ASSOCIATION OF LICHEN PLANUS WITH METABOLIC SYNDROME

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CHENNAI – TAMIL NADU

CERTIFICATE FROM THE DEAN

This is to certify that this dissertation entitled " **ASSOCIATION OF LICHEN PLANUS WITH METABOLIC SYNDROME** " submitted by **DR.S.SUMITHRA** to The Tamil Nadu Dr. M.G.R. Medical University, Chennai is in partial fulfilment of the requirement for the award of M.D. [DERMATO VENEREO LEPROLOGY] and is a bonafide research work carried out by her under direct supervision and guidance. This work has not previously formed the basis for the award of any degree or diploma.

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DECLARATION

I, **DR.S.SUMITHRA,** solemnly declare that the dissertation titled **"Association of lichen planus with metabolic syndrome"** is a bonafide work done by me at Government Rajaji Hospital during 2016 under the guidance and supervision of **Prof.Dr.G.GEETHARANI M.D., DNB.** Professor and Head of the Department of Dermatology, Madurai Medical College, Madurai.

I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree and diploma to any university, board either in India or abroad.

The dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University, towards partial fulfilment of requirement for the award of **M.D. Degree in Dermatology, Venereology and Leprology (BRANCH –XII A).**

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CONTENTS

ABBREVIATIONS

HLA-Human leukocyte antigen

LP-Lichen Planus

LE-Lupus erythematosus

OLP-Oral lichen planus

BMZ-Basement membrane zone

HCV-Hepatitis C virus

HHV-Human herpes virus

VZ-Varicella zoster

NK-Natural killer

MHC-Major histocompatibility complex

LC-Langerhan cell

OPN-Osteopontin

TGF-Transforming growth factor

TNF-Tumor necrosis factor

IFN-Interferon

VEGF-Vascular endothelial growth factor

CVD-Cardio vascular disease

IL-Interleukin

HDL-High density lipoprotein

LDL-Low density lipoprotein

VLDL-Very Low density lipoprotein

TGL-Triglyceride

CRP-C Reactive protein

ESR-Erythrocyte sedimentation rate

PAI-Plasminogen activator inhibitor

MMP-Matrix metallo proteinase

WHO-World health organisation

IDF-International diabetes federation

NCEP-National cholesterol education programme

ATP-Adult treatment plan

TLR-Toll like receptor

FBS-Fasting blood sugar

BP-Blood pressure

INTRODUCTION

INTRODUCTION:

Lichen planus (LP) is a papulosquamous disorder involving the skin, nails, hair follicles and mucous membranes. It has a chronic course with relapse and period of remission[1].The disease was first described by Hebra as Leichen ruber. Erasmus Wilson,in 1869 named the condition as leichen planus.The skin, hair, nails, mucus membrane may be affected.Lichen Planus is rare in children.common in middle aged adult.Itching is variable.The primary lesion is violaceous flat topped papule with several clinical forms.

REVIEW OF

LITERATURE

REVIEW OF LITERATURE

EPIDEMIOLOGY OF LICHEN PLANUS:

Prevalence: 0.5 % of population.[1]

Incidence: The incidence in world population lies between 0.22 to 1%[1] .In India it is 0.38%.

Age: Any age group ,more common in adult frequently affected in 4th to 6th decade[1] .Rare in children.

Sex: LP affects both sexes. Males are affected earlier than females with female preponderance[2]

Race: No racial predilection.

Familial cases: Familial LP are rare but they are reported in association with HLA A3,A5,B7,DR1,DRB *0101[3]

CLINICAL FEATURES:

The classical lesion is violaceous, flat topped ,pruritic ,polygonal papules[1].Common site of predilection is flexor aspect of forearm, legs, thighs and trunk. It also involve oral, genital mucosa, scalp, nail and hair. Oral mucosa without skin involvement can occur .Face, palms and soles are also involved. Wickhams striae is the white reticulate pattern seen over the surface of

the papule, better visualized with hand lens after applying oil over the lesion[1].Lesion appearing at the site of trauma(Koebner phenomenon) also seen.

TYPES OF LICHEN PLANUS:

Based on morphology of the lesion[4]

1.Classical LP-With characteristic feature of LP lesion, the most common site is flexor aspect of the wrist, lumbar region and around ankles.

2.Hypertrophic LP-Common sites are ankle and shin. It start as a small lesion which gradually enlarge and thicken to form hypertrophic lesion. These lesion usually resolve with scarring and atrophy, also associated with severe itching. These lesions are tend to be chronic and persistent. Squamous cell carcinoma reported in long standing cases[5].

3.Atrophic LP-This is a rare form of LP with atrophy at the centre with papules at the margin, the lower extremities being the common site involved ,it is usually seen after resolution of classical LP.

4.Guttate or eruptive LP-Widely scattered discrete,small to larger lesions, with generalized involvement of trunk, both upper and lower limbs.

5.Linear LP-It is common in childhood, occurs along the blaschkos line and the common site involved is extremities and rarely face .It may also follow dermatomes(segmental or zosteriform -LP occurring in linear fashion at the site

of healed herpes zoster(.Isotopic response of Wolff) should not be confused with koebner phenomenon[6].

6.Follicular LP-Follicular lesions are seen during the course of typical LP.LPP presents with irregular patchy loss of hair with loss of follicular ostia lead to scaring alopecia Perifollicular erythema and perifollicular scaling present at the periphery of the scaring alopecia represent the active lesion. .Frontal fibrosing alopecia is a rare variant of LPP which is commonly associated with mucocutaneous LP. Scalp and follicular involvement was reported initially by Graham Little in 1919.

7.LPPigmentosus-Prevalent in India and Middle east described by Bhutani et al[7].This variant seen in Type 3 and Type 4 skin commonly. May or may not be associated with classical LP papules .Common site-face ,neck and upper limb. predominant at intertriginous area. slate grey to brownish black .pattern that are seen are blotchy, reticular and perifollicular. In 1956, Lichen planus pigmentosus was described by Shima.

8.LP Pemphigoides -Described by Kaposi in 1892. It occur as a result of liquefactive degeneration of basal layer. bullous lesion arise on or near the lesion of LP. For the development of bullous lesion from LP lesion it takes around 8weeks.This variant is rare in children but when it occurs, palms and soles are the site of predilection and has got male predilection as against its close differential diagnosis, childhood bullous pemphigoid which has a female predilection..

LPPemphigoide has also been reported with intake of drugs such as cinnarazine, Ramipril, captopril, psoralen and ultraviolet A therapy.

9.Bullous LP-During acute flare vesiculo bullous lesion appear within the lesions of LP. Exaggerated Max joseph space lead to sub epidermal blister. Common site is shin, followed by trunk and thigh. This variant has a chronic course and earlier onset and widespread distribution. Familial cases has also been reported[8].

10.Actinic LP- Known as LP Subtrophicus is common in children and young adults. It is originaly reported from middle east Africa and india[9].common site involved is face.it present as well defined annular patch. hyperpigmentation surrounded by hypopigmentation. erythematous actinic LP is seen in chronic active hepatitis.

11.Annular LP-Has got two types of presentation[10].In one form, annular lesion present with atrophic centre, commonly seen in glans and shaft of the penis. In another form hyperpigmented centre with raised outer border. Unusal variant is annular atrophic LP which has both annular and atrophic features. This variant occur on trunk and limbs. The classical violaceous papules spread peripherally with central atrophy and hyperpigmented border. Histopathologically features of LP seen in raised border, atrophic centre shows degeneration of elastic tissue in dermis which differs from atrophic LP where there is thinning of epidermis with loss of rete ridges and normal elastic tissue.

12.Ulcerative LP-Bulla, erosion and painful ulcers present on the feet and toes lead to atrophic scar and permanent loss of toe nail.

13.LE/LP overlap-Bluish red atrophic plaque or verrucuous papule and nodules which shows clinical, histopathological and immunopathological characteristics of both disorders[11].common site involved are photoexposed and acral portion of extremities.

BASED ON THE SITE OF INVOLVEMENT

1.Oral LP-Seen in 30-70% of cases. In 20-30 % of oral LP buccal mucosa and tongue are involved. The patterns that are seen are reticular, erosive, plaque, atrophic, hypertrophic and ulcerative. The Reticular pattern is common among the them[12]..LP can extend to larynx and oesophagus. For erosive lesion biopsy is important to rule out squamous cell carcinoma.

2.Genital LP-Annular LP is commonly seen over shaft, prepuce, glans penis and scrotum in male and vulva and vagina in female. Second common variant seen in genital is flexural pigmented variant followed by LPPilaris .In females it should be differentiated from lichen sclerosus which shows induration.1982,Pelisse et al described vulvo vaginal gingival lichen planus. In 1993,Cribier et al described peno gingival lichen planus,a male equivalent.

3.Palmoplantar LP-Lesions are firm and have yellowish hue.

4.Inverse LP-Axilla, groin and infra mammary region are involved with classical LP.

5.Nail LP-Reported in 10% of the cases[13].commonly seen in 5th and 6th decade. It,may also cause twenty nail dystrophy. commonly involved are finger nails and the features are as follows

1.longitudinal lines and linear depression due to thinning of nail plate.

2.pterigium unguis –adhesion between the epidermis of dorsal nailfold and nailbed.

3.longitudinal melanoychia

4.hyperpigmentation.

5.subungual hyperkeratosis.

6.onycholysis.

COMPLICATIONS OF LP

1. Post inflammatory hyperpigmentation seen with all variants of LP, take longer time to regress.
2. Erythroderma is reported with generalized LP.
3. Lichen Plano Pilaris is associated with scaring alopecia.
4. Nail involvement in LP lead to dystrophy.
5. Erosive LP is associated with pain on intake of spicy food and hot drinks lead to physical and psychological morbidity.

6. Malignant transformation in long standing cases of hypertrophic LP has been reported.

HISTOPATHOLOGY:

1. In Classical LP-Compact orthokeratosis, wedge shaped hypergranulosis, acanthosis, irregular elongation of rete ridges giving saw toothed appearance, basal cell degeneration are present with dense band like infiltration composed predominantly of lymphocytes in dermoepidermal junction[1]. Civatte bodies (apoptotic keratinocytes) are the special features of this disorder present in lower epidermis[1].civatte bodies are also known as colloid, hyaline or cytoid bodies .Max Joseph space is a small area of artefactual separation between epidermis and dermis[14].

2.Atrophic LP-Thinning of epidermis upto granular layer and effacement of rete ridges.

3.HypertrophicLP-hyperkeratosis,papillomatosis,hypergranulosis,acanthosis,

vacuolar changes are limited to base of rete ridges.

4.LPPigmentosus-Differs from classical features of LP with intense pigmentation and less inflammatory infiltrate.

5.FollicularLP-Orthokeratosis,follicular plugging, wedge shaped hypergranulosis of infundibulum. hydropic degeneration of basal cell layer of external root sheath. Perifolicular lymphocytic infiltrate enveloping upper third

of the hair follicle(infundibulum and isthmus).inter follicular epidermis is normal.in presence of scaring alopecia perifollicular fibrosis and epidermal atrophy at the level of infundibulum give rise to hour glass configuration[14]. The hyperkeratotic papules show similar histological feature, though perifollicular fibrosis is slight and no scaring occur at the end of the process.

6.Actinic LP-Epidermis show atrophy at the centre of the lesion. Intense pigment incontinence. Melanophages are abundant.

7.Ulcerative LP-Biopsy from the skin near to the ulcer show features of LP.
8.LPpemphigoides-Normal skin shows subepidermal bulla without band like infiltrate. .

9.Bullous LP-Features of typical LP with subepidermal bulla heavy dermal infiltrate with colloid bodies.

10.LE/LP overlap-Histological features of LE and LP present in same biopsy.

11.Nail LP-Typical features of LP. Granular layer is normally absent and colloid bodies are rare.

12.Oral LP-Lesions normally show parakeratosis with absence of granular layer. The epithelium is atrophic rather than acanthotic[15]..Ulceration develops by rupture of vesicle or due to necrosis of the atrophic epithelium

SYNDROMES ASSOCIATED WITH LICHEN PLANUS-

1.Graham Little Picarrdi Lassaeur syndrome- Scaring alopecia of scalp ,non scaring alopecia of axilla, groin with follicular lichen planus on body, scalp or both[17]. This was decribed first by Picaardi In 1914 and later in 1915 by Graham Little who reported it in a 55yr old male and was reffered by Lassaeur of Lausanne ,Switzerland. Females are affected more in than males. Common age group affected is 30-60yrs.Cicatricial alopecia of scalp has poor prognosis. Non cicatricial alopecia of axillae and groin resolve spontaneously,whereas follicuar LP show good response to treatment and reccuernce is uncommon.

2.Grinspan syndrome- It is a triad of essential hypertension, diabetes mellitus and oral lichen planus[18]. It is sporadic, non familial and slowly progressive.

3.Jolly syndrome- Grinspan research was confirmed by author Jolly and he confirmed the association of hypertension and diabetes mellitus with oral LP.

4.Good syndrome-seen in 7% of adult with primary immunodeficiency. The characteristic feature of this syndrome are immunodeficiency including thymoma and hypogammaglobulinemia[19].Other features that can be associated with it are oral LP, chronic mucocutaneous candidiasis and pure red cell aplasia.

5.Vulvovaginal gingival syndrome-vulvar lichen planus associated with oral LP[20].

6.Penogingival syndrome- In 1993,Cribier et al described peno gingival lichen planus..Erosive oral LP is associated with erosive penile lesion,causing prepucial adhesion. HPE of oral lesion show typical changes of erosive LP.

DERMOSCOPY IN LICHEN PLANUS

Dermatoscope or dermoscope is a non-invasive, diagnostic tool which helps in the visualisation of subtle clinical patterns of skin lesions and subsurface skin structures which are not visible normally to our unaided eye. It is also called as skin surface microscope, epiluminescence microscope or episcope. Many times the dermoscopic patterns are observed consistently with certain diseases and that help us an aid in diagnosing certain diseases.

In assessing the pattern seen in dermoscopy of various inflammatory condition ,the pioneering work was done by Vazquez Lopez et al[21,22].

Even though LP can be diagnosed clinically,in some cases like LPpilaris causing scaring alopecia, dermoscope helps in arriving at a diagnosis. Wickham striae seen as radiating white line resembling bristles of a comb in dermoscopy helps to differentiate lichen planus from other condition. It is a sign of active disease . Wickhams striae commonly seen in classical LP which

corresponds to hypergranulosis histologically. Morphology of wickhams striae vary from reticular, globular, linear, radial and circular. Colour of the wickham striae observed are white, blue white, yellow.

White dot seen in classical LP correspond to follicular opening surrounded by dermal macrophages. Yellow dot correspond to hyperkeratosis and acanthosis histologically.

Pigmented pattern seen in classical LP may have appearance of dots, globules, peppering , perifollicular. This pattern corresponds to pigment incontinence and dermal melanophages. In early lesion diffuse peppering pattern is seen. Reticulate pattern indicate late lesions.

Vascular pattern seen dermoscopically as red dots, globules, radial and linear. Reticulate vascular pattern was observed commonly in classical LP, which is a marker of active skin lesion. Wickham striae ,pigment ,vascular pattern vary with the variants of LP, duration of the disease and site of the lesion.

In LPpigmentosus –Normal homogenous pigment lines which are smooth forming reticular network are seen as granular pigment lines.[22]

In LPpilaris—In early lesion peripilar cast and scales are seen with follicular plugging .In scaring alopecia white dot surrounded by honeycomb pigmentation seen at the site of follicular loss. Normal reticular pattern in between follicular loss is preserved which differentiate it from discoid lupus erythematosus. Dermoscopy appearance of Lichen Plano Pilaris vary with the

duration of the disease. Wickham striae is seen in early lesion. Lesion of long duration show pigmented pattern[23]

DIRECT IMMUNOFLUORESCENCE IN LICHEN PLANUS:

Done on lesional skin.show features of fibrinogen deposition as shaggy deposit in dermoepidermal junction and is characteristic of LP .Civatte bodies demonstrable in 875 of the cases ,stain mainly for Ig M and also for IgG,IgA,C3. These civatte bodies are also seen in LE ,but they are not seen in abundance and clusters as seen in LP[14]

In LPPilaris, infundibulum and isthumus show deposition of Ig M, IgG IgA and C3.deposition of fibrinogen is seen around the follicle in shaggy pattern.

In LPpemphigoides-DIF of perilesional skin shows linear deposition of IgG and C3 in basement membrane zone.

In LE/LP overlap-presence of cytoid bodies stain for Ig M, IgG present in lower epidermis. IgG and C3 deposit in linear granular pattern is seen in cutaneous LE. shaggy deposit of fibrinogen at dermoepidrmal junction is also seen.[24]

DIF in Oral LP

Diagnosis of OLP depends mainly on both clinical and histopathological features. Direct DIF patterns will be helpful to differentiate OLP from oral LE

lesion showing similar red and white oral lesions , although other investigations such as histopathological study and autoantibodies profiles may also be essential.

DIF is a useful investigation method to distinguish between similar lesions and to confirm diagnosis in cases of uncharacterized features[25]. The histopathological picture in OLP include presence of a lymphocytic band at superficial lamina propria and liquefaction degeneration in the basal cell layer. The histopathological differences between OLP and oral LE are: more pronounced epithelial atrophy in OLP, thicker basement membrane in LE (H&E and PAS), more edema in the lamina propria in LE, deeper perivascular infiltrates, and PAS-positive thickening of vascular walls in LE.

Oral LE picture show positive linear and/or granular IgG, IgA, IgM and complement at BMZ. Laskaris et al., reported the granular pattern of IgG and C3 deposit at BMZ in discoid lupus erythematosus (DLE) in addition to other identical deposits seen in OLP which were positive IgM and C3 at BMZ and colloid bodies[26]. In OLP specimens, positive IgM on colloid bodies were common. , the presence of granular IgG at the BMZ can be used to differentiate oral LE from OLP.

INDIRECT IMMUNOFLUORESCENCE;

Using autologous lesional skin as substrate Fluorescent IgG deposit against lichen planus specific antigen is seen in upper epidermis at stratum granulosum and stratum spinosum is characteristic[2].

Though histopathology and direct immunofluorescence are highly characteristic, they are not specific ,as DIF and HPE also seen in certain condition like systemic lupus erythematosus and dermatomyositis. Lichen planus specific antigen are demonstrated in hypertrophic, vesicular ,actinic, eruptive lesions.

Camisa et al demonstrated Lichen planus specific antigen in bullous LP[27].Olsen et al found Lichen planus specific antigen in LE/LP overlap.[28]

Hence indirect immunofluorescence is helpful in differentiating atypical LP from other dermatoses like lupus erythematosus

ETIOLOGICAL FACTORS:

While LP is known to be autoimmune in its nature, several predisposing, triggering or exacerbating factors have been identified or suspected.

Etiologic factors in the immune pathogenesis of lichen planus (identified or suspected)

- Predisposing factors: Genetic
- Familial occurrence
- HLA haplotypes
- Gene polymorphism

A. Triggers:

Infections

- Hepatitis C
- Hepatitis B

- Human papillomavirus
- Candida

o Trauma

- Mechanical
- Radiation

o Drugs and chemicals

B. Exacerbating factors:

- Oxidative stress
- Psychological stress

A. Genetics

Genetic susceptibility could be the causative in idiopathic LP. Its report in monozygotic twins and family members supports the role of genetic background in the pathogenesis of LP.[30-32] In monozygotic twins association with HLA A3 and HLA A5 has been documented. No association has been reported with other HLA types.The HLA antigen distribution in LP patients of various ethnicities suggests genetic heterogeneity in this disorder.[1] HLA 28,HLA B7 association seen in Jewish people--1 .Associations have been found with HLA-DRI and HLA-DR10(in Arabs);[33] and HLA-DRB1*0101(in the Mexican – Mestizo).

B. Infections

Hepatitis C Virus infection

Hepatitis C virus (HCV) infection has been observed in 10-40% of patients with various clinical types of LP.HCV-RNS and core protein have been detected in lesional keratinocytes of patients with cutaneous LP and chronic HCV hepatitis.[34] HCV-specific CD4+ and CD8 T lymphocytes are also demonstrable in skin lesions of LP.[35] It has been proposed that viral particles may induce altered cytokine expression congenial to the development of LP. However, this association remains controversial.[36]There are many studies regarding association of lichen planus with HCV. Studies conducted in New Delhi, India failed to demonstrate statistically significant association between HCV and LP[37,38] whereas studies conducted in Bangalore and Hyderabad showed significant association. Studies done at Japan and Mediterrean people role of hepatitis C virus has been suggested .Same association is also seen in people of USA, Germany, Italy, Spain, and Iran.Such variations may be attributed to different HLA associations in various populations.[39]

The results of a large multicenter study on the association were inconsistent; the authors suggested further epidemiological studies and basic scientific experiments. In contrast, a recent meta-analysis reported high-quality evidence for this relationship and suggested routine screening for HCV in patients with LP.[40]

Other Viral Infections

implicated in LP are HHV 6,HHV7,Hep B virus, VZ virus

Many studies have reported the association of human papilloma virus (HPV) with oral LP.[41,42] **Vries et al** detected human herpes virus (HHV)-7 DNA in the skin lesions of LP significantly more often than in controls[31]Numerous CD123+plasmacytoid dendrite cells(up-regulated in virus-induced dermatomes')were consistently present in close association with basal cells in lesions of LP.[43]

Candidal Infection

A single study in oral LP patient compared to normal healthy individual reported more frequent colonization of the oral mucosa with Candida species (non-.albicans species).[44]

Vaccination

Some live attenuated vaccines may induce LP. Hep B vaccination trigger LP in some patient. Viral antigens in the vaccine may act as LP specific antigen and trigger cell mediated autoimmune keratinocyte apoptosis. A component present in currently used hepatitis B vaccine, the recombinant protein S, known to participate in the pathogenesis of vaccine induced LP.[45] The occurrence of LP in a healthy adult male following Tdap vaccination[46]

Mechanical Trauma

Tattoo pigments may act as an antigen, triggering the development of LP.A jellyfish sting may cause LP-like cutaneous eruptions.[47]

Generalized eruptive LP has been reported with acupuncture ,starting at the sites of needle insertion.[48]The authors hypothesized that needle prick in acupuncture

might have evoked Koebnerization, which lead to activation of immunological cascade to produce a generalized eruption or it might have been induced subclinical viral infection due to inoculation. Nutmeat et al reported linear LP occurring along Blaschko;s lines following intramuscular injection of triamcinolone for alopecia areta.[49]

Radiation

LP lesions rarely occur following radiation therapy.[43]The term ';isoradiotopic response' was designated to the lesions localised to the site of radiation[50]

Contact allergens:

Chemicals are known to cause lichen planus-like tissue reaction.[51,52] Dental amalgam can cause a lichenoid reaction in experimental animal models[53]as well as in patients with dental fillings. Mercury in dental amalgam act as LP specific antigen causing oral LP. Recent studies show no clear association with it.Betel nut in India and South east Asia is found to be associated with oral LP[1].

Methacrylic acid ester used commonly in car industry, Dimethylfumarate used in sofas act as contact allergen to produce LP[1].Tattoo pigments may act as an antigen, inducing the development of LP.

Drugs:

Cutaneous reaction to certain drugs, chemicals produce lichen planus like or lichenoid drug eruption .lesion look like LP or may be eczematous, psoriasiform or pityriasiform more on photodistribution site. Wickham striae is absent. Associated oral lesion is uncommon. Histopathologically focal parakeratosis, focal absence of granular layer and abundant Colloid bodies with their presence higher up in epidermis are seen .Drugs causing lichenoid reaction are gold,silver,mercury,antimalarials,thiazidediuretics,spironolactone,frusemide ,beta blockers and penicillamine

C. Oxidative Stress

Oxidative stress plays a role in triggering LP. Increase in serum level of reactive oxygen species(nitric oxide, superoxide dismutase) and lipid peroxides(malondialdehyde); with a decrease in the antioxidant defence system(catalase) plays a role in the pathogenesis of both cutaneous and oral LP.[54,55]Barikbin et al found a lower serum level of vitamin C in patients with LP, suggesting the role of free radicals in the pathogenesis.[56]In OLP patients, imbalance in the antioxidant defense system in the salvia and serum may facilitate malignant transformation.[56]

Psychological Stress

In 10-49% of OLP patients mental disorder is recorded.[57]Anxiety and depression are found to be more common in these patients

than in the controls. Study by Lowental et al ,two types :the erosive and bullous types were found to be associated with stressful psychosocial conditions and the reticular type, does not show such an association[58] Shah et al documented an increased salivary cortisol and higher depression, anxiety and stress score in patients with LP irrespective of their gender; there was a positive correlation between these two factors.[59] Stress, anxiety or psychological disorders constituting the etiological or triggering factors in OLP remains unestablished.[57]

Autoimmunity

It is now believed that OLP is an autoimmune disorder. supporting evidences for this hypothesis are adult onset, gender predilection for females, disease chronicity , association with other autoimmune disorders, and presence of auto-cytotoxic T cell clones.[60]Danielsson et al demonstrated increased expression of cyclooxygenase-2 (COX-2), a biomarker for autommunity seen in lesions of OLP.[61]As malignant conversion in OLP is rare, they suggested that this observation may support an antoimmune pathogenesis.[61]

IMMUNOPATHOGENESIS

There are three major steps involved in the immunopathogenesis of LP.[62]

1. LP-specific antigen recognition by CD4+ T cells and NK cells
2. Cytotoxic T cell activation
3. Keratinocyte apoptosis.

1.LP-Specific Antigen Recognition

Autoreactive peptides or certain exogenous factors act as LP-specific self-antigens combine with MHC class I, expressed on the surface of basal keratinocytes.[62]These antigens expressed with MHC class I are recognized by cytotoxic CD8+ T cells and NK cells(antigen recognition) lead to cytotoxic T cell activation. Eventhough autoimmunity plays a central role in Lichen Planus, the exact patho mechanism and exact nature of self antigens is not clear. There are many stimulus like viruses, drugs and contact allergens[60]Some heat-shock proteins also act as auto antigens. The sites of antigen expression in the keratinocyte are very localized and determine the tentative sites of the future clinical lesions.[60] Up-regulation of keratinocyte chemokine formation also occur at the same time.[60]

2.Cytotoxic T cell Activation

The interface infiltrate in LP lesions consists of a mixture of T lymphocytes, NK cells and plasmacytoid dendrites' cells. initially the lesion has both CD4+ and CD8+ T cells ,with disease progression there is predominant CD8+ T cell.[62]

Rana et al studied the distribution of T cell subsets in LP.[64]Cytotoxic T cells were predominant in dermo epidermal junction, whereas CD4T cells were found perivascularly in the dermis.[54]The authors proposed that the cytotoxic T cells in dermoepidermal junction induced the keratinocyte apoptosis[64] The

inducer CD4 T cells present perivascularly assist the cytotoxic T cells in keratinocyte damage by releasing Th1 cytokines.[64]

An immunohistochemical study of cutaneous LP found that infiltration of T lymphocyte in the dermis precedes the histopathological change in epidermis.[60] In well formed lesions these cells present in the lower epidermis and at this stage there are various histopathological changes like vacuolation of basal cells and spongiosis of spinous layer are seen.[60]Vacuolar degeneration of basal keratinocyte result in basement membrane disruption, allowing the entry of further CD8+ cells, there by perpetuate the course of the lesion.[64]

The immunophenotype of infiltrated T cells may be variable. One study found predominantly two subtypes (CD27+ and CD38+ cells) of infiltrated T cells in patients with atrophic OLP, suggesting that even with the same clinical features and histopathology, its pathomechanisms may be variable, mediated by two immunophenotypically different T cells.

The various mechanisms by which T lymphocytes are attracted, retained and accumulated at the lesion site are:

i. Brn2, a transcription factor which is primarily involved in keratinocyte differentiation, is expressed in high concentration in the upper granular layer of the epidermis. This factor probably attract T lymphocytes, thus initiating the pathogenic process.[66] Immuno histochemically this Brn2 factor is demonstrable in the thickened epidermis of LP.

ii. The chemokine receptors(CXCR3 ligand, homeostatic CDCL12 chemokine, CCL20 and its receptorCCR6) help in the accumulation of CD8 cytotoxic cells and plasmacytoid dendritic cells (pDC) at the lesional site[67]The accumulated pDCs secretes large amount of IFN-α which in turn lead to activation of IFN-γ secreting cytotoxic cells and pDCs in the lesion.[67]

iii. In Oral lichen planus the rate of apoptosis in keratinocytes and lymphocytes are different in the tissue.[68] As compared to normal oral mucosa the apoptotic index of keratinocytes is increase whereas for lymphocytes it is decreased in OLP lesions[68] This mechanism helps in the survival of lymphocytes at the lesion contributing to the formation of OLP.[68]

iv. The infiltrated T cells and keratinocytes secrete a chemokine RANTES (Regulated upon Activation, Normal T cell Activated and Secreted),causes mast cell degranulation and release of RANTES by the T cells.[1]This mechanisms plays a role in persistence of T cells at the lesional site and chronicity of the disease.[1]

v. Elevated plasma osteopontin (OPN) level and CD44 levels are documented in patients with OLP.[69] OPN plays important role in the pathogenesis and progression of Th1 mediated immunological disorders and it also prevents T cell apoptosis, thereby facilitate the accumulation of T cells at the lesional site.[60]

Role of NK Cells

Infiltrated NK cells also contribute with its cytotoxic action. There is predominant infiltration of CD3-CD56+cells at the DEJ and papillary dermis in early lichen planus lesion. Whereas in established lesions, NK cells belonging to CD56- subset are present and they are characterized by high positivity for perforin and natural cytotoxic receptors (NKG2D and NKp44) on their surface These cells are also able to secrete TNF- α and IFN-γ.[71]

Role of Langerhans Cells

The CD1a+ Langerhans cells(LC) are involved in the presentation of antigen to T cells and they are demonstrated in excess in the lesional tissue.[1,60]LC activation and differentiation are promoted by TGF-β family member, activin A, whose concentration found to be increased in the affected skin.[1]when compared to controls there is an increase in the number of LC at the lesional site during the initial period of symptoms, suggest their migration at the lesion site and their critical role in the immune response.[70] Though in older lesions, LC migration decreases there is some significant movement of LC from the superficial to the basal part of the lesion[70]

Role of Th1 cytokine

Production of Th1 and Th2 cytokines simultaneously in LP lesions are noted. MHC class II expression and LCs is up-regulated.[70]The antigen presenting cell ,Langerhans cell along with MHC class II cells present an antigen to CD4+

helper T cells. There is expression of a hypothetical cell surface molecule 'request cytotoxic activity (RCA)' on the surface of CD4+ helper T cells.[70] This RCA molecule to the receptor stimulates CD4+cells initiating Th1 cytokine response thereby release interleukin-2 and IFN-γ, TNF-α and transforming growth factor-β causes migration of lymphocyte to the lesional site.[72,73] IL-2,IFN gamma activate CD8+ T producing basal cell degeneration.

Antigens presented by MHC class I to CD8+ T cells takes place through the endosomal pathway whereas antigen presented by MHC class II to CD4+T Cells is through cytosolic pathway.[60]sometimes the same antigen(e.g.viral protein)undergoes modification through both endosomal and cytosolic pathways to activate two subsets of T cells.[60]

Changes that occur in both keratinocyte and activated lymphocyte lead to keratinocyte apoptosis. Activation lead to clonal expansion of activated T cells in lesional tissue and expression of multiple surface receptors on these cells.[62] β_2-integrin and leukocyte function-associated antigen (LFA-1) are expressed and they help in binding intercellular adhesion molecule (ICAM-1) thereby it augment lymphocyte interaction with keratiocytes.[62]

Activated T lymphocyte and keratinocyte interaction has been studied extensively in the pathogenesis of OLP. The activated T lymphocytes may encounter the keratinocyte antigen by chance (chance encounter hypothesis) or may be attracted towards the epithelium under the influence of several chemokines released by keratinocytes (directed migration hypothesis).[60]

The facts that favour for the 'chance encounter hypothesis' are:[60]

1. Presence of T cells in normal human epidermis and there is evidence that that basal cell degeneration occur even in absence of inflammatory infiltrate.
2. Prevalence of OLP is low in the general population (1-2%).
3. Onset of OLP later in life.

Supporting the fact 'directed migration hypothesis are:

1. Constitutive chemokine receptor expression on naïve T cells.
2. T cell infiltrates in the dermis prior to the appearance of intraepithelial lymphocytes and epithelial damage.
3. Antigen-specific CD8T cells are preactivated that up-regulate inflammatory chemokine receptor expression on keratinocytes and attract these cells to the site of future LP formation.
4. The chemokines derived from keratinocyte attract both antigen specific and nonspecific T cells to the site of new developing LP.

Role of Keratinocytes

Basal Keratinocytes also play a role in T cell maturation,activation and infiltration by releasing certain cytokines. They are interleukins(IL-1β,IL-4and IL-6),granulocyte-macrophage colony stimulating factor and TNF-α.[62]Specific keratin genes are also up-regulated on the surface of lesional basal and suprabasal keratinocytes by these cytokines. These include K17, which

normally is expressed only in adnexal structures, K6 and K16[62]K4 and K13 are reduced in orthokeratotic areas while K1 and K10 are enhanced.[62]

3.Keratinoocyte Apoptosis

Activated T cells are gets attached to the basal keratinocyte by its adhesive property because of IFN-γ mediated enhanced expression of adhesion molecules(ICAM-1 and vascular cell adhesion molecule, VCAM-1) on the surface. Activated cytotoxic T cells cause apoptosis in several ways:

- Release of the cytolytic molecule perforin, causing keratinocyte membrane damage by pore formation.[63]
- Release of the serine esterase granzyme B, enters through a porous keratinocyte membrane and causes DNA disruption.[63]
- Release of TNF-α and Fas(CD95), binds to keratinocyte membrane death receptors(TNF-α R-1 and CD95L) initiating keratinocyte caspase activity.
- Inactivate the basement membrane derived anti-apoptotic mechanism, the 'cell-survival-signal; This is mediated by expression of matrix metalloproteinase (MMP-9)mRNA on the surface of T lymphocytes(up-regulated by TNF-α). This is the step involved in the ultimate stage of keratinocyte death.[62]

  Apoptotic keratinocytes are no longer able to perform its function by secreting its components like laminin V and collagen VII in

maintaining basement membrane . The consequences is basement membrane disruption, the ultimate event in the pathogenesis of LP.

Other Mehanisms in the Pathogenesis of LP

are:

i. As there is increased fibrin deposition at the dermo epidermal junction, fibrinogen cascade may play a role. Since the fibrin deposition was more intense in newer lesions, in older lesions it was proposed to be removed by phagocytosis.

ii. Another important factor, angiogenesis is suggested in the pathogenesis of LP.[72]Microvessel density assay (CD34 staining) and VEGF expression are significantly higher in cutaneous lesions of LP than in controls Angiogenesis is increased more in erosive OLP, suggesting its propensity towards malignant transformation.[73]

iii. Nonantigen-mediated mechanisms in the pathogenesis of OLP are MMP activation and mast cell degranulation, facilitate basement membrane disruption and passage of cytotoxic T cells into the epidermis.[74] Infiltrated T cells secrete MMP-9 causes mast cell chemotaxis and degranulation and further release of TNF-α.[1] Chymase a protease released by degranulation of mast cells, in turn

activates MMP-9. Tryptase, chymase and activated MMP-9 lead to basement membrane damage.[74]

iv. Desmoglein 1 and 3 autoantibodies have been detected in patients with OLP and may play a role in the pathogenesis.[74]

Immuno pathogenesis of OLP

The basic immune pathogenesis of OLP is similar to that of cutaneous lesions. There is abundant T cell infiltration and the activated CD8+ T cells trigger the apoptosis of oral mucosal keratinocytes.

Various receptors/ligands and or the related gene that are expressed in OLP tissue include:

1. Bonemorphogenic protein(BM-4):BMP-4 is a member of the TGF-β family and mediates apoptosis.
2. Epidermal growth factor receptors(EGFR):Enhanced EGFR expression on the keratinocytes in OLP lesions and the up-regulation of EGF-like ligands [amphiregulin (AGEG), epiregulin (EREG), and heparin-binding EGF-like growth factor(HB-EGF)], in keratinocytes mononuclear cells could contribute to the carcinogenesis and pathogenesis of OLP.[75]
3. Toll like receptor(TLR): There is over-expression of TLR-2 bin the cells of the spinous layer and infiltrating monocytes in OLP lesions. This favours a Th1 type of response, initiating lesions of OLP.[76]

4. Programmed death-1 molecule(PD-1): Co-stimulatory PD-1 molecule and its ligand PDL-2 expression at both gene and protein level in increased in both peripheral blood and lesions in patients with OLP.[77] These molecules of the local immune response of OLP.

   Micro-RNAs(miR): These are small noncoding RNAs expressed in normal as well as diseased cells (inflammatory and autoimmune).[78] There is alteration of various miR-203 and decreased miR-125b). Some authors n have found significant down-regulation of miR-27b in OLP, Particularly in the atrophic/erosive variant.[79]

ASSOCIATION OF LICHEN PLANUS

Some disorders are associated with LP more frequently than it is expected. There have been studies associating lichen planus with several systemic diseases[80] like diabetesmellitus[81],hypertension and dyslipidemia[82], ,thyroid disorders, myasthenia gravis ulcerative colitis[83], hepatitis C infection[84], thymoma, primary biliary cirrhosis, dermatomyositis and systemic lupus erythematosus.

An increased prevalence of the disease, was found in people with HCV infection.T here have been reports worldwide regarding this association with variable frequencies.[84]

Association with thyroid disorder was studied only in patients with oral lichen planus ,hence further study is needed in cutaneous LP

Population[85] also. There are studies which showed prevalence of thyroid disease in lichen planopilaris, especially hypothyroidism. Autoimmune thyroiditis showed association with lichen plano pilaris in a rare case report.

Prevalence of association of lichen planus with helicobacter pylori infection was reported in many studies. few studies showed less association. Helicobacter pylori most common cause of gastric ulcer, duodenal ulcer, adenocarcinoma of stomach had been studied its link with oral lichen planus. Noninvasive methods are urea breath test, serological test, stool antigen assay, many studies took urea breath test which measure the activity of urease of H.pylori in stomach and found high titre of urea breath test when compared to controls.

Diabetes mellitus has been reported to be associated with lichen planus in which the diabetics exhibited a greater frequency in patients with oral lichen planus on the tongue.In 150 cases of oral LP ,13 percent found to have diabetes mellitus in a study by Anjana Bagewadi et al.[87]

In a prospective study by Silverman et la found no association between diabetes and onset of oral LP[88].. Dilip Kachhawa et al found association of LP with hypertension was 2.4%,polymorphic light eruption .1%,vitiligo 1.9% and diabetes mellitus 1.6% in a clinicoetiological study of 375 cases.

Lichen planus has also been reported in association with cutaneous autoimmune diseases including alopecia areata[90], vitiligo[91], dermatomyositis[92], lichen sclerosus[93], systemic lupus erythematosu[94], pemphigus and paraneoplastic pemphigus[95]

Thomas et al. have also reported morphea to be associated with lichen planus. Lichen sclerosus et atrophicus has also been mentioned in the literature as an associated disorder of lichen planus.

Ahmed et al. have reported 3 of their patients with lichen planus to be suffering from SLE. The coexistence of vitiligo and LP is also described with or without the presence of other autoimmune diseases. Kar and Madris et al have also reported this association of LP with alopecia areata.

ASSOCIATION WITH DYSLIPIDEMIA-

One of the common metabolic disorder is dyslipidemia. Usually it is found on routine investigation. Chronic inflammation in certain dermatological disorder plays crucial role in the development of dyslipidemia. Early recognition of it helps in reduction of the consequences. Abnormal lipoprotein is dyslipidemia which include lipoprotein over production and lipoprotein deficiency. Manifested as increased TGL, increased low density lipoprotein, increased total cholesterol and decreased HDL.

Dyslipidemia may be due to overproduction of lipoprotein or its decreased clearance defect in apo lipoprotein or due to metabolic enzyme deficiencies. May

be primary or secondary. Primary dyslipidemia is due to genetic defect in lipid metabolism, commonly seen in familial cholesterolemia. Secondary dyslipidemia is secondary to diseases like diabetes ,hypothyroidism, obstructive jaundice etc due to medication retinoids,cyclosporine,tacrolimus,corticosteroids,antiretroviral drug especially protease inhibitor, TNF blockers, long term infliximab may be proatherogenic. Dermatological manifestation of dyslipidemia are xanthomas due to lipid laden macrophages. Xanthomas may be tendinous, tuberous, eruptive and planar. Tendinous xanthoma commonly present over Achilles tendon and tendons of the hand. Tuberous xanthoma present as a yellowish nodules over joints. Commonly seen in hypertriglyceridemia and hypercholesterolemia. Eruptive variant present as orange yellow papules seen with hypertriglyceridemia. Also seen in diabetes mellitus. Planar type present as macules with slight elevation. present at any site. common site is periorbital region known as xanthelasma. Xanthoma present at palmar crease is known as xanthoma striatum palmare.

Chronic inflammation in lichen planus explain its association with dyslipidemia. Cytokines released during inflammation contribute to dyslipidemia[96].Many of the studies showed individual with lichen planus had higher level in lipids when they were compared with controls.

Dyslipidaemia was diagnosed among 42.5% of cases of lichen planus compared to 37.8% of controls in a case control study done by Deiher J et al.[97] In another case control study on lipid levels and lichen planus showed that

the prevalence of dyslipidaemia in patients with lichen planus was 61.3% when compared to 32.5% in controls.[86]

A case control study done by Arias-Santiago S et al. showed a significant association between dyslipidaemia and lichen planus. This study also focused on ESR, CRP levels and fibrinogen levels, which were significantly raised in patients with lichen planus. A positive correlation was found between CRP and lipid levels.[98]

Sharrett et al. stated that higher values of triglycerides and low levels of HDL-C were associated with the transition from atheroma to atherothrombosis and therefore control of these two cardiovascular risk factors is essential in patients with subclinical disease.[99]

In a case control study LP was found to be associated with dyslipidemia particularly in age group of 55-64 yrs, people of intermediate status,non smokers,non obese and people without hypertension, diabetes and hypothyroidism

Sezer E et al studied association of lipid peroxidation and antioxidant status in lichen planus in 125 patients and found alteration in lipid metabolism antioxidant status in LP was found to be higher than controls.[100,101]

Few studies found no association exists between LP and dyslipidemia and diabetes.In a study conducted in 2015,Egypt in 20 LP patients showed no association with dyslipidemia.

Dyslipidemia has also been found to be associated with psoriasis pemphigus vulgaris, discoid lupus erythematosus, hyperlipidemia, sea blue histiocytosis, cutaneous necrobiotic xanthogranuloma. Granuloma annulare also reported to be associated with hyperlipidemia.

ASSOCIATION OF LICHEN PLANUS WITH METABOLIC SYNDROME

Metabolic syndrome—It is a group of risk factors accompanying abnormal adipose deposition and function. Skin problems are common in patients with metabolic syndrome, associated with obesity, diabetes, hyperlipidemia and chronic inflammation[102].

PREVALENCE OF THE METABOLIC SYNDROME

The metabolic syndrome is increasing in prevalence over the world as a result of increasing obesity prevalence. India had strikingly high prevalence rate compare to the rest of Asia. In a study conducted in Eastern India by D.S. Prasad et al[105], the Age-standardized prevalence rates of metabolic syndrome were 33.5% overall, 24.9 % in males and 42.3% in females. In another study conducted by Gupta R et al[106], MS was present in 345 (31.6%) subjects; prevalence was 122 (22.9%) in men and was 223 (39.9%) in

women ($p<0.001$); the age-adjusted prevalence was 24.9%, 18.4% in men and 30.9% in women.

RISK FACTORS IN METABOLIC SYNDROME

Overweight-Central obesity major component of metabolic syndrome. There exist strong prevalence between metabolic syndrome and obesity.

Age and sex- Increasing age increases the possibility of metabolic syndrome .Prevalence of metabolic syndrome reported to be higher in females[107].

Low physical action-one of the major risk factor for MS .Physical activity stands first in the treatment of MS. . Studies comparing patients involved in less active activities like television or computer for less than one hour daily to those that carried out these behaviours for more than four hours daily have a several fold increased risk of the metabolic syndrome[108].

Abundance caloric intake- With decreased physical activity contribute to metabolic syndrome.

Factors of systemic aggravation, including C-reactive protein, fibrinogen, interleukin 6 (IL–6), tumour necrosis factor component alpha (TNFα) and others have been observed to be connected with Metabolic disorder. The metabolic risk factors include

i. Elevated triglycerides,

ii. Small LDL particles,

iii. Insulin resistance, glucose intolerance,

iv. Proinflammatory state, and

v. Prothrombotic state

The *important* risk factors include

i. Cigarette smoking,

ii. Hypertension &

iii. Dyslipidemia - elevated LDL cholesterol, low HDL cholesterol,

iv. Positive family history of premature coronary heart disease (CHD)

Old age

Common features of metabolic syndrome are

1. Abnormal body fat distribution-Many studies showed increase risk for non communicable disease associated with increase in abnormal fat distribution .It showed increase in association with dyslipidemia, CVD, type 2 diabetes. With increased waist measurement, fasting hypertriglyceridemia may represent a simple but useful marker of the possibility that the increased girth is due to visceral fat accumulation. Waist circumference found to be superior when compared to BMI for visceral fat accumulation and abdominal obesity. Waist circumference showed differences according to ethnic/country group.

2.Insulin resistance- is present in significant proportion of people with the metabolic syndrome. It strongly co-associates with other known metabolic risk factors and CVD risk. The mechanisms underlying increased prevalence of CVD risk factors are uncertain, hence insulin resistance is categorised as an emerging risk factor. Patients with insulin resistance have glucose intolerance, another emerging risk factor. If glucose intolerance progresses into diabetes, it is independent risk factor for CVD.

3.Atherogenic dyslipidemia-increased triglyceride and decreased cholesterol noted in routine analysis in many patients with metabolic syndrome. other lipoprotein abnormalities include increase in remnant lipoproteins, elevated apolipoprotein B, elevated small LDL, and small HDL particles These abnormalities are atherogenic independently.

4.Elevated blood pressure-commonly seen in patients with insulin resistance,has strong association with obesity varies from one population from another population. . Hypertension is multifactorial in origin

5.Proinflammatory state-in metabolic syndrome patient proinflammatory state can be recognised with elevated CRP plasma level .It has strong association with obesity, the mechanism where the adipose tissue release inflammatory cytokines promoting inflammation explain this strong association. C-receptive protein (CRP) is the inflammatory variable that has been connected with CVD hazard. CRP is a blood test marker for inflammation in the body. The rise of CRP

has been as of late connected to atherosclerosis and cardiovascular sickness, since the pathophysiology of these conditions has been connected with inflammation. However the hoisted CRP alone has not been appeared to be a reason for CVD. In any case CRP can be utilized as indicator of CVD taking into account its connection with other known cardiovascular danger components like insulin resistance. Large amounts of white cell number have additionally been connected with expanded insulin resistance and consequently CVD.

6.Prothrombotic state- Components of the MS are associated with both coagulation and fibrinolytic proteins,shows link which supports with an elevated plasminogen activator inhibitor-1 (PAI)-1 and elevated fibrinogen are present in metabolic syndrome. Fibrinogen, an acute-phase reactant, rises because of inflammatory state. Hence, pro-thrombotic and pro-inflammatory states are metabolically interconnected.

Plasminogen activator inhibitor-1 and CRP have been connected[109] with upgraded hazard for the development of CVD. Plasminogen activator inhibitor (PAI-1) is an inhibitor of fibrinolysis. The PAI-1 restrains the tissue plasminogen activator and comparative chemical urokinase, which initiate plasmin, along these lines inhibit the blood coagulation (fibrin). More elevated amount of plasminogen activator inhibitor - 1 is a causative element for the expanded event of thrombus development.

SIGNS AND SYMPTOMS OF METABOLIC SYNDROME:

Most of the metabolic risk factors have no signs or symptoms, although increase in waist circumference is a visible sign. Some may have symptoms of hyperglycemia –type 2 diabetes are increased thirst, increased urination during night, fatiguability and blurred vision .High blood pressure have no signs and symptoms usually, some may have dull headache, dizziness and nose bleed.

PATHOGENESIS OF METABOLIC SYNDROME

The metabolic syndrome seems to have potential etiological categories:

a. Obesity and disorders of adipose tissue;
b. Insulin resistance; and
c. A constellation of independent factors (eg, molecules of hepatic, vascular, and immunologic origin) that mediate specific constituents of the metabolic syndrome.
d. Other factors—aging, proinflammatory state, and hormonal changes—have been implicated as contributors as well.

Inflammation

Chronic inflammation with persistent elevated level of proinflammatory cytokines is the hallmark of Met S.[110] The proinflammatory

cytokines produced by adipocytes that are involved in metabolic syndrome are Leptin,adiponectin, tumor necrosis factor-α(TNF), interleukin 6 (IL-6), monocyte chemotactic protein-1(MCP-1), and certain other adipocytokines[102] . They are now recognized as a part of the innate immune system, play an important role in the pathogenesis of resistance to insulin. They are also found to be associated with metabolic complications such as dyslipidemia, hypertension, and premature heart disease and their level are also found to be elevated in many dermatological diseases that are associated with Met S. [102] Interleukin (IL)-6 is reduced at the site of inflammation and plays important role in the production of acute phase proteins.. IL-6 in combining with its soluble receptors IL-alpha, lead to the transition from acute to chronic inflammation by changing the nature from polymorphonuclear neutrophils to monocyte/macrophages). In addition, it also exert an stimulatory effect on T- and B-cells, favoring chronic inflammatory responses

It is proposed that cytokines produced during inflammation are released into the systemic circulation thereby alter the function of hepatocytes, vascular cells, and leukocytes and may lead to the formation of atheroma. Role of inflammation associated with metabolic syndrome in many dermatological condition has been proved with therapeutic protocol in lowering the inflammatory cytokines successfully lead to decrease in the development of cardiovascular mortality.

Therapeutic intervention based on drugs such as methotrexate and TNF-α antagonist has been found to decrease the blood level of C-reactive protein, IL-6,and decrease the insulin resistance and an increase in HDL.[103]

Oxidative stress-

Oxidative stress, a condition due to relative imbalance between reactive oxygen species (ROS) and antioxidants enzyme system is believed to play a central role in the pathogenesis of MS. [103]

Obesity is associated with dysregulation of carbohydrate and lipid metabolism. In obesity increased oxidative stress paly important role in the pathogenesis of metabolic syndrome. Not alone in lichen planus, in many diseases oxidative stress plays an important role.

Reactive oxygen species cause increased expression of NADPH oxidase enzyme and decreased expression of antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase).Increase in reactive oxygen species cause dysregulated production of adipocytokines adiponectin,IL-6,TNFalpha,MCP-1,tissueplasminogen activator. Increased production of PAI-1 and TNF-α from accumulated fat contribute to the development of thrombosis and insulin resistance , respectively, in obesity.

Obesity and chronic inflammation play major role in etiology of metabolic syndrome. Not only obesity ,certain xenobiotics such as exogenous chemicals, drugs, environmental pollutants, and dietary components forming major source of ROS are eliminated through the skin. The skin expresses all

known xenobiotic metabolizing enzymes, such as cytochrome P450 enzymes, flavin-dependent mono oxygenase, monoamine oxidase, alcohol dehydrogenase, aldehyde dehydrogenase, nicotinamide adenine dinucleotide phosphate: Quinone oxidoreductase, glutathione S-transferase, and catechol-O methyltransferase.[110,111]In inflammatory skin lesion decreased elimination of xenobiotics through sebum gets dearranged resulting in increased blood level of circulating lipids and cholesterol, thereby increasing the risk of dyslipidemia &MS[110].

Endocrine abnormalities-

Adipocytokines such as adiponectins and leptin, promote inflammation, alter glucose metabolism, and vascular endothelial biology. MS has been consistently associated with decreased plasma adiponectin level[102]. Hypoadipoleptinemia is found in chronic inflammatory diseases like psoriasis compared with healthy controls, therefore contributing toward the development of MS.

Leptin being a hypothalamus modulator of food intake, body weight, and fat stores, exerts important role in acute and chronic inflammatory processes by regulating cytokine expression that modulates the balance of helper T-cell types 1 and 2.

COMPONENTS OF METABOLIC SYNDROME:

1.Central obesity- New IDF definition requires evidence of central obesity for the diagnosis of MS. The important requirement is central

obesity, as it is more strongly correlated with the other MS features and highly correlate with insulin resistance. Many reports support the view that central obesity/insulin resistance are constant features of the MS. With waist circumference ,central obesity is easily measured, with cut-points that are specific for gender and ethnic-group. For example, an abnormal waist circumference for Europe males is ≥ 94 cm and for Europe females is ≥ 80 cm, whereas for Asian population for male it is >90cm and for female it is >80cm.

2.Dyslipidaemia-Dyslipidaemia is defined as either raised TG levels ≥ 1.7 mmol/l (150 mg/dl), low HDL-cholesterol < 0.9 mmol/l (40 mg/dl) for men and < 1.29 mmol/l (50 mg/dl) in women, or specific treatment for previously detected hypertriglyceridaemia and/or reduced HDL-cholesterol. In certain population modification is needed for women HDL level.

3.Raised blood pressure-Raised blood pressure is defined as systolic pressure ≥ 130 mmHg, diastolic ≥ 85 mmHg, or antihypertensive treatment for previously diagnosed hypertension.

4.Hyperglycemia-It is defined as presence of either fasting blood sugar (≥ 5.6 mmol/l or 100 mg/dl) or previously diagnosed diabetes. If fasting plasma glucose is 5.6–6.9 mmol/l (100–125 mg/dl) an oral glucose tolerance test (OGTT) is strongly recommended to diagnose diabetes, but to diagnose metabolic syndrome it is not necessary **.**.

Criterias to diagnose metabolic syndrome.

At least 3 organizations have recommended clinical criteria for the diagnosis of the metabolic syndrome. Their criteria are similar in many aspects, but they also reveal fundamental differences in positioning of the predominant causes of the syndrome

They are ATP-III guidelines[113], WHOcriteria[114] ,IDF criteria separately.

The metabolic syndrome defined by NCEP ATP-III[121] guidelines consists of three or more of the following:

1. fasting plasma glucose ≥110 mg/dl,
2. serum triglycerides ≥150 mg/dl,
3. serum HDL cholesterol <40 mg/dl,
4. BP ≥130/85 mmHg or on BP medication,
5. or waist girth >102 cm.

According to WHO criteria,

1. Hyperglycemia (fasting glucose ≥110 mg/dl) in addition to this, any two of the following
2. Waist girth ≥94 cm,
3. Dyslipidemia (triglycerides ≥150 mg/dl or HDL cholesterol <40 mg/dl), or
4. BP ≥140/90 mmHg or taking BP medication .

The new IDF definition of metabolic syndrome has been divided according to the following age groups: 6 to ,10, 10 to ,16, and16 yr[115]. In all the

three age groups, abdominal obesity is the central feature. Below 10 yrs of age , the metabolic syndrome is not diagnosed, but a strong advice to be given for weight reduction for these children. At the age of 10 yr and more, a diagnosis of metabolic syndrome can be made.

It requires the presence of abdominal obesity plus the presence of two or more of the other components (elevated triglycerides, low high-density lipoprotein (HDL)-cholesterol, high blood pressure, and elevated plasma glucose). The IDF adult criteria can be used for adolescents aged 16 yr and above, but for children from 10 to 15yrs waist circumference should be more than 90th percentile cut off for waist circumference. The waist circumference for his age group is different for different population.

Country/ethnic group	Waist circumference value	
	Male	Female
Europids*	≥94 cm	≥80 cm
South Asians‡	≥90 cm	≥80 cm
Chinese	≥90 cm	≥80 cm
Japanese	≥85 cm	≥90 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available	
Sub-Saharan Africans	Use European data until more specific data are available	
Eastern Mediterranean and Middle East (Arab) populations	Use European data until more specific data are available	

In Asians ,the prevalence of metabolic syndrome increase from 12.2 to 17.9 % on decreasing the waist circumference. NCEP ATP-III criteria will underestimate the people at risk ,hence IDF criteria commonly used in Asian population to diagnose metabolic syndrome.[116]

Other diseases of the skin found to be associated with metabolic syndrome are

1. Psoriasis-It is a immune mediated inflammatory disease, which has the strongest association than any other skin condition. chronic inflammation has strong link between it and metabolic syndrome. Inflammatory marker Th1 cytokine ,TNF alpha ,intercellular adhesion molecule plays important role in

the pathogenesis of psoariasis , metabolic syndrome, obesity, atherosclerosis, myocardial infarction[117,118].Th1 cytokines IL-2,IL-12,TNF alpha, IFN gamma predominate in psoriatic condition plaque and atherosclerotic plaque. Even though so many studies found association, worldwide many studies failed to produce association between psoriasis and metabolic syndrome

2.Androgenic alopecia-mechanism in link between the two is unclear. Genetic factor and family history proposed to be the association between androgenic alopecia and cardiovascular disease. Hyperinsulinemia, hyperaldosteronism, chronic inflammation has been found to be the culprit in association between androgenic alopecia had metabolic syndrome[119].Increase in the proinflammatory cytokines along with microinflammation in hairfollicle seen as local manifestation of systemic inflammation associated with higher risk in metabolic syndrome in these patients.

3.Acanthosis Nigricans -Many number of studies showed association of AN with Metabolic syndrome[120,121].Hyperinsulinemia interacting

with epidermal keratinocyte lead to acanthosis nigricans. 4.Acrochordon -Increase in leptin in these individual proposed to have link in association with obesity and hyperlipidemia[122].As a whole its association with metabolic syndrome has yet to be proved.

5.Hidradenitis suppurativa - It is a chronic destructive ,scarring inflammatory skin disorder .Chronic inflammation has strong link with metabolic syndrome[123].Prevalence of obesity ,hypertriglyceridemia, decreased HDL level,hyperglycemia and metabolic syndrome found to be higher in this condition. 6.Systemic Lupus Erythematosus-Prevalence of metabolic syndrome in these individuals varies between 17-40%.Increase in proinflammatory cytokines,lack of exercise and high dose of prednisolone showed its association with metabolic syndrome[124]

Bhuvana Krishnamoorthy et al ,found chronic inflammation as a component of MS in a descriptive study in lipid profile and metabolic syndrome staus in oral LP patients.[125] Patients with chronic diseases show decreased levels of HDL-C and hypertriglyceridemia, with a positive correlation with cytokine levels. Similar to psoriasis, lichen planus might be a marker for dyslipidemia.

In a case control study of 79 patients by Baykal, L., et al for prevalence of metabolic syndrome in patients with mucosal LP ,they found prevalence of MS was higher in patients with LP with mucosal involvement than without[126].In the MS criteria FBS, Diastolic Blood pressure was higher in LP patients than in control

A descriptive study in lipid profile and metabolic syndrome status in patients with oral LP ,oral lichenoid reaction and healthy individuals attending dental college by Bhuvana krishnamurthy et al found chronic inflammation causes disturbances in the lipid metabolism. When this dyslipidemia becomes prolonged it increases the risk of cardiovascular disease also found . differences in the lipid profiles of patients with OLP and OLR Higher levels of S triglyceride and VLDL-C, lower levels of HDL-C in OLP when compared to OLR .The results insist for careful monitoring of patients with OLP and OLR in order to identify, prevent and modify their cardiovascular risk factors.

AIM OF THE STUDY

AIM OF THE STUDY

1.To determine the association of lichen planus with metabolic syndrome

MATERIALS AND METHODS

MATERIALS AND METHODS

The material for this study was from the patients attending the skin OPD, Govt Rajaji Hospital, Madurai Medical College Madurai during the period from february2016 to july2016.

INCLUSION CRITERIA

Newly diagnosed patients of Lichen Planus who are above 10yrs of age attending the OPD during the study period.

Biopsy proven cases in clinical dilemma.

All variants of Lichen Planus.

EXCLUSION CRITERIA

LP patient of age group less than 10yrs.

Patients who are known diabetic and hypertensive on treatment.

Old cases of LP on treatment.

Patient who did not give consent.

A total of 113 cases who were diagnosed as lichen planus and fulfilled the inclusion criteria were included in the study. Among them 4cases were biopsy proven and in one case of LPPilaris dermoscopy aided in diagnosis, whereas all

others were clinically diagnosed as lichen planus. A detailed clinical history which include the duration, drug history, family history were elicited

.A complete general, systemic and dermatological examination were made.

Their waist circumference were measured in a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest and Blood pressure were measured at the time of examination.

The morphology of the skin lesion ,its distribution and concomitant involvement of hair, nail , palms, soles and mucosal involvement were noted.

Laboratory investigation like FBS ,Fasting TGL,HDL were taken after 8hrs of fasting. Waist circumference and blood pressure were measured at the time of examination .Fasting blood sugar and fasting triglyceride and high density lipoprotein were taken after 8 hours of fasting.

As obesity and inflammation plays major role in the pathogenesis of Metabolic syndrome IDF(International Diabetes Federation) criteria 2015 for diagnosis of metabolic syndrome which included waist circumference as a measure of central obesity was used[115]. The IDF adult criteria can be used for adolescents aged 16yr and above.

A modified version of these criteria was applied to those aged 10 to 16 yr.

Using 90th percentile cut off point of country/ethnic group values for waist circumference was included in this criteria.

For Asian population the waist circumference for male >90cm and for female >80c were considered.

INTERNATIONAL DIABETES FEDERATION (IDF) -2015 CRITERIA

Metabolic syndrome diagnosed with **1. Central obesity**

Plus any two of the following factors

1.TGL>150mg/dl

2.HDL<40mg/dl

3.FBS>100mg/dl

4.BP >130/85mmHg.

Central obesity was measured with WAIST CIRCUMFERENCE >80cm for women,>90cm for men in the age group of 16 and above.

For children aged 10yrs to 16yrs is WAIST CIRCUMFERENCE >90TH PERCENTILE IN INDIAN POPULATION

SEX	AGEs	90^{TH} PERCENTILE
BOYS	3	53.9
	4	55.7
	5	57.8
	6	60.0
	7	62.5
	8	65.2

	9	68.1
	10	71.1
	11	74.2
	12	77.4
	13	80.4
	14	83.4
	15	86.1
	16	88.6
GIRLS	3	54.4
	4	55.8
	5	57.8
	6	60.1
	7	62.8
	8	65.8
	9	68.9
	10	72.0
	11	75.0
	12	77.9
	13	80.4
	14	82.5
	15	83.9
	16	84.7

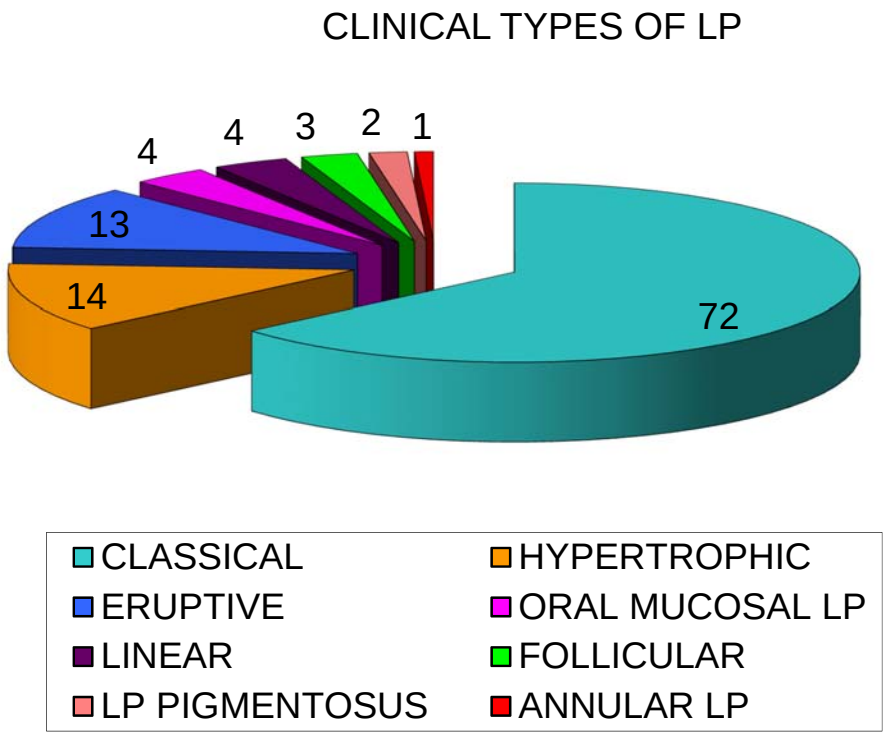
OBSERVATION AND

RESULTS

OBSERVATION AND RESULTS

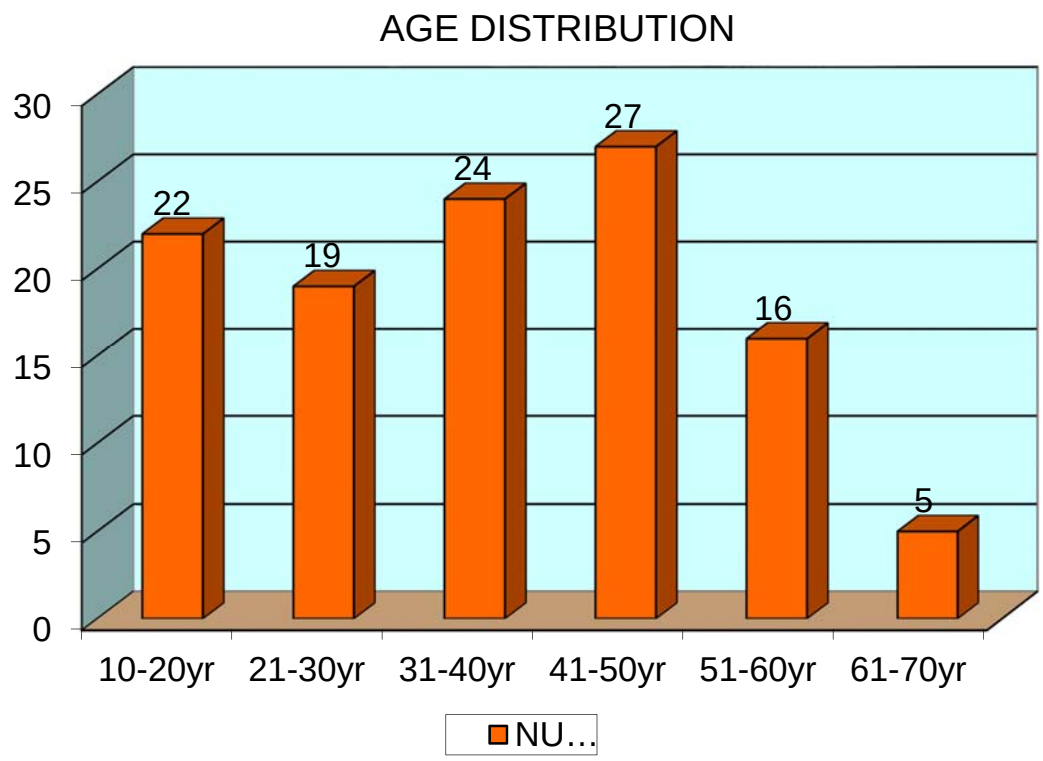
In this study 113 cases of LP were studied from the outpatient department of dermatology, Govt,.Rajaji Hospital, Madurai Medical college from february2016 to july2016.The following observations were made.

TABLE 1.CLINICAL TYPES OF LP



Classical LP was the commonest type (63.72)followed by other types hypertrophic LP(12.39),eruptive LP(11.50),Isolated oral LP(3.54),linear LP(3.54),follicular LP(2.65),lichen planus Pigmentosus(1.77),annular LP (0.88)in decreasing order of frequency.In 3 cases of classical LP concomitant oral mucosal involvement was there.

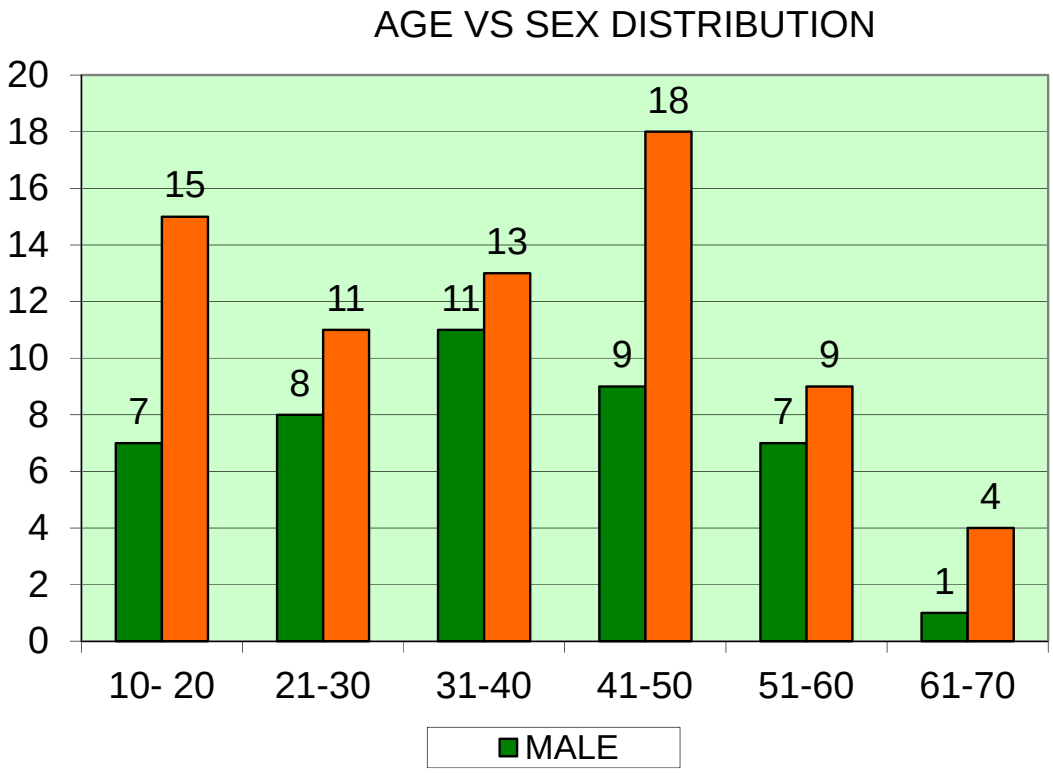
TABLE2.AGE DISTRIBUTION



AGE GROUP	NUMBER	PERCENTAGE
10-20yr	22	19.47
21-30yr	19	16.81
31-40yr	24	21.24
41-50yr	27	23.89
51-60yr	16	14.16
61-70yr	5	4.42

Majority of the patients are in age group 41-50 yrs.followed by 31-40 yrs age group.

TABLE 3.SEX DISTRIBUTION

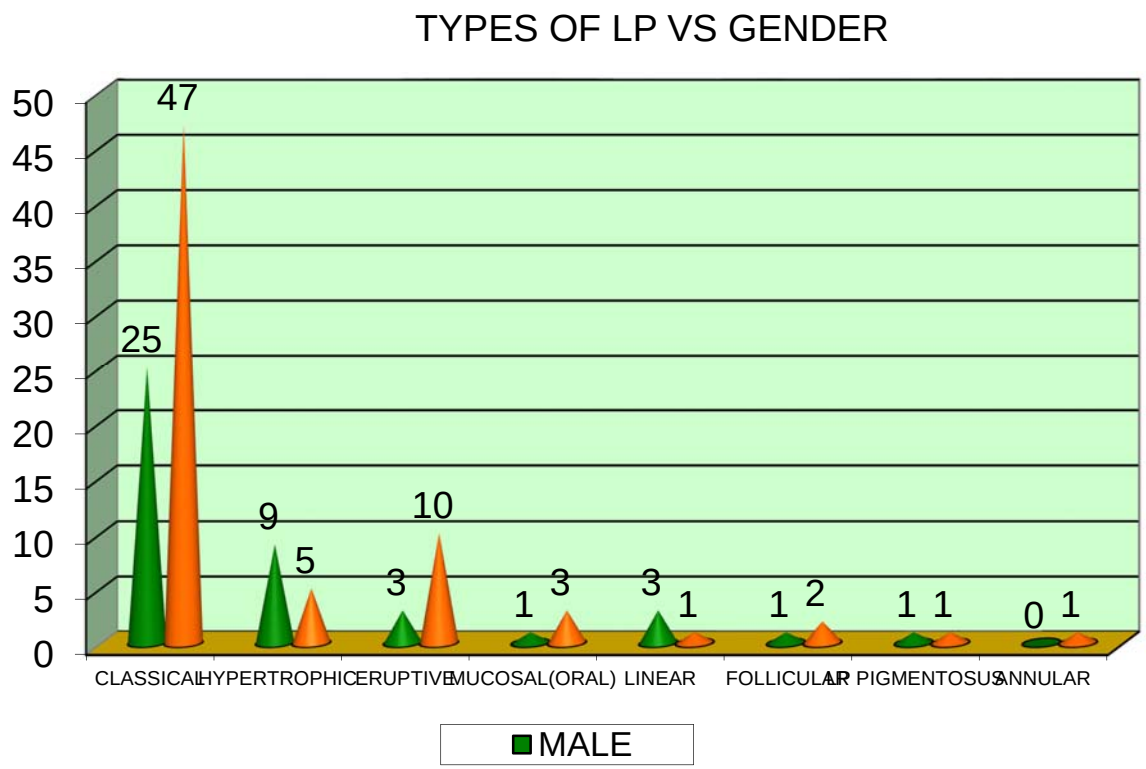


AGE IN YEARS	MALE	FEMALE
10-20	7	15
21-30	8	11
31-40	11	13
41-50	9	18
51-60	7	9
61-70	1	4

Total female cases were 70 and a total of male cases were 43.Majority of the patients were in the age group of 31-50.

Females are affected more than males in all age group.

TABLE 4.TYPES OF LP IN SEX DISTRIBUTION



	MALE	FEMALE
CLASSICAL	20	48
HYPERTROPHIC	9	5
ERUPTIVE	3	10
MUCOSAL(ORAL)	1	6
LINEAR	3	2
FOLLICULAR	1	2
LP PIGMENTOSUS	1	1
ANNULAR	---	1

Females were affected more than male in all variants of LP except in hypertrophic LP and in Linear LP and equally affected in LPPigmentosus.

ORAL MUCOSAL INVOLVEMENT:

In 7 Cases, oral mucosal involvement was seen.Among them 3 cases also had classical skin lesions . Common type seen in oral mucosa was reticular type,followed by erosive type.

NO.OF PATIENTS	RETICULAR	EROSIVE	PLAQUE
7	4	2	1

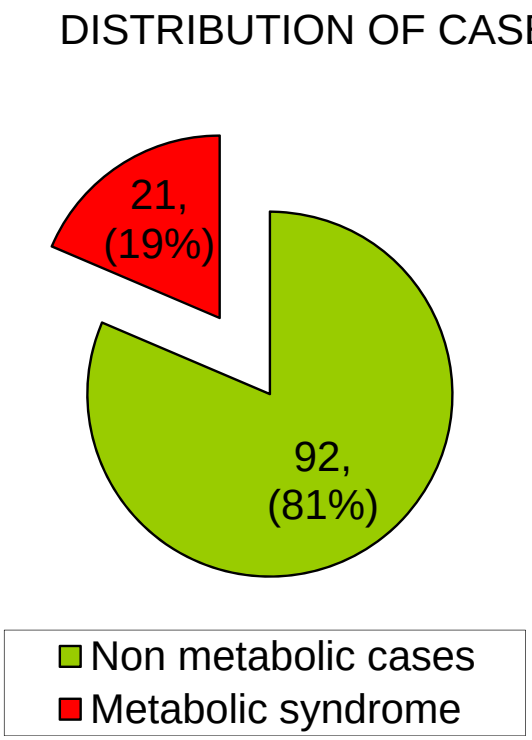
PALMS AND SOLES INVOLVEMENT:

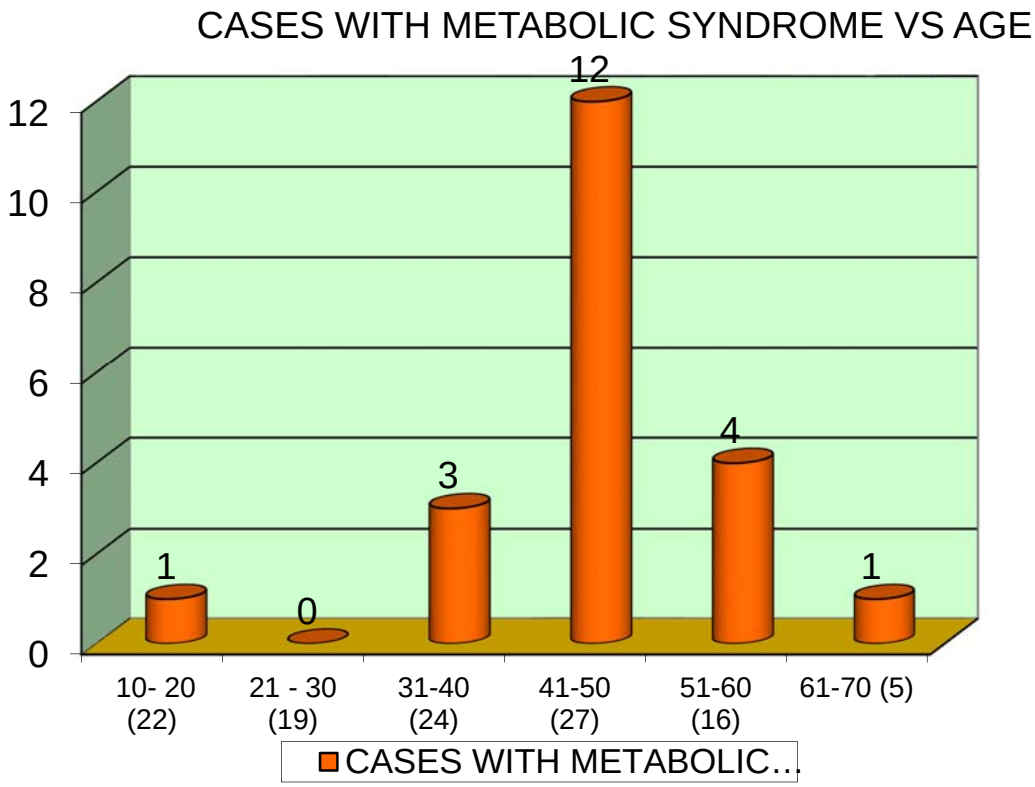
In 3 Cases of classical LP and in 2 cases of hypertrophic LP there was palm and sole Involvement.

NAIL INVOLVEMENT:

FINDING	NO. OF PATIENTS
Longitudinal ridging	4
Pterigium unguis	1
Subungual hyperkeratosis	2
Punctate leuconychia	1

Metabolic syndrome –Out of 113 cases,21 cases were associated with LP.Remaining 92 cases did not show association with MS.



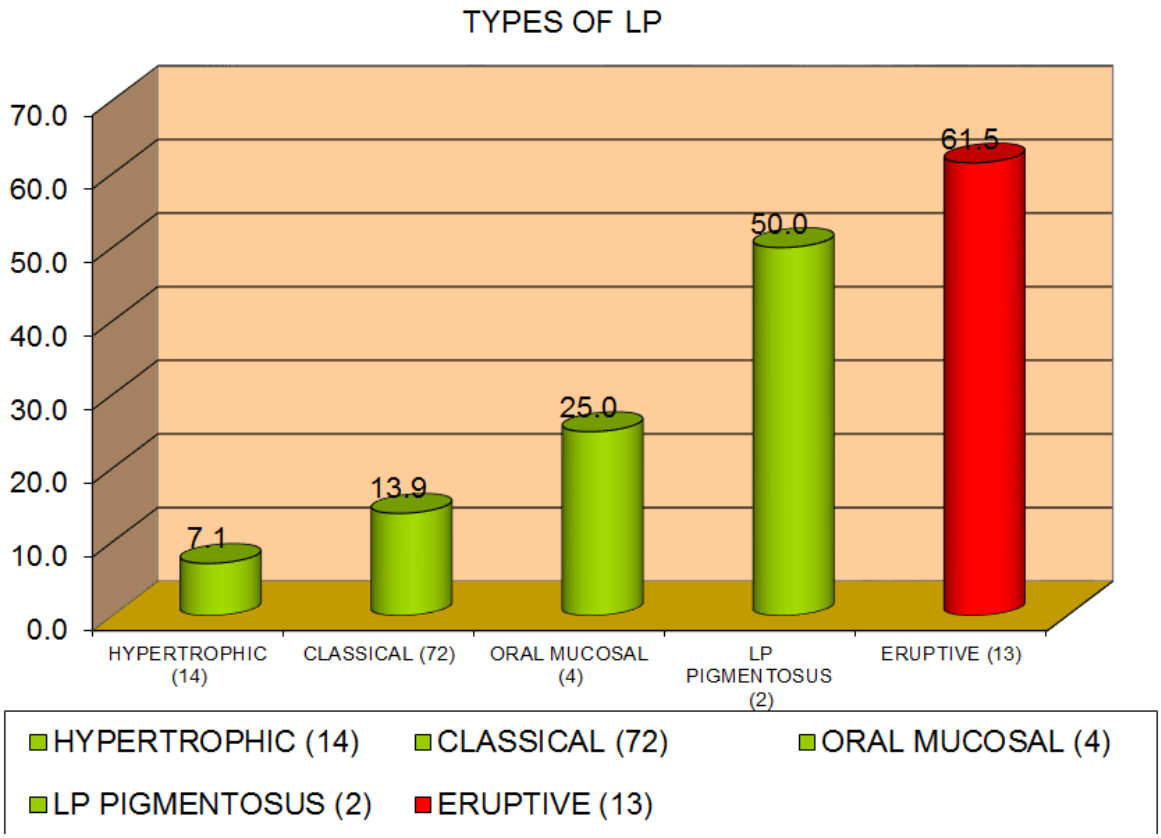


Age in years	TOTAL NUMBER OF CASES	CASES WITH METABOLIC SYNDROME	MALE	FEMALE
10- 20	22	1	0	1
21 - 30	19	0	0	0
31-40	24	3	1	2
41-50	27	12	2	10
51-60	16	4	1	3
61-70	5	1	0	1
TOTAL			4	17

Cases with metabolic syndrome were reported more in the age group of 41-50.Among them females were reported more with metabolic syndrome than males.Total females cases reported were 17, whereas only 4cases were reported to found association with metabolic syndrome.

Metabolic syndrome significantly high in females	
4/21 VS 17/21	0.036 Significant

CLINICAL VARIANTS OF LP WITH MEATABOLIC SYNDROME



TYPES OF LP	Total no.of cases	Metabolic syndrome cases	percentage
CLASSICAL	72	10	13.9
HYPERTROPHIC	14	1	7.1
ERUPTIVE	13	8	61.5
MUCOSAL(ORAL)	4	1	25.0
LP PIGMENTOSUS	2	1	50.0

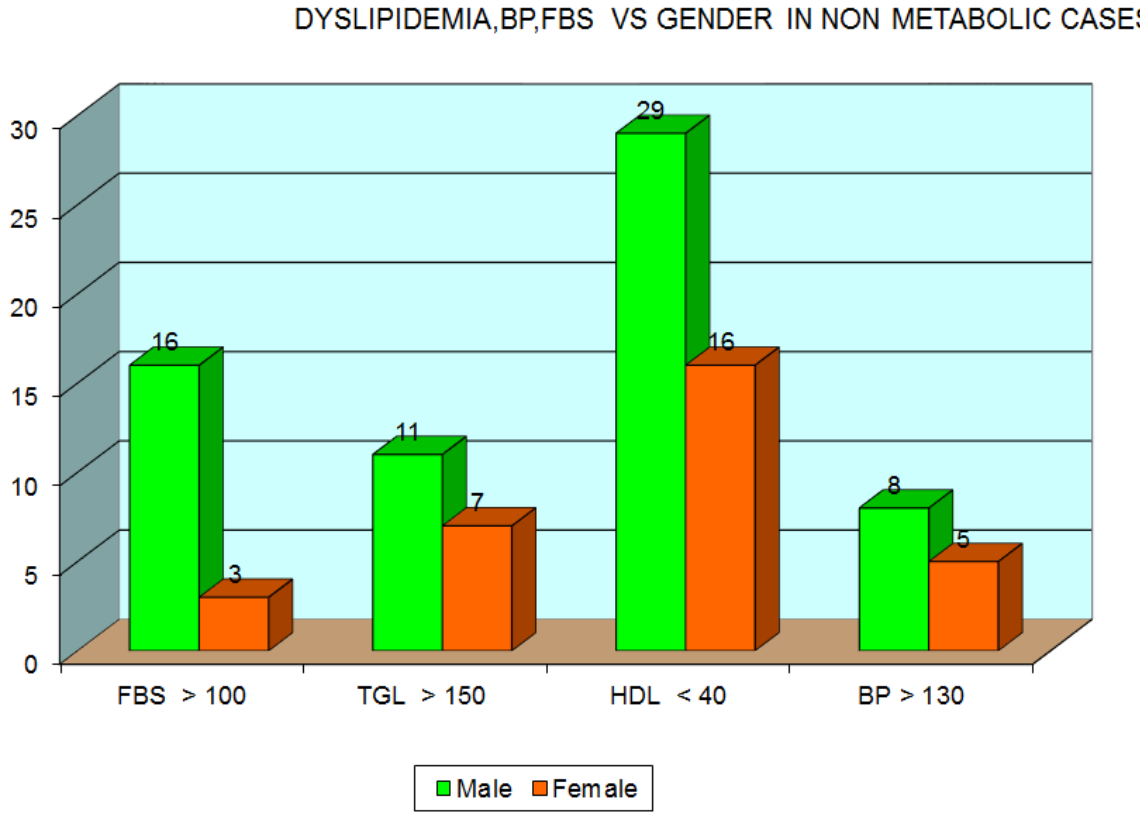
Regarding the variants of LP,eruptive LP cases were found to be associated more with MS when compared to other variants with 61.5%.

Metabolic syndrome

Classical 10 / 72	
Eruptive 8 / 13	p value 0.008 Significant
Others 3 / 28	

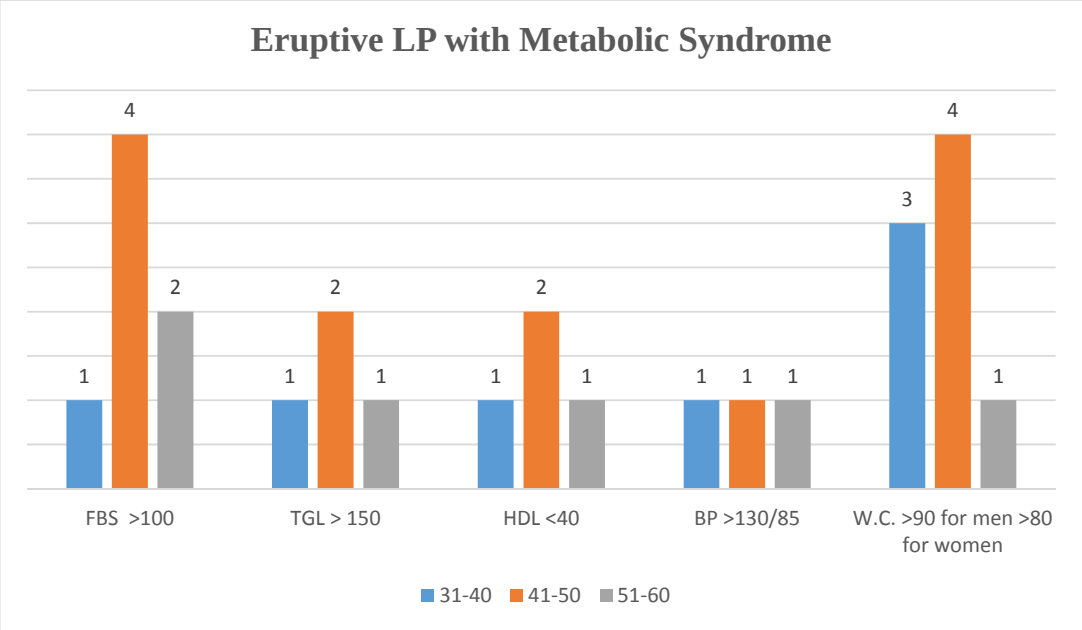
With related to other variants Metabolic syndrome was significantly higher in Eruptive cases(p 0.008)

RELATIONSHIP OF SEX WITH METABOLIC CRITERIA IN LP CASES NOT ASSOCIATED WITH METABOLIC SYNDROME

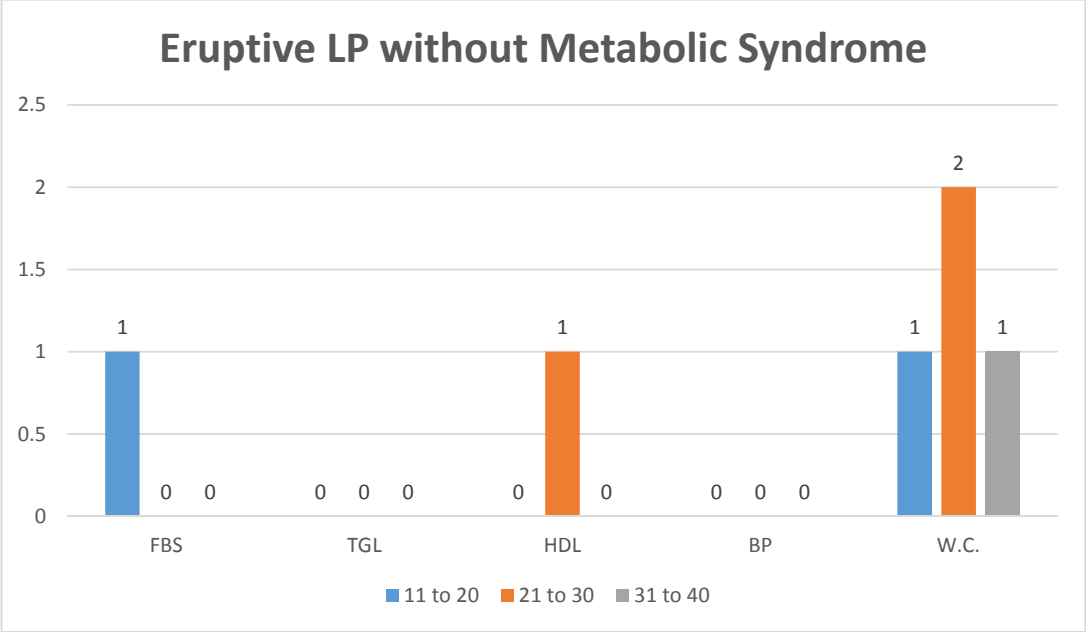


In a total of 53 female cases not associated with metabolic syndrome ,21 cases had dyslipidemia. Though they did not have MS, increased TGL was observed in 7cases,16 cases had decreased HDL .Increased FBS and hypertension was less common when compared to dyslipidemia.

ERUPTIVE VARIANT



Out of 13 eruptive cases ,8 cases with metabolic syndrome in the age group from 31-60 had increased fasting blood sugar in the metabolic criteria.This was found to be common in those age group when compared to increased TGL and decreased HDL. Increased BP was less common.



In 5 eruptive cases not associated with metabolic syndrome in age group 11 to 40 , increased waist circumference was found to be common than increased FBS and low HDL.Hypertension and increased TGL was not found in any of these cases..

DISCUSSION

DISCUSSION

Our study was a epidemiological study where all variants of newly diagnosed Lichen Planus were included to find its association with metabolic syndrome .In our study a total of 113 newly diagnosed cases of LP presented in age group of 10 and above were included.

.**Clinical types of LP-**In our study Classical lichen planus was the commonest type with 63.72% followed by hypertrophic type. This was similar to the 60%of classical LP followed by hypertrophic LP reported in the study conducted by Bhattacharya et al in 145 cases.[1]

Age distribution-Majority of the patients were in the 4th to 6th decade which is supported by the literature[1]

Sex distribution-In our study total female cases were 70 and male cases were 43 which matches with the female preponderance reported by Bhattacharya et al and Boyed AS et al study[2]

Types of LP-All variants of LP presented predominantly in females except hypertrophic LP and linear LP. In studies conducted by Boyed et al hypertrophic LP were reported predominantly in males. Similarly in our study males were reported more in number than female in hypertrophic variant.

Oral LP-Total of 7 cases were reported with oral mucosal involvement.. Isolated LP was seen in 4 cases .Remaining 3 cases showed cutaneous features of LP along

with oral mucosal involvement .Out of 7 cases 4 cases presented with reticular pattern and 2 cases with erosive type and only one case reported with plaque type. Common pattern seen in oral mucosa was reticular type which coincides with the study conducted by Axen et al in 20333 Swedish population[12].

Palms and sole involvement-All the classical LP cases had palm and sole involvement. In hypertrophic type 2 cases showed palms and sole involvement.

Nail involvement- A total of 8 cases showed involvement of nail. Commonest finding was longitudinal ridging followed by subungual hyperkeratosis, pterygium unguis and punctate leuconychia.

Histopathology- Diagnosis was proved whenever there was clinical dilemma. .A case of follicular LP, histopathological examination showed structure of skin with focal area of hyperkeratosis, acanthosis, follicular plugging with basal cell degeneration ,dermis showed pigment incontinence with periadnexal mononuclear infiltrate. The above features confirmed the diagnosis.

In the case of annular LP, histopathological feature showed hyperkeratosis, acanthosis and focal areas of basal cell degeneration .Upper dermis showed dense collection of chronic inflammatory infiltrate with pigment incontinence.

In a case of Lichen Plano Pilaris with scaring alopecia and scalp biopsy was also taken which aided in diagnosis.**Dermoscope -** In a case of lichen

plano pilaris dermoscopy was done which showed peripilar cast in active lesion as observed in the study conducted by Vázquez-López F[21]

Association of Lichen planus with metabolic syndrome- Children less than 10yrs were not included ,as metabolic syndrome could not be diagnosed in these cases[115] In our study metabolic syndrome was diagnosed in 21 cases which constituted 19% of total cases.. Remaining 92 cases with 81 %were not associated with metabolic syndrome. No control was used in the study.

Among the LP patients with Metabolic syndrome in the age group of 10-20 ,only one female case with classical variant was found to be associated with MS. Her waist circumference was more than 90th percentile for that age group in Indian population and she had low HDL and raised BP. Among 22cases in this age group 10 of them showed decreased HDL despite normal waist circumference and blood sugar level.

In the age group between 21-30 yrs no cases were found to be associated with metabolic syndrome. But out of 19 cases, 9 of them had increased waist circumference.

In the age group of 31-40, three out of 24 cases were found to be associated with metabolic syndrome and fifteen cases had only increased waist circumference. Two cases with metabolic syndrome were female with eruptive and classical variant one each and one male case showed eruptive type.

MS was found to be more common in the age group of 41-50 and also more cases of LP were reported in this age group only. In this group 12 cases out of 27 cases were reported in association with metabolic syndrome. With a total of 12 cases 10 were females and 2 were males. Out of the 10 female cases , 5 of them presented with classical variant and 4 of them with eruptive and 1 of them had hypertrophic variant. Both male cases were presented with classical type. In this age group all the females presented with eruptive variant were found to be associated with metabolic syndrome, which carried significance. All the eruptive variant in this age group showed increased fasting blood sugar. In this age group 19 cases were found with increased waist circumference and 12 with decreased HDL.

In the age group of 51-60 four cases were reported in association with MS out of total 16 cases. Out of this 4 cases , 3 were females and 1 case was male presenting with eruptive type. The 3 female cases comprised of , eruptive , classical and lichen planus pigmentosus variant one each .Among the four cases 3 cases were found to have low HDL level. Out of 12 LP cases without associated metabolic syndrome in this age group ,10cases had increased waist circumference and 10 had low HDL value.

In 61-70 age group single case was found to be associated with MS. This is the only cas of mucosal LP which had associated MS. The mucosal pattern

was reticular in this case . With total of 5 cases reported in this age group 4 had decreased HDL.

In a case control study by Arias Santiago et al reported MS showed more prevalence in female when compared to male with LP.[98] In our study the prevalence of MS in female carried significance of p 0.036 when compared with male which was consistent with the study

The metabolic syndrome was found to be associated with LP in the age group of 41-50 was significantly(p 0.007) higher when compared to other age group.

Association of mucosal LP with metabolic syndrome.

Prevalence of MS in oral LP studied by Baykal et al was 34.5% and the prevalence was 8.3% in patients of LP without mucosal involvement[89]. In our study MS in mucosal LP was 14.2 %,but in LP patients without mucous involvement ,the prevalence of MS was 18.8% which did not concur with the previous report. But in our study only 7 cases of oral LP was reported,hence cannot be compared with the previous study where number of cases were large.

Lipid profile and metabolic syndrome in oral lichen planus patients conducted by Bhuvana krishnamurthy et al in 79 patients, and chronic inflammation has been suggested as a component of the MS125. Patients with chronic diseases show decreased levels of HDL-C and hypertriglyceridemia, with a positive correlation with cytokine levels. In our study 7 cases of oral

LP,only 3 cases were associated with decreased HDL which did not concur with the above study.More number of oral LP to be included to show the concurrence.

Association of eruptive LP with metabolic syndrome-

In our study out of 13 cases of eruptive LP,8 cases were found to be associated with metabolic syndrome. A total of 6 eruptive cases belonged to the age group of 41-60 found to be associated with MS. Whereas a total of 3 eruptive cases in the age group of 31-40 , 2 cases were found to be associated with MS. None of the 2 eruptive cases in the age group of 11-20 showed MS association. This association with MS in eruptive LP had significant p value of 0.008 when compared with other variants. There were no studies showing association of MS with specific variants of LP apart from mucosal LP.

In a case control study by Dreiher et al he found prevalence of dyslipidemia was higher in patients with LP with 42.5%. In our study, among the criteria for metabolic syndrome ,57% cases showed dyslipidemia

Lipodystrophy and metabolic syndrome-

One interesting case in our study was a PLHA patient on HAART presented with linear LP had raised triglyceride, low HDL level and raised FBS ,but he was not categorised under metabolic syndrome as he had low waist circumference. The prevalence for the MS in these patients, is really lower than in the all inclusive community due to low WC in this population.Apart from LP,

the role of ART drugs has to be also considered in HIV patients for dyslipidemia due to lipodystrophy.[127]

Most of the patients in the 3rd to 6th decade without metabolic syndrome were associated with increased waist circumference and decrease in HDL level. Increased oxidative stress in accumulated fat is, at least in part, cause dysregulation of adipocytokines and development of metabolic syndrome. Thus obesity carried significance during followup for MS.

SUMMARY

SUMMARY

1.Out of 113 cases of Lichen planus ,metabolic syndrome was found to be associated with 21 cases. Remaining 92 cases had no such association.

2.Metabolic syndrome is high in females with lichen planus when compared to males.

3.In the age group of 41-50 ,12 cases were associated with MS which was significantly high.

4.In 21-30 age group , none of the cases showed association with MS.

5.Among 53 female cases who did not show association with metabolic syndrome

23 cases had dyslipidemia. Out of 23 cases who had dyslipidemia, 16 had low value of HDL and 7 had high value of TGL.

6.Out of total 13 eruptive cases in our study 8 cases had association with metabolic syndrome irrespective of the duration of the disease.

7.Eruptive cases in the age group of 11-20 had no association with MS.

8.In 61-70 age group a single case of isolated oral lichen planus was found to be associated with Metabolic syndrome.

9.Total of 67 cases who were in the age group of 31-60 did not fulfil the metabolic criteria, but most of them had increased waist circumference followed by low HDL level.

CONCLUSION

CONCLUSION

1.Lichen planus occurring in the 4th decade found to be associated with Metabolic syndrome.

2.Association of Lichen planus with Metabolic syndrome was more with females.

3.In a total of 6 eruptive cases in 4th to 5th decade ,all were associated with metabolic syndrome irrespective of its duration. Thus females with eruptive variant in 4th to 5th decade should be evaluated for MS, to reduce its consequences.

4.Though 92 cases did not fulfil the criteria for metabolic syndrome 63 of them had dyslipidemia.

Obesity the main initiator ,in the chronic low-grade inflammatory condition that accompanies the metabolic syndrome has been implicated as an important player in both the installation of the syndrome and its associated pathophysiological consequences . weight loss in obese LP patients is adviced to reduce the consequences.

Obesity is the major inducer of dyslipidemia ,which is the major component of metabolic syndrome. In our study many people had increased waist circumference .On long term follow up of these people, incidence of metabolic syndrome may increase.

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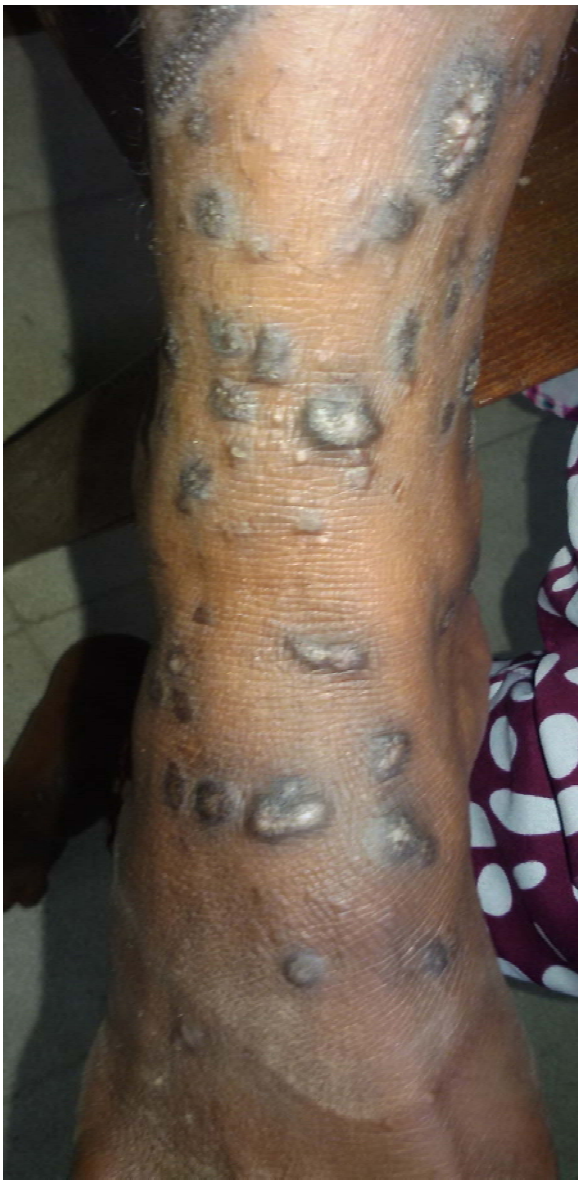
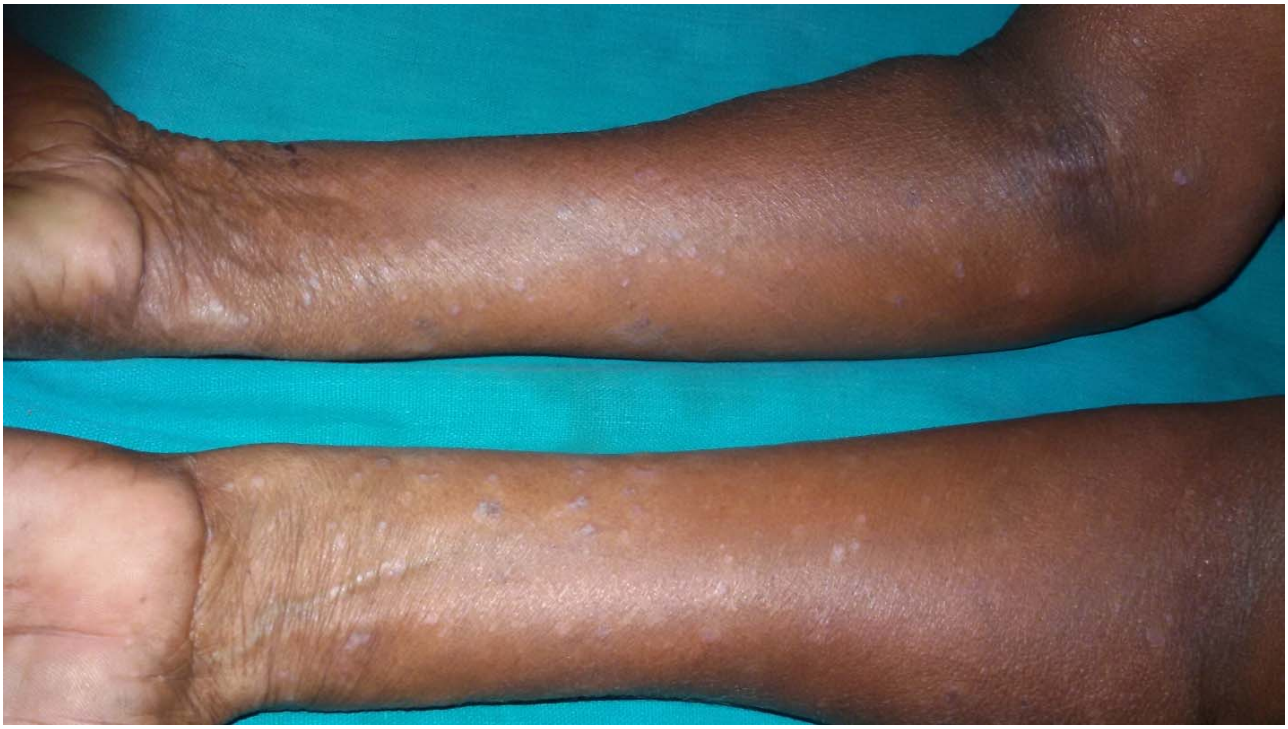
PHOTOGRAPHS

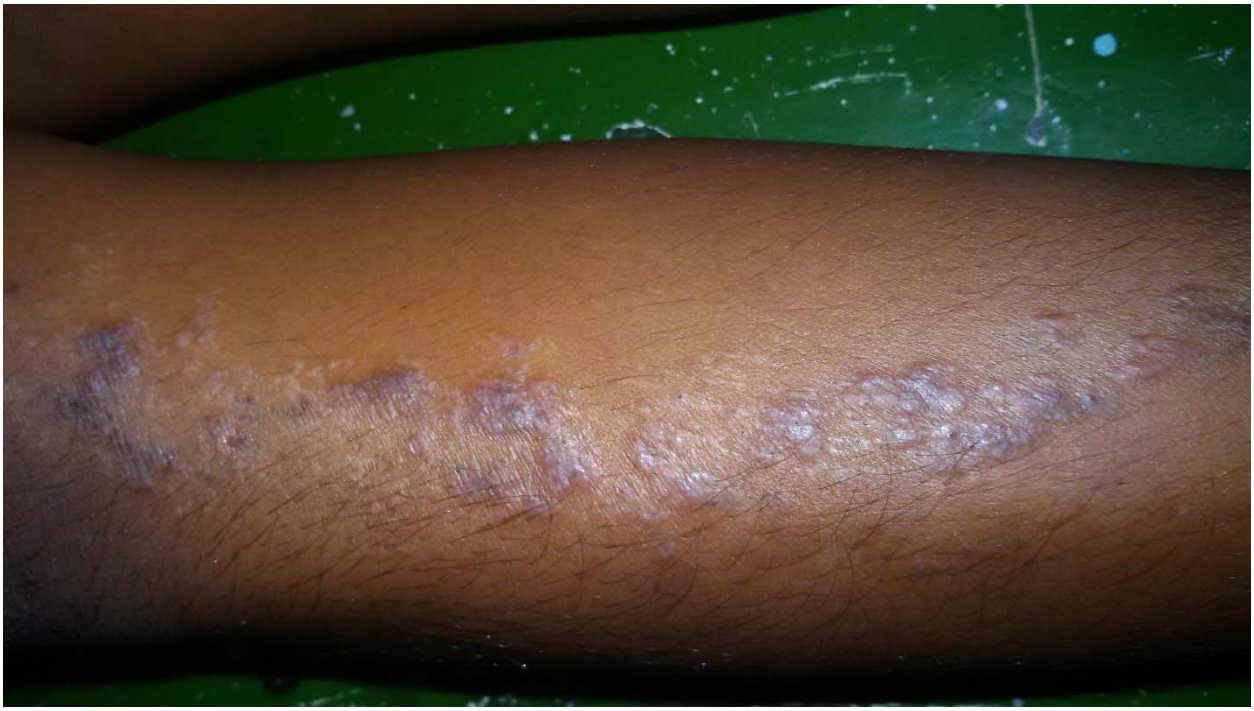
HYPERTROPHIC LICHEN PLANUS



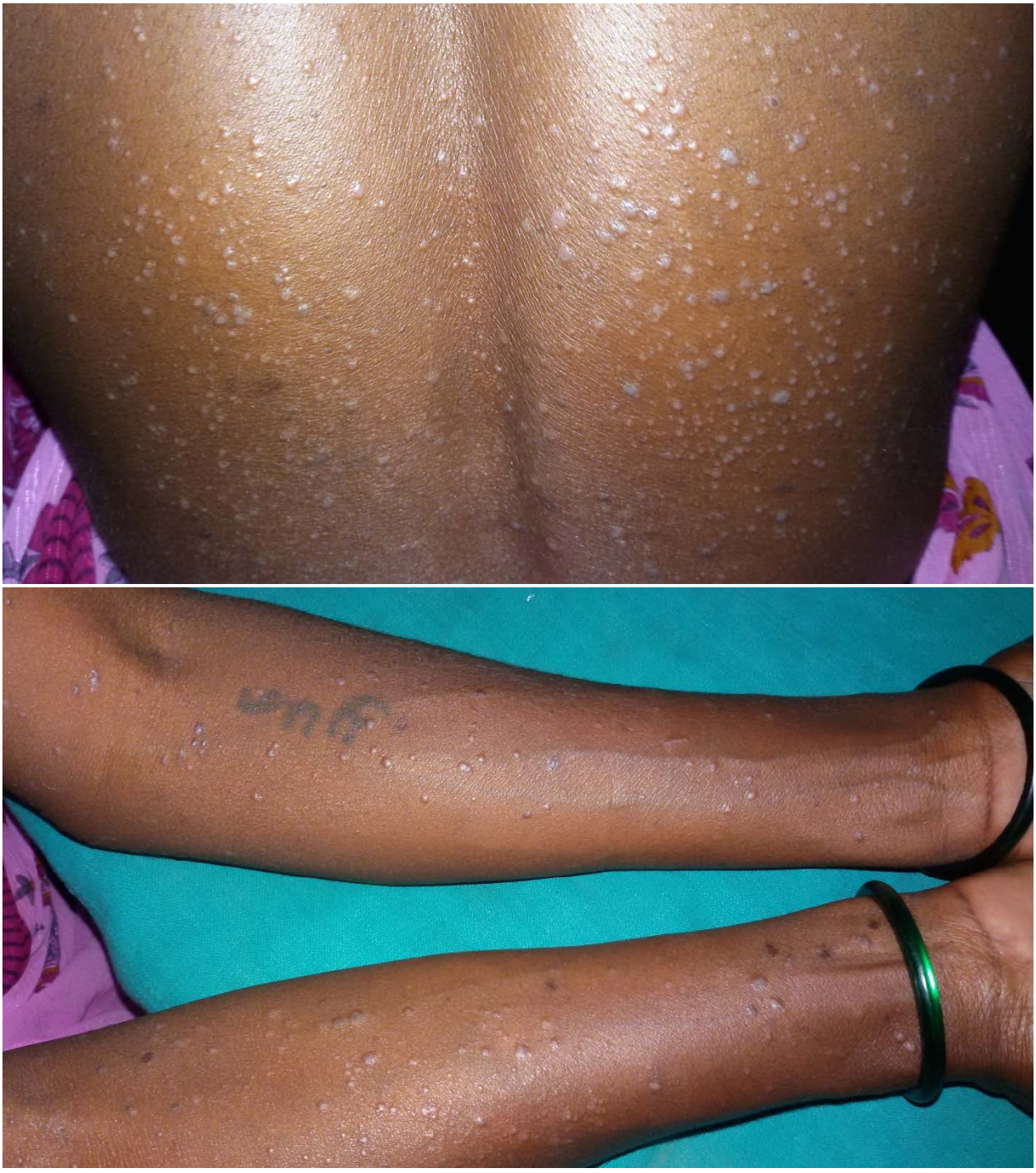
CLASSICAL LICHEN PLANUS



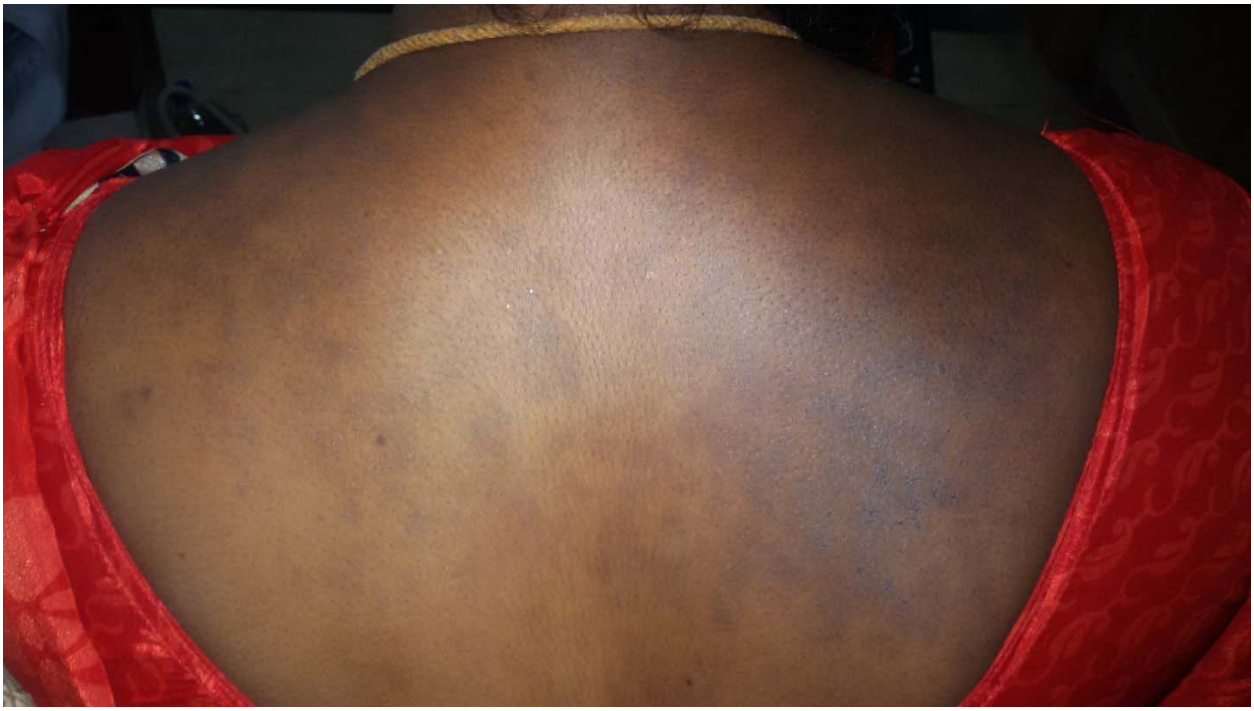
LINEAR LICHEN PLANUS



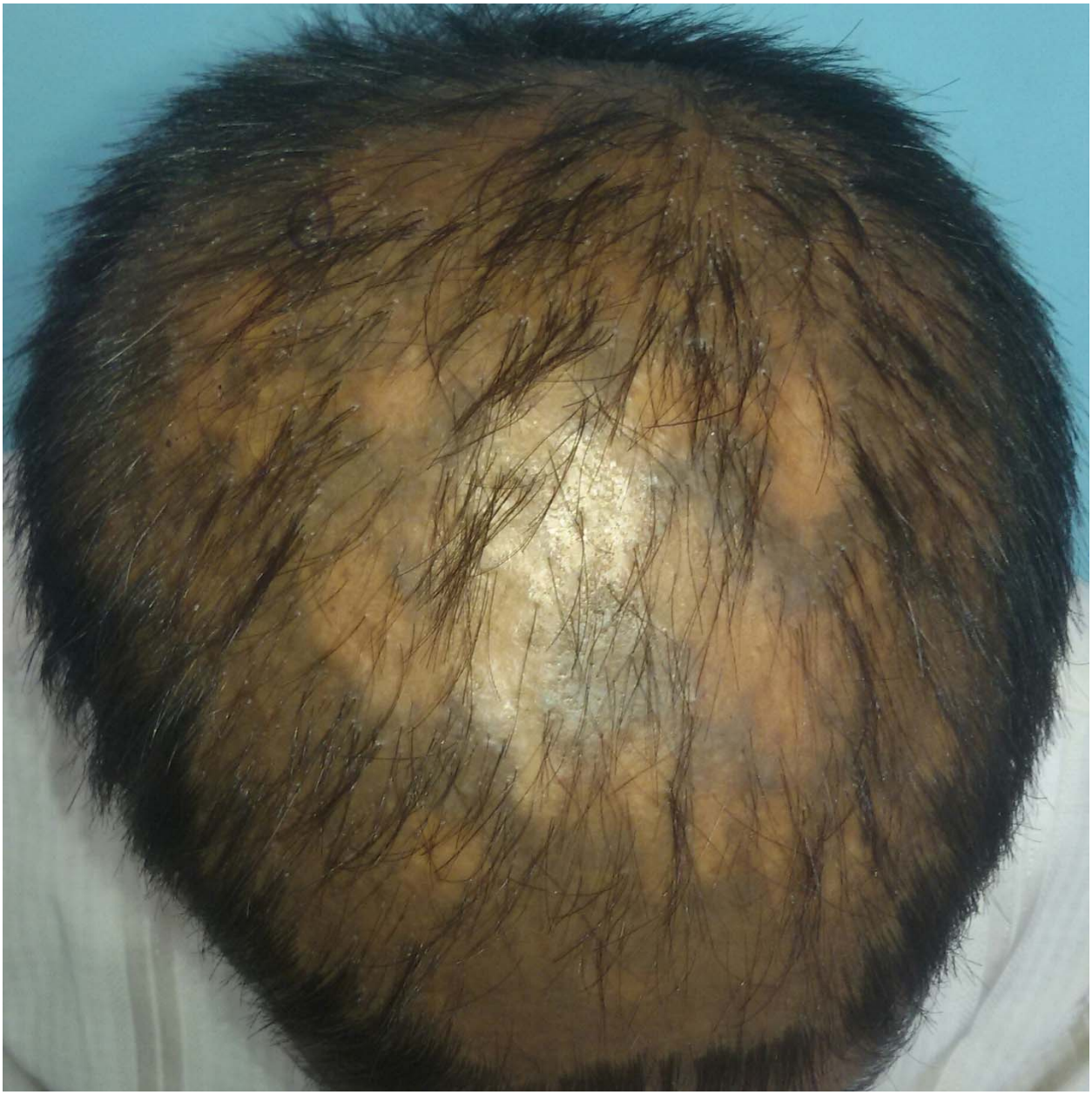
ERUPTIVE LICHEN PLANUS



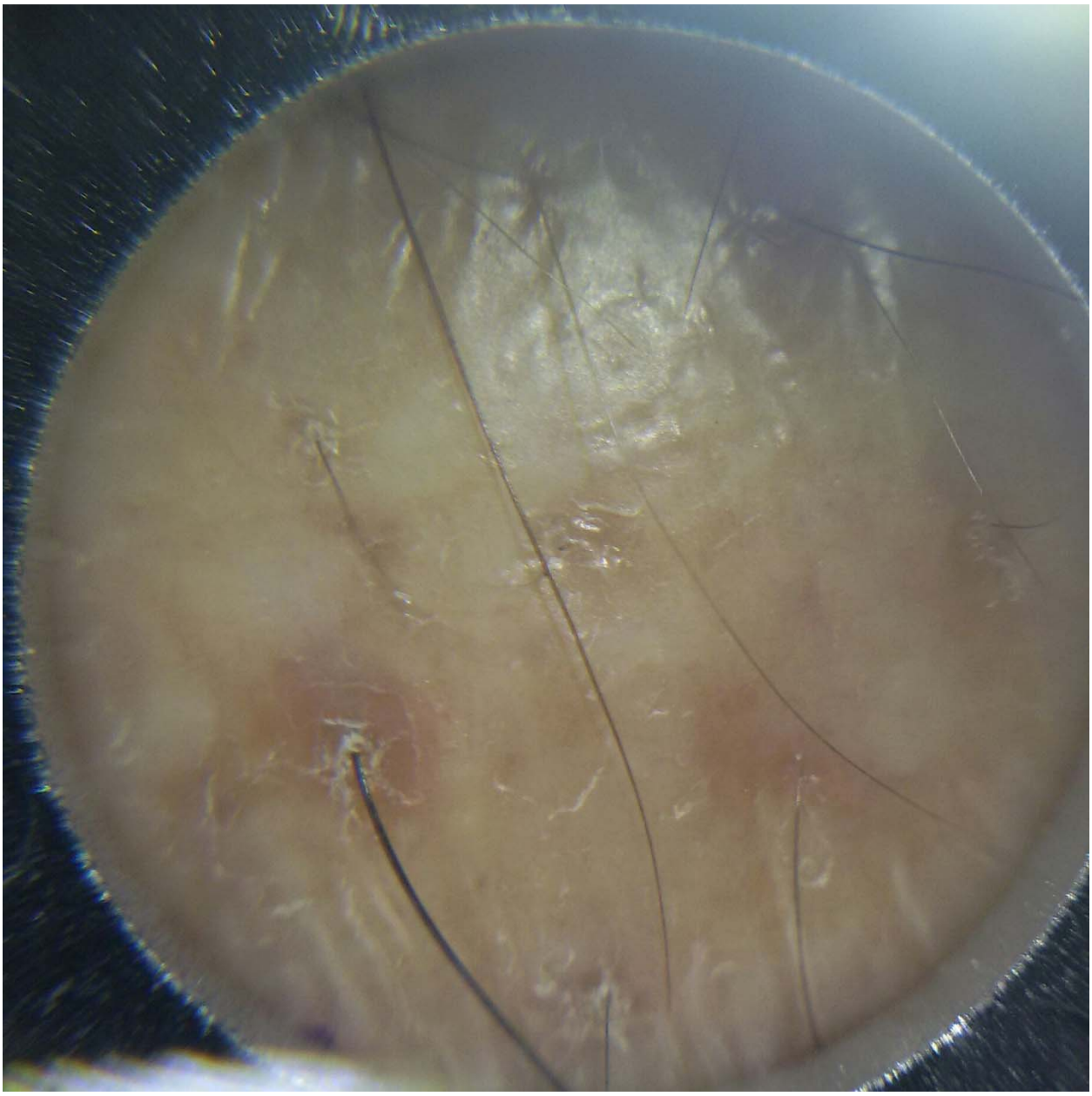
LICHEN PLANUS PIGMENTOSUS



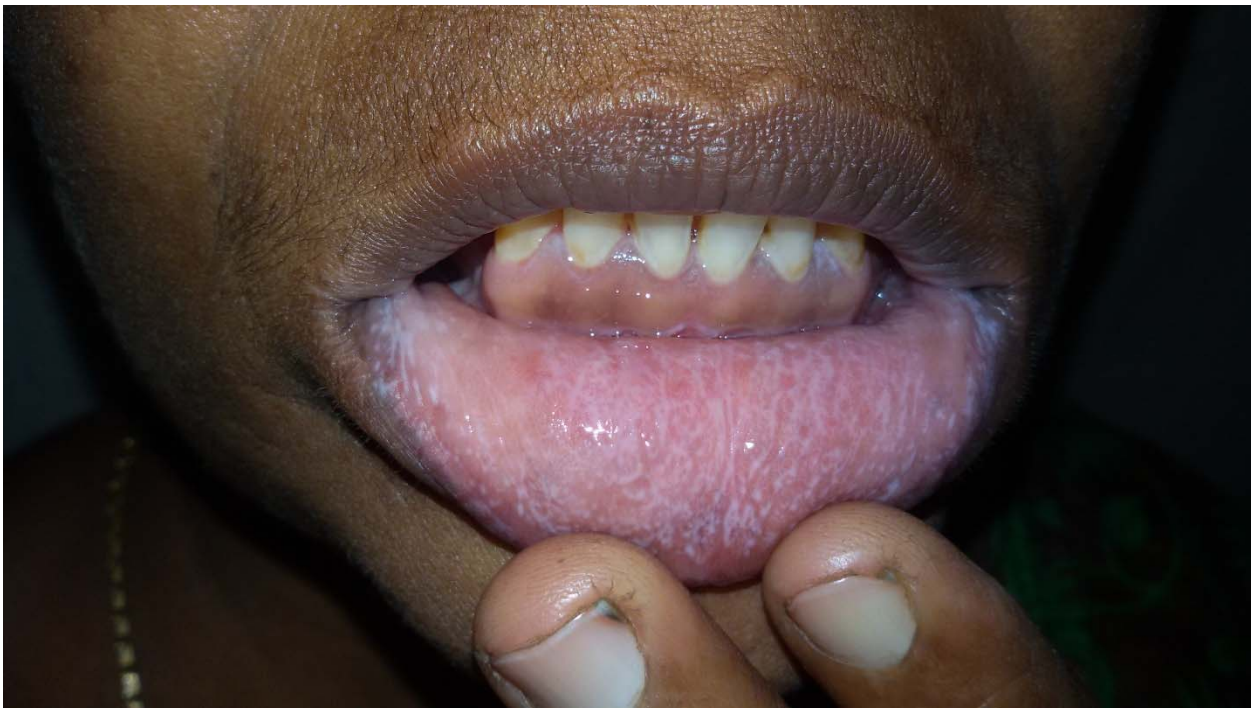
LICHEN PLANO PILARIS WITH SCARING ALOPECIA



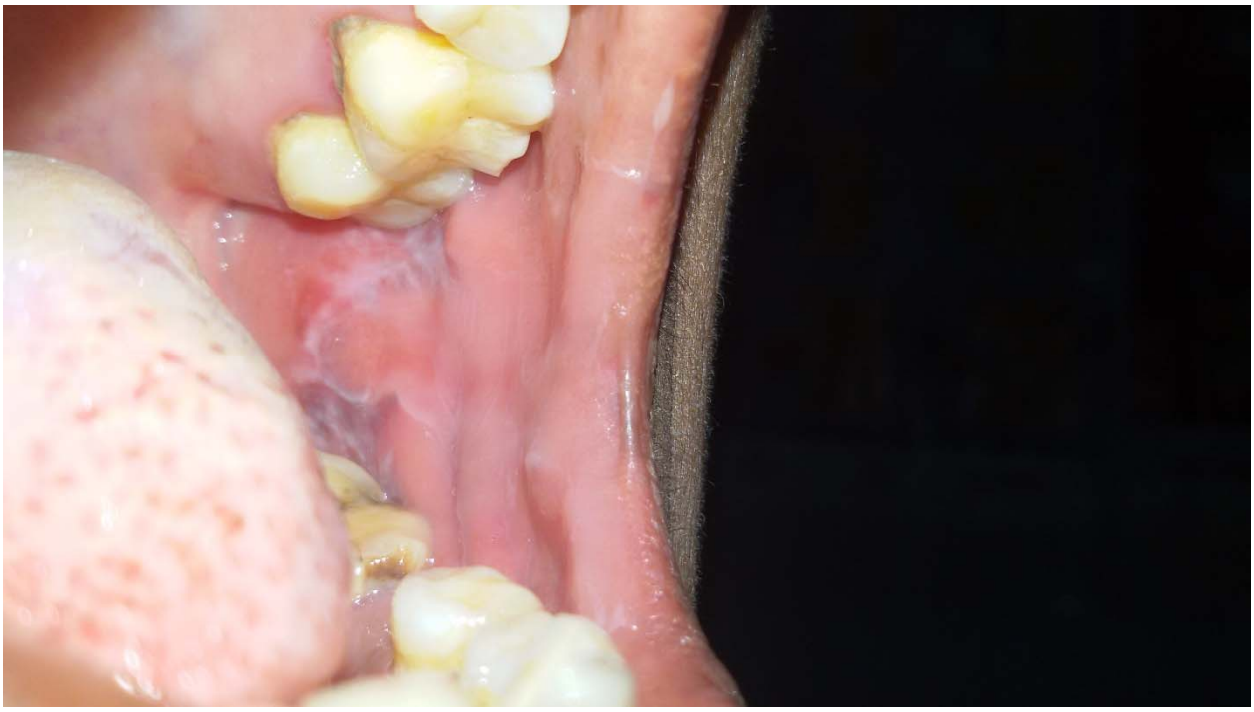
DERMOSCOPY SHOWING PERIPILAR CAST IN LPP



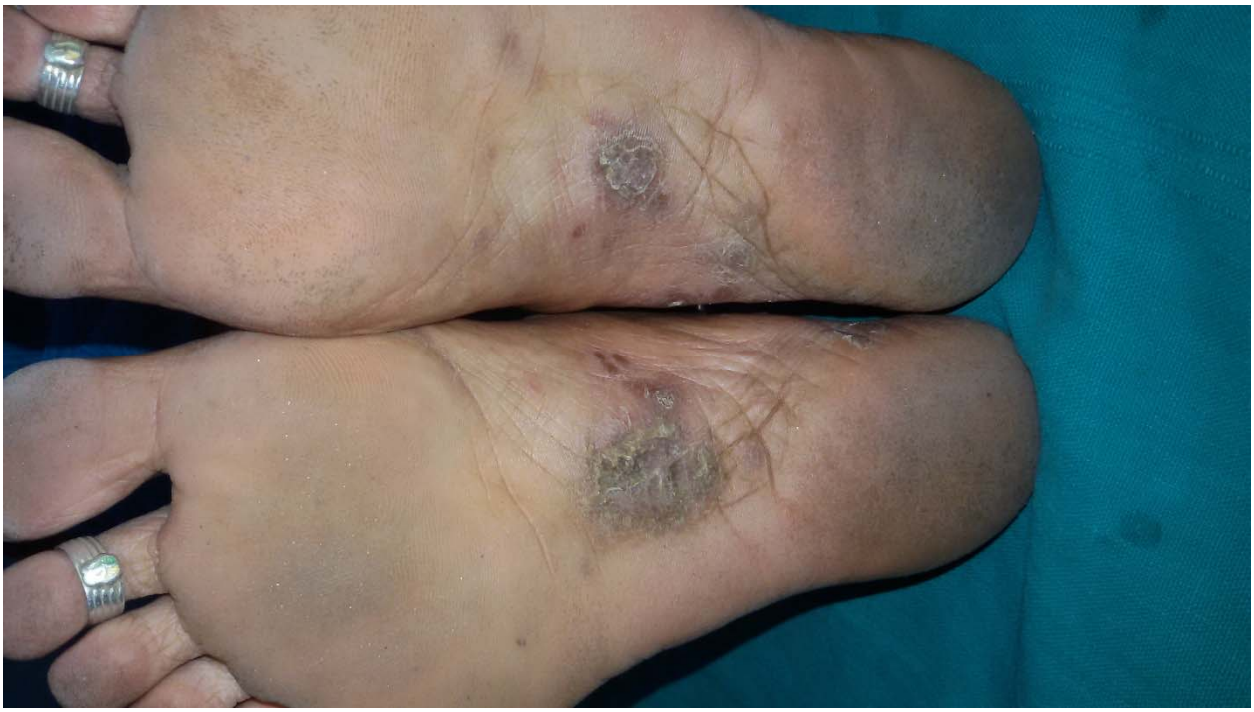
MUCOSAL LICHEN PLANUS

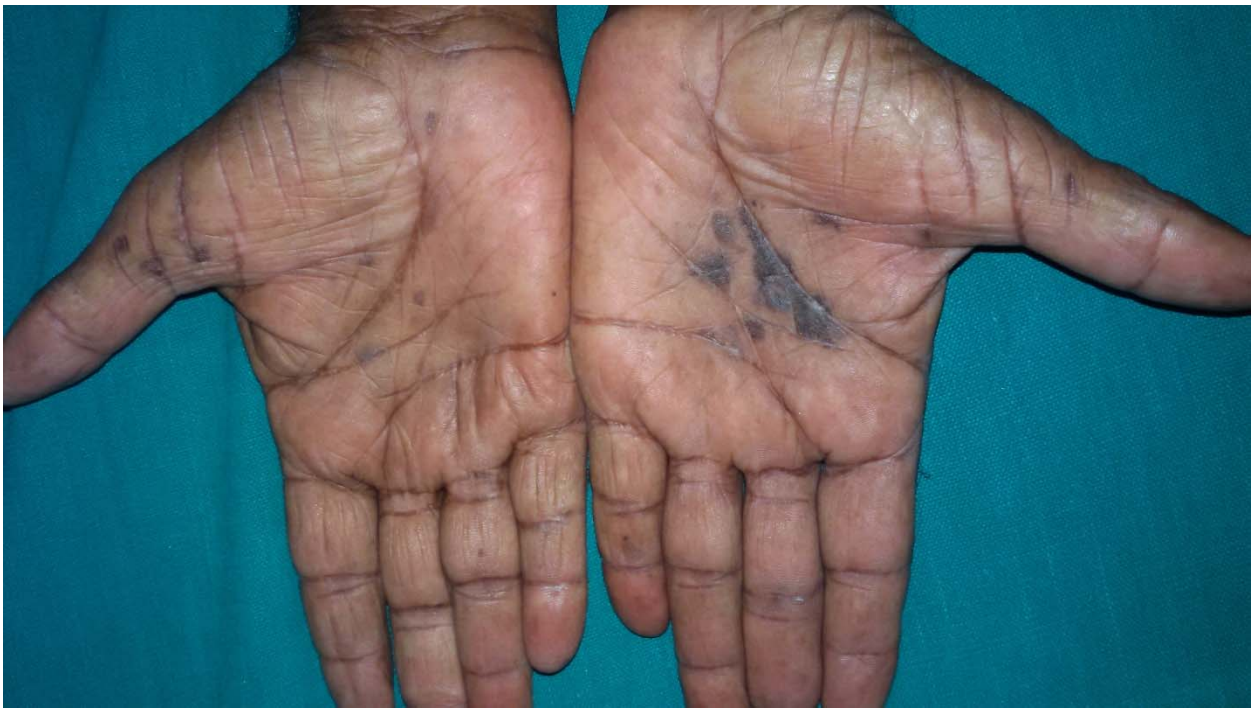


MUCOSAL LICHEN PLANUS WITH RETICULATE PATTERN

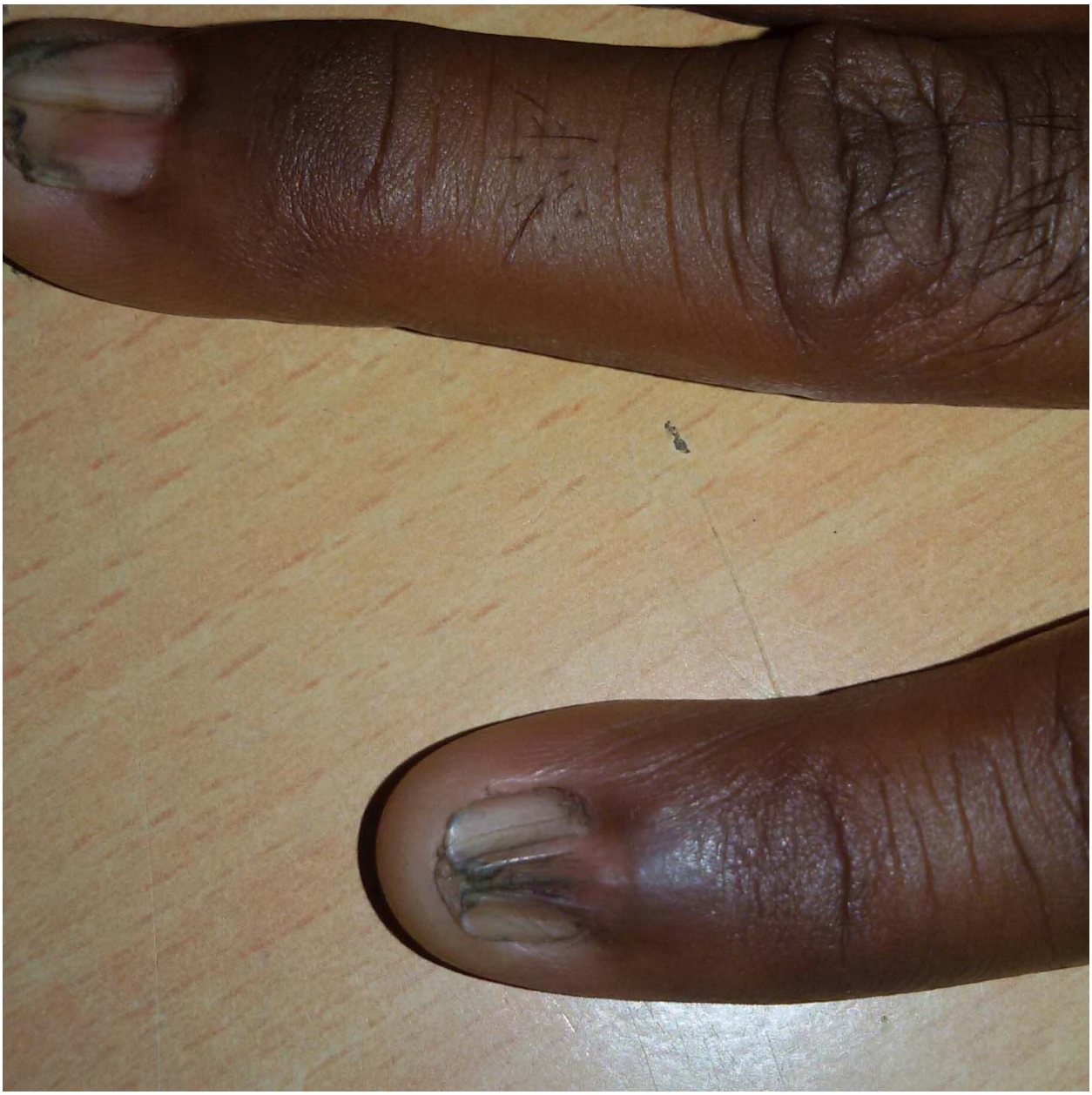


LICHEN PLANUS WITH INVOLVEMENT OF PALMS AND SOLES

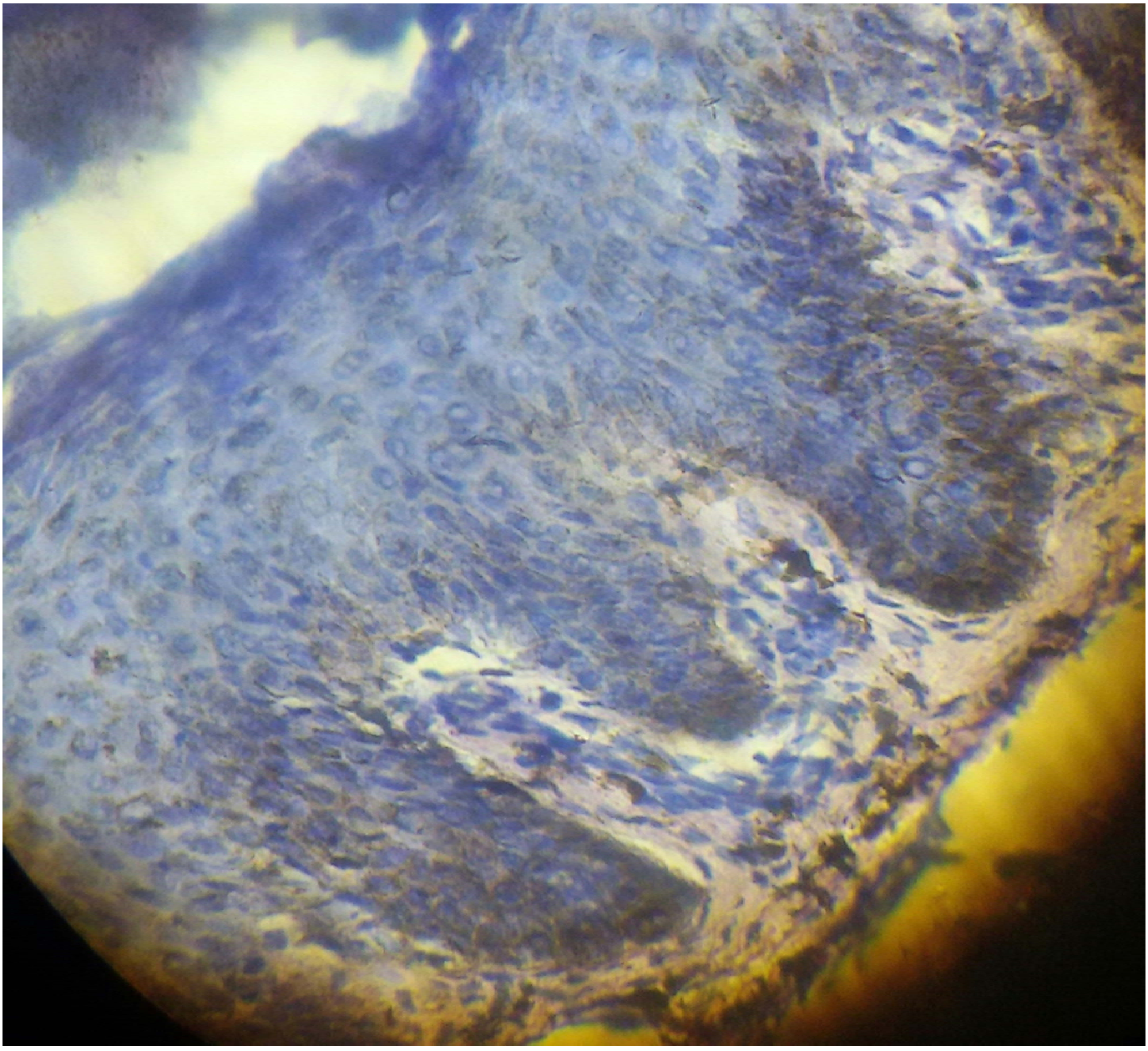




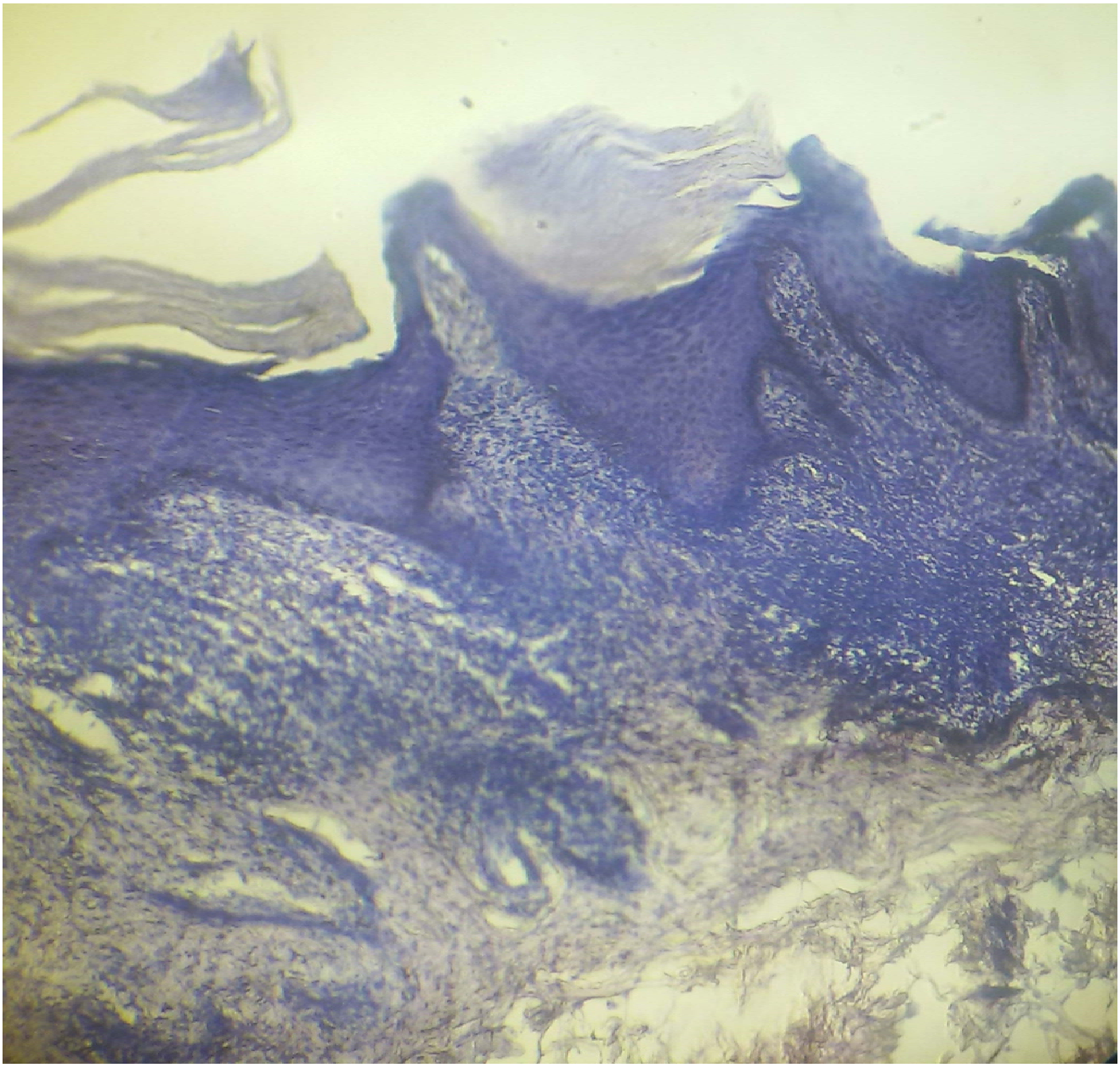
NAIL PTERIGIUM



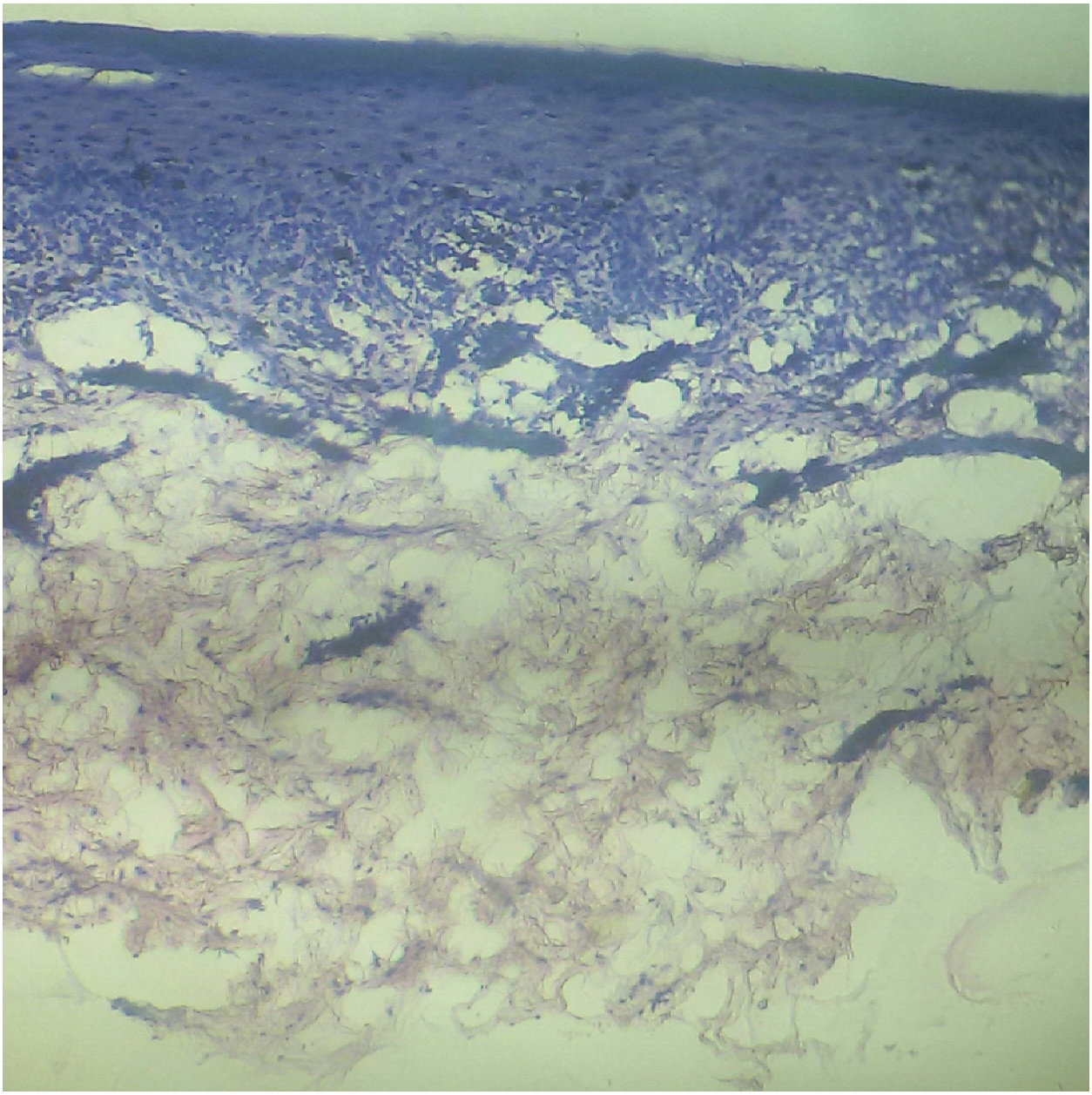
CLASSICAL LP-orthokeratosis, hypergranulosis, saw toothed rete ridges



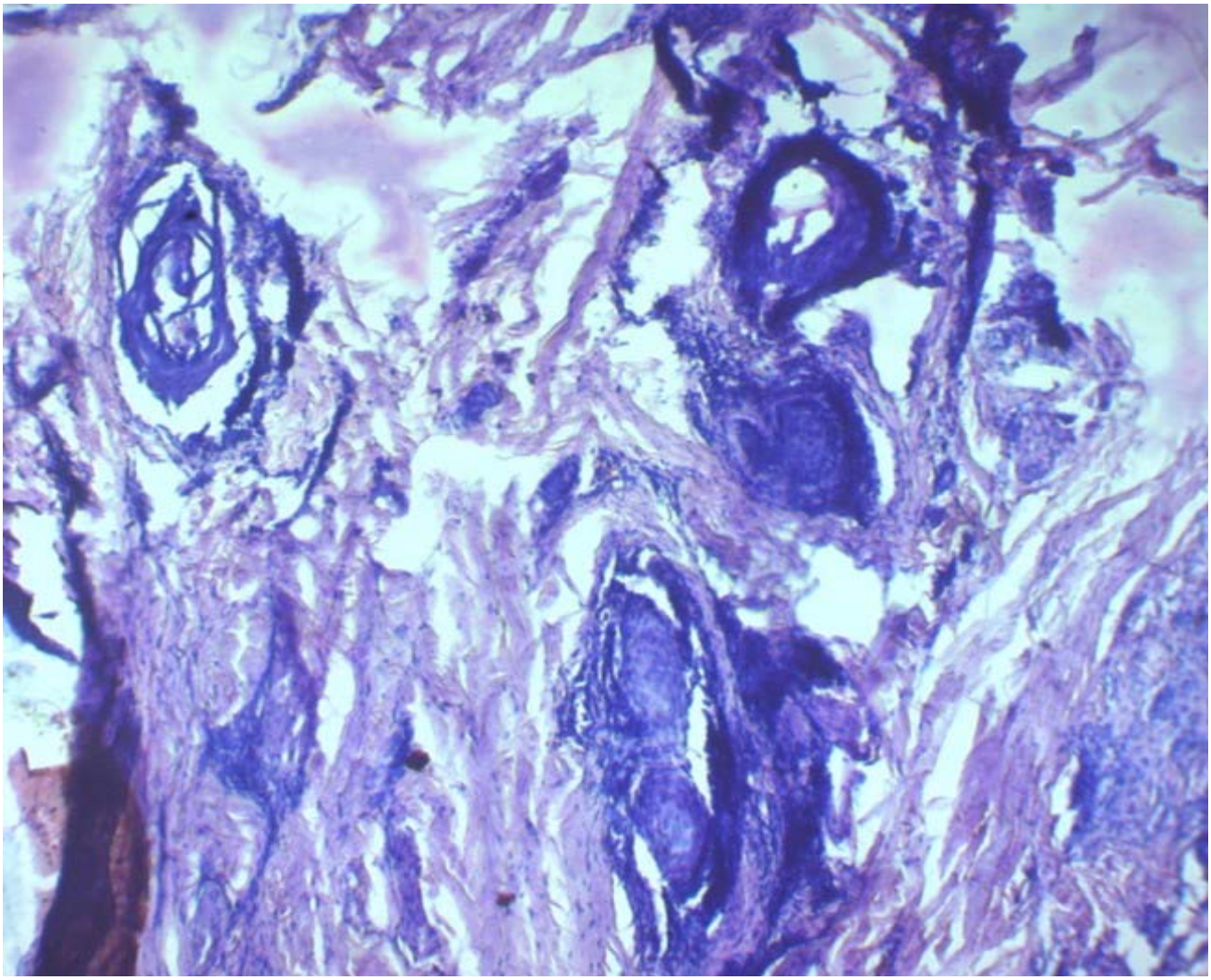
HYPERTROPHIC LP-Hyperkeratosis,acanthosis,band like infiltrate at dermoepidermal junction



ATROPHIC LP-Thinning of epidermis



LICHEN PLANOPILARIS WITH PERIFOLLICULAR FIBROSIS



PROFORMA

Name:

Address:

- Age/sex:
- Occupation:
- Date: Contact no:

- Diagnosis:

HISTORY

- H/o frequent urination
- h/o fatiguability
- h/o blurred vision
- h/o peripheral neuropathy
- h/o giddiness
- h/o headache
- h/o palpitation
- h/o chest pain
- h/o breathlessness
- h/o altered bowel habit

1. PAST HISTORY: DM
   HT
   BA
   THYROID DISORDER
   SEIZURE DISORDER
2. DRUG HISTORY:
3. FAMILY HISTORY:
4. PERSONAL HISTORY: Alcoholic, Smoker-yes/no
5. TREATMENT HISTORY

EXAMINATION

- General Examination:

Conscious

Orientation

Anemia

Jaundice

Cyanosis

Vitals –

Pulse : Blood pressure:

Waist circumference:

- CVS:

- RS:
- P/A

Dermatological examination:

Primary lesions:

Secondary lesions

Configuration and distribution of lesions

Oral mucosal involvement:

Genital mucosal involvement

Hair:

Nail:

INVESTIGATIONS

1. Fasting blood sugar
2. Fasting lipid profile
    i. TGL
    ii. CHOLESTEROL
    iii. LDL
    iv. HDL
    v. VLDL

MASTER CHART

S.NO	NAME	age	sex	DURATION	Type of LP	TRUNK	LL	UL	PALMS SOLES	NAIL	ORAL	SCALP	FASTING BLOOD SUGAR	FASTING TGL	FASTING HDL	B.P mm/Hg	W.C cm
1	Moneesh	21	m	1yr6month	L			+					90	121	54	90/60	59
2	Bobby	21	m	3month	C			+			+		82	110	39	100/60	70
3	Lakshmi	14	f	1month	C			+					98	62	40	110/70	79
4	Paulpandi	16	m	1year	H		+			+			95	94	36	110/60	69
5	Sathya	20	f	3month	C		+						78	98	32	90/60	62
6	Selvarani	17	f	2yr	C			+					85	101	38	100/70	64
7	Meena	12	f	1month	C		+	+					84	139	46	100/70	64
8	Udayakumar	15	m	1month	C	+		+					83	54	39	100/70	64
9	Saravanakumar	11	m	2yr	C			+					76	104	40	100/70	72
10	Sivakami	17	f	1yr	C			+					82	101	39	110/70	70
11	Sakthivel	18	f	20days	C		+						80	90	40	110/60	68
12	Sivanandam	12	m	6month	C			+					81	88	36	100/60	64
13	Sheela	18	f	5month	C			+					88	101	40	100/60	68
14	Sowmiya	13	f	1yr	C		+	+					85	139	46	110/70	84
15	Mookambigai	12	f	3month	C	+		+					85	124	40	110/80	89
16	Brinda	19	f	2month	E			+					108	103	40	120/80	89
17	Subulakshmi	14	f	3month	E			+					97	101	40	110/80	80
18	Sowmiya	11	f	2yr	C			+					79	100	35	132/90	82
19	Manikandan	18	m	1month	C		+						98	98	38	130/80	82
20	Edwin	14	m	1month	L			+		+			90	50	42	110/82	80
21	Sathya	20	f	3month	C	+		+					100	104	36	120/76	78
22	Manimegalai	13	f	2month	C			+					90	108	49	110/80	76
23	Rajan	20	m	2month	C			+					104	108	40	110/70	78
24	Chamu	20	f	1month	C								94	110	42	110/68	76
25	Murugan	27	m	8month	E	+	+	+					90	125	39	110/70	95
26	Saravana	28	m	1month	H		+		+				109	102	45	110/80	78
27	Lurdmary	23	f	1month	H		+						106	163	40	110/80	74
28	Selvi	29	f	2month	E	+	+	+					90	125	40	110/80	82
29	Agnipriya	29	f	6month	C		+						98	120	38	100/80	83
30	Suresh	21	m	3month	H		+						76	72	38	110/72	74
31	Rekha	30	f	1month	C			+					89	82	40	110/80	82
32	Periyasamy	22	m	1yr	C			+		+			89	82	40	130/80	81
33	Pown	25	f	1yr	H		+						78	120	40	110/70	81
34	Madhumita	21	f	1month	C		+	+					76	101	42	110/70	82
35	Sabeena	23	f	1month	C			+					85	100	42	120/80	83
36	Priya	25	f	1month	C			+					80	100	40	110/70	80
37	Stella	23	f	1month	C		+	+					85	120	40	110/70	80
38	Sathya	25	f	2weeks	C			+					80	110	42	110/84	82

39	Sugumar	23	m	11/2month	C			+					82	108	42	110/70	80
40	Riyaz	25	m	1yr	H		+	+					112	135	40	120/80	88
41	Anitha	26	f	1month	F			+				+	100	132	48	110/80	82
42	Gunasekaran	34	m	3month	H		+						89	250	50	110/80	85
43	Kasiprabu	40	m	20days	C		+	+					94	123	40	110/70	84
44	Maniammal	32	f	4month	C			+					109	56	45	110/80	88
45	Jayalakshmi	36	f	4month	C			+					87	44	40	110/80	82
46	Beerunisha	40	f	3month	E	+	+	+					93	88	42	110/82	90
47	Boopathi	39	m	9month	H		+						100	103	103	110/80	90
48	Veerakumar	40	m	3month	H		+						87	63	63	130/90	98
49	Boopalan	41	m	9month	H		+						100	103	43	110/72	103
50	Boomi	35	f	8month	C	+		+					88	92	92	120/80	88
51	Ramachandran	33	m	3month	C			+					95	106	106	120/80	96
52	Murugeswari	33	f	2yr	C			+					83	102	32	120/80	80
53	Kasiprasath	40	m	2month	C			+					94	123	40	122/80	115
54	Selvi	40	f	2month	C		+	+					99	183	38	120/80	95
55	Jayakumari	36	f	7month	C		+	+					80	79	42	112/80	109
56	Sakthi	36	f	3month	C			+					96	62	40	120/80	74
57	Prakash	34	m	1month	E	+	+	+		+			97	284	35	140/80	72
58	Vairamani	39	m	1month	L		+						167	572	40	110/78	82
59	Vasudevan	40	m	7month	C			+					80	92	37	114/80	91
60	Fathima	37	f	2weeks	E	+	+	+					107	123	24	110/70	87
61	Damayanthi	35	f	6weeks	H		+			+			90	103	40	110/80	81
62	Rajan	33	m	1yr	F			+				+	85	83	38	110/80	82
63	Sakunthala	33	f	6month	O						+		78	86	34	130/80	84
64	Saratha	40	f	4month	O						+		83	90	40	130/80	80
65	Banumathy	40	f	3month	A	+							88	132	45	110/80	86
66	Sivajyothi	45	f	4weeks	E	+	+	+					103	210	40	130/80	82
67	Gnaguru	44	m	2weeks	H		+						88	104	38	120/80	88
68	Indirani	44	f	2weeks	E	+	+	+					110	171	35	130/90	86
69	Pitchaimani	44	m	4month	C	+		+					253	233	40	110/80	92
70	Dhanapakiyam	42	f	3month	C			+					80	98	38	130/82	78
71	Rosemary	45	f	1month	C			+					86	60	48	110/70	84
72	Rajendiran	48	m	11/2month	LPPIG	+		+					100	100	42	110/80	88
73	Indirani	51	f	2month	C			+					80	160	33	130/80	89
74	Baskaran	48	m	1month	C			+		+			94	123	40	120/80	115
75	Malaisamy	45	m	4month	C				+				111	147	43	120/80	85
76	Sivasowri	44	f	7month	E	+	+	+					118	139	38	110/80	117
77	Lakshmi	42	f	5month	C			+					181	137	38	110/80	90
78	Sivajothi	44	f	10weeks	C			+					82	139	119	160/100	112
79	Dhavamani	50	f	1month	H		+			+			83	190	38	130/80	110
80	Selvarani	46	f	1weeks	E	+		+					151	115	40	170/100	108

81	Mumtaj	48	f	3weeks	C			+					86	110	38	180/130	82
82	Meena	47	f	11/2month	C	+		+					82	159	35	100/80	100
83	Nasreen	42	f	3month	C		+	+					91	189	38	130/90	112
84	Maha	47	f	1month	C			+					80	86	35	110/70	100
85	Ponnuthai	45	f	6month	C			+					91	189	40	110/80	82
86	Rathinam	43	f	3month	C			+			+		109	102	40	110/74	90
87	Baskar	41	m	2weeks	C			+					82	160	40	110/70	96
88	Raji	50	m	2month	C			+	+				80	77	39	140/90	87
89	Sakthi	45	f	3month	C		+	+					105	106	38	120/80	83
90	Banu	42	f	1month	H		+	+					62	147	40	110/80	92
91	Veeranam	41	m	4month	C			+					106	148	42	140/90	91
92	Maruthupandi	47	m	6month	C			+					126	126	50	110/70	90
93	Thirupalai	60/	m	1yr	E	+	+	+					112	199	39	110/70	108
94	Masthan	60	m	8month	C	+	+						107	121	38	120/80	79
95	Vijaya	55	f	10month	C			+					82	120	32	130/82	78
96	Solaiammal	60	f	1yr	F		+	+					217	140	40	130/80	89
97	Mahalakshmi	60	f	6month	LPPIG	+		+					90	160	38	140/90	85
98	Anbuselvi	54	f	2month	C		+	+		+			92	169	30	120/80	98
99	Lakshmi	53	f	3month	L		+						106	90	40	130/80	104
100	Banumathy	53	f	4month	C	+	+						100	92	38	110/80	82
101	Saraswathy	58	f	1month	C		+	+					106	110	32	110/80	78
102	Mahamayee	58f	f	5yr	E	+		+					108	122	40	132s/90	84
103	Devindran	57	m	1month	C			+					87	120	38	120/80	88
104	Sakunthala	51	f	2month	C			+			+		100	100	32	140/90	80
105	Alipro	55	m	1month	C			+					100	101	40	110/70	101
106	Babu	54	m	4month	C		+	+					110	125	42	130/84	90
107	Bala	58	m	3month	O						+		98	110	48	120/80	98
108	veerapathiran	56	m	3month	C				+				82	123	42	110/80	89
109	Chinnasamy	65	m	1yr	C		+	+					98	104	39	110/70	72
110	Mookayee	65	f	1yr	C		+						87	100	38	110/70	78
111	Pitchaiamal	65	f	1yr	C		+	+					100	100	40	110/80	80
112	Nagarathinam	65	f	1month	C		+						80	120	38	140/80	102
113	Aishamariyam	75	f	2weeks	O						+		146	172	35	130/80	92

KEY TO MASTER CHART

UL-upper limb

LL-lower limb

FBS-fasting blood sugar

B.P-blood pressure

TGL-triglyceride

HDL-high density lipoprotein

W.C-waist circumference

LP-lichen planus

C-classical

H-hypertrophic

F-follicular

L-linear

O-oral mucosal

A-annular

LPPig-lichen planus pigmentosus

ANTI PLAGIARISM

CERTIFICATE

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College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	ASSOCIATION OF LICHEN PLANUS WITH METABOLIC SYNDROME
Ethical Committee as on	:	08.02.2016

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

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8 FEB 2016