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LICHEN PLANUS: FROM DIAGNOSIS TO TREATMENT

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Preface

Lichen planus is a chronic inflammatory mucocutaneous disorder that affects the skin, mucous membranes, hair follicles, and nails. Despite being recognized over a century ago, this condition continues to pose diagnostic and therapeutic challenges due to its complex pathogenesis and varied clinical presentations.

This book, *Lichen Planus: From Diagnosis to Treatment*, was written to provide a comprehensive and practical guide for clinicians, pathologists, and researchers. It integrates current knowledge of disease pathogenesis, histopathological features, clinical manifestations, and treatment strategies. Special emphasis is placed on the pathological perspective, reflecting the author's experience as a practicing pathologist, while bridging the gap between laboratory findings and clinical application.

The motivation for this work arose from the need for a single, accessible reference that combines both clinical and pathological aspects of lichen planus. I hope this book will serve as a valuable tool for diagnosis, management, and education, and encourage further research in this field.

I would like to extend my sincere gratitude to my colleagues, mentors, and the patients who contributed to the understanding of this disease.

CHAPTER 1

LICHEN PLANUS: DEFINITION AND HISTORICAL BACKGROUND

Lichen planus (LP) is an inflammatory dermatosis affecting the skin, skin appendages, and mucous membranes, which usually follows a subacute or chronic course and whose exact etiology remains unknown [1]. Although the precise causative factors are unclear, the disease is believed to be associated with immune system dysregulation.

LP was first described in 1869 by Sir Erasmus Wilson. The term "lichen planus" derives from the Greek word *lichen*, meaning "tree moss," and the Latin word *planus*, meaning "flat." Since its initial description, LP has been extensively studied from both clinical and histopathological perspectives [2] (Figure 1).

The condition predominantly affects middle-aged adults and typically presents with pruritus. Clinically, LP is characterized by small, shiny, flat-topped, violaceous, polygonal papules. On the surface of these papules, fine white reticular lines known as Wickham striae may be observed [3–5].

Understanding the clinical and histopathological features of the disease is crucial for accurate diagnosis and management. Clinically, LP may present with both cutaneous and mucosal lesions, whereas histopathological examination typically reveals hyperkeratosis, irregular acanthosis, hypergranulosis, and basal layer damage. In addition, a band-like lymphocytic infiltrate is commonly observed in the upper dermis. In the lower epidermis or superficial dermis, apoptotic or dyskeratotic keratinocytes

known as Civatte bodies may be present. Pigment incontinence is also frequently encountered [4,6].

Figure 1. Sir William James Erasmus Wilson (1874)
The dermatologist who first described lichen planus.
Source: Wikimedia Commons, "Erasmus_Wilson.jpg" (Public Domain).
https://commons.wikimedia.org/wiki/File:Erasmus_Wilson.jpg

Key Points

- Lichen planus is a chronic inflammatory dermatosis affecting the skin, appendages, and mucous membranes.
- First described by Sir Erasmus Wilson in 1869.
- Clinically characterized by polygonal, violaceous papules with Wickham striae.
- Histopathological hallmarks include hyperkeratosis, acanthosis, basal layer damage, and band-like lymphocytic infiltration.
- Civatte bodies and pigment incontinence are common histological findings.

CHAPTER 2

LICHEN PLANUS: EPIDEMIOLOGY AND ETIOPATHOGENESIS

1-Epidemiology and Demographic Features

LP is an inflammatory skin and mucosal disorder with a worldwide distribution, and its prevalence varies according to geographic region and ethnic background. Available data indicate that the global prevalence of LP ranges from approximately 0.14% to 1.27% [7]. Among patients diagnosed with cutaneous LP, approximately two-thirds also present with oral mucosal involvement, whereas around one-quarter of all LP cases affect only the oral mucosa [8].

Although LP can occur in all age groups, it is most commonly observed in adults aged 30–60 years. Pediatric cases are rare, constituting roughly 5% of all LP patients. Regarding sex distribution, cutaneous LP affects men and women approximately equally, whereas oral lichen planus (OLP) is significantly more frequent in female patients, accounting for 60–75% of cases [9].

Epidemiological studies have shown that about 10% of LP patients have a first-degree relative with a similar disease history. This familial predisposition is generally associated with earlier disease onset, increased frequency of mucosal involvement, and a higher tendency for recurrence. In the literature, cutaneous LP cases have been linked to HLA-DR1**,** and familial OLP cases have been associated with HLA-DR6 and 3p14–3q13 chromosomal mutations [10,11].

However, further comprehensive studies are needed to clarify the mechanisms linking genetic predisposition and LP. Additionally, data on how geographic and ethnic differences affect disease prevalence are limited, emphasizing the need for more region-specific studies.

2-Etiopathogenesis

Although the exact etiology of LP remains unknown, the interaction of genetic susceptibility, immunologic response variations, and environmental triggers is considered a critical factor in disease initiation and progression (Figure 2).

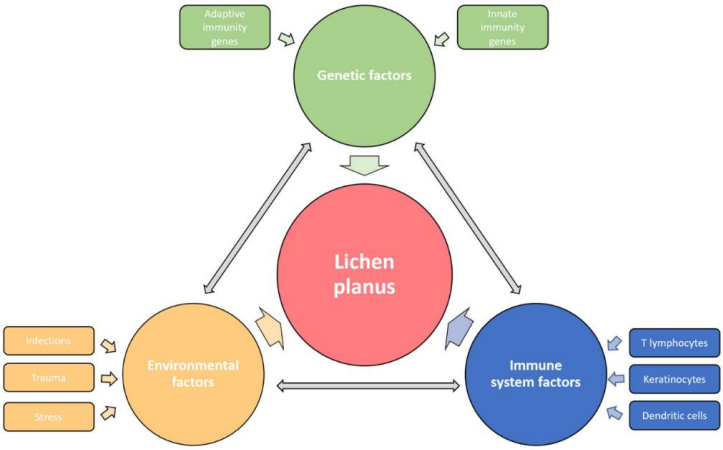

Figure 2. Etiological factors shaping the pathogenesis of lichen planus.

Source: Vičić, M., et al., *Comprehensive Insight into Lichen Planus Immunopathogenesis*, *Int. J. Mol. Sci.* 2023, 24(3):3038; licensed under CC BY 4.0. https://www.mdpi.com/1422-0067/24/3/3038

***Genetic Factors**

The association of genetic susceptibility with LP has primarily emerged from studies on monozygotic twins and the observation that approximately 10% of patients have a first-degree relative affected by the disease [5]. These findings confirm the existence of a familial form of LP, which constitutes roughly 10% of cases and is generally characterized by early onset, frequent relapses, resistance to treatment, and involvement of the oral mucosa [12,13].

Furthermore, genetic susceptibility is not limited to familial cases; similar predispositions have been observed in sporadic LP cases [5]. Analysis of HLA genotypes indicates that certain alleles are particularly prominent as risk factors in familial LP (e.g., HLA-A3, -Aw19, -B7, -B18, -Cw8), whereas others are more evident in sporadic cutaneous LP cases (e.g., HLA-DR1, -DRB1, -DQ1, -Bw35). In oral LP cases, different alleles (e.g., HLA-B8, -B51, -Bw57, -Bw61) are more frequently expressed [5,13].

These findings indicate that genetic factors, together with immune response mechanisms, play a combined role in the pathogenesis of LP and influence the disease's clinical diversity.

More detailed insights into the genetic basis of LP have been obtained through phenome-wide association studies (PheWAS). These studies examined six single nucleotide polymorphisms (SNPs) and identified rs794275, in combination with HLA-DQB1*05:01, as the genetic variation most strongly associated with LP [13,14]. Additionally, a genome-wide association study (GWAS) identified two novel SNPs associated with LP: rs884000 at the NRP2 locus and rs538399 at the IGFBP4 locus [13,15].

These polymorphisms particularly affect genes related to Th1 immune responses, including TNF-α and IFN-γ, while also

influencing mechanisms that regulate inflammatory and cellular responses, such as IL-4, IL-6, IL-10, IL-12, IL-18, oxidative stress-related genes, thyroid hormone synthesis, prostaglandin E2, prothrombin, and NF-κB.

Therefore, genetic predisposition shapes the response of a patient's skin and mucosal tissues to environmental and immunologic triggers, contributing to the diversity of clinical manifestations observed in LP.

***Environmental Factors**

Classic cutaneous LP typically presents with the sudden onset of a single episode and a self-limiting course. Consequently, microorganisms have long been investigated as potential triggers of the disease. The association between hepatitis C virus (HCV) and LP has been confirmed in multiple studies; the prevalence of HCV in LP patients is significantly higher than in healthy individuals, and similar associations have been observed across different geographic regions [16–21]. Although the precise effect of HCV on LP remains unclear, the infection may alter the host immune response, and virus-specific CD8+ T cells can be found in lesions [21,22]. Some studies have reported improvement of OLP lesions following antiviral therapy targeting HCV [22].

In addition, other viral agents have also been linked to LP. Human papillomavirus (HPV) is frequently detected in oral LP lesions [34]; Human herpesvirus 7 (HHV-7), hepatitis B virus (HBV), varicella-zoster virus (VZV), and Epstein-Barr virus (EBV) have been reported as additional agents that may contribute to LP pathogenesis [23–29].

Bacterial and fungal factors may also play a role in LP. Studies have shown that Helicobacter pylori eradication can alleviate disease symptoms [30–32,13]. Fungal species such as Candida and Malassezia may enhance LP antigen expression, thereby triggering a Th17 response [13,33]. Furthermore, the

levels of certain bacterial and fungal species in the saliva of LP patients differ from those in healthy individuals [13,34]. This suggests that disturbances in the oral and salivary microbiome can directly influence the immune system and contribute to OLP development.

Physical factors and psychological stress also influence disease onset. Exposure to radiation, surgical or mechanical trauma can trigger LP's linear form via the Koebner phenomenon [13]. Severe psychological stress, anxiety, and depression can exacerbate both the onset and severity of existing LP [13].

Finally, metabolic alterations may contribute to LP pathogenesis. Research indicates that succinate accumulation and hyperactivation of the mTOR glycolysis pathway can induce apoptosis in cells, potentially playing a role in LP [13].

***Immunopathogenesis**

The mechanisms underlying the development of cutaneous lichen planus have not yet been fully elucidated. One of the main reasons for this is the limited availability of experimental models to explain the pathogenesis of the disease, particularly the insufficient number of animal or human studies [13].

Current evidence indicates that the immune system plays a critical role in disease development. Cytotoxic CD8+ T lymphocytes are thought to be activated by cytokines released from CD4+ T cells, initiating an immune response against basal keratinocytes. In this process, CD8+ T cells cause damage to basal keratinocytes, while their continuous migration along the dermoepidermal junction contributes to the maintenance of the chronic inflammatory cycle. This mechanism has been suggested to be associated with the chronic course of LP [5] (Figure 3).

The innate immune system is also known to play a role in LP pathogenesis. Activation through toll-like receptors (TLRs) leads to an increase in proinflammatory dendritic cells, regulatory T

cells, and polyfunctional T cells [35]. In addition, alterations in the expression levels of various cytokines and growth factors, including IL-1α, IL-6, IL-8, IFN-γ, TNF-α, and vascular endothelial growth factor (VEGF), as well as molecules involved in apoptotic pathways such as caspase-3 and Bcl-2, have been observed [35–38]. These molecules are involved in regulating inflammation, cellular proliferation, and apoptosis.

Chemokines also play an important role in maintaining the inflammatory response. Specifically, chemokines such as CXCL9, CXCL10, and CXCL11 have been shown to support the persistence of inflammation at both the tissue level and in systemic circulation [13]. Furthermore, one of the interferon-α-inducible proteins, known as myxovirus resistance-1 protein, has been reported to be associated with plasmacytoid dendritic cell accumulation and type 1 interferon responses [38–41].

In recent years, the Brn2 transcription factor, which regulates keratinocyte differentiation, has also been suggested to play a role in LP pathogenesis. Experimental studies demonstrated that application of Brn2 to mouse skin produced histopathological changes resembling human LP and increased T lymphocyte migration to the area. Moreover, the majority of thickened epidermal cells in LP lesions were found to exhibit nuclear localization of this factor [42].

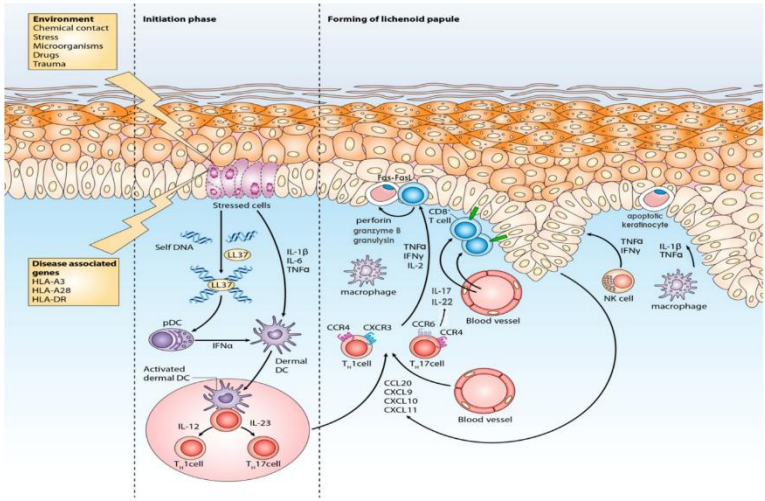

Figure 3. Immunopathogenesis of lichen planus. The disease arises from the activation of T lymphocytes in response to antigen-driven immune reactions. Cytokines released from Th1 and Th17 cells amplify inflammation, while CD8+ cytotoxic T cells induce keratinocyte apoptosis via molecules such as perforin and granzyme. Dendritic cells, macrophages, and NK cells also contribute to the maintenance of the inflammatory process.

Source: Vičić, M., et al., *Comprehensive Insight into Lichen Planus Immunopathogenesis*, *Int. J. Mol. Sci.* 2023, 24(3):3038; licensed under CC BY 4.0. https://www.mdpi.com/1422-0067/24/3/3038

Key Points

- LP is a chronic inflammatory disease affecting the skin and mucosa, with prevalence ranging from 0.14% to 1.27% globally.
- LP occurs most commonly in adults aged 30–60, with oral LP being more prevalent in women.
- Approximately 10% of patients have a first-degree relative affected, indicating a familial predisposition linked to HLA genotypes.
- Genetic susceptibility interacts with environmental triggers and immune mechanisms, contributing to clinical heterogeneity.
- The disease pathogenesis involves both innate and adaptive immune responses, including CD8+ cytotoxic T cells, Th1/Th17 cytokines, dendritic cells, macrophages, and NK cells.
- Brn2 transcription factor may play a role in keratinocyte differentiation and LP lesion formation.
- Environmental factors, including viral (HCV, HPV, HHV-7, HBV, EBV), bacterial, fungal, physical, and psychological triggers, contribute to disease onset and severity.
- Understanding LP's epidemiology and etiopathogenesis is critical for accurate diagnosis, management, and development of targeted therapies.

CHAPTER 3

LICHEN PLANUS: CLINICAL FINDINGS

Cutaneous lichen planus (CLP) is an inflammatory skin disorder that typically presents with violaceous, pruritic papules and plaques. Lesions initially appear as small papules but may coalesce over time to form larger plaques. Fine white lines, known as Wickham striae, are often observed on the surface of papules and plaques, likely due to hypergranulosis [43,44].

Lesions are most commonly distributed on the extremities, particularly on the volar surfaces of the wrists and ankles, although involvement of the trunk may also occur. Less commonly, lesions can appear in Blaschkoid**,** zosteriform**,** or intertriginous areas [44–47].

The clinical course of the disease is often self-limiting, with lesions typically resolving within 6 months to 1 year. Post-inflammatory hyperpigmentation may be observed after lesion resolution. Recurrence is possible. While oral LP may progress without treatment, hypertrophic LP plaques can remain stable for extended periods even without therapy [47,48].

Linear lesions induced by physical trauma, known as the isomorphic response or Koebner phenomenon, may also be observed in LP; however, excoriation marks are uncommon [43,49].

Clinical Types

LP is generally classified into three main groups based on clinical appearance and mucosal involvement:

1. **Mucosal LP** – affecting only mucosa.

2. **Cutaneous LP** – affecting only skin.

3. **Combined LP** – affecting both skin and mucosa.

Additionally, several subtypes are recognized based on histopathological features and clinical course.

1-Cutaneous LP and Its Subtypes

Cutaneous LP usually involves the dorsal hands, ankles, ventral forearms, and dorsum of the feet. Lesions appear as variable-sized, pruritic, shiny, flat-topped papules or plaques [50]. White, reticular patterns called Wickham striae may be present. Specific features can be more easily observed using topical agents (oil- or water-based) and dermoscopy [50].

In fair-skinned individuals, lesions appear reddish-purple, whereas in darker skin types, coloration is less distinct, and post-inflammatory pigmentary changes are more common. Pruritus is often intense, yet secondary excoriation is rare; however, trauma or scratching can trigger lesion formation via the isomorphic response [51].

Subtypes of Cutaneous LP

- **Blaschkoid LP:** Lesions follow Blaschko's lines, typically limited to one part of the body [50,51].
- **Zosteriform LP:** Lesions follow dermatomes, sometimes developing as an isotopic response after herpes zoster [50,51].
- **Inverse LP:** Localized to intertriginous areas [50,51].
- **Actinic LP (LP Subtropicus):** Appears in darker-skinned individuals in sun-exposed areas, with atrophic edges and hyperpigmentation [50,51].
- **Lichen Planopilaris (LPP):** Affects hair follicles, causing scarring alopecia; subtypes include classic LPP,

Graham-Little-Piccardi-Lasseur syndrome, and frontal fibrosing alopecia [17,19].

- **Palmoplantar LP:** Involves palmar and plantar surfaces [50].

- **Hypertrophic LP:** Pruritic, violaceous, nodular, and scaly plaques on distal lower extremities [50,51].

- **Annular, Atrophic, and Annular Atrophic LP:** Central atrophy with raised violaceous borders or plaques expanding due to elastic fiber loss [50,51].

- **Erythrodermic LP:** Widespread involvement of large body areas [50].

- **Follicularis Tumidus LP:** Erythematous plaques with cystic or comedo-like lesions [50].

- **Pigmentosus LP:** Blue-gray or gray-brown lichenoid macules, papules, and plaques in sun-exposed areas; inverse variant appears in skin folds [50–52].

- **Bullous LP:** Tense, multilocular bullae, primarily on the legs; may involve subepidermal blister formation [53].

- **Perforating and Porokeratotic LP:** Rare subtypes characterized by transepidermal elimination or cornoid lamellae [50,51].

- **Invisible LP:** Histopathologically evident but clinically subtle; lesions may be highlighted under Wood's lamp [50,51].

- **Nail LP:** Involves nail matrix and bed, causing nail plate thinning, pterygium formation, onycholysis, atrophy, and subungual hyperkeratosis [50,54].

2-Mucosal Lichen Planus and Its Subtypes

- **Oral Lichen Planus**

OLP typically presents bilaterally on the buccal mucosa [55,56]. Clinically, lesions exhibit various morphologies and are classified into six main forms: reticular, papular, erosive (ulcerative), plaque-type, atrophic (erythematous), and bullous [55] (Figure 4).

The most common form is the reticular type**,** characterized by white-grey, raised, lace-like lesions known as Wickham striae [55,56]. Reticular lesions are often asymptomatic, whereas erosive and atrophic forms may cause burning, stinging, or pain [55].

Erosive OLP presents with painful mucosal erosions and ulcers, potentially leading to permanent scarring [50,51]. Reticular OLP is distinguished by its white, lace-like network pattern [50], while atrophic (erythematous) OLP develops on an erythematous base and resembles the erosive form [50]. Papular OLP presents as small white papules, whereas plaque-type OLP appears as homogeneous white plaques, more frequently observed in smokers [50]. Bullous OLP is a rare form with blister-like mucosal lesions [50].

Lesion density is generally higher on the posterior buccal mucosa and the lateral-dorsal surfaces of the tongue [55,57]. Less commonly, lesions can affect the gingiva, upper lip, vermillion border, floor of the mouth, and palate [55–57]. Gingival involvement is most often observed in atrophic or erosive forms, potentially resulting in desquamative gingivitis. Isolated gingival involvement is noted in approximately 10% of patients [56]. Plaque-type lesions typically involve the buccal mucosa and tongue, while papular and bullous forms are rare [56].

Atrophic and erosive forms often follow a chronic course, rarely resolve spontaneously, and require regular monitoring due

to potential malignant transformation risk [56]. Literature identifies risk factors for malignancy including erosive subtype, tongue localization, advanced age (6th–7th decade), and female sex [56]. Approximately 15% of OLP patients may also exhibit cutaneous LP lesions [58].

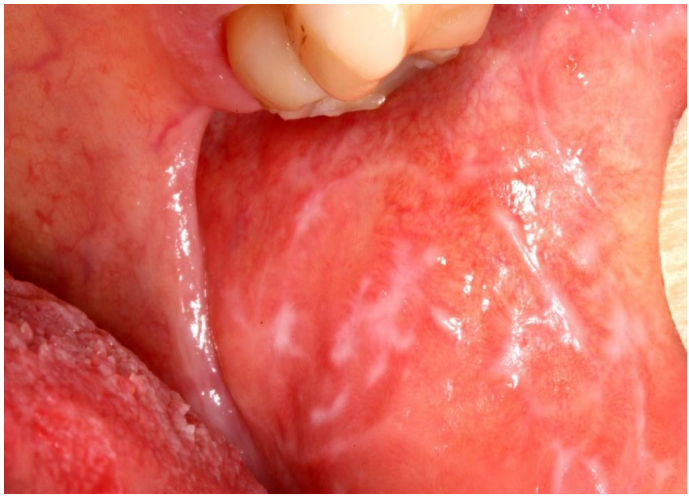

Figure 4. Clinical presentation of oral lichen planus, showing classic reticulated white striations (Wickham striae).

Source: Ian Furst, Wikimedia Commons. Licensed under CC BY-SA 4.0.

- **Genital Lichen Planus**

In women, genital LP is most commonly erosive, potentially causing scarring on an erythematous base [50,58]. Other manifestations include pruritic lichenoid papules, hypertrophic plaques, and variants such as vulvovaginal-gingival syndrome [50,58]. These lesions are often bilateral and symmetric, and may be resistant to therapy with a tendency to recur [59].

Vulvovaginal-gingival syndrome is a special form of erosive LP affecting the vulva, vagina, vestibule, and oral mucosa [59]. Genital mucosal involvement is the second most common site in women after oral mucosa; however, lesion severity does not always progress in parallel between the two regions [58].

In men, genital LP typically presents as annular or papular lesions, and oral-genital co-occurrence is less frequent than in women [50]. The male counterpart of vulvovaginal-gingival syndrome is termed penogingival syndrome [58]. Genital LP may cause burning, pain, dysuria, postcoital bleeding, or bloody discharge, though approximately 25% of cases are asymptomatic with reticular lesions [58,59]. Untreated lesions may lead to scarring, loss of labia minora, and vaginal narrowing or obliteration, necessitating close follow-up due to malignant transformation risk [58,59].

- **Other Mucosal LP Subtypes**

Rarely, patients with oral LP may also present with involvement of **o**cular, laryngeal, anal, otic, nasal, gastric, or bladder mucosa [58].

Esophageal LP primarily affects the upper two-thirds of the esophagus, potentially causing strictures, dysphagia, odynophagia, and weight loss [50,60]. It occurs more frequently in middle-aged women and often coexists with oral or vulvar LP [60]. Due to malignancy risk, monitoring for odynophagia and dysphagia is crucial [60].

Otic LP can lead to external auditory canal stenosis and hearing loss; **anal LP** may cause symptoms related to anal canal narrowing; **ocular LP** can result in scarring conjunctivitis [50].

Key Points

- Cutaneous LP typically presents with violaceous, pruritic, flat-topped papules and plaques, often on the dorsal hands, wrists, and ankles.
- Wickham striae, fine white reticular lines on lesion surfaces, are a hallmark feature.
- Cutaneous LP exhibits multiple subtypes, including Blaschkoid, Zosteriform, Inverse, Hypertrophic, Annular, Erythrodermic, Follicularis Tumidus, Pigmentosus, Bullous, Perforating, and Nail LP.
- Oral LP is commonly bilateral on the buccal mucosa, with six main clinical forms: reticular, papular, erosive, plaque-type, atrophic, and bullous.
- Erosive and atrophic forms of OLP can cause pain, burning, and ulceration, with potential for scarring and malignant transformation.
- Genital LP in women often presents as erosive lesions, with variants including vulvovaginal-gingival syndrome; in men, penogingival syndrome is the corresponding form.
- Rarely, mucosal LP can affect ocular, laryngeal, anal, otic, nasal, gastric, or bladder mucosa, with esophageal involvement leading to strictures and dysphagia.
- Recognition of lesion morphology, distribution, and subtype is crucial for appropriate diagnosis, management, and long-term monitoring due to recurrence and malignancy risk.

CHAPTER 4:

LICHEN PLANUS – HISTOPATHOLOGY

LP is a chronic inflammatory dermatosis targeting the dermal-epidermal junction and exhibits characteristic histopathological findings. The most prominent microscopic feature is the dense inflammatory cell infiltrate along the dermal-epidermal junction extending into the superficial dermis. This infiltrate is typically band-like and predominantly composed of T lymphocytes, occasionally accompanied by histiocytes and, rarely, other inflammatory cells. In some cases, the infiltrate can obscure the precise boundaries of the dermal-epidermal junction, making it difficult to microscopically distinguish the basal cell layer, especially in early lesions [61]. This inflammatory process induces immune-mediated damage in basal keratinocytes and results in various morphological changes in the epidermis. Accurate histopathological diagnosis of LP requires the combined evaluation of epidermal and dermal alterations.

Epidermal Changes

LP lesions typically show irregular epidermal hyperplasia. Epidermal thickening is primarily associated with elongation of rete ridges, which often display irregular, pointed contours described as a “saw-tooth” pattern one of the disease’s distinguishing histopathologic features. At the stratum corneum level, most cases exhibit compact hyperkeratosis or orthokeratosis. Additionally, focal thickening of the granular layer (hypergranulosis) is frequently observed, often in a wedge-shaped distribution. These hypergranulotic areas are thought to correlate with the clinically observed Wickham striae [62]. Vacuolar degeneration in the basal layer is a hallmark histologic

feature of LP. Degenerative changes in basal keratinocytes can weaken the integrity of the dermal-epidermal junction. The spinous layer often exhibits mild intercellular edema (spongiosis) and occasional squamatization. Dermal papillae frequently adopt a dome-shaped morphology [61,63].

Dermal-Epidermal Junction Changes

Basal cell injury can lead to apoptotic keratinocytes, visible at the basal epidermis or the dermal-epidermal junction as necrotic keratinocytes. These structures, with intensely eosinophilic cytoplasm and anucleate appearance, may also be found within the dermis and are histopathologically referred to as colloid or Civatte bodies—classic microscopic features of LP [62]. Vacuolar degeneration of basal cells can also weaken the connection between epidermis and dermis, resulting in small subepidermal clefts or fissures. These structures, known as Max Joseph spaces**,** indicate dermal-epidermal junction damage [61,62,63]. Elongation of rete ridges becomes more pronounced in areas with prominent hypergranulosis, accentuating the saw-tooth pattern. Wedge-shaped hypergranulosis is not only observed in interfollicular epidermis but may also be seen at the acrosyringium (intraepidermal eccrine ducts) or upper segments of hair follicles (acrotrichium) [61,62,63].

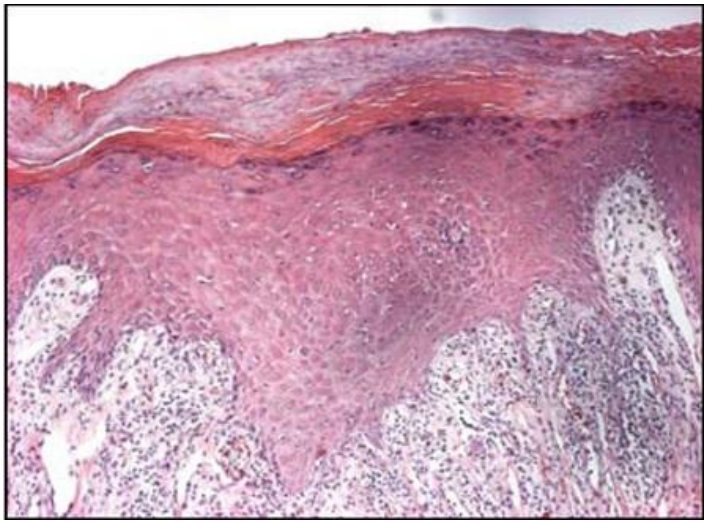

Figure 5. Histopathology of lichen planus showing lichenoid interface dermatitis.
Source: Shi G et al., Wikimedia Commons, licensed under CC BY 4.0**.**

Dermal Changes

The most notable dermal feature is the dense, band-like lymphocytic infiltrate along the dermal-epidermal junction, usually concentrated in the papillary dermis and sometimes sufficiently prominent to distort dermal papillae morphology. In addition to inflammatory infiltration, melanin incontinence can occur, where melanin pigment is phagocytosed by dermal macrophages. This process may contribute to post-inflammatory hyperpigmentation observed clinically as lesions heal.

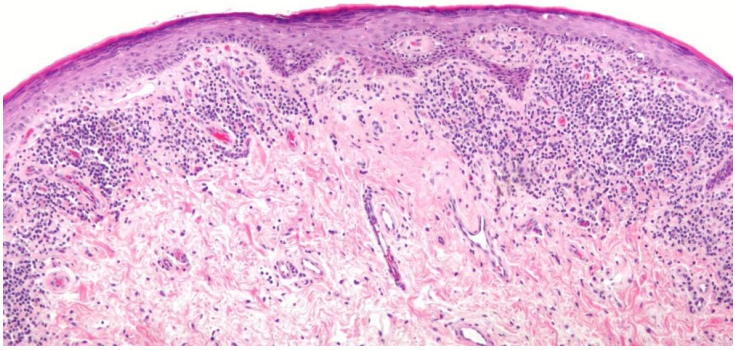

Figure 6. Micrograph of lichen planus (H&E stain) showing loss of rete ridges, basal cell loss, and interface dermatitis with lymphocytes at the dermal-epidermal junction. Source: Nephron, Wikimedia Commons. Licensed under CC BY 4.0

Histopathological Variants of Lichen Planus

Different clinical subtypes of LP can also exhibit certain histopathological variations.

- **Hypertrophic Lichen Planus**

In hypertrophic LP, epidermal changes are particularly pronounced. Hyperkeratosis, parakeratosis, and marked hypergranulosis are commonly observed. Epidermal thickening is characterized by prominent acanthosis, and papillomatosis may develop on the surface. In the dermis, the presence of thicker and denser collagen bundles is notable. These features contribute to the clinically verrucous or hypertrophic appearance of the lesions [48,62,63].

- **Atrophic Lichen Planus**

Atrophic LP is characterized predominantly by epidermal thinning. A marked reduction or complete loss of rete ridges

is typical. Dermal fibrotic changes are more pronounced, serving as a distinguishing feature of this subtype [48,62,63].

- **Vesiculobullous Lichen Planus**

Vesiculobullous LP has a more rapidly progressing clinical course. Consequently, some classical histological features may not always be prominent. For instance, hyperkeratosis or hypergranulosis may be limited, and the dense lymphocytic infiltrate along the dermal-epidermal junction may not consistently appear in all cases [48,62,63].

- **Lichen Planopilaris**

Lichen planopilaris (LPP), characterized by scalp involvement, primarily affects hair follicles histopathologically. In these cases, the band-like lymphocytic infiltrate is concentrated in the peribulge area, including the infundibulum and isthmus regions of the follicle. In early disease stages, the lower segments of the follicles are generally preserved.
Affected follicular segments may exhibit orthokeratosis, hypergranulosis, and follicular obstruction due to keratin accumulation. In contrast, the interfollicular epidermis often appears minimally affected or completely preserved [61,62,63].

- **Mucosal Lichen Planus**

LP lesions developing on mucosal surfaces may show less specific histopathological features compared to cutaneous lesions. This is primarily due to the physiological structural characteristics of the oral mucosa. Normal oral epithelium typically lacks a granular layer and often displays parakeratotic features. Consequently, the characteristic saw-tooth appearance of rete ridges may not always be clearly visible in mucosal LP lesions.
Therefore, the histopathological evaluation of mucosal

lesions should always be interpreted in conjunction with clinical findings and lesion localization to ensure accurate diagnosis [61,62,63].

Key Points

- Lichen planus shows a band-like lymphocytic infiltrate at the dermal–epidermal junction**,** predominantly composed of T lymphocytes**.**
- Basal cell vacuolar degeneration and Civatte bodies (apoptotic keratinocytes) are the hallmark histopathological findings.
- Common epidermal alterations include irregular acanthosis, hyperkeratosis, and focal hypergranulosis**,** which correlate clinically with Wickham striae**.**
- Max Joseph spaces represent focal subepidermal clefts resulting from basal layer damage**.**
- Dermal findings may include melanin incontinence with melanophages and variable fibrosis**,** especially in chronic lesions.
- Histopathologic features may vary according to the clinical subtype (hypertrophic, atrophic, vesiculobullous, follicular/lichen planopilaris, and mucosal variants).

CHAPTER 5:

LICHEN PLANUS – DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of LP is based primarily on clinical findings in most cases. Although the typical morphological features and distribution of lesions are often sufficient for experienced clinicians to establish the diagnosis, histopathological examination plays a crucial role in cases with atypical presentations or when the differential diagnosis is broad. Therefore, a biopsy is recommended to confirm the diagnosis in patients clinically suspected of having LP. Histopathological evaluation is generally supportive and confirmatory in most cases [48].

However, in certain clinical variants, histopathological findings may not fully reflect the classical features of the disease. In particular, conditions such as vesiculobullous cutaneous lichen planus and erosive oral lichen planus may exhibit histologic patterns that resemble other dermatological disorders. In such cases, direct immunofluorescence (DIF) studies may serve as a helpful adjunctive method to support the diagnosis and exclude other diseases [48,64].

In DIF examination, the characteristic finding considered typical for LP is the presence of globular IgM deposition along the dermal–epidermal junction. These immune deposits are often observed around Civatte bodies or in areas with basal cell damage. In addition, fibrin deposition at the mucosal or submucosal interface and fibrin accumulation within vessel walls may also be detected. Furthermore, staining of dermal colloid

bodies with immunoglobulins or complement components is regarded as a supportive finding for LP. However, although these immunologic findings are relatively sensitive, their specificity is limited, and they may also be observed in other lichenoid dermatoses [48,65].

In recent years, non-invasive imaging techniques have increasingly been used in the diagnosis and differential diagnosis of LP. Among these methods, dermoscopy and trichoscopy have gained particular attention. Dermoscopy is a technique that allows magnified visualization of epidermal and superficial dermal structures and may help identify characteristic findings in certain dermatologic conditions. In LP lesions, dermoscopic examination may reveal white reticular structures corresponding to Wickham striae, a violaceous background, and alterations in pigment distribution.

Trichoscopy, on the other hand, is a dermoscopic technique used in the evaluation of hair and scalp disorders. It may provide valuable diagnostic information, particularly in cases with scalp involvement such as follicular lichen planus and lichen planopilaris. Trichoscopic findings that may support the diagnosis include perifollicular erythema, perifollicular hyperkeratosis, and loss of follicular openings. Moreover, dermoscopic characteristics of certain variants, such as lichen planus pigmentosus, are increasingly being defined and reported to contribute significantly to clinical practice. Therefore, dermoscopy and trichoscopy are now considered important complementary and non-invasive diagnostic tools in the evaluation of LP [66–68].

The clinical and histopathological features of LP may resemble those of several other dermatological diseases. For this reason, when establishing the differential diagnosis, the patient's clinical history, lesion distribution, histopathological findings, and, when necessary, immunologic studies should be evaluated

together. The main conditions that may mimic LP include lichenoid drug reactions, lupus erythematosus, lichen sclerosus, psoriasis, chronic graft-versus-host disease, pityriasis rosea, and certain vesiculobullous dermatoses. Careful comparison of the clinical and histopathological characteristics of these diseases is essential for reaching the correct diagnosis. The principal disorders included in the differential diagnosis of LP are summarized in Table 1 [48].

Table 1. Main conditions included in the differential diagnosis of lichen planus according to its clinical variants.

Lichen Planus Subtype	**Diseases to Consider in the Differential Diagnosis**
Cutaneous Lichen Planus	
Classical cutaneous lichen planus	Psoriasis, chronic cutaneous lupus erythematosus, lichen simplex chronicus, graft-versus-host disease, secondary syphilis, pityriasis rosea
Annular lichen planus	Granuloma annulare, dermatophyte infections (tinea)
Linear lichen planus	Lichen striatus, inflammatory linear verrucous epidermal nevus (ILVEN), linear psoriasis, nevus unius lateris
Lichen planus pigmentosus	Ashy dermatosis (erythema dyschromicum perstans)
Bullous lichen planus	Lichen planus pemphigoides, bullous pemphigoid, pemphigus vulgaris

Lichen Planus Subtype	**Diseases to Consider in the Differential Diagnosis**
Atrophic lichen planus	Lichen sclerosus et atrophicus, ashy dermatosis
Generalized lichen planus	Lichen nitidus, drug-induced eruptions, guttate psoriasis, viral exanthems
Mucosal Lichen Planus	
Oral lichen planus	Leukoplakia, oral candidiasis, erythema multiforme, pemphigus vulgaris, secondary syphilis, traumatic mucosal lesions
Vulvar lichen planus	Lichen sclerosus et atrophicus, vulvovaginal bullous dermatoses
Appendageal Involvement	
Follicular cutaneous lichen planus	Lichen spinulosus
Cicatricial alopecia associated with lichen planopilaris	Folliculitis decalvans, perifolliculitis capitis abscedens, discoid lupus erythematosus
Nail lichen planus	Graft-versus-host disease, systemic amyloidosis, trauma, dyskeratosis congenita
Idiopathic nail atrophy	Hereditary anonychia, peripheral circulatory disorders, epidermolysis bullosa

Lichen Planus Subtype	Diseases to Consider in the Differential Diagnosis
Trachyonychia	Alopecia areata, psoriasis
Erosive nail lichen planus	Nail involvement of bullous dermatoses

In the differential diagnosis of lichen planus, not only the clinical appearance but also the histopathological features of other diseases provide important clues during the diagnostic process. In particular, lichenoid dermatoses and certain inflammatory skin disorders may produce lesions that clinically resemble those of lichen planus, which can complicate the diagnostic evaluation. Therefore, comparative assessment of histopathological findings alongside clinical evaluation improves diagnostic accuracy. The clinical and histopathological characteristics of the diseases most frequently confused with lichen planus are comparatively presented in Table 2 [48].

Table 2. Comparison of the Clinical and Histopathological Features of Diseases that May Mimic Lichen Planus

Disease	Clinical Features	Histopathological Features
Lichen Planus	Violaceous, polygonal, flat-topped papules; Wickham striae; commonly located on flexural areas	Band-like lymphocytic infiltrate at the dermal–epidermal junction, basal cell vacuolar degeneration, Civatte bodies, saw-tooth appearance of rete ridges

Disease	Clinical Features	Histopathological Features
Psoriasis	Erythematous, well-demarcated plaques with silvery scales; commonly located on the knees, elbows, and scalp	Regular acanthosis, parakeratosis, Munro microabscesses, elongation of dermal papillae and suprapapillary thinning
Chronic Cutaneous Lupus Erythematosus	Photosensitive plaques with atrophy and scarring; commonly on the face and scalp	Epidermal atrophy, thickening of the basement membrane, perivascular and periadnexal inflammatory infiltrate, dermal mucin deposition
Lichen Sclerosus	Whitish atrophic plaques, particularly in the anogenital region	Epidermal thinning with homogenized collagen and sclerotic changes in the dermis
Lichenoid Drug Reaction	Papular eruptions resembling LP; history of drug exposure may be present	Lichenoid infiltrate similar to LP, but often with deeper inflammation and the presence of eosinophils
Graft-versus-Host Disease	Eruptions developing after allogeneic transplantation;	Basal cell damage, apoptotic keratinocytes, and variable degrees of epidermal necrosis

Disease	Clinical Features	Histopathological Features
	mucosal and cutaneous involvement	
Secondary Syphilis	Generalized maculopapular eruption; palmoplantar involvement is common	Psoriasiform hyperplasia with dermal infiltrate rich in plasma cells
Pityriasis Rosea	Oval plaques on the trunk; "herald patch" and Christmas-tree distribution	Mild spongiosis with superficial perivascular inflammation

Key Points

- The diagnosis of LP is primarily based on clinical findings, particularly violaceous, polygonal, flat-topped papules and the presence of Wickham striae.
- Histopathological examination is recommended in atypical cases or when the differential diagnosis is broad, demonstrating characteristic features such as lichenoid interface dermatitis and basal cell degeneration .
- Direct immunofluorescence (DIF) can aid diagnosis in challenging cases and typically shows globular IgM deposition along the dermal–epidermal junction and around Civatte bodies.
- Non-invasive diagnostic methods, including dermoscopy and trichoscopy, may provide additional clues such as Wickham striae, pigmentary alterations, perifollicular erythema, and follicular hyperkeratosis.
- Several dermatological disorders may clinically and histopathologically mimic LP; therefore, careful evaluation of clinical history, lesion distribution, histopathology, and immunologic findings is essential for accurate diagnosis.
- Common conditions in the differential diagnosis include psoriasis, chronic cutaneous lupus erythematosus, lichen sclerosus, lichenoid drug reactions, graft-versus-host disease, secondary syphilis, and pityriasis rosea.

CHAPTER 6: LICHEN PLANUS – TREATMENT

Since LP may represent a reaction to various exogenous factors such as viruses, medications, or contact allergens, any potential underlying cause should be identified and treated before establishing a definitive diagnosis. Treatment options and management strategies for LP are generally symptomatic or palliative. Therapeutic decisions are determined according to the clinical form and severity of the disease, with erosive variants often being more resistant to treatment.

The primary goal of treatment is the improvement of cutaneous lesions and the associated symptoms. This is particularly important in OLP, where painful erosions may lead to inadequate nutrition and weight loss. In all patients, diseases associated with LP should be evaluated and managed accordingly. Hypertrophic and mucosal LP lesions are considered potentially premalignant, and regular follow-up with periodic biopsies is recommended to exclude malignant transformation [69].

For limited cutaneous LP**,** first-line therapy consists of potent or super-potent topical corticosteroids, often combined with intralesional steroid injections for hypertrophic or treatment-resistant lesions [69,70]. In cases with widespread lesions, systemic corticosteroids administered orally or intravenously may be considered to achieve disease control. Subsequently, the dose can be tapered through oral therapy or by increasing the interval between intravenous administrations [70,71]. Other first-line treatments include systemic retinoids (acitretin or isotretinoin) or cyclosporine [70].

If extensive cutaneous LP remains resistant to treatment, second-line therapies should be considered. These include

sulfasalazine and phototherapy**,** such as broadband UVB, narrowband UVB (NB-UVB), or psoralen plus UVA (PUVA), as well as combinations of UVB/PUVA with retinoids. Third-line therapies include hydroxychloroquine, azathioprine, methotrexate (MTX), mycophenolate mofetil, or biologic agents targeting IL-12/23 [69–71].

The treatment of oral and mucosal LP is often challenging, particularly in cases with widespread erosions. Long-term follow-up is necessary to monitor disease activity and to exclude malignant transformation of erosive lesions. The cornerstone of treatment is topical corticosteroids [70,72]. Super-potent steroids can be applied topically twice daily (often in adhesive paste formulations) for 1–2 months. When lesions are particularly painful or unresponsive to topical therapy, intralesional steroid injections may be considered as an alternative treatment option. For severe, multiple, erosive, ulcerative, or treatment-resistant mucosal LP, systemic corticosteroid therapy may be preferred to achieve faster remission [70,71].

TOPICAL THERAPIES

- ***Topical Corticosteroids***

Class I and II corticosteroids are used as first-line therapy to reduce pruritus and control inflammation [73]. In OLP, topical agents such as clobetasol propionate, betamethasone, and triamcinolone are commonly preferred [74].

- ***Topical Calcineurin Inhibitors***

In patients who do not respond to corticosteroids or in those at risk of adverse effects from long-term steroid use, tacrolimus and pimecrolimus may be used as alternative therapies [73,75–77].

- ***Topical Cyclosporine***

Cyclosporine A exerts its effects by inhibiting T-cell activation. It may be considered as a second-line therapy in OLP cases that do not respond to corticosteroids [78,79].

- ***Vitamin D3 Analogues***

Data regarding their use in cutaneous LP are limited, and their efficacy remains uncertain. Some studies suggest that they may reduce symptoms in OLP; however, strong evidence is lacking [71,73,80].

PHOTOTHERAPY

UVB or PUVA therapy may be used as an alternative treatment option, particularly in cases of cutaneous LP that are resistant to topical or systemic treatments. The effectiveness of phototherapy depends on patient selection and treatment protocols; in some cases, it has been reported to exacerbate lesions [73].

SYSTEMIC THERAPIES

- ***Systemic Corticosteroids***

Systemic corticosteroids are considered first-line therapy in extensive or erosive OLP cases. Rapid clinical improvement can be achieved with methylprednisolone or prednisone; however, long-term use may lead to adverse effects such as weight gain, muscle weakness, and osteoporosis. Mini-pulse regimens may help reduce adverse effects while maintaining therapeutic efficacy [81].

- ***Systemic Retinoids***

Acitretin and alitretinoin are second-line treatment options for patients resistant to corticosteroids. These agents are effective in reducing pruritus and lesions. Alitretinoin may offer a relatively safer teratogenic profile compared with other retinoids [82–84].

- ***Immunosuppressive Agents***

Immunosuppressants such as methotrexate, azathioprine, cyclosporine, and mycophenolate mofetil are used in resistant cutaneous LP cases:

Methotrexate: A safe and effective option in moderate to severe OLP.

Azathioprine: May be used as a steroid-sparing agent.

Cyclosporine and Mycophenolate Mofetil: Have shown promising results in certain LP variants [73,82,85–87].

- ***Immunomodulatory Agents***

Sulfasalazine and thalidomide may improve lesions by modulating the T-cell response. Due to the teratogenic potential of thalidomide, it must be used with caution [71,73,88].

- ***Antibiotics***

Dapsone has shown effectiveness in some patients, whereas metronidazole is generally not recommended due to its limited efficacy [73,89].

- ***Hydroxychloroquine***

Hydroxychloroquine has been reported as a safe and effective monotherapy option, particularly in erosive OLP [90].

- ***Antifungal Therapies***

The efficacy of **griseofulvin and itraconazole** is limited, and they are generally not considered first-line treatments for cutaneous LP [73].

- ***Low-Dose Heparin***

Low-dose heparin may reduce T-cell–mediated inflammation; however, it appears less effective than corticosteroids or methotrexate [73,91].

- ***Biologic Agents***

Biologic agents such as adalimumab, alefacept, infliximab, and anti-IL-17/IL-12/23 therapies may be effective in treatment-resistant LP cases. However, due to their high cost and the lack of long-term safety data, routine use is not currently recommended [73,82].

Key Points

- Management of LP is generally symptomatic and palliative, and treatment decisions depend on the clinical subtype and disease severity. Erosive variants are often more treatment-resistant.

- Identification and management of possible triggering factors (e.g., medications, viral infections, or contact allergens) and associated diseases are recommended before initiating definitive treatment.

- Topical corticosteroids represent the first-line therapy for most patients, particularly in limited cutaneous LP and oral LP.

- Systemic corticosteroids, systemic retinoids (acitretin or isotretinoin), and cyclosporine may be used in patients with extensive or severe disease.

- Second- and third-line treatments for refractory cases include phototherapy (NB-UVB, PUVA), sulfasalazine, hydroxychloroquine, methotrexate, azathioprine, and mycophenolate mofetil.

- Oral and mucosal LP, especially erosive forms, often require long-term follow-up because of their chronic course and the risk of malignant transformation.

- Biologic agents targeting inflammatory pathways (e.g., anti-TNF or anti-IL-17/IL-12/23 therapies) may be considered in

treatment-resistant cases, although their routine use remains limited.

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