Lichen planus and lichenoid dermatoses

Clinical overview and molecular basis

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Learning objectives
After completing this learning activity, participants should be able to recognize clinical features characterizing lichen planus and other lichenoid disorders in patients; classify lichenoid conditions into their respective categories and subtypes; distinguish between the various lichenoid dermatoses despite the significant overlap in clinical presentation; and describe underlying molecular mechanisms for lichenoid skin diseases.

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Deriving from the Greek word λειχήν for "tree moss" and the Latin word *planus* for "planar," lichen planus is a relatively uncommon and heterogeneous cutaneous disorder that typically develops in middle-aged adults. Despite the significant clinical burden associated with the disorder, little well-conducted molecular research has been undertaken, possibly because of heterogeneity impeding consistent and confident phenotyping. The multiple variants of lichenoid disease bear overlapping clinical and pathologic features despite manifesting as distinct clinical disorders. The first article in this 2-part continuing medical education series provides a comprehensive overview of the clinical and pathologic characteristics of cutaneous lichenoid dermatoses and links these manifestations to recent advances in our understanding of the underlying pathobiology of such diseases. (J Am Acad Dermatol 2018;79:789-804.)

Key words: lichen planus; lichenoid inflammation; lichenoid variants; molecular basis of lichenoid inflammation.

CUTANEOUS LICHEN PLANUS

Key points

- **Cutaneous lichen planus represents a relatively uncommon dermatosis, affecting <1% of the population**
- **Consisting of polygonal, pruritic, planar papules or plaques, lichen planus is a heterogeneous papulosquamous eruption of variable morphologic manifestation but a consistent histologic phenotype**

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Abbreviations used:

LP:	lichen planus
LPP:	lichen planopilaris
NLP:	nail lichen planus
HCV:	hepatitis C virus
LDE:	lichenoid drug eruption
LPLK:	lichen planus–like keratosis
LS:	lichen sclerosus
BP:	bullous pemphigoid
LE:	lupus erythematosus
IL:	interleukin
IFN:	interferon
HLA:	human leukocyte antigen
SNP:	single nucleotide polymorphism

- **The etiology of lichen planus remains elusive, although immune dysregulation, infectious, environmental, and genetic factors may play a role in disease pathobiology**

Epidemiology, clinical features, and diagnostic considerations

With an estimated incidence of <1%,[1] cutaneous lichen planus (LP) is thought to make up 0.4% to 1.2% of all dermatology referrals and features.[2-4] It is an inflammatory dermatosis mainly affecting adults of any sex and ethnic origin, and only rarely has it been reported to involve children; the remainder of this series focuses on disease as manifested and treated in adults.[1,5,6]

Cutaneous LP typically presents as a papulosquamous eruption with flat-topped, violaceous, papular lesions of varying size, often described using the "six P's" (purple, pruritic, polygonal, planar, papules, and plaques) and characterized by the classic Wickham striae (Fig 1, *A*).[5,7] The distribution of the eruption is usually localized to the extremities,[8] but may rarely be generalized[4,9] or adopt a Blaschkoid,[10] intertriginous,[5] or dermatomal[11] configuration. The majority of cutaneous LP cases will remit within 1 to 2 years,[12] unlike subtypes involving mucosal and densely follicular sites, where lesions tend to persist for a longer duration. From our perspective, testament to this is the observation that our tertiary specialist clinics are occupied with challenging chronic cases of oral, genital, and appendageal disease, whereas classic cutaneous disease does not appear to be as burdensome, demands less regular clinical input, and is only seen in the general clinic service.

There are a number of characteristic pathologic findings that allow confirmation of a clinical diagnosis of LP.[13,14] The epidermis may show hyperkeratosis without parakeratosis, and apoptotic keratinocytes (Civatte bodies) can be seen at a lower level (Fig 1, *B*).[13,14] The epidermis itself may show "wedge-shaped" hypergranulosis, with a characteristic "saw tooth" appearance of the rete ridges.[13,14] At the dermoepidermal junction, small clefts (known as Max Joseph spaces) may be observed along with band-like lymphocytic infiltration.[13,14] Apoptotic keratinocytes are also found in the papillary dermis, as eosinophilic colloid bodies. As the dermoepidermal junction is disrupted, pigment incontinence occurs, linked to the increased presence of melanophages.[13,14] Direct immunofluorescence staining in the biopsy specimen is helpful, because lesions of LP characteristically and consistently display a bright "shaggy" band of fibrinogen along the dermoepidermal junction, as well as colloid bodies staining with any of the autoantibodies immunoglobulin M (IgM), IgG, IgA, and C3 (Fig 1, *C* and *D*).[13]

Although experienced physicians are able to diagnose cutaneous LP clinically, a biopsy specimen of the skin is useful for confirmation of a clinical diagnosis, and punch or shave biopsy specimens are normally adequate.[15] We tend to resort to histopathologic evaluation in rare cases of diagnostic uncertainty, but we consistently explore possible risk factors for hepatitis C virus (HCV) infection. A systematic drug history to look for culprits is also relevant in the clinical history, as are symptoms suggestive of other regional lichenoid involvement. Such symptoms comprise oral or genital erosions or pain, dysphagia or odynophagia, alopecia, and trichodynia, and the physical examination should comprehensively look for the corresponding and supportive clinical signs at the scalp, oral cavity, and genitalia, respectively. Dermoscopy can be used to highlight Wickham striae,[16] which complement the clinical history, in differentiating idiopathic LP from drug-induced disease (lichenoid drug reaction).[17] The clinical history is also vital in diagnosing clinically reminiscent conditions, such as chronic graft-versus-host disease.[18]

MORPHOLOGIC VARIANTS OF CUTANEOUS LICHEN PLANUS

Key points

- **Being morphologically heterogeneous, lichen planus may be hyperkeratotic, annular, bullous, pigmented, or atrophic**
- **Lichenoid variants are plentiful and comprise lichenoid drug eruption, lichen planus–like keratosis, lichen nitidus, lichen sclerosus, and lichen striatus**
- **Overlap syndromes refer to lichen planus coexisting with a distinct second clinical entity**

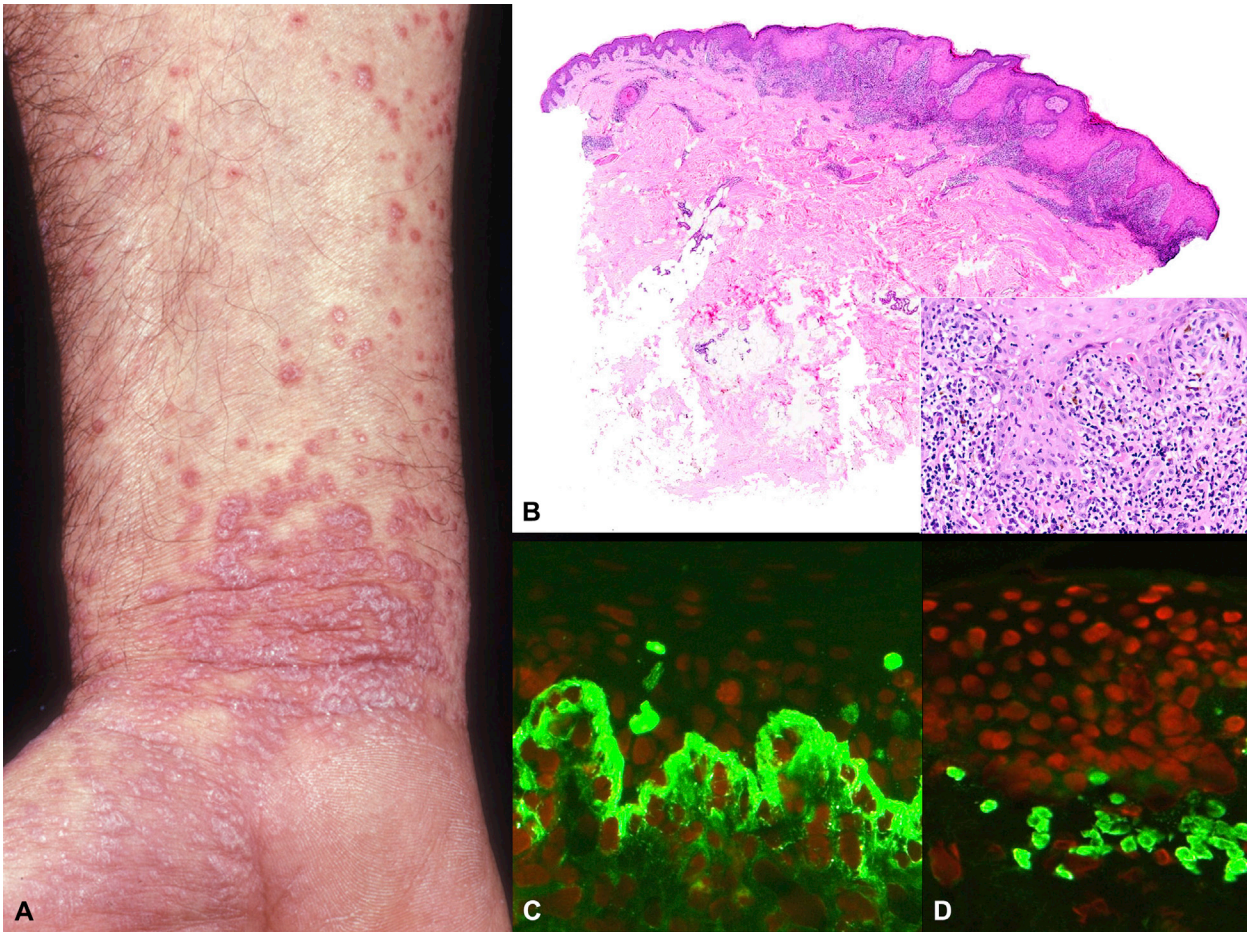

Fig 1. Lichen planus. **A**, Wrist. Characteristic polygonal flat-topped erythematous papules with shiny surfaces coalescing into plaques. **B**, Histopathology of a hypertrophic lesion showing irregular epidermal hyperplasia with a dense lichenoid lympohid cell infiltrate. *Inset*, Higher magnification showing lymphocytic exocytosis with vacuolar interface changes and individual dyskeratotic keratinocytes (Civatte bodies) with papillary dermal lymphocytes admixed with histiocytes and melanophages. **C**, A linear "shaggy" band of fibrinogen deposition at the basement membrane zone. **D**, Colloid bodies in the papillary dermis staining for immunoglobulin A. (**B**, Hematoxylin–eosin stain; **C**, fibrinogen; **D**, immunoglobulin A; original magnifications: **B**, ×40 and inset, ×200; **C**, ×400; **D**, ×400.) Clinical image courtesy of St. John's Institute of Dermatology.

Cutaneous LP does not always manifest in a classic presentation, because there is an array of LP variants that possess distinct clinical characteristics.

Actinic LP is a morphologic variant of high prevalence in tropical countries such as India, East Africa, and the Middle East[8]; therefore, it is sometimes referred to as LP subtropicus. Sun-exposed areas display discoid macules, papules, or plaques with a hyperpigmented focus and encircling hypopigmentation.[5] The violaceous plaques observed in annular LP have a thin rim of activity with a clear, and occasionally atrophic, center. These lesions may develop on the penis (Fig 2), scrotum, and intertriginous regions amongst other sites, including the lips (Fig 3).[19]

Atrophic LP, one of the rarer cutaneous LP variants, typically affects the legs[5] and manifests as small violaceous, annular papules that progressively enlarge. These lesions develop central atrophy and histology of the papillary dermis characteristically shows destruction of elastic fibers, which may or may not be accompanied by a lymphocytic infiltrate.[20-22] In the bullous subtype, bullae or vesicles tend to be restricted to areas already affected by cutaneous LP, and frequently develops on the lower extremities.[5] Bullous LP can resemble an overlap syndrome of LP and bullous pemphigoid (BP) known as LP pemphigoides.[23] The hypertrophic variant of LP presents with extremely pruritic, hyperkeratotic flat-topped plaques affecting the

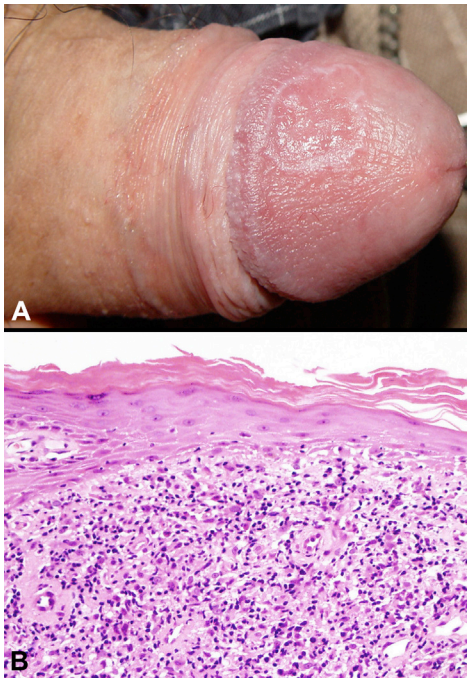

Fig 2. Lichen planus of the penis. **A**, Glans penis. Annular patch with central clearing and white shiny peripheral edge. **B**, Histopathology showing epidermal atrophy with an overlying compact horn and a dense lichenoid lymphoid cell infiltrate in the papillary dermis. (Hematoxylin–eosin stain; original magnification: **B**, ×400.)

wrists, interphalangeal joints or the anterior lower legs (Fig 1, *A*). This subtype can commonly present in a symmetrical pattern. Polygonal papules may encircle the original lesion. A visual clue that can be used to differentiate hypertrophic LP is its resemblance to the extrusive forms of igneous rock.[24] Squamous cell carcinoma may arise in sites affected by chronic hypertrophic LP.[25] Inverse LP manifests as poorly defined erythematous lesions with pigmentation, usually involving the axillae, inguinal creases, inframammary creases, and neck and limb flexures.[5] LP pigmentosus is characterized by minimally pruritic, hyperpigmented macules typically on intertriginous or sun-exposed areas. The degree of pigmentation varies from slate gray to dark brown patches, and inverse LP and LP pigmentosus are more often observed in individuals with darker skin.[26] When lesions are primarily distributed on skin fold areas, this rare variant is known as LP pigmentosus inversus.[27]

Of the above morphologic variants, we most commonly encounter the hypertrophic type, followed by LP pigmentosus, the latter almost exclusively in association with cases of frontal fibrosing alopecia.

Regional and appendageal subtypes

There are 3 different specialty clinics in our center, each devoted to and hosting a large patient cohort for each of these subtypes, and each subtype can be more debilitating and treatment-refractory than classic cutaneous cases of LP.

Oral LP. Oral LP, a lichenoid subvariant affecting the oral mucosa (Fig 4), is a chronic, relapsing and remitting disorder, and is generally thought to confer a higher morbidity than many of its cutaneous counterparts.[28,29] This condition is often diagnosed by dentists, who subsequently refer these patients to dermatologists for treatment. Indeed, given that oral LP is frequently associated with cutaneous lichenoid disease, examination of the oral cavity should therefore be a routine part of patient evaluation in dermatology clinics. Whether asymptomatic reticular or highly distressing erythematous and erosive, specialist assessment and work-up (clinical and histopathologic) is required and should be sought as appropriate.

Genital LP. Genital LP, involving glabrous or mucosal skin, may affect men and women alike and may be encountered by a variety of medical specialties, including gynecology, genitourinary medicine, urology, and primary care, although dermatologists should be involved and lead care as early as possible. Penile LP tends to present with a papular or annular morphology, whereas females tend to develop highly debilitating erosive disease, whether in isolation or as part of erosive vulvovaginogingival syndrome.[30-32] There are many variations in clinical presentation, and it is important to be aware of the more common manifestations of genital LP (Fig 5) while also remembering to consider the genital areas in history-taking and clinical examination when evaluating for LP affecting other body regions. Diagnosis may be reached by clinical assessment, although histopathologic evaluation may be undertaken in challenging cases.

Follicular LP. Follicular LP, or lichen planopilaris (LPP) for loyal Latin scholars, is the prototype of primary lymphocytic cicatricial alopecias and is associated with inflammation-driven hair follicle destruction, culminating in scarring hair loss that involves the scalp and other body areas (Fig 6, *A* and *C*).[33,34] Histopathologically, LPP is characterized by perifollicular lymphoid cell infiltration and perifollicular fibrosis (Fig 6, *B*). It has been postulated that the underlying immune privilege collapse at the level of the hair follicle bulge culminates in epithelial hair follicle stem cell loss and irreversible cicatricial hair loss, in a process germane to alopecia areata but occurring at the more

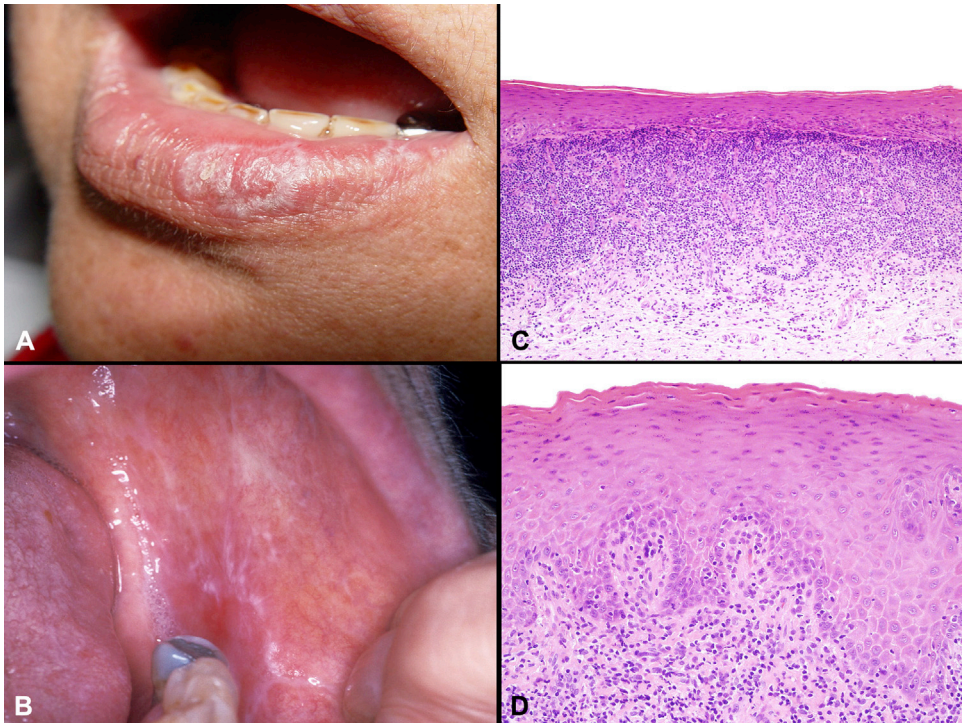

Fig 3. Annular lichen planus. **A**, Lower lip. Annular plaque with central clearing and raised purple to white shiny borders. **B**, Oral lichen planus. Lacy reticular network of white coalescing papules. Clinical image courtesy of St. John's Institute of Dermatology. **C**, Squamous mucosa with confluent parakeratosis and with underlying dense lichenoid lymphoid cell infiltrate. **D**, Higher magnification detail on the lichenoid interface changes and lymphocytic exocytosis. (Hematoxylin-eosin stain; original magnification: **C**, ×100; **D**, ×200.)

superficial anatomic level of the isthmus.[34] LPP is heterogeneous per se and comprises classic multifocal LPP, Graham-Little-Piccardi-Lasseur syndrome, and the distinct and almost exclusively of female predilection and postmenopausal onset frontal fibrosing alopecia variants (Fig 6).[34] We have argued and proposed elsewhere[34] that the term frontal fibrosing alopecia is a misnomer, because it restricts in linguistic terms an immune system–mediated autoinflammatory disease characterized by widespread body, eyebrow, facial, occipital lichenoid, and alopecic involvement to the geographic territory of the frontovertex. By the same token, perhaps LPP should be more precisely defined as classic, frontoparietalis, occipitalis, totalis, and universalis, in a manner on par with its nonscarring, albeit deeper dermal, autoimmune counterpart alopecia areata.

Nail LP. Although the nails show lichenoid involvement in ≤25% of patients with LP,[35-38] isolated nail LP is rare,[39] with no accurate epidemiologic figures. Classic clinical signs comprise nail thinning, longitudinal ridging and fissuring, distal splitting, trachyonychia, and erythema of the lunula.[35,36] Nail LP may lead to severe erosion of the nail bed along with severe and permanent onychodystrophy caused by scarring (Fig 7, *A*).[39] The diagnosis can be reached clinically in most cases, but where there is clinical uncertainty, histopathology of the nail matrix, demonstrating all the classic lichenoid findings (Fig 7, *B* and *C*), is usually conclusive.[39]

Other lichenoid dermatoses

The lichenoid dermatoses discussed below are individually rare eruptions but collectively important clinically. Histologic and dermoscopic evaluation is often essential in diagnosis, and key features thereof are presented in Table I.

Lichenoid drug eruption. Also known as drug-induced LP, lichenoid drug eruptions (LDEs) are often clinically identical to cutaneous LP and occur as an adverse reaction to various medications, while certain drug culprits (Table II) have also been implicated in oral and photodistributed involvement, the latter possibly because their spectrum of activity coincide with the wavelength of ultraviolet B light (290-320 nm).[17,40-47] We find that although LDEs morphologically mirror classic cutaneous LP, they tend to be more polymorphic, lack Wickham striae,

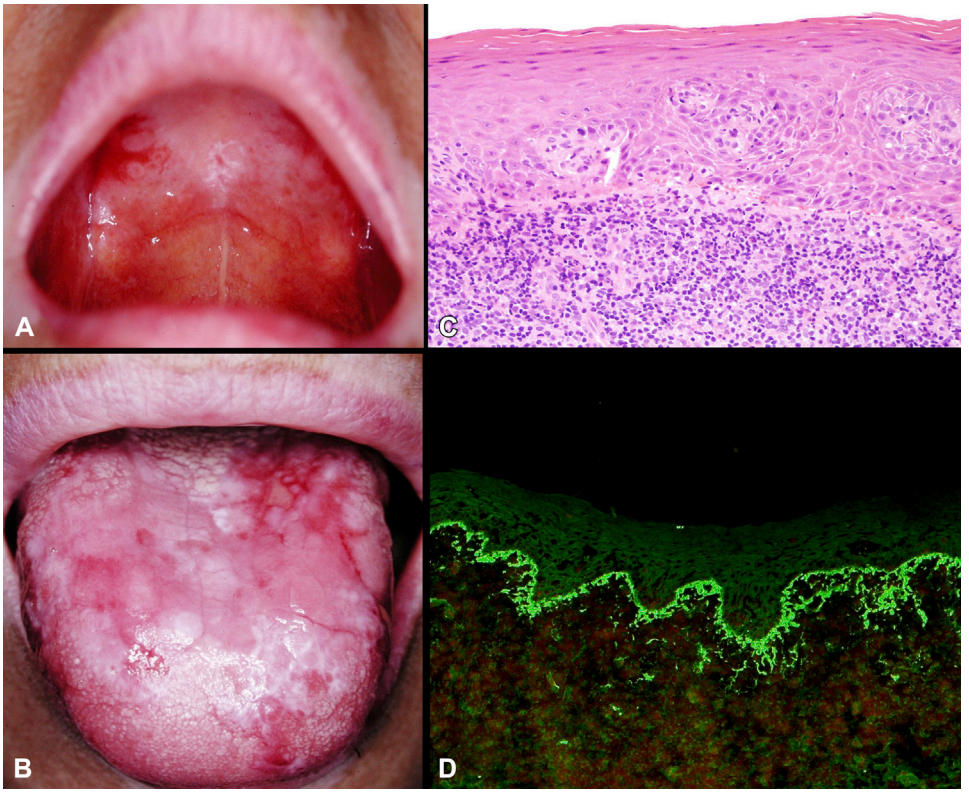

Fig 4. Ulcerative (erosive) lichen planus. **A**, Extensive ulceration involving the hard palate and (**B**) the dorsal aspect of the tongue. **C**, Histopathology showing squamous mucosa with parakeratosis and a dense lichenoid lymphoid cell infiltrate. **D**, A linear "shaggy" band of fibrinogen deposition at the basement membrane zone. (**C**, Hematoxylin-eosin stain; **D**, fibrinogen; original magnifications: **C**, ×200; **D**, ×100.)

and show more pronounced desquamation with psoriasiform or eczematous morphology, as also reported in the litarature.[48] LDEs usually arise several months (or even years) after the initial exposure to the perpetrating medication. The underlying basis for this delay remains unclear but is likely to be influenced by many variables, including the dose, medication class, drug–drug interactions, and other host factors.[43] There is no gender bias and LDEs tend to affect older adults (40-60 years of age).[17,49,50] LDEs typically settle within weeks or months of withdrawing the culprit, although resolution can be seen sooner or while the patient remains exposed to the medication.[51,52]

We routinely perform histologic assessment, and this usually shows lichenoid interface dermatitis,[50,53,54] although there are distinguishing features, such as eosinophilia, which is frequently present (Table I). Patch testing persistently yields high false negative rates and therefore are not regularly performed. At best, only half of all cases receive a meaningful result,[55-57] and we do not often conduct this unless there is dilemma on which drug needs to be discontinued with potentially clinically meaningful implications.

Lichen nitidus. Lichen nitidus, described as inflammatory and often intensely pruritic, is a variant we see relatively uncommonly, especially in isolation. It presents with small, skin-colored papules that can be flat-topped, rounded, shiny (or minimally scaly), hypo- or hyperpigmented (depending on skin tone), and can affect any site, most commonly in children or young adults.[58-65] It has been reported to koebnerize,[66] and nail manifestations, such as pitting and splitting, are common.[67] Lichen nitidus has been associated with a range of diseases, such as Crohn's disease, Down syndrome, atopic dermatitis, and congenital megacolon, and it is important to recognize it in such contexts.[68-70] Familial forms of lichen nitidus have also been reported, lending support to the notion of inherited pathology,[71,72] although no orchestrated attempt at genetic dissection has been reported. For diagnosis, we tend to corroborate clinical evaluation with histologic evaluation: the characteristic lichenoid lymphohistiocytic infiltrate is

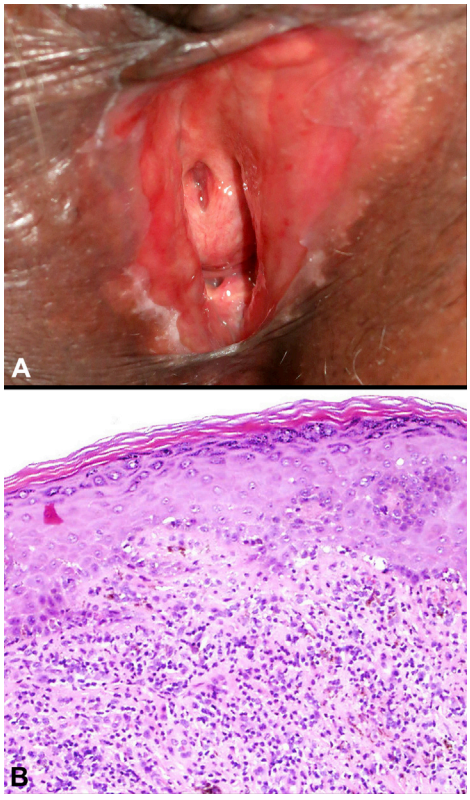

Fig 5. Erosive vulval lichen planus. **A**, Bilateral vestibular erosions with hyperkeratotic lacy edge on lower right labium minus. **B**, Histopathology taken across the edge of the erosions shows compact orthokeratosis, hypergranulosis, irregular "saw-toothing," vacuolar interface change, and a dense lichenoid lymphoid cell infiltrate filling the papillary dermis. (Hematoxylin-eosin stain; original magnification: **B**, ×400.) Clinical image courtesy of Dr Fiona Lewis, St. John's Institute of Dermatology.

seen filling the papillary dermis in a pattern known as the "ball and claw" in dermatopathology (Table I).

LP-like keratosis. We encounter LP-like or benign lichenoid keratosis (LPLK) in mole clinics because these are typically solitary, scaly plaques ranging from pink to violaceous to pigmented[73] on the upper extremities, trunk, and other sun-exposed areas.[74] LPLK is thought to arise from a regressing seborrheic keratosis or solar lentigo. Some of the proposed triggers include dermatitis, medications, mild trauma, and sun exposure. Dermoscopy can be of diagnostic value in LPLK, revealing remnants of the original seborrheic keratosis or lentigo (which fade with time), telangiectatic vasculature, and clusters of gray spots.[75] LPLK may be misdiagnosed as psoriasiform or as superficial basal cell carcinoma, although histologically, it is highly similar to LP but often shows parakeratosis, which can be an important distinguishing feature to bear in mind. Clinicopathologic correlation is essential for accurate diagnosis, because LPLK is frequently a solitary lesion in its distribution and may raise concern of actinic damage of a preneoplastic nature.

Lichen sclerosus. Lichen sclerosus (LS) is a relatively common dermatosis that usually involves the perianal and genital regions but can also manifest extragenitally (Fig 8). Individuals of any age or sex can be affected in a biphasic manner, but the disease is most often detected in later life. Women are thought to be 10 times more likely to be affected than men.[76-81] An association with autoimmune diseases (eg, alopecia areata, pernicious anemia, and thyroid disease) has been reported,[80-82] and our (adult) clinical cohorts do seem to corroborate the published literature. LS may develop in conjunction with or following other immune-mediated cutaneous disorders,[76,81,83-86] although the underlying pathobiology is most likely multifactorial.[87,88] Men who have been circumcised in infancy seldom develop penile LS (also called balanitis xerotica obliterans), lending support to the notion that foreskin may be an obligate part in pathogenesis, whereby susceptible epithelium is allowed to be in prolonged contact with occluded urine.[89] LS may increase the risk of developing squamous cell carcinomas in the involved area[90-94] and, although it can be diagnosed clinically, obtaining a skin biopsy specimen is desirable, especially given the neoplastic transformation potential and warranted surveillance.[93,94]

Lichen striatus. Lichen striatus is a rare, asymptomatic, self-limiting eruption of cryptic pathogenesis that develops most commonly in children (5-15 years of age). Lesions are characterized by red or pink papules that coalesce into a scaly, erythematous linear configuration, often in a Blaschkolinear distribution.[95,96] Lesions may be pruritic and develop most frequently on the neck or limbs, but may also affect the trunk, abdomen, thighs, and buttocks,[97] and a collection of nail signs may be seen.[98] A diagnosis is typically made based on clinical evaluation, but obtaining an accompanying biopsy specimen and histologic analysis are valuable for excluding other differential diagnoses (Table I).[99,100]

Overlap syndromes

Overlap syndromes are conditions where patients present with characteristics of a second and distinct clinical entity alongside cutaneous LP, such as BP and lupus erythematosus (LE). Unlike bullous LP, where blisters are confined to chronic LP erosions, in LP pemphigoides, bullae can arise on existing LP lesions or healthy skin. Clues to distinguish LP pemphigoides from BP include a younger age of

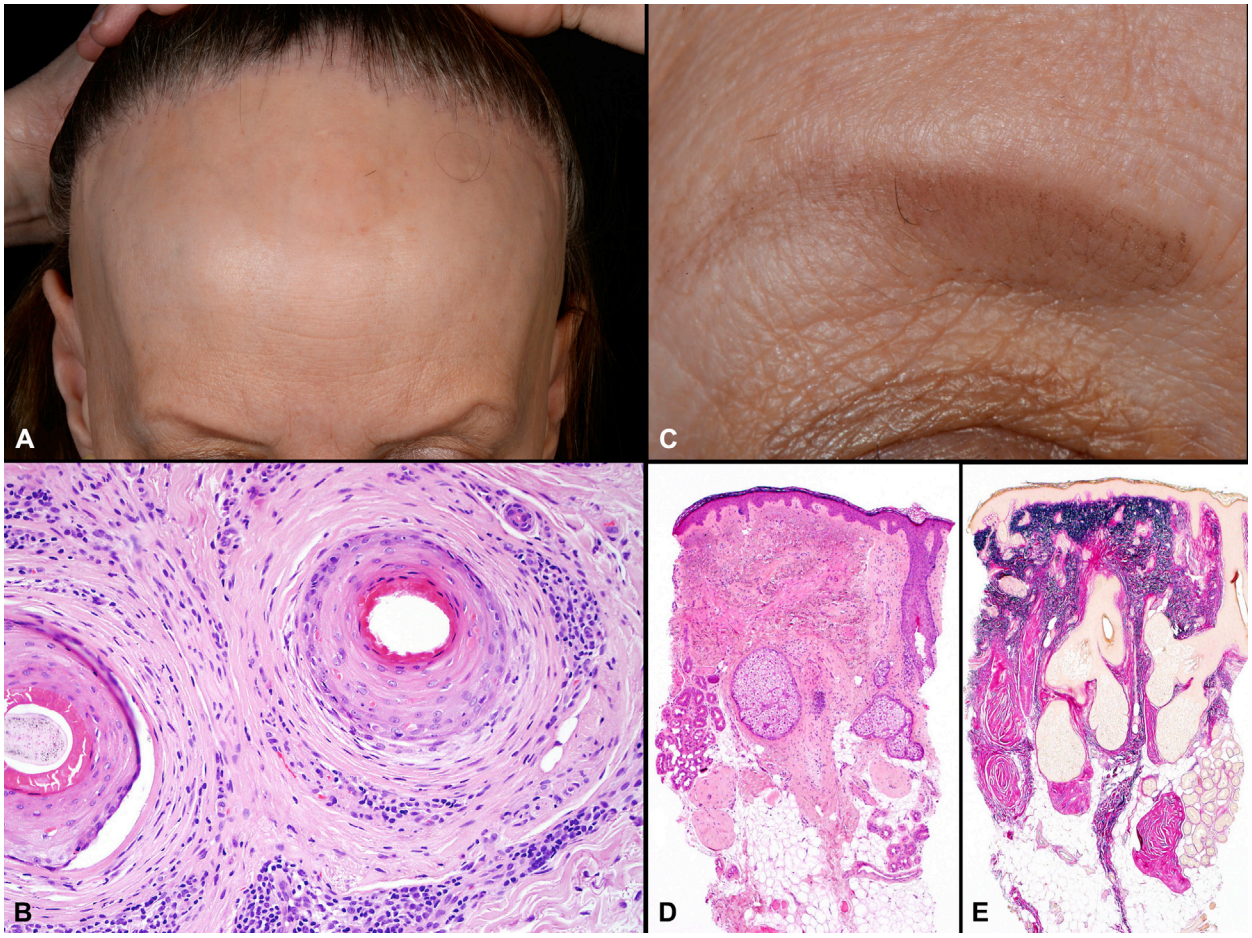

Fig 6. Frontal fibrosing alopecia variant of lichen planopilaris. **A**, Scalp. Recession of the frontotemporal hairline with hyperkeratotic papules perifollicular erythema and loss of eyebrows. **B**, Histopathology of horizontally oriented scalp biopsy specimen. Isthmus. Perifollicular fibrosis with perifollicular lichenoid cell infiltrate. Dyskeratotic keratinocytes are present in the follicular epithelium. **C**, Eyebrow. Higher magnification showing almost complete loss of hair. **D**, Histopathology of vertically oriented eyebrow biopsy specimen. Hair loss with dermal solar elastosis and fibrous tracts (follicular scars) extending into the subcutaneous tissue. **E**, Elastic stain highlighting the solar elastosis in the papillary dermis and demarcating the fibrous tracts with absence of elastic fibers. (**B**-**D**, Hematoxylin–eosin stain; **E**, elastic van Gieson stain; original magnifications: **B**, ×400; **D**, ×40; **E**, ×40.)

onset (40s) and milder lesions principally affecting the extremities,[101] although we invariably resort to obtaining a skin biopsy specimen, in which linear deposits of IgG or C3 at the dermoepidermal junction are detectable by direct immunofluorescence staining, as also reported in the literature.[102] LP–lupus erythematosus is rare and presents with mixtures of verrucous or lichenoid lesions in the head, neck, trunk, and upper extremities. These lesions show clinicopathologic characteristics that resemble both LP and LE.[103]

Etiology and molecular basis

There is relative paucity of well-conducted, hypothesis-driven investigative research in LP, despite its relative prevalence and the therapeutic challenges it often comes with in clinical practice, all stemming primarily from agnosia on molecular targets for drug development. The undertaken studies have focused on the putative role of 4 domains in pathogenesis, and each of these is discussed below.

Immune dysregulation. As with many other inflammatory dermatoses, immune dysregulation has been suggested to be strongly relevant in the pathophysiology of LP. It is postulated that activated T cells, principally cytotoxic $CD8^+$ cells, launch an immune attack against basal keratinocytes, assisted by $CD4^+$ helper T cells via secretion of T_H1 cytokines.[8] The basement membrane is breached

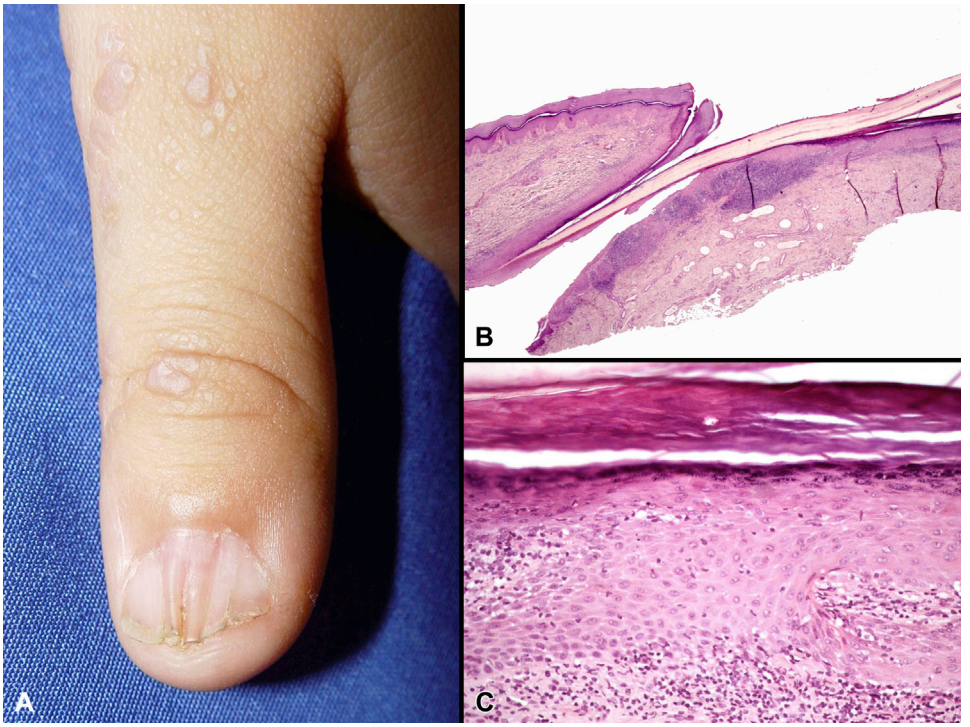

Fig 7. Nail matrix lichen planus. **A**, Nail scarring with dorsal pterygium. Flat-topped polygonal papules of lichen planus are also present on the dorsal aspect of the thumb. **B**, Histopathology showing a dense lichenoid lymphoid cell infiltrate involving the nail matrix. **C**, Higher magnification detail with lymphocytic exocytosis and vacuolar interface changes. (Original magnifications: **B**, ×20; **C**, ×400. Histopathology photographs courtesy of Professor P. A. Fanti, University of Bologna, Bologna, Italy.) Clinical image courtesy of St. John's Institute of Dermatology.

when $CD8^+$ cells inflict injury on keratinocytes, allowing the inflow of additional $CD8^+$ cells in a self-perpetuating process of basal keratinocyte destruction. This vicious loop is presumed to be the underlying basis of the chronicity of LP,[104] although there is no adequate explanation of why classic cutaneous LP is usually self-limiting while its follicular or mucosal counterparts persevere for significantly longer. In LP, Toll-like receptor–mediated activation of the innate immune response results in the production of proinflammatory myeloid dendritic cells, regulatory T cells, and polyfunctional T cells.[105]

Various factors have been shown to be up- and down-regulated in the inflammatory process, comprising a milieu of adhesion molecules, inflammatory and proapoptotic mediators, and cytokines and growth factors (including interleukin [IL]-1α, IL-6, IL-8, interferon [IFN]-γ, tumor necrosis factor–α, vascular endothelial growth factor, transforming growth factor-β1, caspase-3, and Bcl-2).[8,106-118]

From a pharmacologic perspective, important chemokines involved both at tissue and systemic level comprise CXCL9, CXCL10, and CXCL11.[119,120] There is increasing evidence to suggest the important role of type I IFNs and accumulation of plasmacytoid dendritic cells and the IFN-α–inducible protein known as myxovirus resistance 1 protein in the process, has recently been implicated.[121-128] Recently, transcription factor Brn2 has been proposed to be of relevance in keratinocyte differentiation and thus in the pathogenesis of LP. Injection of Brn2 into rat skin leads to histopathologic features that resemble human LP. In addition, Brn2 also attracts T lymphocytes and has been shown to be present in almost all cell nuclei of the thickened epidermis in LP.[129]

It is still unclear what exactly spurs the upstream regulators to action and why it so happens in certain individuals and not others, but dissecting the molecular signature of the process is helpful in identifying "druggable" molecular targets. To add to the complexity, a link between endocrine and immune changes caused by stress and LP has also been postulated, as evidenced by the differential expression of factors such as neopterin, sIL-2R, sFasL, sIL-6R, and IL-18 compared to controls.[130]

Table I. Lichenoid dermatoses and their key histologic features

Lichenoid variant	Key histologic features	Key dermoscopic features
Lichenoid drug eruption	• Lichenoid interface dermatitis; colloid or Civatte bodies, lymphocytic infiltrate in the papillary dermis, pigmentary incontinence with dermal melanophages • Focal parakeratosis with focal interruption of the granular layer, cytoid bodies in the cornified and granular layers, and present eosinophil • Prominent necrotic keratinocytes, plasma cells and eosinophils, exocytosis of lymphoid cells into upper epidermis and deeper perivascular infiltrate would be more typical of lichenoid drug eruption than lichen planus	• Lack of Wickham striae
Lichen planus–like keratosis	• Lichenoid lymphocytic inflammatory infiltrate, similar to lichen planus; parakeratosis can be a key distinguishing feature, clinicopathological correlation is essential to diagnosis	• Fissures and ridges (brain-like appearance) • Milia-like cysts and comedo-like openings • Telangiectatic vasculature • Clusters of gray spots
Lichen nitidus	• "Ball and claw" appearance with focal dense lymphohistiocytic infiltrate in the papillary dermis close to the epidermis; Langerhans giant cells in the infiltrate, elongated rete ridges that "clutch" the infiltrate; erythrocytes subepidermally (if hemorrhagic or purpuric) or eosinophilic material within the dermis with occasional cell in the epidermis (if perforating variant)	• Punctate hemorrhages • Keratin plug surrounded by annular cloud-like, smooth area • Well-demarcated depressions with surrounding thin scale on palmoplantar sites
Lichen sclerosus	• Lichenoid infiltrate in dermoepidermal junction and compact hyperkeratosis • Papillary dermis edema, replaced by dense homogenous fibrotic change as lesions mature	• White structureless foci • Comedo-like openings with telangiectasia
Lichen striatus	• Acanthotic epidermis, dense or sparse lichenoid infiltrate • Numerous melanophages in the superficial dermis, apoptotic keratinocytes throughout all epidermal layers and infiltrate normally extending to involve eccrine structures	• Well delineated white structure • Yellow keratotic, cerebriform structures featuring red dots (corresponding to dermal capillaries)

Association with infection. LP has been associated with HCV infection, but whether there is underlying causality remains ambiguous. Although studies have demonstrated that affected patients are more likely to be HCV positive, this association is highly variable across different populations and countries.[131,132] IFN therapy for HCV has also been tied to the initiation or worsening of LP lesions.[133] And although a contentious issue, routine screening for HCV should probably not be recommended, except in individuals at high risk for HCV infection, due to the risks of morbidity and transmission that exist with this infection.[131-137] We take an individual approach to this issue by performing a focused clinical enquiry to seek high-risk behaviors and thereby screen identified individuals who might be at risk. Numerous other viral pathogens have been associated with LP, including hepatitis B virus,[138] varicella zoster,[139,140] and human herpesviruses-6 and -7.[122] LP eruptions have also been reported to develop after vaccination, especially hepatitis B virus immunization.[141,142]

Genetic associations. There may be a genetic predisposition to idiopathic LP, because multiple

Table II. Drug-induced lichen planus: Drug culprits and their associated lichenoid manifestation

Drug culprit	Association
Angiotensin-converting enzyme inhibitors, antimalarials, β-blockers, gold, lithium; mercury amalgam, methyldopa, penicillamine, quinidine, sulfonylureas, thiazide diuretics, tumor necrosis factor—α, or tyrosine kinase inhibitors	Classic cutaneous lichenoid drug eruption
Angiotensin-converting enzyme inhibitors, allopurinol, anticonvulsants, antiretrovirals, gold, ketoconazole, or nonsteroidal anti-inflammatory drugs	Cutaneous and oral lichen planus
Carbamazepine, chlorpromazine, diltiazem, ethambutol, quinidine, quinine, tetracyclines, and thiazide diuretics	Photodistributed lichenoid drug eruption

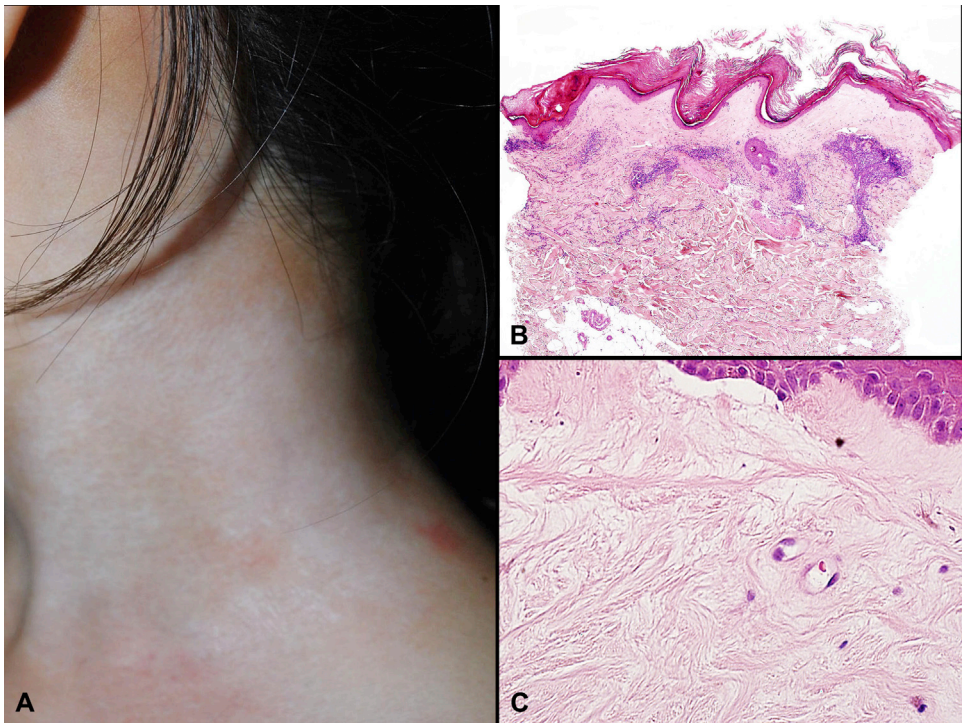

Fig 8. Lichen sclerosus et atrophicus. **A**, Neck. Irregular-shaped white atrophic patches. **B**, Histopathology showing hyperkeratotic horn, epidermal atrophy, and a patchy lichenoid lymphoid cell infiltrate with pale, hyalinized papillary dermis. **C**, Higher magnification on the hyalinized edematous papillary dermis. (Hematoxylin—eosin stain; original magnifications: **B**, ×40; **C**, ×400.)

familial cases have been reported in the literature[143-145] and familial occurrence has been estimated to be as high as 10.7%.[146] Currently, most genetic loci identified for LP have been associations to the HLA region. These include HLA-A5 and HLA-A3,[147,148] HLA-B7,[143] HLA-DR1,[149,150] HLA-DR10 in Arab individuals,[150] and HLA-DRB1*01:01 in Sardinian and Mexican populations.[151,152] Associations to HLA-B5 and HLA-B8 have also been reported.[153] The HLA-A28 haplotype has been associated with nondiabetic Israeli Jewish individuals with LP and carbohydrate intolerance.[154] Though several studies have sought to explore a possible link between the -308 G/A polymorphism in the tumor necrosis factor—α gene with LP, a metaanalysis has concluded that this variant was associated with oral LP (without HCV infection) but not cutaneous LP.[155] This genetic heterogeneity has led to the hypothesis that cutaneous and solely mucosal LP may have distinct pathogenetic mechanisms.

Recently, a phenome-wide association study has comprehensively interrogated the major

histocompatibility complex region and identified novel genetic associations to 8 diseases, including LP.[156] Six single nucleotide polymorphisms (SNPs) were found to be associated (odds ratio 2.0-2.5) and the HLA-DQB1*05:01 haplotype was also strongly associated with LP. These 6 SNPs have previously been implicated in multiple sclerosis, type I diabetes, and other immune disorders.[157-161] Interestingly, LP risk had previously been associated with multiple sclerosis and type I diabetes.[162,163] Four of these SNPs were validated in a replication cohort; however, many of these variants were found to be in partial or strong linkage disequilibrium, leading the authors to suggest that these SNPs probably tag for a single functional variant or haplotype. The most significant SNP, rs1794275, implicated the HLA-DQB1 and HLA-DQA2 haplotypes with an odds ratio of 2.5 (95% confidence interval 1.8-3.4).[156] It is worth noting that the HLA-DQB1*05:01:01 haplotype had previously been implicated in vulvovaginogingival syndrome, a variant of LP.[164]

Environmental risk factors. As discussed in greater detail earlier, a wide spectrum of drugs has been associated with lichenoid eruptions that can greatly resemble LP. Apart from medications, other environmental influences have been associated with cutaneous LP. Psychological factors that have been associated with LP include stress, depression, and anxiety, and they may all play a role in pathogenesis.[130,165,166] LP-like dermatitic eruptions have been associated with exposure to substances in color film developers,[167] methacrylic acid esters,[168] and dimethylfumarate in sofas,[169] and radiotherapy may also trigger LP-like lesions,[170] although we have yet to see a case of a clear-cut environmental association with any of the aforementioned putative triggers.

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