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Lichen planus – a clinical guide

Summary

Lichen planus (LP) is a chronic lichenoid inflammatory disorder of the skin, mucosa and of the appendages. LP is classically characterized by the presence of a rich infiltration of inflammatory T cells, which migrate in the upper part of the dermis, arranged in a band-like pattern. Different sub types of the disease have been so far described. Albeit LP is clinically well defined, the disease still represents a therapeutic enigma. Especially with regard to mucosal or scalp affecting LP types, which often present a recalcitrant and treatment unresponsive course, efficacious therapeutic options are still lacking. Thus, LP represents a disease with a high psychosocial burden. Yet, development in the deciphering of LP pathogenesis reveals possible new druggable targets, thus paving the way for future therapeutic options. In this clinical guide, we summarize the current clinical knowledge and therapeutic standards and discuss the future perspective for the management of LP.

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Introduction

The term lichen planus (LP), also known as lichen ruber planus, originates from likhḗn, something that spreads abruptly and suddenly, with flat, plain and tense papules, therefore planus. Albeit first observations and descriptions of LP on skin are already present in the Greek medical literature [1], the term was firstly introduced by Erasmus Wilson in 1869 [2], slightly modifying the term "leichen ruber", antecedently coined by Ferdinand von Hebra. LP is a model for lichenoid dermatoses, disorders characterized by the presence of a dense cellular dermal infiltrate. This histological hallmark was firstly described by Darier in 1909. Since then, our understanding of LP deeply improved, yet several questions are still open. As many skin conditions, LP represents a high psychosocial burden for affected patients and advances in the understanding of the pathophysiological mechanism, identification of relevant therapeutic targets and development of new therapeutic approaches is needed. Clinically we recognize three major subtypes: cutaneous LP (CLP), mucosal LP (MLP) and LP of the scalp (lichen planopilaris, LPP) [3]. These subtypes can manifest singularly or, in some cases, concomitantly. These three LP entities present many clinical and histological similarities, although studies present evidence of emerging distinctive immunological factors, which differentiate these three disorders and may facilitate the development in the future of more specific therapeutic approaches. In this work, we aim to present an overview of the clinical aspects of the three major forms of LP, with a focus on clinical peculiarities and on established and new emerging therapeutic approaches, thus providing a guidebook for physicians for a better management of these common although often challenging to treat disorders.

Clinical appearance

Cutaneous lichen planus

Cutaneous lichen planus classically presents with red to brown, violaceous, polygonal, slightly scaling and extremely itchy flat papules.

Cutaneous lichen planus classically presents with red to brown, violaceous, polygonal, slightly scaling and extremely itchy flat papules (Figure 1a, b). Extremities are more frequently affected, with a characteristic presence of pruriginous papules on the medial side of the wrist. Dermatoscopy may be of help when Wickham striae are present. These may present as whitish and yellow net-like lines and dots most often surrounded by radial linear and dotted capillaries. In addition, hyperpigmentation is often present with a diffuse brown and grey pattern. LP lesions under effective treatment might be challenging clinically and dermoscopically, and other inflammatory skin diseases may mimic Wickham striae when linear scaling is present [4].

Nonetheless, aside the classical appearance of CLP there is a quite broad spectrum of subtypes and almost every part of the body may be affected. Table 1 summarizes the different LP types. Cutaneous LP may present as generalized (CLP exanthematicus), with violaceous flat-topped papules and plaques eventually merging and developing into a generalized infiltrated exanthema of the skin (Figure 1a). This form has been often reported to be linked to drugs intake (antimalarials, methyldopa, gold, tumor necrosis factor alpha [TNFα] blockers) or vaccines, and should be distinguished from a lichenoid drug reaction, which may clinically resemble idiopathic LP [5]. Actinic lichen planus mostly occurs on light exposed areas and primarily affect darker skinned patients [6]. Cutaneous LP may also occur with treatment resistant, highly pruriginous dark gray-brown papules or nodes (LP verrucosus) (Figure 1c). This form primarily occurs on the lower extremities [7]. This subtype warrants medical follow-ups, since the chronic inflammation may favor the formation of skin cancers [8]. In contrast to the

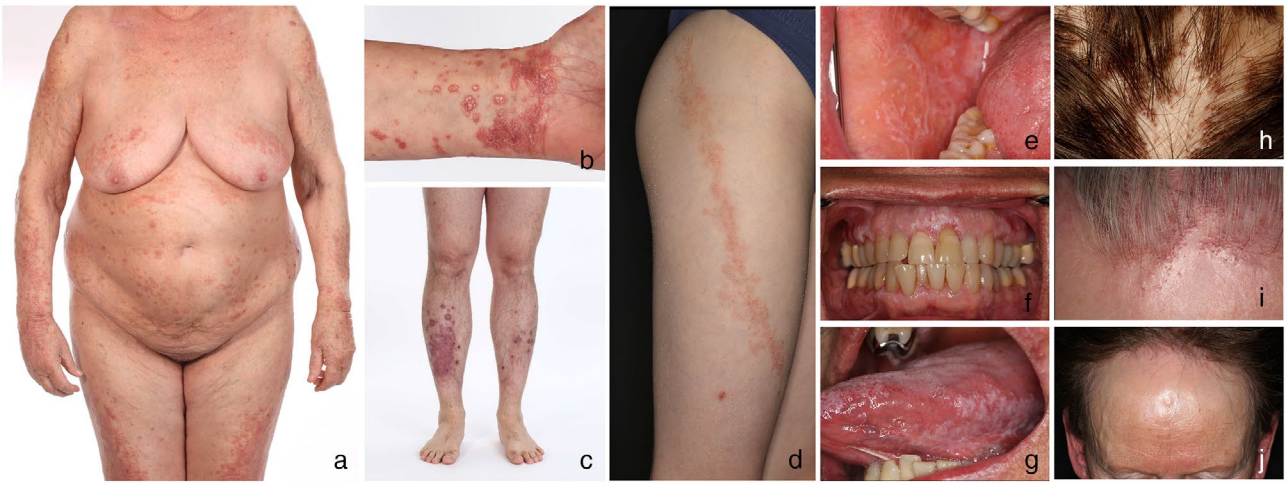

Figure 1 Clinical presentation of lichen planus. Generalized eruption of topped papules in exanthematic lichen planus (LP) (a). Classical presentation of red-violaceous-brown papules with superficial white lacing (Wickham striae) in classic LP (b). Elevated and hypertrophic violaceous pretibial lesions in LP verrucosus (c). Linear papular band with a Blaschko line disposition in a young woman with linear LP (d). Mucosal, gingival and tongue involvement in oral mucosal LP (e–g). Perifollicular erythema and papules in lichen planopilaris (h, i). Upper hairline and loss of eyebrows in frontal fibrosing alopecia (j).

Table 1 Clinical variants of lichen planus and characterizing clinical signs.

Clinical variant	Distinguishing features
Cutaneous lichen planus	
Classic lichen planus	Classic presentation with violaceous brownish infiltrated polygonal papules merging to flat plaques
Exanthematic lichen planus	Violaceous flat-topped papules and plaques eventually merging together and developing into a generalized infiltrated exanthema of the body
Lichen planus actinicus	Chronic, in light-exposed anatomical areas, more frequent in dark skinned young men
Atrophic lichen planus	Annular central atrophic plaque on lower extremities
Lichen planus verrucosus	Hypertrophic, chronic, on lower extremities
Lichen planus inversus	Pigmented asymptomatic lesions in skin-fold areas
Lichen planus pemphigoides	Papules and blisters, serology resembling bullous pemphigoid
Mucosal lichen planus	
Mucosal lichen planus	Classic presentation with white lacing (Wickham striae) and papules
Erosive lichen planus	Painful erosions of mucosa and gingival epithelia
Oral lichenoid reaction	Isolated erythematous/lichenoid reaction in proximity of dental implantations
Lichen planus of the scalp	
Lichen planopilaris	Follicular linked erythema with scaling. Eventually scarring phenotype, destruction of hair follicle. Mostly frontal or parietal area of the scalp
Frontal fibrosing alopecia	Postmenopausal fibrosing band-like alopecia of the forehead. Loss of the eyebrows
Graham-Little-Piccardi-Lasseur syndrome	Multifocal, patchy, scarring alopecia on the scalp, non-scarring alopecia of the axillae, follicular hyperkeratosis of the trunk and extremities

classic or hypertrophic presentation, atrophic LP presents with an annular central atrophic plaque. Typically, this form progresses centrifugally on the legs with a hypopigmented center surrounded by a hyperkeratotic violaceous ring. Rarely CLP can also occur as LP pigmentosus with gray, dark brown maculae eventually merging to form a sketching pattern. This, usually occurring in the flexural and intertriginous areas may reflect Blaschko lines and does not affects children [9, 10]. In contrast, a classical clinical picture in a linear formation along Blaschko represents a linear LP (Figure 1d). Finally, CLP patients may sporadically develop classic polygonal papules accompanied by the presence of sterile tense blisters (LP pemphigoid). This rare variant associates clinical and immunological characteristics of LP with those of the autoimmune blistering disorder bullous pemphigoid. Accordingly, those patients present circulating autoantibodies against BP180 and BP230 and have a strong C3 and IgG deposition along the dermal epidermal junction zone on direct immunofluorescence (DIF) [11, 12].

Classic CLP often presents with spontaneous remission after 1–2 years.

In contrast to MLP – which often has a chronic and recurring course – classic CLP often presents with spontaneous remission after 1–2 years. Commonly, the healing process may be accompanied by long standing hyperpigmentation of affected skin [13]. Lichen planus verrucosus represents an exception, which often has a chronic course and is unresponsive to treatments. Although triggering factors are poorly defined, incidence of CLP seems to occur more frequently among patients with hepatitis B or C infection, although several studies contradict this causal link [14–17]. There are also reports of LP manifestation following to hepatitis B

vaccination [18, 19]. Cutaneous LP occurrence has been also linked to stress factors, depression, anxiety and dyslipidemia [20, 21]. Frequently, in CLP a difficult to treat nail involvement can be seen [22].

Lichen planus of the mucosa

Mucosal involvement in lichen planus is a debilitating disorder, often a therapeutic enigma and due to its chronic recalcitrant course and persistent inflammation, it may function as a fertile ground for neoplastic disorders.

Mucosal involvement in lichen planus is a debilitating disorder, often a therapeutic enigma and due to its chronic recalcitrant course and persistent inflammation, it may function as a fertile ground for neoplastic disorders. Most frequently, it affects the oral cavity and more preferentially, women in the fourth decade. It manifests with a distinctive lacelike white pattern named Wickham striae accompanied by erythematous lesions (Figure 1e–g), presence of plaques or, in some aggressive cases, by extensive erosions (erosive MLP) [23]. In this latter clinical subset, advanced forms may involve the esophagus with strictures and subsequent fibrotic occlusion or involve the lacrimal canal with consequent occlusion following inflammatory and fibrotic processes [24, 25]. An esophageal involvement seems to be present in more than 50 % of patients with LP, especially in females, although the involvement may be subclinical/asymptomatic. Presence of dysphagia or odynophagia (in about 80 % and 30 % of patients with esophageal involvement) in LP patients may indicate esophageal involvement and should be further clarified by esophagogastroduodenoscopy [26–28]. In the setting of genital involvement, erosions, fibrosis, or even phimosis and scarring are possible, with dramatic deterioration on the eating behavior and sexuality of affected patients. Worldwide epidemiological data show a higher incidence among women and in non-Asian countries. A concomitant genital LP is very common in every second women being affected by oral MLP. Mucosal LP has been linked to several triggering factors such as drugs (nonsteroidal anti-inflammatory drugs [NSAIDs], beta blockers, ACE inhibitors, thiazide diuretics, antibiotics, checkpoint inhibitors) [29], viral factors and contact hypersensitivity to dental materials such as amalgam and mercury [30]. In this latter scenario, lichenoid reaction is frequently observed in the proximity of the implanted dental material. In addition oral MLP is more common in smokers and patients with alcohol abuse [31]. Further, human papillomaviruses (HPV) may be involved in the pathogenesis of MLP, indeed HPV DNA has been isolated by PCR in oral lesions of patients with MLP [32]. Although the real risk of malignancy and transformation to a cutaneous squamous cell carcinoma is not clearly established, higher occurrence is present when tongue, oral cavity, esophagus, larynx or vulva are involved [33].

Lichen planopilaris

Lichen planopilaris warrants a rapid therapeutic reaction, since the later treatments are initiated, the more irreversible damage is present.

Lichen planopilaris is a chronic inflammatory disorder of the scalp, though in contrast to MLP and CLP, it comes with red to purple papules and perifollicular erythema due to lymphocytic infiltration. This leads to destruction of hair follicles and eventually scarring of the scalp, clinically represented by the presence of extensive whitish scarring areas in absence of follicular orifices and tufted hair follicles (Figure 1h, i). This process leads to a non-reversible hair loss. This is mostly accompanied by scaling, itching, burning of the scalp and hair fragility. Lichen planopilaris warrants a rapid therapeutic reaction, since the later treatments are initiated, the more irreversible damage is present.

Three major subclinical variants have been described: classic LPP, frontal fibrosing alopecia (FFA) and Graham-Little-Piccardi-Lasseur syndrome. Lichen planopilaris manifests mostly on the parietal areas, possibly in concomitance with skin or oral lesions. Nonetheless, complete scalp involvement is also possible [34].

Although it may manifests at every age, even in children [35–37], LPP mostly affects adult women (1.8 to 1 men-women ratio) between 30 and 75 years [38, 39]. As for other LP forms, inducing factors are largely unknown. Occurrence in association with viral hepatitis (especially hepatitis C) or HIV infection, as well as drugs such as antimalarials and TNFα blockers have been described [40, 41]. In addition to this, stress, neoplastic disorders, concomitance of other autoimmune disorders, especially hypothyroidism, have been reported in patients with LPP [42, 43]. Frontal fibrosing alopecia often occurs as a band like scarring alopecia of the forehead, which mostly occurs in postmenopausal women and may also affect the eyebrows (Figure 1j) Perifollicular erythema and hyperkeratosis are characteristic signs of active inflammation in FFA, whereas tufted hair bundles do not belong to FFA or LPP. In FFA remaining single hairs are seen, the so-called lonely hairs. It is currently debated whether environmental factors such as sunscreen use may trigger FFA [44]. Finally, Graham-Little-Piccardi-Lasseur Syndrome presents multifocal scarring areas on the scalp accompanied by non-scarring alopecia of the groin and axillar region as well as hyperkeratotic plaques on the trunk [45].

Perifollicular erythema and hyperkeratosis are characteristic signs of active inflammation in FFA, whereas tufted hair bundles do not belong to FFA or LPP.

Nail lichen planus

Nail LP may occur alone or in the presence of skin or mucosal changes and affects 10 % of CLP patients.

Nail LP (NLP) is an infrequent manifestation, which may occur alone or in the presence of skin or mucosal changes and affects 10 % of CLP patients, yet it does not show association with age, sex or ethnicity. The nails of the fingers are more frequently affected than the toenails [46]. Causative agents of NLP are not completely known, yet there is evidence of an association with metal allergies. In NLP patients with metal allergies, causative metals following a dental implantation were detected in the affected nail tissue [47]. Clinically, NLP presents with different patterns (Figure 2). When the nail matrix is involved, nails show distal splitting of the nail, longitudinal striae (longitudinal ridging) and thinning (Figure 2a, b). Additionally, other nail changes such as altered pigmentation and onychorrhexis have been reported (Figure 2c). Nail bed involvement is more severe and presents

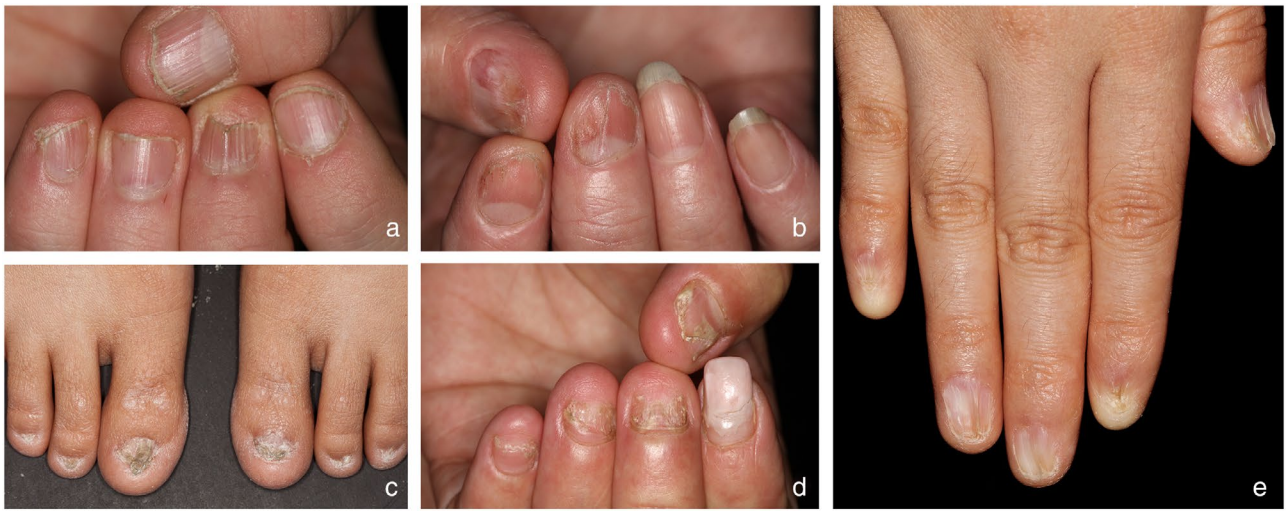

Figure 2 Clinical features of nail involvement in lichen planus. Onychodystrophia with thinning and longitudinal ridging (a). Onychodystrophia with longitudinal ridging (b). Onychorrhexis and onycholysis of the toenails (c). Onychodystrophia with distal splitting (d). Onychodystrophia with pterygium and anonychia (e).

with strong onycholysis and subungual hyperkeratosis, this may evolve in atrophy of the nail bed, erosion of the nail and anonychia or may lead to a painful pterygium (Figure 2d, e).

Epidemiology

The incidence of LP in the general population is between 0.1 and 1.27 % [48, 49]. While LP seems to occur more often between the third and sixth decade, LP can occur at any age, with no sex or racial preferences. Mucosal LP has a prevalence of 0.89 %, with the highest incidence in South America. Additionally, MLP seems to occur more frequently in women [50–53]. Lichen planopilaris and FFA similarly to MLP, more often affects women (approximately 4.9 : 1 and 31 : 1, respectively) [54]. Yet FFA mostly occurs in menopausal women, which are significantly older than LPP patients are. Graham-Little-Piccardi-Lasseur syndrome is extremely rare and epidemiological data are lacking but apparently occurs in middle aged women [55].

Immunologic and genetic mechanisms of disease

Although many studies over the years tried to decipher LP, the pathogenic mechanism of LP still needs to be convincingly explained. This lack of knowledge is reflected by the paucity of appropriate treatments. Yet LP can be seen as an autoimmune disorder. The accumulation of T cells in the upper dermis is the *primum movens* of this disease. T cells, both $CD4^+$ and $CD8^+$, accumulate in the dermis. These inflammatory cells, through the secretion of several cytokines, are responsible for the apoptosis of basal epidermal cells (the so-called colloid bodies) [3, 56]. The present immunological understanding of LP sees it as an overwhelmingly IFNγ driven disorder, thus defining LP as a Th1 dominated disorder. Further, analysis of the signaling cascade revealed the presence of overexpression of the JAK/STAT pathway [57–60]. Findings coming from experimental studies are starting to provide evidence, that CLP, MLP and LPP may present different pathogenesis. Serological analysis and studies of lesional skin show that IL-17 may be more importantly involved in MLP than in other forms [61–68], yet increased levels of IL-17 have been described also in both CLP and LPP [69–71]. However, these IL-17 levels found in CLP are relatively low compared to those found in psoriasis skin [57]. Similarly, LPP presents immunological peculiarities not to be found in other LP forms, like the damage on epithelial stem cells, which is counterpartyed by the scarring evolution of lesions.

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Histology & immunofluorescence

Lichen planus belongs to the group of lichenoid dermatoses, which encompass a larger group also comprehending graft versus host disease (GVHD) and lichen sclerosus.

Distinguishing feature is an interface dermatitis with a band like lymphocytic infiltrate in the upper dermis obscuring the dermoepidermal junction.

Distinguishing feature is an interface dermatitis with a band like lymphocytic infiltrate in the upper dermis obscuring the dermoepidermal junction. Skin biopsy should be taken from a fresh and possibly untreated lesion. Orally, samples should be taken as far away as possible from mechanical stress and therefore the chewing area should be avoided. In most cases, the epidermis is acanthotic with saw-toothed rete ridges. Typically, there is an ortho-hyperkeratotic stratum corneum and a wedge shaped hypergranulosis. The basal layer of the epidermis shows a vacuolar degeneration with apoptotic keratinocytes (Civatte bodies). Pronounced apoptotic cells can lead to small subepidermal clefts (Caspary-Joseph space) [72]. The band like infiltrate is restricted to the upper dermis and consists mainly of lymphocytes and histiocytes with none or only scarce eosinophils (Figure 3a, b) [7, 73]. Mucosal

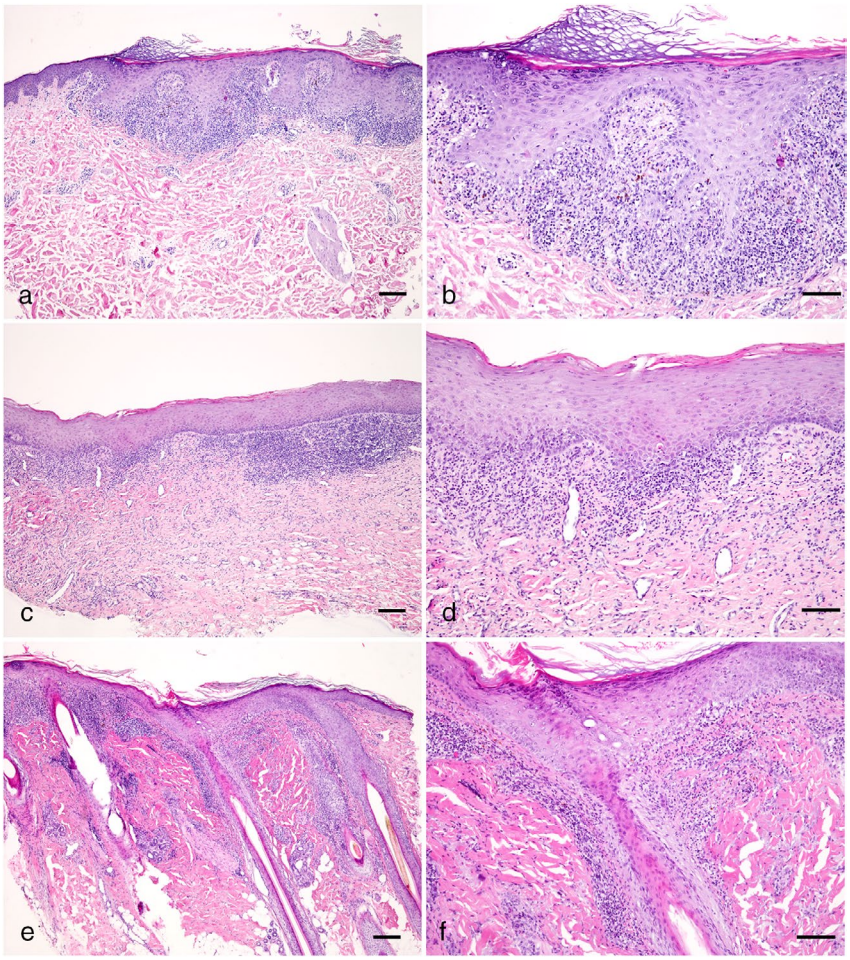

Figure 3 Histological characteristics in lichen planus. Cutaneous lichen planus showing acanthotic epidermis with sawtoothed rete ridges, orthohyperkeratosis, wedge shaped hypergranulosis, basal vacuolar degeneration with apoptotic keratinocytes and a band like subepidermal lymphohistiocytic infiltrate obscuring the dermoepidermal junction (a, b). Mucosal lichen planus (oral lesion) with slightly acanthotic epithelium with a band like lymphocytic lichenoid infiltrate. Suprabasal apoptotic keratinocytes can be seen (c, d). Lichen planopilaris with interface dermatitis of the infundibular epithelium and a dense perifollicular lymphocytic infiltrate (e, f). Hematoxylin-eosin stain, original magnification x 40 (a, c, e), x 100 (b, d, f).

LP shows similar histological changes like lichen planus of the skin. There can be more plasma cells and neutrophilic granulocytes as well as apoptotic keratinocytes in higher levels of the epithelium (Figure 3c, d). In LPP the lichenoid reaction involves the basal layer of the follicular epithelium; infundibular hyperplasia accompanied by a dense perifollicular lichenoid infiltrate and fibrosis of different level may be seen (Figure 3e, f) [73, 74].Direct immunofluorescence (DIF) is not highly specific for MLP, yet it may help to delimit from erythematous lupus and bullous autoimmune disorders such as pemphigus vulgaris or mucous membrane pemphigoid, and should be accompanied by further serological tests.

Direct immunofluorescence may help to delimit from erythematous lupus and bullous autoimmune disorders such as pemphigus vulgaris or mucous membrane pemphigoid.

In chronic MLP some patients may present serological features of patients with blistering diseases [75, 76]. Direct immunofluorescence testing may

reveal cylindrical deposits of any of the immunoglobulins, mainly IgM/IgG and complement, fibrinogen reflect apoptotic keratinocytes (Civatte bodies) or fibrinogen deposition along the dermoepidermal junction [77, 78]. Finally, DIF is useful for the diagnosis of LP pemphigoid and shows the presence of a band-like IgG deposition along the dermal epidermal junction zone.

Differentials and diagnosis of LP

Diagnosis in LP is mostly based on a rigorous analysis of skin appearance and patient's symptoms. A thorough patient's history and clinical examination should imply symptoms being suggestive for other LP manifestations. Those comprise of genital and oral involvement, with pain, dyspareunia and dysphagia, for scalp involvement with scarring alopecia, follicular hyperkeratosis and missensations. Lastly, lid edges, conjunctiva and eyes should also be examined, and an ocular involvement should be excluded [79]. Pharmacologic anamnesis should always be included to exclude drugs involvement and a hepatitis serology is recommended. The clinical diagnosis should be confirmed by histopathology. Histological analysis of skin specimen biopsies, which due to the presence of the classical band like pattern in LP, are often sufficient to rule out other disorders. Especially when differentiating other lichenoid lesions, such as lichenoid graft versus host disease, lichenoid contact dermatitis, lichen Vidal or lichenoid drug reactions a biopsy is indispensable. When violaceous papules occur along with tense blisters, a LP pemphigoides should be considered and additional analysis with Enzyme-linked Immunosorbent Assay (ELISA) will contribute to assess the presence of circulating autoantibodies against BP180 or BP230. The appearance of CLP, MLP and LLP may resemble other inflammatory disorders. In MLP a candidosis or a leukoplakia should be ruled out and lupus should be excluded in patients with LPP through serological and histological investigation. Further, lichenoid lesions resembling oral MLP can be seen in patients with paraneoplastic pemphigus [80, 81]. The battery of diagnostic procedures, above all else the histopathological examination, helps to rule out other possible skin disorders and to start a targeted treatment. Table 2 puts together most important differential diagnoses.

Clinical scores in lichen planus

Assessment of the clinical severity in lichen planus is an important tool to monitor disease activity and response to therapy in patients. The Escudier scoring system was developed to assess severity in MLP and is based on extent of site involvement, disease activity at each site and a subjective pain score [82]. Similarly, the lichen planopilaris activity index (LPPAI) helps to quantify signs and symptoms in LPP and FFA. The lichen planopilaris activity index assigns numeric values to symptoms (pruritus, pain, burning), signs (erythema, perifollicular erythema and scale), a measure of activity (the anagen pull test), and to the extension of disease [83]. Since it is often a gradual process, regular photo documentation is advisable to better assess progress or response to therapy.

Management of lichen planus

Cutaneous lichen planus

The management of LP differs, based on the different subtype. Since CLP often shows a self-limiting disease course, the goal is to reduce duration of symptoms.

Table 2 Differential diagnosis in lichen planus.

Lichen planus of the skin	Lichenoid drug eruptions, erythema exsudativum multiforme, graft-versus-host disease, granuloma anulare, guttate psoriasis, lichen nitidus, lichen sclerosus, lichen spinulosus, lichen amyloidosus, linear lichen planus, pityriasis lichenoides, pityriasis rosea, psoriasis vulgaris, tinea corporis
Mucosal lichen planus (oral)	Candidiasis, leukoplakia, lupus erythematodes, mucous membrane pemphigoid, paraneoplastic pemphigus and pemphigus vulgaris, secondary syphilis
Mucosal lichen planus (genital)	Graft-vs-Host disease, intertrigo, lichen sclerosus, mucous membrane pemphigoid, pemphigus vulgaris, psoriasis
Lichen planus of the scalp	Cicatricial alopecia, lupus erythematodes, inflammatory folliculitis, alopecia areata, bullous pemphigoid
Nail lichen planus	Alopecia areata, atopic dermatitis, psoriasis, onychomycosis, twenty-nail-syndrome

In CLP clinical evidence suggests initial treatment with topical steroid treatments (betamethasone, clobetasol propionate), which can be eventually accompanied by broadband or narrowband UVB phototherapy, or by PUVA.

In CLP clinical evidence suggests initial treatment with topical steroid treatments (betamethasone, clobetasol propionate), which can be eventually accompanied by broadband or narrowband UVB phototherapy, or by PUVA phototherapy [84, 85]. In recalcitrant cases, the treatment may be supplemented by oral prednisone (0.5–1 mg/kg bw/day) treatment or retinoids such as acitretin or isotretinoin [86, 87]. Table 3 provides an overview of recommended first and second line treatments. Physicians should always consider that CLP is among LP subtypes the one with the more benign course, in most of the cases with a self-limiting course and systemic immunosuppressive approaches are rarely needed.

Physicians should always consider that CLP is among LP subtypes the one with the more benign course, in most of the cases with a self-limiting course and systemic immunosuppressive approaches are rarely needed.

An exception is presented by hypertrophic or verrucous LP lesions, which lesions may be more challenging to treat and occlusive application of topical steroids or intralesional steroid injection (Triamcinolone ~10 mg/ml every four weeks for at least six months) may favor healing and need a more regular surveillance for malignancies such as squamous cell carcinoma [8]. In CLP, a concomitant treatment of symptoms is often needed. To control itch, systemic treatment with antihistamines in combination with topical treatments, such as polidocanol or menthol containing ointments may be used [88].

Mucosal lichen planus

Topical treatments

Oral MLP may profoundly undermine the quality of life of patients [89, 90]. The initial topical treatment is based on potent corticosteroids. Clobetasol propionate 0.05 % [91], triamcinolone, betamethasone, fluocinonide, fluticasone, dexamethasone and prednisolone in different forms have been proven to be effective and safe. They have been also used as an ointment, as an oral suspension or aqueous solution, pellets, aerosol or spray, mouthwashes and usually in an adhesive paste. These are usually applied twice daily for 1–2 months, and then tapered. Intralesional injection of corticosteroids (triamcinolone acetonide hydrocortisone, dexamethasone and methylprednisolone) in ulcerative MLP is also an effective treatment approach, although the injections can be painful [92, 93].

Another approach and off-label is the topical application (twice daily for up to 8 weeks) of pimecrolimus or tacrolimus, two calcineurin inhibitors [94]. Yet, in this setting case reports of a possible carcinogenic effect have been published (squamous cell carcinoma, oropharyngeal carcinoma and melanoma) [95–97].

Table 3 Therapeutic options for lichen planus.

Cutaneous lichen planus	
First line treatments	Topical steroids (Class IV–III) Intralesional triamcinolone (LP verrucosus)
Second line treatments	Narrowband UVB311, PUVA, topical calcineurin inhibitors (tacrolimus and pimecrolimus)*, acitretin
Mucosal lichen planus	
First line treatments	Topical steroids (ointment or adhesive cream), intralesional triamcinolone, systemic corticosteroids, acitretin, isotretinoin, topical retinoids, cyclosporine A*
Second line treatments	Topical calcineurin inhibitors (tacrolimus and pimecrolimus)*, azathioprine*, hydroxychloroquine*, methotrexate*, mycophenolate mofetil*
Lichen planus of the scalp	
First line treatments	Topical steroids, triamcinolone intralesional, systemic steroids, hydroxychloroquine*, methotrexate*, topical calcineurin inhibitors*
Second line treatments	Acitretin, isotretinoin, cyclosporine A*, tetracycline*, thalidomide*
Off-label therapies are marked with*.	

These are derived from the carcinogenic effect of calcineurin inhibitors in systemic use. To minimize the risk as far as possible, continuous therapy in topical therapy despite insufficient efficacy if inflammatory activity persists should be avoided. Treatments with topical aloe vera [98–100] or topical tocopherol [101] also showed effectiveness and could be used as adjuvant treatments to steroids or alone in mild cases. A pilot study in 20 MLP patients showed clinical, immunological and quality of life improvement following photodynamic therapy [102].

Frequently, MLP does not sufficiently ameliorate under topical treatment and systemic agents are needed.

Frequently, MLP does not sufficiently ameliorate under topical treatment and systemic agents are needed.

Systemic treatments

Systemic corticosteroids, methylprednisolone or prednisone (30–80 mg/day) is the most effective treatment modality for patients with diffuse recalcitrant erosive oral MLP or multisite lesions of severe erosive MLP. This should be used in short burst to induce remission rather than as a long-term maintenance therapy to avoid steroidal side effects. In addition, intramuscular triamcinolone has been described as an effective treatment. Systemic retinoids, such as acitretin or isotretinoin are being used in the treatment of MLP [88]. Methotrexate also is a valuable option, especially in erosive cases [103]. It may be administered orally once weekly but should be switched to a subcutaneous application when side effects like diarrhea become an issue [104]. Systemic use of cyclosporine A (3–10 mg/kg bw/day) has been found to be effective in different studies and for some authors it is considered the drug of choice [105]. However, due to the unfavorable spectrum of side effects with renal impairment, hypertension and malignancies, the authors advise against use for more than six months. Intravenous immunoglobulins have been also efficaciously used off-label in patients with erosive recalcitrant MLP, although here further studies are warranted [106]. Furthermore, a list of different treatments with immunosuppressive efficacy have been used in MLP patients (cyclophosphamide, dapsone, colchicine, thalidomide) [88, 107–110]. These treatments should

be used as third line treatments in recalcitrant cases, since evidence of their efficacy is lower than for other drugs. Treatment of genital MLP is similar to oral MLP, initial treatment is based on the use of potent corticosteroids (clobetasol) or calcineurin inhibitors, which may be later tapered and used with larger intervals or switch to milder steroid treatments [111]. The inclusion of the sexual history is indispensable, since discomfort and loss of lubrication are indications of disease activity and require an interdisciplinary approach with gynecologists or urologists [112].Lastly, as studies have frequently reported an increased risk of cancer with genital MLP, constant follow-ups to exclude onset of malign lesions are needed [113, 114].

As studies have frequently reported an increased risk of cancer with genital MLP, constant follow-ups to exclude onset of malign lesions are needed.

Management of lichen planopilaris and frontal fibrosing alopecia

In LPP and FFA early and rapid control of inflammation is of central importance to prevent destruction of the follicular units and development of scarring. Initial treatment is mostly based on intensive treatment with potent or class IV steroids, which after disease control may be eventually applied in wider intervals. Alternatively, treatments with topical calcineurin inhibitors or with the topically applied JAK inhibitor tofacitinib have been shown to be effective in single cases or small case series [115, 116]. In FFA, intralesional triamcinolone may halt disease progression [117].

In LPP and FFA early and rapid control of inflammation is of central importance to prevent destruction of the follicular units and development of scarring.

In more aggressive and rapidly progressing cases, a concomitant treatment with systemic prednisone (0.5–1 mg/kg bw/day) is recommended. Alternatively, hydroxychloroquine (up to 6.5 mg/kg/day of ideal body weight, up to a maximum of 400 mg daily) [118] or methotrexate (10–15 mg per week) have proven effective in several studies, although one comparative study between the two drugs showed a better response in the methotrexate group [83, 119]. Mycophenolate mofetil and cyclosporine A (3–10 mg/kg bw/day) may also be used off-label in recalcitrant cases not responding to first and second line treatments [120, 121]. Lichen planopilaris is often associated with comorbid diseases. In particular, depression and anxiety should be inquired about and psychological referral should be sought if needed [122]. More and more often, patients ask about the possibility of hair transplantation in the scarred areas. There is little data on this so far. Hair transplantation in LPP should be planned at the earliest one year after disease control [123]. In particular, the results of hair transplantation in FFA are inferior to those in LPP [124]. Since there are reports of LPP as a result of hair transplantation [125] such a procedure should be discussed in great detail with the patient and potential risks should be pointed out [126].

Hair transplantation in LPP should be planned at the earliest one year after disease control.

Management of nail lichen planus

Treatment of NLP is challenging and relapses are frequently observed, furthermore, treatment options are limited [127]. Based on the severity of the disease and/or concomitant involvement of skin and/or mucosa, topical, intralesional or systemic approaches can be attempted. Topical application of steroids or tacrolimus may be beneficial in mild NLP involvement [128], and patients may benefit from additional bath PUVA treatment of the hands [129]. Intralesional or intramuscular application of triamcinolone at 5 or 10 mg/ml every four weeks for almost six months can be tried in patients with severe nail matrix involvement [130–132]. The treatment is often painful and when first signs of atrophy occur, it should be dismissed. Finally, the JAK1/2 inhibitor tofacitinib is possibly a future candidate for the treatment of NLP [133].

Treatment of NLP is challenging, and relapses are frequently observed.

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Outlook

Lichen planus, in all its different sub types, remains a therapeutic challenge for dermatologist and a stressful psychosocial factor for many patients. New knowledge though may help to enlarge the therapeutic arsenal for these disorders. Studies reported on the presence of increased levels of IL-17, in blood, sera or the skin [61, 64, 67, 69, 71]. Respectively, there are case reports on the beneficial use of anti-IL-17/anti-IL-23 treatment, especially in the treatment of erosive MLP [134, 135]. The JAK/STAT pathway, a pathway used by several inflammatory cytokines to downstream their inflammatory signal, gained attention as a potential therapeutic target [136]. First results coming from small case series and case reports showed efficacy in LPP [135, 137] and hypertrophic CLP [138]. In these first three reports, LP has been treated with tofacitinib, a JAK1/2 inhibitor already approved in the treatment of psoriatic arthritis and rheumatoid arthritis [139, 140]. Based on *clinicaltrials.gov* there are currently different phase II studies testing JAK inhibitors in LP. If further controlled studies will confirm the efficacy of these drugs in the treatment of LP, this would bring dermatologists an important tool, which can be administered both orally and topically. Additionally, some other trials are assessing the efficacy of other drugs which showed efficacy in single cases or small cohort studies, such as the phosphodiesterase-4 inhibitor apremilast [141, 142], the CD2 inhibitor and T cell suppressor alefacept [142–144] and the anti TNFα blocker etanercept [145–147].

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 | JDDG | 1610-0379/2021/1906

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[CME Questions/Lernerfolgskontrolle]

1. Which are the three major forms of Lichen planus?

a) Cutaneous lichen planus, mucosal lichen planus, lichen planopilaris
b) Nail lichen planus, mucosal lichen planus, lichen planopilaris
c) Lichen planus pemphigoides, cutaneous lichen planus, mucosal lichen planus
d) Mucosal lichen planus, lichen planus pemphigoides, lichen planopilaris
e) Cutaneous lichen planus, ocular lichen planus, esophageal lichen planus

2. Which is the main typical histological feature to be found in a skin biopsy of cutaneous lichen planus?

a) Hyperkeratosis
b) Spongiosis of the upper epidermal layers
c) Atrophy of the dermis
d) Band-like dermal infiltrate of immune cells
e) Detachment of the dermal-epidermal junction zone

3. The typical signs of nail involvement in lichen planus are:

a) Distal splitting, longitudinal ridging, nail thinning and partial scarring of the nail matrix
b) Yellow nails with distal hyperkeratosis
c) Nail pitting, leukonychia, oil drops
d) Complete loss of all nails
e) Nail pitting and trachyonychia

4. Patients with esophageal involvement mostly refer with the following symptoms:

a) Acid reflux
b) Nausea, vomiting
c) Bleeding
d) Dysphagia, odynophagia
e) Diarrhea

5. Which are the typical dermoscopic features of lichen planus?

a) Reticular dark pigment with white lines, along with radial arborizing capillaries
b) White lines and dots, dotted pigment and radial linear and capillaries
c) Arborizing vessels in the center of a violaceous papule
d) Radial linear and dotted capillaries on blue signet ring-like circle pigment
e) A starburst pattern of pigmented lines and regularly distributed dotted vessels

6. How do we differentiate between lichen planopilaris and frontal fibrosing alopecia?

a) Lichen planopilaris: rounded hair loss with regeneration; frontal fibrosing alopecia: loss of frontal hairs and eyebrows
b) Lichen planopilaris: circumscribed loss of eyebrows; frontal fibrosing alopecia: loss of eyebrows and body hair
c) Lichen planopilaris: loss of frontal and parietal hairs; frontal fibrosing alopecia: loss of frontal hairs and eyebrows
d) Lichen planopilaris: mostly occurring in young male adults; frontal fibrosing alopecia: mostly occurring in young female adults
e) Lichen planopilaris: loss of axillary hairs and hairs of the groin; frontal fibrosing alopecia: scarring alopecia of the vertex

7. What is first line treatment in oral mucosal lichen planus?

a) IL-17 antagonists
b) Local steroid of class III and IV, combined with UV treatment
c) Cyclosporine A or other systemic immunosuppressive treatments
d) Local steroid of class III and IV, combined with steroid mouth wash solution and if needed systemic immunosuppressive treatment
e) Intravenous immunoglobulins

8. Which blood test could be important to examine in a patient with a newly diagnosed lichen planus?

a) Hepatitis C serology
b) Erythrocyte sedimentation rate
c) Circulating B cells
d) Glomerular filtration rate
e) Platelet count

9. What differentials may mimic Wickham striae?

a) Plaque psoriasis
b) Discoid lupus erythematosus
c) Tinea corporis
d) Oral hairy leukoplakia
e) All of the above

10. What is the expected disease course in lichen planopilaris if therapeutic intervention is delayed or missing?

a) Hair regrowth with initial lack of pigment
b) Scalp ulceration and loss of epidermal tissue
c) Expansion of inflammation with final residual scarring of the scalp
d) Hair loss with patch like scaling lesions
e) Progressive hair loss and joint swelling

Liebe Leserinnen und Leser,
der Einsendeschluss an die DDA für diese Ausgabe ist der 31. August 2021. Die richtige Lösung zum Thema „Autoinflammationssyndrome“ in Heft 3 (März 2021) ist: (1c, 2d, 3c, 4e, 5b, 6e, 7b, 8d, 9c, 10c).

Bitte verwenden Sie für Ihre Einsendung das aktuelle Formblatt auf der folgenden Seite oder aber geben Sie Ihre Lösung online unter http://jddg.akademie-dda.de ein.

 | JDDG | 1610-0379/2021/1906