CLINICAL PRACTICE

Lichen Planus

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 53-year-old woman presents with intensely itchy skin lesions and burning in her mouth, which makes eating difficult. These signs and symptoms have become progressively evident during the past several weeks. Examination of her skin and oral cavity reveals violaceous, polygonal papules, mainly on the flexural aspect of the wrists and ankles and in the lumbar region, as well as erosions associated with a lacelike, white-line network apparent in the posterior buccal mucosa. How should this case be managed?

THE CLINICAL PROBLEM

Lichen planus is a mucocutaneous inflammatory disease of unknown origin. The skin and oral mucosa are the most frequently involved areas.[1] Other mucous membranes (including the genitalia, esophagus, and conjunctiva) and skin appendages (e.g., scalp hair and nails) can also be affected. One or several areas can be involved, either concomitantly or sequentially.[2]

The clinical presentation of lichen planus varies depending on the area involved[3-5] (Fig. 1A through 1F and Table 1). Cutaneous lichen planus is characterized by flat-topped, violaceous papules (Fig. 1A and 1B), the appearance of which may cause embarrassment[1] and which in some cases can be intensely itchy. The lesions may result in long-standing residual hyperpigmentation, especially in dark-skinned patients.[1,6] (Less common variants of cutaneous disease are shown in the figure in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Oral lichen planus is characterized by symmetric reticular lesions that resemble a white, lacelike network, as well as by papules, plaques, erythematous lesions, and erosions (Fig. 1C)[7]; it is a chronic disease, and its erosive form is painful.[3,4] The clinical characteristics of anogenital lichen planus (Fig. 1D and 1E) are typically similar to those of both the cutaneous and the oral forms. The erosive form of mucosal lichen planus may result in fibrosis, with vulvar scarring, vaginal stenosis,[5] phimosis, esophageal stricture,[8] blindness,[9] or obstruction of the lachrymal canal. Progressive scarring can also affect the nails and scalp.[10-12]

According to population-based data from Sweden, the prevalence of cutaneous lichen planus among men is 0.3%[13] and the prevalence of oral lichen planus is 1.5%[14]; the respective prevalences among women are 0.1%[13] and 2.3%.[14] A large study of patients who presented with oral lesions revealed prior or current cutaneous lesions in 16% and genital disease in 19%, with rare cases of esophageal, nail, or conjunctival disease,[2] whereas substantially higher rates of concomitant genital or esophageal disease have been noted on systematic histologic examination in patients with oral or cutaneous disease.[8,15]

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KEY CLINICAL POINTS

LICHEN PLANUS

- Lichen planus is a mucocutaneous inflammatory disease of unknown origin that involves mainly the skin and oral mucosa.
- The major burdens of lichen planus are itching and residual hyperpigmentation in the cutaneous form and pain and difficulties with eating in the oral erosive form.
- With the exception of the cutaneous form, which generally heals within 1 year, lichen planus is a chronic condition.
- Given reports of a significant association between lichen planus and infection with the hepatitis C virus (HCV), HCV serologic testing should be considered in all affected patients.
- In the case of lesions that persist despite treatment, biopsy specimens should be assessed for early dysplasia or squamous-cell carcinoma, since these conditions have been reported in association with lichen planus.
- Data from randomized, controlled trials are limited, and management choices are based mainly on clinical experience.
- Superpotent topical glucocorticoids are the usual first-line treatment for lichen planus.

Women account for 60 to 75% of patients with oral lichen planus[3,4] and 50% of those with cutaneous lichen planus.[6] The mean age at diagnosis is between 50 and 60 years for oral disease[3,4] and between 40 and 45 years for the cutaneous form.[6] Lichen planus is uncommon in children (accounting for less than 5% of cases).[16]

Oral lichen planus is generally considered a potentially premalignant condition[17]; a 1% incidence of squamous-cell carcinoma has been reported among patients with this condition in both retrospective and prospective cohort studies.[18] However, the true risk remains controversial, given the heterogeneous diagnostic criteria for lichen planus across studies (and the difficulty in discriminating it from other premalignant conditions), the variation in the duration of follow-up, and the potential confounding by associated risk factors (e.g., alcohol consumption and smoking).[4,17,18] Case reports have also described squamous-cell carcinomas arising from chronic anogenital,[5] esophageal,[8] or hypertrophic cutaneous lichen planus lesions.[19]

Although the pathogenesis of lichen planus remains unclear, it appears to be an autoimmune disease. The basal keratinocyte degeneration observed in lichen planus is attributed to cytotoxic CD8+ T lymphocytes,[20] which are the major component of the infiltrates located within the epithelium and adjacent to damaged keratinocytes. The triggering antigen is not known.[20] The existence of rare cases of familial lichen planus and the overrepresentation of certain HLA haplotypes (e.g., HLA-DR1 in cutaneous lichen planus) suggest that genetic factors have a role in susceptibility to this disease.[1] Several autoimmune disorders, particularly alopecia areata and ulcerative colitis, have been reported to occur more frequently in patients with lichen planus than in control populations.[21]

There is a significant association between lichen planus and infection with hepatitis C virus (HCV). In two meta-analyses, patients with lichen planus were reported to be approximately 5 times as likely as controls to be HCV-seropositive; moreover, lichen planus was 2.5 to 4.5 times as likely to develop in the HCV-seropositive patients.[22,23]

Lichen planus has adverse effects on both quality of life and psychological status.[24] Factors that contribute to these detrimental effects include pain and difficulties with eating and with sexual function in association with mucosal disease.

STRATEGIES AND EVIDENCE

EVALUATION AND DIAGNOSIS

Lichen planus is usually diagnosed clinically. If a patient has lichen planus at any site, the clinician should examine all potentially involved sites, such as the mucosa, skin, and skin appendages (nails [Fig. 1F] and hair [Fig. 1G]). Specialized otorhinolaryngologic and endoscopic examinations should be considered when related symptoms such as odynophagia or dysphagia are present. Differential

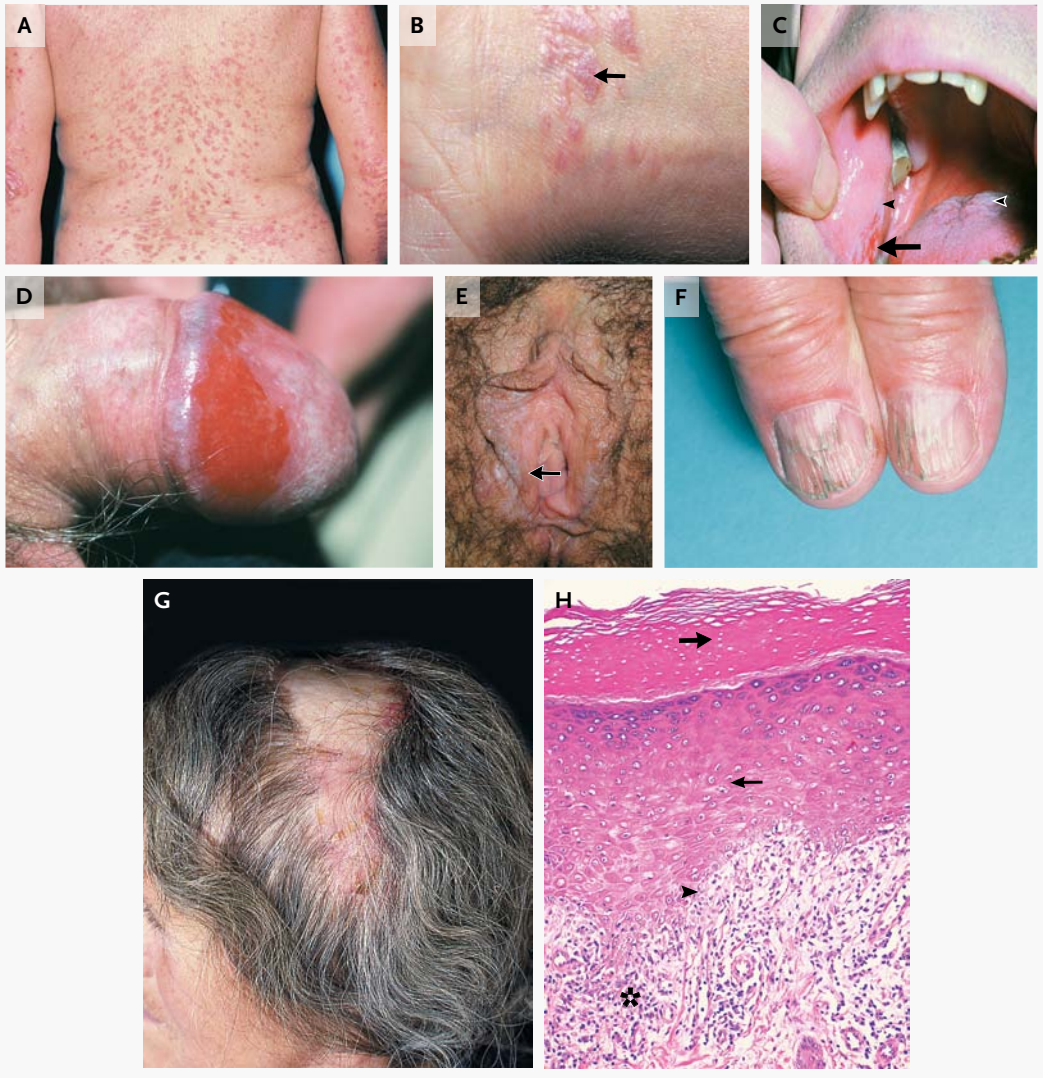

Figure 1. Clinical Presentations of Lichen Planus.

Panel A shows widespread eruption of violaceous, shiny, isolated, flat-topped papules and plaques, which are most profuse on the ankles and in the lumbar region; the legs and neck are also frequently involved. As shown in Panel B, polygonal, violaceous papules, with a lacelike, white-line network (arrow), are most frequently seen on the inner aspect of the wrist. Panel C shows the oral lesions of lichen planus, which are bilateral and symmetric and are associated with a network of white-lined plaques (left arrowhead) and erosive lesions (arrow) in the posterior buccal mucosa and with a white-line network (right arrowhead) on the top of the tongue. Areas of the oral mucosa mainly affect the posterior lining of the cheek (in 73% and 91% of cases), the gingiva (33% and 57%), and the tongue (44% and 54%).[3,4] Panel D shows a white-line network within an erosive plaque on the glans penis. Panel E shows a white-line network (arrow) on the internal aspects of the labia minora and majora, which are the sites that are usually affected in anogenital lichen planus; the vagina is involved in about 50% of cases[5] and the perianal area in about 20% of cases.[5] Panel F shows nail thinning, with longitudinal ridging and distal splitting linked to matrix involvement in these two fingernails; fingernails are involved more frequently than toenails. Panel G shows follicular, violaceous erythema and acuminate keratotic plugs surrounding the zone of alopecia. The plaques are multifocal and occur most frequently on the vertex; other hairy areas can also be involved. The skin specimen in Panel H shows the characteristic histologic features of lichen planus: thickening of the stratum corneum, with orthokeratosis (thick arrow), accentuation of the granular-cell layer (thin arrow), liquefactive degeneration of the basal-cell layer (arrowhead), and bandlike inflammatory-cell infiltrate (asterisk) (hematoxylin and eosin).

Table 1. Typical Symptoms and Particular Patterns of Lichen Planus, with Possible Outcomes and Complications.

Location	Symptoms	Particular Patterns	Outcomes and Complications
Body	Itching	Koebner's phenomenon: lesion at site of traumatic injury (e.g., from scratching); soles affected more frequently than palms, with bilateral involvement; seen as erythematous scaly plaques, hyperkeratosis	Spontaneous healing, usually within 1 yr; long-lasting residual pigmentation
Mouth	Soreness, pain, burning, swelling, irritation, bleeding; isolated reticular form usually asymptomatic	White forms (reticular, papular, plaquelike): white, lacelike network, papules, plaques; seen in 35%[3] and 59%[4] of cases; red forms (erosive, atrophic, bullous): erythematous lesions with or without erosive lesions associated with reticular lesions; seen in 41%[3] and 64%[4] of cases	Poor tendency to heal spontaneously in about 2.5%[3]; periods of exacerbation
Genital area	Burning, itching, pain, dyspareunia, impaired sexual function	Vulvovaginogingival or penogingival syndrome: association between erosive genital lichen planus and gingivitis	Vulvar scarring in erosive forms (95% frequency)[5]; synechiae with vaginal stenosis and labia minora agglutination in females, phimosis in males
Esophagus	Odynophagia, dysphagia	Endoscopic findings: stricture mainly located in whitish papules, erythema, mucosal sloughing	Chronic stricture
Scalp	Itching; pain and burning during inflammatory phase	Frontal fibrosing alopecia: progressive frontal–temporal hairline recession in postmenopausal women; Lassueur–Graham-Little–Piccardi syndrome: patchy, scarring alopecia associated with follicular lichenoid eruption and loss of axillary and pubic hair	Chronic and progressive; atrophic, scarring alopecia with absence of follicular units
Nails	Pain, burning	Lichen planus of the nail bed leading to onycholysis and subungual hyperkeratosis	Recovery with treatment, but with frequent relapses; in rare cases, nail loss or pterygium unguis (permanent advancement of medial skin over the nail plate, bisecting the nail)

diagnoses, which vary depending on the clinical presentation, are reviewed in Table 1 in the Supplementary Appendix.

Drug-induced lichen planus, also known as lichenoid drug eruption, is uncommon and may be indistinguishable from typical idiopathic lichen planus[25-29] (Table 1 in the Supplementary Appendix). A careful drug history is routinely warranted; in rare cases, drugs that have been taken for as long as 2 years before cutaneous lesions develop have been considered to be the likely cause of the lesions.

Histologic examination of skin or mucosal biopsy specimens is useful to confirm the diagnosis in atypical cases, as well as to avoid inappropriate treatment in cases of severe disease. Histologic findings are the same, regardless of the area involved (Fig. 1H). For persistent lesions that do not disappear with treatment, biopsy should be performed to rule out early dysplasia or squamous-cell carcinoma.[18]

Given the recognized associations between lichen planus and HCV infection, screening for anti-HCV antibodies with the use of an enzyme-linked immunosorbent assay (ELISA) is recommended. Some experts believe that for purposes of cost-effectivenesss, such screening should be reserved for patients known to be at risk for acquiring HCV (e.g., intravenous drug abusers),[30] whereas other experts recommend screening all patients with

lichen planus; the choice of screening approach should be based on the local seroprevalence of HCV. Routine screening for other immune-mediated conditions is not thought to be warranted, although these disorders should be considered in patients with suggestive symptoms or signs.

MANAGEMENT

Therapeutic objectives depend on the location and severity of the lesions. Since data from randomized, controlled trials are limited,[31] treatment choices are guided largely by clinical experience. Table 2 summarizes commonly used therapies and their indications. (See Table 2 in the Supplementary Appendix for an expanded list, including therapies used for nail and scalp lichen planus, as well as systemic immunosuppressive therapies.)

Cutaneous Lichen Planus

Because the cutaneous form of lichen planus may resolve spontaneously, the goals of therapy are to shorten the time between onset and resolution of the lesions and to reduce itching. In one study, clearing of lesions occurred within 1 year in two thirds of patients with cutaneous disease who were treated with various regimens.[6] Topical glucocorticoids are used as the first-line treatment, although their efficacy has not been demonstrated in well-designed, randomized, controlled trials. Data from studies in which various topical glucocorticoids are compared are lacking. Topical retinoids are not prescribed for this condition because of the risk of irritation.

When topical glucocorticoids are ineffective, oral glucocorticoid therapy is sometimes used. In a small, randomized, controlled trial[32] in which hydrocortisone 17-butyrate cream alone was compared with oral prednisolone (30 mg per day for 10 days) in combination with twice-daily administration of hydrocortisone 17-butyrate cream, similar numbers of patients in the two treatment groups were reported to have clearing of lesions at 18 weeks, but the time to clearing was significantly shorter in the group given prednisolone (18 weeks, vs. 29 weeks in the group given the topical cream alone); the limitations of this study preclude reliable conclusions.

Oral aromatic retinoids are also used. If these agents are prescribed to women of childbearing age, adequate contraception is mandatory (Table 2). In a randomized, controlled trial, the rates of lesion regression or remission at 8 weeks were significantly higher with acitretin (30 mg per day for 8 weeks) than with placebo.[33]

Another option is phototherapy, although this treatment should be used cautiously in dark-skinned patients, who have an increased risk of residual hyperpigmentation. In a small trial involving 10 patients,[34] psoralen and ultraviolet A (PUVA) therapy three times weekly on one side of the body was compared with no treatment on the other side of the body. After a mean period of 6 weeks, complete clearance (nonpalpable lesions) was noted in half the patients on the treated side only; 2 patients with no response had flares while taking the therapy.[34] Data from randomized trials of narrow-band ultraviolet B therapy are lacking. In a retrospective, observational study, 70% of patients who were treated with narrow-band ultraviolet B therapy had a complete response within a mean of 11 weeks.[35]

Oral Lichen Planus

Reticular oral lichen planus is usually asymptomatic and does not require treatment.[7,17,31] For erosive oral lichen planus, the goals of treatment are to heal erosive lesions and to lessen pain and the associated difficulty in eating and drinking. Topical glucocorticoids are the first-line therapy. In two small, randomized, placebo-controlled trials — one of fluocinonide[36] and the other of betamethasone valerate[37] — the rates of cure or attenuation were significantly higher in the active-treatment group than in the placebo group (80% with fluocinonide vs. 30% with placebo, and 66% with betamethasone vs. 18% with placebo).

Oral glucocorticoids (e.g., prednisone, at a dose of 0.5 to 1.0 mg per kilogram of body weight per day, typically given for 4 to 6 weeks) are generally used for erosive lesions that do not respond sufficiently to topical glucocorticoids and as first-line therapy for severe erosive oral lichen planus associated with eating difficulties. However, data showing the efficacy of this approach are lacking, and side effects are common. In one randomized trial,[38] in which topical triamcinolone was compared with low-dose oral betamethasone (5 mg per day for 3 months, followed by a slow taper during the ensuing 3 months), the only significant between-group difference was a shorter time to healing in the group of patients treated with systemic glucocorticoids (15.5 weeks, vs. 19.0 weeks with triam-

Table 2. Therapies Commonly Used for Lichen Planus.*

Treatment	Uses and Recommendations	Potential Harmful Effects	Comments
Topical glucocorticoids†			
Superpotent topical glucocorticoids (e.g., 0.05% clobetasol propionate ointment)‡	For symptomatic oral lichen planus: first-line treatment applied with gloved finger 3 times daily; patient should avoid eating and drinking for 1 hr after application; for anogenital lichen planus: first-line treatment applied once daily; for thickened lesions of cutaneous lichen planus: first-line treatment applied once daily (under an occlusive bandage for hypertrophic lichen planus)	Oral or genital candidiasis; long-term use can lead to epidermal atrophy and systemic effects (e.g., suppression of the hypothalamic–pituitary–adrenal axis, cushingoid features, diabetes mellitus, bone loss, avascular necrosis)	Glucocorticoids are not formulated for oral or vaginal mucosa, and no randomized, controlled trials have compared the different formulations available; if no improvement after 6 wk, change therapeutic strategy; tailor maintenance therapy to patient's clinical course: reduce frequency of application, use a less potent glucocorticoid, or both
Potent topical glucocorticoids	For less severe forms of lichen planus or for maintenance therapy		
Prednisolone tablet soluble in water	For widespread oral lichen planus: used as mouthwash, 5 mg in 15 ml water, 3 times daily		
Hydrocortisone suppositories, foam, or cream	For vaginal lichen planus: applied every, other day		
Systemic glucocorticoids			
Oral prednisone, 0.5 to 1.0 mg/kg of body weight/day, for 4 to 6 wk, or intramuscular triamcinolone acetonide	For severe mucosal erosive lichen planus or for nail lichen planus that involves more than three nails: first-line treatment; for severe lichen planus that is resistant to topical glucocorticoids: second-line treatment	Characteristic side effects of systemic glucocorticoids	After remission, taper slowly
Topical retinoids			
Retinoic acid or isotretinoin lotion or gel (0.1%)	For oral lichen planus with papular and plaquelike form (without erosive lesions): first-line treatment, either alone or with topical glucocorticoids, 2 times daily	Burning sensation after application; prohibited during pregnancy and breast-feeding; requires adequate birth control	Not indicated for lichen planus at other sites

Systemic Retinoids			
Acitretin, 30 mg/day, for 8 wk	For cutaneous lichen planus: second-line treatment, either alone or with topical glucocorticoids or phototherapy§	Teratogenicity, elevation of liver enzymes, hyperlipidemia	For women of childbearing age, two effective forms of contraception are mandatory during treatment and for 3 yr afterward
Phototherapy			
PUVA or narrow-band ultraviolet B therapy: 2 or 3 times a week, for a total of 12 sessions (i.e., 1 cycle)	For cutaneous lichen planus: second-line treatment, either alone or with acitretin§	Increased risk of skin cancer (but does not appear to be significant if therapy is limited to 1 or 2 cycles of 12 sessions each); increased risk of residual pigmentation	

* Levels of evidence for specific choices of treatment are described in the text. (An expanded version of this table is available in the Supplementary Appendix.) PUVA denotes psoralen and ultraviolet A.
† Gloves should be worn when one is applying topical glucocorticoids in order to prevent side effects of the medication.
‡ Superpotent glucocorticoids in Orabase (Colgate), as a commercial formulation or one prepared by a pharmacist, can also be used.
§ For cutaneous lichen planus, the choice among second-line therapies should be based on the presence or absence of concomitant erosive mucosal lichen planus, the severity of the lesions, childbearing potential, and the availability of phototherapy.

cinolone), and half the patients had side effects (twice the rate in the topical-therapy group).

Topical calcineurin inhibitors (cyclosporine, pimecrolimus, and tacrolimus), although proposed as possible therapy for this disorder, are not recommended. They are not approved by the Food and Drug Administration (FDA) for this indication, and current FDA labeling states that these drugs should not be given to treat premalignant conditions. A recent Cochrane review concluded that evidence to support the contention that topical cyclosporine reduces pain and clinical signs of oral lichen planus is weak and unreliable and that there is no evidence to support the notion that pimecrolimus reduces pain, as compared with topical glucocorticoids or placebo.[39]

For papular and plaquelike lichen planus without erosive lesions, either topical glucocorticoids or topical retinoids are used as first-line treatment. In two small, randomized, placebo-controlled trials in which 0.1% tretinoin lotion was applied for 4 months, twice daily,[40] and 0.1% isotretinoin gel was applied for 8 weeks, twice daily,[41] both the active treatments were superior to placebo. Attenuation was observed in 97% of the lotion-treated patients versus 21% of those given placebo and in 90% of the gel-treated patients versus 10% of those given placebo. A randomized trial comparing a topical glucocorticoid (0.1% fluocinolone acetonide) with topical 0.05% retinoic acid for patients with atrophic and erosive oral lichen planus showed the former treatment to be significantly more effective; however, the retinoic acid concentration was lower than that usually prescribed.[42]

Anogenital Lichen Planus

For erosive genital lesions, the major therapeutic aim is to prevent or limit scarring. In a prospective cohort study of women with erosive vulvar lichen planus,[5] symptoms were attenuated in 71% of the women who applied 0.05% clobetasol propionate ointment (a superpotent topical glucocorticoid) twice daily, but complete resolution (except for scarring) was uncommon. Synechiae formation may be prevented with the use of vaginal dilators and, for uncircumcised men, foreskin retraction. When adhesions form, surgery may be required, but it should be deferred until active lesions are no longer present in order to avoid complications with healing. Since lichen planus has been reported to occur less frequently in circumcised men than in

uncircumcised men,[43] removal of the foreskin is usually recommended.

Nail Lichen Planus

The objectives of treatment in lichen planus of the nails are to lessen pain and to prevent or limit scarring. In two retrospective case series, a total of 142 patients were treated with systemic glucocorticoids (intramuscular injection or oral administration), local glucocorticoids (intralesional injection or topical application), or both.[10,11] Cure or major improvement was reported in two thirds of the patients after an average treatment period of 6 months; however, relapses were common.

Scalp Lichen Planus

Topical glucocorticoids, either alone or combined with an intralesional glucocorticoid injection, are the first-line treatment for lichen planopilaris.[12,44] In a retrospective chart review, 20 of 30 patients who were treated with topical glucocorticoids (potency level not specified) were found to have complete clearing of lesions after 12 weeks.[45] Lichen planopilaris that is severe or is resistant to local glucocorticoid therapy is commonly treated with systemic glucocorticoids, although data on the efficacy of this approach are lacking.

AREAS OF UNCERTAINTY

It remains uncertain whether, and if so to what extent, lichen planus is an independent risk factor for the development of squamous-cell carcinoma, as well as whether, and if so how, patients with lichen planus should be monitored for this neoplasm.[7,17] Randomized trials are needed to provide better guidance in the choice of the various therapies available for the different types of lichen planus[31,39] and to assess the benefits and risks of several medications that have been described to be effective in case reports or small case series. Examples of such medications include topical rapamycin (now known as sirolimus)[46] and extracorporeal photochemotherapy[47] for erosive oral lichen planus; methotrexate for cutaneous lichen planus[48]; a peroxisome proliferator–activated receptor agonist for lichen planopilaris[49]; and anti-CD20 monoclonal antibody for oral, genital, and esophageal lichen planus.[50] Two randomized, controlled trials comparing aloe vera with placebo for the treatment of oral lichen planus yielded inconsistent results,[51,52] so further study is warranted. It remains unclear how long maintenance treatment should be continued for mucosal, scalp, nail, and esophageal disease, for which there are currently no curative therapies.

GUIDELINES

Guidelines for managing oral lichen planus have been published by the British Society for Oral Medicine,[53] and guidelines for managing vulvar lichen planus have been published by the British Association for Sexual Health and HIV.[54] The recommendations provided below are generally consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The woman described in the vignette has oral and cutaneous lesions that appear to be consistent with a diagnosis of lichen planus. In such patients, complete examination of the skin, including the scalp and nails, and of oral, genital, anal, and ocular areas, as well as a thorough gynecologic examination, should be performed to detect any evidence of lichen planus elsewhere. Serologic testing for HCV should be considered. Good oral hygiene should be recommended, and the patient should be told to avoid cigarette smoking, alcohol consumption, and the ingestion of spicy or acidic foods or beverages that can be painful in the presence of oral lesions.

We would initiate treatment with topical 0.05% clobetasol propionate ointment applied three times daily on erosive areas of the oral mucosa (an approach supported by data from randomized trials) and once daily, at night, on involved skin (an approach based largely on clinical experience), with a reevaluation after 6 weeks. If there is no response to treatment or if the response is insufficient and difficulties with eating persist, we would recommend oral glucocorticoids (e.g., prednisone at a dose of 0.5 to 1.0 mg per kilogram per day for 4 to 6 weeks, followed by a slow taper, to minimize the risk of relapse), although data from randomized trials assessing the efficacy of this therapy or comparing it with alternative approaches are lacking. If the patient has intense pain or loses weight, systemic rather than topical glucocorticoids can be considered as first-line treatment. Biopsy is war-

ranted if healing does not occur with treatment. Patients should be educated regarding the potential side effects of glucocorticoids and should be monitored to detect any such effects. Moreover, patients should understand the potentially chronic and relapsing course of oral lichen planus, as well as the need for long-term clinical surveillance.

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