Diagnosis of oral lichen planus: a position paper of the American Academy of Oral and Maxillofacial Pathology

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Despite being one of the most common oral mucosal diseases and recognized as early as 1866, oral lichen planus (OLP) is still a disease without a clear etiology or pathogenesis, and with uncertain premalignant potential. More research is urgently needed; however, the research material must be based on an accurate diagnosis. Accurate identification of OLP is often challenging, mandating inclusion of clinicopathological correlation in the diagnostic process. This article summarizes current knowledge regarding OLP, discusses the challenges of making an accurate diagnosis, and proposes a new set of diagnostic criteria upon which to base future research studies. A checklist is also recommended for clinicians to provide specific information to pathologists when submitting biopsy material. The diagnostic process of OLP requires continued follow-up after initial biopsy, because OLP mimics can manifest, necessitating an additional biopsy for direct immunofluorescence study and/or histopathological evaluation in order to reach a final diagnosis. (Oral Surg Oral Med Oral Pathol Oral Radiol 2016;122:332-354)

Perhaps no disease in the field of oral pathology and medicine has generated more discussion and been associated with more controversy than oral lichen planus (OLP). Although much effort has been invested in clinical, pathologic, and basic science research studies, inconsistent results and diverse opinions still leave many questions unanswered regarding etiology, pathogenesis, and premalignant potential. While this fact obviously points to the need for more research on OLP, any useful investigations must be based on an accurate diagnosis. However, a reliable diagnosis of OLP has proven challenging for a few reasons (as shall be explained later in this article), and significant disagreements concerning its diagnosis continue to be found among pathologists and clinicians. Therefore, the main purposes of this article are to discuss the challenges in making the diagnosis of OLP and to propose a new set of diagnostic criteria by adding additional elements to the existing modified WHO criteria proposed by Van der Meij and van der Waal. 1 A brief review of the current knowledge about OLP is included as background. As we emphasize clinicopathologic correlation in making the diagnosis of OLP, we also recommend that a checklist encompassing all important, relevant, clinical information be provided to pathologists, together with the biopsy, to aid in establishing an accurate diagnosis.

OVERVIEW OF OLP AND ITS COMPLEXITIES

Historical background
The initial clinical description of lichen planus (LP) is generally attributed to Ferdinand Ritter von Hebra, who in 1860 termed the condition “lichen ruber planus.” 2 The clinical definition was refined through the work of Erasmus Wilson and Moritz Kaposi, with the former being the first to simplify the name to “lichen planus.” Wilson offered the first published description of oral lichen planus (OLP) in 1866, noting a white papular eruption of the tongue and buccal and mandibular labial mucosa in a 56-year-old female. 3 This was followed by his report in 1869 of 50 additional patients with OLP. 4 Characterization of white striations in cutaneous LP was provided by Louis Wickham in 1895. 5, 6 It is useful to recognize that from the time of its initial identification, OLP was discussed, studied, and diagnosed for 40 years entirely as a clinical disorder without any histopathologic characterization, as microscopic features would not be delineated until the work of William Dubreuilh in 1906. 7 Efforts to identify key clinical and histopathologic criteria, and to design a valid method of clinicopathologic correlation to ensure accurate diagnosis of OLP, have been both challenging and elusive, occupying the efforts of numerous investigators for over a century.

Epidemiology and clinical features
The prevalence of LP is estimated at 0.22% to 5% worldwide, 6, and the incidence of OLP is estimated at...
up to 2.2%. Patients with cutaneous LP are estimated to exhibit oral disease expression in up to 60% of cases. However, only a minority of OLP patients, approximately 15%, develop cutaneous lesions. Aside from oral and cutaneous disease expression, additional characteristic anatomic distributions of LP are recognized (e.g., peno-gingival syndrome, vulvo-vaginal-gingival syndrome). LP in the genitalia occurs in approximately 20% of patients with OLP, and concurrent oral and esophageal LP is also observed. Scalp lesions with alopecia, and disease expression in nails, glans penis, and conjunctivae are recognized. OLP most often occurs in persons 30 to 80 years of age, with a greater prevalence in females. Although OLP is rare in children, a recent report described 316 pediatric patients with LP (ages 0-14 years), representing 18.76% of all patients attending an LP clinic, and 18% of this childhood LP population were reported to have oral involvement. Interestingly, a slight male predominance was noted in pediatric LP cases. Approximately two-thirds of patients with OLP experience discomfort. Symptom intensity is variable and expressed in some cases only upon contact with spicy or acidic foods. Spontaneous symptoms are also described. A sense of mucosal roughness, reduced mucosal flexibility, and limited opening of the mouth are noted. Significant negative impact on quality of life is emphasized.

Characteristic clinical features of OLP include well-defined looping and intersecting white lines or striae on a background of minimal to substantial erythema. A roughly symmetric distribution is typical, commonly affecting the buccal mucosa, gingiva, and tongue. Six patterns of clinical expression of OLP are recognized—namely: reticular, atrophic, erosive, papular, plaque, and bullous (see Figures 1A-F). When OLP affects gingiva, it often presents as desquamative gingivitis, which can be indistinguishable clinically from some OLP mimics (see “Challenges in Diagnosis of OLP”). The prevalence of a reticular pattern appears to diminish with increased duration of disease. Plaque-type lesions have been reported more commonly in cigarette smokers, with lesion persistence unaffected by tobacco cessation.

In dark-skinned individuals, a pigmented reticular pattern is sometimes seen (Figure 1G).

**Histopathologic features and direct immunofluorescence findings**

Microscopic features of OLP include hyperparakeratosis, hyperorthokeratosis, and combinations of the two; cytoid (Civatte) bodies; basal cell hydropic change; and a band-like chiefly lymphocytic infiltrate in the lamina propria. This pattern of inflammatory change has been termed “interface mucositis,” which is also encountered in oral lesions of lupus erythematosus and in additional oral lichenoid conditions. Figures 2A-C depict characteristic histopathologic alterations in a case clinically presenting with the reticular pattern. Additional findings include saw-tooth rete ridges, atrophy, acanthosis, a homogeneous eosinophilic deposit at the epithelium-connective tissue junction, and ulceration. Compared to cutaneous disease, oral lesions less often exhibit saw-tooth rete ridges and more frequently exhibit atrophy. Biopsy specimens of OLP may show melanosis and melanin incontinence with associated melanophages, particularly in individuals with dark complexion (Figure 2D). Melanin incontinence is not specific to OLP, and is encountered in a wide range of inflammatory disorders sharing a lichenoid inflammatory process.

Direct immunofluorescence (DIF) is a diagnostic adjunct that may be employed to help support a diagnosis of OLP. For example, DIF is often necessary to differentiate OLP from autoimmune blistering diseases that typically present as desquamative gingivitis (see “Challenges in Diagnosis of OLP”). Deposition of fibrinogen in a shaggy pattern along the basement membrane zone (BMZ) in the absence of immunoglobulin (except for cytoid bodies, which are coated by immunoglobulin) and complement is the characteristic immunofluorescence pattern found in OLP. However, fibrinogen at the basement membrane has been reported in premalignant and malignant oral lesions, indicating that this finding is not specific for OLP (see “Challenges in Diagnosis of OLP”). DIF requires submission of fresh tissue for frozen sections or tissue placed in an appropriate transport medium (Michel’s solution). DIF adds cost to the diagnostic process, but may be necessary in situations where available clinical and pathologic information are insufficient to support a definitive diagnosis of OLP. Indirect immunofluorescence (IIF) is negative and not a useful technique in diagnosis of OLP.

**Etiology and pathogenesis**

The etiology of OLP is unknown, and its clinical course suggests that OLP and cutaneous LP may encompass differences in respective pathogenesis mechanisms. A number of potential triggers and contributing factors in OLP have been proposed, including: 1) local and systemic inducers of cell-mediated hypersensitivity; 2) stress; 3) autoimmune response to epithelial antigens; and 4) microorganisms. Hypersensitivity responses generally align with lichenoid mucositis, such as those seen with local reactions to dental restorative...
Fig. 1. Clinical patterns of OLP. A, Reticular. B, Atrophic. C, Erosive. D, Papular (in area close to the retractor, image courtesy of Dr. John Wright). E, Plaque (image courtesy of Dr. Gil Selkin). F, Bullous. G, In dark-skinned individuals, pigmentation can be seen associated with the reticular pattern. OLP, oral lichen planus.
The role of psychological stress is unclear, as the cause and effect relationship between stress and onset of OLP has not been established. Definitive evidence for autoimmunity in OLP has not been demonstrated, although a number of studies point to dysregulated immune responses, which allow for the possibility of autoimmunity. Several microbial agents have been investigated for their possible role in OLP, of which hepatitis C virus has thus far emerged as the only microorganism with a convincing association, and that only in some geographic regions. Whether the destruction of keratinocytes in OLP occurs due to autoreactivity or as a bystander effect (i.e., due to a dysregulated response to an exogenous antigen) has not been resolved. A more detailed account of the current views on etiology and pathogenesis of OLP is described elsewhere.

**Management**

Appropriate management of patients with OLP has been explored in several recently published comprehensive reviews. The importance of patient education before treatment is emphasized. The patient should be advised that therapy is not curative but is directed at controlling inflammation and reducing the associated symptoms. As response to therapy is often delayed and continuous maintenance is necessary, it is
best that patients are prepared for prolonged periods of treatment. Because variation in patient response to specific therapies is well recognized, patients should be warned that sequential use of several treatment regimens may be necessary before effective symptom control is achieved. Patients also should be advised of possible linkages of OLP to development of oral cancer, although this aspect of OLP remains controversial (more discussion in “Controversy regarding malignant transformation”). This knowledge will aid in developing, accepting, and implementing a long-term patient monitoring plan.

The potential for clinicopathologic mimicry of OLP is significant, and the patient should be made aware of this before initiation of therapy (more discussion in “Challenges in Diagnosis of OLP”). It must be made clear that although the presence of oral cancer and epithelial dysplasia are ruled out based on histopathologic findings, continued clinical follow up is still necessary, not only for adequate control of disease, but also for appropriate management of changes that may occur either in response to OLP-specific treatment or in the context of other systemic disorders managed with medications. Confidence in diagnostic validity is most often achieved through patient clinical observation over time, noting responses to therapies and sequential evaluation of oral mucosal status. For example, a pattern of clinical presentation and histopathologic data may fulfill the criteria for OLP, and early patient clinical response to conventional topical therapy may appear to substantiate this diagnosis. However, failure to maintain acceptable control of OLP after continued initial and subsequent alternative therapies would mandate additional patient evaluation and testing (e.g., DIF and IIF studies, rheumatologic evaluation, and patch testing). Positive findings in this process would likely identify a lichenoid clinicopathologic mimic (e.g., chronic ulcerative stomatitis, lichen planus pemphigoids, lupus erythematosus, paraneoplastic pemphigus, contact hypersensitivity), permitting initiation of a more appropriate patient management strategy. The process of patient evaluation, initiation of treatment, assessment of clinical response, and selection of alternative and ultimately effective treatment protocols may require months to years. Both the patient and the clinician should be prepared for this process.

A wide variety of therapies are described for control of OLP, including topical, locally injected, and systemic corticosteroids7,8,12,13; doxycycline; topical retinoids2,8,9; topical calcineurin inhibitors65; hydroxychloroquine; azathioprine; mycophenolate mofetil; methotrexate; dapsone; thalidomide; phototherapy2; biological agents (e.g., efalizumab, etanercept, alefacept, rituximab)66; topical aloe vera; and oral curcuminoids.67 The validity of selection among treatment options is hampered by the paucity of relevant published placebo-controlled double-blind studies, and the absence of consensus-based objective measures of disease activity. Attention to maintenance of good oral hygiene,2,8,12,68 detection and control of candida species infection,69 as well as assessment and management of salivary gland hypofunction70 are required for successful therapeutic outcomes.

Controversy regarding malignant transformation

Ever since the first known clinical report about malignant transformation in OLP was published in the medical literature in 1924,71 there has been an unresolved controversy regarding whether OLP should be considered a premalignant condition. For the purposes of this article, a brief overview of this controversy is described below. Readers interested in detailed discussions of the malignant potential of OLP are encouraged to read the several excellent published reviews.27,72-76

The reported OLP malignant transformation rates vary from 0.4% to 12.5%,27,72-77 with an overall average rate of 1.09% cited in a recent meta-analysis and systematic review of 7,806 patients in 16 studies.72 For this reason, in 2005 the World Health Organization (WHO) in their Global Oral Health Program designated OLP a premalignant condition.78 Many OLP studies have investigated molecular events and mechanisms involved in carcinogenesis, such as telomerase activity, cytogenetic abnormalities, expression of p53, MDM2, p21, SUMO-1, PCNA, argyrophilic nucleolar organizer regions (AgNOR), Ki-67, Bcl-2, BAX, and loss of heterozygosity at the tumor suppressor gene loci.79-96 However, the results of these studies have not shown evidence of premalignant potential as convincing, consistent, or conclusive as that characterizing epithelial dysplasia. Therefore, the controversy regarding the premalignant nature of OLP remains unresolved.

This issue is challenging to resolve for at least the following reasons:

1. A structured, standardized basis for reporting data is lacking, and important clinical information and/or histopathologic evidence are often missing in publications.27,75 In some reports the diagnosis of OLP was made solely on the clinical presentation without histopathologic confirmation. It is therefore difficult or impossible to determine whether the reported cases were accurately diagnosed as OLP, and therefore doubts must be cast upon the validity of outcomes and conclusions.

2. Many other oral diseases may show clinical and microscopic features similar to those found in OLP, including proliferative verrucous leukoplakia (more
<table>
<thead>
<tr>
<th>Pathologic condition</th>
<th>Clinical features</th>
<th>Histopathological features</th>
<th>Immunofluorescent findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OLP</strong></td>
<td>Multifocal, usually bilateral affecting buccal mucosa, tongue, lips, and gingiva; can appear as desquamative gingivitis; white reticular patches with or without erosions and ulcerations.</td>
<td>Reticular form: Hyperkeratosis with basal cell degeneration, necrosis of basal and parabasal keratinocytes, and a band-like predominantly lymphocytic infiltrate adjacent to basal cells. Erosive form: Sub-basal separation with basal cell degeneration; inflammation may contain plasma cells; reactive, regenerative, or reparative epithelial changes may be seen in these cases and, depending on the degree of ulceration, pathologic features may be less distinct.</td>
<td><strong>DIF:</strong> Usually negative, may see shaggy fibrinogen deposition at BMZ and colloid bodies. <strong>IIF:</strong> Negative.</td>
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<td><strong>MMP</strong></td>
<td>Often presents as desquamative gingivitis; erosions and ulcers without a reticular component; rare intact bullae; frequently affects other oral mucosal sites, such as buccal mucosa and palate.</td>
<td>Sub-basal epithelial separation without basal cell liquefaction; inflammation mixed and often sparse.</td>
<td><strong>DIF:</strong> Linear IgG and C3 at BMZ; less often IgA, IgM, and fibrin. <strong>IIF:</strong> Linear IgG and/or IgA at BMZ (low titer); salt split skin shows linear IgG and/or IgA at roof or floor of the split.</td>
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<td><strong>Lichen planus pemphigoides</strong></td>
<td>Combined features of lichen planus and pemphigoid (vesicles or bullae) on oral mucosa, skin, or both. Most often affects buccal mucosa and gingiva, although palate, vestibule, and labial mucosa can also be involved.</td>
<td>Features of OLP (basal cell degeneration, thickening and dissolution of basement membrane, band-like lymphocytic infiltrate in superficial lamina propria), MMP (sub-basal epithelial separation), or both.</td>
<td><strong>DIF:</strong> Same as MMP. <strong>IIF:</strong> Immunoglobulin (most often IgG) at BMZ.</td>
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<td><strong>Chronic graft-versus-host disease</strong></td>
<td>Similar to OLP; history of bone marrow transplant.</td>
<td>Basal cell degeneration with subepithelial lymphocytic infiltrate (may be sparse).</td>
<td><strong>DIF:</strong> May be similar to OLP. <strong>IIF:</strong> Negative. <strong>DIF:</strong> Stratified SES-ANA in lower third of epithelium. <strong>IIF:</strong> SES-ANA positive.</td>
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<td><strong>Chronic ulcerative stomatitis</strong></td>
<td>Similar to OLP.</td>
<td>Similar to OLP.</td>
<td><strong>DIF:</strong> Similar to OLP. <strong>IIF:</strong> Usually negative.</td>
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<td><strong>Oral lichenoid drug reactions</strong></td>
<td>Similar to OLP; may see a temporal relationship with offending drug, but delayed onset of more than 1 year has been reported.</td>
<td>Similar to OLP but mixed inflammation, may extend into the deep lamina propria, may show perivascular inflammation.</td>
<td><strong>DIF:</strong> Similar to OLP. <strong>IIF:</strong> Usually negative.</td>
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<td><strong>Oral lichenoid contact hypersensitivity reactions</strong></td>
<td>Can be unilateral or bilateral; topographic relationship to dental restorations, flavoring agents (Table III).</td>
<td>Similar to OLP but inflammation mixed; may see lymphoid follicles in reactions to dental materials; perivascular inflammation and scattered eosinophils; epithelial acanthosis in cinnamon reaction.</td>
<td><strong>DIF:</strong> Linear band or continuous granular IgG, IgM, IgA, or C3 at BMZ. <strong>IIF:</strong> Negative.</td>
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<td><strong>Lupus erythematosus</strong></td>
<td>Oral involvement in up to 25% of cases and resembles erosive OLP; hard palate often affected; central area of ulceration surrounded by radiating keratotic striae.</td>
<td>Similar to OLP; sometimes deep perivascular inflammation.</td>
<td><strong>DIF:</strong> Similar to OLP. <strong>IIF:</strong> Usually negative.</td>
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<td><strong>Proliferative verrucous leukoplakia</strong></td>
<td>Multifocal keratotic lesions with a predilection for the gingiva, palate, and tongue in elderly females; erosive lesions can occur, mimicking erosive OLP.</td>
<td>Varies, but one pattern may exhibit a lichenoid appearance with a band-like inflammatory cell infiltrate, saw-tooth rete ridges, and inflammatory cell transmigration through the epithelium; hyperchromatic, pleomorphic nuclei with varying degrees of cytologic atypia may be present.</td>
<td><strong>DIF:</strong> Linear band or continuous granular IgG, IgM, IgA, or C3 at BMZ. <strong>IIF:</strong> Negative. <strong>DIF:</strong> May show fibrinogen deposition along BMZ <strong>IIF:</strong> Unknown.</td>
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In fact, it is not uncommon to see microscopic lichenoid features in dysplasia and oral squamous cell carcinoma (OSCC). Therefore, misdiagnosis of OLP can occur, especially when limited clinical information is provided, or when atypical cellular changes that are premalignant in nature are mild in degree and/or accompanied by a lichenoid infiltrate.

3. **There are currently still no widely accepted diagnostic criteria for OLP.** Some pathologists use the WHO criteria, which did not address a way to distinguish or exclude epithelial dysplasia from the OLP diagnosis. Application of WHO criteria has appeared to reveal great interobserver and intraobserver variability. Others use the modified diagnostic criteria proposed by van der Meij and van der Waal, in which the presence of epithelial dysplasia precludes a diagnosis of OLP. Absence of broad consensus in selection of diagnostic criteria has been identified as the major obstacle to assuring the validity of studies investigating OLP potential for undergoing malignant transformation. It is clear that more research is needed to address the complex issues concerning the potential or actual transformation of OLP to oral cancer.

### CHALLENGES IN DIAGNOSIS OF OLP

The challenges in making the diagnosis of OLP include the following:

1. **Various other disorders clinically and/or histopathologically resemble OLP (Table 1).**
2. **The histopathologic features of OLP appear to fall on a spectrum, potentially influenced by the stage of the disease activity at the time of the biopsy, by any recent therapy of the condition, the clinical types (reticular vs erosive), and/or the anatomic sites (buccal mucosa vs gingiva).**
3. **Many microscopic features of OLP are not specific for OLP and can be found in other diseases.**

These challenges are discussed in detail below.

### Various disorders may present with clinical and/or histopathologic features similar to OLP (oral lichenoid lesions)

The terminology, classification, and diagnosis of oral lichenoid lesions have been debated and discussed for decades. Many names have been used in the literature to signify this group of conditions, contributing to confusion surrounding terminology and impeding progress in developing effective approaches to diagnosis and management. The focus of this section is on differentiating OLP from lichenoid lesions. More
detailed information concerning each of the conditions discussed below is available in several previously published articles.28,29 The following conditions can mimic OLP both clinically and microscopically.

**Mucous membrane pemphigoid.** Mucous membrane pemphigoid (MMP) is a chronic autoimmune blistering mucocutaneous disease characterized by subepithelial vesicles and bullae. MMP occurs in all age groups, and is most common between the 6th and 8th decades. Any mucosal site may be affected in MMP; however, the oral and ocular mucosae are most commonly involved. Oral MMP can clinically mimic erosive OLP when presenting as desquamative gingivitis (Figure 3A). Gingiva is involved in more than 60% of cases of oral MMP. The buccal mucosa, palate, alveolar ridge, tongue, and lower lip may also be involved. A positive Nikolsky sign may be affected in MMP; however, the oral and ocular mucosae are most commonly involved. Oral MMP can clinically mimic erosive OLP when presenting as desquamative gingivitis (Figure 3A). Gingiva is involved in more than 60% of cases of oral MMP. The buccal mucosa, palate, alveolar ridge, tongue, and lower lip may also be involved. A positive Nikolsky sign is commonly seen in MMP, but may also be encountered in the bullous form of OLP. Due to frequent minor trauma to the oral mucosa, intact vesicles or blisters are not often seen in oral MMP. Postinflammatory atrophy can mimic the atrophic form of OLP.100

The histopathology of MMP classically shows subepithelial clefting similar to erosive OLP, with specimens usually showing the epithelium detached from the lamina propria (Figure 3B). Biopsies of epithelium which are cleanly detached from the underlying lamina propria or do not contain any connective tissue should cause a pathologist to suspect MMP. In contrast to OLP, the basal epithelial cells affected by MMP do not exhibit hydropic degeneration or colloid bodies.28,29 The patchy and variable subepithelial inflammatory infiltrate found in MMP consists of a mixed population of lymphocytes, plasma cells, and scattered eosinophils. The microscopic appearance of erosive OLP and MMP can overlap greatly, and a definitive diagnosis of MMP requires DIF.

The majority of patients with MMP (80%-100%) will have continuous linear deposits of immunoglobulin (Ig) G, IgM, or IgA, and complement (C3) along the BMZ on DIF,100 distinguishing MMP from OLP (Figure 3C). Most MMP patients do not show detectable circulating antibodies with IIF; however, use of a salt-split skin substrate can increase IIF sensitivity, and the circulating antibody binding site(s) can be localized either at the roof or the floor of the split, depending on the specific distribution of autoantigens of MMP in the BMZ.101-103 Serologic tests, using immunoblot and enzyme-linked
imunosorbet assay (ELISA), have recently been reported to assist immunologic subtyping in the MMP diagnosis.103

**Lichen planus pemphigoides.** Lichen planus pemphigoides (LPP), a member of the pemphigoid family, is a rare mucocutaneous blistering disease that shows clinical and histopathological features of LP and pemphigoid (bullous pemphigoid or MMP).102,104 It can occur in both adults and children.105 In contrast to MMP, which most often occurs later in life (between the 6th and 8th decades), LPP in adults occurs most commonly between the 5th and 6th decades, and the male to female ratio is 4 to 5.104 LPP always arises in LP, and the time from development of LP lesions to vesiculobullous lesions of LPP varies from concomitant to 17 years,106 with a mean duration of 8.3 months.104 The onset of LPP in some cases has been linked to medications (angiotensin converting enzyme inhibitors, statins),104,105,107-109 Chinese herbal medicine,110 psoralen-ultraviolet A therapy,111 and viral infection (varicella zoster virus).112 Association with internal malignancies also has been reported.113

About 24% of LPP patients have oral lesions,104 and oral LPP without any skin or other mucosal involvement has been reported.106,114 A total of 27 cases of LPP with oral involvement were reviewed recently.106 Oral LPP most often affects buccal mucosa and gingiva, and presents with typical OLP features (multifocal white striations, papules, plaques with erosion or ulceration, or desquamative gingivitis) with or without vesicles or bullae.106 These clinical features are indistinguishable from LP. Although LPP may affect oral sites, such as the palate, vestibule, and labial mucosa, interestingly, it rarely affects the tongue.106

Histopathologically, LPP shows features of LP, MMP, or both. DIF shows the same findings as those seen in MMP (linear deposition of immunoglobulins, most often IgG, and C3 at BMZ). IIF showed immunoglobulins deposited at BMZ in 81% (47/58) of the cases cited in a recent literature review.104 The autoantigens found in LPP so far are BP180 and BP230.106 The diagnosis of LPP is based on clinical, histopathologic, and immunofluorescence studies. DIF is essential for the diagnosis.

Because LPP is a disease arising in LP, it is not surprising that a patient could be diagnosed first as OLP (based on clinical, histopathologic, and DIF findings), then the disease evolves into LPP, and the diagnosis of LPP is established later by repeated biopsy during the follow-up period for treatment purposes.106 LPP is an example demonstrating that the diagnostic process of LP does not end after an initial biopsy with a confirmed diagnosis of LP, a concept that is emphasized in this article.

**Chronic graft-versus-host disease.** Oral cavity manifestations of chronic graft-versus-host disease (cGVHD) after allogeneic bone marrow transplantation can be seen in up to 80% of graft recipients.28,115 cGVHD, a major cause of morbidity and mortality in this patient population, exhibits a median onset of 6 months post-transplantation. cGVHD has a more variable clinical presentation than OLP, and may manifest with involvement of skin, eyes, liver, respiratory, and gastrointestinal tracts.116 Lichenoid lesions in cGVHD may be distributed throughout the oral cavity, including the palate, an uncommon site for OLP.117,118 Lesions of cGVHD can present as lacerticulations, thickened plaques, or erosions mimicking OLP (Figure 4A).

The microscopic features of cGVHD and OLP also overlap and require clinical correlation for diagnosis.21,29,117,118 Basal cell degeneration and colloid bodies may be present (Figure 4B). The lymphocytic infiltrate in the subjacent connective tissue often is not as intense as in OLP and may contain a few plasma cells and eosinophils. Due to the varied clinical presentations, the diagnosis of cGVHD is based on the clinical and microscopic findings. DIF findings may be similar to OLP, and IIF is negative.30

**Chronic ulcerative stomatitis.** Chronic ulcerative stomatitis (CUS), a rare mucocutaneous disease, presents with chronic oral ulcerations and may occasionally involve cutaneous sites.119-121 The incidence of CUS is unknown, and only 50 cases have been reported to date in the English language literature since its first description in 1990.21,30,122,123 The demographic characteristics of CUS are virtually identical to OLP, with female predilection and onset in the 5th and 6th decades of life. Oral findings are also indistinguishable from erosive OLP and MMP. Any anatomic sites in the oral cavity may be affected, with expression most commonly on the gingiva, tongue, and buccal mucosa, and less commonly on the palate, lower lip, and lingual gingiva. Gingival involvement is expressed as desquamative gingivitis with erosion and ulceration (Figure 5A).30,119,121 White striations at the periphery of the erosions, similar to erosive OLP, also have been described.

Histopathologic features of CUS vary depending on biopsy site. Often, the features are indistinguishable from those encountered in OLP: atrophic epithelium with saw-tooth rete ridges, basal cell liquefaction, and a dense band-like inflammatory cell infiltrate composed chiefly of lymphocytes.21,122,123 However, ulcerative lesions may exhibit nonspecific features with a mixed inflammatory cell infiltrate.

The diagnosis of CUS requires DIF evaluation of perilesional tissue, demonstrating the presence of IgG.
antibodies in the nuclei of basal and parabasal epithelial cells in a speckled and/or granular pattern. This characteristic finding on DIF is known as the stratified epithelium specific-antineuclear antibody (SES-ANA) pattern (Figure 5B). A shaggy linear band of fibrinogen is sometimes identified in the BMZ, but this DIF finding is not specific for CUS, and indeed is also seen in OLP. However, tangential orientation of tissue sections may render interpretation of IgG localization problematic.

Autoimmune diseases, such as lupus erythematosus, scleroderma, CREST syndrome (calcinosi, Raynaud’s phenomenon, esophageal involvement, spondyloarthritis, and telangiectasia), and mixed connective tissue disease, also may demonstrate an ANA pattern in epithelia; however, these autoantibody deposits are typically found in the spinous cell layer. In CUS, IIF using a tissue substrate, such as guinea pig or monkey esophagus substrate, also exhibits the SES-ANA pattern.

Patient management with CUS is distinct from OLP and some OLP mimics. Corticosteroids and dapsone therapy in CUS are less effective than hydroxychloroquine. Studies have found clinical remission and decreased autoantibody titers after treatment with hydroxychloroquine. Due to the small
The number of cases reported, our understanding of the etiopathogenesis, natural history, and optimal management of CUS is limited.

**Oral lichenoid drug reactions.** Many systemic medications can cause oral lichenoid drug reactions (OLDR) (Table II).21,28-30 Both reticular and erosive patterns may be seen in OLDR with or without cutaneous lesions. The exact incidence of OLDR is unknown, although it is more commonly reported in adults and rarely in the pediatric population.124 The time interval between initiation of a medication and onset of OLDR can vary widely, ranging from weeks to a year or more. OLDR may present as a single oral lesion, unlike the bilateral/multifocal presentation of OLP. The most commonly reported offending medications include nonsteroidal anti-inflammatory drugs, anticonvulsants, antihypertensives, antimalarials, and antiretrovirals.21,28-30 The pathogenesis of OLDR is uncertain, and standardized diagnostic criteria for OLDR have not been established. If a temporal relationship between a medication use and the onset of lesions can be established, discontinuation of the suspected offending medication is recommended. Coordination with the medication prescriber is strongly encouraged. Resolution of the lesions after drug discontinuation may require many months or longer.

The microscopic features of OLDR share similarities to OLP, with some notable differences. The epithelium in OLDR may have a higher number of apoptotic keratinocytes (colloid or Civatte bodies) than in OLP. The inflammatory infiltrate often extends deep into the lamina propria, unlike the superficial band-like infiltrate typical of OLP. A perivascular chronic inflammatory cell infiltrate is frequently seen in OLDR. However, microscopic findings are generally considered nonspecific, and clinical information, including a temporal association with use of any systemic medications and demonstration of cause and effect relationship, are still required to establish the diagnosis of OLDR.

**DIF findings in perilesional tissue in OLDR show shaggy deposition of fibrin at the BMZ and IgM positive colloid or cytoid bodies, similar to OLP.**126 Unlike OLP, IIF testing may detect circulating antibodies directed to the basal cells with an annular fluorescent pattern called a “string of pearls” (arrows). This pattern is not present in OLP.21,28-30 IIF, indirect immunofluorescence; OLD, oral lichenoid drug reactions; OLP, oral lichen planus.

**Table II. Triggers of oral lichenoid drug reactions**21,28-30

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<thead>
<tr>
<th>Type of trigger</th>
<th>Specific examples</th>
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<tr>
<td>Antianxiety/psychotropic agents</td>
<td>Benzodiazepines</td>
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<td>Lithium</td>
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<td>Tricyclic antidepressants</td>
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<td>Isoniazid</td>
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<td>Anticonvulsants</td>
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<td>Antidiabetics</td>
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<td>Nonsteroidal anti-inflammatory drugs</td>
<td>Bismuth</td>
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<td>Dapsone</td>
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<td></td>
<td>Gold</td>
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<td></td>
<td>Penicillamine</td>
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<tr>
<td>Miscellaneous</td>
<td>Allopurinol</td>
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**Fig. 6. IIF for OLDR, showing circulating antibodies directed to the basal cells in an annular fluorescent pattern called a “string of pearls” (arrows). This pattern is not present in OLP.**
Table III. Triggers of oral lichenoid contact hypersensitivity reactions

<table>
<thead>
<tr>
<th>Type of trigger</th>
<th>Specific examples</th>
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<tbody>
<tr>
<td>Metals used in dental restorations</td>
<td>0.1% mercury chloride</td>
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<tr>
<td></td>
<td>1% ammoniated mercury</td>
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<td>Beryllium</td>
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<td>Bismuth</td>
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<td>Cobalt</td>
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<td>Copper</td>
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<td>Gold</td>
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<td></td>
<td>Metallic mercury</td>
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<td></td>
<td>Nickel</td>
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<td></td>
<td>Palladium</td>
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<td></td>
<td>Silver</td>
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<td></td>
<td>Tin</td>
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<tr>
<td>Other dental restorative materials</td>
<td>Acrylate compounds</td>
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<tr>
<td></td>
<td>Composite</td>
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<tr>
<td></td>
<td>Glass ionomer</td>
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<td></td>
<td>Porcelain</td>
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<tr>
<td>Flavoring agents</td>
<td>Balsam of Peru</td>
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<td></td>
<td>Cinnamon (cinnamic aldehyde)</td>
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<td></td>
<td>Eugenol</td>
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<td></td>
<td>Menthol</td>
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<td></td>
<td>Mint (mentha piperita)</td>
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<tr>
<td>Tartar control toothpaste</td>
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</table>

contact hypersensitivity reaction (OLCHR). These include metals, composites, and glass ionomers used in dental restorations (Table III). Amalgam restorations in direct contact with mucosa may cause lichenoid lesions, and are most commonly seen on the buccal mucosa and/or lateral border of tongue (Figure 7A). These lesions are similar in appearance to OLP, but typical unilateral distribution and contact with a restoration contrasts with the usual bilateral/multifocal clinical presentation of OLP without regard to restorations. Upon removal of the restoration, the lesions generally resolve. Flavering agents such as cinnamon, menthol, eugenol, and peppermint have also been associated with OLCHR, with lesions at the site of contact, also most often on the lateral border of the tongue or buccal mucosa (Figure 8A). Cinnamon or cinnamic aldehyde-containing products can induce a cinnamon stomatitis with characteristic histopathology. Resolution of lesions upon discontinuation of the offending agent is rapid.

Similar to OLDR, the microscopic features of OLCHR are not specific and overlap greatly with OLP. Amalgam associated OLCHR may exhibit lymphoid follicles (Figure 7B). Biopsies from cinnamon-induced OLCHR demonstrate marked epithelial acanthosis with elongated rete ridges and a mixed inflammatory infiltrate containing lymphocytes, plasma cells, histiocytes, and eosinophils (Figure 8B). Interface mucositis and characteristic deep perivascular infiltrates are seen (Figure 8C). The DIF may be similar to OLP, and the IIF testing is negative.

Lupus erythematosus. Both systemic and discoid (chronic cutaneous) lupus erythematosus (SLE/DLE) can affect the oral mucosa in 25% of cases. The oral presentation of SLE cannot be distinguished reliably from oral DLE. Oral lesions are typically distributed on the hard palate, buccal mucosa, and gingiva, and the lesions present with a central area of ulceration or atrophy, with erythema surrounded by white radiating striae (Figure 9A). Palatal lesions may be purely erythematous and patchy in distribution. The clinical presentation can mimic OLP, particularly atrophic or erosive OLP. However, unlike OLP, which usually presents with oral lesions alone, patients with oral lesions of lupus erythematosus typically exhibit concurrent cutaneous lesions and clinical indications of photosensitivity. Evidence of systemic inflammatory disease may also be encountered, a finding helpful in guiding the diagnostic process.

The histopathology of oral lupus erythematosus is highly variable and influenced by the anatomic site and the age of the lesion. The microscopic features are not specific and overlap with those found in OLP, OLDR, and OLCHR. The epithelium may exhibit either atrophy or pseudopitheliomatosus hyperplasia, hyperkeratosis with keratin plugging, and a thickened basement membrane showing reactivity with periodic acid Schiff stain. The lamina propria is often edematous, and the inflammatory cell infiltrate in the superficial lamina propria can range from paucicellular to lymphocyte-rich. Colloid bodies sometimes are present. Melanin incontinence may be seen adjacent to the epithelium. Superficial and deep perivascular inflammatory infiltrates are often present.

DIF of both SLE and DLE tissue samples shows granular or shaggy deposits of IgG, IgM, and/or C3 in the BMZ. These findings are helpful in differentiating lupus erythematosus from OLP. Immunoglobulin deposits are found in virtually all cases of SLE. DLE shows positivity on DIF in approximately 70% of the cases, and IIF results in DLE are usually negative.

Proliferative verrucous leukoplakia. Proliferative verrucous leukoplakia (PVL) is an unusual form of oral leukoplakia that can mimic OLP clinically and microscopically. The diagnosis of PVL is often made in retrospect, as this precancerous condition can be difficult to diagnose, particularly in its early stages. The lesions typically grow slowly over a few years to decades. The multifocal presentation of PVL, with propensity for gingiva, palate, tongue, and buccal mucosa, is a feature
common with OLP (Figures 10A and B). Ventral tongue and floor of mouth are uncommon sites affected by PVL. The lesions can vary in appearance, and include hyperkeratotic plaques, erythematous atrophic regions, and ulceration. Histopathologically, PVL typically shows hyperkeratosis associated with interface mucositis, resembling OLP (Figure 10C). However, the presence of a verrucous epithelial architectural change distinguishes PVL from OLP (Figures 10C and D). In addition, the PVL lesions often show basal cell expansion, nuclear crowding, and varying degrees of cellular atypia (Figures 10C and D). Of note, verrucous hyperplasia/hyperkeratosis has been found to show fibrinogen deposition at BMZ on DIF in approximately 42% of cases, and to show both fibrinogen and C3 deposition in approximately 3% of cases. Therefore, DIF cannot be used to distinguish OLP from PVL, and differentiation between these two diseases is based upon histopathological features. The overlapping clinical and histopathological features between OLP and PVL remain one of the greatest challenges in the diagnosis of OLP, especially in the initial stage of PVL, when the verrucous architectural change and/or the degree of cellular atypia are often mild.

Oral epithelial dysplasia. As emphasized previously, OLP tends to be characterized by symmetric multifocal clinical expression. Although oral epithelial dysplasia
usually presents as a solitary lesion with variable proportions of white change (leukoplakia), red change (erythroplakia), and ulceration (Figure 11A). Multifocal expression is well recognized, as seen, for example, in patients with advanced tobacco-related mucosal injury and in PVL. Oral epithelial dysplasia is at times associated with a band-like chronic inflammatory cell infiltrate in the superficial lamina propria which, when viewed with low-power microscopy, may offer substantial histopathologic mimicry of OLP. Such disease has been termed “lichenoid dysplasia” (Figures 11B and C). The incidence of lichenoid features in oral epithelial dysplasia and OSCC has been investigated in a recent study by Fitzpatrick et al., in which lichenoid features (e.g., band-like chronic inflammatory cell infiltrate, saw-tooth rete ridges, infiltration of the basal layer of the epithelium by lymphocytes [interface stomatitis], presence of colloid bodies, and basal cell degeneration) were found at least focally in 29% of the 352 dysplasia or OSCC cases. In the cases that showed lichenoid features, band-like inflammatory cell infiltrate and basal cell degeneration were the most frequent features encountered, accounting for 74% and 30%, respectively, of this group. The authors of this article acknowledged interobserver variability in the interpretation of histopathologic features as a limitation of the investigation.

Microscopic differentiation of epithelial dysplasia from OLP is based on recognition of cytologic atypia in squamous epithelial cells and identification of disturbance in the maturation pattern. However, discrimination of mild epithelial dysplasia with chronic interface mucositis from OLP with reactive cellular atypia can be challenging, requiring subjective assessment of ostensibly objective morphologic features. Evaluation of such factors as the maturation pattern and keratinocyte cytologic distortion are complicated by the impact of chronic interface mucositis on basal cell layer definition, on resolution of lower spinous cell layer maturation sequence, and on keratinocyte degenerative changes, with potential for close mimicry of cytologic atypia. As microscopic alterations supporting a diagnosis of mild epithelial dysplasia are largely restricted to the lower spinous and basal cell regions, the implications of an inflammatory process influencing the microscopic appearance of this zone are apparent. In this situation, the inflammatory cell infiltrates—typically mixed in epithelial dysplasia with lesser proportions of lymphocytes in favor of plasma cells and additional cell types—tend to contrast the lymphocyte predominance of infiltrates found in OLP.

Though a helpful distinction, such data cannot be taken as surrogates for assessment of the epithelial maturation status. Where clinical presentation is as an isolated lesion, a dysplastic disease process should be strongly suspected. The discriminatory value of clinical expression as multifocal disease process is somewhat more problematic, particularly in patients with a history of use of tobacco, and in patients where the clinical appearance of mucosal lesions falls short of a definitively lichenoid pattern. It is emphasized that DIF cannot assist in the differentiation between these two entities, as fibrinogen and/or C3 deposition at the BMZ on DIF is characteristic of OLP, and has been described in 43% of dysplasia or OSCC. We suggest that pathology reports detailing cases judged likely to represent OLP with significant reactive cellular atypia should include a comment...
acknowledging a level of pathologist uncertainty regarding the significance of observed maturational alterations. In such situations, a diagnosis of OLP should be considered provisional, with continuing patient follow-up warranted.

**Challenges in reaching a consensus on the microscopic diagnosis of OLP**

Definitive diagnosis of OLP is important because of implications for therapeutic management. However, many challenges exist in establishing microscopic diagnostic criteria for OLP. The problems and difficulties in making the OLP diagnosis based on histopathologic features alone is evidenced by studies showing inter- and intraobserver variability. This section discusses those challenges, and traces the history of 2 previously proposed OLP diagnostic criteria schemes, with comments on the criteria.

The first set of histopathologic criteria for diagnosis of OLP was published in 1978 by the WHO Collaborating Centre for Oral Precancerous Lesions. This seminal article is frequently referred to in the literature on OLP, although the substance of the article was focused on defining leukoplakia and related lesions. The 1978 WHO histopathologic criteria for OLP (summarized in Table IV) include the presence of either a hyperorthokeratin or a hyperparakeratin layer, with a comment that the degree and type of keratinization and a granular layer is influenced by the site of disease involvement. Epithelial thickness may vary, and saw-tooth rete pegs, indicated to be more common in cutaneous lichen planus, are seen less frequently in OLP. Civatte (colloid) bodies may be present in the basal cell layer, either in the epithelium or in the superficial lamina propria. “Liquefaction degeneration” of the basal cell

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Fig. 10. Clinical and histopathologic features of PVL in a 58-year-old non-smoking male. White, thickened plaques with irregular, rough surface change are noted on the gingiva of the mandible (A) and maxilla (B). The patient had other sites of involvement as well. C, Biopsy of (A) showed hyperorthokeratosis, a prominent granular cell layer, and a verrucoid epithelial architecture associated with interface mucositis. Absence of basal cell degeneration is noted (H&E stain, original magnification ×250). D, Biopsy of (B) revealed different histopathologic features, including a verrucous epithelial architecture with thickened, acanthotic rete ridges (H&E stain, original magnification ×250). Note the lack of inflammation compared with image C. Based on the clinical and histologic findings, the patient was given a working diagnosis of PVL. PVL, proliferative verrucous leukoplakia; H&E, hematoxylin and eosin.
layer and a narrow band of eosinophilic material in the BMZ are cited. A well-defined dense infiltrate comprised predominantly of lymphocytes is confined to the superficial lamina propria.19

In 2003, Van der Meij and van der Waal1 proposed modifications to the WHO criteria for OLP. These modifications were based upon prior studies that found both inter- and intraobserver variability in the histopathologic and clinical assessment of OLP.99 The modified histopathologic criteria include some WHO criteria, namely, a well-defined band-like zone of cellular infiltration confined to the superficial lamina propria consisting mainly of lymphocytes and “liquefaction degeneration” of the basal cells in the epithelium (Table IV). Confirmation of absence of epithelial dysplasia in establishing a diagnosis of OLP is explicitly cited. The authors suggested that pathologists use the term “histopathologically compatible with” when the microscopic features are less obvious. The criteria proposed in 2003 by van der Meij and van der Waal are referred to as the modified WHO diagnostic criteria.

Rad et al.138 compared the correlation between clinical and histopathologic diagnoses of OLP for both the WHO criteria19 and the 2003 modified WHO criteria.1 They found increased agreement between clinicians and pathologists in the diagnosis of OLP when the modified criteria of OLP were used compared with the WHO criteria.1 They also found that clinical assessment by oral medicine clinicians appeared to show less inter- and intraobserver variability compared with histopathologic assessment by pathologists when using the WHO criteria in making OLP diagnosis, a finding attributed to subjectivity in histopathologic interpretation.

The difficulty in reaching consensus on the microscopic diagnosis of OLP is partly due to the variations in the histopathologic features of OLP. The presence of hyperkeratosis in OLP, as mentioned in the 1978 WHO histopathologic criteria, is dependent on the site and type of OLP. Reticular, plaque, and papular types typically exhibit hyperkeratosis, but atrophic and erosive types may not. The mononuclear, mainly lymphocytic, band-like infiltrate in the superficial lamina propria is one of the most characteristic microscopic findings for OLP. However, macrophages and dendritic cell subsets are also present.39 Significant variation in the intensity of the inflammatory infiltrate also has been observed, and may be related to disease activity, as OLP is known to show a waxing and waning pattern clinically, and is influenced by therapeutic intervention before the time of biopsy.

In addition, the subsets of inflammatory cells in the infiltrate may be influenced by the clinical type (for example, reticular vs erosive), the anatomic site (buccal mucosa vs gingiva), or by another concomitant

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**Fig. 11. Clinical and histologic features of a case of epithelial dysplasia that mimics OLP.**

A, Scattered white plaques associated with redness and small ulcers were seen in the left ventral tongue of a 37-year-old male (image courtesy of Dr. Bryan Trump). B, The biopsy of this case showed a “lichenoid” appearance with a band-like inflammatory cell infiltrate (H&E stain, original magnification ×250). C, On higher magnification, hyperchromatic nuclei and significant cellular atypia are evident, but basal cell degeneration is not present (H&E stain, original magnification ×400). OLP, oral lichen planus; H&E, hematoxylin and eosin.
inflammatory process. In the erosive form of OLP, superimposition of neutrophil-rich inflammation related to the ulcer could alter the microscopic features. Similarly, the inflammatory cell infiltrate in gingival OLP lesions is often mixed with plasma cells because of gingivitis or periodontitis associated with dental plaque or calculus. A biopsy tissue demonstrating all typical features of OLP delineated in either the WHO or the modified WHO criteria would not represent a major challenge in histopathologic analysis. However, tissue samples that fulfill some but not all OLP diagnostic features require pathologists to consider mitigating factors, as previously delineated. Such assessment unavoidably involves subjectivity.

The fact that many of the OLP histopathologic diagnostic features are not specific for OLP can also influence accuracy of the diagnosis. The presence of an eosinophilic band at the BMZ, mentioned in the 1978 WHO criteria, does not appear to be a consistent microscopic finding. When identified in an appropriate histopathologic context, this band is generally considered supportive of a diagnosis of OLP. Liquefaction degeneration is one of the characteristic features of OLP, and was included in both the 1978 and the 2003 modified WHO diagnostic criteria. However, this feature is also not specific for OLP, as degeneration of the basal cells could be seen in biopsy materials from cGVHD, lupus erythematosus, OLDR, or OLCHR. The presence of Civatte (also known as colloid, hyaline, or cytoid) bodies, which represent anucleated remnants of epithelial cells, is a feature of OLP and supports the diagnosis, but also can be found in lupus erythematosus, OLDR, cGVHD, and other interface

### Table IV. Comparison of the WHO criteria, the modified WHO criteria, and the proposed criteria for OLP

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>Histopathologic criteria</th>
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<tr>
<td>Usually multiple, and often symmetric in distribution - White papular, reticular (lace-like network of slightly raised gray-white lines), annular, or plaque-type lesions - White lines radiating from the papules - Atrophic lesions with or without erosion - Bullae are rare</td>
<td>Orthokeratosis or parakeratosis Epithelial thickness varies, saw-tooth rete ridges sometimes seen Civatte bodies in the basal layer of the epithelium or superficial lamina propria A narrow band of eosinophilic material in the basement membrane Well-defined band-like zone of cellular infiltration that is confined to the superficial lamina propria, consisting mainly of lymphocytes Liquefaction degeneration in the basal cell layer</td>
</tr>
<tr>
<td>Bilateral, more or less symmetric lesions - Erosive, atrophic, bullous, and plaque-type lesions are only accepted as a subtype in the presence of reticular lesions elsewhere in the oral mucosa - Lace-like network of slightly raised gray-white lines (reticular pattern)</td>
<td>Well-defined, band-like zone of cellular infiltration consisting mainly of lymphocytes and confined to the superficial lamina propria Liquefaction degeneration in the basal cell layer Absence of epithelial dysplasia</td>
</tr>
<tr>
<td>White and red lesions exhibiting one or more of the following forms: - Reticular/papular - Atrophic (erythematous) - Erosive (ulcerative) - Plaque - Bullous</td>
<td>Band-like or patchy, predominately lymphocytic infiltrate in the lamina propria confined to the epithelium-lamina propria interface Basal cell liquefactive (hydropic) degeneration Lymphocytic exocytosis Absence of epithelial dysplasia Absence of verrucous epithelial architectural change</td>
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Lesions are not localized exclusively to the sites of smokeless tobacco placement Lesions are not localized exclusively adjacent to and in contact with dental restorations Lesion onset does not correlate with the start of a medication Lesion onset does not correlate with the use of cinnamon-containing products
dermatitis. The presence of saw-tooth rete pegs is considered supportive but not diagnostic of OLP.

On the other hand, current knowledge and research findings in OLP pathogenesis may help us to correlate the histopathologic features of OLP. Migration of lymphocytes into the overlying epithelium, or lymphocytic exocytosis, is often recognized in OLP and less so in some of the other oral lichenoid conditions, such as MMP. An explanation for this distinction may be that the immune response in MMP targets the adhesion molecules in the BMZ, while the CD8+ cytotoxic T cells in OLP attack the basal epithelial cells.

In addition, eosinophils have not been implicated in the pathogenesis of OLP, but could be found in MMP, and are often seen in contact hypersensitivity. Therefore, the presence of eosinophils suggests OLCHR, rather than OLP. Of note, the absence of eosinophils and migration of lymphocytes into the epithelium were not addressed in the 1978 WHO and 2003 modified WHO criteria.

PROPOSED DIAGNOSTIC CRITERIA

In an attempt to exclude oral lichenoid lesions that are obviously premalignant, and to make the patient group diagnosed as OLP a more homogeneous population of idiopathic OLP for future research, we propose a set of diagnostic criteria that include both clinical and histopathologic criteria (Table IV). We propose that a diagnosis of OLP requires fulfillment of all the clinical and the histopathologic criteria. A decision for diagnosis of OLP is best made by the clinician with access to patient clinical information, applying and incorporating an assessment of histopathologic findings provided by the pathologist. Where doubt may persist, active discussion between the clinician and pathologist is strongly encouraged. Conditions exhibiting chronic interface mucositis but otherwise failing to satisfy this set of diagnostic criteria should be designated by the clinician as oral lichenoid lesions, or the clinician should provide a descriptive diagnosis, such as “lichenoid mucositis” or “chronic mucositis with lichenoid features.”

Regarding the clinical criteria, we propose that OLP should present as multiple white or mixed white and red lesions exhibiting one or more of the 6 clinical forms (Table IV). However, the bullous form is the rarest among all the clinical forms, and a pure bullous form of OLP has never been reported. Therefore, when it does occur, we believe that this form would be seen in combination with one or more of the other clinical forms. If the clinical presentation is a pure bullous form, other vesiculobullous diseases (such as MMP and pemphigus vulgaris), but not OLP, should be considered.

Regarding the histopathologic criteria, we agree with van der Meij and van der Waal that confirming the absence of epithelial dysplasia is necessary before rendering a diagnosis of OLP. In addition, given the capacity for PVL to present clinical and histopathologic features similar to OLP, we also propose that absence of a verrucous epithelial architecture is necessary for a diagnosis of OLP. Significant verrucous architecture is identified by a papillary or verrucous configuration of the spinous cell layer accompanied by variable levels of mucosal surface corrugation. Of note, the absence of a verrucous epithelial architecture was not described in either the 1978 or the 2003 modified WHO criteria.

In some cases, OLCHR may show microscopic features that fulfill all the histopathologic criteria proposed here, and the cause-effect relationship with an inducing agent may not be clearly noted clinically. However, the presence of eosinophils or a finding of perivascular lymphoplasmacytic infiltrate in deep lamina propria generally excludes the diagnosis of OLP.

We recognize that adherence to this proposed guideline may exclude some OLP cases. However, we believe that implementation of the proposed diagnostic system will yield a patient population with enhanced disease homogeneity—composed of individuals more likely to have OLP than one of the several lichenoid mimics. This in turn will enhance the validity of future clinical and basic research studies that investigate OLP. These investigations are urgently needed to elucidate disease pathogenesis and malignant transformation potential, and to develop possible ancillary diagnostic protocols that could guide future efforts to enhance the diagnostic process.

It is also worth noting that even this set of strict criteria cannot exclude a few rare OLP mimics, such as LPP, CUS, or paraneoplastic pemphigus without DIF and IIF. We also cannot exclude the possibility of emerging PVL, as the characteristic verrucous architectural changes in epithelium may not yet be apparent, while the clinical and histopathologic features may fulfill our proposed criteria. Therefore, the diagnostic process of OLP should not be viewed as ending with an initial biopsy. Continued patient clinical follow-up evaluation to monitor therapeutic responses and any alterations in appearance of the lesions are necessary as part of the diagnostic process. Additional biopsy for DIF and/or histopathologic evaluation may be deemed necessary to reach a final diagnosis.

RECOMMENDATIONS TO CLINICIANS

As clinicopathologic correlation is required in the diagnosis of OLP, all patients considered for a
diagnosis of OLP are required to have an oral mucosal biopsy and histopathologic evaluation. A decision concerning the number of tissue samples to be obtained is guided by several considerations. Patients displaying mucosal alterations and lesion distribution fully consistent with OLP may only require a single tissue sample for histopathologic evaluation. As patterns of oral clinical presentation show increasing divergence from the typical clinical features of OLP, justification for multiple site sampling addressing areas with contrasting mucosal clinical features (re: ulceration, verrucous change) is correspondingly increased. This decision process is also influenced by pertinent aspects of the patient history, such as prior diagnosis of cutaneous LP and use of tobacco products. For cases of OLP showing presumably reactive cellular atypia microscopically (see “Oral epithelial dysplasia”), close clinical follow-up is necessary, as the true nature of the cellular atypia may reveal with time.

As specific clinical features are essential in the proposed diagnostic criteria, we recommend the use of a checklist (Table V) to assist the clinician in the identification and collection of data pertinent to the diagnosis of OLP. The completed checklist should be included with biopsy specimens submitted to oral pathologists for evaluation. This checklist is not intended to replace biopsy requisition forms employed by pathology laboratories, nor should it substitute for patient clinical assessment instruments used by clinicians. Rather it is intended that use of this checklist will work to assure that information pertinent to the diagnostic process is readily available to the pathologist. In this way, clinicopathologic correlation is supported, increasing the likelihood of achieving an accurate diagnosis.

**CONCLUSION**

The diagnosis of OLP is based on both clinical and histopathologic features. Therefore, certain clinical information is essential, and clinicians need to work closely with their pathologists to address questions and ambiguities that may arise. In an attempt to form a more homogeneous patient group of OLP patients for future research and to assure diagnostic accuracy in support of favorable patient care outcomes, a set of diagnostic criteria is proposed. Additional immunofluorescence studies may occasionally be needed, and long-term observation of disease behavior and progression is necessary, not only for treatment but also to refine or validate the initial diagnosis of OLP.

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**REFERENCES**


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