

## What Is Your Diagnosis?



A 60-year-old white man with a history of multiple actinic keratoses presented with a slightly erythematous-pink hyperkeratotic plaque on his lower lip of 3 years' duration that occasionally burned. The lesion was not pruritic and there were no lesions on the upper lip. He had been treated with cryotherapy and multiple courses of fluorouracil cream 0.5% without improvement.

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The authors report no conflict of interest.

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## The Diagnosis: Labial Lichen Planus

Lichen planus (LP) is a mucocutaneous autoimmune disorder in which cytotoxic T cells trigger apoptosis of epithelial cells, which leads to chronic inflammation.<sup>1</sup> Lesions commonly affect the hair, skin, and nails. Oral lichen planus (OLP), a variant of LP, clinically presents with lesions occurring most commonly on the buccal mucosa (90%), dorsum of the tongue (30%), and gingiva (13%).<sup>2</sup> It affects 0.1% to 4% of individuals<sup>2</sup> with a female to male ratio of 2 to 1.<sup>3</sup> The typical symptoms include pruritus, pain, burning sensation, and difficulty eating.<sup>1,2,4,5</sup> Labial lichen planus (LLP), which commonly presents in association with other OLP lesions (13%), rarely occurs as an isolated lesion and usually only affects the lower lip (Figure 1).<sup>6</sup> Although a limited number of cases of isolated LLP have been reported in the English-language literature,<sup>6</sup> some evidence suggests that isolated LLP is a precocious form of OLP.<sup>7</sup> Historically, isolated LLP affects individuals with a mean age (standard deviation) of 47.7 (7.8) years with a male to female ratio of 5 to 3.<sup>6</sup> Of the different forms of OLP described by Andreasen,<sup>8</sup> the most commonly described lesion in isolated LLP is atrophic-erosive, while hyperkeratotic and ulcerative lesions occasionally have been observed.<sup>6</sup>

### Associations With Infections

Oral lichen planus has been associated with many diseases or infections with *Helicobacter pylori*, herpes simplex virus type 1, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, human immunodeficiency virus, human papillomavirus, hepatitis C virus (HCV), Wilson disease, hemochromatosis, primary sclerosing cholangitis,  $\alpha_1$ -antitrypsin deficiency, and primary biliary cirrhosis.<sup>9</sup> At this time, the associations with the various herpesviruses (ie, herpes simplex virus type 1, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6) remain uncertain, while the association with human immunodeficiency virus has further implicated treatment with zidovudine and ketoconazole.<sup>9,10</sup> The relationship with HCV seems to be one of the most highly reported in the literature. Following an international consensus meeting held in France in March 2003, Lodi et al<sup>9</sup> emphasized this relationship. Lodi et al<sup>11</sup> also analyzed 25 studies in the literature based on a systematic review, which showed a statistically significant difference in the proportion of HCV-seropositive patients with OLP compared with controls (odds ratio, 4.80; 95% confidence interval, 3.25-7.09;  $P=.04$ ). Interestingly, when OLP/HCV-seropositive patients were

analyzed by geographic location, studies from the Mediterranean region showed an increased proportion, but the proportion was decreased by half in reports from northern Europe.<sup>11</sup> Ironically, the countries with the highest prevalence of HCV—Egypt and Nigeria—showed a negative or insignificant correlation between OLP and HCV seropositivity.<sup>9</sup> In multiple studies, Carrozzo et al<sup>12</sup> attributed this geographic variability to the increased incidence of HLA-DR6 in the Mediterranean population, primarily from Italy.<sup>12,13</sup> Of note, Petrucci et al<sup>6</sup> published a study in 2007 in which 5 of 10 (50%) patients with isolated LLP also were diagnosed with HCV. Unfortunately, there were no data on the ethnicity or HLA type of these patients.<sup>6</sup>

### Malignant Transformation

Oral lichen planus malignant transformation is a highly debated subject in the literature. Until the debate is resolved, this lesion is a cause for concern because transformation has been reported to occur in anywhere between 0% and 12.5% of patients.<sup>14</sup> However, when patients are followed for up to 20 years, a more commonly reported number for malignant transformation is 0.4% to 5%.<sup>1,15,16</sup>

Oral lichen planus lesions that most commonly undergo malignant transformation include the atrophic-erosive form and plaque forms.<sup>14</sup> It is important to consider malignant transformation in isolated LLP due to the aforementioned possibility of LLP as a precocious form of OLP. Following the international consensus meeting in March 2003, Lodi et al<sup>17</sup> also analyzed 3 large-scale retrospective studies and found that OLP progressed to cancer in fewer



**Figure 1.** A slightly erythematous-pink hyperkeratotic plaque on the lower lip that occasionally burned.

than 1.5% of patients followed for 4.5 to 7.5 years. Although these numbers may be incorrect due to the inclusion of patients with lichenoid reactions<sup>16,18</sup> versus true OLP, it is generally accepted that the rate of progression is higher than the general population, and the main debate is how often to screen patients with this premalignant lesion.

### Pathogenesis

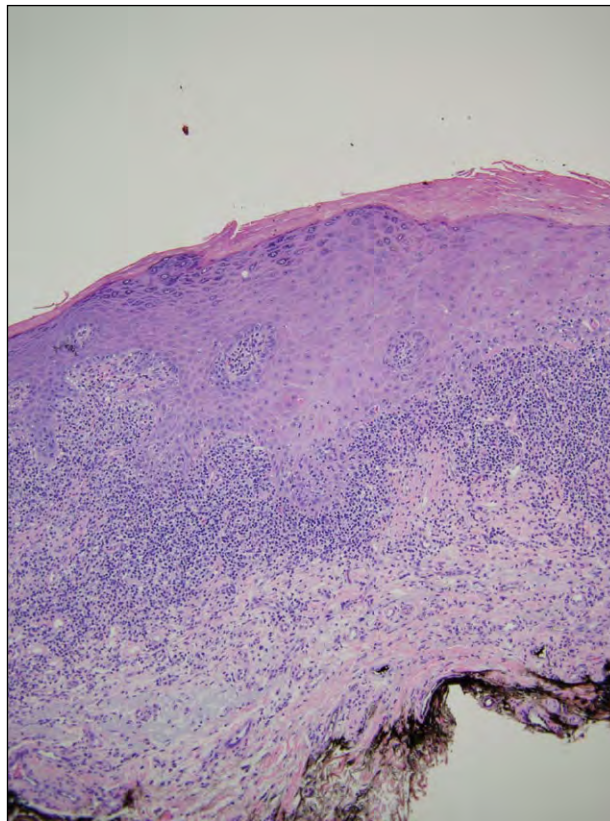
Currently, the exact pathogenesis of LLP/OLP is unknown; however, research suggests dysfunction associated with cellular immunity.<sup>9</sup> Increased numbers of Langerhans cells with upregulated class II major histocompatibility complex (MHC) antigens and keratinocyte expression of class II MHC antigens leads to CD4<sup>+</sup> T-cell activation. Although the origin of this antigen is unknown, it is hypothesized to be a self-peptide, which would make LLP/OLP a true autoimmune disease. In turn, the CD4<sup>+</sup>-activated T cells secrete helper T cells (T<sub>H</sub>1) including IL-2 and IFN- $\gamma$ . CD8<sup>+</sup> T cells may then be activated by IL-2 and IFN- $\gamma$  as well as by antigens presented by class I MHC on basal keratinocytes. Activated CD8<sup>+</sup> T cells lead to keratinocyte apoptosis through an unclear mechanism of action. Possibilities for the mechanism include CD8<sup>+</sup> T-cell secreted tumor necrosis factor  $\alpha$  binding to tumor necrosis factor  $\alpha$  receptor 1 on the surface of the keratinocytes; CD8<sup>+</sup> T-cell FasL (Fas ligand) binding of Fas on the keratinocyte surface; and CD8<sup>+</sup> T-cell secretion of granzyme B that is able to enter the keratinocytes through perforin-induced membrane pores. All of these mechanisms may lead to caspase activation and subsequent apoptosis.<sup>9</sup>

### Histology

Classic LP histologic features include orthokeratotic hyperkeratosis; wedge-shaped hypergranulosis related to the acrosyringium, which causes Wickham striae; and irregular acanthosis with sawtooth rete ridges.<sup>19</sup> Also, there is a bandlike lymphocytic infiltrate along the dermoepidermal junction (DEJ) with scattered apoptotic keratinocytes, melanin incontinence, and small clefts at the DEJ (Caspary-Joseph spaces). Although parakeratosis is not seen in classic LP, OLP can have parakeratosis along with plasma cells due to the mucosal location. If the lesion is ulcerated, the biopsy results typically show an ulcer with nonspecific findings but with classic LP histologic features at the periphery of the ulcer or erosion.<sup>19</sup> Figure 2 demonstrates histology results from a plaque on the lower lip, which demonstrates these pathologic findings.

### Differential Diagnosis

The differential diagnosis of LLP includes actinic cheilitis/squamous cell carcinoma (SCC), discoid



**Figure 2.** Shave biopsy results of the lower labial plaque showed hyperkeratosis, hypergranulosis, some squamatization of the basal layer, Civatte bodies, and a bandlike lichenoid infiltrate with some parakeratosis involving the mucosa (H&E, original magnification  $\times 10$ ).

lupus erythematosus (DLE), hypertrophic lupus erythematosus, contact allergic dermatitis, and lichenoid drug eruption.<sup>6,20,21</sup> Clinically, both LLP and actinic cheilitis/SCC can present with a hyperkeratotic plaque on the lower lip. Basilar cytologic atypia, crowding, and atypical mitoses that can be seen in actinic cheilitis as well as invasive atypical keratinocytes seen in SCC should not be seen in LLP and are helpful distinguishing features. It is noteworthy to mention that SCC has been found in existing lesions of both chronic lupus and LP lesions; therefore, careful scrutiny is required and any concerning areas should be represented on biopsy. The majority of oral DLE lesions are found on the buccal mucosa, followed by gingival mucosa, labial mucosa, and vermillion border. Discoid lupus erythematosus commonly presents with a vacuolar interface dermatitis, thickening of the basement membrane, and an inflammatory infiltrate affecting both the superficial and deep components.<sup>19</sup> It may present with a lichenoid dermatitis and may not display all classic features on the vermillion

border. Examination for other clinical findings and features for LP and lupus should be performed. Direct immunofluorescence also may be helpful. Historically, OLP does not commonly stain as frequently as oral DLE lesions. Labial lichen planus may show an irregular band of fibrinogen and granular IgG along the basement membrane. Discoid lupus erythematosus may show granular deposits of IgG, IgM, complement, and occasionally IgA along the basement membrane zone, and globular IgM deposits at the DEJ.<sup>21,22</sup> However, it often can be difficult to distinguish LLP and lupus erythematosus, even with the assistance of direct immunofluorescence, and some authors have proposed a new entity called mixed LP–lupus erythematosus disease.<sup>23</sup> Additionally, the presence of dental appliances containing mercury, copper, or gold can cause lichenoid oral lesions, which may have histologic findings similar to OLP and if present should first be ruled out as the cause of the concerning lesion. Although lichenoid drug eruptions rarely involve the mucosa, a lichenoid drug eruption could be suggested by recent changes or additions to the patient's medication list, especially nonsteroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors.<sup>1</sup>

### Treatment

In the treatment of isolated LLP, many classes of medications have been used including various topical and oral corticosteroids, antifungals, antimalarials, retinoids, immunomodulators, and immunosuppressants.<sup>6</sup> Although this list may seem extremely diverse, it is similar to how OLP has previously been treated. Additional treatments of OLP include intralesional corticosteroids, tacrolimus, hydroxychloroquine, methotrexate, thalidomide, metronidazole, cyclosporine, azathioprine, dapsone, enoxaparin, griseofulvin, interferon alfa, levamisole, and various biologic therapies including etanercept.<sup>5,24</sup>

### Conclusion

Labial lichen planus is an uncommon form of LP, but it should be included in the differential diagnosis for a hyperkeratotic plaque on the lip. It is a mimicker of actinic cheilitis, DLE, and malignancy. It can be differentiated by immunofluorescence and histologic examination. Failure to recognize LLP can result in unnecessary aggressive treatments of presumed actinic damage, which may ultimately worsen the condition. In addition, because OLP has been associated with HCV and malignant transformation, prompt recognition of the labial form of LP may help decrease morbidity.

*Acknowledgment*—We would like to thank Carlos Nousari, MD, from the Dermopath Diagnostics

Institute for Immunofluorescence, Pompano Beach, Florida, for his expertise in immunofluorescent staining patterns and for his review of this manuscript.

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