



Diagnosis and Management of Oral Lichenoid Reactions

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ABSTRACT Lichen planus is one of the most common mucocutaneous conditions seen in dental practice. A variety of other conditions known as lichenoid reactions can simulate lichen planus either clinically or histologically. This paper will discuss the more common lichenoid reactions seen in clinical practice and review the diagnosis and management of these conditions.

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Lichen planus is a well-known mucocutaneous disorder with well-defined clinical and histologic features. Lesions are typically keratotic (white), often in a striate or reticular pattern (**FIGURE 1**) that may be mixed with erythema (redness) that commonly affects the buccal mucosae and gingivae. Microscopically, lichen planus is characterized by hyperkeratotic epithelium, often with angular rete ridges (saw tooth). There is a band-like infiltrate of small lymphocytes just subjacent to the epithelium and the basal keratinocytes usually show “liquefactive degeneration.” (**FIGURE 2**).

It is now well-documented that other conditions can mimic lichen planus clinically and/or histologically, and this has led to the concept of lichenoid reaction. Dental restorative materials, especially amalgam, will produce lichenoid reaction as well as other allergens producing hypersensitivity reactions. Numerous systemic medications produce lichenoid drug reactions. Premalignant lesions may share clinical and/or histologic features with lichen planus. Other less common condi-

tions producing lichenoid reactions are graft versus host disease, lupus erythematosus, and chronic ulcerative stomatitis.

Further complicating the controversy is the fact that in most instances, lichen planus and lichenoid reaction cannot be distinguished by their histologic features alone. One of the most common lichenoid reactions is amalgam-associated lichenoid reaction, and a recent study concluded the uncertainty of the diagnostic histological differences.¹

It is also known that true lichen planus evolves through cycles of exacerbation and quiescence, and patients may actually have lichen planus, but depending on when and where the biopsy is taken, the histologic features may not confirm the diagnosis. Pathologists will use variable terminology such as “lichenoid mucositis,” “chronic mucositis with lichenoid features,” etc. This can be frustrating to the clinician and the patient since the patient is subjected to the time, discomfort, and expense of a surgical procedure that does not provide a definitive diagnosis. However, such a biopsy is useful because it does confirm and communicate that the patient has an inflammatory condition that has some but not all diagnostic



FIGURE 1. Characteristic clinical pattern of intraoral lichen planus.

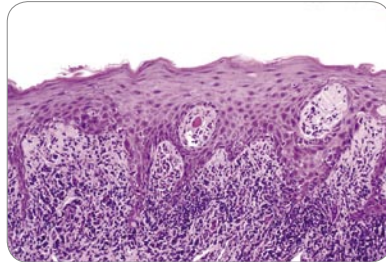


FIGURE 2. Characteristic histologic features of lichen planus showing angular rete ridges with basal cell degeneration and a band-like infiltrate of small lymphocytes.



FIGURE 3. Lichenoid reaction to amalgam.

features of lichen planus. Such lesions may represent lichen planus or lichenoid reaction, and the distinction is often based on the clinical features of the condition.

When a patient presents with lichenoid tissue change clinically, a biopsy should be submitted to board-certified oral pathologists, who, because of their advanced training in diagnosing changes indigenous to the oral cavity, would have the greatest likelihood of rendering an accurate and definitive diagnosis.² It should be noted that distinguishing lichen planus from lichenoid reaction should not rely on histologic features alone, but should be based on clinical correlation to include history, physical findings, and, occasionally, patch testing.

Lichenoid Reactions to Amalgam

Amalgam is the most common dental restorative material to elicit a chronic mucosal reaction similar to lichen planus. Lesions can be plaque-like or striate and may be erosive (**FIGURE 3**). Lesions tend to be persistent and only affect the mucosa in contact with the amalgam, most commonly posterior buccal mucosa, lateral tongue, and, occasionally, gingiva, if the amalgam is placed into the sulcus.

The reaction most likely represents a hypersensitivity reaction, most commonly to mercury. However, depending on the study design, the percent of patients who test positive by patch testing ranges from 6 percent to almost 80 percent.^{5,6} The better-designed studies show patch test reactivity to mercury or amalgam in the 70 percent range.^{5,7} Lack of reactivity may be due to false negative skin reactions or hypersensitivity to constituents other than

mercury. Sensitivity to other materials such as gold or palladium chloride is well-documented.⁵ Dermatologists or allergists would be the appropriate referral for patch testing if one suspects amalgam sensitivity. However, because the materials must be placed in solution, they have a limited shelf life and are therefore not readily available unless the referral office routinely tests for dental materials. However, offices familiar with patch testing will know the commercially available sources for patch testing constituents. They can be instructed to purchase the appropriate testing material for amalgam which is included in **TABLE 1**.

Lichenoid reactions to amalgam should be considered for isolated, persistent mucosal reactions of soft tissue in direct contact with amalgam. Patch testing to mercury can be considered, but it is important to remember that while a positive reaction confirms the diagnosis of hypersensitivity, many patients are nonreactive and a negative patch test does not preclude a diagnosis of amalgam hypersensitivity. One can fabricate a full-coverage mouth-guard, which should be worn as often as possible and re-evaluate the lesion for resolution. Otherwise, the amalgam should be removed and replaced with an alternative restoration. Resolution of lichenoid reactions to amalgam following replacement of the amalgam is also highly variable depending on study design and ranges from below 50 percent to 90 percent. Many studies also do not distinguish between resolution and significant improvement with amalgam removal. The best designed studies show a significant improvement/resolution to amalgam replacement in the

TABLE 1

Amalgam Metals Patch Test

1%	Copper sulfate solution
5%	Cupric nitrate
1%	Stannous chloride
0.01%	Mercury chloride
0.1%	Silver nitrate
5%	Zinc sulfate
5%	Amalgam

90 percent range.^{5,8} Some studies show a better response rate in patients who are patch test positive.⁸ For true lichenoid reaction to amalgam, only the amalgam contacting the lesion needs to be removed. Resolution can be prolonged, and one study showed a mean resolution of 6.4 months.⁸

Other Lichenoid Hypersensitivity Reactions

Besides amalgam, there are numerous other allergens capable of inducing hypersensitivity. One of the most common offenders seen in dental practice today is the flavoring agent cinnamon. Cinnamic aldehyde is widely distributed in various foods and drink, but reactions are more common with prolonged chronic use such as toothpaste, gum, or mints. Toothpaste hypersensitivity is seen most frequently with tartar control toothpaste and the most characteristic clinical presentation is desquamative gingivitis.³

The cinnamon in gum and mints

TABLE 2

Drugs Causing Lichenoid Reactions

Allopurinol
Amiphenazole
Amlodipine
Atorvastatin
Beta blockers
Bismuth
Captopril
Carbamazepine
Chloroquine
Chlorpropamide
Cyanamide
Dapsone
Enalapril
Erythromycin
Fenclofenac
Furosemide
Gabapentin (Neurontin)
Gold
Hydroxychloroquine
Interferon-Alpha-N1
Ketoconazole
Labetalol
Mepacrine
Mercury
Methyldopa
Metopromazine
NSAID
Oxyprenolol
Palladium
Para-amino salicylic acid
Penicillamine
Phenothiazines
Practolol
Propranolol
Pyrimethamine
Quinidine
Quinacrine
Sildenafil
Spirolactone
Streptomycin
Tetracycline
Thalidomide
Thiazides
Tolbutamide
Triprolidine
Zolof



FIGURE 4.



FIGURE 5.

dissolves in saliva and typically produces lesions on the cheek and lateral tongue (FIGURES 4-6). In fact, any lesions discovered on the buccal mucosa and ipsilateral tongue is highly suggestive of hypersensitivity. Reactions to allergens can be Type I hypersensitivity (anaphylactoid reactions) or Type IV (delayed T-cell mediated hypersensitivity). These reactions can produce any combination of red and white tissue change. Patients are usually symptomatic and complain of sensitivity, burning, or mild pain.

Because hypersensitivity reactions are nonspecific in their clinical presentation, a biopsy is often performed. The pattern of inflammation in many hypersensitivity reactions is remarkably lichenoid. While not definitively diagnostic, deep extension of the inflammatory infiltrate, presence of occasional eosinophils or particularly deep perivascular inflammation is very suggestive of hypersensitivity.⁴

Withdrawal of the allergen produces resolution of the clinical reaction.

Lichenoid Drug Reaction

A variety of medications have been documented to produce oral mucosal reactions that are similar clinically and microscopically to lichen planus.⁹⁻¹¹ A full list of drugs producing lichenoid reactions is presented in TABLE 2, but the most common offenders are the nonsteroidal anti-inflammatory drugs, angiotension-converting enzyme inhibitors, and gold salts. Lichenoid drug reactions can be identical to lichen planus but have a tendency to produce more full thickness ulceration and more commonly affect sites not frequently affected by lichen planus, such as ventral tongue (FIGURES 7-13). Lichenoid



FIGURE 6.

FIGURES 4-6. Eighteen-year-old white female with reactions on her lateral tongue and cheek to cinnamon-flavored gum.

drug reaction should be suspected when a new oral reaction follows the administration of a new medication. While there are some histologic and immunofluorescent findings that might suggest lichen planus or lichenoid drug reaction, these are not invariably present and biopsy often cannot distinguish between the two conditions.

The ultimate confirmation of lichenoid drug reaction is resolution of the condition following withdrawal of the drugs. Dentists should never withdraw a medication prescribed by another health care provider, but consultation with the prescriber will often lead to a trial of drug substitution.

Premalignant Lesions Producing Lichenoid Reactions

The most controversial and often confusing of the lichenoid lesions are the ones associated with premalignant lesions. As normal oral mucosa evolves to oral cancer, it progresses through a premalignant stage, which produces clinically detectable lesions. This tends to produce a color change to tissue, which can be a combination of white (leukoplakia) and/or red (erythroplakia). While these lesions



FIGURE 7.



FIGURE 8.



FIGURE 9.

FIGURES 7-9. Lichenoid drug reaction to azulfadine for the management of Crohn's disease.



FIGURE 10. Lichenoid reaction to gold salts for the management of rheumatoid arthritis.

are almost never striate, the pattern of redness and whiteness will have similar features to lichen planus (FIGURE 14). At the cellular level, the morphological cellular changes that characterize premalignancy are known as epithelial dysplasia. The further from normal the dysplastic cell evolves, the more foreign, and therefore antigenic, it becomes. Microscopically, dysplastic cells often induce an immune response. The immune cells are found just under the epithelium, often in a "band-like pattern," which bears a remarkable resemblance to lichen planus (FIGURE 15).

It is common for pathologists to misinterpret the immune reaction to dysplasia

as lichen planus. The resemblance microscopically between the body's immune reaction to dysplasia and true lichen planus has led some authorities to define the former as "lichenoid dysplasia."¹² Because lichenoid dysplasia has nothing to do with lichen planus, the author believes the use of the term adds only controversy and confusion to the debate on the malignant potential of lichen planus. However, it is imperative for pathologists who interpret oral mucosal biopsies to know that reactions to dysplasia will often show histologic features of lichen planus.

There are clearly premalignant lesions that occur orally that show some clinical as well as histological features of lichen planus. These are usually isolated white and/or red lesions that commonly affect the lateral or ventral tongue, or floor of the mouth. True lichen planus is almost always multifocal, and lateral/ventral tongue and floor of mouth are not common sites affected. If one were to biopsy a red and/or white isolated lesion of the lateral/ventral tongue or floor of mouth, and your pathologist renders a diagnosis of lichen planus, that diagnosis must be viewed

with the greatest caution as it most likely represents misinterpretation of dysplasia.

Other Rare Lichenoid Reactions

Several other conditions show clinical and/or histologic similarity to lichen planus.

Twenty to 70 percent of patients who survive allogeneic bone marrow or stem cell transplantation will develop graft versus host disease, which resembles lichen planus clinically and microscopically.¹³⁻¹⁴ The clinical history of transplantation, however, should provide the definitive diagnosis.

Patients with lupus erythematosus also have oral mucosal involvement that clinically and histologically resembles lichen planus. The clinical lesions are usually red and white with characteristic short striae oriented perpendicularly in the margin. While the microscopic features are lichenoid, there are microscopic features to distinguish lupus from lichen planus.¹⁵ Additionally, on direct immunofluorescent testing, lupus shows a deposition of immunoglobulin, usually IgG, at the basement membrane zone and lichen planus usually shows fibrinogen.¹⁶



FIGURE 11.



FIGURE 12.



FIGURE 13.

FIGURES 11-13. Lichenoid reaction to allopurinol for the management of gout.

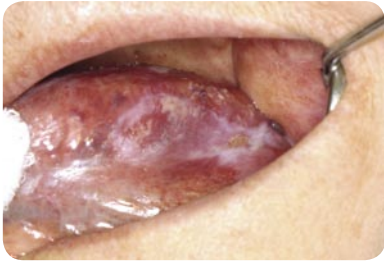


FIGURE 14. Premalignant lesion of lateral tongue with some features of lichen planus. Note lack of striae and the lack of multifocal involvement.

Lastly, chronic ulcerative stomatitis is a relatively new oral mucosal disorder that shows remarkably similar microscopic features to lichen planus. It can only be diagnosed by immunofluorescence because it has circulating as well as tissue bound antinuclear antibodies.¹⁷ Chronic ulcerative stomatitis is exceedingly rare.

Summary

A variety of conditions show clinical and/or histologic features of lichen planus. There are several pathologic conditions seen orally that are not always diagnosed by histologic features alone, but by clinico-pathologic correlation, suggesting that at times the clinical findings and medical/dental history are as important as the histologic features in determining the definitive diagnosis. The author believes this is true of lichen planus and lichenoid reactions. Biopsy, as a means of diagnosing lichen planus, remains the gold standard. Clinicians, at the same time, need to be aware that microscopic features that can definitively separate lichen planus from the various lichenoid reactions are not clearly defined and universally accepted. It is extremely important when performing a biopsy to provide the pathologist with the entire clinical history and accurate description of the clinical tissue change, including which site was chosen to biopsy. "Oral lesion" is not particularly helpful. It makes a significant difference to the pathologist to know that the lesion is a 1 cm white plaque on the ventral surface of the tongue versus a lesion from a patient with bilateral striate keratoses of the buccal mucosae with multifocal

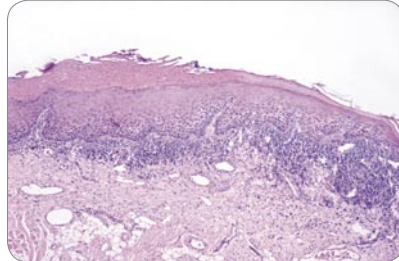


FIGURE 15. Photomicrograph depicting immune reaction to mildly dysplastic epithelium. Such features could easily be misinterpreted as lichen planus.

erosive and keratotic change of the gingiva.

Clinical correlation is extremely important. Because of the cyclical nature of lichen planus, it is not uncommon for the biopsy to fail to definitively confirm the diagnosis. However, the biopsy is invaluable if it can rule out other conditions such as pemphigus vulgaris, epithelial dysplasia, etc., and confirm the pathologic process is at least inflammatory. In such cases, it would be appropriate to use clinical judgment and, as long as the patient's clinical disease is compatible with lichen planus, the author would treat the patient for lichen planus. Conversely, if the biopsy is from a solitary white plaque on the lateral border of the tongue and a diagnosis of lichen planus is rendered, it is appropriate to question the pathologic diagnosis rendered and even ask for a second opinion by consultation.

The clinical features of this group of conditions are as important as the microscopic features. Any condition diagnosed as lichen planus, "lichenoid mucositis," "chronic mucositis with lichenoid features" etc. could represent any of the conditions discussed. If isolated to tissue contacting restorations, reaction to restorative materials, especially amalgam, should be considered. Patients should be questioned about oral allergens, particularly about products they use that may contain cinnamon. Any patient suspected of having lichen planus should be questioned about systemic medications. If a drug reaction is suspected, consultation with the prescriber can often lead to a trial of cessation or drug substitution. It is important to remember that premalignant lesions can sometimes

share clinical and histological features with lichen planus. The clinician's experience with various oral lesions is invaluable in ensuring a dysplastic lesion is not confused with lichen planus. ■■■■

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