



Lichenoid dysplasia – A historical overview and current debates

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Abstract

Oral lichen planus and oral lichenoid mucositis are the two most common lichenoid lesions of the oral cavity. Oral lichen planus is classified as a potentially malignant condition by the World Health Organization, and lichenoid mucositis has also been shown to have malignant potential. However, some argue that lichen planus or lichenoid mucositis is only premalignant when dysplasia has developed in these lesions and that many cases of lichen planus or lichenoid mucositis with cancer development were in fact either a lichenoid lesion with dysplasia or a primary dysplasia misdiagnosed as oral lichen planus or lichenoid mucositis due to the coexistence of lichenoid features. Here, we summarize what is known about the risk of malignant transformation of these lesions and discuss the ongoing controversies surrounding the diagnostic criteria.

Introduction

Lichenoid lesions (as a histological description) refer to lesions characterized by a band-like zone of lymphohistiocytic infiltrate at the epithelial-stromal interface. Oral lichen planus (OLP) and oral lichenoid mucositis (OLM) are the two most common lichenoid lesions in the oral cavity. Differentiation of the two can be impossible both clinically and histologically. Although the current belief is that clinical information, such as bilateral or multiple presentations and no identifiable etiology, is required to make a diagnosis of OLP, such information is frequently not provided on a pathology requisition. When faced with a lichenoid lesion, pathologists will often make a diagnosis of OLP. Classifying lichenoid lesions as OLP, in the absence of this information, could cause the incidence of this diagnosis to be inflated. The differentiation of the two diseases is critical for management. OLP is “idiopathic” and chronic, requiring long-term management, whereas OLM is often caused by identifiable etiologies, such as topical allergens (e.g., toothpaste, chewing gums, food or flavor allergens, and dental filling materials),

medications, and systemic diseases (e.g., chronic liver disease and thyroid diseases). Removal of these etiologies should result in remission of the disease.

OLP is classified as a premalignant condition by the World Health Organization (WHO).^[1] However, this association is controversial. The reported rates of malignant transformation of OLP and OLM in the literature range from 0.3% to 14.3%, with an overall average rate of 1.1%, as cited in a recent meta-analysis of 57 studies.^[2] When taking into account only studies employing the 2003 Modified WHO histopathologic criteria for OLP^[3] in which absence of epithelial dysplasia is required for a diagnosis of OLP, the average rate was lower, at 0.9%.

Inadequate documentation, variability in inclusion criteria, and a lack of universally accepted diagnostic criteria contribute to the ongoing debate.^[4] Other oral diseases may also present with clinical and histological features similar to those of OLP; for example, dysplasia or oral squamous cell carcinoma (OSCC) may present with microscopic lichenoid features.^[5] Some argue that it is not OLP that is potentially malignant, but rather “lichenoid

dysplasia (LD)” – lesions presenting with dysplastic surface epithelium overlying a band-like zone of lymphocytic infiltrate characteristic of OLP.^[6,7] The aim of this review is to summarize what is known about the risk of malignant transformation of OLP and to discuss the ongoing controversies surrounding the diagnostic criteria of LD.

Lichenoid Dysplasia: A Historical Overview

The malignant potential of OLP was a topic of considerable controversy when this designation was first proposed and continues to fuel debate today. In 1978, Krutchkoff *et al.*^[6] investigated the contention that OLP has a potential for malignant transformation by re-examining 223 cases of OLP reported to have progressed to cancer. They found that many of the reports omitted information regarding prior exposure to carcinogens or did not contain enough information to support a diagnosis of OLP. They raised the possibility that the lesions diagnosed as OLP may have been primarily dysplasia but presented with a lichenoid appearance. Thus, the malignant progression of these dysplastic lesions may have resulted in the mistaken impression that OLP is a premalignant condition.^[8] To reduce diagnostic errors, Krutchkoff and Eisenberg^[9] proposed a histopathologic subclassification system for lichenoid lesions and coined the term “LD.” They defined this entity as a lichenoid lesion with the additive presence of two or more histologic features of dysplasia in the overlying epithelium.^[10] They advised that allegations of malignant transformation of OLP should be examined critically, to ensure that the initial diagnosis precludes dysplasia. In 1989, Lovas *et al.*^[10] conducted a case study of three patients with OLP which progressed malignantly. In retrospect, these cases did not present with the clinical features typical of OLP, and after revisiting the initial diagnoses, two cases were deemed LD. They concluded that cases of malignantly transformed OLP were likely dysplastic from the onset and only simulated OLP clinically and histopathologically.

Molecular Studies Supporting the Premalignant Potential of Lichenoid Dysplasia

However, a question remains: Are the subtle dysplastic changes in these lesions reflective of true cellular and architectural changes or are they reactive, as a response to the lymphocytic infiltrate and inflammatory process occurring in OLP?^[10,11] As a result, clinicians and pathologists may be inclined to ignore or downplay the dysplasia in the assumption that the lesion is inflammatory or reactive in nature. To investigate whether dysplasia seen within a lichenoid lesion is a sign of malignant risk, Zhang *et al.*^[11] studied changes in LD through microsatellite analysis. The study analyzed the frequency of the loss of heterozygosity (LOH) in chromosomal regions that contain key tumor suppressor genes in LD compared to that in epithelial dysplasia without lichenoid features. They found that the frequency of LOH in LD did not differ significantly from that of dysplasia without lichenoid features. LOH at any of the

chromosomal loci examined was observed in 54% of mildly dysplastic lichenoid lesions, 53% of moderately dysplastic lichenoid lesions, and 86% of LD with severe dysplasia or CIS, compared to 40%, 46%, and 81% of lesions with the same degree of dysplasia and no lichenoid features.^[11] In contrast, LOH was found in only 6% of OLP lesions.^[12] Thus, they concluded that epithelial dysplasia of any degree is a risk factor for malignant transformation and should not be dismissed as reactive when an inflammatory infiltrate is present.

This finding is supported by Rock *et al.*,^[13] who compared both the frequency and the time to malignant transformation in LD compared to that of dysplasia without lichenoid features. These results showed that a diagnosis of dysplasia, regardless of whether lichenoid changes were present, was significantly associated with progression. Not surprisingly, the degree of dysplasia was associated with progression: Lesions with moderate dysplasia were 2.3 times more likely to progress when compared to those with mild dysplasia. However, interestingly, there was no significant difference in the proportion of malignant progression of LD compared to that of dysplasia, and time to progression did not differ between the groups.^[13]

Kim *et al.*^[14] used chromosomal *in situ* hybridization to assess the degree of genetic instability in OLP and LD. They found that there was an increase in the number of cells exhibiting a loss of genetic material in chromosome 9 in LD that progressed to OSCC. They concluded that LD should be considered as having a high risk of malignant transformation and suggested that the monosomy of chromosome 9 may play a role in malignant progression.^[14]

Lichenoid Dysplasia: A Distinct Entity or Part of the OLP Spectrum?

Two questions arise:

1. Does epithelial dysplasia in OLP represent an entity separate from OLP or do these lesions represent an early phase of OLP malignant transformation?
2. How do these lesions fit within the diagnostic term “LD?”

When the term LD was first introduced, it was categorized as a distinct histopathologic entity, rather than as part of the natural behavior of other essentially benign processes.^[9] According to Eisenberg,^[15] the sharp distinction between LD and OLP resides in the presence of cellular atypia in the former and is indicative of malignant potential. For a diagnosis of OLP, the author proposes that normal epithelial cytomorphology, maturation, and architecture are required and assert that there is no conclusive evidence to support the belief that OLP possesses inherent malignant potential.^[15]

However, other authors assert that the existence of dysplasia in OLP is conceivable.^[4,11,16-18] To clarify whether LD is a step along the linear progression from OLP to malignancy, Czerninski *et al.*^[19] compared clinical characteristics of LD with that of oral epithelial dysplasia (OED) and OLP/OLM. They found that clinical characteristics of LD were more closely aligned to the OLP/OLM group, compared to the epithelial dysplasia group.

They concluded that LD should be considered part of the OLP disorder spectrum.^[19] However, the scientific community has not reached a consensus on this subject.

Pathogenesis

Differences in the pathogenesis of LD and OLP have also been highlighted in the literature. Although both lesions present with a striking, band-like zone of cellular infiltrate, the composition of this inflammatory infiltrate may vary. In OLP, this infiltrate is composed largely of T-lymphocytes, believed to be targeting antigenically altered basal cell surfaces.^[15] In epithelial dysplasia, the infiltrate is typically mixed, often with plasma cells, and a lesser proportion of lymphocytes.^[5] Some authors postulate that this mixed infiltrate is characteristic of lesions with epithelial dysplasia and is a phenomenon associated with a carcinogenic event and thus has an origin that is different from the origin of the infiltrate observed in OLP.^[20,21]

Lichenoid Lesions and Dysplasia: The Chicken or the Egg?

The coexistence of dysplasia and lichenoid reactions is common. Patil *et al.*^[16] investigated the prevalence of LD in previously reported cases of OLP, OLM, and OED. They histologically reevaluated 70 cases of OLP/OLM and 95 OED; dysplasia was observed in 11 of the 70 OLP/OLM cases (11.6%), and lichenoid features were noted in 22 of the 95 OED case (23.2%).^[16] Similarly, Fitzpatrick *et al.*^[22] reviewed 352 cases of dysplasia, carcinoma *in situ*, and OSCC for histopathologic characteristics of lichenoid mucositis and found that 29% of all cases exhibited three or more lichenoid features.^[22] These studies show that lichenoid features may be found in epithelial dysplasia, and epithelial dysplasia can be found in OLP, warranting careful examination of lichenoid lesions for atypia or dysplasia.

One major question in the debate of the entity is whether the presence of dysplasia is a primary event (primary dysplasia misdiagnosed as OLP/OLM) or a secondary event (OLP/OLM

developed dysplasia). Sanketh *et al.*^[4] proposed that OLP with dysplasia represents a lesion that manifests OLP clinically (bilateral presentation and reticular striae) and dysplasia histopathologically. This is separate from LD, in which they consider to be synonymous with OED. This view is supported by a position paper published in 2005 by Lodi *et al.*,^[17] who propose that LD may represent two groups of lesions: those that resemble OLP clinically and display dysplasia histologically; and dysplastic lesions with lichenoid features at the histological level and clinical features that do not resemble classic OLP (unilateral distribution and/or absence of reticulae). They hypothesize that the former could represent an early stage of the malignant transformation in OLP. Raj *et al.*^[23] have proposed that there are two subcategories of OLP/OLM with dysplasia: One in which the lichenoid features are primary and dysplasia is secondary [Figure 1A] and the other where dysplasia is primary and the lichenoid infiltrate is secondary [Figure 1B]. They theorize that if the basal cell layer is intact, the lesion is more likely to represent a primary dysplasia, with the subepithelial infiltrate being a reactionary change to the dysplasia. If the lesion presents with basal cell liquefactive degeneration, the diagnosis is more likely OLP/OLM, though clinicopathological correlation is also needed for the final diagnosis.^[23] However, to date, no research has been conducted to quantify this stratification. Further research is needed to clarify whether the LD entity refers only to epithelial dysplasia with lichenoid features or if it encompasses true OLP lesions manifesting with dysplasia.

Is malignant Risk an Intrinsic Property of Lichenoid Lesions?

The possible molecular mechanisms involved in malignant transformation also require further study. Chronic inflammation has been associated with a variety of cancers^[24] and the presence of infiltrating immune cells has been reported as a risk factor for cancer development in inflammatory conditions such as ulcerative colitis, atrophic gastritis, and chronic obstructive pulmonary disease.^[25,26] The presence of reactive oxygen species

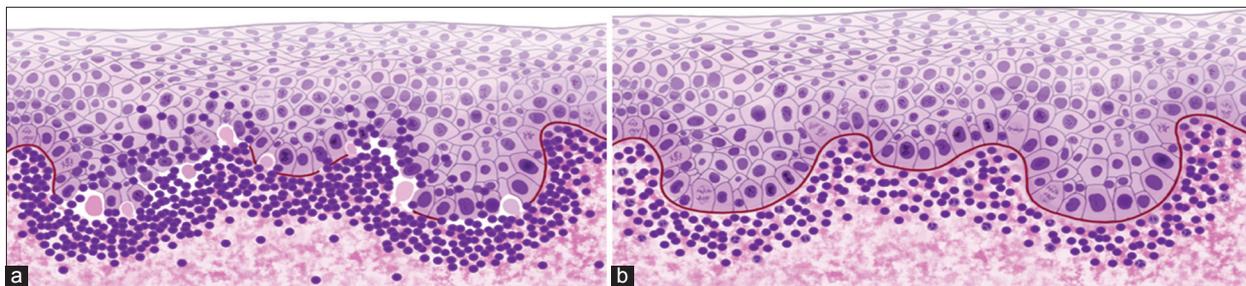


Figure 1: (a and b) Proposed subcategories of oral lichen planus/lichenoid mucositis with dysplasia (lichenoid dysplasia). (a) One in which the lichenoid features are primary and dysplasia is secondary and (b) the other where dysplasia is primary and the lichenoid infiltrate is secondary. The intact basal cell layer (b) is more likely to represent a primary dysplasia, with the subepithelial inflammation being a reactionary change to the dysplasia. If the lesion presents with basal cell degeneration (a), the diagnosis is more likely oral lichen planus (OLP) in nature, though clinicopathological correlation is also needed for the final diagnosis. However, to date, no research has been conducted to quantify this stratification. Further research is needed to clarify whether the lichenoid dysplasia entity refers only to epithelial dysplasia with lichenoid features, or if it encompasses true OLP lesions manifesting with dysplasia.

resulting from these inflammatory cells acts as a mutagenic agent and influences key cell cycle regulatory mechanisms.^[25] In OLP, an immune response comprised mainly of T-lymphocytes which is mounted against the basal epithelial cells, though increased Langerhans and mast cell density are also seen.^[27] It is unknown whether lichenoid inflammation drives malignant transformation or if the inflammation is an immune response to the atypical oral epithelium.^[28] However, some believe that the lymphocytic infiltrate in LD represents a cell-mediated immune response provoked by the oncogenic epithelial alteration in dysplasia, rather than by the surface of the essentially benign epithelial basal cells, as is the case in OLP.^[10,15] Further research investigating the immune microenvironment of LD may lend insight into the risk of malignant transformation of these lesions and clarify the underlying biological mechanisms of such transformation.

Conclusion

The term “LD” continues to elicit debate within the scientific community - is this a separate entity or an early stage in the malignant transformation of OLP? Regardless of this controversy, epithelial dysplasia is a sign of malignant risk, independent of lichenoid changes. Such results suggest that caution should be used when discounting dysplasia as being merely a reactive condition in lichenoid lesions. Clinicians should not ignore dysplasia on a biopsy even if they believe that the patient has presented clinically with OLP. Further research is needed to aid in the separation between OLP/OLM and LD, as each entity requires different management and has a unique prognosis. Further research is needed to further clarify the concept of LD and advance our current knowledge regarding the malignant potential of OLP and OLM.

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