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**Original Research**

# ASSESSMENT OF EPITHELIAL DYSPLASIA AND MALIGNANT TRANSFORMATION IN ORAL LICHENOID LESIONS – A SYSTEMATIC REVIEW

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ABSTRACT

**Aim and objectives:** The article aims a systematic review on malignant transformation of oral lichen planus ,lichenoid lesions as well as those lichenoid lesions with dysplastic features in the clinical and histopathological diagnosis. **Study design :** A review of the international literature was performed to summarize clinicopathological features of oral lichenoid lesions with dysplasia in initial diagnosis progressing to malignancy .**Results:** A total of 27 studies were evaluated to assess the malignancy progression in OLP, OLL and OLD. The average rate of malignant transformation in OLP ranges from 0.07 to 6.57%.The survey of the literature shows that no particular risk groups can be identified. However, OLD exhibit significant risk of malignancy followed by OLL and OLP. **Conclusion:** malignant transformation in oral lichenoid lesions is still a controversy. Only retrospective studies are available till date. Long term multicentre, longitudinal studies must be carried out to assess the progression of dysplasia as well as development of malignancy in those lesions.

## INTRODUCTION

Lichen planus is a common chronic immunologically mediated mucocutaneous disease in which the clinical presentation can vary from keratotic to ulcerative or bullous forms. It is believed to result from an abnormal T-cell-mediated immune response in which basal epithelial cells are recognized as foreign because of changes in the antigenicity of their cell surface.[1] Most of these lesions are benign and respond well to treatment. Oral lichenoid lesions or reactions (OLLs/OLRs) are clinical and histological contemporaries of the classical oral lichen planus (OLP), often associated with a known identifiable inciting factor. The scale of differentiation between the two groups is the association of the former with known inciting factors, which when identified and eliminated, often cause a regression of the lesion. This may not always be so and the differentiation then becomes more difficult. It is well established in literature that the differences between the two groups are almost non-existent and the lesions may be considered subtle variations of the same disease entity, oral lichenoid conditions.[2] However, malignant transformation has been noticed in very few cases of erosive lichen planus as well as that of oral lichenoid lesions.

Certain authors believe that the malignant potential may be attributed to an initial misdiagnosis of coexistent epithelial dysplasia associated with the lesion. There is lack of adequate confirmatory studies regarding this. OLP and epithelial dysplasia are entirely different entities requiring different management modalities. Early intervention is critically essential for good prognosis of epithelial dysplasia.[3]

Krutchkoff and Eisenberg et al in 1985 defined an entity known as lichenoid dysplasia to denote dysplastic features in lesions with lichenoid histomorphology.[4] This term does not imply the presence of dysplastic epithelial changes in lichen planus. Oral lichenoid dysplasia (OLD) is a series of chronic inflammatory process with an autoimmune base that affects epithelium of oral mucosa. In OLP, lichenoid infiltrate represents cell-mediated

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immune response provoked by different antigens, whereas in OLD, lichenoid infiltrate represents immune surveillance mechanism against atypical epithelial cells. OLD is clinically diagnosed as oral lichen planus(OLP) or oral lichenoid reaction(OLR) but have histological features of dysplasia.[3] Dysplastic changes should treat as developing malignant conditions.

OLP, OLL as well as OLD have potential to differentiate into malignancy, and this review aims to explore the malignant potential of each of these lesions. In the light of these findings, the relevance of adequate follow up for these groups of patients as well as modifications in the treatment regimes is outlined.

## METHODS

The review of the literature was carried out using the Pubmed database, limiting the search to references from January 2000 through November 2016. Only full text articles with English translation were selected. Case reports were excluded. In this study, the initial screenings key words were “oral lichen planus”, "lichenoid dysplasia", "oral lichenoid reactions" and “malignant transformation” in various combinations.

MesH term using "oral lichen planus" and "malignant transformation" yielded 137 articles, of which 23 were found to be significant. When adding themesH terms “oral lichenoid lesions" and " lichenoid dysplasia" 57 more articles were obtained, but only 2 studies considered the progression of malignancy in OLP and OLL simultaneously whereas 2 studies compared OLP, OLL and OLD with respect to its malignant potential. The abstracts of these articles were retrieved and examined thoroughly. The search strategy also included cross checking of the reference lists of the included articles.

## RESULTS

Of the 23 studies of malignancy in OLP patients, all were retrospective in nature.[5-27] The range of malignant transformation rate from studies advocating to have included OLP cases alone was 0.07 to 6.57%. At least one patient in each of the study group had developed malignancy. Majority of the studies used modified WHO criteria to sort out OLP patients and cases initially with dysplastic changes were excluded in most of the studies, except five authors.[5,14,17,21,22] In one study 3 patients with clinical diagnosis of OLP developed OSCC within 6 months of diagnosis indicating a misdiagnosed dysplastic change initially.[13] In studies where dysplasia cases were included in the initial sample, malignant transformation was higher in dysplasia cases. Malignant transformation rate was higher in female patients, especially with erosive pattern. One study reported malignant change in reticular OLP.[10] Most commonly encountered malignancy was OSCC in most cases where one reported development of verrucous carcinoma[18]. In majority of the cases malignant transformation occurred at the site of erosive lichen planus were as sites elsewhere showed carcinomatous change in one study.[15] The most common site of malignancy was tongue followed by buccal mucosa and floor of mouth. Definite female prediliction was observed in almost all studies.

In the 4 studies where malignant potential of OLP and OLL were compared, OLL lesions were found to have significantly high malignant potential compared to OLP.[28-31] One study evaluated similarity of OLD with ED and OLP / OLR and concluded that LD is more closely related to OLP/OLR rather than ED. Sex and smoking were significantly associated with the severity of the diagnosis. Mucosal lesions that were ulcerative and those that were located at the tongue and floor of the mouth showed a higher degree of dysplasia or were diagnosed as oral squamous cell carcinoma.

## DISCUSSION

OLP is an immune mediated disease of unknown etiology characterized by persistent chronic inflammation of varying severity that can fluctuate between periods of exacerbation and remission. Officially, the World Health Organization (WHO) classifies OLP as a “potentially malignant disorder” and suggests that OLP patients should be under close monitoring.[32] The risk of malignant transformation of OLP is real, but not high. A number of clinical as well as microscopic mimics of OLP exist making diagnosis challenging at times. This article highlights the inherent malignant nature of OLP. The results reveal that even after excluding dysplastic cases in the inclusion criteria, malignant change was noticed in all the studies. This points towards the innate malignant potential of OLP. The average rate of malignant transformation obtained closely matches with the results of other reviews.[33,34] The most common malignant change was oral squamous cellcarcinoma and the demographic profile resembles that of OLP like female sex and older age group. The common site of malignancy was tongue even though that of OLP is buccal mucosa.

Regarding the clinical subtype of OLP turning to malignancy, erosive or atrophic form was considered at

| Author,Year | Country,sample size | Design | Dysplasia in OLP | Malignant transformation | Mean follow up |
|---|---|---|---|---|---|
| Irani S[5], 2016 | Iran, 112 pts | retrospective | Dysplastic changes were found in 12 samples | One (0.8%) | After 3 years |
| Lauritano D[6] 2016 | Italy, 87 pts | retrospective | NA | one (1.2 %). | After 5 years |
| Budimir V[7], 2014 | Croatia, 563 pts | retrospective | No dysplasia on initial biopsies | Four (0.7% ) | After 7.6 years |
| Gümrü B[8]. 2013 | Turkey, 370 patients | retrospective | NA | One (0.27%) | After 2 years |
| Bardellini E,[9] 2013 | Italy, 204 pts | retrospective | NA | Two (0.98%) | After mean 50 mos |
| Tovaru S[10], 2013 | Romania, 633pts | retrospective | No dysplasia on initial biopsies | Six (0.95%) | NA total follow up of 20 years |
| Shen ZY[11],2012 | China, 518 cases | retrospective | Dysplastic cases were excluded | Five (0.96%) | NA |
| Kaplan I[12],2012 | Israel, 171 | retrospective | No cases of dysplasia was mentioned | Six ( 3.5%) | Mean 4.3 years, 1 to 16 years |
| Bermejo-Fenoll A[13], 2010 | Spain.550 patients | retrospective | three cases were excluded due to MT within 6 mos | Five (0.9 %) | After 20.8 mos to 10.8 years |
| Thongprasom K[14], 2010 | Thailand, 543 pts | retrospective | Nine cases (1.7%) showed dysplasia, | one (0.2%) | |
| Torrente-Castells E[15],2010 | Spain, 65 cases. | retrospective | Dysplastic cases were not included | Two (3.1%), | mean follow-up 18.2 months |
| Fang M[16], 2009 | West China, 2,119 patients | retrospective | NA | Twenty three, MTR 1.1%. | 16 months (range, 1 to 41 months). |
| Pakfetrat A[17],2009 | Iran , 420 patients | retrospective | dysplasia in 7.1% of subjects and All malignant transformations were in cases with mild dysplasia in their first biopsies. | three (0.07%). | NA |
| Carbone M[18], 2009 | Italy, 808 | retrospective | No dysplasia initially | Fifteen (1.85%) | Follow-up ranged from 6 to 204 months in our study population after mean 52.33 months |
| Zhang JH[19] 2007 | China, 724 | retrospective | No dysplasia initially | Fifteen (2.07%). | mean 21 months. |
| Ingafou M[20], 2006 | Britain, 690 pts | retrospective | NA | Thirteen 1.9% | median 35 months |
| Bornstein MM[21], 2006 | Switzerland 145 patients | retrospective | In 3 of these cases, dysplasia was present at the initial diagnosis | Four (2.84%); if the 3 patients with initial dysplasia are excluded, the rate drops to 0.71%. | NA |

TABLE 1: MALIGNANT TRANSFORMATION OF ORAL LICHEN PLANUS

| Author | Study design | Sample size | Mean follow up | Malignant transformation | Results |
|---|---|---|---|---|---|
| Casparis S[28] 2015 | 10-year retrospective study assessed malignant transformation of oral lichen planus (OLP) , dysplasia associated with LP and oral lichenoid lesion (OLL) | 542 patients | | 12 patients malignant transformation to OSCC within an average period of. 1.58 years | The malignant transformation rate (MTR) was higher for OLL (4.4%) than OLP (1.2%). |
| Mares S[29] 2013 | Potentially malignant character of oral lichen planus and lichenoid lesions | 32 patients ,8 were diagnosed with OLP and 24 with LL. | mean follow-up was 164 months | | Malignant transformations were observed only in the LL group |
| van der Meij EH[30] 2007 | a prospective five-year follow-up study of with oral lichen planus and oral lichenoid lesions to assess the malignant potential | 192 patients, 67 patients diagnosed with OLP and 125 patients with OLL, | mean, 55.9 months | 4 out of 192 patients, two men and two women, developed a squamous cell carcinoma | All malignant transformations occurred in the OLL group. The malignant transformation of the OLL group,0.71% per yr |
| van der Meij EH[31] 2003 | the possible premalignant character of OLP and oral lichenoid lesions (OLL) of a prospectively | 173 patients, 62 patients diagnosed with OLP and 111 patients with OLL, , | mean, 31.9 months | three of 173 patients (1.7%), 2 men and 1 woman, developed squamous cell carcinomas | All malignant transformations occurred in the OLL group. The annual malignant transformation rate, 0.65% per year. |

TABLE 2: COMPARISON OF MALIGNANT POTENTIAL IN OLP, OLL AND OLD

the primary risk. But certain authors' demonstrated development of malignancy from reticular lichen planus also in which there was no initial dysplasia.[10] This also favors the innate malignant potential of lichen planus. This finding warns for close review in non ulcerated OLP cases also. It is demonstrated that erosive OLP in older patients with pain and who use tobacco and alcohol is more likely to exhibit malignant transformation. This result calls for an enhanced evaluation of the study population for the prevalence of risk factors or racial predilection. Based on our review also old age appears to be a significant risk factor for malignancy. But most of the studies failed to demonstrate association of tobacco and alcohol with malignancy. OSCC was found to develop in patients without habit use also almost in equal frequency.

There is ambiguity in the differentiation of OLP and OLL in most of the studies, the data are insufficient at this time to determine whether the rate of transformation of these two types of oral lichenoid mucositis differs.[28-31] Oral lichenoid lesions due to systemic drug exposure or local allergic contact hypersensitivity are well documented. There may be a tendency for lichenoid lesions to be unilateral and erosive, and histological examination may show a more diffuse lymphocytic infiltrate with eosinophils and plasma cells, and with more colloid bodies than in classic LP. Kamath et al. had thoroughly searched medical and dental databases and found that OLR are often unrecognized and most of the cases categorized as OLP. In all the studies where the malignant risk of OLP and OLL are compared, OLL was found to be at the higher risk of malignancy.[35] Considering OLP cases without dysplasia initially, there is wide variation in the follow up time period which may affect the uniformity in reporting the malignant transformation rate. The mean follow up ranges from 10 months to 5 years. Dysplasia in the initial diagnosis increased the incidence of malignancy by 3.5%.[28] Generally, higher rates of neoplasia were observed in researches with a longer period of mean follow-up period.

An important diagnostic consideration to pathologists however, is oral epithelial dysplasia with a ''lichenoid'' pattern. Similar to lichen planus, lichenoid dysplasias

exhibit a prominent band-like, chronic inflammatory cell infiltrate subjacent to the basal cells. On closer examination abnormal maturation, mitoses and/or dyskeratosis may be appreciated, features of epithelial dysplasia and not oral lichen planus. Epithelial dysplasia is considered to be a risk factor for malignant transformation into OSCC. A conception that OLP and lichenoid dysplasia should be considered to be different entities is evidently widely accepted.[36] OLD is a series of chronic inflammatory process with an autoimmune base that affects epithelium of oral mucosa. Microscopically dysplastic cells often induce an immune response. The cells become more foreign and antigenic inducing progressive dysplastic changes.[37] Czerwinski R et al 2015 compare the clinical characteristics of lichen planus with dysplasia (LD) cases with oral dysplasia (DYS), and LP/lichenoid reaction (LP/LR). Clinical characteristics of LD are more similar to the LP and LR group than to dysplasia, these findings may indicate that LD should be considered as part of the lichen planus disorder spectrum rather than a separate entity, although further analysis of larger groups is warranted.[38] Patil Sreexamined biopsies of OLP, OLL, and ED and confirmed evidence of lichenoid dysplastic features 14.8% of OLP cases 18.6% of OLL cases and in about 23% cases with diagnosis of ED, suggesting that these features may co exist.[39] Indeed, the possibility of evolving malignancy reflects a series of cell-intrinsic molecular alterations seen in lichenoid dysplasia , as reported by Kim et al.[40] It can be concluded that the presence of dysplasia in a lichenoid lesion should not be diagnosed as lichen planus and rather be diagnosed as epithelial dysplasia. One exception is the presence of a superimposed candidal infection that can cause reactive epithelial atypia. Dysplastic changes should be treated as developing malignancies and close follow up as well as aggressive management modalities should be attempted. To this date no evidence based studies are there in the literature considering the risk factors and the innate malignant potential in these lesions.

## CONCLUSION

Epithelial dysplasia is considered to be a risk factor for malignant transformation into OSCC. An impression that OLP and lichenoid dysplasia should be considered to be different entities is evidently widely accepted. Although the incidence of malignant transformation of OLP remains controversial, careful, regular, and long-term follow-up of patients with OLP is required for the early detection of malignant transformation from OLP. If erosive changes are evident in lesions at follow-up visits or the lesion is recalcitrant, additional biopsies are mandatory and the follow-up intervals should be shortened. A prospective, long-term, follow-up study with strict diagnostic criteria will be required to clarify the malignant potential of OLP. Furthermore, cyto-morphological and histo-chemical markers may act as prognostic tool in predicting the premalignant behaviour of OLP and further researches in these areas may prove beneficial in unveiling the uncertainty associated with malignant potential of lichenoid lesions.

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