Malignant potential of oral lichen planus an analysis of literature over the past 20 years

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Abstract
Aim: The study evaluates and compares the rate of malignant transformation in OLP and OLL and the relevance of initial diagnosis of dysplasia as reported in available literature, since 1995.

Method: An electronic search of literature for retrospective and prospective studies of OLP was performed in the Pub Med MEDLINE database from 1995 to 2014. A total of 38 studies were included for the analysis. Extracted data was tabulated and analyzed.

Results: A total of 16,032 cases of OLP and 236 cases of OLL were reviewed from 38 articles. Of these, 243 cases of OLP and 7 cases of OLL had undergone malignant transformation. The range of malignant transformation rate from studies including OLP cases alone was 0-5.8% whereas, the range for OLL recorded was 0.65-3.2%. The average rate of malignant transformation computed from these studies was 1.25% with a mean follow-up of 1.2-19 years.

Conclusion: The outcome of this study reinforces the need for a mandatory long term follow-up regimen for all cases of OLP and OLL.

Keywords: OLP, malignant transformation, carcinoma

1. Introduction
The potentially malignant nature of oral lichen planus (OLP) has been a subject of discussion and reviews, ever since, a case of carcinoma arising in lichen planus of the oral mucous membrane was first described in 1910, by Hallopeau [1]. Officially, the World Health Organization (WHO) classifies OLP as a “potentially malignant disorder” and suggests that OLP patients should be under close monitoring [2]. Considerable controversy exists in the literature as to whether OLP has an inherent predilection to become malignant. The basis of this controversy lies in the fidelity of the available diagnostic criteria for OLP. Initially, histopathologic confirmation of OLP was not considered mandatory by several researchers. In 1978, WHO put forward a clinicopathologic criterion for diagnosis of OLP [3]. Eisenberg and Krutchkoff suggested that some lesions diagnosed as lichen planus might have, in fact, been epithelial dysplasia with a clinical lichenoid appearance. They applied the term “lichenoid dysplasia” to lesions that could be clinically mistaken for OLP but have histological features of dysplasia [4]. Van der Meij and van der Waal, in 2003, modified the WHO diagnostic criteria, to include a separate entity termed as Oral Lichenoid Lesion (OLL) and epithelial dysplasia was considered an exclusion criterion in the diagnosis of OLP [5].

The aim of this study was to analyze the available literature, since 1995, to evaluate and compare the rates of malignant transformation of OLP and OLL. The relevance of initial diagnosis of dysplasia was assessed. This study also intends to review the malignant cases reported, with respect to sex, type and site of lesion and potential risk of tobacco and alcohol in these cases.

2. Methodology
An electronic search of literature for retrospective and prospective studies of OLP was performed in the Pub Med MEDLINE database from 1995 to 2014 with MeSH terms “Oral Lichen Planus” AND/OR “Malignant Transformation”. Only full text articles with English translation were selected. Case reports were excluded. A total of 38 studies were included for the analysis. Data collection was done in two stages.
The initial stage enumerated the demographic profile, year of study, diagnostic criteria used, total number of cases studied, number of cases with malignant transformation and their rates with mean follow-up duration in years. The second stage was to review the malignant cases reported in each of the included studies under the following subsets: sex, type of lesion, site of malignant transformation, whether dysplasia was diagnosed at the initial stage, and exposure to tobacco and alcohol. The extracted data was tabulated and analyzed.

3. Results
Of the 38 studies analyzed, only two studies had attempted to classify OLP and OLL as two different entities [6, 7]. Thus a total of 16032 cases of OLP and 236 cases of OLL were reviewed. Of these, 243 cases of OLP and 7 cases of OLL underwent malignant transformation. The range of malignant transformation rate from studies advocating to have included OLP cases alone was 0-5.8%. None of the cases diagnosed with OLP, and 0.65% and 3.2% of OLL cases were reported to develop malignancy in the two studies mentioned above. The average rate of malignant transformation computed from these studies was 1.25%. The range of mean follow-up years was calculated as 1.2-19 years with a median of 4.1 years (Table 1). The statistics of individual malignant cases yielded the following results. Malignant transformation rate was slightly higher in females (59.9%) than in males (40%). The clinical varieties of OLP were grouped as ‘Red lichen’ (atrophic, erosive or bullous), ‘White lichen’ (papular, reticular or plaque) and ‘Mixed lichen’, and their rates of malignant transformation were computed. From the available data, the incidence of malignancy was higher in ‘red lichen’ (47.68%) in comparison with the other clinical varieties; ‘white lichen’ (38.21%) and ‘mixed lichen’ (14.11%).

From the cases that reported to develop malignancy, the most affected site was tongue (50.28%) followed by buccal mucosa (42.93%), gingiva (8.47%), palate (4.52%), alveolar mucosa (2.82%), floor of mouth (2.26%), lips (1.69%) and vestibule (0.56%). The presence or absence of risk factors, especially exposure to tobacco and alcohol, was assessed only in 28 studies. From these, only 29.56% of malignant cases were reported to be exposed to tobacco and only 17.80% gave a positive history of alcohol exposure.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Year</th>
<th>Diagnostic Criteria</th>
<th>No. Of Cases</th>
<th>No. Of Malignant Cases</th>
<th>Malignant Transformation Rate</th>
<th>Mean Follow-Up Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. Rode et al. [8]</td>
<td>Slovenia</td>
<td>1994</td>
<td>Clinically and Histologically Proven OLP</td>
<td>75</td>
<td>nil</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>Gorsky M et al. [9]</td>
<td>Israel</td>
<td>1996</td>
<td>Clinically and Histologically Proven OLP</td>
<td>157</td>
<td>2</td>
<td>1.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Markopoulos et al. [10]</td>
<td>Greece</td>
<td>1997</td>
<td>Clinically and Histologically Proven OLP</td>
<td>326</td>
<td>4</td>
<td>1.3</td>
<td>4.8</td>
</tr>
<tr>
<td>Lo Muzio L et al. [12]</td>
<td>Italy</td>
<td>1998</td>
<td>Clinically and Histologically Proven OLP</td>
<td>263</td>
<td>14</td>
<td>4.9</td>
<td>5.7</td>
</tr>
<tr>
<td>Rajentheran R et al. [13]</td>
<td>UK</td>
<td>1999</td>
<td>Krutchkoff et al. Criteria</td>
<td>832</td>
<td>7</td>
<td>0.8</td>
<td>11</td>
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<tr>
<td>Mignogna MD et al. [14]</td>
<td>Italy</td>
<td>2001</td>
<td>Clinically and Histologically Proven OLP</td>
<td>502</td>
<td>24</td>
<td>3.7</td>
<td>NA</td>
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<tr>
<td>Chainani-Wu N et al. [15]</td>
<td>USA</td>
<td>2001</td>
<td>Clinically and Histologically Proven OLP</td>
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<td>4</td>
<td>1.7</td>
<td>NA</td>
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<tr>
<td>Eisen D [16]</td>
<td>USA</td>
<td>2002</td>
<td></td>
<td>723</td>
<td>6</td>
<td>0.8</td>
<td>4.5</td>
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<td>Lanfranchi et al. [17]</td>
<td>Argentina</td>
<td>2003</td>
<td>Clinically and Histologically Proven OLP</td>
<td>719</td>
<td>32</td>
<td>6.5</td>
<td>1.7</td>
</tr>
<tr>
<td>van der Meij EH et al. [17]</td>
<td>Holland</td>
<td>2003</td>
<td>WHO 1978</td>
<td>173 : 62 OLP, 111 OLL</td>
<td>nil in OLP, 3 OLL</td>
<td>0 in OLP, 0.65 in OLL</td>
<td>2.7</td>
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<td>S. Gandolfia et al. [18]</td>
<td>Italy</td>
<td>2004</td>
<td>Krutchkoff et al. Criteria</td>
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<td>9</td>
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<td>2005</td>
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<td>200</td>
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<td>WHO 2003</td>
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<tr>
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<td>Switzerland</td>
<td>2006</td>
<td>WHO 1978</td>
<td>145</td>
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<td>Ingafou M et al. [24]</td>
<td>UK</td>
<td>2006</td>
<td>Clinically and Histologically Proven OLP</td>
<td>690</td>
<td>13</td>
<td>1.9</td>
<td>7</td>
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<tr>
<td>Hsue SS et al. [25]</td>
<td>Taiwan</td>
<td>2007</td>
<td>NA</td>
<td>143</td>
<td>3</td>
<td>2.1</td>
<td>1.2</td>
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<tr>
<td>Van der Meij et al. [6]</td>
<td>Holland</td>
<td>2007</td>
<td>WHO 2003</td>
<td>192 : 192 OLP, 4 OLL</td>
<td>Nil in OLP, 4 OLL</td>
<td>0 OLP, 3.2 OLL</td>
<td>3.3</td>
</tr>
<tr>
<td>Zhang JH et al. [26]</td>
<td>China</td>
<td>2007</td>
<td></td>
<td>724</td>
<td>15</td>
<td>2.1</td>
<td>1.8</td>
</tr>
<tr>
<td>Kesić L et al. [27]</td>
<td>Serbia</td>
<td>2009</td>
<td>Clinically and Histologically Proven OLP</td>
<td>163</td>
<td>2</td>
<td>1.2</td>
<td>NA</td>
</tr>
</tbody>
</table>
4. Discussion

In the past, OLP was considered to be a benign condition. However recently, several cases of malignancy have been reported from previously diagnosed cases of OLP. Several authors have also reported malignancy to arise from unaffected sites in individuals proven with OLP [44-46]. Literature underlines the following controversies: (i) OLP transforms into carcinoma (ii) OLP affected epithelium is more vulnerable to carcinogens (iii) carcinoma could appear in coincidence with OLP [47].

The putative link between OLP and squamous cell carcinoma appears to be magnified due to the errors in initial diagnosis of OLP. Some of the cases reporting carcinomatous changes in OLP could have been other red and white lesions with dysplastic features that mimic OLP clinically and histologically [48]. “Lichenoid Dysplasia”, a separate entity, as explained by Eisenberg and Krutchkoff, represents a potentially precancerous lesion which was frequently overlooked as OLP [4, 48-50]. To avoid this confusion, “epithelial dysplasia” was included as an exclusion criterion by van der Meij and van der Waal in 2003 in the diagnostic criteria for OLP [5]. Nevertheless, researchers who strictly followed this modification have also reported considerable number of neoplastic transformation in their studies.

The results of this review highlight the persisting disputes regarding the inherent malignant nature of OLP. Only 26 studies under review stressed on the initial diagnosis of dysplasia, thus questioning the accuracy of the obtained neoplastic rates. The wide range of malignant transformation rates as obtained in this analysis, 0-5.8%, can be attributed to the diagnostic criteria used, mean follow-up years and the number of cases evaluated. The number of malignant cases reported was nil, in a study by Rode et al., despite an extensive follow-up period of 19 years. [8] Similar results were obtained in three more studies, but the duration of follow-up was not mentioned [34, 41, 43]. Three among these four studies had strictly selected OLP cases and excluded every lichenoid lesions [8, 41, 43]. Generally, higher rates of neoplasia were observed in researches with a longer period of mean follow-up period. In contrary, Ilana Kaplan et al., in their retrospective study in 2011, reported 10 out of the 171 strictly diagnosed cases of OLP, developed malignancy, yielding a high malignant transformation rate of 5.8% with a mean follow-up of 4.3 years [17]. This result calls for an enhanced evaluation of the study population for the prevalence of risk factors or racial predilection.

Owing to the availability of only two studies, in which the investigators have attempted to differentiate OLP and OLL [6, 7], the data is insufficient to compare the risk of malignancy of the two separately. Moreover, many of the initial studies have not attempted to exclude OLL cases, reducing the reliability in effectively separating the two for comparison. However, the
results of these two studies revealed that cases initially diagnosed as OLL developed malignancy, and none of the OLP cases turned neoplastic [6, 7], thus emphasizing the need for stringent guidelines to differentiate the two.

The incidence of neoplasia in OLP is observed to be slightly more in females as compared to men, in accordance with the fact that overall prevalence of OLP is higher in females [51, 52]. Red lichen is at a higher risk of carcinomatous transformation when compared to the other types, as emphasized by majority of the studies reviewed. In contrast, two separate retrospective studies done in Italy and one from Switzerland, reported higher rates of malignancy in white lichen and mixed lichen respectively [12, 14, 23]. Typically, lesions of OLP were observed bilaterally, with buccal mucosa being the most common site of involvement followed by tongue [16, 18, 22, 24, 28, 29, 33, 53, 54]. With reference to the malignant transformation rates, reverse statistics have been observed; the incidence of carcinoma is reported to be higher in tongue followed by buccal mucosa [80]. Epidemiological studies show that the risk of developing oral cancer is five to nine times greater for smokers than for nonsmokers [55]. On scrutinizing the available studies, neoplastic rates were higher in subjects who were not exposed to risk factors like alcohol and tobacco. Nevertheless, considering the many patients with OLP who present risk activities for malignant diseases of the mouth, it would seem essential that all patients with OLP be informed of the potential link between OLP and oral cancer [30].

5. Conclusion
The absence of strict diagnostic criteria is the culprit behind the controversy regarding the premalignant nature of OLP. Researchers should be encouraged to take up similar long term studies to estimate the innate prospective of OLP to turn neoplastic, provided they meticulously diagnose and exclude OLL. Molecular and genetic analysis will provide a more explicit characterization of the potential risk. However, the outcome of this study reinforces the need for a mandatory long term follow-up regimen for all cases of OLP and OLL.

6. References


