Evaluation of Potential Risk Factors that contribute to Malignant Transformation of Oral Lichen Planus: A Literature Review

Farzaneh Agha-Hosseini, Nafiseh Sheykhbahaei, Maryam-Sadat SadrZadeh-Afshar

ABSTRACT

Aim: Many studies have suggested that a lesion originally diagnosed as oral lichen planus (OLP) has different possibilities of undergoing malignant transformation in time, although these findings remain a controversial issue; for example, some studies reported different values of potential malignancy of OLP.

Introduction: World Health Organization (WHO) classifies OLP as a "potentially malignant disorder" with unspecified malignant transformation risk, and suggests that OLP patients should be closely monitored. Numerous studies have attempted to confirm the malignant transformation potential of OLP.

Review results: The Cochrane Controlled Trials Register, Medline and EMBASE databases, PubMed, Google Scholar, Ovid, Up To Date, BMJ Clinical Evidence, MD Consult, and Science Direct were searched for papers published between 1997 and 2015. The medical subject heading search terms were "lichen planus," "oral lichen planus," "erosive oral lichen planus," "dysplasia," "oral precancerous condition," "oral premalignant condition," oral cancer, oral squamous cell carcinoma (OSCC), and atrophic lichen planus. A total of 120 English language abstracts were reviewed, and 50 relevant articles identified. Because of the extensive literature on the association between OLP and SCC, we have divided the data into genetic and non-genetic factors for more accurate assessment.

Conclusion: In this evidence base, malignant transformation ranges from 0 to 37% with a mean of 4.59%. The highest rate of malignancy was noted in erythematosus and erosive lesions. In this way, follow-up of OLP patients could be carried out more efficiently and appropriately.

Clinical significance: Oral lichen planus is a premalignant lesion. All types of OLP in any site of oral mucosa must be monitored regularly.

Keywords: Dysplasia, Malignancy, Oral lichen planus, Precancerous condition, Squamous cell carcinoma.

INTRODUCTION

Classically, oral lichen planus (OLP) has always been considered a chronic inflammatory disease with autoimmune process. It is a mucocutaneous disease, which may simultaneously involve oral and genital mucosa, skin, nail, and scalp. The incidence rate of OLP in the general population ranges between 1 and 2%, affects all races and both sexes, but is more common in females. A total of 70% of affected females are between 30 and 60 years of age. Oral lichen planus is also seen in children, although rarely.

The etiopathogenesis remains unknown, although recent data have shown that immunological mechanisms may play an important role as a causative or contributing factor. Oral lichen planus can be associated with other autoimmune diseases, such as myasthenia gravis, alopecia areata, vitiligo, and ulcerative colitis. Some patients with OLP have a higher concentration of serum antibodies against desmoglein compared to healthy controls, which is another indication of the involvement of autoimmunity in the pathogenesis of OLP. Another feature indicating that OLP is an immunologically mediated disease is the presence of a band-like subepithelial infiltrate of inflammatory cells, predominantly T-lymphocytes. Among these, the CD8+ cells have been suggested to induce apoptosis in epithelial cells within the lesion.

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The main difficulty in studying the malignant transformation of OLP relates to the absence of universally accepted criteria for the diagnosis of OLP.10 The identification of OLP patients in a number of studies has been based on both clinical and histopathological criteria. The clinical criteria are more frequently based on the diagnosis of several characteristic deformities of the oral mucosa, including papular, reticular, atrophic, ulcerative, bullous, and plaque-like lesions,8 of which the most common are papular and reticular lesions.11 The histopathological findings for OLP are a number of epithelial changes, the amount and extension of which vary. They include epithelial orthokeratotic hyperkeratosis, parakeratosis, epithelial atrophy or hyperplasia, acanthosis, saw-toothed rete pegs, liquefaction degeneration, and single-cell necrosis, known as colloid bodies (Civatte, hyaline, or cystoid) in the degenerating basal cell layer. In the basement membrane area, a narrow eosinophilic, periodic acid–Schiff (PAS)-positive zone is frequently present. The superficial dermis shows a dense, well-defined, band-like inflammatory infiltrate composed of lymphocytes and macrophages.10 The use of solely clinical criteria may result in false-positive findings for lesions that are similar to OLP and carry an inherent malignant potential (e.g., erythroplakia, proliferative verrucous leukoplakia, and lichenoid reaction).12

Currently, determining epithelial dysplasia by histologic evaluation is the principle method of identifying malignant conversion of OLP; however, substantial interobserver and intraobserver variation is a problem in the histopathologic assessment of epithelial dysplasia presence and severity. Accordingly, objective indices are necessary to assess malignancy potential of OLP that do not need subjective determination of the morphological changes.13

Since 1910, when Hallopeau14 reported the first case of malignant transformation of OLP to gingival cancer, numerous studies have attempted to confirm the malignant transformation potential of OLP. These studies have suggested that a lesion originally diagnosed as OLP has different possibilities of undergoing malignant transformation in time. However, these findings remain controversial; for example, some studies have reported different values of potential malignancy of OLP.15-17 Officially, the World Health Organization (WHO) classifies OLP as a “potentially malignant disorder” with unspecified malignant transformation risk, and suggests that OLP patients should be closely monitored.18

**REVIEW RESULT**

The Cochrane Controlled Trials Register, Medline and EMBASE databases, PubMed, Google Scholar, Ovid, Up-to-date, BMJ Clinical Evidence, MDConsult and Science Direct were searched for papers published between 1997 and 2015. The medical subject heading search terms were “lichen planus,” “oral lichen planus,” “erosive oral lichen planus,” “dysplasia,” “oral precancerous condition,” “oral premalignant condition,” “oral cancer,” “oral squamous cell carcinoma,” and “atrophic lichen planus.” A total of 120 English language abstracts were reviewed, and 50 relevant articles identified. Further references were obtained through the bibliographies. Full papers were obtained and evaluated. In this study, we divided contributing factors into two subgroups, non-genetic factor and genetic. Also, the related articles are assessed in two subgroups (Tables 1 and 2).

In earlier decades many reports have addressed the question of the malignant potential of OLP. The literatures include case reports, retrospective studies, and prospective follow-up studies. Case reports are of limited value and obviously can only serve as hypothesis generators.19 Examples of these studies are Gándara-Rey et al,20 Katz et al,21 and Tovaru et al,22 Retrospective studies are mostly performed after completion of the surveillance period, and therefore, contain errors, work with incomplete information which has not been defined prior to examination, or in follow-up with the patients.19 Such articles can be found at these references.12,23-28 Prospective clinical studies with strict clinical and histopathological criteria for the definition of OLP are the most beneficial method to answer this question.15,18,29-31 Gonzales-Moles et al32 list the most significant studies of OLP patients published between 1924 and 2007, and show a frequency of malignant transformation ranging from 0 to 12.5%. Although these findings appear to support the potentially malignant character of OLP, it remains a controversial topic. Ismail et al33 summarized the studies in the English literature up to August 2006, calculating the risk of malignant transformation to be between 0 and 3.5%. van der Meij et al34 reviewed studies on the malignant transformation of OLP published from 1977 to 1999, applying the Krutchkoff criteria. During this period, 98 new malignant transformations were reported. Most of the reported transformation rates are strikingly uniform, the ranges being limited to between 0.4 and 5%, despite variations in inclusion criteria. All of these studies investigated patients that had been referred for consultation. Therefore, it is not possible to conclude from them that there is an association between OLP and squamous cell carcinoma (SCC), valid for the total population. Most likely, patients with symptomatic OLP are over-represented in referred patient files, and this can be the
Table 1: Nongenetic articles

<table>
<thead>
<tr>
<th>Authors and years</th>
<th>Type of study</th>
<th>No. of cases</th>
<th>Diagnostic</th>
<th>Follow-up period</th>
<th>Malignant transformation criteria No. of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gandolfi et al 2004</td>
<td>Retrospective</td>
<td>402</td>
<td>Krutchkoff</td>
<td>4.9 years</td>
<td>9 (2.2)</td>
</tr>
<tr>
<td>Loncar Brzak 2012</td>
<td>Retrospective</td>
<td>537</td>
<td>Van Der Wal</td>
<td>10 years</td>
<td></td>
</tr>
<tr>
<td>Shen et al 2011</td>
<td>Retrospective</td>
<td>518</td>
<td>WHO</td>
<td>Mean 40 months</td>
<td>5 (0.96)</td>
</tr>
<tr>
<td>Bermejo-Fennoll et al 2009</td>
<td>Retrospective</td>
<td>550</td>
<td>WHO</td>
<td>24 ± 20.83 months</td>
<td>5 (0.9)</td>
</tr>
<tr>
<td>Bombeccari et al 2011</td>
<td>Prospective</td>
<td>327</td>
<td>WHO</td>
<td>81.7 months</td>
<td>8 (0.36/year)</td>
</tr>
<tr>
<td>Katz et al 1990</td>
<td>Case report</td>
<td>1</td>
<td>Krutchkoff</td>
<td>10 years</td>
<td>1</td>
</tr>
<tr>
<td>Eisen et al 2002</td>
<td>Retrospective</td>
<td>723</td>
<td>Nonstrict</td>
<td>4.5 years</td>
<td>6 (0.8)</td>
</tr>
<tr>
<td>van der Meij et al 2003</td>
<td>Prospective</td>
<td>62</td>
<td>WHO</td>
<td>31.9 months</td>
<td>0</td>
</tr>
<tr>
<td>Hietanen et al 1999</td>
<td>Retrospective</td>
<td>8</td>
<td>WHO</td>
<td>10 years</td>
<td>7</td>
</tr>
<tr>
<td>Mignogna et al 2001</td>
<td>Prospective</td>
<td>502</td>
<td>WHO</td>
<td>5 years</td>
<td>18 (3.7)</td>
</tr>
<tr>
<td>Rajentheran et al 1999</td>
<td>Retrospective</td>
<td>832</td>
<td>Krutchkoff</td>
<td>6 years</td>
<td>7 (0.8)</td>
</tr>
<tr>
<td>Muzio et al 1998</td>
<td>Retrospective</td>
<td>263</td>
<td>WHO</td>
<td>5.7 years</td>
<td>14 (5.32)</td>
</tr>
<tr>
<td>Gandara-Rey et al 2004</td>
<td>Case report</td>
<td>1</td>
<td>WHO</td>
<td>7 years</td>
<td>1</td>
</tr>
<tr>
<td>Van der Meij et al 2007</td>
<td>Prospective</td>
<td>67</td>
<td>WHO</td>
<td>55.9 months</td>
<td>0</td>
</tr>
<tr>
<td>Holmstrup et al 1988</td>
<td>Retrospective</td>
<td>611</td>
<td>WHO</td>
<td>7.5 years</td>
<td>9 (1.5)</td>
</tr>
<tr>
<td>Silverman and Bahl 1997</td>
<td>Retrospective</td>
<td>95</td>
<td>WHO</td>
<td>6.1 years</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>Rödström et al 2004</td>
<td>Retrospective</td>
<td>1028</td>
<td>WHO</td>
<td>6.8 years</td>
<td>5</td>
</tr>
<tr>
<td>Murli et al 1986</td>
<td>Prospective</td>
<td>722</td>
<td>Nonstrict</td>
<td>10 years</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Voûte et al 1992</td>
<td>Prospective</td>
<td>113</td>
<td>Nonstrict</td>
<td>7 years</td>
<td>3</td>
</tr>
<tr>
<td>Tovaru et al 1993</td>
<td>Case report</td>
<td>2</td>
<td>Nonstrict</td>
<td>5 years</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2: Genetic articles

<table>
<thead>
<tr>
<th>Authors and years</th>
<th>OLP criteria</th>
<th>Agent assessment</th>
<th>Pathological assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Szarka et al 2009</td>
<td>Nonstrict</td>
<td>HPV</td>
<td>HPVs may be involved in the development or progression of not only OSCC but also potentially malignant oral lesions.</td>
</tr>
<tr>
<td>Khovidhunkit et al 2008</td>
<td>WHO</td>
<td>HPV</td>
<td>HPV may not play an important role in this group of Thai patients.</td>
</tr>
<tr>
<td>Ishibashi et al 2011</td>
<td>Nonstrict</td>
<td>HPV</td>
<td>HPV may not play a major role in oral lesions although its involvement cannot be completely ruled out.</td>
</tr>
<tr>
<td>Accurso et al 2014</td>
<td>Van der Waal</td>
<td>LOH</td>
<td>OLP genetic profile more similar to a benign or reactive process than a premalignant/malignant one.</td>
</tr>
<tr>
<td>Zhang et al 1997</td>
<td>Krutchkoff</td>
<td>LOH</td>
<td>These findings do not support OLP as a leisinal risk for malignant transformation.</td>
</tr>
<tr>
<td>Kim et al 2001</td>
<td>Krutchkoff</td>
<td>LOH</td>
<td>Tumor suppressor gene residing in chromosome 9 could help to elucidate the premalignant potential of OLP.</td>
</tr>
<tr>
<td>Lee et al 2005</td>
<td>Krutchkoff</td>
<td>p53</td>
<td>PCNA atrophic OLP lesions and AQ chewing habit may have higher risk of malignant transformation.</td>
</tr>
<tr>
<td>Sousa et al 2009</td>
<td>WHO</td>
<td>P53, PCNA, BAX, BCL-2</td>
<td>Alteration in expression of these proteins was a strong indicator of the potential of malignant transformation.</td>
</tr>
<tr>
<td>Holmstrup 2010</td>
<td>WHO</td>
<td>Substance P, NK-1 receptor complex</td>
<td>This complex might play a role in the malignant transformation of OLP.</td>
</tr>
<tr>
<td>Agha-Hosseini et al 2015</td>
<td>WHO</td>
<td>P53</td>
<td>Salivary p53 may have prognostic value for plaque-like form OLP and SCC.</td>
</tr>
<tr>
<td>Agha-Hosseini et al 2013</td>
<td>WHO</td>
<td>P53</td>
<td>Salivary p53 may have prognostic value for plaque-like form OLP.</td>
</tr>
<tr>
<td>Agha-Hosseini et al 2009</td>
<td>WHO</td>
<td>P53 and Ki-67</td>
<td>Proteins high expression of these biomarkers are useful for the identification of OLP lesion with a more aggressive pattern and with a major tendency to OSCC development.</td>
</tr>
<tr>
<td>de Sousa et al 2009</td>
<td>Krutchkoff</td>
<td>p53, bax, and bcl-2, PCNA</td>
<td>PCNA is significantly lower in OLP. p53, bax, and bcl-2: no statistically significant differences.</td>
</tr>
<tr>
<td>Mazzarella et al 2006</td>
<td>Scully</td>
<td>MMP</td>
<td>Expression of MMP was higher in erosive lichen planus than in the reticular forms. Maybe associated with erosion development.</td>
</tr>
</tbody>
</table>

Contd...
Evaluation of Potential Risk Factors that contribute to Malignant Transformation of Oral Lichen Planus

<table>
<thead>
<tr>
<th>Authors and years</th>
<th>OLP criteria</th>
<th>Agent assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al 200860</td>
<td>Cawson and Odell MMPs, TIMP-2, and TGF-β1</td>
<td>MMPs, especially MMP-9, may be useful markers for judging potency of malignant transformation from OLP.</td>
</tr>
<tr>
<td>Sutinen et al 199862</td>
<td>Nonstrict</td>
<td>MMP-1 and -2, TIMP-1, MMPs and TIMPs are up-regulated in SCC.</td>
</tr>
<tr>
<td>Rödström et al 200412</td>
<td>WHO</td>
<td>MMP-13 serum and saliva</td>
</tr>
<tr>
<td>Mignogna et al 200115</td>
<td>Nonstrict</td>
<td>Telomerase activity(Ta)</td>
</tr>
<tr>
<td>O’Flatharta et al 200264</td>
<td>Nonstrict</td>
<td>Telomerase activity(Ta)</td>
</tr>
<tr>
<td>Fujita et al 200465</td>
<td>WHO</td>
<td>Telomerase activity(Ta)</td>
</tr>
<tr>
<td>González Moles et al 200970</td>
<td>WHO</td>
<td>SP,NK-1R, ki-67</td>
</tr>
<tr>
<td>Chaiyarit et al 200571</td>
<td>Nonstrict</td>
<td>8-Nitroguanine and ions</td>
</tr>
<tr>
<td>Neppelberg and Johannessen 200776</td>
<td>Nonstrict</td>
<td>DNA content, (Cox-2)</td>
</tr>
<tr>
<td>Agha-Hosseini et al 201272</td>
<td>WHO</td>
<td>MDA,TAC(8-OHdG)</td>
</tr>
<tr>
<td>Agha-Hosseini et al 201577</td>
<td>WHO</td>
<td>EGF</td>
</tr>
<tr>
<td>Flatharta et al 200866</td>
<td>Nonstrict</td>
<td>Telomerase</td>
</tr>
<tr>
<td>Shi et al 201013</td>
<td>Nonstrict</td>
<td>Telomerase</td>
</tr>
<tr>
<td>González-Moles et al 200959</td>
<td>Nonstrict</td>
<td>p53, p21, ki-67</td>
</tr>
</tbody>
</table>

DISCUSSION

For decades, the progression of OLP to oral squamous cell carcinoma (OSCC) has generated a longstanding controversy about the malignant potential of OLP. It has been postulated that a potential down-regulation of the anti-tumor immune responses induced by immunosuppressive medications could increase the risk of oral cancer in patients with OLP.9 Because of the extensive literature on the association between OLP and SCC, we have divided the data into genetic and nongenetic factors for a more accurate assessment. At the present time, premalignant lesions have been shown to demonstrate many of the genetic alterations present in OSCC.25 They are variable in their malignant potential as well as their genetic background. Among these are leukoplakia, erythroplakia, OLP, and submucous fibrosis.26

cause of the higher rate of malignant transformation of erosive lichen planus.

Nongenetic Risk Factors in Malignant Transformation of Lichen Planus

Tobacco and/or Alcohol Consumption

Some authors have suggested that the development of cancer in OLP could result from an interaction of clinical and histological atrophy with tobacco carcinogens, enhancing the action of these agents.29,35,36 In contrast, many authors found no relationship between tobacco and/or alcohol consumption in patients with malignant transformation in OLP.8,10,27,28,37

Gender and Age

There appears to be a general consensus that the risk is higher in women than in men,10,15,23,25-27,31 but van der Meij et al8 found incidence in men to be double than that in women. Some authors have reported that an oral cancer most frequently develops into LP between the 6th and 7th decade of life.15,6,26 although much lower mean ages have also been documented.29
Modifications in Diet

Some results suggest that a dietary pattern high in fruits, vegetables, and lean meats may reduce the risk of head and neck SCC, while a pattern high in fried foods, high fat and processed meats, and sweets may increase the likelihood of laryngeal cancer. Lower consumption of fruit and fresh vegetables, especially citrus fruit, is probably one of the factors contributing to the development of OLP. Gandolfo et al suggest that this could be one cause of cancer initiation.

Intraoral Localizations of LP

Multiple studies have shown that the tongue is the most common area for the appearance of a cancer, but some authors found that lips, gingiva, and midline of the palate have the highest incidence of cancer. An article by Rajentheran et al even suggested the buccal mucosa as the most common site of cancer.

Infectious Factors

N-nitrosobenzylmethylamine is a substance that can be produced by Candida albicans. Some investigators believe that it can be an important factor in the malignant transformation of OLP. Today, many interesting articles report that OLP patients infected with Hepatitis C virus (HCV) have a greater risk of malignant transformation. Gandolfo et al confirmed this. Nagao et al suggested that the appearance of carcinoma in OLP patients is correlated with HCV secreted in saliva. Geographical heterogeneity is considered a critical factor in the relation between OLP and HCV – it is more common in the Mediterranean area and Japan. There is increased frequency of HLA – DR6 allele in these regions, and the geographical heterogeneity seems to be associated with this phenomenon. In situ hybridization and polymerase chain reaction indicate high replication of the HCV genome in the epithelial cells of OLP lesions; also existence of HCV-specific CD4 and CD8 in the band-like infiltration of lymphocytes in the lamina propria were established. However, Sorensen et al indicate hepatic cirrhosis resulting from HCV infection as a usual cause of oral cancer. At this time, there is no convincing evidence to indicate a possible connection between HCV infection, and OLP progression to OSCC. There is still much debate regarding the exact role of human papilloma viruses (HPV) in the development of premalignant and oral SCC. A solid connection between the HPV DNA, chiefly HPV16, and OSCC was shown by Syrjanen et al in 2011. The present meta-analysis also shows that compared to controls, HPV16 was increased significantly in OL and OLP. Due to lack of sufficient follow-up studies regarding the progression of oral potentially malignant disorders (OPMD) toward malignancy, the role of HPV remains contradictory.

Clinical form of OLP

The malignant transformation of the “atypical” clinical presentation has been classically described as a greater risk, especially the erosive-ulcerative and atrophic types. It was found by Eisen that six (0.8%) patients, who had atrophic-erosive lesions, developed a malignant transformation, while other authors consider the erythematous and erosive lesions as having the highest rate of malignant transformation. The most common form of OLP to transform into carcinoma is the erosive form, but the atrophic form remains a likely predisposing factor. Although still controversial, numerous authors have found the atrophic-erosive forms to be predisposed to cancer development. Some studies also mention a relevancy of keratotic forms (plaques), either when appearing alone, or when associated with atrophic-erosive lesions. Conversely, Gandolfo et al stated that the idea of a higher association of atrophic-erosive or plaque forms to the development of cancer was the result of isolated case reports and noncontrolled studies. It was reported by Mattsson et al that the transformation of this disease cannot be explained by specific clinical features, since different types of OLP showed a similar percentage of transformation.

Genetic Risk Factors involved in Malignant Transformation of Lichen Planus

Allelic Imbalance in OLP

Dysplasia and SCC were significantly associated with increased percentages of loss of heterozygosity (LOH) at more than one locus. In one study, low levels of LOH in OLP were revealed by evidence, while higher levels of LOH in oral SCC and epithelial dysplasia were found. Investigation of LOH at loci 3p, 9p, and 17p by Zhang et al led to confirmation of this hypothesis. Similar results and conclusions, particularly for LOH on chromosome 9, were reported by Kim et al with the use of chromosomal in situ hybridization. It is worth noting that currently our findings regarding LOH are limited to chromosomes 17, 3, and 9. As a consequence, designated cohort studies in this field are needed all over the genome.

Cell Proliferation and Apoptosis

Altered expression of protein, related to cell proliferation and apoptosis, is a strong indicator of the potential malignant transformation of a given lesion.
An important protective mechanism is the activation of p53 right after DNA damage or oncogenic signaling, which stimulates DNA repair and triggers the apoptosis of the condemned cells. Any alterations in p53, which lead to the loss of its proper function, are among the most common genetic changes in human cancers. Other proteins associated with apoptosis and cell proliferation are proliferating cell nuclear antigen (PCNA), Bcl-2, and Bax. It has been suggested by Lee et al that the amount of PCNA and p53 in OLP and hyperkeratosis is very similar, but it is lower in epithelial dysplasia (ED) and SCC, and higher in normal oral mucosa (NOM). The precancerous nature of OLP could not be confirmed by this study. Expression of p53 has been identified as a response to DNA damage. It has also been suggested that high p53 expression can be a sign of increased cell proliferation in OLP. Conversely, in some studies, similar expressions of p53, Bcl-2, and Bax in OSCC and OLP were observed, which may be evidence of malignant transformation potential of OLP. Agha-Hosseini et al have shown that in patients with plaque-like form OLP and SCC, the level of saliva p53 was significantly higher than in healthy and erosive form OLP, and therefore, concluded that the amount of salivary p53 may have a prognostic value for SCC and plaque-like form OLP. They noted Ki-67 and p53 as being statistically significantly different from control group. High expression of these biomarkers is useful for the identification of OLP lesions with a major tendency to OSCC development and with a more aggressive pattern. In 2009, Sousa et al suggested malignant potential in ED and OLP, by showing that altered expressions of PCNA, Bcl-2, Bax, and p53 are similar in both lesions.

Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) are a major category of zinc-dependent endopeptidases, and digestion of the basement membrane portions and extracellular matrix is their main function.

Compared to the reticular forms, the overall levels of expression of MMP mRNAs were shown by Mazzarella et al to be higher in erosive lichen planus. It was indicated by the authors that the amount of inflammation and epithelial cells apoptosis are two major aspects of MMPs function in OLP.

This hypothesis was confirmed by other authors. Sutinen et al were among those who investigated the expression of MMPs and their tissue inhibitors of metalloproteinase (TIMPs) in clinical samples of normal oral mucosa with dystrophic tissue, OLP, and OSCC. Due to the noticeably higher expression in OSCC compared to other lesions, they reported that the value of this marker was significantly higher in OSCC than in other tissues. After studying MMPs, tumor growth factor (TGF)-β, and TIMPs in OSCC, Chen et al concluded that the expression of MMPs increased progressively from normal mucosa to nonatrophic OLP, atrophic OLP, and OSCCs. Furthermore, in the three groups of OSCCs, atrophic OLP, and nonatrophic OLP respectively, the immuno-score of MMP-9 was statistically significant. Moreover, expression of TGF-β1 and TIMP-2 paralleled the increases seen with MMPs. In 2015, Agha-Hosseini and Mirzaai-Dizgah suggested that MMP-13 levels do not differ significantly between OSCC and OLP, which conforms to the description provided by WHO. It is clear that in inflammatory and malignant diseases, the activation cascades are formed by MMPs up-regulated in groups.

Telomerase

Telomerase is a ribonucleoprotein enzyme that synthesizes telomeres. The enzyme resolves the end replication problem and enables cells to proliferate interminably. It has been shown by recent studies that telomerase was expressed in most cases of head and neck SCC. Telomerase activity was demonstrated to be related to the grade of malignancy by Fujita et al and thus acts as a handy prognostic predictor for precancerous conditions and lesions as well. Thongprasom et al detected telomerase expression in 14 out of 20 cases (70%) of OLP. Mild dysplasia phenotype was not correlated with higher frequencies of positive telomerase activity, while erosive OLP has shown a higher frequency of detectable telomerase activity. Therefore, the observed telomerase activity in OLP may be associated with proliferation and inflammation of the lesions. Similar results were reported by Flatharta et al in 2008.

The Relationship between Inflammation and Cancer

Various types of cancer have been linked to chronic inflammatory disorders, such as Barrett’s esophagus, ulcerous colitis, and atrophic gastritis. Recently, it was proposed that this group could include OLP as well. Some radicals and molecules generated by inflammatory cells, e.g., p21, p53, Bcl-2, Ki-67, and caspase-3 proteins, can be mutagenic to epithelial cells, or affect important cell cycle regulation mechanisms, such as cell proliferation, cell cycle arrest, or apoptosis. Chronic inflammation results in oxidative damage to the DNA via the products made by inflammatory-induced enzymes, such as nitric oxide synthase (iNOS). The higher susceptibility of OLP patients to the imbalance of antioxidant-oxidative stress status was demonstrated by Agha-Hosseini et al in three studies. Another inducible inflammation enzyme which inhibits apoptosis
in keratinocytes is cyclooxygenase-2 (COX-2), which by doing so facilitates carcinogenesis. But in 2007 Neppelberg and Johannessen suggested that with the presented patient evidence, the expression of COX-2 was not a reliable marker for the identification of OLP lesions.

Epidermal Growth Factor (EGF)

Epidermal growth factor is a 53-aminoacid polypeptide that is primarily taken from the salivary glands of mice. Although the systematic production of EGF is undertaken by kidneys, saliva is a potential source of EGF in oral milieu since in humans EGF is basically produced by the salivary glands. There is evidence regarding the cytoprotectivity of salivary EGF against injuries that helps in the maintenance of gastrointestinal (GI) mucosa integrity, such as the oral cavity mucosa membrane, and the protection of oral mucosa against various damaging substances. Epidermal growth factor is deemed as one of the high-risk factors in oral cancer. Intrinsic tyrosine kinase activity is stimulated by the binding of EGF with the receptor, resulting in the phosphorylation of the receptor, which generates a signal that eventually leads to changes in gene regulation. Epidermal growth factor receptor (EGFR) (ErbB1) is overexpressed in more than 80% of OSCCs. The EGFR overexpression is associated with metastasis and tumor invasion, refractory to standard therapies (chemotherapy, radiation, and hormonal therapy) and dwindled patient survival. The results by Agha-Hosseini et al showed that the serum EGF level in descending order was: Healthy control group, the reticular form of OLP, low stages of OSCC, the erosive form of OLP, and high stages of OSCC. These results confirm that, as serum EGF levels drop, disease clinical signs increase, and erosive form was closer to malignancy than reticular form. Since the serum EGF levels seem to be similar in OSCC and OLP, according to the statistics, it seems that EGF may play a key role in the carcinogenesis and pathogenesis of OLP.

In this review, transformation to malignancy ranges from 0 to 37% with a mean of 4.59%. The greatest rate of malignancy was reported to be in erosive lesions and erythematous.

Finally, Mignogna et al applied a surveillance protocol for 12 years with periodic examinations every 4 months, since there are definitive and reliable criteria that would let us decide which patients are facing a greater risk of transformation toward malignancy. They applied an excellent dysplasia/neoplasia clinical surveillance to watch for malignant transformation among OLP patients. Through this system, they managed to detect 94.9% of the carcinomas at the initial stage. Another method was designed to perform a simple investigation on OLP patients based on color-coded topography mouth maps (TMMs). In total, three color-coded TMMs were utilized: Red for high-risk oral mucosal areas with OLP lesions, yellow for cases displaying improvement, and green for nonsymptomatic lesions during each follow-up visit. Based on the defined criteria, the areas and extension of lesions were charted on red, yellow, or green TMM. By being simple to use, this time-saving method helps the physicians in terms of patient management. This allows for more efficient and proper follow-up of OLP patients to be carried out.

**CLINICAL SIGNIFICANCE**

Oral lichen planus is a premalignant lesion. All types of OLP in any site of oral mucosa must be monitored regularly.

**REFERENCES**

Evaluation of Potential Risk Factors that contribute to Malignant Transformation of Oral Lichen Planus


