Oral lichen planus: malignant transformation and human papilloma virus: A review of potential clinical implications

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Oral lichen planus (OLP) occurs in from 2% to 3% of the population and may have a risk of malignant transformation into squamous cell carcinoma (SCC). This risk is not necessarily associated with exposure to tobacco and alcohol. An increased awareness of a possible role of human papilloma virus (HPV) and SCC led us to review a possible association between this virus infection and malignant transformation of OLP. The possible linkage between HPV and the risk of transformation of OLP to malignancy is discussed. Furthermore, management of OLP using immunosuppressive drugs may be associated with enhanced viral replication and could theoretically affect the risk of malignant transformation. Implications for clinical care are discussed. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:461-464)**

Oral lichen planus (OLP) is a chronic mucocutaneous disease that occurs in 2% to 3% of the population studied.[1,2] Unlike the clinical behavior of cutaneous lichen planus, which has essentially no risk of malignant transformation,[3-5] OLP has a documented risk for malignant transformation. In a previous publication,[6] we discussed the progress of the disease and the diagnosis and management, including the risk of its malignant potential.

Following a retrospective analysis of published cases of alleged malignant transformation of OLP, the term "lichenoid dysplasia" was used to describe lesions that resemble, clinically, OLP and include dysplastic epithelium.[7] It was also stated that cases of OLP that progress to squamous cell carcinoma (SCC) may be misdiagnosed as OLP from the beginning.[8] Such diagnostic errors have been reported in between 11% and 25% of cases.[9,10] Malignant transformation of histologically diagnosed OLP was not associated with exposure to carcinogens of tobacco and alcohol in one study.[7] Furthermore, a study of tobacco use in OLP patients[11] showed that patients with OLP use less tobacco compared with the general population.

The potential role of human papilloma virus (HPV) in the occurrence of SCC, primarily in oropharyngeal cancer, was first appreciated in 1988 by Syrjanen and colleagues.[12] The purpose of the current article is to discuss a possible association between HPV infection and malignant transformation in OLP lesions.

The risk of malignant transformation of OLP was reported from 1.2% to 3.2% in follow-up of up to 10 years.[6] In a critical review of the literature from 1950 to 1976,[13] it was reported that there was insufficient documented evidence to state with confidence that oral lichen planus, in itself, represents a premalignant condition. A subsequent English language literature review from 1977 through 1999[14] suggested that only 34% of reported cases of malignant transformation of OLP were adequately documented. Whether OLP is associated with an increased risk of malignant transformation was recently reviewed.[15] These findings raise the possibility that other factors not directly related to OLP may play a role in the malignant process and may occur in the mouth of patients who also happened to have OLP. A study of dysplasia diagnosed in oral lesions of lichen planus reported mild or moderate dysplasia in approximately 25% of all cases.[10] Furthermore, a comparison of the rate of malignant transformation between patients diagnosed with OLP-compatible lesions demonstrated that malignant transformation occurred at a rate of 0.65% per year, which represents a 219-fold increase as compared with baseline ($P = .083$). Although these findings were not statistically significant, they do suggest a malignant risk.[16]

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Table I. The prevalence of HPV in OLP cases published in the past 15 years

Author	*Number*	*Subtype*	*Control*	*Number HPV+*	*% HPV (type)*
Szarka et al.[19]	119	NS	NS	39	32.8% (NS)
Szarka et al.[19]	61	A/E	NS	26	42.6% (NS)
Giovannelli et al.[21]	49	NS	NS	12	24.5% (16/18)
Campisi et al.[23]	71	K	5.6%	13	18.5% (16/18)
Campisi et al.[23]	27	A/E	5.6%	6	20.4% (16/18)
O'Flatharta et al.[22]	38	NS	0%	10	26.3% (16)
Ostwald et al.[17]	65	NS	NS	10	15.4% (NS)
Ostwald et al.[17]	65	NS	NS	9	9.2% (16/18)
Sand et al.[20]	22	NS	0%	6	27.3% (18)
Total	517	–	–	131	25.3%

A, atrophic OLP; *E,* erosive OLP; *HPV,* human papilloma virus; *K,* keratotic OLP; *NS,* not specified; *OLP,* oral lichen planus.

Owing to an increased awareness of a role of HPV in oropharyngeal SCC, oral lesions, including oral SCC and oral lichen planus were assessed by polymerase chain reaction (PCR)/Southern blot hybridization for HPV DNA.[17,18] HPV DNA was found in 15.4% of OLP, which is similar to findings in uninvolved clinically benign oral mucosa. However, HPV-16 and -18 were identified in 9.2% of OLP, which suggests the potential for HPV-16 and -18 to be associated with a subset of OLP that may progress to oral SCC. In contrast, another study showed that 34.7% of oral SCC harbored HPV-16 and -18,[17] whereas it has been reported elsewhere that all potentially malignant lesions, including OLP were positive for HPV DNA in contrast to 9% of control sites.[18] In this series, 34% of OLPs were HPV-16-positive and 27% were HPV-18-positive compared with 67% and 39% of the malignant lesions, respectively.[18] More recently (2009) and as shown in Table I, HPV was detected significantly more frequently in OLP lesions than in controls ($P < .001$) and its prevalence increased gradually with increasing severity of the risk for transformation of the lesion from OLP (32.8%) through leukoplakia (40.9%) and SCC (47.7%). Also, these authors noted that HPV prevalence differed significantly between the more risky atrophic and erosive forms of OLP, compared with reticular OLP (42.6% and 22.4%, respectively).[19] Interestingly, the findings showed a similar prevalence in atrophic and erosive OLP to those found in oral leukoplakia (42.6% and 40.9%, respectively).[19] A meta-analysis assessing the prevalence of HPV in oral SCC found a two- to threefold increased probability of HPV in potentially premalignant oral lesions than in normal mucosa.[24] Although this study did not include OLP, these findings may also be relevant for OLP. Other studies have assessed high-risk HPV-16 and -18 in OLP, supporting possible risk of dysplasia and cancer that requires further assessment. Studies have found high-risk HPV types 16, 18, and 31 in 3 (42%) of 7 cases of OLP in Germany,[25] and 6 (27%) of 22 cases of OLP in Sweden where 5 (83%) were type 18.[20] A study from Italy showed that HPV DNA was detected in 12 (25%) of 49 OLP lesions with HPV-18 being the most frequent genotype.[21] HPV was also detected in 6 (26%) of 38 patients (all HPV-16) with OLP in Ireland compared with none of 20 controls.[22] The prevalence of HPV in OLP cases published in the past 15 years (Table I) ranged between 9.2% for HPV-16 and -18 up to 42.6% for not specified types (mean 25.3%). A literature review, based on 1026 individuals, reported a prevalence of 13.5% of HPV in normal oral mucosa.[26] Jontell and coworkers[27] examined patients with erosive LP using PCR and detected HPV in 65% of 20 samples and HPV-16 in 15%. Although the prevalence of HPV in normal oral mucosa, as reported in a literature review, is high (13.5%),[26] it was concluded that the presence of the virus alone is not a prognosticator of progression to malignancy,[26] and most likely other additional factors may play a role in malignant transformation. These findings show that HPV, including its high-risk subtypes, are more commonly present in OLP and may represent a risk factor in oral lichenoid lesions. It is possible that a subset of OLP, possibly those with high-risk HPV subtypes, may carry an increased risk of progression to oral SCC.

OLP lesions that progress to SCC may differ from those of "benign" OLP. Genetic instability is seen in clinically active OLP, and may increase the risk of malignant transformation of OLP.[28] Genetic instability occurring in atrophic and erosive OLP rather than in the keratotic form may be associated with the higher malignant transformation risk reported in those clinical forms of the disease.[29] Molecular changes have been assessed and allelic loss or loss of heterozygosity was shown to represent a potential marker for identifying risk of malignant transformation.[30] Although it has been believed that only lichenoid lesions with epithelial dysplasia are at risk of progressing into carcinoma, loss

of heterozygosity (LOH) also has been assessed in nondysplastic OLP lesions.[31,32] Even though low-risk LOH profiles were demonstrated in OLP, the OLP lesions with dysplasia show similar LOH profiles as dysplastic nonlichenoid premalignant oral lesions.[32] A better distinction between lesions qualified as OLP and lichenoid dysplastic lesions may facilitate more appropriate clinical management and may be supported by molecular study of lesions.

Our clinical experience supports that of others suggesting that SCC may arise rapidly in a subset of cases of OLP. Malignancies that arise in OLP were diagnosed in a mean of 2.6 years following diagnosis of OLP, and during follow-up, 19% of those patients developed another oral cancer within a mean of 11 months from the first occurrence.[33] Furthermore, 50% of the patients with second primaries developed additional oral primaries in a mean of 20 months.[33] Recently, multiple primary oral cancers and recurrences occurring in 4 preexisting OLP patients were presented where three quarters of these patients had multiple oral primary cancers.[34] One 38-year-old female, with a 10-year history of OLP, developed 3 primary oral cancers within 1 year of the original diagnosis. In spite of radiation and surgical management, the patient passed away 2 years from the first diagnosis of the transformed malignancy.[34] Heitanen et al.[35] observed a Finnish series of 8 nondysplastic OLP patients who transformed to carcinoma and reported that the mean time from diagnosis of OLP to progression to SCC was 3.4 years. In their review, persistent clinical painful ulcers not responding to topical steroid treatment preceded clinical signs of possible SCC. A case series of 10 patients with SCC estimated that SCC arose in a mean of 5.5 years following diagnosis of OLP.[36] Of these 10 patients, 3 patients had a further recurrence and 2 a second primary SCC.[36] Interestingly, only 20% of oral cancer subjects with prior OLP were tobacco users and none abused alcohol.[36] This study suggests that some patients with OLP may be at increased risk of developing SCC, clearly documenting the need for close follow-up of patients with OLP. The prognosis of lesions arising from OLP is not known, and the prognosis for second primary lesions is not clearly defined; therefore, very close follow-up is mandatory.

Traditional initial therapy of symptomatic OLP is the use of topical steroids. However, it is possible that the use of immunosuppressive agents in management of OLP may potentially enhance viral replication and could theoretically increase the risk of malignant transformation, as well as alter the progression of SCC.[37] The potential for topical steroids to promote viral expression was seen in a study of genital lichenoid lesions with identified HPV in 20 men treated with topical corticosteroids.[38] High-risk HPV was found in 16% and no low-risk HPV was identified. HPV expression increased following topical steroids to 21%. In 1 case of erosive OLP treated intermittently for 5 years, viral lesions developed and low-risk HPV was identified. The findings suggest that chronic use of high-potency topical steroids may be associated with reactivation of latent HPV, and clinical follow-up was emphasized.[38] The increasing number cases of oropharyngeal and oral cancer linked to HPV further suggest a possibility of a combined and/or synergistic role of immunosuppression and HPV in oral cancer morbidity in OLP patients.[39]

Management options, other than the use of topical steroids, include the application of topical retinoids[6,15] and topical chemotherapy,[6,15,40,41] particularly when dysplastic changes are present. If topical steroids are provided, it appears logical that they should be used with caution, and close clinical follow-up is needed. All clinical forms of OLP require frequent follow-up examinations perhaps on a 4- to 6-month basis and patients should avoid or discontinue tobacco and alcohol use.[37]

In summary, the epidemiology of SCC arising in OLP is not well defined and the molecular changes that increase risk of SCC require further study. Further study should assess the potential role of HPV in a subset of OLP and in lesions that progress to SCC. Lichen planus with dysplasia should be managed as a dysplastic high-risk lesion, rather than an inflammatory condition. OLP lesions transformed into SCC may require aggressive therapy and continuing monitoring owing to risk of recurrence and second primary cancers. Further studies are clearly needed to define pathogenesis, diagnosis, management, and prognosis of OLP, and until defined, close clinical follow-up is necessary to allow early detection of transformation to SCC.

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