Oral lichen planus and malignant transformation: a longitudinal cohort study

Gian Paolo Bombeccari, DDS, a Gianpaolo Guzzi, DDS, b Mauro Tettamanti, PhD, c Aldo Bruno Gianni, MD, d Alessandro Baj, MD, d Francesco Pallotti, MD, e and Francesco Spadari, MD, DDS, a Milan, Italy

UNIVERSITY OF MILAN, ITALIAN ASSOCIATION FOR METALS AND BIOCOMPATIBILITY RESEARCH, AND ISTITUTO DI RICERCHE FARMACOLOGICHE “MARIO NEGRI”

Objective. Oral lichen planus (OLP) is associated with risk for developing oral squamous cell carcinoma (OSCC). We performed a 7-year prospective study to assess the incidence of malignant transformation of OLP among adults.

Study design. Three hundred twenty-seven OLP patients, 229 women (70.0%) and 98 men (30.0%), were observed during the follow-up period.

Results. During a mean follow-up of 81.7 months, 8 of 327 patients developed an OSCC in OLP areas (0.36%/y), yielding the high overall standardized incidence ratio of 17.7 (95% confidence interval [CI] 8.8-35.3). The standardized incidence ratio for OSCC was significantly higher in women (27.0 (95% CI 11.2-64.8]) than in men [11.2 (95% CI 3.6-34.9)]. Six OSCCs were well differentiated (75%) and 2 moderately differentiated (25%). Three subjects (37.5%) developed recurrences within 2 years (mean 16.1 ± 3.5 months). Disease-free survival rate after 69.8 months was 97.3%.

Conclusions. OLP was associated with a significant increase in the risk for OSCC. Close surveillance may help to reduce the morbidity of OSCC arising from OLP at 24 months. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:328-334)

Oral lichen planus (OLP) is a chronic inflammatory mucocutaneous disorder based on immunologic T-cell–mediated process, occurring in 1%-2% of the general population.1 OLP occurs most commonly in women >40 years old.2 OLP lesions are now generally accepted as a truly potentially malignant disorder rather than a precancerous condition.3-8 Pathogenetically, OLP is characterized by a persistent and widespread activation of the stromal environment, and therefore it could play a role in promoting epithelial tumorigenesis of oral mucosa.9,10 The genetic factors implicated in the malignant transformation of OLP have been investigated.11-13 The process of the malignant transformation is still unclear; however, an underlying mechanism that may be involved in this disease suggests the presence of an altered expression of apoptosis-regulating proteins (p53 mutations).13-15 Infection with hepatitis C virus may be a risk factor for both OLP and oral squamous cell carcinoma (OSCC).16,17 Also, the loss of heterozygosity has been identified as a link between OLP and OSCC.18 To date, no reliable biologic markers have been identified.19 Although studies conducted with strict diagnostic criteria have supported a statistically significant risk for OLP patients to develop OSCC,20,21 only a few prospective and/or retrospective studies have investigated the clinical behavior in patients in whom OSCC was subsequently diagnosed.22-24 For this reason, the true incidence of OLP malignant transformation remains controversial and results are somewhat difficult to interpret because of the heterogeneity of the study populations.3,8,25-27 Whether OLP-related OSCC behaves differently than OSCC remains to be studied.

The aim of the present study was to examine the relationship between the clinical features, pathologic staging, and malignant recurrences that occurred in previous OLP lesions.

MATERIAL AND METHODS

The study was conducted using data from a cohort of caucasian patients from Italy with clinical and pathologic diagnosis of OLP, according to revised and modified World Health Organization diagnostic criteria.28
The diagnosis of OLP was established with the following clinical criteria: the occurrence of bilaterally symmetric lesions and the presence of a lace-like network (Wickham striae) of slightly raised gray-white lines (reticular pattern) alone or with erosive, atrophic, bullous, and plaque-like lesions. OLP biopsies were reviewed by 1 expert oral pathologist and were deemed to be eligible when the following histopathologic features were observed: 1) the presence of well-defined band-like zone of cellular infiltration, which was confined to the superficial part of connective tissue; 2) evidence of liquefaction degeneration in the basal cell layer; and 3) absence of epithelial dysplasia. We studied 493 consecutive patients who had been referred to the Department of Oral Pathology and Medicine, University of Milan, between March 2001 and May 2009 for diagnosis and treatment of OLP. Of 493 patients evaluated for OSCC arising from an OLP (OLP-OSCC patients), 327 were eligible for the study. We excluded 166 patients from the study for the following reasons: 11 for refusal of oral punch biopsy, 6 for lichenoid dysplasia, 2 for upper aerodigestive tract cancer, 69 for concurrent smoking or alcohol use, and 78 for ineligible microscopic appearance. However, all patients who were excluded from the detailed statistical analysis because of preexisting risk factors for OSCC (e.g., lichenoid dysplasia, alcohol consumption, use of tobacco), were observed during the same longitudinal follow-up period. The resulting study group of 327 patients was followed prospectively for 9-108 months (mean 81.7 months, SD 11.9) and consisted of 229 women (70%) and 98 men (30%), mean (±SD) age 57.7 ± 10 years. In all of the patients, antibodies to hepatitis C virus (HCV) status was determined by a commercial third-generation enzyme immunoassay test and with the use of an immunoblot assay (Ortho Diagnostic Systems, Raritan, NJ). HCV RNA was detected by reverse-transcription nested polymerase chain reaction (PCR) using primers for the 5′-NC region of the virus.

The follow-up of the patient cohort was started 6 months after OLP diagnosis, and it aimed to exclude the possibility of a concomitant clinical presentation of OLP and OSCC, in accordance with the latency period reported by Gandolfo et al.30 Local Ethical Committee approval was obtained by the Institutional Board, and each of the patients provided oral and written signed informed consent. After diagnosis of OLP, each enrolled subject was followed 3 times per year. In case of exacerbation of OLP lesions, the patients received topical corticosteroid therapy (introral topical applications of clobetasol propionate [0.05%] applied twice daily for 2 weeks, and once daily for other 2 weeks) associated with antimycotic prophylaxis with miconazole gel.

Oral mucosa biopsy samples were taken of all cases with a suspected OSCC arising from OLP. Clinical and histologic analyses collected at the time of initial diagnosis of OLP were as follows: the timing of the first episode of OSCC, the primary site of malignancy, radiologic findings, and treatment regimens, such as surgical approach, radiation treatment, and/or chemotherapy. Criteria for biopsy sampling of OLP lesions were evidence of a loss of keratotic homogeneity associated with red areas of granular appearance and an increased consistency of the OLP lesions. The criteria of the American Joint Committee on Cancer were used to determine the clinical cancer stage.31 After the OSCC diagnosis, long-term follow-up data were recorded to study disease-free interval and overall survival distribution, date, localization of the local recurrences, and concomitant treatment (and were derived by means of the Kaplan-Meier method) within a mean observation period of 69.3 months (SD 10.4). We calculated standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) using the overall and by-site (mouth, tongue) incidence rates of OSCC in the population of the Lombardy region (northern Italy), provided to us by the Lombardy Region Cancer Registry, for the period from 1999 through 2006. Incidence rates were calculated by gender and 5-year classes. The possible effect of local immunosuppressive therapy among 327 OLP patients was investigated by calculating the incidence rate ratio versus patients not treated. Statistical calculations were performed with the use of Stata version 11.1.

RESULTS

During the mean (±SD) follow-up period of 81.7 ± 11.9 months, (median 83, range 9-108), 8 of 327 patients (2.4%; 5 women [1.5%] and 3 men [0.9%]) developed an OSCC in previously affected OLP sites. The mean age of the OLP-OSCC patients was 68.6 years in the women (range 67-71) and 62 years in the men (range 55-68). The rate of annual malignant transformation in 327 OLP patients was 0.36%, at a mean follow-up of 81.7 months [SD 11.9]. The length of follow-up before malignant transformation ranged from 23 to 62 months (mean 39.3 months [SD 12.40]). The overall SIR for OSCC arising from OLP was 17.7 (95% CI 8.8-35.3) compared with a control group. The SIR for OLP-related OSCC among the women was 27.0 (95% CI 11.2-64.8) compared with 11.2 (95% CI 3.6-34.9) among the men. We also elected to consider patients who were excluded from the analysis because they presented with risk factors (e.g., smoke, alcohol) at the time of the diagnosis; the overall SIR for OSCC in
this subgroup of 166 was 15.0, (95% CI 7.8-28.9) but remained highly statistically significant. We also evaluated the exact location of OLP-OSCC lesions. The SIRs for both mouth and tongue were statistically significant, although with wide confidence intervals due to the small number of incident cases (mouth: SIR 13.1, 95% CI 4.2-40.6; tongue: SIR 41.8, 95% CI 17.4-100.3).

The crude incidence rate ratio of the possible influence of local immunosuppressant therapy was estimated by comparing treated and nontreated OLP patients. A relationship was not found (incidence rate ratio 0.71, 95% CI 0.13-3.80). In the entire cohort, the rate of disease-free (DFS) and overall survival among OLP patients at 24 months was 100%. The rate of DFS for 8 patients with OSCC 7 years after resection was 97.3% (Fig. 1). The anatomic sites most commonly involved in subsequent malignant transformations of OLP (8 patients) were tongue (5 patients) and oral buccal mucosa (3 patients). Clinical characteristics of 8 patients with OLP-OSCC, TNM staging (tumor-node-metastasis classification criteria), and treatment options are summarized in Table I. The clinical form of OLP that more frequently underwent malignant transformation was the erosive form, with erosive OLP being observed in 4 of the 8 cases (50.0%) of OSCC and the keratosis form in 3 of 8 patients (37.5%). One of 8 patients (12.5%) displayed a mixed form of OLP, i.e., an erosive variant combined with atrophic and keratotic type. The clinical features of the OLP lesions were substantially the same as those examined at the time of diagnosis.

Histologically, 6 out of 8 cases (75.0%) of OSCC were well differentiated grade with a microinvasive...

---

**Table I. Clinical features of the oral lichen planus (OLP) lesions undergoing malignant transformation during follow-up**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Age</th>
<th>Site of OLP lesions*</th>
<th>Type of OLP lesions</th>
<th>OSCE diagnosis</th>
<th>Follow-up before OSCE diagnosis (mo)</th>
<th>TNM stage at diagnosis</th>
<th>Grading</th>
<th>Subsequent neoplastic events (n)</th>
<th>OLP therapy*</th>
<th>Associated condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>68</td>
<td>BM, T, G, ES</td>
<td>Atrophic, erosive</td>
<td>T1 N0 M0 G1</td>
<td>23</td>
<td>Yes (3)</td>
<td>G1</td>
<td>None</td>
<td>Topical</td>
<td>Hypertension</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>71</td>
<td>BM, T, MF</td>
<td>Keratotic</td>
<td>No</td>
<td>44</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>63</td>
<td>T, G, BM, MF</td>
<td>Atrophic, erosive</td>
<td>T1 N0 M0 G1</td>
<td>28</td>
<td>Yes (1)</td>
<td>No</td>
<td>Topical</td>
<td>Hypertension</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>69</td>
<td>BM, G, ES</td>
<td>Atrophic, erosive</td>
<td>T1 N0 M0 G1</td>
<td>36</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>Topical</td>
<td>Diabetes</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>68</td>
<td>PA, T, BM</td>
<td>Keratotic</td>
<td>No</td>
<td>62</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Diabetes</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>55</td>
<td>G, T, BM</td>
<td>Mixed form</td>
<td>No</td>
<td>32</td>
<td>Yes (2)</td>
<td>No</td>
<td>Topical</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>68</td>
<td>BM, T, G, ES</td>
<td>Keratotic</td>
<td>T1 N0 M0 G1</td>
<td>48</td>
<td>No</td>
<td>None</td>
<td>Topical</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>67</td>
<td>T, BM, G</td>
<td>Atrophic, erosive</td>
<td>T1 N0 M0 G1</td>
<td>42</td>
<td>Yes (2)</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

OSCE, Oral squamous cell carcinoma; BM, Buccal mucosa; ES, tongue; PA, Palatal arch.
*None of the OLP-OSCC patients received systemic immunosuppressive treatment during the follow-up period.
†Topical steroid treatment was clobetasol propionate ointment 0.05%.

Fig. 1. Kaplan-Meier curve showing disease-free survival of oral carcinoma in patients with clinically and histologically diagnosed cases of oral lichen planus.
Table II. Characteristics of patients with OLP-related cancers and timing of developing metachronous neoplastic events

<table>
<thead>
<tr>
<th>Patient, gender, age (y)</th>
<th>Number of tumor events</th>
<th>Secondary sites of OSCC</th>
<th>Staging (TNM)</th>
<th>Grading</th>
<th>Follow-up before multiple OSCC diagnosis (mo)</th>
<th>Status at end of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, F, 68</td>
<td>3</td>
<td>Buccal mucosa (right)</td>
<td>T1 N0 M0</td>
<td>G1</td>
<td>17</td>
<td>Alive with disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maxillary alveolar ridge (left)</td>
<td>T1 N0 M0</td>
<td>G1</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lateral margin of tongue (right)</td>
<td>T1 N0 M0</td>
<td>G1</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>6, M, 55</td>
<td>2</td>
<td>Maxillary alveolar ridge (right)</td>
<td>T1 N0 M0</td>
<td>G1</td>
<td>22</td>
<td>Alive disease free</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Buccal mucosa (right)</td>
<td>T1 N0 M0</td>
<td>G1</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>8, F, 67</td>
<td>2</td>
<td>Mandibular alveolar ridge (right)</td>
<td>T1 N0 M0</td>
<td>G2</td>
<td>18</td>
<td>Alive disease free</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lateral margin of tongue (left)</td>
<td>T1 N0 M0</td>
<td>G1</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

OSCC, Oral squamous cell carcinoma.

DISCUSSION

For decades, the progression of OLP to OSCC has generated a longstanding controversy about the malignant potential of OLP; therefore, we applied strict selection criteria to reduce the variables that can cause confusion with other conditions (e.g., lichenoid dysplasia). In our study cohort, we found that the incidence of malignant transformation of OLP lesions was 2.45% in 6.8 years. The mean time elapsed between OLP diagnosis to the development of OSCC was 3.28 years. The annual malignant transformation rate, based on an average follow-up of 6.8 years, was 0.36% per year. The incidence proportion was decreased to 2.15% at 6.8 years and 0.31% per year when the OSCC diagnostic latency of 2 years was applied in accordance with Krutchoff et al.’s criteria. There are only 3 studies with prospective data and a call-recall system of patients. Two of these studies have reported annual transformation rates of, respectively, 0.31% and 0.22% per year over a mean follow-up period of 7.5 years. Our results are consistent with these percentages, whereas in another study with an observation period of 2.65 years, the percentage of transformation was calculated as 0.65% per year. In those patients, all events of malignancy developed in preexisting oral lichenoid lesions.

In our study, the erosive and atrophic forms of OLP were more prevalent among patients who had OSCC developing in OLP lesions. This outcome is consistent with previously reported association between OLP and OSCC. Nevertheless, an earlier study of OLP patients in northwestern Italy was not able to support nonreticular OLP lesions being more predisposed to malignant change. In addition, the relatively stability of the OLP lesions observed clinically in the present study seems to exclude the direct correlation between neoplastic events and changes in OLP lesions appearance over time. Limited percentages of transformation (15.1%) from oral red lesions to white ones and vice versa.
versa (6%) have also been reported by a recent surveillance study among 808 OLP patients.39

There is a theoretic concern raised in the literature about OLP lesion management. It has been postulated that a potential down-regulation of the antitumor immune responses induced by immunosuppressive medications could increase the risk of oral cancer in patients with OLP.40 In our study, none of OLP patients treated by systemic immunosuppressant for HCV infection or rheumatoid arthritis developed OSCC (ratio 0.71, 95% CI 0.13-3.80). Also, our findings suggest that topical steroid treatment did not seem to influence the risk of oral cancer (Table I), as previously noted.30,39 None of our OLP patients with malignant evolution had HCV infection, compared with 14.7% HCV-positive patients in the whole cohort. Although earlier studies41,42 have demonstrated that there is an association between HCV infection and OLP, it is possible that such an association was mainly due to the allele HLA-DR6 in Italian patients.43 In the present study, we have not seen evidence of a relation between OLP-HCV and malignant transformation. Likewise, regarding relative risk of oral cancer, Gandolfo et al.30 and more recently Carbone et al.39 failed to demonstrate an increase risk for oral cancer in OLP–HCV-infected patients. In particular, the study by Gandolfo et al.30 highlights that the SIR regarding OSCCs was higher and statistically significant in OLP patients compared with the expected risk in the general population. In their study,30 when SIR for OSCC analysis was restricted to nonsmokers, the SIR for OSCC was still high (24.8, 95% CI 6.8-63.4) and equally significant.30 Analogous data were obtained in the present study, which confirms significantly elevated SIRs for OLP patients. Interestingly, the SIR for OSCCs was significantly higher in women than in men, with a rate of oral cancer in women with OLP more than twice that in men. This finding is somewhat unexpected, because the incidence of oral carcinoma in study subjects within the same geographic area was higher in men than women. The conditions that cause OSCC in women with OLP should be further investigated.

Regarding intraoral localization, in our patients the tongue appeared to be the preferential site of primary neoplasia, as previously reported.37 We analyzed a specific SIR for OSCC of the tongue, observing an increased risk of OSCC in OLP patients relative to that expected in the general population. Among excluded patients with lichenoid dysplasia, it is important to note that 1 of 6 (16.7%) developed a stage T1 squamous cell carcinoma of the tongue, in the same area of a previous biopsy of the OLP lesion, after 42 months of latency. This finding is indicative of potentially increased malignancy risk in OLP lesions.

A secondary aim of the present study was to investigate the staging of tumors and relapses of the malignancy events that occurred in previous OLP lesions. Among 3 patients who subsequently developed multiple and metachronous neoplastic events, the prevalent pathologic pattern of the tumors was a well differentiated lesion with subepithelial chronic inflammatory cell infiltrate. Interestingly, we observed in our OLP-OSCC subgroup a high incidence of multiple second primary tumors (37.5% of patients), and there was no topographic relationship between second primary tumors and the primary neoplasia. Thus, second primary tumors did not appear to be associated with a worse prognosis.44,45 None of the 8 patients showed nodal metastases, and local recurrences were classified as T1 lesions (Table II). On the basis of survival data, all these patients were still living after their first oral cancer event. For the pathologic tumor stage (T1) of OLP-unrelated OSCC in the general population, Koo et al.46 have reported ~15% of recurrences associated with a lower overall survival rate in patients who underwent surgery with or without postoperative radiotherapy. The early-detection program recall of patients was intended to reduce morbidity and/or mortality of OLP-related OSCC, but this management is debatable.22 Some authors have indicated that a long-term follow-up after the diagnosis of OLP is not justified.47 By contrast, other investigators have suggested that it is essential to provide a careful long-term follow-up of malignant transformation at early intraepithelial and microinvasive stage of carcinoma in OLP patients.45,48 Our clinical observation study with longitudinal follow-up highlights for the first time the multifocal behavior of neoplastic events diagnosed subsequently to primary OSCCs related to OLP.

Although they are consistent with other reports on this topic, several limitations should be considered in interpreting our results. The present study was conducted within a limited geographic area (northern Italy) with well defined inclusion and exclusion criteria. Further knowledge of rates of OLP-OSCC in different geographic settings of Italy is necessary. Despite these limitations, we were able to find that the risk of relapse was more likely within 24 months after diagnosis of OSCC arising by OLP. According to our analysis, in the first 2 years, we suggest a close observation with bimonthly clinical examinations. Our data lend support to practice guidelines for a close clinical surveillance along with heightened awareness that OLP is a true premalignant condition.

REFERENCES


Reprint requests:
Gianpaolo Bombeccari, DDS
Unit of Oral Pathology and Medicine
Department of Reconstructive and Diagnostic Surgical Sciences
University of Milan
Via Della Commenda 10
20122 Milan
Italy
gpbombeccari@libero.it