FIELD CANCERIZATION OF ORAL LICHEN PLANUS AND PROGNOSTIC ASPECTS OF ORAL SQUAMOUS CELL CARCINOMA OCCURRING ON ITS BACKGROUND

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ABSTRACT

Lichen Planus first described by Erasmus Wilson in 1869 has moved from being regarded as an innocuous benign condition to being considered as a potentially malignant disorder by the World Health Organization and is now defined as an idiopathic immune mediated mucocutaneous chronic inflammatory disease that affects the stratified squamous epithelia and the appendices. Oral lichen planus carries a very small probability of becoming malignant. The objective of the present study was to assess the long term prognostic aspects of oral squamous cell carcinoma/dysplasia and field cancerization occurring on the background of oral lichen planus in a retrospective analysis of 51 OLP patients (mean age=54 years; female, n=35; male, n=16) who between 2001 to middle of 2010 were diagnosed with OLP-related OSCC at the Department of Oral Medicine, Eastman Dental Institute and one major Head and Neck Cancer unit, University College London Hospital, United Kingdom. 1500 OLP patients were analyzed by using a computerized data base (CDR, Clinical Data Repository) and case files of Eastman Dental Institute and UCLH NHS Trust, out of which 53 patients were found to have at least one neoplastic event (intraepithelial neoplasia and / or invasive OSCC). 2 patients were excluded from the study as the case files or CDR did not have sufficient data regarding the histopathological and clinical features of oral lichen planus and / or subsequent neoplastic events. The results of the present study suggest that 3.5% (53 / 1500) of patients with OSCC have a previous history of OLP. The mean interval between the histological diagnosis of OLP and OSCC development was 4.5 years. The observation period following the detection of the first oral malignancy was at least 2.2 years for the majority of patients. 51 oral lichen planus patients suffered a total of 137 neoplastic events (OSCC / dysplasia). Patients with OLP and subsequent development of dysplasia / oral squamous cell carcinoma are at risk of having multiple and multifocal neoplastic events of the oral cavity and therefore worse prognosis.

Key words: Lichen Planus, Field cancerization, Oral squamous cell carcinoma, prognosis.

INTRODUCTION

Little is known regarding the prognosis of oral lichen planus-related oral squamous cell carcinoma and limited information is available to understand whether these carcinomas may be more aggressive than traditional oral cancers (not related to oral lichen planus).

The mean interval between oral lichen planus diagnosis and cancer diagnosis ranges widely from 20.8 months1 to 10.1 years2 although the maximum risk is reportedly between 3 and 6 years after oral lichen planus diagnosis.3,4 But in contrast, Silverman in 1985 concluded that disease duration is not a transformation risk factor. Mignogna et al reported that patients with oral squamous cell carcinoma arising on the background of oral lichen planus were at higher risk of developing second primary tumours then traditional oral squamous cell carcinomas. Moreover, they observed a high incidence of lymph node metastasis in early stage oral squamous cell carcinomas (micro-invasive T1 OSCCs).5 Similarly Munoz et al and co-workers reported a higher rate of local recurrence and second primary oral squamous cell carcinoma in oral...
lichen planus patients compared to controls. These data suggest that patients with oral squamous cell carcinoma occurring on the background of oral lichen planus are more likely to develop recurrences and/or second primary tumours than traditional OSCCs (without prior OLP). Mignogna et al also reported that patients with malignant transforming OLP have a tendency to develop several second primary tumours over the years (2 or more in 53% of cases). They reported an average of 2.6 oral squamous cell carcinomas or dysplasias in each of their 46 patients with malignant transforming OLP (a total of 141 neoplastic events). Among them, 16 presented only one neoplastic event, whereas 30 were affected by one or more second primary intraepithelial neoplasia/invasive carcinomas.

Mignogna and co-workers reported 4 oral lichen planus patients with early stage low risk oral squamous cell carcinoma who developed lymph nodal metastasis after an average of 6 months. Lymphatic spread was unexpected in these patients because of the microinvasive nature of these tumours as well as their low-risk infiltrative pattern.

There remains very little information regarding the survival rates of patients with OLP-related OSCC versus those with traditional OSCC. Hietanen and co-workers reported that 5 of their 8 patients with OLP-related OSCC died within a few months from diagnosis. Though they did not provide further details on recurrences or stage of these tumours. In the case series reported by Munoz et al, no statistically significant differences in mortality rates were found between OLP-related oral cancers and traditional OSCC. Mignogna et al reported that 29 out of 30 patients with OLP-related OSCC were still alive 5 years after their first cancer (5-year survival of 96.7%). Moreover, most of these patients had early oral squamous cell carcinoma and were monitored carefully 3 times per year, and this may explain the very high survival.

Field Cancerization

The concept of ‘field cancerization’ was first introduced by Slaughter et al, in 1953 when studying the presence of histologically abnormal tissue surrounding oral squamous cell carcinoma. Field cancerization is caused by widespread lateral clonal expansion of a single progenitor and/or independent molecular events affecting multiple cells separately. Mignogna and co-workers reported that more than 50% (25 out of 45) of patients with OLP-related OSCC developed at least one metachronous second primary intraepithelial neoplasia/invasive carcinoma. In 5 of these 25 patients, the neoplastic events occurred only in the same site as the first oral squamous cell carcinoma. However, the remaining 20 patients developed subsequent multifocal intraepithelial neoplasias/invasive carcinomas in different anatomical sites of the oral mucosa. The authors suggested that this high incidence of second primary tumours strongly parallels the process of field cancerization.

AIMS AND OBJECTIVES

The aim of this study was to investigate the long-term behaviour of oral squamous cell carcinoma arising on the background of oral lichen planus.

The primary objectives were: The number and location of neoplastic events, mortality/survival, occurrence of field cancerization. Secondary objectives were: Rate of malignant transformation, duration of oral lichen planus before oral squamous cell carcinoma occurrence, clinical features of malignant transforming OLP.

METHODOLOGY

The study group consisted of 53 patients who were diagnosed with oral lichen planus and eventually developed one or more oral cancers/dysplasias. These patients belong to a larger cohort of 1500 patients (53/1500=3.5%) with OLP who had attended the Oral Medicine Unit of UCL/UCLH, Eastman Dental Institute/Hospital and the H&N Cancer Unit of UCLH between 2001 and 2010.

An electronic database (CDR- Clinical Data Repository) and patient’s case files were used for retrospective data collection.

Details of demographics, diagnosis of clinical features of oral lichen planus, histopathological features, diagnosis of primary and second primary oral squamous cell carcinoma and dysplasia as well as relevant treatment were extracted. 2 patients were excluded from the study as the case files or CDR did not have sufficient data regarding the histopathological and clinical features of OLP and/or subsequent neoplastic events. (Fig 1) The diagnosis of OLP was based upon WHO criteria: typical clinical manifestations (plaque and/or reticular lesions alone or in association with erosive/ulcerative lesions, mostly but not exclusively bilateral and symmetrical) and histopathological features (hyperortho-hyperparakeratosis of the superficial epithelial layers, vacuolar degeneration of the germinative layer of the epithelium, and subepithelial lymphocytic band-like infiltrate. Patients sus-
expected to have lichenoid lesions related to drugs or oral restorations were not included. The diagnosis of neoplastic events was based upon clinical examination confirmed by histopathological examination of lesional tissue. Dysplasia/oral carcinoma was graded according to the criteria of WHO. The criteria of AJCC (American Joint Committee on Cancer) was used to determine the tumour stage. The International Classification of Diseases for Oncology (ICD-O) was used to identify the sites of carcinomas: the ICD-O codings were confirmed by a standardized drawing provided with each patient file.

Inclusion criteria of the study is summarized in Table 1.

Intraepithelial neoplasia and early invasive oral carcinoma were treated by surgical excision including, whenever allowed by anatomical and functional factors, at least 0.5 cm of healthy tissue at the lateral margin of resection and about 0.3-0.5 cm of sub-mucosal tissue as deep margin. Subsequent cancers which occurred after treatment were defined as second primary tumours when previous resection margins were free of intraepithelial neoplasia (severe dysplasia/carcinoma in situ) and/or invasive carcinoma, defined as negative margins. In instances when carcinoma and/or intraepithelial neoplasia was present at the resection margins (defined as positive margins) further wider surgical extension to clinically healthy mucosa was undertaken. Patients with mild dysplasia at resection margins were not re-operated but carefully observed by increased frequency of periodic clinical examinations. Advanced stage oral carcinomas were treated, whenever possible, with resective maxillofacial surgery and at least 1 cm of healthy tissue of the deep and lateral margins. Neck dissection, orofacial reconstruction and postoperative radiotherapy and/or chemotherapy were provided where needed.

RESULTS

53 patients out of 1500 (3.5%) developed at least one neoplastic event on the background of OLP. However data from only 51 of them was available for long term analysis. At the time of diagnosis of oral lichen planus, mean age was 54.2 years and there were 35 women (68.6%) and 16 men (31.4%). 13 (4 males and 9 females) out of 51 (25.5%) OLP patients were affected by only one neoplastic event (dysplasia/invasive carcinoma). The remaining 38 OLP patients (74.5%) developed more than one synchronous/metachronous second primary neoplastic events. In particular the neoplastic events were distributed as follows: 2 neoplastic events in 14 patients (Group 1), 3 neoplastic events in 9 patients (Group 2), 4 neoplastic events in 5 patients (Group 3), 5 neoplastic events in 4 patients (Group 4) and 7 neoplastic events in 6 patients (Group 5). The characteristics of one patient from each group is detailed in table 2. The observation period following the detection of the first oral malignancy was at least 2.2 years for the OLP patients (mean 4.5 years, range 1-8.2 years). 38 out of 51 patients developed multiple neoplastic events along the years. In some cases each neoplastic event was characterized by one single dysplasia/OSCC involving one oral ICD-O site. However in most patients malignant disease occurred as synchronous or metachronous multifocal malignant transformation, involving different ICD-O sites. The topographic relation between primary and subsequent neoplastic events of some of these patients is presented in figure 2. In 11 patients with multiple oral squamous cell carcinoma the neoplastic events occurred only in the same location as the previous ones. The remaining 27 patients developed subsequent multifocal dysplasias/invasive carcinomas in ICD-O sites distant to that of the preceding tumours. Tumours mostly occurred in the same mucosal areas where OLP lesions were already present, although occasionally they occurred in areas of mucosa which clinically appeared to be non-involved by oral lichen planus (Fig 2B). With regard to the clinical form of OLP, the majority of patients were affected predominantly by the mixed form of oral lichen planus (Reticulations and...
3. Among 137 neoplastic events subsequent to the diagnosis of OLP in 51 patients, 55 (40%) neoplastic events were intraepithelial neoplasias (dysplasias/carcinoma in situ) and the rest (82, 60%) were invasive moderate to well differentiated OSCC. 5 and 7 patients developed stage I (T1N0M0) and stage II tumours (T2N0M0) respectively and the remaining 25 patients developed stage IV tumours (T4N0M0) with 7 patients having lymph nodal metastasis as well (T4N1M0). There were no cancer-related deaths at the time of data collection, corresponding to a cancer specific mortality of 0% (0/51). 3 year survival analysis was available in only 13 patients out of 51 (25%) and was 100%. 1 year survival analysis was available in all the 51 patients; and was 100%. The survival rate of those patients who developed only one neoplastic event was the same as

TABLE 1: INCLUSION CRITERIA

| 1 | OLP diagnosed on the basis of WHO criteria |
| 2 | Absence of dysplasia at the time of OLP diagnosis |
| 3 | Occurrence of at least one neoplastic event, namely one dysplasia and/or OSCC |
| 4 | Development of OSCC/dysplasia at least 6 months after OLP diagnosis |
| 5 | Exclusion of dental restoration-related or drug-related lichenoid reactions |

A (A) Topographical relationship of OLP patients shown by brown circles described in table 2

B (B) Topographical relationship between primary and subsequent neoplastic (intraepithelial/invasive carcinoma) events in the above patients. The blue circles indicate the primary and subsequent neoplasia occurring at the same site. The red circles indicate neoplastic events occurring at distant sites showing field cancerization. The number indicates the patient and small letter with the number indicates the time of neoplastic event.

Fig 2: Topographical relationship between oral lichen planus, primary tumour and subsequent neoplastic events
### TABLE 2: CHARACTERISTICS OF OLP OF ONE PATIENT OF EACH OF THE FIVE GROUPS WITH MALIGNANT TRANSFORMATION

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Gender</th>
<th>Age</th>
<th>OLP Type + Age at OLP diagnosis</th>
<th>OLP clinical sites</th>
<th>OLP Therapy</th>
<th>Site &amp; staging of Primary OSCC</th>
<th>Treatment</th>
<th>Further Neoplastic events</th>
<th>Field changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>76</td>
<td>Mixed (Reticular + plaque) 68</td>
<td>Left buccal mucosa, left retromolar trigone, left ventral surface of tongue, left floor of mouth and gingival tissues (left lower 3 to left lower 6)</td>
<td>Topical</td>
<td>Right anterior tonsillar pillar and right lateral soft palate. Stage II ($T_2N_0M_0$)</td>
<td>Radiotherapy</td>
<td>Yes (1)</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>69</td>
<td>Mixed (Erosive + plaque) 62</td>
<td>Right posterior maxillary alveolar mucosa, buccal mucosa bilaterally, dorsum of tongue, bilateral retro commissural area, gingival tissues, upper anterior labial and palatal + lingual gingiva of right lower 2, 3.</td>
<td>Topical</td>
<td>Right posterior maxillary alveolar mucosa. Stage II ($T_2N_0M_0$)</td>
<td>Surgery</td>
<td>Yes (2)</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>72</td>
<td>Mixed (Erosive + plaque) 68</td>
<td>Bilateral buccal mucosa, upper and lower labial mucosa, left hard and soft palate, uvula and floor of mouth</td>
<td>Topical</td>
<td>Left posterior maxillary alveolus, left buccal mucosa and left sulcus. Stage IV ($T_1N_0M_0$)</td>
<td>Surgery + Radiotherapy</td>
<td>Yes (3)</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>57</td>
<td>Mixed (Erosive + plaque) 49</td>
<td>Right buccal and labial mucosa, left buccal mucosa, floor of mouth, lower lip right inner surface and lower labial gingiva</td>
<td>Topical</td>
<td>Right buccal mucosa and left floor of mouth. Stage I ($T_1N_0M_0$)</td>
<td>PDT (Photo dynamic therapy)</td>
<td>Yes (4)</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>75</td>
<td>Mixed (Erosive + plaque + ulcerative) 64</td>
<td>Right angle of mouth, right lateral border of tongue, right buccal mucosa and left lower labial mucosa with vestibular region.</td>
<td>Topical</td>
<td>Right angle of mouth. Stage IV ($T_1N_0M_0$)</td>
<td>Surgery + PDT</td>
<td>Yes (6)</td>
<td>Yes</td>
</tr>
</tbody>
</table>
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those patients who developed multiple oral tumours (100%).

No significant post-surgical complications were recorded, with the exception of mild to moderate deficit of oral functions due to intra oral scarring in patients treated with multiple resections.

DISCUSSION

The present study aimed at investigating long-term behaviour of oral squamous cell carcinoma arising on the background of oral lichen planus.

Since the first report of the malignant transformation of oral lichen planus\textsuperscript{21}, numerous studies have investigated the association between oral squamous cell carcinoma and oral lichen planus. The topic has been controversial as there remain a number of confounding factors and methodological biases in the previous studies that have the potential to jeopardise available evidence.\textsuperscript{22,23} Indeed, meta-analysis of published data is difficult because of differences in study design, diagnostic criteria of OLP, time of follow up, information on exposure to known carcinogens (e.g. smoking)\textsuperscript{24} or medications (e.g. cyclosporine).\textsuperscript{25} The results of the present study suggest that a small percentage (3.5%, 53/1500) of patients with oral lichen planus may develop oral squamous cell carcinoma. This is in agreement with the majority of authors\textsuperscript{2,26,27,28,29,30,31,32,33,34} although there remain reports of cohorts of patients with very low (<1%)\textsuperscript{35,36,37,39,40} or very high (7-12.5%) \textsuperscript{41,42} malignant transformation rate.

This study shows that 74% of the patients with malignant transforming OLP (38/51) developed more than one neoplastic event during the years with a maximum of 7 OSCC’s/dysplasias. This is in agreement with the data reported by Mignogna et al who highlighted that 56% of their patients had multiple episodes of OSCC/dysplasia.\textsuperscript{8} In addition, 27 out of 38 patients (71%) developed tumours in different and unrelated sites of the oral mucosa. The present study can therefore confirm that malignant transforming OLP is characterized, in the majority of cases, by multiple and multifocal neoplastic events, thus paralleling the process of field cancerization. However, the occurrence of second primary tumours and field cancerization in patients with traditional OSCC is strictly related to the stage of primary tumour, with the risk being higher in individuals with advanced stage OSCC.\textsuperscript{8} On the contrary, the present study shows that also OLP patients (Total=13) with stage I and II primary tumours developed an average of 2.25 second primary tumours (range 1-4).

This is in agreement with the data reported by Mignogna et al who also observed an unexpected high rate of second primary tumours in OLP patients with early stage primary OSCC.\textsuperscript{5}

CONCLUSION

This study provides a snapshot of the malignant potential of oral lichen planus, prognosis of OLP-related OSCC and field cancerization. There is a need for a much more rigorous investigation that should include patients attending several medical and dental units throughout the country and indeed the entire globe to establish the exact risk of OSCC and the process of field cancerization arising in patients with OLP.

REFERENCES

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