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Field cancerization in oral lichen planus

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Abstract

Background: The concept of field cancerization describes the tendency of patients with premalignant and malignant lesions of head and neck mucosal sites to develop multiple carcinomas of the upper aerodigestive tract. Here we address whether this concept should be extended also to patients affected by oral lichen planus (OLP), an inflammatory disorder associated with an increased risk of cancer development.
Methods: Data from a cohort of 45 patients with OLP who subsequently developed severe dysplastic changes and/or oral squamous cell carcinoma were retrospectively reviewed. Patients who presented more than one oral neoplastic event were considered for further data analysis as regards incidence, localization, management and prognosis.
Results: Twenty (44.4 %) patients were affected by one single neoplastic event while 25 (55.6 %) developed multiple and often multifocal oral dysplastic and/or malignant events. In most cases, a careful surveillance programme led to diagnosis and effective treatment of oral neoplasias at an early intraepithelial and microinvasive stage, leading to long-term survival. In some patients, however, additional primary tumours occurred suddenly with rapid invasion, leading to advanced stage diagnosis and poor prognosis. Overall, three patients (12 %) died due to malignant oral disease.
Conclusions: 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, a phenomenon which parallels the concept of field cancerization of traditional head and neck cancers. If detected at an early stage, these neoplasias can be managed with superficial and complete resection. However a small number of patients have loco-regional tumour spread despite a standard surveillance protocol.

Keywords: Field cancerization; Oral cancer; Oral lichen planus; Inflammation; Prognosis; Precancerous lesions

Introduction

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.[1,2] It was proposed to explain the development of multiple neoplasms of the upper aerodigestive tract (UAT) observed in head and neck cancer patients as a consequence of continuous exposure of these areas to carcinogenic agents. Since then, the concept has been further extended to include not only a higher-than-expected prevalence of multiple local second primary tumours and the presence of synchronous distant tumours within the UAT, but also the occurrence of multiple oral premalignant lesions.[3] Oral leukoplakia, oral submucous fibrosis and erythroplakia, generally considered the three major clinical types of premalignant oral lesions, share with oral squamous cell carcinoma (OSCC) the same risk factors as well as the same events underlying the process of field cancerization, namely widespread lateral clonal expansion of a single progenitor and/or independent molecular events affecting multiple cells separately.[4–6] An important clinical implication of such a process is that fields

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of oral mucosa, apparently healthy but proven to be altered via histological and molecular studies, remain beyond the limits of resection and may lead to new potentially malignant and malignant lesions.[3] Even if these second primary lesions and/or local recurrences are not considered a major cause of mortality in head and neck cancer patients,[7,8] they could have a significant impact upon the need for and type of treatment, and overall prognosis of patients. Furthermore, recent studies have suggested that a subgroup of potentially malignant lesions with gross genomic aberrations (aneuploid erythroplakia and leukoplakia) are characterized by a high incidence of multiple and multifocal subsequent tumours and associated mortality.[9,10] It is not known whether the concept of field cancerization should be extended to oral lichen planus (OLP), a chronic inflammatory disorder which is increasingly considered to have malignant potential unrelated to common risk factors (e.g. tobacco and alcohol usage) of oral cancer development.[11–16] However, a few preliminary studies have suggested that some patients with OLP-related OSCC have a poor prognosis due, at least in part, to a tendency to develop second primary metachronous oral cancers.[17,18]

Paralleling this, multifocal and synchronous or metachronous areas of malignant transformation (e.g. high-grade dysplasia and invasive carcinomas) characterize other chronic inflammatory conditions associated with cancer development, such as Barrett's oesophagus and ulcerative colitis.[19–21] This might thus support the view that the concept of field cancerization may be applied also to these disorders, probably as a consequence of persistent and widespread activation of their stromal inflammatory microenvironment, given that activated inflammatory cells and the cytokine network can act as oncogenic agents, hence promoting epithelial tumorigenesis.[22–25]

If OLP is a potentially malignant disease linked to chronic inflammation, it would be expected that some patients will have disease that behaves in a manner similar to that of oral epithelial dysplasia and the other chronic inflammatory conditions associated with cancer development, giving rise to malignant disease that is recurrent and aggressive. The aim of the present retrospective study was to determine the incidence, nature and locations of multiple neoplastic events in patients with a previous history of OLP to establish if there is a potential of field cancerization of the oral mucosa associated with OLP.

Materials and methods

A cohort of 45 patients diagnosed with OLP at the Oral Medicine Section of University ''Federico II'' and who subsequently developed severe epithelial dysplasia/carcinoma in situ, defined here as oral intraepithelial neoplasia,[26] and/or invasive OSCC were retrospectively analysed. All the patients did not have clinical/histological signs of dysplasia or OSCC at the time of OLP diagnosis and all developed at least one neoplastic event, namely one intraepithelial neoplasia and/or invasive OSCC. Among them, patients presenting multiple synchronous and metachronous neoplastic events were considered for further data analysis with focus on tumour incidence and locations, clinical management, and prognosis. The study cohort belongs to a bigger group of 700 patients who have been diagnosed and regularly reviewed during a period of 16 years (1990–2006).

The diagnosis of OLP was based upon clinical manifestations (papular, plaque and/or reticular lesions alone or in association with erosive/ulcerative lesions, mostly but not exclusively bilateral and symmetrical) confirmed by incisional biopsy demonstrating characteristic microscopic features including hyperortho-hyperparakeratosis of the superficial epithelial layers, vacuolar degeneration of the germinative layer of the epithelium, and subepithelial lymphocytic band-like infiltrate.[27,28] Patients suspected 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 the World Health Organization.[29] The criteria of the American Joint Committee on Cancer were used to determine the clinical stage.[30] 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.[31]

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 submucosal 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 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. When considered clinically useful, tolonium chloride staining was used as an adjunctive diagnostic aid.[32,33] In all cases, OLP diagnosis, dysplasia grading and status of resection margins were determined after consensus had been reached independently by two pathologists. Advanced stage oral carcinomas were treated, whenever possible, with resective maxillofacial surgery. Neck dissection, orofacial reconstruction and postoperative radiotherapy and/or chemotherapy were provided where needed. Patients were routinely recalled and clinically observed every 4 months, except those needing closer surveillance due to recent development of dysplasia or intraepithelial neoplasia/invasive carcinoma.[34] Clinical