Challenges in predicting which oral mucosal potentially malignant disease will progress to neoplasia

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Probably the greatest challenge to those managing patients with oral diseases is the dilemma of attempting to predict which oral erythroplakias, leukoplakias, lichenoid and other potentially malignant mucosal disease (PMD) such as oral submucous fibrosis will progress to neoplasia – notably oral squamous cell carcinoma (OSCC). The paper reviews progress over the past decade and the application to the clinical situation.

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Introduction

Probably the greatest challenge to those managing patients with oral diseases is the dilemma of attempting to predict which oral erythroplakias, leukoplakias, lichenoid and other potentially malignant mucosal disease (PMD) such as oral submucous fibrosis will progress to neoplasia – notably oral squamous cell carcinoma (OSCC) (Table 1). This difficulty in prognostication was certainly recognized up to a decade ago (Lee et al., 2000; Scully et al., 2003), and even 5 years ago, it was reiterated that, despite numerous studies, accurately predicting which patients or lesions of PMD would develop OSCC was still impossible (Lodi and Porter, 2008). Indeed, malignant transformation may be present in a lesion which presents clinically as a leukoplakia, and this may even not be detected on histopathological examination of a biopsy specimen. There can be issues as to the reliability of the biopsy in representing what might be the behaviour in the lesion or elsewhere. Already half a century ago, it had been recognized that, in OSCC, the epithelium elsewhere in the area was abnormal with ‘field cancerization’ and 11% contained another cancer and the concept of ‘second primary tumours’ (SPTs) arose (Slaughter et al., 1953). Of concern also is a study on oral leukoplakias reported three decades ago, in which patients with PMD were biopsied pre-operatively and then treated by laser excision to obtain a histopathology specimen (Chiesa et al., 1986). Despite pre-operative biopsies
negative for malignancies, the postoperative histopathology revealed malignancy in 6 of 59 lesions (10.2%). Speckled and erosive leukoplaikias had the highest cancerization rate. A different study of 26 consecutive hitherto untreated patients presenting with a unilateral OSCC (18) or a PMD (8) examined ‘mirror image’ biopsies from clinically normal mucosa at corresponding anatomical sites and found that 15 patients (58%) had histologically abnormal tissue there (Thomson, 2002). Of the 15 with abnormalities, six had reactive change/cellular atypia associated with chronic irritation and seven had frank dysplasia, while two had carcinoma in situ or microinvasive carcinoma. A study of 101 mucosal lesions in 96 patients which examined the histopathological findings in the preoperative biopsies compared with the histopathological findings of the complete lesions showed that seven lesions (7%) harboured a carcinoma and 70 lesions (69%) showed a degree of epithelial dysplasia or carcinoma in situ (Holmstrup et al, 2007). It is evident therefore, from several studies, that a negative biopsy result may not completely reliably exclude carcinoma or its potential; indeed, up to ~10% may contain malignant or dysplastic tissue. The evidence thus indicates that these lesions cannot be guaranteed to be innocent, even once a pre-operative biopsy result has shown no concern.

To date, possibly the most important marker of malignant development is a non-homogeneous clinical appearance (Reibel and Holmstrup, 2010), but this is typically supported by biopsy and histopathological assessment of epithelial dysplasia. In one Danish study however, neither the site, demarcation, tobacco smoking nor degree of epithelial dysplasia influenced the risk of malignant development (Holmstrup et al, 2006). Nevertheless, it is dysplasia that has been the focus of most recognized and accepted practice.

### Dysplastic changes

The criteria for grading epithelial dysplasia are based on architectural features and cytology; the presence, degree and significance of individual criteria are typically taken into account in pathologists’ interpretations (Manchanda and Shetty, 2012). Pathologists play a significant role in identifying and grading the severity of dysplasia in PMD lesions. Consideration of three oral epithelial dysplasia classification systems (oral epithelial dysplasia scoring system, squamous intraepithelial neoplasia and Ljubljana classification) recommended epithelial dysplasia scoring for routine use while recognizing that a major limitation of using histological criteria for dysplasia is the subjectivity of the grading system (Warnakulasuriya et al, 2008).

Assessment of epithelial dysplasia can be of some prognostic help (Mithani et al, 2007). The risk of cancerous change in oral PMD is generally lower with mild dysplasia than with severe dysplasia. A recent workshop noted that the presence of dysplasia as assessed by light microscopic examination is one of the various prognostic predictors of malignant transformation long-used in PMD, but it is recognized that not all dysplastic lesions become malignant, while apparently non-dysplastic lesions may occasionally develop into cancer (Brennan et al, 2007). There are also other potential outcomes for a PMD in that it may persist clinically unchanged, it may enlarge or it may shrink or even disappear (Napier and Speight, 2008).

Nevertheless, to expect any pathologist to guarantee from examination of an incisional biopsy specimen, which probably contains a heterogeneous cellular picture (Califano et al, 2000; Braakhuis et al, 2004), that there is no carcinoma in situ or frankly invasive carcinoma present in the specimen is perhaps unrealistic and unreasonable. And the discussion above notes the extent to which the biopsy specimen may or may not in any event represent the whole lesion. The reliability of dysplasia grading has also been questioned after a number of studies over the past two decades demonstrated low-to-moderate interpathologist, and even intrapathologist, consensus for the presence or absence of and the grading of dysplasia, even among specialist oral pathologists (Abbey et al, 1995; Karabulut et al, 1995; Fischer et al, 2004; Kujan et al, 2006). Other dysplasia grading systems may conceivably have advantages (Nankivell et al, 2013).

It is evident then that neither clinical nor the histological features can reliably prognosticate in PMD, but cellular and molecular studies have been long recognized to have a better potential (Zhang and Rosin, 2001). DNA studies such as ploidy, after initial enthusiasm (Scully et al, 2003) and then a chequered history and even suggestions they were of little benefit (Bremmer et al, 2011) are now indeed proving to be of some value (Torres-Rendon...
et al., 2009; Bradley et al., 2010; Sperandio et al., 2013; Giaretti et al., 2012a,b, 2013) as are some of the molecular changes thus far characterized – especially chromosomal loss of heterozygosity profiles (Mithani et al., 2007; Pitiyage et al., 2009; Smith et al., 2009; Lingen, 2010; Zhang et al., 2012).

Molecular changes

The hypothesis that chromosomal loss of heterozygosity (LOH) might be a potential tool in the management of oral PMD was raised by the group in British Columbia, Canada, over a decade ago (Zhang and Rosin, 2001). This and their further studies have helped stimulate a number of other groups, several of whom have produced evidence of the potential usefulness of molecular markers (reviewed by Mithani et al., 2007; Pitiyage et al., 2009; Zhang et al., 2012) (Box 2). There are hundreds of research reports in this field, but one meta-analysis has shown that LOH on chromosomes 3p and/or 9p, DNA content, survivin and matrix metalloproteinase-9 can help predict progression in PMD (Smith et al., 2009). Chromosomal 3p and/or 9p loss in leukoplakias after attempts at lesional treatment may also be helpful predictors of prognosis because they were associated with a 26.3-fold increase in risk of developing oral SPT compared with those that retained both of these arms (P < 0.001), with 60% of cases with LOH developing SPT in 2 years (Rosin et al., 2002). In contrast, histological diagnosis (moderate or severe dysplasia vs hyperplasia or mild dysplasia) had only a 1.7-fold increase in risk (P = 0.11).

Other prognostic indicators in PMD (reviewed by Arduino et al., 2013) that may help include the degree of expression of tumour suppressor genes (p53 and p16), epidermal growth factor receptor (EGFR), phosphatidylinositol-3-kinase and cyclins D1 and B.

Management of leukoplakia

It is evident therefore that the foundation of using dysplasia grade to make management choices is not as firm as one would wish. This is one of the main challenges for oral histopathology (Kujan et al., 2006), but the outcomes of research on molecular changes should make significant headway in this area and should improve management.

Management attempts for the treatment of leukoplakias have included non-surgical and surgical approaches. There is no evidence that any non-surgical treatments are effective in preventing dysplastic mucosal lesions progressing to carcinoma (Lodi et al., 2006). Therefore, moderate and/or severely dysplastic lesions are usually managed by removing the clinical lesion surgically by scalpel, sometimes by laser (van der Waal, 2010) or photodynamic therapy (Saini and Poh, 2013) or other techniques, but reliable randomized controlled clinical trials to assess the effect of these methods in preventing the development of carcinoma are lacking. Indeed, some reports on the effectiveness of various surgical modalities in preventing malignant transformation have produced contradictory outcomes. Even a retrospective study to evaluate the long-term outcome of leukoplakias and erythroplakias treated either surgically or without surgical interventions showed that surgical treatment was insufficient to prevent malignant transformation of the dysplastic lesions treated (Holmstrup et al., 2006). Thus, the concept that removing PMD surgically (by scalpel, laser or cryosurgery) can prevent the onset of carcinoma remains unproven – by no means a new conclusion (Einhorn and Wersall, 1967). There is indeed no evidence that surgical intervention reduces the risk of malignant transformation (Holmstrup, 2009). Indeed, one workshop concluded, ‘Because of the lack of randomized controlled trials that have shown effectiveness in the prevention of malignant transformation, no recommendations can be provided for specific surgical interventions of dysplastic oral lesions either’ (Brennan et al., 2007). Furthermore, recent studies have also confirmed the concept of field cancerization by demonstrating molecular abnormalities in clinically normal oral mucosa from patients with PMD (Giaretti et al., 2012a,b, 2013), which raises questions about precisely which area warrants treatment.

Clinicians are thus still faced with a series of dilemmas, a summation of which should always underpin full discussions with the patient and their advocates, in order for patients to be in a position to give valid consent to the management offered. Meantime, on the positive side, it would appear that we are on the verge of a major breakthrough in prognostication using DNA and molecular studies as evidenced also by a prospective real-time study using LOH profiling in a clinical trial [http://clinicaltrials.gov/ct2/show/NCT00402779?term=oral+cancer+prevention&r

References


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