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SYMPOSIA

Update on Oral Epithelial Dysplasia and Progression to Cancer

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Introduction

Precursor lesions of the upper aerodigestive tract are similar regardless of site and can be defined as altered epithelial lesions, which have an increased likelihood of progressing to squamous cell carcinoma. In the oral cavity the most common lesions recognised as potentially malignant are *leukoplakia* and *erythroplakia*, but it is also apparent that as many as 50% of oral squamous cell carcinomas arise from apparently clinically normal mucosa. The prognostic significance of an individual lesion is difficult to determine, and none of the currently available molecular markers have proved to be prognostically significant and none have yet been evaluated in large prospective studies. At present therefore, the gold standard for the assessment of oral potentially malignant lesions is microscopic evaluation of haematoxylin and eosin stained sections for the presence of architectural and cytological changes, which are generally referred to as *epithelial dysplasia*. Some texts use the terms squamous intraepithelial neoplasia (SIN) or squamous intraepithelial lesions (SIL; Table 1) [1]. The categories under each scheme are similar, but the terminology is not exactly synonymous. In the oral cavity, use of the SIL terminology of 'atypical hyperplasia' may lead to confusion because of the large number of common benign hyperplastic lesions, which may be encountered. In oral and maxillofacial pathology therefore, *oral epithelial dysplasia* is regarded as the standard terminology [2, 3].

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Criteria for the Diagnosis of Oral Epithelial Dysplasia

In the assessment of oral potentially malignant lesions, much reliance is put upon the microscopic diagnosis and grading of the changes of cytological atypia. It can be seen from Table 1, that the various grading schemes are not exactly synonymous. 'Atypical hyperplasia' and 'keratosis with dysplasia' correlate with both moderate and severe epithelial dysplasia as used in the oral scheme. Not all schemes use the term 'carcinoma in situ'. The oral scheme has the advantages of clear terminology and five grades, which suggest that it may be more discriminatory. The new WHO classification [1] advocates the use of the oral scheme and also applies it to lesions elsewhere in the upper aerodigestive tract.

The diagnosis and grading of oral epithelial dysplasia is based on a combination of architectural and cytological changes (Table 2), but evaluation of these is subjective and has been subject to considerable inter- and intra-observer variations in the grading of lesions (e.g. [4]). More recently there has been an attempt to more carefully define the criteria for grading of epithelial dysplasia [1, 2, 3]. In cervical pathology it has been traditional to grade cervical intraepithelial neoplasia (CIN) according to the thickness or levels of involved epithelium. Such a scheme has been resisted in oral and maxillofacial pathology because, even in the presence of severe cytological changes, there is often evidence of normal maturation with a thick surface layer of keratin. Thus, full-thickness change analogous to CIN3 is rarely seen in the mouth. Nevertheless, the latest WHO classification now recommends a more objective grading, which does, to some extent, take account of levels of involvement. The criteria for grading of oral epithelial dysplasia are summarised in Table 3. It should be noted at the outset that in the histological evaluation of oral potentially malignant lesions

Table 1 Classification schemes for epithelial dysplasia

Oral epithelial dysplasia	Squamous intraepithelial neoplasia (SIN)	Squamous intraepithelial lesions (ljubljana system)	Classic laryngeal system
Epithelial hyperplasia	N/A	Simple hyperplasia	Laryngeal keratosis
Mild dysplasia	SIN 1	Basal/parabasal hyperplasia	Hyperplasia
Moderate dysplasia	SIN 2	Atypical hyperplasia	Keratosis with dysplasia
Severe dysplasia	SIN 3		
Carcinoma in situ		Carcinoma in situ	Carcinoma in situ

Based on Refs. [1, 2]

(usually clinical Leukoplakia) only about 50% of lesions show evidence of dysplasia, the remainder showing non-specific hyperplasia and hyperkeratosis.

Mild dysplasia (grade I) demonstrates proliferation or hyperplasia of cells of the basal and parabasal layers which does not extend beyond the lower third of the epithelium (Fig. 1). Cytological atypia is generally slight with only mild pleomorphism of cells or nuclei. Mitoses are not prominent, and when present are usually basally located and normal. Architectural changes are minimal.

Moderate dysplasia (grade II) demonstrates a proliferation of atypical cells extending into the middle one-third of the epithelium (Fig. 2). The cytological changes are more severe than in mild dysplasia and changes such as hyperchromatism, and prominent cell and nuclear pleomorphism may be seen. Increased and abnormal mitoses may be present, but these are usually located in the basal layers. Architectural changes may be seen in the lower half of the epithelium where there may be loss of basal polarity and hyperplasia leading to bulbous rete pegs. However stratification and maturation are relatively normal, often with hyperkeratosis

Table 2 Cytological and architectural features of oral epithelial dysplasia

Cellular changes
Abnormal variation in nuclear size and shape (anisonucleosis and pleomorphism)
Abnormal variation in cell size and shape (anisocytosis and pleomorphism)
Increased nuclear/cytoplasmic ratio
Enlarged nuclei and cells
Hyperchromatic nuclei
Increased mitotic figures
Abnormal mitotic figures (abnormal in shape or location)
Increased number and size of nucleoli
Architectural (Tissue) changes
Loss of polarity
Disordered maturation from basal to squamous cells
Includes top-to-bottom change of carcinoma in situ
Increased cellular density
Basal cell hyperplasia
Dyskeratosis (premature keratinization and keratin pearls deep in epithelium)
Bulbous drop shaped rete pegs
Secondary extensions (nodules) on rete tips

In *severe dysplasia* (grade III) there is abnormal proliferation from the basal layer into the upper third of the epithelium (Fig. 3). Cytological and architectural changes can be very prominent. All the changes seen in mild and moderate dysplasia are seen but in addition there is marked pleomorphism often with abnormally large nuclei with prominent or even multiple nucleoli. Prominent and suprabasal mitoses are usually evident and abnormal tripolar or star-shaped forms may be seen. Apoptotic bodies may also be prominent. Architectural changes are severe, often with complete loss of stratification and with deep abnormal keratinisation and even formation of keratin pearls. Abnormal forms of rete pegs are usual and we regard bulbous rete pegs as particularly significant in the diagnosis of severe dysplasia. Abnormal shaped rete pegs may also be seen, with lateral extensions or small branches. These are quite abnormal and may be the earliest signs of invasion. Occasional lesions may show prominent acantholysis with severe disruption of the architecture. Although the epithelium may be thickened, severe dysplasia is sometimes accompanied by marked epithelial atrophy. This is especially prominent in lesion from the floor of mouth, ventral tongue or soft palate and may be a feature of lesions which have presented clinically as erythroplakia. In these cases there may be minimal evidence of stratification or keratinisation, and atypical cells may extend to the surface.

Carcinoma in situ, is the most severe form of epithelial dysplasia and is characterised by full thickness cytological and architectural changes. In the oral cavity such changes are rare, and often, even in the presence of the most severe atypia, there is still an intact keratinised surface layer (Fig. 4). Carcinoma in situ is thought by some to be a premalignancy but others regard it as evidence of actual malignant change but without invasion.

When grading epithelial dysplasia the pathologist should take into account both the cytological and architectural

Table 3 Criteria for grading of oral epithelial dysplasia

Grade	Levels involved	Cytological changes	Architectural changes
Hyperplasia	N/A	None	Thickened epithelium
			Hyperkeratosis
			Normal maturation
Mild (I)	Lower third	Cell and nuclear pleomorphism	Basal cell hyperplasia
		Nuclear hyperchromatism	
Moderate (II)	Up to middle third	Cell and nuclear pleomorphism	Loss of polarity
		Anisocytosis and anisonucleosis	Disordered maturation from basal to squamous cells
		Nuclear hyperchromatism	Increased cellular density
		Increased and abnormal mitotic figures	Basal cell hyperplasia
			Bulbous drop shaped rete pegs
Severe (III)	Up to the upper third	Cell and nuclear pleomorphism	Disordered maturation from basal to squamous cells
		Anisocytosis and anisonucleosis	Increased cellular density
		Nuclear hyperchromatism	Basal cell hyperplasia
		Increased and abnormal mitotic figures	Dyskeratosis (premature keratinization and keratin pearls deep in epithelium)
		Enlarged nuclei and cells	Bulbous drop shaped rete pegs
		Hyperchromatic nuclei	Secondary extensions (nodules) on rete tips
		Increased number and size of nucleoli	Acantholysis
		Apoptotic bodies	
Carcinoma-in situ	Full thickness	All changes may be present	Top-to-bottom change
			Loss of stratification

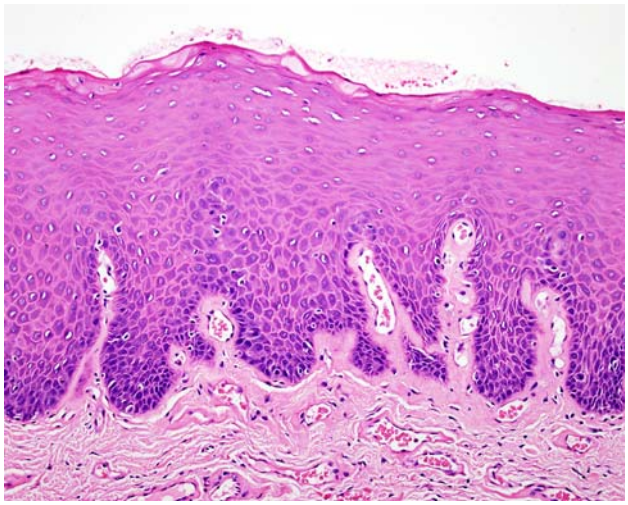

Fig. 1 Mild epithelial dysplasia. Cells in the basal layer show cytological atypia including pleomorphism and hyperchromatism, but there are no architectural changes and stratification is normal

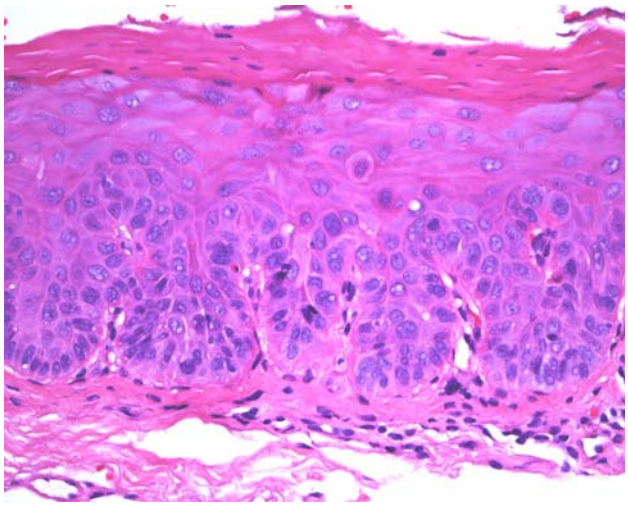

Fig. 2 Moderate epithelial dysplasia. There is considerable cytological atypia which extends into the middle third of the epithelium

changes. Changes regarded as particularly significant include marked cell and nuclear pleomorphism, drop shaped rete pegs and abnormal mitoses. When the cytological changes are very marked this may indicate that a lesion should be upgraded. For example in Fig. 5, although the changes are limited to the lower two thirds of the epithelium, the cytological changes are marked. The lesion should be upgraded to severe dysplasia.

Progression to Squamous Cell Carcinoma

Although it is established that oral potentially malignant lesions and epithelial dysplasia are statistically more likely to progress to cancer, the actual mechanisms are poorly understood and it is not inevitable that a dysplastic lesion will progress to cancer. At present, there are no molecular markers which enable us to distinguish lesions that may

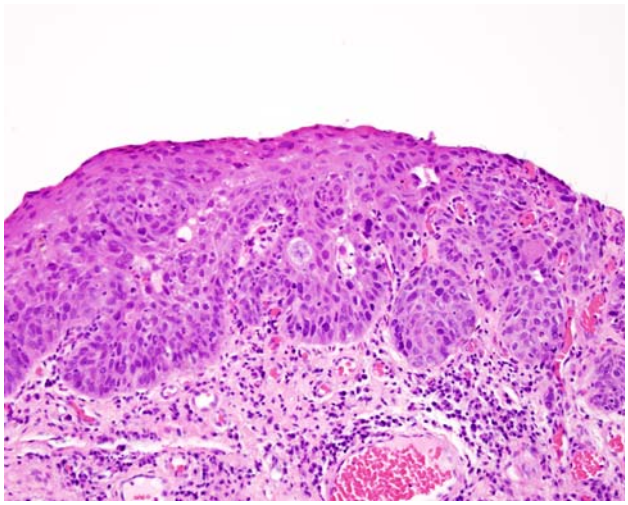

Fig. 3 Severe epithelial dysplasia. Cytological atypia extends to the upper third of the epithelium. There is disruption of the normal architecture of the epithelium and bulbous rete pegs are prominent

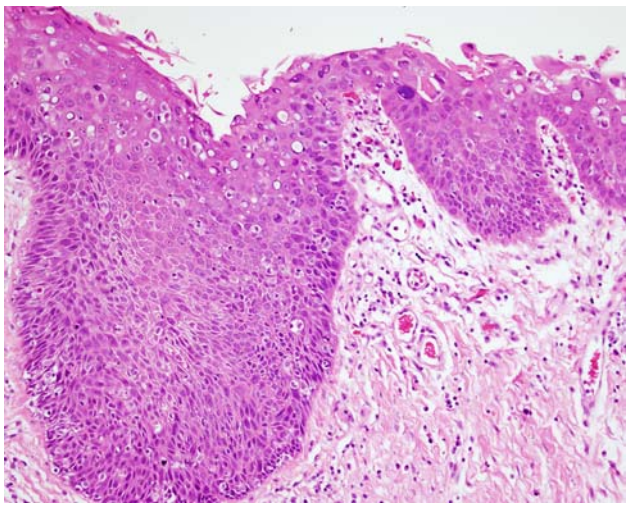

Fig. 4 Carcinoma in situ. The architecture of the epithelium is almost completely disrupted and cells with atypical and hyperchromatic nuclei are seen among the superficial cells. Note however that there is still some evidence of maturation with some keratin on the surface

progress from those that will not [5]. Potential markers include analysis of p53 mutations, and loss of heterozygosity, especially at chromosomes 3p and 9p. Gross genomic aberrations, assessed by DNA ploidy status, also have promise as a predictor of malignant progression, but recent studies need to be repeated. None of these markers have been evaluated in long term prospective studies.

At present, therefore the degree of dysplasia is the best guide to potential progression of oral lesions. Severe epithelial dysplasia has an overall malignant transformation rate of about 16% but studies show a wide range of 7–50% [2]. Moderate dysplasias have a malignant transformation

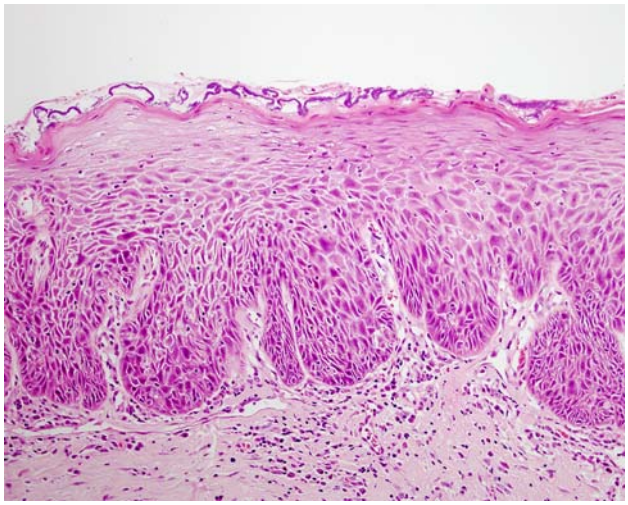

Fig. 5 In this cases, the atypical cells are confined to the lower two thirds of the epithelium but the cytological changes are severe and bulbous rete pegs are prominent. The lesion should be upgraded to severe dysplasia

potential of 3–15%, whereas mild epithelial dysplasia shows a very low risk (<5%). It is always assumed, however, that there is a temporal progression of disease, analogous to multistage carcinogenesis, and that mild dysplasia will progress to severe dysplasia and then to carcinoma. There is very little empirical evidence however to support this attractive model.

With regards to the clinical lesion it is apparent that even fewer lesions actually progress. Only about 50% of biopsied leukoplakias show dysplasia and overall the malignant transformation rate for leukoplakia is only about 0.1–2% per year. Ironically rates are lower in the developing world where tobacco chewing habits are most prevalent. In the west malignant transformation is estimated at about 5% of leukoplakias. Higher rates of about 20% have been reported in non-homogeneous lesions, which are also more likely to show dysplasia on biopsy.

Micro-Invasive Carcinoma

An area of particular diagnostic difficulty is the decision as to whether or not a severely dysplastic lesion shows the earliest signs of invasion into the underlying connective tissue. Often interpretation is hampered by heavy inflammatory infiltrates or by the plane of section through bulbous or branching rete pegs. Identification of breaches in the basement membrane are helpful, but difficult to identify. There are no objective criteria for a diagnosis of early invasion and pathologists must use their judgement and experience. In some cases (Fig. 6) there is clear evidence of small islands of epithelium, sometimes with keratinisation, in the superficial lamina propria. In other

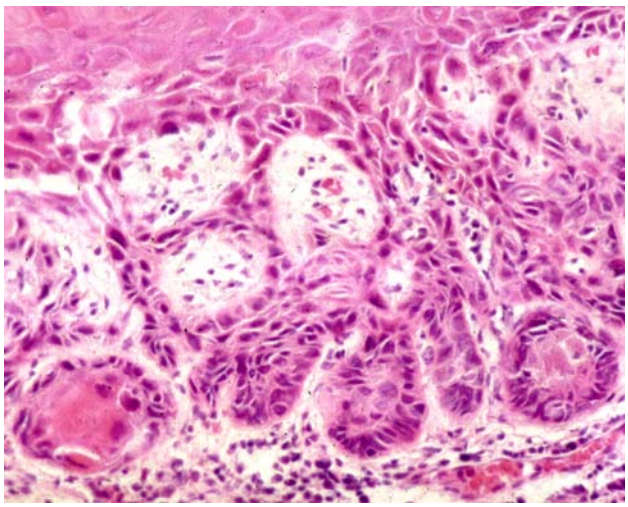

Fig. 6 Micro-invasive carcinoma. In this lesion there are small branching bulbous rete pegs, but small islands of epithelium one of which is keratinizing appear to be 'dropping off' into the superficial lamina propria

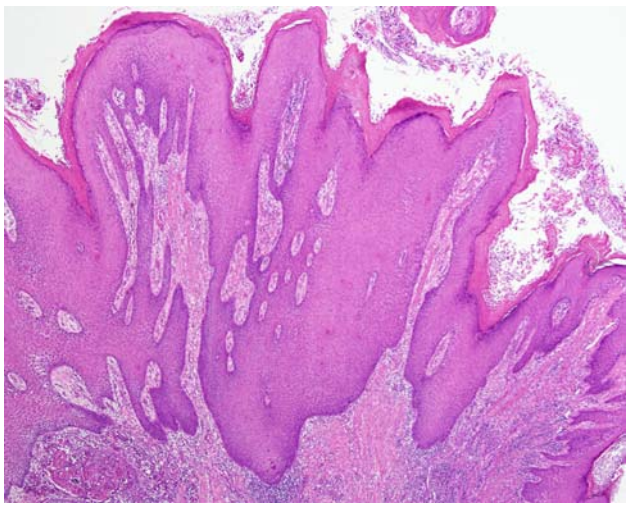

Fig. 7 Histology of a lesion of proliferative verrucous leukoplakia. The lesion is exophytic with marked hyperkeratosis and a verruciform surface. Cytological atypia is minimal

lesions there may be a pushing front, with intact epithelium proliferating downwards in an endophytic manner.

Verrucous Hyperplasia and Proliferative Verrucous Leukoplakia

Most oral potentially malignant lesions fall easily into one of the above categories, but occasional lesions show marked architectural changes with minimal cytological atypia. These lesions are characterised clinically by gross hyperkeratosis with a verrucous or papillomatous surface pattern. The lesions tend to be exophytic and spread laterally to encompass large regions of the oral mucosa. Localised lesions are usually referred to as verrucous hyperplasia but the extreme form of this lesion is characterised by recurrent multifocal and progressive lesions and is called *proliferative verrucous leukoplakia* [1, 6].

Histologically the lesions are characterised by massive hyperkeratosis and a verrucous folded surface. There may be basal cell hyperplasia and acanthosis with wide bulbous rete pegs (Fig. 7), but features of cytological atypia are rarely prominent and only about 50% of lesions show any significant epithelial dysplasia.

However the lesions progress and in time over 70% of patients develop a conventional squamous cell carcinoma [6, 7]. In the early stages these lesions are very difficult to diagnose since the lack of dysplasia makes them difficult to distinguish from papillomas and other benign verruciform lesions. The clinical history is important and the extent of the lesion, and a history of progression, multifocality and recurrence all lead to a diagnosis of proliferative verrucous leukoplakia. The exophytic nature and lack of pushing invasion distinguishes it from verrucous carcinoma.

Pseudoepitheliomatous Lesions

Further areas of diagnostic difficulty are reactive lesions in which the pattern of epithelial hyperplasia results in an appearance, which may be mistaken for invasive carcinoma. The classic lesion in which this occurs is granular cell tumour [8], which in 30% of cases shows marked pseudomalignant changes in the overlying epithelium. Since this lesion is common on the tongue, misdiagnosis as carcinoma is a not infrequent occurrence.

Other lesions, which may be characterised by pseudoepitheliomatous hyperplasia include chronic hyperplastic candidiasis, median rhomboid glossitis and necrotising sialometaplasia.

Cytological atypia may also be seen in a range of reactive lesions and care needs to be taken not to over interpret such changes as dysplasia. Reactive atypia is often seen associated with inflammation and regenerative epithelium, for example at the margin of an ulcer, in traumatic lesions and in lichen planus. The context of the lesions, the clinical history and histological evidence of reactive change are all clues to the correct diagnosis.

A peculiar form of cytological atypia may be seen in lesions associated with human papilloma virus infection [9]. Lesions usually present as flat warts and in our experience are almost exclusive to HIV positive individuals. The atypia is bizarre and prominent and is characterised by large pleomorphic nuclei and giant cells. The nuclei may be hyperchromatic and angular (Fig. 8). Typically the

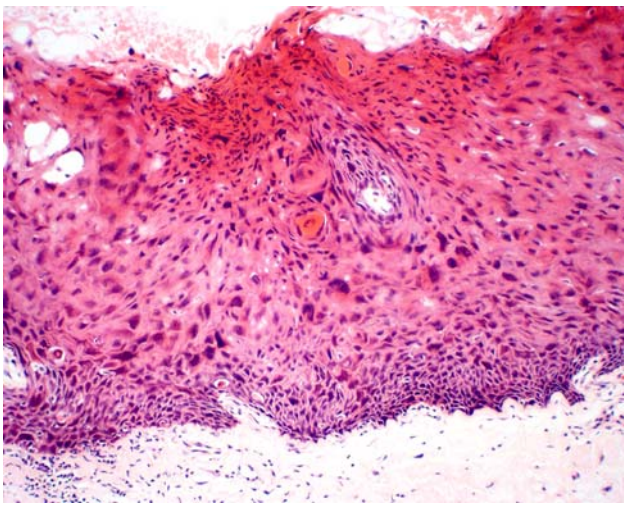

Fig. 8 Viral atypia. There is marked cytological atypia, but this is localized primarily in the prickle cell layer. Large hyperchromatic and angular nuclei are typical

atypical cells appear high in the epithelium and the basal layers may be little affected. This feature and the prominent and bizarre nature of the changes serve to distinguish it from conventional dysplasia. In our department all cases have been positive for HPV and after over 10 years of follow up, none have progressed to cancer.

Summary and Conclusions

Oral potentially malignant lesions are characterised most frequently by the appearance of white patches (leukoplakia) on the oral mucosa. Overall malignant progression in these lesions is only of the order of 5% and there are no currently accepted markers to distinguish those that may progress from those that may not. The current gold standard is the finding of epithelial dysplasia on a tissue biopsy. Diagnosis of dysplasia is subjective and considerable experience needs to be accrued before the significance of the variable features become fully apparent. The WHO guidelines are helpful in providing more objective criteria for grading. Overall however only about 50% of biopsied clinical leukoplakias show epithelial dysplasia and not all lesions progress. A maximum of 50% of severe dysplasias, 30% of moderate dysplasias and very few (<5%) mild dysplasia are thought to progress to cancer.

Apart from the diagnosis and grading of dysplasia other significant diagnostic challenges include the evaluation of exophytic verruciform lesions and the diagnosis of benign reactive lesions that may mimic epithelial dysplasia or early invasive carcinoma.

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