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MINI-SYMPOSIUM: HEAD AND NECK PATHOLOGY

Problems and pitfalls in oral mucosal pathology

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Summary The oral mucosa is affected by a number of reactive, infective, inflammatory and immune-mediated disorders and distinguishing between them can be challenging. This review will concentrate on two histological patterns: the lichenoid tissue reaction and pseudoepitheliomatous hyperplasia. For each pattern the histological features are described, the differential diagnosis is discussed and the essential diagnostic features are given. Discussion on the lichenoid tissue reaction covers the entities of lichen planus, lichenoid reactions to drugs and dental materials, discoid lupus erythematosus, graft versus host disease and erythema multiforme, while that on pseudoepitheliomatous hyperplasia covers granular cell tumour, chronic hyperplastic candidosis, median rhomboid glossitis, necrotizing sialometaplasia and papillary hyperplasia of the palate.

Introduction

The oral mucosa is affected by a number of reactive, infective, inflammatory and immune-mediated disorders and distinguishing between them can be challenging not only for the clinician but also for the pathologist. This review will concentrate on two histological patterns that frequently cause difficulties for the non-specialist pathologist: the lichenoid tissue reaction and pseudoepitheliomatous hyperplasia. For each pattern the histological features are described, the differential diagnosis is discussed and the essential diagnostic features are given.

Lichenoid tissue reactions

One of the areas of greatest confusion and perhaps also disagreement lies in the diagnosis of lesions that are characterised by the so-called 'lichenoid tissue reaction'. This pattern was originally described by Pinkus[1] in the skin as 'epidermal basal cell damage with associated changes in the epidermis' and has since been expanded by Weedon.[2] There is a general consensus that this pattern is the result of a cell-mediated immune response directed against antigenic changes within the epithelium.[3] Almost all lesions are characterised by a T-cell dominated infiltrate that is closely associated with basal cell damage and it seems likely that the other epithelial changes are secondary to this. There appear to be multiple triggers to this type of response including drugs, dental materials and viruses, although in some

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diseases such as lichen planus the cause is unknown.[4]

In the oral cavity, basal epithelial cell damage and loss is associated with infiltration of immune and inflammatory cells in the lamina propria and changes in the differentiation and thickness of the epithelium. This type of basal cell damage has often been described as liquefaction degeneration, which refers to the formation of vacuoles and oedema in the basal epithelial cells. In clinical practice it is often difficult to determine what type of basal cell destruction has occurred since the basal epithelial cells may be lost and the prickle cells abut directly onto the basement membrane. Keratinocyte apoptosis is a common finding and results in the formation of Civatte or colloid bodies. These appear as rounded, eosinophilic masses either in the basal or lower layers of the epithelium or in the upper lamina propria. They appear to adsorb immunoglobulins particularly IgM onto their surfaces. Thickening and hyalinization of the basement membrane zone may be evident and using a periodic acid schiff (PAS) stain, it appears as a thick or thin continuous or discontinuous band beneath the epithelium.

The infiltrate appears to be intimately associated with the basal cell destruction and usually comprises lymphocytes and macrophages, which typically form a band-like infiltrate in the upper lamina propria that is closely associated with the epithelium. In some cases the infiltrate may obscure the basement membrane zone and extend into the basal epithelial cell layers. Here focal areas of epithelial destruction may be associated with lymphocytes at their margins—so-called satellite cell necrosis. It is extremely unusual for the infiltrate to extend higher than the lower third of the epithelium. Plasma cells, eosinophils and neutrophils may also be present in the infiltrate even in the absence of ulceration or candidal superinfection and the infiltrate may extend more deeply into the underlying lamina propria in a focal and perivascular or more diffuse distribution.

Apart from basal cell loss, the epithelial changes are typically those of hyperkeratosis. Strictly speaking those sites in the oral cavity that are non-keratinized, such as the buccal mucosa and lateral borders of the tongue, show keratosis and those that are normally keratinized, such as the gingivae, show hyperkeratosis (both may be either para- or orthokeratosis). It is these changes in keratinisation that are responsible for the white appearance clinically. In addition to changes in keratin production, the epithelium may be markedly atrophic and show total loss of the normal rete peg pattern with areas of ulceration. Occasionally flame or saw tooth-shaped rete ridges may be evident, but these are less common than in skin lesions. In some cases the epithelium is acanthotic and shows marked rete proliferation into the underlying lamina propria, giving an appearance that is almost pseudoepitheliomatous with apparently detached epithelial islands in the lamina propria. In other lesions atrophy may alternate with acanthosis. Multinucleate epithelial cells have been described and are usually binucleate, although rarely cells with more than three nuclei are seen.

Table 1 Lesions characterised by a lichenoid tissue reaction

Lichen planus
Lichenoid reactions associated with drugs
Lichenoid reactions associated with dental materials
Systemic or discoid lupus erythematosus
Graft versus host disease
Erythema multiforme

A number of lesions in the oral cavity are characterised by a lichenoid tissue reaction and these are shown in Table 1.

All these lesions show the essential features of the lichenoid tissue reaction, namely basal cell destruction and keratosis/hyperkeratosis associated with an infiltrate in the lamina propria. One of the challenges in oral mucosal pathology is whether it is possible to distinguish between them on the basis of the detailed histological characteristics. As a general rule this is difficult and almost all are a clinico-pathological diagnosis. However, there are some histological parameters that may be helpful in establishing the diagnosis and these will be discussed below together with the relevant clinical features. They are summarised in Table 2.

Lichen planus

The clinical and histological features of lichen planus were defined by the World Health Organization (WHO)[5] and although the criteria have not been validated there is general agreement in the literature as to what constitutes the clinical diagnosis of lichen planus. Clinically lesions are bilateral and symmetrical, usually multiple and affect the buccal mucosa, gingivae and/or lateral and dorsal aspects of the tongue. Rarely the hard palate may be affected. The oral lesions may occur with or without skin lesions and are typically reticular white striations (Wickhams striae) that may coalesce to form papules or plaques. Erosive

Table 2 Clinical features and histology of lesions characterised by a lichenoid tissue reaction

	Clinical features	Specific diagnostic histological features
Lichen planus	Bilateral, symmetrical lesions affecting buccal mucosa and/or tongue and gingivae	Band-like inflammatory infiltrate Absence of a deep infiltrate Absence of a perivascular infiltrate Absence of plasma cells and neutrophils No dysplasia
Lichenoid drug reactions	Temporal association with drug ingestion	None
Lichenoid reaction to dental materials	Typically unilateral	Deep infiltrate in some or all areas
	Associated with large amalgam restorations	Perivascular infiltrate Plasma cells and neutrophils in infiltrate
Discoid lupus erythematosus	Associated systemic or skin lesions Occasionally oral lesions may precede skin lesions	Keratin plugging Atrophy of rete processes Deep inflammatory infiltrate Oedema in lamina propria
Graft versus host disease	History of allogenic bone marrow transplant	None

and atrophic forms may often be seen and the oral mucosa appears erythematous and, in severe cases, ulcerated. Rarely, bullous forms occur. The cause of the lesions is not known and there is no association with drugs, amalgam restorations or other dental materials.

The histological features defined by the WHO[5,6] are essentially keratosis/hyperkeratosis, variable epithelial thickness but with atrophy predominating, saw tooth rete pegs, Civatte or colloid bodies, liquefaction degeneration of the basal cell layer, a thin band of eosinophilic material in the position of the basement membrane zone and a well-defined cellular infiltrate composed predominantly of lymphocytes in the superficial lamina propria. However, these criteria have not been validated and all these features may be seen in almost all the lichenoid reactions of the oral mucosa. Nevertheless certain histological features, particularly of the infiltrate, appear to be able to distinguish lichen planus from lupus erythematosus and at least some lichenoid reactions to dental materials. The infiltrate in lichen planus is composed predominantly of lymphocytes and macrophages and does not contain plasma cells, eosinophils or neutrophils. In addition it is band-like and closely associated with the epithelium and deep and perivascular infiltrates are not evident (Fig. 1).[7] However, when evaluating this, it is important to exclude the presence of candidal super-infection and ulceration which may complicate the histological picture.

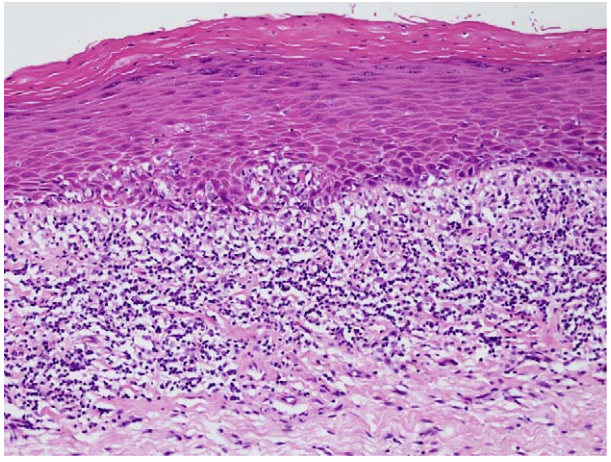

Figure 1 Lichen planus affecting the buccal mucosa. Note the marked parakeratosis and atrophy with loss of the normal rete peg pattern, basal cell destruction, Civatte bodies in the lower epithelial layers associated with intra-epithelial lymphocytes and a band-like infiltrate in the upper lamina propria.

There are no specific epithelial changes in lichen planus that are not seen in other lichenoid reactions and the epithelium may be atrophic or hyperplastic and acanthotic. However, keratin plugging is not usually evident and is more in keeping with a diagnosis of lupus, as is the presence of atrophy alternating with hyperplasia and a thick (>basal cell nucleus) sub-epithelial PAS deposit. This is discussed in greater detail below.

There is evidence that oral lichen planus is a pre-malignant lesion and shows a higher risk of malignant transformation than normal mucosa. The WHO estimates this risk to be between 2% and 3%,[6] but other authors consider it to be lower and between 0.04% and 1.74%.[8] This whole area has been controversial as many have argued that histological lichenoid tissue reactions may occur in pre-existing dysplastic lesions of the oral mucosa and that many cases of so-called malignant transformation are misdiagnoses.[9] Nevertheless there do appear to be some cases of true malignant transformation.[10] This, however, poses difficulties for the diagnostic pathologist as to whether epithelial dysplasia is an allowable diagnostic feature of lichen planus. The WHO states that dysplastic features are sometimes seen[6] but give no details on the type or degree of epithelial changes that are acceptable. Other authors argue that dysplasia negates a diagnosis of lichen planus.[8] Until this area is finally resolved the most sensible course of action is to diagnose any lesion showing a lichenoid tissue reaction and dysplastic changes as dysplasia and not as lichen planus. Accordingly clinicians will be able to ascertain the probable risk of malignant transformation and treat the patient appropriately. Ascribing the diagnosis of lichen planus with dysplasia runs the risk of inappropriate treatment. The histological features of dysplasia and their grading are discussed by Bouquot et al. in the chapter dealing with pre-malignant lesions of the oral mucosa.

Lichenoid reactions to drugs and dental materials

The clinical features occurring in patients with lichenoid drug reactions are similar to those occurring in lichen planus but in some cases lesions may be unilateral. The onset of the lesions corresponds to the commencement of medication and drugs that have been commonly associated are antihypertensive agents, oral hypoglycaemic drugs, antimalarial drugs, gold and penicillamine.[11]

Lichenoid lesions associated with dental material and, in particular, amalgam restorations are not uncommon. The clinical characteristics appear similar to lichen planus, but they are almost always unilateral and occur on the buccal mucosa and lateral border of the tongue in association with large amalgam restorations. These lesions tend to heal following removal and replacement of the amalgam. A proportion of patients may show skin contact hypersensitivity reactions to components of amalgam, in particular mercury, but this does not appear to be a particularly good indicator of response to amalgam removal.[12]

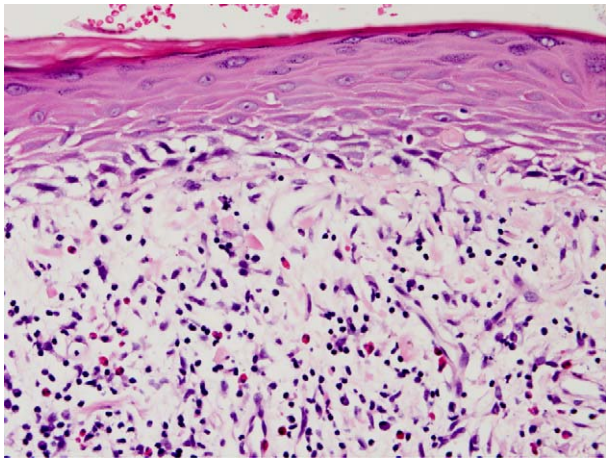

Figure 2 Lichenoid reaction of the gingivae. Note orthokeratosis, marked vacuolar degeneration of the basal cell layers with Civatte body formation and a diffuse infiltrate in the lamina propria containing eosinophils and plasma cells.

It is not possible to reliably distinguish lichenoid reactions to drugs and dental materials from lichen planus on histology alone. However, there are some indications that these lesions resemble discoid lupus erythematosus more closely than lichen planus.[13] The infiltrate is often not band-like but extends into the deeper connective tissue in a perivascular or diffuse distribution. Furthermore, neutrophils and plasma cells in the absence of ulceration have been described (Fig. 2).[7] However, without adequate clinical information these features are not sufficient to establish either diagnosis, which should be made primarily on clinical grounds.

Systemic and discoid lupus erythematosus

Oral mucosal lesions may occur in both systemic and cutaneous forms of lupus erythematosus and have been reported to appear before lesions elsewhere on the body.[14] Typical lesions in discoid lupus are characterised by central atrophy, small white keratinized plaques with elevated borders, radiating white striae and telangectasia and may occur primarily on the buccal and labial mucosa, alveolar processes and vermillion border of the lip. However, the spectrum of presentation is very broad and other lesions may resemble erosive lichen planus and show striae and erosions. Thus

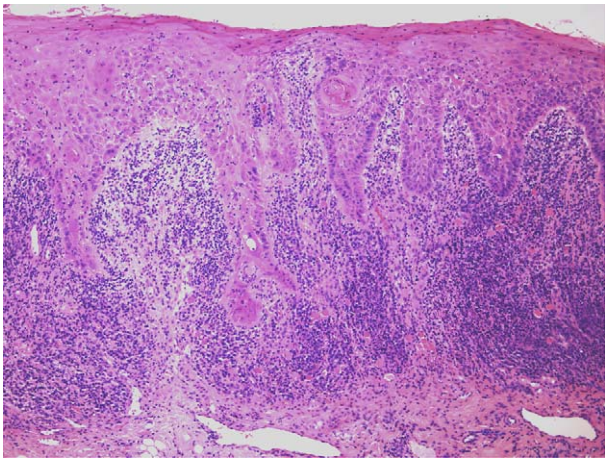

Figure 3 Discoid lupus erythematosus affecting the buccal mucosa. Note parakeratosis, atrophy alternating with hyperplasia, keratin plugging and a dense mixed chronic inflammatory cell infiltrate in the lamina propria with extension of the infiltrate into the deeper connective tissue and oedema in the superficial lamina propria.

the diagnosis of discoid lupus erythematosus can present difficulties particularly as the systemic and multi-system involvement is limited.

The histological appearance of oral lesions is variable and may be difficult to distinguish from lichen planus or lichenoid reactions to dental materials or drugs. Lesions are characterised by a lichenoid reaction and the following features have been described as characteristic: hyperkeratosis with keratin plugging, epithelial atrophy or atrophy alternating with hyperplasia and pseudoepitheliomatous hyperplasia, multinucleate epithelial cells containing three or more nuclei, liquefaction degeneration of the basal cell layers, deep patchy and/or perivascular lymphocytic infiltrate in the connective tissue and PAS-positive deposits in the basement membrane zone (Fig. 3). One study has analysed the histopathological features of discoid lupus erythematosus compared to lichen planus and found that any two of the following features have a sensitivity of 92% and 96% against lichen planus and leukoplakia, respectively: hyperkeratosis with keratin plugging, atrophy of the rete processes, deep inflammatory infiltrate, oedema in the lamina propria and a thick (>basal cell nucleus) continuous or patchy PAS-positive deposit juxta-epithelially.[13] In the skin, immunofluorescence is a useful diagnostic tool for lupus since deposits of immunoglobulin are characteristically found at the basement membrane zone.[15] However, in the oral mucosa, although immunoglobulin deposition has been found in 100% of lesions in systemic lupus only 73% cases of discoid lupus are positive.[16] Thus the sensitivity of using the above-mentioned histological criteria is greater than that of immunofluorescence.

Graft versus host disease

Graft versus host disease (GVHD) may develop following allogenic bone marrow transplantation and may be either acute or chronic. Oral lesions with white striations resembling lichen planus are most common and are found in up to 85% patients with chronic GVHD. The histological appearance is that of basal cell destruction and Civatte body formation often associated with lymphocytes at their margins—'satellite cell necrosis'—as well as a moderate lymphocytic cell infiltrate in the upper lamina propria and the lower epithelial layers. These features do not differ significantly from those of lichen planus, but one study has reported partial cleavage between the epithelium and connective tissues in 32% of cases.[17] However, it should be cautioned that this feature may sometimes be seen in lichen planus. The diagnosis is therefore essentially clinico-pathological.

Erythema multiforme

Erythema multiforme is an acute inflammatory reaction that may affect the skin and/or mucous membranes. It usually affects young individuals and the clinical features are variable with a spectrum of changes that vary from mild to severe. These have been classified as erythema multiforme minor, erythema multiforme major, Steven Johnson syndrome and toxic epidermolysis necrosis (TEN).[18] The oral lesions may precede the skin lesions and are typically macules or bullae that progress to ulceration, in particular affecting the non-keratinized mucosa of anterior parts of the mouth. The lips may be blood encrusted and show bullae or ulceration. Some lesions are recurrent and these, as well as a proportion of non-recurrent lesions, are triggered by herpes virus infection. The more severe forms of the disease—Steven Johnson syndrome and TEN—tend to be drug related.

The histological features of erythema multiforme are variable and diagnosis is often difficult. The epithelium is usually oedematous and there is a lymphocytic infiltrate in the upper lamina propria that may extend into the epithelium. The epithelial destruction may be very marked and there is often both sub and intra-epithelial bullae containing mononuclear cells (Fig. 4). The extent of the

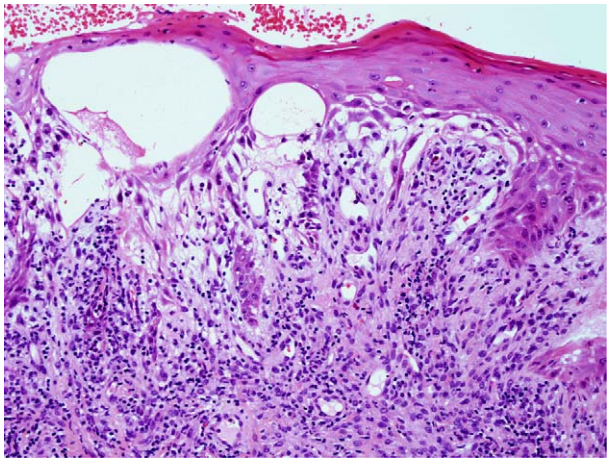

Figure 4 Erythema multiforme affecting the buccal mucosa. Note parakeratosis, marked epithelial destruction with sub- and intra-epithelial separation and oedematous lamina propria containing lymphocytes and macrophages.

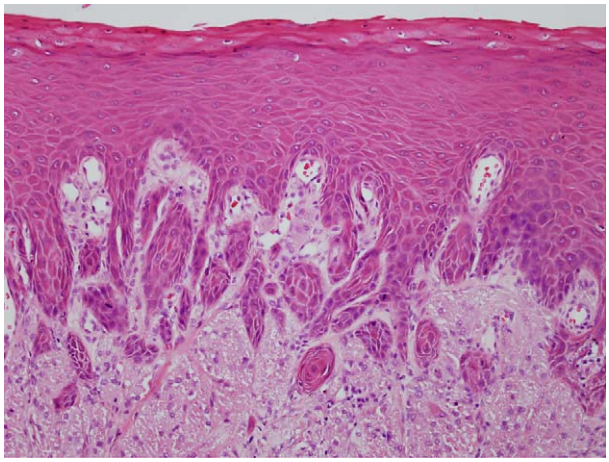

Figure 5 Pseudoepitheliomatous hyperplasia occurring in a granular cell tumour. Note the large polygonal cells with eosinophilic granular cytoplasm extending up beneath the epithelium.

infiltrate varies and does not necessarily correlate with the degree of epithelial destruction. Immunofluorescence shows granular staining for IgG at the basement membrane zone and around vessels.[19]

Lesions associated with pseudoepitheliomatous hyperplasia

Pseudoepitheliomatous hyperplasia of the oral mucosa is a common cause of diagnostic difficulty. It is characterised by marked epithelial hyperplasia with extension of rete pegs deeply into the underlying connective tissue. These may give the appearance of invasion if very extensive and may even show keratin pearl formation (Fig. 5). Cytologically the epithelium is usually normal with very little cellular atypia and although mitotic figures may be evident these are not abnormal. Five lesions of the oral mucosa are commonly associated with pseudoepitheliomatous hyperplasia: granular cell tumour, chronic hyperplastic candidosis, median rhomboid glossitis, necrotizing sialometaplasia and papillary hyperplasia of the palate. However, there have been other rare reports of pseudoepitheliomatous hyperplasia associated with pleomorphic adenoma of the minor salivary glands[20] and an intra-mucosal naevus.[21] Only the first five of these lesions will be discussed.

Granular cell tumour

These lesions may arise in a number of sites but 50% occur in the head and neck where the most common site is the tongue. They have also been described on the buccal mucosa, lower lip and sublingual papilla. They are slow growing, smooth, sessile swellings and usually occur in adults with a peak incidence between 40 and 60 years. The histological appearance shows that the underlying lamina propria is replaced by large polygonal cells with eosinophilic granular cytoplasm that typically stains positively with PAS. These cells are intimately associated and appear to merge with the underlying skeletal muscle. Immunostaining shows they are strongly positive for S100 but may also express CD68, neurone-specific enolase, calretinin, inhibin-alpha and PGP 9.5[22,23] and it is thought that they are derived from Schwann cells. In up to 30% of cases the epithelium may show marked pseudoepitheliomatous hyperplasia, which may be mistaken for squamous cell carcinoma (Fig. 5).

Chronic hyperplastic candidosis

Chronic hyperplastic candidosis (candidal leukoplakia) presents clinically as an adherent white or red and white patch and occurs most commonly at the commisure of the lips where it is often bilateral. However, it may also be unilateral and occur at other intra-oral sites such as the palate and lateral border of the tongue. It is often associated with angular cheilitis, denture stomatitis and smoking.

Histologically, it is characterised by atrophy alternating with acanthosis and typically the epithelium has elongated broad-based rete ridges that extend deeply into the underlying lamina propria (Fig. 6). In a few cases the proliferation

Figure 6 Typical example of chronic hyperplastic candidosis affecting the commisures of the lip. Note parakeratosis, disruption of the superficial epithelial layers by neutrophils, broad-based rete rides alternating with atrophy and a diffuse chronic inflammatory cell infiltrate in the lamina propria.

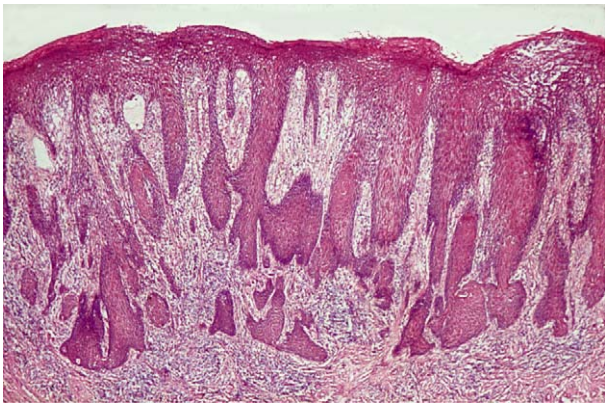

Figure 7 Marked pseudoepitheliomatous hyperplasia occurring in chronic hyperplastic candidosis.

may be very marked and give the appearance of invasion (Fig. 7). The surface usually shows mild parakeratosis and is disrupted by accumulations of neutrophils. These may be scattered or form micro-abscesses. Associated with these are fungal hyphae that typically invade the epithelium at right angles to the surface (Fig. 8). They may be very difficult to see on a routine haematoxylin and eosin (H/E) stained section but are more obvious using periodic acid schiff and appear either as an elongated tube-shaped structure or, if in cross-section, as a disc. Care should be taken to distinguish them from bacterial rods, which are smaller. The hyphae do not invade the epithelium below the level of the upper prickle cell layer and are often associated with loss of glycogen. A chronic inflammatory cell infiltrate including plasma cells is usually present in

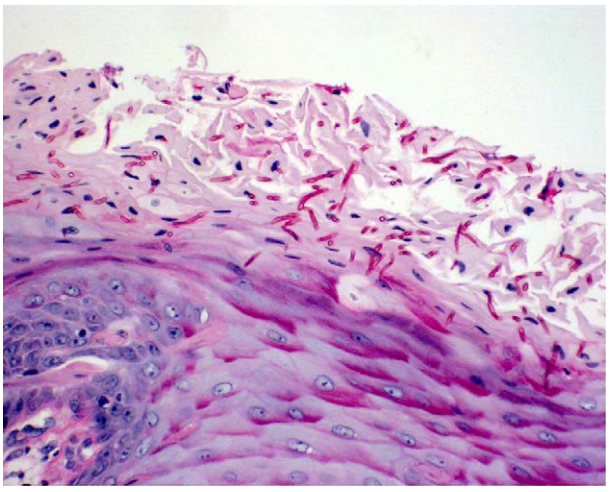

Figure 8 Chronic hyperplastic candidosis. Candidal hyphae infiltrate the superficial epithelial layers.

the upper lamina propria and lymphocytes may extend into the lower epithelial layers.

Basal cell proliferation is a common finding and mitotic figures may be numerous. Some cases are associated with cellular atypia and it is controversial whether this dysplasia is reactive to the candidosis. However, there is good evidence that candida is able to cause epithelial hyperplasia[24] and clinical studies have shown that treatment with antifungal agents may result in at least partial resolution of some lesions.[25] For the histopathologist it is important to recognise that marked epithelial proliferation may occur in response to candidal infection and in the absence of significant epithelial dysplasia should not be mistaken for a squamous cell carcinoma. If, however, cellular atypia is present then the lesion should be designated as chronic hyperplastic candidosis with dysplasia graded according to established criteria (see chapter by Bouquot et al. on pre-malignant lesions).

Median rhomboid glossitis

This lesion occurs characteristically in the midline on the dorsum of the tongue at the junction of the posterior third and anterior two thirds and appears as a reddened rhomboid-shaped patch. Histopathologically lesions resemble chronic hyperplastic candidiasis and show atrophy alternating with acanthosis and marked rete proliferation. There is loss of the normal filiform papillae on the epithelial surface and often candidal hyphae associated with neutrophils and micro-abscesses are present in the superficial epithelial layers. A chronic inflammatory

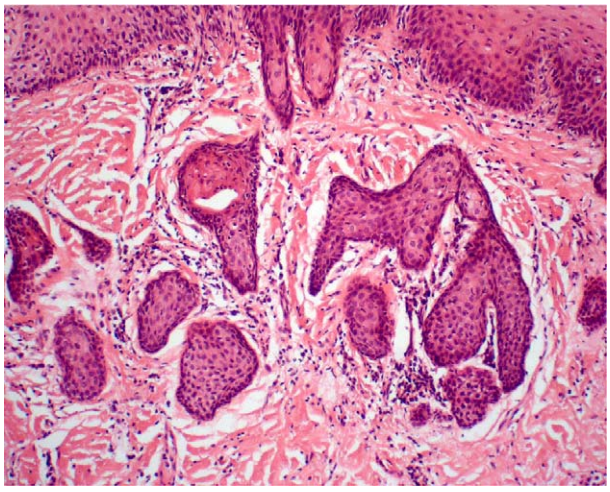

Figure 9 Necrotizing sialometaplasia. In this superficial part of the lesion the metaplastic ducts may be mistaken for invading carcinoma.

cell infiltrate is usually found in the upper lamina propria, which may show evidence of fibrosis. Cellular atypia is a not a feature and the lesion is not pre-malignant.

Necrotizing sialometaplasia

Necrotizing sialometaplasia is a rare, benign self-limiting lesion affecting the minor salivary glands. It typically presents as a long-standing, deep, crater-like ulcer on the hard palate and affects men more than women. It may be mistaken for carcinoma both clinically and histologically.[26] The lesion shows necrosis of the minor salivary gland acini with marked proliferation and squamous metaplasia of the ducts. Superficially these metaplastic ducts may resemble invading carcinoma (Fig. 9), but the epithelium is cytologically bland and duct lumina can usually be seen. In addition the overlying epithelium is typically ulcerated but may show marked pseudoepitheliomatous hyperplasia at the ulcer margin with epithelial islands extending deeply into the underlying connective tissue. The lesions are frequently inflamed and densely infiltrated by chronic inflammatory cells. The pseudoepitheliomatous hyperplasia and the ductal proliferation may be easily mistaken for a squamous cell carcinoma but the epithelium is cytologically bland and squamous cell carcinoma is relatively rare on the hard palate.

Papillary hyperplasia

This lesion occurs typically on the palate of patients who wear dentures that are ill-fitting or that are worn continuously. It is characterised by numerous erythematous papillary nodules. Histologically the lesion shows multiple papillary nodules of mucosa showing fibrous hyperplasia and epithelial acanthosis and parakeratosis. Occasionally there is marked pseudoepitheliomatous hyperplasia with keratin pearl formation.

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