Surgical pathology of the mouth and jaws

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9. White, red and pigmented lesions of the oral mucosa

Oral white lesions

The appearance of most oral white lesions is due to hyperkeratosis. Apart from the lingual filiform papillae, visible keratinization of any significant degree is abnormal in the mouth. Any excess keratin, becoming sodden with saliva, appears white. *Leucoplakia* literally means no more than a white plaque, but in the past was widely but incorrectly regarded as virtually synonymous with premalignancy. The term 'leukoplakia' should therefore be used only as defined by a World Health Organisation committee as 'a white patch of plaque which cannot be characterized clinically or pathologically as any other condition'.

A minority of white lesions can undergo malignant change, but hyperkeratosis *per se* is of no significance, except in so far as it may be associated with epithelial dysplasia. By no means all leucoplakias are premalignant, nor are all premalignant lesins white. As discussed later, erythroplastic (red) lesions are more frequently dysplastic than white lesions.

White sponge naevus

White sponge naevus is a developmental anomaly inherited as an autosomal dominant trait.

Clinically, the appearance is distinctive. The affected mucosa is white, soft and irregularly thickened. Unlike other white lesions, this anomaly can spread so widely as to involve the whole oral mucosa. It lacks well-defined borders and its edges fade imperceptibly into normal tissue. The anus and vagina can also be affected.

Microscopy

The epithelium is hyperplastic, with uniform acanthosis and the rete ridges having a smooth lower border. Shaggy hyperparakeratosis and intracellular oedema with abnormally prominent cell membranes produce a so-called basket-weave appearance. There is no dysplasia and inflammatory infiltration in the corium is typically absent.

Management

The appearance is readily recognized, particularly when there is widespread mucosal involvement. A positive family history is virtually confirmatory. If there is any doubt, a biopsy will confirm the diagnosis. Occasionally, patients relate that antibiotic treatment has caused the whiteness to disappear, but any such response is unreliable. The main requirement is to reassure the patient of the benign nature of the anomaly.

Pachyonychia congenita

Pachyonychia congenita is an uncommon congenital disorder, characterized by hypertrophy of the nail beds, skin lesions (particularly hyperkeratosis of the palms and soles) and oral white lesions. Premature eruption, including natal teeth, may be associated.

The oral lesions typically comprise areas of soft whitish mucosal thickenings (leucokeratosis). Typically, the leucokeratosis appears as widespread, translucent thickening of the mucosal surface, sometimes with localized white plaques. Leucokeratosis may be present in infancy but becomes prominent, especially in areas subject to trauma, over years. White sponge naevus, by contrast, produces considerably more diffuse and widespread white mucosal thickening and lacks ungual or cutaneous abnormalities.

Microscopically, the oral plaques show acanthosis and widespread hyperparakeratosis. The epithelial cells show intracellular vacuolation, somewhat like those of white sponge naevus, but in a more limited zone in the spinal cell layer and surrounded by normal cells. No treatment other than reassurance is required.

Fordyce's spots

Sebaceous glands may appear in the oral mucosa as creamy white spots a few millimetres in diameter. They are soft, symmetrically distributed and, increasing in number and size with age, may become conspicuous. The buccal mucosa is the main site, but sometimes the lips and rarely even the tongue are involved.

If these glands are mistaken for disease, patients can be reassured.

Dyskeratosis congenita

Dyskeratosis congenita is heritable as a rare recessive or dominant trait. Dysplastic lesions of the oral mucosa, dermal pigmentation, dystrophies of the nails and, occasionally, aplastic anaemia are the main features.

Clinically, oral white patches are seen in over 80% of patients or there may be inconspicuous erythematous areas. The cutaneous pigmentation is greyish brown, reticulate and predominantly affects the neck, arms and upper chest. The nails become dystrophic early and, by adolescence, may be completely destroyed. Alopecia is present in over 30% and haematological abnormalities in 51% of patients. Many patients also appear to be immunodeficient or have other abnormalities: the findings in 104 cases of the disease have been reviewed by Davidson and Connor (1988).

Microscopy

However slight the symptoms and however innocent oral lesions appear clinically, they frequently show epithelial atypical microscopically and the risk of carcinomatous change is high. Multiple oral carcinomas can result and the expectation of life is poor. Close observation and repeated biopsies should be prompted by the slightest symptoms to enable each tumor to be treated as early as possible.

The management is the same as for other dysplastic lesions, as discussed later, but overall the prognosis is poor. The mean expectation of life is less than 25 years. Causes of death include cancers of the mouth or other sites, and bleeding (gastrointestinal or cerebral), but in 50% of cases from infections, which are frequently opportunistic.

Frictional keratosis and cheek biting

This is caused by prolonged mild abrasion of the mucous membrane by such irritants as a sharp tooth, cheek biting or dentures.

Clinically, in the early stages the patches are pale and translucent, but later become dense and white, sometimes with rough surface. Habitual cheek-biting causes an area of buccal mucosa to appear patchily red and white with a rough surface.

Microscopy

The epithelium is moderately hyperplastic with a prominent granular cell layer and thick hyperkeratosis but no significant dysplasia. There are often scattered chronic inflammatory cells in the corium.

Management

Removal of the irritant causes the patch quickly to disappear and should make biopsy unnecessary. Frictional keratosis is completely benign, and there is no evidence that continued minor trauma alone has any carcinogenic potential.

Smoker's keratosis ('nicotinic stomatitis')

Smoker's keratosis is seen among heavy, long-term pipe smokers and some cigar smokers. The appearances are distinctive in that the palate is affected, but any part covered by a denture is spared. Changes are then seen only on the soft palate.

The lesion has two components, namely hyperkeratosis and inflammatory swelling of minor mucous glands; either may predominate, but typically, white thickening of the palatal mucosa is associated with small umbilicated swellings with red centres. The white plaque is sometimes distinctly tessellated.

Microscopy

The white areas show hyperorthokeratosis and acanthosis with a variable inflammatory infiltrate beneath. The diagnostic feature is the swollen, inflamed mucous glands with hyperkeratosis extending up to the duct orifice.

Management

The clinical appearances and history are so distinctive that biopsy should not be necessary. Though epidemiological evidence suggests that pipe smoking increases the risk of cancer, when oral cancer develops in associated with pipe smoking it typically appears not

in the keratotic area on the palate (one of the least common sites for cancer), but low down in the mouth, often in the lingual retromolar region. This may be the result of carcinogens pooling and having their maximal effect in drainage areas of the mouth. It also suggests that there are different causes for the hyperkeratosis and any carcinomatous change.

By contrast, there is no characteristic type of hyperkeratotic lesion association with cigarette smoking. The role of tobacco in the aetiology of oral cancer is discussed in Chapter 10.

The main requirement is to persuade the patient to stop smoking. The lesion then resolves remarkably quickly. Persuasion is reinforced by warning of the risk of malignant change and pointing out the damage already done.

Snuff dipper's keratosis and other smokeless tobacco lesions

Tobacco chewing or snuff dipping (holding flavoured tobacco powder in an oral sulcus) causes a white hyperkeratotic lesion. Oral snuff appears to cause more severe changes than tobacco chewing (Daniels et al, 1992) and is probably the main way in which smokeless tobacco is currently used in Western countries.

Clinically, the habit of snuff dipping may be maintained for decades and gives rise to keratoses in the area against which the tobacco is held - in the buccal or labial sulcus. Early changes are erythema and mild, whitish thickening. Long-term use gives rise to extensive leucoplakia-like thickening and wrinkling of the buccal mucosa.

Microscopy

The main changes are thickening of the epithelium with plump or squared-off rete ridges. There are varying degrees of hyperorthokeratosis or parakeratosis. Chevron keratosis is sometimes regarded as characteristic, but was seen in only 17% of 132 biopsies examined by Daniels et al (1992). Dysplasia may eventually by seen and, occasionally, malignant change can follow several decades of use. A high proportion of these carcinomas are verrucous.

The heaviest users of oral snuff in the Western world are in Sweden, but Larsson et al (1991), in an extensive study, found no carcinomas among them and stated that they have never been seen in the great number of biopsies from all parts of Sweden over many years.

Management

Diagnosis is based on the history of snuff use and the leucoplakia-like lesion in the area where the tobacco is held. Biopsy is required to exclude dysplasia or early malignant change.

Larsson et al (1991) have shown that snuff dipper's lesions will resolve on stopping the habit, even after 25 years of use. This therefore is the main measure. If this fails, regular follow-up and biopsies are required.

Syphilitic leucoplakia

Leucoplakia of the dorsum of the tongue is a characteristic complication of tertiary syphilis but is of little more than historical interest now.

Clinically, syphilitic leucoplakia has no distinctive features, but typically affects the dorsum of the tongue and spares the margins. The lesion has an irregular outline and surface. It is usually regarded as having a high risk of malignant change, and cracks, small erosions or nodules may be foci of invasive carcinoma. Carcinoma developing near the centre of the dorsum of the tongue is typically a sequel to syphilitic leucoplakia and, as a consequence of the great decline in late-stage syphilis, is exceedingly rare in this site now.

Microscopy

In addition to hyperkeratosis and acanthosis, often with dysplasia, the characteristic late syphilitic chronic inflammatory changes, with plasma cells predominating, may be seen. Giant cells and, rarely, more or less well-formed tuberculoid granulomas may be present. Endarteritis of small arteries is particularly characteristic. However, any distinctive features of a syphilitic tissue reaction may be totally lacking.

Management

The diagnosis is confirmed mainly by the serological findings. However, even if positive, biopsy is still essential as minute areas of malignant change may be found, and the management is affected accordingly. In particular, the presence of syphilitic endarteritis may be a contraindication to radiotherapy.

Antibiotic treatment of syphilis does not cure the leucoplakia, which persists and can undergo malignant change even after serology has become negative.

Candidosis

Candidosis can cause acute and chronic whitish lesions (thrush and chronic hyperplastic candidosis) and also red lesions such as denture stomatitis, as discussed later.

Thrush

Thrush, a disease recognized in infants by Hippocrates, can also affect adults and is then, as it was termed in the nineteenth century, a 'disease of the diseased'. This has been dramatically confirmed by its frequency in HIV infection.

Factors predisposing to thrush or chronic candidosis include immunodeficiency, anaemia and suppression of the normal flora of the mouth by antibacterial drugs. However, any adult male who develops thrush without apparent cause should be suspected of having HIV infection.

Clinically, the distinctive feature of thrush is that the patches can be wiped off to expose an erythematous mucosa. The patches are soft, friable, and creamy in colour. Their extent varies from isolated small flecks to widespread confluent plaque.

Microscopy

A Gram-stained smear shows large masses of tangled hyphae, detached epithelial cells and leucocytes. Biopsy shows hyperplastic epithelium infiltrated by inflammatory oedema and cells, predominantly neutrophils. Staining with PAS shows many candidal hyphae growing down through the epithelial cells to the junction of the plaque with the spinous cell layer. At this level there is a concentration of inflammatory exudate and inflammatory cells forming, in places, micro-abscesses. More deeply, the epithelium is hyperplastic but attenuated, with long slender processes extending down into the corium, surrounded by a light, predominantly lymphoplasmacytic infiltrate.

The microscopic appearances explain both the friable nature of the plaques of thrush and their ready attachment.

Management

If any local cause such as topical antibiotic treatment can be controlled, this alone may allow thrush to resolve. If not, a course of nystatin, amphotericin lozenges or miconazole gel should allow the oral microflora to return to normal. If the patient has HIV infection, the infection may respond to fluconazole or itraconazole, but candidosis is indicative of a poor prognosis.

Chronic hyperplastic candidosis (candidal leucoplakia)

Clinically, chronic oral candidosis produces a plaque, distinguishable only by biopsy from other leucoplakia-like conditions and may have malignant potential.

Adults, typically males of middle age or over, are affected. The usual sites are the dorsum of the tongue and the post-commissural buccal mucosa. The plaque is variable in thickness and often rough or irregular in texture, or nodular with an erythematous background, giving it a speckled appearance. Angular stomatitis may be associated, is sometimes continuous with intraoral plaques and suggests the candidal nature of the lesion.

Microscopy

The plaque cannot be wiped off, but fragments can be detached by firm scraping and, when Gram stained, shows clumps of epithelial cells with embedded hyphae.

Like thrush, the plaque of chronic candidosis is parakeratotic, but more coherent, containing only beads of inflammatory exudate which give it a psoriasiform appearance. In haematoxylin and eosin stained sections, hyphae appear as no more than clear or faintly basophilic trachs through the upper epithelium. Periodic acid-Schiff stain clearly shows the hyphae growing (as in thrush) through the full thickness of the plaque to the glycogen-rich

zone where the inflammatory exudate tends to be more concentrated and can form micro-abscesses.

Electron microscopy shows *Candida albicans* to be an intracellular parasite growing within the epithelial cytoplasm (Cawson, 1972): the hyphae, therefore, grow in relatively straight lines and do not follow a tortuous path along the intercellular spaces.

Acanthosis of the epithelium can sometimes be extensive with rounded down-growths, and there may be dysplasia. Induction of epithelial proliferation by *C. albicans* infection has been demonstrated experimentally (Cawson, 1973).

The chronic inflammatory infiltrate in the corium is variable in density, but may not break into the deeper epithelium. The basement membrane then remains intact and may appear to be thickened. This unusual feature in an oral keratotic lesion is typical of chronic candidosis.

Management

After confirmation of the diagnosis by biopsy, treatment should be with a systemically acting antifungal agent such as fluconazole, but this may have to be continued for several months. Other factors likely to perpetuate candidal infection should be controlled. Stopping the patient from smoking and elimination of candidal infection from under an upper denture are important. Any iron deficiency should also be treated.

Excision of candidal plaque alone is of little value, as the infection can recur in the same site even after skin grafting. Vigorous antifungal therapy is therefore essential, but sometimes some residual (uninfected) plaque may persist after treatment and probably, once the process has been initiated, it may become (as in syphilitic leucoplakia) autonomous.

Chronic mucocutaneous candidosis (CMCC) syndromes

These syndromes are all rare, but difficult to manage. The following classification is mainly based on that of Higgs and Wells (1974):

- familial (limited) type

- diffuse type (candida 'granuloma')

- endocrine candidosis syndrome

- late onset (thymoma syndrome).

Clinically, these syndromes differ from each other mainly in their extraoral features. Only the diffuse type shows significantly more severe candidal infection and may, therefore, be distinguishable from the other clinically. The microscopic features are essentially as described above.

The main features of these variants are as follows:

Familial (limited) mucocutaneous candidosis. Inheritance is by an autosomal recessive trait, though rarely the trait may be dominant. The onset is in infancy, with thrush-like plaques in childhood. Later the oral lesions become indistinguishable from those of sporadic cases of chronic hyperplastic candidosis, but there may be mild cutaneous involvement and sideropenia is characteristically associated.

Diffuse-type mucocutaneous candidosis. Most cases are sporadic, but there appear to be rare familial cases. This is the most severe type and was earlier termed 'monilial granuloma' by Hauser and Rothman (1950) because of the extensive, warty and often disfiguring overgrowths on the skin. However, there is no granuloma formation microscopically. Rather, the lesions are produced by epithelial proliferation and an extreme expression of the same process that produces oral epithelial plaques in response to candidal invasion.

These patients are usually also abnormally susceptible to bacterial diseases, particularly pulmonary and superficial suppurative infections.

Endocrine candidosis syndrome. In this variant, chronic mucocutaneous candidosis is associated with multiple glandular deficiencies and organ-specific autoantibody production. Nevertheless, there is no direct cause-and-effect relationship between the candidosis and the endocrine deficiency. The candidal infection can precede the onset of endocrine deficiency by as long as 15 years, but occasionally this sequence is reversed. Treatment of the candidosis does not affect the endocrine deficiency and vice versa.

The most common associated endocrine deficiency is hypoparathyroidism. For quite different reasons, hypoparathyroidism and chronic candidosis may also be associated in Di George's syndrome. A myth has therefore arisen that hypoparathyroidism confers susceptibility to candidosis.

Endocrine candidosis syndrome is a manifestation of type I chronic polyendocrinopathy. In the latter, Addison's disease and hypoparathyroidism are present in the great majority, and other glandular deficiencies can develop, but cadidosis is often so mild as to pass unnoticed.

Late onset mucocutaneous candidosis. This syndrome has a clear immunological basis, in that there is a persistent defect of cell-mediated immunity produced by a thymoma. In the full syndrome, myasthenia gravis and pure red cell aplasia are associated.

Management of mucocutaneous candidosis syndromes

Microscopic diagnosis of the candidal infection has been described earlier, but precise categorization may have to await development of other features of one of these syndromes, such as endocrine deficiency or elucidation of a relevant family history.

Immunological investigation, apart from detection of autoantibodies to glandular tissues in the endocrine candidosis syndrome, is not generally helpful, though detection of impaired or absent cell-mediated immunity to *C. albicans* strongly suggests that the patient

has one of the mucocutaneous candidosis syndromes rather than limited oral chronic hyperplastic candidosis.

The principles of management are, therefore, to treat the candidal infectin with antifungal drugs such as itraconazole and to deal with associated disorders as appropriate. Thus, antibacterial chemotherapy is necessary in diffuse-type CMCC, and endocrine replacement is essential in endocrine candidosis.

Lichen planus

Lichen planus occasionally causes plaque-like lesions, particularly on the dorsum of the tongue and in long-standing cases. The plaques may be thick, are characteristically snowy white and may have ill-defined margins giving them a fluffy or cottonwool-like outline. The microscopic features, management and possible risk of malignant change have been discussed in Chapter 8.

Lupus erythematosus

Both discoid and systemic lupus erythematosus can produce white lesions. These are rarely plaque-like, but are often associated with erosions. However, occasional cases of carcinoma developing in long-standing lesions of lupus erythematosus have been reported (Chapter 8).

Sublingual keratosis

A white soft plaque with a wrinkled surface, with an irregular but well-defined outline and sometimes with a butterfly shape, may appear in the sublingual region. The plaque typically extends from the anterior floor of the mouth to the undersurface of the tongue. There is usually no associated inflammation.

Microscopically, sublingual keratosis is not distinctive, but malignant change was associated in 24% of 29 cases reported by Kramer et al (1978). Such a high risk of malignant change has not been widely confirmed and it is puzzling that more than 20 years should elapse between the reporting of this potential and the description of sublingual keratosis as a harmless naevus by Cooke (1956).

Psoriasis

Psoriasis is a common skin disease estimated to affect 2% of the population. Oral psoriatic plaques are rare, but there is a significant associated between both benign migratory glossitis (geographical tongue) and stomatitis areata migrans (the counterpart in other parts of the oral mucosa), and cutaneous psoriasis, which these lesions closely resemble histologically.

Clinically, oral psoriatic plaques are typically associated with severe pustular psoriasis but occasionally with psoriasis vulgaris. The appearance of the oral lesions is variable. Whitish translucent plaques are most characteristic or there may be the circinate white lesions of migratory glossitis or stomatitis areata migrans. Macules, diffuse erythema and pustules

may occasionally be seen. Oral lesions are frequently asymptomatic and probably often unnoticed.

Microscopy

Oral lesions have essentially the same appearance as dermal lesions. There is parakeratosis, superficial spongiosis and an inflammatory infiltrate which can form spongiform pustules (Monro micro-abscesses) superficially in the epithelium. There may also be the characteristic pattern of acanthosis with long, slender, square-tipped or club-shaped epithelial downgrowths. The inflammatory infiltrate in the corium is usually sparse.

Like migratory glossitis, chronic candidosis and Reiter's disease can have a psoriasiform microscopic appearance. The diagnosis of oral psoriasis should only, therefore, be made when it has the characteristic microscopic features and is associated with cutaneous psoriasis.

Management

Since oral psoriatic plaques are so rare, biopsy should be carried out for any oral white plaque in a patient with psoriasis to exclude a coincidental disease. If, however, microscopy confirms the oral lesion to be psoriasis, no more than reassurance is required.

HIV-associated hairy leucoplakia

Patients with HIV infection may develop a clinically and histologically distinctive type of leucoplakia. The lateral margins of the tongue are usually affected, and the plaque is soft, white and usually asymptomatioc. The surface is vertically corrugated but only occasionally has hair-like filamentous projections of keratin.

Microscopically, hairy leucoplakia is characterized by hyperkeratosis with a ridged surface or, sometimes, hair-like extensions of keratin. Secondary invasion of the surface by candidal hyphae is relatively common, but microscopic features of candidosis are lacking. More important is the presence of *koilocytes,* which are vacuolated and ballooned prickle cells with pyknotic nuclei surrounded by a clear halo. There is little or no inflammatory infiltrate in the corium.

Epstein-Barr virus (EBV) capsid antigen can be identified in the epithelial cell nuclei and viral particles resembling EBV can be seen by electron microscopy. This finding appears to be unique to hairy leucoplakia, and the likelihood that the EBV is the aetiological agent is suggested by reports by Resnick et al (1988), among others, that hairy leucoplakia responds to treatment with acyclovir or its analogues. Langerhans cells may be few or absent, so that a defect of local immunity may contribute to the development of this lesion.

Management

The differential diagnosis is from other types of leucoplakia and from candidosis in particular. Other features of HIV infection or serum positivity are strongly suggestive, but biopsy is necessary if confirmation is required or serology is not permissible. Hairy

leucoplakia can rarely be seen in immunodeficient patients such as those receiving renal transplants and is not completely unique to HIV infection. However, patients with hairy leucoplakia are, with rare exceptions, HIV positive and 60-70% of them develop the full syndrome of AIDS within very few years. HIV-associated hairy leucoplakia is, therefore, an indication of a poor prognosis. Hairy leucoplakia does not appear to be precancerous, but the short expectation of life may preclude the realization of any such potential. Hairy leucoplakia has a remittant course and can regress spontaneously. If troublesome, acyclovir may be beneficial but Lozada-Nur and Costa (1992) recommend topical application of podophyllum resin sol as safe and avoiding the risk of development of tolerance to acyclovir.

Oral keratosis of renal failure

Leucoplakia-like oral lesions are an occasional and unexplained complication of long-standing renal failure.

The plaques are soft, have a crenated surface and are typically symmetrically distributed.

Microscopy

The features do not appear to be sufficiently distinctive to enable a diagnosis to be made without knowledge of the underlying disease; there is irregular acanthosis with mild atypia of the epithelial cells and moderate parakeratosis. The appearances are somewhat similar to those of hairy leucoplakia. Biopsy may be useful also to distinguish these lesions from adherent bacterial plaques, which may also develop in patients with renal failure.

Management

Since these plaques are secondary to renal failure, correction of the latter by effective dialysis or renal transplantation resolves the lesion spontaneously. No local treatment is necessary or likely to be effective.

Verruciform xanthoma

Verruciform xanthoma is a rare proliferative lesion which can have a white, hyperkeratotic surface.

Clinically, verruciform xanthoma is most common in the fifth to seventh decades. It is usually found on the gingiva but can form in almost any site in the mouth. It can be white or red in colour, be sessile or pedunculated, have a warty surface, and range in size from one to several centimetres across. It may be mistaken for a papilloma, leucoplakia or carcinoma clinically, but is readily recognizable histologically.

Microscopically, the warty surface is due to the much infoled epithelium which, in white variants, is hyperkeratinized, but may be merely parakeratinized. In haematoxylin and eosin stained sections, the parakeratin layer stains a distinctive orange colour. The rete ridges are uniformly elongated and extend to a straight well-defined lower border.

The diagnostic feature is the large, foamy, xanthoma cells which fill the connective tissue papillae but extend only to the lower border of the lesion. These cells contain lipid and PAS-positive granules.

Management

Verruciform xanthoma is benign and has no known associations with diseases such as hyperlipidaemia or diabetes mellitus associated with cutaneous xanthoma formation. Simple surgical excision is curative.

Oral submucous fibrosis

In oral submucous fibrosis (Chapter 8), affected areas of the oral mucosa such as the palate or buccal mucosa appear almost white. This is not a leucoplakia-like lesion, but the mucosa is typically smooth, thin and atrophic, and the pallor due to the underlying fibrosis and ischaemia, is symmetrically distributed. However, the epithelium may show dysplasia and leucoplakia may be associated. Murti et al (1985) reported the development of oral carcinoma in 7.6% of 66 patients with submucous fibrosis followed up for a median period of 10 years (Chapter 10).

Idiopathic (including dysplastic) leucoplakia

No aetiological factor can be identified for the majority of persistent white plaques. The histopathology is also highly variable, ranging from hyperkeratosis and hyperplasia to severe dysplasia.

The most extensive follow-up studies on leucoplakia suggest that this idiopathic group now has the highest risk of developing cancer. In most lesions of definable cause, the risk of malignant change is low, especially now that late-stage syphilis forms a negligibly small group.

Though there is no doubt about the malignant potential of leucoplakias, the level of risk cannot be accurately assessed from the histopathology. The largest study was carried out by Einhorn and Wersall (1967) and based on no fewer than 782 cases of histologically unspecified oral white lesions followed for an average of 12 years; of these, only 2.4% underwent malignant change in 10 years and less than 5% after 20 years. However, even this low rate represents a risk of malignant change 50-10000 times that in the normal mouth. It was also conspicuous that in this large study the rate of malignant change in oral leucoplakias was 10 times higher in non-smokers than in smokers. By contrast, in a study of 257 patients with leucoplakia who had been followed for an average of 8 years, Silverman et al (1984) found malignant transformation in 17.5%. However, malignant change was also more frequent among non-smokers. Earlier, Silverman et al (1976) had reported transformation rates of 0.12% in India and 6% in the USA. Other, smaller, series have suggested rates of 30% or more, though in many cases no time scale has been indicated, and the wide variation in the rate of malignant change in these different series suggests that the findings have been significantly affected by selection of cases.

It must be emphasized that these large-scale studies have been on histologically unspecified oral keratoses. Because of the rarity of dysplastic oral lesions there are very few studies, and none on a large scale, that have followed their progress for adequate periods. In the study by Mincer et al (1972), 45 patients with oral dysplastic lesions were followed for up to 8 years. Only 11% underwent malignant change in this period and up to 30% of them regressed or even ultimately disappeared spontaneously. Eveson (1983), in a review of published surveys, found that dysplastic lesions appeared to regress more frequently than to undergo malignant change. As a consequence, it is not possible to prognosticate soley on the basis of the histopathological changes. An additional problem is that, apart from the subjective nature of the assessment, if part is taken for biopsy purposes, there is no certainty that it is representative of the whole. The aetiology of cancer and of precancerous lesions overlap on many points and they are therefore discussed in the next chapter.

Clinical features

Idiopathic leucoplakias and dysplastic lesions do not have any specific clnical appearance. Small and innocent-looking white patches are as likely to show epithelial dysplasia as large and irregular ones. However, red (erythroplastic) lesions or erythroplasia in leucoplakias (speckled leucoplakia) are usually dysplastioc or frank carcinomas.

Microscopy

The epithelium may or may not be hyperplastic and is often thinner than normal. The plaque may show hyperortho- and parakeratosis in different parts, and the two may alternate along the length of the specimen. The epithelium is characterized by any of the cytological changes of dysplasia, namely:

- *Nuclear hyperchromatism.* The nuclei stain more densely due to increased nucleic acid content.

- *Nuclear pleomorphism and altered nuclear/cytoplasmic ratio.* The nuclei are variable in size, out of proportion to that of the cell; there may then be little cytoplasm surrounding the nucleus.

- *Mitoses.* They may be frequent or abnormal and at superficial levels.

- *Loss of polarity.* The basal cells in particular may lie higgledy-piggledy at angles to one another.

- *Deep cell keratinization.* Individual cells may start to degenerate long before the surface is reached and show eosinophilic change deeply within the epithelium. The term *dyskeratosis* applies only to this particular cellular change.

- *Differentiation.* The organization of the individual cell layers becomes lost and no clearly differentiated basal and spinous cell layers can be identified. Drop-shaped rete ridges are regarded as a particularly adverse feature.

- *Loss of intercellular adherence.* The boundaries of the cells may become separated.

A lymphoplasmacytic infiltrate of highly variable intensity is usually present in the corium.

Carcinoma-in-situ

Carcinoma-in-situ is a controversial term used for severe dysplasia where the abnormalities extent throughout the thickness of the epithelium - a state sometimes graphically called 'top-to-bottom change'. All the cellular abnormalities characteristic of malignancy may be present; only invasion of the underlying connective tissue is absent.

Top-to-bottom epithelial dysplasia, like other dysplastic lesions, has no characteristic clinical appearance. Erythroplasia, however, as discussed below, often proves to be carcinoma-in-situ or early invasive carcinoma.

Management of dysplastic lesions

The management of dysplastic oral lesions remains controversial, as their relative rarity has made it impossible as yet to accumulate enough data to make reliable predictions. It is frequently also assumed that dysplasia is no more than an early stage in the development of carcinoma which will subsequently behave like any other carcinoma. This leads to the assumption that treatment of dysplastic lesion provides an opportunity to treat carcinoma at an exceptionally early, and potentially curative, pre-invasive stage.

In contrast to an optimistic viewpoint of this sort, are the findings (discussed earlier) in the large survey where Einhorn and Wersall (1967) discovered, after prolonged follow-up, that lesions which had been treated by surgery more frequently became frankly malignant than those which had not. Though selection of patients may have biased these results, they certainly do not endorse the value of surgery.

From the histological viewpoint it is also noticeable that the degree of atypia in many dysplastic lesions is considerably more severe than that seen in many frank carcinomas of the mouth. This may possibly be an indicator (on the assumption that the degree of differentiation of carcinomas is a guide to prognosis) of particularly aggressive behaviour.

Further, small dysplastic lesions, despite excision, can be followed by multiple carcinomas and a fatal outcome, as confirmed by the report of Shibuya et al (1986) of 522 cases of carcinoma or carcinoma-in-situ (severe dysplasias) of the tongue. They found that the risk of multiple carcinomas was 5 times greater in patients with carcinoma preceded by leucoplakia than those carcinomas which had no such precursor. This large study, therefore, appears to confirm the possibility that some dysplastic leucoplakias may have a worse prognosis than isolated carcinomas without leucoplakia. Though such phenomena may be described as 'field change', this hardly helps either the patient or the surgeon.

By contrast, there is the evidence, discussed earlier, that many dysplastic lesions can regress spontaneously. It is clear, therefore, that the behaviour of dysplastic lesions is unpredictable and that there is no reliable protocol of management. If they are of manageable

size, it is tempting to excise them - this can presumably do no harm, but it is essentially a treatment of hope rather than certainty. Prolonged, close follow-up is therefore essential. Even then, the prognosis may be poor. An alternative policy is to avoid surgical intervention unless there are signs of progression and deterioration.

Another approach is cryotherapy ablation. In the short term the area usually heals rapidly to leave an apparently normal mucosa. However, there is some uncertainty about the risk of invasive carcinomas subsequently arising in sites previously treated by cryotherapy. Carbon dioxide laser ablation has also been advocated, but the same objections may apply.

Treatment with systemic or topical retinoids has also been tried. Topical retinoids are largely ineffective and though a proportion of white lesions resolve with systemic treatment, the toxic effects are usually unacceptable. Further, lesions which resolve with treatment, recur on withdrawal of the drugs. More recently Lippman et al (1993) have reported that high-dose induction followed by low-dose systemic isoretinoin did not cause an unacceptable degree of toxicity, stabilized the majority of lesions and was more effective than beta-carotene in preventing malignant change in oral leucoplakia. This seems an approach worth pursuing for lesions which are so readily accessible for clinical and pathological assessment of progress.

With regard to possible predictors of malignant change in leucoplakias, there is good evidence that such change is more common in women. This also appears to apply to malignant change in lichen planus, as disccess earlier.

In summary, frequent clinical observation, preferably with photographic records, and immediate biopsy of any suspicious or changing areas is the best that can be offered.

Speckled leucoplakia

This term applies to lesions consisting of white flecks or fine nodules on an atrophic erythematous base. They can be regarded as a combination of or transition between leucoplakia and erythroplasia; speckled leucoplakia also more frequently shows dysplasia than lesions with a homogeneous surface. The histological characteristics are usually, therefore, intermediate between leucoplakia and erythroplasia.

Many cases of chronic candidosis have this appearance.

Erythroplasia ('erythroplakia')

In contrast to the foregoing lesions, erythroplasias are red. The surface is frequently velvety in texture and the margin may be sharply defined. Lesions of this type typically do not form plaques (hence the term 'erythroplakia' is inappropriate) but, instead, their surface is often depressed below the level of the surrounding mucosa. Erythroplasia is uncommon in the mouth.

Microscopy

Erythroplastic lesions usually show epithelial dysplasia which may be severe. In other cases, there may be micro- or frankly invasive carcinoma. The risk of development of cancer is, therefore, highest in these lesions if they are not already carcinomas.

Early squamous cell carcinoma

Occasionally, early carcinomas produce sufficient surface keratin to appear as white plaques. They should not be confused with carcinomatous change in pre-existing leucoplakia. These carcinomas are always small (5-7 mm across), since further progress produces a more typical mass or ulcer.

Red, purple and pigmented mucosal lesions

One of the most important considerations is to exclude erythroplasia as the cause of a localized red area by biopsy. Other possible causes include the following.

Vitamin B_{12} deficiency. Exceptionally rarely, pernicious anaemia can cause red areas simulating erythroplasia. However, they are transient, only to reappear in another site. These are associated with a raised mean corpuscular volume in the blood picture or, later, the typical haematological features of pernicious anaemia.

More characteristic of pernicious anaemia is a pattern of red streaks on the dorsum of the tongue (Chapter 8). Generalized redness of the dorsum of the tongue can be seen in any type of anaemia.

Candidosis. Candidal infection can cause patchy or widespread erythema according to the following circumstances. Angular stomatitis may be associated with any of them and is a sign of candidosis.

- *Denture-induced stomatitis.* Occlusion of the mucosa under a well-fitting upper denture cuts it from the protective effects of saliva and creates a localized area of xerostomia. In susceptible patients this can promote candidosis. This is seen as an area of erythema sharply limited to the area of mucosa covered by the upper denture. Microscopically, direct Gram-stained smears show candidal hyphae and some yeast forms which have proliferated in the interface between denture base and mucosa. Histologically, there is mild acanthosis with prominent blood vessels superficially and a mild chronic inflammatory infiltrate. There is no plaque formation unless anaemia or any immune defect promotes the formation of patches of thrush in the erythematous area or elsewhere.

- *Generalized candidal erythema.* Xerostomia promotes candidal infection and in conditions such as Sjögren's syndrome, the whole of the oral mucosa becomes red and sore. Resolution follows use of nystatin suspension or miconazole gel held in the mouth.

A clinically similar condition, *antibiotic stomatitis,* can follow overuse or topical oral use of antibiotics, especially tetracycline, as a result of suppression of normal, competing oral

flora, but is infrequently seen now. Resolution may follow withdrawal of the antibiotic, but is accelerated by topical antifungal treatment.

- *Erythematous candidosis.* Though this term can be, and sometimes is, applied to any of the foregoing forms of candidosis, it is frequently now restricted to patchy, red mucosal macules due to this infection in HIV-positive patients. It is a sign of depletion of T-helper lymphocytes and may precede any of the other types of candidosis. If resistant to topical nystatin, resolution may be obtained with fluconazole or itraconazole, but development of full-blown AIDS must be anticipated within a few years.

Amelanotic melanoma. As discussed below, approximately 15% of oral melanomas are amelanotic and appear red but are equally malignant.

Haemangiomas. These may form localized purple malformations, but mucocutaneous angiomatosis (Chapter 13) typically forms large red areas of mucosa sharply delimited by the midline.

Isolated haemangiomas form flat or nodular lesions which are typically sharply defined and blanch on pressure. If small, this can readily be demonstrated by compressing them with a glass microscope slide.

Kaposi's sarcoma. This tumour must be excluded in any patient with a red or purple area or nodule on the palate or any other mucosal site. Kaposi's sarcoma in a male below the age of about 50 who is not having immunosuppressive treatment is pathognomonic of HIV infection (Chapters 13 and 14).

Telangiectases. Telangiecatases are small, localized abnormalities of superficial blood vessels. They are usually either a manifestation of hereditary haemorrhagic telangiectasia (HHT) or may be the result of previous irradiation. HHT is readily recognizable by the multiple small (pinhead) purplish lesions scattered about the oral mucosa and also on the lips and skin. Significant oral bleeding from this cause is rare. Irradiation telangiectasia is recognizable not merely from the history but also by the pallor of the surrounding mucosa due to ischemia secondary to obliterative endarteritis and fibrosis.

Lingual varices. Varices form on the underside of the tongue in the elderly and if they are noticed and alarm the patient, reassurance should be given.

Purpura and blood blisters. Purpura can cause blood blisters or more extensive macular ecchymoses in the oral mucosa, particularly where there is pressure, as under the post-dam line of an upper denture. Haematological investigation and assessment of haemostatic function are necessary to find the underlying cause before there is a more severe bleeding episode, and to start treatment if necessary. The main conditions to be considered are idiopathic (autoimmune) thrombocytopenic purpura, acute leukaemia or drug-associated purpura. Autoimmune thrombocytopenic purpura is typically more common in women, but when AIDS-associated, is more frequent in men.

Localized oral purpura. In this harmless condition, blood blisters form in the oral mucosa as a result of minor or unnoticed trauma without any abnormality of haemostasis. It is probably due to abnormal fragility of oral mucosal blood vessels.

Rupture of these blisters leaves a sore area, but healing is otherwise uneventful. Occasionally such blisters can form in the palate or throat and cause a choking sensation ('angina bullosa haemorrhagica'). A long history of recurrent oral blood blisters without either skin purpura or any other haemorrhagic episodes is usually enough to exclude systemic purpura. However, the latter should be excluded by haematological examination and the patient can then be reassured.

Bullous diseases. In bullous diseases, particularly mucous membrane pemphigoid, the blisters can become filled with blood. Biopsy should make the diagnosis clear (Chapter 8) and it is rarely necessary to have a blood picture to exclude purpura.

Melanomas and pigmented naevi

Malignant melanoma of the oral cavity has a poor prognosis and must be distinguished from other pigmented lesions such as naevi and the common amalgam tattoos.

Terminology. Melanocytes are of neuroectodermal origin, but migrate to the basal cell layer of the skin and oral mucosa where they form variable amounts of melanin and transfer it via dendritic processes to adjacent keratinocytes.

Heavier pigmentation may be due to more rapid synthesis and formation of coarser granules of melanin (as in coloured races) or to proliferation of melanocytes, or both.

Junctional activity is the term given to proliferation of melanocytes at the epitheliomesenchymal junction and protrusion of such foci into the corium. In adults, junctional activity suggests the possibility of malignant change.

Compound naevi show junctional activity together with clusters of naevus cells in the corium. In such cases, melanocytes appear to be dropping off the basal layer. Compound naevi are benign, but intraoral malignant melanomas are invariably compound in character.

Oral melanotic naevi

Pigmented naevi far more frequently affect the skin than the mouth. They are well circumscribed and most commonly macular or slightly raised and only very rarely polypoid. They can be brown, bluish, grey or almost black and only about 15% are non-pigmented and reddish. The palate is the most common site and women seem to be affected in the ratio of 2 to 1.

Microscopically, most melanotic naevi are intramucosal and show the naevus cells lying freely or in circumscribed groups (theques) in the corium.

Compound mucosal naevi are rare and may be difficult to distinguish from malignant melanoma if trauma has induced proliferative cellular activity. Junctional naevi of the oral mucosa are even more uncommon.

Blue naevus

Blue naevi form about 35% of all oral naevi and are characterized by normal epithelium, but spindle-shaped pigmented melanocytes and melaning-containing macrophages (melanophages) are loosely grouped together in the corium and are typically well separated from the epithelium.

Oral melanotic macule

These freckle-like pigmented macules are most commonly of the lip or buccal mucosa.

Microscopically, pigmentation is confinred to the basal cell layer or immediately adjacent keratinocytes, but the epithelium and corium are otherwise normal.

Oral and labial melanotic macules may be associated with HIV infection and have been found in 2-6% of these patients.

Melanoacanthoma

Melanoacanthoma is an exceptionally rare pigmented lesion which may also show papillomatous proliferation. It may be a sequel to trauma, and may regress after incomplete excision. Melanoacanthoma may therefore, be reactive rather than neoplastic.

Microscopically, the epithelium is acanthotic and contains clear cells and melanin-producing melanocytes with dendritic processes.

Management of benign pigmented lesions

All pigmented lesions need to be treated by excision biopsy to exclude the possibility of malignant melanoma. Since most benign lesions are small, excision is curative. As a general guide, naevi are more common in younger people (aged up to 40 years), are usually small, and appear to be static.

Malignant melanoma

Oral melanomas are rare. The peak age incidence is between 40 and 60 years; nearly 50% are on the hard palate and about 25% are on the upper gingivae. About 30% of melanomas are preceded by an area of hyperpigmentation, often by many years. Pigmentation varies from black to brown, while rare non-pigmented melanomas (15% of oral melanomas) are red. Oral melanomas may be flat but are usually raised or nodular, and asymptomatic initially, but may later become ulcerated, painful or bleed. Because of their rapid growth, most oral melanomas are at least a centimetre across, and approximately 50% of patients have metastases at presentation.

Microscopically, malignant melanocytes invade both epithelium and connective tissue. Malignant cells may be round, spindle-shaped or both and there may be associated pseudoepitheliomatous hyperplasia.

Superficially spreading melanomas, which are considerably more rare in the mouth than on the skin, have a pre-invasive phase when atypical melanocytes with clear areas of cytoplasm (pagetoid cells) are clustered along the epitheliomesenchymal junction. Growth is radial rather than invasive, and there may be a few scattered melanocytes in the superficial corium associated with sparse inflammatory cellular infiltrate. Active invasion follows after a variable period.

Lentigo maligna, although not uncommon in the facial skin, is an exceptionally rare oral variant of melanoma, and is distinguished only but its microscopic features. A better prognosis for this variant when in the mouth has not been confirmed.

Prognosis and management

Clinically, size and rapid growth, particularly if associated with destruction of underlying bone or presence of metastases, are obvious indicators of a poor outcome.

Microscopically, tumour thickness, measured in millimetres from the granular cell layer to the deepest identifiable melanocyte (the Breslow thickness), is the main guide to prognosis. With cutaneous melanomas the 5-year survival rate is inversely proportional to the Breslow thickness. The poor prognosis of oral melanomas is probably due to their late detection tham more conspicuous skin tumours.

Other indicators of poor prognosis are malignant melanocytes in blood vessels and multiple, or atypical, mytoses. The morphology of the melanocytes or the amount of melanin does not appear to affect the outcome.

Once the diagnosis has been confirmed, the only hope of cure is provided by the widest possible excision followed by radical radiotherapy. There is no evidence that chemotherapy is of significant value except for palliation. The overal 5-year survival rate appears to be about 5%.

Secondary melanomas

Secondary melanomas have very occasionally been reported in the oral cavity and in the parotid gland. If unpigmented and anaplastic, they may pass unrecognized if the possibility is not suspected. S-100 protein is a marker for melanocytes, but not specific to these cells. More specific antibodies such as HMB 45 are now available.

Melanotic neuroectodermal tumour of infancy (progonoma)

This rare tumour appears almost exclusively in the first year of life. It is intraosseous but the pigmentation may show through the mucosa and appear as a purplish area. It has been discussed more fully in Chapter 5.

Miscellaneous oral pigmentations

Amalgam tattoo

Amalgam tattoos are the most common cause of localized oral pigmentation. They form painless, bluish black macules usually less than a centimetre in diameter, with well-defined, or diffuse and irregular, margins. The mucosa close to the teeth or floor of the mouth are the common sites. They usually arise from mucosal abrasions during cavity preparation contaminated with amalgam fragments, from fractured restored teeth at the time of extraction, or from apicectomies sealed with retrograde amalgam restorations.

Microscopy typically shows dark, refractile particles of amalgam in the corium. The granules are black or brownish and tend to be deposited along collagen bundles and around small blood vessels. They are also found in nerve sheaths, around elastic fibres and in muscle, and may be present in the cytoplasm of macrophages, multinucleated giant cells or fibroblasts. Frequently there is no tissue reaction, but in about 30% of cases there may be a foreign body reaction or macrophage accumulations.

Intraoral radiographs with low penetration may sometimes show a small fragment of amalgam within the lesion and, when present, confirms the diagnosis. The only importance of these pigmentations is to distinguish them from naevi or melanomas and for this reason they should be excised for microscopy whenever there is doubt.

Peutz-Jeghers syndrome

This syndrome comprises intestinal polyposis and melanotic macules of the face, mouth, and less commonly of hands and feet. It is inherited as an autosomal dominant characteristic, but only about half the patients have a family history of the syndrome.

There are multiple freckles on the lips and oral mucosa, particularly the mucosal aspect of the lower lip and the buccal mucosa and around the nares. Facial pigmentation is mainly around the mouth, eyes and nose; it usually fades after puberty, but the mucosal pigmentation persists. Microscopy shows increased melanin in the basal keratinocytes.

Polyps may be present throughout the gastrointestinal tract, and in the small bowel can cause recurrent abdominal pain and minor intestinal obstruction. The polyps, which are hamartomas, have a low malignant potential and malignant transformation is rare.

Addison's disease (hypoadrenocorticism)

Addison's disease is rare. Bilateral destruction of the adrenal cortices was usually due to tuberculosis in the past, but the majority of cases are now due to organ-specific autoimmune disease or to histoplasmosis in immunodeficient patients. Addison's disease, therefore, occasionally now appears in AIDS patients as a result of opportunistic infections of the adrenal glands.

Clinically, pigmentation of the skin and oral mucosa is an early sign. The skin becomes bronzed, particularly in exposed parts, areas subjected to friction or trauma, skin folds and scars. Occasionally vitiligo is the predominant feature.

Oral pigmentation varies from light brown to almost black and can affect the gingivae, tongue (particularly the lateral margins), buccal mucosa and lips. Microscopy shows increased melanotic pigmentation, mainly of basal keratinocytes.

Weakness, lassitude, gastrointestinal disturbance, weight loss and hypotension may develop. Occasionally, oral white lesions of chronic mucocutaneous candidosis are present and indicative of polyendocrinopathy syndrome type I, as discussed earlier.

Investigation typically shows low serum levels of sodium and chloride but raised potassium and urea. The diagnosis can be confirmed by a tetracosacrtin (a synthetic ACTH-like polypeptide) test to measure the plasma cortisol response half an hour after an injection. Low plasma cortisol (< 5 microg/dL) is diagnostic. However, Addison's disease is probably the least common cause of intraoral pigmentation, and such investigations should not be initiated in the absence of other suggestive clinical features.

Mucosal pigmentation in AIDS

Diffuse oral pigmentation can be seen in some patients with HIV infection. Pigmentation may be drug-associated or due to Addison's disease. In others, no cause other than HIV infection can be found. As mentioned earlier, oral melanotic macules may also be seen.

Racial pigmentation

This is the most common cause of widespread oral mucosal pigmentation and is seen particularly in Blacks, Asians and people of Mediterranean origin. Brown to almost black pigmentation is symmetrically distributed on the gingivae, palate, buccal mucosa and elsewhere, but its intensity is not directly related to the darkness of the skin. About 5% of adult Caucasians show similar pigmentation. Microscopy shows increased melaning pigmentation of the basal, and to a much lesser extent, suprabasal, keratinocytes.

Lichen planus

Degenerative changes in the basal keratinocytes may lead to pigmentary incontinence, particularly in coloured races, and this can result in an area of brownish pigmentation which persists long after the lichen planus has resolved.

Oral pigmentation and lung disease

Pigmentation of the soft palate may develop in patients with malignant or suppurative lung disease and is seen in nearly 25% of patients with bronchogenic carcinoma. Although most such patients are long-term smokers, the incidence of oral pigmentation appears to be much higher than in smokers without lung cancer.

Drug-associated pigmentation

Gingival pigmentation by heavy metals (mercury, lead, antimony, bismuth) was, in the past, a feature of industrial or therapeutic exposure to these agents. These metals caused blue, brown or black lines typically just short of the gingival margins and due to formation of sulphides as a result of reaction with plaque products. The cytotoxic drug cisplatin can cause a bluish gingival platinum line. Drugs which may cause diffuse mucosal pigmentation include the antimalarials, amodiaquine, chloroquine and mepacrine, busulphan, some contraceptive pills and phenothiazines. In patients with HIV infection, zidovudine, clofazimine, ketoconazole and pyrimethamine have been implicated in mucosal pigmentation.

Antibiotics and antiseptics used topically may cause pigmentation, particularly of the dorsum of the tongue due to overgrowth of pigment-forming bacteria.

Smoker's melanosis, with increased melanin formation, particularly in the attached gingivae, has been described but is less common or conspicuous than might be expected from the number of habitual smokers.

Black hairy tongue

This condition (see Chapter 3) is due to elongation of the filiform papillae which form hair-like overgrowths and become stained brown or black due to proliferation of chromogenic microbes. The causes are unknown, but heavy smoking and the use of antiseptic mouthwashes may contribute. The dorsum of the tongue may also become blackened without overgrowth of the filiform papillae in patients using antibiotic mouthwashes, particularly tetracycline.

Black hairy tongue only rarely resolves on stopping the underlying habit or antibiotic. Treatment is largely ineffective but the patient should be instructed to scrub the dorsum of the tongue daily with a toothbrush.