

CHAPTER 4

Tumours of the Oral Cavity and Oropharynx

Squamous cell carcinomas amount to more than 90% of malignant tumours of the oral cavity and oropharynx. As in other parts of the upper aerodigestive tract, there is a strong and synergistic association with tobacco smoking and alcohol abuse. In some regions, particularly the Indian subcontinent, oral cancer is among the most frequent malignancies, largely due to tobacco chewing.

The WHO Working Group has made an attempt to unify the terminology used to define the histological features of precursor lesions throughout the head and neck region. Although there has been considerable progress in the understanding of the genetic and molecular events underlying the progression of precancerous lesions to invasive carcinomas, this has yet to be translated into novel therapeutic strategies.

WHO classification of tumours of the oral cavity and oropharynx

Malignant epithelial tumours		Myoepithelial carcinoma	8982/3
Squamous cell carcinoma	8070/3	Carcinoma ex pleomorphic adenoma	8941/3
Verrucous carcinoma	8051/3	Salivary gland adenomas	
Basaloid squamous cell carcinoma	8083/3	Pleomorphic adenoma	8940/0
Papillary squamous cell carcinoma	8052/3	Myoepithelioma	8982/0
Spindle cell carcinoma	8074/3	Basal cell adenoma	8147/0
Acantholytic squamous cell carcinoma	8075/3	Canalicular adenoma	8149/0
Adenosquamous carcinoma	8560/3	Duct papilloma	8503/0
Carcinoma cuniculatum	8051/3	Cystadenoma	8440/0
Lymphoepithelial carcinoma	8082/3		
Epithelial precursor lesions		Soft tissue tumours	
Benign epithelial tumours		Kaposi sarcoma	9140/3
Papillomas	8050/0	Lymphangioma	9170/0
Squamous cell papilloma and verruca vulgaris		Ectomesenchymal chondromyxoid tumour	
Condyloma acuminatum		Focal oral mucinosis	
Focal epithelial hyperplasia		Congenital granular cell epulis	
Granular cell tumour	9580/0	Haematolymphoid tumours	
Keratoacanthoma	8071/1	Diffuse large B-cell lymphoma (DLBCL)	9680/3
		Mantle cell lymphoma	9673/3
		Follicular lymphoma	9690/3
		Extranodal marginal zone B-cell lymphoma of MALT type	9699/3
		Burkitt lymphoma	9687/3
		T-cell lymphoma (including anaplastic large cell lymphoma)	9714/3
		Extramedullary plasmacytoma	9734/3
		Langerhans cell histiocytosis	9751/1
		Extramedullary myeloid sarcoma	9930/3
		Follicular dendritic cell sarcoma / tumour	9758/3
		Mucosal malignant melanoma	8720/3
		Secondary tumours	

¹ Morphology code of the International Classification of Diseases for Oncology (ICD-O) {821} and the Systematized Nomenclature of Medicine (<http://snomed.org>). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

TNM classification of carcinomas of the oral cavity and oropharynx

TNM classification of carcinomas of the lip and oral cavity^{1,2}

T – Primary tumour

- TX Primary tumour cannot be assessed
- T0 No evidence of primary tumour
- Tis Carcinoma in situ
- T1 Tumour 2 cm or less in greatest dimension
- T2 Tumour more than 2 cm but not more than 4 cm in greatest dimension
- T3 Tumour more than 4 cm in greatest dimension

T4a (lip)

Tumour invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin (chin or nose)

T4a (oral cavity)

Tumour invades through cortical bone, into deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face

T4b (lip and oral cavity)

Tumour invades masticator space, pterygoid plates, or skull base; or encases internal carotid artery

Note: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumour as T4.

N – Regional lymph nodes##

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
- N2 Metastasis as specified in N2a, 2b, 2c below
- N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
- N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
- N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
- N3 Metastasis in a lymph node more than 6 cm in greatest dimension

Note: Midline nodes are considered ipsilateral nodes.

M – Distant metastasis

- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis

Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T3	N0, N1	M0
Stage IVA	T1, T2, T3	N2	M0
	T4a	N0, N1, N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

The regional lymph nodes are the cervical nodes.

TNM classification of carcinomas of the oropharynx^{1,2}

T – Primary tumour

- TX Primary tumour cannot be assessed
- T0 No evidence of primary tumour
- Tis Carcinoma in situ
- T1 Tumour 2 cm or less in greatest dimension
- T2 Tumour more than 2 cm but not more than 4 cm in greatest dimension
- T3 Tumour more than 4 cm in greatest dimension

T4a Tumour invades any of the following: larynx, deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), medial pterygoid, hard palate, and mandible

T4b Tumour invades any of the following: lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base; or encases the carotid artery

N – Regional lymph nodes##

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
- N2 Metastasis as specified in N2a, 2b, 2c below
- N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
- N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
- N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
- N3 Metastasis in a lymph node more than 6 cm in greatest dimension

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Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T3	N0, N1	M0
Stage IVA	T1, T2, T3	N2	M0
	T4a	N0, N1, N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

The regional lymph nodes are the cervical nodes.

¹ {947,2418}.

² A help desk for specific questions about the TNM classification is available at www.uicc.org/index.php?id=508.

Tumours of the oral cavity and oropharynx: Introduction

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Tumours of the oral cavity and oropharynx may be either epithelial, mesenchymal, or haematolymphoid. The epithelial tumours may be classified as those originating within the epithelium lining of the oral cavity and oropharynx and those derived from salivary gland tissue. Both will be included in this chapter, including precursor lesions where appropriate.

For the haematolymphoid diseases, the reader is referred to the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues {1197}, for mesenchymal ones to the WHO Classification of Tumours of Soft Tissue and Bone {775}.

Oral Cavity

The oral cavity extends from the lips to the palatoglossal folds. The outer vestibule is enclosed by the cheeks and lips and forms a slit-like space separating it from the gingivae and teeth. It is limited above and below by mucosal reflections from the lips and cheeks.

The space bordered by the teeth and gingivae is the oral cavity proper. It is bounded inferiorly by the floor of the mouth and tongue and superiorly by the hard palate. The buccal mucosa extends from the commissure of the lips anteriorly to the palatoglossal fold posteriorly. It is lined by thick, non-keratinized stratified squamous epithelium and contains variable numbers of sebaceous glands (Fordyce spots or granules) and minor salivary glands. The duct of the parotid gland (Stensen's duct) opens on a papilla or fold opposite the upper second permanent molar tooth.

The mucous membrane related to the teeth is the gingiva. The gingival mucosa surrounds the necks of the teeth and the alveolar mucosa overlies the alveolar bone and extends to the vestibular reflections. The junction between these two parts is marked by a faint scalloped line called the mucogingival junction. The gingival mucosa is pink and firmly attached to the underlying bone and necks of the teeth (attached gingiva) except for a free marginal area. It is usually non-keratinized or parakeratinized. The alveolar mucosa is reddish and covered by thin, non-keratinized stratified squamous epithelium.

Minor salivary glands may be seen in the alveolar mucosa and occasionally the attached gingiva.

The hard palate is continuous anteriorly with the maxillary alveolar arches and posteriorly with the soft palate. A median raphe extends anteriorly from this junction to the incisive fossa into which the nasopalatine foramen opens. Most of the palatal mucosa is firmly bound to the underlying bone forming a mucoperiosteum. It is covered by orthokeratinized stratified squamous epithelium and posteriorly contains many minor mucous salivary glands.

The oral part of the tongue (anterior two thirds) lies in front of the V-shaped sulcus terminalis. It is mobile and attached to the floor of the mouth anteriorly by a median lingual fraenum. The dorsal part is covered by stratified squamous epithelium and contains several types of papillae. The most numerous are the hair-like filiform papillae which are heavily keratinized. There are less numerous and evenly scattered fungiform papillae which form pink nodules and contain taste buds. Taste buds here and in other oral sites are occasionally mistaken for junctional melanocytic proliferation or Pagetoid infiltration. In front of the sulcus terminalis there are 10-12 circumvallate papillae. These contain many taste buds on the surface and in a deep groove that surrounds each papilla. In addition, the ducts of minor serous salivary glands

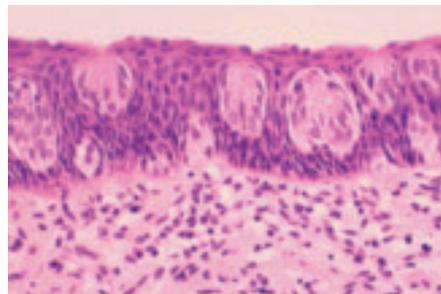


Fig. 4.1 Taste buds. Normal intraepithelial taste buds are sometimes confused with melanocytic lesions and pagetoid infiltration..

(von Ebner's glands) open into the base of the groove. At the postero-lateral aspect of the tongue where it meets the palatoglossal fold there are the leaf shaped foliate papillae. These also may contain taste buds on the surface and the core of the papillae often contains lymphoid aggregates similar to those in the rest of the Waldeyer ring. In addition, there are minor salivary glands in the underlying lingual musculature. The ventrum of the tongue is covered by thin, non-keratinized stratified squamous epithelium which is continuous with similar mucosa in the floor of the mouth. Minor salivary glands (glands of Blandin and Nuhn) are present, predominantly towards the midline and deep within the lingual musculature. They can extend to involve the tip of the tongue.

The floor of the mouth is a horseshoe-shaped area between the ventrum of the tongue medially and the gingivae of the lower teeth anteriorly and laterally. It extends to the palatoglossal folds distally and is in continuity with the retromolar pad behind the lower third molar tooth. The mucosa covers the major sublingual glands and the submandibular (Wharton's) ducts which open anteriorly onto the submandibular papillae on either side of the median sublingual fraenum. It is important to note that 75% of oral squamous cell carcinomas have been reported to arise in an area that comprises the floor of the mouth and adjacent lingual mucosa, sublingual sulcus and retromolar region {1767}. This region forms only about 20% of the total mucosal area. The zone of increased susceptibility has been called the 'drainage area' as it is thought that any carcinogens present in the mouth pool there before being swallowed. It is obvious, therefore, that any precursor lesions in these areas should be regarded as highly suspicious.

Oropharynx

The oropharynx lies behind the oral cavity. It is bounded superiorly by the soft palate and inferiorly by a hypothetical

horizontal line level with the tip of the epiglottis. Anteriorly are the isthmus of the fauces and the posterior third of the tongue, and the lateral wall is formed by the palatopharyngeal arches and the palatine tonsils. The posterior wall contains the pharyngeal tonsils.

The palatine tonsils are two masses of lymphoid tissue situated in the triangular recess (tonsillar sulcus) between the anterior and posterior faucial pillars. They extend from the soft palate to the dorsum of the tongue. The surface is convoluted and deep clefts or crypts can penetrate almost its full thickness. The bulk of the tonsil consists of lymphoid tissue arranged in nodules or follicles. There are no afferent lymphatics and no subcapsular sinuses. Squamous cell carcinomas at this site can invade deeply into the underlying tissues, base of tongue and lateral pharyngeal wall. They also have a particular tendency to extend upwards into the nasopharynx.

The soft palate is a mobile, muscular flap attached to the posterior edge of the hard palate and extending to a free margin posteriorly. The uvula forms a small, conical, midline process. The oral surface of the soft palate is covered by non-keratinized stratified squamous epithelium and contains many minor mucous glands. The uvula contains mainly fat and a few muscle fibres but minor salivary glands may also be seen and occasionally salivary gland tumours develop at this site.

The pharyngeal part of the tongue is immobile and has a bossellated surface due to the presence of underlying lymphoid tissue forming the lingual tonsils. Minor salivary glands are also present.

Lymphatic drainage of mouth and oropharynx

The main sites of lymphatic drainage from the mouth and oropharynx are the jugulodigastric, submandibular and submental lymph nodes. Lymph vessels from the gingiva usually drain to the submandibular lymph nodes but those in the lower incisor region run to the submental nodes. Most of the vessels from the palate run to the jugulodigastric group but some involve the retropharyngeal nodes. There is a rich lymphatic plexus in the tongue and the main vessels can be subdivided into marginal and central. The marginal vessels drain the lateral third of the dorsum and contiguous later-

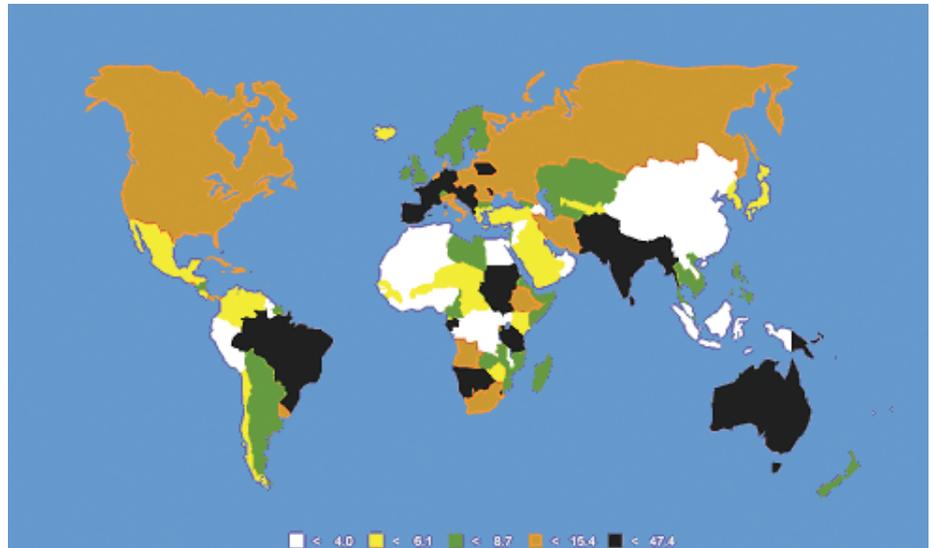


Fig. 4.2 Global incidence rates of tumours of the oral cavity and oropharynx (all ages) in males. Age-standardized rates (ASR, world standard population) per 100,000 population and year. From J. Ferlay et al., *Globocan 2000* {730}.

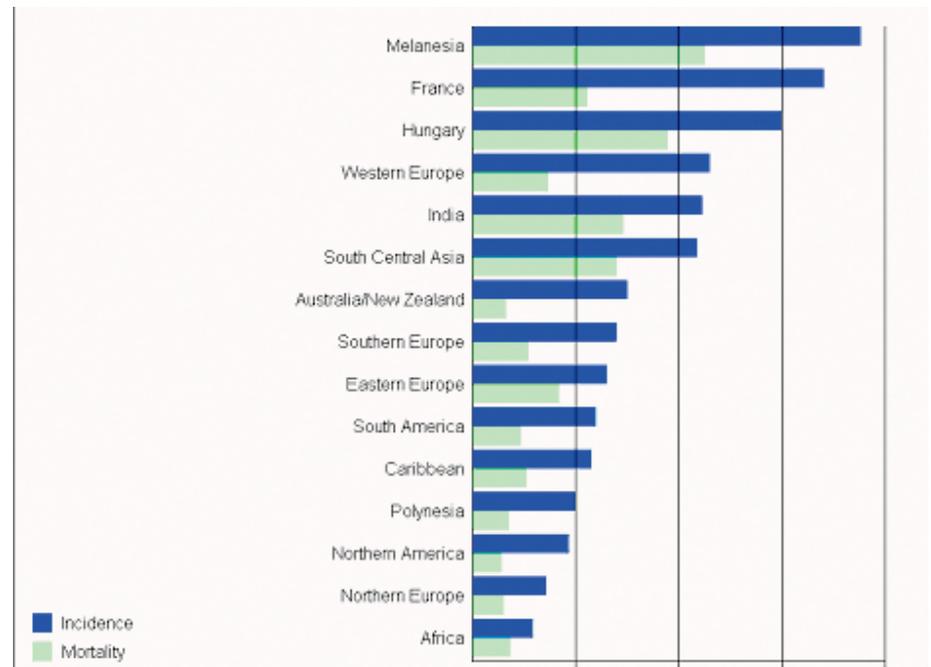


Fig. 4.3 Incidence and mortality rates for tumours of the oral cavity and pharynx (excl. nasopharynx), all ages, in males. Age-standardized rates (ASR, world standard population) per 100,000 population and year. From J. Ferlay et al., *Globocan 2000* {730}.

al border and part of the ventrum of the tongue. They run to the ipsilateral submandibular nodes. Those towards the tip of the tongue drain to the submental nodes. Central lymph vessels drain to the submandibular nodes on both sides. Some marginal and central vessels run directly to the jugulodigastric group but some can pass direct to the jugulo-omohyoid nodes. Vessels from the area of the circumvallate papillae and posterior third

of the tongue drain to the jugulodigastric, jugulo-omohyoid or intermediate nodes, either unilaterally or bilaterally. Most of the lymphatics of the palatine tonsils drain to the jugulodigastric nodes.

Squamous cell carcinoma

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Definition

An invasive epithelial neoplasm with varying degrees of squamous differentiation and a propensity to early and extensive lymph node metastases, occurring predominantly in alcohol and tobacco-using adults in the 5th and 6th decades of life.

ICD-O code 8070/3

Epidemiology

More than 90% of malignant neoplasms of the oral cavity and oropharynx are squamous cell carcinomas of the lining mucosae with relatively rare neoplasms arising in minor salivary glands and soft tissues. It is important to specify which anatomical sites are included in epidemiological data. Separate assessment of incidence rates for the oral cavity and oropharynx is complicated by the difficulty of assigning a site of origin to tumours that are often advanced.

Males are affected more often than females because of heavier indulgence in both tobacco and alcohol habits in most countries: in India the highest rates of intraoral cancer may be found in women who chew tobacco heavily. The male to female ratio is, however, globally lower for cancer of the oral cavity than for cancer of the oropharynx, perhaps suggesting that higher exposure to tobacco smoking and alcohol drinking are required to induce oropharyngeal than oral cancer {796}.

Globally some 389,650 cases occurred in the year 2000; 266,672 for the oral cavity (ICD-9 140-5) and 122,978 for the oropharynx (ICD-9 146,8-9) {1981}. This represents 5% of all cancers for men and 2% for women.

In males, the country with the highest rate in the western world is currently France, with extremely elevated rates also in French-speaking Switzerland, Northern Italy, Central and Eastern Europe (especially Hungary) and parts of Latin America. Rates are elevated amongst both men and women throughout South Asia. In the USA incidence rates are two-fold higher in Black men

than White men {1981}. Very high rates in the IARC database for Melanesia, presumably associated with areca nut and tobacco habits, are based on small numbers and need confirmation {730,1981}. The high incidence rates in Australasia are explained by lip cancer in fair-skinned races which has a comparatively low mortality rate.

Much of Europe and Japan is experiencing alarming rises in incidence, with a strong cohort effect, those born from approximately 1930 onwards showing significantly increased incidence and mortality. In North America there are statistically significant falls in Whites, but Blacks continue to show worse outcomes. Globally, with the exception of the most highly specialized treatment centres, survival rates have not improved for decades.

Significant increases in incidence in younger subjects, particularly males, have been reported from many western countries in recent decades {1534,2259}.

Etiology

Tobacco smoking and alcohol

The dominant risk factors are tobacco use and alcohol abuse, which are strongly synergistic {228}. Alcohol and tobacco account for 75% of the disease burden of oral and oropharyngeal malignancies in Europe, the Americas and Japan {227,1862}. For the highest levels of consumption compared to the lowest ones relative risks from 70 to over 100 have been shown {287,1811}. Relative risks in case-control studies showing a supermultiplicative effect in the oral cavity, between additive and multiplicative in the oesophagus, and multiplicative in the larynx, reflecting degree of contact with both these agents at these sites {797}.

Most of the rise in western countries in recent years has been attributed to rising alcohol consumption in northern Europe {1597 and rises in tobacco consumption in parts of southern Europe. Significant risk increases have also been reported amongst non-drinking smokers and, to a lesser extent, non-smoking heavy

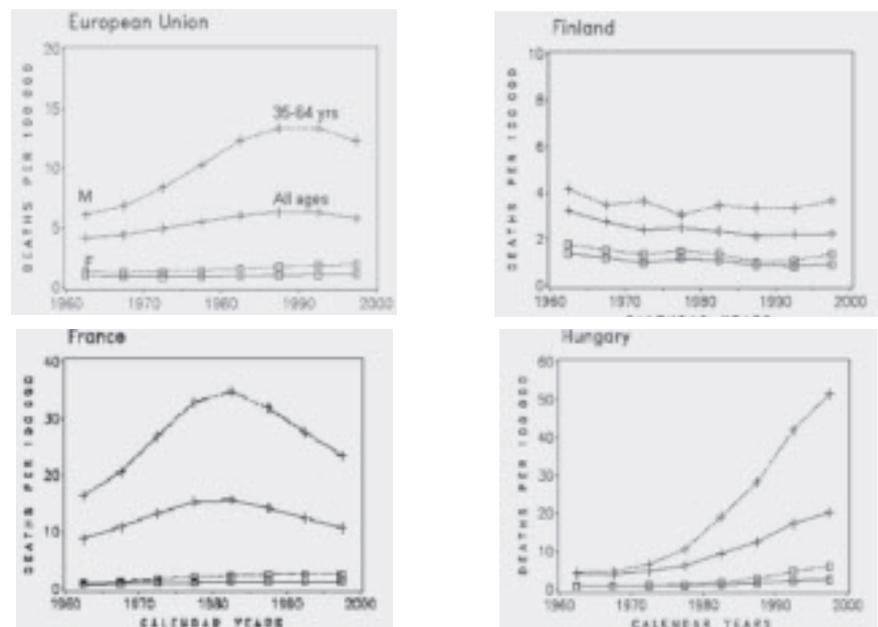


Fig. 4.4 Trends in mortality from cancer of the oral cavity and pharynx in some European countries. The large differences observed (currently 10-fold in between Hungary and Finland) largely reflect past success and failure in tobacco and alcohol control. From F. Levi et al. {1483}.

drinkers {1406}. Studies that have attempted to estimate a difference between wine, beer and hard liquors generally indicate that heavy consumption of all types of alcoholic beverage confers risk, the differences in risk estimates being largely due to socio-cultural correlates of drinking patterns in various populations {142,1404}. Ultraviolet light and contact with smoking appliances are important for lip vermillion.

Tobacco chewing

Oral smokeless tobacco is a major cause of oral {969} and oropharyngeal {2908} squamous cell carcinoma in the Indian subcontinent, parts of South-East Asia, China and Taiwan and in emigrant communities therefrom, especially when consumed in betel quids containing areca nut and calcium hydroxide (lime). Areca nut has been declared a known human carcinogen by an IARC Expert Group (2003). In India chewing accounts for nearly 50% of cancers of the oral cavity and oropharynx in men and over 90% in women {108}. Traditional tobacco products used in Sudan and the Middle East, which are powdered and fermented and mixed with sodium bicarbonate, contain very high levels of tobacco-specific nitrosamines and are highly carcinogenic {1171}. Those forms of non-flue cured smokeless tobacco used as oral snuff in Scandinavia and North America is less carcinogenic {1230} – though they cause nicotine addiction.

Human papillomavirus (HPV) infection

HPVs, especially those genotypes of known high oncogenic potential in uterine cervix and skin such as HPV 16 and 18, are found in a variable but small proportion of oral, and up to 50% of tonsillar and oropharyngeal SCCs, especially the tonsil. Recent studies suggest that HPV may be responsible for a small fraction of oral, and up to 40% of oropharyngeal, cancers {888,1077}. This has led to speculation that HPV infection, perhaps arising from oral/genital contact, might be important in some cases {2284}. Of interest is the observation that HPV-containing cancers at these sites do not generally show TP53 mutations, contrary to HPV DNA-negative cancers {660,1077}. It is well known that HPV 16 E6 protein inactivates p53 protein, suggesting that HPV and smoking might operate, in part, on the same criti-

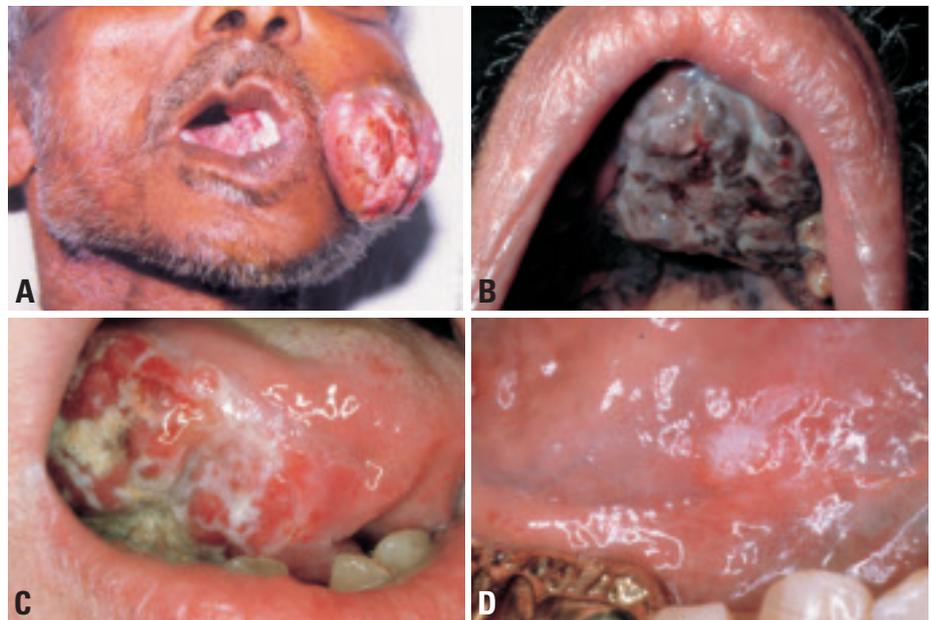


Fig. 4.5 Squamous cell carcinoma. **A** Exophytic growth involving the left buccal mucosa and overlying skin in a 65 year old male who chewed betel quid and smoked tobacco. **B** An exophytic growth arising from the left palate. **C** Squamous cell carcinoma of the tongue. **D** Early squamous cell carcinoma of lateral border of the tongue.

cal step in the multistage process of carcinogenesis at these sites.

Prevention

Recent work on risk factors in younger cases emphasises the importance of early and heavy tobacco and alcohol use, the protective effect of diets rich in fresh fruits and vegetables, but with a substantial minority without these established risk factors {1534}.

The protective effect of diets rich in trace elements and antioxidant vitamins is well demonstrated in many countries, especially in Italian studies {1628,2563}. Though more controversial, a contribution from poor oral hygiene is also suggested {108,2548}.

Second primary tumours

It has been recognised for a long time that patients with oral cancer are at risk of second tumours in the upper aerodigestive tract. This has been reported to occur in 10-35% of cases {2676}. These may be synchronous with the index tumour or, if occurring after an interval of longer than six months are described as metachronous. Recurrence of the index tumour after treatment can be diagnosed by the pathologist where the tumour is in deeper tissue and not associated with the epithelial surface. However, the most frequent situation of second tumours is when they

arise from surface epithelium adjacent to the treated index tumour. On morphological grounds these are diagnosed as second primary tumours. The increasing use of molecular biological techniques has allowed distinction to be made between molecularly distinct second primary tumours and second field tumours derived from the same genetically altered field as the index tumour {248}.

Localization

Tumours may arise in any part of the oral cavity. The most common sites vary geographically reflecting different risk factors. Lip SCC arise almost exclusively on the lower lip. Within the oral cavity, the subsites at which tumours may be located include: buccal mucosa, upper and lower gingiva, hard palate, anterior two-thirds of the tongue, including dorsal, ventral and lateral surfaces, and the floor of mouth. Many tumours are large at presentation and the tumour site is then recorded as essentially the centre of the tumour. Analysis of small symptomless tumours shows the highest frequency in floor of mouth, ventrolateral tongue and soft palate complex {1655}. This suggests that tumours arise at these sites, but spread preferentially to involve other sites such as tongue, being then recorded as lingual lesions. The clinical relevance of this observation is to emphasise the

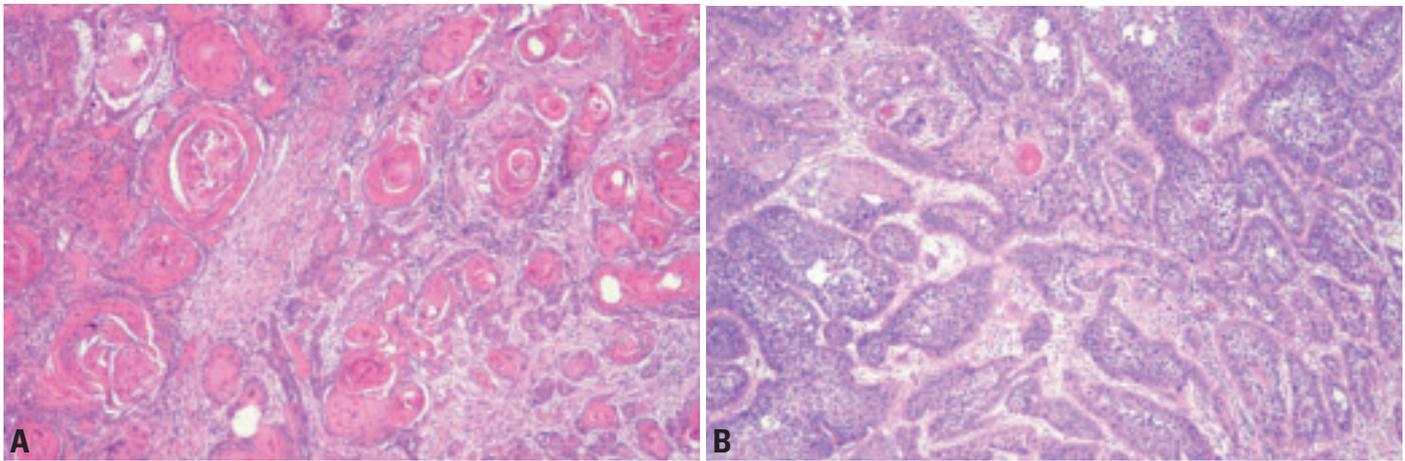


Fig. 4.6 **A** Well-differentiated squamous cell carcinoma (SCC), characterized by abundant formation of keratin pearls. **B** Moderately differentiated SCC. Cells form large anastomosing areas in which keratin pearls are formed. They are not very numerous and the main component consists of cells with pronounced cytonuclear atypia.

importance of close examination of high-risk sites. The oropharynx consists of the base of the tongue (posterior third), vallecula, tonsil with tonsillar fossae and pillars, glossotonsillar sulci, posterior wall and superior wall composed of the inferior surface of the soft palate and the uvula. The most common oropharyngeal site of involvement for SCC is the base of tongue.

Clinical features

Signs and symptoms

Patients with small oral and oropharyngeal SCC are often asymptomatic or may present with vague symptoms and minimal physical findings. Hence, a high index of clinical suspicion is needed to diagnose small lesions, especially if the patients have tobacco and alcohol habits. Patients may present with red

lesions, mixed red and white lesions, or white plaques. Co-existing white plaques (leukoplakia) may be observed adjacent to carcinomas and this implies an origin in a pre-existing white lesion though the prevalence of this association varies considerably in different populations. However, most patients present with signs and symptoms of locally advanced disease. The clinical features may vary according to the affected intraoral subsite. Mucosal growth and ulceration, pain, referred pain to the ear, malodour from the mouth, difficulty with speaking, opening the mouth, chewing, difficulty and pain with swallowing, bleeding, weight loss, and neck swelling are the common presenting symptoms of locally advanced oral and oropharyngeal cancers. Occasionally, patients present with enlarged neck nodes without any symp-

toms from oral or oropharyngeal lesions. Extremely advanced cancers present as ulceroproliferative growths with areas of necrosis and extension to surrounding structures, such as bone, muscle and skin. In the terminal stages, patients may present with oro-cutaneous fistula, intractable bleeding, severe anaemia and cachexia.

Cancer of the buccal mucosa may present as an ulcer with indurated raised margin, exophytic or verrucous growth or with the site of origin depending upon the preferential side of chewing and placement of betel quid. In advanced stages, these lesions infiltrate into the adjacent bone and overlying skin. Cancer of the tongue may appear as a red area interspersed with nodules or as an ulcer infiltrating deeply, leading to reduced mobility of the tongue. These tumours are

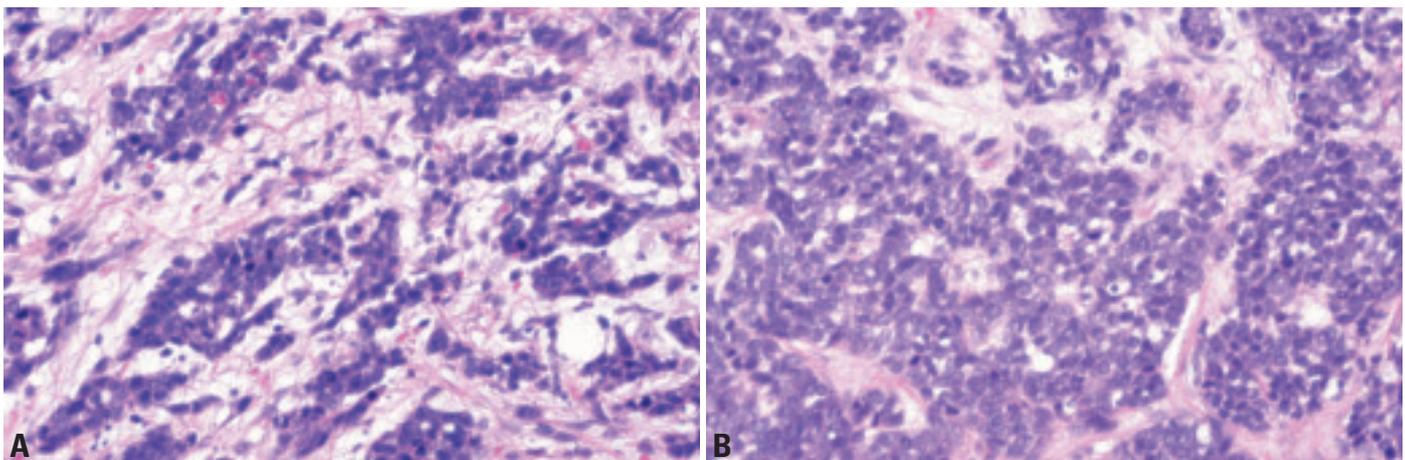


Fig. 4.7 Poorly differentiated SCC. **A** Cells with atypical nuclei and a small rim of eosinophilic cytoplasm form strands and small nests. **B** Cells in a poorly differentiated SCC tend to have more vesicular nuclei. The cells in this tumour are more cohesive, forming larger tumour areas than the lesion shown in A.

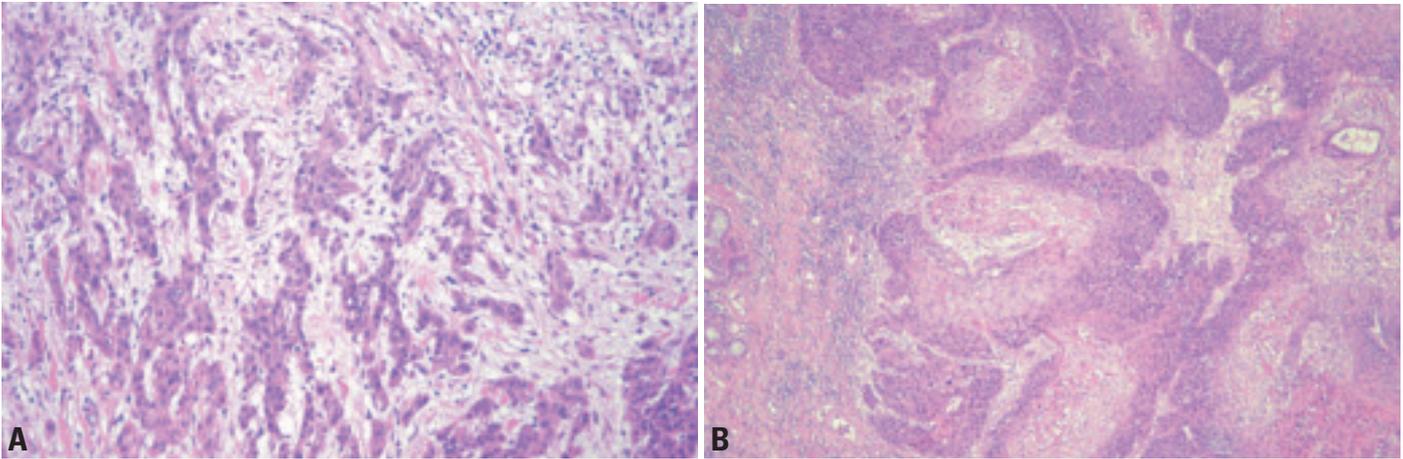


Fig. 4.8 Squamous cell carcinoma (SCC). **A** Growth pattern of a diffusely infiltrating SCC. In this moderately differentiated lesion, the tumour cells form tiny strands. This growth pattern is a prognostically unfavourable feature. **B** Moderately differentiated SCC growing in large cohesive fields. This pattern is prognostically more favourable than the diffuse growth shown in Figure A.

painful. Cancers of the floor of mouth may arise as a red area, a small ulcer or as a papillary lesion. Most patients present with discomfort or irritation at the site of the tumour. Advanced stages are associated with drooling. Cancers of the lower lip usually arise in the vermilion border and appear as a crusty indurated or ulcerated lesion. Cancers of the upper lip are rare, often originate on the skin and spread to the mucosa. Cancer of the gingiva usually presents as an ulceroproliferative growth. Tumours of the alveolar ridge may occasionally present as difficulty in wearing denture plates or as loosening of teeth associated with pain and bleeding during brushing of teeth. Tumours of the hard palate often present as papillary or exophytic growths, rather than a flat or ulcerated lesion. Cancer of soft palate and uvula often

appear as an ulcerative lesion with raised margins or as fungating masses. Tonsillar cancers generally appear as an exophytic or ulcerative lesion. Sometimes they can present as enlarged neck nodes without any other signs and symptoms. Cancer of the base of tongue presents late in the course of the disease as a grossly ulcerated, painful, indurated growth.

More than two-thirds of the patients with buccal mucosal and gingival cancers in South Asia present with submandibular lymph node enlargement. More than three fourths of patients with tongue, floor of mouth and oropharyngeal cancers in South Asia present with neck swellings implying clinically obvious lymph node metastasis. In the West lymph node involvement is common at presentation in oropharyngeal SCC.

Imaging

Intraoral and dental radiographs, in combination with orthopantomography, may help in identifying involvement of the underlying bone. Three-dimensional imaging with computed tomography (CT) and magnetic resonance imaging (MRI) is frequently used to supplement the clinical evaluation and staging of the primary tumour and regional lymph nodes. CT scan or MRI give more information about the local extent of the disease and also help to identify lymph node metastases. CT scanning is useful in evaluating involvement of cortical bone. MRI is more informative when evaluating the extent of soft tissue and neurovascular bundle involvement. The combination of soft tissue characterisation and anatomical localization afforded by CT and MRI make them valuable tools in the

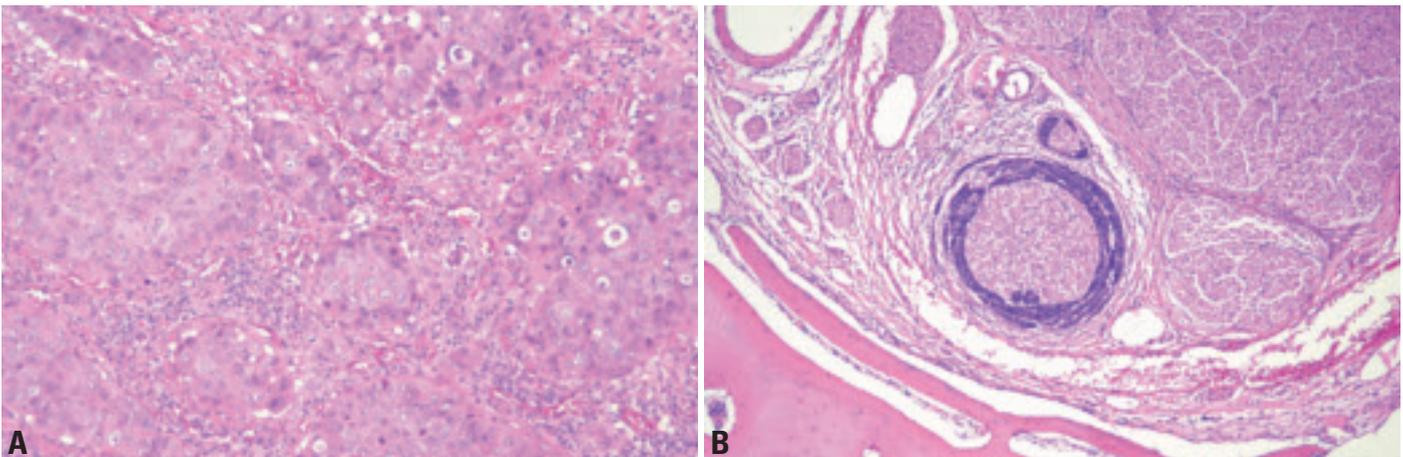


Fig. 4.9 Squamous cell carcinoma (SCC). **A** In this moderately differentiated SCC, the tumour stroma contains a dense lymphoplasmacytic infiltrate. **B** SCC with perineural growth, spreading alongside the inferior alveolar nerve.

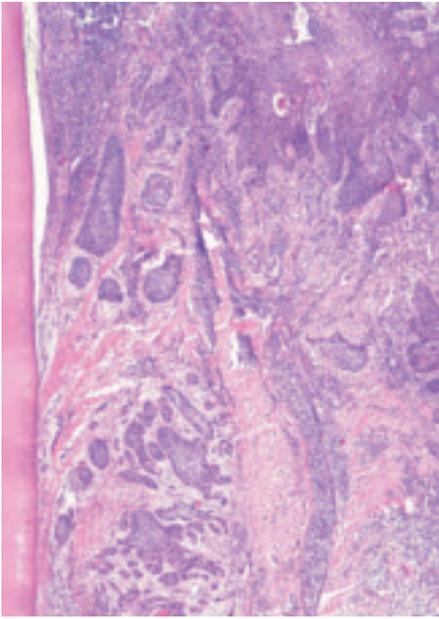


Fig. 4.10 Periodontal ligament involvement by a squamous cell carcinoma (SCC).

preoperative assessment of patients with oral or oropharyngeal cancers. Distant metastasis from oral and oropharyngeal cancer is uncommon at presentation. At minimum, a routine radiograph of the chest is performed to rule out lung metastases.

Relevant diagnostic procedures

Optimal therapy and survival from oral cancer depend on adequate diagnosis and assessment of the primary tumour and its clinical extent. Physical examination should include visual inspection and palpation of all mucosal surfaces, bimanual palpation of the floor of the mouth, and clinical assessment of the neck for lymph node involvement.

The diagnosis is confirmed by biopsy. The specimen is taken from the clinically most suspicious area, avoiding necrotic or grossly ulcerated areas, and more than one biopsy site may need to be chosen. In patients with enlarged cervical lymph nodes and an obvious primary in the oral cavity or oropharynx, the biopsy is always taken from the primary site and not from the lymph node. In such situations, fine needle aspiration cytology may be carried out to verify the involvement of the node.

If no obvious primary site is found in patients presenting with neck nodes, fine-needle aspiration of the lymph node can be performed to help establish the diag-

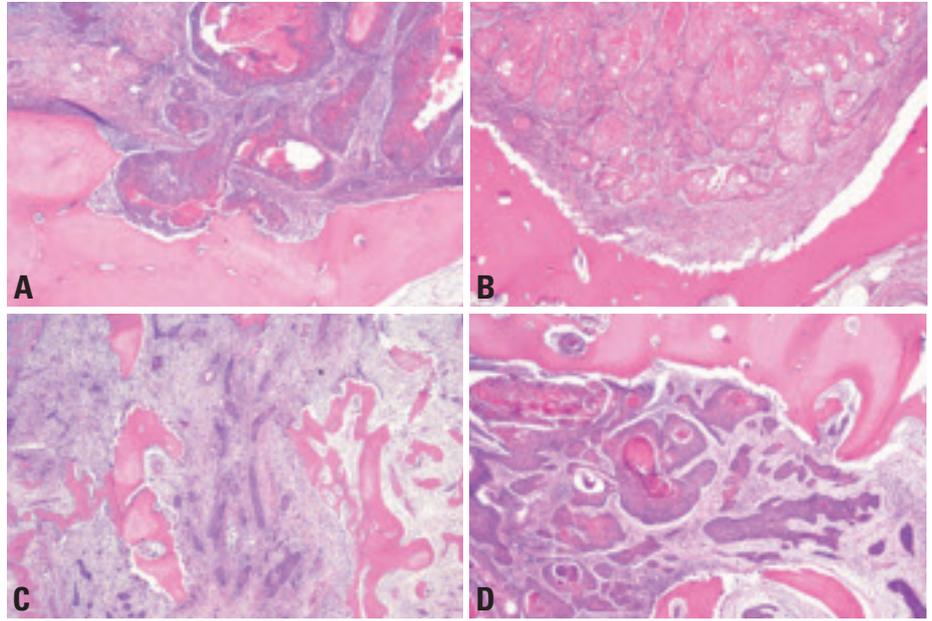


Fig. 4.11 Squamous cell carcinoma (SCC). **A** Superficial erosion of the mandibular bone has perforated the cortical bone. As there is no spread in the bone marrow, this case of SCC does not meet the requirements for classification as T4. **B** Saucerization by SCC. In this case of, there is substantial loss of bone due to endocortical tumour growth (meets the requirements T4). **C** Permeative infiltration of bone by SCC growing diffusely in the marrow cavities of the mandibular bone (T4). There is also heavy osteoclast-mediated bone resorption. **D** Bone invasion by SCC with diffuse growth in the mandibular bone.

nosis. In patients for whom fine needle aspiration is non-diagnostic and SCC is strongly suspected, excisional lymph node biopsy is a last resort, as subsequent curative therapy may be compromised by this procedure. The search for an occult primary tumour may include direct pharyngolaryngoscopy with biopsy of high-risk sites like base of tongue, nasopharynx, and usually a diagnostic tonsillectomy, as well as other imaging modalities. Open lymph node biopsy is carried out only when the lesion cannot be identified by aspiration biopsy or in patients with suspected lymphoma.

Patients with SCC of the oral cavity or oropharynx have a risk of multiple primary tumours in the pharynx or larynx, as well as in the tracheobronchial region and oesophagus so routine panendoscopy is often performed to evaluate these sites.

Tumour spread and staging

Staging is carried out according to the TNM classification {947,2418}. Recent additions to the coding have been provided for micrometastases, isolated tumour cells, findings in sentinel nodes and tumour detection by molecular methods. Some of these are discussed in the following sections.

Local spread of oral SCC, in the early

stages, is relatively predictable in tissues that have not been previously irradiated. It is influenced by local anatomical features. Lip SCC spreads superficially and then into deeper tissues. Floor of mouth SCC spreads superficially rather than in depth, being unlikely to invade into the mylohyoid muscle or the sublingual gland until a late stage. Tumour involving the lateral margin of tongue, whether arising there directly or by superficial spread from the floor of mouth, tends to spread in depth. The intrinsic muscles of tongue run in small bundles in all directions such that invading tumour encounters some muscle running at right angles to the surface. The line of least resistance to tumour spread is therefore along these muscle bundles and into the tongue. Tumours of palate spread superficially rather than in depth and this is also true for more posterior tumours of the oropharynx.

For most oral SCC other than tongue, the extent of spread in an area can be predicted from the extent of surface involvement. Tongue and tonsil tumours can spread beneath intact normal appearing surface, giving a larger area of tumour involvement. Spread of oral SCC into bone is a frequent problem. The mandible is involved much more frequently than the

maxilla. In dentate jaws the usual route of entry into mandible is along the periodontal ligament. In edentulous areas of mandible the tumour spread is through the crest of the alveolus directly into the marrow spaces between trabeculae of cancellous bone {1682}. This occurs because of failure of formation of an intact cortex of alveolar bone as resorption of edentulous alveolus progresses. Tumours in the mandible can involve the inferior alveolar nerve {1683} with a particular likelihood of spread posteriorly along the nerve, sometimes extending well beyond the mandibular foramen. Cancers arising in gingiva or alveolus and those involving these sites by extension from adjacent sites are unlikely to invade into the mandible other than by periodontal ligament or the crest of edentulous alveolus. Extension into the mandible through foramina, for example the mental foramen from lip cancer, does occur, but is uncommon.

Spread in previously irradiated tissues

Tumour spread in previously irradiated soft tissues tends to be more extensive and less predictable than in normal tissues and as a consequence requires more extensive surgery if excision is attempted. Tumour invasion into irradiated mandible tends to occur wherever the tumour approaches bone, often at multiple sites {1682}.

Lymphatic spread

Spread to local lymph nodes worsens the prognosis in oral and oropharyngeal cancer. The mechanism of spread from the primary site to lymph nodes is almost always by embolism. Permeation in lymphatics adjacent to tumours is uncommon and it is debatable if this spread extends as far as lymph nodes. Once tumour is present in the neck, however, spread between nodes may be embolic or by permeation. The lymph nodes in the neck are divided into levels. The lymphatic drainage from different head and neck sites is relatively predictable {1789}. Levels at high risk for metastasis from oral cavity SCC are Levels I, II and III, and to a lesser extent Level IV. Although Level II is the most frequently involved, some tumours spread to Level III or IV, with or without involvement of Level I. This has given rise to the concept of skip metastasis. In reality the lymphatic drainage is complex and does not follow a regular sequence of lev-

els of involvement in many patients {2817}. Bilateral spread to the neck is likely to occur from tumours involving the midline, especially tumours of posterior tongue or soft palate. Extracapsular spread of tumour involving lymph nodes is associated with a poor prognosis {2819}.

There have been many studies attempting to predict the presence of lymphatic spread from features of the primary tumour {872,2820}. Tumour size and site are relevant. Tumour differentiation is not a reliable predictor. The pattern of the invasive front is a useful predictor in that a non-cohesive front is associated with increased likelihood of metastasis. Other factors associated with increased risk of metastasis are perineural spread at the invasive front, lymphovascular invasion and tumour thickness. The tumour thickness is measured from the deepest tumour invasion to the presumed original surface level, that is, ignoring exophytic growth or assessing the original surface level in ulcerated tumours. For diagnostic purposes a thickness of 5mm or greater is used as indicating increased risk of nodal spread {395}.

Haematogenous spread

Until relatively recently, haematogenous spread of oral and oropharyngeal cancer has been regarded as less important than local and lymphatic spread. However, its importance is increasing as loco-regional control improves. Blood borne spread most often involves lung {754,1958}. The best predictor of the likelihood of this spread is involvement of the neck at multiple levels. This suggests that the route of entry of tumours into the circulation is most often via the large veins in the neck and that haematogenous spread is in effect tertiary spread following extracapsular spread from neck nodes.

Sentinel node biopsy

This is currently an experimental technique {2057} that is under active evaluation by prospective clinical trials and it is not practised at all centres. It is a technique used primarily for staging a clinically N0 neck. In an effort to avoid a neck dissection. If a clinically N0 neck is followed untreated until tumour development occurs, the prognosis can be very poor {57,977}. Studies on the incidence of occult metastases in N0 necks {753} have shown tumour spread in only a small

minority of patients. Therefore, if neck dissection is undertaken either prophylactically or as a staging procedure, on patients with N0 necks, a large majority will have unnecessary surgery, as the neck will be found to be free from tumour. The sentinel node is the first draining lymph node from a tumour. It is assumed that if the sentinel node can be shown to be free from tumour, then the lymphatic basin is free from tumour and neck dissection is not required. By contrast, sentinel node positive patients can be selected for further therapy. Sentinel nodes are identified by a combination of lymphoscintigraphy and injection of blue dye in the tumour bed and then sampling draining nodes identified. In reality, more than one sentinel node is found in many cases {2345} indicating that tumours drain to more than a single first echelon node, presumably from different parts of the tumour.

Sampled sentinel nodes should be fully examined by the pathologist. This usually involves bisecting the node in the largest diameter and then undertaking extensive sampling. Some pathologists undertake frozen sections on bisected fresh nodes. If this is done it is important to use a technique whereby the cut surface is frozen on a flat surface and only early sections are examined. This is to ensure that as little node as possible is examined at this stage in order not to compromise full examination of the node. Paraffin processed blocks are then examined with H and E sections of the early sections of the blocks. If these show no tumour, more detailed sampling with immunocytochemistry for cytokeratins and sampling through the block is required. True serial sectioning is impracticable for routine use. A compromise is step sectioning at intervals of 150µm with examination of H and E sections and AE1/3 reacted sections {2202}. The importance of these sections is that suspicious areas on immunocytochemistry can be identified in the H and E sections. These may be viable tumour cells, but other possible causes of cytokeratin positivity, such as inclusion of normal salivary gland epithelium or thyroid follicles, either occult metastases or lateral aberrant thyroid, need to be identified. Another not infrequent finding is areas of cytokeratin positivity which on H and E appear as densely eosinophilic apparently non-viable tumour cells.

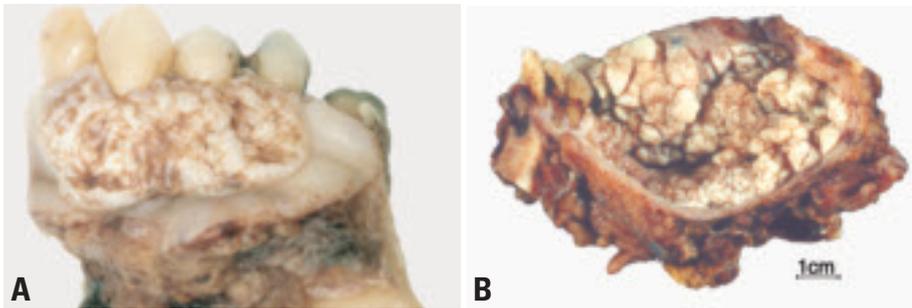


Fig. 4.12 **A** Verrucous carcinoma (VC) of the gingiva. **B** VC of the gingiva, spreading laterally to involve the cheek mucosa.

Interpretation of sentinel nodes can demand considerable pathological expertise. The outcome of the pathological assessment may be the presence of metastasis; micrometastasis, less than 2mm diameter tumour deposits, or isolated tumour cells {2477}. Micrometastasis has been defined {1073} as cells which have arrested and implanted. These may be in contact with a vessel or lymph sinus wall or may be extravascular. Single or small clusters of cells within lymph or blood vessels, but not in contact with the wall are defined as isolated tumour cells.

Histopathology

The histological features of SCC have been discussed in Chapter 3 on tumours of the hypopharynx, larynx and trachea. The findings in the oral cavity and oropharynx do not differ significantly from those of the larynx and hypopharynx. A minority of oral and oropharyngeal cancers show different histological subtypes that can be associated with differences in prognosis. These are discussed below. It is clearly important that pseudo epitheliomatous hyperplasia (PEH) is distinguished from SCC. PEH can occur in mucosa overlying a granular cell tumour, in necrotising sialometaplasia and in papillary hyperplasia of palate. PEH occurring with mucositis, particularly after irradiation, may be difficult to distinguish from squamous cell carcinoma.

The majority of cases of SCC present no difficulty in diagnosis for the experienced pathologist. However, the recognition of the earliest stages of invasion can be problematic. No consistent guidelines for this exist. The deepest layers of the epithelium and the interface between the epithelium and the lamina propria need to be examined in detail. This is frequently made more difficult where there is a prominent inflammatory infiltration.

Relevant features include the loss of a histologically well-defined interface, described previously as loss of basement membrane and disturbed architecture of the basal layers of the epithelium, particularly the replacement of basal cells by larger irregular cells with cytoplasmic processes extending into connective tissue. In some cases the degree of cytological atypia and mitotic feature may suggest malignancy, but these are not always present. To an extent the judgement about early invasion is subjective and it can be important for the pathologist to communicate the difficulty in interpretation to the clinician. Some pathologists will indicate that while no unequivocal evidence of invasion is demonstrated, they nevertheless feel that the lesion should be regarded as early invasive carcinoma.

Somatic genetics

There is some variation in the genetic profile of oral and oropharyngeal SCC that reflects the site-specific impact of various casual agents and differences in clinical presentation. The carcinogens in tobacco smoke, for example, increase the prevalence and spectrum of TP53 mutations {268}. Compared to carcinomas that arise in patients who smoke, carcinomas in patients who have never smoked harbour fewer p53 mutations, disproportionately involve women, typically arise from the oral tongue, and affect very young or very old patients {1351,2258}. For carcinomas of the oropharynx, oncogenic human papillomavirus (HPV), particularly the HPV-16 subtype, is an important causative agent: More than 50% of oropharyngeal carcinomas harbour integrated HPV DNA {60,888,1999}. The E6 and E7 viral oncoproteins bind and inactivate the TP53 and retinoblastoma gene products respectively, disengaging two of the more critical pathways involved in

cell cycle regulation {2788}. These HPV-positive oropharyngeal tumours compose a distinct pathological entity with its own clinical spectrum and basaloid morphology {888,1012,2072}, illustrating the emerging role of genetic characterization as a potential means of determining prognosis and influencing management {1691}.

Genetic evidence has clarified the vague concept of “field cancerization”. Most, if not all, multiple primary carcinomas of the upper aerodigestive tract derive from a common clonal progenitor cell that undergoes a common early genetic alterations {187,2271}. Genetic evidence has helped account for the perplexing problem of local tumour recurrence following seemingly complete tumour resection. In many instances, local tumour recurrence reflects extension of genetically damaged cells beyond the clinical and microscopic boundaries of carcinoma to the margins of surgical resection {268,1626,1983,2777}.

Microsatellite analysis of exfoliated cells swabbed or rinsed from the oral cavity of patients with head and neck squamous carcinomas consistently harbour genetic changes that are identical to those in the primary tumours, suggesting a non-invasive test for specific DNA-sequence variants in saliva as a means of identifying patients with pre-invasive or invasive neoplasms {2430}. Clonal genetic changes identical to those found in primary head and neck SCC have been identified in circulating plasma or serum, suggesting a mechanism for early cancer detection and tumour surveillance {1853}. The use of highly sensitive genetic assays for detecting rare cancer cells at the margin of tumour resection shows promise for predicting the likelihood of tumour recurrence {268,1983}.

Prognosis and predictive factors

Tumour size and nodal status are the most significant prognostic factors {2060}. Histological grade correlates poorly with patient outcome {1292,2195}. The value of grading improves when only the deeply invasive margins of the tumour are evaluated {291,292,1927, 2818}. Tumours invading with pushing borders are less aggressive than tumours showing a non-cohesive front showing diffuse spread with tiny strands or single cells. {1325,2132,2342,2653, 2841} Major risk factors that adversely influence prognosis

are two or more positive regional nodes, extracapsular extension of nodal disease, or positive margins of resection {1429}. Other important histologic features associated with poor prognosis are tumour thickness and vascular invasion.

Molecular markers with unequivocal prognostic and/or predictive significance have not been identified {428,1052,1561,2106}.

Verrucous carcinoma

ICD-O code 8051/3

Although uncommon, 75% of all cases of VC occur in the oral cavity. It is an exophytic, warty, slowly growing variant of SCC with pushing margins. It typically involves older males {950,1251,1677,1695,2621}. Chronic smokeless tobacco use is accepted as the primary etiological factor for oral VC. Human papillomavirus subtypes 16 and 18 have been identified in up to 40% of oral VC {1927,2349}. Oral VC begins as a well-demarcated, thin white keratotic plaque which quickly thickens and develops papillary (blunted tips) or verruciform (pointed tips) surface projections. Occasional lesions present as erythaematous or pink papular masses. The colour depends on the amount of keratin produced and the degree of host inflammatory response to the tumour. This cancer almost always remains broad-based or sessile and can become quite extensive from lateral growth by the time of diagnosis. Rare fungating examples, however, may appear to be somewhat pedunculated. Smokeless tobacco keratosis (tobacco pouch) is often seen on adjacent mucosal surfaces in patients who chew tobacco or use snuff. Unless the tumour is infected or is encroaching on alveolar nerves in the jawbones, VC is an asymptomatic lesion. Surface ulceration and haemorrhage are not seen, unless a focus of SCC is present in the mass.

VC consists of thickened club-shaped papillae and blunt stromal invaginations of well-differentiated squamous epithelium with marked keratinization. The squamous epithelium lacks the usual cytologic criteria of malignancy, and by morphometry, the cells are larger than those seen in SCC {489}. Mitoses are rare, and observed in the basal layers; DNA synthesis (S-phase) is also limited primarily to the basal layers {737}. VC invades the

stroma with a pushing, rather than infiltrating border. Dense lymphoplasmacytic host response is common. Intraepithelial microabscesses are seen, and the abundant keratin may evoke a foreign body reaction.

The surrounding mucosa shows progressive transition from hyperplasia to VC. A downward dipping of epithelium often “cups” the VC periphery, and is the ideal site for deep biopsy {174,1192}. With extensive surgical removal, and without neck dissection, the 5-year disease-free survival rate is 80-90%, although 8% of patients require at least one additional surgical procedure during that time {1870,1927}. Treatment failures usually occur in patients with the most extensive involvement or in those unable to tolerate extensive surgery because of unrelated systemic diseases. No molecular or other markers have yet shown prognostic significance for oral VC. However, one-fifth of these tumours contain a co-existing SCC which may not be identified without extensive histologic sectioning {1927}. Such hybrid tumours have a greater tendency to recur locally and a slight tendency to metastasize to the ipsilateral neck.

Basaloid squamous cell carcinoma

ICD-O code 8083/3

This is uncommon in the oral cavity, slightly more common in the oropharynx. It is described in the chapter on tumours of the hypopharynx, larynx and trachea.

Papillary squamous cell carcinoma

ICD-O code 8052/3

This is rarely recognized in the oral cavity and oropharynx other than as a component of a large SCC. It is described in the chapter on tumours of the hypopharynx, larynx and trachea.

Spindle cell carcinoma

ICD-O code 8074/3

This unusual variant is more common in the larynx than in the oral cavity and oropharynx, and is described in detail in the chapter on tumours of the hypopharynx, larynx and trachea.

Acantholytic squamous cell carcinoma

ICD-O code 8075/3

The lip is the most frequent oral site. There are no distinguishing clinical signs and the microscopical features are considered in the chapter on tumours of the hypopharynx, larynx and trachea. A variant of this tumour has been referred to as pseudovascular SCC.

Adenosquamous carcinoma

ICD-O code 8560/3

In the oral cavity this is a SCC with clear-cut areas of adenocarcinoma, most frequently seen as a component of a large SCC. It is described in the chapter on tumours of the hypopharynx, larynx and trachea.

Carcinoma cuniculatum (epithelioma cuniculatum)

ICD-O code 8051/3

This rare variant of oral cancer has similarities to the lesion more commonly described in the foot in which tumour infiltrates deeply into bone. The oral tumours show proliferation of stratified squamous epithelium in broad processes with keratin cores and keratin filled crypts which seem to burrow into bone, but lack obvious cytological features of malignancy {40}. Diagnosis on biopsy specimens can be very difficult and correlation with the clinical and radiographic features is required.

Lymphoepithelial carcinoma

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Definition

Lymphoepithelial carcinoma (LEC) is a poorly differentiated squamous cell carcinoma (SCC) or undifferentiated carcinoma, accompanied by a prominent reactive lymphoplasmacytic infiltrate. The morphological features are indistinguishable from those examples of nasopharyngeal nonkeratinizing carcinoma with a rich lymphoplasmacytic infiltrate.

ICD-O code 8082/3

Epidemiology

LEC is rare at these sites, and accounts for 0.8-2% of all oral or oropharyngeal cancers {1339,2741}. See Chapter 2.

Etiology

Epstein-Barr virus (EBV) has been tested in only a limited number of cases {819, 856,1802,1875,2405}, but it appears that tumours occurring in Chinese are usually positive for EBV, while those occurring in Caucasians are usually negative. The racial difference in the association with EBV is similar to LEC occurring in the major salivary glands (see Chapter 5).

Clinical features

The patients present with an intra-oral mass, which may be ulcerated. Some tumours can be bilateral {801,2038}. A proportion of patients present with neck mass due to regional lymph node involvement {119}.

Location and metastatic spread

More than 90% of all oral and oropharyngeal LEC occur in the tonsil and tongue base areas. The remaining cases are found in the palate and buccal mucosa {444,694,2822}. The tumour has a high propensity for regional cervical lymph node involvement (approximately 70% of cases at presentation) {119,444,1339}. Distant metastasis tends to occur in the liver and lung {119}.

Histopathology

LEC of the oral cavity and oropharynx shows morphologic features indistinguishable from its nasopharyngeal and sinonasal counterparts. The surface epithelium is often intact. The tumour is invasive, and comprises syncytial sheets and clusters of carcinoma cells with

vesicular nuclei, prominent nucleoli and ill-defined cell borders. A rich lymphoplasmacytic infiltrate is present within the tumour islands and the surrounding stroma, which may appear desmoplastic.

The tumour cells are immunoreactive for pan-cytokeratin and epithelial membrane antigen. EBV encoded RNA (EBER) has been demonstrated by in-situ hybridization in oral / oropharyngeal LEC occurring in Chinese patients.

Prognosis and predictive factors

LEC of the oral cavity and oropharynx are radiosensitive, and in a high percentage of cases local control can be achieved even in the presence of regional lymph node metastasis {1339}. Local, regional and distant failures occur in 3%, 5% and 19% of cases respectively {444}. Distant metastasis is associated with a poor prognosis.

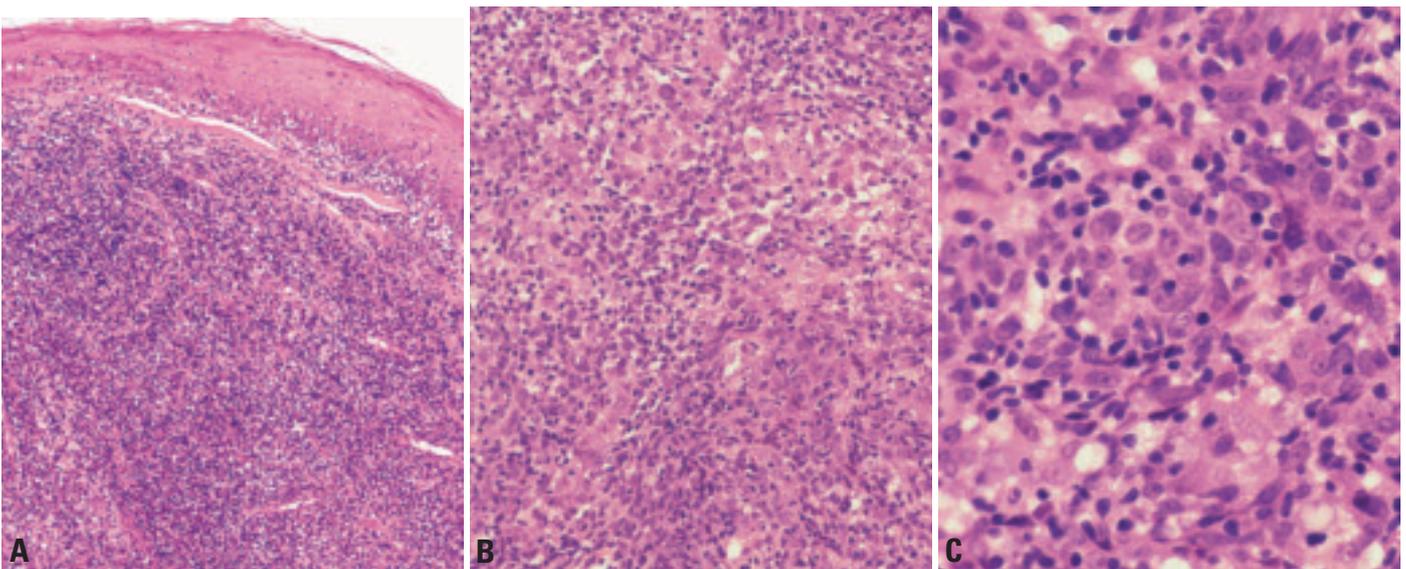


Fig. 4.13 **A** Lymphoepithelial carcinoma of the tonsil. The tumour infiltrates beneath an intact surface epithelium. In this example, the tumour islands are obscured by the heavy lymphoplasmacytic infiltrate. **B** Sheets and islands of tumour cells intimately admixed with lymphocytes and plasma cells. **C** Lymphoepithelial carcinoma of the palate. Carcinoma cells exhibit indistinct cell borders, pale chromatin and distinct nucleoli. Many lymphocytes are found among the carcinoma cells.

Epithelial precursor lesions

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The pathologic assessment of precursor lesions is similar throughout the upper aerodigestive tract. It is described in detail in the Chapter 3 on tumours of the hypopharynx, larynx and trachea (page 140).

Clinical features

The principal oral and oropharyngeal lesions which may be precursor lesions are white patches (leukoplakia) and red patches (erythroplasia/erythroplakia) or mixed red and white lesions. The majority of leukoplakias will not show dysplasia and correspond to the hyperplasia category. Red and mixed lesions (speckled leukoplakia) show a higher frequency of dysplasia, often of higher grade. The majority of leukoplakias will not undergo malignant change and may even regress particularly if apparent aetiologic factors are removed.

Histopathology

The epithelium of precursor lesions may be thick, but in the oral cavity it can also be atrophic. By definition, there is no evidence of invasion. The magnitude of surface keratinisation is of no importance. Allocation to categories within each of the classifications requires consideration firstly of architectural features and then of cytology.

Hyperplasia

Hyperplasia describes increased cell numbers. This may be in the spinous layer (acanthosis) and/or in the basal/parabasal cell layers (progenitor compartment), termed basal cell hyperplasia. The architecture shows regular stratification without cellular atypia.

Dysplasia, / squamous intraepithelial neoplasia / atypical hyperplasia

When architectural disturbance is accompanied by cytologic atypia, the term dysplasia applies. The terms squamous intraepithelial neoplasia (SIN) and atypical epithelial hyperplasia are used synonymously.

There is a challenge in the recognition of

Table 4.01 Classification schemas that histologically categorize precursor and related lesions

2005 WHO Classification	Squamous Intraepithelial Neoplasia (SIN)	Ljubljana Classification Squamous Intraepithelial Lesions (SIL)
Squamous cell hyperplasia		Squamous cell (Simple) hyperplasia
Mild dysplasia	SIN 1	Basal/parabasal cell hyperplasia*
Moderate dysplasia	SIN 2	Atypical hyperplasia**
Severe dysplasia	SIN 3***	Atypical hyperplasia**
Carcinoma in-situ	SIN 3***	Carcinoma in-situ

* Basal/parabasal cell hyperplasia may histologically resemble mild dysplasia, but the former is conceptually benign lesion and the latter the lower grade of precursor lesions.
 ** 'Risky epithelium'. The analogy to moderate and severe dysplasia is approximate.
 *** The advocates of SIN combine severe dysplasia and carcinoma in-situ.

the earliest manifestations of dysplasia and no single combination of the above features allows for consistent distinction between hyperplasia and the earliest stages of dysplasia. Dysplasia is a spectrum and no criteria exist to precisely divide this spectrum into mild, moderate and severe categories.

Mild dysplasia

In general architectural disturbance limited to the lower third of the epithelium accompanied by cytological atypia define the minimum criteria of dysplasia.

Moderate dysplasia

Architectural disturbance extending into the middle third of the epithelium is the initial criterion for recognizing this category. However, consideration of the degree of cytologic atypia may require upgrading.

Severe dysplasia

Recognition of severe dysplasia starts with greater than two thirds of the epithelium showing architectural disturbance with associated cytologic atypia. However, as noted in the previous para-

Table 4.02 Criteria used for diagnosing dysplasia

Architecture	Cytology
Irregular epithelial stratification	Abnormal variation in nuclear size (anisonucleosis)
Loss of polarity of basal cells	Abnormal variation in nuclear shape (nuclear pleomorphism)
Drop-shaped rete ridges	Abnormal variation in cell size (anisocytosis)
Increased number of mitotic figures	Abnormal variation in cell shape (cellular pleomorphism)
Abnormally superficial mitoses	Increased nuclear-cytoplasmic ratio
Premature keratinization in single cells (dyskeratosis)	Increased nuclear size
Keratin pearls within rete pegs	Atypical mitotic figures
	Increased number and size of nucleoli

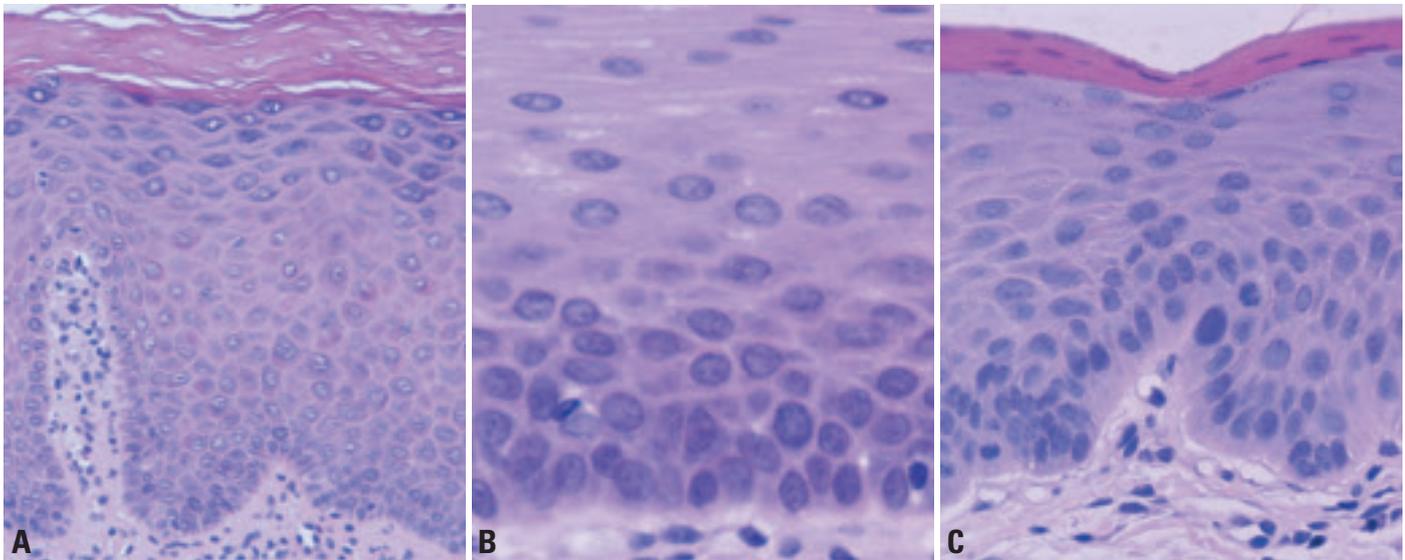


Fig. 4.14 **A** Acanthosis. Hyperplastic epithelium with thickened stratum spinosum. **B** Basal cell hyperplasia. Increase in progenitor compartment without dysplasia. **C** Mild dysplasia. Basal cell hyperplasia with relatively mild cytological change confined to lower third of epithelium.

graph architectural disturbance extending into the middle third of the epithelium with sufficient cytologic atypia is upgraded from moderate to severe dysplasia.

Carcinoma in-situ

The theoretical concept of carcinoma in-situ is that malignant transformation has occurred but invasion is not present. It is not possible to recognize this morphologically. The following is recommended for the diagnosis of carcinoma in-situ: full thickness or almost full thickness architectural abnormalities in the viable cellular layers accompanied by pronounced cytologic atypia. Atypical mitotic figures and abnormal superficial mitoses are commonly seen in carcinoma in-situ.

Differential diagnosis

Reactive, regenerative or reparative squamous epithelium, for example in response to trauma, inflammation, irradiation or

ulceration, may manifest atypical cytology or architectural disturbance. Nutritional deficiencies such as iron, folate, and vitamin B12, can also simulate dysplasia. Such lesions are not considered precursor lesions and should be distinguished from them. Clinical history is helpful and morphological changes suggestive of the inciting event, such as ulceration, inflammation, haemorrhage, radiation-induced mesenchymal and/or endothelial nuclear enlargement and hyperchromatism, may be present. The epithelial changes in these cases are generally less pronounced than in dysplasia.

Relevance of dysplasia. It is reasonable to assume that the changes described in dysplasia are due to genetic changes in the epithelium occur, but it is unlikely that the mutations involved are the same ones as are associated with development of malignancy. More severe dysplasia has been traditionally believed to be associat-

ed with a greater likelihood of progression to malignancy. This might indicate that the greater the accumulation of mutations in tissue, the greater the chance that the critical mutations for malignancy will be present. The corollary is also true in that malignancy can arise from non-dysplastic epithelium [2493] presumably because these critical mutations can be present in the absence of the mutations causing dysplasia.

Genetics

There are no individual markers that reliably predict malignant transformation. The molecular biology techniques which show most promise as predictors of development of SCC are large scale genomic status (DNA ploidy) and loss of heterozygosity (LOH) at defined loci [2286].

Dysplasia has been reported to be present in from 10-25% of leukoplakias

Table 4.03 Malignant transformation of oral leukoplakia (Reibel [2145])

Authors/Year	Country	Material (no. of cases)	Observation period (years)	Cases with malignant transformation (%)
Pindborg et al., 1968 {2049}	Denmark	248	3.9	4.4
Silverman and Rosen, 1968 {2362}	USA	117	1-11	6.0
Kramer et al., 1970 {1368}	UK	187	-	4.8
Mehta et al., 1972 {1699}	India	117	10	0.9
Silverman et al., 1976 {2358}	India	4762	2	0.13
Bánóczy, 1977 {118}	Hungary	670	9.8	6.0
Silverman et al., 1984 {2361}	USA	257	7.2	17.5
Lind, 1987 {1517}	Norway	157	9.3	8.9
Schepman et al., 1998 {2261}	Netherlands	166	2.5	12.0

{2286,2490}. Ploidy studies of dysplastic leukoplakias showed that the great majority of aneuploid lesions developed SCC in the follow-up period, by contrast with 60% of tetraploid lesions and only about 3% of diploid lesions {2490}. No correlation was found between the degree of dysplasia and DNA ploidy. Similar studies on erythroplasias {2491} confirmed the high predictive potential of aneuploidy in identify-

ing cases which progressed to SCC. Non-dysplastic white patches have also been studied {11} and although there was a much lower incidence of malignant transformation, 80% of such cases were aneuploid.

LOH studies have been undertaken contrasting oral lesions which progressed to SCC or carcinoma in-situ during follow-up with corresponding lesions which did not

progress. LOH on two chromosome arms, 3p and 9p seemed to be particularly important in predicting progression {2201}.

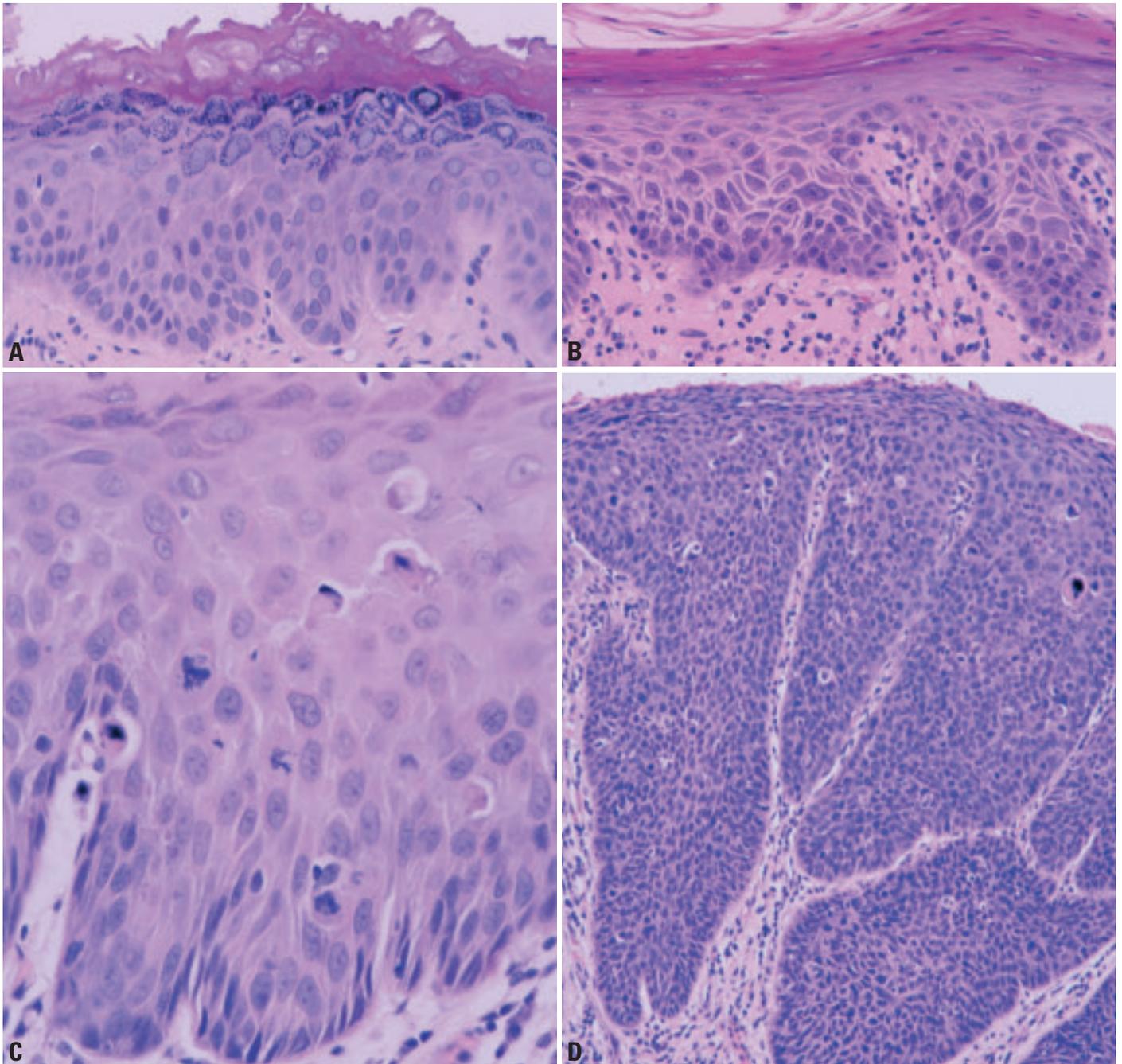


Fig. 4.15 **A** Moderate dysplasia. Drop shaped rete ridges, dysplasia extending to mid-third and moderate cytological changes **B** Severe dysplasia into upper third of epithelium with marked cytological change **C** Severe dysplasia into upper third of epithelium with prominent cytological change including abnormal mitoses. **D** Carcinoma in-situ. Abnormal cells seen throughout the full thickness of epithelium.

Proliferative verrucous leukoplakia and precancerous conditions

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P.A. Reichart

Definition

Proliferative verrucous leukoplakia (PVL) is a rare but distinctive high-risk clinical form of oral precursor lesions. Because of the lack of specific histologic criteria, the diagnosis is based on combined clinical and histopathologic evidence of progression. Sequential biopsies show progressive dysplasia and the acquisition of aberrant TP53 protein.

Clinical features

PVL is an aggressive form of oral leukoplakia with considerable morbidity and strong predilection to malignant transformation {174,1005,1797,2360}. The etiology of this entity is unknown. The condition develops initially as focal clinical hyperkeratosis (leukoplakia) that progressively becomes a wide multifocal disease with gross exophytic features {174}. The aver-

age age at diagnosis is 62 years; women are more commonly afflicted (ratio, 4:1). Typically, multiple oral sites are affected. The most common site in women is the buccal mucosa and the tongue in men. Carcinoma develops after a protracted period of time. The most common sites of the carcinoma are gingiva and tongue. PVL is characterized by high recurrence rate and histological progression. Many cases are resistant to all forms of treatment, including laser microsurgery, surgical excision and radio- and chemotherapy. Conservative management of these lesions has been unsuccessful and wide surgical excision is the best hope for control.

Other precancerous conditions

Precancerous conditions (PCs) are generalized clinical states associated with a

significantly increased risk for SCC. Epithelial atrophy, increased mitotic activity and impaired epithelial repair mechanisms are fundamental to PCs of different etiology.

Iron deficiency

Originally described in the context of sideropenic dysphagia, it is an important cause of epithelial atrophy. The association of iron deficiency with oropharyngeal squamous cell carcinomas has been observed since the mid-thirties of the 20th century {21}. However, a significant decrease of cases with hypopharyngeal cancers and iron deficiency was noted in Sweden in the seventies {1433}. Few cases of oral cancer and iron deficiency have been published in the last 20 years.

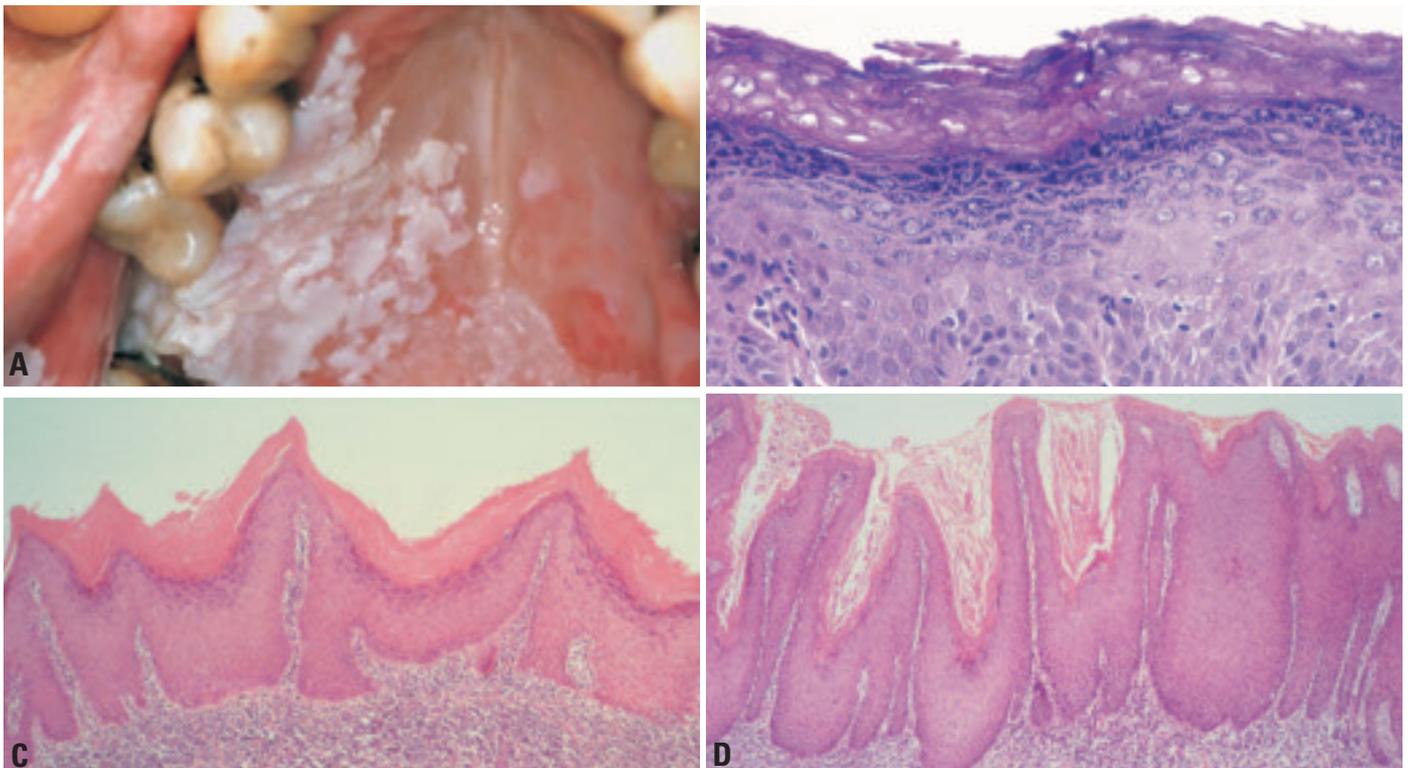


Fig. 4.16 Proliferative verrucous leukoplakia (PVL) **A** Extensive, thick, white plaques. **B** Hyperplasia and dense hyperkeratosis of early PVL. **C** Histology from a clinical case of PVL showing verrucous surface with hyperkeratosis, hypergranulosis and a dense inflammatory infiltrate in the corium. **D** Same case as shown on fig. C two years later showing more florid verrucous hyperplasia illustrating the progressive nature of the condition.

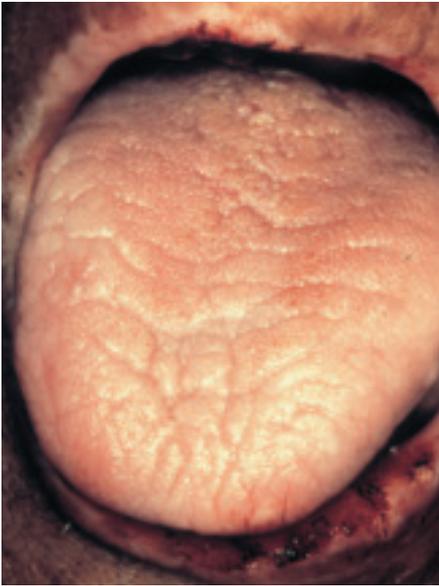


Fig. 4.17 Sideropenic dysphagia. Iron deficiency anaemia with depapillated tongue, depigmentation of the upper lip and epithelial erosion of the lower lip.



Fig. 4.18 Erythroplasia / erythroplakia associated with oral lichen planus (precancer).



Fig. 4.19 Syphilis. Interstitial glossitis due to late stage syphilis with squamous cell carcinoma at the left tip of the tongue (Collection of J.J. Pindborg, M.D., Copenhagen).

Oral lichen planus

OLP is a chronic mucocutaneous immune inflammatory condition. Malignant transformation is still controversial {639,2359}; one review reporting malignant transformation rates between 0% and 5.6% {2116}.

The controversy is due to lack of uniform

clinical and histological criteria for OLP and oral lichenoid lesions (OLL). The latter have also been termed interface mucositis or lichenoid mucositis. Oral lichenoid lesions have been considered by some to represent the lesion at risk if associated with dysplasia. In a recent study {2664} it was shown that all cases of malignant transformation (1.7%) involved cases of OLL and not OLP. Similarly, a study {2896} investigating whether OLP without dysplasia is premalignant by using microsatellite analysis for loss of heterozygosity (chromosomes 3p, 9p, 17p) did not support OLP as a lesion at risk.

However, until distinct clinical and histological criteria have been developed on how to differentiate OLP from OLL, both lesions have to be considered as 'at risk for malignant transformation'.

Oral submucous fibrosis (OSF)

This chronic, progressive condition of the oral mucosa {2115} is etiologically strongly associated with the chewing of areca nut which has recently been categorized by IARC as a human carcinogen {1}. It is almost exclusively seen in ethnic groups using areca nut alone or as a component of betel quid.

Clinically there is mucosal rigidity of varying intensity due to fibroelastic transformation of the juxtaepithelial connective tissue. Fibrous bands and mucosal pallor are characteristic {498}. Histologically, there is epithelial atrophy, keratosis and dysplasia in up to 25% of cases {498}. In a population-based prospective study, in India, SCC developed in 7% of patients with OSF over a period of 17 years {1798}.

Syphilis

Late stage (tertiary) syphilis associated with leukoplakia had a high risk of malignancy, but this is now largely of historical interest {1721}.

Xeroderma pigmentosum

This is a rare neurocutaneous disease with an autosomal-recessive mode of inheritance. The syndrome is caused by deficient nucleotide excision repair mechanisms {2090}. The skin, including the lips, is affected and shows epithelial atrophy and hyperpigmentation. Patients are extremely sensitive to light and show an increased predisposition to UV-associated malignancies of the skin. Carcinomas of the tongue have also

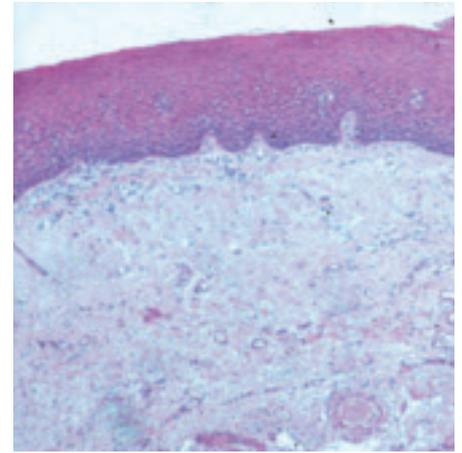


Fig. 4.20 Oral submucous fibrosis with a broad band of subepithelial collagenous tissue.

been described {1306,1994,2704}.

Lupus erythematosus

This is a chronic autoimmune disease of unknown etiology. Carcinomas, mainly of the lips, have been described in affected individuals {2264,2696}.

Epidermolysis bullosa dystrophicans (Hallopeau-Siemens type)

This disease of the skin and oral mucosa has an autosomal dominant pattern of inheritance. Oral leukoplakia and occasional cases of SCC have been observed in association with epidermolysis bullosa {226,2288}.

Papillomas

E.W. Odell

Definition

These form a range of localised hyperplastic exophytic and polypoid lesions of hyperplastic epithelium with a verrucous or cauliflower-like morphology. Lesions of fibroepithelial hyperplasia are not generally included. Not every papilloma can be allocated to one of the diagnostic categories described below.

ICD-O code 8050/0

Epidemiology

Papillomas are common, with a prevalence of approximately 0.1%-0.5% [94,1342,2569].

Etiology

HPV infection causes some papillomas [2076] and at least types 1,2,3,4,6,7,10,11,13,16,18,30,31,32,33,35,38,45,52,55,57,59,69,72,73 sequences have been detected in benign oral lesions. Clinically, latent HPV is common in oral mucosa and HPV DNA sequences can be detected in over 80% of individuals. There is no absolute association between the virus type and the type of papilloma [866] though focal epithelial hyperplasia is almost exclusively associated with types 13 and 32. HPV infection of oral tissue may be transmitted horizontally, including venereally, perinatally and possibly in utero [2518].

Histopathology

Histological differential diagnosis for all types includes lesions of fibroepithelial hyperplasia: fibroepithelial polyps, fibrous epulis and papillary hyperplasia associated with candidal infection or dentures. These have a more prominent fibrous component and no viral change. Verruciform xanthoma is a solitary lesion with a very similar clinical and histological presentation.

Extensive multiple papillomas or diffuse papillomatous change raise the possibilities of HPV lesions in immunosuppression, acanthosis nigricans, naevus unius et lateris, focal dermal hypoplasia, Cowden syndrome, papillary and verru-

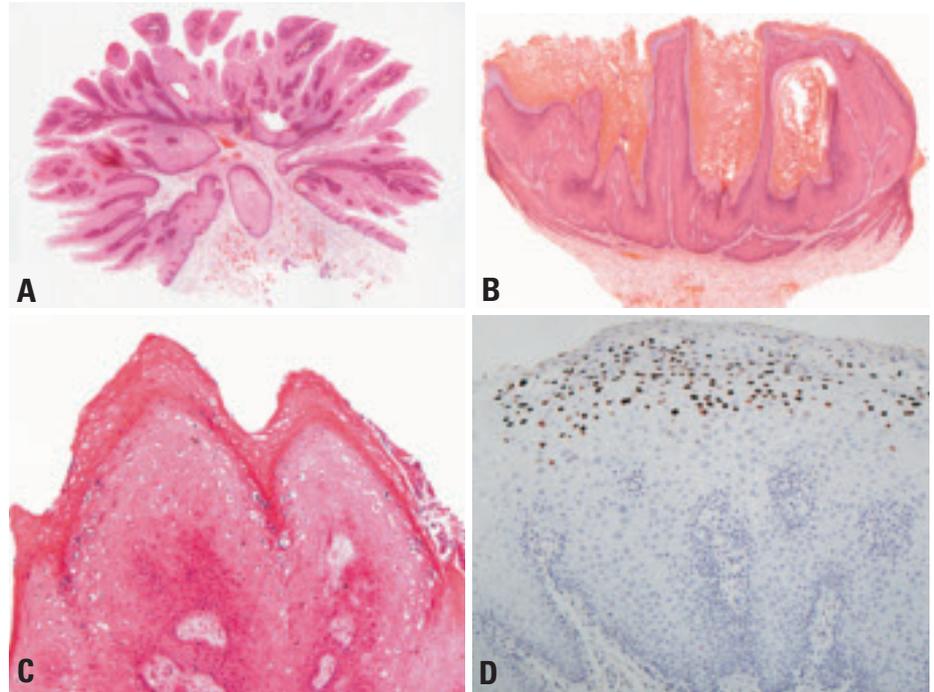


Fig. 4.21 Papilloma. **A** Typical papillary structure of squamous papilloma. This example is only lightly keratinised and negative for papilloma virus on immunocytochemistry. **B** Papilloma from the vermilion border showing extensive keratinisation. Note the inwardly facing rete ridges at the periphery. **C** Moderately keratinised papilloma of verruca vulgaris type showing koilocytic change in the upper prickle cell layers. **D** Strong and extensive staining for papilloma virus in a flat papilloma from an HIV infected individual. There is widespread infection in the upper prickle cell layer but the architecture of the epithelium is little changed. Note the sharp lesion margin on the left.

cous dysplastic lesions and papillary squamous [2488] or verrucous carcinoma. Florid oral papillomatosis is a clinical term for diffuse papillomatous change of the mucosa for which no specific cause can be identified and is not a defined clinico-pathological entity.

Squamous cell papilloma and verruca vulgaris

Definition

A benign, hyperplastic wart-like localised proliferation of the oral epithelium [2076].

Epidemiology

Squamous papillomas are common in children and in adults in the 3rd to 5th decades but may be found at any age. There is an almost equal sex incidence with a slight male predominance.

Etiology

Evidence of causative HPV infection can be found in less than half of oral squamous papillomas [866,2516,2747], and these lesions are the intraoral counterpart of verruca vulgaris. Many HPV subtypes have been detected including 2,4,6,7,10,40. The presence of HPV virion components ultrastructurally and immunocytochemically indicates active viral replication in the lesion. Virus transmission appears to be mostly horizontal or by autoinoculation. Lesions in children tend to arise at anterior oral sites and the source of infection is often verruca vulgaris on the skin, particularly on the fingers. Infectivity is low.

The remainder of squamous papillomas are of unknown etiology. HPV sequences may be detected by PCR but the significance of this is unclear.

Localization

Any oral site may be affected but the most common are the hard and soft palate, labial mucosa, tongue and gingiva.

Clinical features

Squamous papillomas are soft, pedunculated lesions formed by a cluster of finger-like fronds or a sessile, dome-shaped lesion with a nodular, papillary or verrucous surface. The surface may be white or of normal mucosal colour depending on the degree of keratinization {2076}. Lesions are usually single but fairly frequently multiple, particularly in children and for verruca vulgaris. Squamous papillomas grow rapidly over a period of a few months to a maximum of about 6mm diameter and then remain a constant size.

Histopathology

Lesions are exophytic and comprise folds of hyperplastic stratified epithelium that are usually thickly para- or orthokeratinized but may be non keratinised. Squamous papillomas associated with HPV (oral verruca vulgaris) comprise a cluster of finger-like projections from a narrow base, each with a sharp keratinised tip, supported on ramifying cores of connective tissue containing dilated capillaries. Stratification of the epithelium is well ordered. Mitoses may be frequent and there may be mild anisonucleosis consistent with hyperplasia, but no atypia. The fronds are thickly keratinised, often with a prominent keratohyaline layer of large coarse granules. Small foci of HPV-infected cells (koilocytes) can usually be found in the upper prickle cell layer. These keratinocytes have crumpled, darkly stained nuclei with perinuclear haloes but appear very similar to vacuolated keratinocytes that are common in the normal oral mucosa. Koilocytes may be more frequent in early lesions. Less frequently, viral inclusions are found. Rete processes at the base often turn inwards and are symmetrical. Small foci of lymphocytic inflammation may lie in the fronds or at the base but inflammation is usually sparse unless the lesion is subject to trauma or other irritation {4,1929}. HPV may be identified by immunocytochemistry or in-situ hybridisation but this is not necessary for diagnosis {2076}.

Papillomas without detectable active HPV replication show more variation.

They may appear identical to verruca vulgaris but without koilocytes or prominent keratohyaline granules, or form rounded broad-based dome shaped lesions similar to condyloma. The hyperplastic epithelium may form papillary exophytic fronds or arborising rete processes. Some are flat zones of acanthotic hyperplastic epithelium with increased numbers of dermal papillae similar to plane warts of the skin.

Prognosis and predictive factors

Oral verruca vulgaris may regress spontaneously, particularly in children, but responds to simple excision or ablation by laser or cryosurgery. Recurrence is unusual provided all lesional tissue is removed and there is no malignant potential.

Condyloma acuminatum

Definition

Oral counterpart of anogenital condyloma acuminatum

Synonyms

Venereal wart; venereal condyloma

Epidemiology

Lesions are usually diagnosed between the mid 2nd and 5th decade with a peak in teenagers and young adults {2916}.

Etiology

Epithelial infection by HPV, most commonly types 6,11,16 and 18 though others have been detected {700,1380}. Transmission is usually venereal or by autoinnoculation from concomitant genital lesions {1975}.

Histological appearance is not an accurate indicator of a genital origin.

Localization

Most lesions arise on the labial mucosa, tongue and palate in anterior oral sites though any area may be affected {700, 2916}.

Clinical features

Condylomas are painless, rounded, dome-shaped exophytic nodules up to 15 mm in diameter, larger than squamous papillomas and verruca vulgaris. They have a broad base and a nodular or mulberry-like surface that is slightly red, pink or of normal mucosal colour. Lesions may be multiple and are then usually clustered {2076,2916}.

Histopathology

Condylomas are similar to squamous papillomas but with short blunt rounded fronds of hyperplastic epithelium of even length forming a smooth or nodular, flat or rounded surface. Keratin is usually absent or sparse, occasional examples show moderate keratin and are white clinically. Between the folds, crypts or clefts lined by epithelium extend close to the broad base and may be filled with keratin debris in keratinised lesions. Clusters of koilocytes identical to those described above are much commoner than in squamous papillomas and are usually a prominent feature. Unlike squamous papilloma, rete processes are bulbous and short, of even length and do not curve inwards {700,2076}.

Prognosis and predictive factors

Condyloma acuminatum often responds to simple excision or ablation by laser or cryosurgery but appears to carry a higher risk of recurrence than squamous papilloma. Unlike ano-genital condyloma, there is no documented risk of malignant transformation, regardless of the presence of high-risk HPV types.

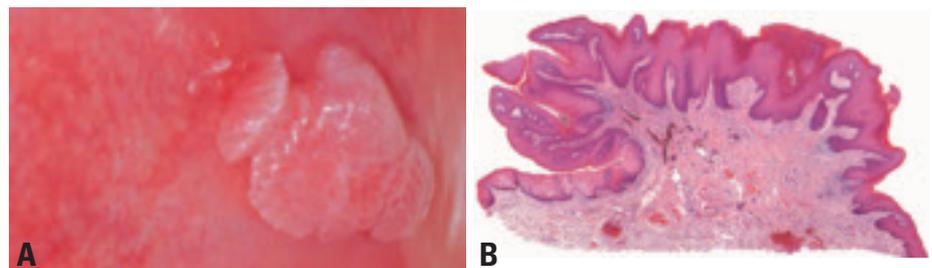


Fig. 4.22 Condyloma acuminatum. **A** Several sessile, cauliflower-like swellings forming a cluster. **B** Typical papilloma structure in condyloma showing the more rounded architecture in comparison with verruca vulgaris. Note a verrucous area on the left; many of these lesions have features of both types of papilloma.

Condyloma acuminatum in children raises the possibility of sexual abuse, but non-sexual transmission is possible {1380} and probably frequent.

Papillomas and papillomatosis in immunodeficiency

More florid presentations of HPV-induced lesions are found in immunosuppression, particularly in HIV infection. Lesions may be larger, multiple and coalesce to form extensive patches of affected mucosa. Occasionally the entire oral mucosa may become papillomatous and some of these presentations are not easily classified. Unusual HPV subtypes and multiple HPV subtypes are more frequent in immunosuppression. Occasional lesions in HIV infection are dysplastic and are of uncertain malignant potential.

Focal epithelial hyperplasia

Definition

Multiple oral papillomas induced by HPV 13 and 32

Synonym

Heck disease

Epidemiology

This is primarily a disease of children, adolescents and young adults. Originally described in Inuit and native Americans {69} but now recognised worldwide. The condition is endemic in some countries and prevalence may be as high as 40% of children in localised areas {94,332, 1014}.

Etiology

Infection by HPV types 13 and 32.

Localization

All areas of the oral cavity may be affected but the lesions are most common on the labial and buccal mucosa and the tongue {69,332,1014}.

Clinical features

Typically there are multiple asymptomatic lesions, each a soft rounded or flat plaque-like sessile swelling with a slightly nodular surface. They are usually pink in colour or sometimes white, and 2-10mm in diameter. Lesions develop in clusters or confluent patches {332}.



Fig. 4.23 Focal epithelial hyperplasia. Typical clinical appearance of multiple papillomatous nodules.

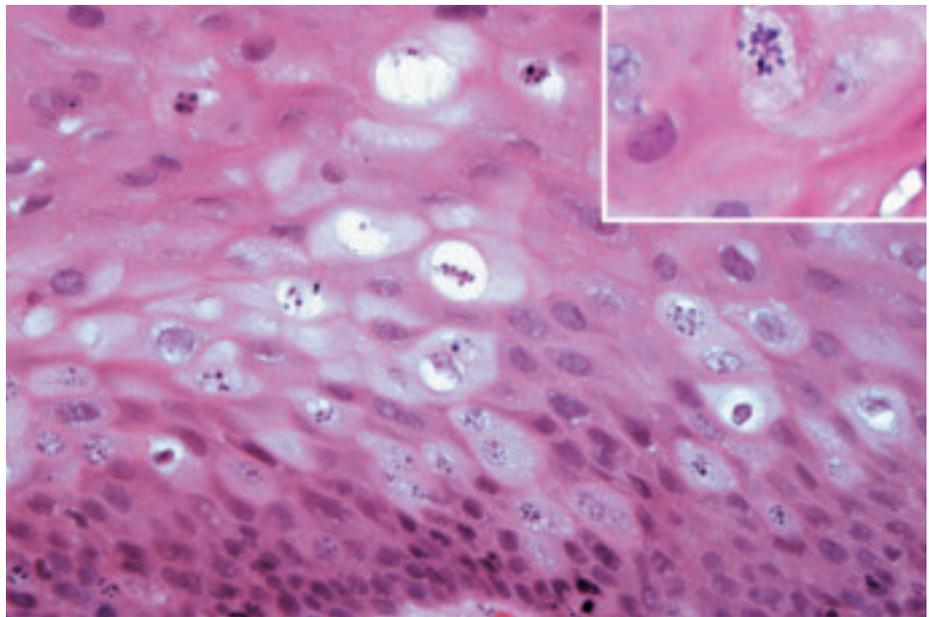


Fig. 4.24 Focal epithelial hyperplasia, viral change and mitosoid body (inset).

Individual lesions may appear and disappear during the course of the disease {1014}.

Histopathology

The histological features are more distinctive than squamous papilloma or condyloma. Each lesion is a slightly raised or rounded sessile swelling formed by a sharply demarcated zone of epithelial acanthosis, similar to condyloma acuminatum but with a less prominent papillomatous structure. The bulk of lesion is formed by exophytic acanthosis, without formation of well-defined projections of epithelium and the lesion contains minimal connective tissue papillae. Koilocytes similar to those of squamous papilloma are usually present and, in addition, there are usually characteristic "mitosoid bodies", which are nuclei with coarse clumped heterochromatin resembling a mitotic figure. Mitosoid bodies are characteristic but not specific for focal epithelial hyperplasia. The base of the

lesion is flat and level with the adjacent epithelium without rete process enlargement {332,2076}. HPV may be detected on immunocytochemistry or by in-situ hybridisation but this is not necessary for diagnosis if the clinical presentation is typical {2076}.

Genetic susceptibility

Familial clustering and endemic areas may result from horizontal transmission.

Prognosis and predictive factors

The condition appears to resolve spontaneously after a period of years and is rarely found in adults. It has no malignant potential.

Granular cell tumour

P.M. Speight

Definition

A benign tumour of soft tissues which most often arises in the tongue and is thought to be of Schwann cell origin. It is composed of a poorly demarcated accumulation of plump granular cells which are often intimately associated with skeletal muscle.

ICD-O code 9580/0

Synonym

Granular cell myoblastoma

Epidemiology

Granular cell tumours are rare. Approximately 50% of all lesions arise in the head and neck and over half of these are found in the tongue. They arise in all age groups, with a peak between 40 and 60 years. In about 10-20% of patients the lesions are multiple. Females are affected more often than males with an M/F ratio of 2:1.

Etiology

No etiological factors are known. The lesion is thought to arise from Schwann cells. The granularity may be a senescent change associated with accumulation of lysosomes.

Localization

Granular cell tumours may arise in the skin, soft tissues, breast and lungs, but over 50% involve the head and neck and the tongue is the most common single site. Oral lesions may also be found in the buccal mucosa, floor of oral cavity or palate. Lesions may be multiple, affecting more than one intraoral site, or involving oral and extraoral sites [477]. Rare lesions have been reported in the salivary glands [331].

Clinical features

The lesion typically presents as a smooth, sessile mucosal swelling 1-2 cm in diameter with a firm texture. The overlying epithelium is of normal colour or may be slightly pale. Occasionally there is candidal infestation of the superficial



Fig. 4.25 Granular cell tumour. The typical presentation of granular cell tumour: a sessile swelling on the tongue covered by normal appearing epithelium.

epithelium and the lesion may then present as a discrete, white plaque.

Macroscopy

Tumours are usually 1-2 cm in diameter with a smooth surface. The cut surface shows a poorly demarcated lesion which is pale yellow or cream and firm on cutting.

Histopathology

The lesion is composed of plump eosinophilic cells with central small dark nuclei and abundant granular cytoplasm. The cells may be polygonal or elongated and have indistinct cell membranes, often giving the impression of a syncytium. The lesion is not encapsulated and the granular cells extend into adjacent tissues, typically skeletal muscle,

where they appear to merge with muscle cells [477,2791]. Granular cells extend up to the epithelium, often forming small islands in the connective tissue papillae. The granules stain positively with periodic acid Schiff (PAS).

A characteristic feature of granular cell tumour is that in up to 30% of cases the overlying epithelium shows pseudoepitheliomatous hyperplasia that may be misdiagnosed as carcinoma.

Immunoprofile

The lesion is strongly and uniformly positive for S-100 protein. Cells also express neurone-specific enolase, calretinin, inhibin-alpha and PGP 9.5, and show fine granular cytoplasmic positivity for the lysosome related antigen CD68 [764, 2791].

Prognosis and predictive factors

Granular cell tumours are benign and rarely recur, even after conservative removal. Occasional lesions have behaved aggressively and malignant granular cell tumours have been described.

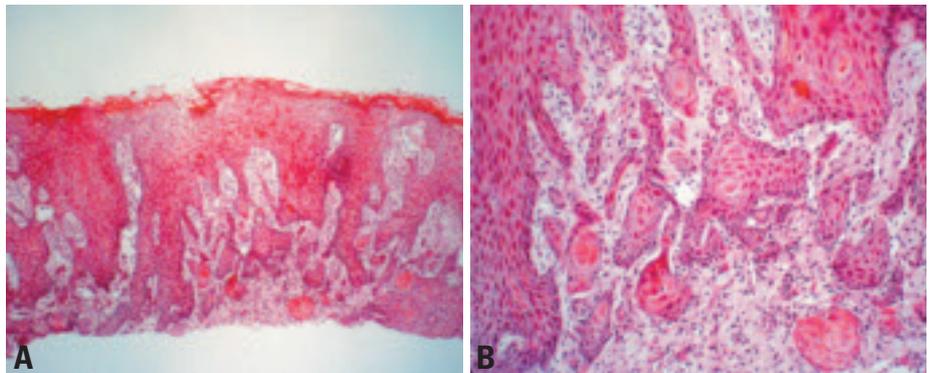


Fig. 4.26 Granular cell tumour. **A** Prominent pseudoepitheliomatous hyperplasia of the oral epithelium overlying a granular cell tumour. **B** The pseudoepitheliomatous hyperplasia can be mistaken for carcinoma, but careful examination shows eosinophilic granular cells in the connective tissues.

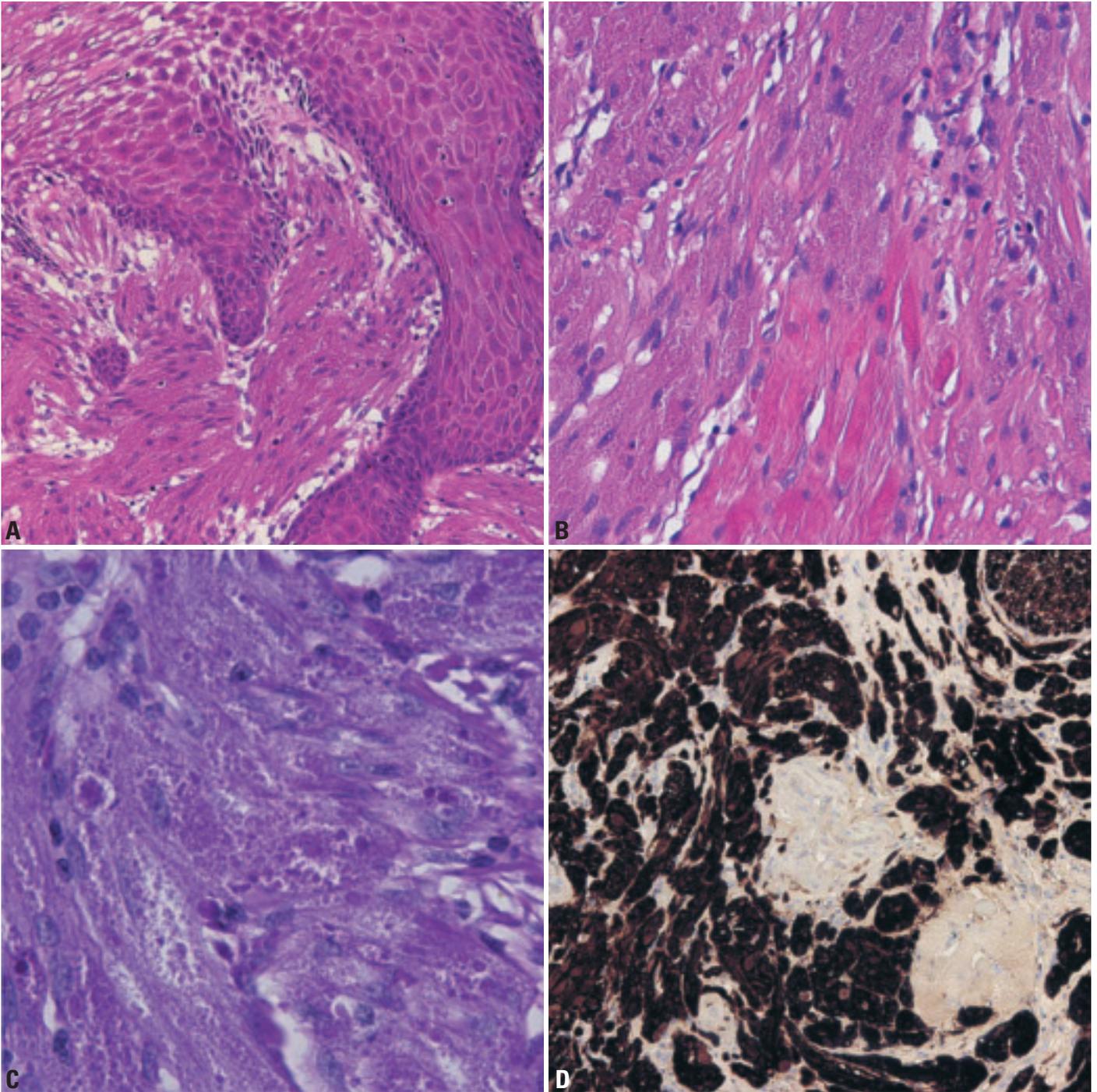


Fig. 4.27 Granular cell tumour. **A** The granular cells frequently extend close to the overlying epithelium, but do not fuse with it. **B** The granular cells infiltrate widely and often appear to merge with striated muscle cells. **C** The granules are PAS positive (Periodic acid Schiff stain). **D** The granular cells are strongly and uniformly positive for S-100 protein.

Keratoacanthoma

T. Löning
K.T. Jäkel

Definition

Keratoacanthoma is a benign tumour that is believed to arise from the epithelium of hair follicles.

ICD-O code 8071/1

Synonyms

Molluscum sebaceum, molluscum pseudocarcinomatousum, self-healing primary squamous carcinoma, tumour-like keratosis, idiopathic cutaneous pseudoepitheliomatous hyperplasia.

Epidemiology

Keratoacanthoma occurs more often in whites, and is almost twice as frequent in men as in women. Although they have been seen in infants, keratoacanthomas are rare in persons under 20 years of age and the peak incidence is between the sixth and seventh decade {881}.

Etiology

Interestingly, the uptake of carcinogens (e.g. via particular smoking habits) may be relevant in human tumours {641}. No other risk factors are known. The concept of a common viral origin (papillomaviruses), popular for some years, has been abandoned.

In addition to the solitary type, clinical variants with multiple keratoacanthomas have been described, sometimes with a unilateral distribution {881}. Genetic factors may be involved in these cases, for familial clustering occurs, with multiple keratoacanthomas in affected individuals.

Localization

Keratoacanthomas preferentially occur on sun exposed hairy skin {881}. Thus, they are frequent on the skin of the face, including the lips (8% of cases), and extremely rare at hairless sites. Whether or not a "true keratoacanthoma" of the oral mucosa exists or not remains controversial {1929}. However, a small number of cases of the solitary form have been reported in intraoral sites {414,973}, and mucocutaneous linings may also be

affected in the generalized forms (e.g. the Ferguson-Smith, Grzybowski and Witten and Zak types) {881}.

Clinical features

Keratoacanthoma is characterised by rapid growth followed by slow, spontaneous involution over several months {881}. Exact figures about regression time, however, are difficult to obtain, since the common mode of treatment is excision. The mature lesion is usually bud- or dome-shaped and is brownish or slightly reddish. Over time a central keratinous crater appears at the expense of the surrounding softer tumour tissue until finally a cup- or saucer-shape lesion develops that appears ulcerated, but is, in fact, lined by tumour epithelium and often covered with horn masses. An eruptive variant can be distinguished which is multifocal and often lacks the central keratin-filled crater. Following trauma and/or infection, true ulceration may occur, especially in areas like the lips, probably due to repeated scratching or biting. In the oral cavity, the above-described phenotypes rarely occur. Instead, the puta-

tive oral lesion mimics a broad spectrum of pseudoneoplastic and neoplastic lesions {1929}.

Macroscopy

The basic gross features of epidermal lesions have been already described. However, such prototypic lesions are rarely seen in the oral cavity. Instead, as in cases at the inner side of the vulva and within the anal canal, oral keratoacanthomas present as verrucous, speckled or even ulcerated lesions. Also, they may produce deep projections, which can extend through minor salivary glands and reach the surface of underlying bone.

Histopathology

Keratoacanthomas show a verrucous surface, and underneath keratinized clefts and penetrating squamous rete processes are found with deep keratin pearls. Atypia is minimal, and mitotic figures are rare or absent. Dense inflammatory infiltrates, including granulocytes typically are found in the adjacent stroma and within the deep parts of the tumour, so that the margins seem ill defined. The

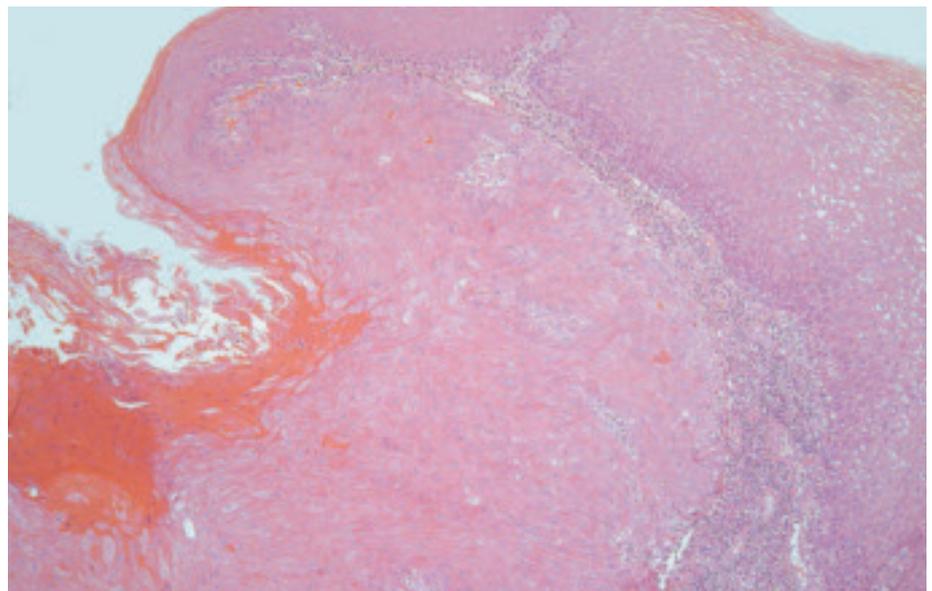


Fig. 4.28 Keratoacanthoma of the mucosal aspect of the upper lip with the cup-shape margin on the right, and the keratin-filled crater that is in the centre of the lesion on the left.

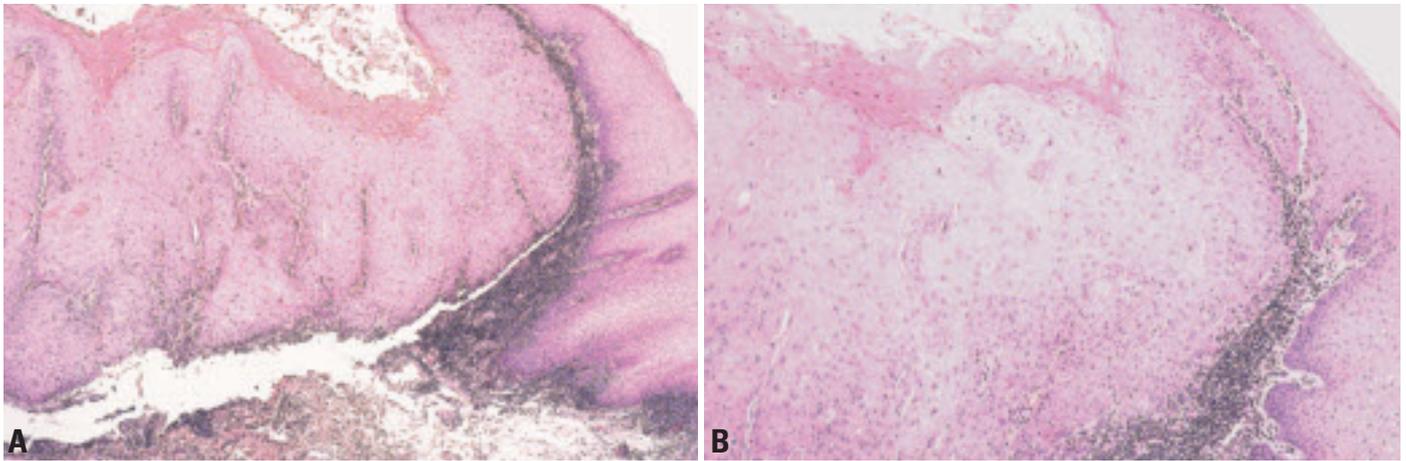


Fig. 4.29 Keratoacanthoma. **A** Intraoral keratoacanthoma with a marginal lip and a cup-shaped lesion, in this case with parakeratotic keratin, and the typical dense inflammatory infiltrate at the epithelial-stromal interface. **B** The higher magnification reveals the inflammatory infiltrate in detail, and the absence of cellular atypia in the lesional epithelium.

hallmark of keratoacanthoma is the overall architecture, with a cup-shaped appearance and a collar-like circumference.

A major diagnostic problem arises when destructive infiltration takes place as has been reported, including some cases in young individuals. When this kind of tumour growth occurs in the elderly, it is of course extremely difficult or even impossible to distinguish the lesion from carcinoma, particularly from carcinoma cuniculatum, which also shows minimal atypia despite its destructive growth pattern [1929].

Histogenesis

A large body of evidence exists pertaining to the histogenesis of keratoacanthomas [881]. In fact, it is their origin from pilosebaceous follicles which has led some authors to deny the existence of intraoral keratoacanthomas [1929]. This standpoint may be acceptable for sites

of the oral cavity where pilo-sebaceous rudiments are rarely seen (e.g. gingiva). However, there are also cases reported in areas such as the buccal mucosa, which is a preferential site for the ectopic sebaceous glands (Fordyce spots). In addition, as also suggested for skin lesions, preprogrammed progenitor cells of the most superficial (intraepidermal) parts of the pilosebaceous unit may be sufficient as a source of (intraoral) keratoacanthoma.

Prognosis and predictive factors

Epidermal keratoacanthomas are clearly benign lesions [881]. However, for similar tumours of the external openings (oral cavity, vulva, anal canal) there are no reliable data, since these lesions are extremely rare, present diagnostic problems and therefore are usually completely excised. Recurrences after surgical excision do not occur.

Papillary hyperplasia

E.W. Odell

Papillary hyperplasia is an asymptomatic nodular or papillary mucosal lesion typically seen in the palate of patients who wear dentures. Most patients wear ill-fitting dentures, wear dentures continuously {2645} or have poor denture hygiene. Lesions also arise in non-denture wearers, in xerostomia or individuals with a high arched palate. Florid and extensive presentations occur in immunosuppression {937} and HIV infection {2150}. There is sessile nodular papillomatous hyperplasia of epithelium and supporting underlying fibrous tissue. There is usually parakeratinisation or less frequently orthokeratinisation. Rete processes are

usually rounded or sharply defined at the base of the lesion but there may be pseudoepitheliomatous hyperplasia with keratin pearls and a poorly defined deep margin. Differential diagnosis includes diffuse HPV-induced papillomatosis, periorificial plasmacytosis {937} and verruciform xanthoma. Other multinodular lesions such as focal epithelial hyperplasia, acanthosis nigricans and Cowden syndrome appear similar histologically but have distinctive clinical presentations.

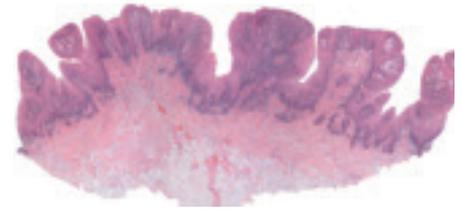


Fig. 4.30 Papillary hyperplasia. Low power view showing the overall architecture with nodular fibroepithelial hyperplasia and apparently detached islands of epithelium in the upper corium. Inflammation is slight in this example but depends on candidal infection and whether a denture overlies the lesion. It may be a very prominent feature.

Median rhomboid glossitis

E.W. Odell

Median rhomboid glossitis typically forms a patch of papillary atrophy near the midline of the dorsum of the tongue at the junction of the anterior two thirds and posterior third in the region of the embryological foramen caecum. It is no longer thought to be a developmental defect but the result of chronic candidal infection {719,2825}. The epithelium lacks papillae, and shows

psoriasiform hyperplasia and sometimes areas of pseudoepitheliomatous hyperplasia. A mild degree of atypia may be present. Fungal hyphae are present in the superficial epithelium but are usually sparse and revealed only in multiple sections. Scarring and nodularity persist after antifungal treatment. Differential diagnosis is aided by knowledge of the specific site and includes reactive

fibroepithelial hyperplasia, granular cell tumour and other nodular lesions of the tongue. Occasionally the lesion can be difficult to differentiate from squamous cell carcinoma {931, 1932}, particularly when hyperplasia is extensive and epithelial processes reach or penetrate the underlying muscle.

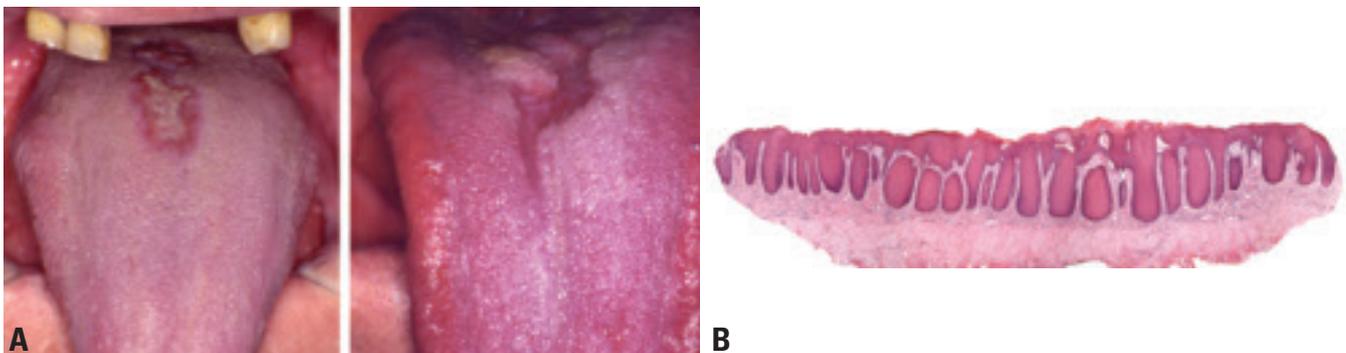


Fig. 4.31 Median rhomboid glossitis. **A** Two lesions of chronic candidiasis of the median rhomboid glossitis form. That on the left is flat and more typical, that on the right more nodular and irregular. **B** Typical median rhomboid glossitis with active candidal infection showing long bulbous rete hyperplasia and suprapapillary atrophy. Note the broad band of dense fibrosis separating the inflamed superficial corium from the underlying muscle.

Salivary gland tumours

J.W. Eveson

Epidemiology

Tumours of the oral cavity and oropharynx account for 9-23% of all salivary gland neoplasms in major series {669,704,2301}. The most common sites are the palate (44-58%), lips (15-22%) and buccal mucosa (12-15%) {669,704,2301,2711}. Variations in these series probably reflect patterns of referral in different institutions, together with geographical and ethnic differences.

Tumours of the oropharynx are relatively uncommon and form only 1.1-3.3% of all minor gland tumours {669,704,2448}. Most studies show a female to male ratio in the range of 1.2:1-1.5:1 {2711}.

Location

Nearly half of all oral and oropharyngeal salivary tumours are malignant, and in some sites, such as the lower lip, tongue and floor of the oral cavity, the large majority are carcinomas. It is interesting to note that while 80-90% of labial salivary gland tumours involve the upper lip, there is a 3-5x greater risk of neoplasms in the lower lip being malignant {400,669,704,1871,1963}.

Most of the principle types of salivary gland tumour have been reported in the oral cavity. In some tumours such as canalicular adenoma, duct adenomas and polymorphous low-grade adenocarcinoma, the minor glands are by far the most frequent site of involvement. Whether there are genuine cases of intra-oral Warthin tumour, or whether reported examples represent oncocytic hyperplasia and metaplasia with reactive lymphocytic infiltration, is contentious {2669}.

ICD-O codes

Acinic cell carcinoma	8550/3
Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/3
Polymorphous low-grade adenocarcinoma	8525/3
Epithelial-myoepithelial carcinoma	8562/3
Clear cell carcinoma, NOS	8310/3
Basal cell adenocarcinoma	8147/3
Cystadenocarcinoma	8450/3
Mucinous adenocarcinoma	8480/3
Oncocytic carcinoma	8290/3
Salivary duct carcinoma	8500/3
Myoepithelial carcinoma	8982/3
Carcinoma ex pleomorphic adenoma	8941/3

Acinic cell carcinoma

These are uncommon in minor glands {9,280,340,410,734,864,2886} and form 2-6.5% of all intraoral salivary gland tumours {669,704,2711}. In one series, the age range was from 11-77 years, with a mean of 45 years, and a male to female ratio of 1.5:1 {2711}. The most common sites are the buccal mucosa, upper lip and palate where the tumours usually form non-descript swellings. The microscopical features are similar to those in major glands. However, in one series there appeared to be more areas consisting of solid sheets of epithelium with secretory material and fewer areas show-

the minor glands {2711}.

Mucoepidermoid carcinoma

This most common malignant salivary gland tumour involves minor glands, and accounts for 9.5-23% of all minor gland tumours {669,704,2711}. About half of the cases arise in the palate and other common sites include the buccal mucosa, lips, floor of oral cavity and retromolar pad. They appear to be much more frequent in the lower lip than the upper lip {1871}.

The tumour is often asymptomatic and detected during a routine dental examination. Many appear as bluish, domed swellings that resemble mucoceles or haemangiomas. Less commonly, the surface appears granular or papillary. Tumours of the base of tongue or oropharynx may cause dysphagia and sublingual tumours can lead to ankyloglossia and dysphonia. High-grade tumours are uncommon but can result in ulceration, loosening of teeth, paraesthesia or anaesthesia. Mucoepidermoid carcinoma is the most common salivary gland tumour to develop in a central location within the bone of the mandible or, less frequently, the maxilla {280}.

The microscopical features of minor gland mucoepidermoid carcinomas are the same as those seen in the major glands.

Adenoid cystic carcinoma

This lesion is relatively common in the minor glands. In the AFIP series 42.5% of all adenoid cystic carcinomas were in minor glands and 20.5% of the total was

Table 4.04 Percentage of malignant minor salivary gland tumours in different sites in published series.

	Upper Lip	Lower Lip	Lip NOS	Palate	Tongue	Cheek	Retro-molar	FOM*	Tonsil	Other
Auclair et al {669}	22.5	60.2	17.2	46.8	85.7	50.5	89.7	88.2	41.4	65.6
Waldron et al {2711}	14	86	-	42	-	46	91	80	-	69
Eveson & Cawson {704}	-	-	14.8	47	91.7	50	33.3	-	50	-
* Floor of the mouth										

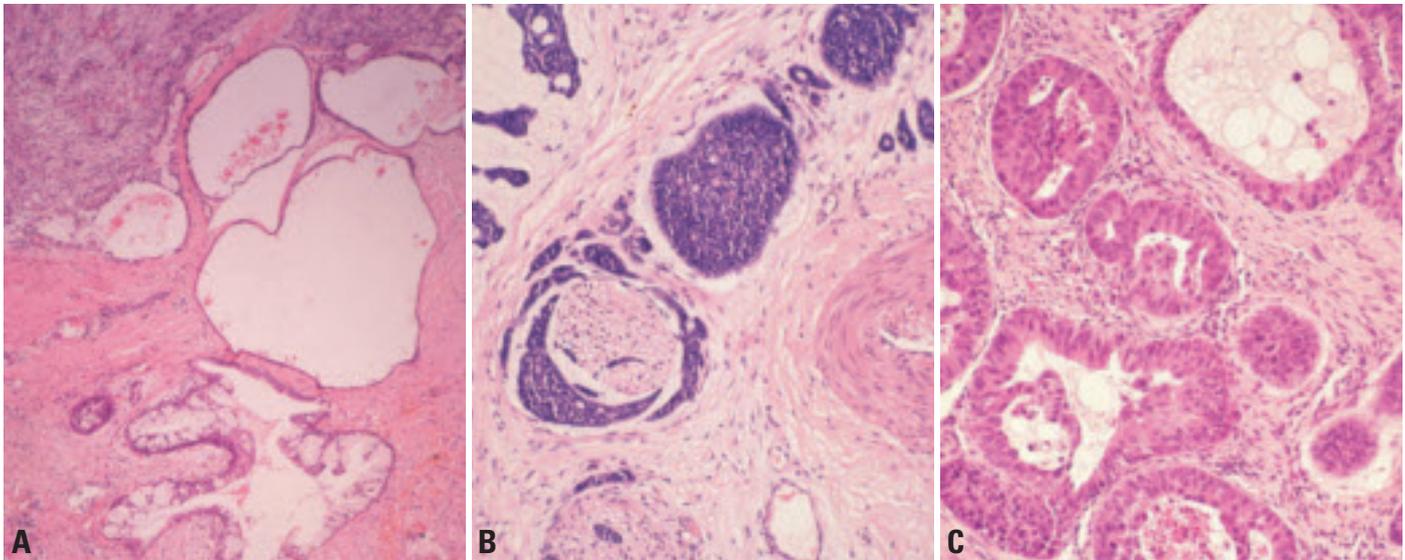


Fig. 4.32 **A** Mucoepidermoid carcinoma. Low power showing low-grade tumour with both cystic and solid areas and an inflamed, fibrous stroma. **B** Adenoid cystic carcinoma. This predominantly solid variant shows peri- and intraneural invasion. **C** Salivary duct carcinoma with large, somewhat oncocyctic cells, cribriform areas, small papillae and comedo-type necrosis.

the tongue, tonsil and oropharynx, cheek, lips, retromolar pad and gingiva {899}. They are much more frequent in the upper lip than the lower lip {669,1871,2711}. Intraoral adenoid cystic carcinomas usually present as slow growing submucosal masses and ulceration may be seen, particularly in the palate. Pain, or evidence of nerve involvement, is usually only present in advanced tumours. Most tumours show the typical cylindromatous or cribriform variant microscopically, but some may have tubular areas and a few are predominantly solid {2711}.

Polymorphous low-grade adenocarcinoma

This tumour is seen almost exclusively in minor glands and is considered in detail in Chapter 5.

Epithelial-myoepithelial carcinoma

This tumour is rare in minor glands and the literature consists mainly of single cases or short series {154,436,493,784,981,992,1177}. Tumours of the oral cavity and oropharynx formed only 10.3% of the AFIP series {669}. The palate is the most common site. The clinical presentation is non-specific and the microscopical features are the same as those in major glands.

Basal cell adenocarcinoma

This tumour is rare in minor glands. There were none in the AFIP series {669} but

there have been isolated case reports {563,785,1211,1540,2059,2703}. The most common sites are the palate, buccal mucosa and lip. They usually form asymptomatic, smooth or lobulated submucosal masses apart from one case that presented with dull pain and inflamed overlying mucosa {2703}. Microscopically they are similar to basal cell adenocarcinomas of the major glands.

Cystadenocarcinoma

These tumours are uncommon and about 32% developed in the minor glands where they are frequently papillary {411,790}. The most frequent sites are the palate, lips, buccal mucosa, tongue {1834} and retromolar regions. They are usually slow growing and painless but some palatal tumours have eroded the underlying bone and invaded the sinonasal complex. This tumour is considered in detail in Chapter 5.

Oncocytic carcinoma

This tumour is rare and there were only two cases involving the oral cavity in the AFIP series of 26 cases {669}. One was in the palate and the other the buccal mucosa. Reported cases also include an additional case in the palate {274} and the AFIP case from the buccal mucosa {922}. The microscopical features are considered in Chapter 5.

Salivary duct carcinoma

This tumour is rare in minor salivary glands. A recent review documented 20 cases {1147} and a further 6 cases have been reported {1559,2673}. The most common location was the palate (65%). Other sites included the buccal mucosa and vestibule (19%), tongue (8%), retromolar pad (4%) and upper lip (4%). The age range was 23-80 years (mean 56 years). Some tumours formed painless swellings but many in the palate were painful and ulcerated or fungated. There were metastases to regional lymph nodes in 25% of cases and this was associated with a poor prognosis. The range of microscopical appearances was similar to that seen in the major glands.

Myoepithelial carcinoma

This is a rare salivary gland tumour and 26% of cases in a review of the literature (9 cases) involved the oral cavity or oropharynx {668} and only isolated cases have been published since this review {1827}. The most common location is the palate. The clinical signs and symptoms are non-specific and the microscopical features are considered in Chapter 5.

Carcinoma ex pleomorphic adenoma

Lesions involving the oral and oropharyngeal minor glands formed 17.5% of the AFIP series {669}. 63% of cases were in the palate and 10.5% were in the upper lip. There were no cases in the lower lip. Other sites included the tongue, buccal



Fig. 4.33 Pleomorphic adenoma which started at palate involving the mid face and entire oral cavity.

mucosa and tonsil/oropharynx. They usually form a painless mass of long duration and there may be a history of recent rapid growth, often with ulceration. The microscopical features are similar to those of major glands.

Mucinous adenocarcinoma is very rare while *clear cell carcinoma* is a controversial entity; both are discussed in Chapter 5.

Salivary gland adenomas

ICD-O codes

Pleomorphic adenoma	8940/0
Myoepithelioma	8982/0
Basal cell adenoma	8147/0
Canalicular adenoma	8149/0
Duct papilloma	8503/0
Cystadenoma	8440/0

Pleomorphic adenoma

These amount to 40-70% of minor gland tumours, the large majority of cases being located in the palate, lips and buccal mucosa [2711]. They usually present as painless, slow-growing, sub-mucosal masses, but occasionally they are traumatised and bleed or ulcerate. They rarely exceed 3 sphere cm in diam-

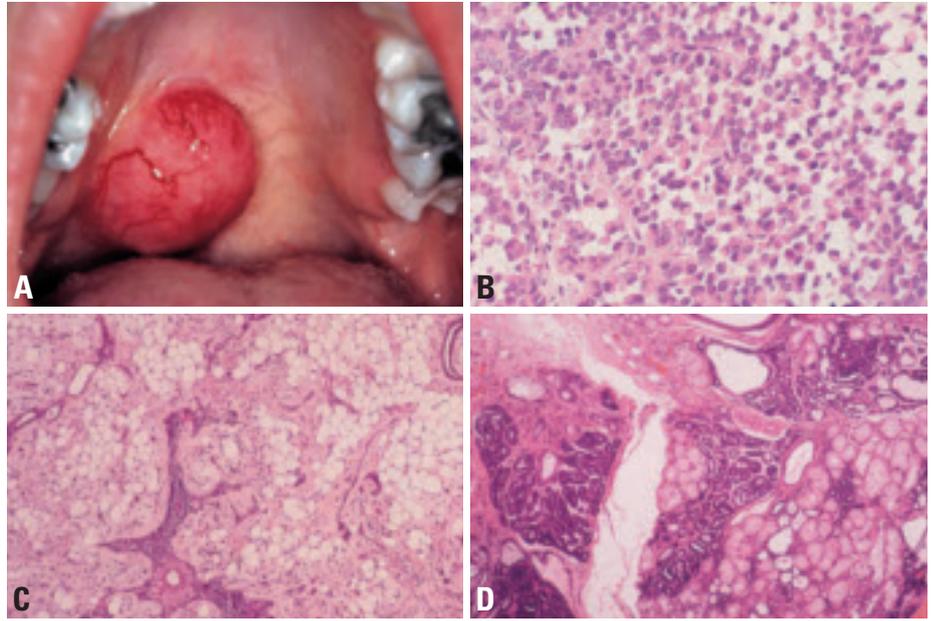


Fig. 4.34 **A** Pleomorphic adenoma. Tumour presenting as a firm swelling on the lateral aspect of the junction between the hard and soft palate. **B** Plasmacytoid, or hyaline myoepithelial cells are often a conspicuous feature of pleomorphic adenomas of minor glands. **C** Tumors may have an abundant lipomatous component that is occasionally misinterpreted as invasion. **D** Multifocal adenomatosis. Both basal cell adenoma and canalicular adenoma can show multifocal tumours and evidence of duct transformation within salivary gland lobules.

eter. Oral pleomorphic adenomas are similar microscopically to tumours elsewhere but frequently lack encapsulation, especially in the palate. They tend to be cellular, and hyaline or plasmacytoid cell types are common. Squamous metaplasia is also frequently seen and may be extensive. Some tumours have a strikingly lipomatous stroma and this should not be misinterpreted as tumour invading fat. Cases of intraoral pleomorphic adenoma with florid pseudoepitheliomatous hyperplasia of the overlying mucosa have been reported following incisional biopsy [2541].

Myoepithelioma

The minor glands are the common site for and myoepitheliomas account for about 42% of all of these tumours. Two thirds of the intraoral cases involve the palate [899]. They show the same range of morphological variation described in Chapter 5, but predominantly plasmacytoid tumours have a predilection for the palate of younger individuals [546].

Basal cell adenoma

About 20% of basal cell adenomas involve the oral cavity and the upper lip and buccal mucosa are the most common sites [669]. They are histologically similar to those in major glands.

Cystadenoma

These lesions are uncommon and form 7% of benign minor gland tumours [668]. Of these, 30% arose in the lips, 23% in the cheek, 20% in the palate and 26% in other oral and oropharyngeal sites. Clinically they resemble mucocèles and rarely exceed 1cm in diameter. The pathology is discussed in Chapter 5.

Canalicular adenoma and duct papillomas arise almost exclusively in the minor salivary glands and are discussed in detail in Chapter 5.

Kaposi sarcoma

I. van der Waal
J. Lamovec
S. Knuutila

Definition

Kaposi sarcoma (KS) is a locally aggressive tumour that typically presents with cutaneous lesions in the form of multiple patches, plaques or nodules but may also involve mucosal sites, lymph nodes and visceral organs. The disease is uniformly associated with human herpes virus 8 (HHV-8) infection. KS rarely metastasizes and belongs to the group of intermediate type vascular tumours.

ICD-O code 9140/3

Epidemiology

Four different clinical and epidemiological forms of KS are recognized: 1. classic indolent form occurring predominantly in elderly men of Mediterranean/East European descent, 2. endemic African KS that occurs in middle-aged adults and children in Equatorial Africa who are not HIV infected, 3. iatrogenic KS appearing in solid organ transplant recipients treated with immunosuppressive therapy and also in patients treated by immunosuppressive agents, notably corticosteroids, for various diseases {2629}, 4. acquired immunodeficiency syndrome-associated KS (AIDS KS), the most aggressive form of the disease, found in HIV-1 infected individuals, that is particularly frequent in homo- and bisexual men. The relative risk of acquiring KS

in the latter patients is > 10,000 {909}; it has been reduced with the advent of highly active antiretroviral therapy (HAART) {212}, although this has not been proven yet for oral KS {1993,2120}.

Etiology

The disease is the result of a complex interplay of HHV-8 with immunologic, genetic, and environmental factors {392}. Oral exposure to infectious saliva seems to be a potential risk factor for the acquisition of HHV-8 {1995}. HHV-8 is found in KS cells of all epidemiological-clinical forms of the disease {2242} and is detected in the peripheral blood before the development of KS. Nevertheless, it has been observed that a declined incidence of KS did not appear to be caused by a decline in HHV-8 transmission {1959}.

Localization

The most typical site of involvement by KS is the skin, particularly of the face and lower extremities. During the course of the disease or initially, mucosal membranes such as oral mucosa, lymph nodes and visceral organs may be affected, sometimes without skin involvement. Oral KS most frequently occurs on the palate, followed by the gingiva and the tongue.



Fig. 4.35 Kaposi sarcoma of the palate.

Clinical features

Classic type of KS is characterized by the appearance of purplish, reddish blue or dark brown macules, plaques and nodules that may ulcerate. They are particularly frequent in distal extremities and may be accompanied by lymphoedema. The disease is usually indolent, lymph node and visceral involvement occurs infrequently. Classic KS may be associated with haematolymphoid malignancies. In the endemic form of KS, the disease may be localized to skin and shows a protracted course. A variant of endemic disease, a lymphadenopathic form in African children is rapidly progressive and highly lethal. Iatrogenic KS is relatively frequent. It develops in a few months to several years after the transplantation of solid organs or immunosuppressive treatment for a vari-

Table 4.05 Epidemiological-clinical types of Kaposi sarcoma

Type	Risk groups	Skin lesions -predilection sites	Visceral involvement	Course
Classic	Elderly men of Mediterranean/ East European descent	Lower legs	Rare	Indolent
Endemic	Middles-aged men and children in Equatorial Africa	Extremities	Fairly common - adults Frequent - children (lymph nodes)	Indolent - adults Aggressive - children
Iatrogenic	Immunosuppressed patients (post-transplant, other diseases)	Lower legs	Fairly common	Indolent or aggressive
AIDS-associated	Younger, mainly homo- and bisexual HIV-1 infected men	Face, genitalia, lower extremities	Frequent	Aggressive

From: WHO Classification of Tumours of Soft Tissue and Bone {775}.

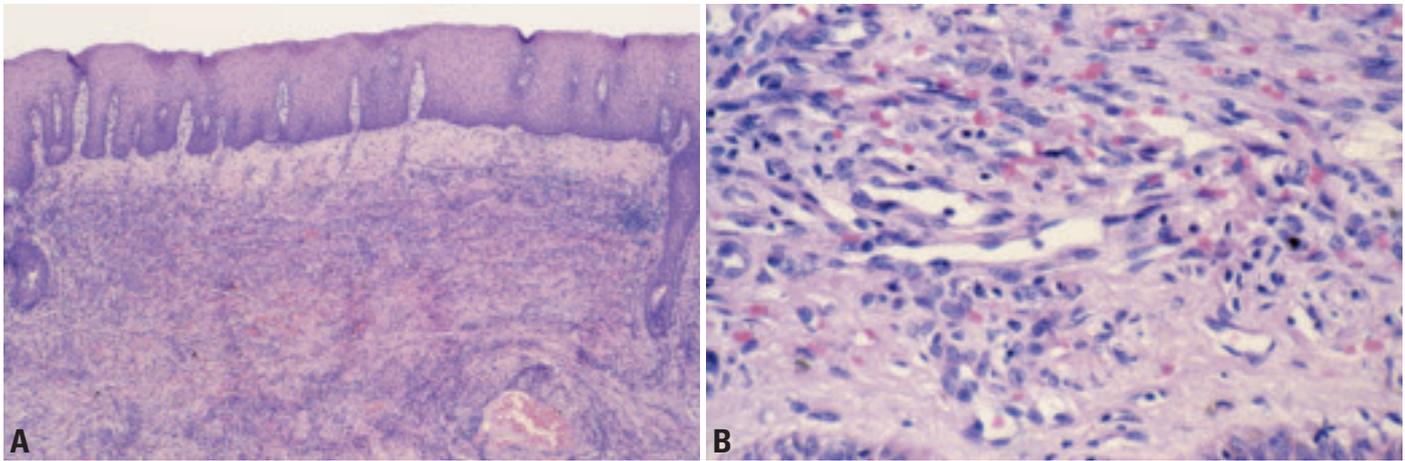


Fig. 4.36 Kaposi sarcoma. **A** Inflammatory-like aspect of palatal Kaposi sarcoma. **B** Vascular slits and sparsely distributed lymphocytes.

ety of conditions. The disease may resolve entirely upon withdrawal of immunosuppressive treatment although immunosuppressive treatment although its course is somewhat unpredictable. AIDS-related KS is the most aggressive type of KS. Early oral KS is represented by solitary or multiple red or bluish flat lesions, while the later stage is characterized by a nodular, sometimes massive appearance with or without secondary ulceration.

Histopathology

Microscopic features of all four different epidemiological-clinical types of KS do not differ. Early lesions of the skin or the mucosa are uncharacteristic and present with subtle vascular proliferation [2216]. In the patch stage, vascular spaces are increased in number, of irregular shape, and may dissect collagen fibres in the superficial corium. They often run parallel to the epithelium. The vascular proliferation is often perivascular and periadnexal. Endothelial cells lining the spaces are flattened or more oval, with little atypia. Pre-existing blood vessels may protrude into the lumen of new vessels. Admixed are sparse lymphocytes and plasma cells; frequently, extravasated erythrocytes and deposits of hemosiderin surround the vas-

cular structures. Slits lined by attenuated endothelial cells between collagen bundles are also seen. In some cases, there is a proliferation of spindle or oval endothelial cells around pre-existing blood vessels in the dermis or submucosa. Slit-like spaces, lymphocyte and plasma cell infiltration and extravasated erythrocytes are also observed.

In plaque stage, all characteristics of patch stage are exaggerated. There is more extensive angio-proliferation with vascular spaces showing jagged outlines. Inflammatory infiltrate is denser and extravascular red cells and siderophages are numerous. Hyaline globules (likely representing destroyed red blood cells) are frequently found.

Nodular stage is characterized by well-defined nodules of intersecting fascicles of spindle cells with only mild atypia and numerous slit-like spaces containing red cells. Peripherally, there are ectatic blood vessels. Many spindle cells show mitoses. Hyaline globules are present inside and outside the spindle cells. Some patients, usually with endemic nodular type KS, develop lesions that closely resemble lymphangioma.

The main differential diagnosis includes Kaposiform haemangioendothelioma [775].

Immunoprofile

The lining cells of clearly developed vascular structures are usually positive for vascular markers, while the spindle cells consistently show positive reaction for CD34 and commonly for CD31 but are factor VIII negative. All cases, irrespective of epidemiologic subgroup, are HHV-8 positive. The new marker FLI1, a nuclear transcription factor, appears to be expressed in almost 100% of different vascular tumours, including KS [780].

Prognosis and predictive factors

The evolution of disease depends on the epidemiological-clinical type of KS and on its clinical extent. It is also modified by treatment that includes surgery, radio- and chemotherapy. Patients with oral KS who did not receive triple antiretroviral therapy had a higher death rate than those having exclusively cutaneous manifestations of the disease [2192].

Lymphangioma

I. van der Waal

Definition

A benign, cavernous/cystic vascular lesion composed of dilated lymphatic channels.

ICD-O code 9170/0

Epidemiology

Lymphangiomas are common paediatric lesions, which most often present at birth or during the first years of life. Lymphangiomas appear mostly in the head and neck area but may be found in any other part of the body.

Etiology

Early or even congenital appearance in life and lesional architecture are in favour of a developmental malformation, with genetic abnormalities playing an additional role in cystic lymphangioma of the neck in association with Turner syndrome {416}.

Clinical features

The lesion presents as a somewhat circumscribed painless swelling, which is soft and fluctuant on palpation. In oral involvement, the tongue is the site of predilection, the majority of lymphangiomas being located on the dorsal surface of the anterior part of the tongue. The size may vary from pinhead dimensions to massive lesions involving the entire tongue and surrounding structures. The typical lymphangioma of the



Fig. 4.37 Lymphangioma on the dorsum of the tongue.

tongue is characterized by irregular nodularity of the dorsum of the tongue with grey and pink, grapelike projections. Secondary haemorrhage in lymphangiomas is not a rare occurrence. CT scan reveals homogeneous non-enhancing areas {775}.

A staging system of lymphatic malformations of the head and neck based on the anatomic location has shown to be of relevance in predicting prognosis and outcome of surgical intervention {561,991}.

Macroscopy

Lymphangiomas form a multicystic or spongy mass, the cavities of which contain watery to milky fluid.

Histopathology

Lymphangiomas are characterized by thin-walled, dilated lymphatic vessels of different size, which are lined by a flat-

tened endothelium. There is no encapsulation. The lumina may be either empty or contain proteinaceous fluid, lymphocytes and sometimes a few erythrocytes. Longstanding lesions show interstitial fibrosis.

Immunoprofile

The endothelium demonstrates variable expression of FVIII-rAg, CD31 and CD34 {781}.

Electron microscopy

The endothelium of thin-walled vessels is not enveloped by a basement membrane and no pericytes are attached to it, thus directly contacting with the interstitium. With increasing calibre the vessels may acquire pericytes and smooth muscle, respectively.

Prognosis and predictive factors

Recurrences are due to incomplete removal. Current interest is centred on treating these lesions with sclerosing agents {2117}, interferon {1953} or bleomycin {2903A}. Malignant transformation does not occur. There is an exceedingly rare case report of a squamous cell carcinoma arising in a lymphangioma of the tongue {203}.

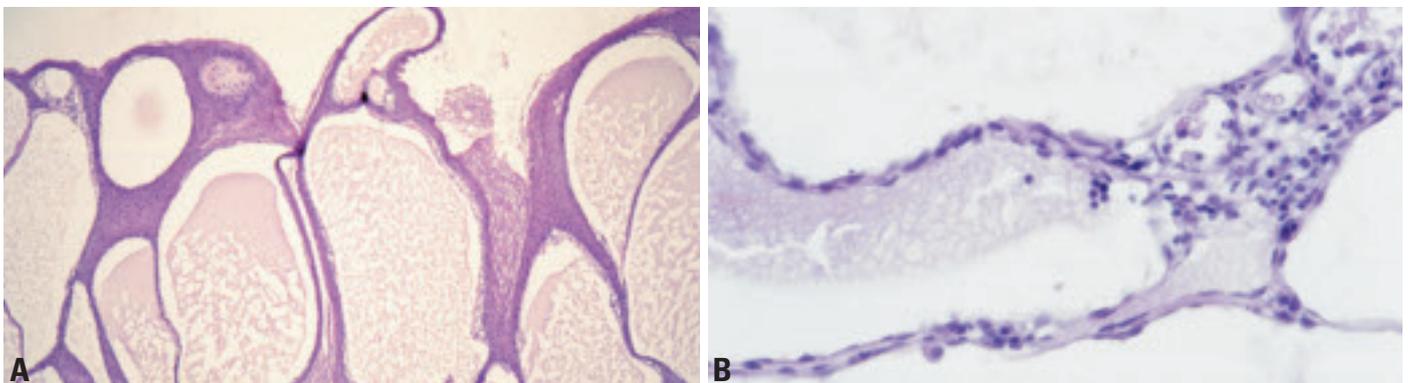


Fig. 4.38 Lymphangioma. **A** Cavernous lymphangioma. **B** Flattened endothelial lining in lymphangioma.

Ectomesenchymal chondromyxoid tumour of the anterior tongue

I. van der Waal

Definition

A benign ectomesenchymal chondromyxoid tumour that arises in the anterior tongue.

Epidemiology

In 1995, nineteen cases of the previously undescribed entity were reported. Ever since, a few additional case reports have been published {1169}. The reported age range varies from 9-78 years; there is no distinct sex predilection.

Clinical features

Most tumours presented as an otherwise asymptomatic, slow growing solitary nodule in the anterior dorsal tongue. The consistency may vary from firm to soft elastic.

Macroscopy

The cut surface has a gelatinous consistency with occasional foci of haemorrhage.

Histopathology

The tumour is usually well-circumscribed, but not encapsulated. Occasionally, muscle fibres and nerve branches may be entrapped within the tumour. It is composed of round, cup-shaped, fusiform, or polygonal cells with uniform small nuclei and moderate amounts of faintly basophilic cytoplasm; some tumours may show nuclear pleomorphism, hyperchromatism, and multinucleation, while mitotic figures are scarce {2410}. In addition, the presence of myxoglobulosis-like changes has been reported {1169}. Alcian blue stains at pH 0.4 and 2.5 are positive, while mucicarmine is usually faintly positive in the extracellular matrix. The tumour cells do not stain with the periodic acid-Schiff (PAS). In the histological differential diagnosis other myxoid and chondroid lesions should be excluded, such as focal oral mucinosis, the mucous retention phenomenon, soft-tissue myxoma, nerve sheath myxoma, myxomatous changes in fibrous lesions, chondrosarcoma, chondroid choristoma, and variants of pleomorphic adenoma or myoepithelioma arising from minor salivary glands.



Fig. 4.39 Ectomesenchymal chondromyxoid tumour of the anterior tongue presenting as a small nodule.

Immunoprofile

Reactivity with polyclonal and monoclonal anti glial fibrillary acidic protein (GFAP) is positive in almost all reported cases; reactivity with anti-cytokeratin monoclonal antibody has been positive in the majority of cases as well, while variable staining results were observed for S-100, CD57 and smooth muscle actin {2410}.

Histogenesis

The tumour cells are possibly derived from undifferentiated ectomesenchymal progenitor cells that have migrated from the neural crest {2410}.

Prognosis and predictive factors

Surgical excision is the treatment of choice. The recurrence rate is apparently low.

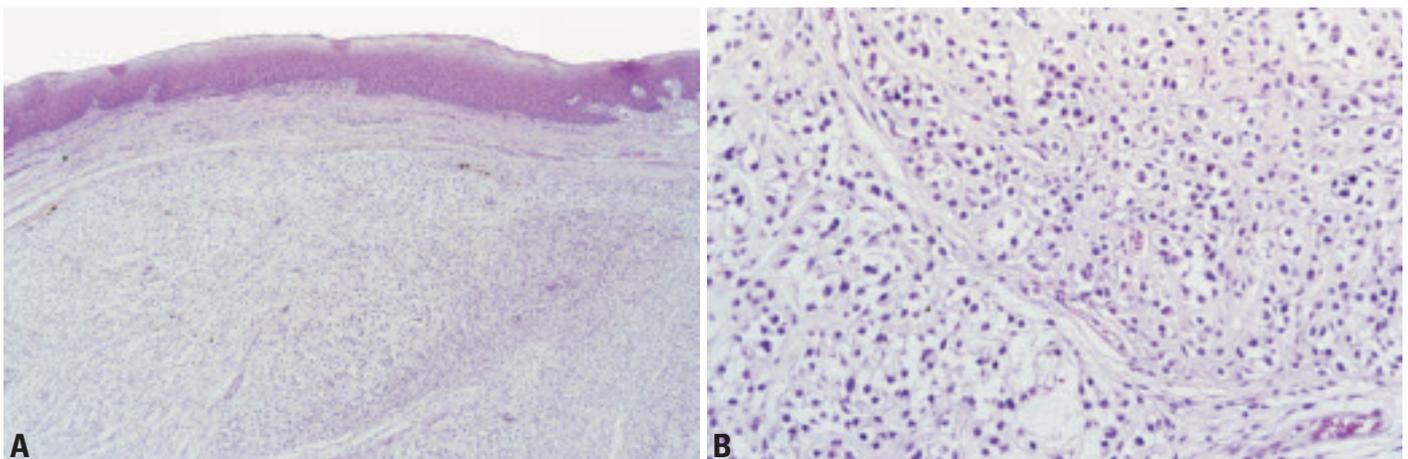


Fig. 4.40 **A** Rather well demarcated ectomesenchymal chondromyxoid tumour. **B** Net-like pattern of round or ovoid cells in a chondromyxoid background.

Definition

Focal oral mucinosis (FOM) is the oral counterpart of focal cutaneous mucinosis and cutaneous myxoid cyst. It is postulated that FOM develops as the result of a fibroblastic overproduction of hyaluronic acid due to an unknown cause [2615].

Epidemiology

Today, fewer than fifty cases have been reported. The lesion may occur at all ages, but it is rare in children [906]. There is no distinct sex predilection.

Clinical features

The clinical presentation is usually that of an otherwise asymptomatic fibrous or cystic-like lesion. The most common site is the gingiva; less common sites include the palate, cheek mucosa and tongue. The consistency may vary from soft elastic to firm.



Fig. 4.41 Focal oral mucinosis. Fibroma-like swelling of the cheek mucosa based on focal oral mucinosis.

Histopathology

The histopathology is characterized by a well-circumscribed area of myxomatous tissue in which fusiform or stellate fibroblasts are present [299]. Reticular fibres are sparse or absent. The mucinous material shows alcianophilia at pH 2.5. The histologic differential diagnosis includes soft-tissue myxoma, myxomatous change in fibrous lesions, nerve

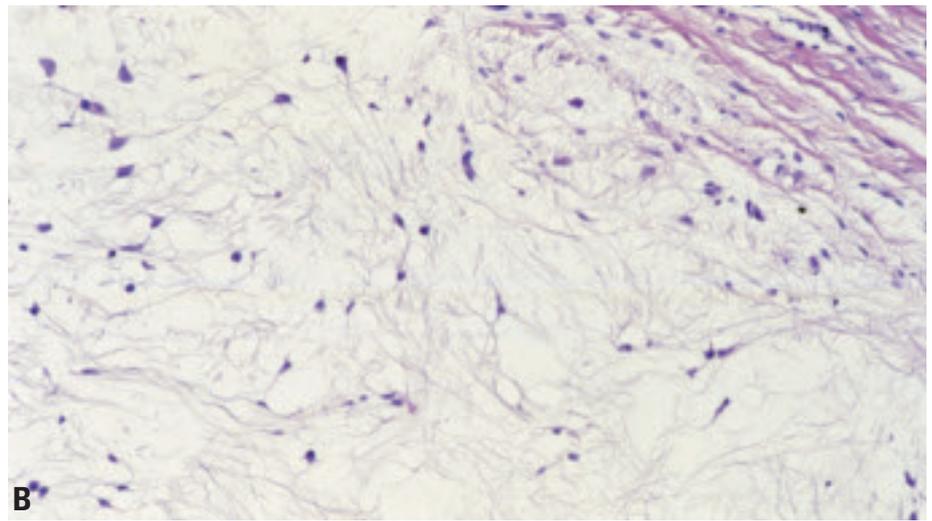
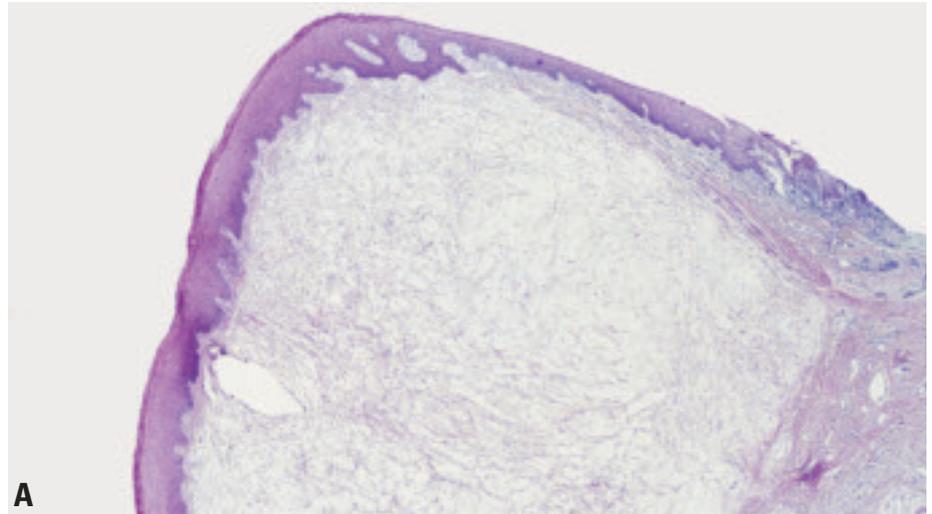


Fig. 4.42 Focal oral mucinosis. **A** Well-demarcated area of myxomatous connective tissue. **B** Delicate fibrillar processes extending from fibroblast cytoplasm.

sheath myxoma, and mucous retention phenomenon. The lack of reticular fibres and the sharp delineation distinguishes FOM both from soft-tissue myxoma and from myxomatous changes in fibrous lesions [2615]. Nerve sheath myxoma usually shows a lobular architecture and, conspicuously, contains numerous mast cells. The mucous retention phenomenon is surrounded by a wall of granulation tis-

sue or an epithelium-lined wall, while the mucoid material contains histiocytic cells; such features are lacking in FOM.

Prognosis and predictive factors

The lesion is treated by conservative surgical excision and has no tendency to recur.

Congenital granular cell epulis

I. van der Waal

Definition

A benign tumour arising from the alveolar ridges of newborns and composed of nests of cells with granular cytoplasm set in a prominent vasculature {2744}.

Synonym

Congenital epulis of the newborn

Epidemiology

In a review of the literature 216 cases have been collected since its first description in 1871. Females are affected ten times more often than males {2152}.

Clinical features

Congenital granular cell epulis (CGCE) occurs twice as often in the maxilla as in the mandible, usually presenting as a solitary, somewhat pedunculated fibroma-like lesion attached to the alveolar ridge near the midline. A few cases of simultaneous occurrence of a CGCE and a granular cell tumour of the tongue have been reported {1564,2848}. The size of a CGCE may vary from a few millimetres up to several centimetres.

Since the availability of ultrasound examination techniques, a number of cases have been diagnosed in the prenatal stage {1839,2000}.



Fig. 4.43 Congenital granular cell epulis of the maxilla.

Histopathology

CGCE consists of large, slightly eosinophilic cells with granular cytoplasm set in a prominent vasculature. There is no cellular or nuclear pleomorphism, and mitotic activity is not usually observed. The presence of odontogenic epithelium scattered throughout the lesions has been reported. Immunohistochemically, the tumour cells are positive for vimentin and neuron specific enolase; there is no reactivity with cytokeratin, CEA, desmin, hormone receptors or S-100 {1968}. Pseudoepitheliomatous changes in the overlying epithelium, although common in the granular cell tumour, do not occur in CGCE. An extremely rare case of a

congenital leiomyomatous epulis has been reported {2542}.

Histogenesis

The histogenesis is unknown. The lack of immunoreactivity with S-100 protein suggests that the tumour is derived from a cell line different from granular cell tumour. Furthermore, the hypothesis of a non-neoplastic lesion can be raised.

Prognosis and predictive factors

Spontaneous regression may occur, but surgical removal is usually indicated due to interference with feeding or respiration. The tumour has no tendency to recur after surgery.

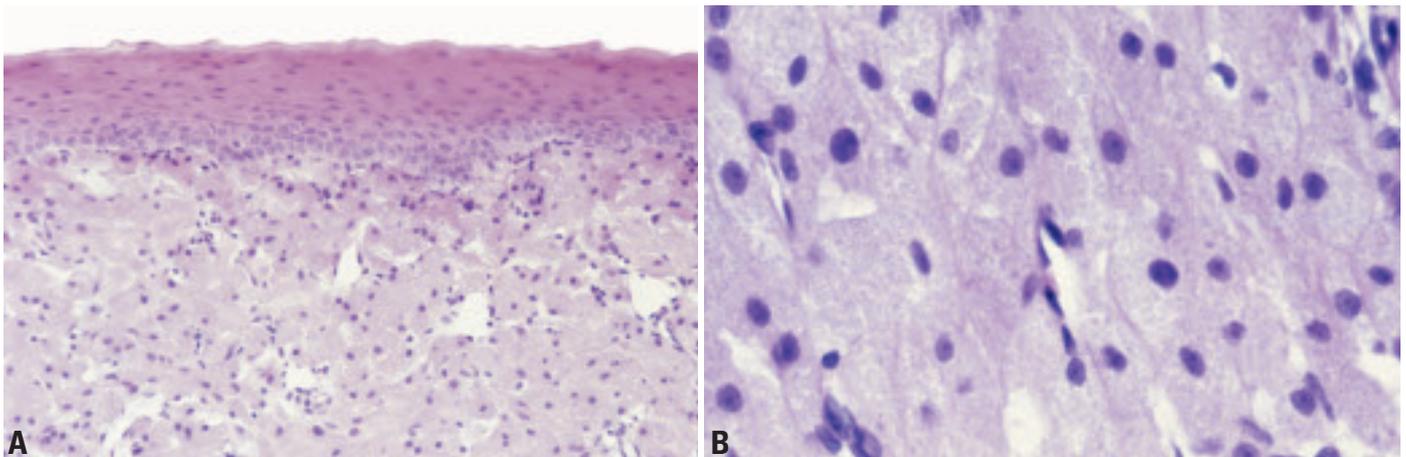


Fig. 4.44 Congenital granular cell epulis. **A** Slightly eosinophilic cells with granular cytoplasm in a prominent vasculature. **B** Absence of nuclear and cellular pleomorphism.

Haematolymphoid tumours

A.C.L. Chan
J.K.C. Chan

Non-Hodgkin lymphoma

Definition

Non-Hodgkin lymphomas (NHL) of the oral cavity and oropharynx are defined as lymphoid cell neoplasms in which the bulk of the disease occurs in the palate, tongue, floor of mouth, gingiva, buccal mucosa, lips, palatine tonsils, lingual tonsils or oropharynx.

ICD-O codes

Diffuse large B-cell lymphoma (DLBCL)	9680/3
Mantle cell lymphoma	9673/3
Follicular lymphoma	9690/3
Extranodal marginal zone B-cell lymphoma of MALT type	9699/3
Burkitt lymphoma	9687/3
T-cell lymphoma (including anaplastic large cell lymphoma)	9714/3

Epidemiology

Although NHL is the second most com-

mon cancer of the oral cavity, it only accounts for 3.5% of all oral malignancies {683}. NHL of the oral cavity and oropharynx account for 13% of all primary extranodal NHL, with approximately 70% of these occurring in the tonsils {809}. They affect patients over a wide age range (including children), but most patients are in the 6th and 7th decades. Burkitt lymphomas occur predominantly in children and young adults. Patients with an underlying immunodeficiency state (e.g. HIV Infection) are also usually younger.

Etiology

There is no known etiology in most patients. A minority of patients have an underlying immunodeficiency state (e.g. HIV infection, post-transplantation), which predisposes to the development of NHL. There is a strong association with Epstein-Barr virus (EBV) for lymphomas occurring in the setting of immunodeficiency as well as in extranodal NK/T cell

Table 4.06 Frequency of the various types of primary lymphoma of the tonsil {1704}

Diffuse large B-cell lymphoma (DLBCL) ICD-O code 9680/3	64%
Mantle cell lymphoma ICD-O code 9673/3	10%
Follicular lymphoma ICD-O code 9690/3	8%
Extranodal marginal zone B-cell lymphoma of MALT type* ICD-O code 9699/3	6.5%
T-cell lymphoma (including anaplastic large cell lymphoma) ICD-O code 9714/3	6.5%
Burkitt lymphoma ICD-O code 9687/3	5%
* Reported as monocytoid B-cell lymphoma and immunocytoma in the original series.	

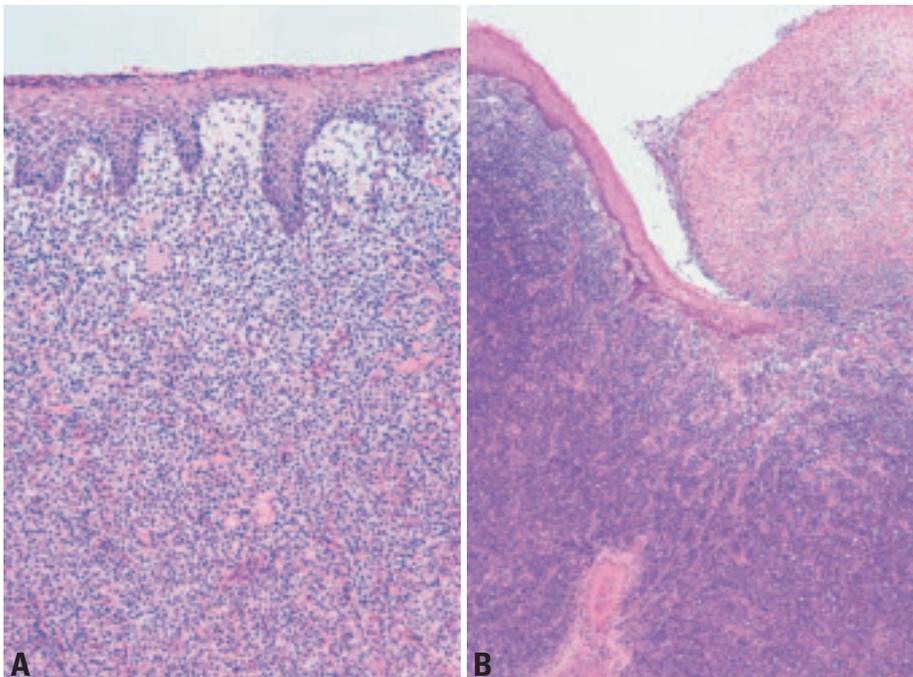


Fig. 4.45 **A** Primary large B cell lymphoma of the lip. The mucosa shows a diffuse infiltrate of lymphoma cells beneath an intact stratified squamous epithelium. **B** Primary large B cell lymphoma of the tongue. In this example, the mucosa is partly ulcerated.

lymphoma of nasal-type {371,962,1476,2850}. Extranodal marginal zone B-cell lymphoma of MALT type may be associated with Sjögren syndrome {2476}.

Localization

The palatine tonsil is the most frequently involved site, followed by palate, gingiva and tongue {683,809,1476,2532}.

Clinical features

Patients with NHL of the lip, buccal mucosa, gingiva, floor of mouth, tongue or palate usually present with ulcer, swelling, discoloration, pain, paraesthesia, anaesthesia, or loose teeth. Those with NHL of the Waldeyer ring (tonsils) or oropharynx usually present with a sensation of fullness of the throat, sore throat, dysphagia, or snoring. The high-grade tumours often show rapid growth. Systemic symptoms such as fever and night sweat are uncommon {201}.

Clinical examination reveals solitary or multiple lesions, in the form of an exophytic mass, ulcer or localized swelling. Some cases may mimic inflammatory

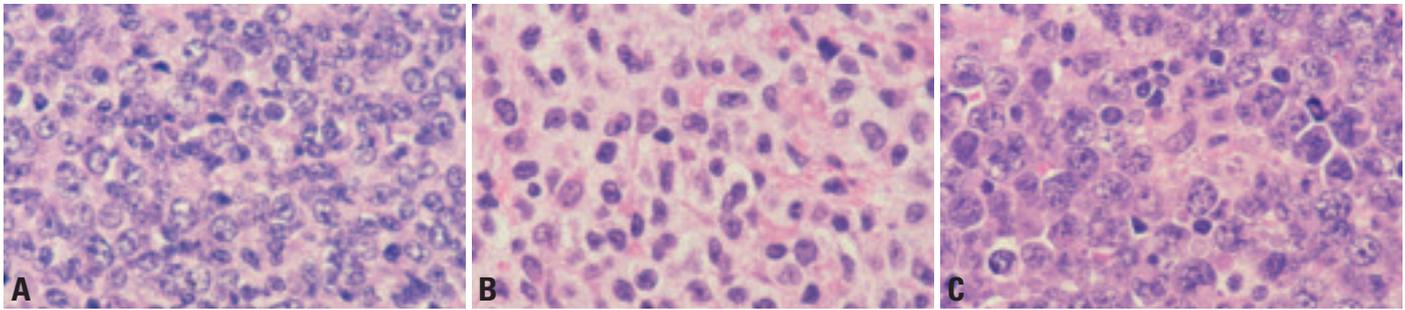


Fig. 4.46 Primary large B cell lymphoma of the oral cavity and oropharynx: cytological spectrum. **A** Large cells with predominantly round nuclei and membrane-bound nucleoli, consistent with centroblastic morphology. **B** Predominantly medium-sized cells with abundant pale cytoplasm. **C** Large cells with round or multilobated nuclei.

conditions, such as periodontitis. Tonsillar lymphoma usually manifests as asymmetric tonsil enlargement, although the disease can be bilateral in up to 9% of cases [2250]. The regional lymph nodes can be enlarged as a result of lymphoma involvement or reactive changes secondary to ulceration.

Tumour spread and staging

Three-quarters of patients have localized disease, with or without accompanying cervical lymph node involvement at presentation (Stage IE/IIIE). Patients with lymphoma of the tonsil are prone to metachronous or synchronous gastrointestinal tract involvement, suggesting a homing mechanism among different mucosal sites [1998,2139,2250].

Histopathology

Most NHL of the oral cavity and oropharynx are of B-cell lineage, with DLBCL being the commonest (>50%) [370,1476,1704,2142,2530]. The surface stratified squamous epithelium is either intact or ulcerated. The stroma is densely infiltrated by lymphoma cells, which vary in appearance depending on the histologic

type. In the tonsil, not uncommonly there are some residual lymphoid follicles due to incomplete involvement of the tissue.

Diffuse large B-cell lymphoma (DLBCL)

DLBCL is characterized by large to medium-sized cells which may resemble centroblasts. Nuclear multilobation is prominent in some cases. There can be areas of coagulative necrosis. In DLBCL of the tonsils, a focal follicular pattern may be present [2138], and it has been argued that the follicles result from colonization of pre-existing follicles rather than de novo neoplastic follicle formation. In some cases, there may be an associated component of extranodal marginal zone B-cell lymphoma of MALT type or follicular lymphoma, indicating that the DLBCL represents high-grade transformation of the latter [1998].

Mantle cell lymphoma

Lymphoma cells are usually monotonous, and frequently have small irregular nuclei, dense chromatin and scanty cytoplasm. They may show a mantle zone distribution around residual follicles. Rare cases can have a blastic appearance

and are associated with a higher proliferation rate [19].

Follicular lymphoma

Follicular lymphoma is characterized by follicles that frequently lack polarity and mantle zone. The neoplastic follicles consist of a mixture of centrocytes and centroblasts, often without accompanying tingible-body macrophages.

Extranodal marginal zone B-cell lymphomas of MALT type

These lymphomas most often involve the tonsil, and less commonly the palate, gingiva, buccal mucosa, tongue and lip [295,962,1476,1507,1629,1998,2225,2531]. The surface epithelium is often intact. In a background of reactive lymphoid follicles, there is an interfollicular and perifollicular infiltrate of small to medium-sized cells with roundish or indented nuclei. Some cells have a moderate amount of clear cytoplasm, resembling monocytoid B-cells. There can be clusters of admixed plasma cells. Follicular colonization can be seen in some cases. A distinctive feature is invasion of the epithelial component (e.g. sur-

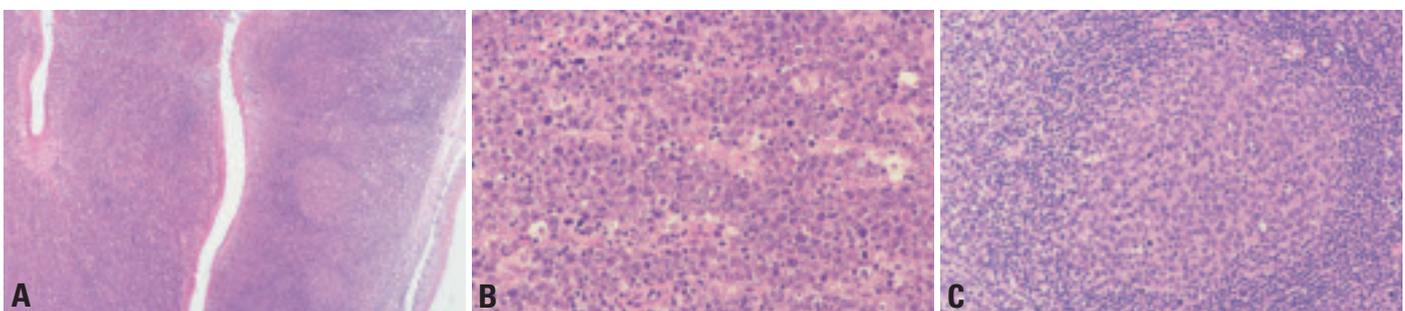


Fig. 4.47 Primary large B cell lymphoma of the tonsil with focal follicular features. **A** The left field shows the predominant component of diffuse large cell lymphoma. The minor component with follicles is shown in the right field. **B** The diffuse large B cell lymphoma component comprises large cells effacing the normal architecture of the tonsil. **C** Focally, there are follicles comprising a monotonous population of large cells. It is unclear whether this represents a grade 3 follicular lymphoma with diffuse large B cell lymphoma, or a diffuse large B-cell lymphoma with follicular colonization.

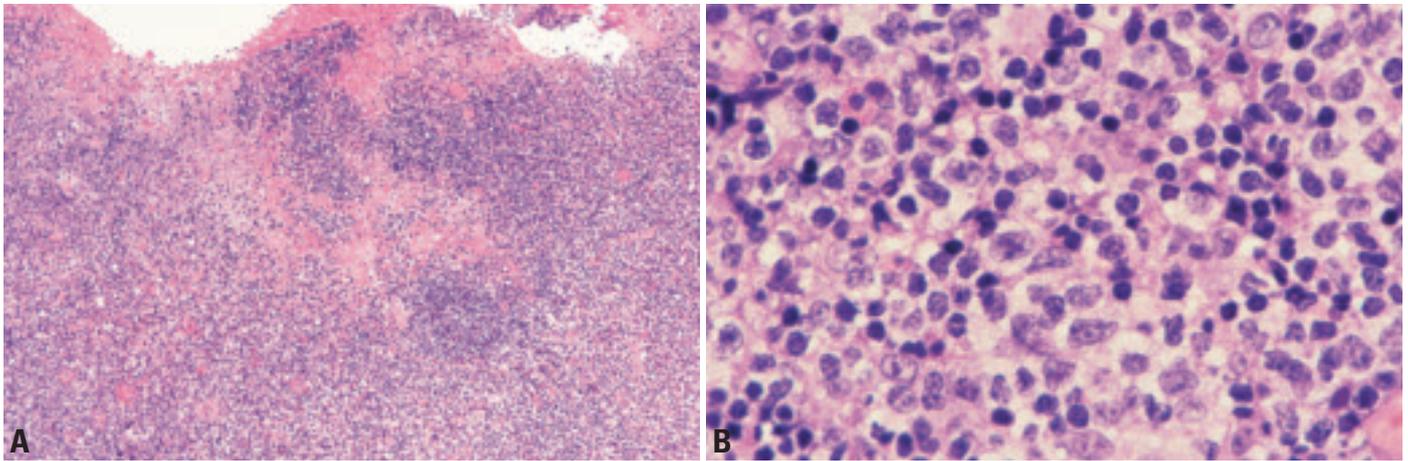


Fig. 4.48 Extranodal NK/T cell lymphoma of the palate. **A** The mucosa, which is densely infiltrated by lymphoma cells, shows ulceration. **B** The lymphoma cells comprise small, medium-sized and large cells with irregular nuclear foldings.

face or crypt epithelium, minor salivary glands), forming lymphoepithelial lesions.

Burkitt lymphoma

There is typically a starry sky pattern created by interspersed histiocytes. The lymphoma cells appear monotonous and medium-sized, with coarse chromatin, multiple small nucleoli and a small amount of basophilic cytoplasm. The cellular outline usually appears squared off. Frequent mitotic figures and apoptotic bodies are constant features.

Immunoprofile. B-cell lymphomas express pan-B markers such as CD19, CD20, CD22 and CD79a. Some DLBCLs can express CD10 and/or BCL6. Within the group of low-grade B-cell lymphomas, follicular lymphoma is characterized by CD10 and BCL6 expression,

mantle cell lymphoma CD5 and cyclin D1 expression, and extranodal marginal zone B-cell lymphoma none of these markers. Bcl-2 Immunoreactivity is helpful for distinction of follicular lymphoma from reactive follicular hyperplasia.

Extranodal NK/T cell lymphoma of nasal-type

Extranodal NK/T cell lymphoma of nasal-type can present primarily as an intraoral tumour in the palate, tonsil, oropharynx or lip {371,2639}. Please refer to the section of 'non-Hodgkin lymphoma' in 'Tumours of the nasal cavity and paranasal sinuses' for details.

T-cell lymphomas

Peripheral T-cell lymphomas, including anaplastic large cell lymphomas, can occasionally involve the oral cavity

{1476,2200,2530}. Some anaplastic large cell lymphomas (CD30+ T-cell lymphoproliferative disorder) of the oral cavity can regress spontaneously {760}. HTLV-1-associated adult T-cell lymphoma/leukaemia may also present as NHL of the Waldeyer ring {2616}.

Immunodeficiency-associated lymphomas

The lymphomas that develop in the oral cavity of patients with HIV infection are most commonly DLBCL with frequent EBV association (75%) {962,2141}, although EBV-associated T-cell lymphomas have also been reported in this setting {1476,2589}. A distinctive form of DLBCL, plasmablastic lymphoma, has recently been shown to exhibit a predilection for the oral cavity of HIV-positive subjects. It differs from the usual

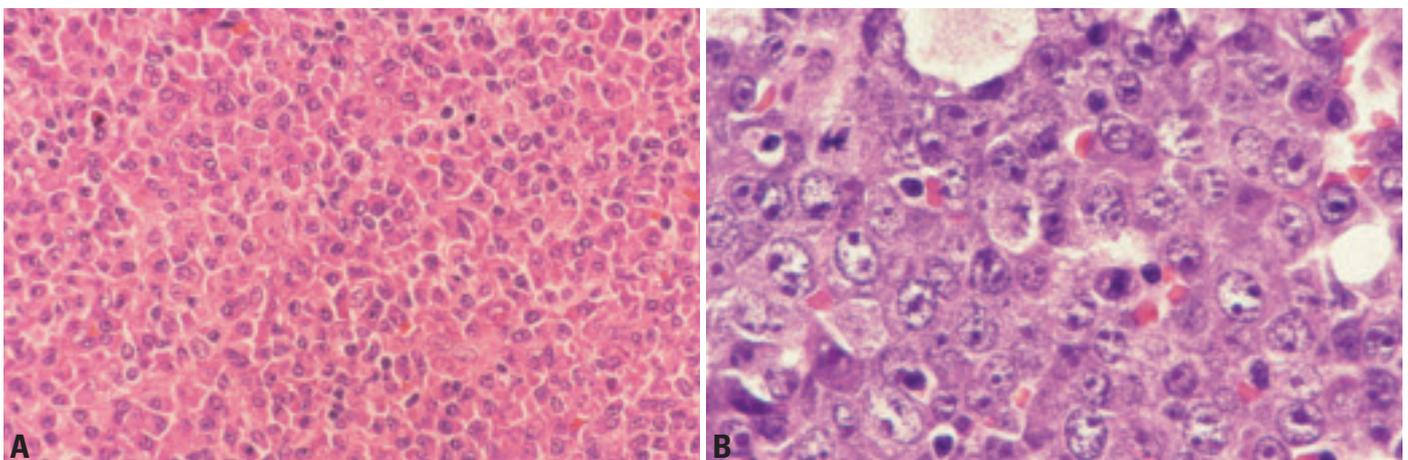


Fig. 4.49 Immunodeficiency-associated lymphoproliferative disorders. **A** Post-transplant lymphoproliferative disorder, plasmacytic hyperplasia, involving tonsil. **B** Plasmablastic lymphoma of the oral cavity in HIV-positive subject. The cells possess slightly eccentrically-located large vesicular nuclei, prominent nucleoli, and amphophilic cytoplasm.

DLBCL by the plasmablastic morphology, frequent lack of expression of CD45 and the pan-B marker CD20, and expression of plasma cell-associated markers (e.g. VS38c and CD138) [576]. EBV is identified in 60% of cases. Histologically, the tumour shows a starry-sky appearance and a high proliferation index. The large tumour cells have eccentric vesicular nuclei, central prominent nucleoli, abundant basophilic cytoplasm and paranuclear hof. There is no maturation into plasma cells.

Post-transplant lymphoproliferative disorder (PTLD) can also affect the oral cavity, and they are frequently associated with EBV (>80%). The 'early' lesions, including plasmacytic hyperplasia and infectious mononucleosis-like PTLD, commonly involve the tonsils of children or younger adults [355,356,2830]. The architecture of the tonsil is preserved, with expansion of the interfollicular areas by small lymphocytes, polyclonal plasma cells, plasmablasts and immunoblasts. Clonal immunoglobulin gene rearrangement is rare [355,2830]. Most lesions regress with reduction in immunosuppression, but rare cases may progress to polymorphic PTLD [2830]. Polymorphic and monomorphic PTLD can also present in the oral cavity (e.g. tonsil, gingiva, alveolus): the former shows architectural effacement, necrosis, cytologic atypia together with a full range of B-cell maturation, while the latter is indistinguishable from conventional DLBCL, and less commonly Burkitt lymphoma [1301,1926,2131,2850]. Clonal immunoglobulin gene rearrangement is frequently demonstrated in polymorphic and monomorphic PTLD. Regression after reduction in immunosuppression may still be possible in some cases of polymorphic PTLD, but progression is usually the rule for monomorphic PTLD. (Please refer to 'Post-transplant lymphoproliferative disorders' in 'WHO classification of tumours: Tumours of haematopoietic and lymphoid tissues' for details).

Differential diagnoses

In *infectious mononucleosis*, the tonsils may appear histologically worrisome, with necrosis, partial effacement of architecture, and striking immunoblastic proliferation, mimicking DLBCL [431]. In contrast to the latter, there is usually a spectrum of lymphoid cells in different stages of differentiation and activation

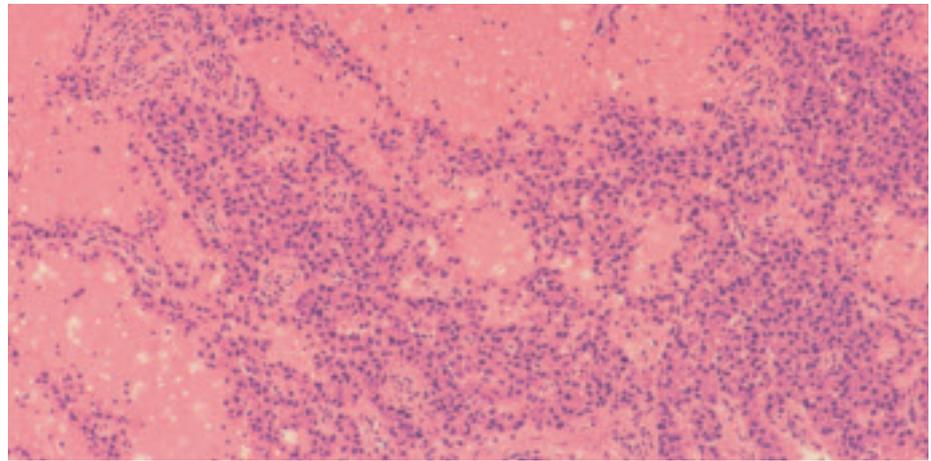


Fig. 4.50 Plasmacytoma of the tongue. The plasmacytoma is accompanied by blood lakes.

(immunoblasts, plasmablasts and plasma cells). On immunostaining, the large cells usually consist of a mixture of B- and T-cells, and there is no immunoglobulin light chain restriction. As a rule of thumb, infectious mononucleosis has to be seriously excluded before making a diagnosis of DLBCL in young patients.

Some cases of DLBCL (especially those in the tonsil) can exhibit deceptively cohesive growth and a sharp interface with the uninvolved mucosa, closely mimicking poorly differentiated carcinoma or malignant melanoma. Marked irregular nuclear foldings and amphophilic cytoplasm, if present, should point more towards a diagnosis of lymphoma. Appropriate immunostains can readily solve this diagnostic problem.

Anaplastic plasmacytoma can be difficult to distinguish from DLBCL, including the plasmablastic variant. An important clue to the diagnosis is the presence of coarsely clumped 'clock-face' chromatin in the few differentiated cells that are present. There are often intermingled atypical plasma cells. There is usually no association with EBV. A prior history of multiple myeloma, if present, would be a strong point to substantiate a diagnosis of plasmacytoma.

Extramedullary myeloid sarcoma (granulocytic sarcoma) is commonly misdiagnosed as large cell lymphoma. The clues to diagnosis are the fine chromatin, presence of cytoplasmic eosinophilic granules in some cells, and interspersed eosinophilic myelocytes. The diagnosis can be confirmed by immunoreactivity for myeloid or monocytic markers (e.g. myeloperoxidase, CD13, CD33, CD117, neutrophil elastase, lysozyme, CD68).

The differential diagnosis between extranodal marginal zone B-cell lymphoma of MALT type in the tonsil and *reactive lymphoid hyperplasia* can be extremely difficult, because of the presence of reactive lymphoid follicles, minimal atypia of the lymphoid cells in the former and presence of numerous plasma cells. Furthermore, lymphoepithelial lesions in the tonsil are difficult to assess since the tonsillar epithelium is normally extensively infiltrated by small lymphoid cells. The following features would favour a diagnosis of lymphoma: lymphoid cells infiltrating beyond the fibrous band at the base of the tonsil, presence of sheets of CD20+ B-cells between the lymphoid follicles, immunoglobulin light chain restriction, and molecular evidence of clonal immunoglobulin gene rearrangement.

Some *extranodal NK/T cell lymphomas of nasal-type* comprise predominantly small lymphoid cells with minimal atypia, rendering it difficult to distinguish from a reactive lymphoid infiltrate. Histologic clues to the diagnosis are the extensive necrosis and angiocentric growth. Demonstration of sheets of CD56+ or EBER+ cells would strongly support the diagnosis.

There is some morphologic overlap of anaplastic large cell lymphoma with *eosinophilic ulcer* (traumatic eosinophilic granuloma; atypical histiocytic granuloma) [645,674,701], which is characterized by a rich inflammatory infiltrate (especially eosinophils) and occasional large cells [760]. Anaplastic large cell lymphoma can be distinguished from it by the presence of at least large aggregates of large atypical cells in areas and strong CD30 expression.

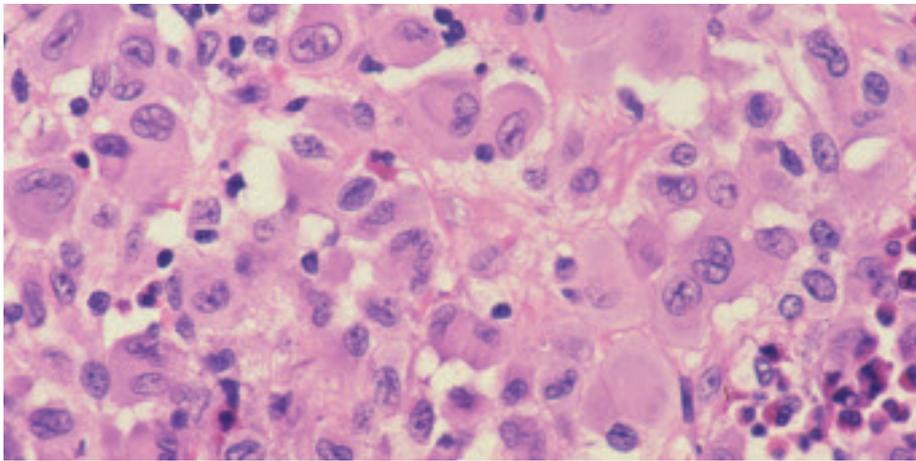


Fig. 4.51 Langerhans cell histiocytosis involving gingiva. The infiltrate comprises ovoid Langerhans cells with deeply grooved nuclei, thin nuclear membranes and abundant eosinophilic cytoplasm. There are typically many admixed eosinophils.

Prognosis and predictive factors

Patients with NHL of the oral cavity and oropharynx are treated by radiotherapy, chemotherapy or a combination of the two. Some studies have shown that adjuvant chemotherapy is associated with a better clinical outcome compared to radiotherapy alone {832,1009}. The five-year overall survival rate for localized disease ranges from 50% to more than 80% {146,832,1009,1614,2505}. High clinical stage, high histologic grade (large cell lymphoma), and T-cell or NK/T cell phenotype are poor prognostic indicators {146,1009,2250,2340,2809}.

Extramedullary plasmacytoma

ICD-O code 9734/3

Extramedullary plasmacytoma can occur in the oral cavity and oropharynx, see Chapter 1 for details.

Langerhans cell histiocytosis

ICD-O code 9751/1

Oral involvement occurs in 10% of patients with Langerhans cell histiocytosis (LCH). 78% of these patients have eosinophilic granulomas clinically, while the rest have multifocal multisystem disease {1021}. Common oral symptoms include swelling, pain, gingivitis, loose teeth and ulceration. The majority of patients with intraoral lesions have intraosseous lesions in the jaw bone, more commonly in the mandible. The intraoral soft tissues may be secondarily affected, especially the gingiva, but the palate, floor of mouth, buccal mucosa and tonsil can also be involved {1021,2043}. In a minority of patients with intraoral soft tissue involvement, there is no

associated bony lesion {241,460,1731}. See chapter 7 for details.

Hodgkin lymphoma

Hodgkin lymphoma (HL) is predominantly a nodal-based disease, and primary extranodal presentation is very rare. When it presents in extranodal tissues, the Waldeyer ring, particularly the palatine tonsil, is a common site {1274,1756}. Most patients present with localized disease (stage I/II), with symptoms of chronic tonsillitis or tonsillar enlargement, with or without enlarged cervical lymph nodes. Other reported sites include the oropharynx {44,1756}, alveolar crest of mandible {1659}, and maxillary gingiva {2554}.

Most cases represent classical HL, as detailed in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues {1197}, frequently of mixed cellularity subtype and showing strong association with Epstein-Barr virus (EBV) {1274}, although nodular lymphocyte predominant HL may also rarely present in the Waldeyer ring (palatine and lingual tonsils) {391,1274}.

Extramedullary myeloid sarcoma

ICD-O code 9930/3

Gingival infiltrates occur in 3.5% of patients with acute myeloid leukaemia, predominantly in the monocytic or myelomonocytic subtypes {622}. Clinically, there is diffuse enlargement of the interdental papillae, marginal gingiva and attached gingiva. The swollen gingiva has a spongy to firm consistency, bright red to purple in colour. There is no correlation between gingival leukaemic infiltrate and oral hygiene or peripheral white blood cell count {622}.

Rare cases of extramedullary myeloid sarcoma may present as an isolated tumour-forming intraoral mass. The most frequently involved sites are the palate and gingiva {52,761,2189,2614,2618}. While the tumour most often develops while the patient has active disease, it may precede the development of acute myeloid leukaemia, or arise as blastic transformation of an underlying chronic myeloproliferative disease or myelodys-

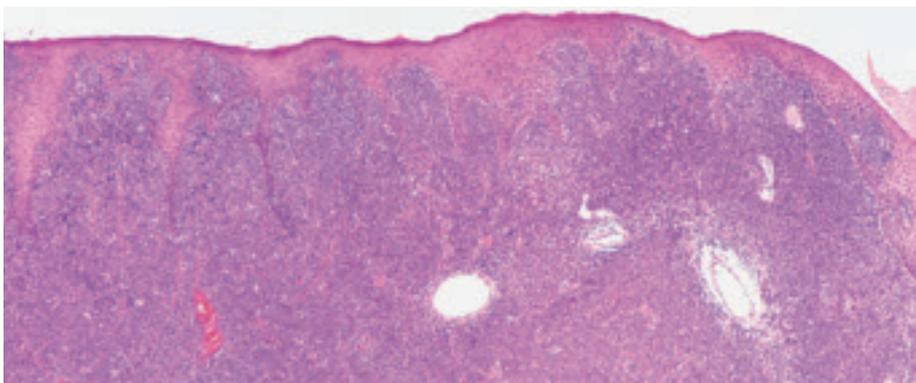


Fig. 4.52 Extramedullary myeloid sarcoma of the gingiva as the first sign of relapse of acute myeloid leukaemia. Beneath an intact stratified squamous epithelium, there is a diffuse and dense infiltrate of primitive myeloid cells.

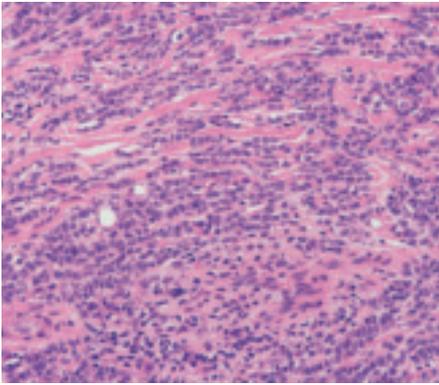


Fig. 4.53 Extramedullary myeloid sarcoma of the gingiva as the first sign of relapse of acute myeloid leukaemia. In areas, there is typically an Indian-file pattern of infiltration.

plastic syndrome. Histologically, there is a dense infiltrate of immature myeloid cells in the subepithelial soft tissue of the gingiva. Please refer to the section of 'Other uncommon haematolymphoid tumours' in 'Tumours of the nasal cavity and paranasal sinuses' for further details on extramedullary myeloid sarcoma.

Follicular dendritic cell sarcoma / tumour

Definition

Follicular dendritic cell (FDC) sarcoma/tumour is a rare neoplasm showing morphologic and phenotypic features of FDC.

ICD-O code 9758/3

Epidemiology, localization and clinical features

It is an uncommon tumour of adulthood, and can affect patients over a wide age range {368,2010,2043}. It can arise in nodal and extranodal tissues, and the oral cavity is among the more commonly involved extranodal sites {67,368,375,2010,2043,2249}. The patients usually present with a painless mass involving the tonsil, palate or oropharynx.

Etiology

Occasional FDC sarcomas/tumours appear to evolve from an underlying hyaline-vascular Castleman disease; the two lesions can present simultaneously or the latter can precede the appearance of the former by several years {359,368,374}. Overgrowth of FDC in the interfollicular

zone or 'dysplasia' of FDC may represent the precursor lesion.

Histopathology

Histologically, the tumour usually grows beneath an intact stratified squamous epithelium. It usually exhibits pushing borders and comprises fascicles, whorls, nodules, storiform arrays or diffuse sheets of spindly to ovoid tumour cells sprinkled with small lymphocytes. The tumour cells usually show ill-defined cell borders, distinct nucleoli, and sometimes nuclear pseudoinclusions. There is a tendency for some nuclei to be haphazardly clustered, and scattered multinucleated tumour cells are common. While nuclear pleomorphism is usually mild, some

cases can show significant nuclear atypia and pleomorphism. The cytoplasm is eosinophilic, and often exhibits a fibrillary quality as a result of the presence of interdigitating cell processes. Very rarely, the tumour cells have distinct cell borders, and are polygonal or oval in shape. The mitotic count ranges from low to high, and some cases can show coagulative necrosis. Occasional cases may show irregular interspersed cystic spaces. Besides being intermingled among the tumour cells, the lymphocytes can show cuffing around the blood vessels.

The diagnosis has to be confirmed by demonstration of FDC markers (e.g. CD21, CD23 and CD35), although the staining can be patchy. Typically a mesh-

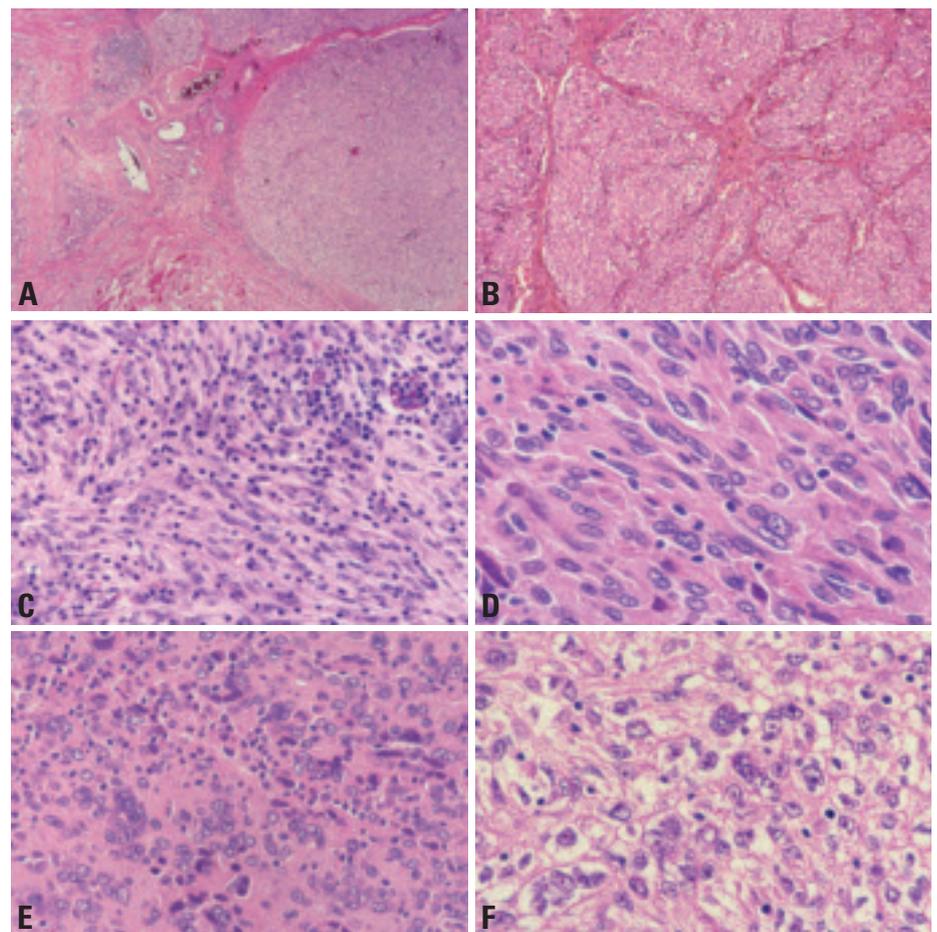


Fig. 4.54 Follicular dendritic cell sarcoma / tumour of oral cavity and oropharynx. **A** This palatal tumour invades in pushing fronts. The main tumour is seen in the right. Smooth-contoured nodules (upper field) invade the adjacent normal structures. **B** Uncommon nodular growth pattern, recapitulating the ability of follicular dendritic cells to form follicles. **C** Typical storiform pattern, accompanied by a sprinkling of lymphocytes. **D** This tumour consists of spindle cells with elongated nuclei, fine chromatin and small distinct nucleoli. Some cells have ill-defined cell borders, while others exhibit well-defined borders. **E** The tumour cell nuclei often appear haphazardly distributed, with some focal clustering. A few multinucleated tumour cells are also evident. The cytoplasm exhibits a fibrillary quality. **F** This example, composed of plump ovoid cells, shows a moderate degree of nuclear atypia and pleomorphism. Nucleoli are prominent.

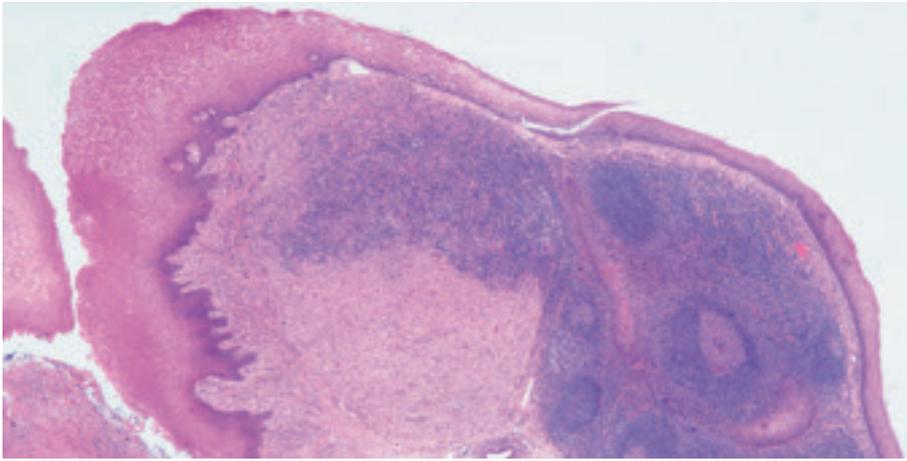


Fig. 4.55 Follicular dendritic cell sarcoma/tumour of the oral cavity. The surface epithelium is intact. This tumour shows partial involvement of the tonsil (left field).

work pattern is highlighted. Cytokeratin is negative. A proportion of cases express epithelial membrane antigen or muscle-specific actin. Occasional cases can weakly express the pan-B marker CD20 {2043}. Ultrastructurally, the tumour cells possess interdigitating long slender cytoplasmic processes and intercellular desmosome junctions. Differential diagnoses include soft tissue sarcoma, poorly differentiated carcinoma, meningioma, and malignant melanoma.

Prognosis and predictive factors

Most cases of FDC sarcomas/tumours have been treated by surgery, with or without adjuvant chemotherapy and

radiotherapy, with variable success. FDC sarcomas/tumours are low to intermediate grade malignant tumours, with an overall local recurrence rate of at least 40% and a metastatic rate of at least 28% {368,2010,2043}. Since some patients can develop late metastasis (such as after more than 20 years) {438}, long-term follow up is essential. Poor prognostic factors include significant cytologic atypia, extensive coagulative necrosis, high proliferative index and large tumour size {368,2010}.

Mucosal malignant melanoma

P.M. Speight

Definition

Malignant melanoma is a malignant neoplasm of melanocytes or of melanocyte precursors. It is characterized by proliferation of atypical melanocytes at the epithelial-connective tissue interface associated with upward migration into the epithelium and by invasion of the underlying connective tissues. Although usually seen in the skin, melanomas may also arise from melanocytes in mucosae.

ICD-O code 8720/3

Epidemiology

Mucosal melanomas of the head and neck comprise just over 1% of all melanomas and of these about 50% arise in the oral cavity. Oral mucosal melanomas are therefore rare, representing about 0.5% of oral malignancies {1085} and less than 0.01% of all oral biopsies {122}. The annual incidence in the USA is about 0.02 per 100,000 {170}, but the lesion may be more common in other parts of the world including Japan where the oral cavity has been reported as the most common site for melanomas {2528}.

They arise in adults with an average age of about 55, but with a uniform age distribution from 20–80 years {122,617,1085,2080,2127}. Very rare cases have been reported in children. In most large series there is a male predominance in a ratio of about 3:1 {122,617,2080} and some reports show males and females are almost equal {144,1843}.

Etiology

No etiological factors are known to be associated with oral melanoma.

Localization

Eighty percent of oral melanomas arise on the palate, maxillary alveolus or gingivae. Other sites include the mandibular gingivae, buccal mucosa, floor of mouth and tongue.

Clinical features

Oral melanomas are usually asymmetric



Fig. 4.56 Malignant melanoma. multiple or widespread areas of dark macular pigmentation affecting the palate. Irregular nodular areas are also seen.

with irregular outlines. They may be black, grey or purple to red, and rarely amelanotic. Typical lesions are composed of multiple or widespread areas of macular pigmentation with areas of nodular growth. Purely macular lesions may be seen but over 50% of lesions present as nodules or as a pigmented epulis. Ulceration is seen in about one third of cases and invasion of bone is common. Many reports document long-standing 'melanosis' before the onset of nodular lesions, with a history of up to 10 years. Oral lesions are usually advanced at presentation with up to 75% of patients having metastases to cervical lymph

nodes, and 50% with distant metastases, usually to lung or liver {144,617,1085}.

Macroscopy

Tumours are usually 1.5–4 cm in diameter with a black, macular or nodular surface. The cut surface is often homogeneously black or darkly pigmented.

Histopathology

Oral melanoma may have in-situ (radial) and invasive growth phases, but the histological classification is not analogous to cutaneous lesions. Mucosal lesions are similar to acral lentiginous melanoma of the skin {2652}, with junctional activity and upward migration but Pagetoid invasion is unusual. Atypical melanocytic lesions may progress to malignant melanoma but there is little evidence for progression of oral benign melanocytic naevi to invasive malignancy {1085,2652}. Oral mucosal melanoma is, therefore, classified as in-situ oral mucosal melanoma, invasive oral mucosal melanoma, and mixed in-situ and invasive lesions. Borderline lesions may be termed atypical melanocytic proliferations {122,1085,2652}.

Most lesions at presentation are invasive or have mixed invasive and in-situ com-

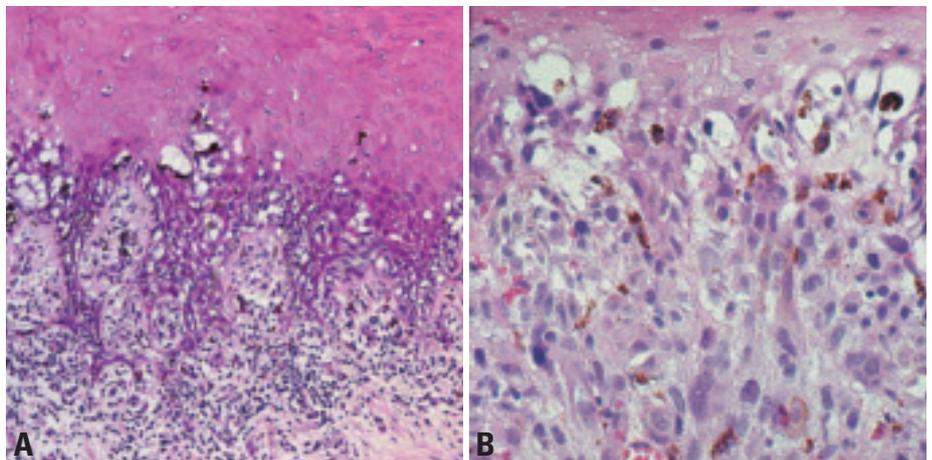


Fig. 4.57 **A** in-situ growth phase showing atypical and enlarged melanocytes at the epithelial-connective tissue interface. Melanocytes may show upward migration into the epithelium. **B** Invasive lesions showing considerable junctional activity, with atypical melanocytes invading into the underlying connective tissues.

ponents. Less than 20% are solely in-situ lesions. Typically, an oral melanoma is composed of sheets or islands of epithelioid melanocytes, which may be arranged in an organoid, or alveolar pattern. The cells have pale cytoplasm and large open nuclei with prominent nucleoli and occasionally they may be plasmacytoid. Sheets and fascicles of spindle cells may also be seen, but are usually a minor part of the lesion. Occasional lesions may be predominantly or wholly spindled. Over 90% of lesions contain melanin pigment that can easily be demonstrated with stains such as Masson-Fontana or Schmorl's.

When present, the in-situ component shows atypical naevoid cells arranged singly or in nests at the epithelial-connective tissue interface. Upward migration of the cells is common, but Pagetoid islands, similar to those of superficial spreading cutaneous melanomas, are not frequent. Invasion may be difficult to determine but the presence of obviously malignant cells in the lamina propria indicates invasion and islands of cells larger than those seen within the epithelium suggest an invasive growth phase.

Mitoses are surprisingly sparse but are seen more frequently in invasive lesions. The overlying epithelium is usually atrophic and just over half of lesions are ulcerated.

Immunoprofile

Over 95% of lesions are S100 positive and negative for cytokeratins {144}. Although sensitive, S100 is not specific. More specific markers include HMB45, Melan-A or anti-tyrosinase, which stain about 75% of lesions {2079}.

Genetics

Cutaneous melanomas may be associated with familial melanoma syndromes, and melanoma-prone kindreds show frequent loss of heterozygosity or mutations at several sites. Two tumour suppressor genes, CDKN2A (at 9p21, which codes for P16INK4A) and PTEN (at 10q23), and the oncogene CDK4 have been identified as important melanoma

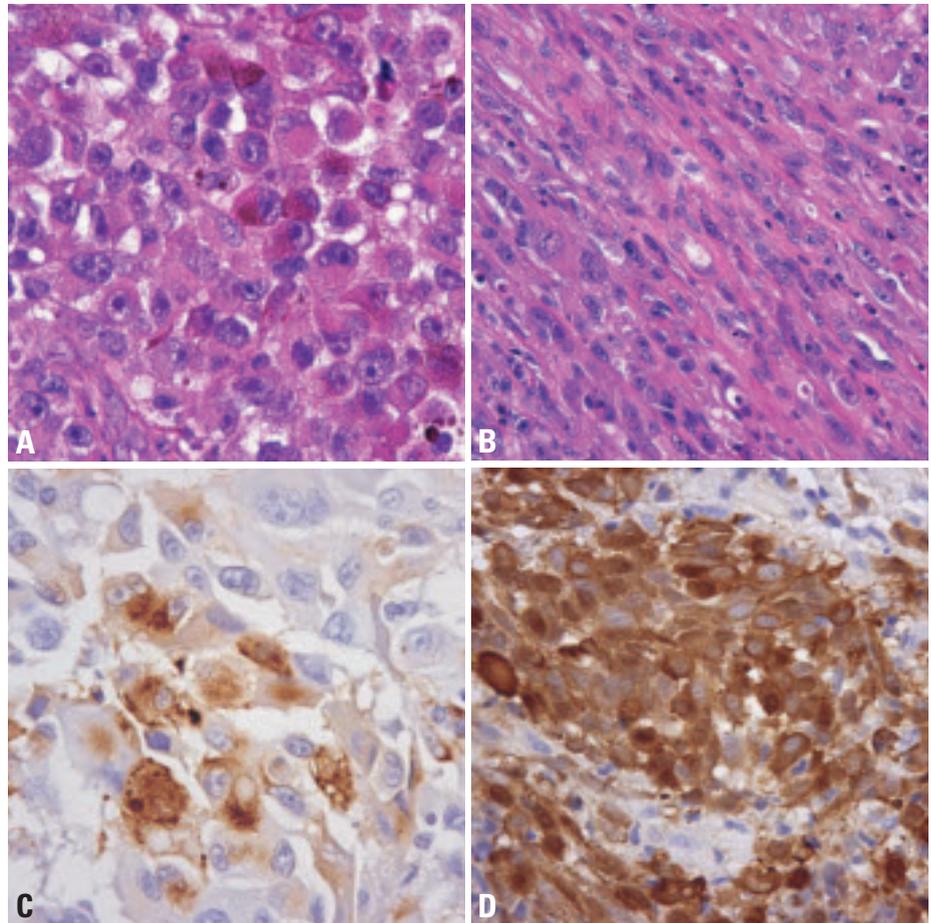


Fig. 4.58 Malignant melanoma **A** Invasive lesions are typically composed of sheets of plump epithelioid melanocytes. **B** Spindle cell areas are often seen. **C** HMB45 is one of the most specific markers for melanoma, but staining may be patchy. **D** S-100 antibodies are expressed strongly and uniformly in almost all lesions.

susceptibility genes {269,1252,2713}. However, associations with these genes have not yet been shown for oral melanomas, and expression of various tumour suppressor genes or oncogenes is variable and heterogeneous {1085,2555}.

Prognosis and predictive factors

The prognosis for oral melanoma is poor with an overall median survival of about 2 years and 5-year survival of less than 20% {122,170,1085}. Stage is a predictor of survival but even localized tumours (stage I) show a 5-year survival of less than 50%. Depth of invasion (Breslow

thickness and Clark's levels) is of limited value in oral lesions. This is due to lack of adequate studies and the fact that most oral melanomas are deeper than 4 mm at presentation {1085,1843,2080}. Nevertheless, lesions thicker than 5 mm may have a significantly worse prognosis. Other factors associated with poor prognosis include, vascular invasion, necrosis, a polymorphous tumour cell population, and increasing age {170,1085,1843,2080}.

Secondary tumours

E.W. Odell

Metastases to bone

Definition

Distant spread of malignant neoplasm to the head and neck from other parts of the body. This is almost exclusively via a haematogenous route.

Epidemiology

The most common malignant neoplasms within the jaws, apart from direct spread from mucosal carcinomas, are metastases and the most frequent primary sites are carcinomas of, in order of decreasing incidence, breast, kidney, lung, prostate and thyroid or colon {1098}. Maxillary and sinus metastases most frequently arise from renal carcinoma {202}.

Metastasis accounts for approximately 4% of all upper aerodigestive tract carcinoma {246}. The great majority of patients are elderly, with mean age at diagnosis of 55 years and the sex incidence varies from equal {2877} to a female preponderance accounted for by the prevalence of breast carcinoma. Asymptomatic mandibular metastases have been found in 16% of carcinoma patients at autopsy {1025} but only approximately 1% of carcinomas develop clinical metastasis to the jaws during the course of the disease. Sarcomatous metastases are extremely rare, usually Ewing sarcoma or osteosarcoma and arise in the second or third decade. Childhood malignant neoplasms also occasionally metastasise to the jaws.

Localization

The ratio of metastases in mandible to maxilla is 5:1 or greater. Most mandibular metastases develop in the angle of the mandible below the inferior dental nerve canal, a minority affect the alveolus.

Clinical features

Common signs and symptoms include loosening of teeth, swelling, failure to heal of a dental extraction socket {1101}, pathological fracture or nerve signs, particularly paraesthesia and anaesthesia in the mental region. Pain may be the only evidence of metastasis. After cortical perforation, a soft tissue mass may be present. Some metastases are asymptomatic chance radiographic findings.

The majority of jaw metastases are radiolucent and poorly defined but occasional lesions are circumscribed. A minority are osteosclerotic or mixed radiolucencies and these are usually breast or prostate carcinomas. Some show only subtle changes such as widening of the periodontal ligament or may be invisible on panoramic tomographic views and plain films. In such cases a bone scan may reveal the metastasis. Radiography has low diagnostic yield for metastases {1025}.

Tumour spread and staging

Jaw metastases are the presenting sign of malignancy in 20-30% of cases {1098,2877} but in most the primary lesion is known. Sometimes metastasis develops many years after treatment for the primary lesion, particularly with renal carcinoma. Metastatic spread to the jaws indicates UICC/AJCC Stage IV disease.

Histopathology

Histopathological appearances vary. Metastases are usually poorly-differentiated. If immunocytochemistry is required to aid clinical identification of sites of an occult primary lesion, prostate specific antigen and thyroglobulin are the most useful stains.

Prognosis and predictive factors

Metastasis to the jaws usually indicates widely disseminated disease and a poor prognosis with a 4-year survival of 10% {458}. Two thirds of patients die in less than 1 year {1101}. Depending on lesion type and dissemination, radiotherapy or hormone therapy may be provided. Surgery may occasionally be of value in palliative care.

Metastases to oral soft tissues

Metastasis to soft tissues is much more rare. It affects a similar age group, 40-70 years old, and the commonest sites for primary lesions in males are lung (one third of cases) followed by kidney and skin. The commonest primary site in females is breast {1100}. The commonest site for metastasis is gingiva (55%) because of its fine capillary bed, followed by tongue (30%), though any site may be affected. The predilection for gingiva is mostly lost after teeth are extracted {1100}. Lesions present as soft tissue masses, often ulcerated, resembling traumatic or reactive hyperplastic lesions.