Occasional articles

Troublesome tumours 2: borderline tumours of salivary glands

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Introduction

Salivary gland tumours are relatively uncommon, comprising less than 3% of all neoplasms of the head and neck.¹ Coupled with this is a bewildering range of differentiation among individual tumours and frequently within the same tumour mass. The complexity of this group of tumours is illustrated by the fact that in the second revision of the World Health Organisation Histological Classification of Salivary Gland Tumours^{2,3} there are over 30 types of epithelial tumours alone and several of these have major subtypes. As the borderline between many of these tumours is blurred I have had to be very selective in the tumours I have chosen to discuss. I have, therefore, grouped a number of tumours and non-neoplastic lesions into broad topics which include clear cell tumours, oncocytic lesions of salivary glands, basal cell tumours, and squamous metaplasia and squamous tumours of salivary glands. I have also considered as a separate entity a relatively recently recognised tumour, the polymorphous low grade adenocarcinoma, which can simulate several other salivary gland tumours but has a relatively good prognosis. Throughout the paper I have used the revised terminology proposed in the second revision of the WHO classification.³

Clear cell tumours

Many salivary gland tumours have focal areas of clear cells which rarely complicate the diagnosis. In some tumours, however, the clear cells may predominate and the diagnosis can then be very difficult. The reasons for cells in salivary gland tumours appearing clear include a sparsity of organelles, cytoplasmic constituents such as glycogen, mucus, lipid or clear secretory granules, and fixation artefact. Clear cell tumours can be classified (table 1). It must be emphasised that most predominantly clear cell tumours of salivary glands, even when they are cytologically bland, are malignant.

PLEOMORPHIC ADENOMA

Clear "myoepithelial" cells occasionally constitute a large part of pleomorphic adenomas. This can be in the form of extensive sheets or double layered, duct-like structures with inner, dark staining, cuboidal cells and outer clear cells. Very similar duct-like structures can be seen in adenoid cystic carcinoma and epithelial-myoeplithelial carcinomas (fig 1). In pleomorphic adenomas and adenoid cystic carcinomas typical features are usually found elsewhere in the specimen which make the diagnosis obvious. But this appearance may be an insoluble problem when interpreting limited biopsy material. In salivary tumour diagnosis it is always wise to issue a circumspect report on small incisional biopsy specimens unless they are absolutely typical—even then the excision specimen can come as an unpleasant surprise.

Figure 1 Double layered duct-like structures with dark staining inner cuboidal cells and clear outer myoepithelial type cells. This is from an adenoid cystic carcinoma but similar appearances can be seen in pleomorphic adenomas and epithelial-myoeplithelial carcinomas.

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Table 1 Salivary gland tumours with clear cells

Benign	Malignant
Pleomorphic adenoma	Primary:
Clear cell oncocytoma	Muco-epidermoid carcinoma
Multifocal nodular oncocytic hyperplasia	Acinic cell carcinoma
Sebaceous adenoma	Epithelial-myoeplithelial carcinoma
	Adenoid cystic carcinoma
	Sebaceous carcinoma
	Secondary:
	Renal
	Thyroid
	Others

ONCOCYTOMA

Clear cell oncocytoma is a very rare tumour usually seen in the parotid.⁴ It forms a circumscribed mass of polyhedral cells with clear cytoplasm and small, hyperchromatic nuclei which, typically, are eccentric. These cells may form an organoid arrangement, separated by thin fibrous septa. PTAH staining may show focal areas of positive granular staining but is unreliable and electron microscopic examination shows a sparsity of organelles and swollen mitochondria which are usually concentrated at the periphery of the cytoplasm. Some of these appearances are thought to be due to fixation artefact.

MULTIFOCAL NODULAR ONCOCYTIC HYPERPLASIA

This very rare condition, which may be associated with clear cell oncocytoma, consists of nodules of oncocytic or clear cells. These nodules may be lobular and appear to engulf normal acinar tissue (fig 2), giving the false impression of invasion.⁵

SEBACEOUS ADENOMA

Although sebaceous differentiation is common in the parotid gland, sebaceous neoplasms are very rare.⁶ Sebaceous adenomas, which may be cystic, consist of sebaceous cells with abundant foamy cytoplasm, arranged in nests, with variable amounts of stratified basilar epithelium. The stroma is fibrous. The diagnosis is usually straightforward.

MUCOEPIDERMOID CARCINOMA

Foci of clear cells are very common in mucoepidermoid carcinoma but can occasionally form the bulk of the tumour, and careful examination may be needed to find evidence of epidermoid differentiation. The clear cells are

Figure 2 Multifocal nodular oncocytic hyperplasia of parotid gland giving the appearance of an infiltrating clear cell tumour.

Figure 3 Clear cell area in an acinic cell carcinoma showing areas of persistent granularity.

often mucin negative but may contain glycogen, typically in the form of droplets rather than granules.

ACINIC CELL CARCINOMA

Although the cells in acinic cell carcinoma may become vacuolated, they only rarely appear crystal clear, and such areas are often focal and the typical basophilic or granular cells can usually be seen (fig 3). The cells are usually periodic acid Schiff positive and diastase resistant. Clear cells in acinic cell carcinomas may be an artefact caused by prolonged formalin fixation.

EPITHELIAL-MYOEPITHELIAL CARCINOMA

This important clear cell tumour has had a somewhat chequered terminological career.⁷ In both the 1972 WHO Classification and the AFIP Fascicle, as well as in many standard texts, it is called a clear cell adenoma or a glycogen rich adenoma. The tumour consists of two cell types in widely varying proportions. There are inner, dark staining cells and outer clear cells. The outer clear cells stain strongly for glycogen and are positive for S-100 antigen and actin and myosin.⁸ Electron microscopical examination also shows features consistent with a myoepithelial origin. There is a wide range of variation in this tumour group. Sometimes the duct-like structures are widely separated in an abundant fibrous stroma, while in others they are packed together to form continuous sheets (fig 4). The duct-lining cells may be extremely rare so that the whole tumour may initially seem to consist of clear cells, and some of those have been called clear cell myoepitheliomas.⁹ The cells are often

Figure 4 Epithelial-myoeptithelial carcinoma showing sheets of clear cells and darker duct lining cells.

Figure 5 Sebaceous carcinoma showing sheets of pleomorphic sebaceous cells. Some are foamy and others are clear.

cytologically bland, giving the tumour a deceptively innocent appearance. But these are carcinomas and can show local spread, perineural, and vascular invasion. Recurrence or metastasis has been reported in over a third of cases.

SEBACEOUS CARCINOMA

This rare tumour consists of sebaceous cells in sheets or thèques with variable nuclear atypia, pleomorphism, and mitotic activity.¹⁰ The

cytoplasm of the cells is usually foamy but sometimes there are foci where the cytoplasm is clear (fig 5). They are usually located in the parotid gland and are slow growing, but about a third of patients in one major series died from the tumour.¹¹

METASTATIC CLEAR CELL TUMOURS

Clear cell renal and thyroid metastases have been reported in the salivary glands, and occasionally clear cell squamous carcinomas or melanomas are seen.¹² Clear cell renal carcinomas contain abundant glycogen and lipid and often look remarkably bland. The vascularity said to be so typical of renal carcinomas may not be a conspicuous feature. Thyroid secondaries are negative for both glycogen and lipid, but are usually positive with antibodies against thyroglobulin. It is feasible for a signet-ring cell microfollicular adenoma of ectopic thyroid to be mistaken for a clear cell variant of an intraoral salivary gland.¹³ Sometimes, however, it is impossible to distinguish between metastatic clear cell tumours by histological or immunocytochemical means and further investigations such as radioimaging may be necessary.

Oncocytic lesions of salivary glands

Oncocytic change is where cells develop intensely eosinophilic granular cytoplasm due, typically, to increased numbers of mitochondria. The criteria for defining oncocytes have recently been reviewed.^{5 14} Many non-neoplastic lesions and tumours of salivary glands can show focal or generalised oncocytic change (table 2).

BENIGN LESIONS

Focal and diffuse oncocytosis

Focal areas of oncocytosis, usually of ducts but occasionally also acini, are increasingly common with advancing age. Diffuse oncocytosis of the parotid, however, is extremely rare and virtually the whole gland can show oncocytic metaplasia of ducts and acini. Diffuse oncocytosis, like most other oncocytic lesions, shows two types of cells: light and dark cells. Light cells are large and round or polygonal and have finely granular, pink cytoplasm and a vesicular nucleus. The dark cells are usually more sparse and have deeply eosinophilic, compressed cytoplasm and densely hyperchromatic nuclei.

Table 2 Oncocytic lesions of salivary glands

Benign:
Focal and diffuse oncocytosis
Ductal oncocytosis
Larynx
Cheilitis glandularis
Multifocal nodular oncocytic hyperplasia
Oncocytoma (oxyphil adenoma)
Warthin's tumour
Papillary cystadenoma
Oncocytic tumour metaplasia
Pleomorphic adenoma
Basal cell adenoma
Others
Malignant:
Mucoepidermoid carcinoma
Oncocytic carcinoma

Ductal oncocytosis

Extensive oncocytic metaplasia of ducts, often with cystic dilation, is seen mainly in the larynx, usually in patients over 50, and some regard these lesions as oncocytic papillary cystadenomas.¹⁵ They are microscopically identical with Warthin's tumour without any lymphoid stroma. Although rare cases of papillary cystadenomas of this type can be seen in the parotid, the oncocytic lesions of the larynx and other oropharyngeal minor glands are usually small and are probably due to oncocytic metaplasia and hyperplasia of existing salivary gland ducts.¹⁶ Similar oncocytic metaplasia and duct dilatation have been reported in a condition known as cheilitis glandularis which can rarely affect other intraoral minor glands and would be better termed stomatitis glandularis. This is a disorder of uncertain cause characterised by enlargement of the minor salivary glands usually the lips.¹⁷ There are multiple nodules and puncta which exude viscous mucus. The histopathological changes are not specific but include acinar distention or fibrosis, and ectasia of the ducts which may be florid. The dilated ducts can show oncocytic metaplasia and simulate a papillary cystic neoplasm.

Multifocal nodular oncocytic hyperplasia

This is discussed in the section on clear cell tumours. These uncommon lesions frequently consist almost exclusively of clear cells and do not show the characteristic light and dark cells.⁵ This lesion has been reported to co-exist with a pleomorphic adenoma which itself showed oncocytic change.

Oncocytoma

These are very rare tumours and in a review of 26 oncocytic lesions of salivary glands,⁵ excluding Warthin's tumour, only eight tumours fulfilled the criteria for oncocytoma and half of these were associated with multifocal nodular oncocytic hyperplasia. The tumour comprises a well demarcated mass consisting entirely of oncocytic cells with a solid, trabecular, or tubular configuration, and usually contains both light and dark cells. There is a fibrous capsule which may not be complete and little internal fibrous stroma. Warthin's tumour has several variants, one being the so-called stroma poor type^{18,19} which has a sparse lymphoid stroma and can form a solid tumour nodule of oncocytic cells rather than a papillary cystic lesion. The diagnosis of this variant is made on the basis of finding areas of lymphoid stroma, which may be patchily distributed. The only value in making the distinction from oncocytoma is that Warthin's tumour is much more likely to be multifocal or bilateral.

Oncocytic tumour metaplasia

Oncocytic metaplasia in other benign salivary gland tumours seems to be more common than oncocytoma itself. In a study of 26 benign oncocytic tumours nine were pleomorphic adenomas and four were oncocytic metaplasia in trabecular or tubulo-trabecular basal cell adenomas.⁵ The distinction between oncocytic

metaplasia and oncocytoma was most readily appreciated by examining the capsule and looking for the presence or absence of clinically important internal fibrous stroma. Thus the capsule of pleomorphic adenoma was thicker than oncocytoma, had an irregular internal margin, and often showed areas of capsular invasion. Satellite nodules were sometimes present. A third of oncocytic pleomorphic adenomas contained psammoma bodies, but none of the oncocytomas showed this feature. The oncocytic monomorphic adenomas showed the typical growth patterns of basal cell adenomas but the cells were intensely oncocytic.

MALIGNANT ONCOCYTIC TUMOURS

Muco-epidermoid carcinoma

Oncocytic change, either focally or throughout, is a rare feature of mucoepidermoid carcinomas. The tumours are usually of the solid type and the oncocytic cells are enlarged with distinct cell boundaries. There is usually not a high degree of cellular atypia and the presence of duct-like structures and mucus cells aid the diagnosis. Occasionally it may be difficult to distinguish such tumours from oncocytic pleomorphic adenomas on haematoxylin and eosin stained sections, but periodic acid Schiff or mucicarmine usually permit distinction.

Oncocytic carcinoma

This is an extremely rare tumour^{20,21} which is seen principally in the parotid gland. In a review of oncocytic carcinomas Goode and Corio²² considered the following histological features to be important in establishing this diagnosis: (1) Oncocytic features together with dysplasia including mitoses and nuclear pleomorphism; (2) perineural or vascular invasion; (3) infiltration of the surrounding tissues or paraparotid lymph nodes.

Oncocytic carcinoma seems to be a very aggressive tumour and over half of the reviewed cases either died from the tumour or were alive with active disease. However, in the recent review by Brandwein and Huvos²¹ apparently aggressive histological features, including perineural infiltration and capsular invasion by oncocytic tumours, were not always associated with a poor prognosis. They felt, therefore, that it was unjustified to classify oncocytic tumours as malignant based only on these two features. Further case reports or series with adequate follow up will be needed to clarify the nature of these, admittedly, rare tumours.

BASAL CELL TUMOURS

Several types of benign and malignant salivary gland tumours are characterised by a predominance of basal cells (table 3).

Embryomas

This very rare group of tumours has a variety of names including sialoblastoma, congenital basal cell adenoma, embryonal carcinoma and congenital basal cell adenoma-adenoid cystic carcinoma.^{23,24} The tumours are usually seen at birth or shortly after and the submandibular

Table 3 Basal cell tumours of salivary glands

Embryomas (sialoblastoma)
Benign (? hamartoma)
Malignant
Basal cell adenoma
Solid
Trabecular
Tubular
Membranous (dermal analogue type)
Basal cell adenocarcinoma
Solid (basaloid) adenoid cystic carcinoma

gland is the most common site. The benign tumours, which may well be hamartomas, resemble solid basal cell adenomas but are usually confined within lobules of relatively normal overall architecture and frequently show terminal acinar differentiation. Most are cytologically bland, but occasional cases, which have been called malignant sialoblastomas, have shown aggressive cytological features and behaviour.

Basal cell adenoma

Most basal cell adenomas arise in the parotid gland of elderly patients. These tumours have a unicellular, isomorphic cell type together with a prominent basal cell layer. There are several morphological variants including solid (fig 6), trabecular, tubular (fig 7), and membranous types.² The tumours may have distinct basement membrane-like structures and usually have a fibrous stroma. An uncommon variant of the tubulo-trabecular type has been described with abundant myoepithelial cell-derived stroma.²⁵ The membranous variant is uncommon but distinctive (figs 8 and 9). The epithelium may show peripheral palisading and contains intercellular hyaline droplets and there is a thick, hyaline basement membrane zone. The tumour thus closely resembles dermal cylindroma (trichoepithelioma). These tumours are not infiltrative but can be bilateral and may be associated with scalp cylindromas.²⁶

Basal cell adenocarcinoma

These rare tumours, which are mainly seen in the parotid gland, are considered to be the malignant equivalent of basal cell adenomas, particularly the membranous type.²⁷ The tumour consists of multiple solid islands of darkly stained epithelial cells, often with a distinct hyalinised basal membrane zone. Peripheral palisading is not a feature and the cells may show frequent mitoses but variable pleomorphism and necrosis. Squamous differentiation and occasional small lumina are also seen and the stroma is typically fibroblastic. The principal distinction between basal cell adenoma and basal cell adenocarcinomas, however, is invasion of surrounding tissue, including nerves and blood vessels (fig 10). Such invasion can be seen in tumours which appear to be cytologically benign. Basal cell adenocarcinomas are low grade malignancies with local recurrence in about 25% of cases and metastasis in less than 10% of cases.

Solid (basaloid) adenoid cystic carcinoma

This pattern rarely forms the total mass of an

Figure 6 Solid type basal cell adenoma.

Figure 7 Tubulo-trabecular basal cell adenoma with cellular stroma.

adenoid cystic carcinoma, and more typical cribriform or tubular areas are often present. The small, darkly staining epithelial cells form discrete islands often with central necrosis and frequently with artefactual splitting of the epithelial islands from the surrounding stroma (fig 11). Mitoses are not usually frequent.

Figure 8 Membranous type basal cell adenoma with thick, hyaline basement membranes and intercellular hyaline droplets. Low power.

Figure 10 Basal cell adenocarcinoma showing islands resembling basal cell adenoma but invading adjacent lymphoid tissue.

Figure 9 Membranous type basal cell adenoma. High power.

Figure 11 Solid adenoid cystic carcinoma showing dark staining cells and small duct-like spaces.

Although the tumour islands appear solid, usually small true ducts can be seen within the islands and these may contain eosinophilic secretion. This is an important distinguishing feature from basal cell adenocarcinomas or the

uncommon undifferentiated carcinomas with basaloid morphology.²⁸ The latter can show a very high mitotic frequency. The solid variant of adenoid cystic carcinoma has a relatively poor prognosis.²⁹⁻³¹

Squamous metaplasia and tumours of salivary glands

Squamous differentiation is common in reactive salivary gland lesions and can be seen in several benign and malignant tumours, either as metaplasia, or as an integral feature of the tumour (table 4).

NECROTISING SIALOMETAPLASIA

Necrotising sialometaplasia is a benign, self limiting cause of ulceration or swelling, mainly in minor glands, first described by Abrams *et al* in 1973.³² It is important because it can simulate malignancy both clinically and histologically. Typically, a single but sometimes bilateral ulcer forms on the palate or less commonly in other intraoral sites.³³ Microscopical examination shows lobular necrosis of the minor glands with regenerative hyperplasia of the adjacent salivary ducts which become solid and can simulate islands of invading squamous epithelium (fig 12). When there is ulceration there can also be pseudoepitheliomatous hyperplasia of the overlying epithelium. This can lead to a diagnosis of squamous cell carcinoma or mucoepidermoid carcinoma with the consequent therapeutic implications. The cause is unknown but the consensus is that the condition is primarily due to salivary gland infarction as a result of ischaemic injury.

METAPLASIA IN SALIVARY GLAND TUMOURS

Areas of squamous metaplasia are commonly seen in pleomorphic adenomas, particularly in the lip. The dilated duct structures may show a layer of squamous differentiation or this may progress so that solid islands of squamous epithelium form, with or without keratin pearls. The cells are cytologically bland. If mucous cells are seen in conjunction with these areas, it would be easy to make an erroneous diagnosis of mucoepidermoid carcinoma. But keratin pearl formation is uncommon in the latter and careful examination of the stromal elements should avoid confusion.

Squamous metaplasia is sometimes seen in Warthin's tumours which have undergone extensive necrosis, probably due to infarction or infection.^{18 34} In the series of Seifert *et al* squamous metaplasia was common and sometimes florid and the possibility of a misdiagnosis of a malignant squamous neoplasm had to be considered.¹⁸ Over 40% of these patients had received irradiation which may have been a contributory factor. The picture is further complicated by reports of squamous carcinomas in Warthin's tumours.^{35 36} The general configuration of the tumour, the inflam-

Figure 12 Necrotising sialometaplasia showing regenerating squamous epithelium adjacent to necrotic mucous glands.

matory overlay, and the lack of cellular atypia should help avoid any confusion. Very occasionally, squamous metaplasia can be seen in an otherwise typical cribriform adenoid cystic carcinoma.

MUCOEPIDERMOID CARCINOMA

This tumour has a variety of cell types including squamous cells, mucous cells, intermediate cells, and sometimes clear cells in varying proportions and configurations. The low grade tumours tend to be predominantly cystic with many mucous cells and scanty intermediate and squamous cells. The squamous cells show little pleomorphism and few mitoses. There may be dyskeratosis and keratin pearl formation, but these are not common.^{37 38} Higher grade tumours tend to be solid, have many fewer mucous cells, and often the squamous cell element resembles squamous cell carcinoma. The mucous cells may then be so rare that they can only be detected with special stains.

SQUAMOUS CELL CARCINOMA

This uncommon salivary tumour shows no specific features in salivary glands but is often poorly differentiated and carries a poor prognosis. It is important to distinguish these from metastases to the intraparotid lymph nodes from cutaneous, oral, or nasopharyngeal carcinomas and an examination under anaesthesia may be necessary to accomplish this. It is also worthwhile staining all such tumours for mucus to exclude the possibility of high grade mucoepidermoid carcinoma, which carries a slightly better prognosis. Some squamous carcinomas show malignant acantholysis and can then resemble adenocarcinoma (fig 13). Such

Table 4 Squamous metaplasia and tumours of salivary glands

Metaplasia:
Necrotising sialometaplasia
Tumours
Pleomorphic adenoma
Warthin's tumour
Others
Tumours:
Mucoepidermoid carcinoma
Squamous cell carcinoma
Adenoid squamous carcinoma
Adenosquamous carcinoma

Figure 13 Adenoid squamous carcinoma—an appearance produced by malignant acantholysis in a squamous carcinoma.

Figure 15 Polymorphous low grade carcinoma showing papillary cystic area.

Figure 14 Adenosquamous carcinoma with severe dysplasia and early squamous carcinoma overlying a duct adenocarcinoma.

Figure 16 Polymorphous low grade carcinoma showing characteristic neurotropism.

tumours, which are most common in the lip, are termed adenoid squamous carcinomas.

ADENOSQUAMOUS CARCINOMAS

This rare carcinoma shows both glandular and squamous differentiation, and appears to be a tumour of minor salivary glands.³⁹ Unlike mucoepidermoid carcinoma, where the glan-

dular and epidermoid elements form integrated components, in adenosquamous carcinoma there are separate areas of adenocarcinoma and squamous carcinoma, or carcinoma in situ in the epithelium overlying an adenocarcinoma which is typically ductal in type (fig 14). The few reported cases of this tumour would suggest that it is aggressive.

Polymorphous low grade adenocarcinomas

This distinctive clinicopathological entity has only been reported in the past few years.^{40,41} It was described independently by several workers and has thus been called lobular carcinoma,⁴² terminal duct carcinoma,⁴³ and polymorphous low grade adenocarcinoma of minor salivary gland.⁴⁴ Recent reviews include those by Mitchell⁴⁵ *et al* and Batsakis and El-Naggar.⁴⁶ It is an important tumour because it can easily be confused with several other salivary tumours but has a very good prognosis.

The histological hallmark of this tumour is cytological uniformity and morphological diversity. Cells are small to medium in size with pale, vesicular nuclei and frequently the tumours look as though they have failed to take up the haematoxylin stain or have been bleached. Mitoses are uncommon. Tumours can present many patterns in a single case including lobular, tubular, trabecular, cribriform and papillary areas (fig 15). The stroma may show hyalinisation, containing both collagen and elastic tissue, mucinous areas, and foci of interstitial and stromal haemorrhage. A very characteristic feature, which is not seen in all tumours, is concentric targetting or whorling of small duct-like cells around nerves and sometimes ducts (fig 16). This, together with cribriform areas, causes confusion with adenoid cystic carcinoma. But this neurotropism seems to be confined to the main tumour mass and does not show the relentless perineural spread of adenoid cystic carcinoma. It is not clear whether so-called low grade papillary adenocarcinomas, which also largely affect the minor glands, are a distinct entity or merely reflect a predominantly papillary variant of polymorphous low grade adenocarcinoma.⁴⁵ However, such tumours are certainly more clinically aggressive than the classic polymorphous adenocarcinoma, with a greater liability to local recurrence and regional lymph node metastases.

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