SALIVARY PATHOLOGY.
Roderick HW Simpson.

INTRODUCTION.

The salivary glands can be affected by a variety of non-neoplastic conditions and produce a very wide range of different tumours, both benign and malignant. Some of these conditions will have been dealt with by Prof. Skálová. It is not possible to cover all of the rest of salivary gland pathology during this presentation, which will concentrate on the more important lesions, mainly neoplastic. Comprehensive accounts of diseases and neoplasms of the salivary glands will be found in standard textbooks, as well as a variety of new atlases, all of which are of a high standard.

SOME NON-NEOPLASTIC CONDITIONS

Chronic sclerosing (atrophic) sialadenitis of submandibular gland (Küttner tumour).

Chronic sclerosing sialadenitis (Küttner tumour) occurs in the submandibular gland. Its exact aetiology is unknown, but up to 80% are associated with sialoliths in the excretory ducts, although it is uncertain whether these are the cause of the disease or a secondary process. Some patients also have increased numbers of IgG4-positive plasma cells, and this can be localized to the salivary glands, or be part of other IgG4-related systemic sclerosing diseases such as autoimmune pancreatitis. The histopathological picture of chronic sclerosing sialadenitis varies from just scattered lymphoplasmacytic aggregates to severe changes of acinar atrophy and heavy chronic inflammation with germinal centre formation to an end stage of destruction of the lobular architecture and scarring. The inflammation is centred on the acini rather than ducts, although minor intraductal aggregates of neutrophils are often present. IgG4-positive plasma cells and sometimes eosinophils are numerous in the non-sialolith cases, both in the systemic and localized forms. Only exceptionally are lymphoepithelial lesions (LELs) found.

Necrotising sialometaplasia (salivary gland infarction).

Necrotising sialometaplasia (salivary gland infarction), is a benign self-healing process, affecting especially the minor salivary glands of the palate. Some cases follow surgery (about 1 to 8 weeks post-operatively) or even relatively minor trauma, such as from an ill-fitting denture, but often no predisposing factor is apparent, although the underlying process is generally considered to be ischaemic. Microscopy shows lobular coagulative necrosis of acini (particularly in the early stages), squamous metaplasia of ducts, a chronic inflammatory cell infiltrate and pseudoeplitheliomatous hyperplasia of the overlying surface. There is a superficial resemblance to either mucoepidermoid or squamous cell carcinoma, but the overall lobular architecture of the involved gland is preserved. A similar reaction can be seen in the major glands after surgery or radiotherapy.

Multifocal nodular oncocytic hyperplasia (MNOH).

Oncocytic change is where cells develop intensely eosinophilic granular cytoplasm due, to increased numbers of mitochondria. MNOH is rare and consists of nodules of varying size, composed of oncocytic cells, often with relatively clear cytoplasm. The nodules appear to engulf normal acini giving a false impression of invasion, but there is no stromal or other response by the acini. MNOH can be mistaken for a clear cell neoplasm with satellite deposits when one nodule is
much larger than the others. MNOH can also be bilateral, and it has been reported to co-exist with a pleomorphic adenoma which itself showed oncocytic change.

**Tissue changes following fine needle aspiration (FNA).**

FNA is an important technique in the investigation of salivary disease, particularly tumours, but the procedure itself can have adverse effects, causing difficulties in histological assessment and even simulating malignancy. The effects are classified as tissue injury with repair, infarction and reactive pseudomalignant changes. Some or all of these can occur in any tumour including pleomorphic adenoma, but are most frequent in Warthin’s tumour, where infarction may be total and squamous metaplasia florid. Possible causes include trauma by the needle and an increased sensitivity to hypoxia of oncocytic cells.

**BENIGN SALIVARY GLAND NEOPLASMS.**

**Pleomorphic Adenoma.**

Most authors accept that there is a spectrum of benign salivary adenomas, including pleomorphic adenoma. Benign myoepithelioma, which is composed almost entirely of myoepithelial cells represents one end of the spectrum, whereas basal cell adenoma and canalicular adenoma are at the other end. The particular morphology of any particular tumour reflects the different proportions of the constituent cells.

Pleomorphic adenoma (PA) is the most common tumour of the salivary glands. Although most often found in young to middle-aged women, they can occur in either sex and at any age. Up to 80% occur in the superficial lobe of the parotid gland, and it typically presents as a painless swelling. PAs are usually well-circumscribed masses of 20–40 mm. The cut surface is white, and grey glistening areas are commonly seen. Histologically, PA is as “a tumour of variable capsule characterised microscopically by architectural rather than cellular pleomorphism. Epithelial and modified myoepithelial elements intermingle most commonly with tissue of mucoid, myxoid or chondroid appearance.” The pattern varies from case to case, and also from area to area within any individual tumour. All are composed of a mixture of ductal epithelial cells, basal and myoepithelial cells and variable amounts of stroma, both hyaline and chondromyxoid. Attempts have been made to subclassify PA based on the proportions of cell types and stroma, but because of the variation in any tumour, this is difficult and probably has no prognostic value. Ducts are lined with flat, cuboidal or columnar epithelial cells, with little or no atypia. The ducts are usually small tubules, but can be cystically dilated and also arranged in a cribriform basaloid pattern, resembling adenoid cystic carcinoma, but mitotic figures are rare and the proliferation index low. Squamous metaplasia with or without keratinisation is seen in up to 25% of PAs. Myoepithelial cells are arranged in sheets, smaller islands and trabeculae, and also surround epithelium-lined spaces. As in benign myoepithelioma, neoplastic myoepithelial cells may take several forms – epithelioid, spindle, plasmacytoid, clear and oncocytic, as well as transitional forms with features of two or more of these types. The stroma varies in amount and is either dense eosinophilic hyaline material or chondromyxoid tissue. The former is composed of basement membrane material and stains with PAS diastase and collagen type IV; the chondromyxoid material only rarely resembles true cartilage and is Alcian blue-positive. Calcification and bone formation can occur in long standing tumours. Occasionally, collagenous spherules and crystalloids are seen, particularly in tumours rich in myoepithelial cells of the plasmacytoid type. Nuclear atypia is not common, but can be seen in tumours where epithelial or myoepithelial cells display oncocytic features. Occasional myoepithelial cell nuclei are enlarged and bizarre, somewhat analogous to “ancient” change in schwannomas. Mitotic figures are generally sparse, but can occur as part of the repair process after FNA. Similarly, areas of necrosis or haemorrhage may follow surgical manipulation, FNA or other trauma, and these neoplasms should also be sampled thoroughly. Tumour cells in
lymphatics (“vascular invasion”) are occasionally seen in benign PAs, but this does not necessarily indicate malignancy. None of the reported cases were followed by metastases. PAs are often completely or partly surrounded by a fibrous capsule of variable thickness, but it can be absent, especially in tumours of the minor glands. Neoplastic elements may extend into and even through the capsule in the form of microscopic pseudopodia or apparent satellite nodules. They may be the cause of future recurrence after apparent surgical removal, and their presence should be noted in the surgical pathology report. Special stains and immunohistochemistry are not necessary for the diagnosis in most cases, but can be used to identify the different cell types and also early malignant change. Recurrent PA occurs after incomplete surgical excision and is usually composed of multiple nodules completely separate from each other. In the first recurrence the nodules are usually seen within salivary gland tissue, but in further recurrences tumours are found in the soft tissue of the surgical bed. Histologically, the nodules show similar features to ordinary PA, and in particular they lack any cytological atypia. In spite of this, confluent nodules of recurrent PA can still kill the patient. As discussed later multiply recurrent PAs may rarely metastasise to distant sites, and in addition are more prone to developing malignant changes.

**Benign Myoepithelioma.**

Myoepithelioma represents one end of a spectrum that also includes pleomorphic adenoma and possibly even some basal cell adenomas. Nevertheless, myoepithelioma displays particular microscopic features that pose specific practical problems in identification and differential diagnosis, and on this basis it can be accepted as a separate diagnostic category. It can be defined as “a benign salivary gland tumour composed almost exclusively of sheets, islands or cords of cells with myoepithelial differentiation that may exhibit spindle, plasmacytoid, epithelioid or clear cyttoplasmic features.” Criteria to distinguish a PA with a predominance of myoepithelial cells from a myoepithelioma are largely arbitrary and most salivary pathologists allow up to 5% of the tumour to be composed of ductal epithelium in an otherwise typical myoepithelioma. With more than this, our preference is to designate such tumours as PAs with myoepithelial predominance. Benign myoepitheliomas arise in the parotid glands (48%), the submandibular glands (10%) and the minor salivary glands (42%) (especially the palate), as well as in seromucinous glands in the nasal cavity and larynx. Tumours with a similar morphology have also been described in the breast and soft tissues. Salivary myoepitheliomas occur approximately equally in both sexes. The patients have ranged in age from 6 to 98 years with a mean age in the early to mid-forties. As with pleomorphic adenoma, myoepithelioma is a well-circumscribed or encapsulated tumour. Microscopically, the neoplastic cells are arranged in sheets, irregular collections, nests, interconnecting trabeculae, or ribbons, giving typical solid, myxoid, reticular, micrrocystic and cribriform growth patterns. The component cells may be spindle-shaped, plasmacytoid (hyaline), polygonal (epithelioid), or less frequently, clear, basalaroid or oncocytic. In addition, overlap forms may be seen, such as elongated epithelioid cells similar to short, stubby spindle cells. Also, many tumours show more than one growth pattern or cell type. In addition, overlap forms may be seen, so that epithelioid cells may be elongated and thus have a similar appearance to those spindle cells, which are shorter and plumper. Rarely, the spindle cells can show lipomatous metaplasia. Benign myoepitheliomas do not usually show necrosis, or more than an isolated mitotic figure, but reparative foci with increased proliferation may follow infarction or trauma, particularly from fine needle aspiration (FNA). The stroma in myoepithelioma may be minimal or abundant and is usually acellular and mucoid, myxoid, or hyalinized. It can occasionally contain mature fat cells, and extracellular collagenous crystalloids. Immunohistochemically, there may be considerable variability of staining within the same tumour and between different tumours. However, almost all express S-100 protein, as well as broad spectrum cytokeratins (e.g AE1/AE3, MNF116), and some keratin subtypes, especially 14, and also the nuclear transcription factor, p63. Alpha smooth muscle actin (αSMA), muscle-specific actin, Calponin, Smooth Muscle Myosin Heavy Chain
(SMMHC) positivity is seen to some degree in most spindle cell myoepitheliomas, but only occasionally above 10%. Electron microscopic studies have also confirmed both epithelial and smooth muscle differentiation. Since benign myoepitheliomas are considered to represent one extreme of the histological spectrum of pleomorphic adenoma, the treatment and prognosis are essentially the same as for benign PA. Patients with these neoplasms should be treated by a complete excision that ensures a tumour-free margin, for example superficial parotidectomy; in minor gland sites, this will usually involve surgical excision with a rim of normal surrounding tissue. Neither growth pattern nor cell type appears to carry prognostic significance. Malignant change to myoepithelial carcinoma in a benign lesion has been described, but too little information is available about the percentage of cases involved. However, it is not unreasonable to postulate that it is probably similar to that of pleomorphic adenoma.

**Striated duct adenoma.**
Striated duct adenomas are unilayered ductal tumors that recapitulate normal striated ducts, which are lined by a single layer with patchy or absent basal or myoepithelial cells, unlike intercalated or excretory ducts. The cases arose in parotid and palate. They were encapsulated and were composed of back-to-back ducts with virtually no stroma. The ducts varied in size with some showing cysts up to 1 mm. The cells were eosinophilic and bland. Prominent cell membranes, reminiscent of “striations” of normal striated ducts were seen. All tumours were positive for keratins. S100 positivity was present in most, but no myoepithelial cells were found with SMA. Two tumors showed focal bilayered ducts with calponin or SMMHC, but the tumors were largely unilayered. Only isolated cells in 3 tumors were positive with p63, which was a pattern identical to the normal striated ducts. In contrast, the normal excretory and intercalated ducts all contained diffuse bilayering with basal (p63 positive) or myoepithelial (SMA, calponin, SMMHC positive) cells, respectively.

**Warthin’s Tumour - metaplastic subtype.**
Warthin’s tumour (adenolymphoma) is the second commonest neoplasm of the parotid gland, and is the easiest salivary tumour to diagnose by microscopy. One of the few diagnostic pitfalls is the rare subtype variously termed infarcted, infected or metaplastic. It accounted for 6.2% (20/323) of Warthin’s tumours in one series and 7.5% (21/275) in another. The histopathological definition is a Warthin’s tumour in which much of the original oncocytic epithelium has been replaced by squamous cells, and it thus resembles a ruptured epidermoid or lymphoepithelial cyst. Other microscopic features include extensive necrosis, in which a ghost architecture of papillary structures is often identified. Non-keratinising squamous metaplasia is prominent, consisting of tongues and cords of often spongiotic squamous cells extending into surrounding tissues in a pseudoinfiltrative pattern. Cytological atypia can be prominent and mitotic figures numerous, although none is abnormal. Goblet cells can also be seen, but should not be numerous. At the periphery of the lesions, there is extensive fibrosis, with dense hypocellular collagen and myofibroblastic spindle cell proliferation. There is a heavy mixed inflammatory infiltrate, comprising neutrophils, chronic inflammatory cells, as well as sheets of macrophages, some with foamy cytoplasm. Lipogranuloma, with or without cholesterol clefts, are not uncommon. The definition of metaplastic Warthin’s tumour does not encompass minor microscopic foci of inflammation, necrosis and fibrosis, as these findings can be commonly seen in any Warthin’s tumour. The diagnosis is easy if residual tumour is present, but it will not always be so, particularly if there is complete necrosis. Several cases have been reported following fine needle aspiration (FNA) acting on an ordinary Warthin’s tumour to produce the infarcted subtype. The most likely mechanism would be direct injury of a blood vessel by the needle, as Warthin’s tumours tend to contain few blood vessels within the substance of the tumours.
Therefore, they could be at risk of anything harming a limited number of feeder arteries. Another possibly important factor is cell type; in the well-documented injuries from FNA in other organs, tumours rich in oncocytic cells, such as Hürthle cell adenoma of the thyroid, feature prominently. Similar infarction has been reported in salivary oncocytoma. 

Sclerosing polycystic adenosis.

Sclerosing polycystic adenosis (SPA) is a recently described, rare lesion of the salivary glands that bears a resemblance to epithelial proliferative lesions of the breast. The true nature of the lesion is unknown, but until recently, it had generally been believed to represent a pseudoneoplastic sclerosing and inflammatory process. However, local recurrences developed in about one third of the reported cases, and in addition, superimposed atypical changes ranging from low-grade dysplasia to carcinoma in situ have been described. Although no metastases and/or disease related patient deaths were documented, these clinical and histopathological features raise the possibility that SPA might represent a neoplastic lesion. A recent study assessing clonality of the human androgen receptor (HUMARA) locus found that all six cases of SPA satisfied the criteria for monoclonality, thus providing further supporting evidence that SPA is a neoplasm, and not just a reactive process.

SPA affects females twice as often as men, and the age range is 9 to 75. Most of the about 50 reported cases have been described as slow-growing masses in the parotid gland, with rare examples of submandibular gland and minor gland involvement. Most patients present with a painless mass, although about 15% report mild pain or parasthaesia. A review of the literature reveals that pathological gross examination shows that the excised gland is largely replaced by multiple discrete firm, rubbery nodules, with a maximum size of 70 mm. Microscopic examination shows a well-circumscribed, partly encapsulated mass composed of a lobular arrangement of proliferating ducts and acini with cystic ducts containing viscous secretion and, on occasions, aggregates of foamy macrophages. There is often intraluminal epithelial proliferation occasionally with a cribriform pattern and these may contain small droplets of basement membrane material. The lining comprises a spectrum of apocrine, mucous, squamous cells and ballooned sebaceous-like cells, although true goblet cells are not seen. Some acinar cells contain prominent large, intensely eosinophilic PAS-positive cytoplasmic granules of varying sizes, representing aberrant zymogen granules. On occasions there is nuclear pleomorphism, suggesting dysplasia, resembling low grade ductal carcinoma in situ, but there is no significant mitotic activity. Flattened myoepithelial cells are present around ductal and acinar structures, and there is periductal sclerosis and intense hyaline sclerosis of the surrounding soft tissue. Sometimes, a patchy lymphocytic infiltrate is noted. Immunohistochemistry shows that the ductal and acinar cells are positive for cytokeratin (AE1/AE3 and CAM5.2), variably positive for EMA, S-100 protein, antimitochondrial antibody, but negative for CEA, p53 and HER-2/neu. The acinar cells with coarse granules react with GCDFP-15. About 20% of the epithelial cells express progesterone receptors, and oestrogen receptors can be detected in about 5% of ductal cells in the dysplastic and hyperplastic foci. Ducts filled with hyperplastic and dysplastic epithelium are surrounded by an intact myoepithelial layer, positive for smooth muscle actin, p63, and calponin.

The differential diagnosis of SPA includes polycystic dysgenetic disease, chronic sclerosing sialadenitis and low grade carcinoma, particularly acinic cell or mucoepidermoid carcinoma. Polycystic dysgenetic disease is a rare development disorder characterised by a diffusely honeycombed, lattice-like network of cysts with inspissated intracystic secretions replacing the normal parenchyma. Unlike SPA, fibrosis is not prominent and ductal and acinar proliferation is not seen. Chronic sclerosing sialadenitis has prominent fibrosis with varying degrees of chronic inflammation, but unlike SPA, there is acinar atrophy and cystic change is minimal. Unlike acinic cell or mucoepidermoid carcinoma, the lobular architecture is typically maintained in SPA, and there is no destructive growth.
Studies with clinical outcome data have shown that about one third of cases recur, but no patient has as yet developed metastases or died of disease.

References.


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MALIGNANT SALIVARY GLAND NEOPLASMS.

Acinic cell carcinoma

Acinic cell carcinoma is a malignancy in which at least some neoplastic cells demonstrate serous acinar cell differentiation. About 90% of acinic cell carcinomas arise in the parotid gland; there is an equal sex incidence and a wide age range, and children may be affected. Whilst serous acinar cell differentiation (PASD positive zymogen granules) is diagnostic for AcCC, the spectrum of growth patterns and cellular features is very variable. Growth patterns include solid, microcystic (microfollicular), follicular and papillary-cystic. The cell types are acinar (serous; blue dot), vacuolated, hobnail, clear and non-specific glandular and intercalated-duct epithelium. The most useful special stain is PASD. Immunohistochemistry is generally unhelpful in its diagnosis.

The clinical course is characterized by local recurrences in 30-50% of patients, metastases in fewer and death from tumour in about 16%. Clinical stage at the time of diagnosis and completeness of excision are the best predictors of outcome. Attempts at histological grading have not been successful, although poor prognostic factors include necrosis, extraglandular extension, increased pleomorphism, high mitotic rate and prominent infiltration of nerves and blood vessels. A particularly aggressive variant is those tumours with high grade transformation (dedifferentiation), in which a poorly differentiated adenocarcinoma develops in an ordinary acinic cell carcinoma. Most patients die with widespread metastases. In contrast, circumscribed well differentiated, microfollicular acinic cell carcinomas with abundant lymphoid stroma have an excellent prognosis; however, lymphocytic infiltration by itself is common in acinic cell carcinoma and has no predictive value. The most useful prognostic indicator in all acinic cell carcinomas is the Ki-67 (MIB1) proliferative index. In a series of thirty cases, no patient with an index <5% developed a recurrence or metastasis, in contrast to those with >5%, most of whom suffered tumour progression.

Mammary analogue secretory carcinoma

Mammary analogue secretory carcinoma (MASC) was first recognized in 2010 by Skálová et al, but most salivary pathologists realise that we have probably been misdiagnosing it as an “odd looking acinic cell carcinoma”. However, they are different entities.

The Skálová et al study described 16 salivary gland tumours with histomorphological and immunohistochemical features reminiscent of secretory carcinoma of the breast. The sex distribution was approximately equal and the mean age was 46 years (range 21-75). Most cases occurred in the parotid gland, with a few also in the minor salivary glands.

Microscopic examination showed that the tumours were usually circumscribed but not encapsulated, and invasion within the salivary gland was often present, sometimes with extension to extra-glandular tissues. The architecture consisted of a lobulated growth pattern composed of tubular and solid structures with microcystic and glandular spaces. The tumour cells had low grade vesicular nuclei with finely granular chromatin and distinctive centrally located nucleoli, surrounded by pale pink granular or vacuolated cytoplasm. Cellular atypia was mild, and mitotic figures were in most cases rare. Then no evidence of perineural or vascular invasion, or necrosis was identified, and no serious acinar differentiation was seen. Abundant eosinophilic homogenous
bubbly secretion was present within microcystic and tubular spaces. This material was positive for PAS (±diastase), mucicarmine, MUC1, MUC4 and mammaglobin. The neoplasms also showed diffuse strong staining with vimentin and S-100 protein, as well as with cytokeratins, EMA and GCDFP-15. Basal cell/myoepithelial cell markers, such as p63, calponin, CK14, smooth muscle actin, and CK5/6 were negative. Proliferative activity was variable with MIB1 indices ranging between 5 and 28%.

All testable cases harboured a t(12;15) (p13;q25) ETV6-NTRK3 translocation, identical to that found in breast secretory carcinoma. This translocation was not found in normal tissue or any other salivary tumour, including acinic cell carcinoma.

MASC appears to be more aggressive than its breast counterpart, as 4/13 patients suffered local recurrences; two died, one of them due to multiple local recurrences and extension to the temporal bone, and another due to widespread metastatic dissemination.

More recently, the clinical and morphological profile of MASC has been expanded to include origin in submandibular and minor glands, as well as the presence of macrocysts, hobnail cells, intra-cytoplasmic mucin (focal), an incomplete p63+ basal layer and thyroid colloid-like areas.

Also, Chiosea et al have reviewed 81 tumours originally diagnosed as acinic cell carcinoma, and reclassified most cases of zymogen granule poor, intercalated duct cell predominant tumours as MASC, based on the demonstration of the ETV6 translocation.

**Mucoepidermoid carcinoma.**

Mucoepidermoid carcinoma (MEC) is “a malignant glandular epithelial neoplasm characterized by mucous, intermediate and epidermoid cells, with columnar, clear cell and oncocytic feature”. It is the commonest primary salivary carcinoma worldwide, although not in Britain. There is a wide age distribution with a mean of 45 years, but it can be seen in children. There is a slight 3:2 female predominance. Approximately half (53%) of cases arise in major glands, mainly the parotid, and the most frequent intraoral sites are the palate and buccal mucosa. Occasionally, MEC arises in minor glands of the nose or larynx and within the body of the mandible. Tumours are usually 10-60 mm in size. Microscopically, the proportion of the different cell types and their architectural configuration (including cyst formation) vary between tumours and sometimes within any individual neoplasm. Mucous cells are cuboidal, columnar or goblet-like and form solid masses or line cysts, where they may be single or multi-layered. The mucin stains with PASD and mucicarmine, and these are particularly useful in cases where mucous cells are few. Mucus-filled cysts may rupture and elicit an inflammatory response. Epidermoid cells usually have intercellular bridges, but it should be noted that the term epidermoid does not indicate squamous differentiation, but simply a squamous-like appearance. Consequently, keratinisation is exceptionally rare in MEC and indeed, the presence of keratinisation should make one doubt a diagnosis of MEC, as it is much commoner as part of squamous metaplasia in pleomorphic adenoma or myoepithelial carcinoma, and in metastatic squamous carcinoma from the skin or upper aerodigestive tract. Squamous cells may be sparse in MECs, and high molecular weight cytokeratin stains (e.g. 34βE12, CK14, CK5/6) and p63 can help identify them. Intermediate cells are small with dark-staining nuclei and they often form the stratified lining of cysts beneath the mucous cells. Clear cytoplasm may be seen in either the squamous or intermediate cells, and MEC may take the form of a clear cell carcinoma; similarly oncocyes can be plentiful, and even bland spindle cells have been described. All mucoepidermoid carcinomas are malignant with metastatic potential, regardless of their microscopic appearance. Nevertheless, histological features can predict outcome to some degree, and a grading system has been developed based on the extent of the cystic component, necrosis, cytological pleomorphism, patterns of invasion (e.g. perineural) and mitotic activity. Histological grading is agreed to be prognostically useful, but there is no agreement on the best scheme. Special techniques of value include MIB1 index and expression
of different membrane-bound mucins: MUC4 is related to a much better prognosis than MUC1\textsuperscript{16}. Most cases of MEC (including three cases studied of the clear cell variant\textsuperscript{17}) harbour a recurrent t(11;19) (q21; p13) translocation resulting in a MECT1-MAML2 fusion. The median survival of fusion positive patients appears to be better than those without it, but its value remains uncertain\textsuperscript{18}.

**Adenoid cystic carcinoma.**

Adenoid cystic carcinoma (AdCC) is defined as “a basaloid tumour consisting of epithelial and myoepithelial cells in variable morphologic configurations, including tubular, cribriform and solid patterns. It has a relentless clinical course and usually a fatal outcome”\textsuperscript{19}. It arises in all age groups, although more often in older people. There is an equal sex incidence. It can arise in both major and minor salivary glands, particularly the palate and submandibular glands. Presentation is usually as a slow growing mass, and nerve paralysis is common. Microscopic examination shows an extensively infiltrative biphasic malignancy composed of epithelial and abluminal cells, the latter usually being much more abundant. Although the histological appearance is much more basaloid than myoepithelial, a proportion of the abluminal cells show ultrastructural and immunohistochemical evidence of myoepithelial differentiation. The most characteristic microscopic feature is the presence of densely cellular cribriform structures, which include true lumina lined by epithelial cells and pseudo-lumina containing hyaline or basophilic mucoid material. The nuclei are usually dark, hyperchromatic and angulated. Mitotic figures are easy to find and may be abundant; the MIB1 proliferation index exceeds 10%\textsuperscript{20}. On occasions, tumour cells may be sparse and bland, and thus the lesions may mimic a pleomorphic adenoma, as can the finding of basaloid cribriform foci, but myxochondroid matrix and plasmacytoid or spindle-shaped myoepithelial cells are usually present\textsuperscript{21}. Tumours can also be composed of small tubules lined with one or two cell types, luminal and abluminal without significant cytological atypia. Because of this bland cytological appearance it may be mistaken for basal cell adenoma, except for the presence of infiltration. Other tumours can be dominated by large solid sheets of tumour cells, sometimes with comedo-like central necrosis. Within the solid masses of tumour cells, there are small duct-like spaces surrounded by a definite layer of epithelial cells. This latter finding distinguishes solid variant AdCC from (relatively low-grade) basal cell adenocarcinoma and the aggressive basaloid squamous cell carcinoma, which in addition often shows intraepithelial dysplastic changes. A rare finding in all types of AdCC is squamous metaplasia, either as single cells or with keratin pearl formation\textsuperscript{12}. A system of three grades based on the presence of tubular, cribriform and solid pattern\textsuperscript{22} has shown that outcome is better in tubular ACC, while the worst prognosis is seen in solid AdCC. Nevertheless, clinical stage appears to be a better predictor than grade\textsuperscript{23}. Another unfavourable feature of AdCC is the frequent involvement of resection margins in the surgical specimen, particularly as the result of extensive perineural infiltration. Immunohistochemistry shows patchy non-specific positivity with αSMA, although conversely, S-100 protein is generally negative. Peripheral staining with p63 and cytoplasmic positivity for CD117 are helpful, but not specific\textsuperscript{24}. The best way to distinguish AdCC from polymorphous low grade adenocarcinoma is by identifying the much higher MIB1 proliferation index in the former\textsuperscript{20}. Recently, it has been shown that activation of the MYB gene, mainly as a result of the MYB-NFIB fusion is typical, but not quite specific to adenoid cystic carcinoma\textsuperscript{25}. However, in spite of often apparently slow growth, outcome over the long term is poor. The average 5 and 10 year survival rates are about 60% and 40% respectively, but most patients eventually die of or with their disease. AdCC is an extensively infiltrative tumour with characteristic perineural invasion, and this is partly responsible for the clinical presentation of late, but repeated local recurrences. Metastases occur in 40-60% of patients, but unlike other salivary gland malignancies, when AdCC metastasises, it tends to involve distant organs (lung, bone) rather than local lymph nodes\textsuperscript{26}. As complete excision of AdCC is difficult, patients often require postoperative radiotherapy.
Polymorphous Low Grade Adenocarcinoma.

Polymorphous low grade adenocarcinoma (PLGA), also known as terminal duct or lobular carcinoma, is defined as “a malignant epithelial tumour characterized by cytological uniformity, morphologic diversity, an infiltrative growth pattern and low metastatic potential”\textsuperscript{27}. It is the second commonest intra-oral salivary carcinoma. It is more frequent in women and has a wide age range (range 21–94 years), mean 59\textsuperscript{12}. Most arise in minor salivary glands, particularly the palate, with only rare examples in the parotid\textsuperscript{28}, sometimes developing in a pleomorphic adenoma\textsuperscript{29}. The characteristic histological picture of PLGA is an infiltrating tumour with cytological uniformity and morphological diversity\textsuperscript{27}. The architecture comprises a variety of patterns, including ducts, streams, and micropapillary, cribriform and solid structures. Diffuse infiltration of tumour cells with Indian filing and concentric growth around nerves is reminiscent of lobular carcinoma of the breast. Cytologically, there is a uniform population of small to medium sized cells, each of which having a single regular round, ovoid or fusiform bland nucleus, sometimes with intra-nuclear vacuoles\textsuperscript{30} and absent or small nucleoli. Variably present are oncocytic, clear or mucous cells. Mitotic figures are scanty, and never atypical. The stroma varies from fibromyxoid to densely hyaline, but the chondroid matrix of a pleomorphic adenoma is not seen. The most useful immunohistochemical markers are cytokeratins (broad spectrum, CK7) and S-100 protein. Positivity is also seen with EMA, vimentin, bcl-2 and sometimes with CEA, αSMA and GFAP; MIB1 proliferation is low – mean 2.4% (range 0.2–6.4) in one study\textsuperscript{20}. PLGA behaves as a low-grade malignancy; a literature review found a recurrence rate of 21%, regional nodal metastasis in 6.5%, distant metastasis in 1.8%, and death due to cancer in 0.9%\textsuperscript{31}. However, after 10 years late recurrences and metastases are perhaps more common than that\textsuperscript{32}, although in another study with a long follow-up, recurrence was in large part due to incompleteness of excision – only one of the 22 excised tumours recurred or caused death\textsuperscript{33}. In a larger series of 164 PLGA, more than 95% of the patients had no evidence of disease after a long-term follow-up\textsuperscript{34}. The recommended treatment of PLGA is wide, but conservative surgical excision, postoperative radiation and chemotherapy have little place. The most important histopathological differential diagnosis is from the much more aggressive adenoid cystic carcinoma. Although both are diffusely infiltrating (including perineural spread) carcinomas that display morphological diversity, at a cytological level the nuclei in AdCC are seen to be hyperchromatic, angulated, pleomorphic and densely packed with more frequent mitotic figures, in contrast to the nuclei in PLGA, which are uniform with finely speckled chromatin. In addition, staining with S-100 protein is usually more diffuse and stronger in PLGA than AdCC\textsuperscript{20,35}. Other markers such as c-kit (CD117) are of little use in practice, as staining can be seen in AdCC and most PLGAs\textsuperscript{36}. Much more reliable marker is the MIB1 proliferation index, which is almost always significantly lower in PLGA\textsuperscript{20,35}. Other differential diagnoses include pleomorphic adenoma, which in minor salivary glands can be poorly circumscribed. The presence of chondroid matrix and any circumscription favours PA, but it is sometimes not possible to distinguish these tumours, particularly on a small biopsy. Papillary structures form part of the spectrum of growth patterns seen in PLGA\textsuperscript{37}, but when extensive, there is evidence that these tumours have slightly more frequent nodal metastases\textsuperscript{32,38}, although the same long-term outlook. Genuine high-grade malignancy can occur rarely, as either a poorly differentiated version of the low grade carcinoma or as a salivary duct carcinoma\textsuperscript{39}.

Cribriform adenocarcinoma of the tongue and other minor salivary glands\textsuperscript{40}.

CATS has been accepted for publication with the unwieldy title of "cribriform adenocarcinoma of minor salivary gland origin principally affecting the tongue", but CATS is our favoured designation. This is a distinctive type of adenocarcinoma clinico-pathologically distinct from PLGA. Most cases arise in the tongue, but it can also occur at other minor glands such as in
the soft palate. Fifteen of the 23 patients had synchronous metastases in the cervical lymph nodes at the time of diagnosis. However, none has developed distant metastases or died of disease.

Histologically, the tumours are covered by intact squamous epithelium devoid of ulceration, although a degree of pseudoepitheliomatous hyperplasia is frequently seen. They infiltrate surrounding tissues and lymphovascular invasion is present in about one third of cases. The tumour architecture consists mainly of a generally solid mass, often divided by fibrous septa into irregularly shaped and sized nodules composed of solid, cribriform, glomeruloid and microcystic structures in variable proportions. The most prominent microscopic feature, however, is the appearance of the nuclei. These often overlap one another, and are pale, optically clear and vesicular with a ground glass appearance, giving a strong cytological resemblance to papillary thyroid carcinoma. Cellular atypia is mild and mitotic figures generally rare. The cervical lymph node metastases have an identical appearance to the primary tumours, and thus in those patients presenting with a neck mass, the initial diagnosis is generally metastatic papillary thyroid carcinoma. All tumours express broad-spectrum and low molecular weight cytokeratins, including CK7, as well as S-100 and vimentin. Basal and myoepithelial cell markers, such as p63, calponin, CK14, smooth muscle actin, and CK5/6 are positive with variable proportions of up to 60% of cells; in particular, the palisaded cells surrounding the glomeruloid structures are usually highlighted. Importantly, all tumours are completely devoid of any staining for TTF1 or thyroglobulin.

Epithelial-myoeipithelial carcinoma

Epithelial-myoeipithelial carcinoma (EMC) is defined by the WHO as “a malignant tumour composed of variable proportions of two cell types, which typically form duct-like structures. The biphasic morphology is represented by an inner layer of duct lining, epithelial-type cells and an outer layer of clear, myoepithelial-type cells”\(^{41}\). EMC is rare with a wide age range (8-103, mean 60 years) and a slight female predominance. It can occur in any salivary gland, but mainly the parotid. Analogous neoplasms have been described in the breast (adenomyoepithelioma) and elsewhere. EMC usually arises de novo, but occasionally develops in a pre-existing pleomorphic adenoma\(^{42}\). There are no known aetiological factors\(^{43}\). EMC usually presents as a slow-growing mass, and those arising in mucosal minor glands may ulcerate. The duration of symptoms before diagnosis has ranged from a few months to many years\(^{44}\). Rapid growth, pain or facial weakness are rare and suggestive of high grade areas. Imaging findings are non-specific. The usual macroscopic appearance of EMC is that of a multinodular mass, with expansive borders, but lacking a capsule. The size is usually 20-30 mm, but can be as large as 120 mm\(^2\). They are usually solid, but cystic change is seen in 30%. Often, tumours appearing grossly circumscribed are revealed by microscopy as invading surrounding structures, including nerves (34%) and vascular spaces (11%). EMC is composed throughout of lumina lined by an inner layer of epithelial cells, surrounded by an outer mantle of myoepithelial cells, beyond which is a PASD positive basement membrane of variable thickness. Cytological pleomorphism is generally mild at most. The biphasic pattern is reproduced throughout most of the tumour (and indeed, is retained in cell cultures\(^{45}\)), though each element may vary in prominence between cases as well as within any given lesion\(^{46}\). Myoepithelial cells with clear cytoplasm usually dominate the picture, often giving the tumour the appearance of a clear cell tumour, but on occasions the epithelial cells or a stroma of plentiful hyaline basement membrane material with relatively inconspicuous bi-layered ducts can be prominent. The epithelial cells are generally small and cuboidal to low columnar, and composed of scanty pale to eosinophilic cytoplasm and a round to oval nucleus. The myoepithelial cells typically are larger and polygonal in shape and have plentiful clear cytoplasm. Recently, a large series from the USA showed the morphological range is more extensive than previously documented: myoepithelial cells may be pale and amphophilic, oncocytic, spindled or plasmacytoid, and more than 20% of cases lacked clear cells altogether\(^{13}\). A proportion of the
epithelial cells can show sebaceous differentiation. Cytological pleomorphism is usually mild at most, but was classed as severe in 6.6% of cases; Schwannoma-like “ancient change” has also been described. Mitotic figures may be quite numerous. Although most tumours are minimally invasive, extensively infiltrating margins are seen in about 13%. Areas of necrosis are found in about 20% of cases. The stroma is usually scanty but on occasions, it consists of plentiful hyaline basement membrane material with relatively inconspicuous bi-layered ducts; the tumour can then be mistaken for a pleomorphic adenoma. Some lumina contain PAS positive secretions. Immunohistochemical studies have shown that the inner cells express low molecular weight cytokeratin and the outer α smooth muscle actin, SMMHC, calponin and p63. S100, CD10 and cytokeratin 14 are less specific and sometimes react with both layers. The surrounding stroma of PAS positive basement membrane material reacts with collagen type IV. Ki-67 proliferative activity is variable with a range 0 to 50 and a mean of 17%. The differential diagnosis depends on the predominant component, e.g. other clear cell tumours [Table 1]. Tumours with abundant stroma and inconspicuous bi-layered ducts resemble pleomorphic adenoma, but invasiveness indicates EMC. Areas resembling EMC can be seen in myoepithelial carcinoma (particularly the clear cell variant), and also in AdCC. Therefore, any tumour resembling an EMC must be sampled widely in order to identify areas of other more aggressive neoplasms. The behaviour of EMC in most series is low grade, typically with recurrences in 31%, cervical node metastases in 18%, distant metastases and death due to tumour in 7%. Higher rates of recurrence (50%) and death (40%) in a series from a large referral centre in Portugal probably reflect a patient population with advanced disease. Morphological features found to correlate with a poor prognosis include positive margin status, presence of angiolymphatic invasion, presence of necrosis and myoepithelial anaplasia. EMC can occasionally dedifferentiate as a high grade myoepithelial neoplasm or adenocarcinoma.

Table 1: Classification of Clear Cell Tumours of the Salivary Glands.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign</strong></td>
<td>Pleomorphic adenoma, myoepithelioma, sebaceous adenoma, oncocytoma and oncocytic hyperplasia (MNOH).</td>
</tr>
<tr>
<td><strong>Malignant, primary</strong></td>
<td>a) Carcinomas not usually characterized by clear cells, but with rare clear cell variants; e.g. mucocoeplidermoid and acinic cell carcinomas.</td>
</tr>
<tr>
<td></td>
<td>b) Carcinomas usually characterized by clear cells;</td>
</tr>
<tr>
<td></td>
<td>i. Dimorphic epithelial-myoepithelial carcinoma.</td>
</tr>
<tr>
<td></td>
<td>ii. Monomorphic hyalinizing clear cell carcinoma.</td>
</tr>
<tr>
<td></td>
<td>iii. Sebaceous carcinoma.</td>
</tr>
<tr>
<td><strong>Malignant, metastatic</strong></td>
<td>Carcinomas, especially kidney, thyroid. Also melanoma.</td>
</tr>
</tbody>
</table>

**Possible precursor lesions.**

Cases of EMC (and other tumours such as basal cell adenoma) have been associated with multiple nodules of intercalated duct adenomas and hyperplasia in the surrounding parotid gland. This suggests a ductal origin of EMC, and also why in hybrid carcinomas of the salivary glands, themselves very rare, the most frequent combination is that of EMC and AdCC.

**Clear cell carcinoma, NOS.**

Monomorphic clear cell carcinomas are either epithelial or myoepithelial (clear cell variant of myoepithelial carcinoma). The former is included in the 2005 WHO classification as clear cell carcinoma, not otherwise specified (NOS), a malignant epithelial neoplasm composed of a single
population of cells having optically clear cytoplasm on H&E. The diagnosis requires the exclusion of other salivary tumours with a clear cell component. The sex incidence is equal, and the age range wide. Most arise in minor salivary glands, mainly the palate, and less frequently elsewhere such as the parotid. Patients typically present with a long-standing painless mass, usually <30 mm in diameter. Exceptionally, cervical lymph node metastases are seen at initial presentation. Microscopy shows invasive nests, sheets and trabeculae of polygonal glycogen rich cells separated by dense collagen bands or thin fibrous septa, hence the alternative name, hyalinizing clear cell carcinoma. The nuclei display generally mild pleomorphism and inconspicuous nucleoli; mitotic figures are rare. In some cells, particularly in deeper parts of the tumours, the cytoplasm appears weakly eosinophilic rather than clear. Occasional tumours demonstrate squamous or ductal differentiation, with rare intracellular mucin droplets. Otherwise, mucin stains are negative. Clear cell carcinomas express epithelial markers, including cytokeratin 7 (but not 20), and EMA, as well as p63, but other myoepithelial markers (e.g. S-100 protein, actin) are consistently negative. Ultrastructural studies have demonstrated epithelial but not myoepithelial features. Recently, it has been shown that most cases harbour a rearrangement of the EWSRA1 gene. Clear cell carcinoma, NOS is one of several salivary tumours composed of clear cells. [Table 1]. In addition to primary salivary neoplasms composed of clear cells, the differential diagnosis also includes metastases, principally from renal cell carcinoma, which can present as a parotid mass. It has a prominent vascular background and usually some nuclear atypia. It usually expresses broad spectrum cytokeratins, vimentin and CD10, but not CK7 or CEA. Imaging of the kidneys also identifies any primary with metastatic potential. Other metastases sometimes composed of clear cells include melanoma, positive with S-100 protein, HMB45 and other markers. The treatment of clear cell carcinoma is surgical excision. The prognosis of this low-grade malignancy is generally good; a few patients have developed metastases in the neck nodes and rarely the lungs, but no deaths have been reported.

**Basal cell adenocarcinoma.**
Definition: “dominated by basaloid epithelial cells, basal cell adenocarcinoma is cytologically and histomorphologically similar to basal cell adenoma but is an infiltrative neoplasm with potential for metastasis.” This rare tumour arises in adults with no sex predilection, and over 90% of cases arise in the parotid glands. Microscopically it has the architecture of basal cell adenoma, but displays infiltrative growth. Four architectural patterns are recognized: solid (composed of variably sized nests), tubular (contains luminal spaces), trabecular and membranous. In all patterns, there is a mixture of small basal-type and large pale cells; nuclei are often palisaded at the periphery of tumour islands; focal squamous eddies are seen in some tumours. Nuclear pleomorphism and mitotic figures are usually minimal. Hyalinized eosinophilic basal lamina material is present in variable amounts, but is abundant in the membranous subtype, together with hyaline intercellular droplets. The most important differential diagnosis is the solid variant of adenoid cystic carcinoma, which as described above shows nuclear pleomorphism and mitotic activity. Also, it is much commoner in the submandibular and minor glands, in contrast to the usual parotid location of basal cell adenocarcinoma. Basal cell adenocarcinoma is a low grade malignancy with local recurrences in 37%, nodal and distant metastases in 8% and 4% respectively.

**Salivary duct carcinoma and variants.**
Salivary duct carcinoma (SDC) was defined in the 2005 WHO Classification as “an aggressive adenocarcinoma which resembles high-grade breast ductal carcinoma.” Previously thought to be extremely rare, it is now recognised as not infrequent, and in Exeter accounts for about 2% of all salivary tumours. Most patients are over 50 years old and there is an at least 4:1 male to female ratio. It arises mainly in the parotid, though cases have been described in the submandibular gland and occasionally in the minor glands. Most cases arise de novo, although
some develop as the malignant component of carcinoma ex pleomorphic adenoma, and a single case has been reported arising in (or in association with) a polymorphous low grade adenocarcinoma of the palate. All histological studies on SDC have noted the strong morphological resemblance to in situ and invasive ductal carcinoma of the breast. The former component comprises expanded salivary ducts with solid, papillary, “Roman bridge”, cribriform and comedo patterns and the infiltrating tumour can include small ducts, cribriform structures, small nests of cells and trabeculae, all accompanied by stromal desmoplasia. Perineural and lympho-vascular invasion are frequent as well. SDC is composed mainly of cells with eosinophilic cytoplasm and often vesicular nuclei containing prominent central nucleoli. Frequently, there is marked nuclear pleomorphism, also apparent on FNA cytology. Mitotic and MIB1 indices are usually high. In addition to the usual type of salivary duct carcinoma, a few rare morphological variants have been reported: micropapillary, sarcomatoid, mucin-rich and oncocytic, as well as pure in situ cases. In the micropapillary variant, clusters of cells without fibrovascular cores are each surrounded by a clear space, and there is an “inside-out” pattern of EMA staining. The mucin-rich variant includes areas of typical SDC and mucin lakes containing malignant cells. The sarcomatoid type is a composite of usual salivary duct and spindle cell sarcomatoid carcinomas. It may account for some tumours previously classified as carcinosarcoma (“true malignant mixed tumour”). A few oncocytic cells can be seen in any SDC, but a genuine oncocytic variant has only been described in outline, in which most cells in a neoplasm with morphological and immunohistochemical features of SDC show evidence of oncocytic differentiation. Although pure in situ salivary duct carcinoma was not recognized as an entity by the 2005 WHO classification, occasional cases have been described, characterized by an intraductal proliferation of malignant cells, similar to ductal carcinoma in situ of the breast. The diagnosis requires strict criteria, particularly the absence of local invasion, determined by adequate sampling of the whole tumour and the presence of an intact myoepithelial layer around all tumour islands, ideally confirmed by immunohistochemistry. SDC is mainly an H&E diagnosis and immunohistochemical stains such as androgen receptors (AR) are at present mainly confirmatory.

Molecular classification. Ductal carcinoma of the breast can be classified into three main molecular subtypes (with some additional subgroups) - luminal, HER2+ and basal, by using a surrogate immunohistochemical panel of a hormone receptor, HER2 and basal/myoepithelial markers. The luminal subtype is characterised by positivity for hormone receptors, particularly oestrogen receptor (specifically, the α isoform - ERα) and sometimes androgen receptor, the HER-2 type by a combination of immunohistochemistry and FISH for the HER-2/neu protein or amplified gene and the basal type by markers such as high molecular weight cytokeratins.

Given the morphological similarity to mammary ductal carcinoma, a recent study speculated that SDC could also be classified into similar molecular subtypes. Whereas expression of ERα in SDC is exceptional, several studies have demonstrated androgen receptor (AR) staining in a high proportion of invasive SDCs. Two recent large series identified that 83% and 67% of cases were AR positive, and in addition, the second of these series showed that 73% of SDCs expressed oestrogen receptor β isoform (ERβ), a receptor in which androgens participate in its regulation. Consequently, it is not unreasonable to postulate that AR expression in SDC is analogous to ERα reactivity in breast carcinoma, and can be used as a marker of the luminal phenotype.

HER-2 protein overexpression has been reported in SDC for some years, but only in 2003 was this more accurately quantified in an immunohistochemical study of several different HER2 protein antisera together with FISH gene analysis. This showed that protein overexpression is usually, but not always (even when 3+) associated with gene amplification. Although one possible
CK5/6 positive SDC had been reported in the German literature, two of the 42 SDCs in our series satisfied the criteria for basal phenotype.

Extrapolating from these data, it is suggested that invasive and in situ SDCs can be classified into three main groups; these are luminal androgen receptor positive, HER2+ and basal phenotype, based on positive nuclear staining of AR, HER2 protein overexpression (and/or gene amplification) and positive cytoplasmic staining for basal markers such as cytokeratins types 5/6, 14, 17, and epidermal growth factor receptor (EGFR). In our study the relative percentages for each subtype were 69% luminal, 17% HER2, 5% basal and 10% indeterminate. There was no correlation between nuclear grade and subtype, except that both basal subtype SDCs were high grade.

Outcome and treatment.

Overall, SDC is one of the most aggressive salivary malignancies. At present, death occurs in 60-80% of patients, usually within 5 years; about 33% develop local recurrence and 50% distant metastases, at sites including lungs, bone, liver, brain and skin. The outcome for pure SDCIS should be good, provided it is completely excised. The standard treatment at present is complete surgical excision with radical neck dissection followed by radiotherapy to the tumour bed and possibly chemotherapy.

The prognostic impact of the proposed molecular classification of SDCs is yet to be fully determined, but the subdivision of SDCs into distinct molecular subtypes could possibly help refine the therapeutic approaches for patients with these cancers. Linking their findings to outcome, Williams et al found that SDCs negative for both AR and ERβ were more aggressive than tumours which expressed one or both of these markers. The same study also found that carcinomas which were HER2 protein 3+ had a worse outcome than those which were HER2 protein 0-2+.73

Given that luminal androgen receptor positive SDCs by definition consistently express AR, anti-androgens may constitute an interesting therapeutic strategy for this subgroup of patients, and preliminary studies on limited numbers of patients have shown a positive result in some.74 In addition, given the lines of evidence to demonstrate that HER2 is an effective therapeutic target for patients with HER2 amplified breast cancers and the fairly promising results with Trastuzumab for some individuals with advanced SDCs, patients with HER2 subtype SDCs may benefit from targeted therapies with anti-HER2 monoclonal antibodies (Trastuzumab, Pertuzumab) or HER2 tyrosine kinase inhibitors (Lapatinib).75 Further studies are warranted to determine whether basal-like SDCs, in a way akin to basal-like breast cancers, are sensitive to platinum salts and inhibitors of the poly(ADP) ribose polymerase (PARP).

Oncocytic carcinoma.

Only a few dozen cases of oncocytic carcinoma have been reported, mostly in the parotid glands of patients with an average age of 63 years (range 29-91) and male predominance. A few cases have arisen in Warthin’s tumours. The diagnosis requires evidence of oncocytic differentiation (by PTAH, immunohistochemistry or electron microscopy) and demonstration of malignant behaviour. The literature is limited, but the consensus is that oncocytic carcinoma is an aggressive tumour with over half of reported patients either dying of disease or suffering recurrences. My own view is that it is probably not a single entity but a mixture of several carcinomas showing oncocytic differentiation, most often salivary duct carcinoma.

Mucinous adenocarcinoma.

Mucinous (colloid) adenocarcinoma arises most often in the major glands of adults. It is composed of round and irregularly shaped clusters of epithelial cells floating in mucus-filled cysts, themselves separated by fibrous strands. The cells are cuboidal, columnar or irregular in shape.
usually possessing clear cytoplasm and small dark nuclei; signet ring cells may be present. Mitotic figures are sparse. The mucus is PASD and mucicarmine positive. The carcinoma cells express epithelial markers, but not high MW cytokeratins or actin. The differential diagnosis includes mucoid adenocarcinoma, in which there are also squamous-like and intermediate cells. Mucin-rich salivary duct carcinoma includes areas of the usual type of SDC, and usually expresses GCDPF15 and Androgen receptors. Mucinous cystadenocarcinoma arises more often from the minor glands and can be separated from colloid carcinoma. The mucin pools are more often lined by carcinoma cells, which have larger nuclei than in colloid carcinoma. It is unclear whether low grade signet ring cell (mucin-producing) adenocarcinomas of minor salivary gland are related, as they lack mucous pools. From the relatively few published cases, mucinous adenocarcinoma has a relatively favourable clinical behaviour.

**Low-grade cribriform cystadenocarcinoma (low grade salivary duct carcinoma).**

Low-grade cribriform cystadenocarcinoma is defined as “a rare, cystic, proliferative carcinoma that resembles the spectrum of breast lesions from atypical ductal hyperplasia to micropapillary and cribriform low-grade ductal carcinoma in situ”. It was previously named “low-grade salivary duct carcinoma”. The average age of patients is 64 years (range 32-93), with an equal sex incidence. All but one case arose in the parotid glands, the other in the submandibular. Microscopically, it is unencapsulated and generally displaces rather than truly invades salivary tissue. It is formed of multiple cysts and solid structures of varying sizes, which are composed of small, bland ductal cells with regular nuclei and clear to eosinophilic cytoplasm. They proliferate to form papillae or cribriform structures, but no necrosis or comedocarcinoma are seen. Mitotic figures are sparse. Occasional cells contain lipofuscin pigment. At the periphery of the tumour islands, there is often a population of flattened myoepithelial cells. The stroma is partly sclerotic with occasional microcalcifications. Moderate amounts of extracellular mucus are found, but goblet cells only rarely. The predominant cells express cytokeratins 7, 8, 18, 19, EMA and S-100 protein, and the peripheral cells react with myoepithelial markers. Cytokeratin 14 shows strong staining at the periphery, but also in some inner cells. The MIB1 proliferation index is usually <1%. No significant staining is seen with CEA, GCDFP-15 or HER2/neu, and variable results have been found with androgen receptors. Occasional tumours have demonstrated foci of stromal invasion, and three neoplasms have shown transition from low to intermediate or high-grade cytology, with scattered mitotic figures and focal necrosis. The main differential diagnosis is salivary duct carcinoma of usual type, particularly pure in situ lesions. They display nuclear atypia and the same immunoprofile as their invasive counterparts, i.e. negative S-100, expression of AR, GCDFP-15. Intraductal proliferation is common to both tumours, but it is not clear whether they represent two different entities or different ends of the cytological spectrum of a single entity. Among other differential diagnoses, the papillary cystic variant of acinic cell carcinoma includes at least some cells with PASD positive granules and is usually S-100 negative. Other variants of cystadenocarcinoma lack the resemblance to atypical ductal hyperplasia or carcinoma-in-situ of the breast. Generally, low grade cribriform cystadenocarcinoma follows a non-aggressive clinical course; all but one patient were recurrence-free after 6-144 months (median 32 months). One recent case transformed to a higher grade neoplasm and developed cervical nodal metastases. Thus, conservative resection of the involved gland, without neck dissection or adjuvant radiotherapy is adequate treatment, unless there is histological evidence of high grade disease.

**Other forms of Cystadenocarcinoma.**

The WHO fascicle defines cystadenocarcinoma as “a rare malignant tumour characterized by predominantly cystic growth that often exhibits intraluminal papillary growth. It lacks any additional specific histopathological features that characterize the other types of salivary carcinomas showing cystic growth. It is conceptually the malignant counterpart of benign cystadenoma”. However, it is not universally accepted as a specific entity. Microscopically,
there are numerous cysts of different sizes, some of which contain mucin, separated by fibrous connective tissue. The cell types include small and large, cuboidal and columnar, but mucous, clear and oncocytic cells are rare. The nuclei are typically bland and mitotic figures few. Cystadenocarcinoma is a low grade malignancy, and no deaths have been reported, although a few patients have developed regional nodal metastases.

**Myoepithelial carcinoma (malignant myoepithelioma).**

Myoepithelial carcinoma is defined as “a neoplasm composed almost exclusively of tumour cells with myoepithelial differentiation, characterized by infiltrative growth and potential for metastasis. The tumour represents the malignant counterpart of benign myoepithelioma”85. The average age of patients is 55 years (range 14-86), with an equal sex incidence. They arise at any site (mostly the parotid), sometimes de novo, but at least 50% develop in pre-existing pleomorphic adenomas or benign myoepitheliomas86. Myoepithelial carcinomas often form multiple cellular nodules containing plentiful myxoid or hyaline material, and central necrosis. Small cysts and cleft-like spaces are frequent, and some authors allow a few small true lumina. The cells can be monomorphic or a mixture of epithelioid (the most frequent), clear, vacuolated (resembling lipoblasts), hyaline (plasmacytoid), spindle to stellate, or occasionally oncocytic. The nuclei vary from small and bland to large and pleomorphic. Mitotic figures may be plentiful, including atypical forms. Metaplastic changes are frequent, most often squamous with keratinization24. All cases stain to some degree with S-100, vimentin and broad-spectrum cytokeratins. Myoepithelial markers such as CK14, αSMA, SMMHC, calponin and p63 are positive in most, but by no means all cases. The mean MIB1 index is high, with any count above 10% said to be diagnostic of malignancy in a myoepithelial neoplasm87. It has recently been shown that myoepithelial carcinomas secrete compounds with anti-invasive properties, and although as yet poorly understood, they could affect the biological aggressiveness of any particular tumour88. The variable appearance leads to a wide differential diagnosis, including other salivary carcinomas. The spindle cell type mimics soft tissue sarcomas and the plasmacytoid cell type must be distinguished from melanoma. The clear cell variant resembles the many other salivary tumours composed of clear cells88,89 [Table 1]. Extensive squamous differentiation suggests mucopidermoid or metastatic squamous carcinoma. The prognosis of myoepithelial carcinoma is variable, but approximately one third of patients die of disease, another third have residual tumour or recurrences (often multiple) and the remaining third are disease free24,86,87. There is only a weak statistical correlation for outcome with cytological atypia (high grade), but other parameters (tumour size, site, cell type, mitotic rate, presence of a benign tumour, necrosis, perineural and vascular invasion) are not helpful. Tumours arising in ordinary pleomorphic adenomas behave the same as de novo carcinomas86, but those developing in recurrent pleomorphic adenomas may pursue a prolonged course90.

**Malignancy in a pleomorphic adenoma.**

Malignancy in pleomorphic adenoma encompasses three entities: carcinoma ex pleomorphic adenoma, carcinosarcoma and metastasizing pleomorphic adenoma. The latter two are exceedingly rare. Published figures for incidence vary considerably from series to series: those quoted in the 2005 WHO fascicle are 3.6% of all salivary gland tumours (range 0.9-14%) and 12% of malignancies (range 2.8-42.4%). Malignancy develops in 6.2% of all pleomorphic adenomas (range 1.9-23.3%), and the incidence increases with the length of history, but can still be short91.

a. Carcinoma In Pleomorphic Adenoma.

This is defined as “pleomorphic adenoma from which an epithelial malignancy is derived”91. The malignancy in carcinoma ex pleomorphic adenoma is restricted to the epithelial or myoepithelial component, and metastases are composed solely of carcinoma. CaXPA occurs over a
wide age range, with the majority of cases in the 6th-8th decades, approximately 10 years later than uncomplicated pleomorphic adenoma; most series report a slight female predominance. Any gland can be involved, though the parotid is most common. The tumour typically presents with a long history (usually >3 years) of a nodule that suddenly increases in size. The main histological requirement for the diagnosis is the presence of a benign pleomorphic adenoma and a carcinoma. The former is often largely hyalinized and/or calcified, and may require extensive sampling to detect it, but sometimes the origin can only be inferred from the history. Most types of carcinoma have been described, the commonest being poorly differentiated adenocarcinoma and undifferentiated carcinoma. There is evidence that many of the former are salivary duct carcinoma and the latter myoepithelial. The most important feature to assess is whether the carcinoma has breached the capsule; it is thus classified as non-invasive, minimally invasive (<1.5 mm penetration beyond the capsule) or invasive (>1.5 mm). Non-invasive carcinoma (the terminology preferred to “intracapsular carcinoma” and “carcinoma in situ”) is defined as “pleomorphic adenoma with multifocal areas containing carcinoma”. Despite its malignant microscopic appearance, it generally behaves indolently, with only one report of a patient developing lymph node metastases. In invasive carcinomas, the extent is important: one study found that no patient whose tumour penetrated <6 mm beyond the capsule died of disease, whereas all patients with invasion of >8 mm succumbed. Immunohistochemical and molecular studies of HER-2/neu proto-oncogene have shown protein overexpression and gene amplification in all high grade invasive carcinoma ex pleomorphic adenoma. Similar findings have been demonstrated in the malignant component of non-invasive carcinomas (protein overexpression in 55%, gene amplification in 37%). In these studies, benign areas of the original tumour were constantly negative. Thus, staining for HER-2/neu can be used to detect early carcinoma in a pleomorphic adenoma. The main practical difficulties with carcinoma ex pleomorphic adenoma are:

a) Its rarity, which makes it an unfamiliar feature for most pathologists.
b) If the capsule of the pleomorphic adenoma is ill-defined, assessment of the extent of invasion becomes less reliable.
c) Sampling of the capsule must be extensive to ensure identification of maximum invasion.
d) It can be difficult to separate non invasive carcinoma from a pleomorphic adenoma with atypical histological features. Focal nuclear atypia in oncocytic and myoepithelial cells is seen occasionally and is probably not of clinical significance. Necrosis, squamous metaplasia and epithelial atypia may follow FNA of a benign tumour, as perhaps can focal vascular permeation. Immunohistochemical staining for MIB1 and HER-2/neu can differentiate true malignant cells from bizarre nuclear changes in benign cells.
e) The differential diagnosis includes a wide range of other salivary carcinomas, and the main problem results from the under-recognition of the pre-existent pleomorphic adenoma.

The treatment is radical surgery and neck dissection, perhaps with radiotherapy. The prognosis for widely invasive carcinoma ex pleomorphic adenoma is poor, with a 5-year survival of approximately 50%. Regional and distant metastases are frequent.

b. Carcinosarcoma in a Pleomorphic Adenoma (True Malignant Mixed Tumour).

Carcinosarcoma is an exceedingly rare malignant tumour composed of a mixture of carcinomatous and sarcomatous elements, with either component capable of metastasis. The mean age at presentation is 58 (range 14-87), and most cases are found in the parotid gland. It may arise in a pre-existing pleomorphic adenoma, or de novo. Microscopy shows a biphasic tumour in which the epithelial component is generally a poorly differentiated adenocarcinoma. The mesenchymal element is usually chondrosarcoma, but osteosarcoma and other differentiation have been described. Epithelial markers are detected in the epithelial component and sometimes the mesenchymal; both elements have similar p53 and genetic profiles. In a subset with osteoclast-type giant cells, the same mutation was found of the same allele on chromosome 17p13, a known
mutation of salivary duct carcinoma\textsuperscript{96}. This suggests that carcinosarcomas are metaplastic carcinomas, possibly sarcomatoid salivary duct carcinomas. The differential diagnosis includes spindle cell squamous carcinoma, primary salivary sarcomas and carcinoma ex pleomorphic adenoma. The first arises from the mucosal surface and may simulate carcinosarcoma of minor salivary glands. Its epithelial component is epidermoid, not glandular; dysplasia of the surface squamous epithelium is diagnostic. Primary salivary sarcomas are exceptionally rare and must be well sampled to identify any minor carcinomatous component. The outcome of carcinosarcoma is usually poor with 60\% of patients dying of disease.

\textit{c. Metastasizing Pleomorphic Adenoma.}

Metastasizing pleomorphic adenoma is defined as “a histologically benign pleomorphic adenoma that inexplicably manifests local or distant metastasis”\textsuperscript{97}. Common factors in most reported cases were long time intervals (up to 50 years) between the primary and metastases, and simultaneous occurrence of distant metastases and local recurrences, usually multiple. This suggests that surgical manipulation of recurrences could cause vascular implantation, but in many cases that later metastasized, it was not possible histologically to demonstrate actual vascular permeation. The microscopic picture is that of the usual mixture of mesenchyme, epithelial and myoepithelial cells of any pleomorphic adenoma, and there are no predictive histological features. Metastases can be found in bone, lung, lymph nodes and rarely other sites such as kidney. They are generally indolent tumours, and patients may survive for extended periods with metastatic disease. Recommended therapy is wide local excision for both primary and metastases.

\textbf{Undifferentiated carcinoma.}

Undifferentiated carcinomas of the salivary glands are uncommon malignant epithelial neoplasms that are too poorly differentiated by their light microscopic features to be placed into a specific category. They are generally subclassified into three groups: lymphoepithelial, small cell and large cell carcinomas. Almost all small cell and some large cell carcinomas exhibit neuroendocrine differentiation\textsuperscript{98}.

\textbf{a) Lymphoepithelial carcinoma.}

Lymphoepithelial carcinoma is exceptionally rare, except for a high incidence among Eskimos and Chinese, in whom it is consistently linked with EBV infection\textsuperscript{99}. There is no clinical association with Sjögren’s syndrome. It is histologically almost identical to analogous nasopharyngeal neoplasms, and syncytial nests of carcinoma cells infiltrate the surrounding salivary tissue accompanied by lymphoid stroma. The cells are anaplastic, large and polygonal or sometimes spindled with a vesicular nucleus and prominent eosinophilic nucleoli. In non-Caucasian patients, EBV-encoded small RNA (EBER) is generally detected in the tumour cells by in situ hybridization. The 5-year survival rate is 75-86\%, even though nodal and distant metastases are common\textsuperscript{99}.

\textbf{b) Small cell carcinoma.}

Small cell carcinoma of the salivary glands is a very rare malignant epithelial tumour characterized by proliferation of small anaplastic cells with scanty cytoplasm, fine nuclear chromatin, and inconspicuous nucleoli\textsuperscript{98}. Most are positive for cytokeratin, sometimes showing a paranuclear dot-like pattern, and also react with neuroendocrine markers. All are negative for S-100, HMB-45, myoepithelial and lymphoid markers. In addition, about three-quarters of cases express cytokeratin 20, and on this basis, salivary small cell carcinoma may be subdivided into Merkel cell and pulmonary varieties. The 2 and 5 year survival rates are 38-70\% and 13-46\%
respectively, although patients with the Merkel cell subtype (i.e. CK20+) have a better prognosis than CK20- cases.

c) **Large cell carcinoma.**
Large cell carcinoma is exceptionally rare and composed of invasive sheets of large pleomorphic cells (>30 μm in diameter), with abundant eosinophilic or clear cytoplasm. They usually express cytokeratins (not CK20) and EMA, but never lymphoid, melanoma or myoepithelial markers. About one in five exhibits neuroendocrine differentiation - i.e. large-cell neuroendocrine carcinoma^{100}. It is aggressive with frequent local recurrences, nodal and distant metastases. The 2 year survival rate is 36%^{100}.

**Sialoblastoma.**
Most sialoblastomas are identified in the perinatal period or first year of life^{12}. The male to female ratio is 2:1; three-quarters of tumours arise in the parotid glands, the remainder in the submandibular. Tumours are well circumscribed, up to 150 mm in diameter and composed of numerous solid hypercellular islands of primitive basaloid cells, some with peripheral palisading, and often with small central ducts, bud-like structures and solid organoid nests. The tumour cells have large round to oval vesicular nuclei and variable amounts of eosinophilic cytoplasm. Immunohistochemistry and electron microscopy show both epithelial and myoepithelial cells^{12,101}. There is diffuse expression of S-100 protein and vimentin, with cytokeratin highlighting any ducts. Mitotic figures may be numerous (especially in recurrences), but none is atypical. The intervening stroma appears loose and immature. Criteria for malignancy include invasion of nerves or vascular spaces, necrosis and marked cytological atypia. Of fifteen reported cases, four recurred and another metastases to regional lymph nodes. One death has been recorded, but most cases are cured by excision^{101}.

**Miscellaneous Other Carcinomas**^{24,48}
Sebaceous carcinoma and lymphadenocarcinoma are both very rare and high grade. Primary squamous cell carcinoma must be distinguished from metastases, which are far commoner.
References.


LYMPHOID LESIONS OF SALIVARY GLANDS.

INTRODUCTION.
Salivary gland lymphoid infiltrates include a variety of benign conditions, especially autoimmune disease, important because of its association with extranodal malignant lymphoma. Salivary disease is simulated clinically by inflammatory processes and neoplasms of lymph nodes within or adjacent to the major glands, particularly nodal type lymphomas¹.

NON-AUTOIMMUNE LYMPHOID INFLTRATES.

Chronic sclerosing sialadenitis (Küttner tumour) occurs in the submandibular gland. Its exact aetiology is unknown, but up to 80% are associated with sialoliths in the excretory ducts, although it is uncertain whether these are the cause of the disease or a secondary process. Some patients also have a similar sclerosing pancreatitis, an IgG4-related disease. The histopathological picture of chronic sclerosing sialadenitis varies from just scattered lymphoplasmacytic aggregates to severe changes of acinar atrophy and heavy chronic inflammation with germinal centre formation to an end stage of destruction of the lobular architecture and scarring. The inflammation is centred on the acini rather than ducts, although minor intraductal aggregates of neutrophils are often present. IgG4-positive plasma cells and sometimes eosinophils are numerous in the non-sialolith cases, both in the systemic and localized forms². Only exceptionally are lymphoepithelial lesions (LELs) found.

Infectious diseases (e.g. mumps, CMV) are rarely biopsied; an exception is AIDS-related cystic lymphoid hyperplasia probably due to direct HIV infection. The cysts are lined by squamous epithelium accompanied by lymphoid tissue showing follicular hyperplasia, but with lysis of germinal centres and loss of mantle zone lymphocytes. LELs may be present³, and a few cases appear identical to autoimmune sialadenitis, but with negative serology. Other inflammatory infiltrates include granulomatous diseases such as sarcoidosis and tuberculosis. Kimura’s disease, seen predominantly in Oriental patients, frequently affects the salivary glands. Microscopy shows acinar atrophy and fibrosis, often surrounding ducts, and a heavy lymphoid infiltrate with formation of irregularly shaped follicles, together with numerous eosinophils often forming abscesses, typically within germinal centres. There is also a proliferation of high endothelial venules with slit-like lumina lined by non-vacuolated cuboidal or atrophic endothelial cells containing pale oval nuclei. Recurrences sometimes occur after excision⁴.

Chronic inflammation may accompany any tumour (e.g. acinic cell carcinoma), due to secondary obstruction, infection, or a host reaction. In particular, lymphoepithelial carcinoma (often EBV-related) closely resembles its better known counterpart in the nasopharynx, comprising syncytial aggregates of cytokeratin-positive large cells intimately associated with a dense infiltrate of lymphocytes and plasma cells.

BENIGN AUTOIMMUNE LYMPHOID INFLTRATES.
The preferred term for the histopathological condition is lymphoepithelial sialadenitis (LESA)⁵, which has replaced the older synonyms, myoepithelial sialadenitis, benign lymphoepithelial lesion and Mikulicz disease.

Sjögren’s syndrome (SS) is a clinical term describing the combination of dry eyes and mouth due to autoimmune infiltrates of the lacrimal and salivary glands. It is often associated with other autoimmune or connective tissue diseases, particularly rheumatoid arthritis but also others. Most patients with SS develop LESA, but not so the reverse, as up to 50% of patients with LESA do not display the clinical features of SS.

The aetiology of LESA is probably autoimmune, but the pathogenetic process is not understood. Nevertheless, it is likely that an interaction of genetic, environmental, viral (HCV in some patients) and immunological factors determines its onset and progress.
About 80% of patients with LESA are female, with a mean age at presentation of 55 years (range 1 to 86). The parotids are affected in over 80% of cases (20% bilaterally), the submandibular and minor glands alone in 11% and 6% respectively, although they are involved more often in conjunction with parotid disease. Tumour-like lesions of the lips, palate and floor of mouth are relatively rare, but sub-clinical foci of lymphocytes and plasma cells are frequently seen in the labial glands in SS, and a semi-quantitative assessment of a lip biopsy may have a place in the investigation of a patient with a dry mouth.

Microscopic examination of the earlier stages of LESA shows that the salivary ducts are dilated and surrounded by an increasing lymphoid infiltrate with germinal centres. Unlike in non-autoimmune chronic inflammatory conditions, B-cells focally infiltrate the duct epithelium itself. In many examples of LESA, some of the B-cells are characteristic, and are known as marginal zone or monocytoid B-cells, or centrocyte-like (CCL) cells. These cells tend to be cytologically uniform in any given lesion, and may take one of three forms: 1. small mature cells similar to, but slightly larger than mantle zone lymphocytes; 2. cells containing irregularly shaped nuclei often with clefts; 3. cells with more abundant pale cytoplasm. These cells are seen immediately beneath the epithelium where they merge into the mantle zones of the germinal centres. Plasma cells are also concentrated around the ducts; they and the B-cells are usually polytypic for light chains. T-cells, often numerous, are seen throughout the infiltrate, particularly around germinal centres. In time, the ducts condense, with partial or complete loss of their lumina, to form lympho-epithelial lesions (LELs), previously known as epimyoepithelial islands. These consist of cohesive aggregates of epithelium with hyalinized basal lamina material containing variable numbers of B-cells, but myoepithelial cells are relatively inconspicuous. As the disease progresses the acini become atrophied and then totally replaced by lymphoid tissue leading to clinical enlargement of the salivary glands. Monoclonality by PCR can be demonstrated in over 40% of patients with LESA, but this alone is probably insufficient for a diagnosis of lymphoma, and stronger evidence is required from the demonstration of monoclonality by immunohistochemistry or flow cytometry.

MALIGANT LYMPHOMA.

Lymphomas represented 16.3% of all malignant tumours of the major salivary glands at the AFIP from 1985-95. Most occur in women, usually over the age of 50. They are either nodal or extranodal: the former involve intraparotid lymph nodes and are the same as those found in other nodes. Most arising in the salivary parenchyma are extranodal marginal zone lymphomas (EMZLs), also known as mucosa-associated lymphoid tissue (MALT) lymphomas.

Extranodal marginal zone lymphoma (MALT lymphoma).

EMZLs usually present clinically as parotid enlargement, sometimes bilateral. There is often a history of SS, but not always. In one series, 46% of patients had this association, and a further 29% had positive HCV serology. Cases have been reported in other autoimmune diseases and in post-transplant patients. In contrast to nodal lymphoma, in a series of 33 salivary EMZLs, only 12% had bone marrow infiltration at presentation, 21% regional node involvement and 6% widespread lymphadenopathy; one case had lymphoma in the stomach.

Grossly, the gland in EMZL is firm, with a homogenous white or beige cut surface. The lobular structure may be retained, or there may be a multiple nodules separated by normal tissue. In 3% of cases, the ducts are dilated giving a multicystic appearance.

The microscopic picture evolves with time; the earliest morphologically recognizable feature of at least borderline malignancy is proliferation of CCL cells to form a distinct halo around the LELs of LESA; monoclonality can be demonstrated at this stage. Admixed with the CCL cells are plasma cells (sometimes very numerous) and transformed blast cells, and surrounding these zones in turn is a heavy lymphoid infiltrate with prominent reactive follicles. As the lymphoma evolves in a background of LESA, a decreasing proportion of the total mass is reactive. The CCL cell halos expand and coalesce to form extensive sheets, destroying the LELs. They displace then replace the follicles, or they may colonize the germinal centres replacing the normal
cells with a uniform infiltrate of CCL cells, so that areas may assume a follicular-like architecture\textsuperscript{13}. In addition, there may be foci of sclerosis, and infiltration by epithelioid histiocytes, which can form granulomas. Small numbers of large transformed blast cells may be seen in low grade EMZL, but when they comprise diffuse areas, the tumour is considered to be high grade\textsuperscript{7}. This occurred as a late event in 12\% in one series\textsuperscript{11}. The CCL cells may involve local lymph nodes, first by expanding the area between follicles and in due course by replacing large parts of the affected node by sheets of lymphoma cells, giving an appearance identical to monocytoid B-cell lymphoma.

The CCL cells express B-cell markers, e.g. CD20, CD79a, and there is surface immunoglobulin with light chain restriction; bcl-2 staining is usual. They do not react with CD5, CD10 (with very rare exceptions), CD23 or bcl-1 (cyclin D1). Cytokeratin highlights the LELs; reactive histiocytes and T-cells express their appropriate markers\textsuperscript{14}. Several cytogenetic abnormalities are found in EMZLs, with differences between primary sites. In the salivary gland, 74\% of cases show one or more genetic aberrations, most frequently trisomy 3 (in 55\%), trisomy 18 (in 19\%) and the t(14;18) (q32;q21) translocation in 12\%\textsuperscript{15}. The last of these juxtaposes the \textit{MALT1} gene next to the promoter region of the immunoglobulin heavy chain genes with subsequent \textit{MALT1} overexpression.

The risk of EMZL evolving in LESA is estimated at 4-7\%\textsuperscript{5}, and the two conditions are intimately linked. It would appear that a sustained B-cell inflammatory response directed against a relatively narrow range of antigens facilitates the selection of a single clone of neoplastic B-lymphocytes\textsuperscript{1} and then, with the acquisition of secondary genetic changes, to EMZL. Histological criteria alone cannot identify exactly when a clonal B-cell population emerges in LESA, and in practice the process is not so much a sharp change from one (benign) entity to another (malignant) one, but rather as a spectrum of lymphoma gradually evolving from a purely inflammatory process\textsuperscript{7,10}. \textbf{[Table 1]}. Cytogenetic investigation shows an increased frequency of abnormalities in high grade EMZLs compared to low grade neoplasms and in LESA, but there are no clear cut distinctions to be of diagnostic use.

Low grade EMZLs restricted to the salivary glands are relatively indolent, usually remain localized, and are often curable with local treatment\textsuperscript{9}. In one series, 10\% of patients died of disease, but only after histological transformation to high grade B-cell lymphoma\textsuperscript{11}.

\textbf{Lymphomas other than extranodal marginal zone lymphoma.}

Primary non-MALT extranodal salivary lymphomas are very rare. Most are T-cell neoplasms, including CD30+ large cell tumours, CD56+ NK/T-cell lymphomas and a lesion resembling enteropathy associated lymphoma. Histologically, neoplastic T-cells can infiltrate epithelium mimicking LELs\textsuperscript{16}.

Primary and disseminated nodal Hodgkin’s and non-Hodgkin’s lymphomas can involve the intra-salivary and adjacent lymph nodes, and should be classified using the appropriate scheme, e.g. WHO\textsuperscript{17}. Few diagnostic difficulties arise with a nodal lymphoma confined to the nodes, but if a follicular lymphoma invades into the gland itself, it must be distinguished from apparently similar structures in EMZL, i.e. reactive follicles (an integral component of the disease process), or pseudofollicles (germinal centres colonized by tumour cells)\textsuperscript{13,19}. This distinction is important as EMZL and nodal lymphomas behave differently. The differential diagnosis is usually obvious from the morphology. The presence of residual LELs containing aggregates of CCL cells points strongly to EMZL. Immunohistochemistry may help: cytokeratins highlight LELs. CD10 stains some mainly low grade follicle centre cell lymphomas, whereas EMZLs are almost always negative\textsuperscript{18}. 

35
SELECTED REFERENCES.

<table>
<thead>
<tr>
<th>Table 1. Overview of autoimmune and neoplastic salivary lymphoid proliferations.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign</strong></td>
</tr>
<tr>
<td>LESA, non-clonal.</td>
</tr>
<tr>
<td><strong>Borderline</strong> (histological or clonal evidence of neoplasia, but unlikely to disseminate).</td>
</tr>
<tr>
<td>LESA, clonal.</td>
</tr>
<tr>
<td>LESA with halos of CCL/monocytoid B-cells.</td>
</tr>
<tr>
<td><strong>Low grade lymphoma</strong> (potential for spread to nodes and less often, systemically).</td>
</tr>
<tr>
<td>Low grade EMZL (confluent proliferation of CCL/monocytoid B-cells).</td>
</tr>
<tr>
<td>Low grade EMZL with plasmacytic differentiation.</td>
</tr>
<tr>
<td><strong>Intermediate/high grade lymphoma</strong> (arises de novo or in low grade lymphoma)</td>
</tr>
<tr>
<td>High grade EMZL, with diffuse areas of large B-cells.</td>
</tr>
</tbody>
</table>

Adapted from Quintana et al⁷.
HIGH GRADE SINONASAL MALIGNANCIES AND NASOPHARYNGEAL CARCINOMA.
Roderick HW Simpson.

Introduction
Malignant tumours of the nasal cavity and paranasal sinuses are relatively rare, accounting for about 3% of all malignancies of the head and neck region, although there are considerable geographical differences. A great variety of primary tumours are of high histological grade: squamous cell carcinoma (including variants), adenocarcinoma (intestinal and non-intestinal types), some salivary carcinomas (arising from minor seromucous glands), sinonasal undifferentiated carcinoma (SNUC), NUT rearrangement carcinoma, lymphoepithelial carcinoma (nasopharyngeal type), neuroendocrine carcinoma, malignant melanoma, olfactory neuroblastoma, teratocarcinosarcoma, PNET- Ewing’s sarcoma, high grade sarcoma (including embryonal rhabdomyosarcoma) and high grade malignant lymphoma. Of these, the most problematic for histopathological diagnosis are the poorly differentiated ones 1,2,3.

Sinonasal Squamous Carcinoma.
Keratinising squamous carcinoma is the same as elsewhere in the upper aero-digestive tract. Non-keratinising squamous carcinoma (Cylindric cell carcinoma) is often an exophytic mass. It arises from maxillary antrum, ethmoid and the lateral nasal wall.
Microscopically, it comprises papillary fronds and invaginations, comprising thick ribbons of multilayered epithelium. It often displays expansile invasion with “pushing” edges.
The cells are often cylindrical in shape with basal palisading. Some are mixed with keratinising squamous carcinoma. About 50% are p16+3a.

Sinonasal Adenocarcinoma.
Adenocarcinoma of the nose can be considered as: Salivary or non-salivary; the non-salivary are intestinal or non-intestinal; all can be either low or high grade3b.
Intestinal adenocarcinoma (ITAC) has an equal sex incidence and a mean age at diagnosis of 58 (range 12-86). The most frequent sites of origin are: ethmoid 40%, nasal cavity 27% and maxilla 20%. Patients usually present with unilateral nasal obstruction, epistaxis or rhinorrhoea; 10% have lymph node metastases at presentation.
There is a strong aetiologial association with exposure to wood or leather dust.
Microscopically, it resemble adenocarcinomas of the large intestine, with a variable amount of mucin production. Two sub-classifications have been proposed:

Table 1:

<table>
<thead>
<tr>
<th>Barnes</th>
<th>Kleinsasser &amp; Schroeder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary</td>
<td>PTCC-I (papillary tubular cylinder cell).</td>
</tr>
<tr>
<td>Colonic</td>
<td>PTCC-II</td>
</tr>
<tr>
<td>Solid</td>
<td>PTCC-III</td>
</tr>
<tr>
<td>Mucinous</td>
<td>Alveolar-goblet</td>
</tr>
<tr>
<td>Signet-ring cell</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>Transitional</td>
</tr>
</tbody>
</table>
Immunohistochemistry shows positivity with panCK, EMA and Ber EP4. Most react with CK20 (73%), CK7 (43-93%), CDX-2 (usually, but can be focal) and CEA (variable). There are often scattered cells or groups that react with Synaptophysin and Chromogranin A. ITAC tends to be locally aggressive, but nodal and distant metastases are seen in up to 20%. Clinical staging is not so helpful. Prognosis depends to some degree on morphology.

Table 2:

<table>
<thead>
<tr>
<th>Barnes</th>
<th>Kleinsasser / Schroed</th>
<th>3 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary</td>
<td>PTCC-I</td>
<td>82%</td>
</tr>
<tr>
<td>Colonic</td>
<td>PTCC-II</td>
<td>54%</td>
</tr>
<tr>
<td>Solid</td>
<td>PTCC-III</td>
<td>36%</td>
</tr>
<tr>
<td>Mucinous</td>
<td>Alveolar-goblet</td>
<td>48%</td>
</tr>
<tr>
<td>Signet-ring cell</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Mixed</td>
<td>Transitional</td>
<td>71%</td>
</tr>
</tbody>
</table>

The main differential diagnosis of low grade adenocarcinoma include hamartomas and papillomas. Sinonasal Undifferentiated Carcinoma (SNUC).

Sinonasal undifferentiated carcinoma (SNUC) is defined as “a highly aggressive and clinicopathologically distinctive carcinoma of uncertain histogenesis that typically presents with locally extensive disease. It is composed of pleomorphic tumour cells with frequent necrosis, and should be differentiated from lymphoepithelial carcinoma and olfactory neuroblastoma”. It is found equally in both sexes with a wide age range. It typically presents as a widely invasive malignancy in the nasal cavity and/or maxillary antrum and ethmoid sinus, often with invasion of the orbit and anterior cranial fossa. Microscopy shows lobules, sheets, nests and trabeculae of cells with medium to large nuclei and scanty cytoplasm, and there is no evidence of glandular or squamous differentiation. The mitotic rate is high and tumour necrosis often prominent. SNUC expresses broad spectrum cytokeratins and EMA, but apart from NSE on occasions, neuroendocrine markers are negative. The prognosis is poor, with a median survival of <18 months.

NUT Rearrangement Carcinoma.

A recently recognised entity is the NUT rearrangement carcinoma, defined by the rearrangement of the NUT (nuclear protein in testis) gene on chromosome 15q14. Previously thought to occur in children, cases have now been recognised in a wide age range (3-78 years). Although examples have been described in the salivary glands, most are found in the midline of the upper aerodigestive tract. Microscopy shows sheets of undifferentiated malignant cells resembling SNUC, but with occasional well differentiated squamous islands; p63 staining is seen beyond these islands, suggesting a squamous lineage. Areas of necrosis are frequent and the mitotic rate is high. Published cases are few, but the behaviour is probably aggressive.

Neuroendocrine Carcinoma.

All neuroendocrine neoplasms, including carcinoids are rare in the sinonasal tract. High grade neuroendocrine carcinoma resembles analogous neoplasms of the lung and larynx. The cells vary from small to intermediate and occasionally are large; there is often nuclear moulding. Necrosis is prominent, and the “Azzopardi smear effect” can be present. The tumours express cytokeratins (but not CK20), EMA and neuroendocrine markers such as synaptophysin, CD56 and chromogranin A. Most patients die of disease with widespread metastases.
**Malignant Melanoma.**

The mucosal surfaces of the sinonasal region account for about 1% of all malignant melanomas, and melanoma accounts for 2.4% of all nasal malignancies. The sex incidence is equal and the mean age is 64 (range 13-93). Melanomas may be found in black patients. Presenting symptoms include epistaxis, mass and/or obstruction. In decreasing order of frequency, the sites are the nasal cavity (especially the anterior nasal cavity and middle or lower turbinates), maxillary antrum, ethmoid sinuses and the sphenoid sinus. They rarely, if ever, involve the nasopharynx or olfactory mucosa higher in the nasal cavity. The typical macroscopic appearance is that of a polyp, often grossly necrotic or haemorrhagic. Sinonasal melanoma can exhibit a wide variety of histological appearances. It can be composed of small round cells mimicking lymphoma or small cell carcinoma, large cells similar to large cell carcinoma (epithelioid), or rhabdoid cells resembling rhabdomyosarcoma or rhabdoid tumour, or sarcoma-like spindle cells. It can particularly resemble olfactory neuroblastoma (even with poorly formed rosettes), and the differentiation is partly based on the exact location of the tumour. Melanin pigment may or may not be present. Junctional involvement of the surface epithelium is seen in only about a third of cases. Vascular and perineural infiltration are frequent. Immunohistochemistry shows positivity for S-100 protein and HMB45, although spindle cell melanomas may sometimes be negative. There may also be spurious staining with cytokeratins. Newer markers such as Mel A, D5 (microphthalmia-associated transcription factor) and especially tyrosinase (T311) are some value, but S100 remains the best. Mucosal melanomas are aggressive neoplasms. Chemo- or radiotherapy are of little value, and median survival is 18 months. Nevertheless, some patients have long disease free intervals or no further recurrence or metastasis. Poor prognosis has been related to advanced age, size (>30 mm), inaccessibility and delay in diagnosis, but other factors including depth of invasion have not convincingly been correlated with prognosis. Staging systems for other sinonasal tumours do not work for melanoma, and a separate scheme has been proposed (Table 22-1).

**Table 3: Proposed staging for sinonasal and nasopharyngeal malignant melanoma.**

<table>
<thead>
<tr>
<th>Primary Tumour</th>
<th>T1</th>
<th>Single anatomical site</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>Two or more sites.</td>
<td></td>
</tr>
<tr>
<td>Regional Lymph Node</td>
<td>N1</td>
<td>Any lymph node metastasis</td>
</tr>
<tr>
<td>Distant Metastasis</td>
<td>M1</td>
<td>Distant metastasis.</td>
</tr>
<tr>
<td>STAGE GROUPING</td>
<td>Stage I</td>
<td>T1, N0, M0.</td>
</tr>
<tr>
<td></td>
<td>Stage II</td>
<td>T2, N0, M0.</td>
</tr>
<tr>
<td></td>
<td>Stage III</td>
<td>T1 or 2, N0 or 1, M1.</td>
</tr>
</tbody>
</table>

**Olfactory Neuroblastoma.**

Olfactory neuroblastoma is defined as “a malignant neuroectodermal tumour thought to originate from the olfactory membrane of the sinonasal tract.” Patients range in age from 2-90 years, with two peaks in 2nd and 6th decades. The usual site is the upper nasal cavity in the region of the cribiform plate. Typically the tumours are localised to the submucosa, growing in circumscribed lobules or nests separated by a richly vascularised fibrous stroma. The neoplastic cells have uniform small round to oval nuclei with scant cytoplasm, dispersed chromatin and inconspicuous nucleoli. Nuclear pleomorphism, mitotic activity and necrosis are usually seen only in high grade tumours. The cells do not have distinct borders, and they are surrounded by variable amounts of a neurofibrillary matrix. Homer-Wright or Flexner-Wintersteiner rosettes are relatively uncommon. The nests and islands are surrounded by thin spindle-shaped sustentacular cells, which can be hard to identify in high grade neoplasms. The majority of cells express synaptophysin and chromogranin A, with S-100 reacting just with the surrounding sustentacular cells. About 10% of
cases show a few cells staining for cytokeratin. EMA and CD99 are negative. The Hyams’ grading system recognises four grades, based principally on architecture (mainly degree of lobularity), cytological pleomorphism, neurofibrillary matrix, rosette formation, necrosis and mitotic activity. It is prognostically useful – tumour necrosis is particularly important. Other factors said to be prognostically important include the proliferation index. The prognosis olfactory neuroblastoma largely depends on clinical stage, in particular the local extent. Therefore, tumours confined to the nasal cavity have a 75-91% five year survival, whereas the comparable figures for those extending beyond the nose and sinuses is 41-47%. Overall, local recurrence will be seen in about 30% of patients, cervical lymph node metastases in 10-25% and distant metastases in 16-46%.

Sinonasal Teratocarcinosarcoma.

This extremely uncommon tumour is defined as “a complex malignant sinonasal neoplasm combining features of teratoma and carcinosarcoma. Benign and malignant epithelial, mesenchymal and neural elements are typically present, including immature tissue with blastomatous features, while embryonal carcinoma, choriocarcinoma or seminoma are absent”\textsuperscript{15}. Reported patients are adults (range 18-79 years, mean 60), with a male predominance. It arises in the ethmoid sinus and maxillary antrum. Histopathological examination shows multiple tissues derived from two or three germ layers, exhibiting variable degrees of maturity. In addition, there are intermingled carcinoma and sarcoma components. The epithelial tissues include squamous (keratising and non-keratinising) and glandular structures lined by cuboidal or ciliated columnar cells. Mucous and clear cells may be present. Neuroepithelial elements are neuroblastoma-like areas often with rosettes. The mesenchymal tissue includes immature cartilage and sarcoma-like areas (e.g. spindle cell sarcomaNOS, rhabdomyosarcoma). There is a variable immune-reaction, reacting with the different tissues present. The prognosis is poor, with an average survival of 2 years\textsuperscript{15}. Because of the variable appearances, the correct diagnosis may require thorough sampling of the specimen, as different areas can resemble a variety of tumour types\textsuperscript{2}.3.13.14.

Ewing’s sarcoma(EWS)/Primitive neuroectodermal tumour (PNET).

Ewing’s sarcoma/PNET is defined as “a high grade, primitive, round cell tumour of neuroectodermal phenotype......”\textsuperscript{13}. Ewing’s sarcoma and PNET, originally regarded as separate, are now considered to represent a group of small round cell neoplasms with variable degrees of neuroectodermal differentiation, and part of the same histopathological spectrum. They arise mostly in children and young adults with a peak in the third decade. Approximately 20% of all EWS/PNETs arise in the head and neck region, and 20% of those in the sinonasal tract, especially the maxillary sinus. The tumour is composed of lobules and sheets of closely packed, uniform, small to medium sized round cells with a high nuclear-cytoplasmic ratio. Mitotic figures are numerous, and areas of necrosis frequent. The cells react with CD99, vimentin, and occasionally with low molecular weight cytokeratin. More than 90% of cases harbour the translocation t(11;22)(q24;q12) (EWS-FLI1), and Fli-1 (one portion of the gene fusion product) can be detected with immunohistochemistry. EWS/PNET has a better prognosis in the head and neck region than in other anatomical sites. Gene fusion positive tumours also have a better outcome. The overall 10 year survival of paediatric patients treated with multimodality therapy is 60-70%\textsuperscript{13,16}.

Embryonal Rhabdomyosarcoma.

This is the most common sarcoma of childhood, and the nasopharynx is more frequently involved than the sinonasal tract. Some tumours are polypoid (sarcoma botryoides). Most patients are under 5 years of age. Microscopy shows primitive mesenchymal cells, varying from round to spindle shaped with hyperchromatic nuclei. Cross-striation are usually difficult to identify. Larger ganglion-like rhabdomyoblasts are seen on occasion. The spindle cells are often arranged in fascicular to storiform patterns, and can be deceptively bland, particularly if plentiful myxoid
stroma is present. Sub-epithelial hypercellularity (“cambian layer”) is a helpful clue. Mitotic figures are plentiful, and areas of necrosis are usual. The cells express desmin, muscle specific actin, myoglobin, MyoD1 and other specific muscle markers. Prognosis depends on several factors, for example, younger patients have a more favourable prognosis than older ones.16,17

**Nasopharyngeal Carcinoma.**

Nasopharyngeal carcinoma is defined by the WHO as a carcinoma arising in the nasopharynx. It encompasses squamous cell carcinoma, non-keratinising carcinoma (differentiated or undifferentiated) and basaloid squamous cell carcinoma. Adenocarcinoma and salivary gland-type carcinoma are excluded.18 There is no mucin production or evidence of glandular differentiation. Electron microscopy shows squamous characteristics such as tonofilaments and desmosomes. These carcinomas are divided into three subtypes: keratinising squamous, non-keratinizing squamous and undifferentiated. The last is commonly referred to as nasopharyngeal (or lymphoepithelial) carcinoma (NPC). Although NPC is rare in Western white patients of northern European origin, it is much more common in southern Chinese, as well as to a lesser extent elsewhere such as Africa, the Mediterranean region and amongst Eskimos. In China it accounts for 18% of all cancers, and until recently in Hong Kong 1 in 40 men developed NPC before the age of 75. A steady decline in incidence has been noticed in Hong Kong over the past quarter century.18 It becomes much rarer in second and third generation Chinese people living in the West. It is twice as common in men as women. The aetiology is partly genetic (perhaps related to HLA-A2), but NPC is intimately associated with Epstein-Barr virus (EBV). In China, NPC occurs most commonly in patients between 30 and 70 years old, but elsewhere it is often seen in younger patients. NPC can also present as a metastasis in a neck lymph node, and the diagnosis must always be born in mind, particularly in a patient from a high risk population group. The primary may cause hearing loss or otitis media due to involvement of the Eustachian tube. Most NPCs are located in the lateral walls of the nasopharynx, particularly the fossa of Rosenmüller.20 Identical carcinomas can arise in the sinonasal on rare occasions and most cases have been reported from Southeast Asia. Like its much commoner nasopharyngeal tumour, nearly all cases have shown a strong association with Epstein-Barr virus. Histologically, the usual type of NPC has an unusual, striking and potentially confusing morphology that has prompted several classification schemes over the years. Light microscopic evidence of squamous differentiation is totally or almost completely absent. The cells are arranged in a syncytial pattern with indistinct cell borders. Nuclei are large and vesicular, and nucleoli are prominent. The tumour cells may be arranged in nests or distributed individually among the reactive lymphoid cells. Some cells may be more spindle-shaped. Crush artefacts are common and may cause diagnostic problems in practice. The inflammatory cell response may include large numbers of eosinophils, as well as epithelioid cell granulomas. Amyloid globules are seen in about 10% of cases.21 Immunohistochemically, NPCs stain strongly with broad spectrum cytokeratin stains such as AE1/AE3 and most are positive with CK5/6, CK8, CK13 and CK19, but most are negative with CK7 and CK14. Among other markers, EMA is positive, but S-100, CD45, HMB45 and synaptophysin are negative. HER2 is negative and the C-KIT protein (CD117) is found in >50% of patients.23 EBV positivity can also be demonstrated in the nuclei, using EBER (EBV encoded early RNA) in situ hybridization. NPC is particularly radiosensitive, and consequently the outcome is often surprisingly good for such an aggressive-looking neoplasm, and survival rates at 3 and 5 years are 70% and 59%. As may be expected, patients with disease limited to the nasopharynx do better than those in whom it is more advanced.
References


Midline destructive lesions of the nose.

Fungal Infection.

Sinonasal fungal disease can be divided into four groups\(^1,2,3\):

a). Non-invasive colonization of paranasal sinuses (“fungus ball”).

b). Non-invasive hypersensitivity reaction to fungi (allergic fungal sinusitis).

c). Invasive indolent sinusitis.

d). Invasive fulminant fungal rhinosinusitis.

Patients with non-invasive colonization typically have chronic sinusitis, and only a few will suffer facial pain or sense of fullness. Imaging often shows a single opacified sinus. Almost all cases are due to Aspergillus sp. Treatment is debridement, and there is no role for antifungal drugs.

Allergic fungal sinusitis is a non-invasive fungal pansinusitis that occurs in immunocompetent individuals with a history of atopy and peripheral eosinophilia. Although Aspergillus can cause this in a similar way to bronchopulmonary aspergillosis, most sinonasal cases are due to other fungi. Microscopy shows abundant laminated mucin containing cell debris and inflammatory cells, particularly eosinophils with Charcot-Leyden crystals. Fungal hyphae are present, but there is no invasion of bone or mucosa.

Chronic invasive fungal sinusitis (invasive indolent sinusitis) patients are usually immunocompetent and have a protracted clinical course.

Invasive fulminant fungal rhinosinusitis is a medical emergency. Patients are usually immunocompromised secondary to poorly controlled diabetes mellitus, post-transplantation, HIV infection, malignancy and/or chemotherapy or corticosteroid therapy. There are typically thrombosed blood vessels due to the tendency of the fungi to invade blood vessel walls, tissue necrosis and acute inflammation, although in some cases there is little inflammatory reaction. Many fungi can be involved, but the most frequent are Aspergillus species, and non-hyphal organisms such as cryptococcus may occur. Mucormycosis (phycomycosis) is usually seen in poorly controlled diabetics, although it can occur in non-immunocompromised hosts. The most often involved sinus is the maxillary antrum, followed by the ethmoid, sphenoid and frontal paranasal sinuses. Fulminant infection may spread to the cranial cavity by direct extension, vascular emboli, perineural invasion or through the cribriform plate. The mortality rate for this form is 25% and is higher if there is a predisposing systemic disease, such as diabetes. Treatment should be aggressive with surgical debridement and systemic antifungal drugs.

Other infections.

**Rhinoporidiosis.**

This disease is endemic in India, but also found elsewhere including South America, Africa and rural parts of the USA. It is associated with stagnant pools of water, dust and trauma, and there is animal to human transmission. It is characterised by hyperplastic polyps in the nasal cavity with a chronic lymphoplasmacytic infiltrate. Microscopically, there are numerous globular cysts up to 200 μm in diameter, each containing multiple spores. The organism is not a typical fungus, and is now thought to be a blue-green alga.

**Rhinoscleroma.**

This disease is endemic to Africa, parts of Latin America, Egypt, north and central Africa and east/central Europe (particularly Ukraine and Belarus). It is associated with crowded dwelling and poor sanitary conditions, and the cause is Klebsiella rhinoscleromatis, a Gram negative cocccobacillus. The disease starts in the nasal septum, later involving the nasopharynx. It may cause nasal obstruction in up to 94% of cases, nasal deformity, upper lip swelling or ulceration of
the palate. Histologically, there are three stages (exudative, proliferative and fibrotic). In the exudative phase, there is a dense lymphoplasmacytic infiltrate, together with oedema, suppurative necrosis and squamous metaplasia of the overlying epithelium. In the proliferative phase, there are numerous foamy macrophages containing bacilli (Mikulicz’s cells). In the fibrotic phase, there is scarring and chronic inflammation, but Mikulicz’s cells are rare to absent. The organisms are best demonstrated by Giemsa or Warthin-Starry stains, and cultures have only a 50% yield. A diminished T-cell response explains the chronicity, and cases have been reported in AIDS. Treatment is surgical ablation and antibiotics, such as Tetracycline or rifampicin.

**Wegener’s granulomatosis.**

Wegener’s granulomatosis is a chronic systemic disease of unknown aetiology. It is characterized by a granulomatous vasculitis of the upper and lower respiratory tracts together with glomerulonephritis. In addition, variable degrees of disseminated vasculitis involving small arteries and veins may occur. The mean age of onset is about 40 years and the sex incidence is roughly equal. ENT involvement occurs in 92% of patients during the course of their disease, and other sites affected include the kidneys (77%), lungs (85%), skin (46%) and joints (67%).

Involvement of the ENT areas includes sinusitis, nasal disease (obstruction and rhinorhoea and eventually cartilage and bone destruction), otitis media, hearing loss, and less frequently subglottic stenosis, ear pain or oral lesions. The most important clinical test is cANCA (anti-neutrophil cytoplasmic antibody), but this is not specific or sensitive enough to identify every case.

Histologically, Wegener’s granulomatosis shows a variety of changes mainly in two patterns: these are destructive necrosis with inflammation and fibrinoid change, and acute necrotizing vasculitis involving all types of vessels, later evolving to scarring. The inflammation is partly granulomatous with necrosis, and there is often an acute and chronic inflammatory infiltrate including giant cells and eosinophils. None of these changes is really specific, and the diagnosis is made taking into account the clinical features, as well as the serology and histopathological findings. An important practical point is that any sinonasal biopsy must be deep enough, as the overlying crust will just show necrosis, granulation tissue and non-specific acute on chronic inflammation.

The mean survival without treatment is only 5 months. The recommended therapy is cyclophosphamide and steroids, and 75% of patients will achieve complete remission.

**NK/T-cell Lymphoma.**

Previously known by a variety of names, such as lethal midline granuloma/reticulosis and angiocentric lymphoma, the present terminology is NK/T-cell lymphoma. It is most common in Asia, Africa and Latin America, but cases do occur in Europeans, as here. By definition, all cases are associated with EBV infection.

It is commoner in men with a wide age range at presentation (13-80). Approximately 50-60% of patients have localised disease at presentation, although this may include bone and nasal septum destruction. 25% have involvement of lymph nodes, bone marrow or other sites.

There is a broad morphological spectrum of lymphoid cells, admixed with plasma cells, histiocytes, eosinophils and neutrophils. The atypical cells vary in number and size, and often show invasion or clustering around blood vessels. Necrosis is usual and may be extensive, and several biopsies may be needed to identify the neoplastic cells. The cells are usually positive for CD56, but less frequently with CD57, CD16. They are also positive with CD2, CD45RO, CD3 (CD3ε) and CD43.

The differential diagnosis includes destructive lesions of the nasal septum such as infections (especially fungi), Wegener’s disease, cocaine abuse and other lymphomas.

Patients with localised disease often respond well to radiotherapy or chemotherapy.
References.


