# Selected recent advances in the pathology of salivary neoplasms

Roderick H W Simpson

Silvana Di Palma

## Abstract

This review concentrates on significant developments in salivary pathology since the 2005 WHO classification was written.

- Sclerosing polycystic adenosis is a rare lesion often mistaken histologically for carcinoma. Previously thought to be a reactive fibro-inflammatory process, recent evidence of clonality suggests it may be neoplastic.
- Histological grading of mucoepidermoid carcinoma has been shown to have clinical relevance, but it is not clear yet which is the best method. Also, other prognostic indices, particularly MIB1 proliferation may be useful in practice.
- Epithelial–myoepithelial carcinoma has been known as mainly a clear cell tumour, but it has now been recognized to have a much wider spectrum of histological appearances.
- Various morphological variants of salivary duct carcinoma have been described, and a possibly clinically significant molecular classification has been proposed.
- The relationship between low-grade cribriform cystadenocarcinoma and salivary duct carcinoma remains unclear.

**Keywords** epithelial–myoepithelial carcinoma; grading; low-grade cribriform cystadenocarcinoma; molecular classification; mucoepidermoid carcinoma; salivary duct carcinoma; salivary neoplasms; sclerosing polycystic adenosis

## Introduction and classification

The 2005 revised WHO classification is an excellent summary of the current state of knowledge of salivary neoplasms, updating previous classifications.[1] Compared to previous editions, it includes several new entities: clear cell carcinoma NOS, sialoblastoma and low-grade cribriform cystadenocarcinoma (low-grade salivary duct carcinoma). Cribriform adenocarcinoma of the tongue is included as a variant of polymorphous low-grade adenocarcinoma. The classification also subdivides what was previously known as undifferentiated carcinoma into the entities of small cell, large cell and lymphoepithelial carcinoma.[1]

Space does not allow this review to cover all salivary pathology, so it will concentrate on significant developments that have happened since 2005. The topics to be covered are the nature of sclerosing polycystic adenosis, prognostic indices for mucoepidermoid carcinoma, the spectrum of epithelial–myoepithelial carcinoma, molecular classification of salivary duct carcinoma and further knowledge on the relationship between low-grade cribriform cystadenocarcinoma and salivary duct carcinoma.

### Sclerosing polycystic adenosis

Sclerosing polycystic adenosis (SPA) was first described in 1996 as a tumour-like lesion of the salivary glands reminiscent of fibrocystic change in the breast.[2] It affects females twice as often as men, with an age range of 9–75 years. Most of the approximately 50 reported cases have been described as slow-growing masses in the parotid gland, with rare examples of submandibular and minor gland involvement.[3,4] Microscopically, SPA is a well-circumscribed, partly encapsulated mass composed of a lobular arrangement of proliferating ducts and acini with cysts containing viscous secretion and, on occasions, aggregates of foamy macrophages (Figure 1). A particular feature is that some acinar cells contain prominent large, intensely eosinophilic PAS-positive cytoplasmic granules, representing aberrant zymogen granules (Figure 2). Flattened myoepithelial cells surround ducts and acini, and there is periductal sclerosis with hyaline areas of the stroma. Ductal hyperplasia is frequent with varying degrees of cytological atypia (Figure 3a), at times amounting to low-grade ductal carcinoma in situ, thus resembling proliferative lesions of the breast.[3] Although generally believed to represent a pseudoneoplastic sclerosing and inflammatory process, a recent study found evidence of clonality, thus suggesting that SPA could in fact be a neoplasm.[5]

The differential diagnosis of SPA includes polycystic dysgenetic disease, chronic sclerosing sialadenitis and low-grade malignancy, particularly acinic cell and mucoepidermoid carcinomas. Helpful features to distinguish SPA from carcinoma are the maintenance of the lobular architecture and the lack of destructive growth.

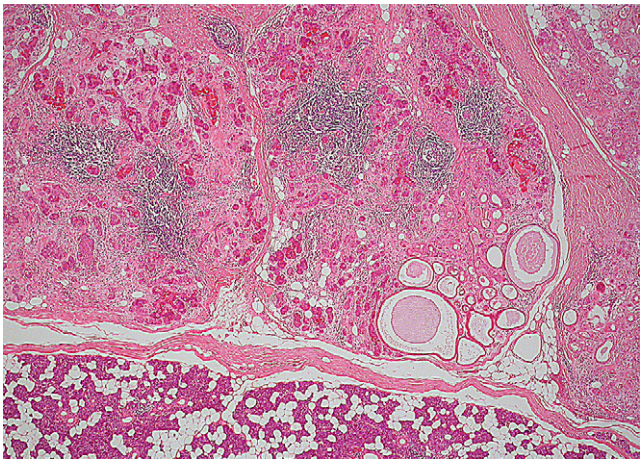

**Figure 1** SPA is a well-circumscribed proliferation of cysts, ducts and acini in a fibro-inflammatory stroma.

***Roderick H W Simpson*** *FRCPath is a Consultant at the Department of Histopathology, Royal Devon and Exeter Hospital, Exeter, UK. Conflicts of interest: none declared.*

***Silvana Di Palma*** *FRCPath is a Consultant at the Department of Histopathology, Royal Surrey County Hospital and a Lecturer in Histopathology at the Postgraduate Medical School, University of Surrey, Guildford, UK. Conflicts of interest: none declared.*

 

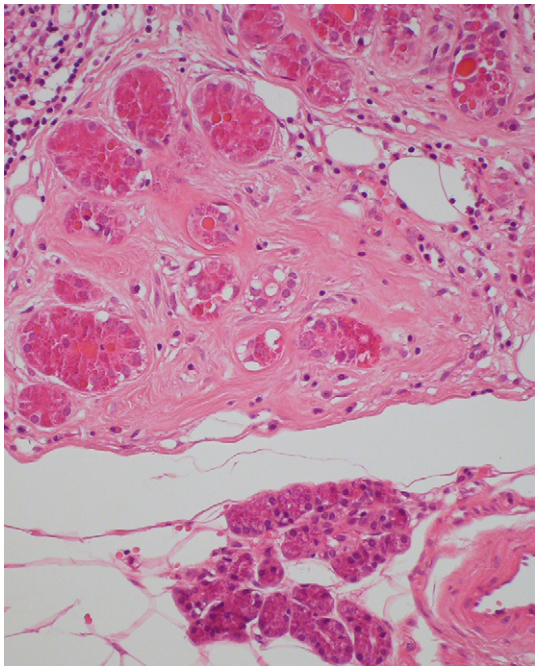

**Figure 2** SPA: large cytoplasmic granules in acinar cells, with normal acini for comparison.

About one third of cases recur, but no patient has as yet developed metastases or died of disease.

### Mucoepidermoid carcinoma

Mucoepidermoid carcinoma (MEC) is an epithelial malignancy characterized by mucous, intermediate and (non-keratinising/squamous-like) epidermoid cells, with additional clear and oncocytic populations. The proportions of the different cell types and their architectural configuration (including cyst formation) vary between tumours and within any individual neoplasm. It is the commonest primary salivary malignancy worldwide,[6] but not in Britain,[7] can occur at any age (range 3–95 years, mean 46 years) with a slight female predominance.[6] About 53% of cases have been reported from the major glands, but MEC is also frequent in the palate and other minor glands.[6]

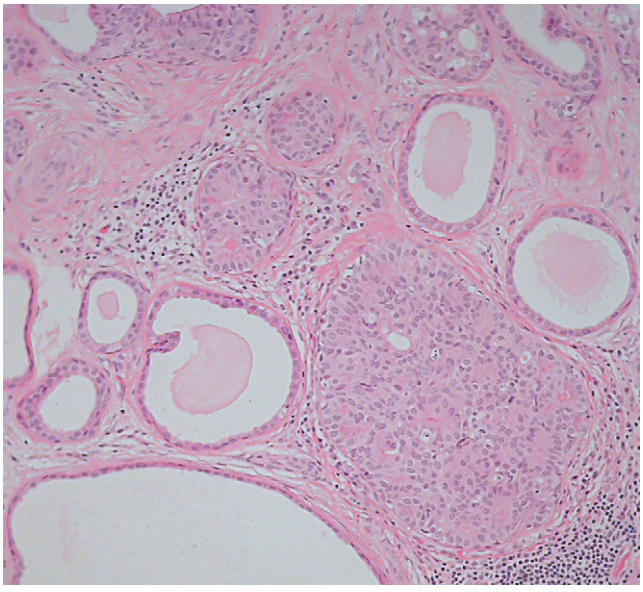

**Figure 3** SPA: intraductal epithelial proliferation.

Microscopic examination shows variable proportions of the three main cell types, but in most tumours intermediate cells predominate. While mucous (goblet) and squamous-like cells are relatively easy to characterize, intermediate cells range from small basal type cells to larger round or polygonal cells, often with clear cytoplasm. All cell types can show degrees of nuclear pleomorphism and mitotic activity. The stroma is variable, but can be fibrous and hyalinized; a lymphoid reaction is often prominent with germinal centre formation. Histological variants include clear cell predominant,[8] oncocytic,[9] sebaceous,[10] as well as sclerosing MEC without[11] and with prominent eosinophils,[12] the latter resembling similar thyroid tumours.

Recent developments have considered histological and molecular features that may predict clinical outcome. All MECs are thought to be malignant with a metastatic potential, regardless of their microscopic appearance. Nevertheless, histological features predict outcome and grading systems have been developed based on the extent of the cystic component, neural invasion, necrosis, cytological pleomorphism and mitotic activity (Figure 4a,b and c). The AFIP scheme reported death rates from disease of 3.3%, 9.7% and 46.3% for low, intermediate and high grades respectively, also noting that grading MECs in the submandibular glands was less reliable that at other sites.[6] Brandwein et al. have proposed modifications by adding vascular invasion and the pattern of infiltration, as well as changing the scoring of different factors.[13] A critical review of current grading systems showed that the AFIP scheme was more reproducible and overall had a better correlation with disease survival than the Brandwein system, but the latter more successfully predicted an indolent course for low-grade MEC. An ideal grading system that marries the respective strengths of each system has yet to be developed.[14] A series of 12 cases of the oncocytic variant found a favourable outcome independent of grade.[9]

For all MECs, special techniques appear to have independent value. The MIB1 proliferative index[15] is related to prognosis as 11 of 12 patients with an index <5% had no further disease in follow up periods of up to 14 years (mean 7.1), with only one patient having cervical nodal micrometastases followed by 6 years without further disease. In contrast, only six of 18 tumours in this study with an index >10% had a favourable outcome and 10 patients died or had persistent disease. In a study of membrane-bound mucins, cases showing MUC4 expression had a better prognosis than those expressing MUC1.[16] At the molecular level, MEC can be grouped according to the presence of absence of a recurrent t(11;19) (q21; p13) translocation resulting in a MECT1-MAML2 fusion. The median survival of *fusion positive* patients was >10 years compared to 1.6 years for those without the fusion.[17] The latter two techniques have yet to enter general use. In practice, it is advisable to use a mixture of histological grading and the MIB1 index.

### Epithelial–myoepithelial carcinoma

Epithelial–myoepithelial carcinoma (EMC) has been defined 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''.[18]