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Salivary Duct Carcinoma: New Developments—Morphological Variants Including Pure In Situ High Grade Lesions; Proposed Molecular Classification

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Abstract Salivary duct carcinoma (SDC) is an aggressive primary salivary malignancy which microscopically resembles high-grade ductal carcinoma of the breast, with both in situ and invasive patterns. It is typically found in older men, most often in the parotid. It can arise de novo or as the malignant component of carcinoma ex pleomorphic adenoma. SDC is generally a hematoxylin and eosin stain-based diagnosis, with special stains and immunohistochemistry acting mainly in a confirmatory role. Other than epithelial markers, SDC expresses androgen receptors in most cases, with true HER2 positivity seen in about 15 %. Based on these data and analogous to similar schemes in the breast, it is suggested that SDCs can be classified into three main groups: luminal androgen receptor positive, HER2+ and basal phenotype. This may form the basis for prognostic information and new therapeutic possibilities. In addition to the usual type of SDC, a few less common morphological variants have been reported: papillary, micropapillary, mucin-rich, sarcomatoid and oncocytic, as well as pure in situ cases.

Keywords Salivary duct carcinoma · Morphological variants · Molecular classification · Androgen receptors · HER2/neu, basal phenotype

Introduction

Salivary duct carcinoma (SDC) is a clinicopathologically distinct primary malignancy of the salivary glands which was first described by Kleinsasser et al. in 1968 [1], although on later review two of the five cases were probably epithelial-myoepithelial carcinomas [2]. It was defined in the 2005 WHO Classification as "an aggressive adenocarcinoma which resembles high-grade breast ductal carcinoma" [3].

Previously thought to be extremely rare, it is now recognised as not infrequent, and accounts for up to 2 % of all primary salivary epithelial neoplasms. Most patients are over 50 years old and there is an at least 4:1 male to female ratio [4]. It arises mainly in the parotid glands, though cases have been described in the submandibular gland and occasionally in the minor glands [5]. Most cases develop *de novo*, although some represent the malignant component of carcinoma ex pleomorphic adenoma—the exact proportion is uncertain, as it is not infrequent to find a hyalinized area of stroma in a SDC, which may or may not be the remnants of a benign tumor; in addition, a single case has been reported arising in (or in association with) a polymorphous low grade adenocarcinoma of the palate [6].

Patients typically present with a fast-growing mass often involving the facial nerve. SDCs are aggressive tumors, frequently recur locally and give rise to nodal and distant metastases [2]. In fact, over 60 % of patients die of disease within 5 years of the initial diagnosis, despite radical surgery and adjuvant chemo-radiotherapy [2, 7]. There are no known etiologic factors, although one case was reported in a patient with long-standing chronic obstructive sialadenitis [8, 9], and another in a patient with IgG4-related sclerosing disease of the parotid [10].

Pathologic Findings in the Usual Type of Salivary Duct Carcinoma

Macroscopically, SDC is usually a firm ill-defined mass infiltrating the surrounding gland and soft tissue. A well-

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circumscribed nodule within the tumor may indicate a pre-existing pleomorphic adenoma.

All histological studies on SDC have confirmed the strong architectural and cytological resemblance to in situ and invasive grade 2–3 ductal carcinoma of the breast. The former component comprises expanded salivary ducts with solid, papillary, "Roman bridge", cribriform and comedo patterns (Fig. 1a). It should be noted that sometimes, the in situ lesions can be masked by extensive growth of invasive carcinoma and are morphologically subtle, although they can be highlighted by using basal-myoepithelial markers [11, 12].

Infiltrating SDC includes a mixture of small ducts, cribriform structures, small nests of cells and trabeculae, all accompanied by stromal desmoplasia (Fig. 1b) [2, 3, 7, 13–18]. Occasionally, there is a diffuse growth of single cells and small ill-defined clusters (Fig. 1c). Perineural and lympho-vascular invasion are frequently seen. The component cells of SDC mainly have moderate amounts of eosinophilic and granular cytoplasm, containing nuclei which are often vesicular with coarse chromatin and in which central nucleoli may be prominent [2]; frequently, there is marked nuclear pleomorphism, also apparent on FNA cytology [19]. In better differentiated areas, cells may show definite apocrine features, such as luminal snouts (Fig. 1d). Mitotic and MIB1 indices are usually high.

Special Stains and Immunohistochemistry

Salivary duct carcinoma (SDC) is generally a hematoxylin and eosin stain-based diagnosis, with special stains and immunohistochemistry acting mainly in a confirmatory role [8], although some immunomarkers may in future be therapeutically important [*see below*]. Other than in the genuine mucin-rich variant [20], epithelial mucus may still be found in small quantities, although not goblet cells.

Immunohistochemically, SDC is positive with broad spectrum and low molecular weight cytokeratins and epithelial membrane antigen (EMA) [3]. It is also strongly and diffusely positive with CK7, and there is occasionally focal staining with CK20 [21]. It is typically negative with S-100 protein and basal-myoepithelial markers, such as cytokeratins 5/6 and 14, p63, calponin and smooth muscle myosin heavy chain (SMMHC), although these highlight surrounding non-neoplastic cells of in situ lesions. In most examples of SDC, the MIB1 proliferative index is over 25 %.

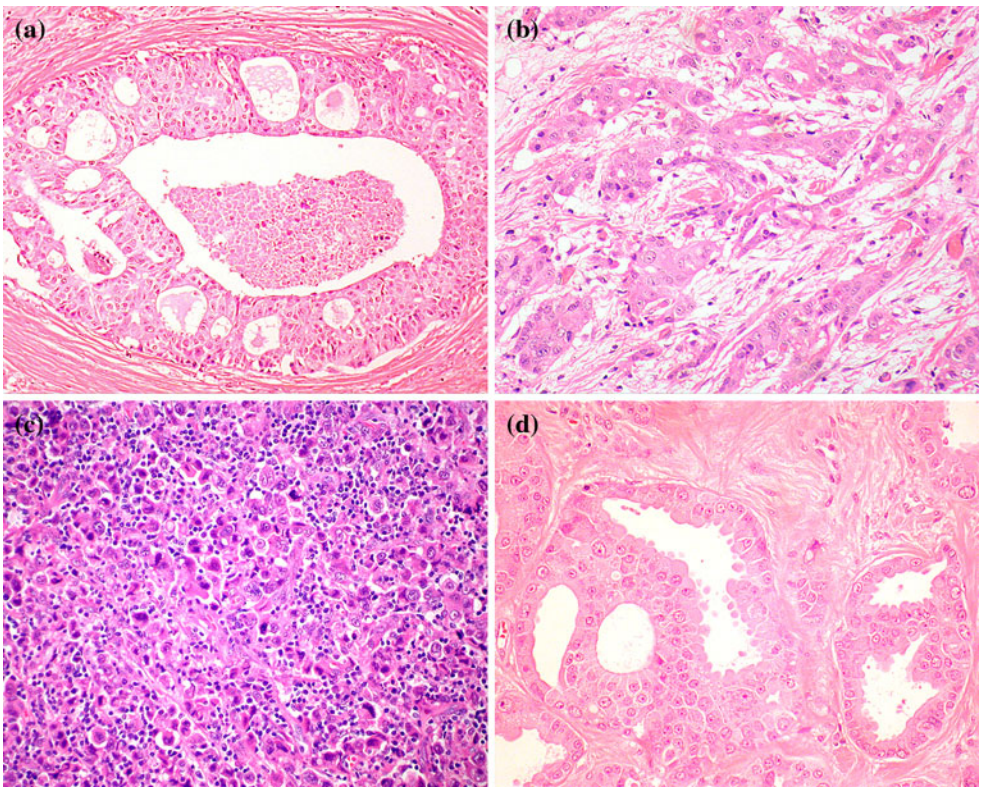

Fig. 1 Usual type SDC. **a** DCIS lesion with central comedo-necrosis. **b** Invasive tubulo-trabecular pattern. **c** Invasion as single cells in a tumor with more usual SDC areas elsewhere. **d** Invasive tubules with apocrine-type snouts

As SDC resembles breast carcinoma morphologically, not surprisingly there are immunohistochemical similarities, but also some important differences. For instance, gross cystic disease fluid protein-15 (GCDFP-15), a marker of apocrine differentiation in breast cancer, is reported to be found in >80 % of SDCs [2, 7, 14, 22]. HER2 protein overexpression has been reported in up to 90 % of cases [17, 23–27], although there is considerable variation between different antibody clones and scoring systems [25]. However, when stricter criteria (e.g. American Society of Clinical Oncologists (ASCO)/College of American Pathologists (CAP) or the Herceptest® scoring system) [28] are used or when HER2 positivity is defined by fluorescence or chromogenic in situ hybridisation amplification, HER2 positivity is reported to be found in only 15 % to a maximum of 40 % [25, 27, 29–31].

On the other hand, there are still significant differences between SDC and invasive ductal carcinoma of the breast in their hormone receptor profile: whilst in breast cancer, estrogen receptor α (ERα) and progesterone receptor (PR) are found in >75 % of cases, positivity for these markers is exceptional in SDC. ERα expression is extremely rare [22, 32–34] and PR expression is usually absent, with only focal positivity being found in at most 20 % of SDCs [33–35]—in contrast, 73 % of SDCs have been shown to express estrogen receptor β isoform (ERβ). Conversely, a similar prevalence of androgen receptor (AR) expression has been reported in SDCs (67 to 83 %) [22, 29, 31, 36], and in breast carcinomas (47 to 88 %) [37, 38]. Owing to the high frequency of AR expression in SDCs and its near absence in other tumor types [39], this hormone receptor is often used as a marker to confirm the diagnosis.

On occasions, staining with prostatic markers has been found [36], but only one tumor of a series of 40 from the Mayo Clinic was positive [40], and all cases studied in Exeter, UK have been negative [18, 19, 29]. A high frequency of transforming growth factor α (TGF-α) and epidermal growth factor receptor (EGFR) suggests a possible mechanism of carcinogenesis similar to that of prostatic carcinoma [41]. Also, peroxisome proliferator-activated receptor gamma (PPARγ) is often strongly expressed in the cytoplasm of SDC, the biological significance of which is as yet uncertain [42].

Electron Microscopy

The tumor cells in SDC have ultrastructural features of ductal differentiation with basal lamina, luminal microvilli, desmosomes and tight junctions, rough endoplasmic reticulum, a moderate number of mitochondria (plentiful in the oncocytic variant) and some glycogen [2, 32, 43].

Genetics

Other than work on the *HER-2/neu* gene [*see above*], relatively few studies have been published. A high incidence of LOH has been found at the chromosomal locus 9p21, which contains the *CDKN2A/p16* tumor suppressor gene. It has been suggested that inactivation of this gene is associated with progression of SDC [44]. In another study, a high incidence of LOH was found at the 6q, 16q, 17p and 17q regions [45]. Mutations and overexpression of the TP53 gene and protein are frequent [45, 46]. LOH at microsatellite loci, TP53 point mutations and frequent alteration of certain loci on chromosome arm 6q have also been described [45]. Expression of p53 has been linked to more aggressive behavior [47]. Leivo et al. [48] used a cDNA array to study the gene expression profiles of 13 salivary carcinomas, including SDC, mucoepidermoid and acinic cell carcinomas. They were able to demonstrate overexpression of five genes in all cases: fibronectin 1 (*FN1*), tissue metalloproteinase inhibitor 1 (*TIMP1*), biglycan (*BGN*), tenascin-c (*HXB*) and insulin-like growth factor binding protein 5 (*IGFBP5*), whereas 16 other genes were under expressed. Each carcinoma entity was clustered together, but SDC could be separated from the other two tumor types. Apoptosis-related genes *CASP10* and *MMP11* were overexpressed in SDC.

Amongst other genetic abnormalities found in salivary tumors, the MECT1/MAML2 translocation characteristic of mucoepidermoid carcinoma is not found in SDC, even those with some squamoid morphology [49]. Brill et al. [50] found 2 out of 18 SDCs showed immunohistochemical staining for MYB, but all were negative for the MYB-NFIB gene fusion, in contrast to 86 % of adenoid cystic carcinomas.

Morphological Variants

As more experience is accumulated with SDC, it is becoming increasingly clear that the morphology may be as variable as it is in ductal carcinoma of the breast. In addition to the usual type of SDC, a few less common morphological variants have been reported: papillary, micropapillary, mucin-rich, sarcomatoid and oncocytic, as well as pure in situ cases.

Papillary-cystic invasive growth is not usually seen in SDC. However, Brandwein et al. [14] reported a series of SDCs, one of which included papillary structures with psammoma bodies.

The micropapillary variant of SDC is composed of morula-like small clusters of cells, or less commonly duct-like structures, without fibrovascular cores each surrounded by a clear space, separating it from the surrounding stroma (Fig. 2a). Lymphovascular and perineural invasion are

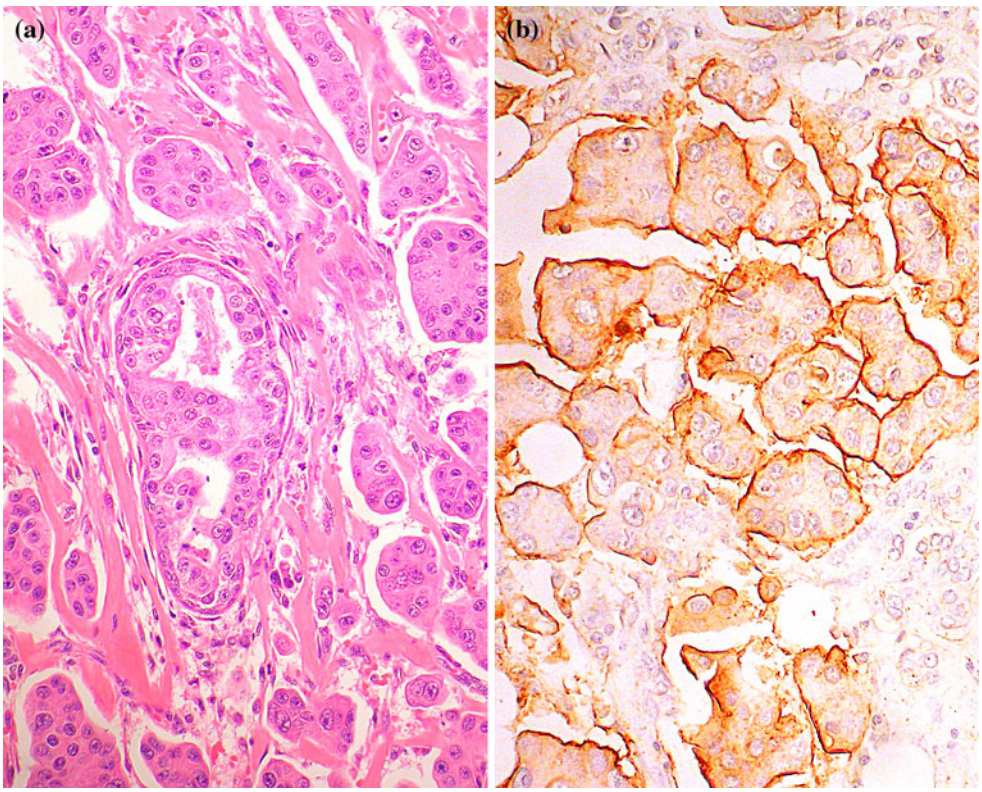

Fig. 2 Micropapillary SDC. **a** Invasive cellular morules each surrounded by a clear space; there is also a small central in situ lesion. **b** Peripheral "inside-out" staining with EMA

common. The micropapillary growth can constitute almost all of a particular tumor or represent a significant minority component. One particular immunohistochemical feature is an "inside-out" pattern of EMA staining on the outer rim of the cell clusters (Fig. 2b). The micropapillary pattern can be retained in lymph node metastases [51, 52].

Small quantities of mucin staining with PASD and mucicarmine are not infrequently seen in many SDCs. In the mucin-rich variant there are substantial lakes of such epithelial mucin containing islands of malignant cells, i.e. mucinous (colloid) carcinoma, in addition to areas of typical SDC, both in situ and invasive (Fig. 3a, b) [20, 53, 54]. The mucinous component resembles colloid carcinoma as described in detail by Yakirevich et al. recently [55], but any such tumor should be fully sampled to identify any areas of typical SDC, which would probably indicate a more aggressive clinical course.

The sarcomatoid type is a combination of usual type SDC and sarcomatoid elements (Fig. 4) [56]. The latter is usually a proliferation of highly atypical spindle cells, often admixed with bizarre multinucleated giant cells, but in addition, osteoid production has been noted on occasions [57]. The immunohistochemical profile of the usual type component is the same as for any SDC, but in one series the sarcomatoid areas showed focal or diffuse staining for EMA in all instances and broad-spectrum and high molecular weight cytokeratins in about half of cases [57]. This variant may account for some tumors previously classified as carcinosarcoma ("true malignant mixed tumor"). To differentiate between the two, the term sarcomatoid SDC is used to designate a biphasic malignant neoplasm with or without heterologous elements, when the carcinomatous component fulfils the diagnostic criteria for SDC [57]. Probably related is the osteoclast-type giant cell neoplasm of the salivary gland, which bears some morphologic similarity to giant cell tumor of bone, but in addition there is often a component of SDC. Also unlike the bone neoplasm, the mononuclear cells in the salivary tumor have the same immunoprofile as SDC and a similar microsatellite pattern on genotypic analysis [58].

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 [59]. The proportion of such cells needed to establish the diagnosis of oncocytic SDC is arbitrary, but should be more than 50 %. It is probable that this variant accounts for many neoplasms previously diagnosed as "oncocytic carcinoma".

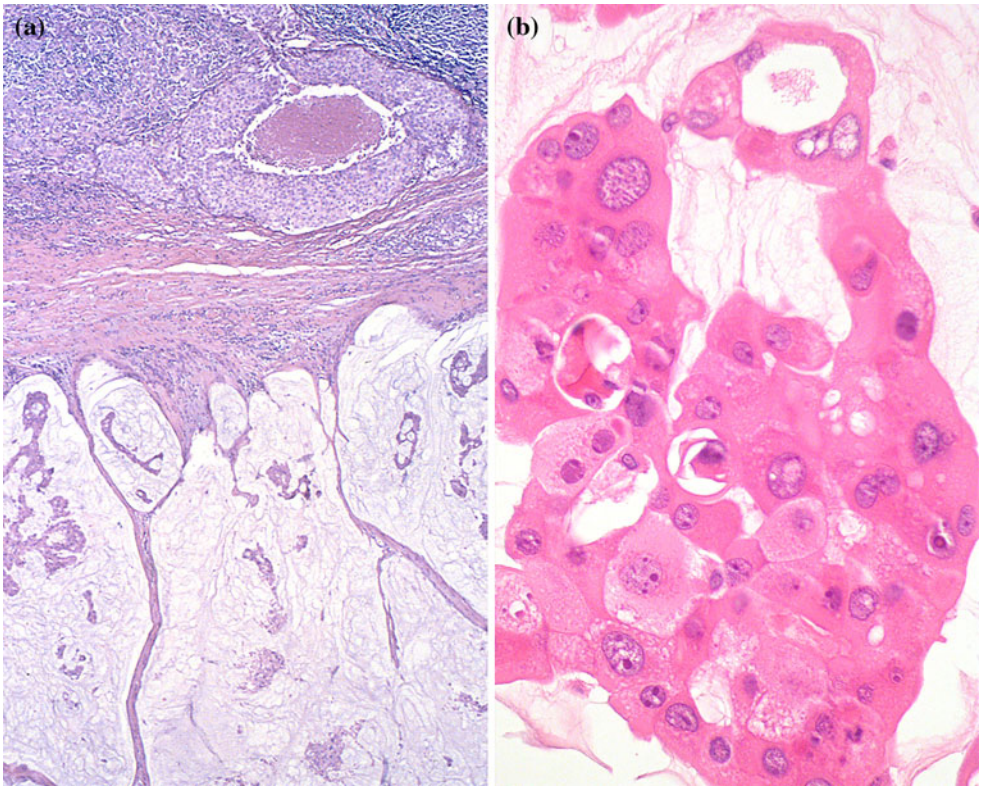

Fig. 3 Mucin-rich SDC. **a** Both components: area of usual type SDC and an area of colloid carcinoma. **b**. Group of carcinoma cells surrounded by epithelial mucin

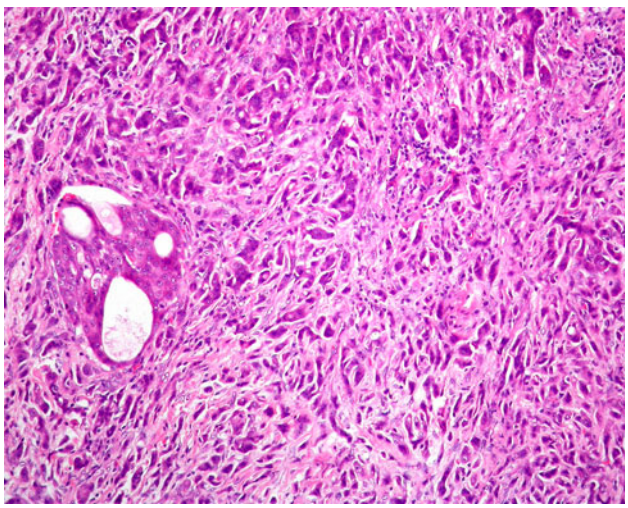

Fig. 4 Sarcomatoid SDC; glandular area and a population of spindle-shaped carcinoma cells

Salivary Duct Carcinoma In Situ

Although pure in situ salivary duct carcinoma (SDCIS) was not recognized as an entity by the 2005 WHO classification, occasional cases have been described in both major and minor glands, characterized by an intraductal proliferation of malignant cells, similar to ductal carcinoma in situ of the breast [60–66]. The rarity is not surprising, as SDC usually presents at an advanced and invasive stage, and furthermore, there is no system for early detection analogous to mammographic screening programs for breast cancer.

The SDCIS lesions comprise ducts and cysts often containing comedo-like necrotic debris (Fig. 5a), sometimes with calcification. The lumina are lined throughout by atypical cells varying in thickness from one to several layers. In some of the smaller ducts the proliferation can fill the whole lumen, but in the larger cysts a variety of architectural patterns are evident, including "Roman bridges", papillary and cribriform structures. The lining cells display variable degrees of nuclear pleomorphism and central nucleoli may be prominent. The cytoplasm is generally plentiful and eosinophilic, occasionally vacuolated, and some cells have apocrine snouts. Mitotic figures are fairly frequent, and the MIB1 proliferation index is generally above 10 %. Varying amounts of luminal PAS positive diastase resistant mucus are seen, but true goblet cells are absent. Foci where malignant cells grow along small ducts into acini, i.e. cancerization of acini, can be present (Fig. 5b).

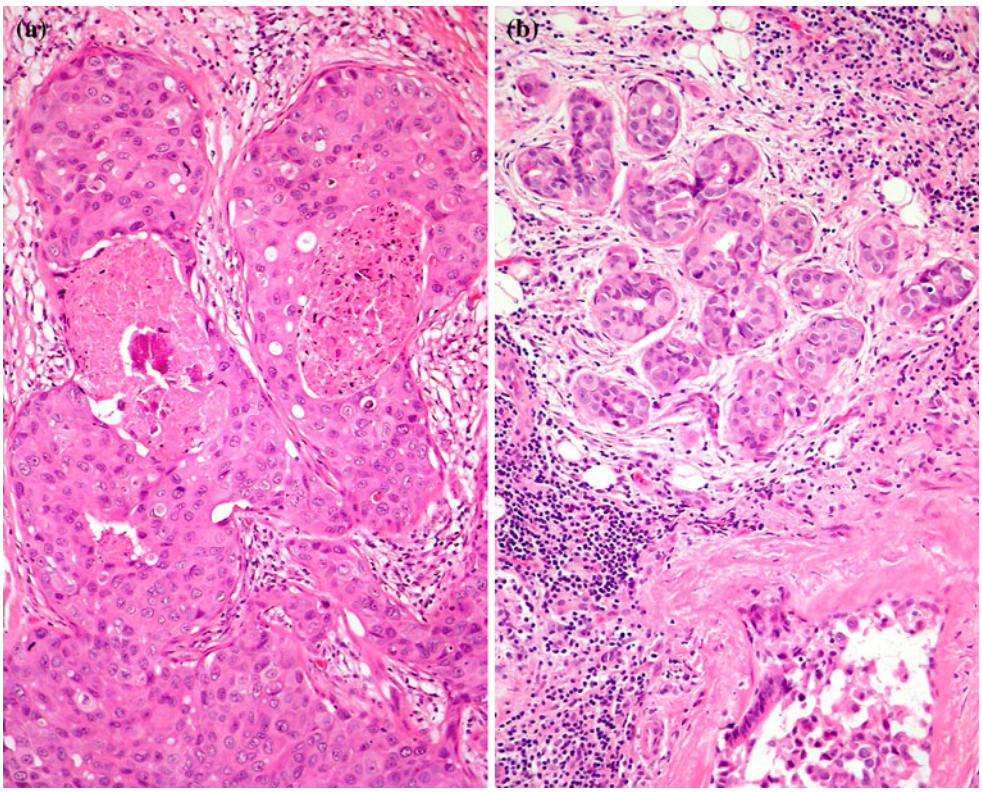

Fig. 5 Pure SDCIS. **a** Comedocarcinoma with cytological atypia. **b** Cancerization of acini

The diagnosis of SDCIS requires strict criteria, particularly the absence of local invasion, determined by adequate sampling of the whole lesion and the presence of an intact myoepithelial layer around all tumor islands. This comprises a mantle of small cells, usually flat and inconspicuous, and therefore ideally confirmed by immunohistochemistry for basal-myoepithelial markers such as cytokeratins 5/6 and 14, p63, calponin and SMMHC [65, 66].

As so few cases have been described, little is known about the natural history of pure SDCIS and it cannot be stated whether the examples described would eventually have progressed to invasive SDC. However, it is noteworthy that one of the patients in the paper of Simpson et al. [66] had a mass "present for many years". The tumor was incompletely excised, but there was no recurrence after more than 8 years.

The relationship of SDCIS to low grade cribriform cystadenocarcinoma (LGCCC) remains unclear [67–69]. They could be separate entities as there are significant immunohistochemical differences, but equally, LGCCC might well represent the extreme low grade end of the spectrum of salivary DCIS. In favor of the latter is the overlap of architectural patterns with SDCIS, together with the occasional case showing progression to higher grade cytology and/or invasion [70, 71]. This tumor is described in greater detail in another paper in this special issue.

Differential Diagnosis

Whilst most cases of SDC resemble high grade ductal carcinoma of the breast and are relatively straightforward to recognize, others can be more problematic. The histopathologic differential diagnosis of SDC includes primary oncocytic, mucoepidermoid and myoepithelial carcinomas, as well as metastatic melanoma, squamous, breast and prostate carcinomas.

The oncocytic variant of SDC probably accounts for many cases previously diagnosed as oncocytic carcinoma, which is a rare and usually high grade malignancy, unlikely to represent a single entity. High grade mucoepidermoid carcinoma is also invasive and displays nuclear pleomorphism and increased mitotic activity. It is composed of mucinous goblet cells, cells showing epidermoid differentiation and intermediate forms; about half are *MECT1-MAML2* translocation positive [49]. In myoepithelial carcinoma, neoplastic lobules with central necrosis can bear a superficial resemblance to the DCIS lesions of SDC, but these areas usually contain increased amounts of hyaline stromal material. The immunohistochemical profile is also very different. High grade adenocarcinoma NOS is a diagnosis of exclusion in neoplasms where it is not possible to establish a more accurate categorization; this is particularly

the case with small biopsies subject to insufficient sampling. Many turn out to be examples of SDC.

Metastatic melanoma with an epithelioid pattern can mimic a predominantly solid SDC, but can be excluded by appropriate immunomarkers. Metastatic squamous (poorly differentiated, non-keratinizing), prostate or breast carcinoma all have the appearance of a high grade salivary carcinoma. Squamous carcinoma lacks an infiltrating cribriform pattern and displays evidence of epidermoid differentiation such as intercellular bridges. Metastatic breast carcinoma is microscopically very similar to invasive SDC and differentiation can only be made on clinical grounds, although ERα positivity in >25 % of tumor cells would strongly favor a metastasis, particularly in the absence of sialodochodysplasia, the presence of which would support a primary salivary origin. In metastatic carcinoma of the prostate, positive staining for prostate specific antigen (PSA) is usually diagnostic, although it has rarely been demonstrated in SDC [36]. Cytokeratin 7 is positive in SDC [21], whereas it is negative in 90 % of prostatic adenocarcinomas [72]. Androgen receptor staining is a good marker for SDC, but not quite specific. It is positive in metastatic prostatic carcinoma and only infrequently in some other salivary carcinomas [33].

Molecular Classification

Pioneering studies by Perou et al. [73] revealed that breast cancer can be classified into at least four main molecular subgroups: luminal, HER2, basal-like and normal breast-like cancers. Subsequently, Farmer et al. [74] described the existence of a molecular apocrine group of breast cancers, which would to some extent overlap with a subgroup of luminal and HER2 cancers described by Perou et al. [73]. These groups have been shown to have distinct clinical behavior and response to chemotherapy [75, 76]. More recently, Nielsen et al. [77] have described an immunohistochemical panel of four markers which can be used as a surrogate of gene expression analysis to classify breast carcinomas in the molecular subgroups.

Given the morphologic similarity to mammary ductal carcinoma, a recent study speculated that SDC could also be classified into three similar molecular subtypes [29]. Whereas expression of ERα in SDC is exceptional, several studies have demonstrated AR staining in up to 83 % of invasive SDCs. 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 [25]. This showed that protein overexpression is usually, but not always (even when 3+) associated with gene amplification.

Extrapolating from these data, it is suggested that invasive and in situ SDCs can be classified into three main groups; these are luminal AR positive, HER2+ and basal phenotype, based on positive nuclear staining of AR (Fig. 6a, b), HER2 protein overexpression (and/or gene amplification) (Fig. 7a, b) and positive cytoplasmic staining for basal markers such as cytokeratins types 5/6 (Fig. 8a, b), 14, 17, and epidermal growth factor receptor (EGFR). In our recent 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 [29]. Two of the 42 SDCs in our series satisfied the criteria for basal phenotype; these may be the first published cases, although one possible CK5/6 positive SDC had previously been reported in the German literature [78].

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 [2]. The behavior of the morphologic variants is probably similar to the usual type of SDC, although there is some evidence that the micropapillary variant is more aggressive [52]. The outcome for pure SDCIS should be good, provided it is completely excised. The standard treatment at present for invasive SDC is complete surgical excision with radical neck dissection followed by radiotherapy to the tumor 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. [31] found that SDCs negative for both AR and ERβ were more aggressive than tumors 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+.

Given that luminal AR 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 [79]. Our

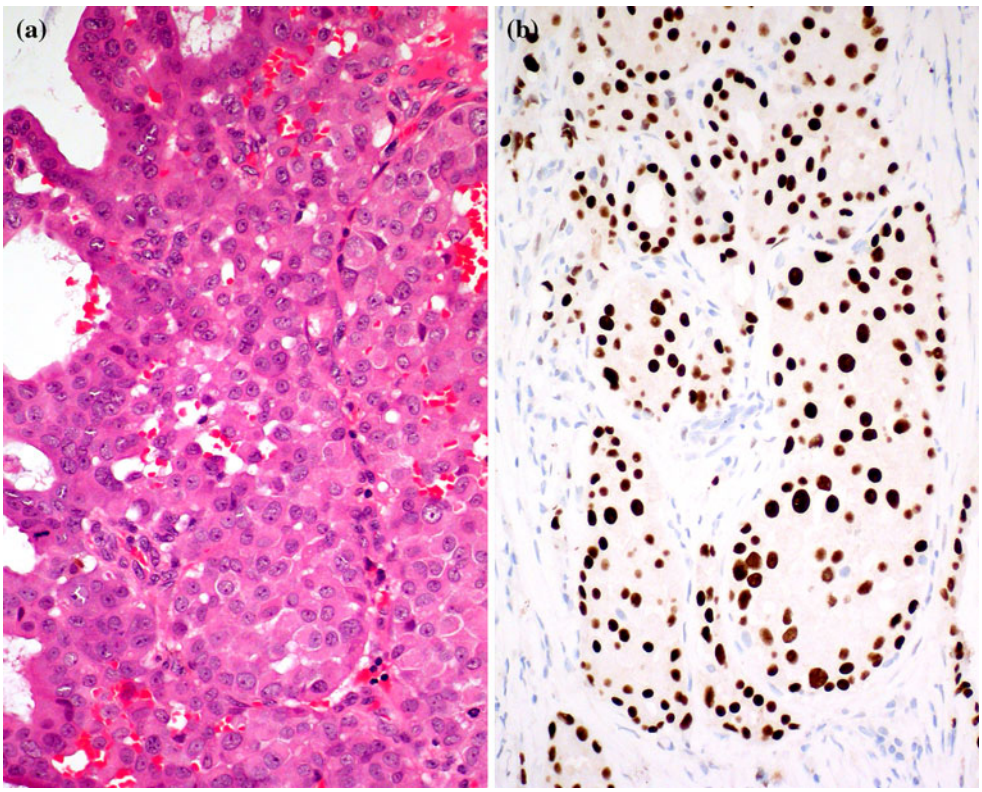

Fig. 6 Molecular subtypes: luminal androgen receptor positive. **a** Typical invasive SDC. **b** Strong reaction for AR in almost every nucleus

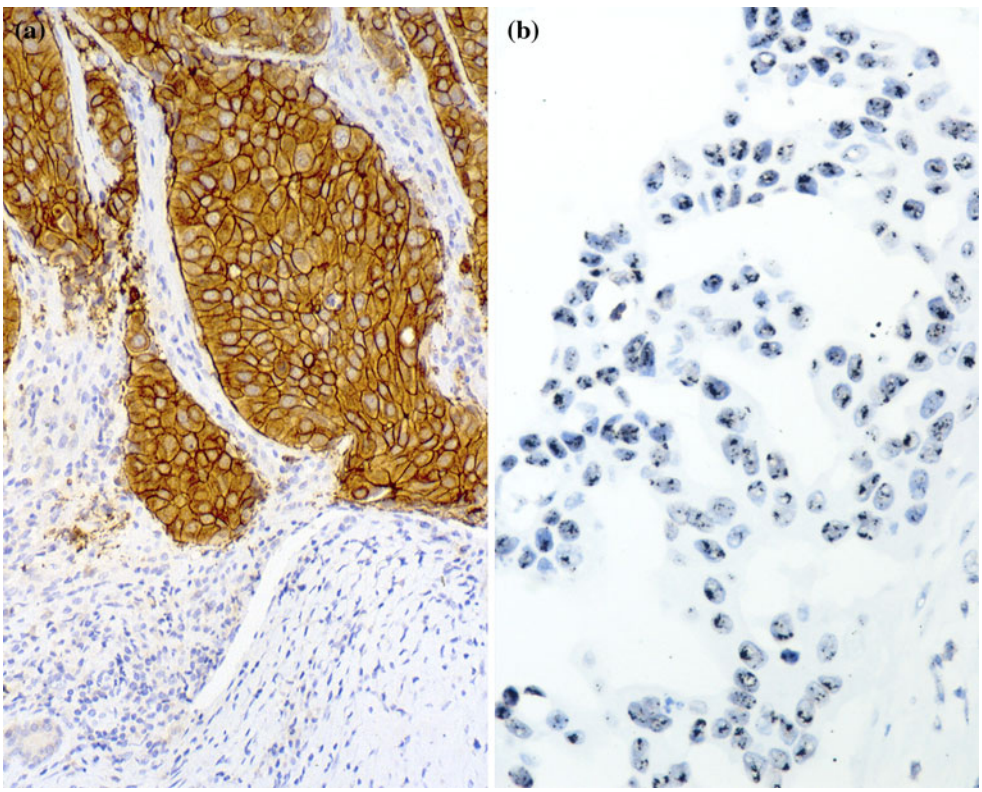

Fig. 7 Molecular subtypes: HER2 positive. **a** 3+ immunostaining for HER2 protein (with normal negative staining ducts as internal control). **b** Amplification of the HER2/neu gene (SISH)

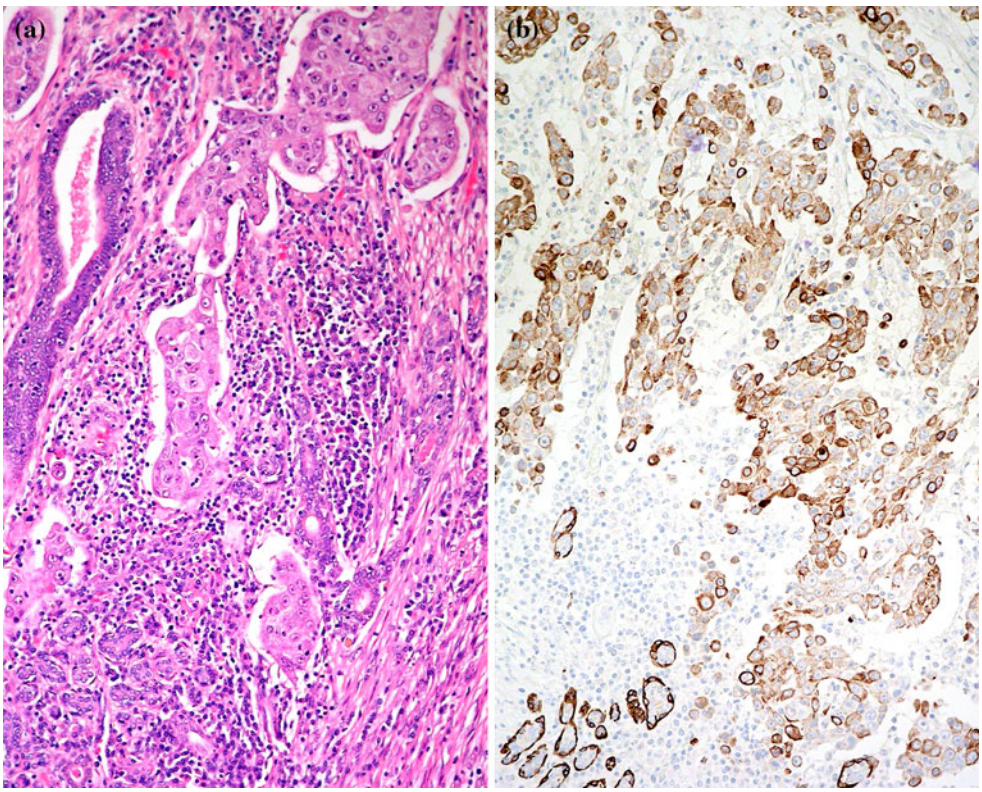

Fig. 8 Molecular subtypes: Basal phenotype. SDC invading normal gland (**a** HE and **b** CK5/6)

own limited experience in Exeter with a small number of patients has shown that some patients show at least a temporary improvement of their symptoms and tumor shrinkage. 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) [80]. 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).

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