Head and Neck Cancer

Chapter 2

Salivary Duct Carcinoma: Old but New Aspects

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Abstract

Salivary duct carcinoma (SDC) is a relatively rare malignant neoplasm of the salivary glands. In many cases, it arises as the carcinomatous component of carcinoma ex pleomorphic adenoma (CXPA). SDC exhibits morphological similarity to invasive ductal carcinoma of the breast, but it displays negativity for the estrogen and progesterone receptors, and most cases of SDC demonstrate positivity for the androgen receptor (AR). On the other hand, approximately half of SDC overexpress the human epidermal growth factor receptor (HER)2, and HER2 gene amplification is seen in 20–40% of cases. Sarcomatoid, mucin-rich, and invasive micro papillary subtypes are well-known histological subtypes of SDC. We report SDC with rhabdoid-like features (SDCRF) as a new histological subtype. SDCRF is the salivary counterpart of pleomorphic lobular carcinoma of the breast. We collected SDC cases, including CXPA, in a large Japanese cohort study and subclassified them into 7 subtypes: apocrine A (AR+/HER2-/Ki-67low), apocrine B (AR+/HER2-/Ki-67high), apocrine-HER2 (AR+/HER2+), HER2-enriched (AR-/HER2+), basal-like (epidermal growth factor receptor [EGFR]+ and/or cytokeratin [CK]5/6+), HER2-basal (HER2+/EGFR+), and unclassified (AR-/HER2-/EGFR-/CK5/6-). Statistically, apocrine A exhibited a better prognosis than the other subtypes. Apocrine-HER2 and HER2-enriched were common in cases of CXPA. Recently, PTEN gene deletion and mutations in the PIK3CA, HRAS, and KRAS genes, which are related to the HER2 pathway, have
been detected in SDC, and RET gene arrangements have been reported in some cases, especially cases of intraductal carcinoma. Molecular-targeted therapies, such as trastuzumab in HER2+ cases or androgen-deprivation therapy in AR+ cases, has been employed in recurrent or unrespectable cases of SDC and demonstrated better therapeutic effects in terms of survival and prognosis. We summarize novel clinicopathological and genetic aspects of SDC.

1. The Original Entity of Salivary Duct Carcinoma

Salivary duct carcinoma (SDC) is a clinicopathologically distinct malignancy of the salivary glands, which was first described by Keinsasser et al. in 1968 [1], but on later review it was found that two of the five cases were probably epithelial-myoepithelial carcinomas. It was defined in the 2005 World Health Organization (WHO) Classification as “an aggressive adenocarcinoma which resembles high-grade ductal carcinoma of the breast” [2].

Previously, SDC was considered to be an extremely rare malignancy, but now it is encountered relatively frequently; i.e., it accounts for up to 2% of all primary salivary epithelial neoplasms [3,4]. SDC is frequently detected as a carcinomatous component of carcinoma ex pleomorphic adenoma (CXPA). In particular, when a hyalinized nodule is observed in an SDC lesion, it is considered to be a pre-existing pleomorphic adenoma (PA) [5,6]. Most patients with SDC are over 50 years old, and the male to female ratio of the disease is at least 4:1 [4,7]. Most SDC occur in the major salivary glands, especially the parotid gland; some cases arise in the submandibular gland; and SDC occasionally affects the minor salivary glands.

As SDC is a high-grade aggressive tumor, rapid growth and facial nerve paralysis are frequently seen. After surgery, local recurrence, regional lymph node metastasis, and distant metastasis often occur [8]. Over 60% of patients die of the disease within 5 years after radical surgery [4,8,9]. The etiology of SDC remains unknown.

2. Conventional Histopathology of SDC

All histological studies of SDC have confirmed that it exhibits a strong architectural and cytological resemblance to grade 2–3 in situ and invasive ductal carcinoma of the breast (IDCB) [4,7]. The architecture of SDC involves expanded salivary ducts with papillary, solid, “Roman bridge”, and cribriform structures and/or comedonecrosis (Figure 1), whereas SDC cells mainly display moderate amounts of eosinophilic and granular cytoplasm, and their nuclei contain coarse chromatin and sometimes possess prominent central nucleoli. SDC frequently demonstrates marked nuclear pleomorphism, and its characteristics are particularly obvious on fine-needle aspiration cytology. Moreover, SDC cells often exhibit apocrine differentiation; i.e., apical snout/decapitation secretion, eosinophilic and granular cytoplasm, and positivity
for the gross cystic disease fluid protein (GCDFP)-15 and the androgen receptor (AR), as described by Dr. E. Leon Barnes et al. in a pair of seminal studies in 1998 and 2000 [10,11]. The immunohistochemical characteristics of SDC are outlined in the next chapter. Cases of SDC that displayed a basal-like phenotype [12]; i.e., relatively dark cytoplasm, marked cellular pleomorphism, and/or squamoid differentiation, have also been reported.

**Figure 1:** Histological findings of SDC
Some SDC exhibit Roman bridge structures (A), whereas other cases display comedonecrosis (B).

### 3. Immunohistochemical Characteristics of SDC

As SDC frequently demonstrates apocrine differentiation, they are positive for GCDFP-15, which is a marker of apocrine carcinoma (Figure 2A). The GCDFP-15 expression level of SDC varies from case to case. Recently, some subtypes of salivary gland cancers, including SDC, have been reported to be immunopositive for mammaglobin (MGB1) [13] (Figure 2B) and GATA-binding protein (GATA)-3 [14], but the status and significance of MGB1 and GATA-3 expression in SDC remain unknown. However, as breast cancer and secretory carcinoma of the salivary glands frequently express MGB1 and/or GATA-3 [15], these molecules may not be useful for diagnosing SDC.

Immunohistochemically, SDC is usually positive for the AR, but not the estrogen receptor (ER) or progesterone receptor (PgR) [16,17]. Although SDC is almost negative for ERα, which we usually call the “ER”, approximately 70% of SDC cases were reported to be positive for ERβ [18,19]. Previous studies have shown that the proline, glutamic acid, and leucine-rich protein (PLEP)1/MNAR, a novel ER co-activator, is expressed in SDC [19,20]. At the genomic level, PLEP1 enhances targeted transcription by binding to the promoter regions of ER target genes. Williams et al. reported that 94% of SDC expressed PLEP1, 73% expressed ERβ, and 67% expressed the AR (Figure 2C). AR expression is significantly more common in males than females [19], whereas ERβ expression is more common in females than in males, although the difference is not statistically significant. On the other hand, the risk of local and regional recurrence is significantly greater in cases of SDC that do not involve ERβ expression. Moreover, ERβ-negative and AR-negative cases of SDC exhibit decreased survival compared...
with cases that co-express ERβ and the AR [19]. We previously reported a case of “low-grade SDC” [21], which should have been called low-grade cribriform cystadenocarcinoma (LGCCA) or adenocarcinoma, not otherwise specified (AdNOS) [22-24], that was diffusely positive for the PgR and focally positive for the ER in addition to being partially positive for the AR. However, “LGCCA-type” SDC is usually negative for the ER and the PgR, despite exhibiting relatively high positivity (62%) for the AR [25,26].

On the other hand, approximately 40% of SDC overexpress (3+) human epidermal growth factor receptor (HER) 2 or exhibit HER2 gene amplification [12,19,27-29]. When SDC arises as a carcinomatous component of CXPA, it often overexpresses the epidermal growth factor receptor (EGFR), HER2, HER3, and Ki-67 compared with the levels of these molecules seen in de novo SDC [30] (Figures 2D, E, and F). High HER2 positivity (3+) was reported to be significantly associated with an increased rate of distant metastases and with stage III or IV disease, and 12% of SDC co-express high levels of both HER2 and the EGFR (3+) [19].

These findings suggest that the biological behavior of SDC is controlled by the AR, HER2, and/or EGFR.

Figure 2: Immunostaining characteristics of SDC
SDC is frequently immunopositive for GCDFP-15, whereas some cases of SDC are positive for MGB1. Most cases of SDC are positive for the AR (C). Approximately half of SDC cases are positive for HER2 (D), whereas SDC is sometimes positive for the EGFR (E). SDC frequently exhibits a high Ki-67 labeling index (F).
4. Histological Variants of SDC

The histology of conventional SDC has already been described in chapter 2. Several histological subtypes of SDC have been reported, including sarcomatoid, mucin-rich, invasive micropapillary, and rhabdoid-like variants. The sarcomatoid variant of SDC exhibits a spindle-shaped, bizarre polygonal, or giant cell tumor-like morphology, usually within foci of conventional SDC (Figure 3A), in which the co-expression of cytokeratin (CK) and vimentin is observed [31,32]. The giant cell tumor-like subtype co-expresses vimentin and CD68, and it remains unclear whether this subtype is derived from the epithelial cells of SDC or is a giant cell tumor of the salivary glands [33,34] (Figure 3B). Most of the previously reported cases about carcinosarcoma or spindle cell carcinoma of the salivary glands could be subclassified into sarcomatoid SDC [35,36].

The mucin-rich variant of SDC involves tumor nests floating in a mucin pool [37] (Figure 4A). The carcinoma cells in the mucin-rich variant of SDC are cytologically similar to those of conventional SDC; i.e., they exhibit eosinophilic cytoplasm, swollen nuclei, and marked cellular atypia. More rarely, some cases demonstrate a signet-ring cell morphology [38] (Figure 4B), and this subtype contains large amounts of intracellular mucin and extracellular mucin. As mucin pools act as barriers to anti-cancer drugs, this variant of SDC frequently displays resistance to chemotherapy. Mucins are positively stained by Alcian blue and mucicarmine stain.
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The invasive micropapillary variant of SDC is a rare subtype, which is histologically characterized by morula-like small cell clusters arranged in solid patterns or, less commonly, duct-like structures without fibrovascular cores [39,40] (Figure 5A). A clear space surrounds each tumor-cell cluster, separating it from the intervening stroma, which results in a similar appearance to lymphatic vessels. Invasive micropapillary structures usually account for 10% to >90% of such tumors. The cytological features of the invasive micropapillary variant of SDC, which include high-grade cytological atypia, are similar to those of conventional SDC. Immunohistochemically, the invasive micropapillary structures exhibit the reverse polarity or inside-out pattern during staining of epithelial membrane antigen and/or mucin-1 (MUC1) (Figure 5B), whereas CD31 immunostaining of the clear spaces surrounding the micropapillary tumor cell nests produces negative results, which confirms that endothelial tissue is absent from these spaces [41]. This subtype frequently demonstrates lymphatic invasion at numerous sites, as well as regional lymph node metastasis and distal metastasis. Patients with invasive micropapillary SDC display significantly worse prognoses than patients with conventional SDC, despite the small size of such tumors [4,39].

Figure 4: Mucin-rich variant of SDC
(A) Eosinophilic atypical cell clusters are seen floating in a mucin pool.
(B) Signet-ring cells, which contain intracellular mucin and eccentric nuclei, are observed in rare cases of this variant.

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Figure 5: Invasive micropapillary variant of SDC
(A) Solid nests without fibrovascular cores are seen in blood vessel-like spaces.
(B) Signals for MUC1 are observed outside of the tumor cell nests.
Recently, SDC was named based on its histological similarity to IDCDB. Breast cancer is frequently accompanied by in situ lesions, which is called ductal carcinoma in situ (DCIS). Although in situ SDC lesions, which are considered to be caused by “intraductal spread”, are sometimes seen near the main invasive tumor in the surrounding salivary glands, pure in situ lesions are rarely observed [4]. Simpson et al. proposed “pure SDC in situ (SDCIS)” as an entity. SDCIS usually exhibits a high-grade histology inside ducts, which are rimmed by CK5/6+/p63+/calponin+ normal myoepithelial cells. On the other hand, cases of low-grade SDC have also been reported [2,11,22,23], which frequently included an intraductal component. Moreover, in the 4th version of the WHO blue book, intraductal carcinoma was described as a new entity [42] (Figure 6). This entity includes low-grade SDC, LGCCA, and SDCIS, which involve the intraductal proliferation of atypical glandular cells with low- to high-grade cytology [42]. The distinct differences among these tumor subtypes remain unclear, although these carcinomas exhibit better outcomes than conventional SDC.

![Figure 6: Intraductal carcinoma](image)
(A) Atypical eosinophilic cells are observed in ductal structures.
(B) Calponin-positive/myoepithelial cells surround the proliferating atypical cells.

Recently, we proposed “SDC with rhabdoid-like features (SDCRF)” as a novel subtype of SDC [43-45] (Figures 7A and B). SDCRF involves the diffuse proliferation of less cohesive, ovoid, or round atypical cells with eosinophilic cytoplasm and eccentric nuclei. Most cases of SDCRF emerge as a carcinomatous component of CXPA, whereas small numbers of de novo SDCRF have been reported. Moreover, in rare cases SDCRF occurs as an intracapsular lesion; i.e., rhabdoid-like cells proliferate inside the neoplastic ducts of PA. These neoplastic cells usually do not co-express CK and vimentin, or exhibit intracytoplasmic round eosinophilic globular bodies, unlike the true “rhabdoid cells” of malignant rhabdoid tumors and/or vimentin-positive carcinomas of other organs, but they do express SMARCB1 [44]. The loss or aberrant expression of E-cadherin and β-catenin is a particular characteristic of SDCRF cells (Figures 7C and D), and approximately half of SDCRF cases demonstrate genetic changes (point mutations and/or insertions) in the CDH-1 gene, which codes for the E-cadherin molecule [44] (personal communication). Based on its histological characteristics, immunophenotypes, and genetic changes, we propose that SDCRF is the salivary counterpart of pleomorphic lobular
carcinoma of the breast (PLCB) [44]. As SDC was originally characterized by its similarity to IDCBC, it is ironic that SDCRF is akin to PLCB. The outcomes of SDCRF seem to be a bit worse than those of conventional SDC.

SDC frequently exhibits squamous differentiation to varying extents, but no keratinization is usually seen [7]. In such cases, it is necessary to differentiate SDC from mucoepidermoid carcinoma (MEC). MEC is usually composed of mucous cells, intermediate cells, and/or squamous cells, whereas cases of SDC that demonstrate squamous differentiation, most of which belong to the basal-like phenotype of SDC, also display the typical histological features of SDC [12]. Both SDC and MEC are frequently positive for CK5/6 and/or p63, whereas MEC is usually negative for the AR, which is a specific marker of SDC. On the other hand, salivary carcinomas that display high-grade transformation (HGT) frequently demonstrate comedonecrosis, but the presence of a component with the typical histology of a low-grade carcinoma (adenoid cystic carcinoma, acinic cell carcinoma, secretory carcinoma, or epithelial-myoepithelial carcinoma) is important for differentiating SDC from carcinomas with HGT [46].

**Figure 7:** Salivary duct carcinoma with rhabdoid-like features (SDCRF)
The dense and diffuse proliferation of less cohesive atypical cells is seen (A), which contain eosinophilic cytoplasm and eccentric nuclei (B). The SDCRF cells exhibit the loss of E-cadherin (C) and β-catenin (D). Normal salivary gland

5. Immunoprofiles of SDC and their Relationships with Outcomes

Based on the expression patterns of the hormone receptors HER2 and the EGFR, various subclassifications of SDC have been suggested. Di Palma et al. subclassified de novo SDC into
On the other hand, Boyle et al. attempted to classify breast tumors into three groups according to their p53 expression patterns; i.e., into extremely negative, extremely positive, and non-extreme groups [47] (Figures 9A, B, and C). They found that extremely negative/positive p53 expression was significantly associated with worse overall survival (OS) than non-extreme p53 expression, and that combining extremely negative and extremely positive p53 expression resulted in better predictions of OS than using either pattern alone. Extremely negative and extremely positive p53 expression might be related to nonsense mutations or deletions that abrogate protein expression of the TP53 gene and missense mutations in the TP53 gene, respectively. Therefore, Boyle et al. reported that extremely negative/positive p53 expression is an independent prognostic factor in patients with SDC [30]. In the near future, more precise prognostic factors for SDC might be found.

Figure 8: The immunoprofiles of SDC

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6. Genetic alterations and characteristics of SDC

Most SDC express the AR, and SDC are controlled by the AR pathway. The AR requires its co-regulator protein forkhead box protein A1 (FOXA1) to form a productive transcription complex on chromatin in order to mediate the cell- and tissue-specific regulation of target gene expression and to bring about the diverse biological actions of androgens [48-50]. Recently, Urano et al. reported that cases of SDC that exhibited high FOXA1-labeling indices (L.I.) displayed early T classifications more frequently than cases of SDC with low FOXA1-L.I. [51]. The FOXA1-L.I. was significantly correlated with the AR expression level, whereas it was not related to HER2 or Ki-67 expression. Approximately 18% of SDC cases harbor FOXA1 gene mutations (missense mutations, 13 cases; deletions, 9 cases), but no associations were detected between FOXA1 mutations and clinicopathological factors [51]. On the other hand, AR splicing variant 7 (AR-V7), which includes exons 1–3 and a cryptic exon 3 instead of exons 1–8, was detected in prostate cancer [52]. Although AR-V7 lacks the ligand-binding domain, but is transcriptionally active, the ratio of AR-V7 to full-length AR is quite low in SDC [53]. Therefore, it is unclear whether AR-V7 is really related to the resistance to androgen-deprivation therapy (ADT) exhibited by SDC.

Approximately half of SDC cases overexpress HER2 (Figure 10A), whereas the amplification of HER2 gene signals is only found in 15–40% of cases [4,12,29,41,54]. It is well known that phosphatase and tensin homolog (PTEN) (Figure 10B); phosphatidylinositol 4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA); v-Akt murine thymoma viral oncogene homolog (AKT1); and the mammalian target of rapamycin (mTOR) act downstream of the HER2 pathway (the AR-independent pathway) [55-57], and various HER2 pathway mutations are seen in SDC. The most commonly mutated genes in previous SDC cohorts were TP53 (10/15 cases or 68%), PIK3CA (18–53%), PTEN (53%), F-Box and WD repeat domain containing 7 (FBXW7) (53% cases), ATM serine/threonine kinase (ATM)(47% cases), guanine nucleotide-binding protein G subunit alpha (GNAQ) (40% cases), GTPase HRas (HRAS) (16–
A recurrent nuclear receptor coactivator 4 (NCOA4)-RET fusion signal has been found in SDC [59,60], but recently this novel fusion signal was identified in the index case of the intercalated duct type of intraductal and invasive carcinoma, which has been referred to as LGCCA or low-grade SDC. On the other hand, DNA fragmentation factor subunit alpha (DFFA)-AT-rich interactive domain-containing protein 1A (ARID1A) and kinesin family member 13B (KIF13B)-erythrocyte membrane protein band 4.1 like 4B (EPB41L4B) fusion signals were detected at low frequencies in invasive apocrine SDC/SDC with intraductal components, in addition to the PIK3CA and HRAS mutations found in conventional SDC [61]. Notably, a subset the apocrine variant of intraductal carcinoma harbors a novel tripartite motif containing 27 (TRIM27)-RET fusion gene [59, 60], but its significance in tumorigenesis remains unclear; however, a RET gene-targeted therapy might be developed in future.

On the other hand, approximately 50–70% of PA display pleomorphic adenoma gene 1 (PLAG1) or high mobility AT-hook 2 (HMGA2) gene abnormalities; i.e., rearrangements or amplification [62,63]. Bahrami et al. reported that 23% of SDC ex-PA exhibited PLAG1 gene abnormalities (a balanced translocation pattern, an unbalanced translocation pattern, or polysomy), and 18% of SDC ex-PA showed balanced translocation or amplification of the HMGA2 gene [62]. However, SDC ex-PA has been reported to demonstrate the loss of PLAG1 immunopositivity [64]. Although PA is one of the precursors of SDC, the discrepancies between

Figure 10: The HER2 pathway in SDC
The overexpression of the HER2 protein (A) and the loss of PTEN (B) are observed.
the PLAG1-related genetic changes and immunostaining patterns seen in these two lesions require further investigation.

Leivo et al. used a cDNA array to study the gene expression profiles of 13 salivary carcinomas, including SDC, MEC, and acinic cell carcinoma [65]. They detected the overexpression of five genes in all cases: fibronectin 1 (FN1), tissue metalloproteinase inhibitor 1 (TIMP1), biglycan (BGN), tenascin-C (TN-C), and insulin-like growth factor-binding protein 5 (IGFBP5). A few cases of SDC also overexpressed the apoptosis-related genes caspase 19 (CASP19) and matrix metalloproteinase 11 (MMP11).

7. Future Treatments for SDC

There is no standard first-line chemotherapy for recurrent/metastatic or unresectable locally advanced salivary gland carcinoma. Fushimi et al. conducted a mono-institutional, open-label, single-arm, phase II trial of combined androgen blockade (CAB) for AR+ SDC and AdNOS, which indicated that the best overall response rate was 41.7%, and the clinical benefit rate was 75.0%. These findings suggested that compared with conventional chemotherapy CAB exhibited equivalent efficacy and less toxicity for patients with AR+ SDC or AdNOS [66]. Okada et al. performed a retrospective study of 24 patients, which included 6 patients with AR+ SDC who developed progressive disease after being treated with CAB. In the latter study, carboplatin and docetaxel were administered for 6 courses every 3 weeks [67]. The overall survival rate was 42%, the median progression-free survival time was 8.4 months, and the median overall survival time was 26.4 months. They suggested that carboplatin/docetaxel combination therapy might be a chemotherapeutic option for patients with recurrent/metastatic or unresectable/locally advanced SDC and could be a valuable second-line chemotherapy for CAB-resistant AR+ SDC. Similarly, Boon et al. indicated that in advanced AR+ SDC, ADT is effective [68]; i.e., 18% of patients showed partial responses, and 32% of patients had stable disease, leading to a clinical benefit rate of 50%. Therefore, AR+ SDC could be treated similarly to prostate cancer.

Recently, Takahashi et al. conducted a single-center, single-arm, open-label, phase II study of trastuzumab and docetaxel in patients with HER2+ SDC (HER2 score: 3+ or gene amplification detected during fluorescence in situ hybridization) [69]. The overall response rate was 70.2%, and the clinical benefit rate was 84.2%. The median progression-free and overall survival times were 8.9 months and 39.7 months, respectively. In the latter study, trastuzumab plus docetaxel therapy exhibited encouraging efficacy and a manageable toxicity profile in patients with HER2+ SDC.

These reports suggest that pathologists should assess the AR and/or HER2 status of SDC, and that CAB, ADT, and/or trastuzumab therapy are fully effective, even in recurrent/metastatic or locally advanced/unresectable cases of SDC.
8. References


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