Salivary Duct Carcinoma

The Predominance of Apocrine Morphology, Prevalence of Histologic Variants, and Androgen Receptor Expression

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Abstract: Salivary duct carcinoma (SDC) is a prototypic aggressive salivary gland carcinoma. Our aim is to determine the prevalence of histologic variants (micropapillary, basal-like) and androgen receptor (AR) expression in a large multi-institutional series of SDC. AR status was determined by immunohistochemistry (IHC). Most SDCs were characterized by an apocrine phenotype and AR expression. Cases with a non-apocrine phenotype and AR-negative status were studied by additional IHC and fluorescence in situ hybridization for *ETV6* or *MYB*/*NFIB*. The diagnosis of SDC was confirmed in 187 of 199 (94%) cases. Variant morphologies were identified in 12 cases: micropapillary (n = 6), sarcomatoid (n = 3), mucinous (n = 2), and basal-like (n = 1). AR IHC was performed in 183 cases, of which 179 (97.8%) showed AR expression. On the basis of morphologic appearance and results of additional studies, 12 cases were reclassified as squamous cell carcinoma (SCC) (n = 4), epithelial-myoepithelial carcinoma with high-grade transformation (HGT) (n = 2), myoepithelial carcinoma (n = 2), mammary analogue secretory carcinoma, high grade (*ETV6* translocated; n = 1), adenoid cystic carcinoma with HGT (n = 1), acinic cell carcinoma with HGT (n = 1), and adenosquamous carcinoma (n = 1). AR-negative SDC is extremely rare, and the majority of such cases are more accurately classified as other entities. HGTs of other salivary carcinomas and squamous cell carcinoma are the most common mimics of SDC. SDCs with variant morphologies still show at least a minor component of conventional apocrine appearance. Thus, apocrine morphology defines SDC.

Kew Words: salivary duct carcinoma, androgen receptor, mammary analogue secretory carcinoma, epithelial-myoepithelial carcinoma, high-grade transformation

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Salivary duct carcinoma (SDC) is the prototypic aggressive salivary carcinoma.[1] Usually, SDC patients present with bulky disease, extraglandular extension, and regional spread.[2,3] As the name would suggest, SDC is phenotypically ductal, and virtually all cases are characterized by abundant eosinophilic granular cytoplasm and pleomorphic nuclei with prominent nucleoli. Tumor cells are arrayed in various combinations of tubular, cribriform, solid, and papillary components. SDCs often have areas with apocrine morphology defined by the presence of decapitation secretions. In situ components delimited by basal/myoepithelial cells are fairly common, and it is now increasingly obvious that SDC is the most common carcinoma type that arises from pleomorphic adenoma (PA). [4–6]

The dismal clinical outcome and the failure of conventional chemoradiotherapy to adequately manage SDC require a more nuanced approach. Some attempts at targeted therapy exploited the expression of androgen receptor (AR) by SDC.[7,8] As SDC and ductal carcinoma of the breast show morphologic similarities, new therapies discovered for patients with breast carcinomas have been tested on patients with SDC. For instance, anti-HER2/neu therapy has been tried with varying success in some SDC patients.[9,10] Similarly, phosphoinositide 3-kinase pathway inhibitors are now sporadically used in SDC patients. [11,12]

Extrapolating discoveries from breast oncology to SDC has been a productive way to advance our understanding of SDC. To further the ongoing analogy between SDC and breast carcinoma, a basic question has to

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be addressed: Are SDCs sufficiently heterogenous to be subcategorized into several breast carcinoma–like groups, or do all SDCs resemble just one type of breast carcinoma—luminal AR positive?[13] To this end, SDCs were recently stratified into several groups.[14,15] Although these studies relied primarily on immunohistochemical (IHC) markers, possible morphologic correlates were identified (ie, basal-like phenotype). Over the years, several variant morphologies of SDC have been described: micropapillary,[16] sarcomatoid,[17,18] mucin-rich,[19] and basal-like.[15,20] The need for accurate morphologic inclusion criteria has been increasingly recognized, with Di Palma et al[15] specifically excluding poorly differentiated salivary carcinomas. Another observation that raises concern about the "purity" of SDC as reported in the literature is the significant variation (67% to 97%) in reported AR positivity by IHC.[3,14,15,21]

To study the morphologic variety of SDC and in an attempt to identify the morphologic criteria for SDC classification, we reviewed 199 cases diagnosed as SDC at multiple institutions. As AR expression by IHC objectively correlates with the apocrine phenotype, AR IHC was used to complement morphologic review.

MATERIALS AND METHODS

Patients

Cases diagnosed as SDC (n = 199; regardless of morphologic appearance) were identified by the authors. Some cases were previously reported.[4,22] Tumors were staged according to the seventh edition of the American Joint Committee on Cancer.[23] For staging purposes, tumor size was based on the entire tumor including PA and SDC components. In 17 cases, only metastases to regional lymph nodes or distant metastases were available for evaluation, precluding assessment for preexisting PA. Variant morphologies were diagnosed as per prior reports.[16,18,19] For instance, micropapillary morphology consisted of small tufts (without fibrovascular cores) and clusters of cells that appeared to float within clear spaces. This study was approved by the Institutional Review Boards (UPMC, IRB# IRB991206; Southern California Permanente Medical Group, #5968).

Immunohistochemistry

IHC for AR was performed per the manufacturer's recommendations (clone AR441, monoclonal mouse, dilution 1:100; Dako, Carpinteria, CA). IHC studies with other antibodies were carried out according to the manufacturer's recommendation (Table 1, Supplemental Digital Content, http://links.lww.com/PAS/A268). Quantification of AR staining was performed using the Allred system.[24] The Allred total score (TS; ranging from 0 to 8) is reached by adding an intensity score (0, 1, 2, or 3, corresponding to negative, weak, moderate, or strong staining, respectively) to a proportion score (0, 1, 2, 3, 4, or 5, corresponding to negative, $\leq$1%, >1% to 10%, >10% to 33%, >33% to 66%, >66% of carcinoma cells with positive staining).

Fluorescence In Situ Hybridization

Fluorescence in situ hybridization (FISH) for *MYB*/*NFIB* translocation was performed with RP11-104D9 and RP11-349J5/RP11-280O24 clones (cytogenetic Location: 6q22-24/9p24.1; CHORI, Oakland, CA). *MYB*/*NFIB* translocation was detected as follows: normal cells without the translocation show green and orange signals separately. Cells with the *MYB*/*NFIB* translocation show 1 pair of signals (green and orange) in juxtaposition and 1 green and 1 orange signal separated. *MYB*/*NFIB* FISH analysis was manually performed and quantitatively assessed by analysis of a minimum of 60 cells using the *MYB* SpectrumOrange and the *NFIB* SpectrumGreen probes and Leica Biosystems FISH Imaging System (CytoVision FISH Capture and Analysis Workstation) (Buffalo Grove, IL). *ETV6* FISH was performed as previously described.[25]

RESULTS

The diagnosis of SDC was confirmed in 187 of 199 cases (Table 1). Among the patients with confirmed SDC, 7 patients presented with distant metastases, whereas additional 49 patients developed distant metastases after surgery. The 3 most common sites of metastasis were bone (n = 28), lung (n = 24), and the central nervous system (n = 12). Other sites included nonregional lymph nodes, liver, pleura, pericardium, orbit, skin, adrenal, and thyroid glands. In 29 patients, multiple sites of metastatic disease were identified. Owing to the small number and short follow-up for cases with variant morphology (see

TABLE 1. Demographic and Clinicopathologic Features of 187 Patients With Confirmed SDC

Clinicopathologic Feature	N (%)
Sex, male (%)	158/187 (84.5)
Age, mean (range) (y)	67.4 (33-92)
Site* (n = 187)	
Parotid	158 (84.5)
Submandibular	23 (12.3)
Lacrimal	3 (1.6)
Maxilla	1 (0.5)
Palate	1 (0.5)
Tumor size (n = 148), mean (range) (cm)	3.2 (0.5-9)
Origin (n = 187)	
De novo	89 (47.6)
Ex PA	81 (43.3)
Unknown	17 (9.1)
pT (n = 147)	
1	23 (15.6)
2	44 (29.9)
3	41 (27.9)
4	39 (26.5)
pN (n = 131)	
0	22 (16.8)
1	15 (11.5)
2	93 (71.0)
3	1 (0.8)

*The primary tumor site could not be determined in 1 small biopsy designated only as "left neck."

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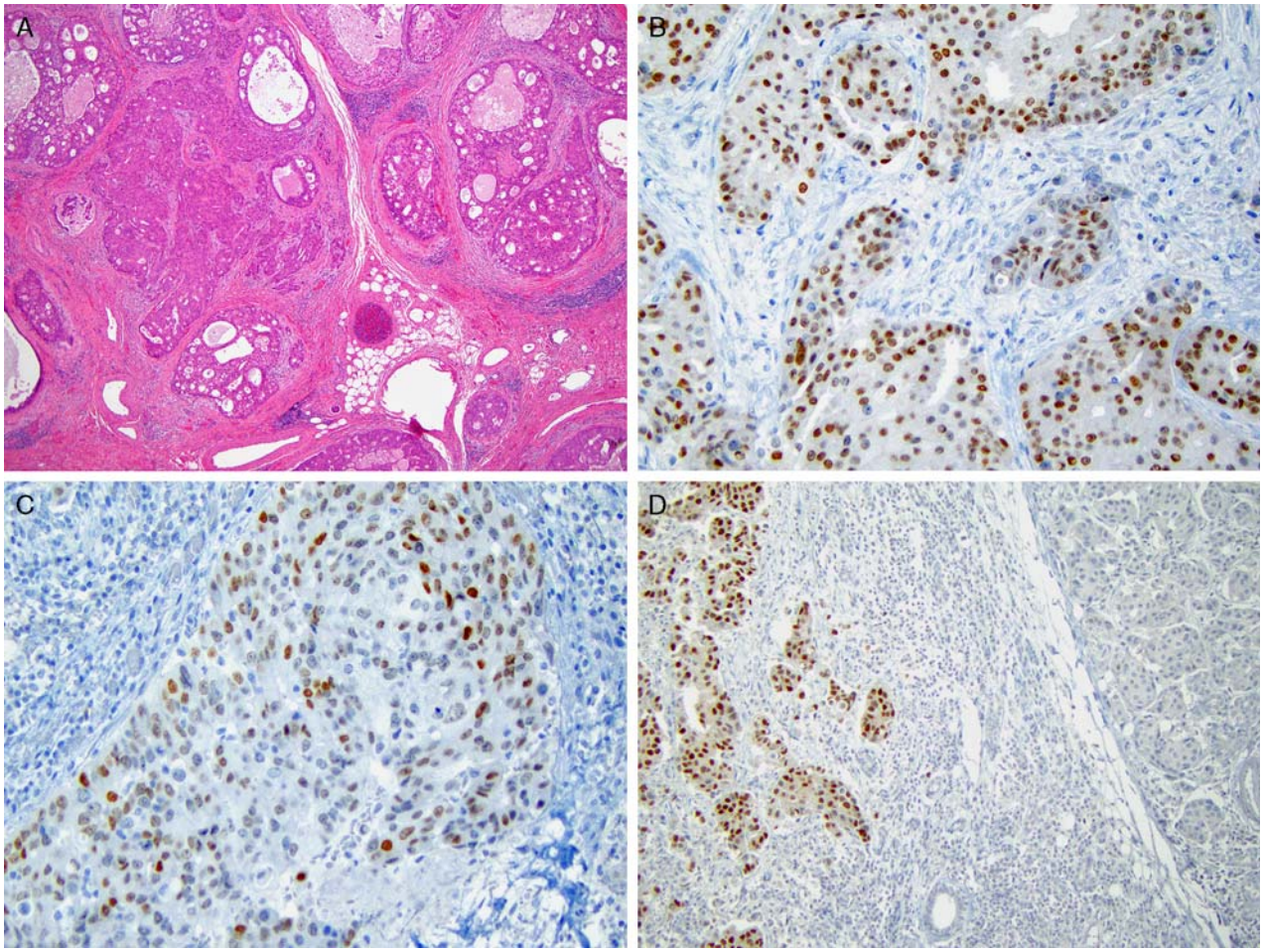

FIGURE 1. SDC and AR expression. A, Prototypical SDC with eosinophilic appearance, cribriform growth, and rounded cystic and solid tumor lobules of variable size (hematoxylin and eosin, [H&E]). B, The majority of SDCs showed AR staining with an Allred total score (TS) of 6 to 8. Representative case with Allred TS 8, consisting of an intensity score of 3 (strong staining) and a proportion score of 5 (staining in >66% of cells) (AR IHC). C, Representative case with an Allred TS of 5, consisting of an intensity score of 2 (moderate staining) and a proportion score of 3 (staining in >10% to 33% of cells) (AR IHC). D, Technical issues encountered during fixation, processing, and/or IHC staining procedures or focal antigen expression by some tumors may result in SDC with partial, localized AR staining. Distribution of AR positivity in this case is suggestive of a fixation issue: the left half of the field shows strong staining, whereas the right half is negative (AR IHC).

below), outcome analyses will be attempted in a later publication.

High-grade adenocarcinomas metastatic to a major salivary gland are routinely considered in the differential diagnosis of SDC. Five patients had a prior history of adenocarcinomas at the time of the SDC diagnosis: prostate origin (n = 3), lung and breast origin (n = 1), and of breast origin only (n = 1). In 3 of these cases, the SDC arose ex PA, and in 1 remaining de novo case an in situ component was present, essentially excluding consideration of metastatic disease in these cases. In 1 patient with de novo SDC without an in situ component, prostate adenocarcinoma was diagnosed 11 years before the development of a submandibular SDC. In this case, IHC for prostate-specific antigen and prostate-specific acid phosphatase was negative. In this series, 3 patients developed adenocarcinoma of the prostate 8 to 10 years after the diagnosis of SDC.

In all 187 cases of confirmed SDC, at least part of the tumor was represented by high-grade apocrine histology (Figs. 1A, 2B). Part of the tumor was represented by micropapillary, sarcomatoid, mucinous, or basal-like morphologies in 12 cases (Table 2). Clinicopathologic features, AR IHC, and the proportion of the tumor represented by variant morphology are summarized in Table 2. All SDCs with variant morphology developed in parotid glands. In all cases variant morphology was intimately admixed with conventional areas. None of the cases showed >1 variant morphology.

In our series, 6 of 187 cases (3.2%) demonstrated an invasive micropapillary component, ranging from 10% to 70% of the primary tumor. One additional case showed

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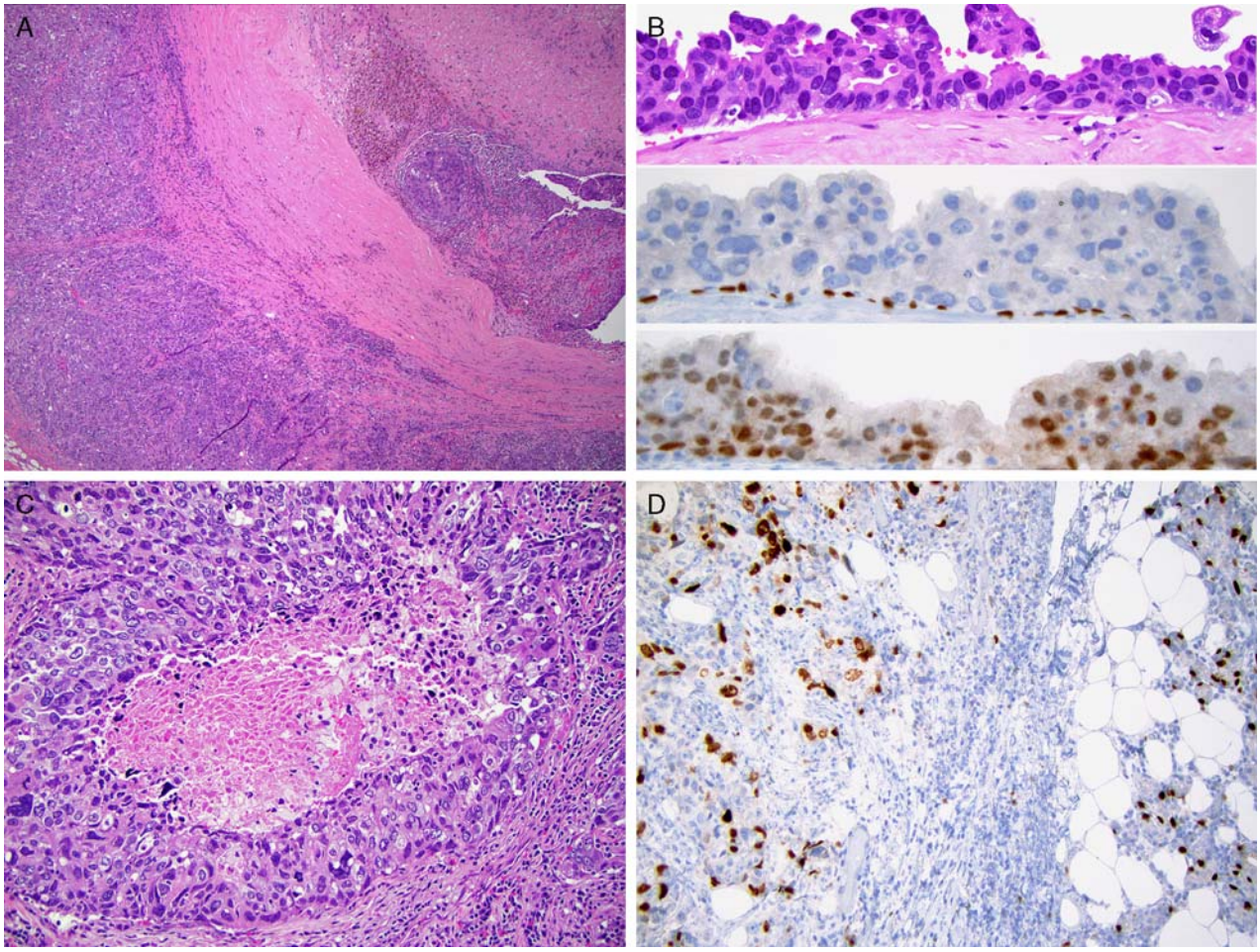

FIGURE 2. Predominantly nonapocrine AR-negative invasive SDC with minor apocrine in situ component adjacent to a hyalinized nodule (HN). A, Invasive SDC, capsule, and HN in the right upper corner (H&E). B, A 0.5 cm SDC in situ adjacent to an HN. The upper one third shows eosinophilic neoplastic cells with apical snouts (H&E). In the middle, IHC stain for p63 highlights basal cells (IHC). The lower one third shows AR IHC (IHC). C, The entire invasive component was represented by solid proliferations of amphophilic, AR-negative neoplastic cells with comedo necrosis (H&E). D, A randomly distributed subset of neoplastic cells (left half) was highlighted by p63 (IHC). Of note, compared with the basal/myoepithelial cells in the adjacent normal parotid tissue (right half), the p63-positive neoplastic cells have larger and more irregular nuclei. H&E indicates hematoxylin and eosin.

micropapillary architecture in the in situ component only (ie, club-shaped projections), comprising approximately 30% of the in situ SDC component. No psammoma bodies were seen.

Sarcomatoid features were identified in 3 cases, 1 of which has been previously described in detail.[21] These cases were characterized by enlarged, bizarre, hyperchromatic nuclei, atypical mitotic figures, and spindled cells.

We identified 2 cases with extracellular mucin comprising 30% and 20% of the primary tumor (Table 2).

Finally, in 1 case, apocrine morphology was limited to an area adjacent to a hyalinized nodule. The remaining tumor was AR negative and focally p63 positive (Fig. 2). The cells in the AR-negative areas demonstrated higher nuclear to cytoplasmic ratios with amphophilic cytoplasm. This is the only case we would characterize as "basal-like."

SDC and AR Expression by IHC

Overall, AR IHC staining was technically adequate in 183 SDCs. In 3 cases, there was insufficient material to perform AR IHC. In 1 additional case, AR IHC failed after repeated attempts using different tissue blocks (IHC for other antibodies failed as well). When selecting tumor blocks for AR IHC, we opted for areas with skin involvement (when present) to include dermal sebaceous glands as a built-in internal positive control. Over 85% of cases demonstrated AR IHC staining with an Allred TS from 6 to 8 (Fig. 1B). The complete results of AR IHC scoring are summarized in Table 3.

Potential technical issues encountered during fixation and/or IHC staining complicated AR IHC

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TABLE 2. Clinicopathologic Features of 12 Patients With Morphologic Variants of SDC

Case #	Variant Morphology Type	%	Sex	Age	Ex PA	pT	pN	Distant Metastasis, Site	Postop. Therapy	AR (TS)
1	Micropapillary	70*	M	56	+	1	2b	—	CT, RT	3
2		10	M	45	+	4a	2b	—	CT, RT	6
3		20	F	77	–	3	2b	—	NA	8
4		30	M	77	–	3	2b	—	RT	3
5		20	F	61	–	4a	0	—	NA	8
6		50	M	79	–	4a	2b	—	NA	4
7	Sarcomatoid	10	M	60	–	3	2b	Lung	RT	8
8		80	M	68	–	4a	0	—	RT	3
9		60	M	71	+	3	x	Brain, lung, spinal cord, ribs	RT	8
10	Mucinous	30	M	72	+	3	1	—	NA	5
11		20	M	72	–	2	2b	Pleura	NA	0
12	Basal-like	95	F	66	+	2	2b	—	CT, RT	4

*In this case, the primary tumor demonstrated purely conventional morphology, and only lymph node metastases showed an invasive micropapillary growth pattern (70% refers to the proportion of tumor in lymph nodes with micropapillary morphology).

AR indicates androgen receptor; CT, chemotherapy; F, female; M, man; NA, not available; PA, pleomorphic adenoma; postop, postoperative; RT, radiotherapy; TS, total score.

interpretation in 5 cases. We identified 3 cases with a conventional apocrine appearance in which the initial AR IHC was negative. Repeat staining (in 2 cases on a different tissue block) showed TS of 6 (n = 1) and TS of 8 (n = 2). Two other cases showed strong staining in one half of the tissue section sharply juxtaposed to completely negative staining in the other half (Fig. 1D).

Four SDCs were AR IHC negative. Three of these SDCs occurred in women. Three of the 4 occurred in the parotid gland, and 1 case arose in the lacrimal gland.

IHC evaluation for cytokeratin (CK7) revealed that 104 of 105 (99.1%) tested cases were positive. Among cases with variant morphologies, 3 of 3 cases with invasive micropapillary growth, 2 of 2 cases with sarcomatoid features, and 1 of 1 case with extracellular mucin were CK7 positive. The only CK7 IHC-negative case showed conventional morphology. Thirty-two of 38 tested cases were positive for GCDFP 15.

TABLE 3. Results of AR IHC Allred Scoring in 183 Patients With SDC

Combination of Intensity Score and Proportion Score			
Intensity Score	Proportion Score	TS	N (%)
3	5	8	115 (63)
2	5	7	24 (13)
3	4	7	8 (4)
2	4	6	7 (4)
3	3	6	1 (0.5)
1	5	6	1 (0.5)
2	3	5	6 (3)
1	4	5	2 (1)
3	2	5	1 (0.5)
2	2	4	8 (4)
1	3	4	1 (0.5)
1	2	3	5 (3)
0	0	0	4 (2.2)

Mimics of SDC

Twelve of 199 cases with an original diagnosis of SDC were recharacterized by the coauthors as summarized in Table 4. The main reason for our reclassification was recognition of a better-differentiated component diagnostic of other salivary tumors (Figs. 3–5) or recognition of subtle but evenly distributed predominantly nonkeratinizing squamous differentiation. Such morphologic findings prompted additional IHC or FISH studies (Table 4). All reclassified cases were AR IHC negative.

TABLE 4. Revised Diagnoses in 12 Cases

Revised Diagnosis and No. Cases	Justification
EMCA with HGT (n = 2)	Dual-cell population in the distinct well-differentiated component (Fig. 3D) or throughout the entire neoplasm (Fig. 5); myoepithelial cells highlighted by p63 and smooth muscle actin IHC
Myoepithelial carcinoma (n = 2)	Plasmacytoid cells, droplets of hyalinized stroma (Fig. 3C); strong, diffuse p63 and S100 IHC
Adenoid cystic carcinoma with HGT* (n = 1)	Cribriform growth pattern, pseudolumina filled with basement membrane material (Fig. 3A); pulmonary metastases with conventional cribriform-tubular growth
Acinic cell carcinoma with HGT (n = 1)	Zymogen granules (Fig. 3B) highlighted by periodic acid-Schiff with diastase histochemistry; positive DOG1 by IHC
MASC (n = 1)	Microfollicular growth with colloid-like secretions in lower-grade areas (Fig. 4); presence of *ETV6* translocation by FISH
Predominantly NK SCC (n = 4)	Subtle keratinization; strong, diffuse p63 expression by IHC
Adenosquamous carcinoma (n = 1)	Subtle keratinization and glandular differentiation; strong, diffuse p63 expression by IHC

*No evidence of *MYB*/*NFIB* translocation by FISH.

EMCA indicates epithelial-myoepithelial carcinoma; MASC, mammary analogue secretory carcinoma; NK, nonkeratinizing.

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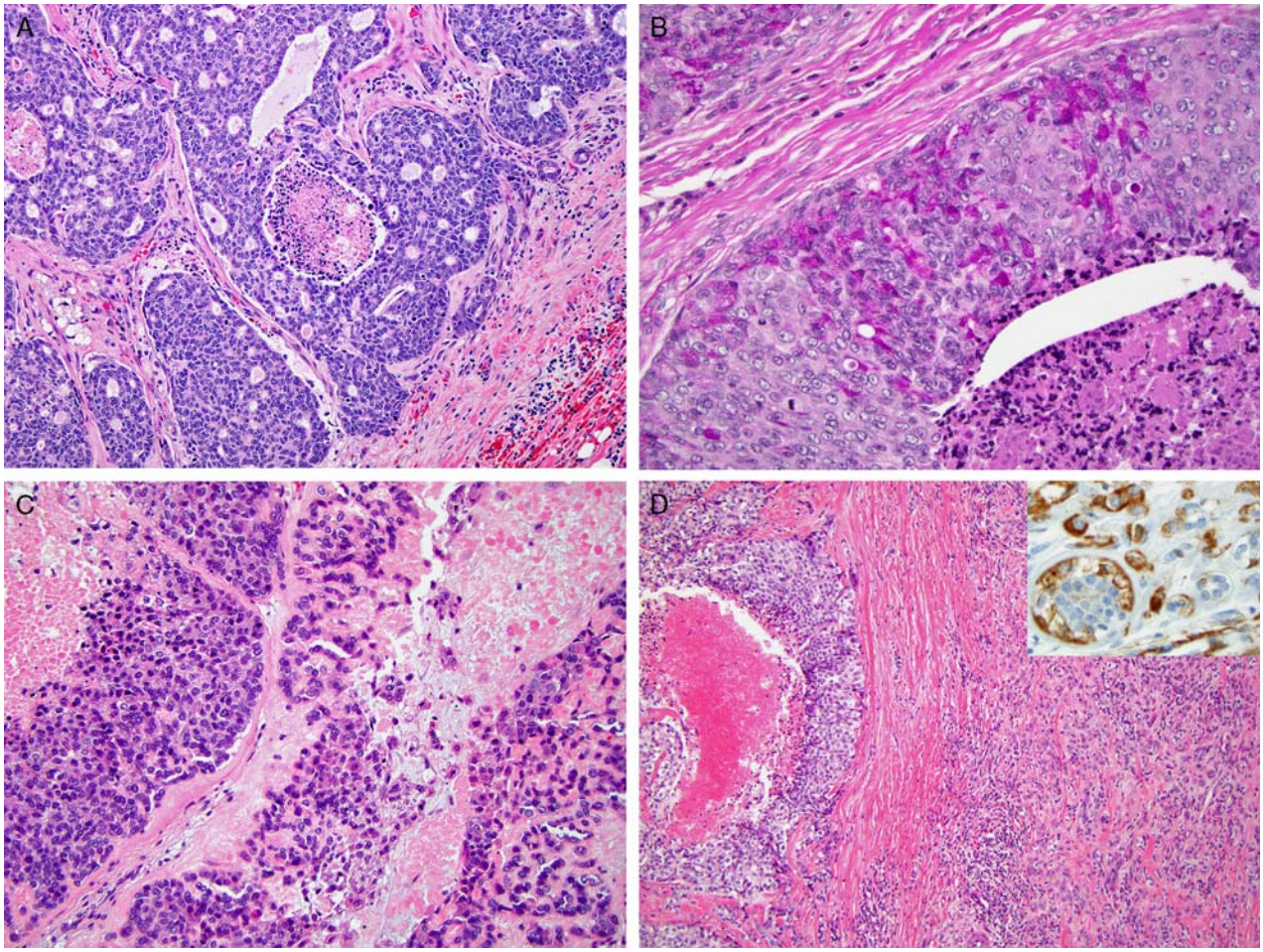

FIGURE 3. Distinguishing high-grade salivary tumors with comedo-type necrosis from SDC. A, Adenoid cystic carcinoma (AdCC) with high grade transformation (HGT). Basophilic appearance, cribriform growth pattern, and pseudolumina filled with basement membrane–like material raise the possibility of an AdCC. Fourteen months after the initial diagnosis of SDC, this patient developed pulmonary metastases with cribriform-tubular AdCC (H&E). B, Acinic cell carcinoma with HGT. A minority of cells surrounding foci of necrosis have numerous cytoplasmic zymogen granules, best appreciated on periodic acid-Schiff with diastase histochemical stain. C, Myoepithelial carcinoma ex PA. Solid sheets of neoplastic cells do not form glands and are accompanied by droplets of hyalinized material. Nuclear palisading was absent (H&E). D, Epithelial-myoepithelial carcinoma with HGT: an area with comedo-type necrosis is accompanied by a better-differentiated component with dual-cell population: smooth muscle actin IHC highlights the outer layer of myoepithelial cells (right upper corner inset) (H&E). H&E indicates hematoxylin and eosin.

DISCUSSION

In agreement with prior reports, this study shows that SDC affects predominantly major salivary glands of older men, who usually present at an advanced stage.[3,26,27] All cases demonstrated high nuclear grade. Therefore, in SDC, the histologic classification defines the grade and precludes any need for further grading. [28]

Prior studies of SDC identified micropapillary, sarcomatoid, and mucinous variants.[16–19] By reviewing the largest collection of SDC from multiple institutions, we aimed to determine the prevalence of these histologic variants and the proportion of variant morphology in a given case. The histologic variants of SDC appear to be less frequent than previously reported. For instance, SDC with micropapillary growth represented 17% (14 of 82) of SDC in Mayo Clinic experience.[16] It is unclear why the prevalence of micropapillary growth in this study is lower (3.2%). Partly, it could be because of the variation in the proportion of micropapillary growth; both in this and prior reports, micropapillary growth comprised as little as 10% of the tumor volume. We identified no cases with >90% micropapillary growth. It appears that SDCs with micropapillary or other variant morphologies are exceedingly rare and do not seem to be found in "pure" form, and determining an evidence-based minimal proportion that would define this histologic SDC variant will be very challenging.

The diagnosis of the basal-like variant of SDC remains to be most challenging, and the difficulties of identifying a basal-like phenotype in SDC have been previously recognized.[15,20] Di Palma and colleagues highlighted the need to exclude "poorly differentiated"

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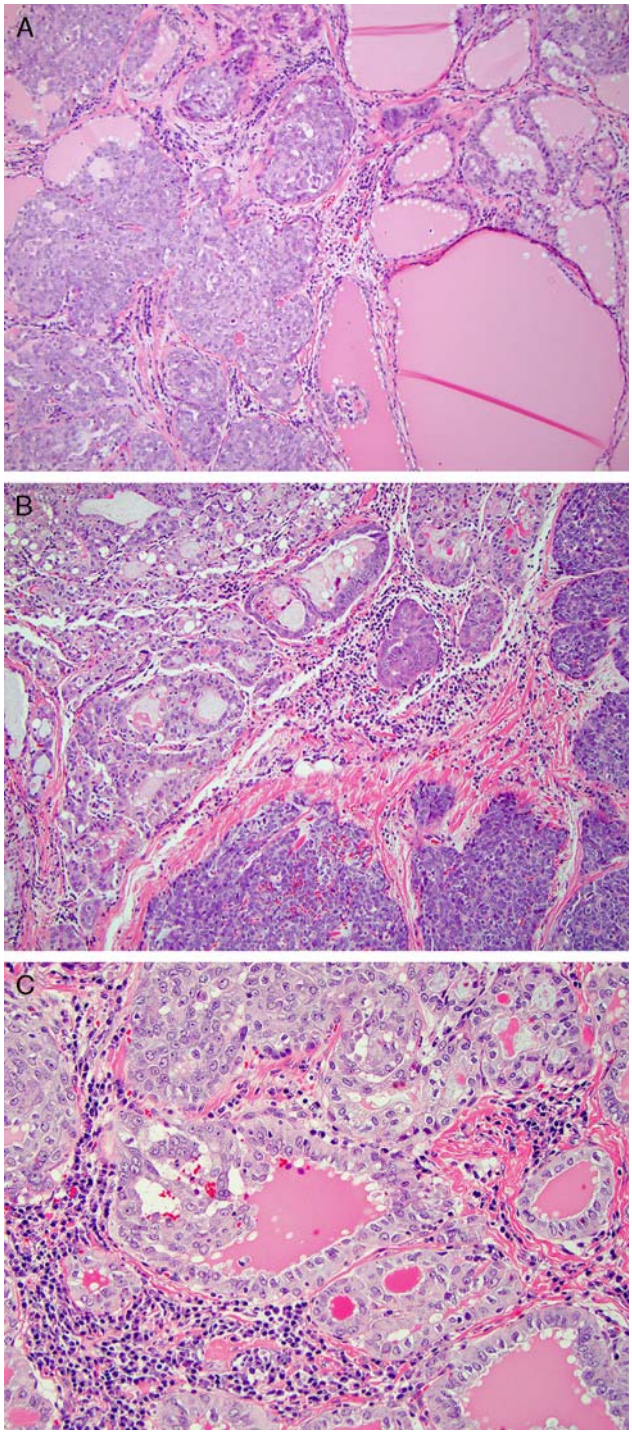

FIGURE 4. Mammary analogue secretory carcinoma (MASC), high grade. Two carcinomatous components—conventional microcystic with abundant eosinophilic colloid-like secretions and solid basophilic with minimal secretory activity—were intermingled in some areas (A, H&E) and sharply demarcated in others (B, H&E). C, Even conventional MASC areas with secretory activity are characterized by columnar rather than cuboidal cells. There was no necrosis (H&E). H&E indicates hematoxylin and eosin.

carcinomas, especially those with a myoepithelial component. The best candidate for an SDC with a basal-like phenotype in our study is illustrated in Figure 2. Like all other SDCs, it had a focus of conventional apocrine component. However, the bulk of the tumor had amphophilic cytoplasm and acquired p63 and lost AR expression. Importantly, there were no features of other types of salivary carcinomas. Interestingly, the most recent other candidate for basal-like SDC illustrated in the English literature appears to resemble an epithelial-myoepithelial carcinoma with high-grade transformation (HGT) (figure 3 in Di Palma et al[15]). Although we did not review the actual glass slides, our impression is based on photomicrographs demonstrating dual-cell population (highlighted by cytokeratin 5/6), clear polygonal cells surrounding gland-like structures, and presumed absence of more conventional SDC areas.

AR expression correlates with the apocrine phenotype, and AR IHC showed a TS of 6 to 8 in the vast majority of our cases. If ASCO/CAP guidelines for interpretation of estrogen receptor were applied to AR IHC in SDC and cases with a TS of "3" were accepted as "positive,"[29] the AR IHC positivity in this study would be higher than previously reported.[3,15] This may be attributed to the explicit attention to the technical issues of AR IHC and the application of strict criteria to diagnose SDC. For instance, we repeated AR IHC on cases with conventional apocrine morphology if the first AR stain was negative. Rereview by several study pathologists and additional workup of some AR-negative cases resulted in reclassification to other entities.

The lack of AR expression was reportedly associated with a trend toward worse outcome.[3,14] Considering how aggressive SDCs are, we were interested in identifying carcinomas that appeared to be more aggressive than SDC. Our findings indicate that squamous cell carcinomas (SCCs) involving major salivary glands and non-SDC salivary tumors with HGT represent the AR-negative group of cancers that appeared to be clinically more aggressive than SDC.

Primary SCCs of salivary glands are extremely rare. Cutaneous SCC usually involves the parotid gland by direct extension or by extensive extranodal spread after initial metastasis to intraparotid lymph nodes. Distinguishing SDC from SCC can be made more objective and reliable with two IHC stains: AR and p63. We showed that most SDCs express AR. Almost all SCCs are p63 positive, whereas SDC, like most other adenocarcinomas, are expected to be p63 negative.

Before accepting the diagnosis of AR-negative SDC, the possibility of another type of salivary carcinoma with HGT has to be evaluated. Areas of HGT of adenoid cystic carcinoma or epithelial-myoepithelial carcinoma are characterized by necrosis and may closely mimic SDC. Some well-differentiated areas with biphasic cellular populations (ie, inner ductal cells and outer basal/myoepithelial cells) are usually preserved in adenoid cystic carcinomas and epithelial-myoepithelial carcinomas. In such areas, the outer basal/myoepithelial cells will be highlighted by p63 IHC.

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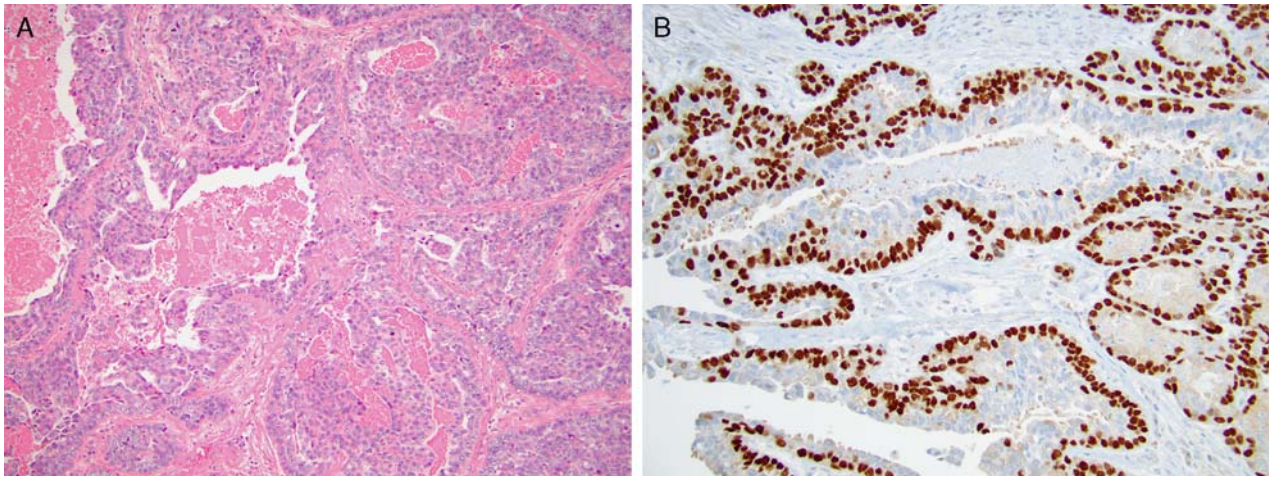

FIGURE 5. Epithelial-myoepithelial carcinoma (EMCA) with high grade transformation (HGT). A, The tumor has an overall eosinophilic appearance with glands, pink secretions, and abundant necrosis (hematoxylin and eosin). B, p63 IHC highlights the dual-cell population. Unlike residual basal/myoepithelial cell outlining SDC in situ, these myoepithelial cells show an architecturally complex trabecular arrangement and in areas of myoepithelial overgrowth are multilayered. The nuclei of myoepithelial cells of EMCA are enlarged and irregular (p63 IHC).

Inspired by studies of breast carcinomas and on the basis of morphology and expression of IHC markers (including AR), two recent reports categorized SDC into several groups.[14,15] Although we did not formally attempt such classification here, our results highlight the difficulties of identifying truly AR-negative SDC and the exceptional rarity of morphologic variants, particularly those with a basal-like phenotype. On the basis of morphology and AR IHC expression, almost all SDCs appear to resemble just one type of breast carcinoma—luminal AR-positive type (first described as "molecular apocrine" type).[13,30–32]

In summary, we contend that apocrine phenotype and AR expression define SDC and that nonapocrine tumors can almost always be better classified as other entities. Nonkeratinizing SCCs and salivary-type carcinomas with HGT are the most common tumor types that masquerade as "nonapocrine and AR-negative" SDC. Micropapillary and other variant morphologies are rare and are accompanied by conventional apocrine areas.

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REFERENCES

1. Kleinsasser O, Klein HJ, Hubner G. Salivary duct carcinoma. A group of salivary gland tumors analogous to mammary duct carcinoma. *Arch Klin Exp Ohren Nasen Kehlkopfheilkd*. 1968;192:100–105.
2. Hosal AS, Fan C, Barnes L, et al. Salivary duct carcinoma. *Otolaryngol Head Neck Surg*. 2003;129:720–725.
3. Williams MD, Roberts D, Blumenschein GR Jr, et al. Differential expression of hormonal and growth factor receptors in salivary duct carcinomas: biologic significance and potential role in therapeutic stratification of patients. *Am J Surg Pathol*. 2007;31:1645–1652.
4. Bahrami A, Perez-Ordonez B, Dalton JD, et al. An analysis of PLAG1 and HMGA2 rearrangements in salivary duct carcinoma and examination of the role of precursor lesions. *Histopathology*. 2013;63:250–262.
5. Katabi N, Gomez D, Klimstra DS, et al. Prognostic factors of recurrence in salivary carcinoma ex pleomorphic adenoma, with emphasis on the carcinoma histologic subtype: a clinicopathologic study of 43 cases. *Hum Pathol*. 2010;41:927–934.
6. Lewis JE, Olsen KD, Sebo TJ. Carcinoma ex pleomorphic adenoma: pathologic analysis of 73 cases. *Hum Pathol*. 2001;32:596–604.
7. Kapadia SB, Barnes L. Expression of androgen receptor, gross cystic disease fluid protein, and CD44 in salivary duct carcinoma. *Mod Pathol*. 1998;11:1033–1038.
8. Jaspers HC, Verbist BM, Schoffelen R, et al. Androgen receptor-positive salivary duct carcinoma: a disease entity with promising new treatment options. *J Clin Oncol*. 2011;29:e473–e476.
9. Nashed M, Casasola RJ. Biological therapy of salivary duct carcinoma. *J Laryngol Otol*. 2009;123:250–252.
10. Kaidar-Person O, Billan S, Kuten A. Targeted therapy with trastuzumab for advanced salivary ductal carcinoma: case report and literature review. *Med Oncol*. 2012;29:704–706.
11. Nardi V, Sadow PM, Juric D, et al. Detection of novel actionable genetic changes in salivary duct carcinoma helps direct patient treatment. *Clin Cancer Res*. 2013;19:480–490.
12. Piha-Paul SA, Cohen PR, Kurzrock R. Salivary duct carcinoma: Targeting the phosphatidylinositol 3-kinase pathway by blocking mammalian target of rapamycin with temsirolimus. *J Clin Oncol*. 2011;29:e727–e730.
13. Farmer P, Bonnefoi H, Becette V, et al. Identification of molecular apocrine breast tumours by microarray analysis. *Oncogene*. 2005;24:4660–4671.
14. Masubuchi T, Tada Y, Maruya SI, et al. Clinicopathological significance of androgen receptor, HER2, Ki-67 and EGFR expressions in salivary duct carcinoma. *Int J Clin Oncol*. 2015;20:35–44.
15. Di Palma S, Simpson RH, Marchio C, et al. Salivary duct carcinomas can be classified into luminal androgen receptor-positive, HER2 and basal-like phenotypes. *Histopathology*. 2012;61:629–643.
16. Nagao T, Gaffey TA, Visscher DW, et al. Invasive micropapillary salivary duct carcinoma: a distinct histologic variant with biologic significance. *Am J Surg Pathol*. 2004;28:319–326.
17. Henley JD, Seo IS, Dayan D, et al. Sarcomatoid salivary duct carcinoma of the parotid gland. *Hum Pathol*. 2000;31:208–213.

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18. Nagao T, Gaffey TA, Serizawa H, et al. Sarcomatoid variant of salivary duct carcinoma: clinicopathologic and immunohistochemical study of eight cases with review of the literature. *Am J Surg Pathol*. 2004;122:222–231.
19. Simpson RH, Prasad AR, Lewis JE, et al. Mucin-rich variant of salivary duct carcinoma: a clinicopathologic and immunohistochemical study of four cases. *Am J Surg Pathol*. 2003;27:1070–1079.
20. Hungermann D, Roeser K, Buerger H, et al. Salivary duct carcinoma. *Pathologe*. 2005;26:353–358.
21. Griffith CC, Seethala RR, Luvison A, et al. PIK3CA mutations and PTEN loss in salivary duct carcinomas. *Am J Surg Pathol*. 2013;37:1201–1207.
22. Griffith CC, Thompson LD, Assaad A, et al. Salivary duct carcinoma and the concept of early carcinoma ex pleomorphic adenoma. *Histopathology*. 2014;65:854–860.
23. Edge SB, Byrd DR, Compton CC, et al. *AJCC Cancer Staging Handbook: From the AJCC Cancer Staging Manual*. New York: Springer; 2009.
24. Harvey JM, Clark GM, Osborne CK, et al. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. *J Clin Oncol*. 1999;17:1474–1481.
25. Chiosea SI, Griffith C, Assaad A, et al. The profile of acinic cell carcinoma after recognition of mammary analog secretory carcinoma. *Am J Surg Pathol*. 2012;36:343–350.
26. Jaehne M, Roeser K, Jaekel T, et al. Clinical and immunohistologic typing of salivary duct carcinoma: a report of 50 cases. *Cancer*. 2005;103:2526–2533.
27. Lewis JE, McKinney BC, Weiland LH, et al. Salivary duct carcinoma. Clinicopathologic and immunohistochemical review of 26 cases. *Cancer*. 1996;77:223–230.
28. Jayaprakash V, Merzianu M, Warren GW, et al. Survival rates and prognostic factors for infiltrating salivary duct carcinoma: analysis of 228 cases from the Surveillance, Epidemiology, and End Results database. *Head Neck*. 2014;36:694–701.
29. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *Arch Pathol Lab Med*. 2010;134:907–922.
30. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature*. 2000;406:747–752.
31. Hirshfield KM, Ganesan S. Triple-negative breast cancer: molecular subtypes and targeted therapy. *Curr Opin Obstet Gynecol*. 2014;26:34–40.
32. Lehmann BD, Bauer JA, Chen X, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *J Clin Invest*. 2011;121:2750–2767.

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