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Dr. S. Chiosea declares he has no conflict of interest to disclose.

Salivary Duct Carcinoma: Its Apocrine Nature, Mimics, and Androgen Receptor Immunohistochemistry

S. Chiosea
University of Pittsburgh Medical Center

Salivary Duct Carcinoma (SDC): its Apocrine Nature and Androgen Receptor (AR) Expression

1968: SDC was first described by Kleinsasser et al.
1991: SDC was recognized as a distinct entity by the World Health Organization (WHO)
1998, 2000: Dr. Barnes and colleagues reported several novel findings regarding the morphology of and AR expression in SDC
2015: Multi-institutional study of SDC on predominance of apocrine morphology, histologic variants, and AR expression.

Expression of AR in SDC was an incidental discovery. When a pathology resident was asked to request ER and PR immunostains in a case of SDC, he also inadvertently ordered an AR immunostain. Surprisingly, all neoplastic cells were diffusely and strongly stained with the anti-AR antibody. This discovery led to a study by Kapadia and Barnes, in which 12 SDCs were stained for AR and 11 (92%: 7 men, 4 women) were found to be positive.
Salivary Duct Carcinoma (SDC): its Apocrine Nature and Androgen Receptor (AR) Expression

1998, 2000, Dr. Barnes and colleagues:

#1: “Papillary-cribriform areas, necrosis, pleomorphism, apocrine appearance,… and diffuse, strong nuclear immunoreactivity … for AR… are characteristic of SDC.”

#2: “The magnitude of the AR expression in SDC approaches that seen in prostate carcinoma. By contrast, AR expression in breast carcinoma remains sporadic, except for apocrine breast carcinoma.”

#3: “… hormonal profile (i.e., ER-PR-AR +) suggests that SDC… is immunophenotypically related to prostatic carcinoma. The expression of AR in SDC raises the possibility that anti-androgen therapy might have a role in the management of patients with disseminated disease”.

Salivary Duct Carcinoma: its Apocrine Nature and Androgen Receptor Expression

1998, 2000, Dr. Barnes and colleagues:

#1: “… apocrine appearance,… and diffuse, strong immunoreactivity … for AR… are characteristic of SDC.”

SDC: An Apocrine High Grade Adenocarcinoma

Apocrine Phenotype AR Expression

The Knowledge Of Nearly Uniform AR ‘+’ in SDC Has Affected UPMC Practice:

- High skepticism about cases of non-apocrine AR ‘-’ salivary duct carcinoma
- Intraductal carcinoma (Low grade cribriform cystadenocarcinoma, LGCCA) is unrelated to SDC
  - All SDC are high grade
  - Avoid the use of "low grade SDC" (as a synonym to LGCCA)

Is there a Non-Apocrine/ Androgen Receptor Negative SDC?

<table>
<thead>
<tr>
<th>HER2</th>
<th>ER (o)</th>
<th>PR</th>
<th>AR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDC</td>
<td>17- 44%</td>
<td>0-8%</td>
<td>0-4%</td>
</tr>
</tbody>
</table>

What is the morphology of an AR-negative SDC?

2015, Multi-institutional study of 199 cases of SDC

Mimics of SDC: Adenoid Cystic Carcinoma with High Grade Transformation (HGT)

Young female; Non-apocrine, AR-negative; pulmonary metastasis with unequivocal morphology of adenoid cystic carcinoma; no MYB/NFIB translocation by FISH
Mimics of SDC: Epithelial Myoepithelial Carcinoma, High Grade

Dual cell population in conventional area (with p63/p40 ~+) 
Myoepithelial overgrowth and Comedo-necrosis in High grade area

Mimics of SDC: Acinic Cell Carcinoma with High Grade Transformation (HGT)

Zymogen granules highlighted by PASD; Focal DOG1 positivity

Comedo-Type Necrosis ≠ Salivary Duct Carcinoma

Other types of salivary carcinomas with high grade transformation mimic SDC

Mimics of SDC: Non-Keratinizing Squamous Cell Carcinoma (AR “-” & p63 “+”) Metastatic to Parotid

Micropapillary SDC

Micropapillary: Rare - 6/187
All AR IHC “+”

EMA, “inside-out” pattern seen in 1 of 6 cases

SDC: An Apocrine High Grade Adenocarcinoma

• The most common mimics of SDC are:
  -- SDC is mimicked by other types of salivary carcinomas with high grade transformation:
  -- Squamous cell carcinomas metastatic to parotid area
• 98% of SDC are apocrine and AR IHC+
• Variant morphologies are rare and are not found in “pure” form

Sarcomatoid SDC and AR Expression
3/187; all 3 cases AR “+” in conventional component

Mucinous SDC and AR Expression
Mucinous: 2/187
1 of 2 AR “-”

Basal-Like SDC and AR Expression
1/187
SDC component within the pre-existing PA
Extensive sampling key to identifying apocrine component

98% of Salivary Duct Carcinomas are Apocrine/AR-positive

No Relationship Between SDC & Intraductal Carcinoma (Low Grade Cribriform Cystadenocarcinoma)

Intraductal Carcinoma (Low Grade Cribriform Cystadenocarcinoma)
### SDC vs. Intraductal Carcinoma (Low Grade Cribriform Cystadenocarcinoma)

<table>
<thead>
<tr>
<th></th>
<th>AR</th>
<th>$S_{10}$</th>
<th>SOX10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salivary duct carcinoma</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Intraductal carcinoma/LGCCA</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mammary analogue secretory carcinoma</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Acinic cell carcinoma</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

A subset of LGCCA harbour RET rearrangement. I. Weinreb et al., USCAP 2016

### SDC, Comparison to Breast Carcinoma

1998, 2001, Dr. Barnes and colleagues:

1. "Papillary-cribriform areas, necrosis, pleomorphism, apocrine appearance, ... and diffuse, strong nuclear immunoreactivity ... for androgen receptor ... are characteristic of salivary duct carcinoma."

2. The scale and magnitude of the androgen receptor (AR) expression in salivary duct carcinoma approaches that seen in prostate carcinoma. By contrast, AR expression in breast carcinoma remains sporadic, except for apocrine breast carcinoma.

### SDC Resembles A Specific Type of Breast Carcinoma: Luminal AR “+”

#2: The scale and magnitude of the AR expression in SDC approaches that seen in prostate carcinoma. By contrast, AR expression in breast carcinoma remains sporadic, except for apocrine breast carcinoma.

<table>
<thead>
<tr>
<th></th>
<th>Salivary Duct Carcinoma</th>
<th>Luminal AR+ breast carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER/PR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AR</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Prevalence of PIK3CA, TP53 mutations</td>
<td>Comparable</td>
<td></td>
</tr>
<tr>
<td>PLAG1, HMGA2 rearrangements</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Chiosea, et al, AJSP, 2015; Dalin et al., CCR, 2016; Chiosea et al, Cancer 2016

### SDC, Comparison to Prostate Carcinoma

1998, 2001, Dr. Barnes and colleagues:

1. Apocrine appearance, ... and diffuse, strong nuclear immunoreactivity ... for AR ... are characteristic of SDC.

2. "The scale and magnitude of the AR expression in SDC approaches that seen in prostate carcinoma. By contrast, AR expression in breast carcinoma remains sporadic, except for apocrine breast carcinoma.

3. "The ... expression of AR in SDC raises the possibility that anti-androgen therapy might have a role in the management of patients with disseminated disease."

### Salivary Duct Carcinoma & Androgen Deprivation Therapy (ADT)

1993 – first inadvertent attempt to treat SDC with ADT:

Van Krieken JH, Van der Hulst RW et al., Lancet, 1994: Although provided photomicrographs and histologic description are most consistent with SDC, the authors did not actually use the term “salivary duct carcinoma”, complicating the literature search.

### Salivary Duct Carcinoma & Androgen Deprivation Therapy

1993 – first inadvertent attempt of ADT for SDC:

66-year-old man with a 5 cm retro-auricular mass. A 1 cm biopsy revealed an adenocarcinoma positive for prostate specific antigen (PSA) and prostatic acid phosphatase (PAP).

PAS+/PAP+ immunoprofile was believed to be indicative of prostatic adenocarcinoma.

The patient was treated with an anti-testosterone (goserelin), without clinical evidence of primary prostatic carcinoma (benign prostate biopsies, negative bone scan, and normal PSA serum level).

The retro-auricular tumor regressed.
Salivary Duct Carcinoma (SDC) or Prostate Adenocarcinoma? New markers

Dr. Barnes et al showed that PSA and PAP may be positive in a number of SDCs.

Salivary Duct Carcinoma & Androgen Deprivation Therapy

Similarities and differences between AR pathway activation in SDC and prostate cancer have been delineated:

<table>
<thead>
<tr>
<th>SDC</th>
<th>Prostate Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncogenic AR splice variants</td>
<td>+</td>
</tr>
<tr>
<td>(AR-V7) associated with</td>
<td>+</td>
</tr>
<tr>
<td>resistance to ADT</td>
<td></td>
</tr>
<tr>
<td>Activating AR mutations</td>
<td>-</td>
</tr>
<tr>
<td>AR amplification</td>
<td>-</td>
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</table>

In the future, SDC patients may be selected for ADT clinical trials based on AR isoforms.

Summary: Evolution Of Observations Made By Dr. Barnes and Colleagues


References:

Important Information Regarding CME/SAMs

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No claims can be processed after that date!

After September 30, 2017 you will NOT be able to obtain any CME or SAMs credits for attending this meeting.

THANK YOU
Mimics of SDC: Mammary Analogue Secretory Carcinoma, High Grade

AR **+, S100 ++ IHC; positive for ETV6 translocation by FISH