NEXT GENERATION LEARNING

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Dr. Simon Chiosea declares he has no conflict(s) of interest to disclose.
A 60-year old Man with Left Jaw Mass

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A 60-year old Man with Left Jaw Mass

- Asymptomatic, painless
- Unknown duration
- Imaging - 5.8 cm lobulated heterogeneous hypoechoic indeterminate mass in left deep lobe parotid gland, likely neoplastic
- Parotid Fine Needle Aspiration (FNA)
Fine Needle Aspiration of Parotid Mass

Scant cellularity, clean background, metachromatic fibrillary stroma

FNA Diagnosis:
Satisfactory for interpretation; Positive for neoplasm
Favor pleomorphic adenoma (PA) or other salivary neoplasm with myoepithelial component

Left Deep Lobe Parotidectomy with Facial Nerve Dissection
Well Circumscribed 5.8 cm Parotid Mass
Partially Encapsulated, Satellite Nodule
Cellular Pleomorphic Adenoma Component
Well Circumscribed Parotid Mass

Cellular Pleomorphic Adenoma Component
The Non-Pleomorphic Adenoma Component
Non-PA Component: Complex Architecture & High Grade Cytology
Androgen Receptor IHC: Positive Only in Carcinomatous Component & Confirms It’s Apocrine Nature

>95% of salivary duct carcinomas are AR positive

Williams L., et al., AJSP, 2015
Final Diagnosis

LEFT PAROTIDECTOMY AND PARAPHARYNGEAL SPACE, EXCISION

A. SALIVARY DUCT CARCINOMA EX PLEOMORPHIC ADENOMA, 5 CM.

B. THE SALIVARY DUCT CARCINOMA COMPONENT IS INTRACAPSULAR, BUT IS < 0.1 CM FROM THE POTENTIAL MARGIN.

C. PERINEURAL AND VASCULAR INVASION IS ABSENT.

D. THE FRAGMENTED NATURE OF THE SPECIMEN PRECLUDES EVALUATION OF THE ADEQUACY OF EXCISION.

E. pT3 N0.
Challenges of Reporting Intracapsular Salivary Duct Carcinoma ex PA

• pT3?
  – What proportion of the 5 cm mass is SDC?
  – Intracapsular! Intraductal?
  – No “pTis” category

• Margin status? (Fragmentation ➔ close or unknown)

• pN0, but:
  – Only 6 lymph nodes sampled
  – Level II

• No PNI
Distribution of SDC component – Periphery of Pre-existing PA
Challenges of Reporting Intracapsular Salivary Duct Carcinoma ex PA

• pT3:
  – SDC component is likely to be about 5 cm mass is SDC
    • Unevenly distributed, mostly at the periphery of PA
  – Intracapsular! Intraductal or extraductal?
  – No “pTis” category
• Margin? (Fragmentation. Margin status: close or unknown)
• pN0, but:
  – Only 6 lymph nodes sampled
    – Level II
• No PNI
Intracapsular and Mostly Extra-Ductal

P63 IHC
Practical Challenges of Determining the Extent of Invasion (Intracapsular)

Details of our case

- Fragmented specimen
  - Unknown or close margin
- **High grade** carcinoma ex PA

General Limitations, Not Applicable to Our Case

- Absence of PNI or vascular invasion
- pN0
- Non-recurrent PA
- Site – PAs from minor salivary glands lack capsule
- Reference point - Multinodularity or lobulated growth, pseudopodia and satellite nodule
Clinical Follow-up

• Salivary duct carcinoma is a high grade carcinoma and was treated as such:
  – Cisplatin
  – Concomitant radiation therapy
• No recurrence at 12 months
The Value of Recognizing Pre-existing Pleomorphic Adenoma

• Correlation with clinical history
  – 15 years of parotid mass [=PA] with recent rapid growth [=SDC]

• Helps to exclude metastases from occult distant primary (breast, prostate)
Orbital Mass and History of Pulmonary and/or Breast Carcinomas – Validation of *PLAG1* and *HMGA2* FISH and Work-up of Carcinomas with Unknown Primary

**Case #2: Larger Biopsy With Hyalinized Nodule**

**Case #3: Smaller Biopsy, No Morphologic Evidence of PA**
Evidence of Pre-existing Pleomorphic Adenoma

Morphology

Molecular

Pleomorphic Adenoma Gene 1 (PLAG1), Zinc Finger Transcription Factor
- 1/3 of SDC ex PA harbor PLAG1 rearrangement

High Mobility Group A2 (HMGA2), Non-histone component of chromatin
- about 1/5 of SDC ex PA harbor HMGA2 rearrangement
Morphologic Spectrum of Salivary Duct Carcinoma ex PA: Recognizable PA Component with Chondromyxoid Stroma is Rare

Intracapsular (n=5)

- Intraductal (n=4)
  - n = 2
  - n = 2

- Extraductal
  - n = 1

Extracapsular (n=39)

- Invasive, <5 mm (n=5)
  - (22 of 27 with +LN)

- Invasive, >7 mm (n = 27)
  - SDC

Hyalinized Nodule

SDC with *PLAG1* Rearrangement, FISH

**Intact HMGA2**

**PLAG1 rearranged:**

*PA component: 67% of cells*

*SDC component: 83% of cells*

Possible Fusion partners
- *FGFR1 (intact in our case)*
- *β-catenin (CTNNB1)*
- *leukemia inhibitory factor receptor*
- *coiled-coil-helix-coiled-coil-helix domain containing 7*
- *transcription elongation factor A*
Beta-Catenin Cellular Localization Does Not Correlate *PLAG1-CTNNB1* Rearrangement

- The t(3;8) results in promoter swapping between *PLAG1* and the β-catenin (CTNNB1):
  - PLAG1 over-expression
  - No change in CTNNB1 cellular localization

I. Fonseca et al, Histopathology, 2007
Timing of Genetic Alterations

Malignant transformation of PA into SDC:

• It probably takes at least 20 years
• Timing of genetic events?
• Which PA will undergo transformation?

<table>
<thead>
<tr>
<th>Patients with PLAG1 rearrangement</th>
<th>Histologic Diagnosis</th>
<th>Patients’ Age, average, years</th>
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<tbody>
<tr>
<td>PA</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>SDC</td>
<td>61 (33-75)</td>
<td></td>
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</tbody>
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Bullerdiek J et al., Cancer Genet Cytogenet. 1993
Malignant Transformation of PA into a Salivary Duct Carcinoma: Next Gen. Sequencing of Both Components

PA component: ATM p.V410A


p53 IHC
Malignant Transformation of PA into a Salivary Duct Carcinoma: Next Gen. Sequencing of Both Components

PA component: ATM p.V410A


p53 IHC
**ATM & TP53 Mutations and Response to Conventional Chemotherapy**

In triple-negative breast cancer, TP53 mutations are associated with good cisplatin response.

Doxorubicin is most effective in ATM- and TP53-deficient tumors.

Combined ATM- and TP53-deficiency is rare in human tumors.

Silver DP, et al., J Clin Oncol. 2010 Mar 1;28(7); Jiang H, et al., Genes and Development, 2009
Conclusions

• Challenges of reporting intracapsular carcinomas ex PA:
  – Sampling issues – cytology
  – Histologic subtype
  – Extent of invasion
  – pTis?

• Potential use of PLAG1 in work–up of small biopsies of carcinomas (unknown primary?)

• Timing of genetic alterations and potential response to conventional chemotherapy:
  – ATM and TP53
  – Mutational testing of salivary FNAs?
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