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Disclosure Information

I hereby declare that I have had business or personal interests in the following industrial enterprises since 1 September 2017:

Name of the enterprise / Nature of the interest

<table>
<thead>
<tr>
<th>Enterprise</th>
<th>Interest</th>
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<tbody>
<tr>
<td>None</td>
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Many Thanks to the
Congress Organizing Committee
ESP Head and Neck Pathology Working Group
Case that might be presented...

- EBER (+) metastatic carcinoma to the neck... Primary is not nasopharynx but parotid gland!!!
- Triple masses of a patient: at the nasopharynx, neck and parotid gland. Nasopharyngeal bx: EBER+ carcinoma and FNA from the parotid gland: not high grade, probably malignant tumor EBER (-)
  - proving to be intraductal carcinoma after parotidectomy. Neck dissection was not performed as the metastatic neck masses were accepted from nasopharyngeal primary.
- Verrucous carcinoma of the maxillary sinus arising from Inverted papilloma; infiltrating the hard palate (Nice case I prefer this one)
- Isolated neurofibroma of the band ventricle
- Myxoma of the middle ear.
- The chosen case (I’ll present now)
My case...

• Is not very rare
• Is not the greatest diagnostic challenge
• Is not prognostically important
• Is not very unexpected
• The problem is...
  • *What is the name of the lesion?*
• 60-year-old male patient
• A history of left parotid region swelling of three years duration.
• No pain
• 30 package/year smoking: quitted 18 years ago.
Axial, contrast computed tomography
P: Parotid gland
mss: masseter muscle
*: Mass
Arrow: The deliniation of the mass from the parotid gland
Low-grade neoplasm, an adenoma
• Superficial parotidectomy was performed and 27x25x22 mm nodular mass was observed at the macroscopic examination.
Basal cell adenoma? Myoepithelioma reticular Pattern?
Myoepithelioma?
Oncocytoma
S100 (-) oncocytic cells

Actin (-) oncocytic cells

PTAH (+)

p63 (-) oncocytic cells

MITO
Clear cell adenoma/carcinoma?
Sebaceous metaplasia?
Sebaceous, oncocyctic, squamous metaplastic regions
Squamous metaplasia
ki67
Summary (HC, IHC) Muci carmine (-), CK20 (-), DOG-1(-), β-catenin (-), CK43 (-)

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<tbody>
<tr>
<td>PTAH/MITO</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
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<tr>
<td>PAS</td>
<td>BM like material</td>
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<td>BM like material</td>
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<tr>
<td>Pan-CK</td>
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<td>CK7 - CK5/6</td>
<td>++</td>
<td>Focal+</td>
<td>+</td>
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<td>S100/ SOX10</td>
<td>Luminal++ , patchy+</td>
<td>Strong/Patchy+++</td>
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<td>Actin/ Calponin</td>
<td>Abluminal++ ,</td>
<td>Patchy+++</td>
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<tr>
<td>GFAP</td>
<td>Focal+</td>
<td>-</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>p63</td>
<td>Luminal++ , patchy+</td>
<td>+++</td>
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</table>
• What is your diagnosis?
<table>
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<tr>
<th>Tumor Type</th>
<th>&gt;90%</th>
<th>50-90%</th>
<th>10-50%</th>
<th>&lt;10%</th>
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<tbody>
<tr>
<td>Oncocytoma</td>
<td>CK7, CK8, CK18, CEA, GATA-3</td>
<td>P63</td>
<td></td>
<td>Actin</td>
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<tr>
<td>Myoepithelioma</td>
<td>S100, CK5/6/14, CALPONİN, SOX10, Vimentin</td>
<td>CK19, EMA, P63, GFAP, Actin, caldesmon</td>
<td></td>
<td>CEA, CK7</td>
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<tr>
<td>Basal cell adenoma</td>
<td>Luminal: CK7, CK8, CK18, EMA Myoepithelial: S100, actin, calponin, vimentin, CK5/6/14, p63</td>
<td>CEA</td>
<td></td>
<td>CD43, Vimentin</td>
</tr>
<tr>
<td>Sebaceous adenoma</td>
<td>Adipophilin, EMA</td>
<td>Perilipin, CK5/14, CK8/18, CK7, CK19, CD15</td>
<td></td>
<td>CK20, CEA, S100</td>
</tr>
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Basal Cell Adenoma

• 1-3.7 of salivary gland tumors; 57-70 years, female predominance
• >80% parotid gland
• FNA: basaloid cells with round-oval nuclei, scant cytoplasm
• 8p22, 19q13.4, 16q12-13, t7;13, inv(13)
• Pattern:
  • solid, trabecular, tubular and membranous
  • Basaloid cells with palisading at the periphery of the cell groups.
  • PAS positive basement mambrane like material
  • Centrally located cells may have larger cytoplasm, but the rest have scant cytoplasm and indistinct cell borders.
Basal Cell Adenoma

- May be associated with oncocytic and squamous metaplasia
- The membranous patterned tumors resemble the dermal anlage tumor and the two tumors may be associated and 16q12.1, CYDL LOH/mutation; Brooke-Spiegler Syndrome.
- CTNNB1 mutation is identified in tubule-trabecular variant Basal cell adenoma may be associated with oncocytic and squamous metaplasia (10,11).
- Luminal cells are positive for CK7, CK8, CK18, EMA while myoepithelial cells express S100, actin, calponin, vimentin, CK5/6/14, p63 as well as CEA is expected to be positive. CD117, CD43 and vimentin may be rarely positive.

Myoepithelioma

- 1.5% of salivary gland tumors; 9-85 years, female=male
- >80% parotid gland
- FNA: bland cells which may be spindled, epitheloid or plasmacytoid.
- Cells: Spindle, plasmacytoid, hyaline, epitheloid, clear cell, signet ring cell
- Patterns: Epitheloid, organoid, reticular
Myoepithelioma

- Cell types:
  - Plasmocytoid (most frequently), hyaline, epitheloid, clear cells (glycogen rich) arranged in nests and cords;
- Pattern:
  - Glandular structures and chondromyxoid stromal elements should be sparse if any.
  - *Reticular pattern may mimic basal cell adenoma, which is recognized by net-like arrangement of interconnected cell cords.
  - Rare cases with oncocytic or lipomatous metaplasia and signet ring shaped (mucin rich) cells may be observed.
- Smooth muscle actin expression is strong in spindle cells but negative in plasmocytoid and clear cells.
- Cases with positive S100, CK5/6/14, CALPONIN, SOX10, Vimentin CK19, EMA, P63, GFAP, actin, caldesmon expressions are frequent while CEA, CK7 may also be positive.
- Not many mutations, aberrations at chromosome 8

Oncocytoma

- Large granular eosinophilic cytoplasm and vesicular nuclei
- PTAH or MITO positivity reflects thousands of mitochondria many times the normal amount.
- _Focal or extensive clear cell changes may be seen related to cystic dilatation of the mitochondria._
- _The oncocytes are vulnerable to trauma and this may be the reason for frequent squamous metaplasia._
- Impairment of mitochondrial genes (OXPHOS) seem to induce the proliferation of the mitochondria; either related to low protein expression or mutations.
- In neoplasms, the mutations are not restricted to the mitochondrial genes; probably the high concentration of reactive oxygen species related to mitochondrial malfunction, lead to the mutations of the cellular DNA.
- These alterations may lead to malignant transformation.
- *In tumors with partial oncocyctic changes, the mitochondrial changes are probably acquired following cellular DNA changes.*

Sebaceous Adenoma

- Sebaceous cell nests in a fibrous stroma is the typical morphology.
- *Squamous and oncocyctic metaplasia is frequent.*
- Adipophilin, EMA perilipin, CK5/14, CK8/18, CK7, CK19, CD15 expression is frequent but CK20, CEA, S100 is positive in rare cases.

Metaplasia

What is metaplasia?
- Stem cell origin?
- Epigenetic changes?
- Relation with dysplasia?
Metaplasia in salivary gland tumors

- Microdissection of oncocytic metaplastic and non metaplastic regions of a pleomorphic adenoma
- Microarray based comparative genomic hybridization
- A similar amplification in both components, mapping to 12q13.3–q21.1, which was further validated by chromogenic in situ hybridisation (A hotspot region for PA).
- The foci of oncocytic metaplasia showed an additional low-level gain of 6p.

How do we diagnose?
Approach with focus on Patterns of Recognition

- Basaloid Markers: p63, p40
- Myoepithelial markers: SMA, S100, Calponin
- Five broad categories of salivary gland tumors:
  - **Acinar differentiation:** Acinic cell carcinoma
  - **Biphasic ductal and myoepithelial differentiation:** Mimicking intercalated ducts; pleomorphic adenoma, basal cell adenoma, intercalated duct adenoma, carcinoma ex pleomorphic adenoma, epithelial-myoepithelial carcinoma, adenoid cystic carcinoma, basal cell adenocarcinoma
  - **Oncocytic features:** Mimicking striated ducts; Warthin’s tumor, oncocytoma, oncocyctic carcinoma
  - **Epidermoid and glandular features:** Mimicking excretory ducts; salivary duct carcinoma, clear cell carcinoma, adenocarcinoma NOS, mucoepidermoid carcinoma
  - **Myoepithelial:** Polymorphous adenocarcinoma, myoepithelioma, myoepithelial carcinoma
• Strict diagnostic criteria in salivary tumors?
IHC in salivary gland tumors

- Ductal: epithelial-luminal cells: LMWK: CAM5.2, EMA, CK7, CK19
- Basaloid Markers: p63, p40
- Myoepithelial (abluminal) HMWK: CK5/6, 34βE12, p63, p40 and SMA, SOX10, S100, Calponin, GFAP
- Biphasic or monophasic pattern may be appreciated
- Myoepithelioma: One cytokeratin marker and a myoepithelial marker: S100 and/or SOX10
- Squamous differentiation; Clear cell carcinoma, Mucoepidermoid carcinoma: HMWK (CK5/6, 34βE12) and p40, p63
- S100 positive: exclude: Salivary duct carcinoma, clear cell carcinoma, mucoepidermoid carcinoma
- Androgen receptor +: Salivary duct carcinoma (75%-95%+)
- P63+/p40-: Secretory carcinoma, Polymorphous adenocarcinoma
- P63-/p40-: Salivary duct carcinoma
- P63+/p40+: Adenoid cystic carcinoma
- SOX10: Usually negative in salivary duct carcinoma, clear cell carcinoma, lymphoepithelial carcinoma, oncocytoma, oncocytc carcinoma, Warthin tumor. Positive in pleomorphic adenoma, epithelial myoepithelial carcinoma, basal cell adenoma and basal cell adenocarcinoma
- S100 negative but SOX10 positive mucoepidermoid carcinoma and acinic cell carcinoma

Katabi N, Xu B. Salivary Gland Neoplasms: Diagnostic Approach with focus on Patterns of Recognition and useful ancillary tools Mini-Symposium: Head and Neck Pathology Diagnostic Histopathology 24:5
Diagnosis

- *There is adenocarcinoma, NOS*
- *There isn’t adenoma, NOS…*
- *There is polymorphous adenocarcinoma*
- *There isn’t polymorphous adenoma…*
• *Myoepithelioma*

• with metaplasia and some unexpected patterns...
• *Thanks for your attention...*