Clinical History:
A 45-year-old man is noted to have a soft palate lesion on routine dental examination. The mass is 1.5 cm, soft, non-ulcerated, and non-tender. He has no history of malignancy, and he is a non-smoker. Fine needle aspiration was performed, and a ThinPrep slide from the aspiration material is provided for review.
Fine needle aspiration of oncocytoid neoplasms of the salivary gland

Mammary analogues and their evolving classifications
Objectives and goals

• Develop a differential diagnosis of oncocytoid salivary gland neoplasms based on cytologic features

• Identify key immunohistochemical and molecular findings that aid in the fine needle aspiration diagnosis of oncocytoid salivary gland neoplasms

• Recognize newly categorized and/or reclassified entities with oncocytoid features in the 2017 World Health Organization Classification of Head and Neck Tumours
Case 1
45 year old male with a painless right soft palate lesion

• 1.5 cm, soft, non-ulcerated, non-tender

• No history of malignancy

• Fine needle aspiration performed
Oncocytoid salivary gland neoplasms

• Broad range of benign → malignant salivary neoplasms

• Marked by tumor cells with abundant eosinophilic cytoplasm on H&E

  • Distinct from “basaloid” neoplasms (e.g. pleomorphic adenoma, adenoid cystic carcinoma)

  • Not necessarily “true oncocytes”
Oncocytoid salivary gland neoplasms

- Benign
  - Warthin tumor
  - Oncocytoma
  - Nodular oncocytic hyperplasia
  - Sclerosing polycystic adenosis
  - Myoepithelioma

- Malignant, typically low-grade
  - Acinic cell carcinoma
  - Secretory carcinoma
  - Mucoepidermoid carcinoma
  - Oncocytic carcinoma
  - Intraductal carcinoma, low grade

- Malignant, high grade
  - Salivary duct carcinoma
  - Carcinoma ex pleomorphic adenoma (often)
  - Squamous cell carcinoma
Differential diagnosis by background

- **Oncocytoid neoplasms with lymphoid background**: Warthin tumor
- **Oncocytoid neoplasms with clean cystic background**: Oncocytoma, Warthin tumor, Sclerosing polycystic adenosis, Less common: carcinomas
- **Oncocytoid neoplasms with mucoid or dirty background**: Warthin tumor, Carcinomas, including salivary duct ca, mucoepidermoid ca, acinic cell ca, and secretory ca
Differential diagnosis by cytology

- Oncocytoid neoplasms with granular/vacuolated cytoplasm
  - Secretory carcinoma
  - Acinic cell carcinoma
  - Salivary duct carcinoma
- Oncocytoid neoplasms with marked pleomorphism
  - Salivary duct carcinoma
  - Mucoepidermoid carcinoma
  - Metastatic carcinoma
Secretory carcinoma


Cancer Cytopathol. 2013 May;121(5):228-33.
Acinic cell carcinoma
Salivary duct carcinoma
### Immunohistochemistry

<table>
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<th></th>
<th>SOX-10</th>
<th>DOG-1</th>
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<th>Mammaglobin</th>
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Resection
Final diagnosis: SECRETORY CARCINOMA
Secretory carcinoma

- First described in 2010 as “Mammary analogue secretory carcinoma”
- M:F = ~1:1, wide age range, most common 5\(^{th}\)-6\(^{th}\) decade
- Occurs in major and minor salivary glands
- Tumor cells with eosinophilic, vacuolated cytoplasm, present in multiple growth patterns
- Luminal secretions of mucoid material
Secretory carcinoma

• Included in 2017 W.H.O. classification

• “Mammary analogue” terminology dropped
  • Conserved morphology / molecular characteristics across multiple sites

• Culled from acinic cell carcinoma and adenocarcinoma, NOS
  • Significant overlap with ACC in growth patterns and cytoplasmic features
ETV6-NTRK3 : t(12;15)(p13;p25)

• ETV6 – encodes transcription factor promoting function and survival in a wide range of somatic cell types

• NTRK3 – tyrosine kinase predominantly regulation of neuronal growth and survival

• Fusion protein constitutively induces cyclin D1 expression, activation of TK function and activation of MAP pathways
FIGURE 1. MASC of salivary gland. A, MASC is composed of microcystic and solid areas with abundant vacuolated colloid-like PAS-positive secretory material within the microcystic spaces. B, FISH analysis of ETV6 gene. C, Part of the ETV6-NTRK3 fusion transcript sequence. FISH indicates fluorescence in situ hybridization; PAS, periodic acid Schiff.
ETV6-NTRK3– targeted therapy

• Translocation seen in infantile fibrosarcoma, mesoblastic nephroma, acute myeloid leukemia, radiation-associated papillary thyroid carcinoma

• Tyrosine kinase inhibitors of potential benefit in these malignancies
Case 2
53 year old female with right parotid mass

• 8 month history of painless nodule at angle of jaw

• Ultrasound revealed a well circumscribed, solid, 2 cm mass within parotid gland
Surgical excision
Sclerosing polycystic adenosis

- Rare tumor-like salivary gland lesion
- Likely a neoplastic process, but exhibits benign behavior
- Presents as painless mass in parotid or submandibular gland
- Histology simulates sclerosing adenosis and fibrocystic changes of the breast

Head and Neck Pathol (2013) 7:S97–S106
Sclerosing polycystic adenosis

- Consider when multiple types of epithelium are present
  - Varying proportions of oncotypoid cells, but often prominent
  - Sebaceous differentiation is particularly characteristic on FNA
  - Coarse red zymogen granules frequently encountered

- IHC of limited benefit
  - Staining similar to other salivary “mammary analogues”

- Local recurrence not uncommon, but benign behavior
Case 3
60 year old female with left parotid mass

• 1 year history of a painless nodule at angle of jaw

• History of smoking

• Cyst fluid obtained
Intraductal carcinoma, low grade

• Previous names include
  • Low grade salivary duct carcinoma
  • Low grade cribriform cystadenocarcinoma

• Histologic and cytologic resemblance to low grade DCIS of breast

• Often oncocytoid, but monomorphic, bland, and evenly spaced
  • Tightly cohesive
  • “Roman bridge” architecture on cell block
Salivary “ductal” carcinomas

• Confusing and varied terminology used

• INTRADUCTAL CARCINOMA
  • LOW GRADE
    • No or minimal infiltration, benign behavior
    • RET translocations, S-100 +++, AR -/+  
  • HIGH GRADE
    • No infiltration, excision curative
    • AR and HER2 amplification, S-100 -/+ , AR +++

• SALIVARY DUCT CARCINOMA
  • Invasive, poor prognosis
  • AR and HER2 amplification, S-100 -/+ , AR +++
Oncocytoid neoplasms - summary

• Neoplasms with oncocytoid features represent a broad range of benign, low grade malignant, and high grade malignant neoplasms

• Cytomorphology and ancillary studies often allow for specific diagnosis
  • If a SPECIFIC entity cannot be established, a diagnosis of “neoplastic cells present” with a differential diagnosis should be rendered
Oncocytoid neoplasms - summary

• Secretory carcinoma has distinct morphologic, immunohistochemical, and molecular features from acinic cell carcinoma

• Sclerosing polycystic adenosis is a polymorphous, benign lesion prone to recurrence

• Low grade intraductal carcinoma has a benign course, and is distinct high grade ductal lesions such as salivary duct carcinoma
Case 7
Richard Cantley, MD
New Frontiers in Pathology

References and Suggested Readings:

Fine needle aspiration diagnosis of oncocytoid neoplasms:


Updates on classification of salivary gland neoplasms:


Skalova A, Michal M, Simpson RH. Newly described salivary gland tumors. Mod Pathol. 2017 Jan;30(s1):S27-S4