Introduction

- Papilloma = finger-like epithelial proliferation with fibrovascular cores.

Sinonasal Papillomas

- Uncommon, benign epithelial neoplasms.
- Arise from the ectodermally-derived pseudostratified ciliated (Schneiderian) epithelium that lines the nasal cavity and sinonasal tract.

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Dr. Bishop declares he has no conflict(s) of interest to disclose.
Sinonasal Papilloma History

- Probably first described by Nathaniel Ward in 1854 and by Theodor Billroth in 1855.
- Subsequent reports and small series followed.
  - Many emphasized potential to recur and some recognized cases of carcinomatous transformation.

In 1971 Capt. Vincent Hyams published an exhaustive description of 315 cases from the AFIP archives.

Up to that point, had been variably referred to as papilloma durum, papillary sinusitis, Ewing's papilloma, Ringertz papilloma, papillary adenoma, and many others.

Hyams Classification - 1971

- Inverted
- Fungiform
- Cylindrical cell
Sinonasal Papilloma History

- Barnes and Bedetti 1984.
- Expanded on Hyams’ work by providing additional descriptions of cylindrical cell papilloma.
- Determined this subtype was truly oncocytic (i.e., possessed abundant mitochondria resulting in a granular eosinophilic cytoplasm) and thus introduced oncocytic Schneiderian papilloma as a synonym of cylindrical cell papilloma.

Current Terminology

- In 2017 WHO Classification:
  - “Sinonasal” (not Schneiderian) papilloma
  - Inverted sinonasal papilloma (ISP), oncocytic (OSP), and exophytic (ESP).
- Although similar, they are distinct entities in many ways and a precise diagnosis should be attempted.

Poor Schneider...

- Conrad Victor Schneider
- German anatomist at University of Wittenberg
- Published in 1660 about nasal mucous membrane (not pituitary) as the source of nasal secretions.

Clinical Features

- ISP (~60%) > ESP (~30%) > OSP (~10%).
- Usually unilateral.
- Nasal obstruction, discharge, epistaxis.

Clinical features

- ISP and OSP similar profiles:
  - 5th-6th decades.
  - Lateral wall and/or sinuses.
  - M=F
  - ISP rarely in weird sites.
- ESP:
  - 3rd-5th decades.
  - More common in men
  - Nasal septum.
Histology

- Features shared among subtypes:
  - Epithelial thickening
  - Scattered mucous cells or cysts
  - Intraepithelial neutrophils +/- microabscesses

Exophytic sinonasal papilloma
Inverted sinonasal papilloma
Oncocytic sinonasal papilloma
Etiology

- Given frequent association with inflammatory polyps, historically theorized:
  - Papillomas simply a metaplastic change?
  - Polyps a precursor lesion to papillomas?
- Subsequent studies showed that sinonasal papillomas are truly clonal neoplasms

Etiology

- No clear association to smoking, ethanol or occupational exposures.
- What about HPV?

Role of HPV

- Viral etiology hypothesized from earliest descriptions.
- Newer HPV detection methods have elucidated role (to some extent...):
  - ESP: usually positive for low-risk HPV.
  - OSP: always negative for HPV.

HPV in ISP?

- Literature remains confusing and contradictory.
- Meta-analysis by Lawson, et al: 22-26% of ISPs LR or HR HPV+, increased rate of HR HPV in ISPs with dysplasia (56%) or SCC (55%).
- Many previous studies utilized suboptimal detection methods unable to distinguish biologically active HPV from “passenger” virus.
- Also, invasive NK SCC may be mistaken for SCC ex ISP.
HPV in ISP?

- Bishop, et al. 2012: 1 of 16 SCCs ex-ISP were HR HPV+ using p16+DNA ISH.
- Rooper, et al. 2017: 0 of 53 ISPs and SCCs ex ISP were HR HPV+ using RNA ISH.
- But... Stoddard, et al. 2015 found HR HPV in 100% of ISPs (though signals very focal...).

Molecular Insights

- Udager, et al. 2015: activating EGFR mutations in most of ISPs (88%) and carcinomas arising from ISPs (77%).
- Udager, et al. 2016: OSPs and SCC ex-OSP consistently (56 of 56 in their series) harbor activating KRAS mutations, ISPs and ESPs negative.

Clinical

- All types treated with complete surgical excision
- All prone to recur (20-30%) following incomplete removal of the tumor
- ISP and OSP of the frontal sinus particularly prone to recurrence given difficulties in reaching this sinus
- Malignant transformation...

Malignant Transformation

- ESP: almost never.
- ISP and OSP: 5-17%.
  - 2/3 are synchronous.
- No known histologic features predictive of subsequent malignant transformation.
<table>
<thead>
<tr>
<th>Location</th>
<th>Histologic Features</th>
<th>Rate of Malignant Transformation</th>
<th>Molecular Alterations</th>
<th>Association with HPV</th>
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</thead>
<tbody>
<tr>
<td>ISP (Lateral nasal wall and paranasal sinuses)</td>
<td>- Thickened epithelium, scattered mucous cells or cysts, intraepithelial neutrophils, microabscesses. - Epithelium variably squamous, squamoid/transitional, or ciliated columnar. - Prominent downward growth of rounded, elongated, and anastomosing epithelial nests from surface epithelium.</td>
<td>5-15% EGFR mutations</td>
<td>Unclear association.</td>
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<tr>
<td>ESP (Nasal septum)</td>
<td>- Thickened epithelium, scattered mucous cells or cysts, intraepithelial neutrophils, microabscesses. - Epithelium usually squamous, sometimes squamoid/transitional. - Broad, branching fronds of epithelium surrounding fibrovascular cores. +/- koilocytes.</td>
<td>Close to 0</td>
<td>No known association.</td>
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<tr>
<td>OSP (Lateral nasal wall and paranasal sinuses)</td>
<td>- Thickened epithelium, scattered mucous cells or cysts, intraepithelial neutrophils, microabscesses. - Both inverted and exophytic growth. - Epithelium pseudostratified columnar epithelial cells, with abundant, granular eosinophilic cytoplasm and small, hyperchromatic nuclei.</td>
<td>4-17% KRAS mutations</td>
<td>No association.</td>
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**Future directions?**
- HPV role in ISP?
- Predictors of malignant transformation?
- "Metastasizing ISP"