### Sinonasal Papillomas

*aka Schneiderian papilloma*

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Location</th>
<th>Risk of transformation</th>
<th>Molecular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exophytic</td>
<td>Nasal septum</td>
<td>Very low risk</td>
<td>Low-risk HPV subtypes</td>
</tr>
<tr>
<td>Inverted</td>
<td>Lateral wall and sinuses</td>
<td>Low to Intermediate risk</td>
<td>EGFR mutations or low-risk HPV subtypes</td>
</tr>
<tr>
<td>Oncocytic</td>
<td>Lateral wall and sinuses</td>
<td>Low to intermediate</td>
<td>KRAS</td>
</tr>
</tbody>
</table>

**Modified from:** Weindorf et al. *Arch Pathol Lab Med—Vol 143, November 2019*

---

**Oncocytic Sinonasal Papilloma**

Note the abundant oncocytic epithelium with numerous neutrophils

---

**Inverted Sinonasal Papilloma**

Note the inverted, “ribbon-like” growth
**Respiratory Epithelial Adenomatoid Hamartoma**

Sinonasal glandular proliferation arising from the surface epithelium (i.e., in continuity with the surface). Invaginations of small to medium-sized glands surrounded by hyalinized stroma with characteristic thickened, eosinophilic basement membrane.

Exists on a spectrum with seromucinous hamartoma, which has smaller glands.

Should be able to draw a circle around all of the glands though, if too confluent → consider a low-grade adenocarcinoma.

**Inflammatory Polyp**

Surface ciliated, sinonasal mucosa, possibly with squamous metaplasia.

Edematous stroma (without a proliferation of seromucinous glands).

Mixed inflammation (usu. Lymphocytes, plasma cells, and eosinophils).

**Pituitary adenoma**

Benign anterior pituitary tumor

Although usually primary to sphenoid bone, can erode into nasopharynx or be ectopic.

Can result in endocrine disorders, such as Cushing’s disease or acromegaly.

Solid, nested, or trabecular growth of epithelioid cells with round nuclei and speckled chromatin and eosinophilic, granular chromatin.

Express CK, and neuroendocrine markers.

NO S100 sustentacular pattern

Can stain with hormone-specific markers (e.g., prolactin).

Can recur.
**Squamous cell carcinoma**

**Most common carcinoma!**
Can be Keratinizing or Non-keratinizing
Associated with tobacco exposure.

High-risk HPV subtypes in a subset of tumors;
EGFR or KRAS mutations if papilloma–associated

---

**Sinonasal Undifferentiated Carcinoma (SNUC)**

**Poorly differentiated carcinoma** without squamous, glandular, or neuroendocrine differentiation (Dx of exclusion!).

Open to hyperchromatic nuclei. Somewhat monotonous. Often prominent nucleoli.

CK+, but squamous markers negative
IDH2 codon R172 mutations in most tumors

Aggressive high-grade malignancy → poor outcome

---

**NUT (Midline) Carcinoma**

**Poorly-differentiated carcinoma** (often small-round blue cells), with often “abrupt keratinization” or squamous differentiation.

Often younger patients, in the midline, often in the head and neck.

NUT gene rearrangement → stain with NUT IHC!

Aggressive high-grade malignancy → poor outcome
Lymphoepithelial Carcinoma

Poorly-differentiated carcinoma with high N:C ratios

**Similar morphology to SNUC** but may show prominent plasmacytoid/rhabdoid features

Biallelic **inactivation of SMARCB1** (loss of INI-1 staining by IHC)

Poor long-term outcomes

---

HPV-related multiphenotypic sinonasal carcinoma

High-grade carcinoma with **morphologic and immunohistochemical evidence of myoepithelial differentiation** → often Adenoid cystic-like

Shows associated surface squamous dysplasia

Positive for **HPV: High-risk subtypes** (especially type 33) → P16 IHC block positive, but must do additional, more specific testing.

Although typically advanced disease at presentation, clinical course is **relatively indolent**

---

Lymphoepithelial Carcinoma

Essentially **non-keratinizing nasopharyngeal carcinoma, undifferentiated type** (if in the sinonasal cavity, just call it NPC if in nasopharynx)

Sheets of malignant cells with **vesicular chromatin**, indistinct cytoplasm, and **abundant tumor-infiltrating lymphocytes**.

**EBV-positive.** Positive for CK, CK5/6, p40, p63

More common in **Asians**.

---

Teratocarcinosarcoma

Malignant tumor with features of **teratoma** (e.g., squamous or glandular epithelium, often including immatures fetal-appearing squamous epithelium, and immature neuroepithelium, sometimes with rosette formation) and **carcinosarcoma** (with spindled cells, possibly with rhabdomyoblastic, or other differentiation) without germ cell components
Mucosal Melanoma
Distinct from cutaneous melanomas biologically (but must exclude metastatic melanoma clinically!)
Epithelioid to spindled cells with pleomorphic nuclei and often prominent nucleoli.
Intracytoplasmic melanin
Melanoma markers: S100, SOX10, HMB45, MelanA, MITF, Tyrosinase. Do many (as can be loss)!
Poor prognosis: Staging starts at T3-4.
No need for Clark/Breslow depth.

Neuroendocrine Carcinoma
Like Poorly-differentiated neuroendocrine carcinomas of the lung.
Divided into: 1) Small cell neuroendocrine carcinoma
2) Large cell neuroendocrine carcinoma
Strong staining with a neuroendocrine stain (e.g., synaptophysin or chromogranin). Often perinuclear “dot-like” keratin expression.

Adenocarcinoma
Salivary gland adenocarcinomas are the most common (particularly adenoid cystic → see separate guide)

Sinonasal Adenocarcinomas
Intestinal type
Causal relationship with wood dust and leather dust (so, mostly men)
Morphology and IHC identical to colonic adenocarcinoma
(CK7-, CK20+, CDX2+)

Non-intestinal type
(CK7+, CK20-, CDX2-)
Low-grade:
Very bland cytologically (to the point where you wonder if it is malignant!)
Excellent prognosis

High-grade
Cytologically malignant. Diagnosis of exclusion (must exclude metastasis, etc...)
Poor prognosis

Nasopharyngeal papillary adenocarcinoma
Low-grade adenocarcinoma of the nasopharynx with predominantly papillary architecture
Papillae are lined by a single layer of bland cuboidal cells with scant cytoplasm
Complex, arborizing papillae (sort of looks like ovarian micropapillary serous borderline tumor)
Olfactory Neuroblastoma

Malignant neuroectodermal neoplasm

Confined to the cribriform plate (and surrounding region)

Lobulated, nests to sheets of cells with speckled chromatin. High N:C ratio

Fibrillar cytoplasm → Neuropil!

Can see pseudorosettes.

IHC: Diffuse Synaptophysin/Chromogranin

S100 → Sustentacular pattern. CK negative.

Ewing Sarcoma

Malignant tumor of neuroectodermal differentiation

Often have EWSR1 translocation (with FLI-1 or ERG)  t(11;22)

Usually uniform, small, round, blue cells with sheet-like to lobular, growth pattern with variable necrosis

Strong, membranous CD99 staining

(Sensitive, but not Specific staining)

Cytoplasmic glycogen stains with PAS

“Adamantinoma-like” variant can show diffuse staining with CK and p40!

Lymphoma

Extranodal NK/T-cell lymphoma

IHC: CD3, CD56, EBER +

Most common in Asians

Plasmacytoma

IHC: CD138+ with light chain restriction

May or may not be associated with multiple myeloma

Rhabdomyosarcoma

Malignant tumor with primary skeletal muscle differentiation, several types

Stain with Desmin, MyoD1, Myogenin

Embryonal Rhabdo:

Variable numbers of round (“rhabdoid”), strap-, or tadpole-shaped eosinophilic rhabdomyoblasts in a myxoid stroma

Can see cytoplasmic cross striations

Alveolar Rhabdo:

Larger, more rounded undifferentiated cells with only occasional rhabdomyoblasts

Often arranged in an alveolar (nested) pattern

Distinctively strong and diffuse myogenin positivity

Characteristic FOXO1 translocations

Olfactory Neuroblastoma

aka “Esthesioneuroblastoma”

Malignant neuroectodermal neoplasm

Confined to the cribriform plate (and surrounding region)

Lobulated, nests to sheets of cells with speckled chromatin. High N:C ratio

Fibrillary cytoplasm → Neuropil!

Can see pseudorosettes.

IHC: Diffuse Synaptophysin/Chromogranin

S100 → Sustentacular pattern. CK negative.

Lymphoma

Extranodal NK/T-cell lymphoma

IHC: CD3, CD56, EBER +

Most common in Asians

Plasmacytoma

IHC: CD138+ with light chain restriction

May or may not be associated with multiple myeloma
Glomangiopericytoma

Patternless proliferation of regular, syncytial spindled cells with ovoid nuclei.

Prominent vascularity with perivascular hyalinization. Can see “staghorn” vessels (hemangiopericytoma-like, hence the name, in part)

Perivascular myoid phenotype (like a glomus tumor, hence the name)

IHC: SMA+, Nuclear β-catenin (CTNNB1 mutations)

Relatively indolent with good survival

Biphenotypic Sinonasal Sarcoma

Low-grade spindle cell sarcoma.

Cellular, submucosal spindle-cell proliferation. Arranged in intersection fascicles, often herringbone.

Infiltrate into bone often. Can induce epithelial proliferation.

“Biphenotypic” because has evidence of both neural and muscular differentiation.

- Neural → S100 (focal to diffuse)
- Muscle → SMA (focal to diffuse)

PAX3-MAML3 translocations.

Slow, continuous growth, but no metastases.

Nasopharyngeal Angiofibroma

Richly vascular tumor with variably sized blood vessels set in fibrotic stroma.

Vessels are usu. thin-walled and often dilated with variable smooth muscle.

Stroma is myxoid to dense with stellate fibroblasts.

Almost exclusively young to adolescent boys (“Juvenile angiofibroma”) → classically causes epistaxis & obstruction

Nuclear expression of β-catenin and AR in stromal cells

Locally aggressive and can recur. Treat with embolization and surgery
<table>
<thead>
<tr>
<th>Immunohistochemistry</th>
<th>Squamous cell carcinoma</th>
<th>Sinonasal Undifferentiated Carcinoma (SNUC)</th>
<th>SMARCB1(INI-1)–deficient sinonasal carcinoma</th>
<th>NUT carcinoma</th>
<th>HPV-related multi-phenotypic sinonasal carcinoma</th>
<th>Nasopharyngeal carcinoma</th>
<th>Neuroendocrine Carcinoma</th>
<th>Mucosal melanoma</th>
<th>Rhabdomyosarcoma</th>
<th>Lymphoma</th>
<th>Olfactory Neuroblastoma</th>
<th>Ewing Sarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK (AE1/AE3)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>CK5/6</td>
<td>+</td>
<td>-</td>
<td>α</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>P63 and p40</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>Synapto/Chromo</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>±</td>
<td>-</td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>CD56</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>CD99</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>P16</td>
<td>±</td>
<td>±</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S100 SOX10</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD45</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Myogenin/Desmin</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NUT</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>INI-1</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>EBER</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Note:** Weak/focal staining with synaptophysin, CD56, and CK can be seen with many tumors and should be taken in context. Look for strong, diffuse staining (think Christmas tree).
Algorithm for Nasal Small Round Blue Cell Tumors

Starting IHC Panel: 1) AE1/AE3, 2) p40, 3) synaptophysin, 4) SOX10, 5) CD45, 6) CD99, and 7) Desmin

Adapted from a presentation from Justin A. Bishop, MD Chief of Anatomic Pathology UT Southwestern Medical Center

Start with the whole panel, and then work through the algorithm and get additional stains/studies if necessary.