Prepared by Kurt Schaberg

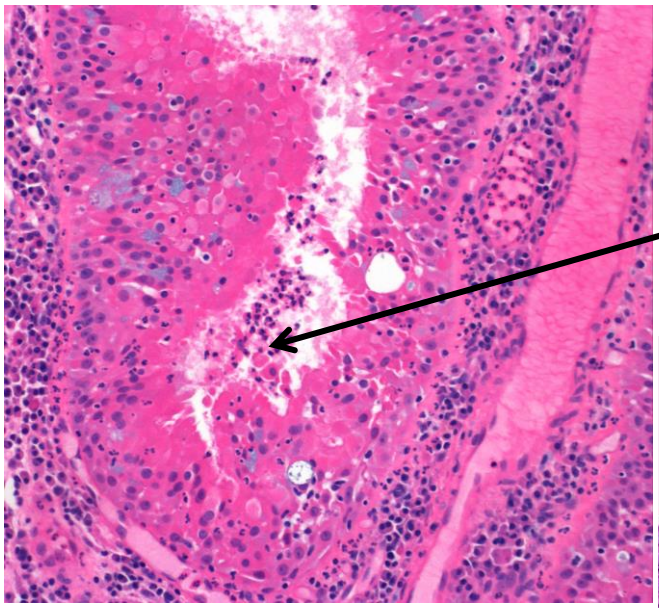
Sinonasal/Nasopharyngeal Tumors

Benign

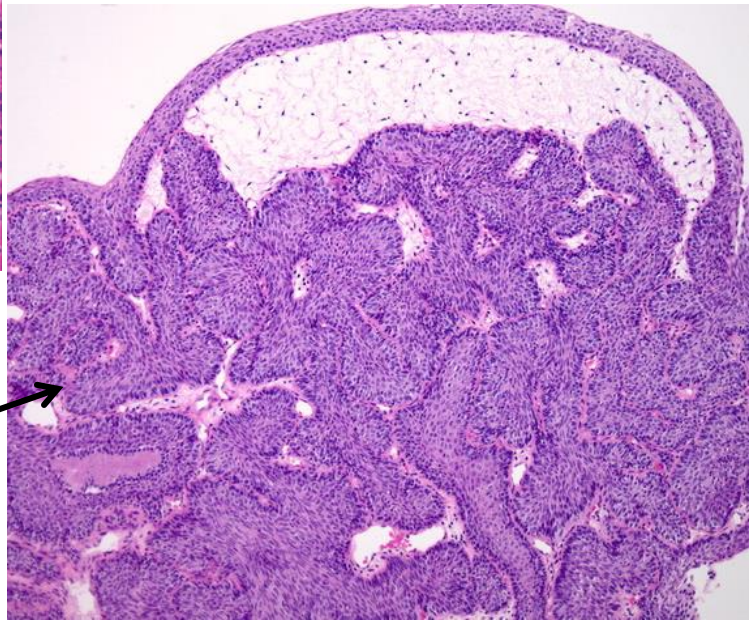
Sinonasal Papillomas *aka Schneiderian papilloma*

	Morphology	Location	Risk of transformation	Molecular
Exophytic	Exophytic growth; immature squamous epithelium	Nasal septum	Very low risk	Low-risk HPV subtypes
Inverted	Inverted ‘‘ribbonlike’’ growth; immature squamous epithelium; transmigrating intraepithelial neutrophilic inflammation	Lateral wall and sinuses	Low to Intermediate risk	EGFR mutations or low-risk HPV subtypes
Oncocytic	Exophytic and endophytic growth; multilayered oncocytic epithelium; microcysts and intraepithelial neutrophilic microabscesses	Lateral wall and sinuses	Low to intermediate	KRAS

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

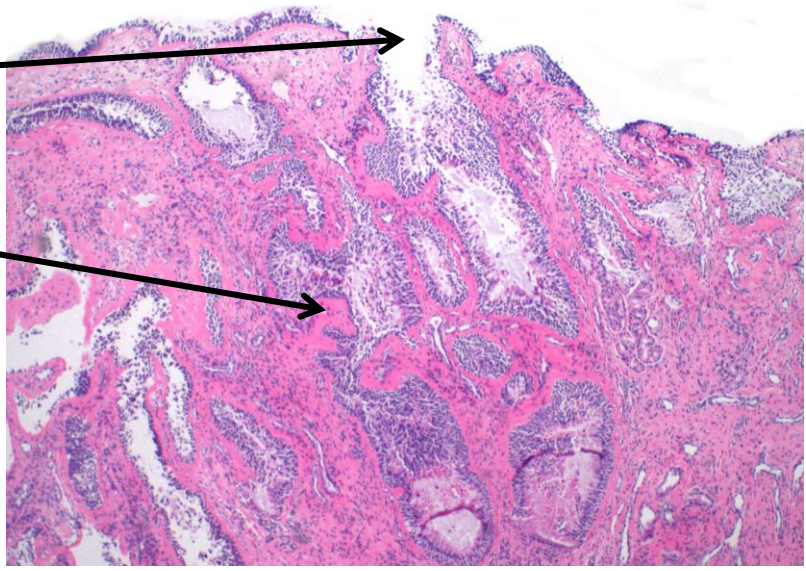
Respiratory Epithelial Adenomatoid Hamartoma

aka "REAH"

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

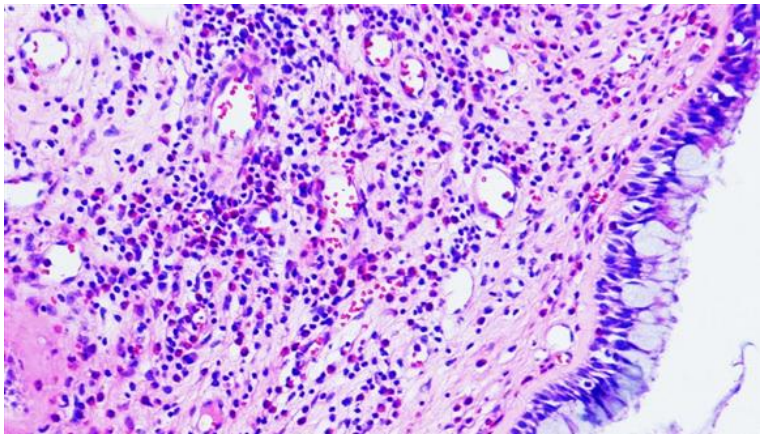


Inflammatory Polyp

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**

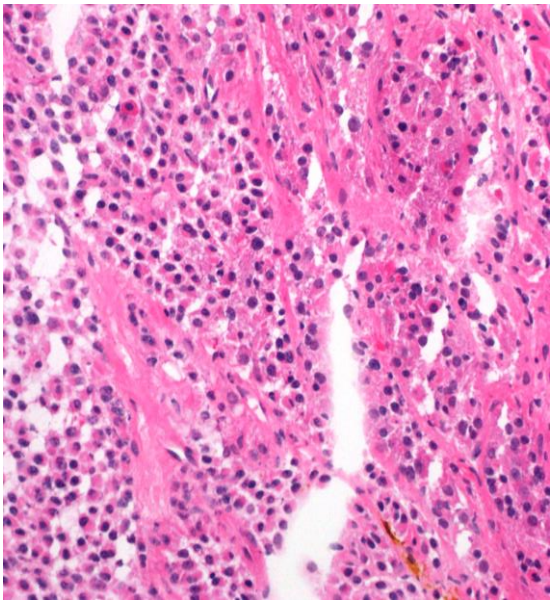
Although usually primary to sphenoid bone, can erode into nasopharynx or be **ectopic**

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

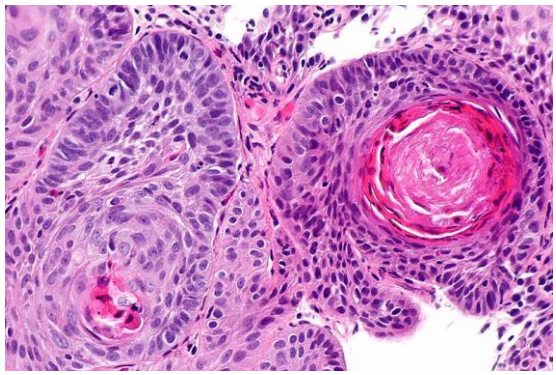


Malignant

Small Round Cell DDX: MR. SLEEP'N

M: Melanoma, Mesenchymal chondrosarcoma
R: Rhabdomyosarcoma
S: SNUC, SCC, SMARCB1-deficient sinonasal carcinoma
L: Lymphoma
E: Esthesioneuroblastoma
E: Ewing sarcoma
P: Pituitary adenoma, Plasmacytoma
N: NUT Carcinoma, Nasopharyngeal Carcinoma, NEC,

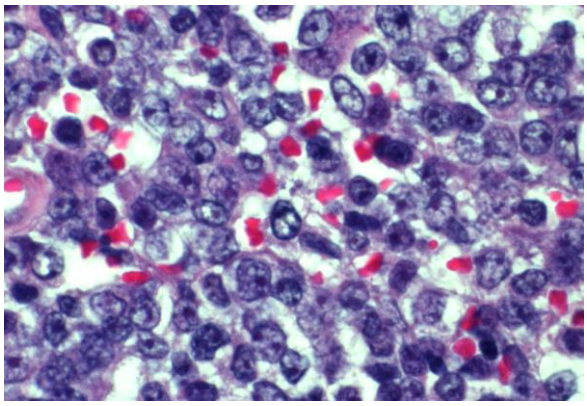
Squamous cell carcinoma



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)



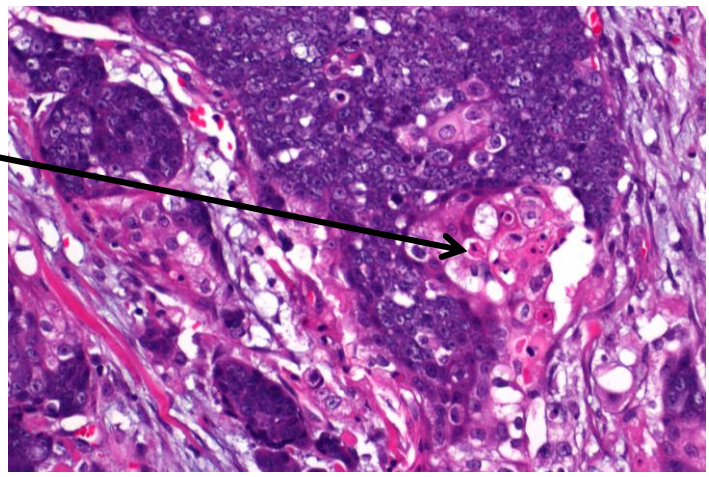
Poorly differentiated carcinoma without squamous, glandular, or neuroendocrine differentiation (Dx of exclusion!).

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

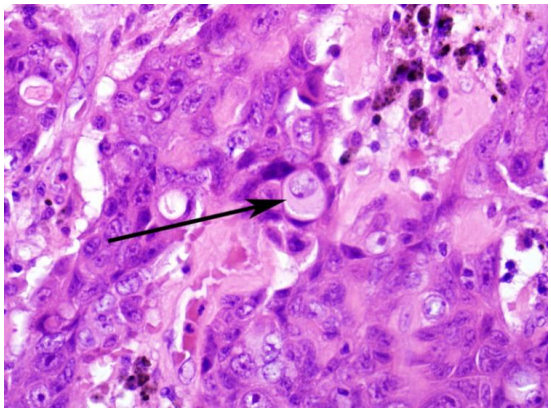
SMARCB1(INI-1)–deficient sinonasal carcinoma

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



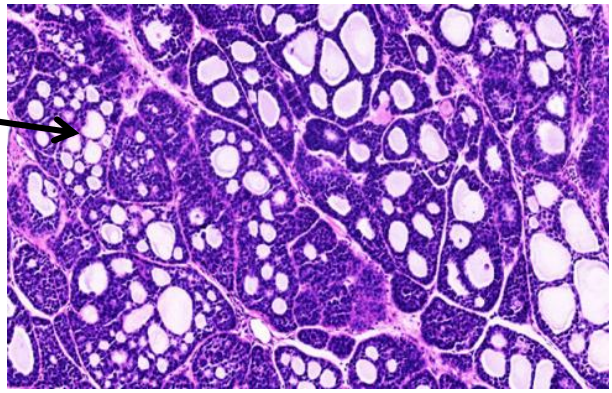
HPV-related multiphenotypic sinonasal carcinoma

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**



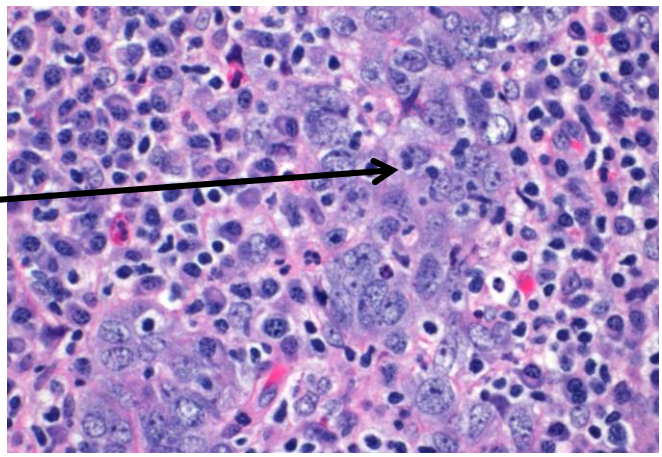
Lymphoepithelial Carcinoma

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**, indististinct cytoplasm, and **abundant tumor-infiltrating lymphocytes**.

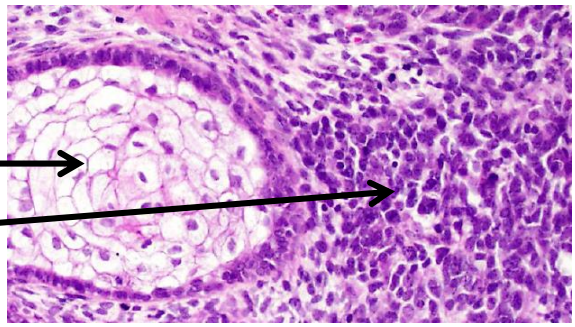
EBV-positive. Positive for CK, CK5/6, p40, p63

More common in **Asians**.

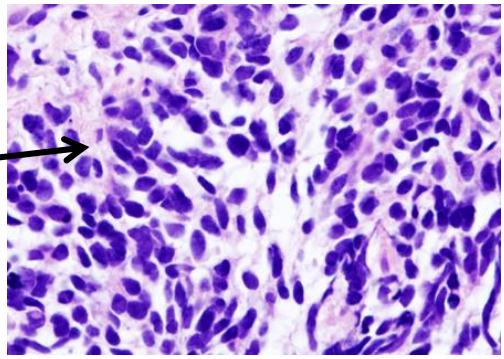


Teratocarcinosarcoma

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



Neuroendocrine Carcinoma

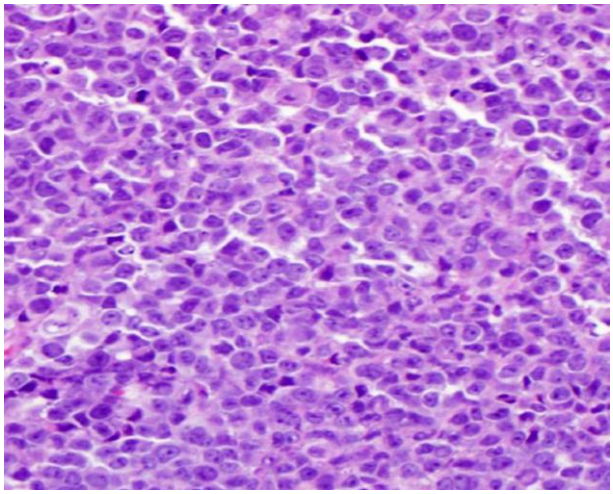


Like Poorly-differentiated neuroendocrine carcinomas of the lung.

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.

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.

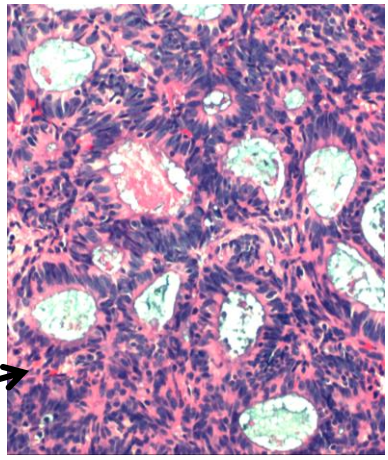
Adenocarcinoma

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

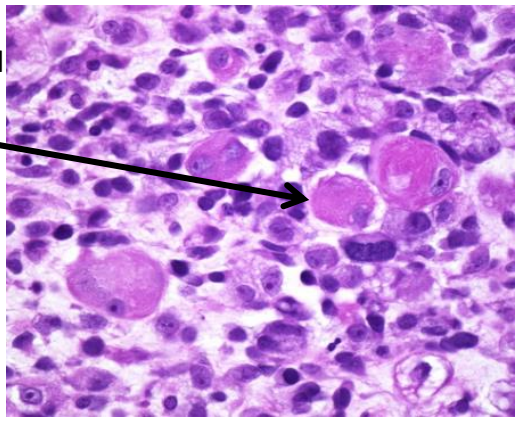
Nasopharyngeal papillary adenocarcinoma

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)

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



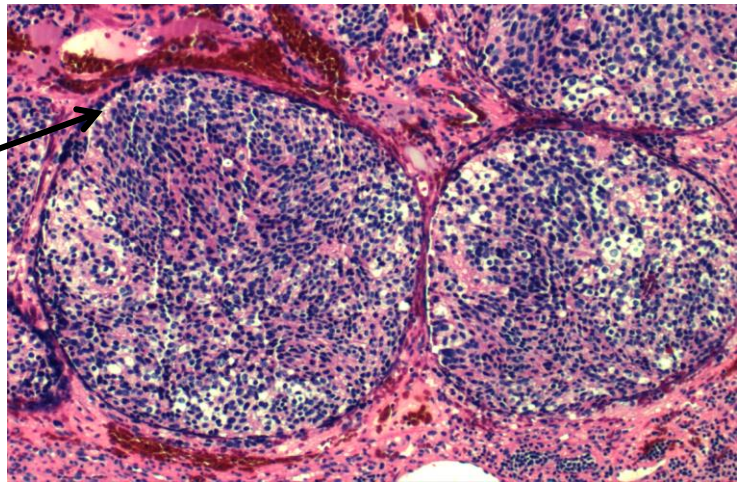
Alveolar Rhabdo:
Larger, more rounded undifferentiated cells with only occasional rhabdomyoblasts
Often arranged in an alveolar (nested) pattern
Distinctively strong and diffuse myogenin positivity
Characteristic **FOXO1** translocations

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.

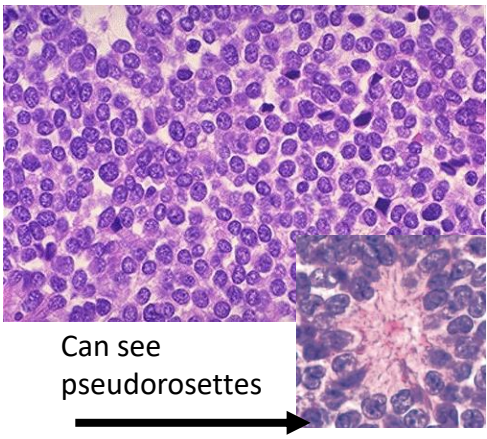
IHC: Diffuse Synaptophysin/Chromogranin
S100→ Sustentacular pattern. CK negative.

Ewing Sarcoma *aka Primitive Neuroectodermal Tumor (PNET)*

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!



Can see pseudorosettes

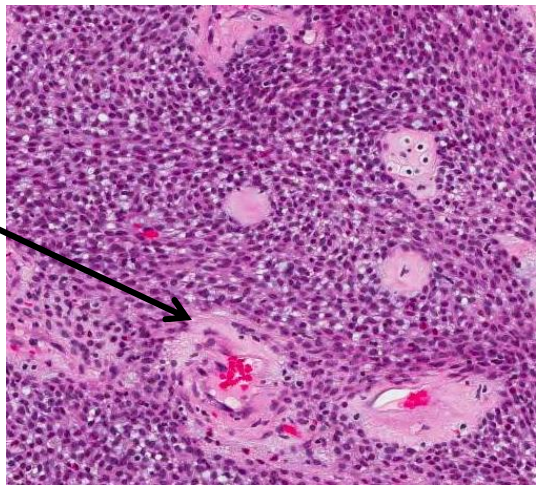
Lymphoma

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

Unique (not benign) Mesenchymal Tumors

Glomangiopericytoma



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

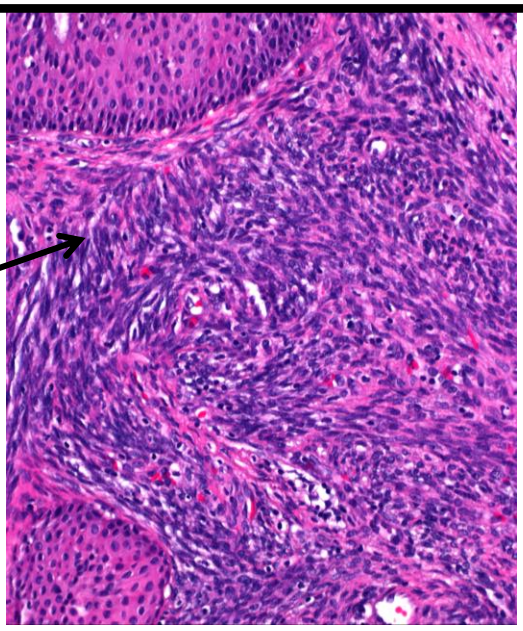
Prominent vascularity with perivascular hyalinization. Can see "**staghorn" vessels** (hemangiopericytoma-like, hence the name, in part)

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

IHC: SMA+, Nuclear ß-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.

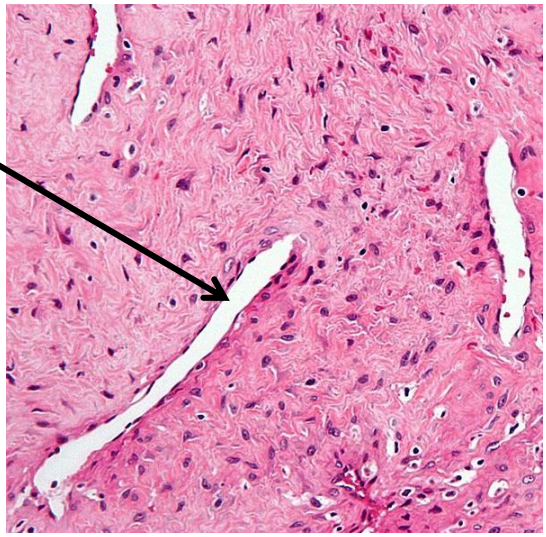
"**Biphenotypic**" because has evidence of **both neural and muscular differentiation.**

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 ß-catenin and AR in stromal cells

Locally aggressive and can recur.
Treat with embolization and surgery

Immunohistochemistry

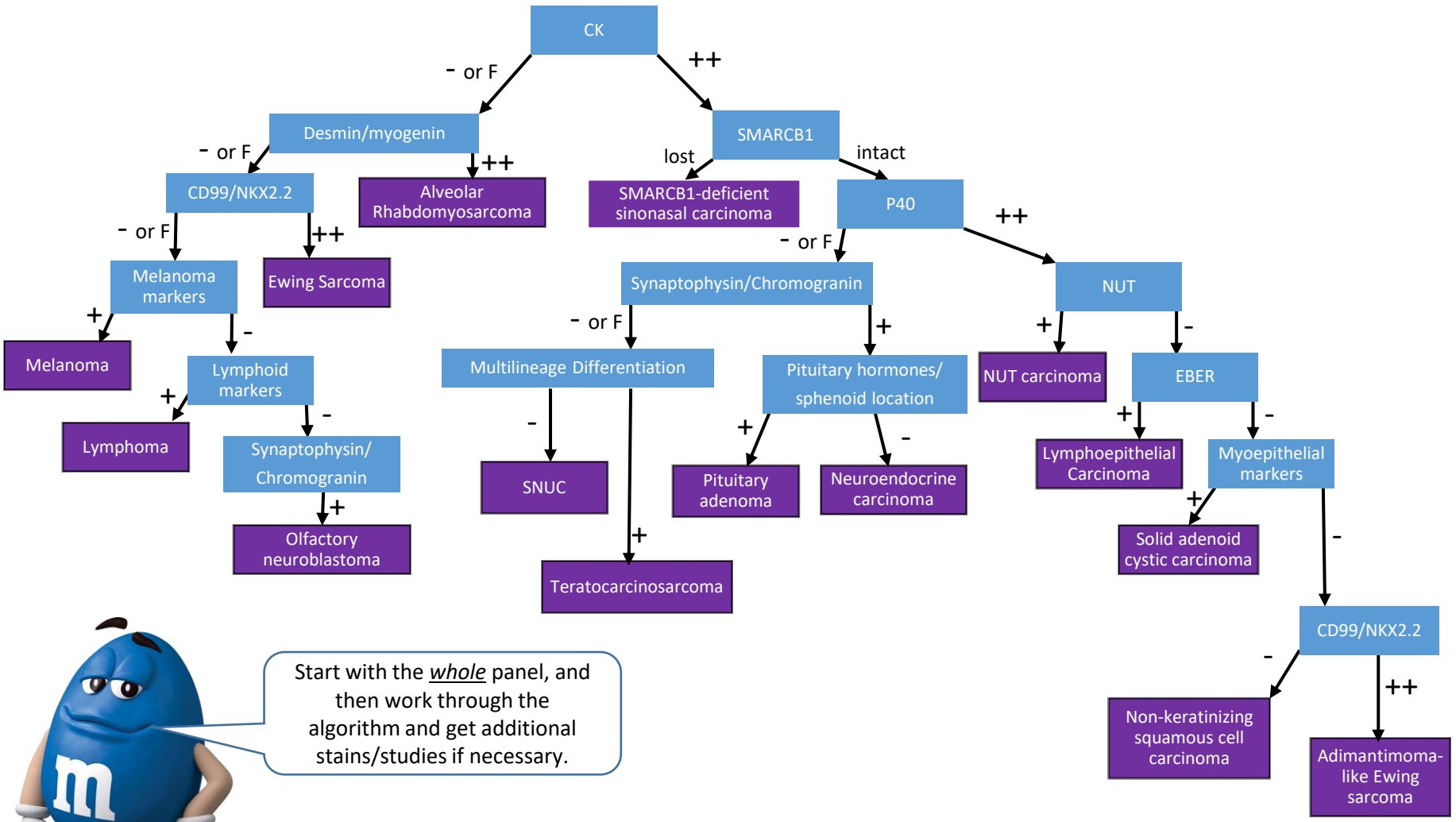
	Squamous cell carcinoma	Sinonasal Undifferentiated Carcinoma (SNUC)	SMARCB1(INI-1)–deficient sinonasal carcinoma	NUT carcinoma	HPV-related multiphenotypic sinonasal carcinoma	Nasopharyngeal carcinoma	Neuroendocrine Carcinoma	Mucosal melanoma	Rhabdomyosarcoma	Lymphoma	Olfactory Neuroblastoma	Ewing Sarcoma
CK (AE1/AE3)	+	+	+	+	+	+	+	-	-	-	-	±
CK5/6	+	-	±	+	+	+	-	-	-	-	-	±
P63 and p40	+	-	±	+	+	+	-	-	-	-	-	±
Synapto/ Chromo	-	-	-	-	-	-	+	-	±	-	+	±
CD56	-	-	-	-	-	-	+	-	±	±	+	±
CD99	-	-	-	-	-	-	-	-	-	±	-	+
P16	±	±	-	-	+	-	±	-	-	-	-	-
S100 SOX10	-	-	-	-	+	-	-	+	-	-	+	-
CD45	-	-	-	-	-	-	-	-	-	+	-	-
Myogenin/ Desmin	-	-	-	-	-	-	-	-	+	-	-	-
NUT	-	-	-	+	-	-	-	-	-	-	-	-
INI-1	+	+	-	+	+	+	+	+	+	+	+	+
EBER	-	-	-	-	-	+	-	-	-	±	-	-

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.