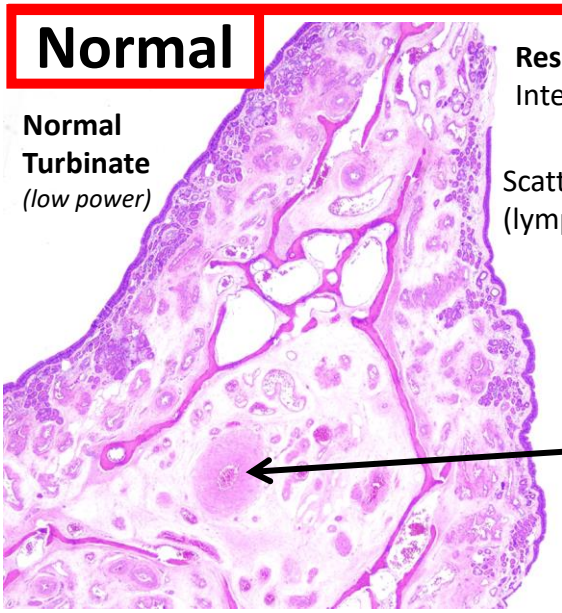
*Prepared by Dr. Kurt Schaberg*

# Sinonasal and Nasopharyngeal Lesions

## Normal



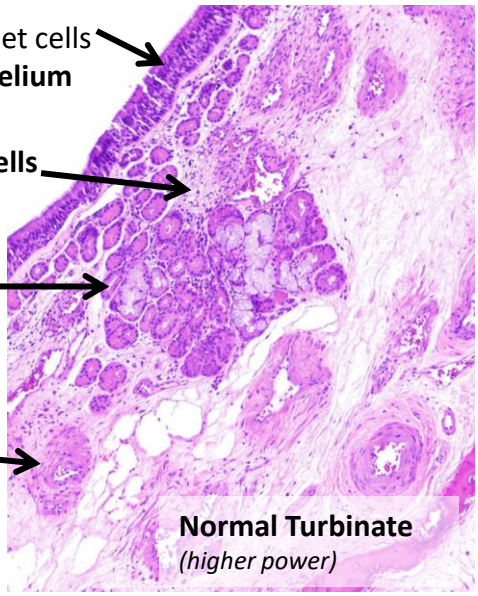
**Normal Turbinate** *(low power)*

**Respiratory Epithelium** with goblet cells Intermixed with **Squamous epithelium**

Scattered **chronic inflammatory cells** (lymphocytes, plasma cells, etc..)

**Minor salivary gland**, arranged in lobules

Numerous large, thick-walled **blood vessels**. *Pitfall alert: these can be mistaken for vascular lesions, but are normal!*



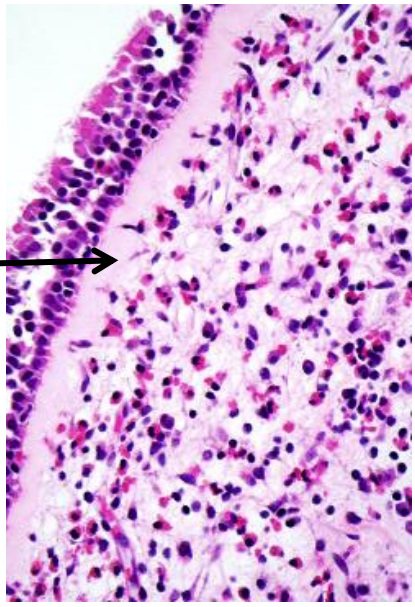
**Normal Turbinate** *(higher power)*

## Inflammatory

### Rhinosinusitis

In adults, allergies are the most common cause of rhinosinusitis (in kids, it's viral URIs).

**Submucosal chronic inflammatory infiltrate**, generally composed of lymphocytes, plasma cells, macrophages, and eosinophils
**Thickened, hyalinized basement membrane**
Stromal edema→ can develop into inflammatory polyps (see later)



**Allergic Sinusitis**
Exposure to allergen (pollen, dander, etc.)→ IgE-mediated reaction
Eosinophils predominate histologically. Can see Charcot Leyden crystals.
If lots of Eos→ stain for fungi (GMS) to evaluate for Allergic fungal sinusitis.

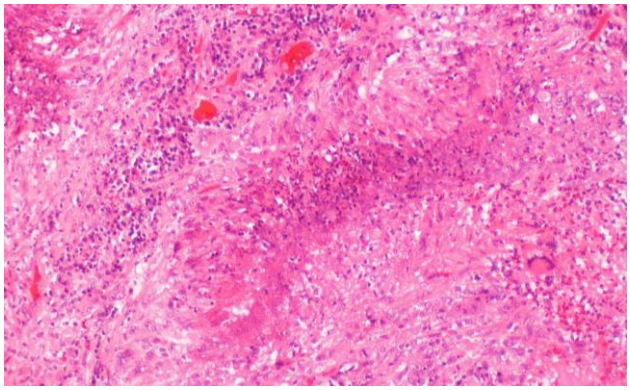
**Bacterial Sinusitis**
Mucopurulent discharge, headache, fever. Neutrophils predominate.

### Granulomatosis with Polyangiitis

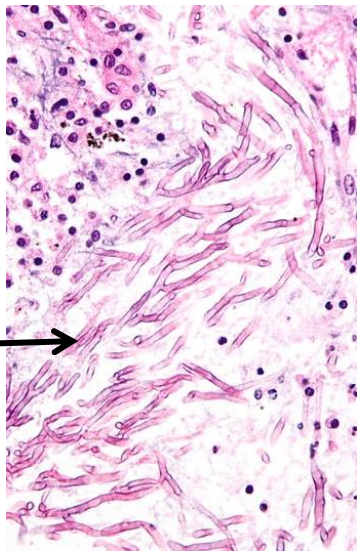
***aka Wegner's granulomatosis***

**Vasculitis** with necrotizing granulomatous inflammation.

Commonly impacts lung, nasal cavity, and kidney.
In lung/head see granulomas with geographic central necrosis and associated vasculitis→ form ulcers and nodules. In kidney can see crescentic glomerulonephritis.
PR3-ANCA positive.



# Fungal Infections

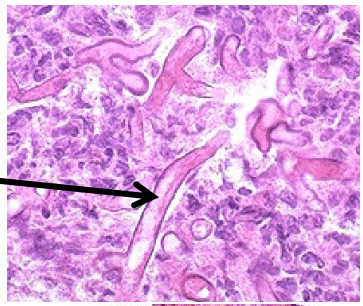


**Aspergillus** (3 forms of infection)
Thin (2 to 5 µm) hyphae with acute angle (45 degrees) branching and septation

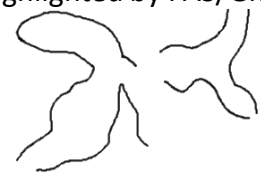
***Allergic fungal sinusitis***
Noninvasive fungus causing an allergic response with inspissated mucus, abundant eosinophils, Charcot-Leyden crystals, and debris.
Fungi may be scant→ consider getting a GMS if there are a lot of Eosinophils

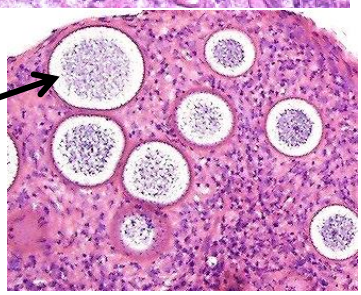
***Aspergillus mycetoma ("fungus ball")***
Indolent mass-forming ball of fungus.

***Invasive fungal sinusitis***
Destructive invasion with necrosis. Angioinvasion.
Often immunocompromised. Requires surgical debridement.



**Mucormycosis**
Zygomycetes fungus that classically infects those with diabetic ketoacidosis and/or immunocompromised. Rapidly progressive invasive infection with necrosis that often requires urgent surgical debridement.
Large/broad in diameter (10 to 20 µm), ribbon-like, non-septated hyphae with branching at haphazard angles. See well on H&E (highlighted by PAS/GMS, but special stains often unnecessary)



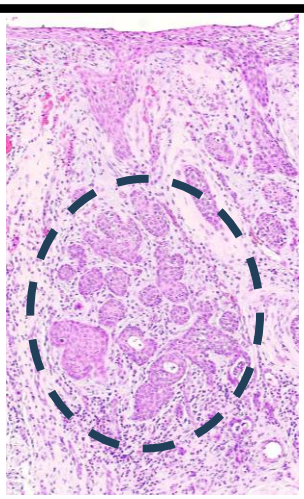


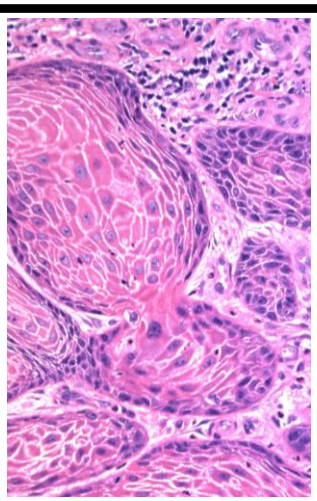
**Rhinosporidiosis**
Polypoid masses caused by the sporulating organism Rhinosporidium seeberi. Rare in US (more common in India and Brazil). Cysts (sporangia) ranging in size from 10 to 300 µm in diameter, containing innumerable sporangiospores (endospores) seen on H&E.

# Mucocele

Sinus outlet obstruction → build up of mucus → fills and distends sinus walls. **Clinical/radiographic Dx.**
Histologic findings *nonspecific*: flattened epithelium and squamous metaplasia, inflammation, bone remodeling, and other reactive changes.

# Necrotizing sialometaplasia





**Squamous metaplasia** of minor salivary glands
(just a fancy name for it! ;-)

*Classic Mimic of SCC!*

Lobular architecture is maintained
Smooth, rounded contours
Often associated inflammation and reactive changes
Acinar coagulative necrosis

(vs SCC, which does *not* have lobular architecture, has infiltrative, irregular contours, and is more atypical and less inflamed)

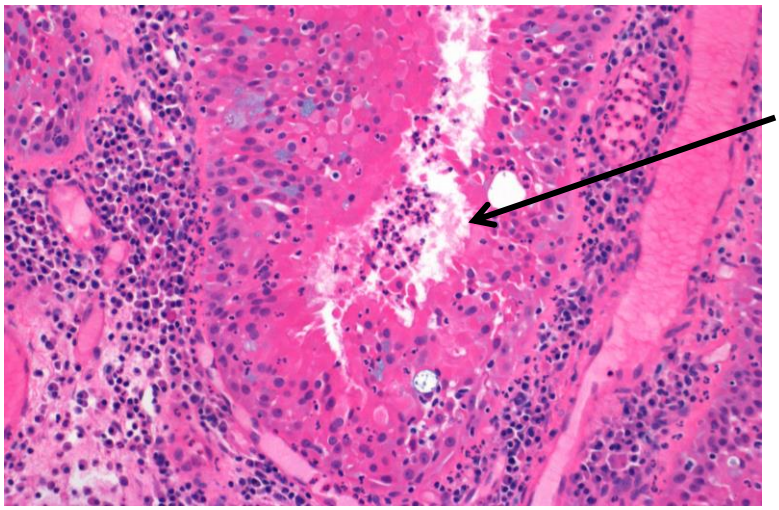
# Benign Tumors

## Sinonasal Papilloma

***aka "Schneiderian papilloma"***

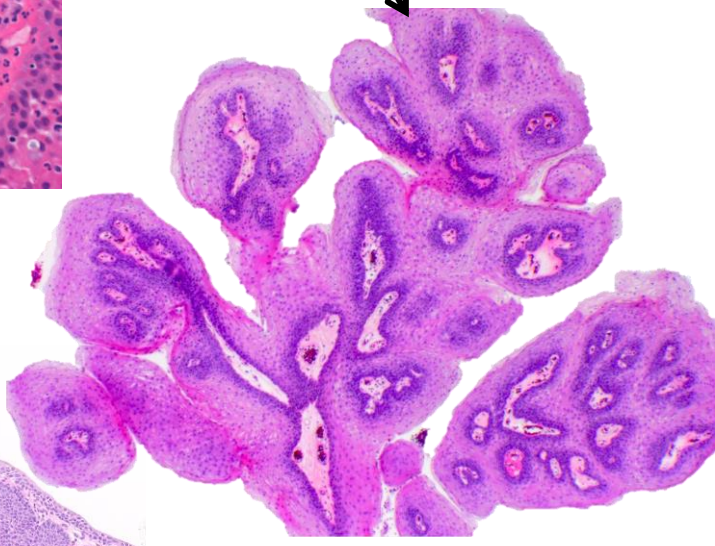
| Type | Morphology | Location | Risk of transformation | Molecular |
|---|---|---|---|---|
| **Exophytic** | Exophytic and papillary growth; immature squamous epithelium | Nasal septum | Very low risk | Low-risk HPV subtypes |
| **Inverted** | Inverted ''ribbonlike'' endophytic, non-destructive growth; 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 |

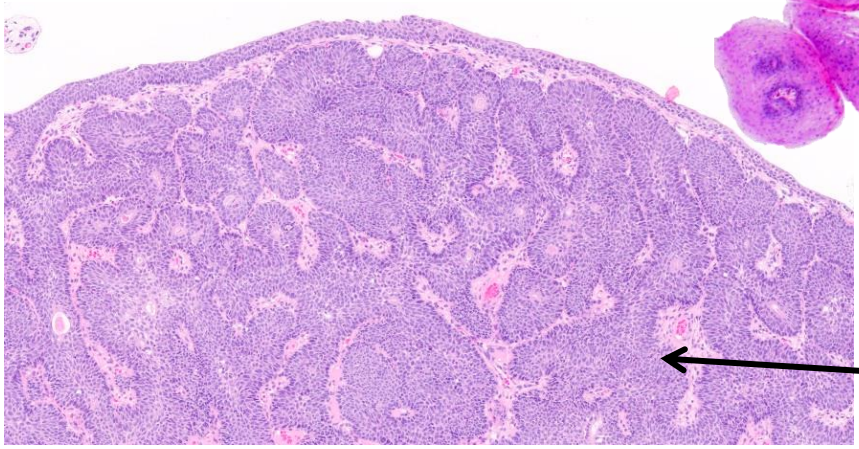
*Modified from: Weindorf et al. Arch Pathol Lab Med—Vol 143, November 2019*



**Oncocytic Sinonasal Papilloma**
Abundant oncocytic epithelium with numerous neutrophils

**Exophytic Sinonasal Papilloma**
Papillary growth





**Inverted Sinonasal Papilloma**
Inverted, "ribbon-like" growth

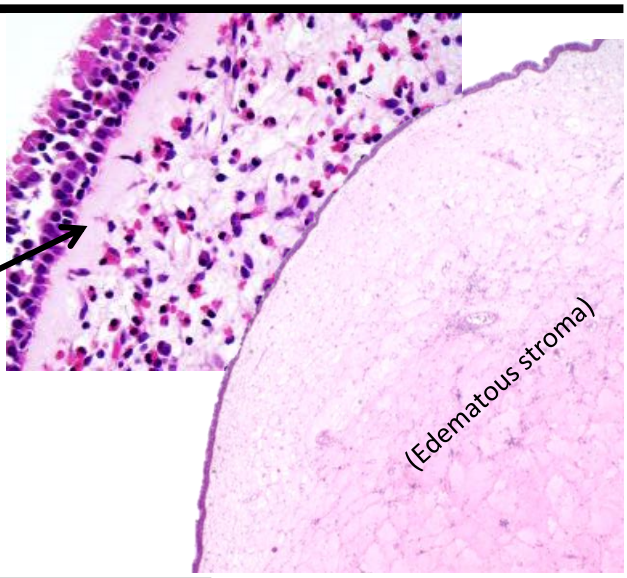
# Inflammatory Polyp

**Non-neoplastic** inflammatory swellings of the sinonasal mucosa (secondary to/overlapping with chronic sinusitis).

Surface ciliated, respiratory/sinonasal mucosa, possibly with squamous metaplasia.
May have thickened, eosinophilic basement membrane.

**Markedly edematous stroma** (without a proliferation of seromucinous glands).

Mixed **chronic inflammation** (usu. Lymphocytes, plasma cells, and eosinophils) with occasional neutrophils.




# Respiratory Epithelial Adenomatoid Hamartoma

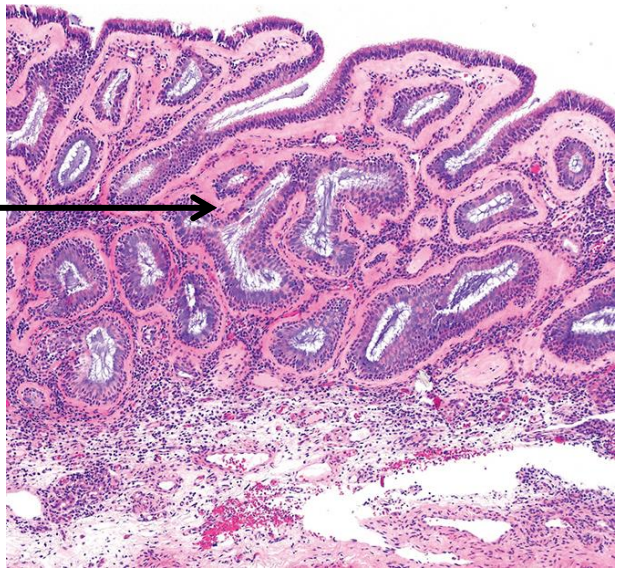
***aka "REAH"***

**Glandular proliferation arising from the surface epithelium** (i.e., in continuity with the surface). Pseudostratified, ciliated epithelium.

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.

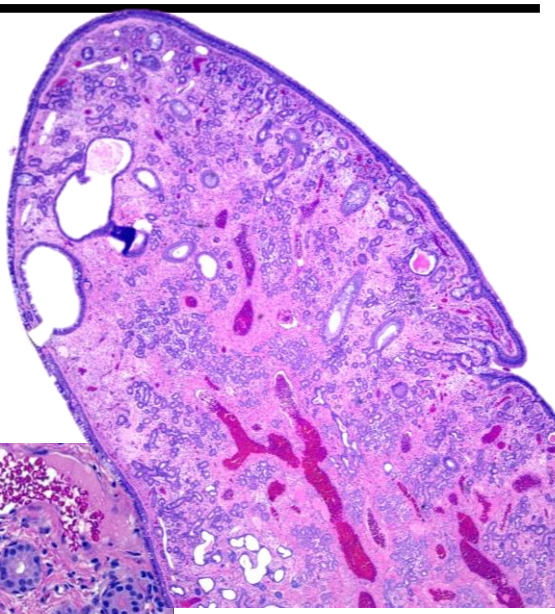
Chondro-osseous respiratory epithelial (CORE) hamartoma is a subtype with an admixture of cartilaginous and/or osseous trabeculae that are intimately associated with the glandular proliferation.

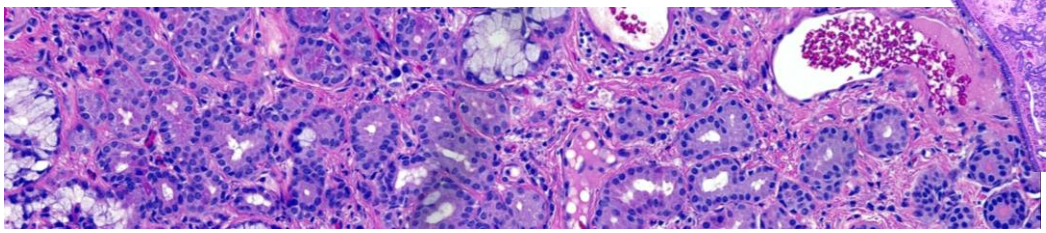


# Seromucinous hamartoma

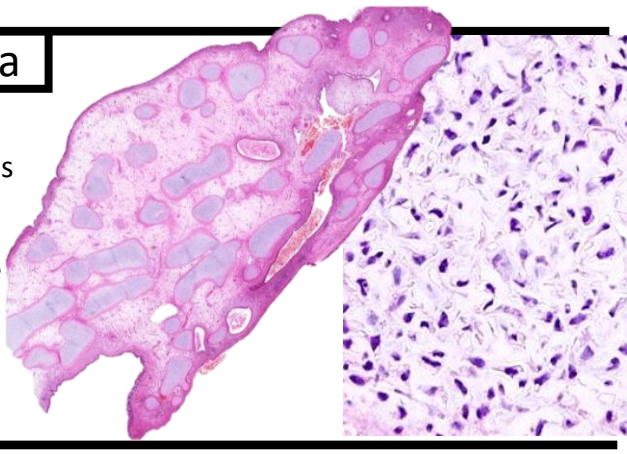
**Monotonous proliferation of small pink tubules with lobular architecture** (resembles microglandular adenosis in the breast); absent/rare myoepithelial/basal cells; discernible basal lamina; no infiltrative pattern; no papillary architecture or gland fusion. Can have eosinophilic secretions.

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





# Nasal chondromesenchymal hamartoma



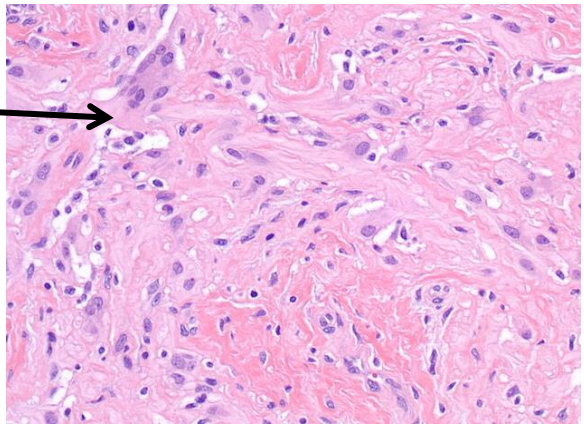
Benign mesenchymal sinonasal tract tumor composed of **cysts** lined by respiratory epithelium associated with nodules of **cartilage** and a variably **myxoid spindle cell stroma**.

**DICER1 mutations**→ associated with DICER1 syndrome (like pleuropulmonary blastoma, etc…

Usually seen in **kids**.

# CNS Lesions

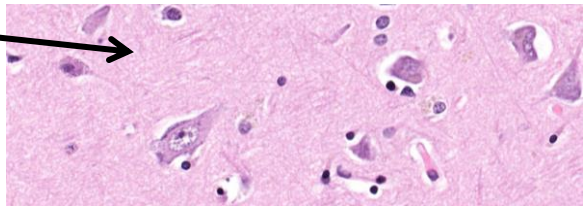
## Heterotopic CNS tissue



***aka Glial heterotopia***

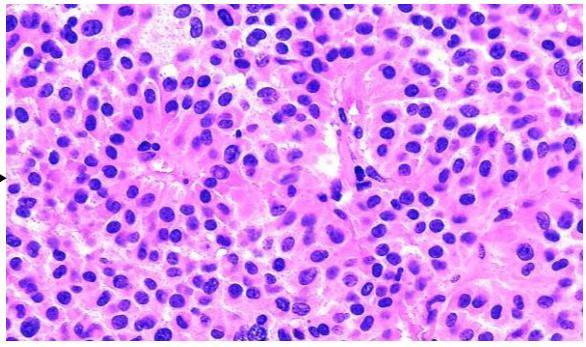
Congenital developmental, displacement of neuroglial tissue in extracranial sites *without* connection to the cranial cavity. Astrocytes and neuroglial fibers associated with a fibrous, vascularized connective tissue. Neurons are usually rare/few. May resemble plump fibroblasts (Does NOT really look like normal brain). IHC: (+) GFAP and S100.

DDX: **Encephalocele**→ Herniation of brain outside of cranium (*connected* to the brain). Closely resembles normal brain tissue with neurons. Must exclude "surgical misadventure."



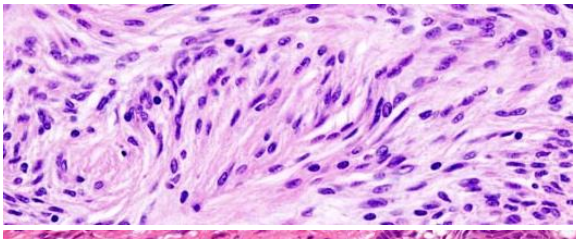
## Pituitary Adenoma

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.
IHC: (+)CK, and neuroendocrine markers.
(-) *No* S100 sustentacular pattern.
Can stain with hormone-specific markers (e.g., prolactin).
Can recur.



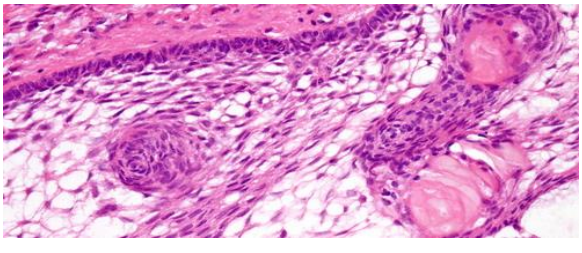
## Meningioma

Dural-based. Oval nuclei, pseudoinclusions. Syncytial tumor cells with whorls and psammoma bodies.
IHC: (+)SSTR2A, EMA, PR.



## Adamantinomatous craniopharyngioma

Epithelial tumor derived from embryonic remnants of Rathke's pouch. Basal palisading. Stellate retinaculum. "Wet Keratin."
IHC: nuclear β-catenin

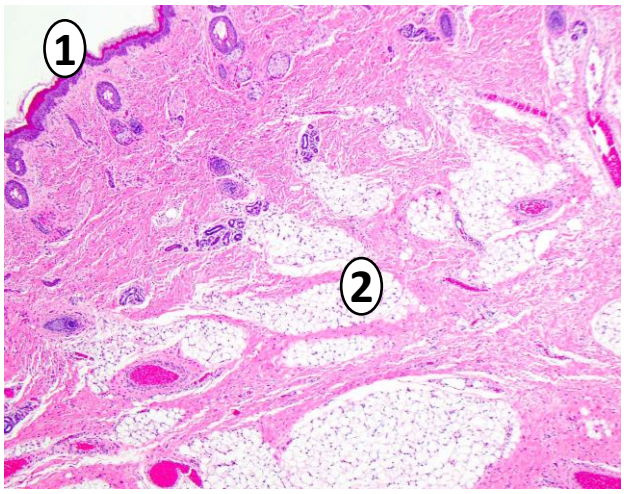


## Hairy Polyp

**Polypoid** structure with **1) ectodermal outer layer resembling skin** (keratinizing squamous epithelium with adnexal structures, including hair), covering **2) mesodermal tissue** (always fibroadipose tissue, with bone, cartilage, and/or skeletal muscle); no endodermal tissue should be present.

**Developmental** abnormality→ mostly diagnosed in **<u>kids</u>**.

*Think: looks like skin and dermis, including <u>hair</u>*

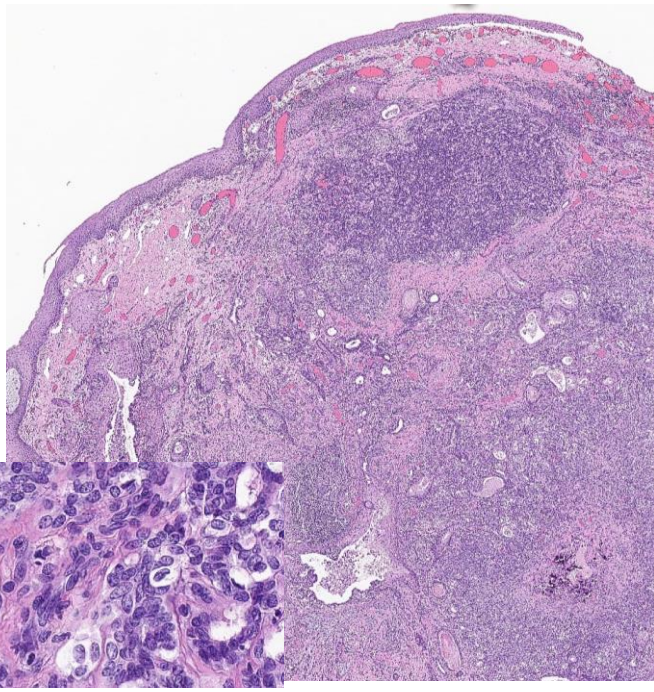


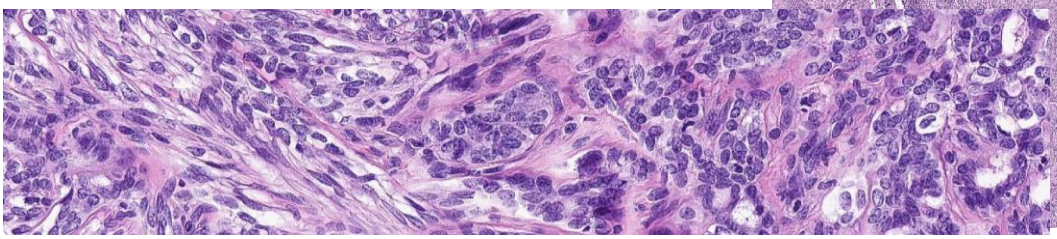

## Salivary gland anlage tumor

**Very rare**. Predominantly **<u>infants</u>**.

Biphasic squamoid epithelial and myoepithelial complex network of tubules and ducts continuous with the surface epithelium, resembling developing salivary gland. Stroma hypocellular, with more cellular stromal nodules in the center of the polyp→ myoepithelial cells, IHC: (+) CK & SMA

Old name: congenital pleomorphic adenoma of nasopharynx





## Malignant

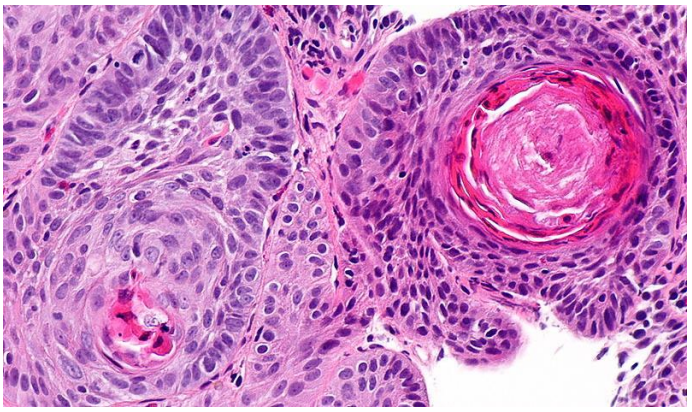
The most common malignancy in the sinonasal region is **squamous cell carcinoma**.

However, there are a lot of other tumors that can arise there—including some unique ones—many of which have relatively "small round blue cell" morphology. To help with these cases, I use this mnemonic.

### *Small Round Blue Cell: MR SLEEP 'N*

**M:** Melanoma, Mesenchymal chondrosarcoma
**R:** Rhabdomyosarcoma
**S:** SNUC, SCC, SWI/SNF-deficient sinonasal carcinoma
**L:** Lymphoma
**E:** Esthesio(olfactory)neuroblastoma
**E:** Ewing sarcoma
**P:** Pituitary adenoma, Plasmacytoma
**N:** NUT Carcinoma, Nasopharyngeal Carcinoma, NEC,

# Squamous cell carcinoma



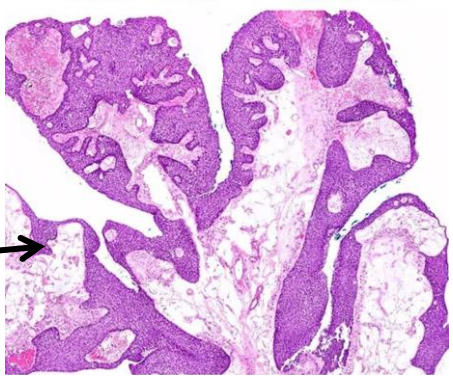
**Most common sinonasal malignancy!**
Can be Keratinizing or Non-keratinizing

*Like elsewhere*: malignant infiltrative epithelial cells with squamous differentiation.

Arise from squamous metaplasia and/or inverted papillomas.

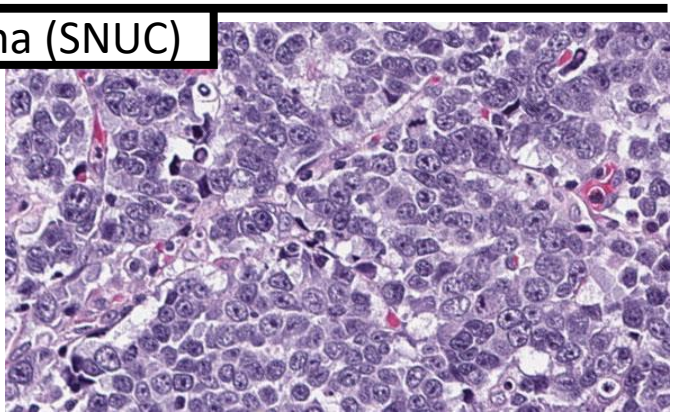
Associated with **tobacco** and occupational exposure.
High-risk HPV subtypes in a subset of tumors;
EGFR or KRAS mutations if papilloma–associated

IHC: (+)CK, p40, p63, CK5/6 and 34βE12
(-) Neuroendocrine markers, INSM1, S100, NUT, CD99, with intact INI1 and BRG1



*Rare/emerging subtype:*
***DEK-AFF2* fusion-associated papillary squamous cell carcinoma**
Exophytic and inverted patterns, broad papillary fronds, acantholytic change, cellular monotony, dense neutrophilic infiltrates, and peripheral palisading. Can be deceptively bland. Prolonged locoregional spread.
Molecular: DEK-AFF2 fusion.

# Sinonasal Undifferentiated Carcinoma (SNUC)



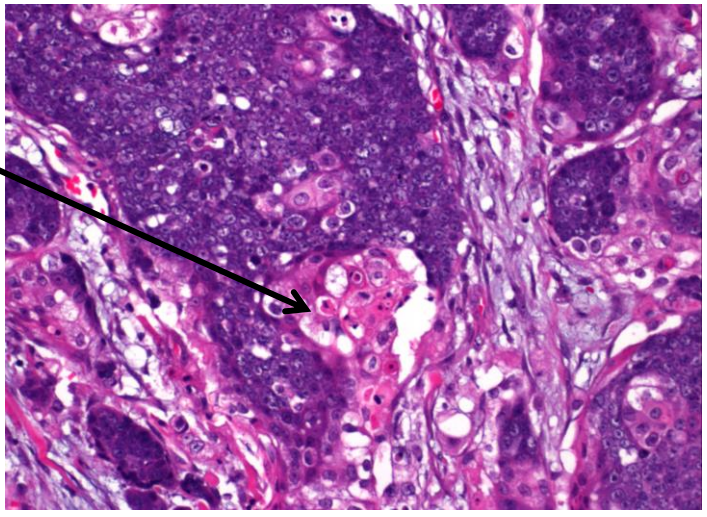
**Poorly differentiated carcinoma without squamous, glandular, or neuroendocrine differentiation.**
***(Dx of exclusion!)***

Somewhat monotonous. Often prominent nucleoli.
Usually older men.

**IHC: (+) CK, but squamous markers negative**
Molecular: IDH2 codon R172 mutations often

Aggressive high-grade malignancy→ poor outcome

# NUT Carcinoma



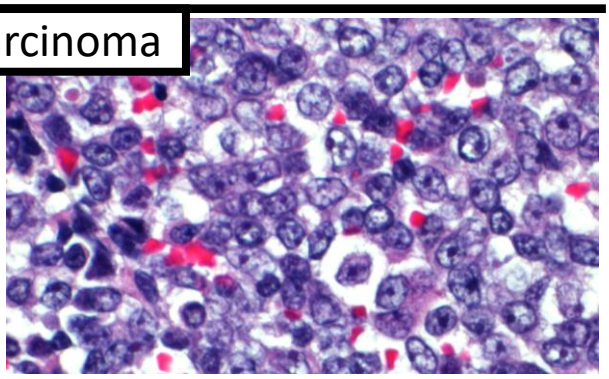
Poorly-differentiated carcinoma (often small-round blue cells), classically with "abrupt keratinization" (1/3 of cases) or squamous differentiation.
Vesicular chromatin with prominent nucleoli

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

Molecular: **NUTM1 fusions** (most often with BRD4)
**IHC: (+)NUT,** CK (usually), (+/-)PRAME, p63, CD34
*Need positive NUT IHC or molecular to make Dx*

Aggressive high-grade malignancy→ poor outcome

# SWI/SNF complex-deficient sinonasal carcinoma

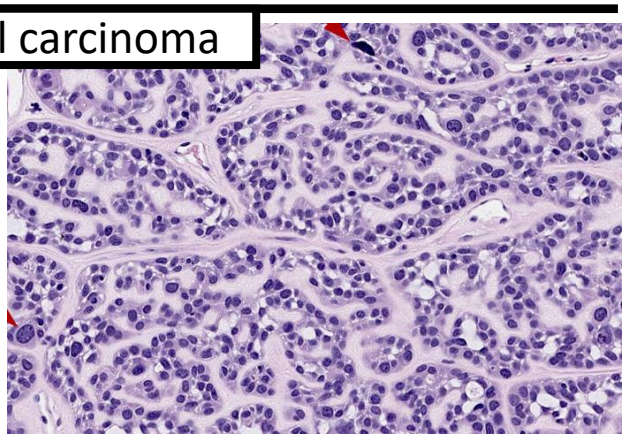


Poorly-differentiated carcinoma with high N:C ratios
May show basaloid, plasmacytoid, or rhabdoid features

***Required to show loss of SWI/SNF complex subunit***
**IHC: Loss of INI-1 or BIRG1 protein expression**
**Molecular: inactivation of SMARCB1 or SMARCA4**

Aggressive→ Poor long-term outcomes

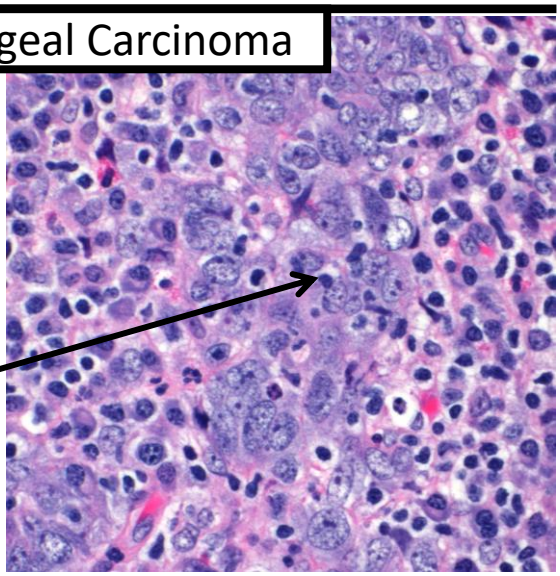
# HPV-related multiphenotypic sinonasal carcinoma



HPV-mediated 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, seems to be **indolent**.

# Lymphoepithelial Carcinoma/Nasopharyngeal Carcinoma

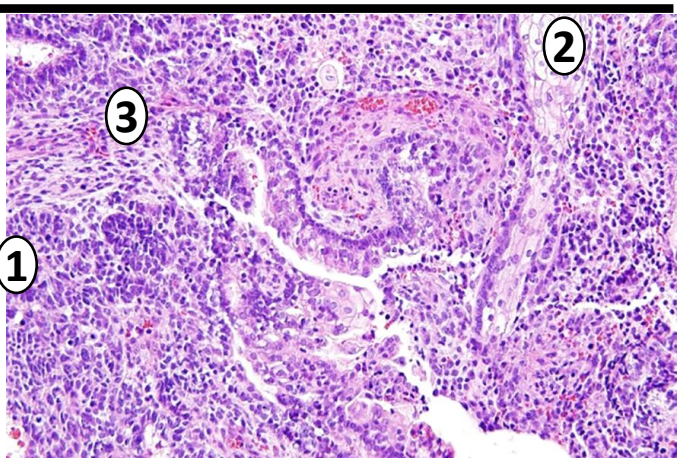


**Undifferentiated carcinoma with prominent non-neoplastic lymphoplasmacytic cell infiltrate, strongly associated with EBV.**

Sinonasal cavity→ Lymphoepithelial carcinoma
Nasopharynx→ Nasopharyngeal carcinoma, Non-keratinizing squamous cell carcinoma
*(there are separate keratinizing and basaloid SCCs in the nasopharynx, less related to EBV)*

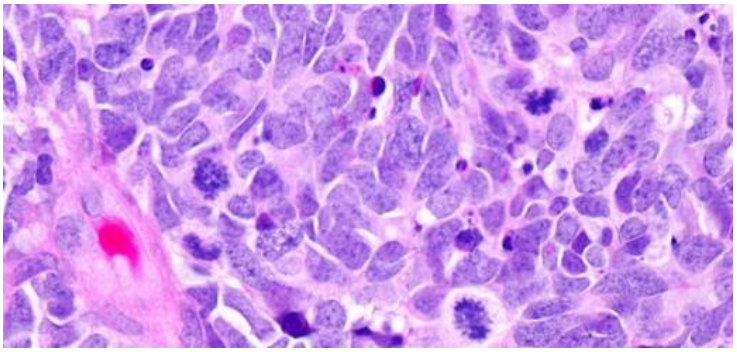
Sheets of malignant cells with vesicular chromatin, indististinct cytoplasm, and abundant tumor infiltrating lymphocytes.
IHC: (+) CK, CK5/6, p40, p63, **EBER** ISH
More common in **Asians**

# Teratocarcinosarcoma



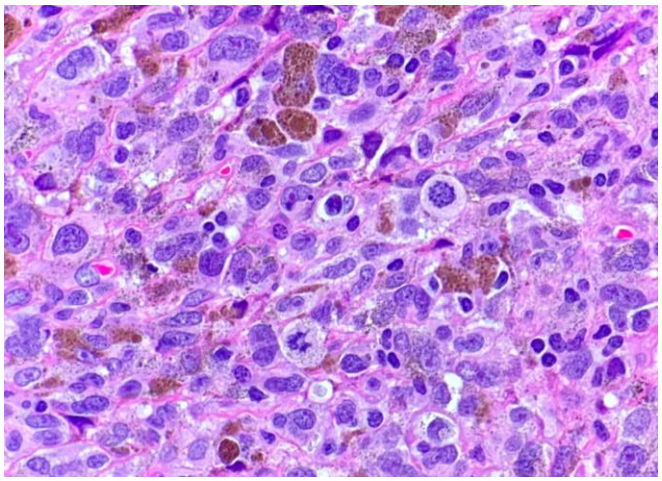

**Malignant tumor with:**
**1) Immature teratoma:** Primitive neuroepithelial elements with fibrillary matrix and rosettes
**2) Carcinoma**: Squamous or glandular, often with fetal clear cell appearance
**3) Sarcoma**: usually fibroblastic, but can show heterologous differentiation
Many have SMARCA4 (BIRG1) loss and/or nuclear β-catenin.
Usually older men.

# Neuroendocrine Carcinoma



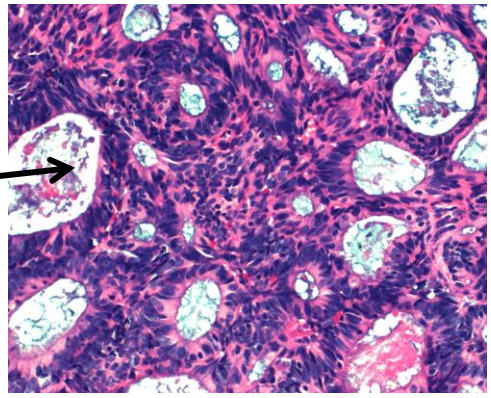
Like Poorly-differentiated neuroendocrine carcinomas of the lung.
Divided into:
1) Small cell neuroendocrine carcinoma
2) Large cell neuroendocrine carcinoma
Strong staining with a neuroendocrine stain (e.g.., synaptophysin or chromogranin). Often perinuclear "dot-like" keratin expression.

# Mucosal Melanoma



**Epithelioid to spindled cells with pleomorphic nuclei and often prominent nucleoli.**
Distinct from cutaneous melanomas biologically (but must exclude metastatic melanoma clinically!)
Intracytoplasmic **melanin**
Melanoma markers: (+) S100, SOX10, HMB45, MelanA, MITF, Tyrosinase. Do many (as can be loss)!
Molecular: Frequent RAS mutations
**Poor prognosis**: Staging starts at T3-4.
*No* need for Clark/Breslow depth.

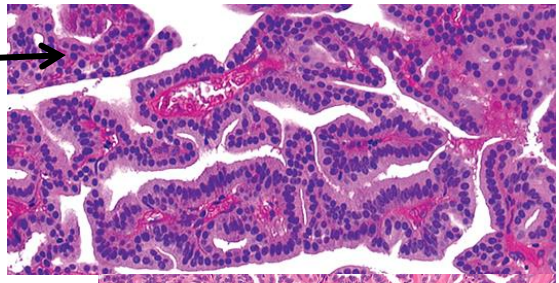
# Adenocarcinoma



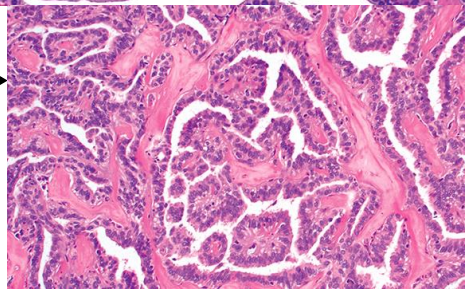
**Salivary gland adenocarcinomas are the most common!!**
(particularly adenoid cystic→ see separate notes)

**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 complex papillary and glandular growth with infiltration of the submucosa; low-grade cytology. Indolent.
IHC: (+)TTF1, CK, CK7; (-)Thyroglobulin, PAX8

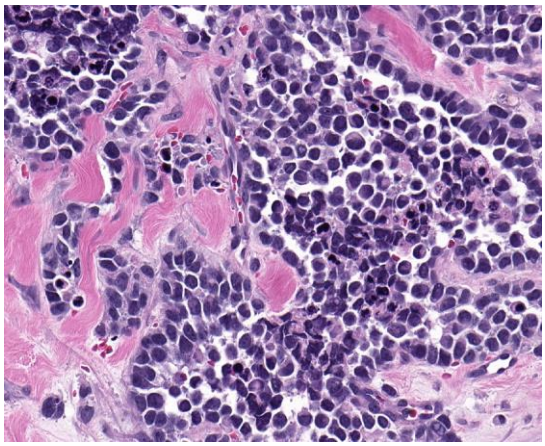


# Rhabdomyosarcoma

Malignant tumor with **skeletal muscle** differentiation, several types.
IHC: (+) Most specific are MyoD1, Myogenin. Also, Desmin

**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



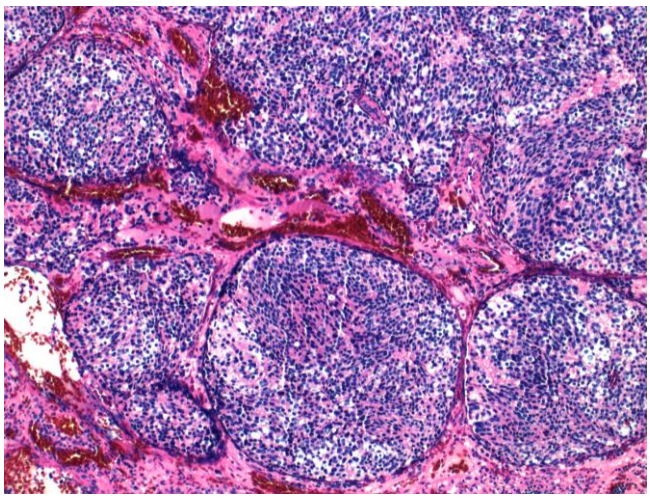
# Olfactory Neuroblastoma

***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 (small round blue cells).
Fibrillary cytoplasm→ **Neuropil**!
Can see **rosettes** and pseudorosettes.

**IHC: (+) Diffuse Synaptophysin/Chromogranin**, SSTR2A
**S100→ Sustentacular pattern**.
**(-/focal) CK**

Grade using Hyams system.



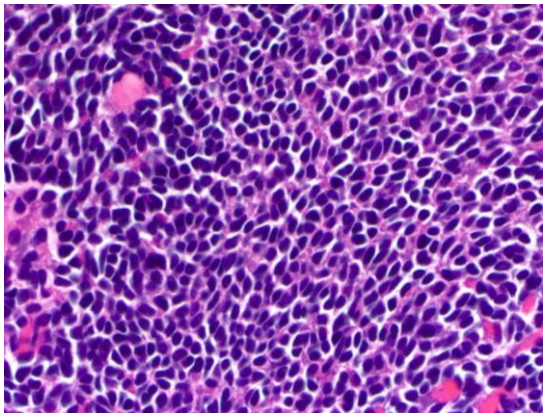
# Ewing Sarcoma

***aka Primitive Neuroectodermal Tumor (PNET)***

Malignant tumor of neuroectodermal differentiation.
**EWSR1 translocations** (with FLI-1 or ERG). t(11;22)
**Usually uniform, small, round, blue cells** with sheet-like to lobular growth pattern with variable necrosis

IHC: (+) Strong, membranous CD99 staining
(Sensitive, but not Specific staining)
Cytoplasmic glycogen stains with PAS

***Pitfall Alert:*** **"Adamantinoma-like" variant can show diffuse staining with CK and p40!**



# Lymphoma

*Always consider a hematologic malignancy and throw on heme stain or two (particularly if it's not staining with other stains ;-)!*

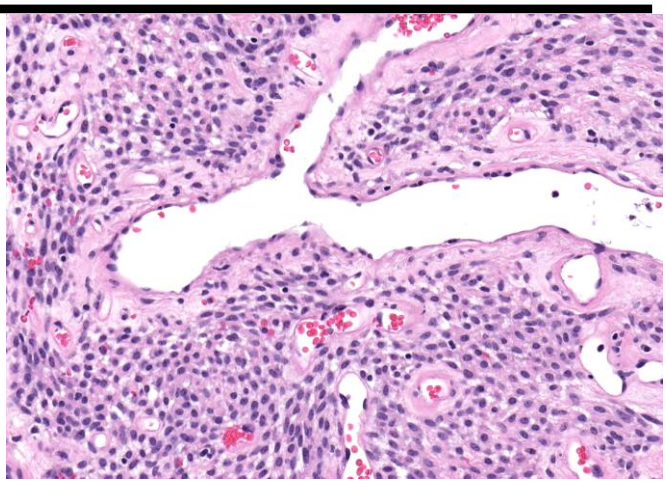
**Extranodal NK/T-cell lymphoma**
IHC: CD3, CD56, EBER +
Most common in Asians

**Plasmacytoma**
IHC: CD138+ with light chain restriction
May or may not be associated with multiple myeloma

# Unique (Low-grade) Mesenchymal Tumors

**Note:** Spindle cell tumors may *not* be Mesenchymal!
Consider salivary gland tumors, melanoma, spindle cell SCC, etc..!

## Glomangiopericytoma

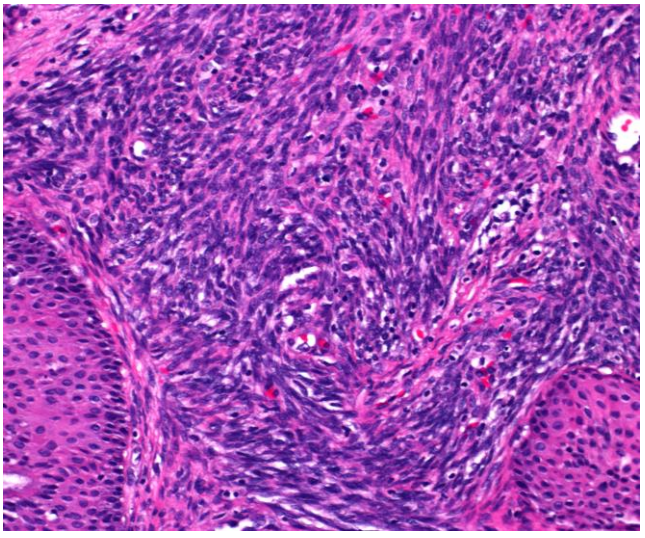


Patternless proliferation of regular, syncytial **ovoid to spindled myoid-type cells within a richly vascularized stroma and ovoid nuclei.**
Prominent vascularity with perivascular hyalinization.
Can see "staghorn" vessels (*"hemangiopericytoma-like")*
Extravasated erythrocytes, mast cells, and eosinophils.

**IHC: SMA+, Nuclear ß-catenin** (CTNNB1 mutations)
(-) STAT6, S100, CK

Relatively indolent with good survival.

## Biphenotypic Sinonasal Sarcoma



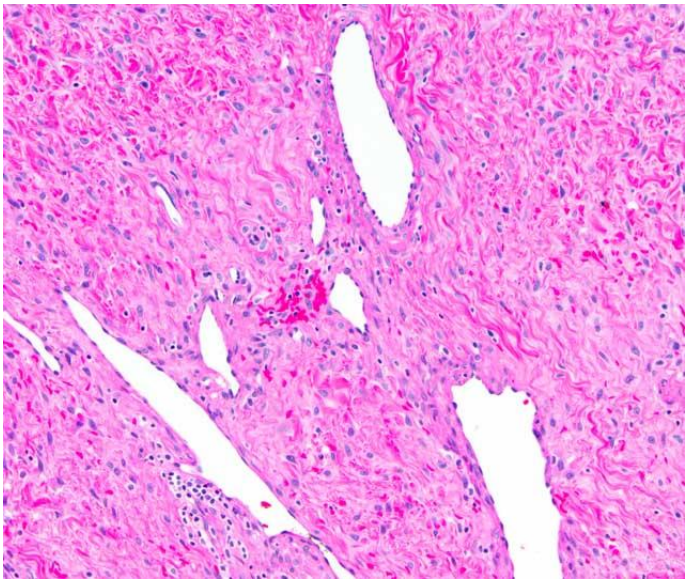
Low-grade spindle cell sarcoma.
"Biphenotypic" because has evidence of both **neural and muscular differentiation.**
Cellular, submucosal spindle-cell proliferation.
Arranged in intersection fascicles, often herringbone.
Infiltrate into bone often.
Can induce epithelial proliferation.

IHC: Neural→ + S100 (focal to diffuse) (SOX10 negative)
Muscle→ + SMA (focal to diffuse) (Desmin +/-)

**Molecular: PAX3 rearrangements** (usu. with MAML3**)**

Slow, continuous growth/recurrence, but no metastases.

## Sinonasal Tract Angiofibroma



**Locally aggressive**, variably cellular fibrovascular neoplasm.

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

Richly vascular tumor with variably sized blood vessels set in fibrotic stroma.
Vessels are usu. thin-walled and often dilated with variable smooth muscle.

IHC: **(+) Nuclear expression of ß-catenin** and AR

Treat with embolization (to reduce bleeding) and surgery.

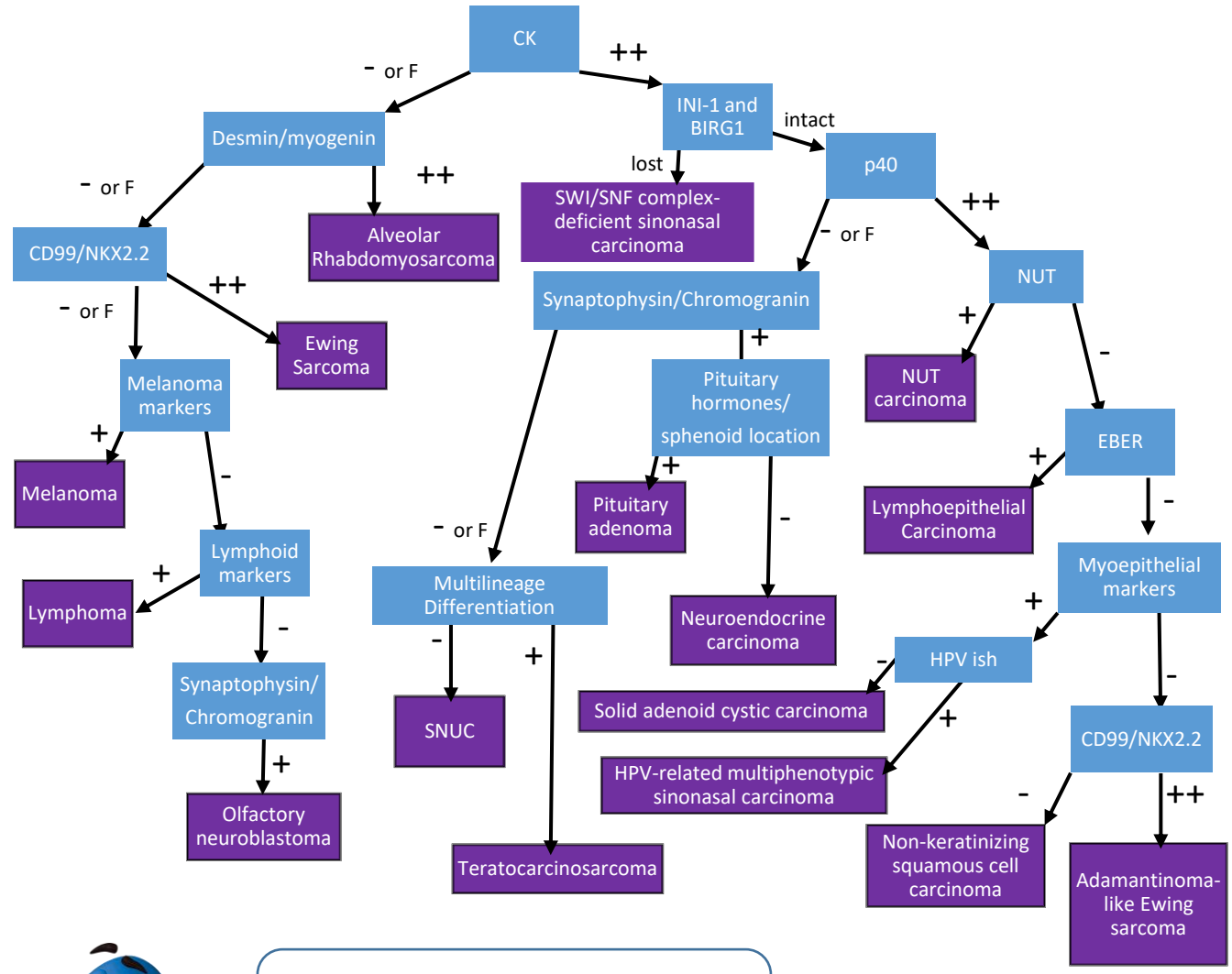
# Small Round Blue Cell Immunohistochemistry

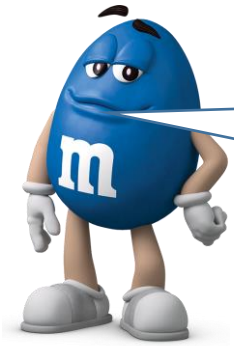
| | Squamous cell carcinoma | Sinonasal Undifferentiated Carcinoma (SNUC) | SMARCB1(INI-1)–deficient sinonasal carcinoma | NUT carcinoma | HPV-related multiphenotypic sinonasal carcinoma | Lymphoepithelial/Nasopharyngeal carcinoma | Neuroendocrine Carcinoma | Mucosal melanoma | Rhabdomyosarcoma | Lymphoma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

**Note:** Weak 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



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

***Potential Pitfalls:***

Many non-neuroendocrine tumors can show some staining with synaptophysin (e.g., rhabdomyosarcoma)

Many of these lesions can stain with PRAME!

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