SINONASAL TUMORS

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Broad Types

- Epithelial Tumors
  - Schneiderian Papillomas
  - Hamartomas
  - Adenocarcinomas
- Round blue cell tumors
- Soft tissue tumors
- Recently described entities

SCHNEIDERIAN PAPILLOMA

Inverted type

- Lateral nasal cavity and sinuses; endophytic growth of markedly thickened squamous epithelial proliferation growing downward
- Thickened squamous epithelial proliferation with admixed mucocytes, intraepithelial mucous cysts

Exophytic type

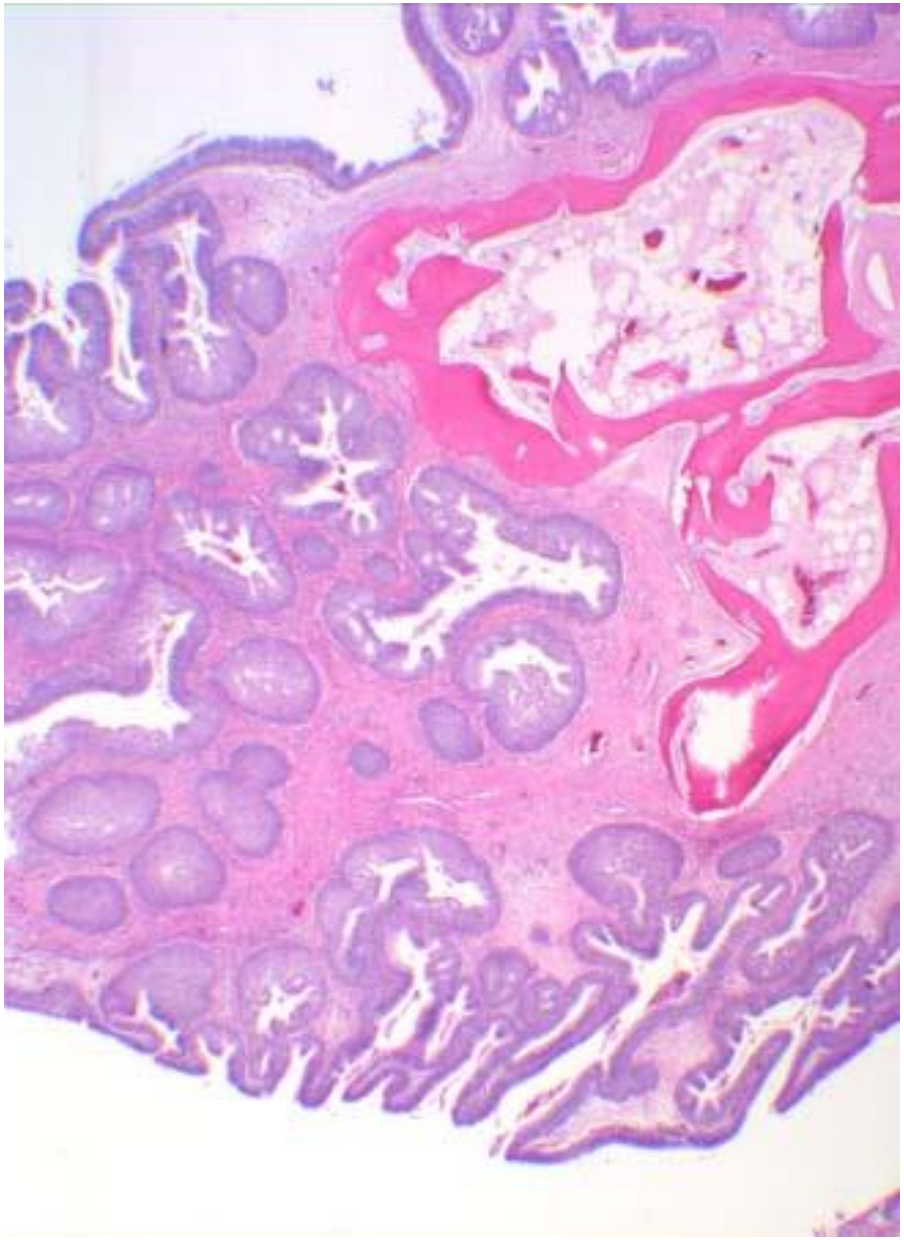
- Exophytic (papillary) growth, almost invariably of septum
- Thickened squamous epithelial proliferation with admixed mucocytes, intraepithelial mucous cysts

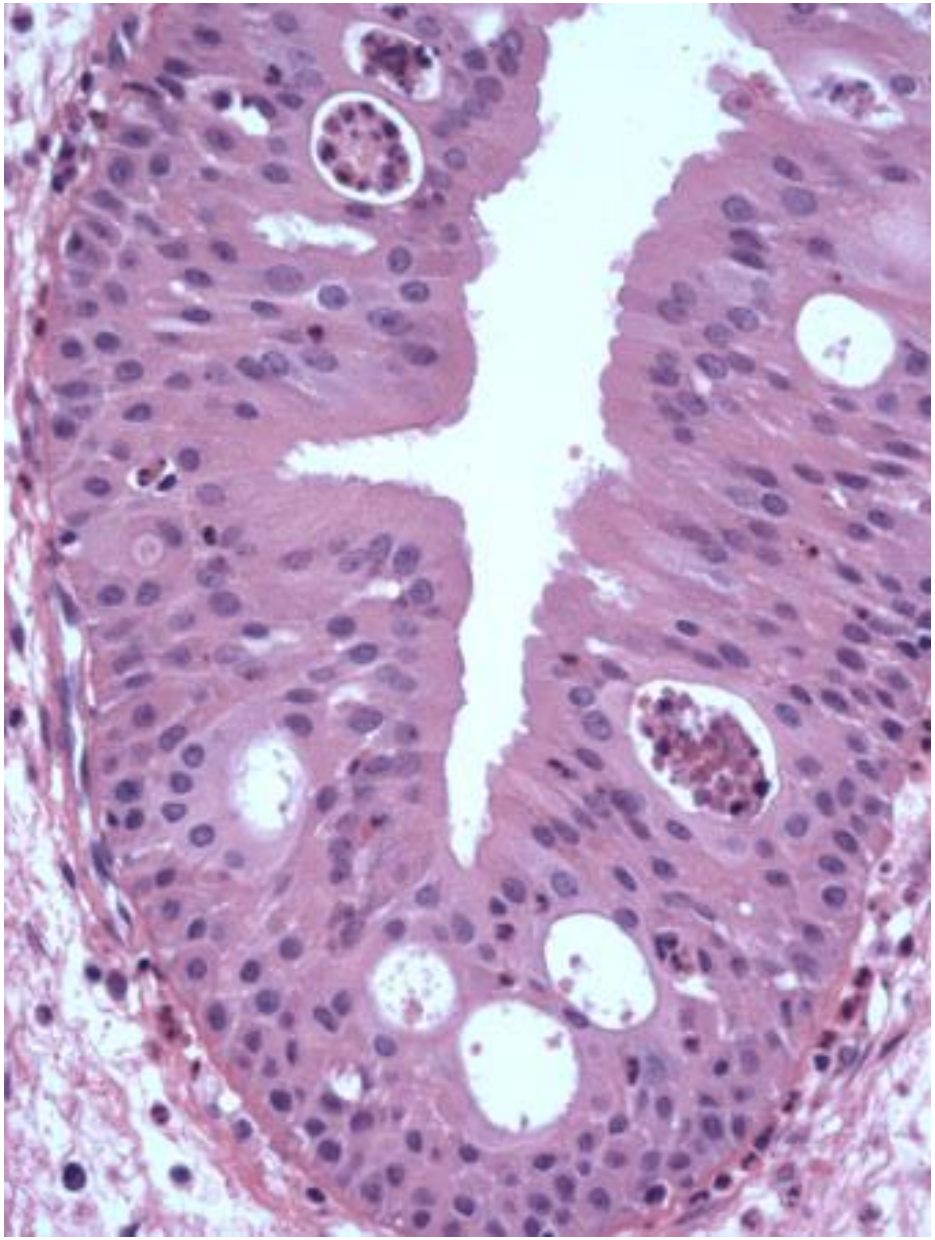
Oncocytic type

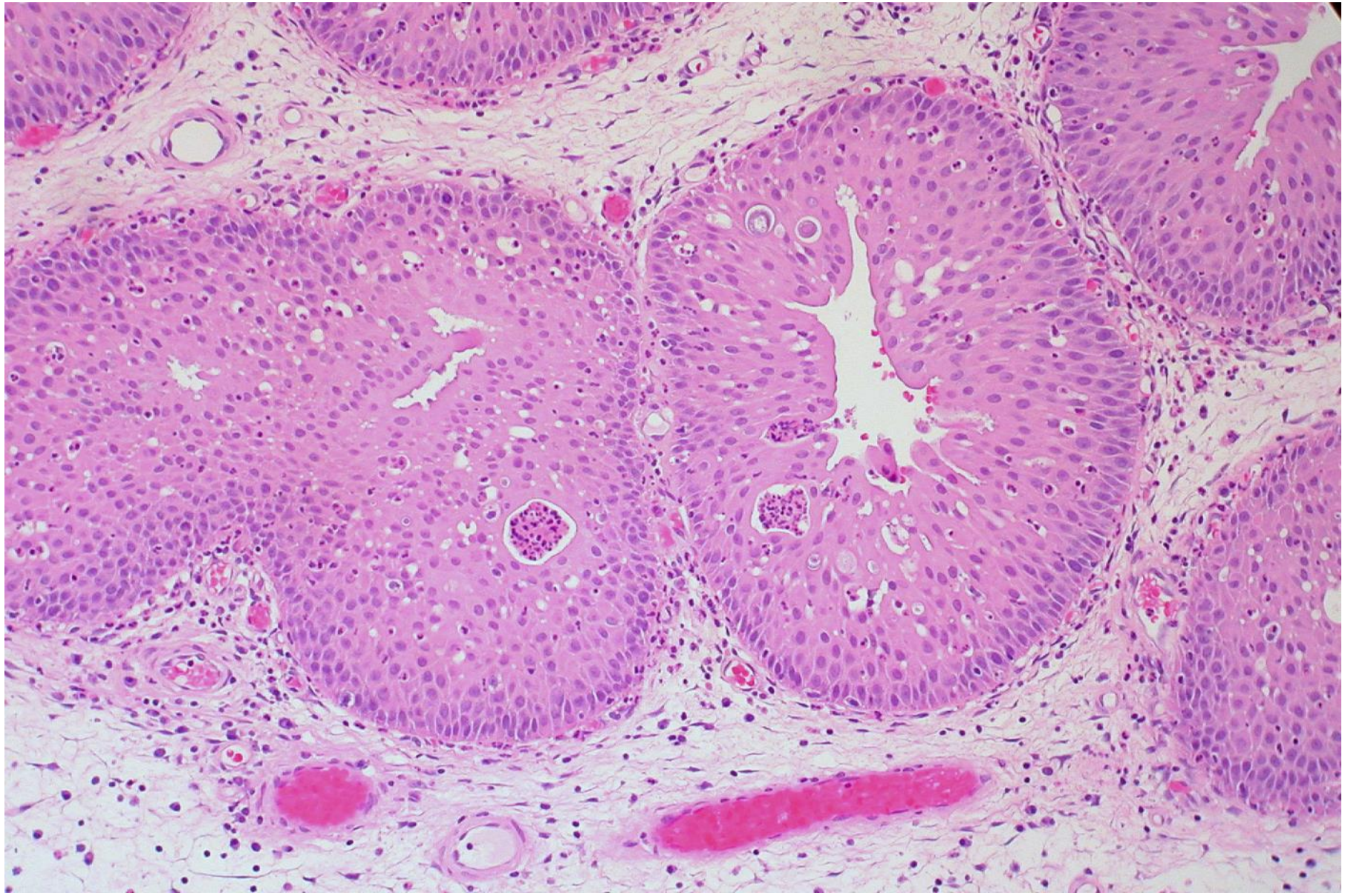
- Exophytic &/or endophytic growth usually lateral nasal cavity and sinuses
- Multilayered epithelium composed of columnar cells with abundant eosinophilic and granular cytoplasm
- Admixed mucocytes (goblet cells) and intraepithelial mucous cysts with neutrophil

Malignant transformation uncommon (bone invasion, disorganization, loss of transepithelial inflammatory infiltrate, increased mitoses (> 25/10 HPF), atypical mitoses, necrosis)

HPV association ~25%; controversial wrt etiology







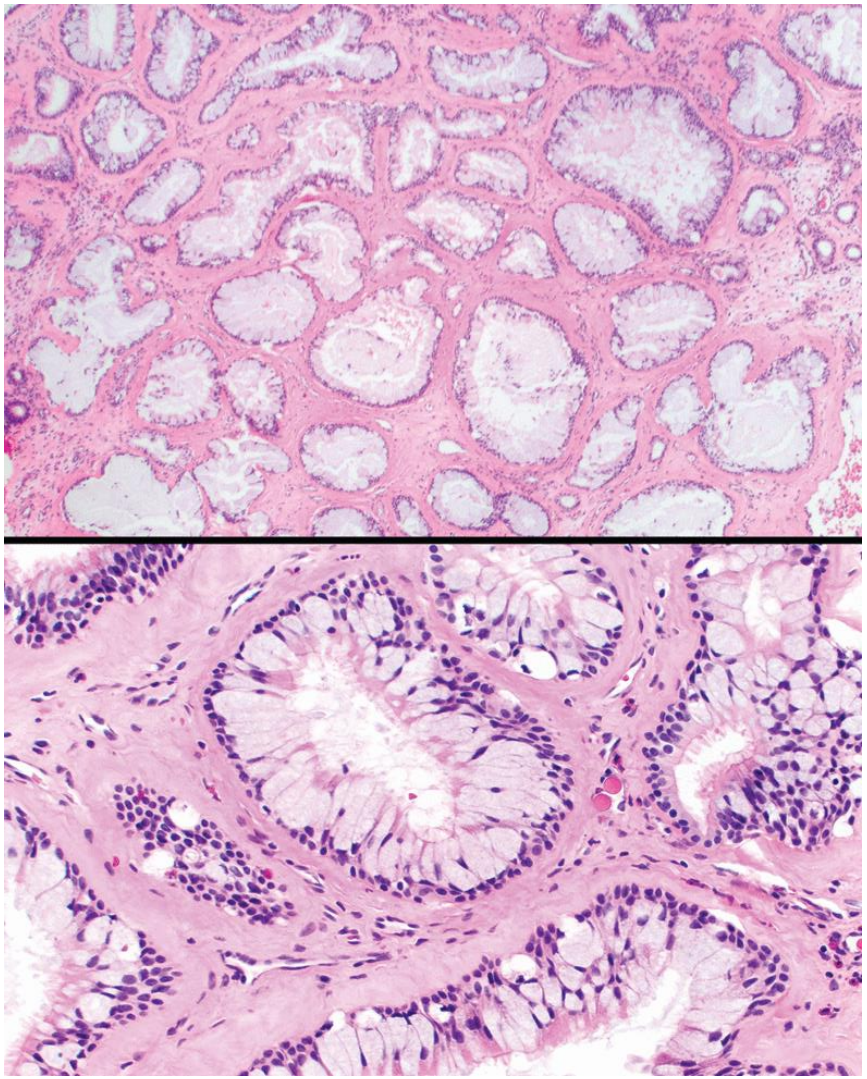
HAMARTOMAS

- Respiratory epithelial adenomatoid hamartoma (REAH)
- Chondroosseous and respiratory epithelial (CORE) hamartoma
- Seromucinous hamartoma (SH)
- Nasal chondromesenchymal hamartoma (NCH)

Hamartomas

- Most occur in nasal cavity, especially posterior septum
- Present with nasal obstruction or polypoid masses
- May be related to inflammatory polyps
- Except NCH, most present in adult life

REAH



- Glandular proliferation of widely spaced, small- to medium-sized glands separated by stromal tissue
- Connected to surface epithelial invaginations
- Lined by multilayered ciliated respiratory epithelium often with admixed mucin-secreting (goblet) cells
- Characteristic stromal hyalinization with envelopment of glands by thick, eosinophilic basement membrane
- May show ‘atrophic’ glands and stroma inflammation/osseous metaplasia

From: Lee JT et al. Am J Rhinol Allergy 2013; 27:322-8.

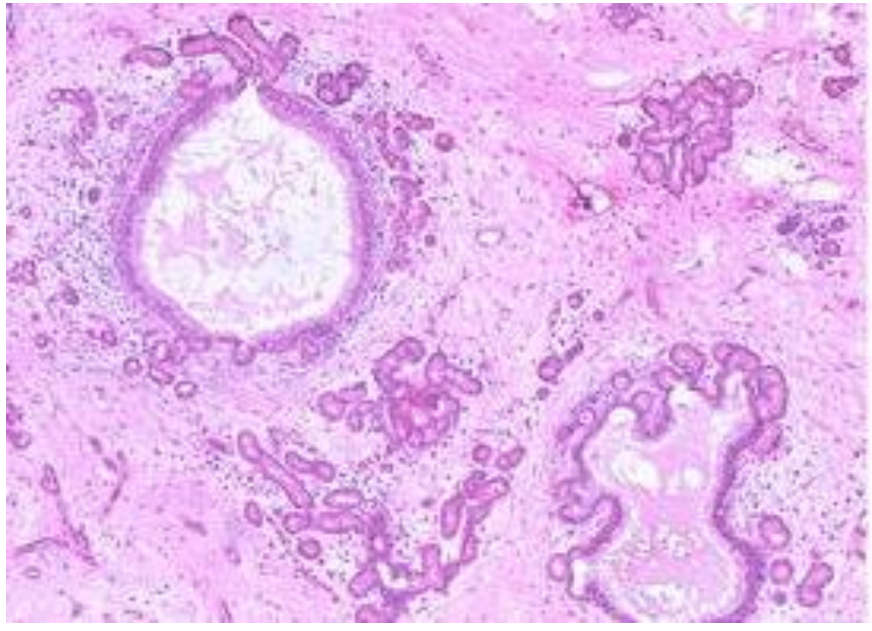
REAH

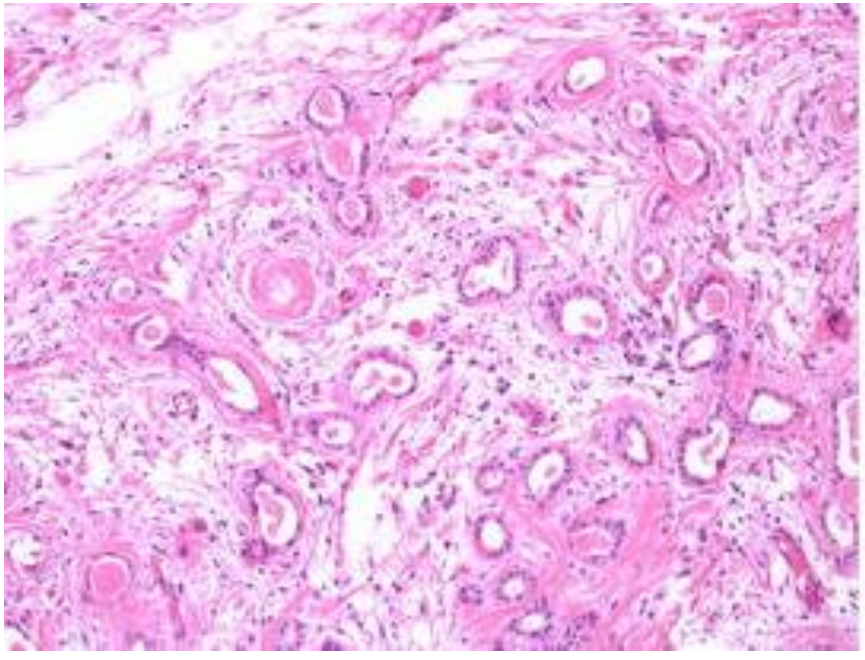
Feature	No.
Isolated	16
Bilateral	4
Unilateral	12
OC	9
Posterior nasal cavity/NP	7
Associated	35
Bilateral	15
Unilateral	20
SNP	20
CRS without polyps	12
Allergic fungal rhinosinusitis	3

CRS = chronic rhinosinusitis; OC = olfactory cleft; NP = nasopharynx; SNP = sinonasal polyposis.

From: Lee JT et al. Am J Rhinol Allergy 2013; 27:322-8.

SH





- Submucosal lobular proliferation of small glands, serous acini, and tubules
- Low cuboidal/flat serous-type epithelium; lack myoepithelial layer
- Lack significant mucinous cells
- No nuclear pleomorphism, increased mitoses, or necrosis
- No micropapillae, epithelial tufting or invasive growth
- Background mixed inflammation, edema, fibrosis
- Focal REAH morphology ±

ADENOCARCINOMAS

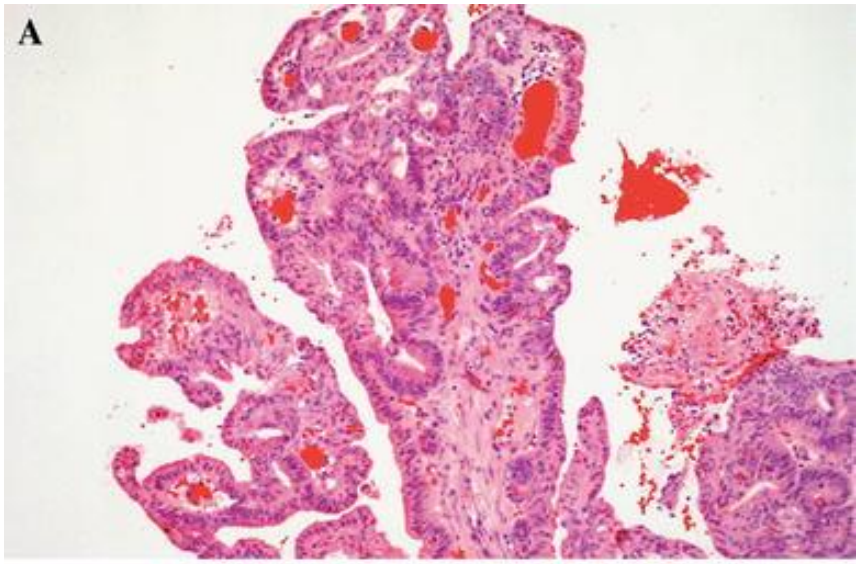
- Salivary-type
  - All salivary tumors (except Warthin and purely sebaceous types) occur in sinonasal region; pleomorphic adenoma is most frequent
  - Adenoid cystic carcinoma is the most common salivary-type carcinoma (second most common sinonasal malignancy, ~20%)
  - Mucoepidermoid carcinoma is next common (~5%)
- Intestinal type
- Non-intestinal type

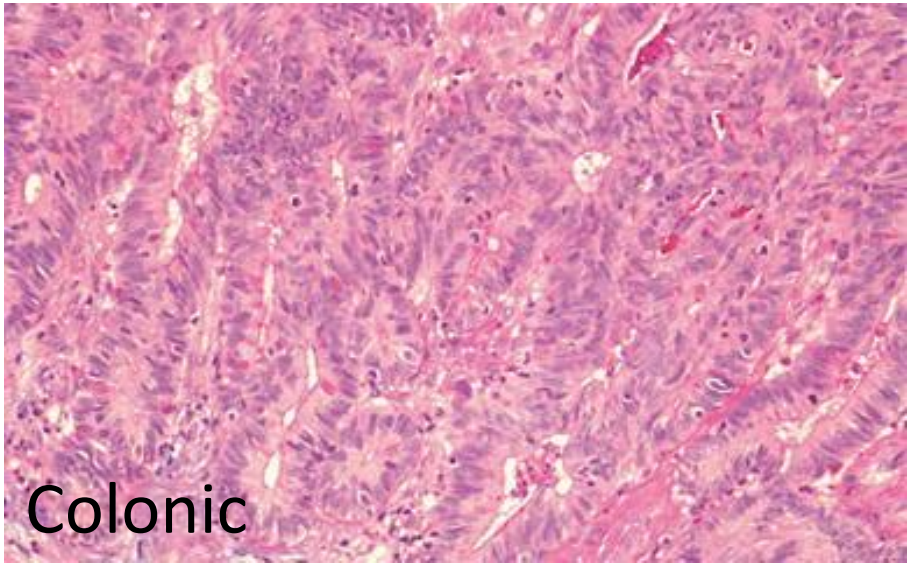
Intestinal-type AdCa

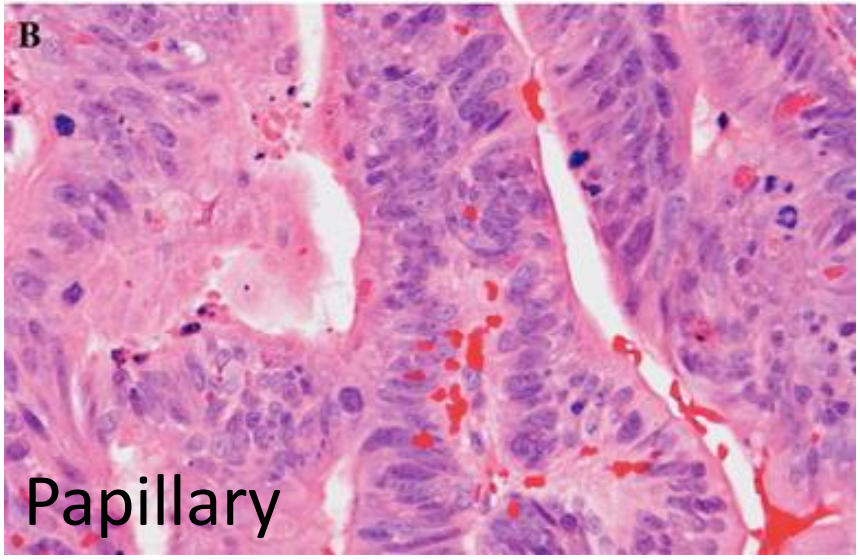
- ITAC is the 2nd most common sinonasal AdCa
- Resembles intestinal adenoma/carcinoma
- Typically in males
- ITACs associated with wood dust exposure occur mostly in ethmoid sinus; sporadic ITACs often arise in the maxillary antrum
- ITACs are aggressive malignancies

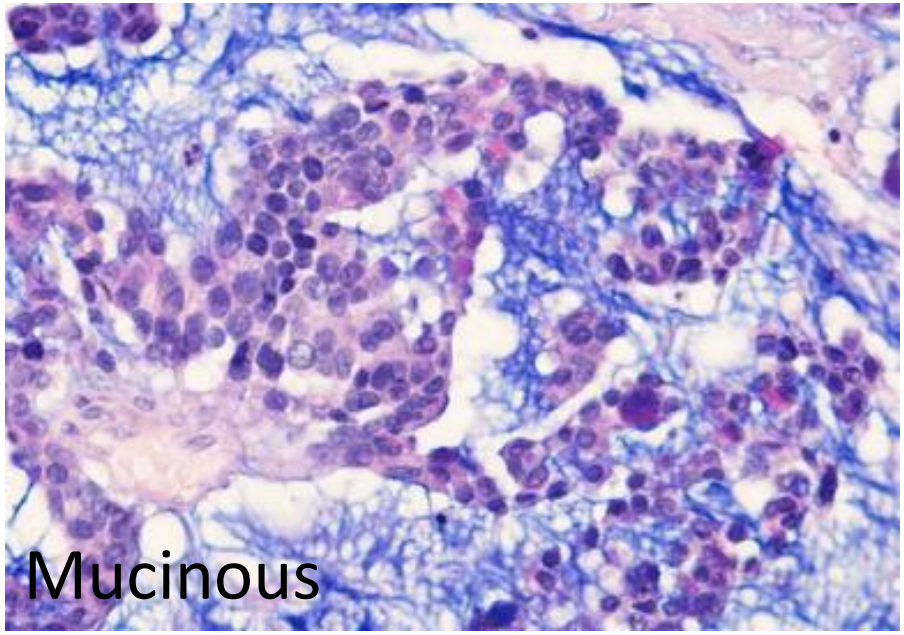
ITAC classification

- Barnes classification: papillary, colonic, solid, mucinous, and mixed types
- Kleinsasser and Schroeder classification: papillary-tubular cylindrical cell type (corresponding to papillary, colonic, and solid types), alveolar goblet cell type, signet-ring cell type (corresponding to mucinous type), and transitional cell type (corresponding to mixed type)
- Histologic subtypes have been found to correlate with clinical behavior









From: Leivo I. Head Neck Pathol. 2016 Mar;10(1):68-74

ITAC

- IHC:
  - Positive for CK20, CDX2, villin, and MUC2
  - Variable positivity for CK7
  - Focal chromogranin/synaptophysin in NE cells
- Unlike CRC, activating mutations of K-RAS and BRAF in the signal route of EGFR are rare (may respond to anti-EGFR therapies)
- Preserved expression of MMR proteins, β-catenin and E-cadherin; , overexpression of MET protein; Annexin A1 and A2 down-regulated
- In woodworkers, a subset of ITACs expressed high levels of EGFR protein and high prevalence of *TP53* mutations is reported

Nonintestinal type adenocarcinoma

- Look like neither ITAC nor salivary-type cancer

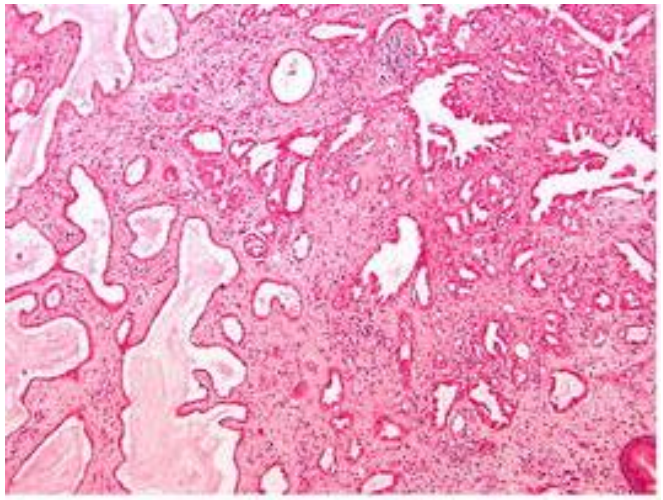
High-grade nonintestinal-type adenocarcinomas

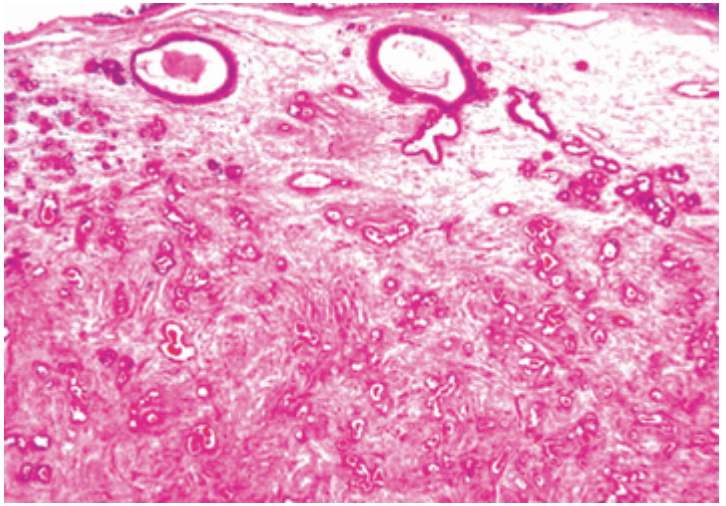
- Rare – typically in males
- Diverse histology (blastomatous, apocrine, oncocytic, mucinous, poorly differentiated/undifferentiated)
- Pleomorphic and anaplastic appearing
- Lack CDX-2 and CK20 staining
- Their heterogeneity makes it difficult to differentiate from other malignanies (especially salivary adenocarcinoma, NOS)

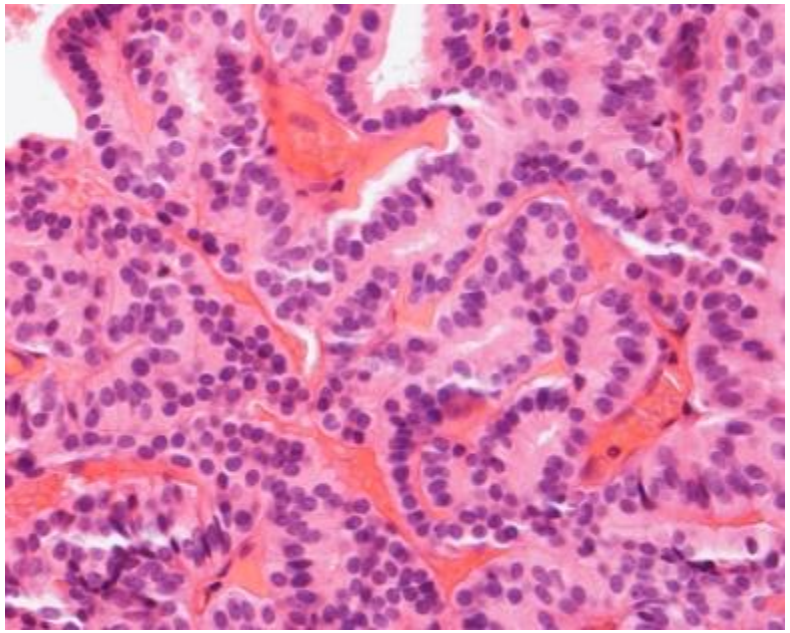
Low-grade non-ITAC

- ~15 % of sinonasal AdCa; no known environmental association
- Ethmoid sinus, nasal cavity, and maxillary sinus
- Many synonyms - terminal tubulus AdCa, sinonasal tubulopapillary low-grade AdCa, sinonasal low-grade AdCa, and sinonasal seromucinous AdCa
- Varied architecture - exophytic papillae, tubular, trabecular, cribriform, clear cell and mucinous patterns
- Papillae and glands lined by a single layer of uniform columnar or cuboidal cells with bland low-grade cytology
- Complexity of growth pattern and local invasive growth are clues to diagnosis
- Constantly positive for CK7, but negative for CK20 and CDX-2
- May also be positive for markers of seromucinous differentiation - DOG1, SOX10, and S-100

Low grade non-ITAC





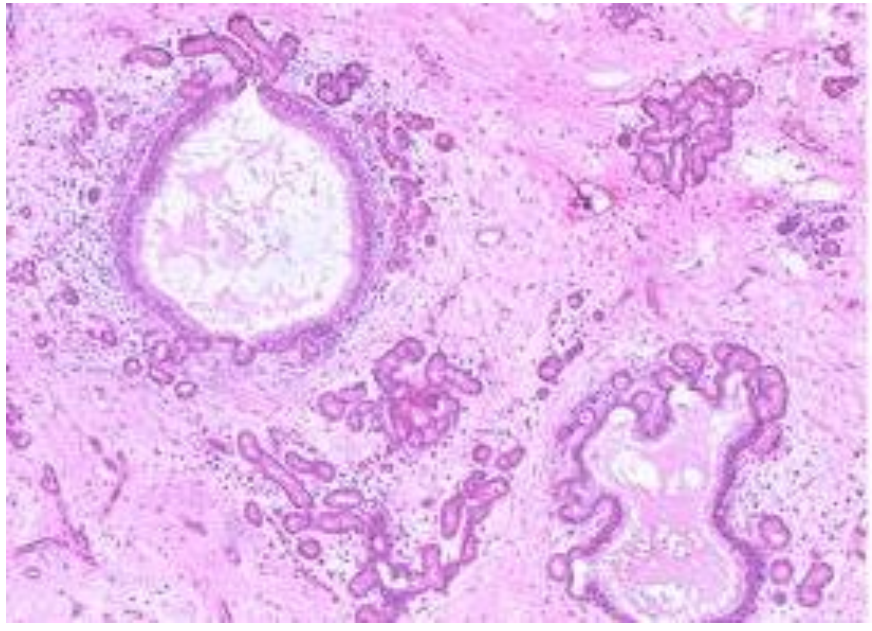


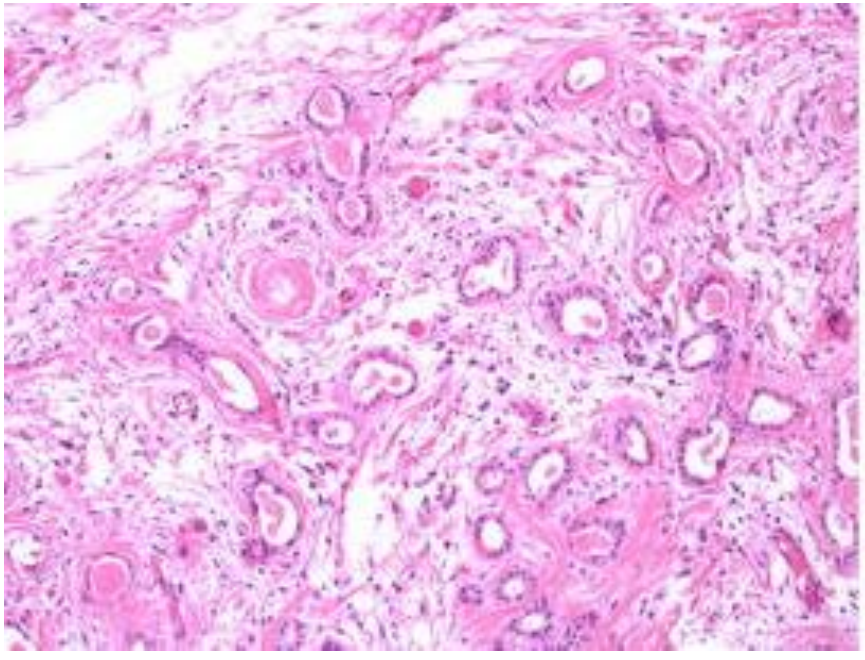
Haphazard growth

Tubulopapillary and complex architecture

Low grade cytology

SH





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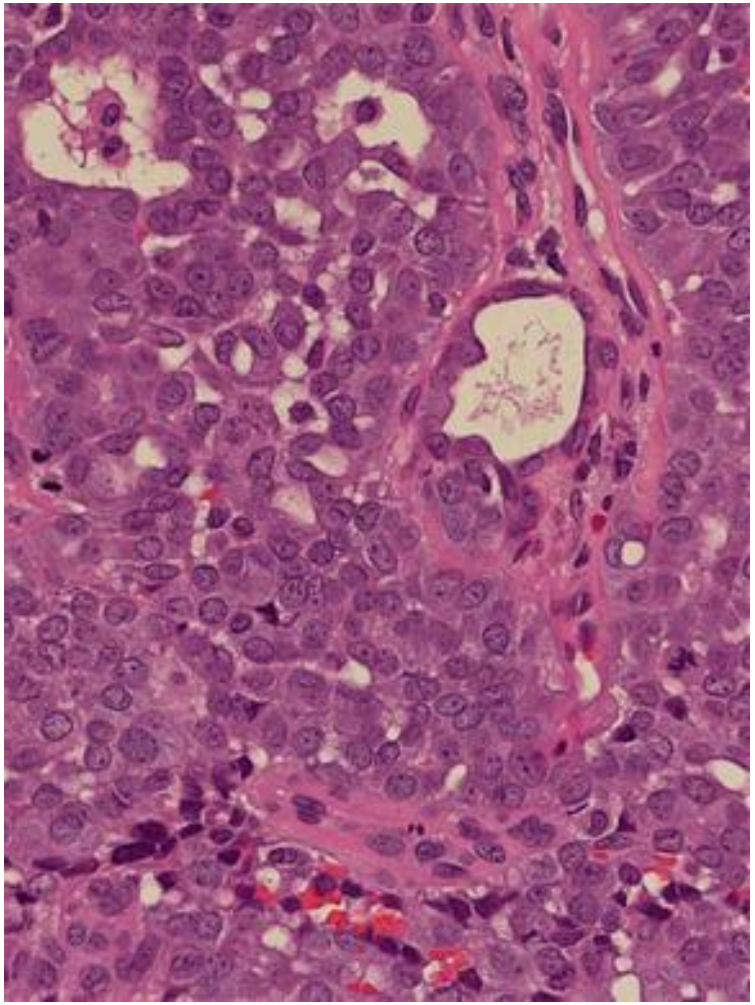
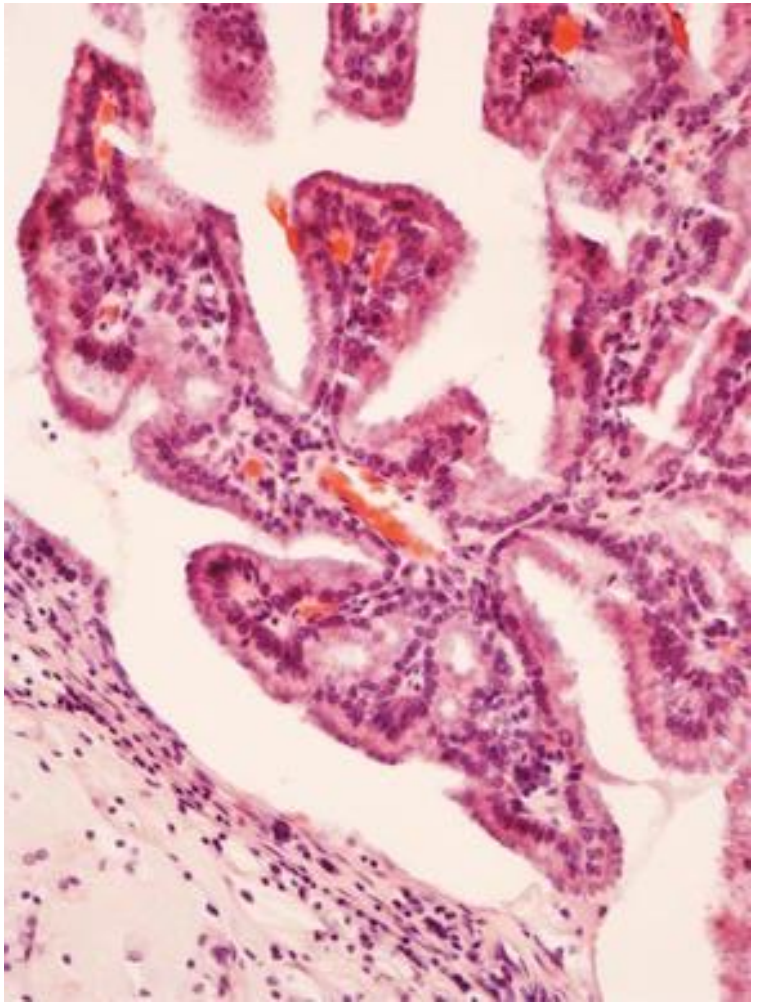
Nonintestinal type AdCa





From: Leivo I. Head Neck Pathol. 2016 Mar;10(1):68-74

Thyroid-like, low-grade nasopharyngeal papillary adenocarcinoma

- Rare surface epithelial tumor of nasopharynx (esp posterior and lateral nasopharyngeal walls and roof)
- Unencapsulated, infiltrative tumor with complex papillae and glands
- PTC-like (but no pseudoinclusions)
- Keratin, TTF-1 +; Thyroglobulin neg; <5% Ki67

Small round blue cell tumors

- *Epithelial differentiation*
  - SqCC (nonkeratinizing, basaloid, NPC)
  - Solid adenoid cystic carcinoma
  - Small cell carcinoma
  - Sinonasal undifferentiated carcinoma (SNUC)
  - NUT midline carcinoma
- *Neuroectodermal differentiation* : olfactory neuroblastoma (ONB); Ewing sarcoma family; mucosal melanoma
- *Soft tissue differentiation* : RMS and Synovial Sa
- *Hematopoietic differentiation* : NK/TCL; DLBCL; myeloid sarcoma
- *Secondary malignancies* : usually by extension and occasionally by metastasis

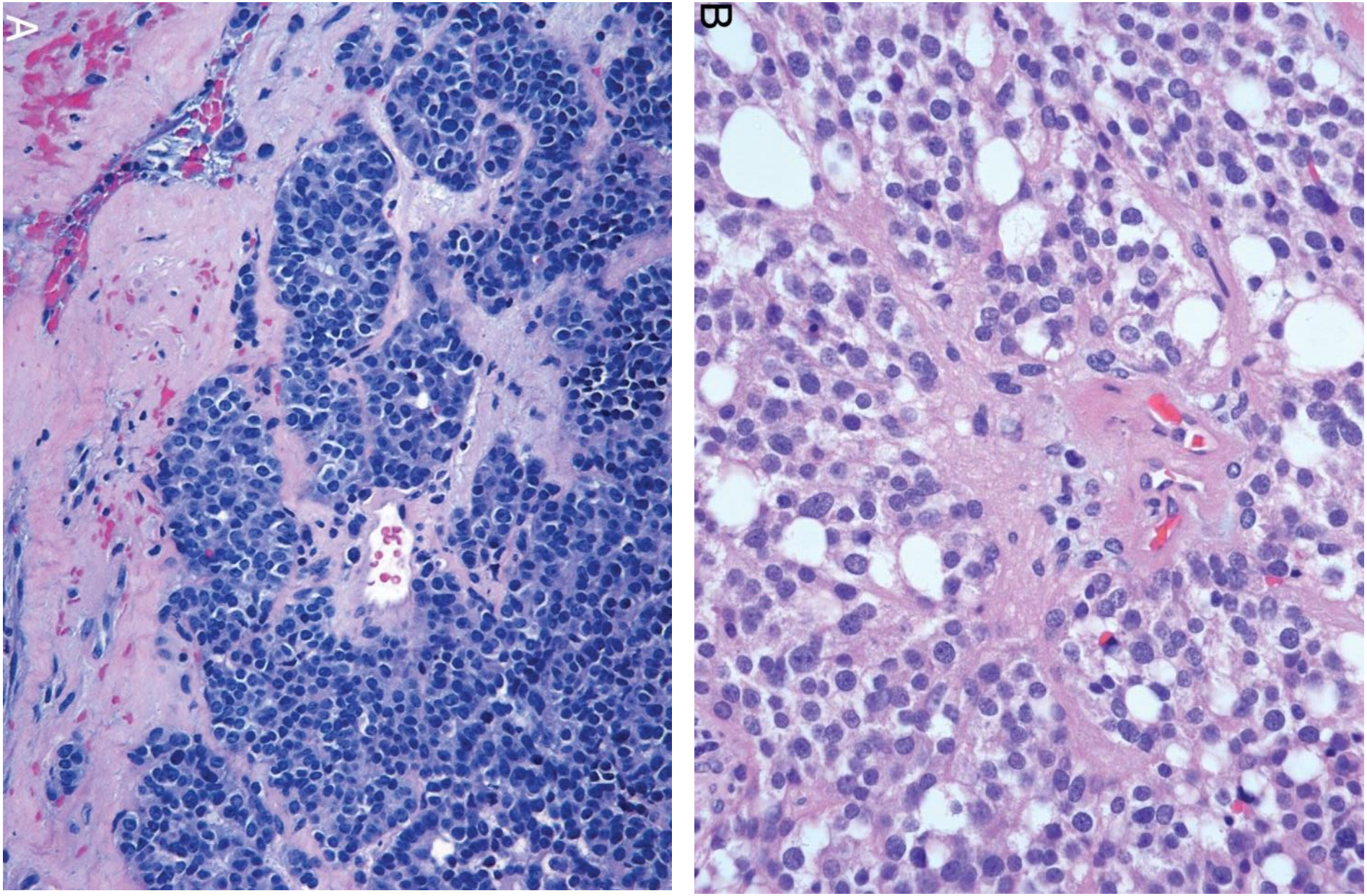
ONB

- Rare (<5%) malignant tumor of neuroectodermal origin; arises from olfactory epithelium lining the superior-third of nasal septum, cribriform plate, and superior turbinates
- Either gender; Bimodal age (ages 11–20 and 51–60 years)
- Imaging: Dumbbell shaped mass across cribriform plate; peripheral cysts at intracranial margin

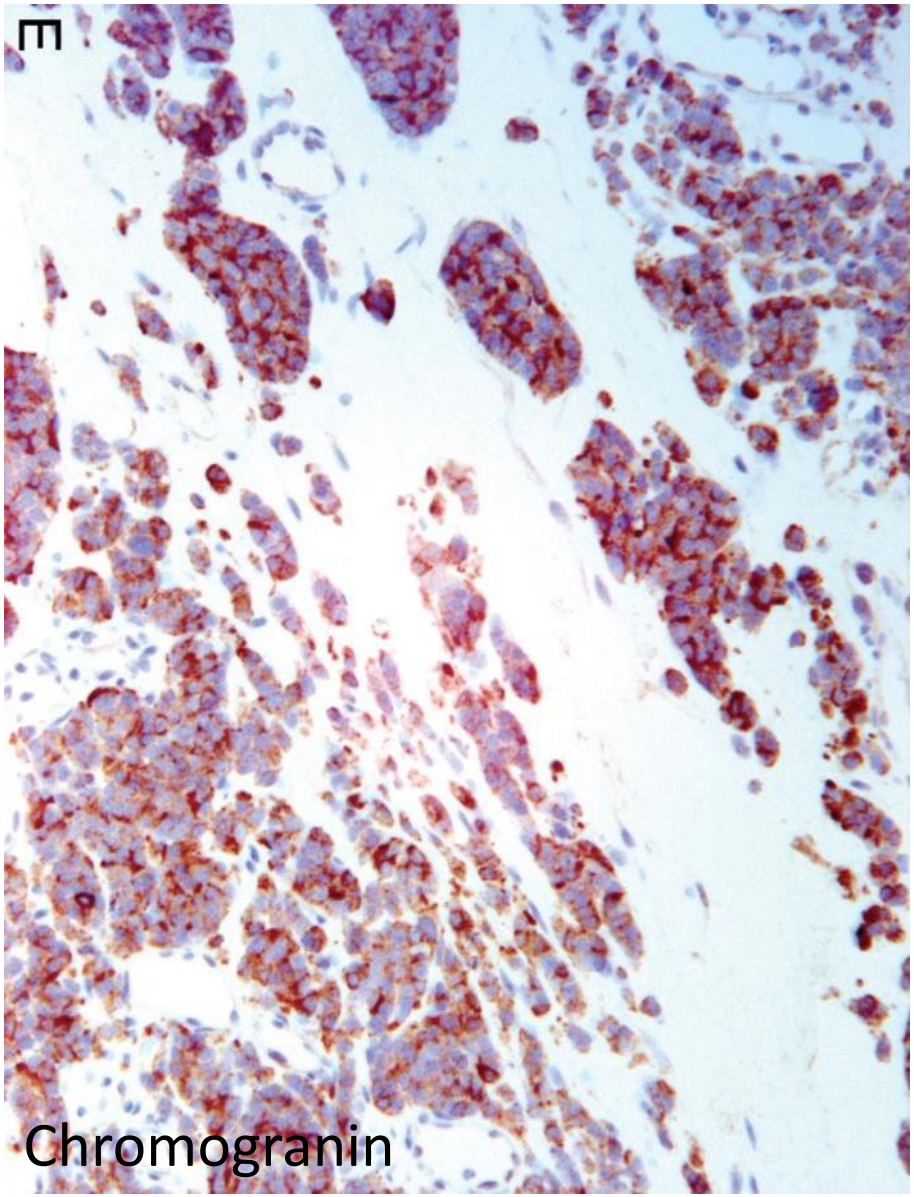
ONB -histology

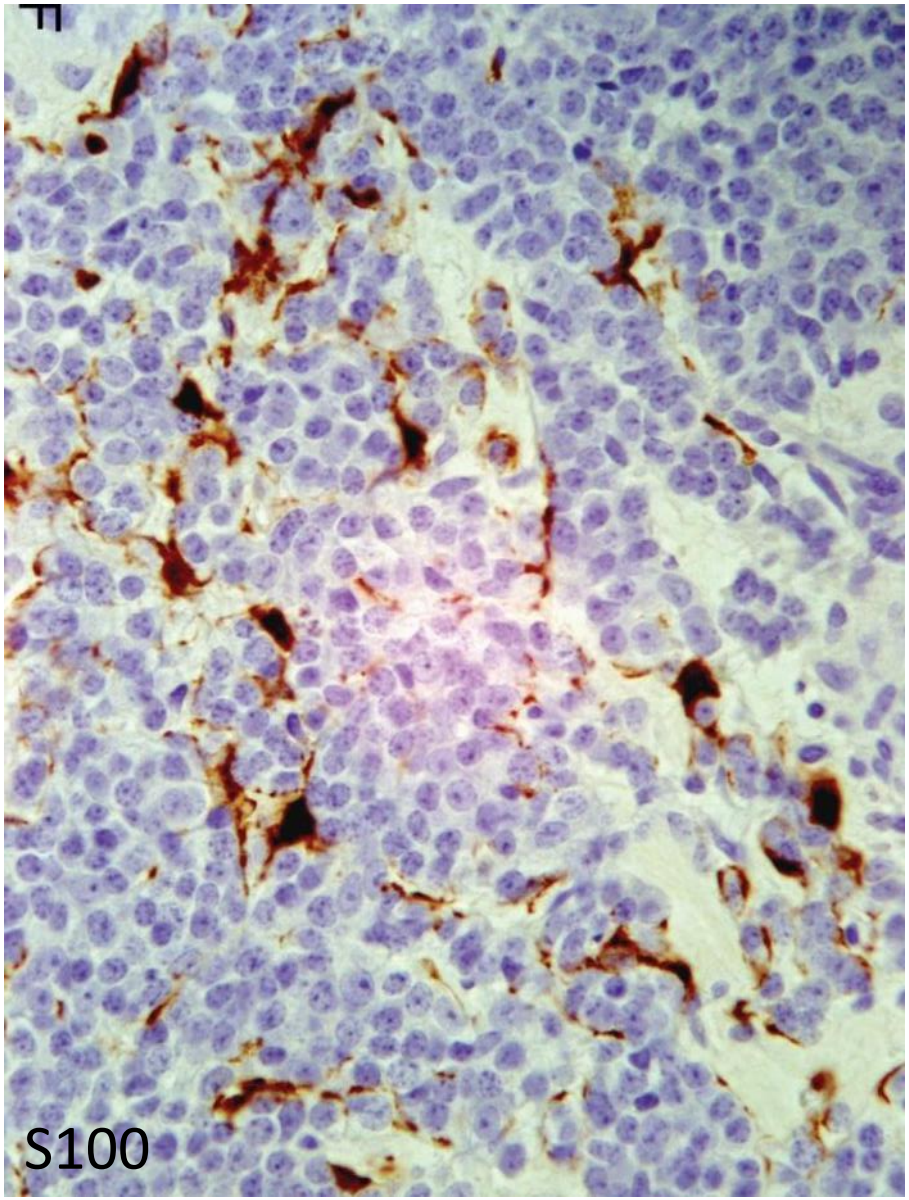
- Lobular architecture
- Well-differentiated ONBs are composed of nests of small cells with uniform, round to oval nuclei and speckled chromatin pattern admixed with a neurofibrillary matrix; HW rosettes
- Poorly differentiated ONBs are characterized by cells with hyperchromatic, atypical nuclei with coarse chromatin, scant cytoplasm, and minimal fibrillary matrix; FW rosettes
- Hyams grading system includes grades I to IV
  - Grades I and II have lobular architecture and prominent to appreciable fibrillary matrix
  - Grade III has no lobular pattern, but has FW rosettes
  - Grade IV is undifferentiated

ONB



Montone KT. Arch Pathol Lab Med. 2015 Dec;139(12):1498-507.





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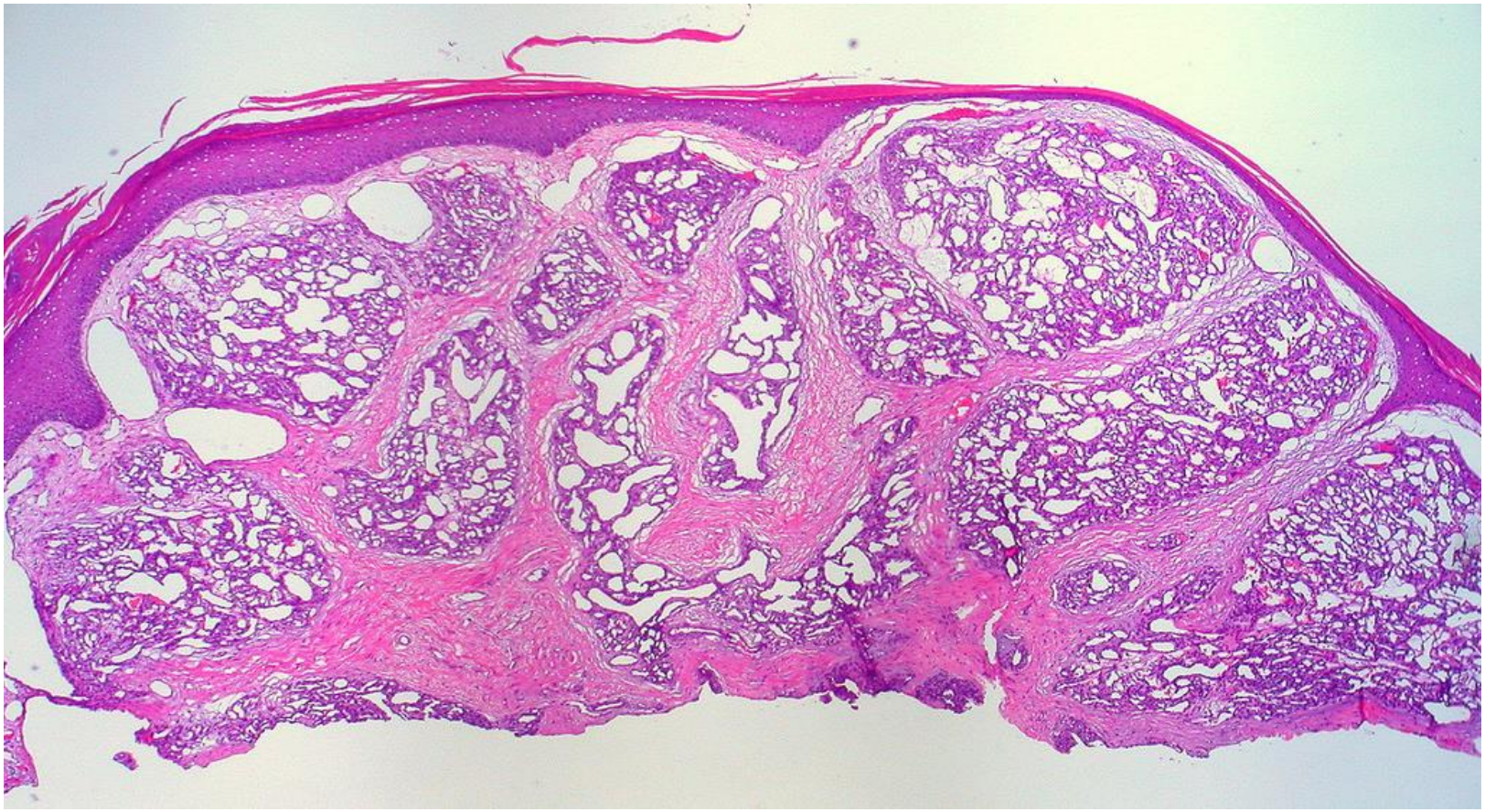
ONB

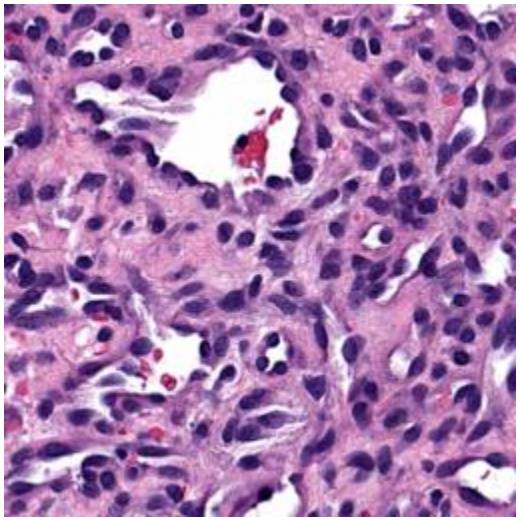
- IHC
  - NSE, chromogranin, synaptophysin, CD56 +
  - S100, GFAP highlight sustentacular cells
  - Almost always cytokeratin negative (rare CAM+)
  - Strongly calretinin positive and p63 negative
- *hASH1* RT-PCR may be specific

- Prognostic factors include Hyams grade, Kadish stage, neck node & distal metastasis
- 75% 5-yr survival; Metastasis 25-30%

Soft Tissue Tumors

- Lobular capillary hemangioma
- Nasopharyngeal angiofibroma
- Schwannoma
- Sinonasal glomangio/hemangiopericytoma
- Biphenotypic sinonasal sarcoma
- MPNST
- RMS
- Phosphaturic mesenchymal tumor

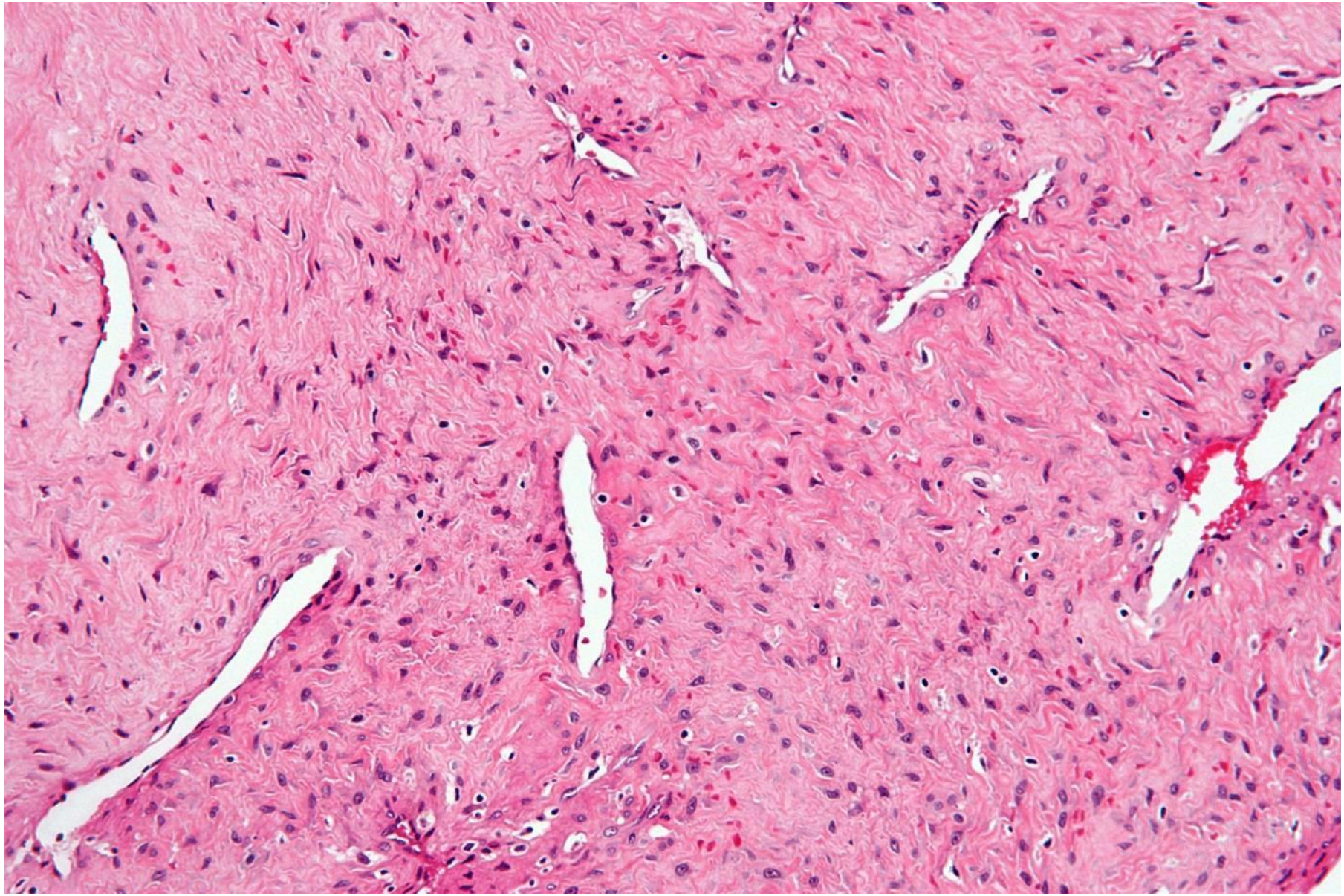




Nasopharyngeal angiofibroma

- Rare (<1% head-neck) tumor; locally aggressive; ~25% recur
- Hormonally driven (adolescent males and expression of AR)
- Imaging suggests vascular lesion and presumptive diagnosis. Biopsy is often avoided

- Grossly tan-white sessile or lobulated masses
- Unencapsulated with a variably sized, irregularly shaped vessels set in a hyalinized and collagenous stroma
- Vessels are thin-walled, and the walls show a variable smooth muscle component that is occasionally absent or discontinuous
- Moderately cellular stroma, with haphazardly arranged bland spindle and stellate cells
- Occasionally multinucleated stromal cells, mild reactive atypia, stromal predominance, and myxoid stromal change
- Extensive stromal fibrosis in long-standing tumors



NPA (contd)

- Diagnosis based on morphology; IHC nonspecific
- Vascular markers positive; SMA highlights variable muscle component
- AR positive in both the endothelial and stromal cells
- Stroma positive for SMA, with perivascular accentuation
- β-Catenin overexpression in stromal cells and *CTNNB1* mutations have been reported
- Differential diagnosis of nasopharyngeal angiofibroma includes LCH and sinonasal hemangiopericytoma
  - LCH with prominently hyalinized stroma is circumscribed and lacks stromal cell component. Also LCH vessels are small and compressed in lobules
  - Sinonasal HPC shows a fascicular growth pattern of spindle and epithelioid cells encircling thin-walled vessels and diffuse SMA positivity

Sinonasal Glomangiopericytoma (HPC)

- Rare (<0.5%), mostly in ages 50-70; no gender bias
- Unilateral mass - nasal cavity or sinuses (ethmoid)
- Indolent behavior, >90% 5-year survival; ~ 30% recur locally
- Shows perivascular myoid differentiation
- Red-tan polypoid masses
- Submucosal, well-circumscribed but unencapsulated, often with a “Grenz” zone between tumor and intact epithelium
- Spindled and epithelioid tumor cells are arranged in short fascicles; occasionally storiform, whorled, palisaded, or solid growth, that often encircle thin-walled HPC-like vessels
- Perivascular hyalinization is typical
- Uniform bland cytology
- Background inflammation (mast cells and eosinophils)
- Necrosis absent; but degenerative features (fibrosis or myxoid change) may be seen

GPC (contd)

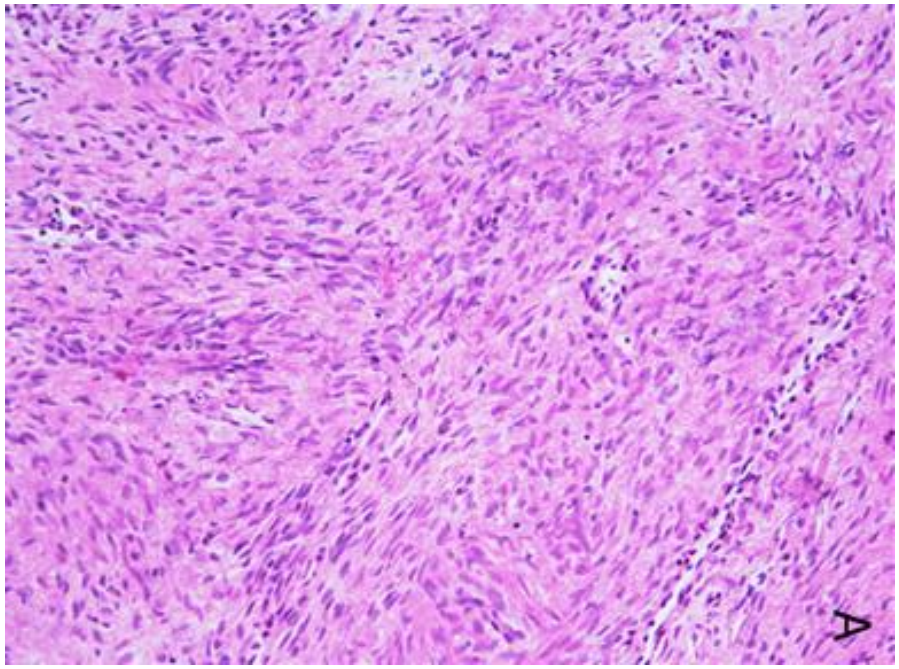
- Actins + (SMA, HHF-35); vascular IHC neg
- Desmin and keratin negative
- Nuclear β-catenin positive; *CTNNB1* gene mutations are consistent
- D/D - SFT, synovial sarcoma, MPNST, and meningioma
- Sinonasal HPC rarely shows overt cytologic atypia and can be distinguished from most high-grade sarcomas
  - SFT is rare in the sinonasal tract; CD34 and STAT6 positive
  - Synovial sarcoma – keratin, TLE1 +, SMA neg, SS18 FISH+
  - Meningioma – consistent perivascular whorled growth, nuclear pseudoinclusions, psammoma bodies, and positivity for EMA and Claudin-1

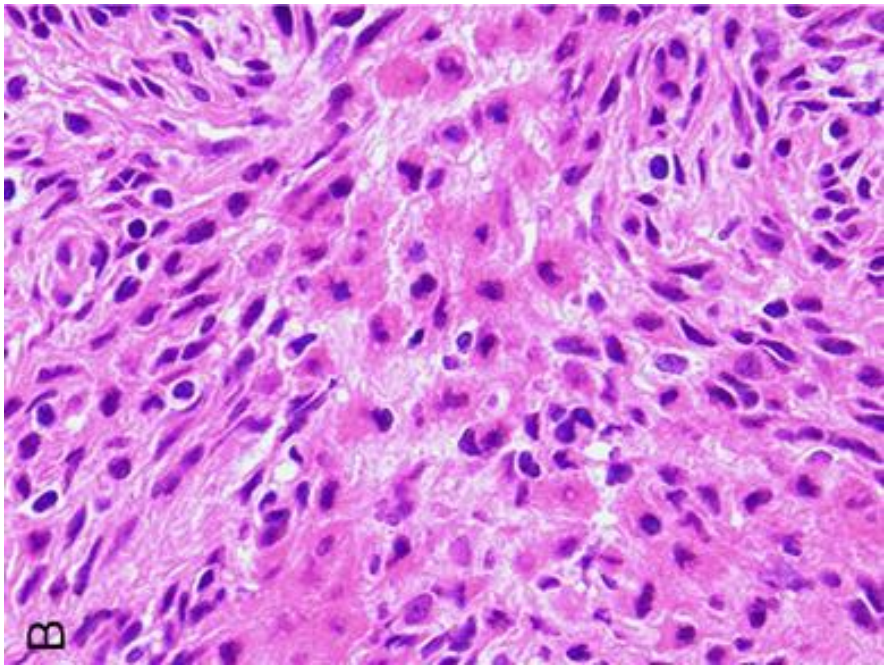
Biphenotypic Sinonasal Sarcoma

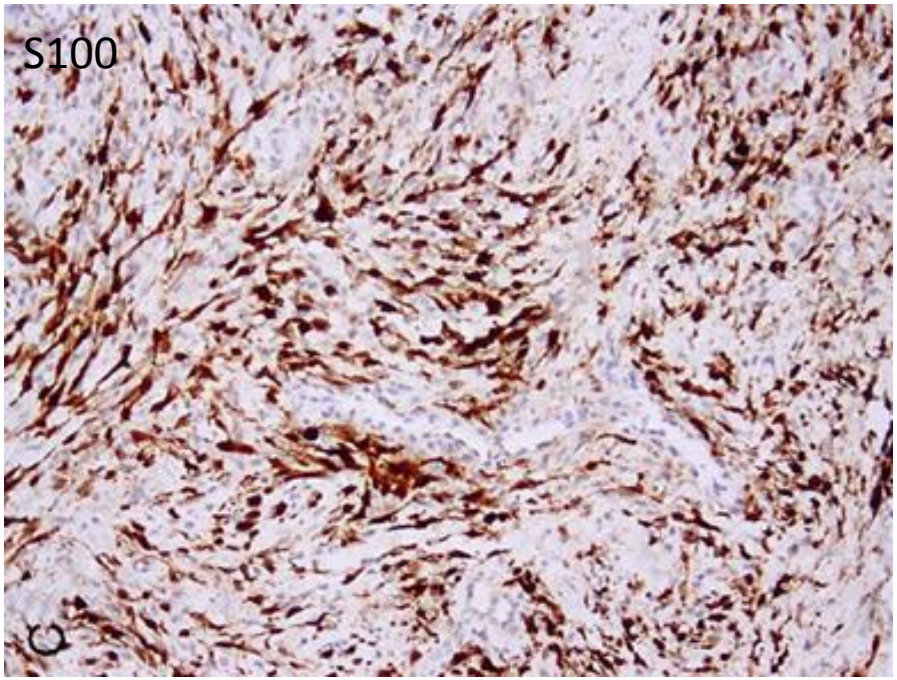
- “Low-grade sinonasal sarcoma with neural and myogenic features”
- Mostly adult females; mostly in nasal cavity and ethmoid sinus
- 40% recur; no metastasis reported
- Polypoid masses with infiltrative growth, including into orbit, cribriform plate, or cranial vault
- Low grade spindle cells in fascicles (“herringbone”)
- HPC-like vessels are interspersed within fascicles
- Delicate stromal collagen pattern frequent
- Foci of rhabdomyoblastic differentiation may be seen
- Mitotic activity low and necrosis is rare
- ~70% show simultaneous proliferation of the overlying respiratory epithelium, with invagination and intermingling with the spindle tumor cells (REAH-like)

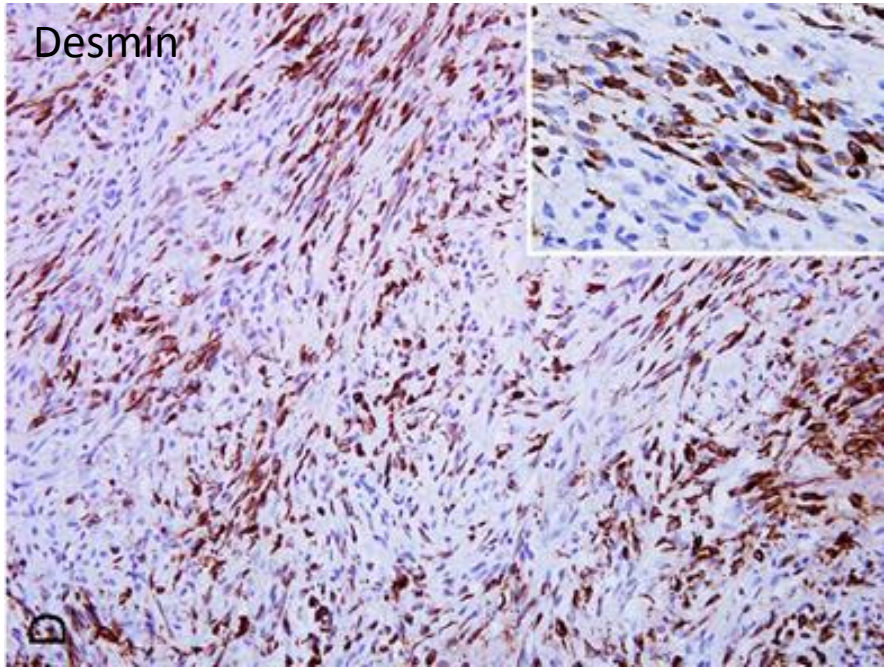
BSS

- Positive for both S-100 and myogenic markers.
- Consistent +: S100, actin, calponin, *β*-catenin, F-XIIIa
- S-100 ranges from diffuse to more focal
- Occasionally +: desmin, myogenin, CKs, EMA
- Consistently SOX10 negative
- *PAX3–MAML3* fusion, t(2; 4)(q35; q31.1), has been identified as a recurrent aberration in biphenotypic sinonasal sarcoma





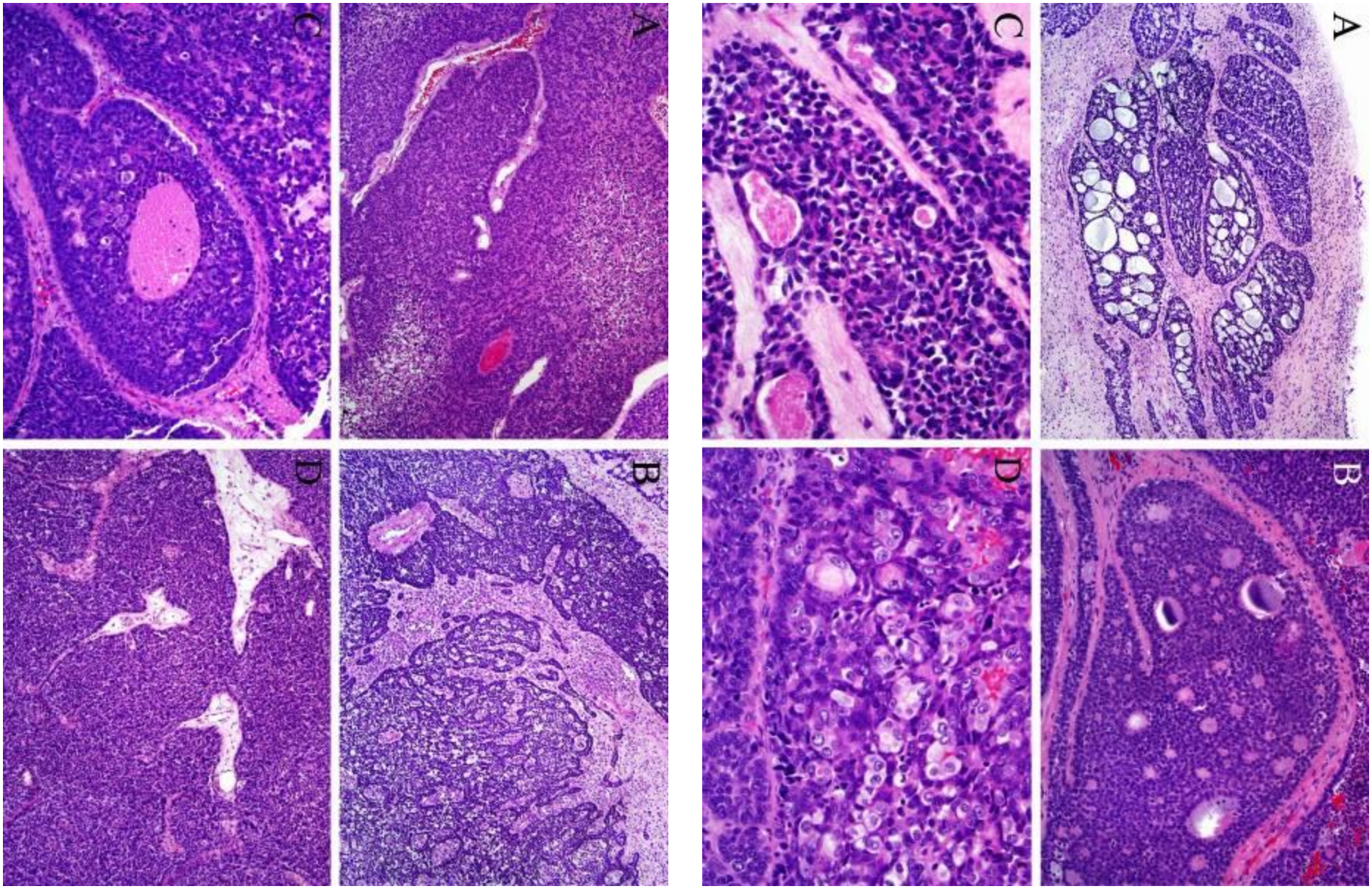




Huang, S-C et al. Am J Surg Pathol. 40(1):51-59

HPV-related Ca with ACC-like features (Multiphenotypic HPV-related Sinonasal Carcinoma)

- Sinuses involved (mostly ethmoid)
- Morphologically resembles adenoid cystic carcinoma
  - Lobular/nested proliferation of basaloid cells
  - Peripheral palisading, cribriforming, focal ductal-like profiles
- Overlying dysplastic squamous mucosa
- AE1/AE3 strong in ductal cells, and relatively weaker in the abluminal basaloid cells
- Basaloid cells strongly positive for myoepithelial markers (S100, calponin, p63, actin)
- C-kit staining positive, usually in ductal cells
- p16 diffuse, and HPV-ISH positive
- *MYB* rearrangement negative



Lobular growth pattern of basaloid cells with focal ductal profiles and cribriforming

From- Bishop JA. Am J Surg Pathol. 2013 Jun; 37(6): 836–844.

INI1-deficient sinonasal carcinoma

- Malignant destructive epithelioid neoplasm
- Basaloid morphology without squamous or glandular differentiation
- No in-situ component/dysplasia.
- NOT very pleomorphic nuclei (unlike SNUC)
- Prominent nucleolus
- Focal rhabdoid and plasmacytoid cells
- INI1-deficient by IHC
- NUT1 negative (unlike NMC)
- May show p40, p63, p16, synaptophysin staining

Adamantinoma-like Ewing family tumor

- Nests of basaloid tumor cells with peripheral palisading; prominent tumoral fibrosis; squamous differentiation; may show surface epithelial involvement (“in-situ”) – thus resembles squamous carcinoma
- But monotonous appearance should prompt CD99 IHC which is diffusely positive
- May also be diffuse + for CK, p40, p63 and focal S100, synaptophysin positive
- EWS-FISH required for diagnosis

Summary

- Epithelial Tumors
  - Schneiderian Papillomas
  - Hamartomas
  - Adenocarcinomas
- Round blue cell tumors
- Soft tissue tumors
- Recently described entities