Navigating the Border: Skull Base and Head and Neck Pathology for the Practicing Neuropathologist

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Disclosures

- I have no relevant financial relationships to disclose

Learning Objectives

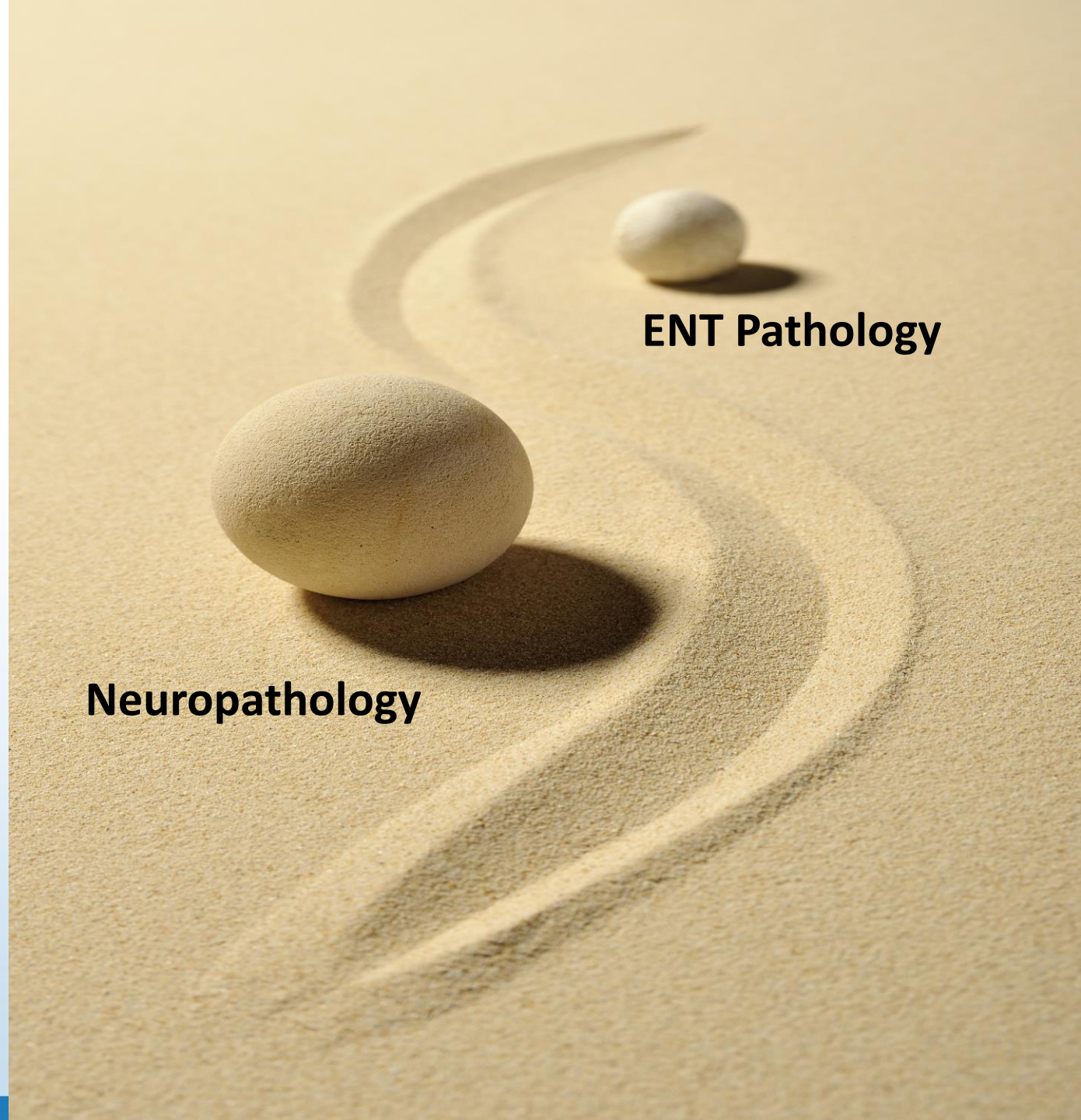
- Recall basic anatomy, histology, and developmental abnormalities of the skull base
- Examine tumors of the sella and contrast them with histologically similar tumors of the head and neck
- Formulate a histologic and immunohistochemical approach to epithelioid and spindle cell neoplasms of the skull base
- Examine molecular alterations in carcinomas and sarcomas affecting the skull base

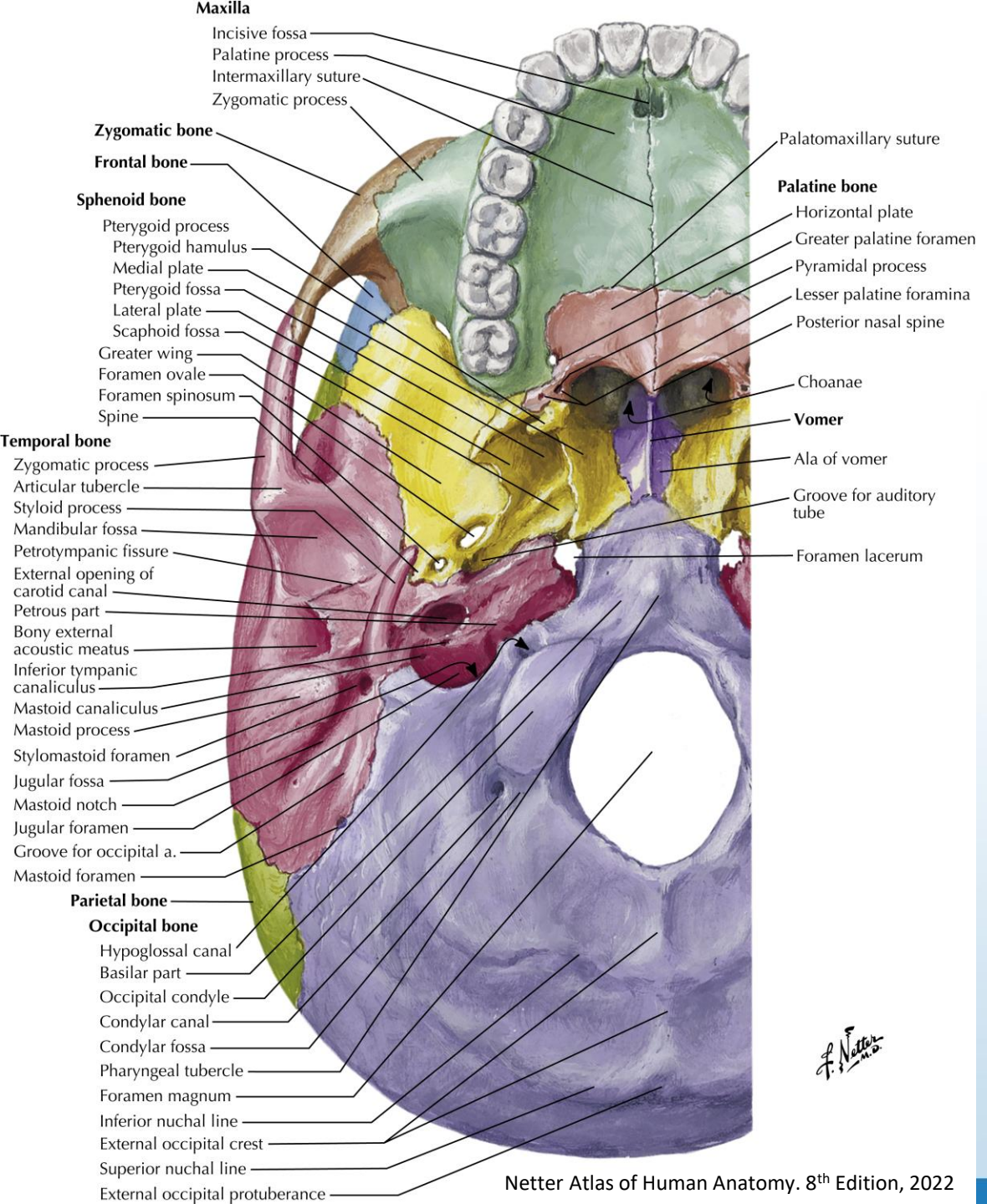
Outline

- Skull base overview
- Developmental abnormalities
- Inflammatory lesions of the skull base
- Epithelial and epithelioid neoplasms of the skull base
- Mesenchymal neoplasms of the skull base

Skull Base

- Complex anatomical region
- Rare neoplasms with overlapping features
- Staging and treatment implications
- Optimal patient care facilitated by knowledge of neuropathology and ENT pathology





Netter Atlas of Human Anatomy. 8th Edition, 2022

Skull Base Anatomy Overview

- Divided into anterior, middle, and posterior cranial fossas
- Many foramina allowing passage of nerves and vessels
- Embryologically complex, derived from mesoderm and ectoderm, including development and migration of neural crest cells
- Pituitary gland and related structures

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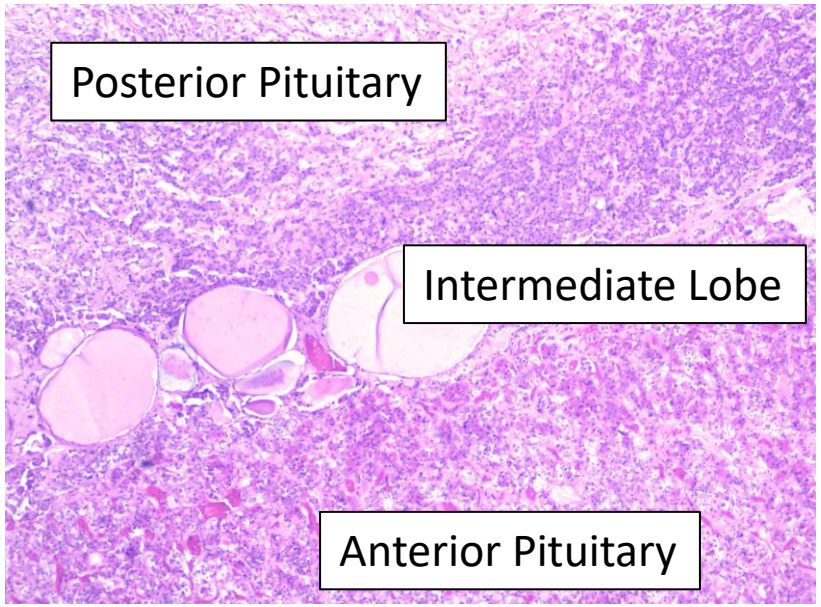
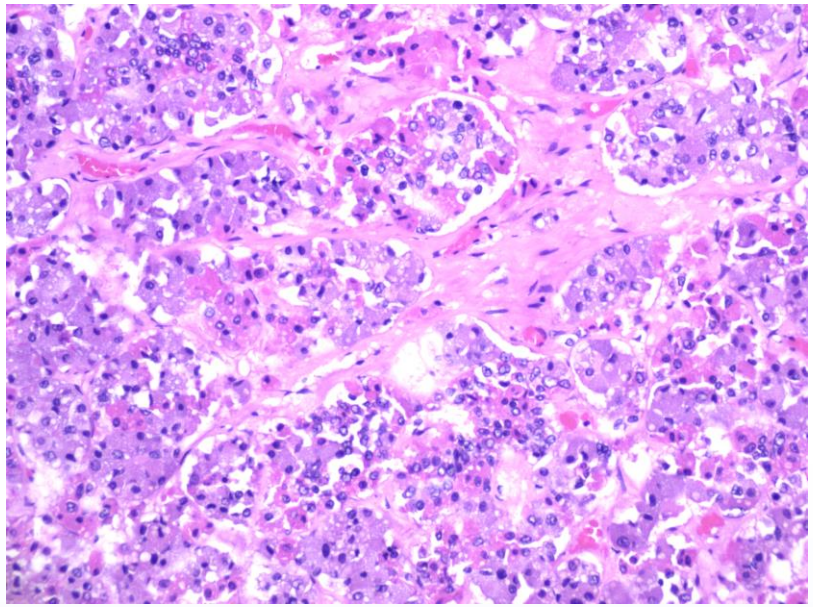
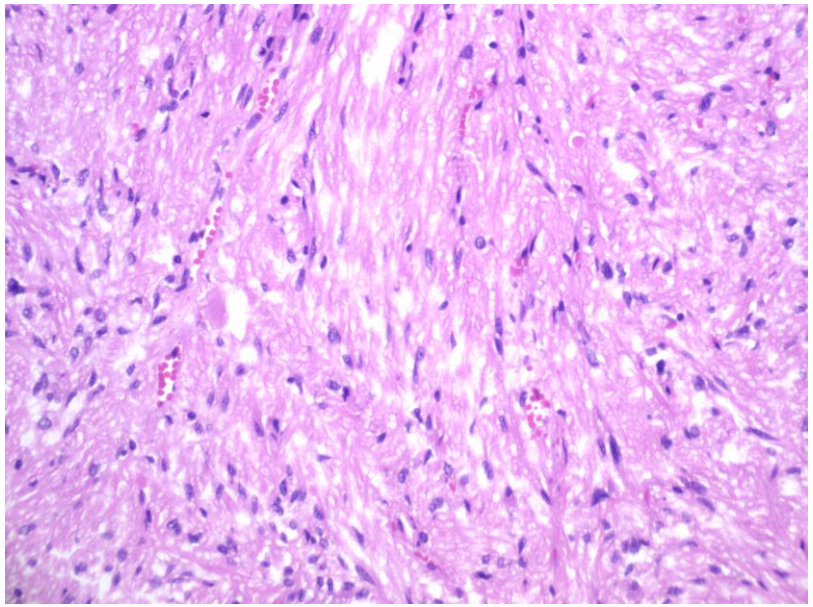
Normal Histology of the Skull Base and Related Anatomic Sites



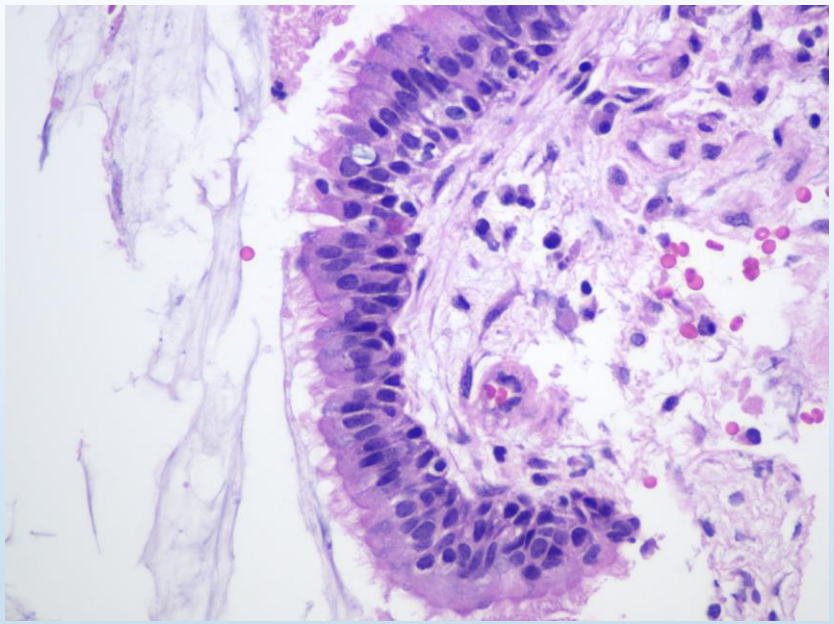
Pituitary gland overview



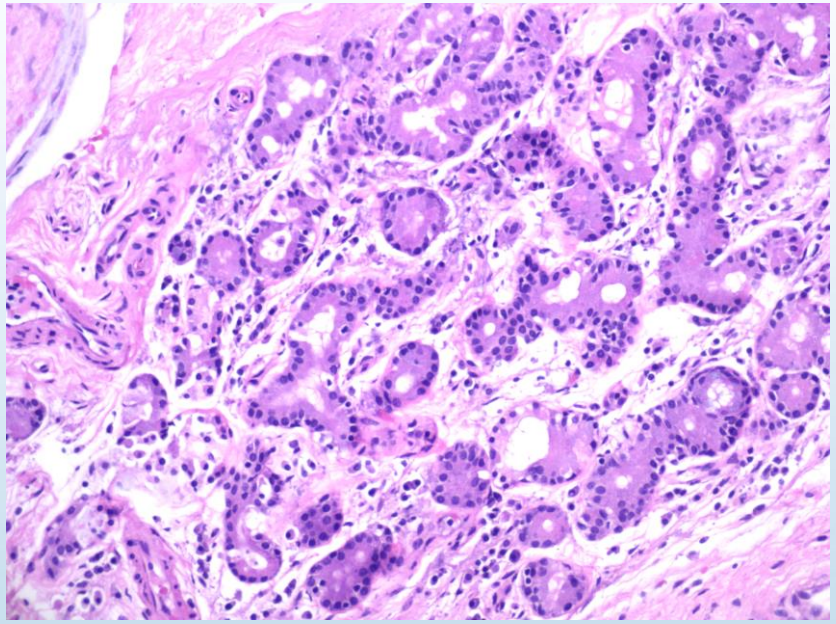
Anterior pituitary



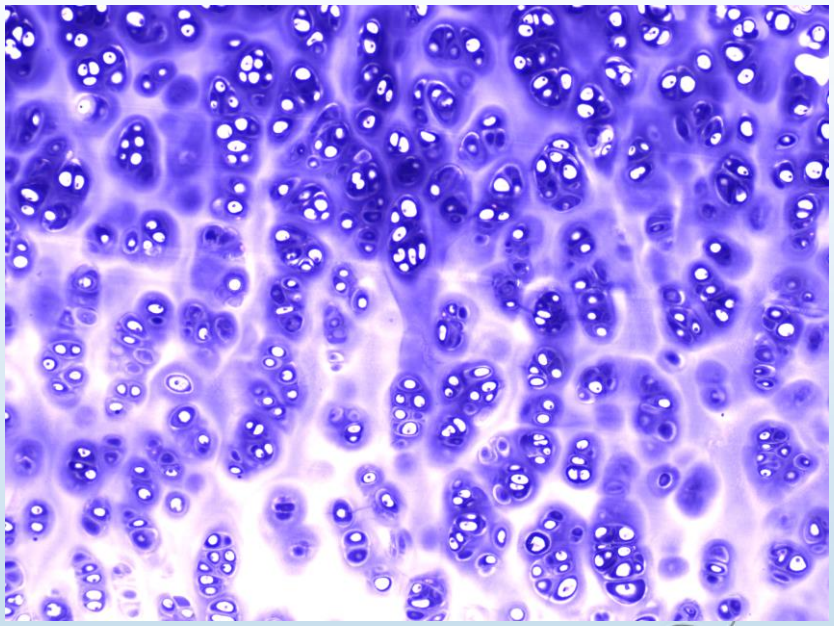
Posterior pituitary



Respiratory mucosa



Seromucinous glands



Nasal (hyaline) cartilage

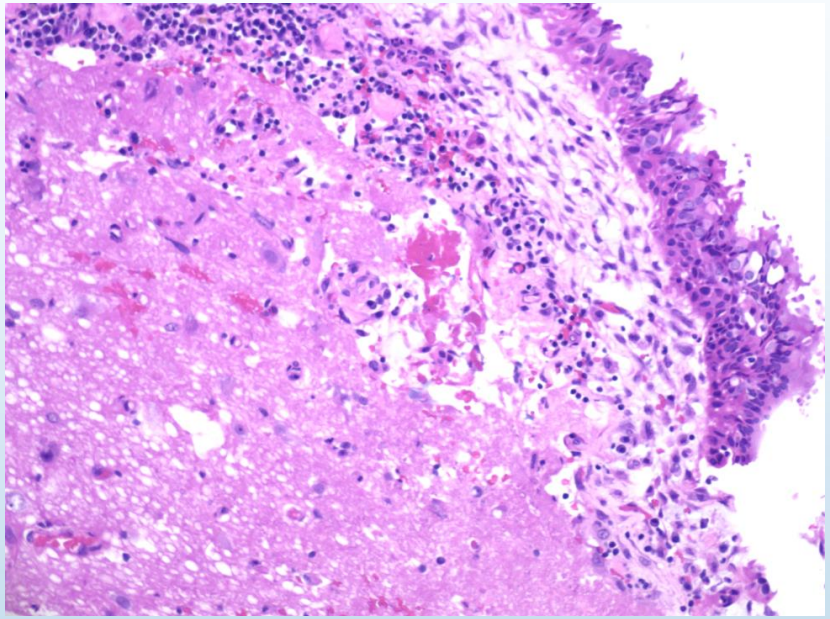
Developmental Abnormalities and Related Lesions of the Skull Base

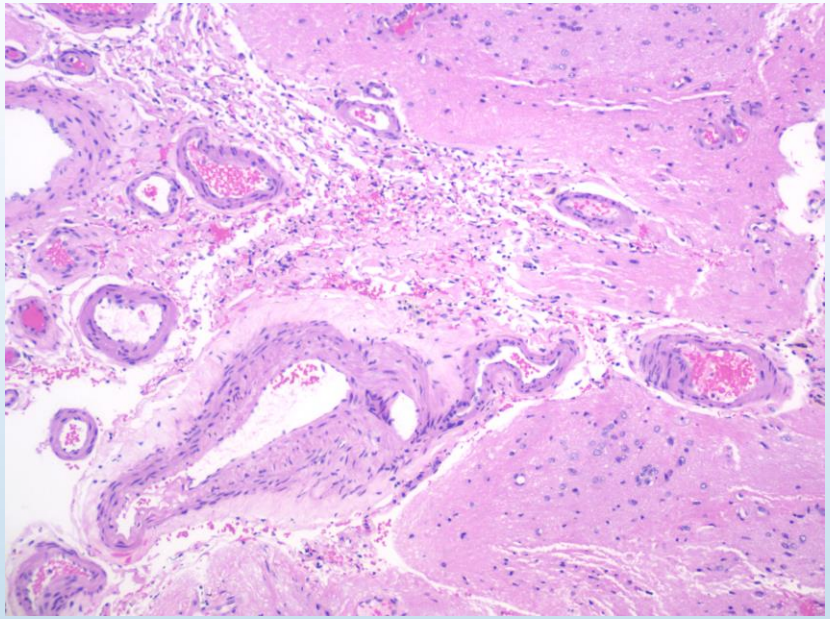
Nasal Glial Heterotopias and Glial Encephaloceles

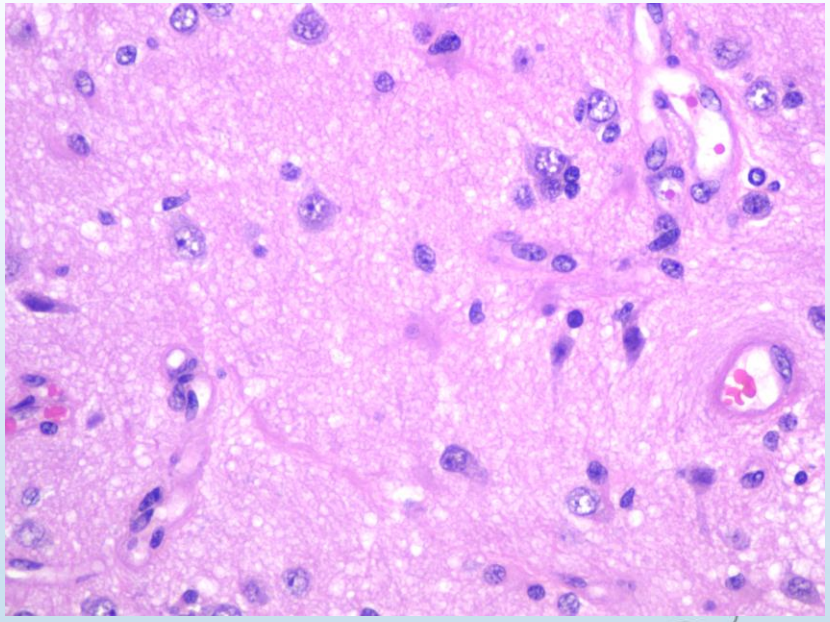
- Nasal glial heterotopia (“nasal glioma”)
  - Etiology: thought to arise from entrapped, non-neoplastic neuroectodermal tissue and present at birth
  - Locations: Nose and nasal cavity, facial region
  - Clinical features: pediatric and adult patients presenting with a mass, nasal obstruction, or non-specific symptoms, such as chronic sinusitis

Nasal Glial Heterotopias and Glial Encephaloceles

- Histology: mature glioneuronal tissue and fibroconnective tissue, may include leptomeninges



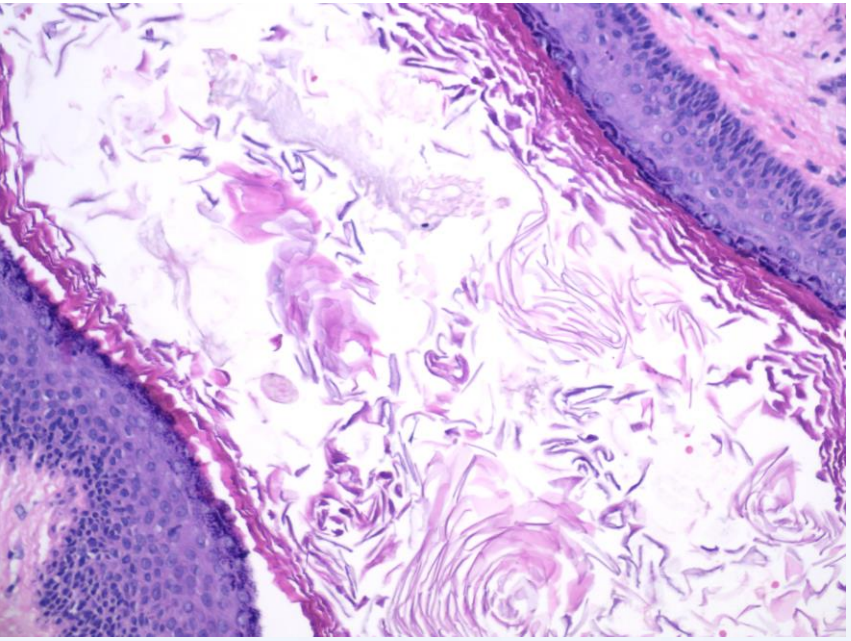




Nasal Glial Heterotopias and Glial Encephaloceles

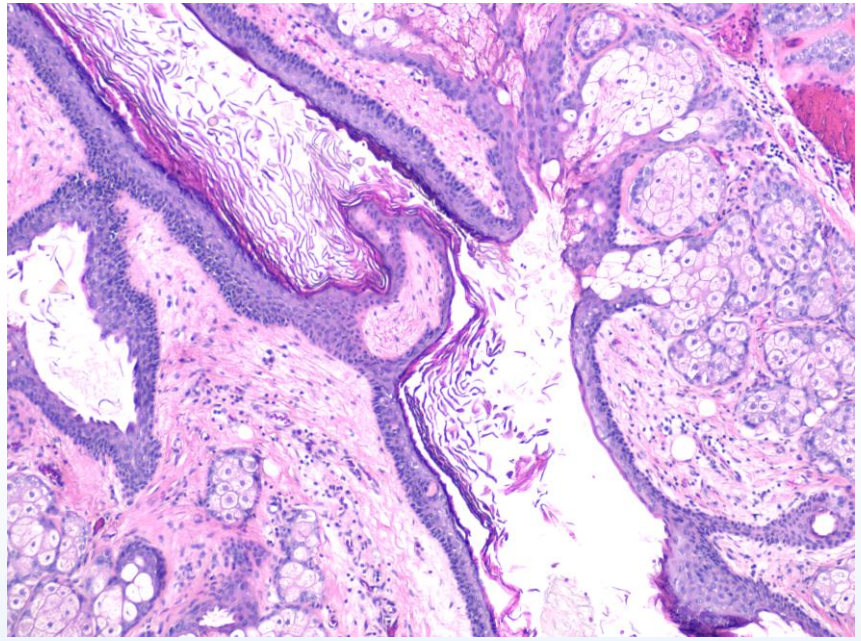
- Nasal glial heterotopia (“nasal glioma”)
  - Imaging critical to exclude connection to the central nervous system (CNS), which would confirm a diagnosis of glial encephalocele, requiring surgical attention to prevent cerebrospinal fluid (CSF) leakage
  - Overlapping molecular alterations (copy number variations of chromosomes 16, 17, and 19) between glial heterotopias and encephaloceles suggest a spectrum of disease (Gilani and Kleinschmidt-DeMasters. Childs Nerv Syst. 2022)
  - Treatment: Surgical excision for glial heterotopia, additional craniofacial repair for glial encephalocele

Epidermoid Cysts



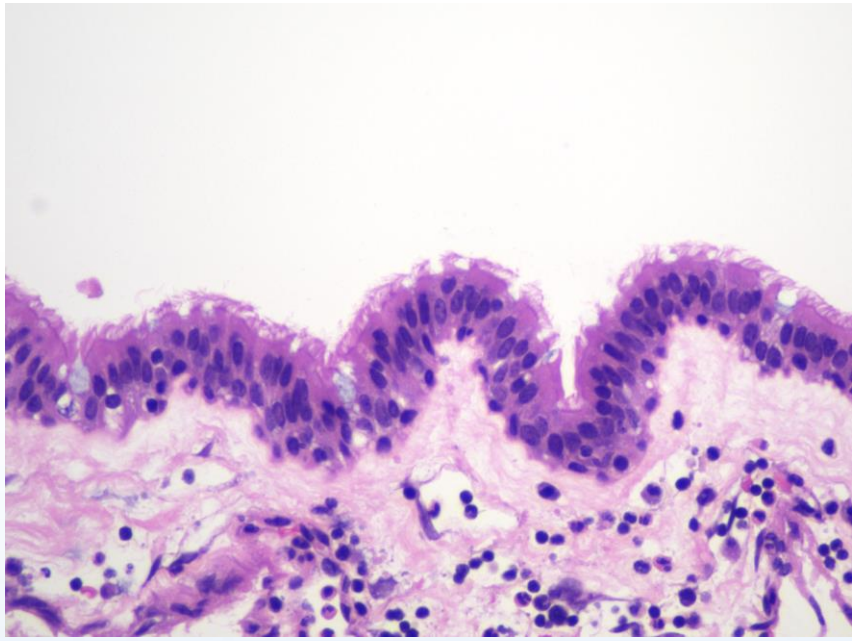
Locations: cerebellopontine angle, parasellar region, and fourth ventricle
Histology: stratified squamous cyst lining with granular layer, often keratin debris

Dermoid Cysts



Locations: predilection for midline location, posterior fossa, and superotemporal orbital rim in periocular examples (most common orbital mass in children)
Histology: stratified squamous cyst lining with adnexal structures, such as hair, sebaceous glands, and sweat glands

Rathke Cleft Cysts



Location: sella
Histology: ciliated, columnar epithelium with goblet cells (may attenuate)

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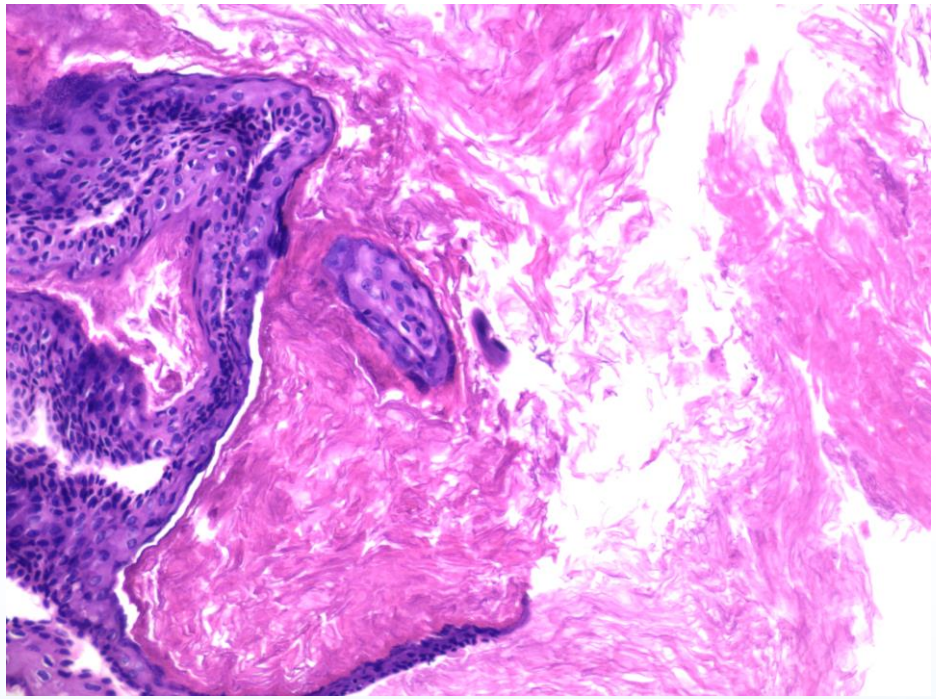
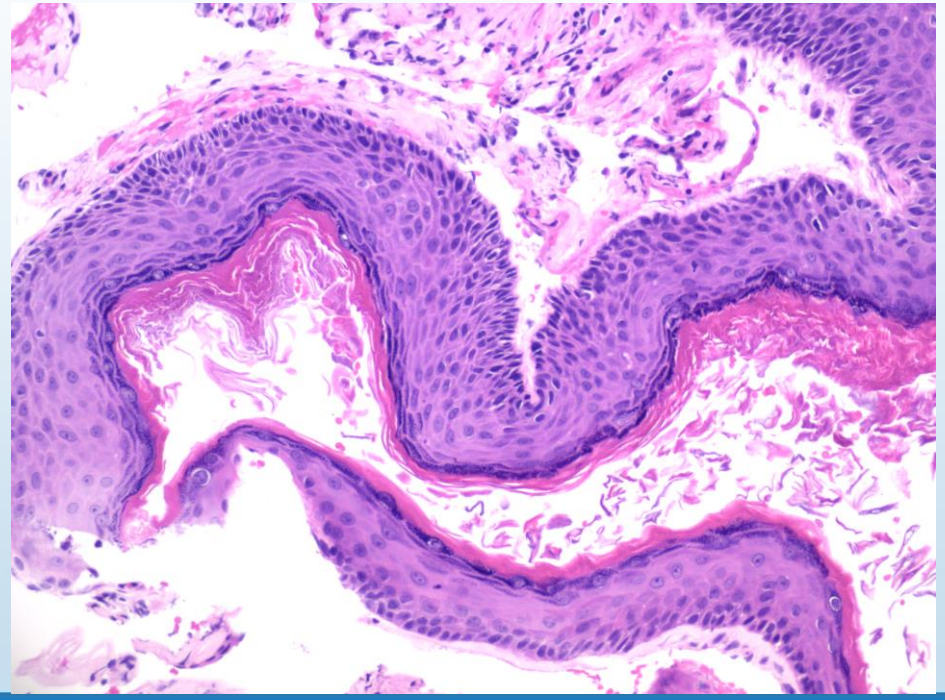
Cholesteatoma

- Etiology
  - Congenital: entrapped epithelial rests, similar to epidermoid cysts
  - Acquired: trauma, associated with otitis media (majority of examples)
- Location: middle ear
- Clinical features: odorous otorrhea, tinnitus, hearing loss
- Imaging shows local, bony destruction
- Histology: keratinizing squamous epithelium with granular layer, keratin debris, and variable inflammatory reaction
- Treatment: curettage, recurrences common

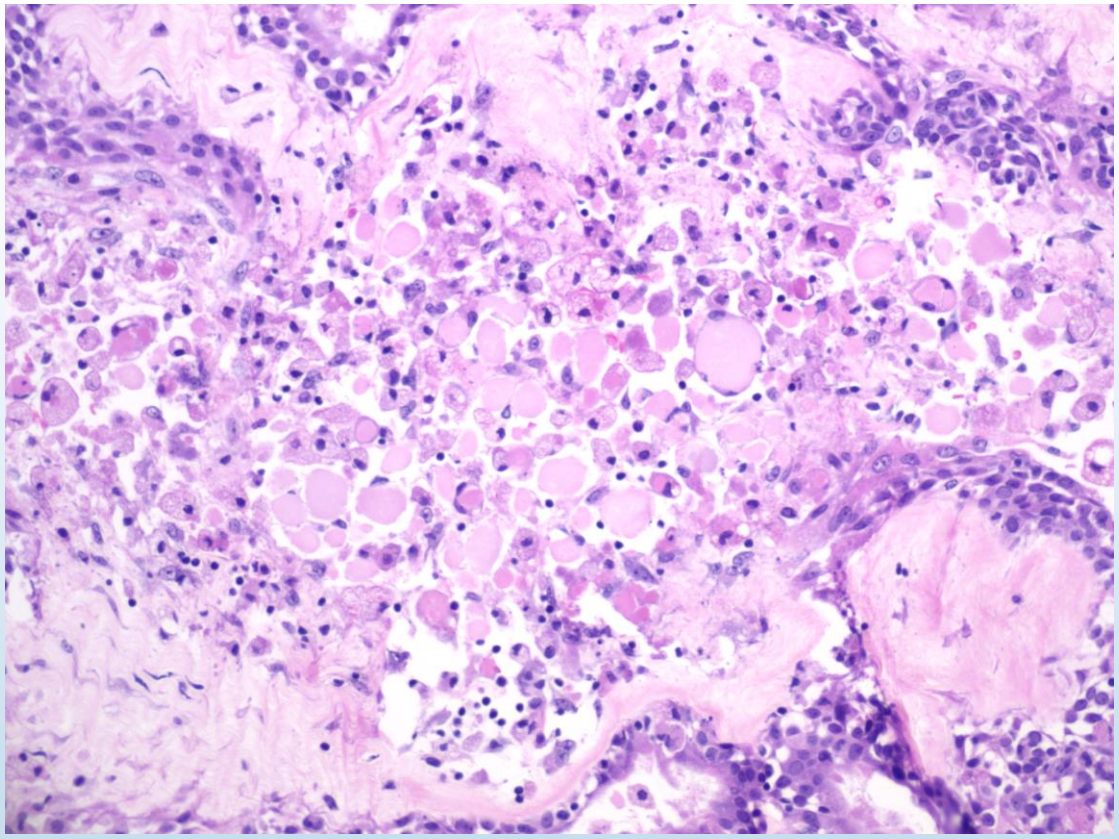




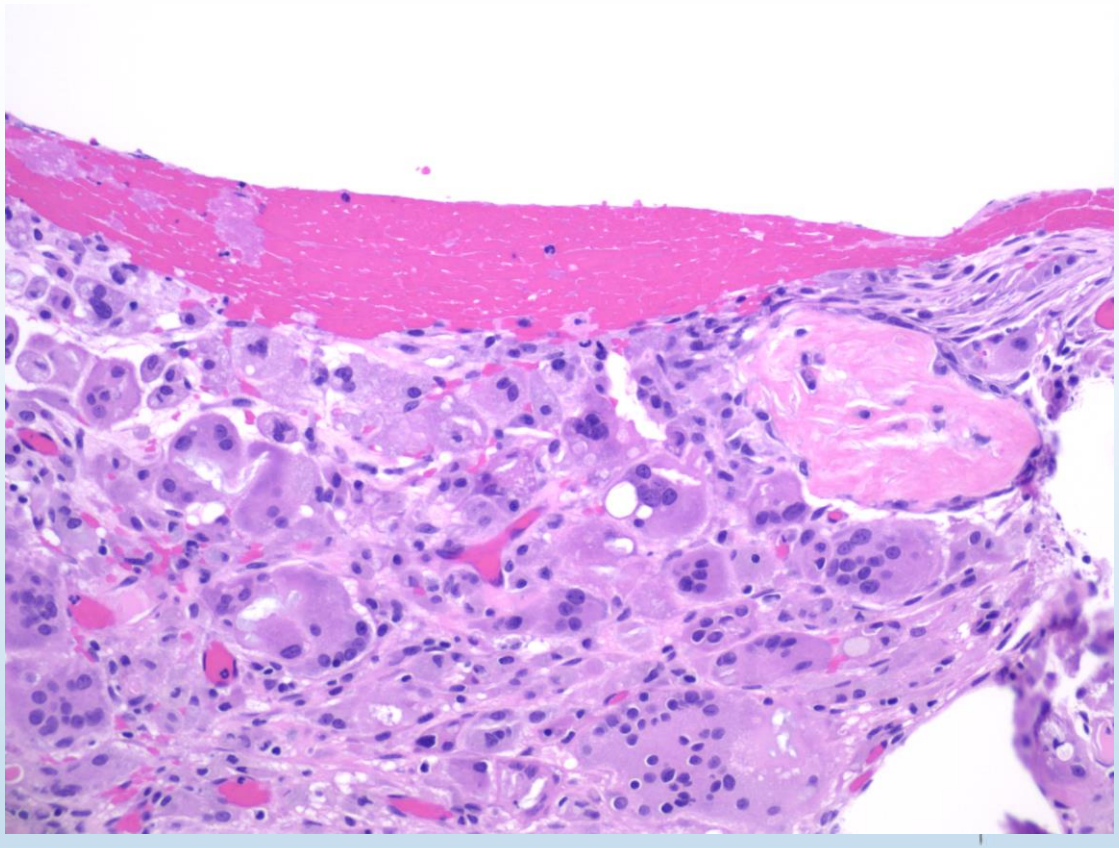
Pitfall: Inflammation Associated with Cyst Rupture

- Cyst rupture can result in inflammatory reactions, including robust histiocytic reactions and multinucleated giant cells

Ruptured Rathke Cleft Cyst



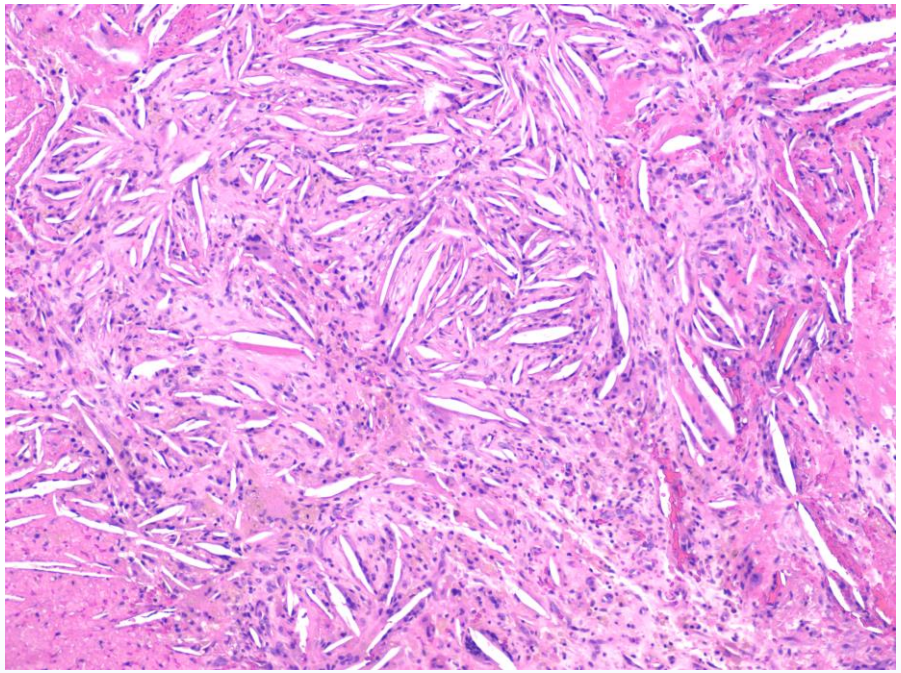
Ruptured Dermoid Cyst

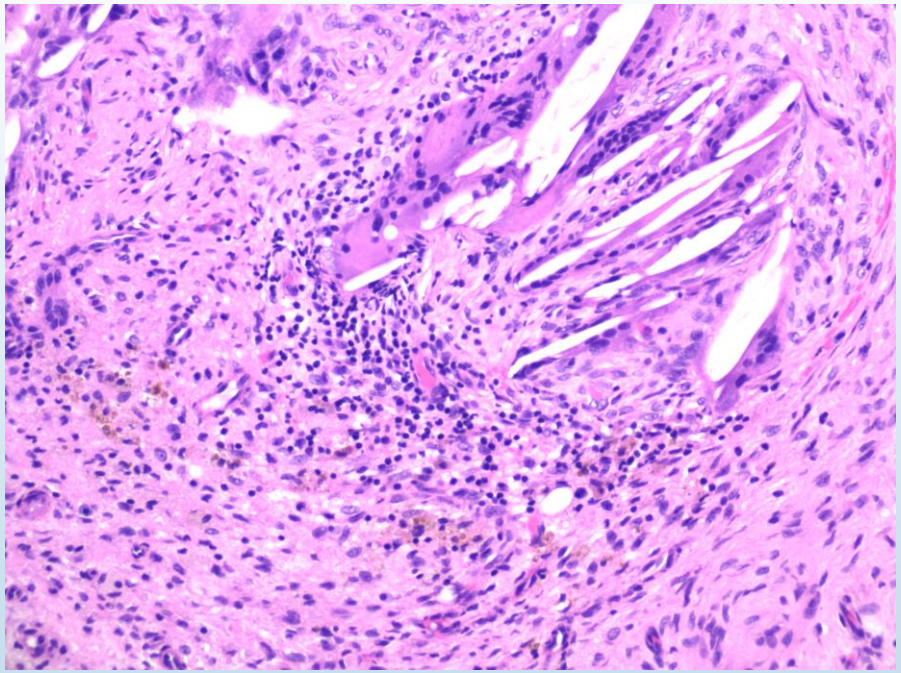


Inflammatory Lesions of the Skull Base

Cholesterol Granuloma

- Etiology: foreign body reaction to blood and lipid breakdown products
- Location: middle ear, mastoid, petrous apex
- Clinical features: chronic otitis media, trauma, hearing loss, tinnitus
- Imaging: well-delineated cystic lesion
- Histology: foreign-body giant cell reaction, granulation tissue, cholesterol clefts
- Treatment: drainage

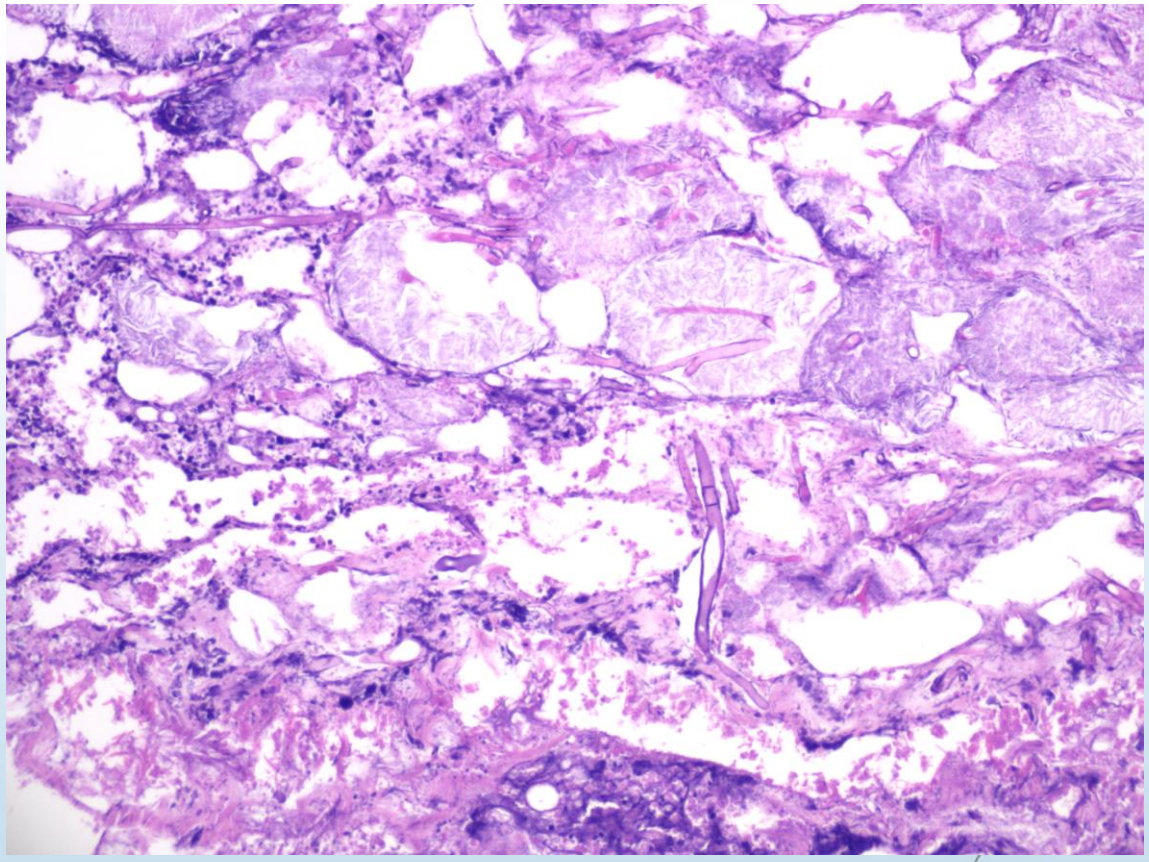




Invasive Fungal Rhinosinusitis

- Clinical presentation: rapid and aggressive invasive fungal disease
- Common pathogens: *Mucor* species, *Aspergillus* species
- Risk factors: immunocompromised patients and uncontrolled diabetes mellitus
- Histology: tissue destruction, identification of hyphal forms in vessels (angioinvasion) and viable tissue
- Treatment: aggressive surgical debridement and antifungal therapy
- Prognosis: High mortality rate, ranging from 33-80% (Alkhateb et al. Arch Pathol Lab Med. 2021)

Mucor species with broad, ribbon-like, aseptate hyphae and right-angle branching



Challenges in Fungal Disease: Identification

- How good are we at correctly identifying fungus?
  - 10-year retrospective study
    - 79% of fungal organisms correctly identified
    - 21% of fungal organisms misidentified
    - 2 potential adverse outcomes
    - (Sangoi. Am J. Clin. Pathol. 2009)
  - Cultures or other ancillary testing are needed for definitive fungal identification

Challenges in Fungal Disease: Identification

Am J Clin Pathol. 2009 Mar;131(3):364-75. doi: 10.1309/AJCP99OOOZSNISCZ.

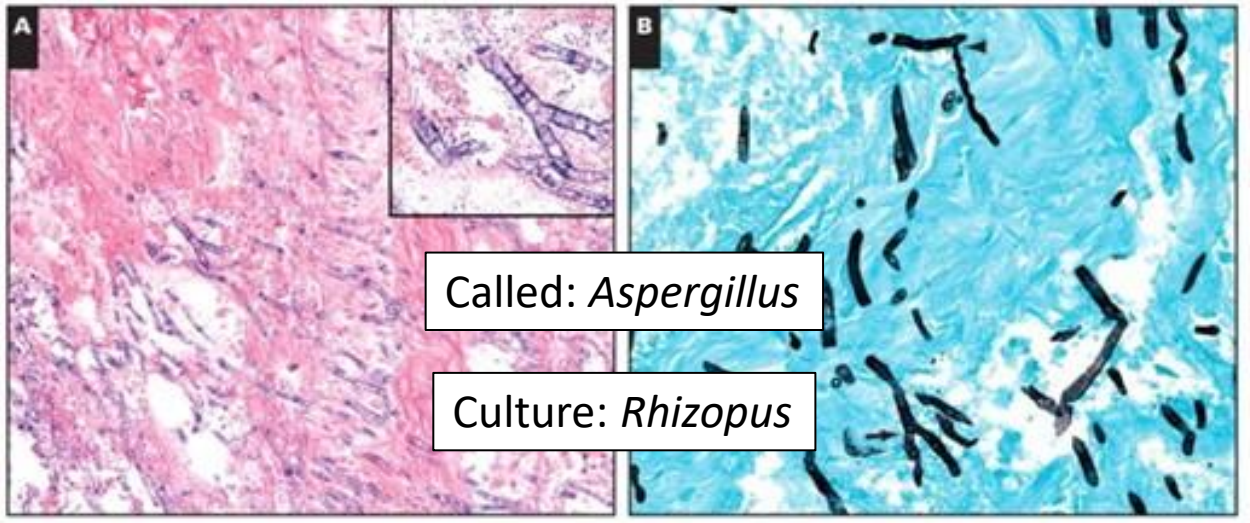
Challenges and pitfalls of morphologic identification of fungal infections in histologic and cytologic specimens: a ten-year retrospective review at a single institution

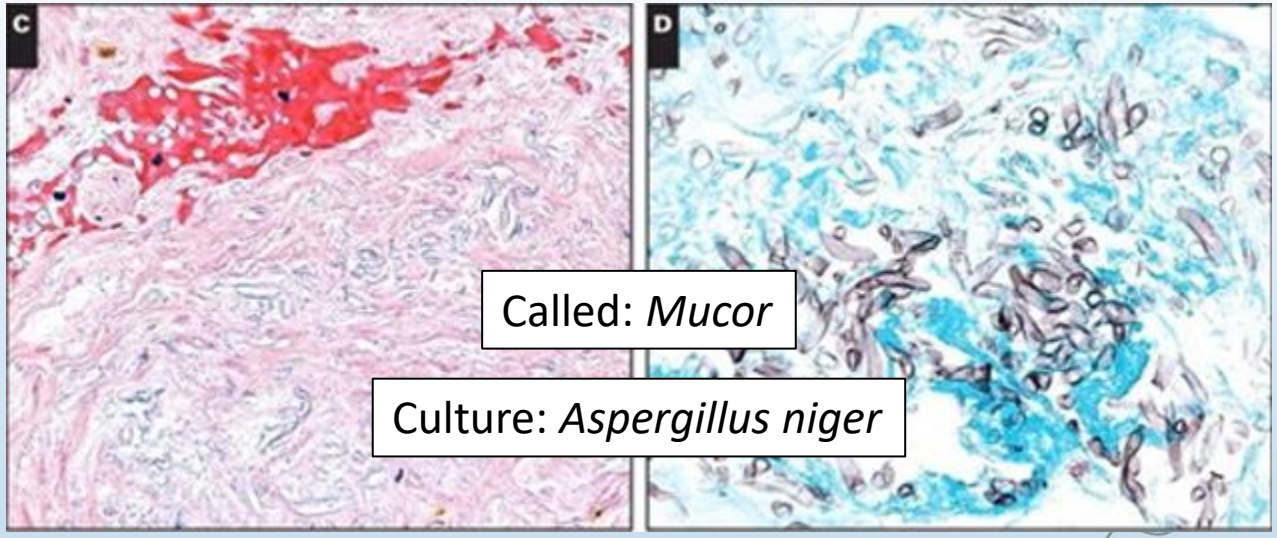
Ankur R Sangoi [1], William M Rogers, Teri A Longacre, Jose G Montoya, Ellen Jo Baron, Niaz Banaei

Affiliations + expand

PMID: 19228642 DOI: 10.1309/AJCP99OOOZSNISCZ

Conclusion: exercise caution to avoid possible inappropriate pharmacotherapy





Sangoi. Am J. Clin. Pathol. 2009

Challenges in Fungal Disease: Frozens

- Delay in therapy associated with poor outcome
- Aggressive surgical debridement could be harmful to the patient
- How good are we at identifying invasive fungal rhinosinusitis on intraoperative consultation?
  - 10-year retrospective study (Alkhateb et al. Arch Pathol Lab Med. 2021)
    - 90% of patients had at least 1 intraoperative consultation positive for acute invasive fungal rhinosinusitis
    - 88.5% of positive cases were diagnosed on intraoperative consultation
    - 100% of negative specimens called negative
    - Sensitivity: 88.5%
    - Specificity: 100%

› Arch Pathol Lab Med. 2021 Jun 1;145(6):736-743. doi: 10.5858/arpa.2019-0696-OA.

Accuracy of Intraoperative Frozen Section in Detection of Acute Invasive Fungal Rhinosinusitis

Rahaf Alkhateb [1], Preethi Dileep Menon [1], Hamza Tariq [1], Sarah Hackman [1], Alia Nazarullah [1], Daniel D Mais [1]

Affiliations + expand

PMID: 33091928 DOI: 10.5858/arpa.2019-0696-OA

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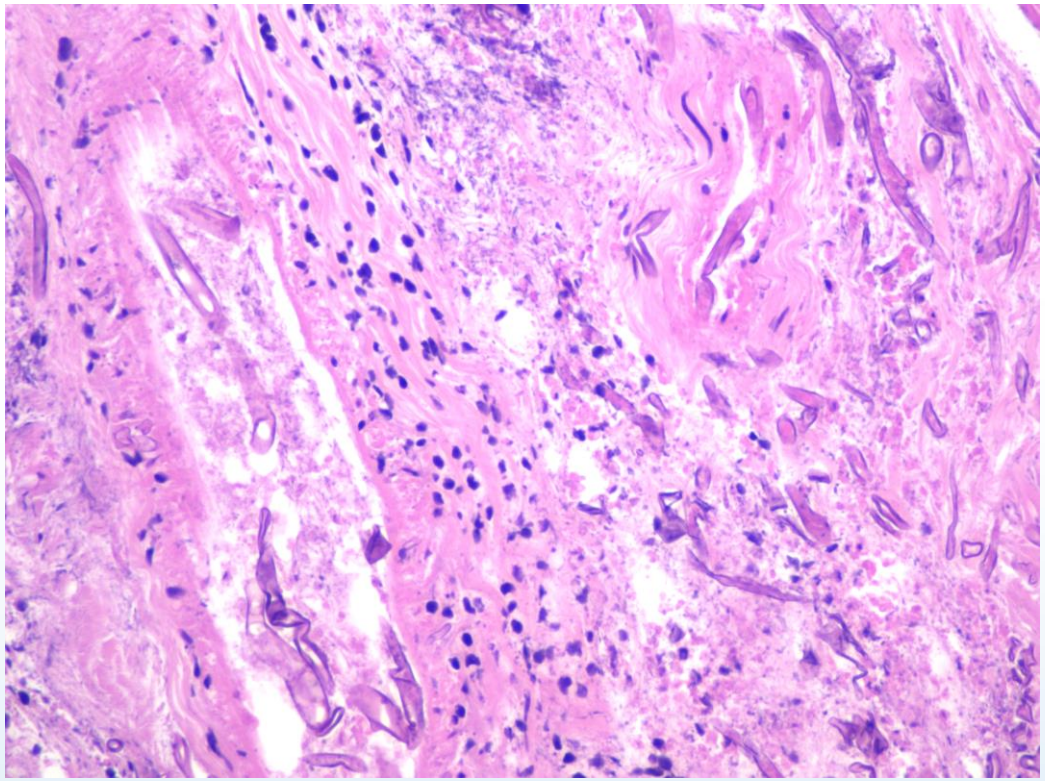
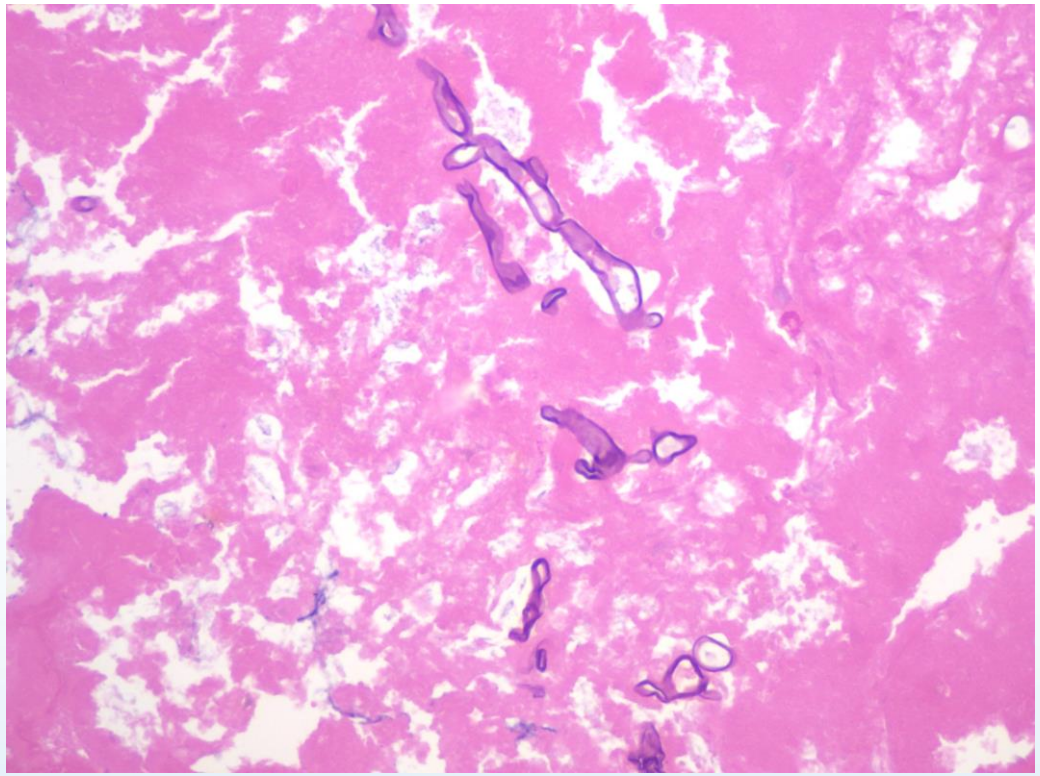
Challenges in Fungal Disease: Frozens



Positive for invasive fungal rhinosinusitis, suspicious for *Mucor* species



Positive for hyphal forms suspicious for *Mucor* species in non-viable/necrotic tissue, (highly) suspicious for invasive fungal rhinosinusitis

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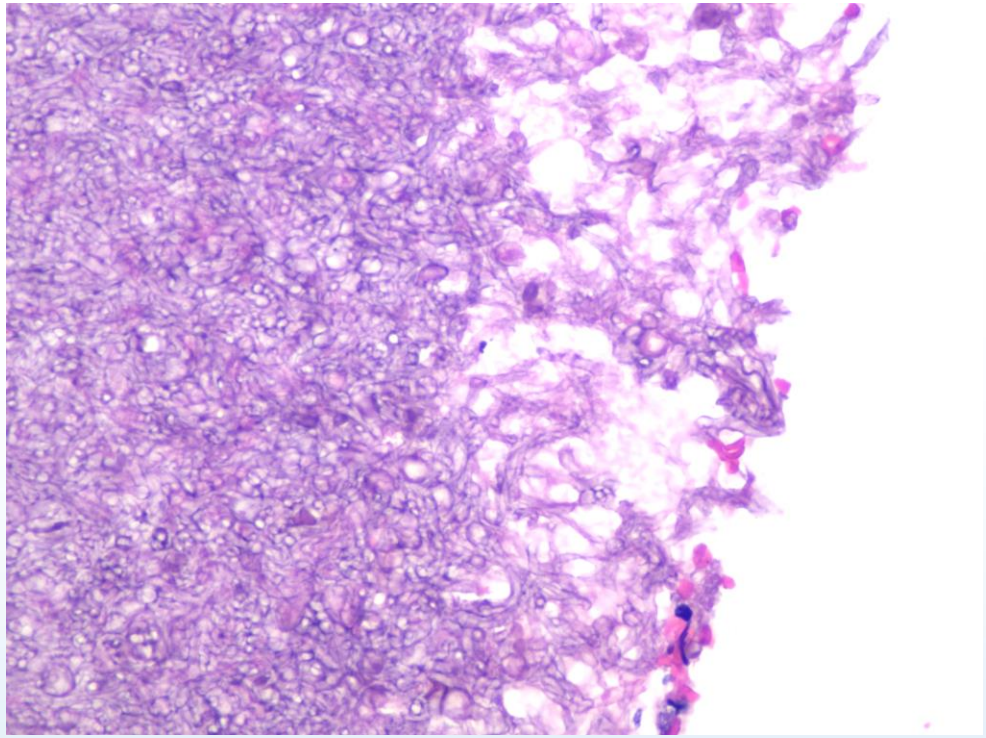
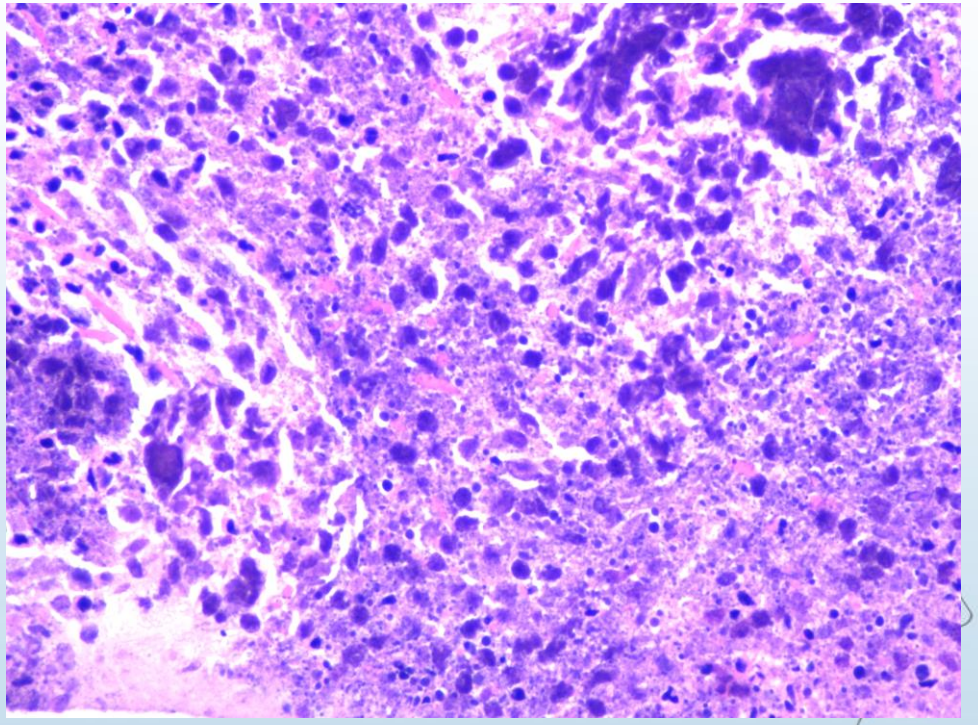
Challenges in Fungal Disease: Non-invasive fungal disease



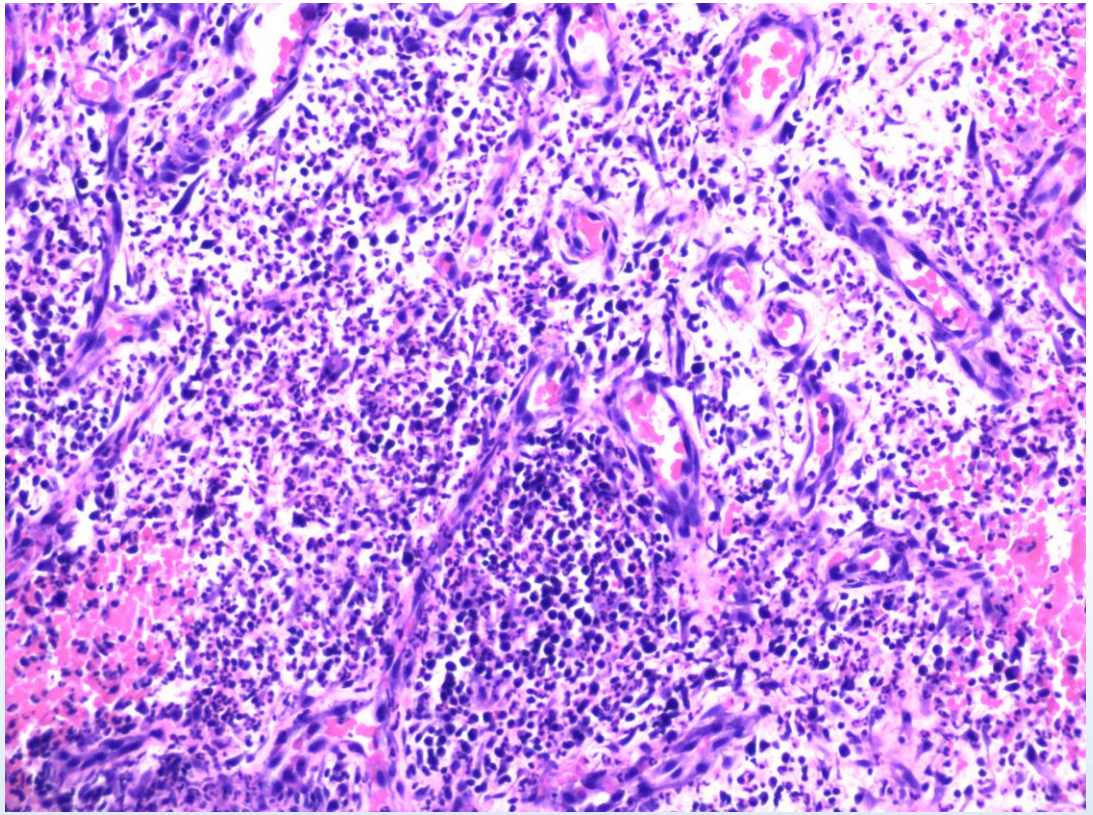
Mycetoma, “Fungus ball”
Clinical: Non-specific sinus symptoms
Imaging: sinus opacification, maxillary sinuses most common
Histology: Dense accumulation of non-invasive fungal hyphae

Allergic fungal rhinosinusitis
Clinical: longstanding chronic sinusitis
Imaging: sinus opacification
Histology: thick, allergic mucin with degenerated/inflammatory debris, eosinophils, Charcot-Leyden crystals, and non-invasive fungal organisms



Necrotizing “Malignant” Otitis Externa

- Severe infection that can affect the skull base and temporal bone, most commonly caused by *Pseudomonas aeruginosa*
  - Gram negative bacteria that lives in water and wet surfaces
- Associated with diabetes mellitus, debilitation, immunodeficiency
- Histology: exuberant granulation tissue and necrosis
- Treatment: systemic and local antimicrobials, may be complicated by drug resistance, surgery needed in refractory cases



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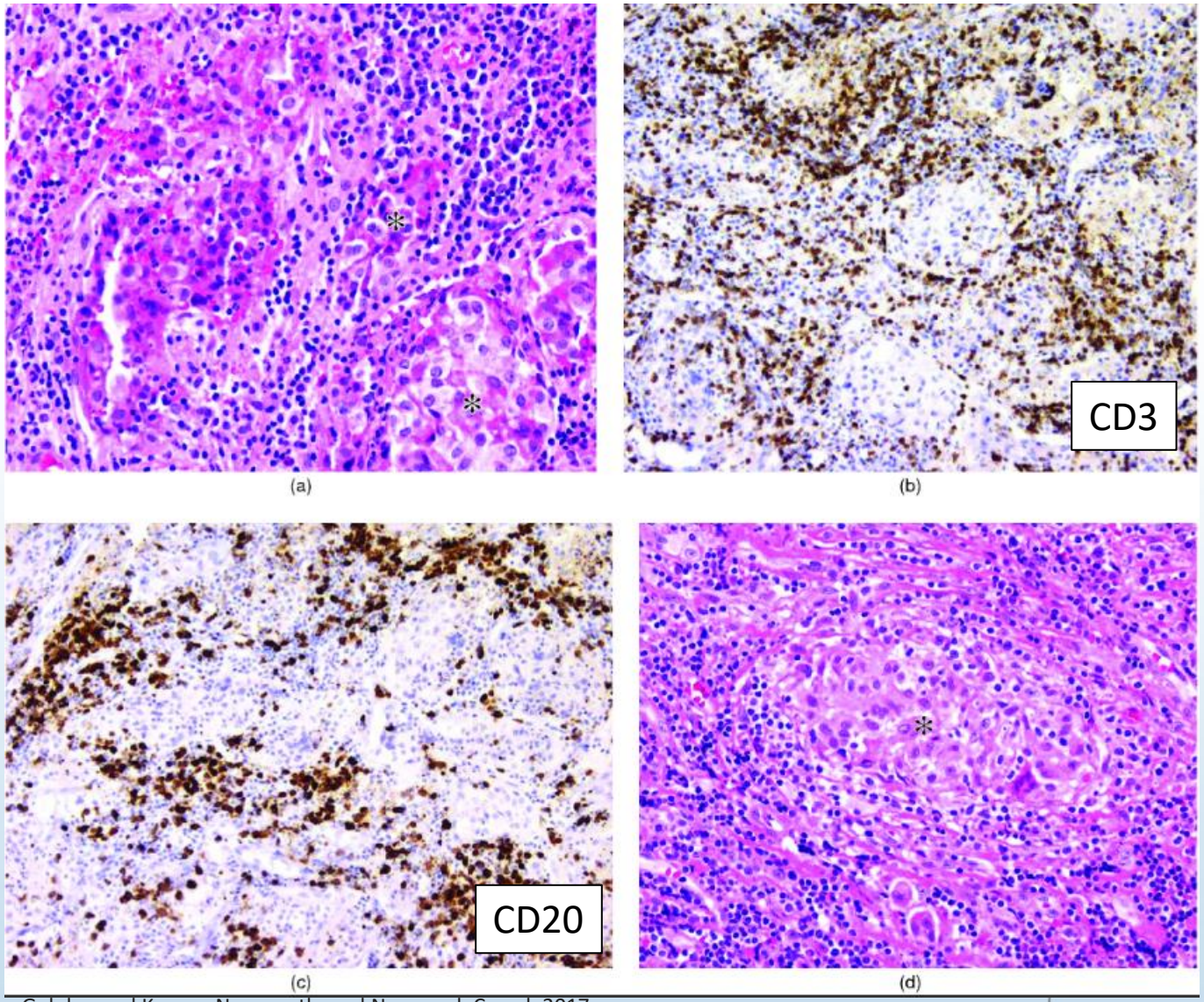
Primary Lymphocytic Hypophysitis

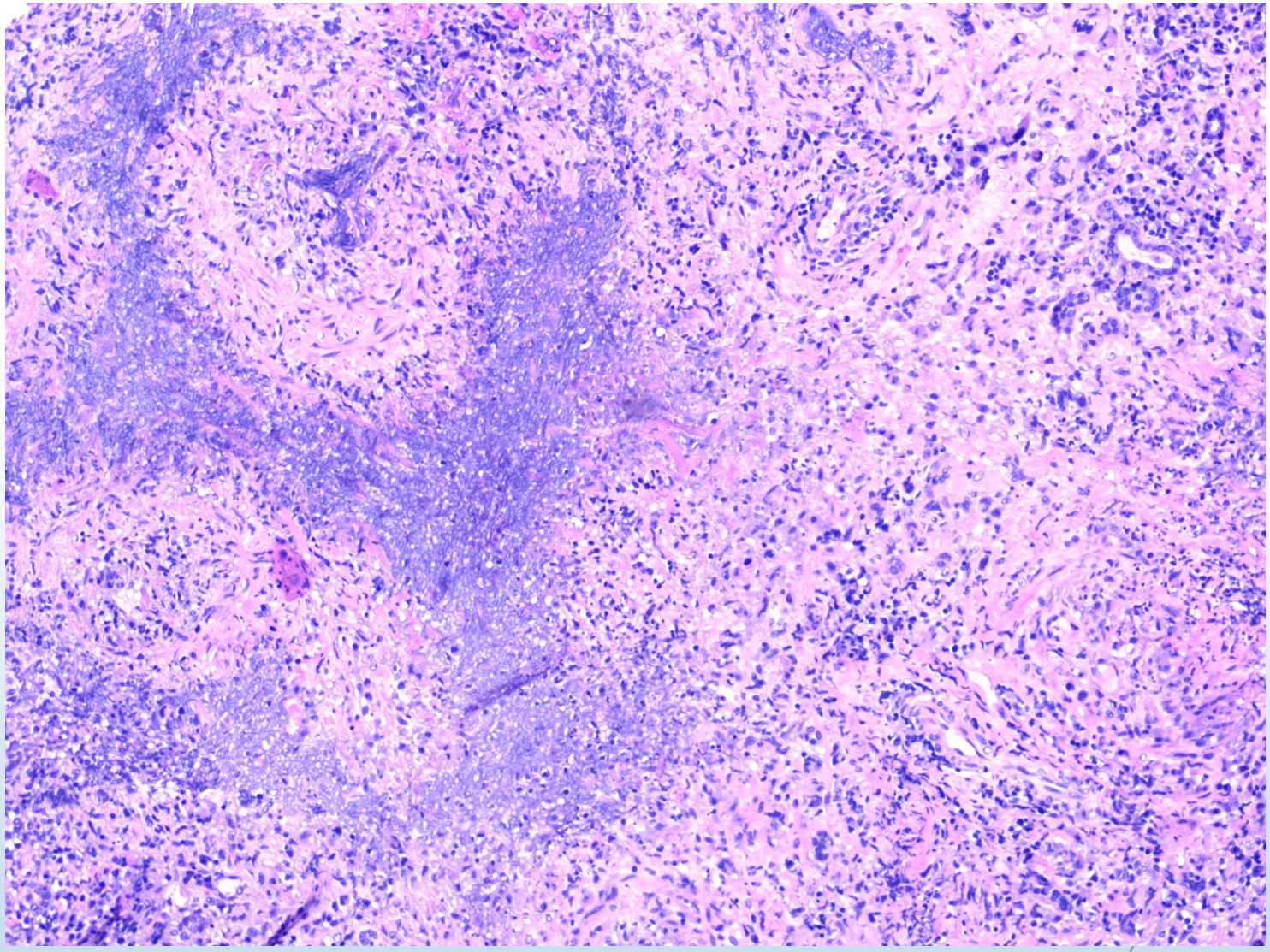
- Rare, idiopathic condition thought to be autoimmune
- Post-partum and pregnant women
- Non-specific signs, symptoms, and imaging findings that may mimic pituitary neuroendocrine tumors (PitNETs)
- Histology: lymphoplasmacytic infiltrate
- Treatment may involve steroids and anti-inflammatory agents
- Diagnosis of exclusion
  - IgG4-related disease
  - Infection
  - Granulomatous (panel d) and xanthomatous hypophysitis
  - Sarcoidosis
  - Neoplasms



Gokden and Kumar. Neuropath. and Neurorad. Correl. 2017.

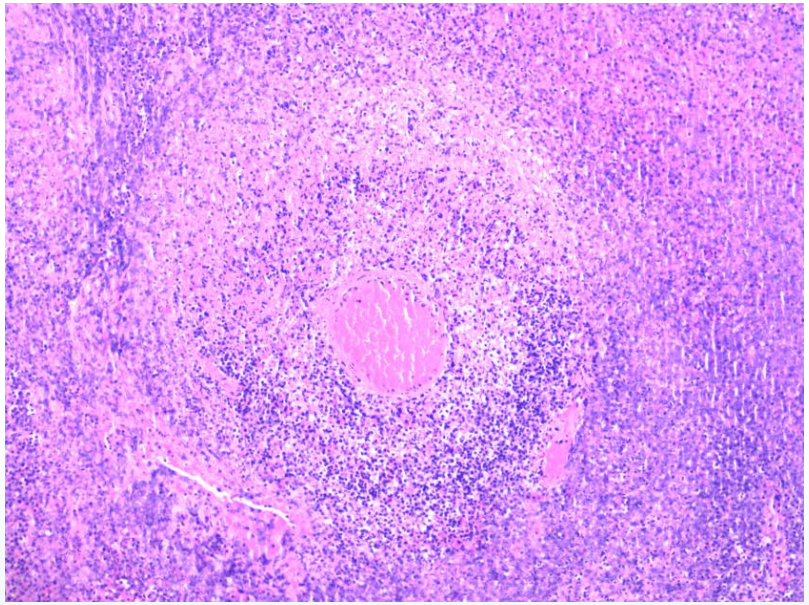
Granulomatosis with Polyangiitis

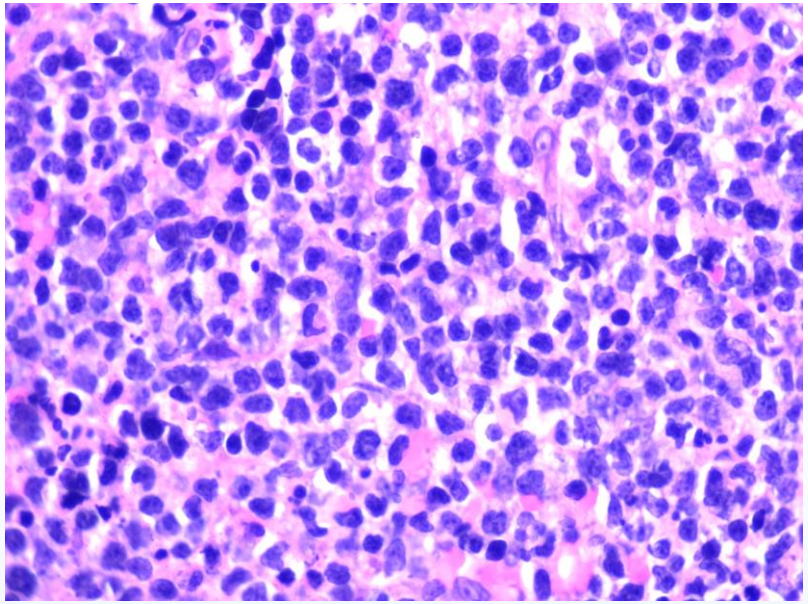
- Necrotizing vasculitis of small and medium-sized blood vessels
- Anti-neutrophilic cytoplasmic antibodies (ANCA), specifically cytoplasmic-ANCA (c-ANCA) against proteinase 3 in most cases
- Clinical: usually adults, classic involvement of upper respiratory tract, lungs, and kidneys
- Classic histologic triad: vasculitis, granulomatous inflammation, and necrosis (often “geographic” or “zonal” necrosis with a basophilic, granular quality)
  - Classic triad may not be seen (particularly on limited biopsies/fragments)

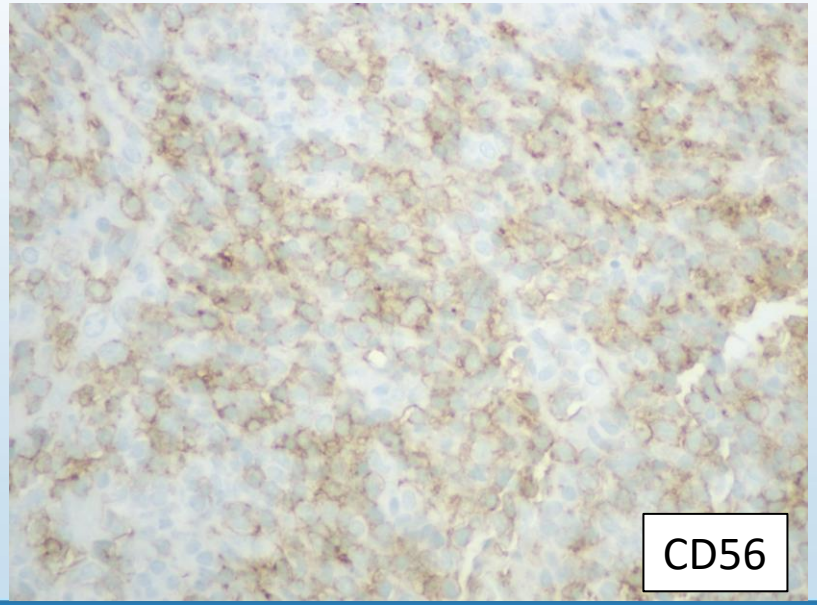


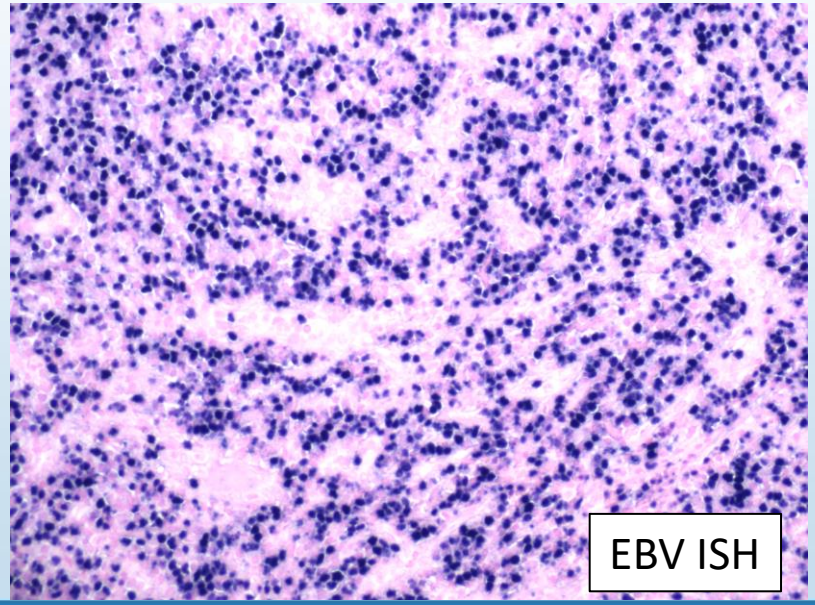
Extranodal NK/T Cell Lymphoma

- Epstein-Barr Virus (EBV)-associated natural killer or cytotoxic T-cell lymphoma, formerly called “lethal midline granuloma” and “angiocentric lymphoma”
- Clinical: adults, male predominance, East Asia, Central and South America, majority in head and neck, particularly in nasal cavity
- Histology: diffuse and angiocentric growth of medium-to-large neoplastic cells with irregular nuclei as well as associated necrosis
- Immunohistochemistry: typically, CD3 and CD56 expressing cells with positivity for cytotoxic molecules (TIA-1, granzyme B, and perforin) and EBV demonstrable with in situ hybridization

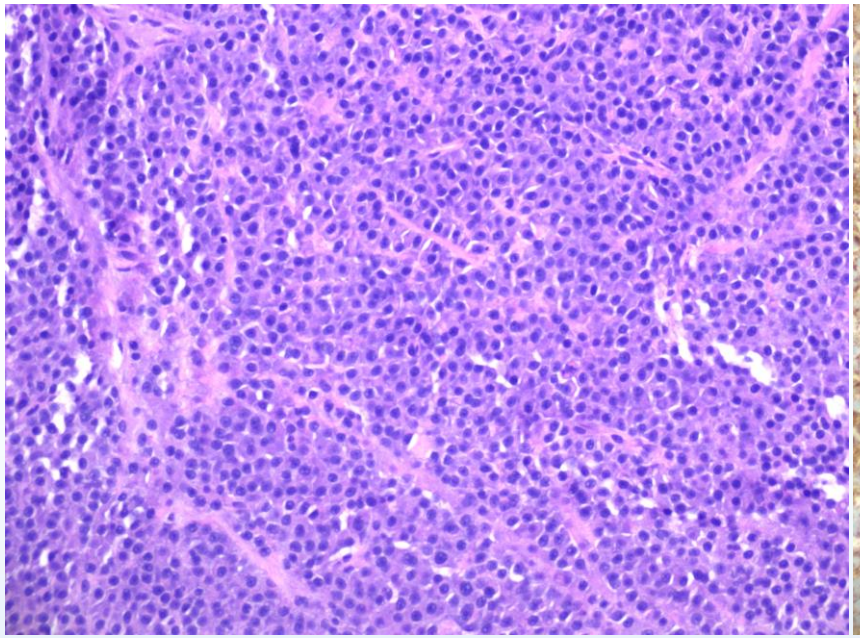




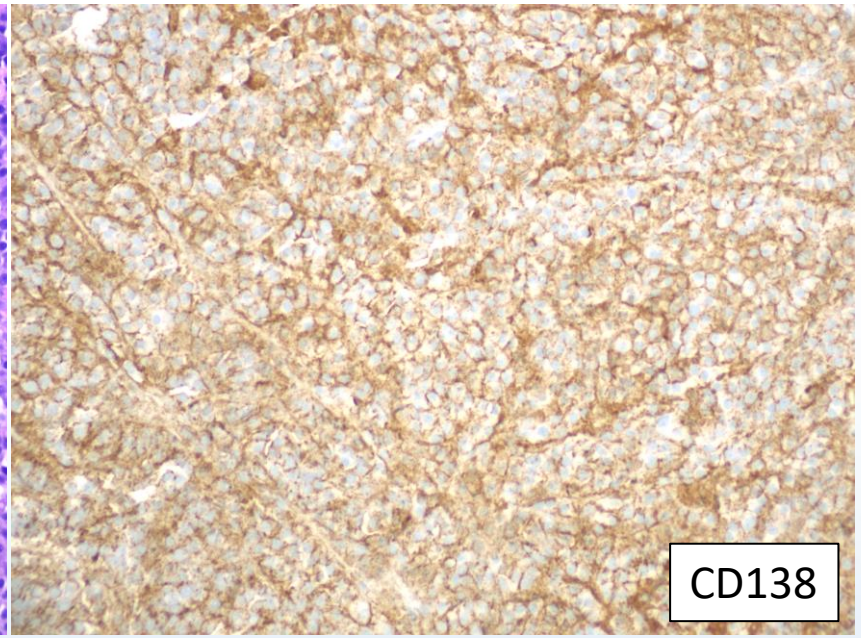


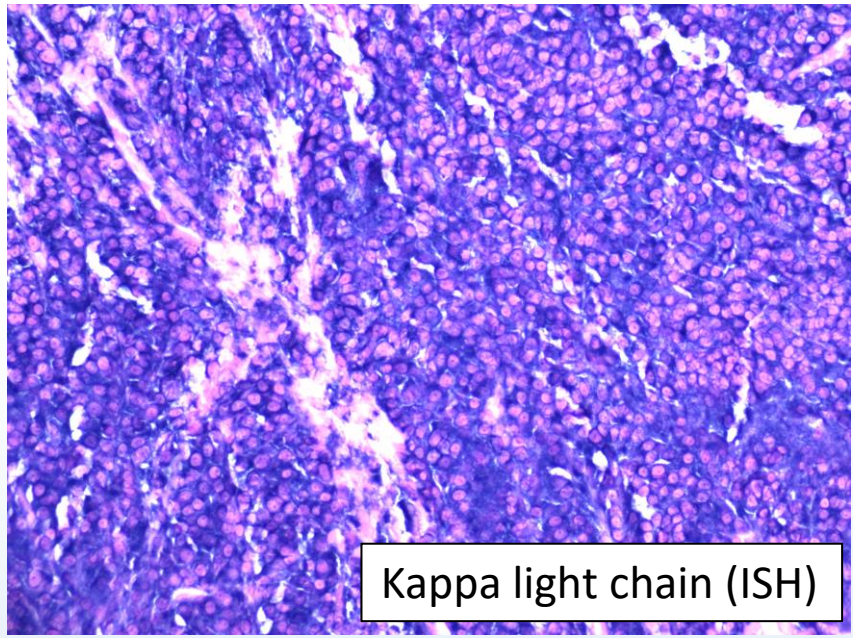


Other Hematolymphoid Neoplasms and Proliferations



Sellar mass clinically thought to be pituitary neuroendocrine tumor





Plasma cell neoplasm, kappa-restricted

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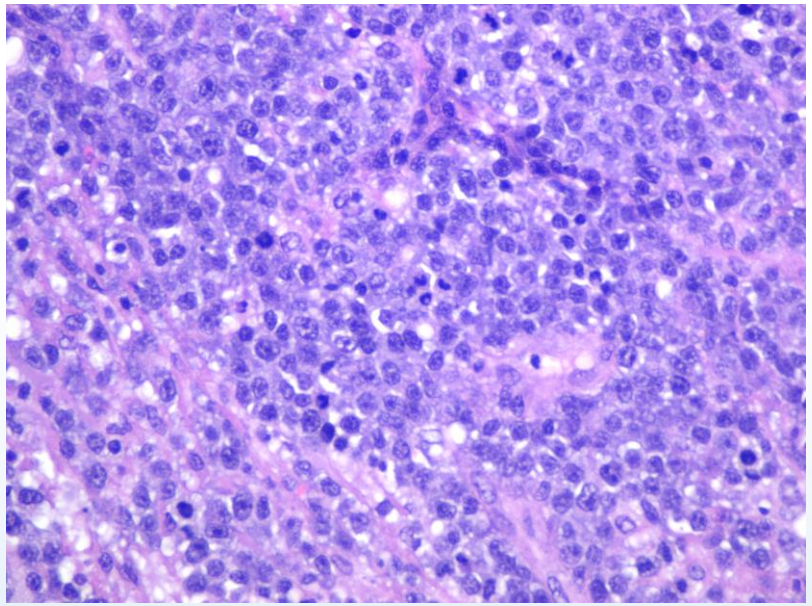
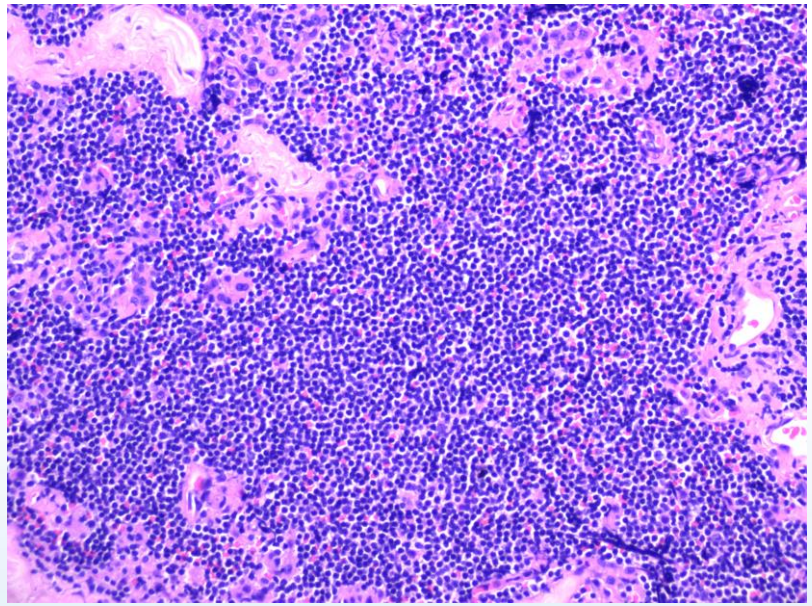
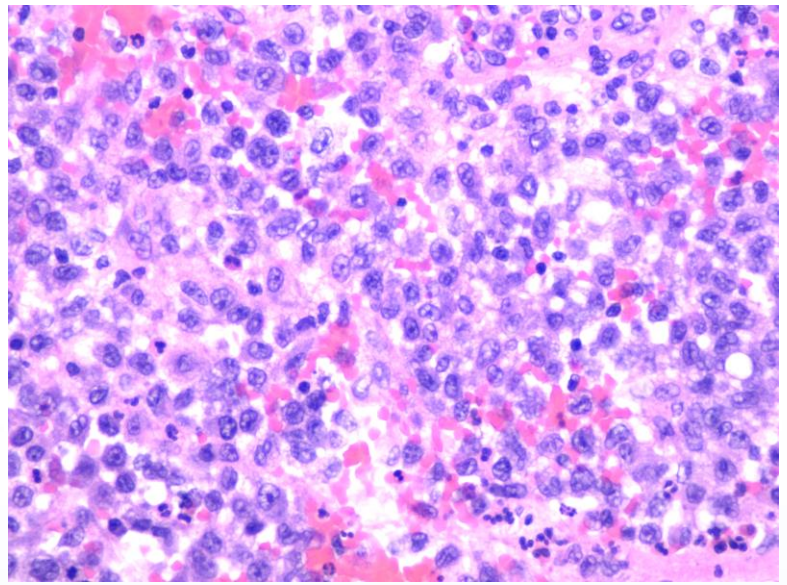
Other Hematolymphoid Neoplasms and Proliferations



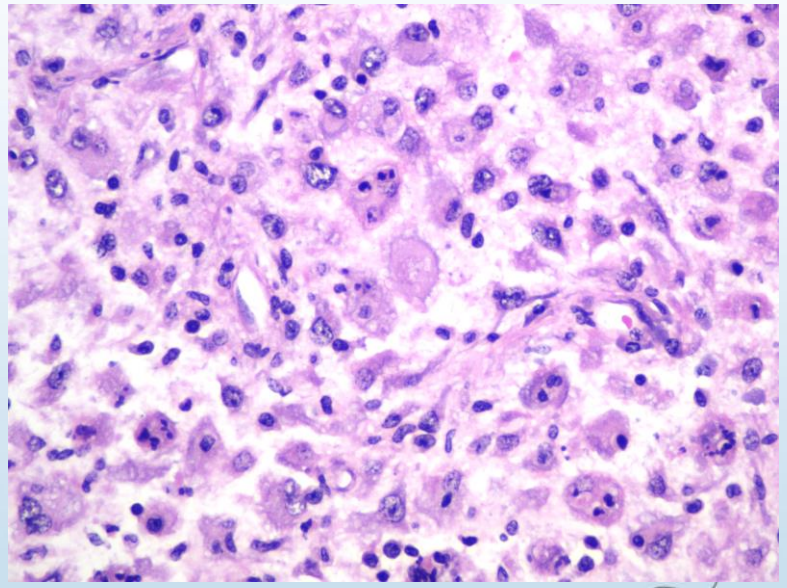
Diffuse large B-cell lymphoma
Most common lymphoma of head and neck overall



Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Ocular region and salivary glands, most commonly



Langerhans cell histiocytosis
Craniofacial bones

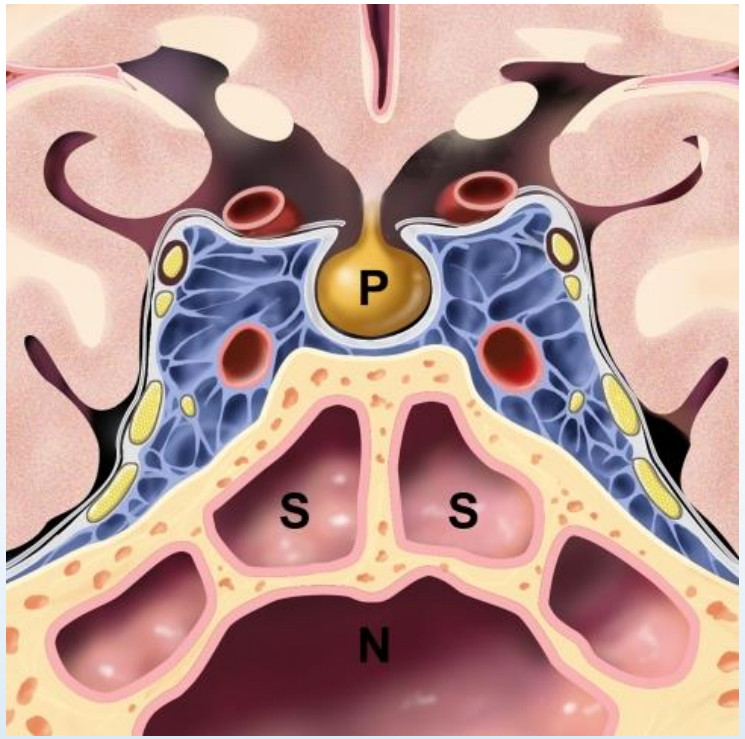


Rosai-Dorfman Disease, sinonasal tract, orbit

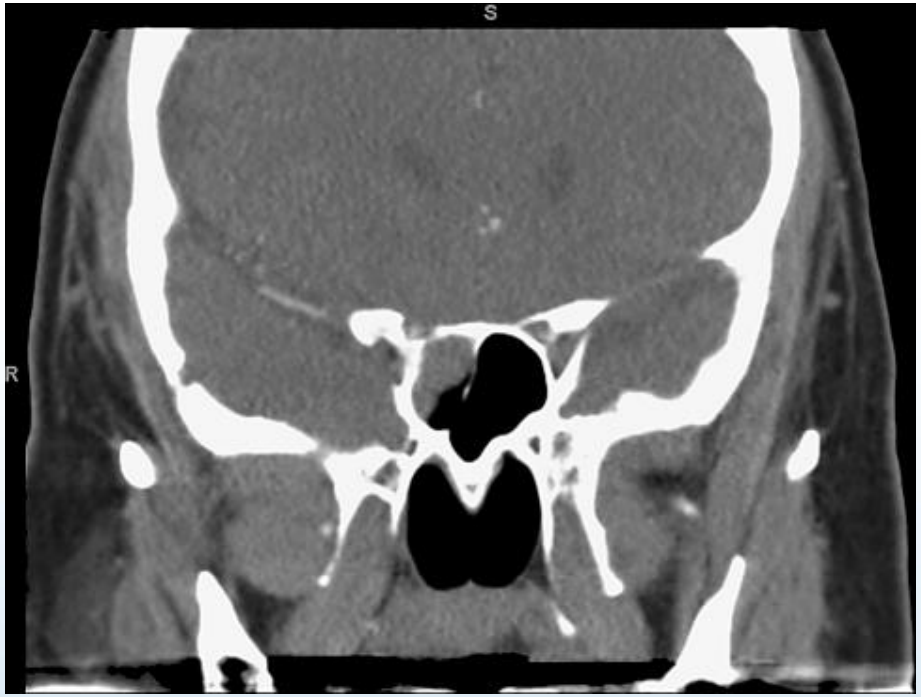
Epithelial and Epithelioid Neoplasms of the Skull Base

Ectopic Pituitary Neuroendocrine Tumors (PitNETs)

- Pituitary neuroendocrine tumor of adenohypophysial cells within the sinonasal tract without evidence of direct invasion from the sella
- Ectopic sphenoid sinus examples most common, may also involve nasopharynx and nasal cavity
- Etiology may be related to Rathke's pouch remnant
- Symptoms: hormone-related dysfunction (Cushing symptoms), sinusitis, headache



S=sphenoid sinus, P=pituitary, N=nasopharynx



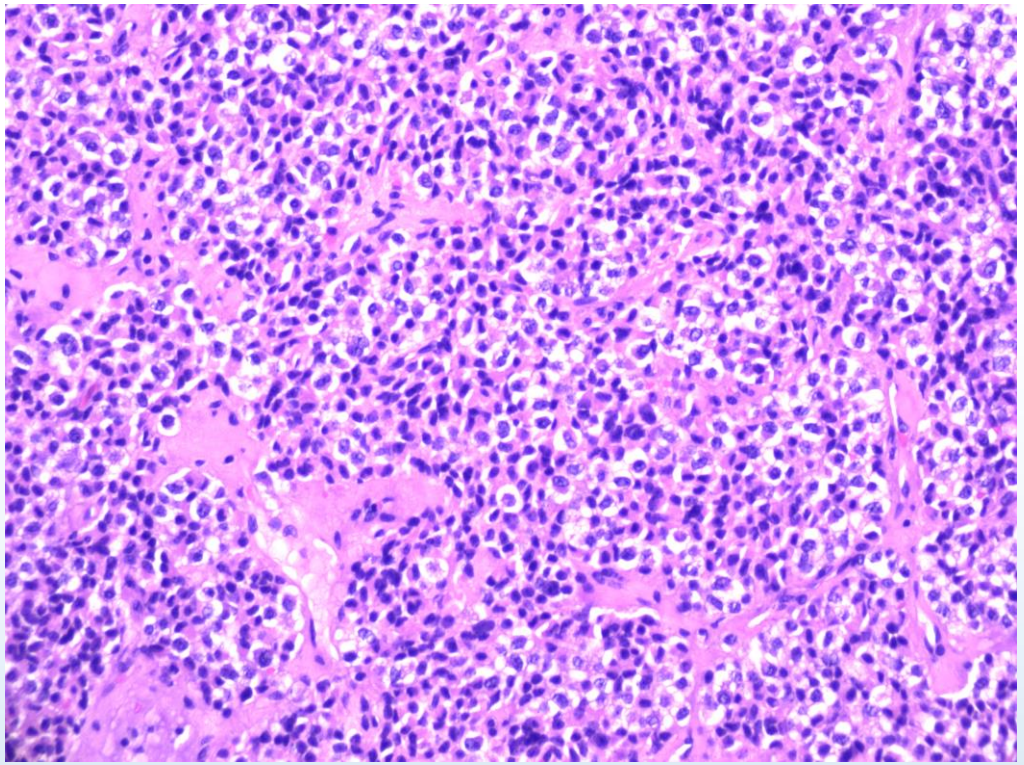
Right sphenoid sinus mass

AANP

Thompson. Head Neck Pathol. 2012

Ectopic Pituitary Neuroendocrine Tumors (PitNETs)

- Classified similarly to those arising within the sella
- Confirmation of adenohypophyseal differentiation (lineage markers, hormones) is essential for the diagnosis
- Differential includes
  - Well-differentiated neuroendocrine tumors
  - Paraganglioma
  - Olfactory neuroblastoma
- Treatment: surgical removal +/- radiotherapy
- Prognosis: dependent on tumor subtype, difficulty in resection can lead to recurrence

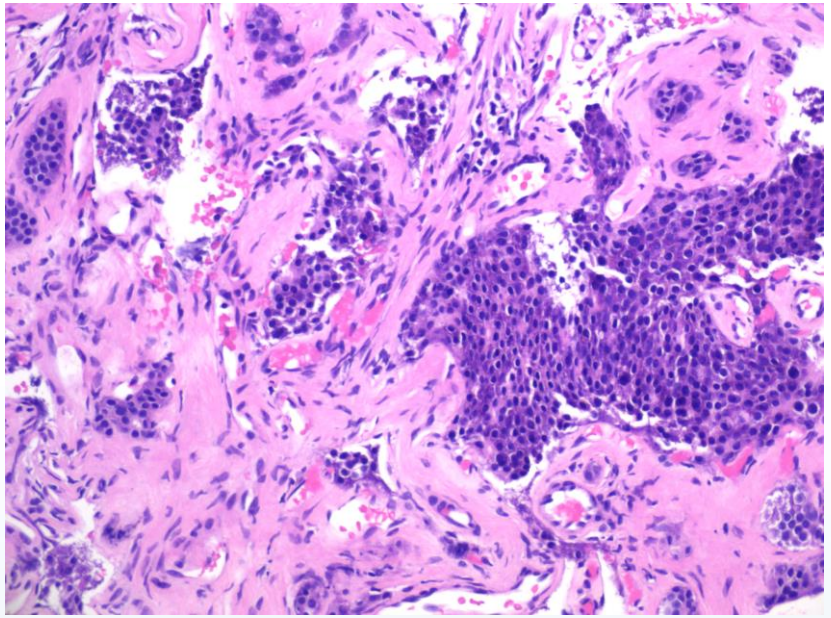


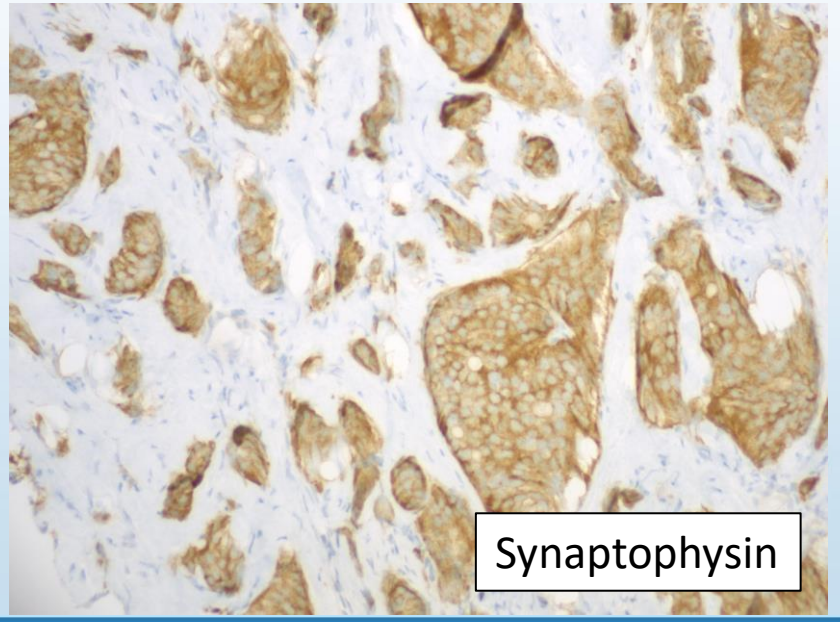
AANP

(Well-differentiated) Neuroendocrine Tumors

- Rare, <5% of neuroendocrine neoplasms in sinonasal region
- Monotonous cells with salt-and-pepper nuclei
- Positive for neuroendocrine markers
- WHO Grade 1
  - <2 mitoses per 2mm^2
  - No necrosis
- WHO Grade 2
  - 2-10 mitoses per 2mm^2

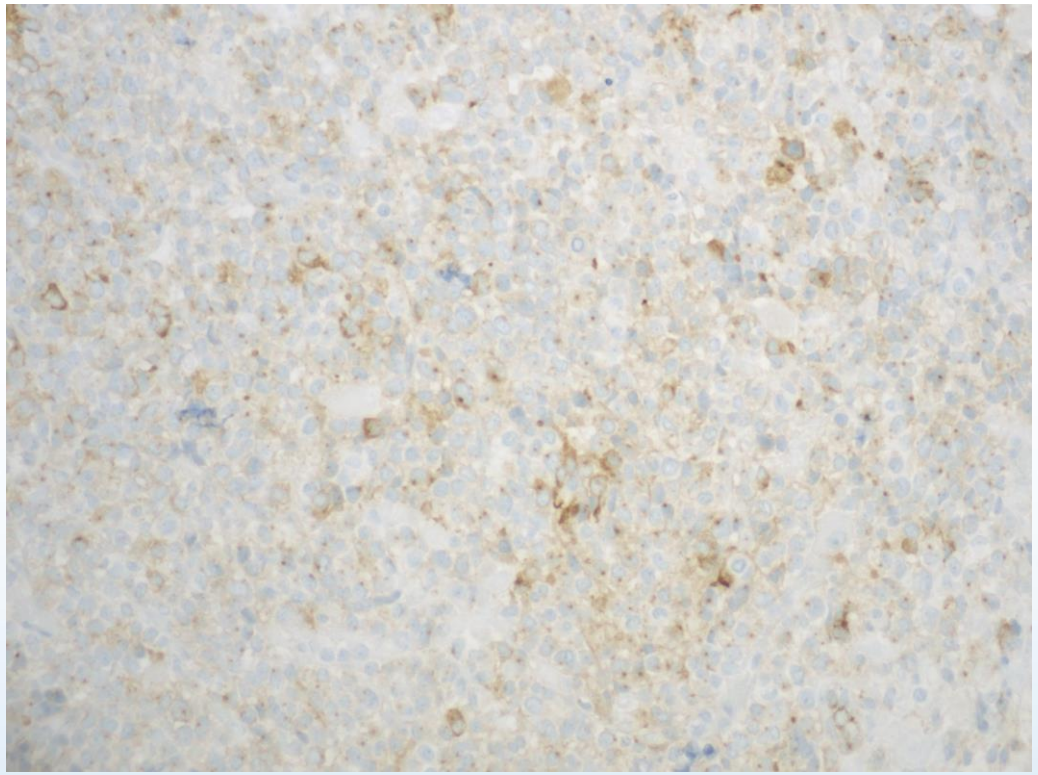
  and/or
  - Necrosis
  - Desirable: Ki-67 proliferation index <20%





Pitfall: Neuroendocrine markers in the sinonasal region

- Neuroendocrine markers are notoriously unreliable in the sinonasal region and can be expressed in non-neuroendocrine tumors, such as
  - Melanoma
  - Rhabdomyosarcoma
  - SWI/SNF-deficient sinonasal carcinomas
  - Teratocarcinosarcoma
  - Sinonasal undifferentiated carcinoma
  - Meningioma

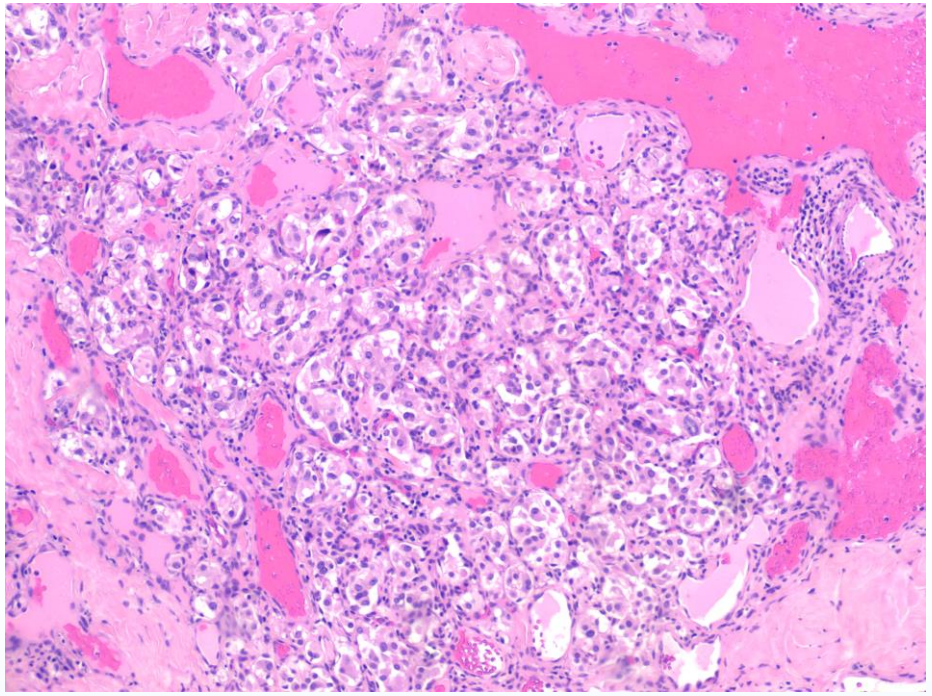


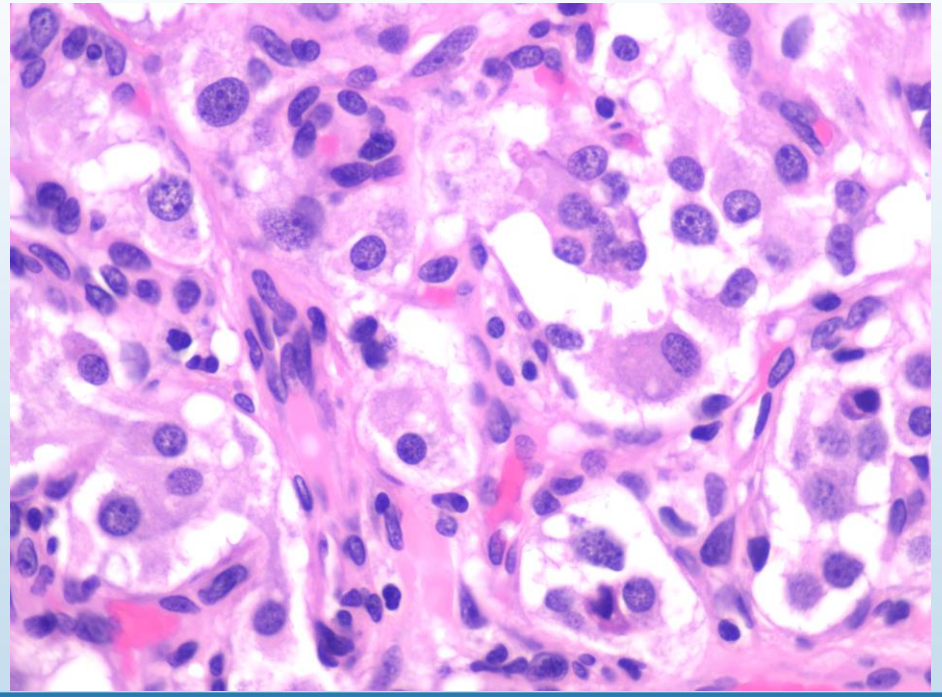
Synaptophysin in a sinonasal alveolar rhabdomyosarcoma

AANP

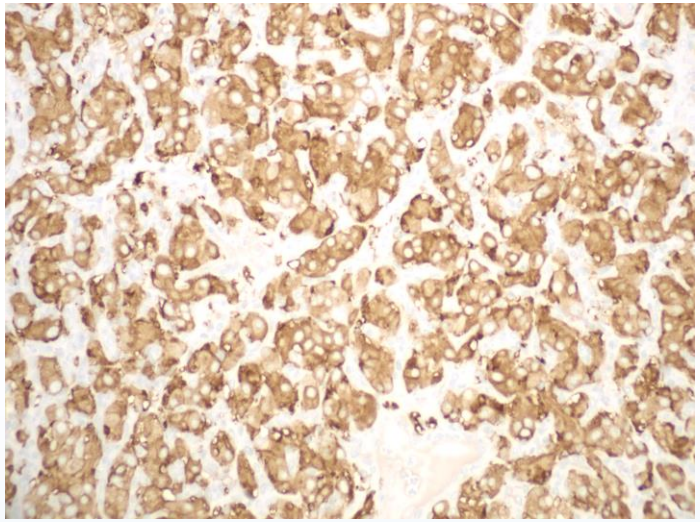
Head and neck paraganglioma

- Tumor of autonomic nervous system paraganglion cells
- Clinical: vagus and glossopharyngeral nerves, carotid body, middle ear, sinonasal tract/skull base
- Histology: Zellballen, nested architecture with peripheral sustentacular cells

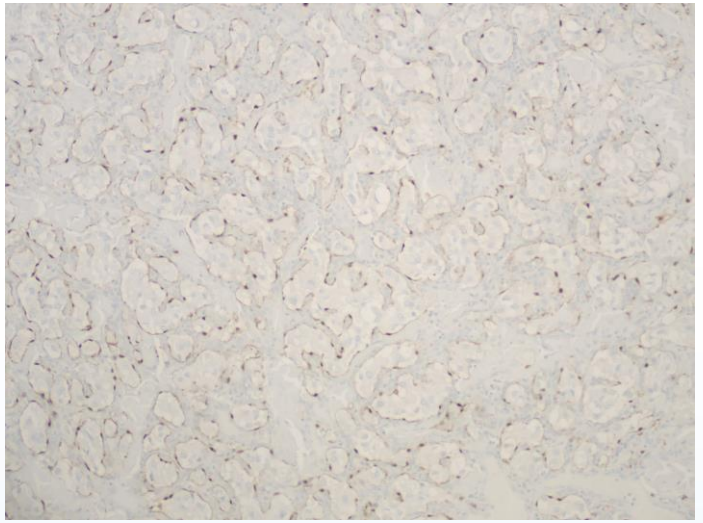




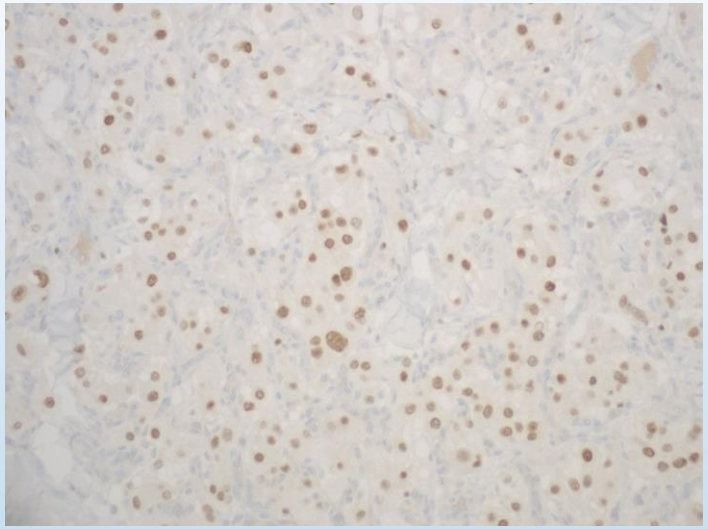
Paraganglioma Immunohistochemistry



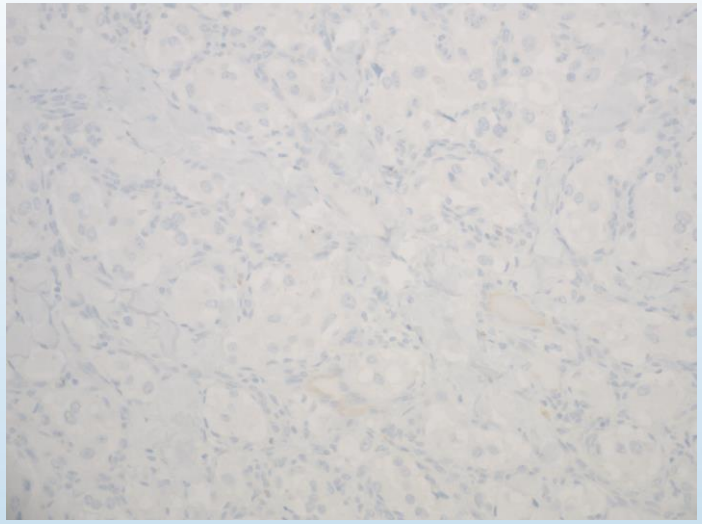
Synaptophysin



S100 (sustentacular pattern)



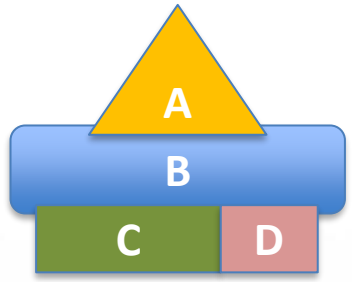
GATA3



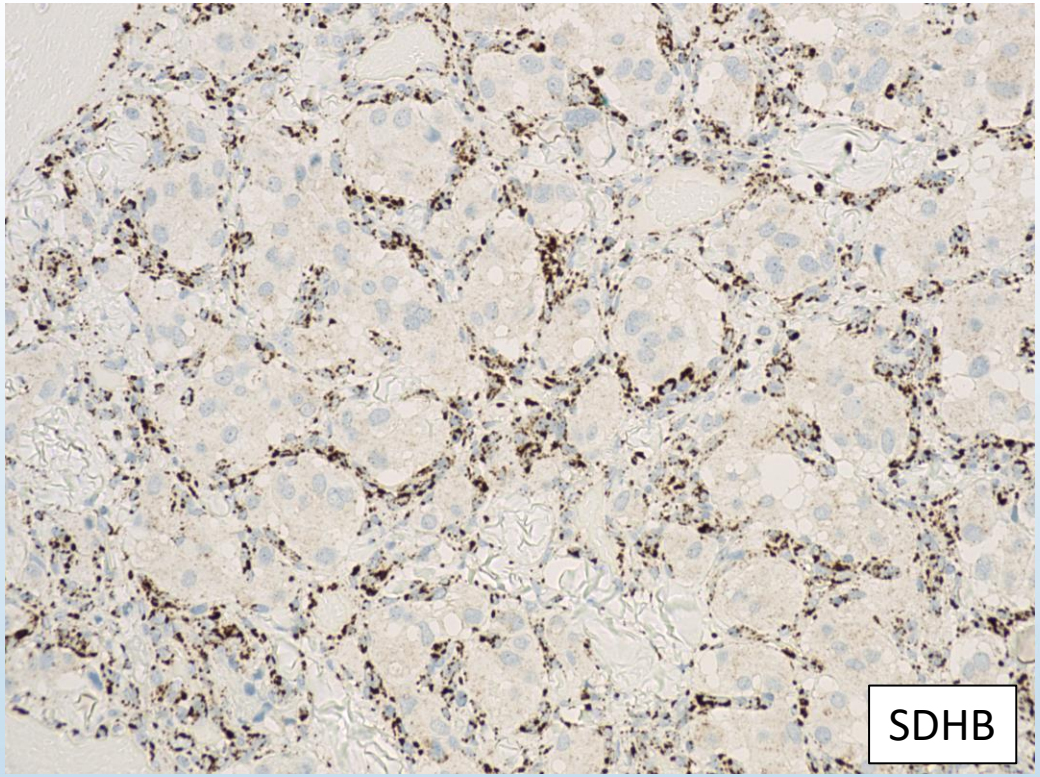
AE1/3

Paraganglioma and the succinate dehydrogenase complex

- 40% of patients with paraganglioma have hereditary predisposition
- Germline mutations most commonly involve *SDHD* (47%), *SDHB* (30%), and *SDHC* (16%)
  - Head and neck paragangliomas less likely to be associated with *VHL, RET,* or *NF1* mutations (Offergeld et al. Clinics. 2012)
- SDHB immunohistochemistry is a helpful screen for *SDH* mutations
- *SDHB* mutations are a risk factor for metastasis



SDH Complex converts succinate to fumerate (Krebs Cycle) and transfers electrons (Electron transfer chain)



CNS WHO Terminology Change: Cauda equina neuroendocrine tumor (previously paraganglioma)

- Tumor of neural crest cells in the cauda equina/filum terminale
- Molecularly distinct from paragangliomas in other sites
- Most are sporadic as opposed to those paragangliomas arising outside the CNS
- Negative for GATA3 (unlike autonomic nervous system paragangliomas)
- Overexpression of HOXB13

Table 3

Summary of histologic and immunohistochemical findings in seventeen CEPs.

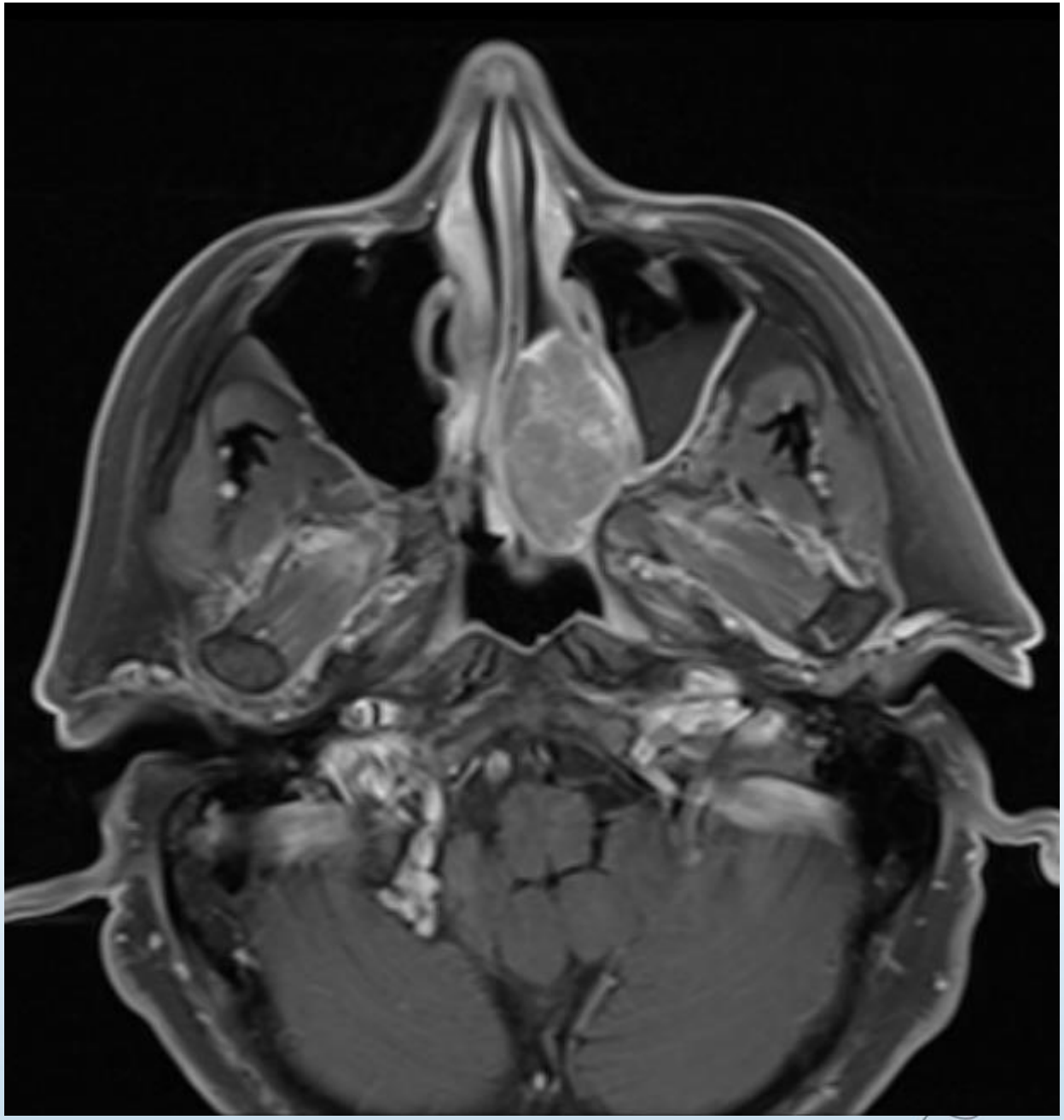
Gangliocytic differentiation	6/17 (35%)
Ganglioneuromatous differentiation	3/17 (17%)
Chromogranin expression	17/17 (100%)
SDHB loss of expression	0/17 (0%)
GATA3 expression	0/17 (0%)
Keratin cocktail positivity	17/17 (100%)
S100 positivity in sustentacular cells	16/17 (94%)

Ramani et al. Acta Neuropathol. 2021

AANP

Olfactory Neuroblastoma

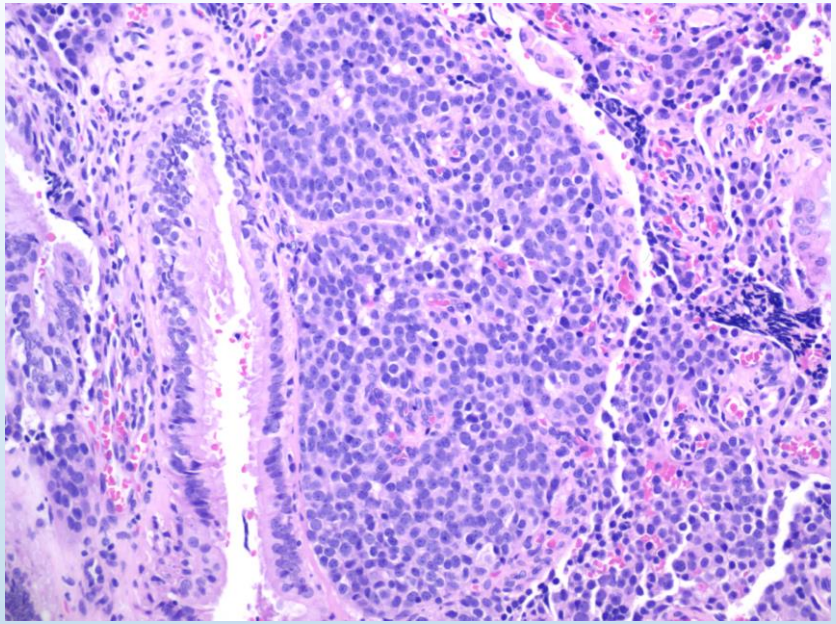
- Malignant tumor of olfactory neuroepithelium
- Clinical: usually adults, cribriform plate, superior turbinate, and superior nasal septum
- Kadish Staging System
  - Nasal cavity alone (A)
  - Extension to paranasal sinuses (B)
  - Extension beyond paranasal sinuses (C)
- Morita Modified Kadish System
  - Tumors with metastases (D)

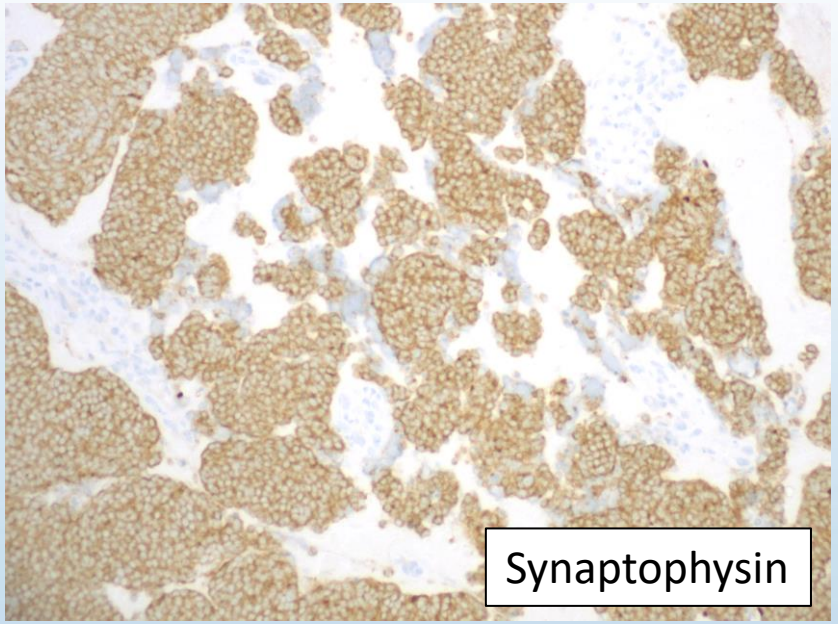


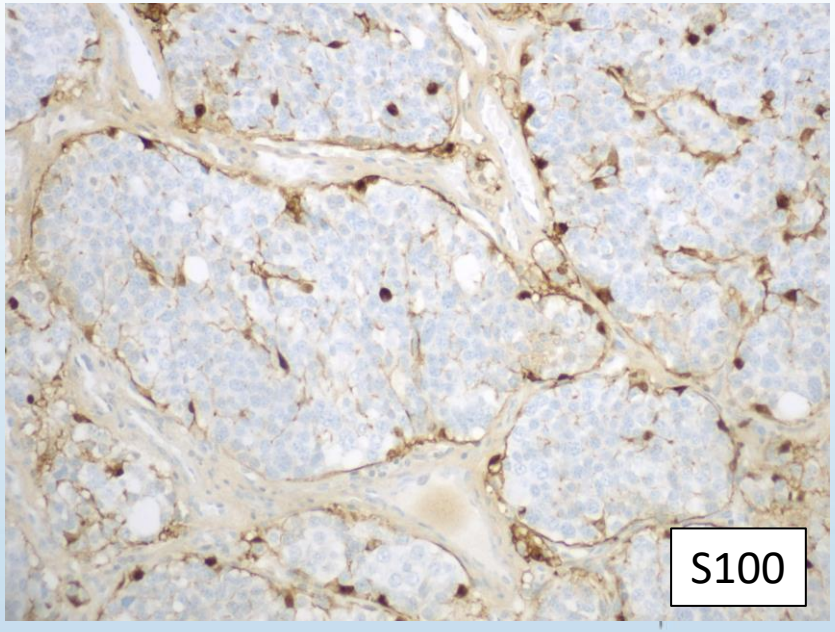
Left expansile nasal mass (MRI T1 post-contrast)

Olfactory Neuroblastoma

- Histology: Lobules of uniform cells with “salt-and-pepper” chromatin and variable fibrillary, neuropil background/matrix
- Positive for neuroendocrine markers (may show focal pancytokeratin)
- S100 highlights a sustentacular pattern

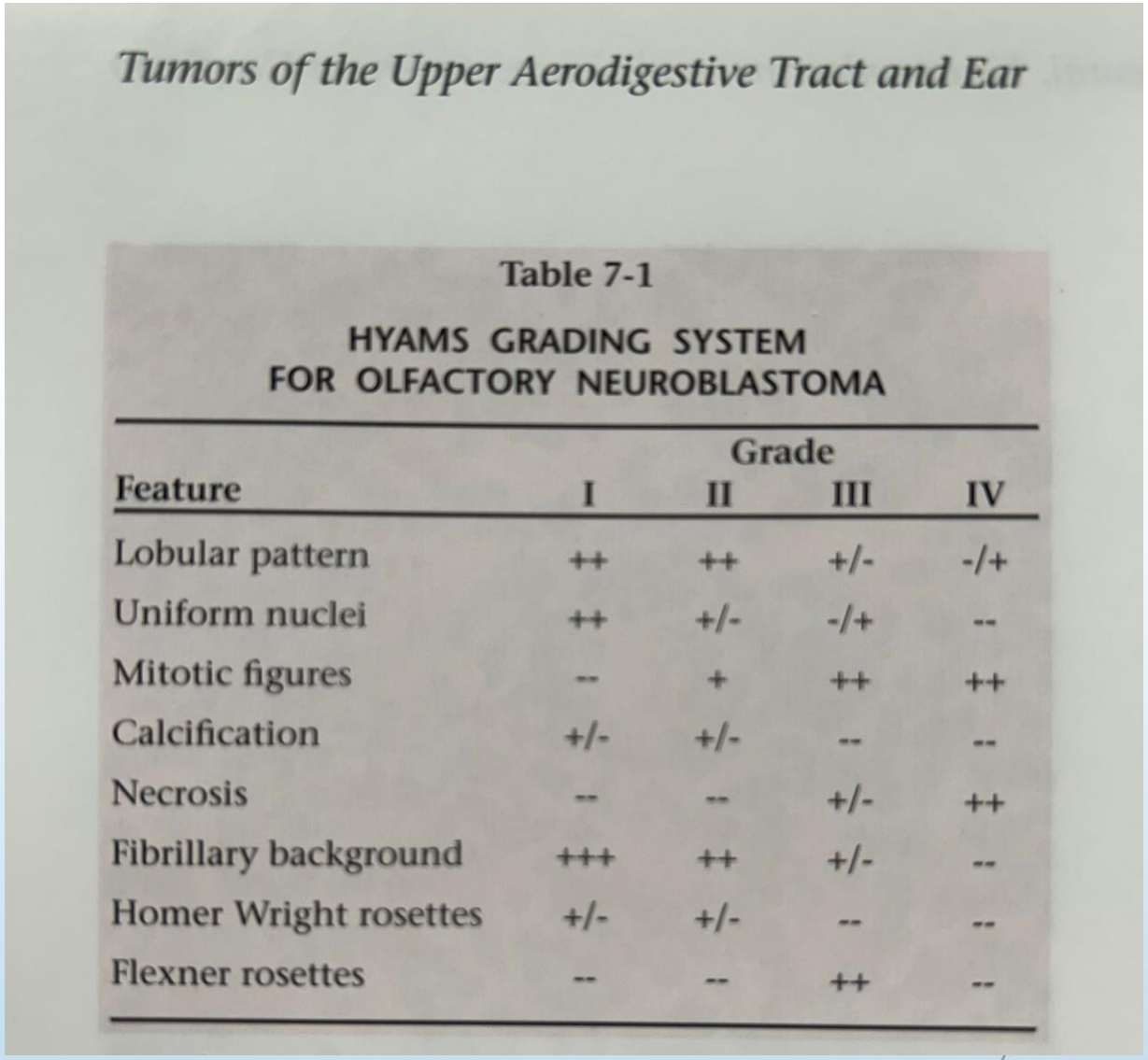






Hyams Grading System

- Hyams grading system (Armed Forces Institute of Pathology, AFIP) is the most widely used system but is subjective
- Most divide into low-grade and high-grade categories using the Hyams system for prognostic purposes
  - High-grade (III/IV) have higher rates of metastases and lower overall survival



Tumors of the Upper Aerodigestive Tract and Ear

Table 7-1

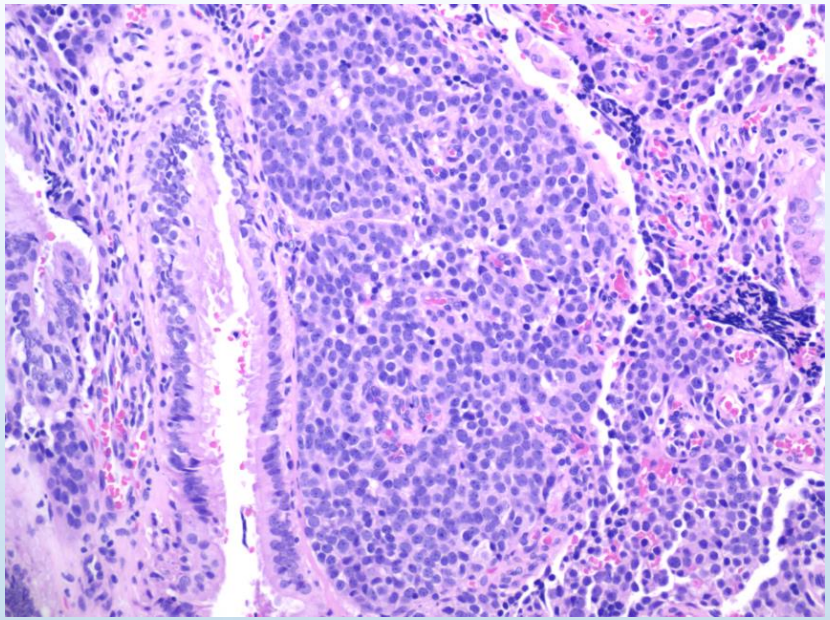
HYAMS GRADING SYSTEM FOR OLFACTORY NEUROBLASTOMA

Feature	Grade I	II	III	IV
Lobular pattern	++	++	+/-	-/+
Uniform nuclei	++	+/-	-/+	--
Mitotic figures	--	+	++	++
Calcification	+/-	+/-	--	--
Necrosis	--	--	+/-	++
Fibrillary background	+++	++	+/-	--
Homer Wright rosettes	+/-	+/-	--	--
Flexner rosettes	--	--	++	--

Mills. Tumors of the Upper Aerodigestive Tract and Ear. AFIP. 2012

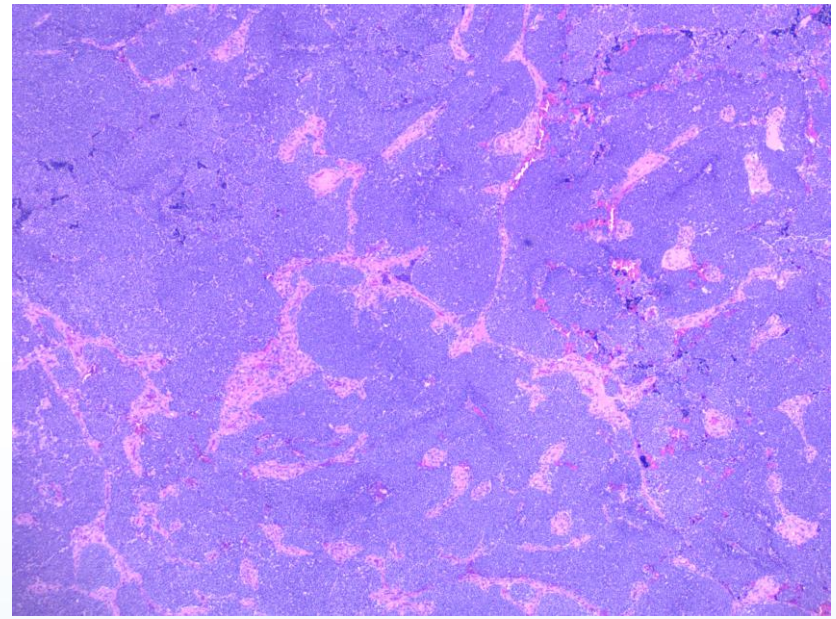
Low-Grade (Hyams I/II)

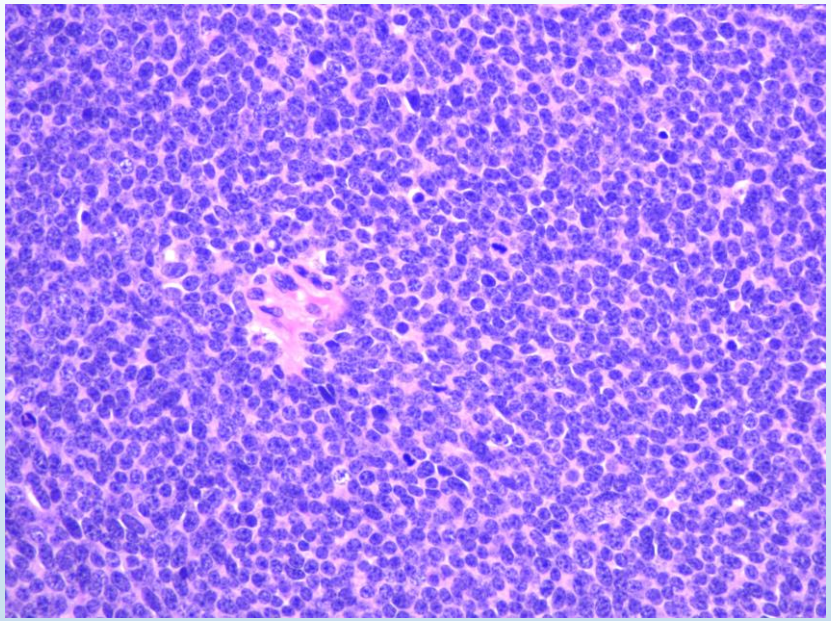
- Lobular pattern retained
- Zero-to-limited mitoses
- Lacks nuclear pleomorphism
- No necrosis

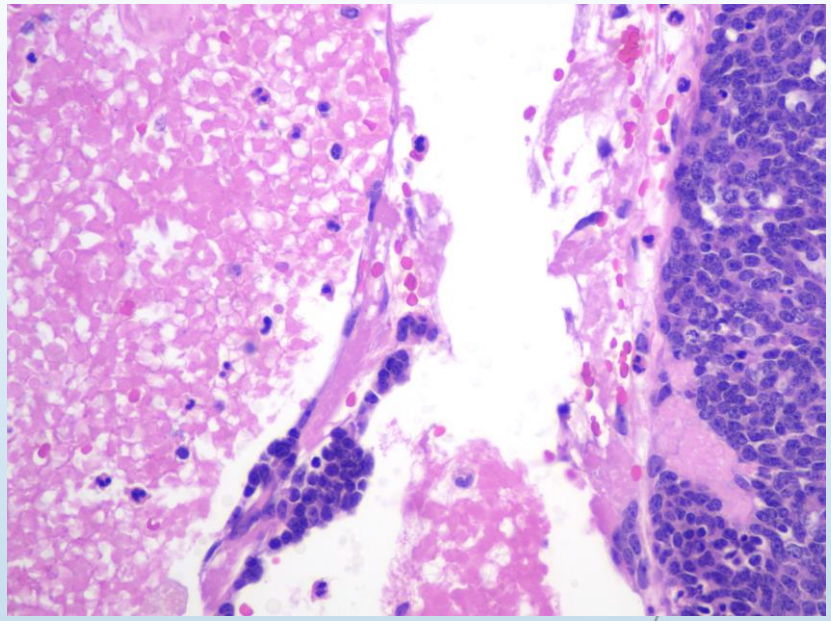


High-grade (Hyams III/IV)

- Loss of lobular pattern
- Increased mitoses
- Nuclear pleomorphism
- Necrosis



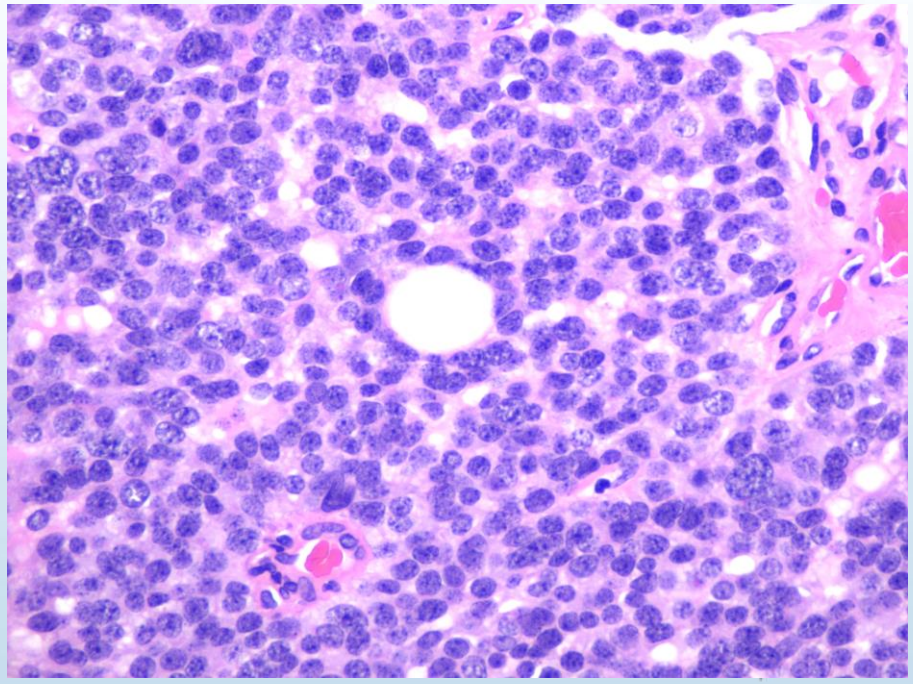




Pitfall: Rosettes in Olfactory Neuroblastoma Grading

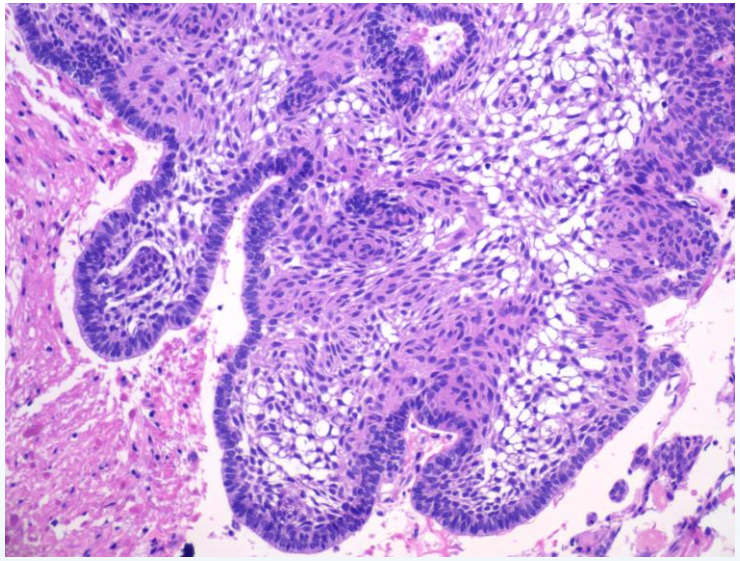
- Homer Wright rosettes with neuropil centers can be seen in low-grade examples of olfactory neuroblastomas
- Flexner-Wintersteiner rosettes with central lumens are listed as a feature seen in grade III olfactory neuroblastomas
- However, olfactory neuroblastomas can have glandular differentiation and other changes that mimic rosettes
- Exercise caution in using this feature for grading

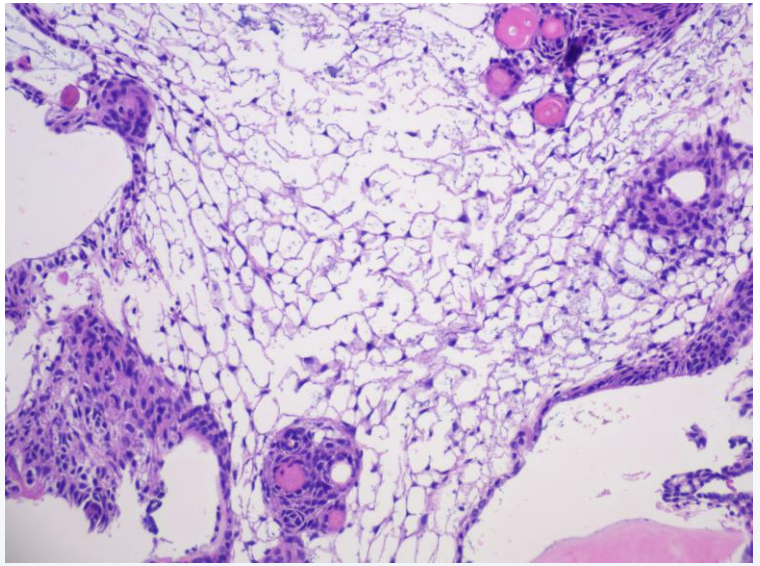
This mimic, seen in olfactory neuroblastoma, lacks the extending cytoplasmic processes of Flexner-Wintersteiner rosettes

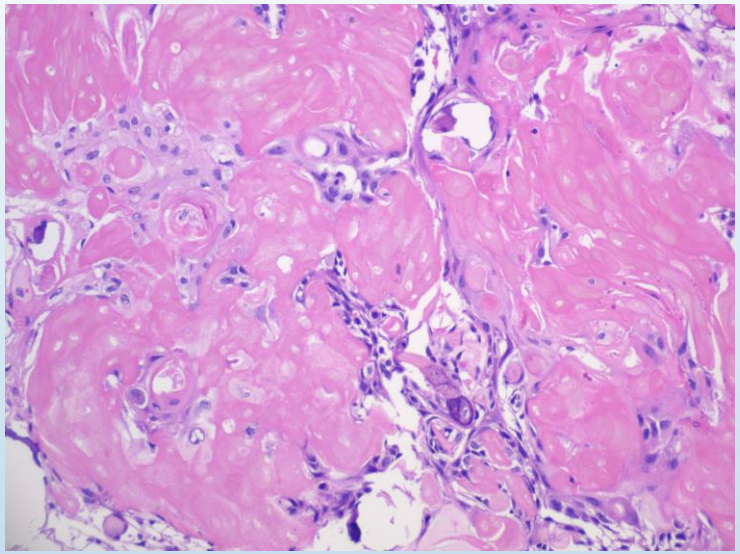


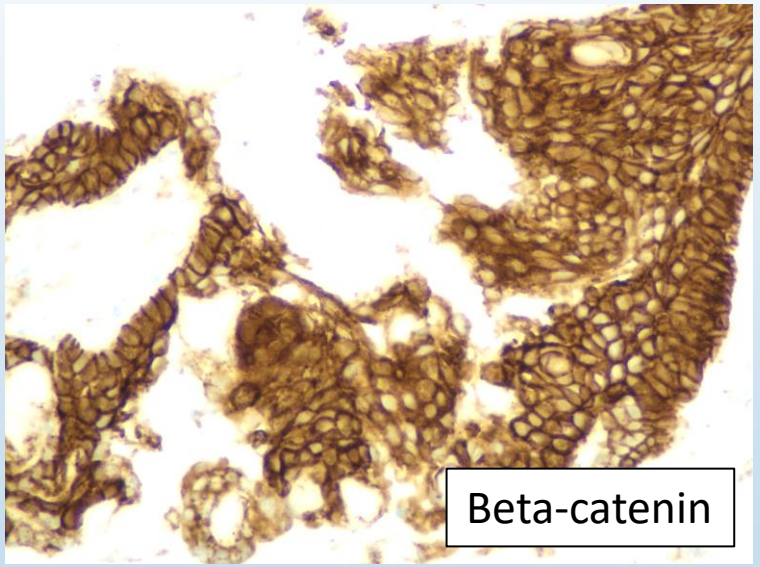
Adamantinomatous Craniopharyngioma

- Thought to arise from Rathke pouch remnants
- Clinical: bimodal distribution in children and adults
- Imaging: Solid and cystic sellar/suprasellar mass
- Gross: “machine” or “motor” oil cyst fluid
- Histology: peripheral palisading nuclei, stellate reticulum, and “wet keratin,” or “ghost cells”
- IHC: Nuclear beta catenin due to *CTNNB1* mutations in exon 3



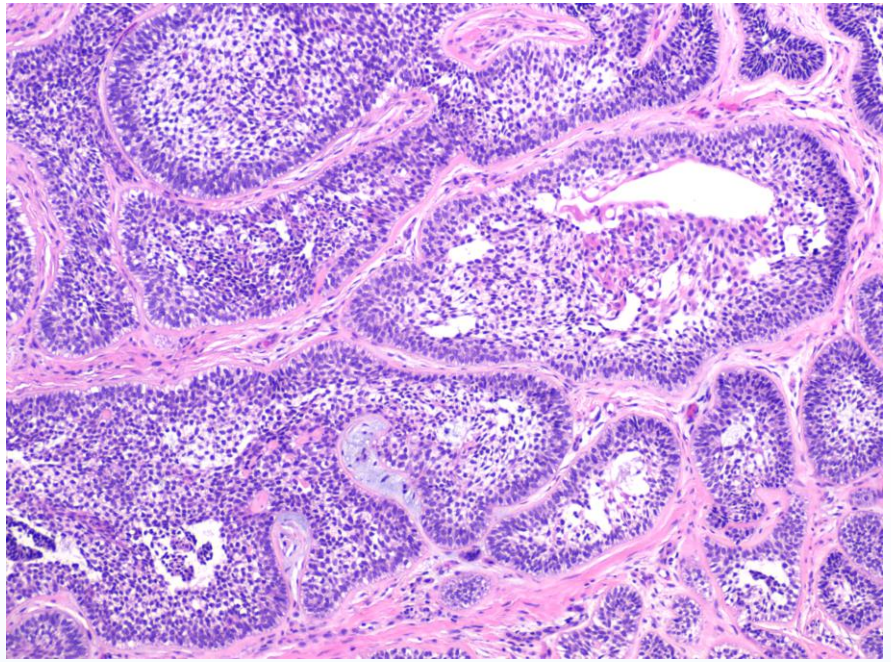


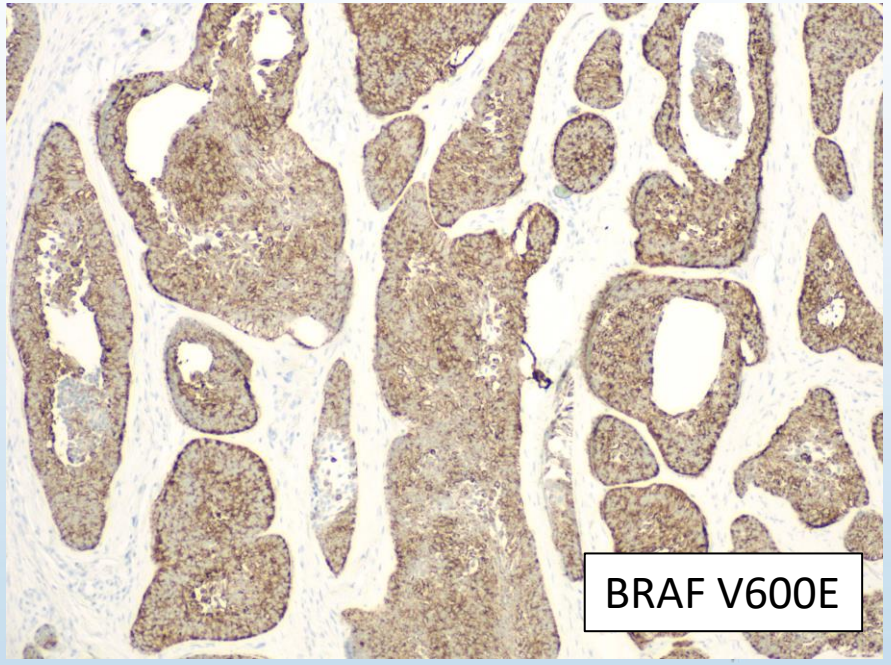




Sinonasal Ameloblastoma

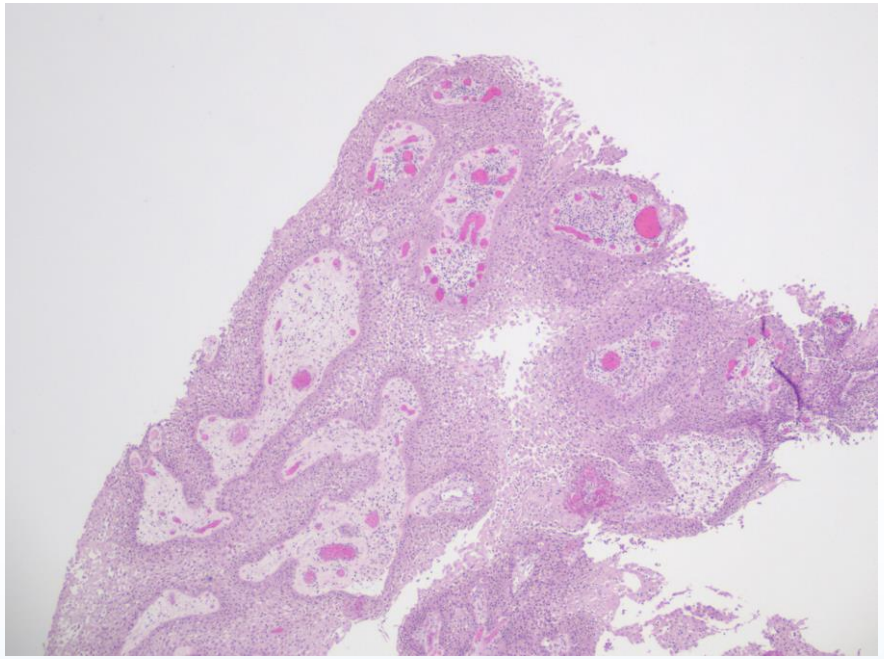
- Odontogenic tumor that can rarely arise in the sinonasal tract, including the paranasal sinuses
- Clinical: very rare, usually men
- Imaging: solid appearance
- Histology: peripherally palisading cells with reverse polarity and stellate reticulum
- Molecular: *BRAF* (including p.V600E) and *RAS* mutations (conventional, odontogenic examples

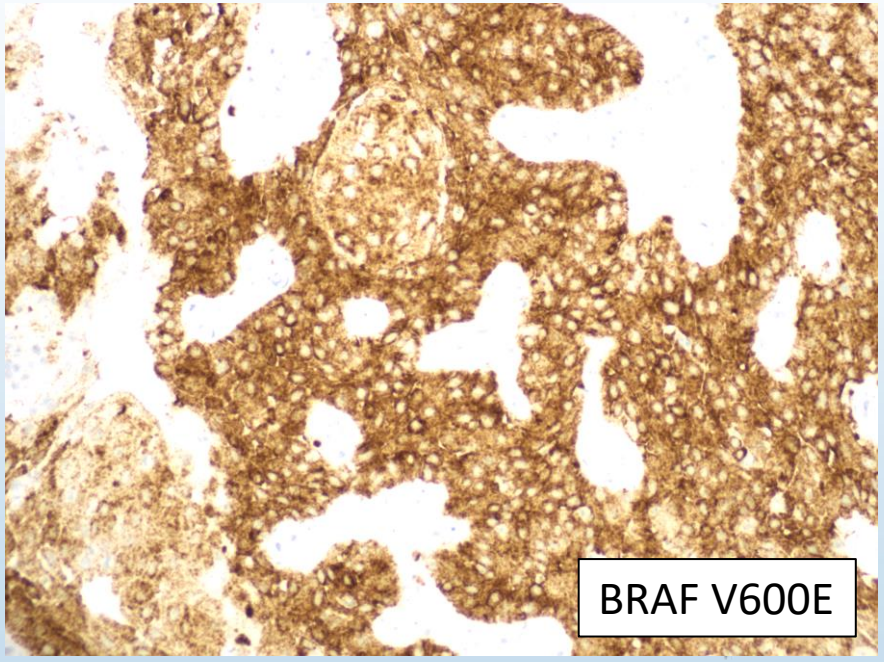




Papillary Craniopharyngioma

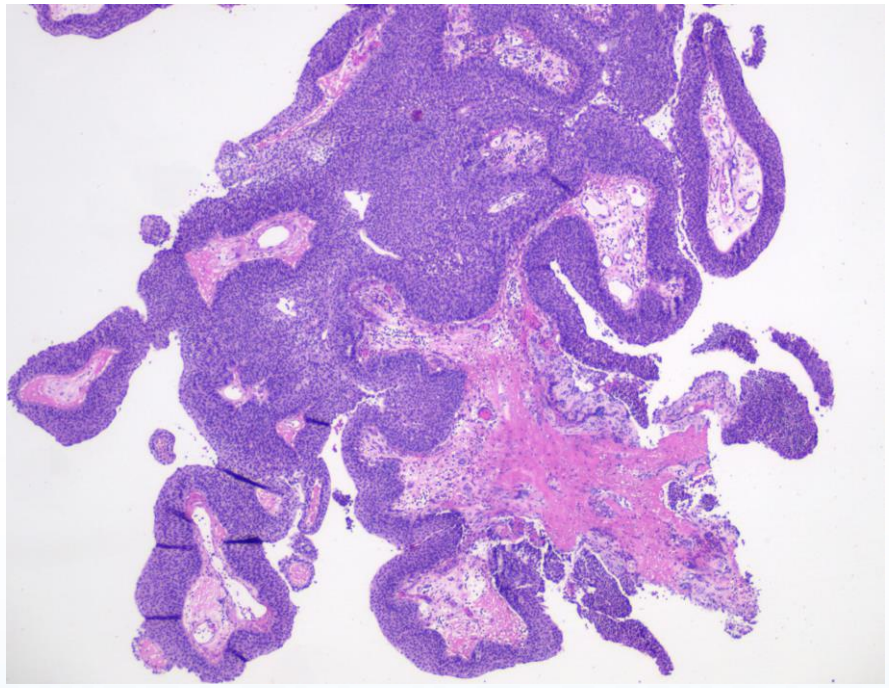
- Thought to arise from Rathke pouch remnants
- Clinical: Adults (less common than adamantinomatous craniopharyngiomas)
- Imaging: more solid, cauliflower-like characteristics
- Histology: bland, non-keratinizing squamous epithelium and fibrovascular cores
- Molecular: *BRAF* p.V600E mutations

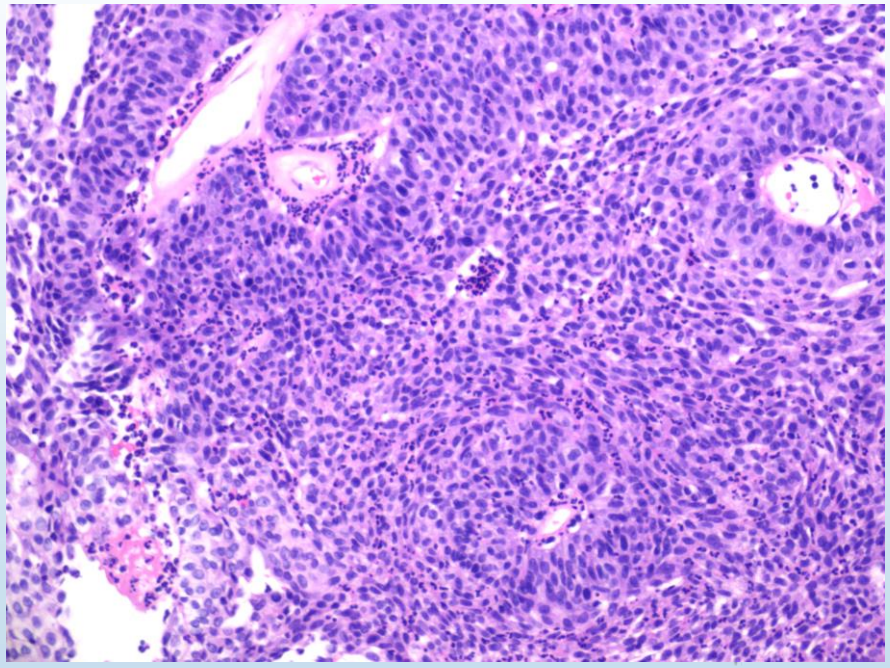




DEK::AFF2 squamous cell carcinoma

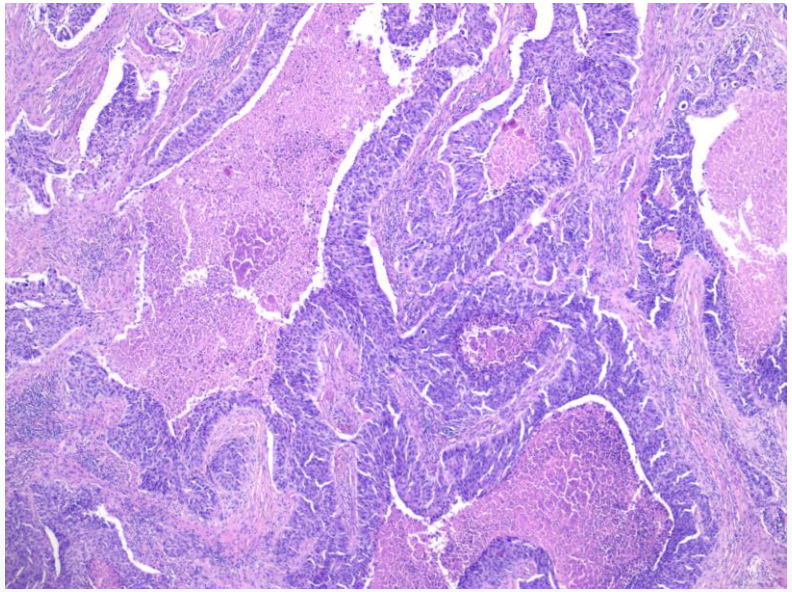
- Subset of non-keratinizing squamous cell carcinoma with *DEK::AFF2* fusions
- Clinical: Adults
- Locations: sinonasal tract, middle ear, temporal bone, nasopharynx, orbit
- Exophytic and endophytic growth and papillary formation, can resemble an inverted sinonasal papilloma/carcinoma
- Cells tend toward the monotonous and bland
- Tumor-infiltrating neutrophils are a common finding
- Prognosis: frequent local recurrence (limited data)

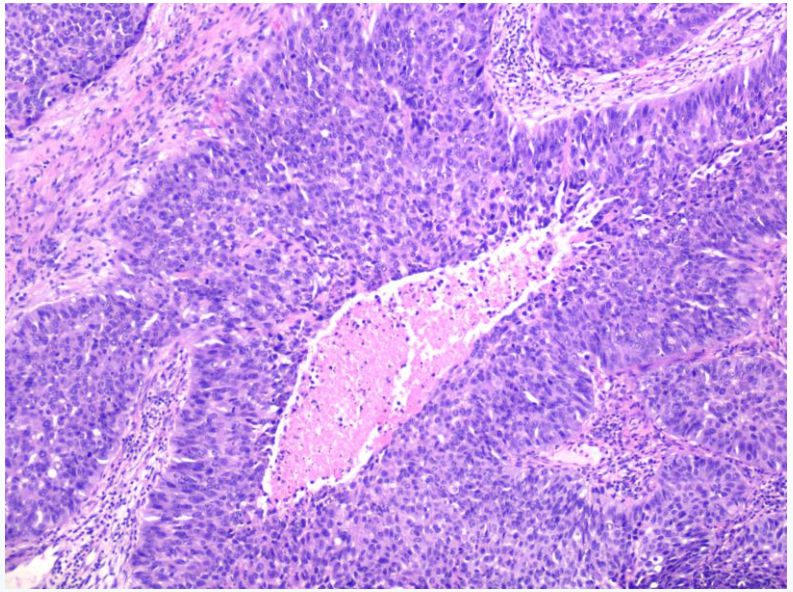


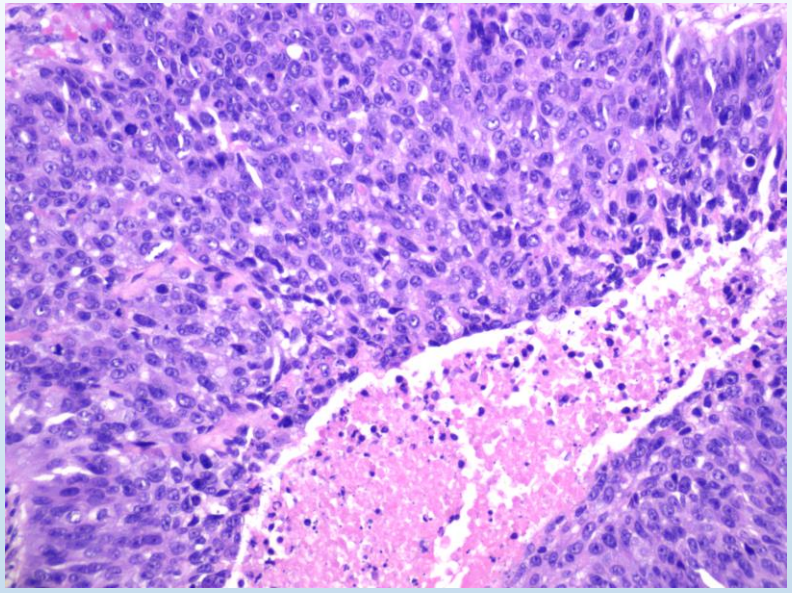


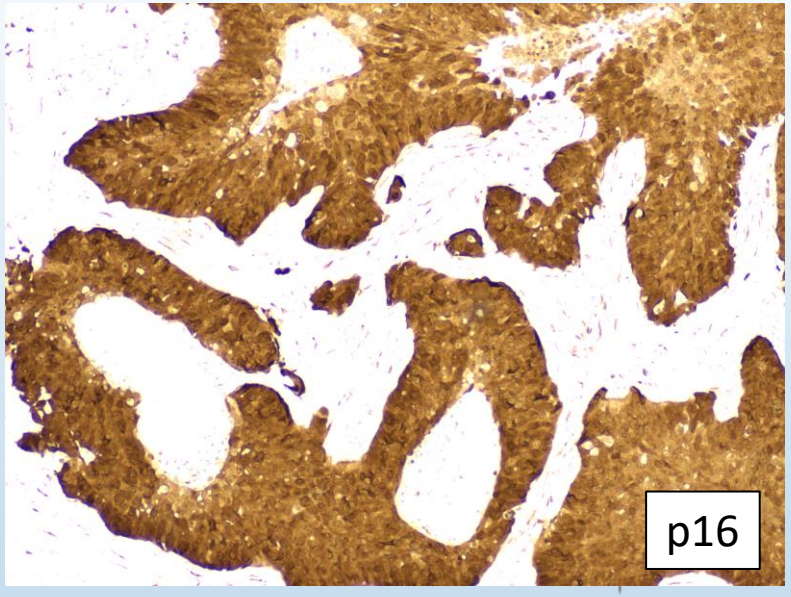
Non-keratinizing Squamous Cell Carcinoma of the Sinonasal Tract and Skull Base

- High-risk human papillomavirus implicated in 41-82% of cases
- Often a more aggressive appearance than those harboring *DEK::AFF2* fusions
  - Increased mitoses, necrosis, cytologic atypia)
- Strong and diffuse p16 immunohistochemistry needs to be confirmed with high-risk HPV RNA in situ hybridization
- Uncertain whether HPV status is clinically significant for prognosis, treatment, or follow-up









Pitfall: Exclusion of Histologic Mimics is Essential to a Diagnosis of Non-keratinizing Squamous Cell Carcinoma of the Sinonasal Tract and Skull Base

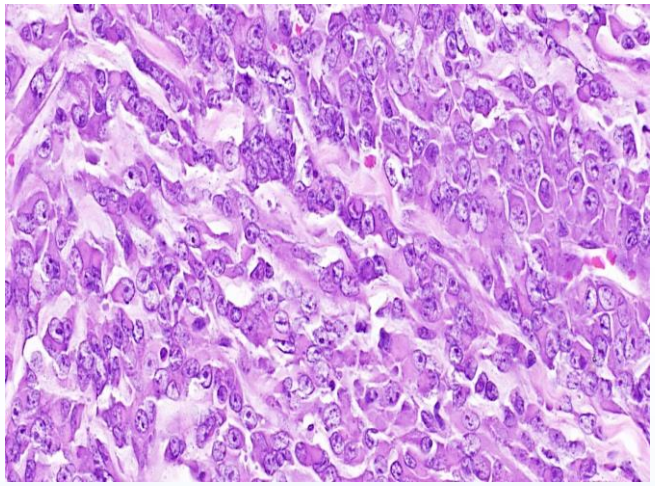
- SWI/SNF complex-deficient sinonasal carcinoma
- NUT carcinoma
- Adamantinoma-like Ewing sarcoma
- Other epithelioid neoplasms

SWI/SNF Complex-Deficient Sinonasal Carcinoma

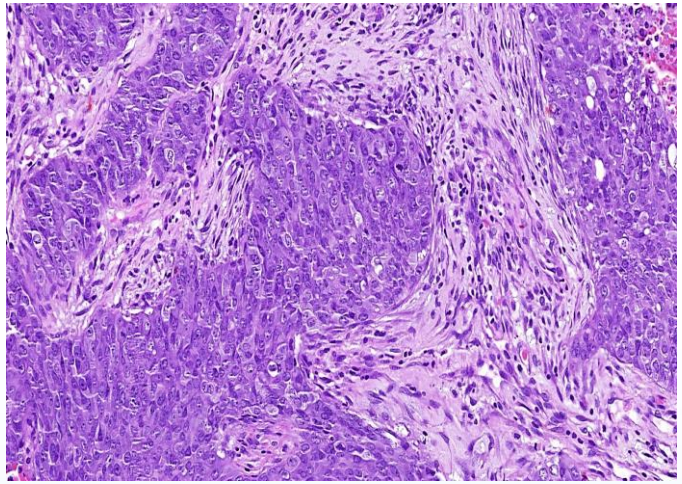
- Sinonasal carcinoma with either *SMARCB1* or *SMARCA4* alterations
- Clinical: Adults, predominantly males, often present with advanced disease
- Behavior: Highly aggressive (>50% mortality in 2 years)

Histology: SWI/SNF complex-deficient sinonasal carcinoma

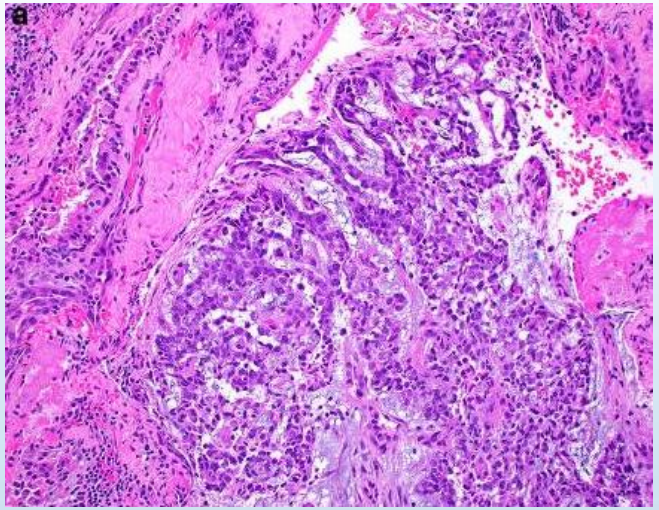
SMARCB1-deficient carcinoma

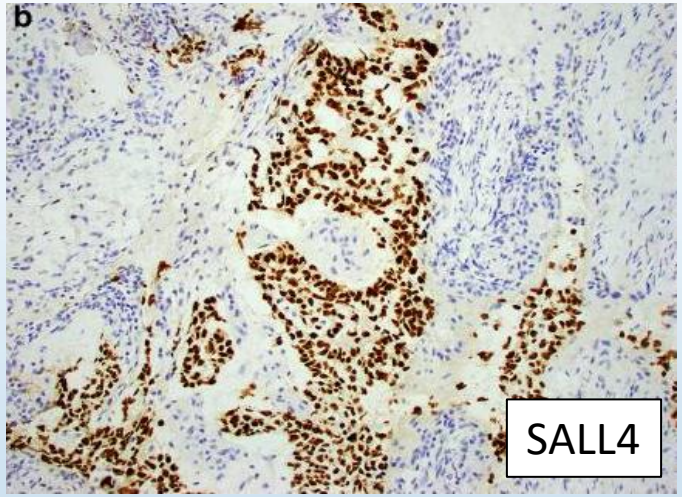


Pink, plasmacytoid, rhabdoid



Blue, basaloid

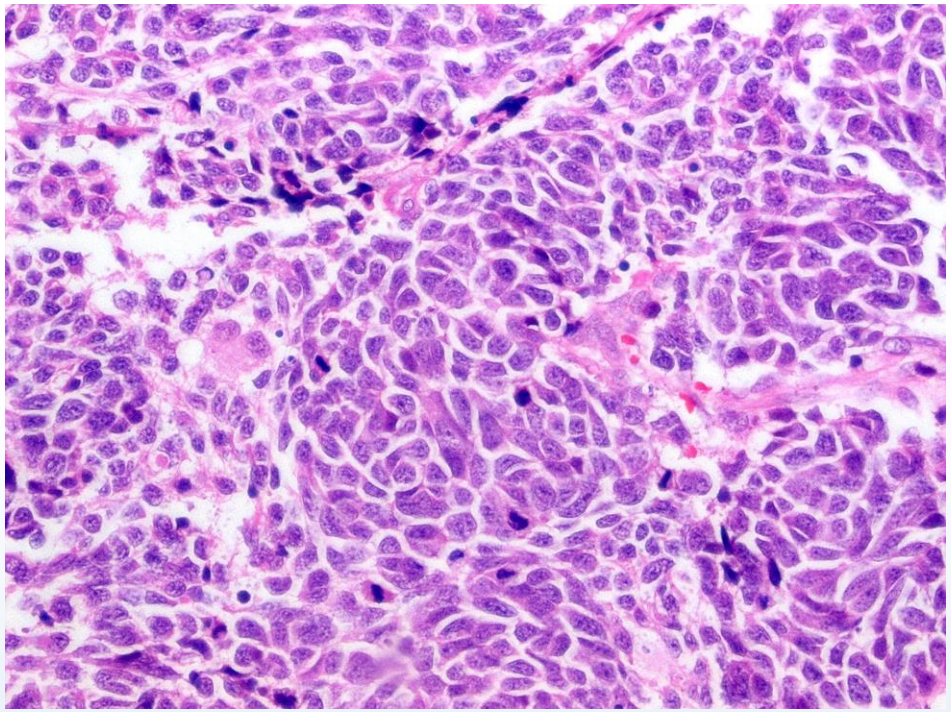




Adenocarcinoma, including yolk sac tumor-like with SALL4 and glypican-3 positivity

Shah. Head Neck Pathol. 2020

SMARCA4-deficient carcinoma

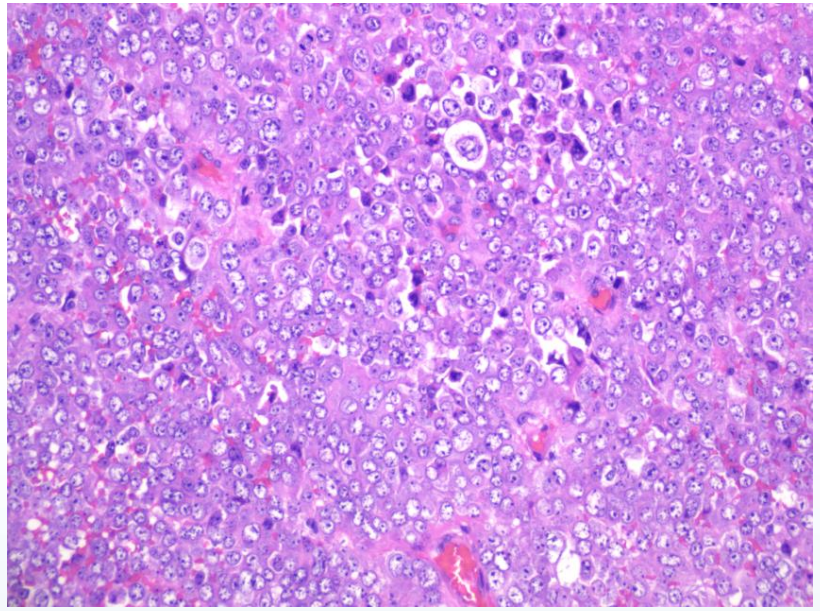


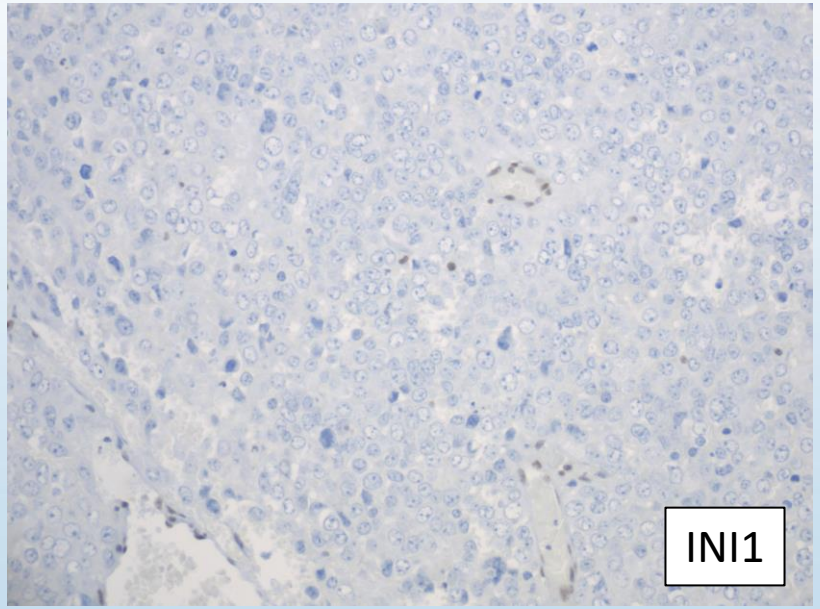
Greater anaplasia, tend toward undifferentiated and neuroendocrine-like appearance

WHO. Head and Neck Tumours. 5th Ed.

Immunohistochemistry: SWI/SNF Complex-Deficient Sinonasal Carcinoma

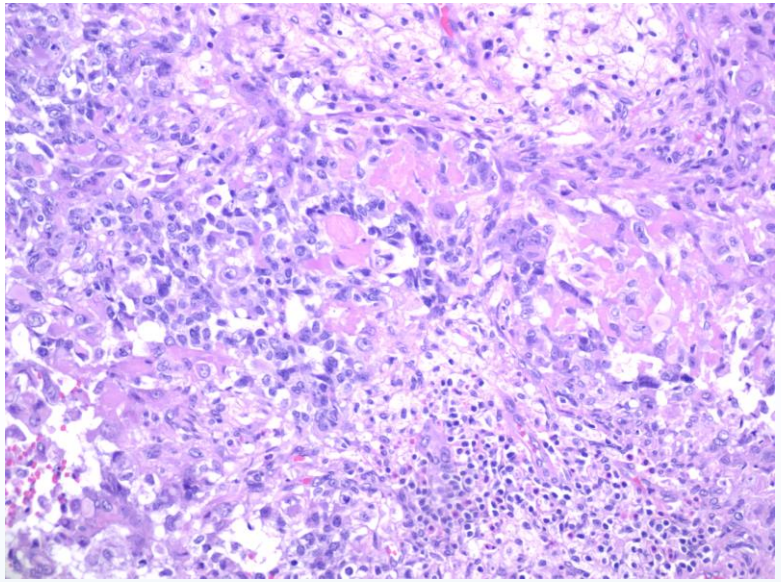
- *SMARCB1*-deficient sinonasal carcinoma
  - Positive: pancytokeratin, CK7, variable p63 and p40
  - INI1 loss
- *SMARCA4*-deficient sinonasal carcinoma
  - Positive: pancytokeratin, focal synaptophysin
  - Negative: CK5, p63, and p40
  - BRG1 loss

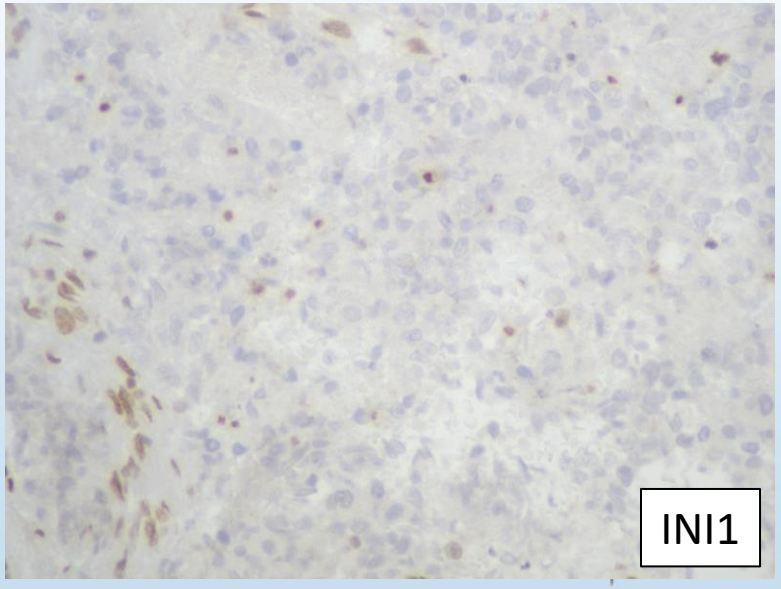




Sellar Region Atypical Teratoid/Rhabdoid Tumors (AT/RT)

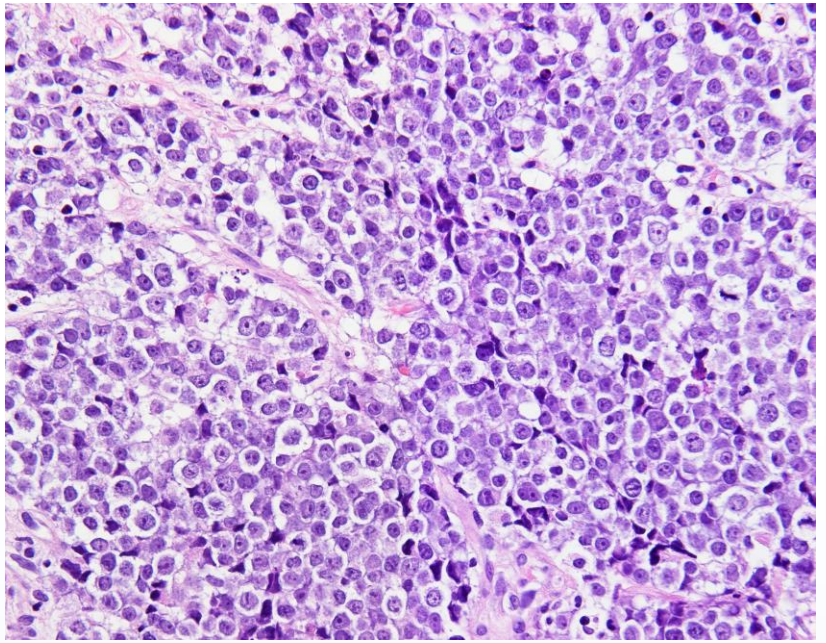
- AT/RTs are malignant, embryonal neoplasms with inactivation of *SMARCB1* (rarely *SMARCA4*)
- Sellar examples occur in adults with a female predominance
- Though clinically distinct, methylation profiling clusters sellar region AT/RTs as ATRT-MYC and not a distinct epigenetic group (Johann et al. Am J Surg Pathol. 2018).

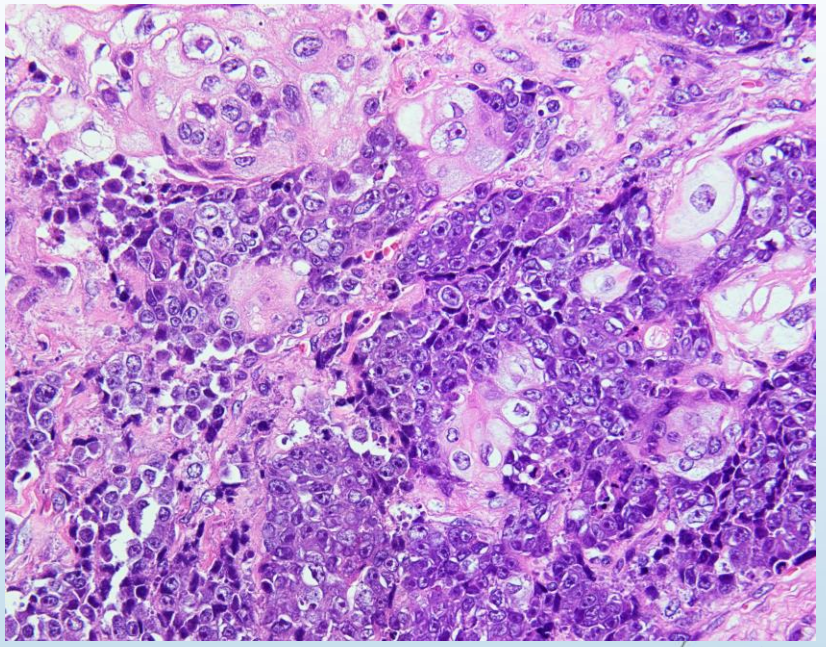




NUT Carcinoma

- Carcinoma with *Nuclear Protein in Testis* (*NUTM1*) gene rearrangements
- Sinonasal tract accounts for most head and neck examples, rarely orbit
- Clinical: young adults, rapidly enlarging mass
- Histology: monotonously malignant undifferentiated cells, may encounter “abrupt keratinization” (bottom panel)
- Immunohistochemistry: NUT antibody, cytokeratins, p63, may express CD34 (possible pitfall)

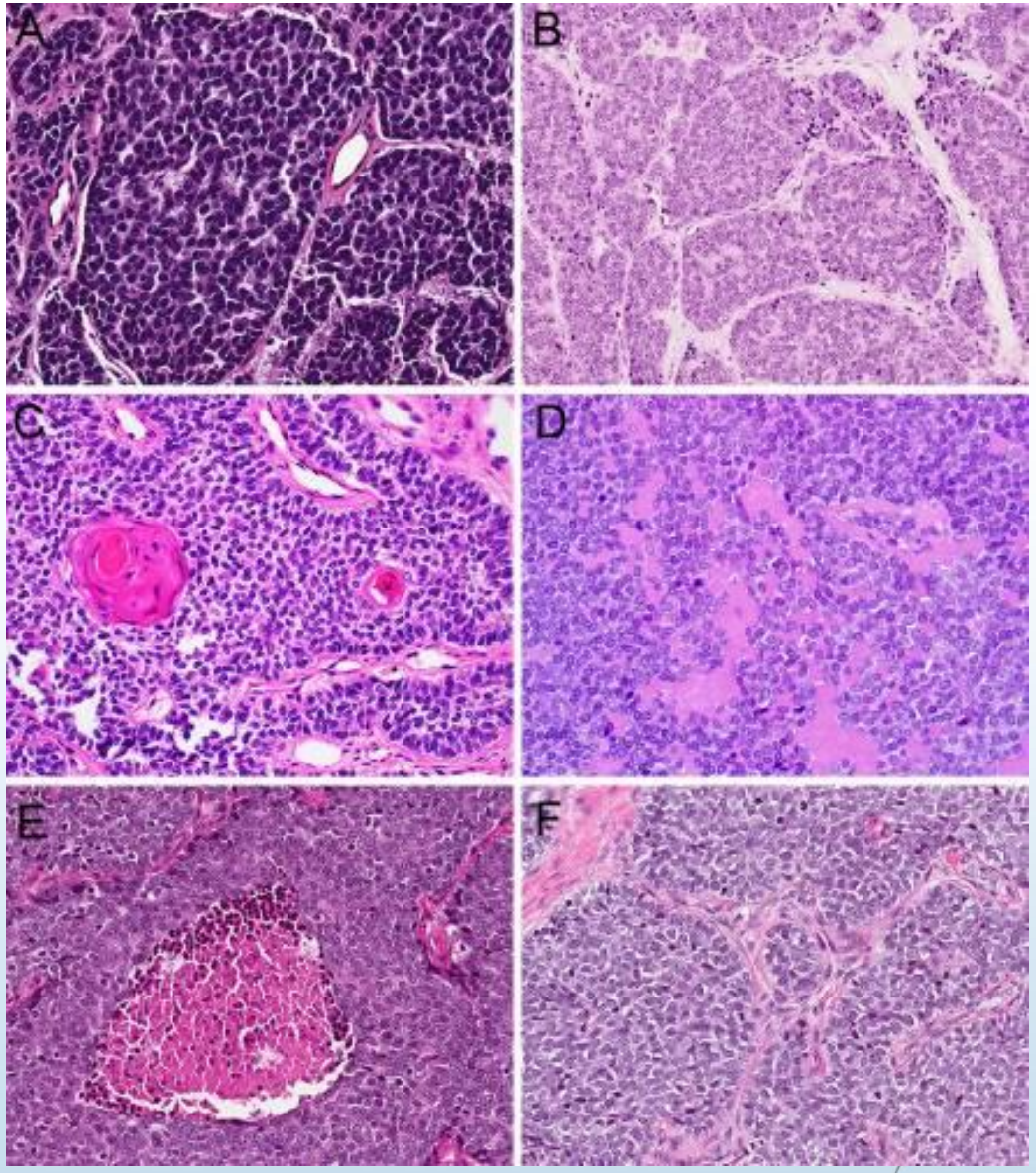




WHO. Head and Neck Tumours. 5th Ed.

Adamantinoma-like Ewing Sarcoma

- Rare Ewing sarcoma variant with cytokeratin and p40 positivity
- Sites include sinonasal tract and orbit
- Clinical: young-to-middle aged adults, generally presenting with a large, destructive tumor
- Histology: Infiltrating basaloid cells with myxoid-to-fibrous stroma
  - Additional features include rosette formation and keratinization
- Immunohistochemistry:
  - Positive: AE1/3, p63, p40, strong, membranous CD99, variable neuroendocrine markers, p16 (subset)
  - Negative S100, desmin, NUT, high-risk HPV
  - Molecular: t(11;22) *EWSR1::FLI1* rearrangement



Rooper. Head Neck Pathol. 2020

Teratocarcinosarcoma

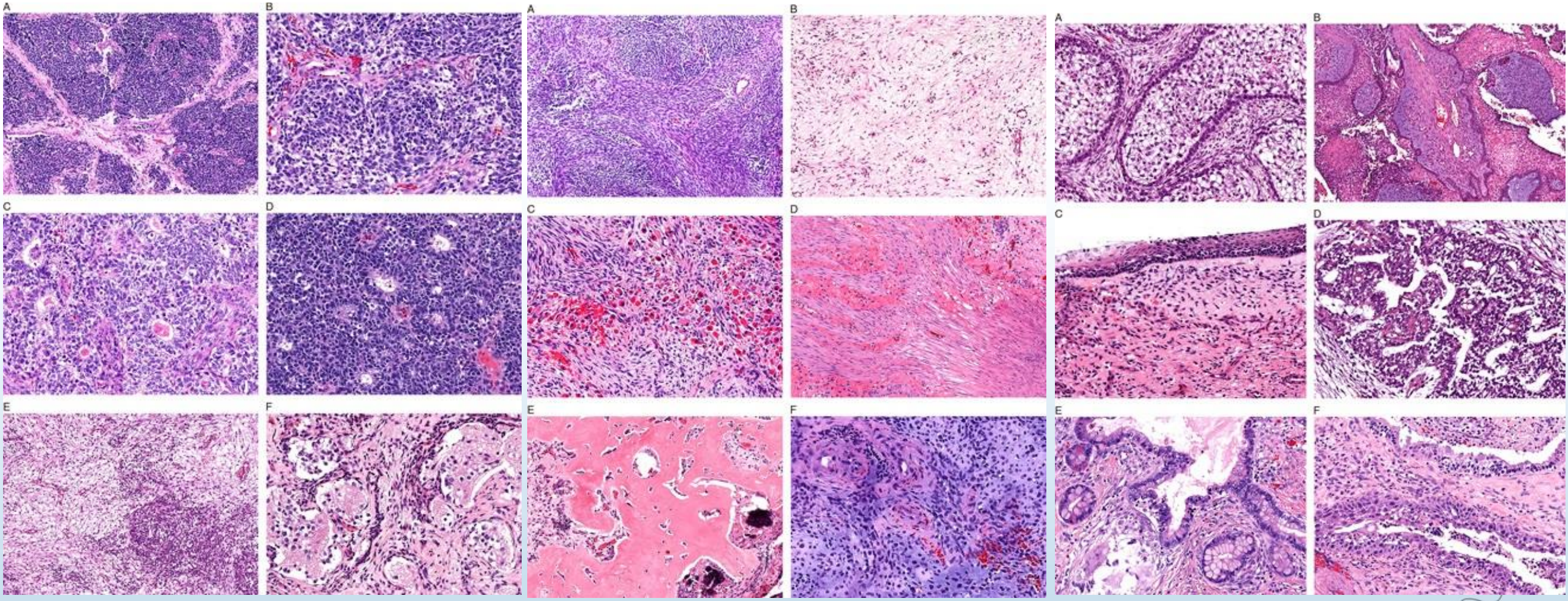
- Malignant neoplasm with epithelial, mesenchymal, and primitive neuroepithelial elements
- Sites include the sinonasal tract, orbit, skull base, cribriform plate, nasopharynx, and anterior cranial fossa
- Clinical: adults with a male predilection
- Immunohistochemistry: mirrors histologic elements
- Molecular alterations:
  - *SMARCA4* mutations (BRG1 loss)
  - *CTNNB1* mutations (nuclear beta-catenin in subset, usually in epithelial component)

Teratocarcinosarcoma Histology (Rooper et al. 2023)

Neuroepithelial elements, including neurofibrillary stroma and ganglion-like cells (E-F)

Mesenchymal elements

Epithelial elements



Rooper et al. Am J Surg Pathol. 2023

Other mimics

Sinonasal rhabdomyosarcoma

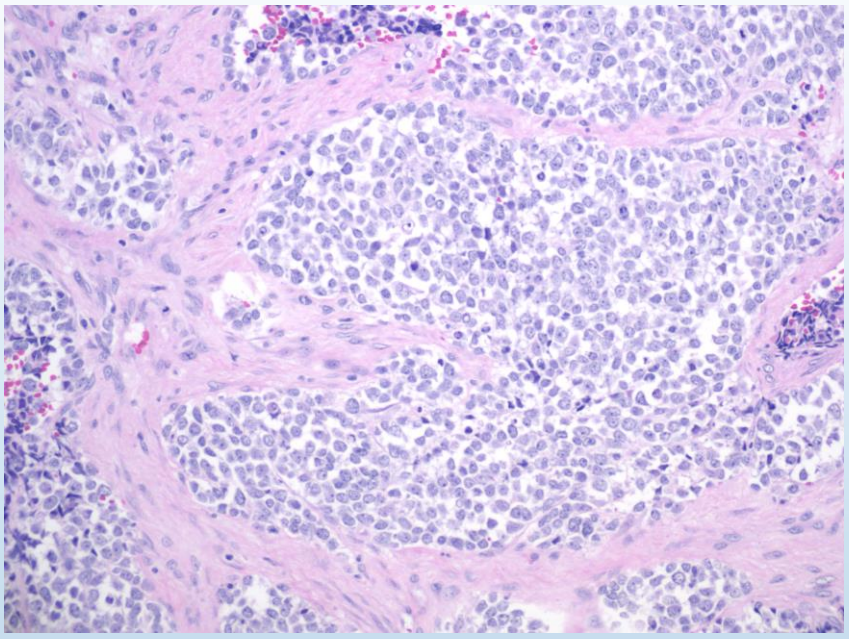
- Most common sinonasal sarcoma
- Sites: orbit, ear and temporal bone, sinonasal tract
- IHC: desmin and myogenin

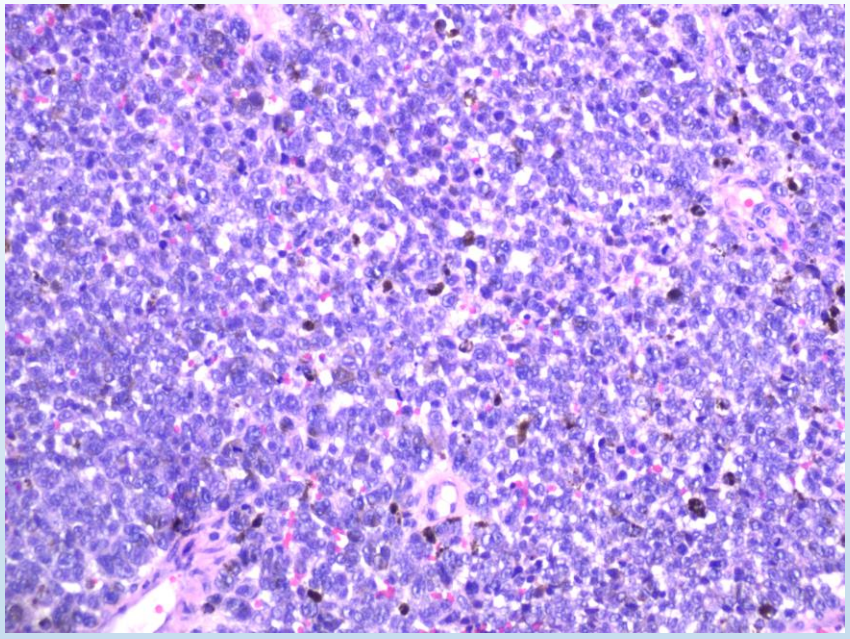
Sinonasal mucosal melanoma

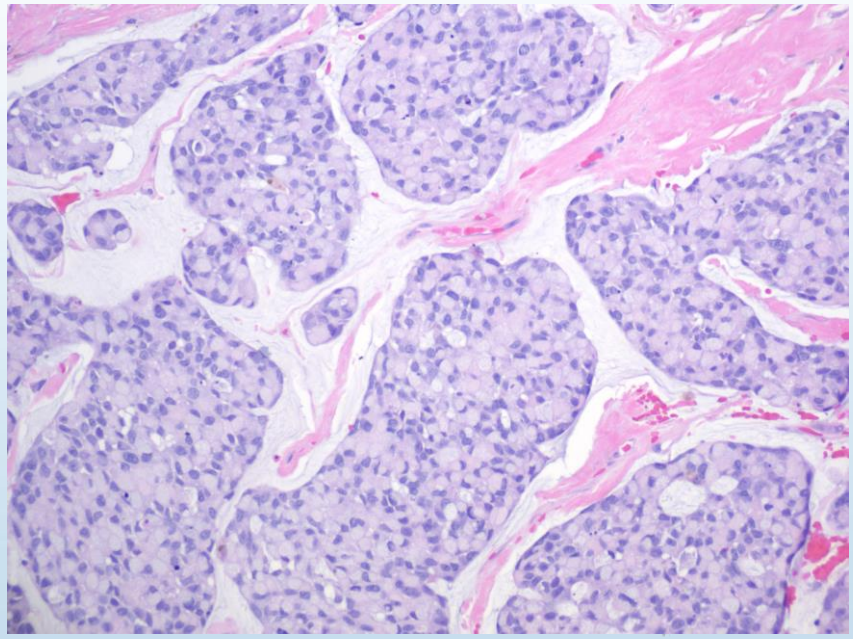
- Mucosal melanocyte malignancy
- Nasal cavity, septum, sinuses
- Multiple melanoma markers helpful due to variable staining

Sinonasal adenocarcinomas

- Non-intestinal and intestinal types (intestinal with signet ring differentiation shown below, involving dura)
- Sites: nasal cavity and sinuses, possible extension into orbit and skull base
- Exclude metastases and salivary gland neoplasms



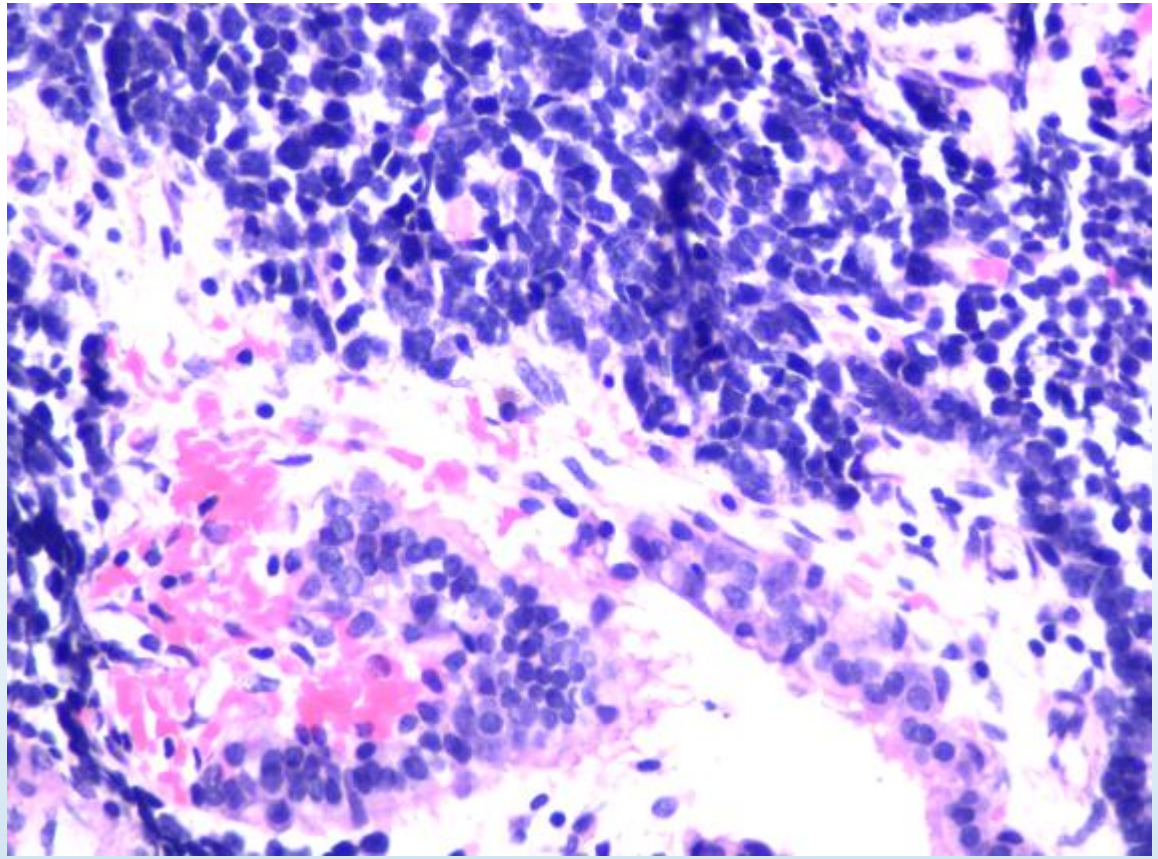




Sinonasal Undifferentiated Carcinoma (SNUC)

- Undifferentiated carcinoma and diagnosis of exclusion
- Clinical: adults, large destructive mass at presentation
- Histology: malignant yet relatively same-looking epithelioid cells
- Immunohistochemistry
  - Positive for pan-cytokeratin, CK8/18, p16 (subset)
  - Negative for CK5/6, p40, high-risk HPV, and specific markers of differentiation (CD45, S100, SOX10, desmin)
- Molecular: *IDH2* hotspot mutations (p.R172M most common)

Pitfall: Diagnosing SNUC in the Expanding Molecular Landscape of the Sinonasal Region and Skull Base



Diagnosed as sinonasal undifferentiated carcinoma >5 years ago

Molecular result: *EWSR1::C11orf93* (*COLCA2*)

› Am J Surg Pathol. 2023 Mar 1;47(3):361-369. doi: 10.1097/PAS.0000000000002000. Epub 2022 Nov 14.

Recurrent EWSR1::COLCA2 Fusions Define a Novel Sarcoma With Spindle/Round Cell Morphology and Strong Predilection for the Sinonasal Tract

Abbas Agaimy [1], Martina Baněčková [2 3], John De Almeida [4], Brendan C Dickson [5 6], Arno Dimmler [7], Wolfgang Hartmann [8 9], Marick Laé [10], Jessica Pablik [11], Christoph Schubart [1], Alena Skálová [2 3], Robert Stoehr [1], Marcel Trautmann [8 9], Eva Wardelmann [8], Michel Wassef [12], Ilan Weinreb [13]

Affiliations + expand

PMID: 36580038 DOI: 10.1097/PAS.0000000000002000

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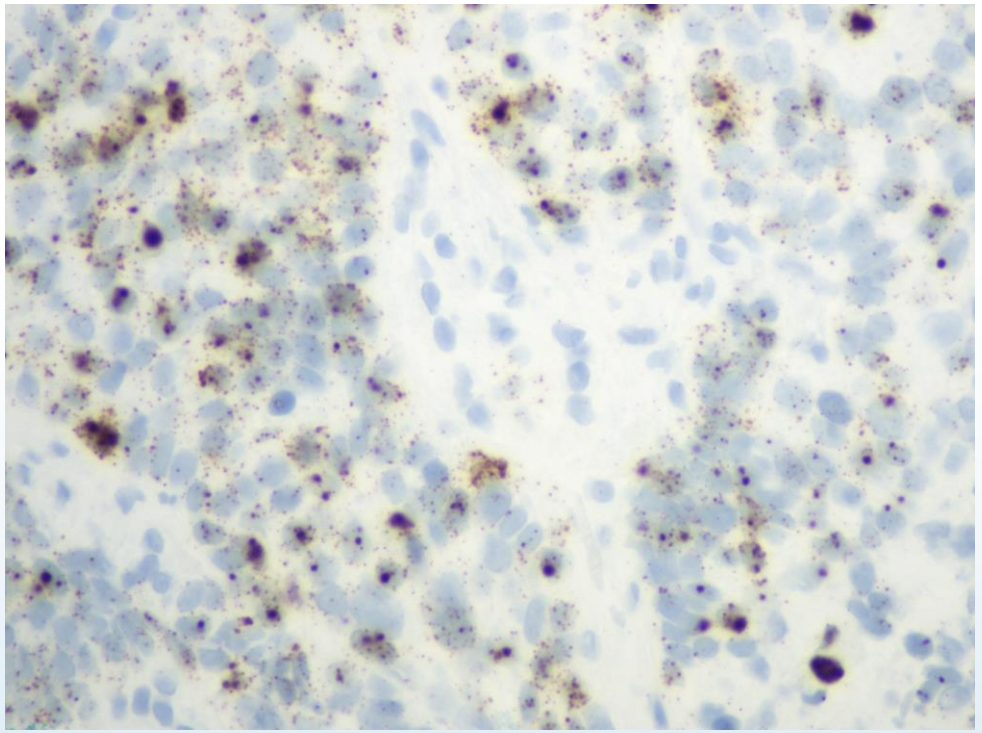
Immunohistochemical Approach to Epithelial and Epithelioid Neoplasms of the Sinonasal Tract and Skull base

- Step 1: lineage markers
  - Keratins, p63, and p40 for epithelial and squamous differentiation
  - S100 and SOX10 for melanoma and investigation of salivary gland neoplasms
- Step 2: refinement
  - INI1, BRG1, NUT
  - Desmin and myogenin if rhabdomyosarcoma suspected
  - Additional melanoma markers
  - CD99 if adamantinoma-like Ewing sarcoma suspected
  - p16 if high-risk HPV process suspected (needs confirmation)
- Step 3: confirmation
  - High-risk HPV RNA in situ hybridization in select cases
  - Molecular testing as needed



High risk HPV E6/E7 RNA ISH in a nonkeratinizing squamous cell carcinoma

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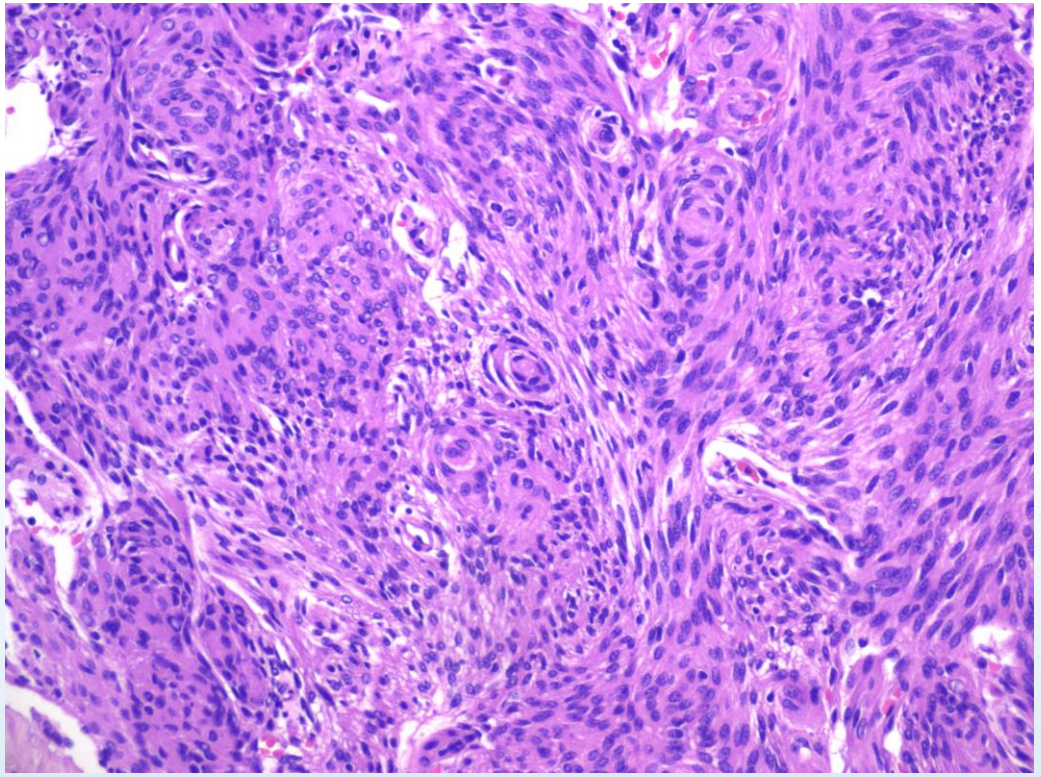
Mesenchymal and Related Neoplasms of the Skull Base

Meningioma of the Sinonasal Tract and Skull base

- Ectopic meningiomas may arise in the sinonasal tract and ear/temporal bone
  - Extension from an intracranial lesion should be excluded
- Similar histologic findings to other meningiomas, meningothelial subtype is most common
- Growth pattern around native glands and through bones imparts an infiltrative appearance but does not correlate with worse patient outcome (Lester and Gyure. Am J Surg Pathol. 2000).
- >4 mitoses per 10 high power fields (2.5 mm^2) and/or 3 or more atypical features may correlate with lower 10-year survival (Rushing et al. Head Neck Pathol. 2009)
- Similar staining to CNS examples, positive for EMA, somatostatin receptor 2a (SSTR2a), and progesterone receptor



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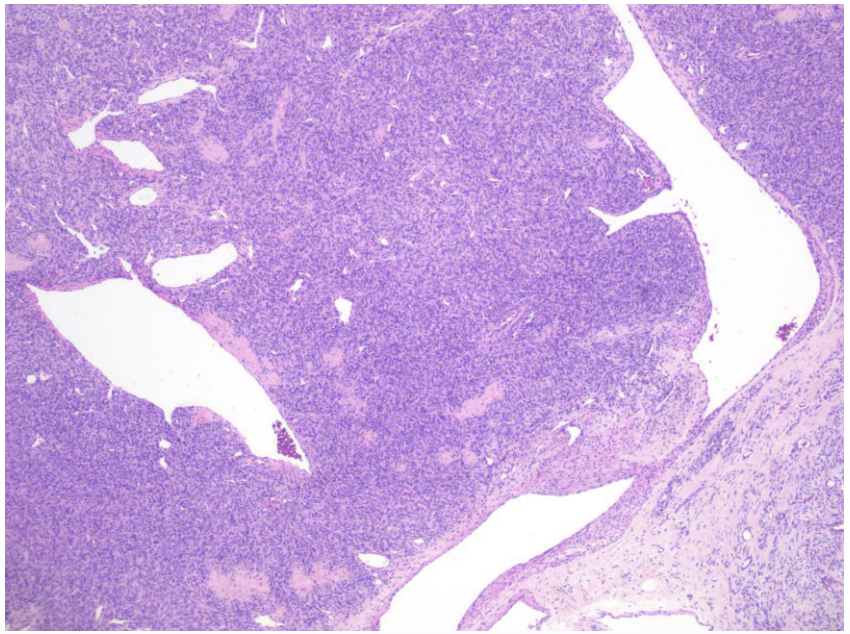
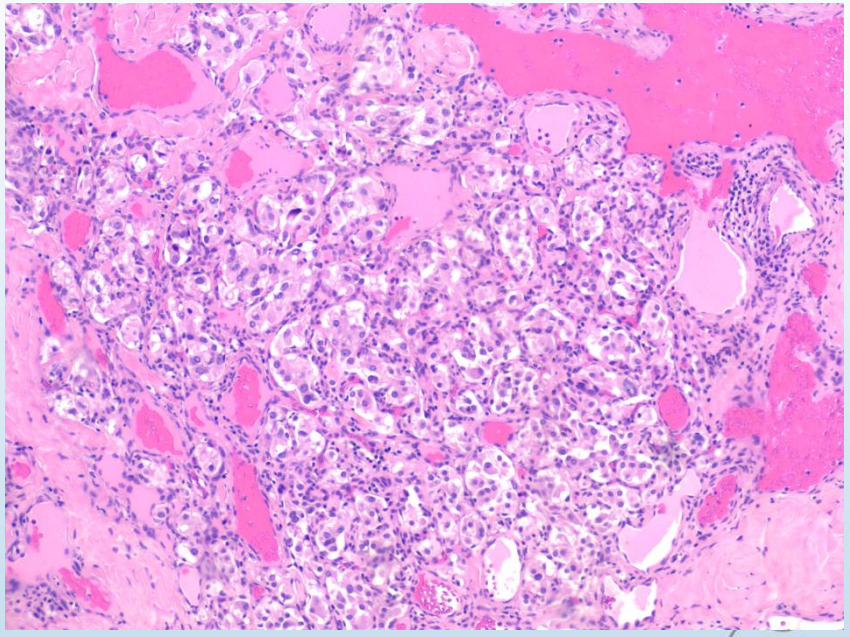
Differential Diagnosis for Meningioma

- Solitary fibrous tissue
  - CD34 and STAT6 positivity
- Paraganglioma
  - Synaptophysin and GATA3 positivity with a sustentacular pattern of staining
- Pituitary neuroendocrine tumor
  - Hormonal and lineage markers, synaptophysin positivity
- Sinonasal glomangiopericytoma



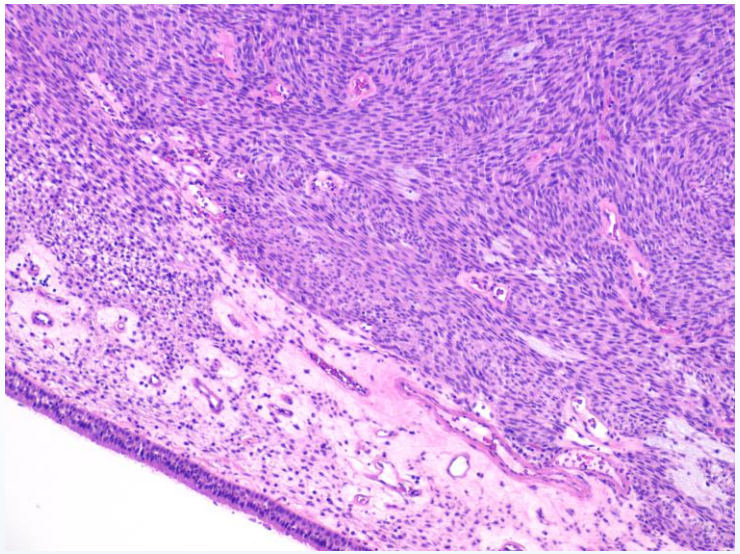
Solitary fibrous tumor with gaping vessels

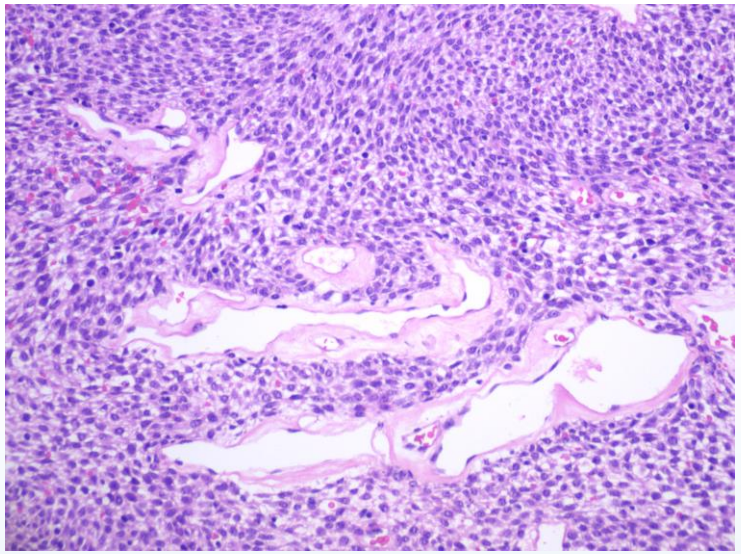


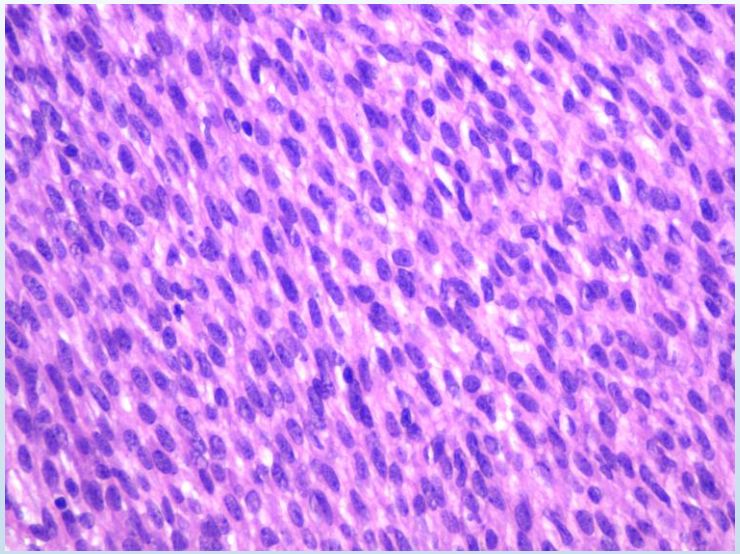
Paraganglioma with Zellballen, nested pattern

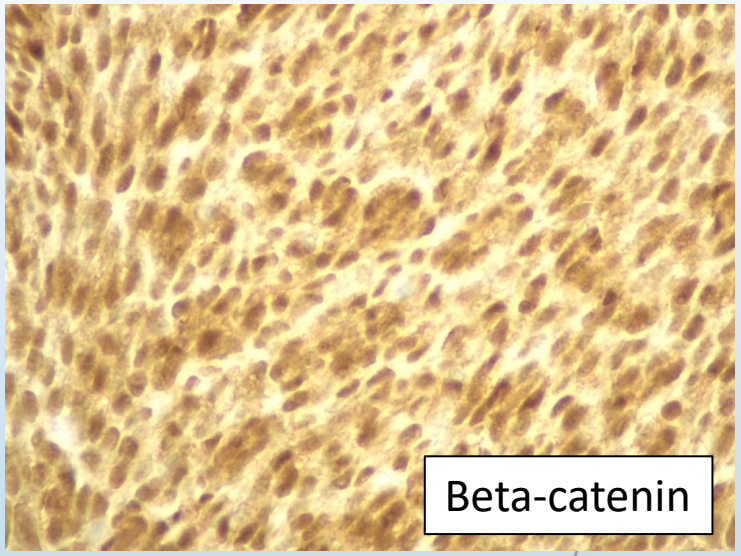
Sinonasal Glomangiopericytoma

- Soft tissue tumor with perivascular myoid differentiation (formerly “sinonasal hemangiopericytoma”)
- Nasal cavity with extension into sinuses, any age
- Unencapsulated, patternless, syncytial-like arrangement of bland, ovoid cells
- Vessels with peritheliomatous hyalinization are a classic clue
- Molecular: *CTNNB1* mutations
- Positive: SMA, nuclear beta catenin
- Negative: STAT6, S100, SOX10, cytokeratins



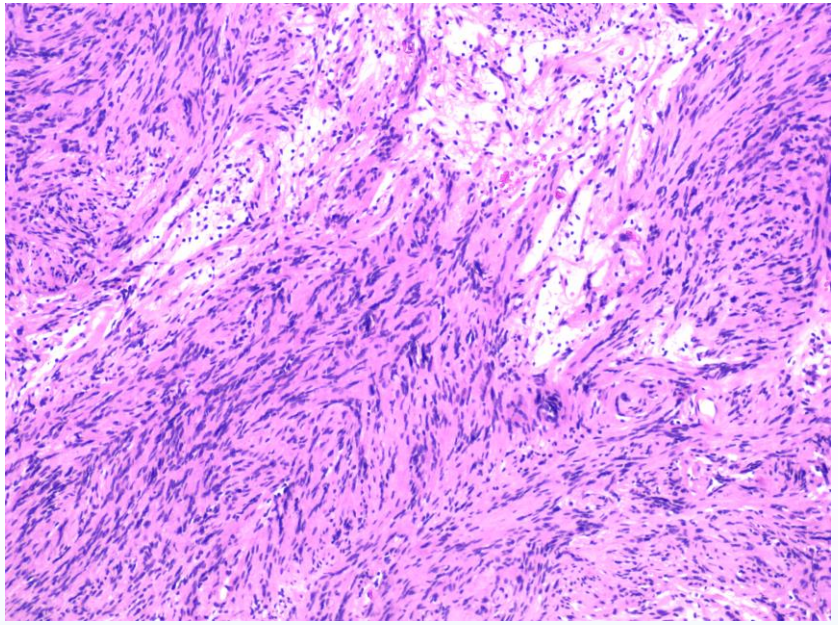


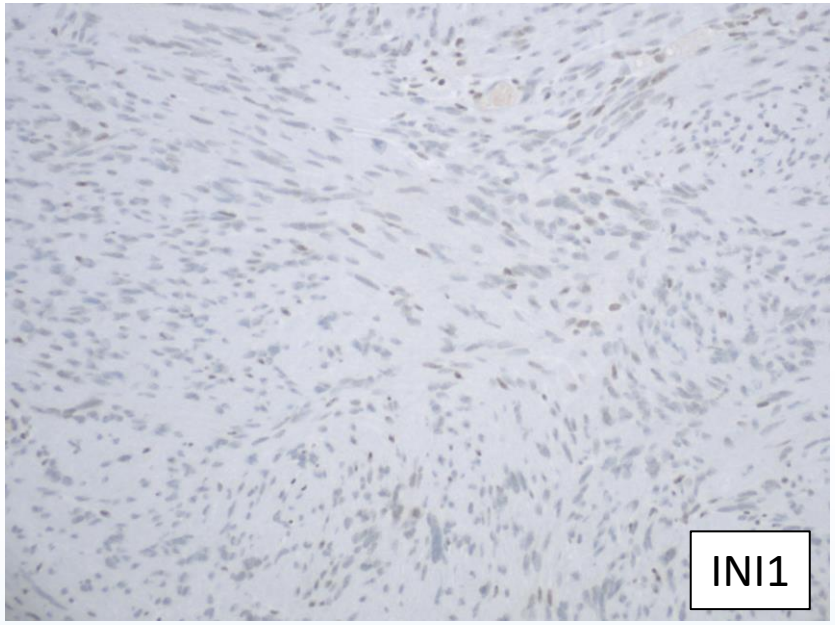


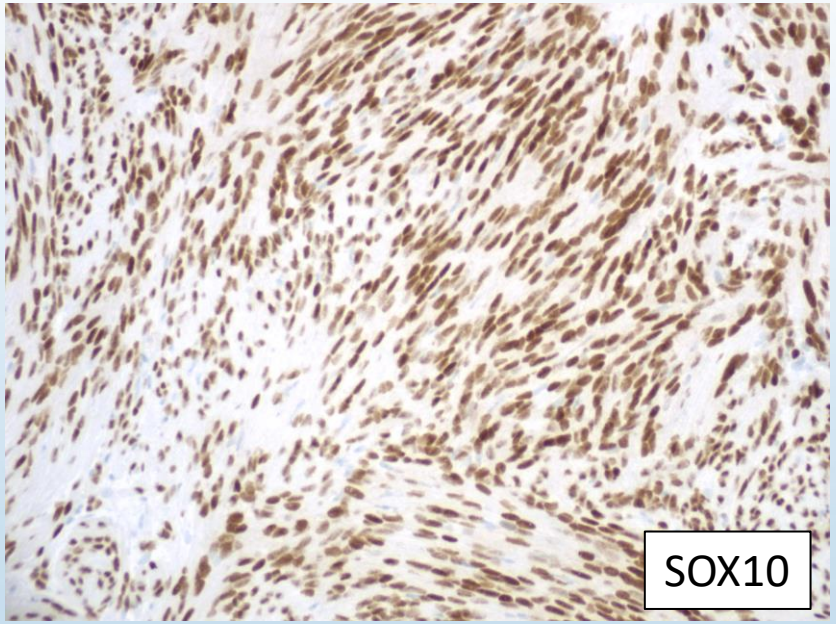


Schwannoma

- Benign peripheral nerve sheath tumor of Schwann cell differentiation
- Most are sporadic but may arise in familial syndromes
  - Neurofibromatosis 2 (NF2): *NF2* mutations
  - Schwannomatosis: *SMARCB1, LZTR1* mutations
- Histology: well-circumscribed tumors with compact (Antoni A) and loose (Antoni B) areas
- IHC: Diffuse S100 and SOX10 positivity
- Pitfall: a mosaic pattern of INI1 loss can be seen in both schwannomatosis and NF2







(Above) Mosaic pattern of INI1 loss in a familial schwannoma

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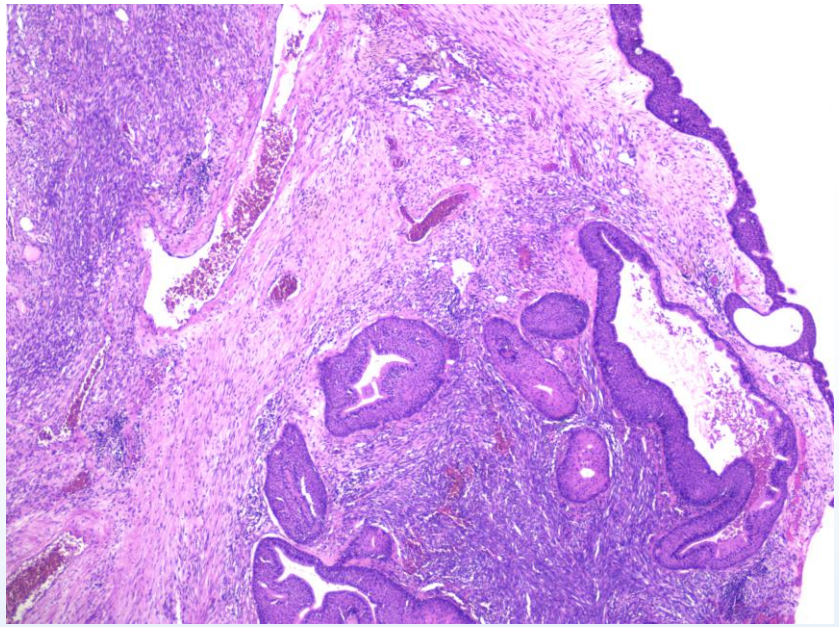
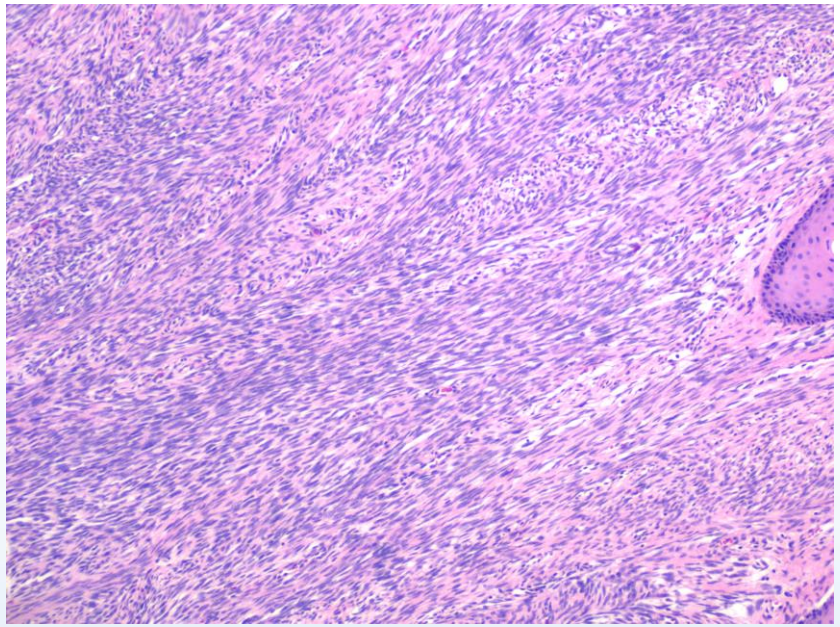
Biphenotypic Sinonasal Sarcoma

- Malignant, spindle cell neoplasm of the sinonasal tract with neural and myogenic differentiation
- Sites: nasal cavity and sinuses with local infiltration, including skull base, orbit, and brain
- Clinical: adults with female predominance

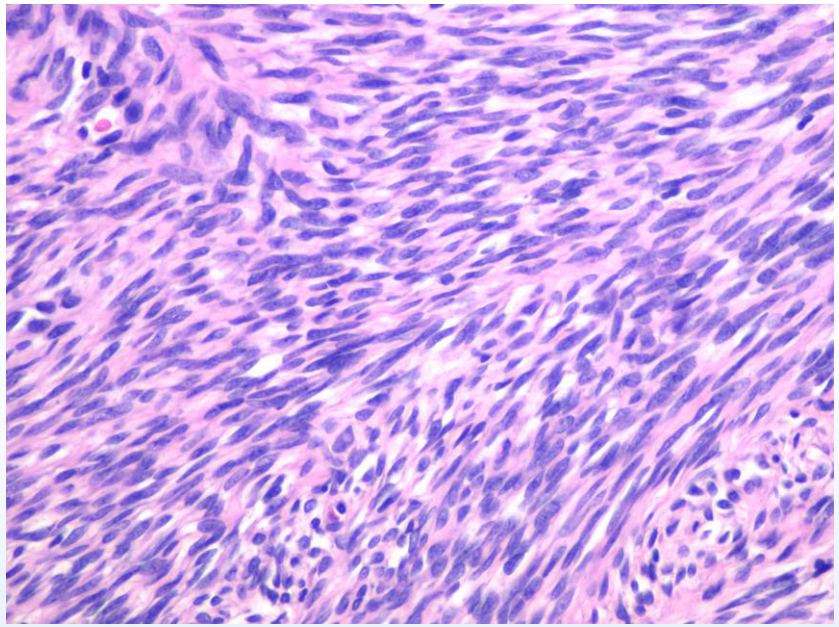
Biphenotypic Sinonasal Sarcoma Histology



Unencapsulated tumor with entrapped, hyperplastic sinonasal elements



Fascicles of eosinophilic, spindled cells



Overlapping, oval-to-wavy nuclei, lacking significant mitotic activity or necrosis

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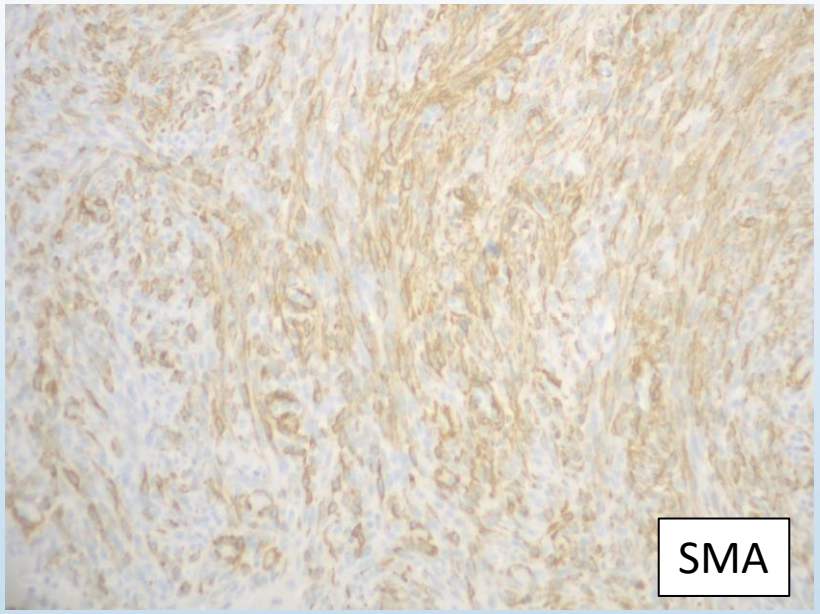
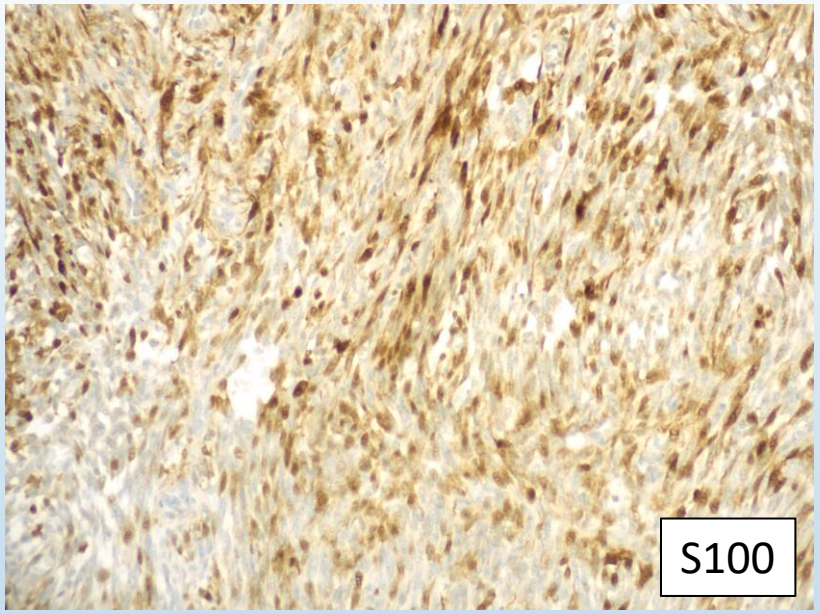
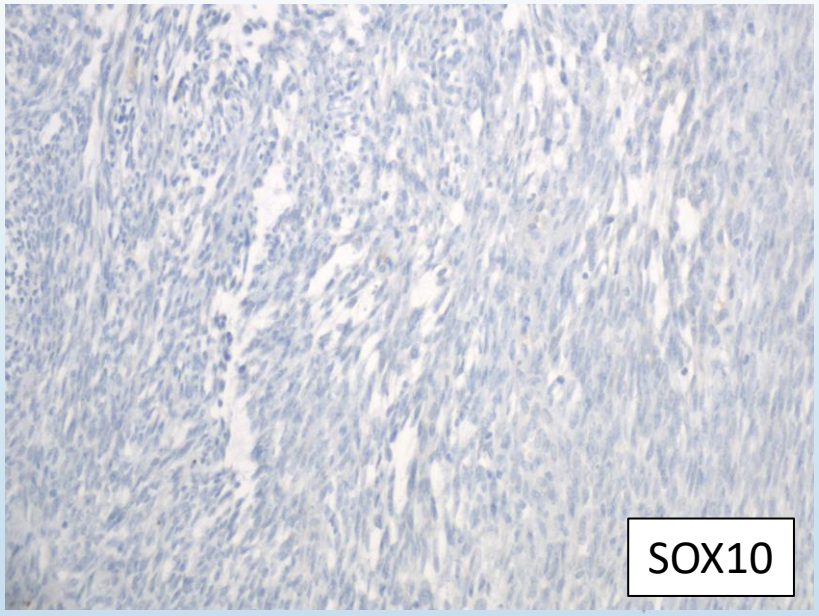
Biphenotypic Sinonasal Sarcoma Ancillary Studies

- Myogenic differentiation: SMA and desmin (subset) positivity
- Neurogenic differentiation: S100 positivity (may be patchy)
- SOX10 is always negative
- *PAX3::MAML3* fusions in most cases

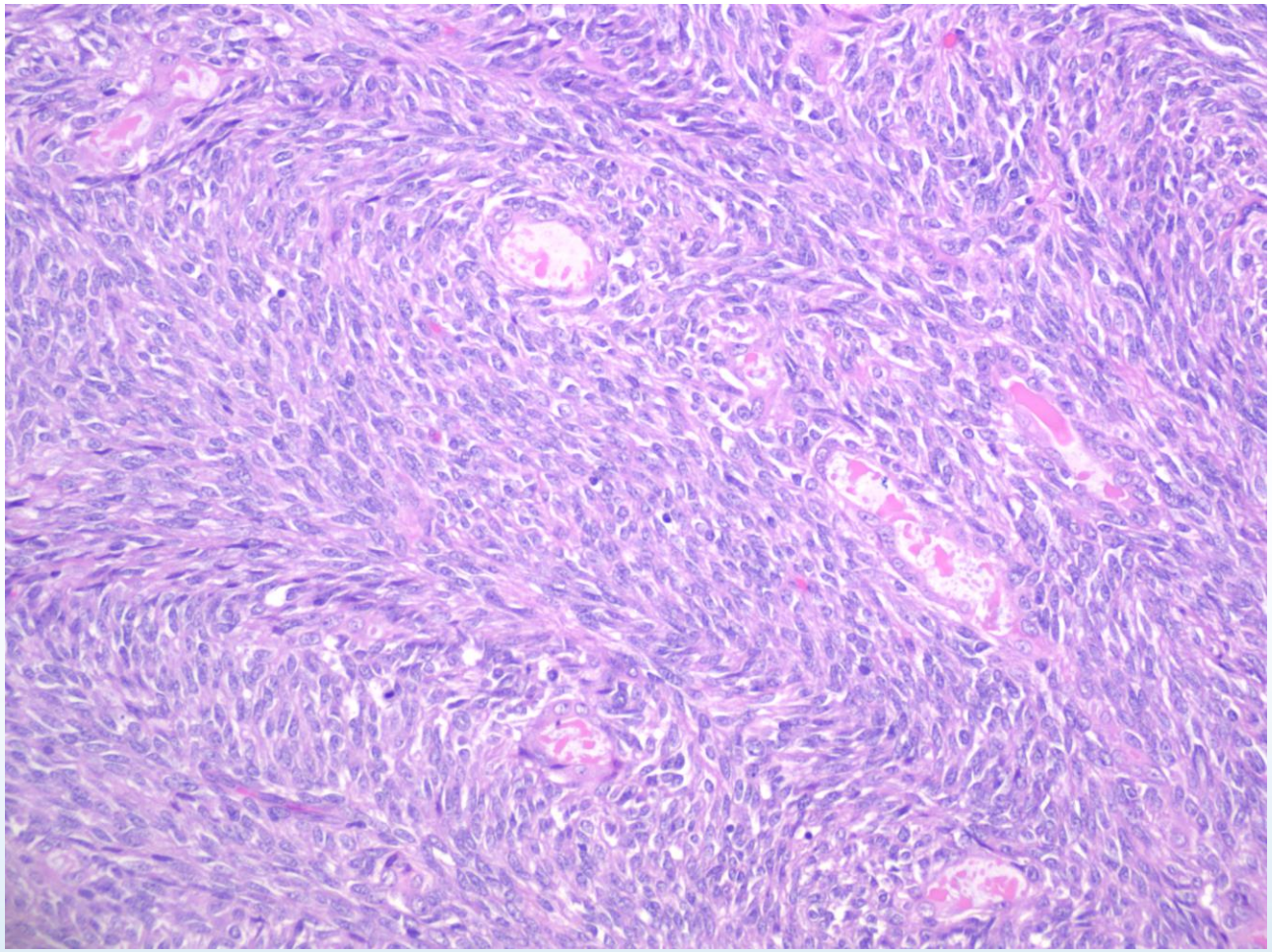






Synovial Sarcoma

- Spindle cell neoplasm with *SS18::SSX1*, *SSX2*, or *SSX4* gene fusions
- Young adults and pediatric patients most commonly affected, small subset occur in head and neck
- Histology
  - Monophasic: spindled cells
    - Ossifying, calcifying, and myxoid appearances can be encountered
  - Biphasic: glandular and epithelial differentiation
- Variable Immunohistochemistry
  - TLE1 positivity (not specific)
  - Cytokeratin (patchy)
  - Negative for S100



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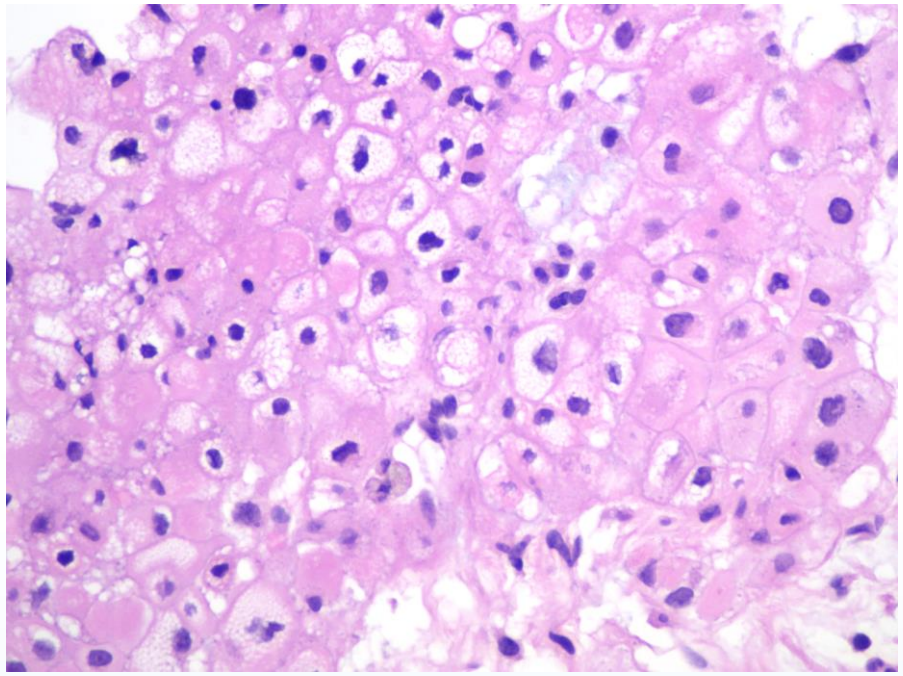
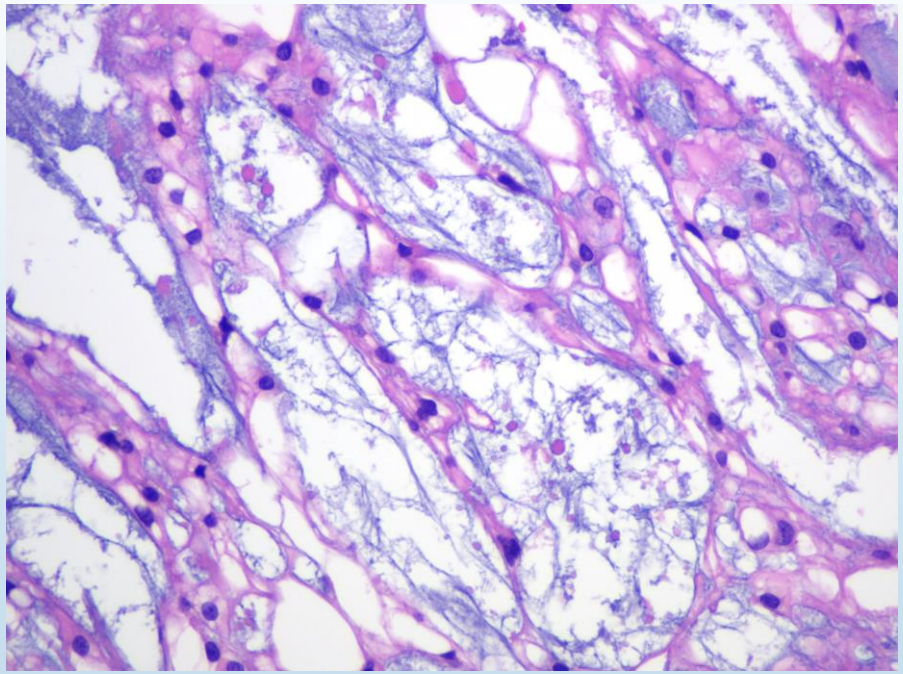
Chordoma

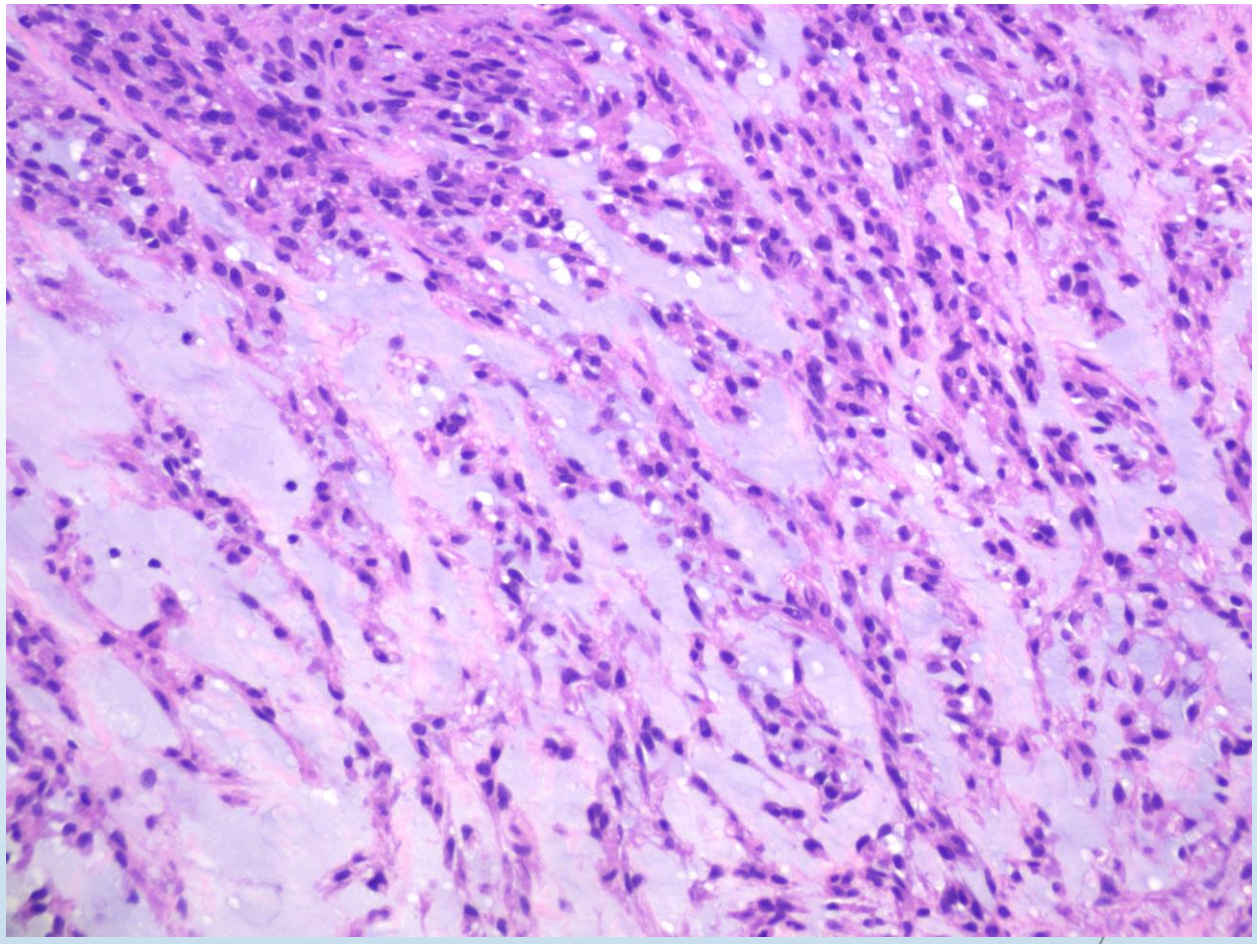
- Neoplasm of notochordal differentiation
- Arises in axial skeleton, skull base
- Lobules, fibrous septae, and cords of tumor cells in a chondroid/myxoid background as well as bubbly, physaliphorous cells
- IHC: Positive for brachyury, EMA, pan-cytokeratin (AE1/3), S100
- INI1 is retained in conventional examples (lost in poorly differentiated chordomas, which still retain brachyury)





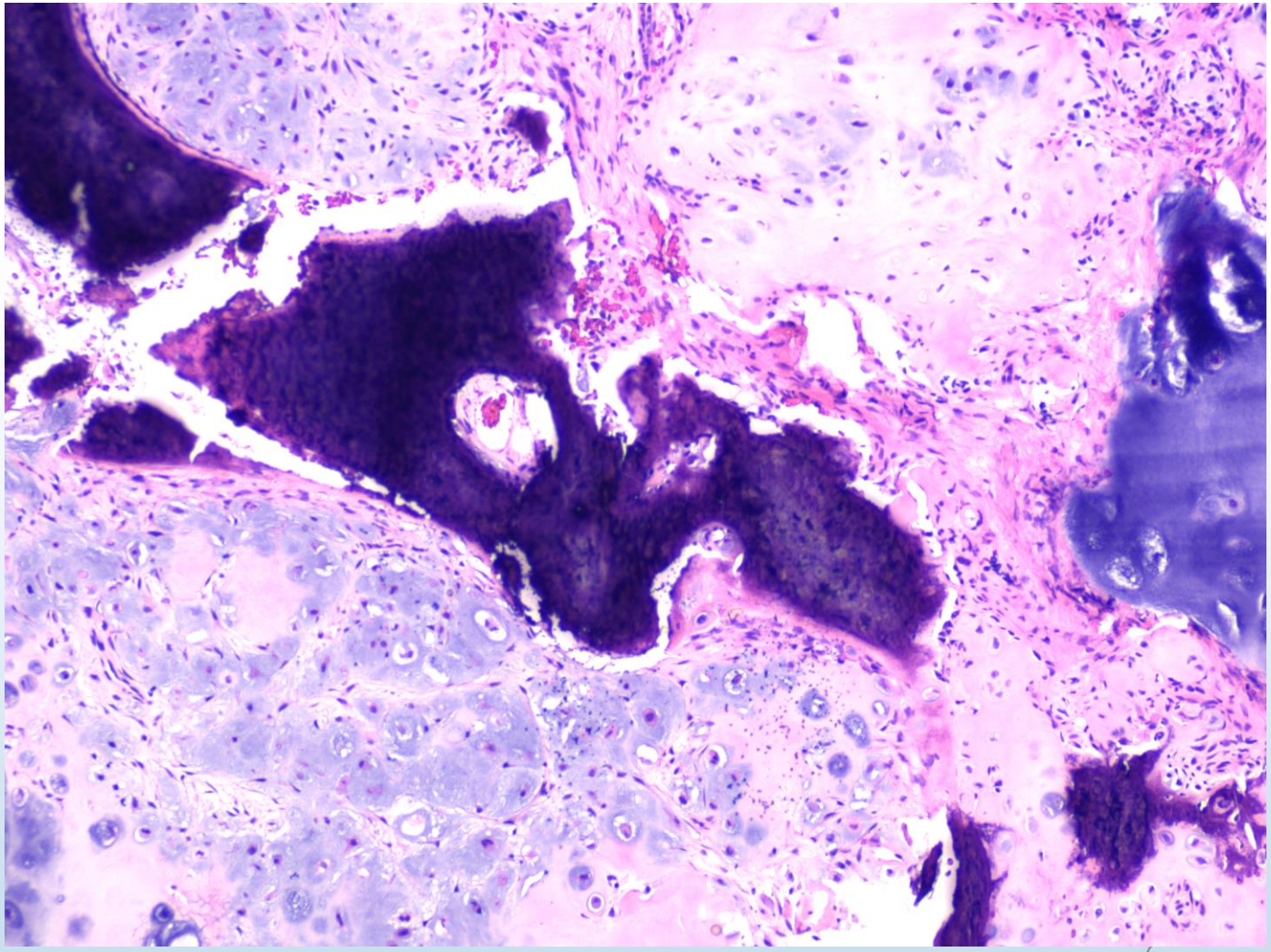
Extraskeletal Myxoid Chondrosarcoma

- Malignant mesenchymal tumor of uncertain differentiation
- Sites: sinonasal tract, intracranial sites, and orbit (rarely)
- Histology: lobular architecture, cords, clusters, and cribriform arrangements of eosinophilic-to-vacuolated cells in a chondromyxoid background
- Variable, unreliable IHC
- *NR4A3* gene rearrangements



Conventional Chondrosarcoma

- Rarely occurs in the maxilla and facial skeleton
  - Consider chondroblastic osteosarcoma (look for osteoid matrix), which is more common in maxillofacial bones
- Histology: invasive lobules of hyaline cartilage
- IHC
  - Positive: S100
  - Negative: Brachyury, pan-cytokeratin, EMA
- Molecular:
  - Skull base examples have a high *IDH1* mutation rate (R132C, most commonly) while examples in facial bones are *IDH1*-wildtype in one study (Tallegas et al. Human Pathol. 2019)



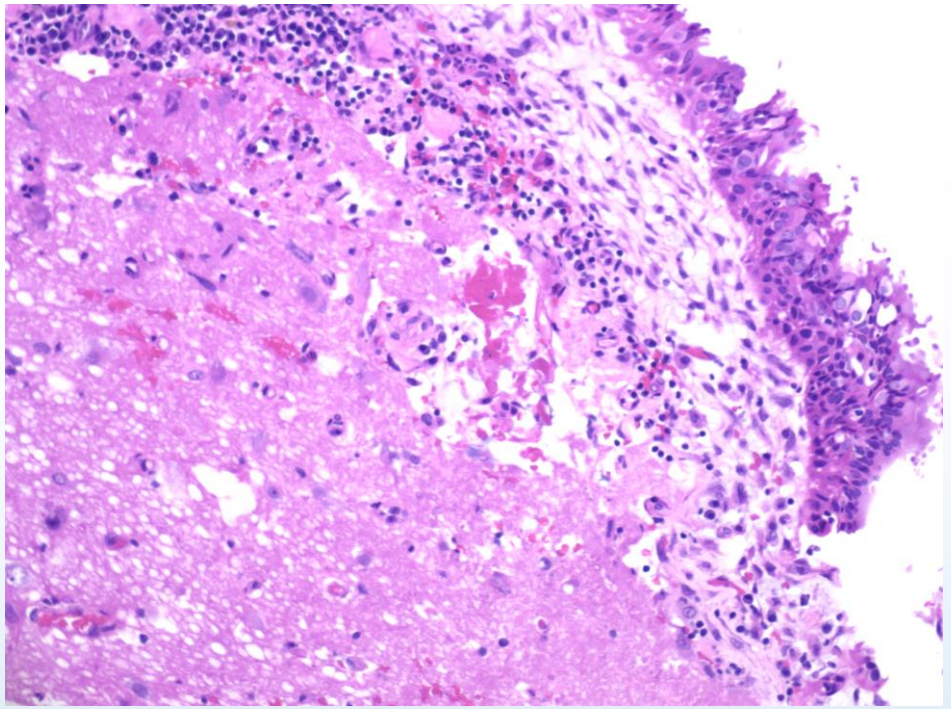
Digital Slides

- Case 1: 40F with a 2.0 cm heterogeneously enhancing mass of pterygopalatine fossa with extension into the foramen rotundum
- Case 2: 60F with a 2.0 cm nasopharyngeal mass
- Case 3: 72F with a 2.6 cm nasal cavity mass

- Link: https://pathpresenter.net/public/presentation/display?token=80cbfed3

Summary and Conclusion

- Skull base is a complex site with developmental, epithelial, mesenchymal, and lymphoid lesions
- Assessment benefits from an expanded neuropathology and ENT pathology differential
- Familiar neuropathologic entities, histologic findings, and developmental abnormalities may occur in the sinonasal tract and skull base
  - Ectopic pituitary neuroendocrine tumor
  - Meningioma of the sinonasal tract
  - Schwannoma
  - Nasal glial heterotopia/encephalocele
  - Dermoid and epidermoid cysts, Rathke cleft cyst, cholesteatoma



Nasal glial heterotopia

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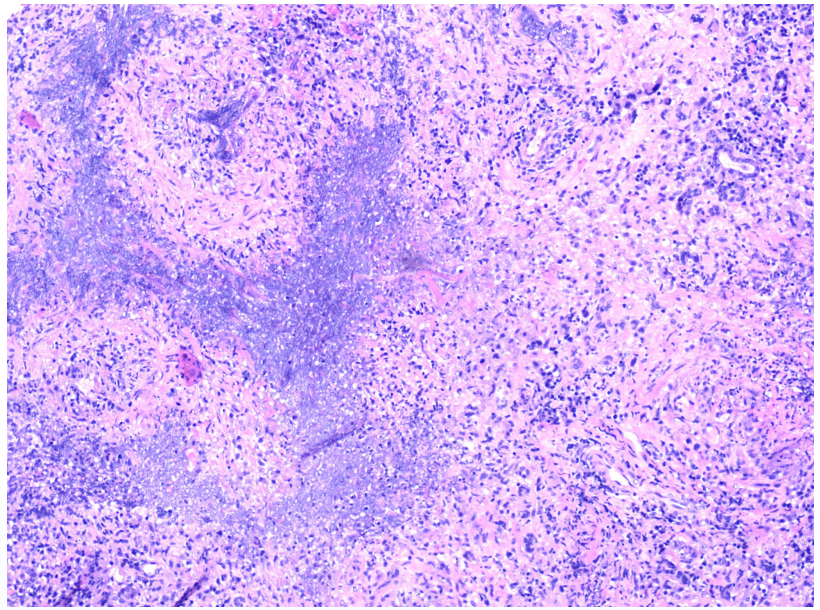
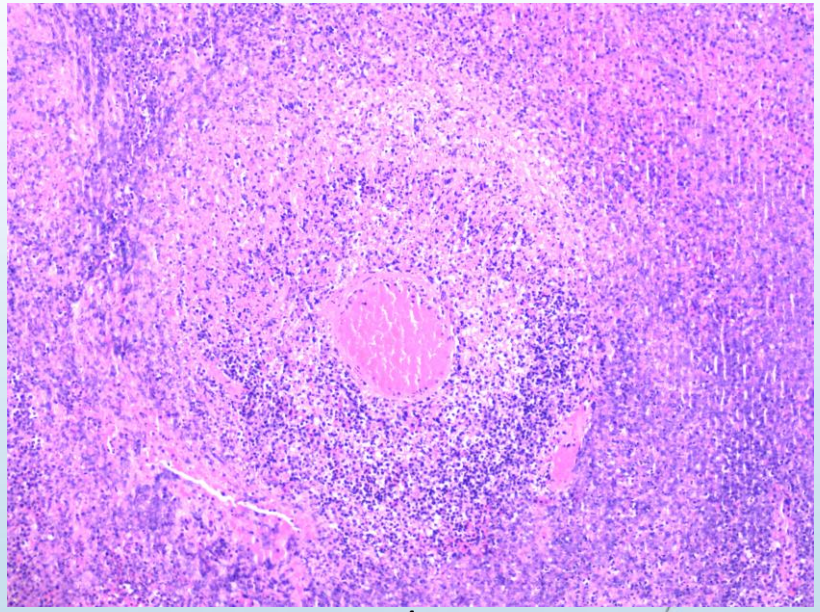
Summary and Conclusion

- Inflammatory lesions
  - Infectious diseases
    - Consider invasive fungal sinusitis and extension of necrotizing “malignant” otitis externa (*Pseudomonas*)
  - Granulomatosis with Polyangiitis
    - c-ANCA against proteinase 3
    - Vasculitis, granulomatous inflammation, basophilic necrosis
  - Extranodal NK/T Cell Lymphoma
    - Formerly “lethal midline granuloma” and “angiocentric lymphoma”
    - Diffuse and angiocentric neoplastic cells and necrosis
    - EBV positive by in situ hybridization
  - Other lymphomas, IgG4-related disease, sarcoidosis



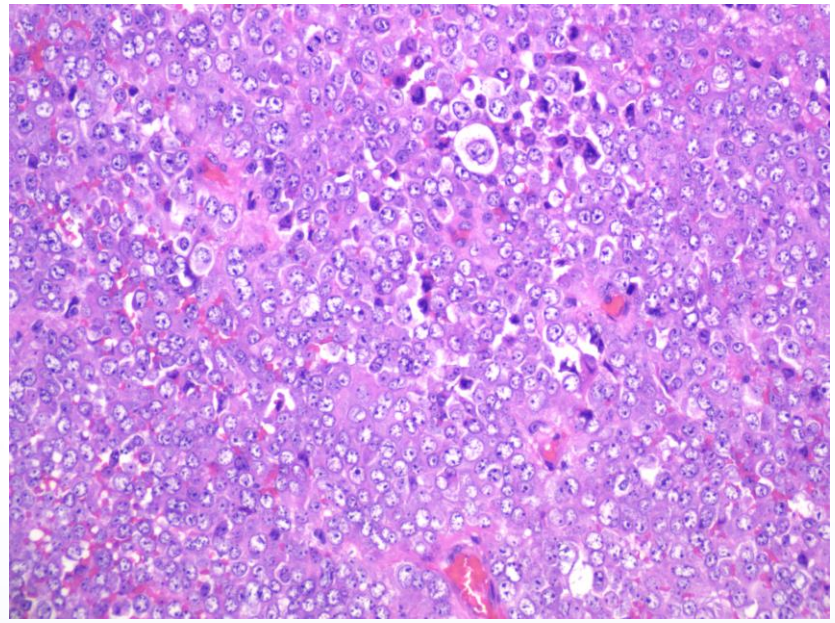
Granulomatosis with polyangiitis



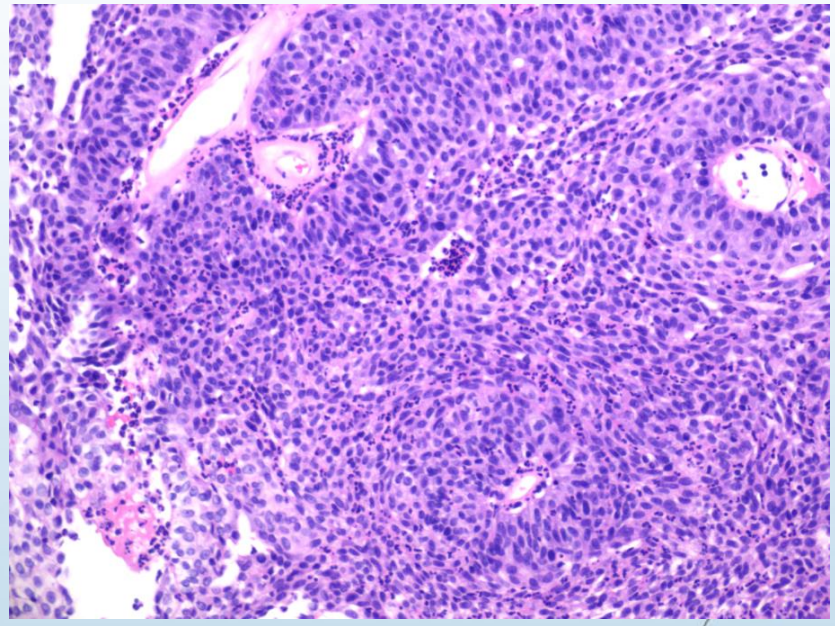
Extranodal NK/T cell lymphoma

Summary and Conclusion

- Sinonasal and skull base epithelial and epithelioid neoplasms require workup due to overlapping histologic features
  - Non-keratinizing squamous cell carcinoma (*DEK::AFF2*, high risk-HPV)
  - SWI/SNF complex-deficient sinonasal carcinomas
  - NUT carcinoma
  - Teratocarcinosarcoma
  - Sinonasal undifferentiated carcinoma
  - Mimics: adamantinoma-like Ewing sarcoma, sinonasal rhabdomyosarcoma, sinonasal mucosal melanoma



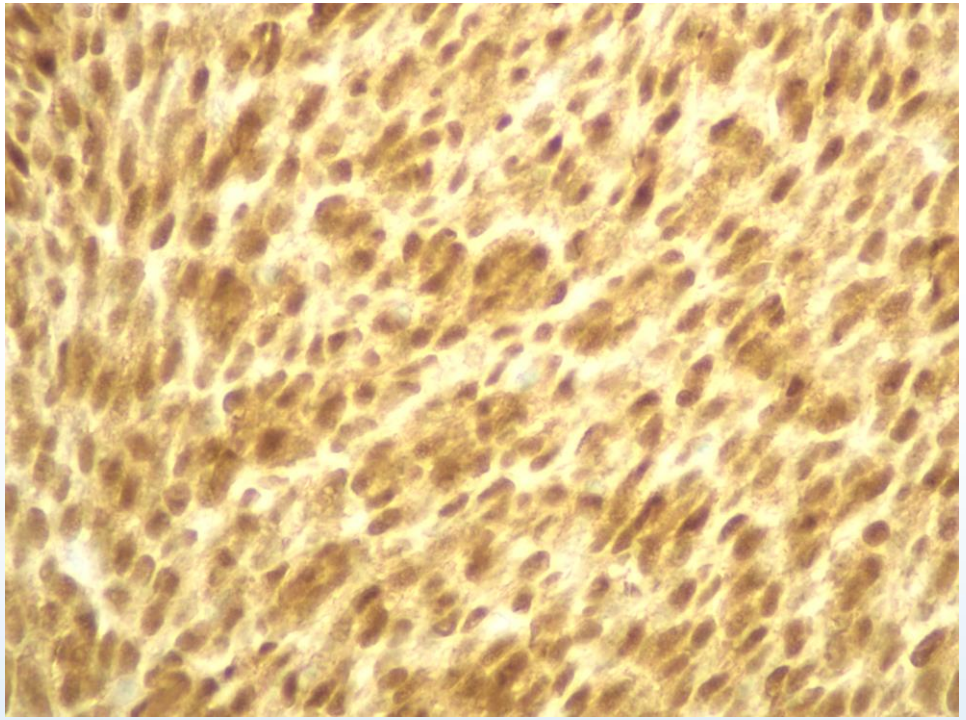
SMARCB1-deficient sinonasal carcinoma



DEK::AFF2 squamous cell carcinoma

Summary and Conclusion

- Mesenchymal neoplasms may mimic neuropathologic entities
- Recurrent molecular alterations and related immunsotains are helpful in difficult cases
  - Sinonasal glomangiopericytoma: *CTNNB1* mutations
  - Biphenotypic Sinonasal Sarcoma: *PAX3::MAML3* fusions
  - Synovial Sarcoma: *SS18::SSX1*, *SSX2*, or *SSX4* gene fusions
  - Extraskeletal myxoid chondrosarcoma: *NR4A3* gene rearrangements



Nuclear beta-catenin in sinonasal glomangiopericytoma

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Thank You

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