FNA of Basaloid Neoplasms of the Head and Neck

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Overview

- Case based approach
- Basaloid tumors and closely related entities
- Review
  - Common clinical presentations
  - Cytologic features
  - Adjunctive techniques as appropriate

Basaloid Tumors

- Sparse cytoplasm confers an immature appearance
- Need to rely on other clues to classify
  - Chromatin
  - Matrix
  - Architecture/Smear pattern
  - Non-basaloid areas

Two Main Scenarios

- Basaloid salivary gland tumors
- Basaloid metastases in neck lymph nodes

Salivary Gland Tumors

Salivary gland neoplasms

Clinical Management

- Superficial parotid gland is most common site
- Benign tumor/Low-grade carcinoma
  - Excision of the mass (partial parotidectomy)
- High-grade carcinoma
  - Radical surgery (complete parotidectomy)
  - Neck dissection?
  - Radiation therapy

Challenging Salivary Gland Patterns

Benign/LG Malignant

- Oncocytic/Clear cell
- Spindle cell
- Cystic/Mucinous

HG Malignant

- High-grade

Basaloid neoplasms

Basaloid pattern is most problematic

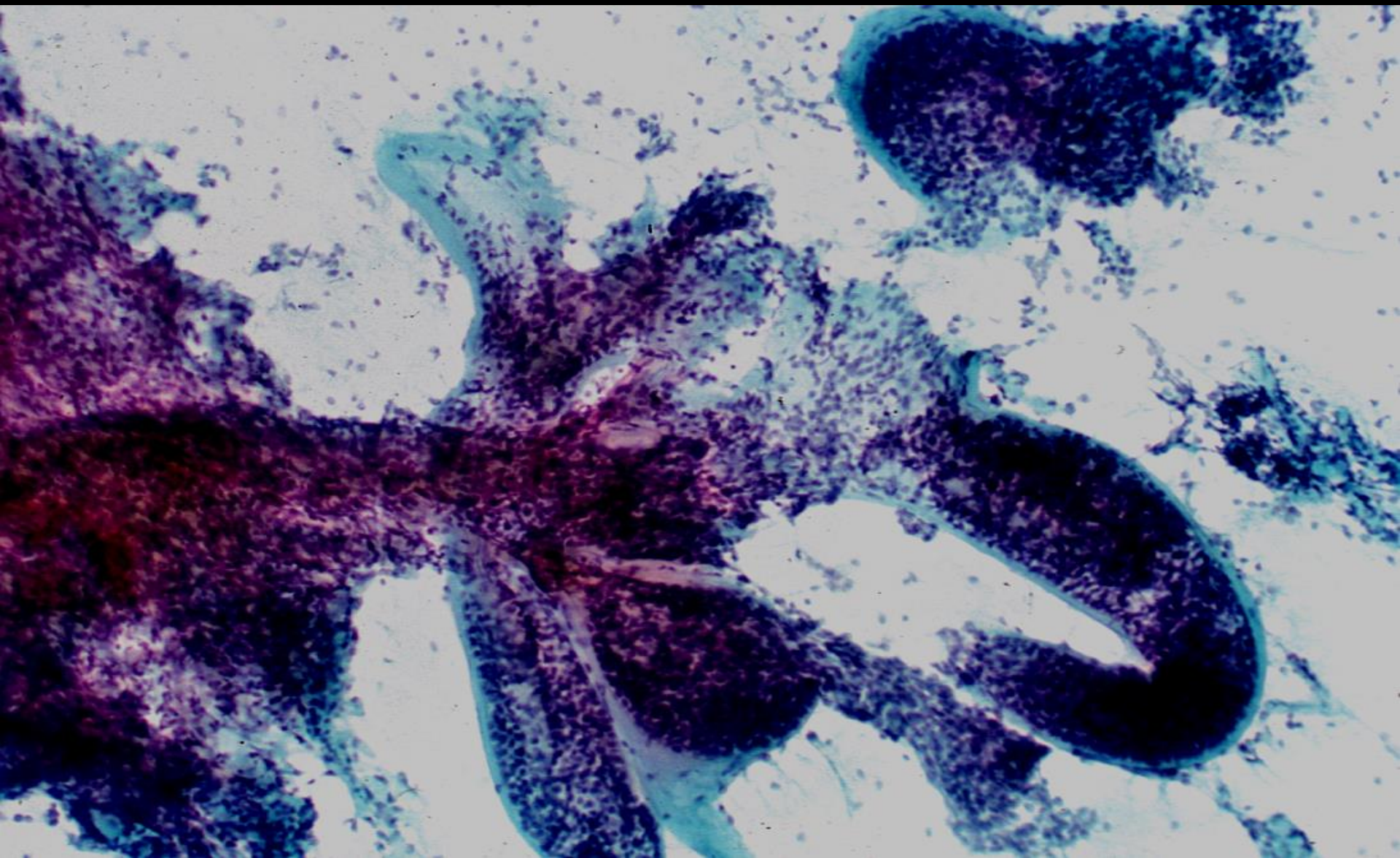
Differential diagnosis spans benign,

low-grade and high-grade carcinomas

Case 1: History

- A 79 year-old woman with a 5 month history of a firm, mobile 2 cm non-tender parotid mass.

Case 1



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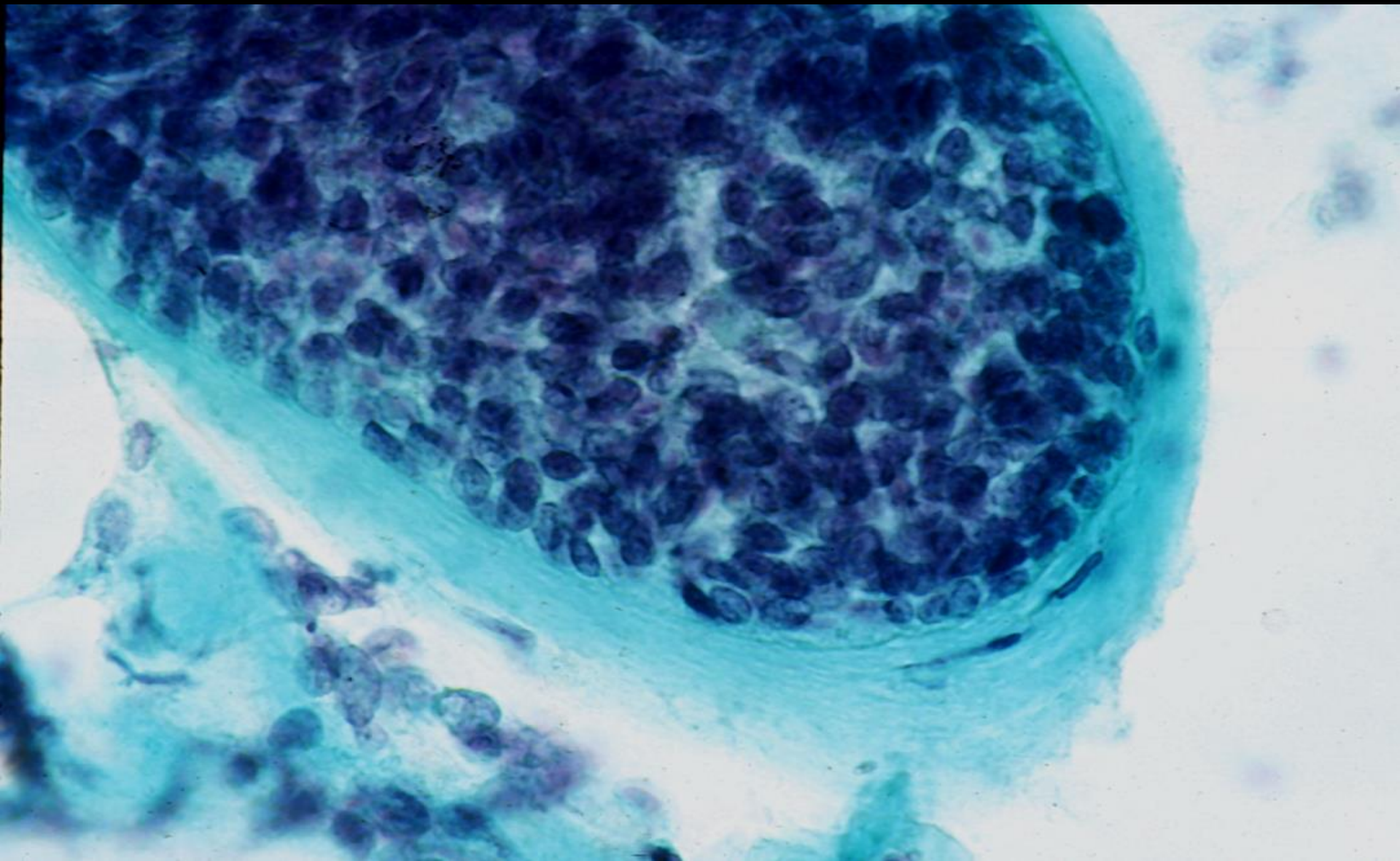

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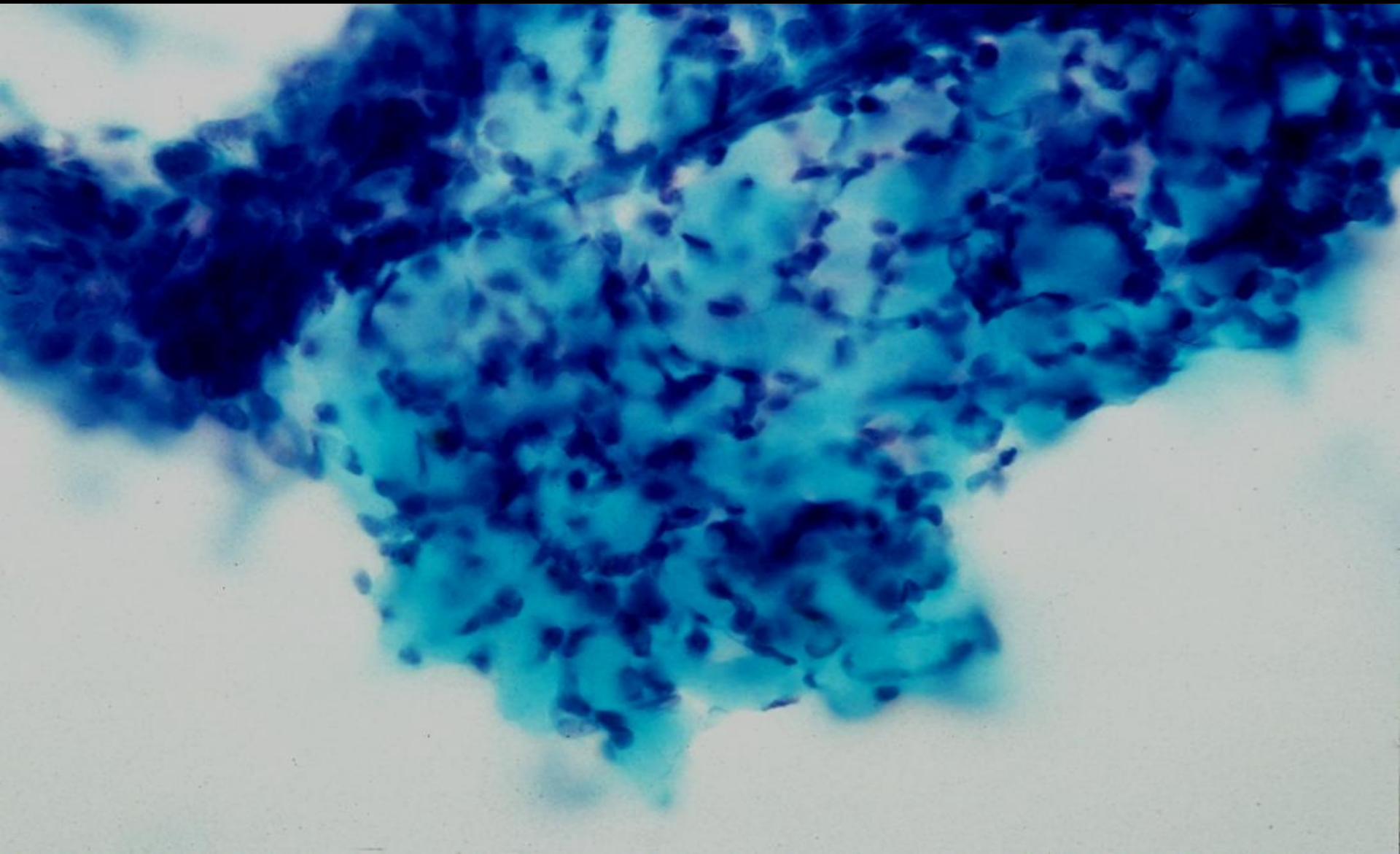

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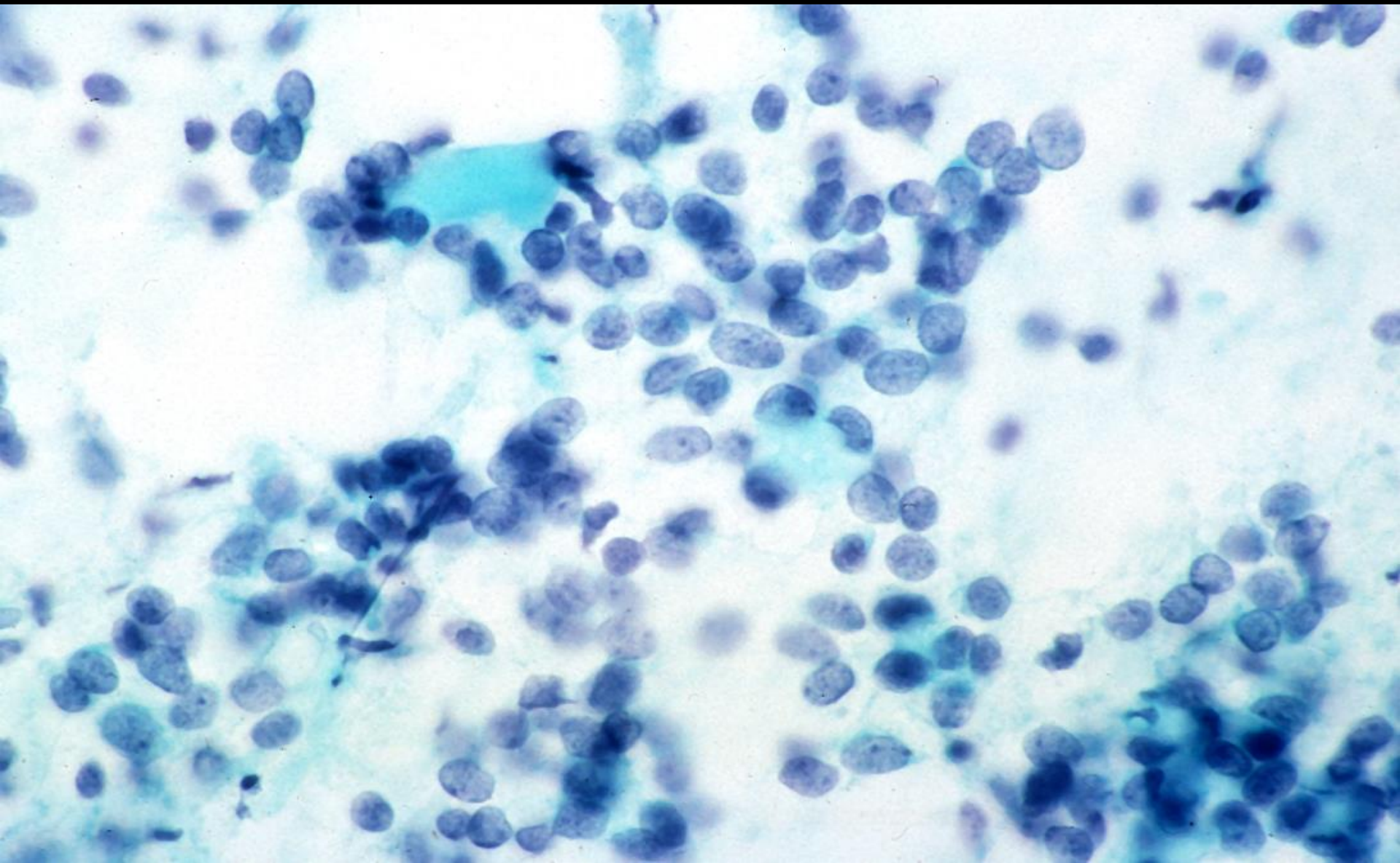

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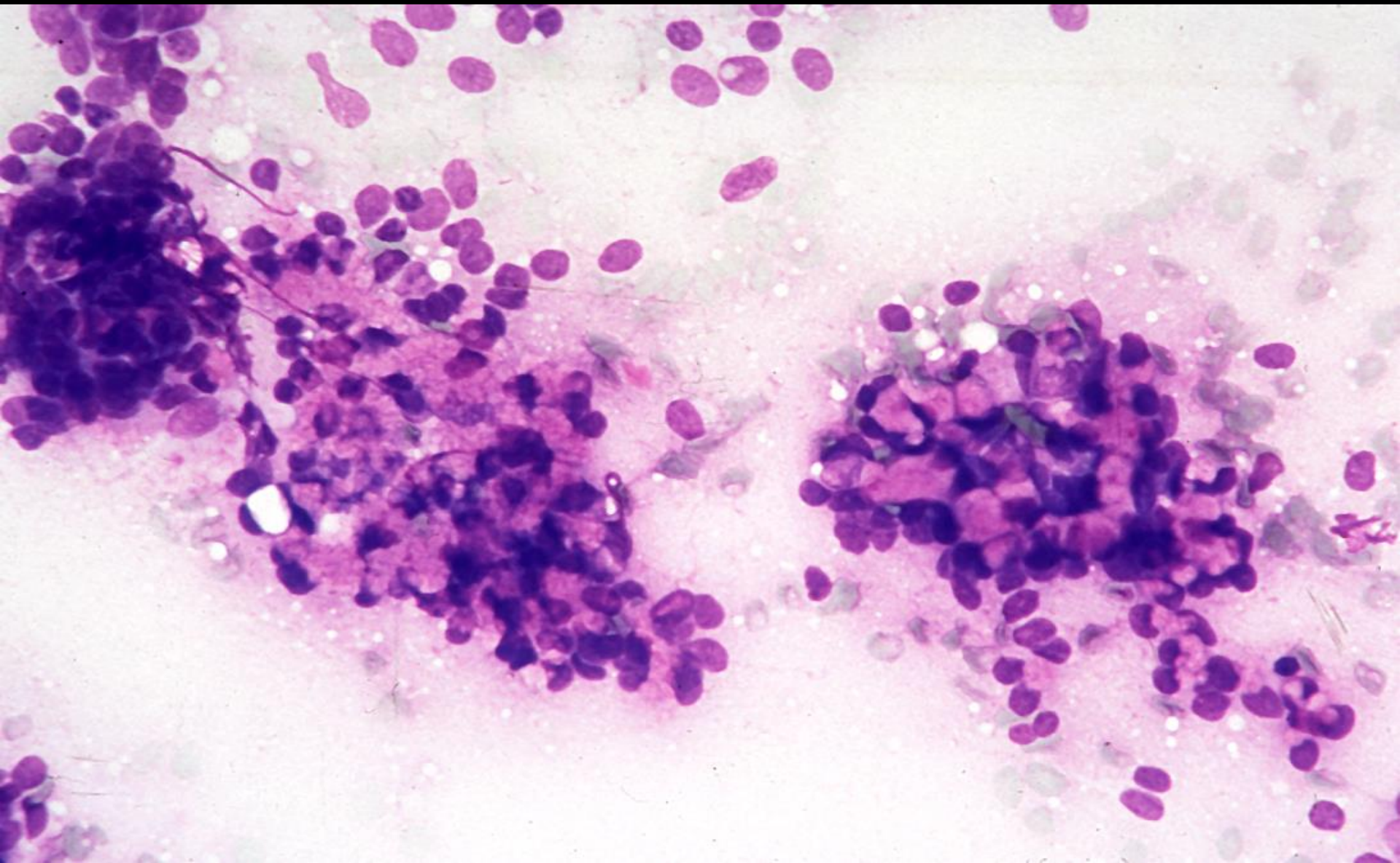

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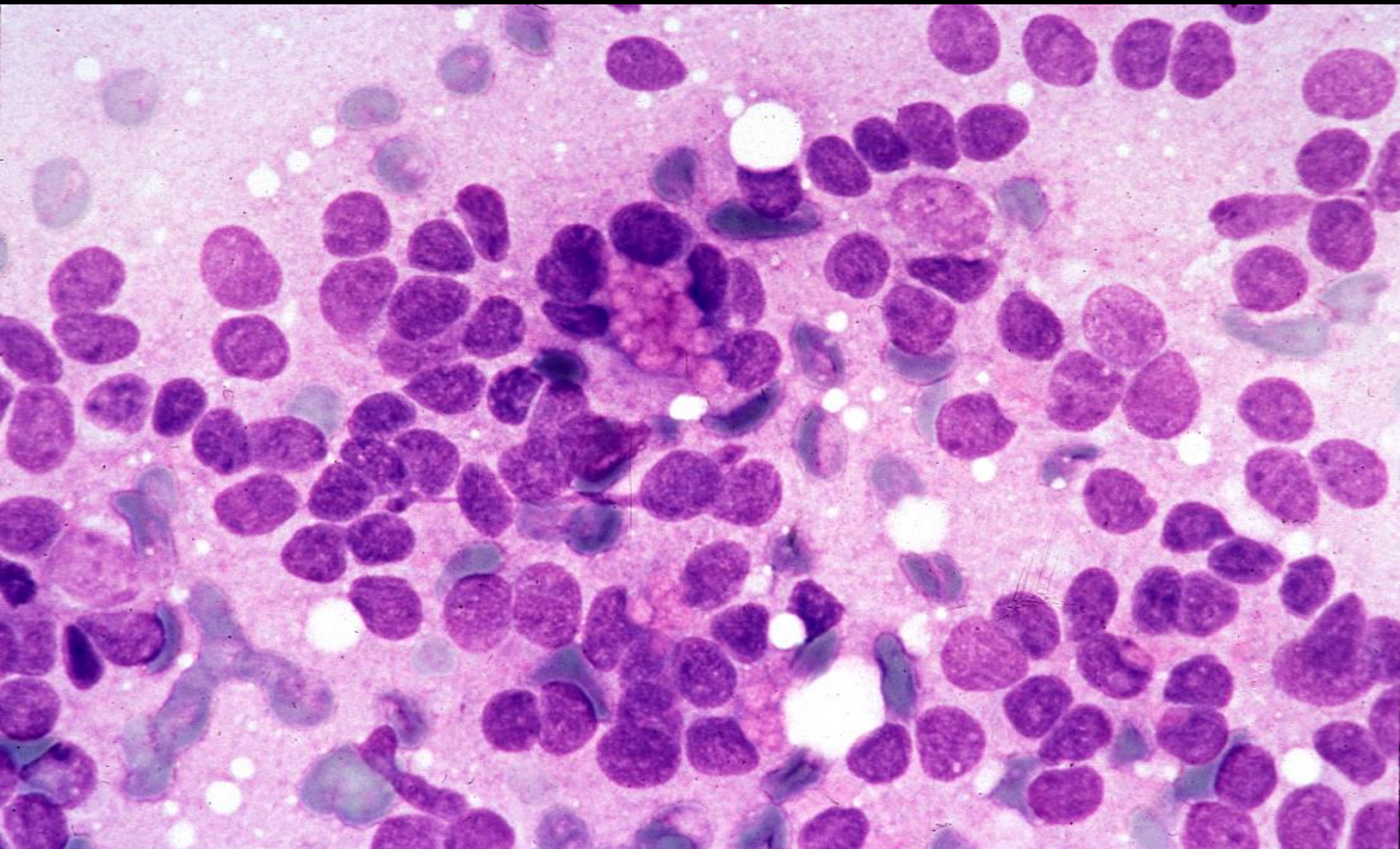
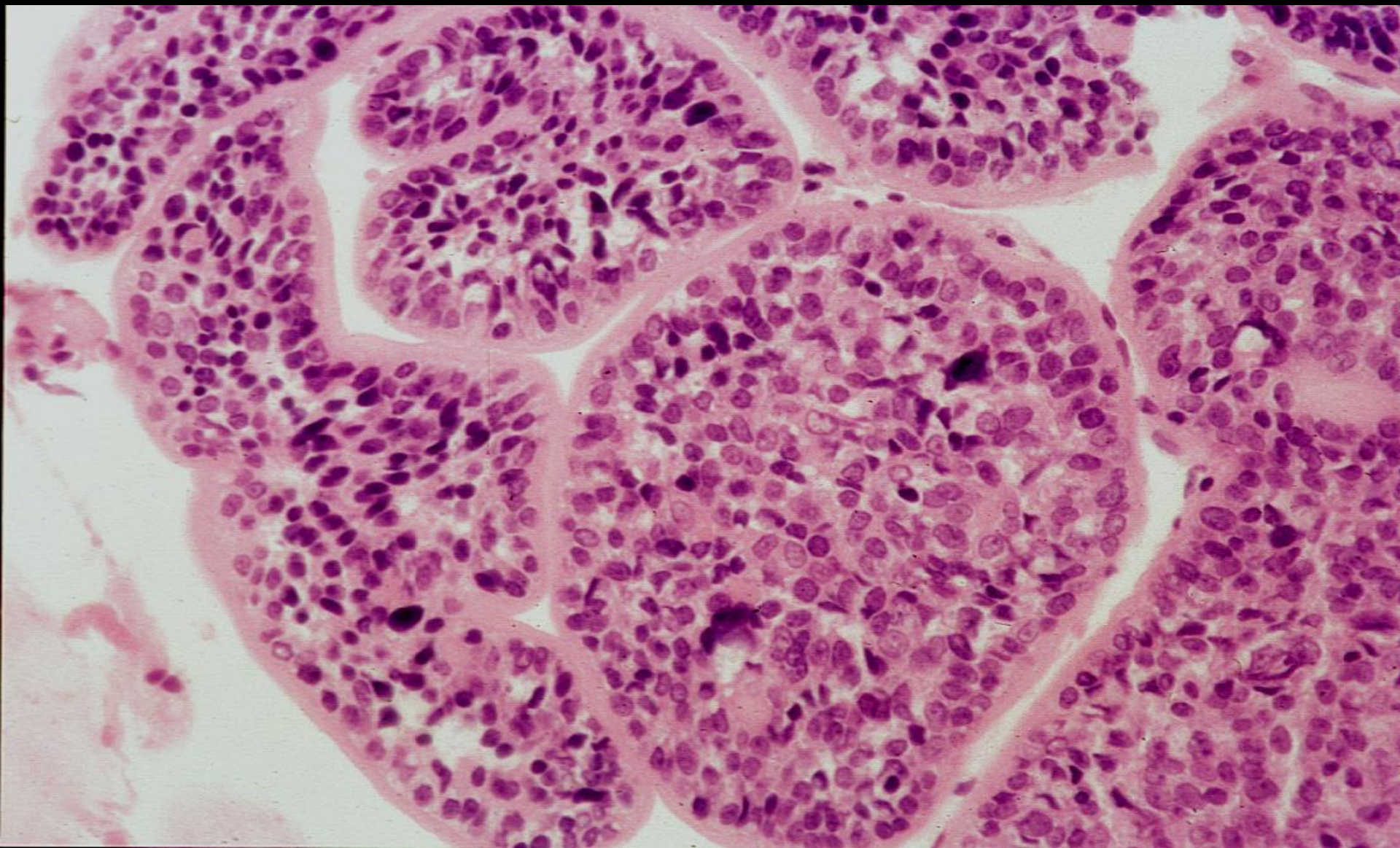


Case 1: Diagnosis?

A. Adenoid cystic carcinoma
B. Basal cell adenoma
C. Skin adnexal neoplasm
D. Basaloid squamous cell carcinoma

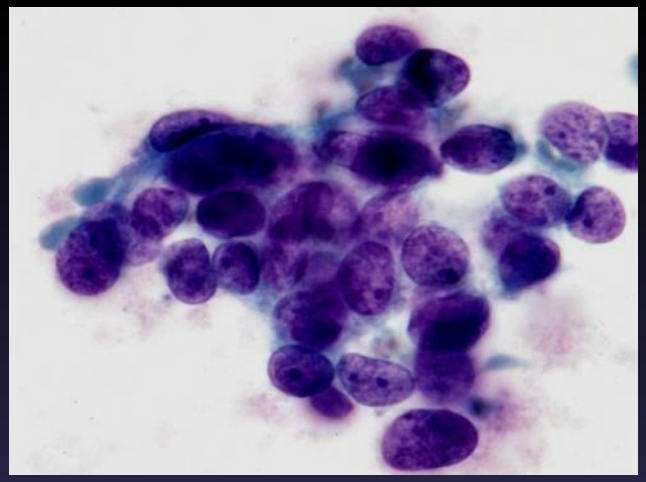
Case 1

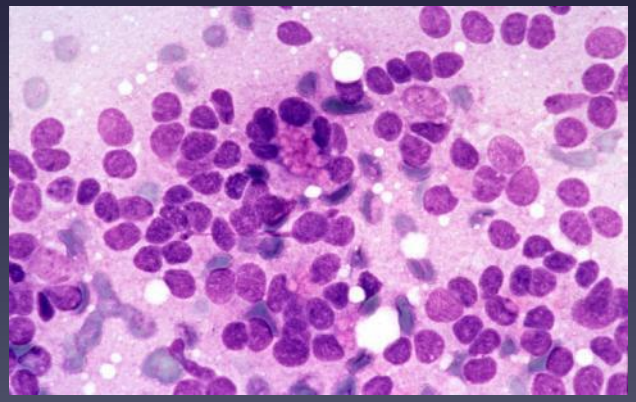


Case 1: Diagnosis?

Basal cell adenoma, membranous type

Basaloid neoplasms:
Differential Diagnosis

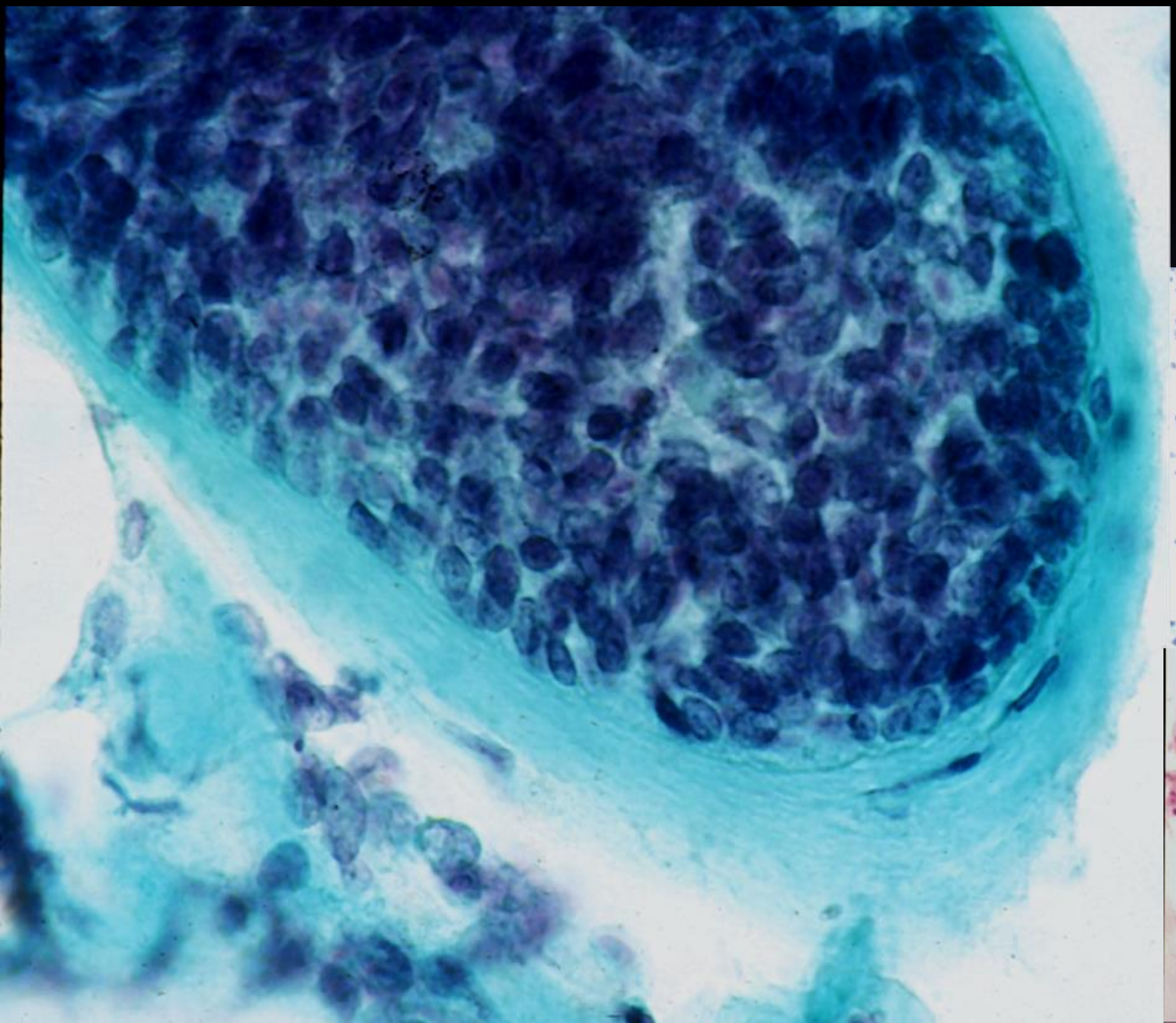




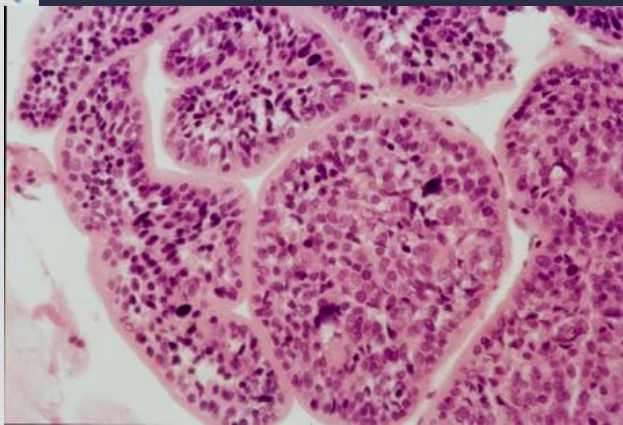
- Benign: Basal cell adenoma, myoepithelioma, pleomorphic adenoma, pilomatrixoma
- Low-grade malignant: Basal cell adenocarcinoma, basal cell carcinoma
- High-grade malignant: Adenoid cystic carcinoma, metastatic small cell carcinoma/Merkel cell carcinoma, primary neuroendocrine carcinoma, metastatic basaloid squamous cell carcinoma
  - Adenoid cystic carcinoma may be deceptively bland

Basaloid neoplasm

Basal cell adenoma, membranous type



- Distinguished by dense matrix material surrounding groups

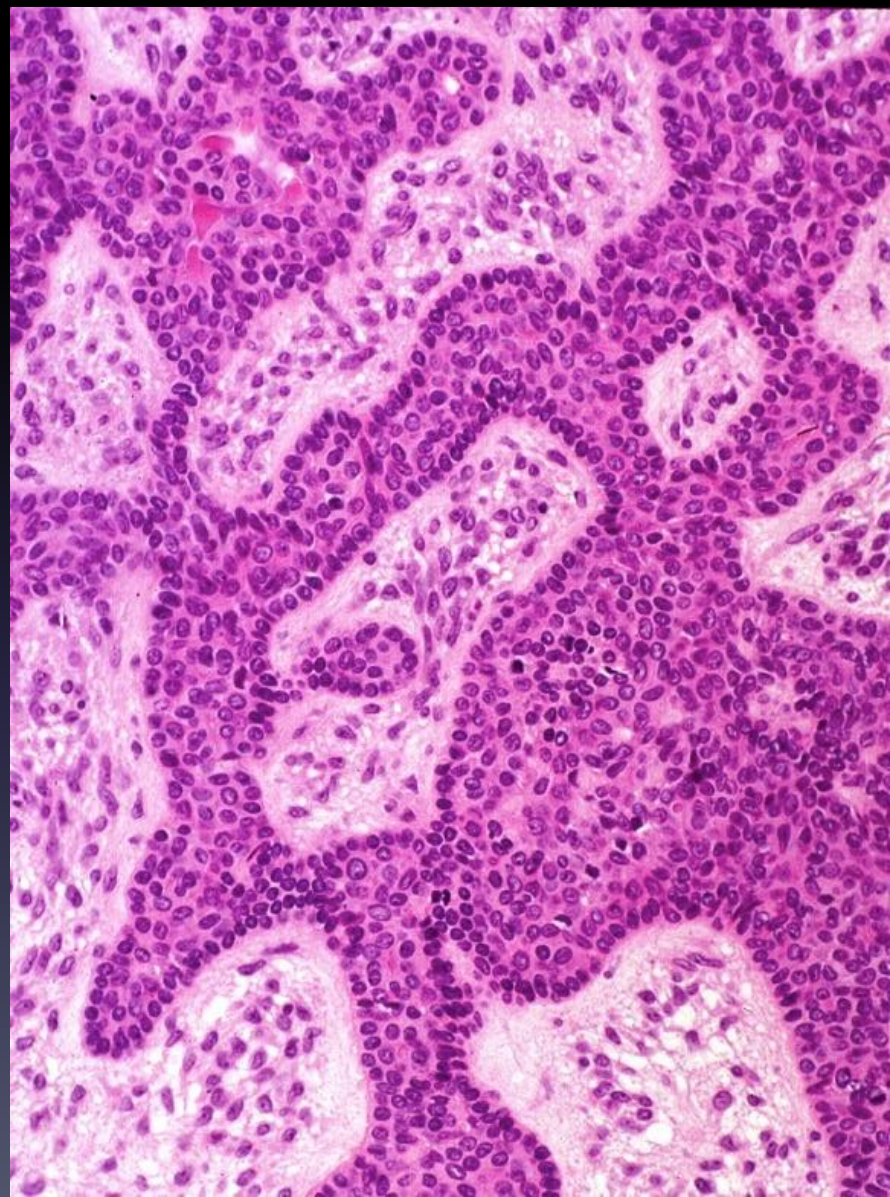


Basal cell adenoma, membranous type

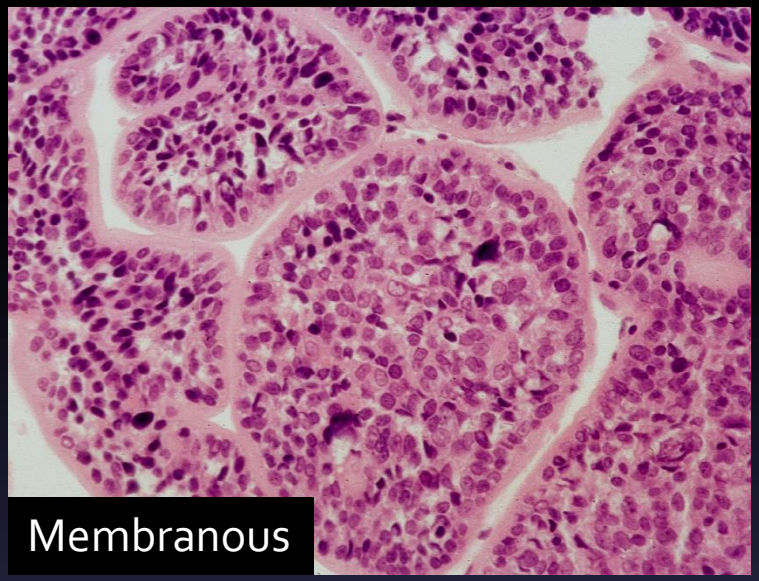
- Conspicuous basal lamina
- Similar to dermal cylindroma
- More aggressive behavior:
  - Recurrence 25%
  - Malignant transformation 28%

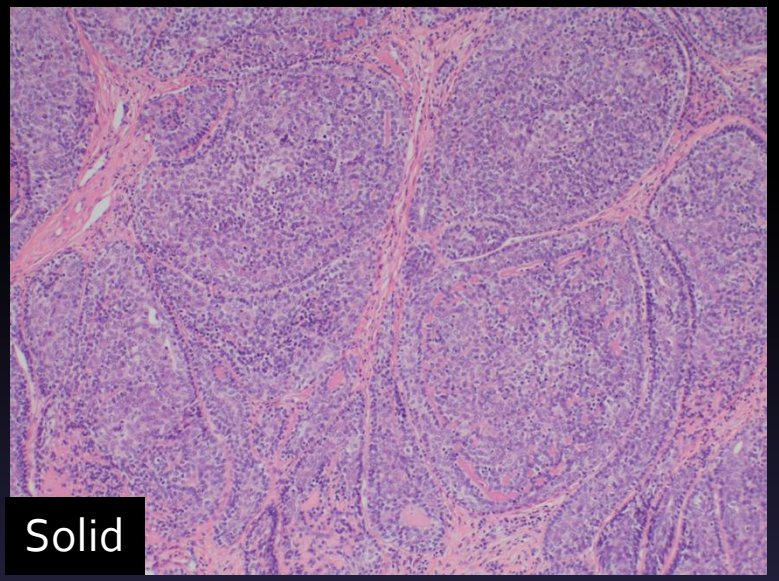
Basal Cell Adenoma

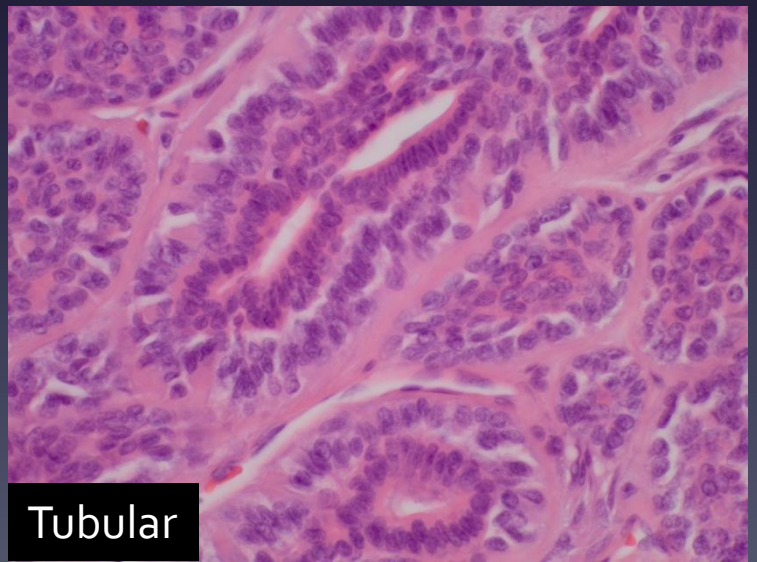
- 2% of benign salivary gland tumors
- Adults
- Parotid (>80%)
- Pathology
  - Basaloid/myoepithelial cells
  - No chondromyxoid matrix
  - Nuclear palisading
  - Ductal component

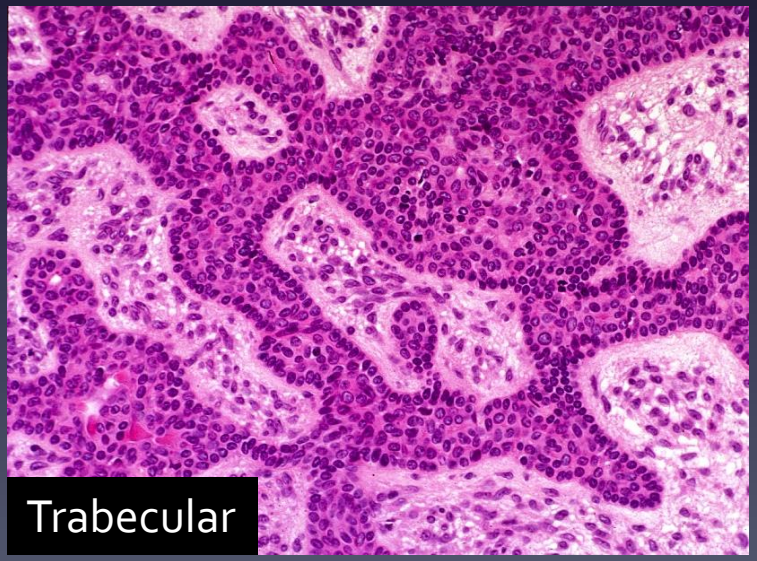


Basal cell adenoma


Membranous

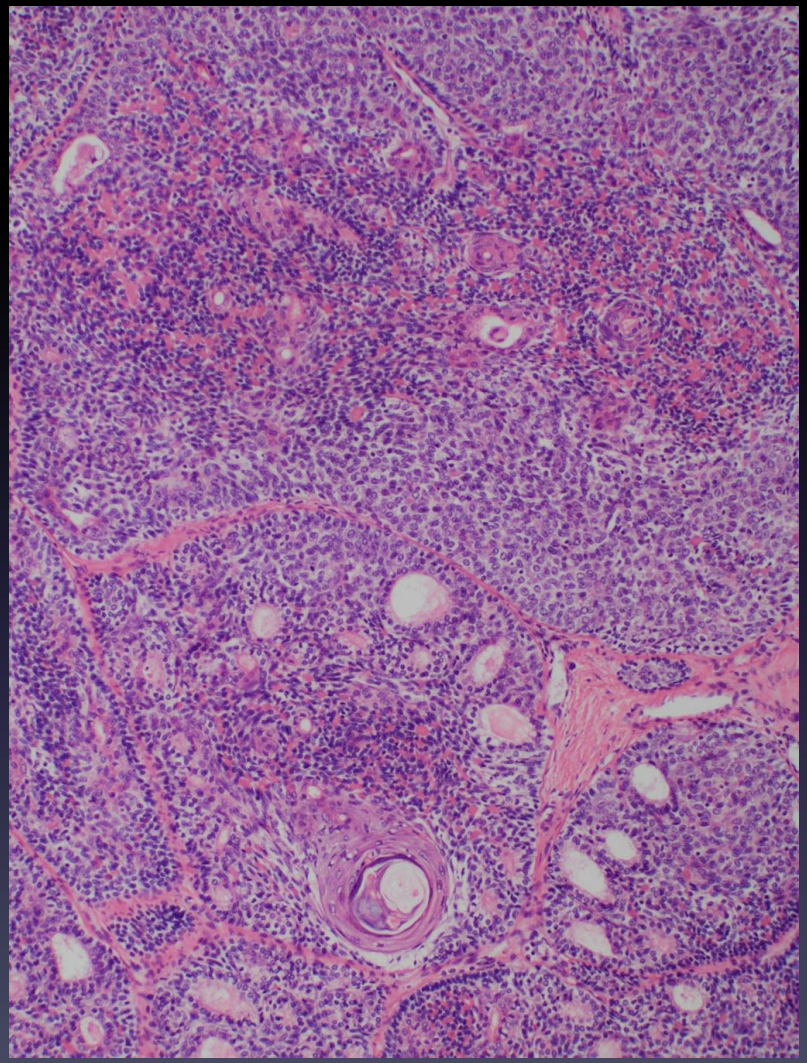

Solid


Tubular

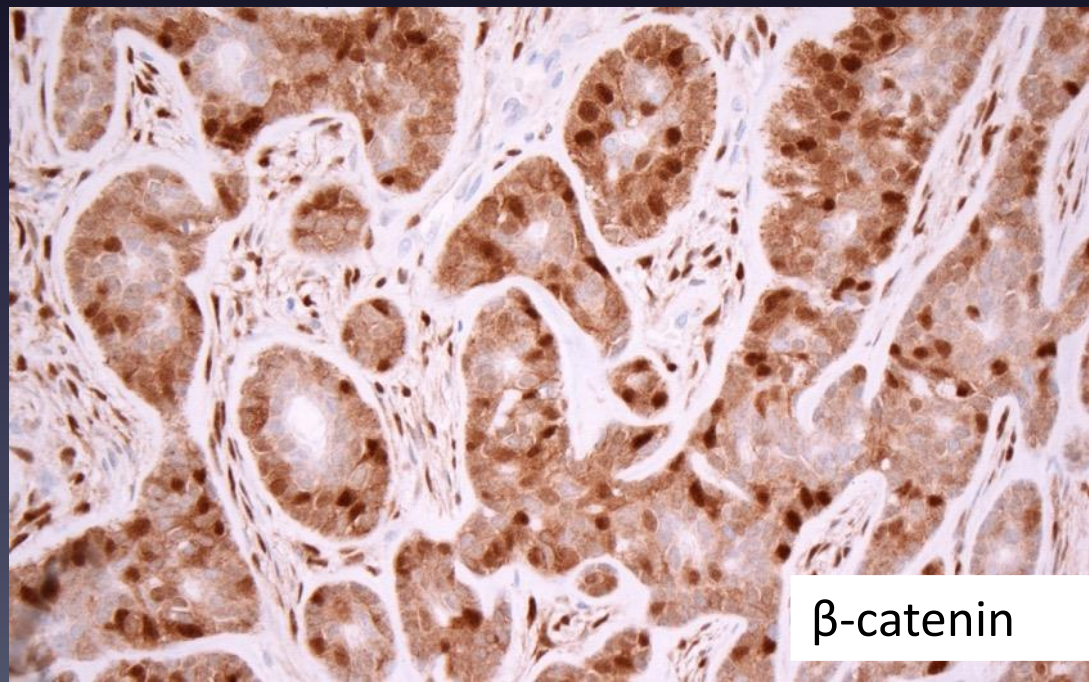

Trabecular

Basal Cell Adenoma

- Tubular/trabecular
  - *CTNNB1* I35S mutations
  - β-catenin expression (82%)
  - Highly specific (96%)
- Membranous
  - *CYLD* alterations
  - Brooke-Spiegler syndrome
  - Multiple familial trichoepithelioma



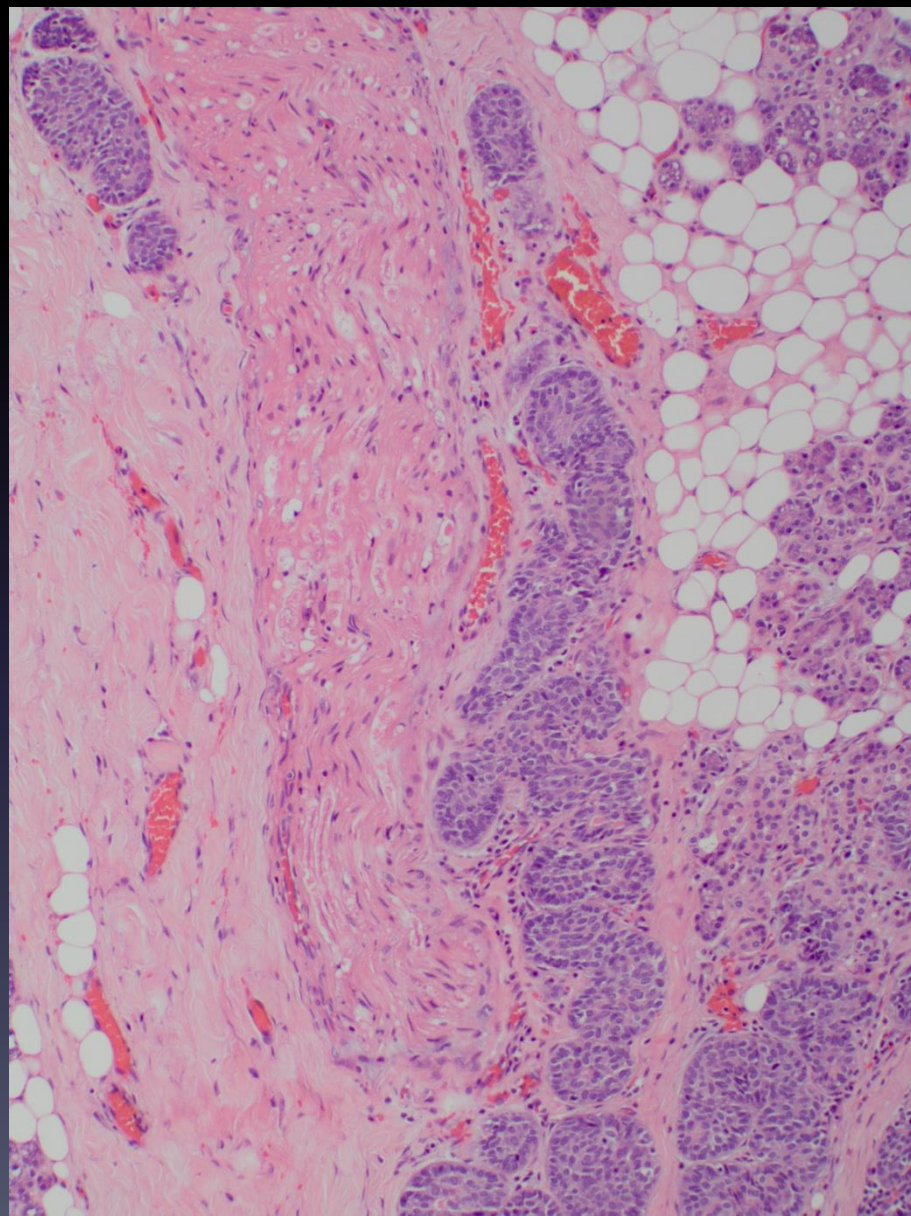
Jo et al *Am J Surg Pathol* (2016)



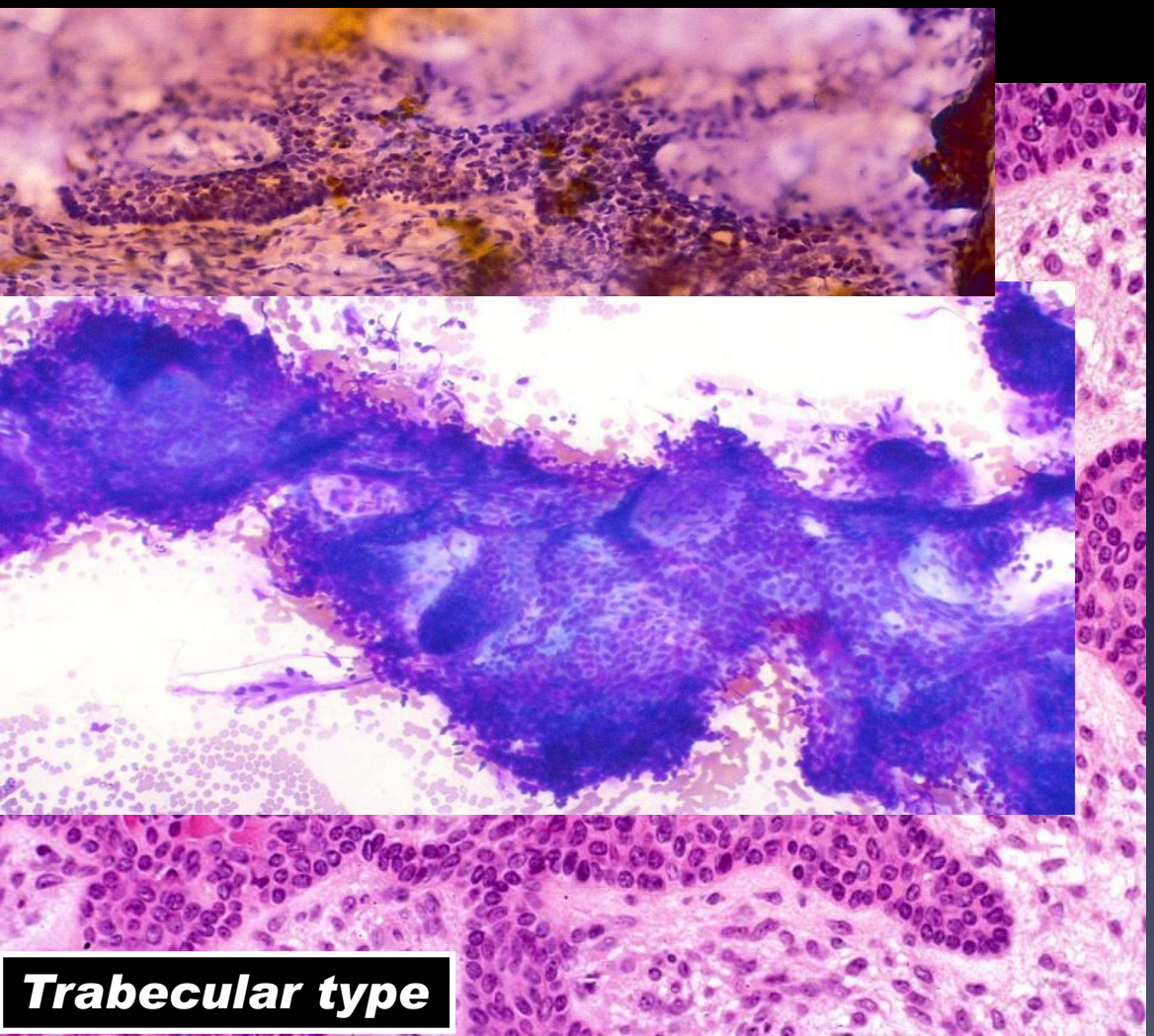
β-catenin

Basal cell adenocarcinoma

- Low-grade malignant counterpart
- Infiltrative growth
- 90% parotid
- About ¼ have lymphovascular or perineural invasion
- Mainly local recurrence
- Rarely fatal



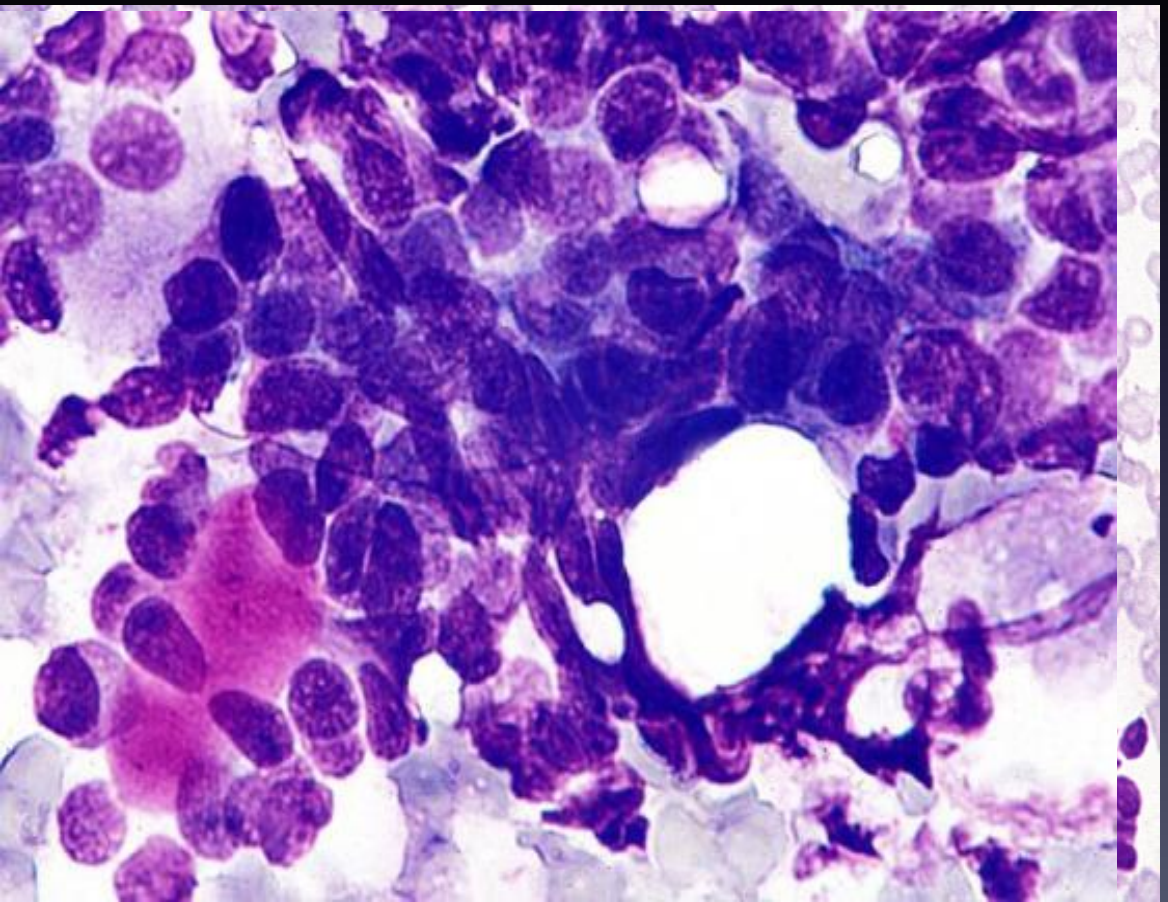
Basal cell adenoma/adenocarcinoma Cytologic features



- Can only distinguish benign vs malignant by infiltrative growth in resected specimen

- Basaloid cells
- Nuclear pallisading
- No atypia
- No necrosis
- No mitoses
- Lacks PA matrix material

Adenoid cystic carcinoma, solid variant



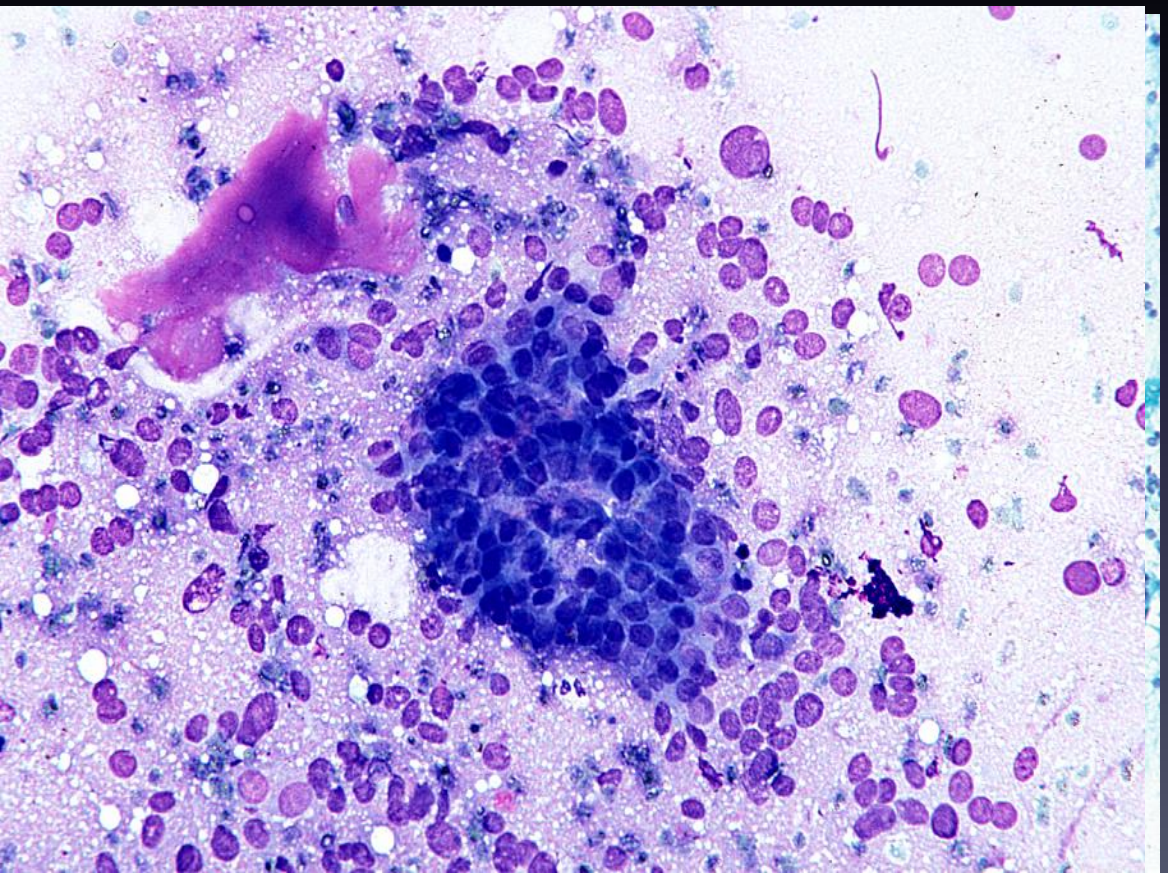
- More aggressive clinically
- Most difficult variant to identify on cytology
- Can only identify by finding characteristic matrix material

Adenoid cystic carcinoma

Stromal mimics

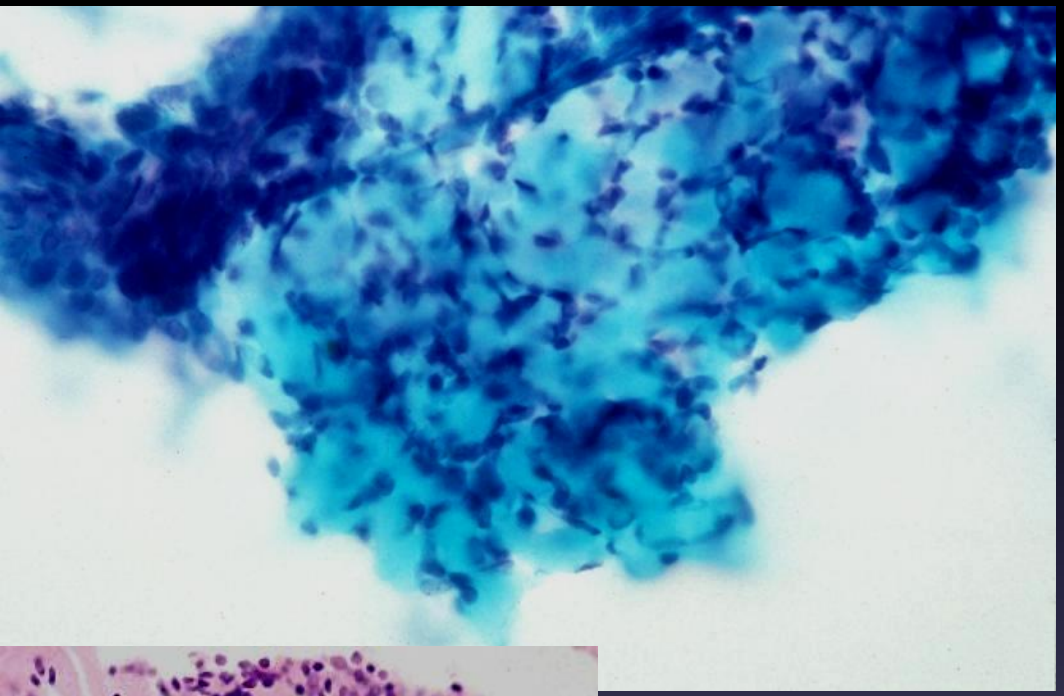
- Pleomorphic adenoma
- Epithelial-myoepithelial carcinoma
- Basal cell adenoma
- Polymorphous adenocarcinoma

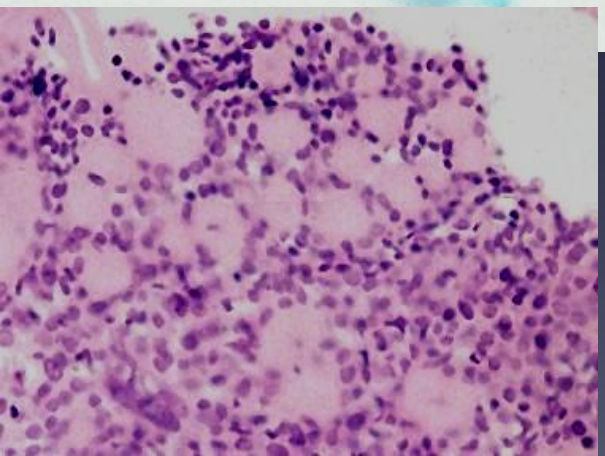
Epithelial-myoepithelial carcinoma



- Biphasic
  - Ductal cells
  - Clear myoepithelial cells
- Background bare nuclei
- Acellular, peripherally located, basement membrane material

Non-specific matrix material





- Lattice-like matrix material with small, interdigitating, coalescing hyaline globules
- Basaloid myoepithelial cells
- This pattern is non-specific
  - Pleomorphic adenoma
  - Myoepithelioma
  - Basal cell adenoma/adenocarcinoma
  - Adenoid cystic carcinoma
  - Basaloid squamous cell carcinoma

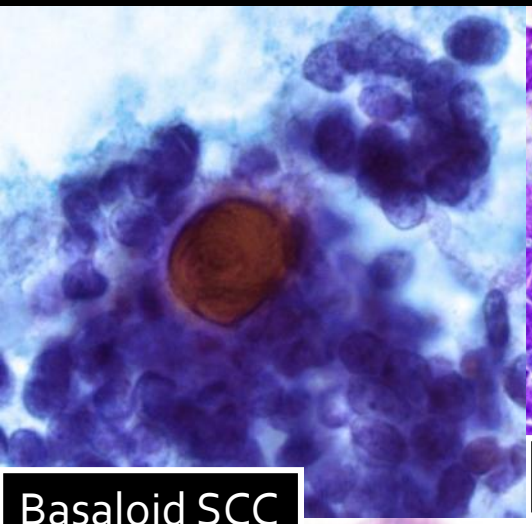
Basaloid neoplasms

Diagnostic limitations

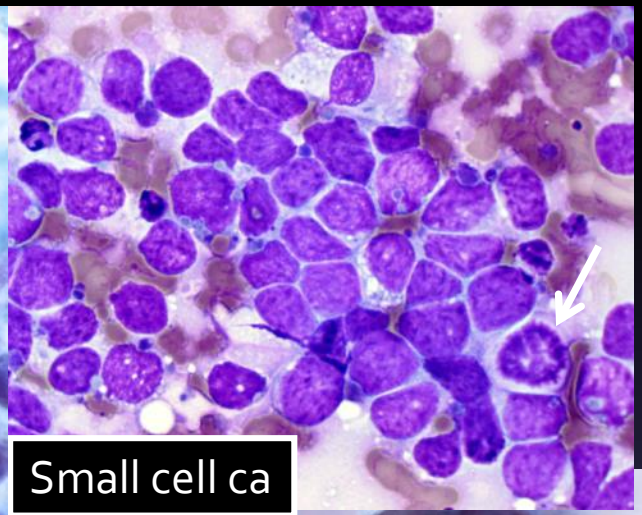
- Often cannot be definitive or exclude adenoid cystic carcinoma
- Sign out descriptively:
  - SUMP.
  - BASALOID NEOPLASM. NOTE: Although overt cytologic features of malignancy are not seen, the differential diagnosis includes both benign and malignant salivary gland neoplasms, including BCA and adenoid cystic carcinoma. Surgical excision is recommended for precise classification.

Basaloid neoplasms

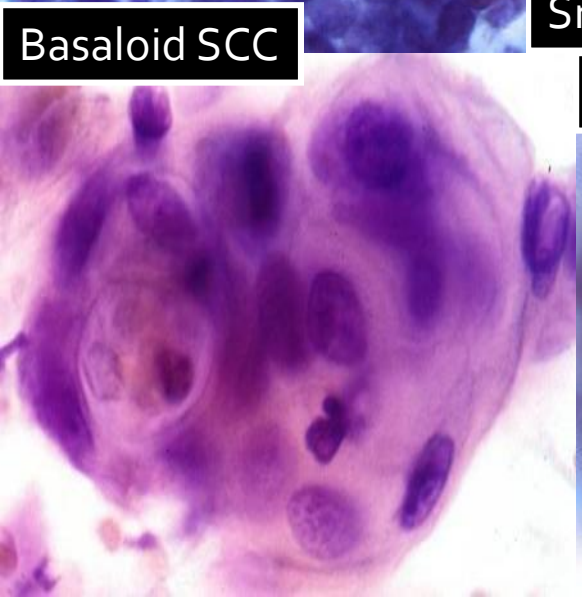
Diagnostic clues

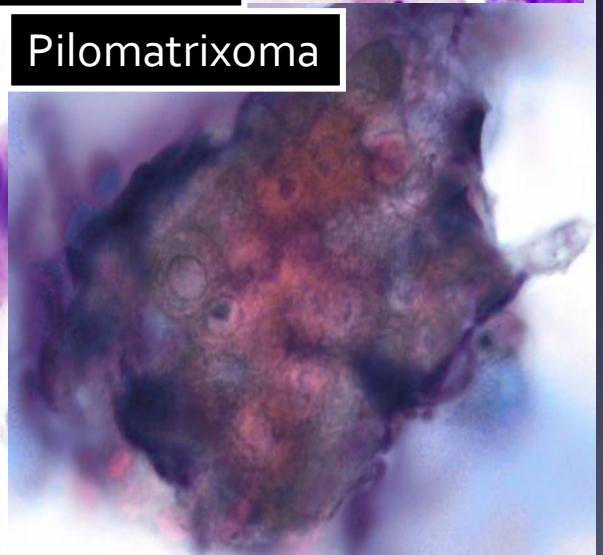


Basaloid SCC



Small cell ca



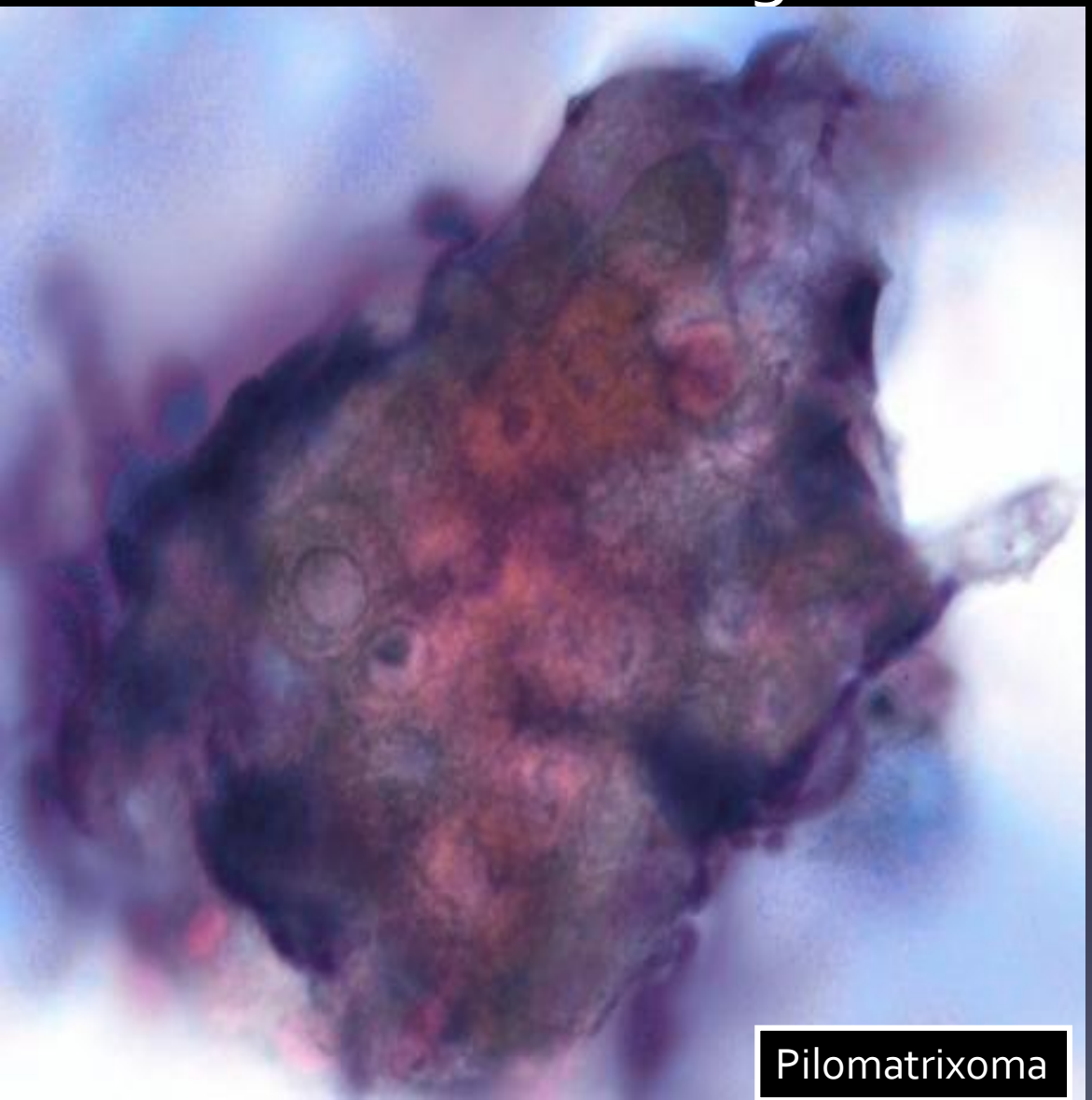


Pilomatrixoma

- Look for atypia, necrosis, and mitotic activity in high-grade malignancies
- Squamous whorls
  - Basaloid squamous cell carcinoma
  - Basal cell adenoma/adenocarcinoma
  - *Not seen in adenoid cystic carcinoma*
- Characteristic matrix material of adenoid cystic
- Ghost cells in pilomatrixoma
- History, clinical, and radiologic findings

Basaloid neoplasms

Diagnostic clues



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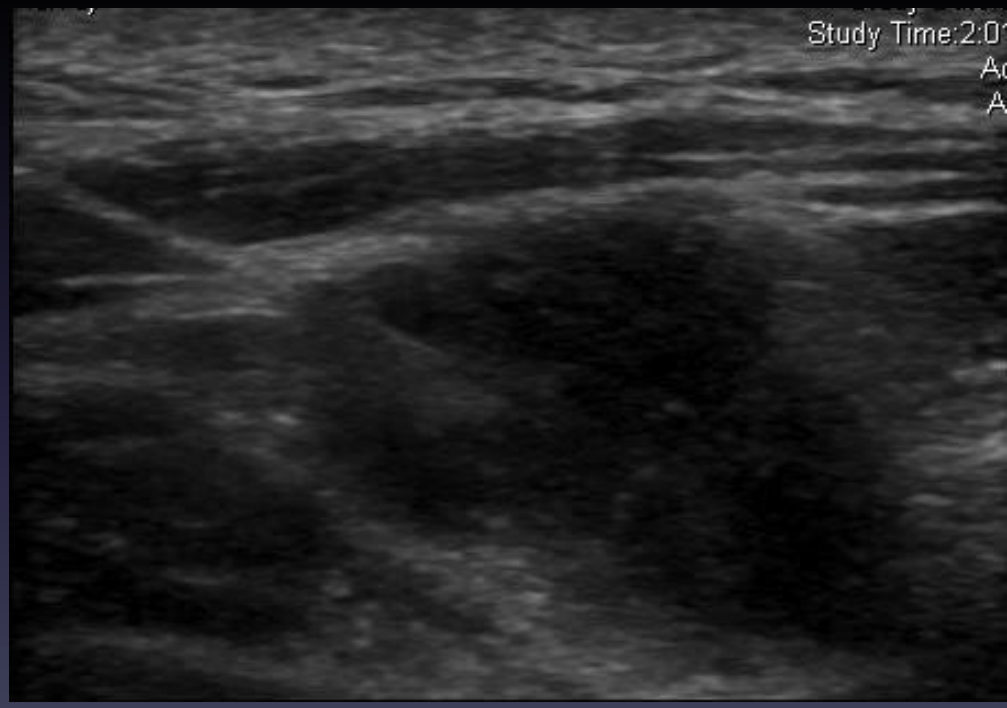
Case 2: History

- A 62 year old man presents with a necrotic 2.2 cm left neck mass



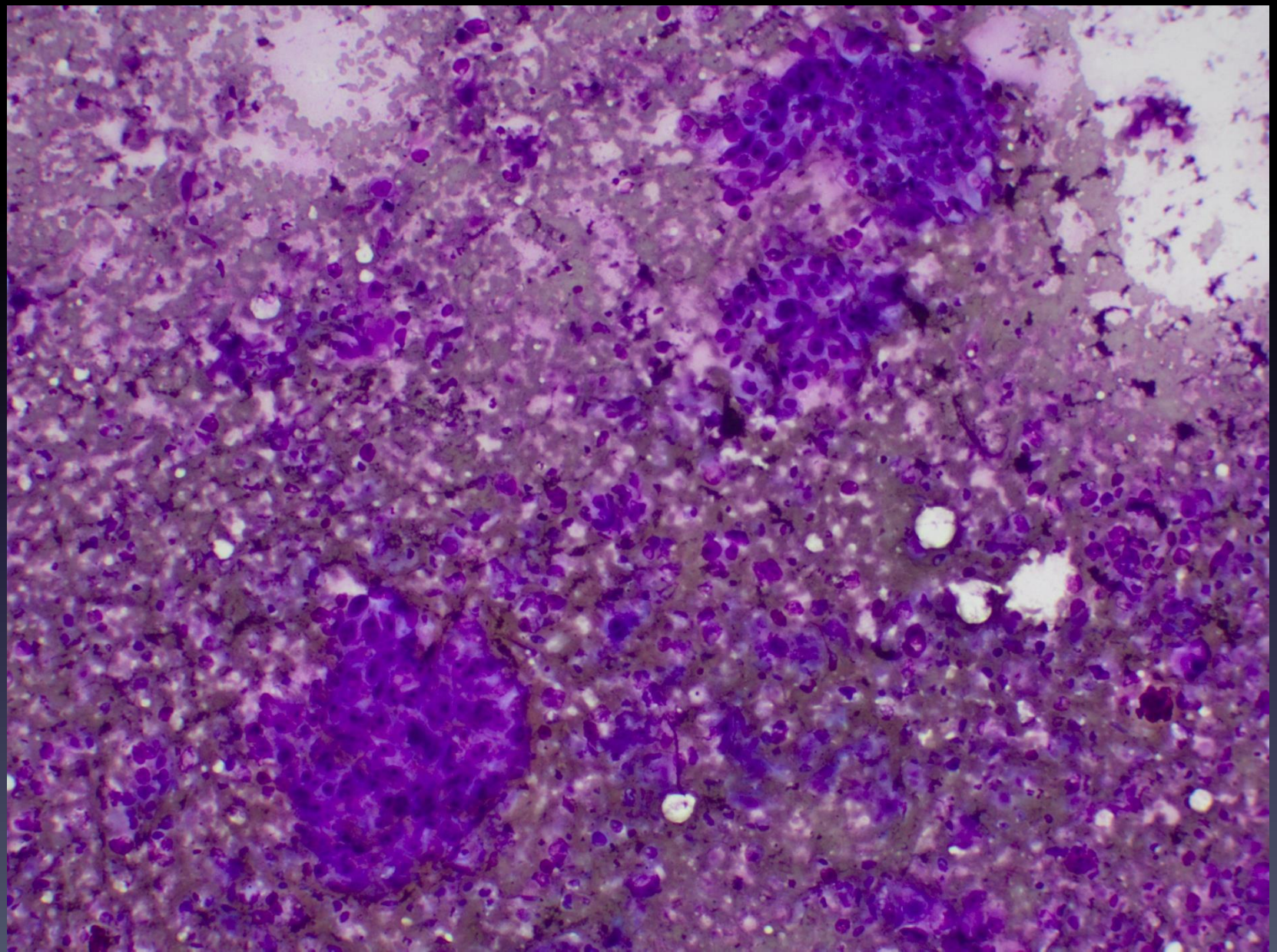
I cheated (a little)

- Primary is unknown but…
- 5 yrs earlier: T2N2 base of tongue SCC, post chemo/XRT
- 2 years earlier: Cutaneous SCC in scalp region
- 1 year earlier: T2N2 esophageal adenocarcinoma, post chemo and esophagectomy

General cytologic principles

- Critical to know as much history as possible
- Known history of malignancy, before you even look at the specimen consider the scenario
  - Does the pattern of spread make sense for the primary?
  - What do the clinician and radiologist think is most probable explanation?
  - What is your idealized vision of what this tumor will look like?
  - What is the spectrum of what this tumor typically looks like?
  - Is there a history of multiple malignancies?

Case 2



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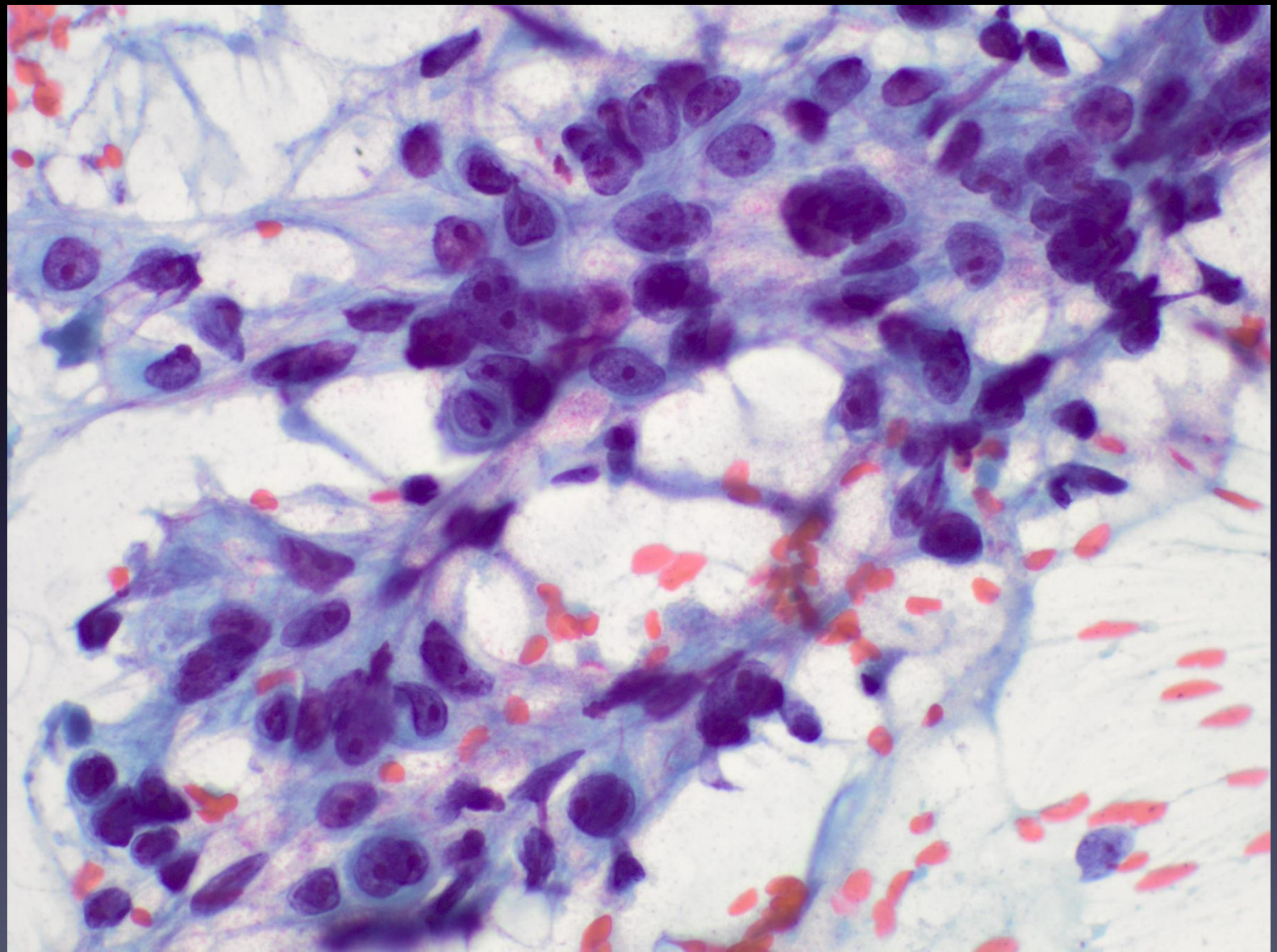

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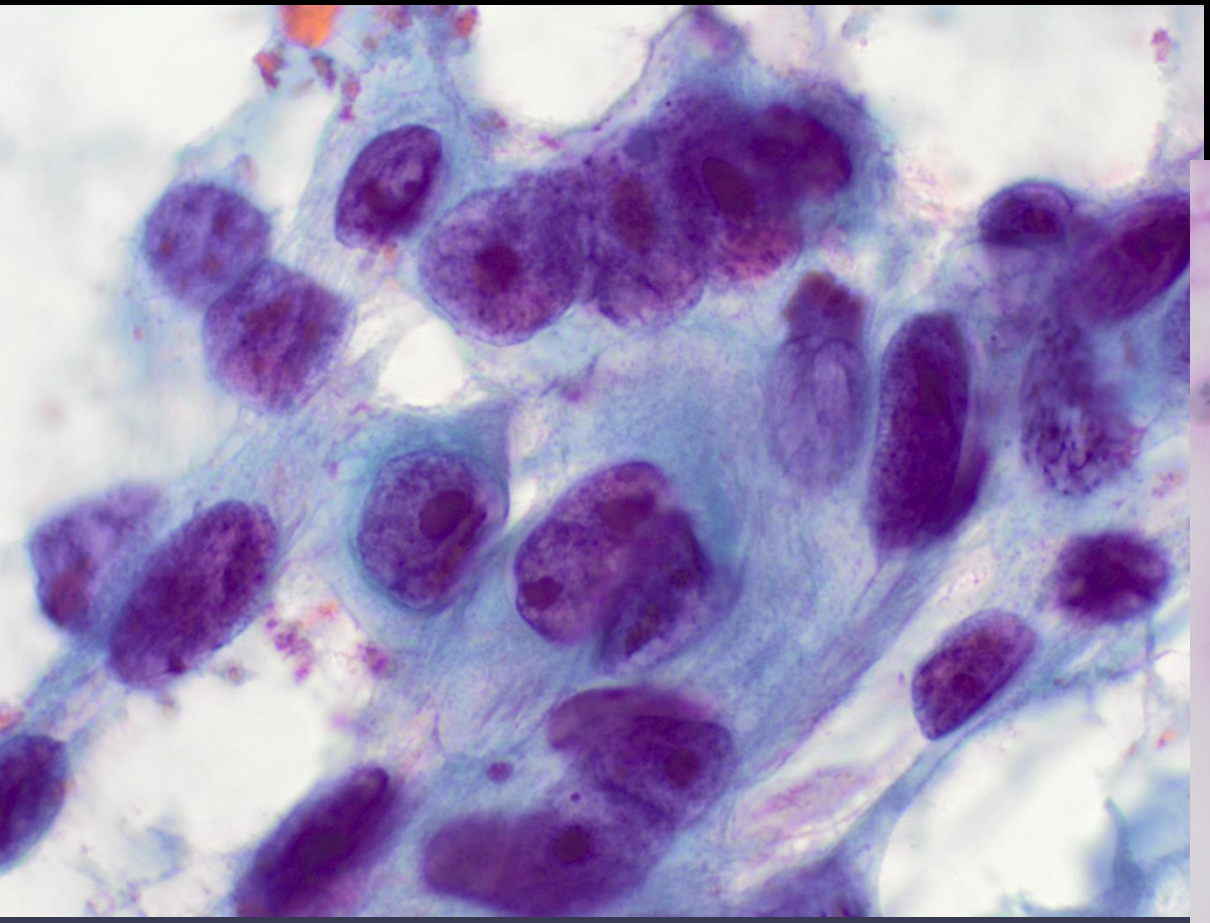
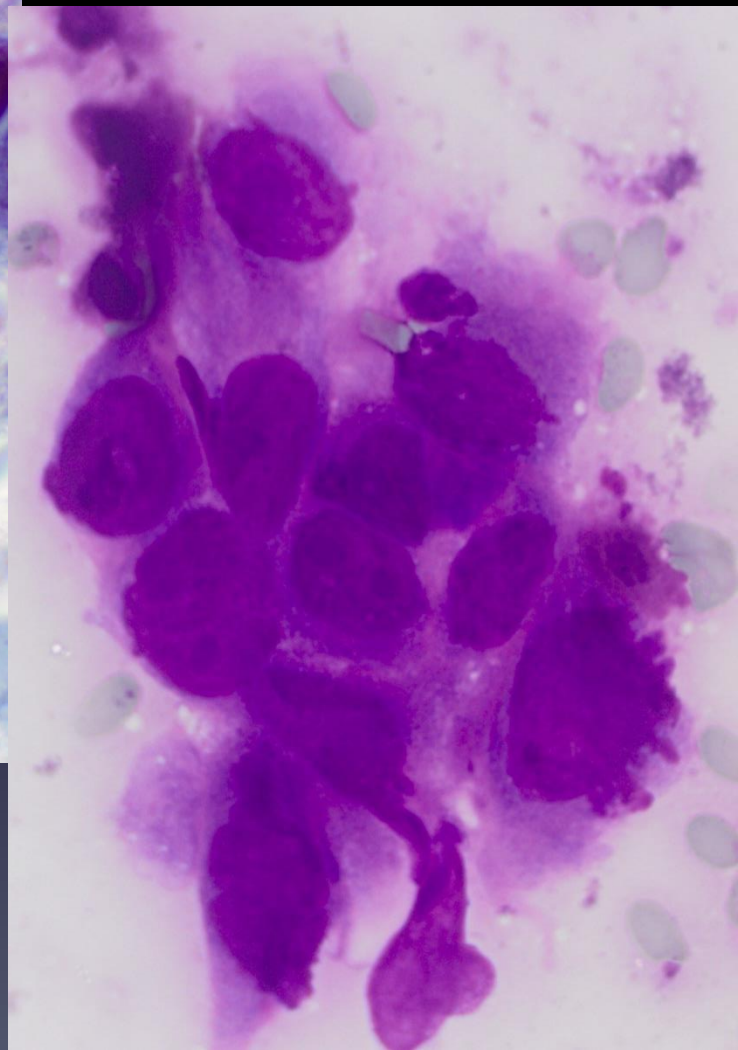




Case 2: Diagnosis?

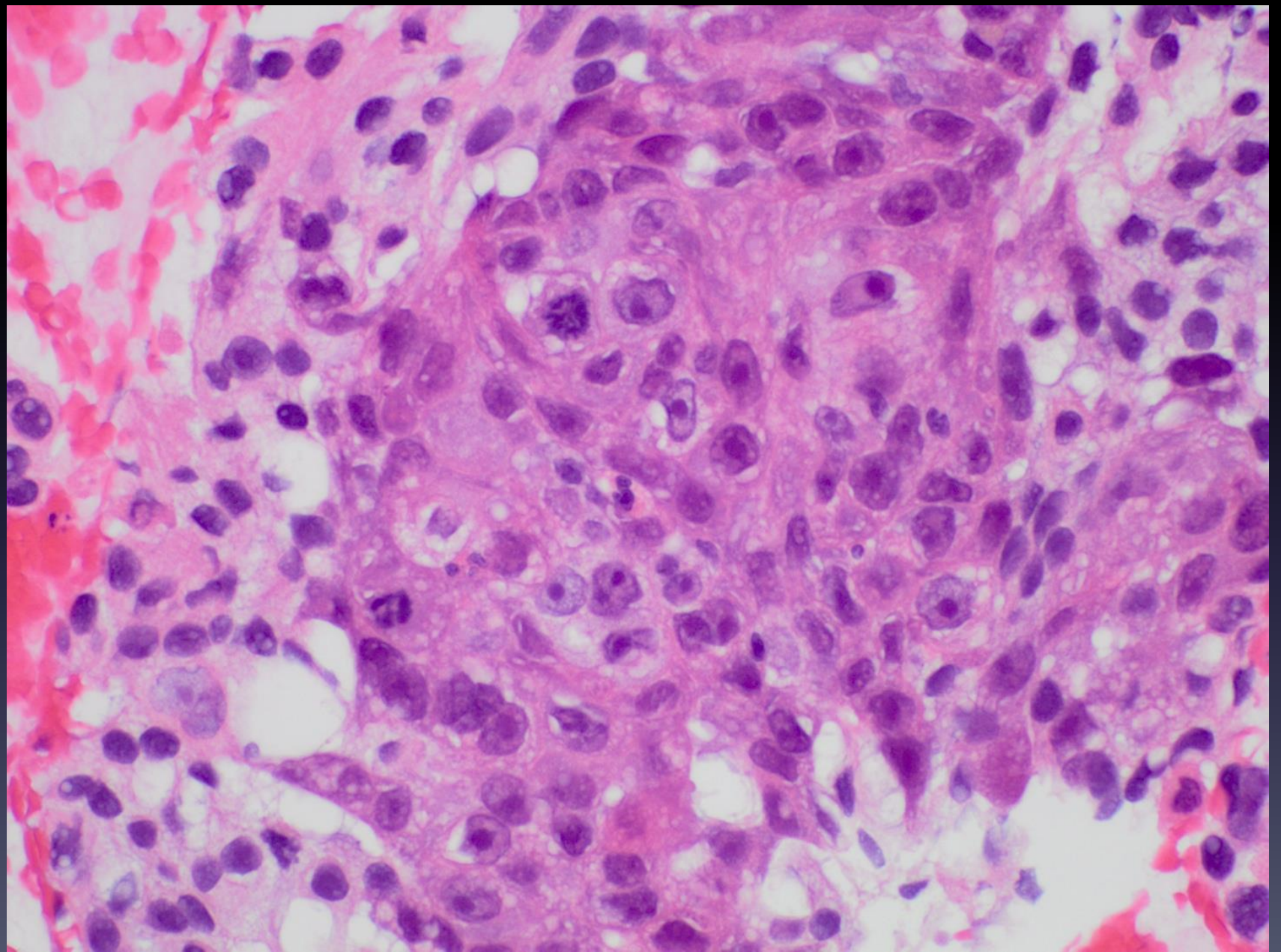
A. Metastatic SCC from tongue base

B. Metastatic SCC from scalp

C. Metastatic esophageal adenocarcinoma

D. A new primary carcinoma

Case 2



Case 2: Diagnosis

Poorly differentiated SCC

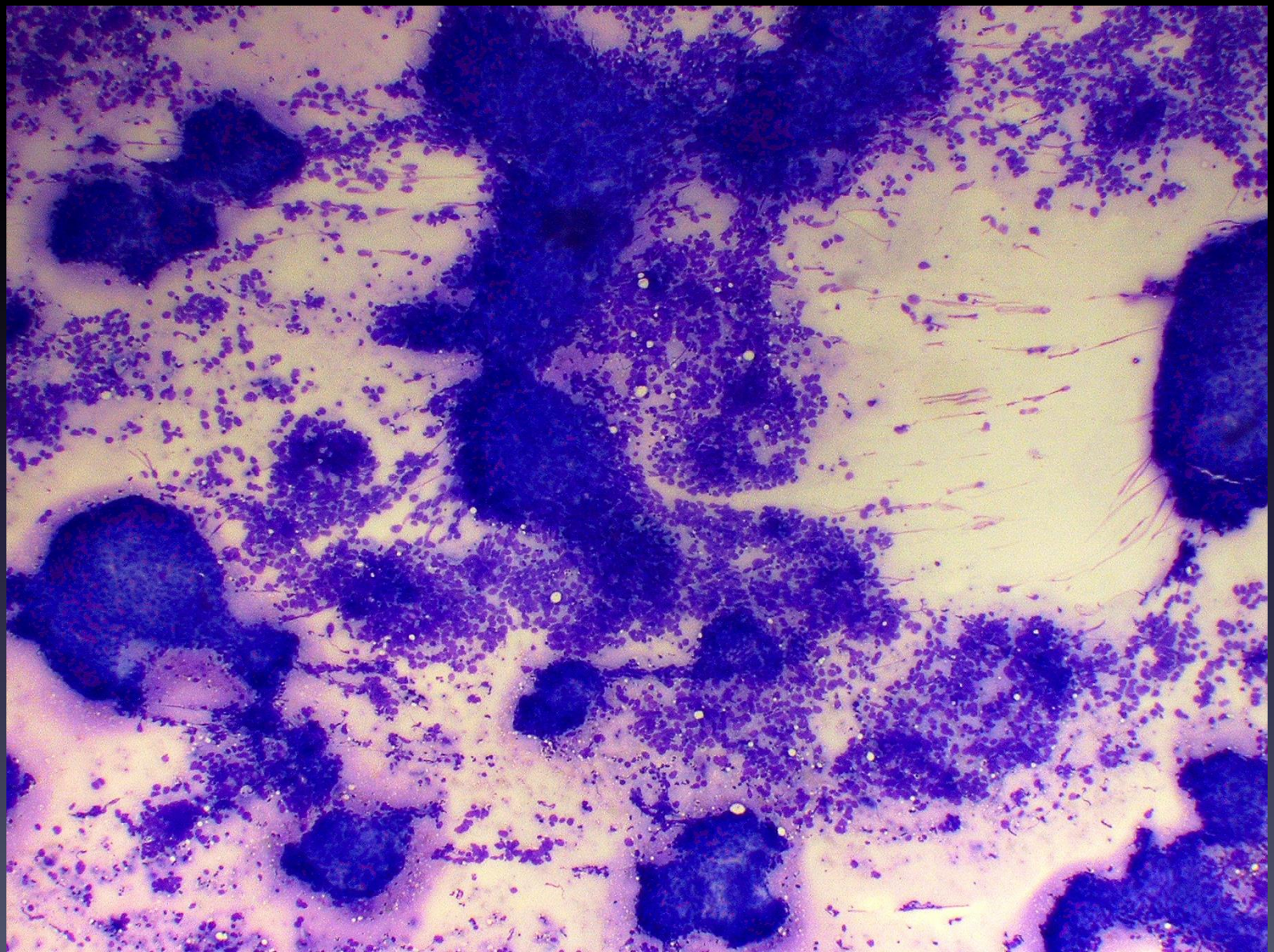
What about primary site?

We'll come back to this later…

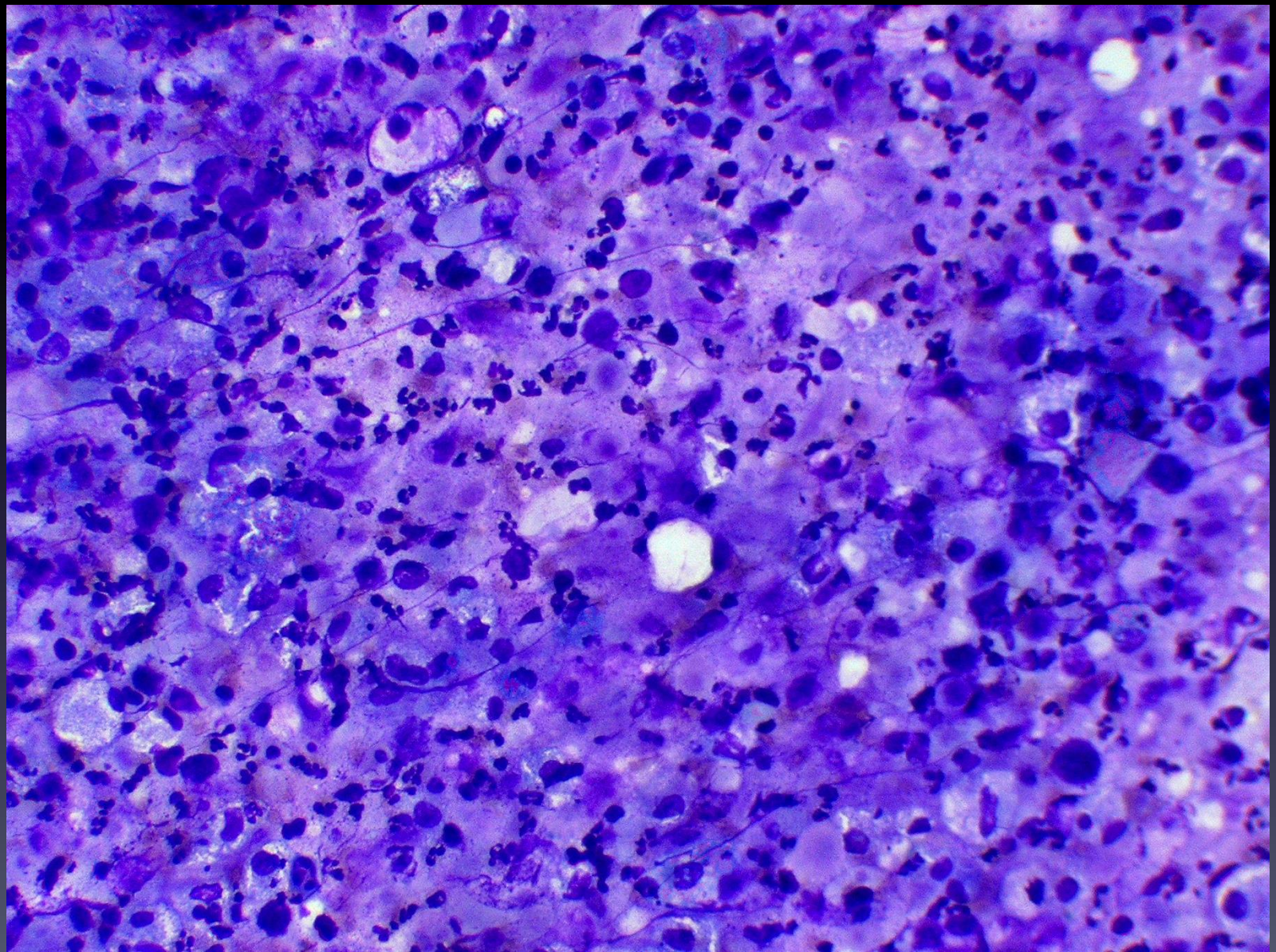
Case 3

A 77 year old man and his 75 year old wife each present with a right neck mass. Both have "minimal" smoking histories. The man had an FNA performed.

Case 3



Case 3



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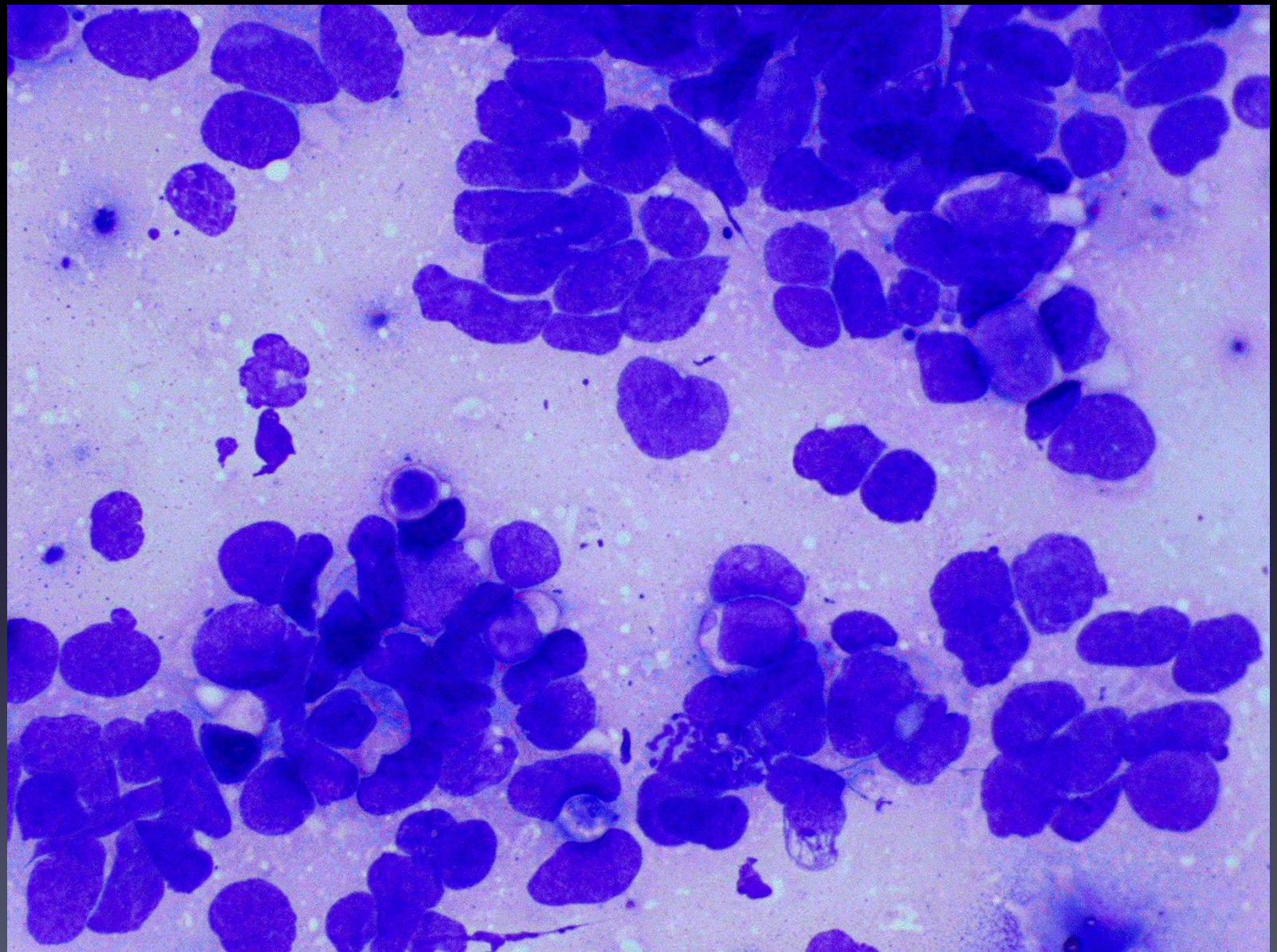

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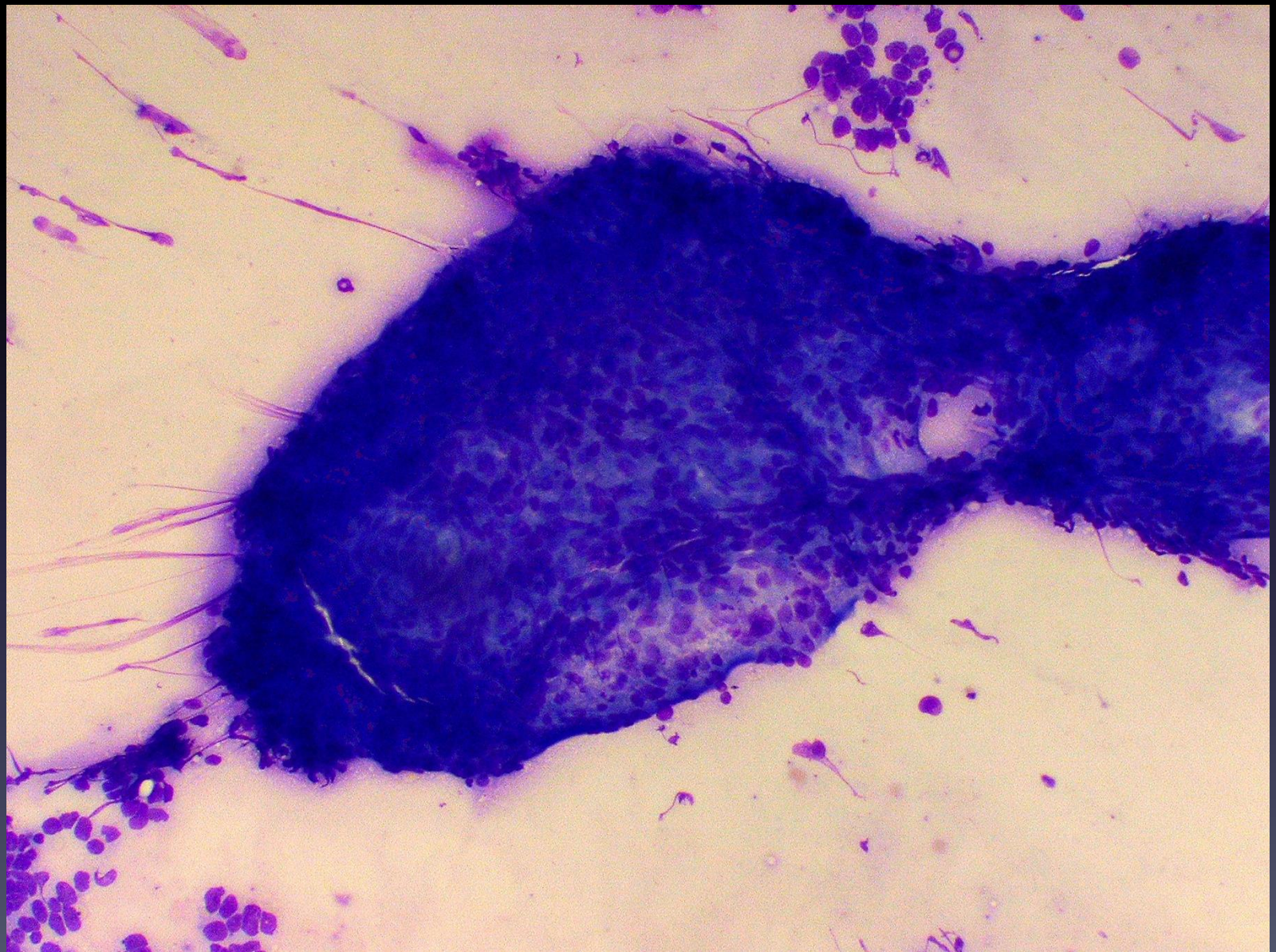


Case 3: Diagnosis?

A. Adenoid cystic carcinoma, solid type

B. Other salivary gland carcinoma

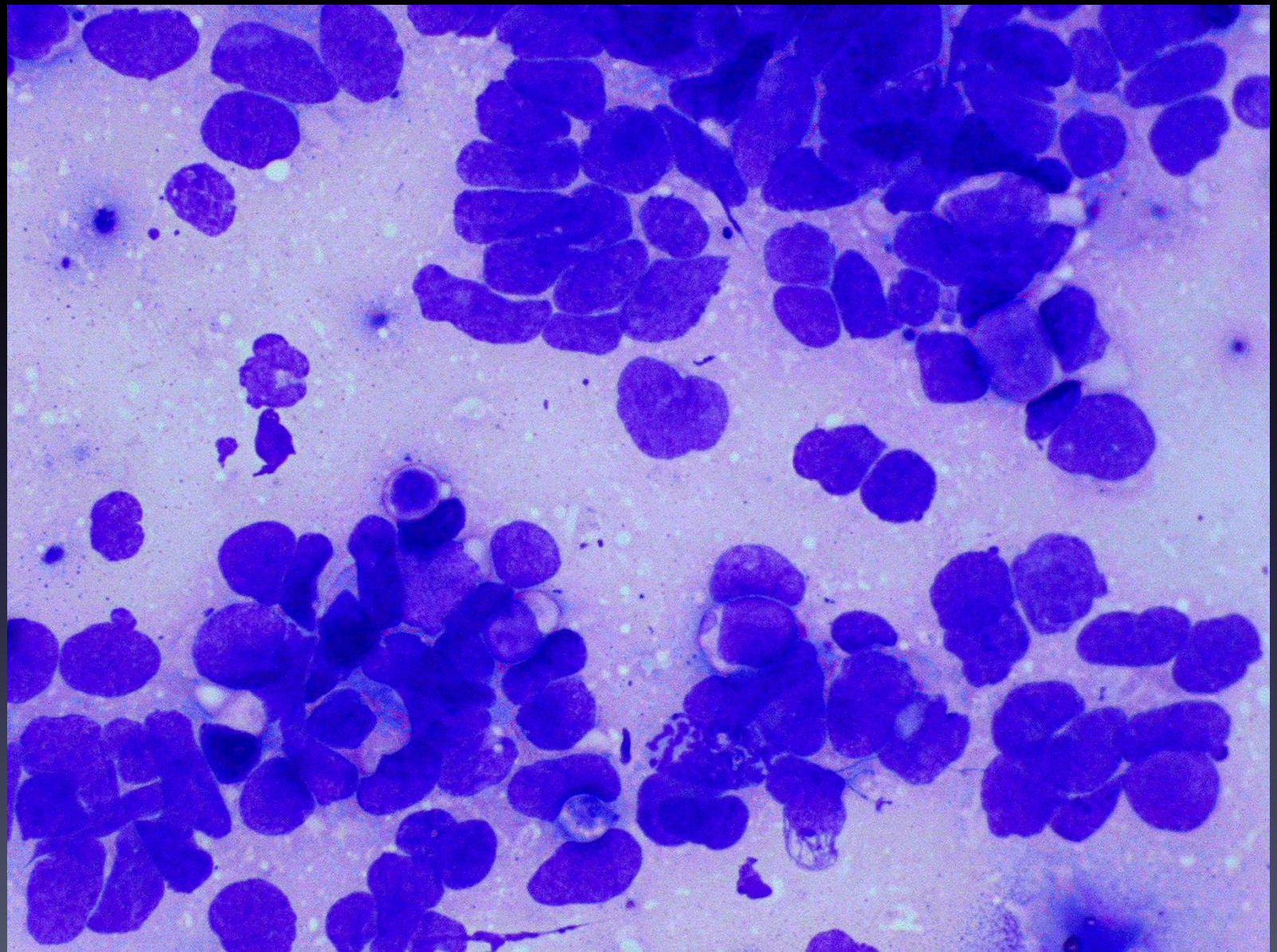
C. Metastatic small cell carcinoma

D. Squamous cell carcinoma with basaloid features

Case 3: Diagnosis

SCC with basaloid features

Case 3



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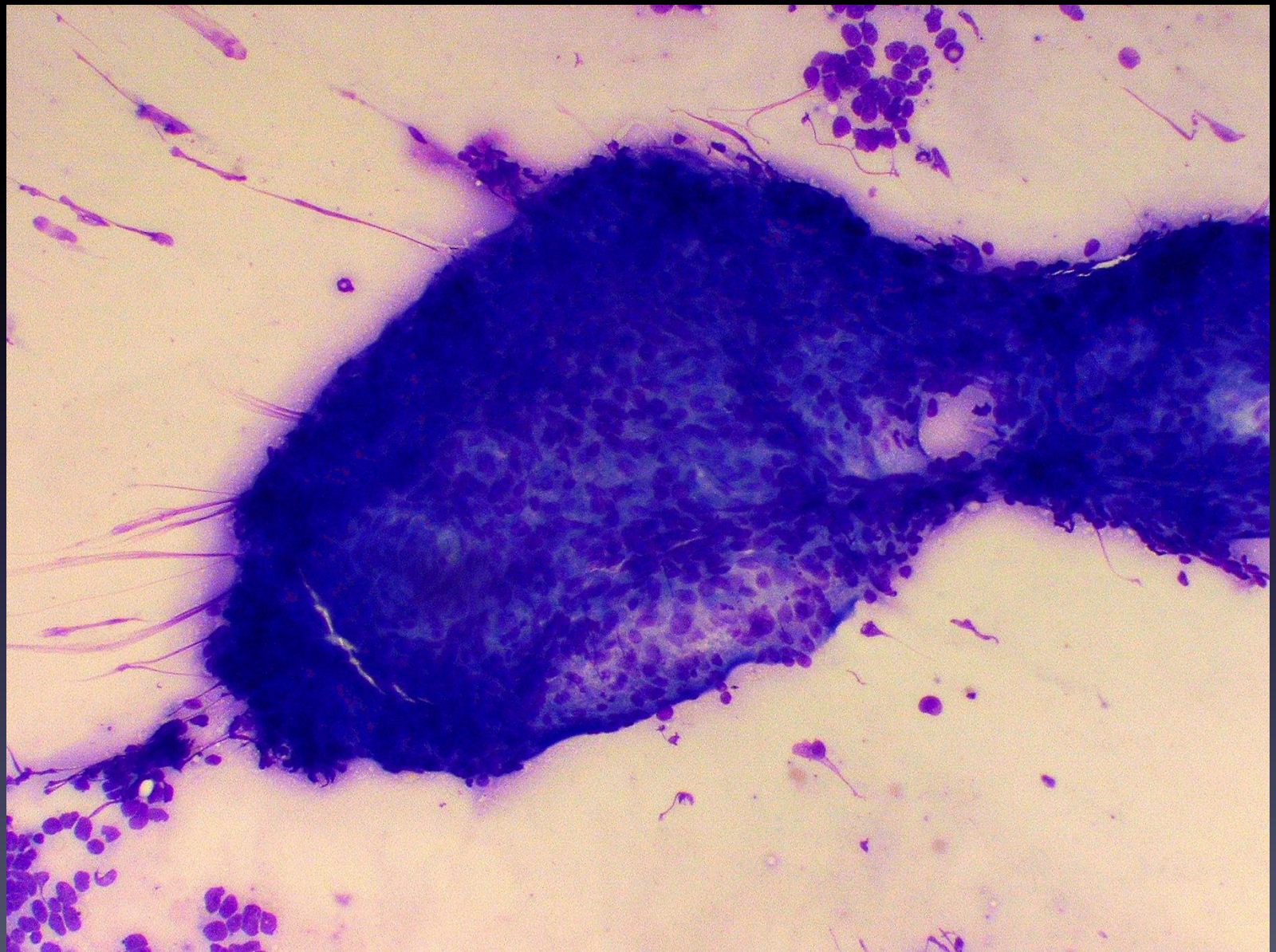
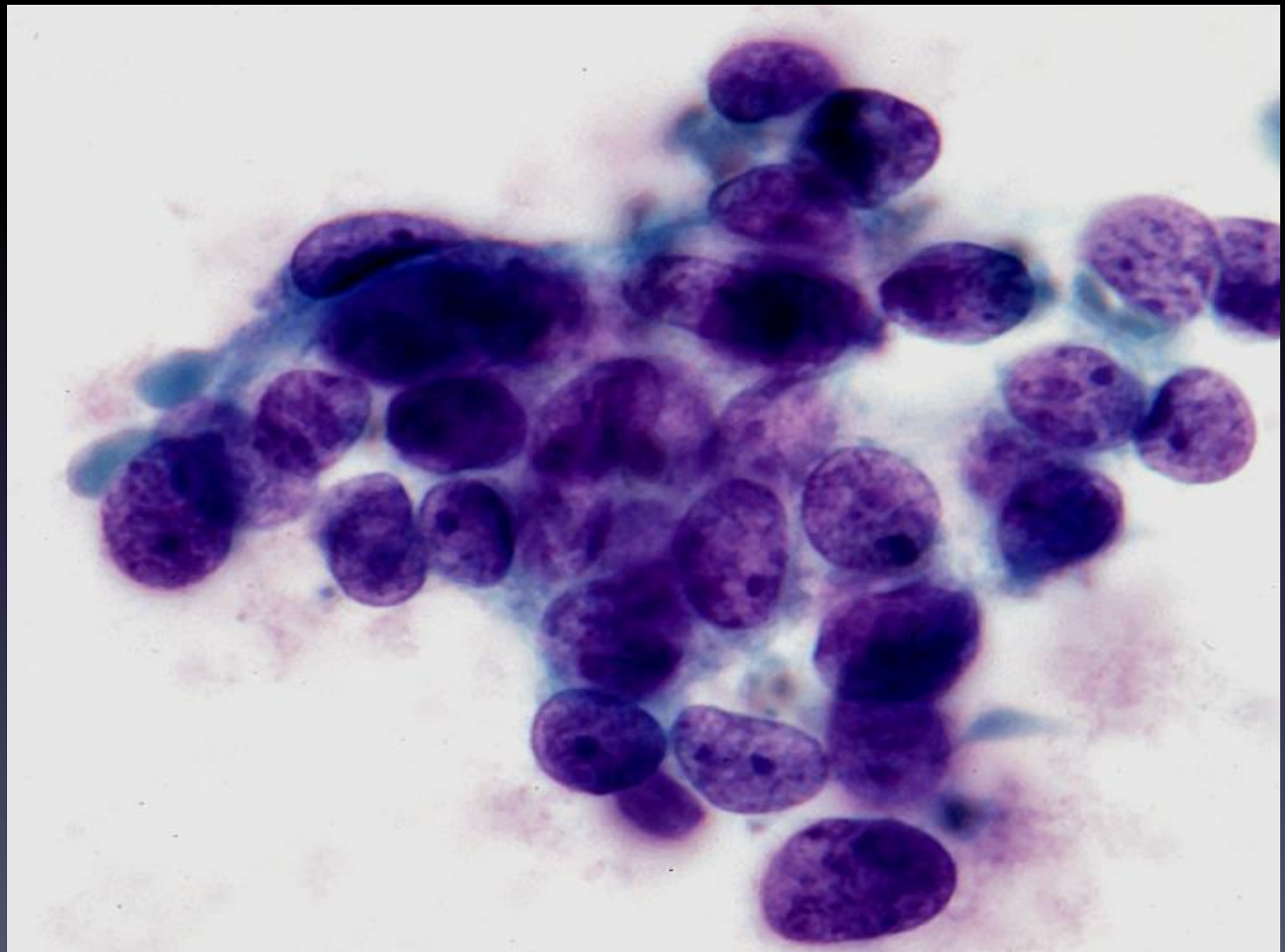
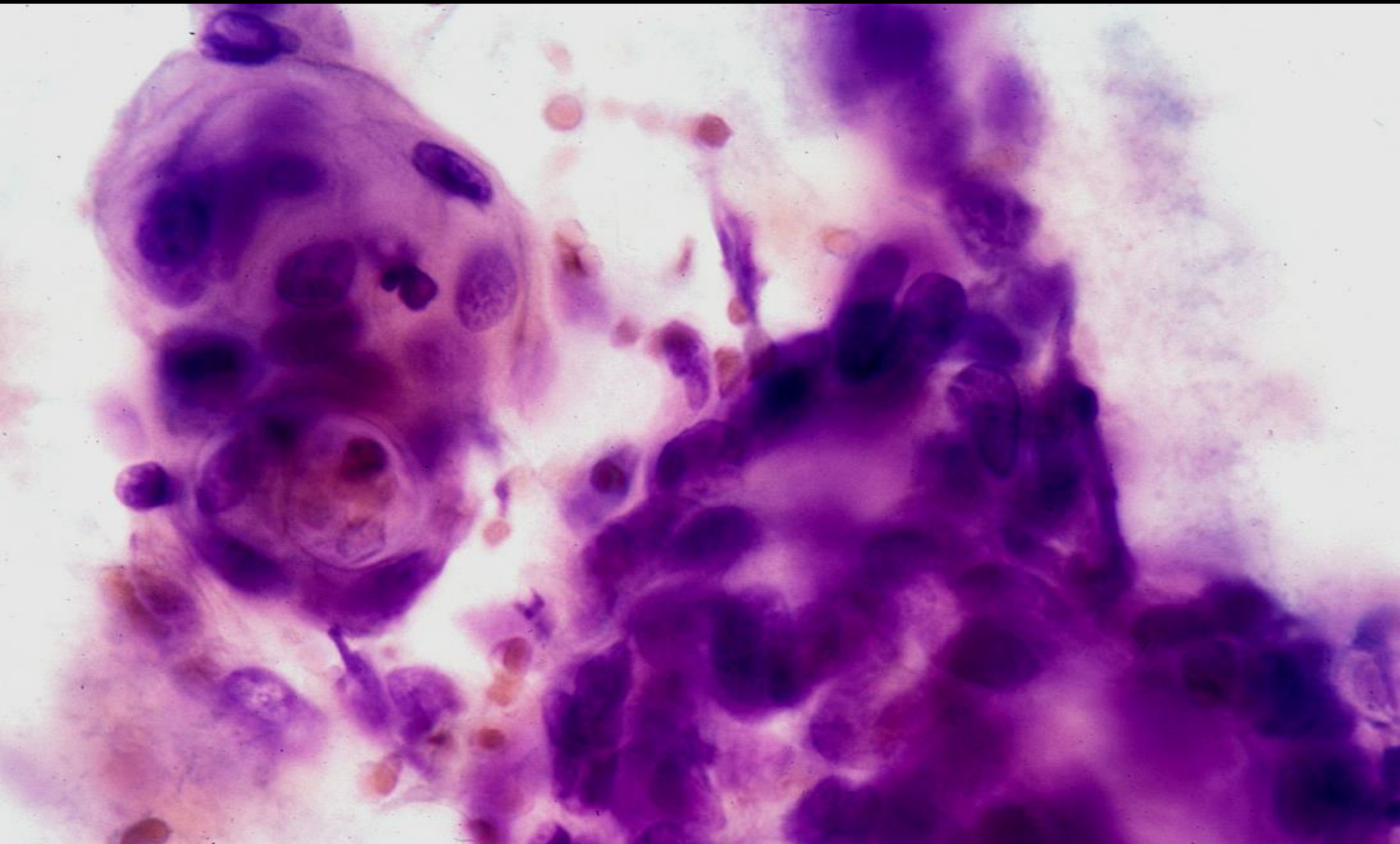


Basaloid squamous cell carcinoma

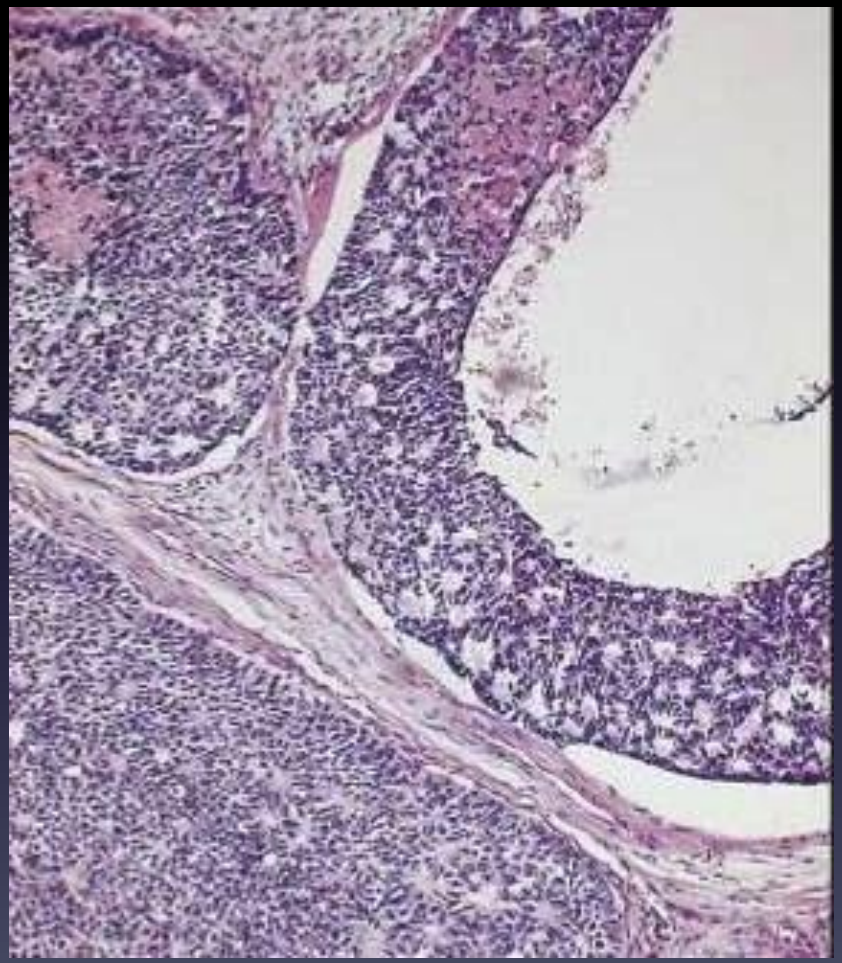


Basaloid squamous cell carcinoma

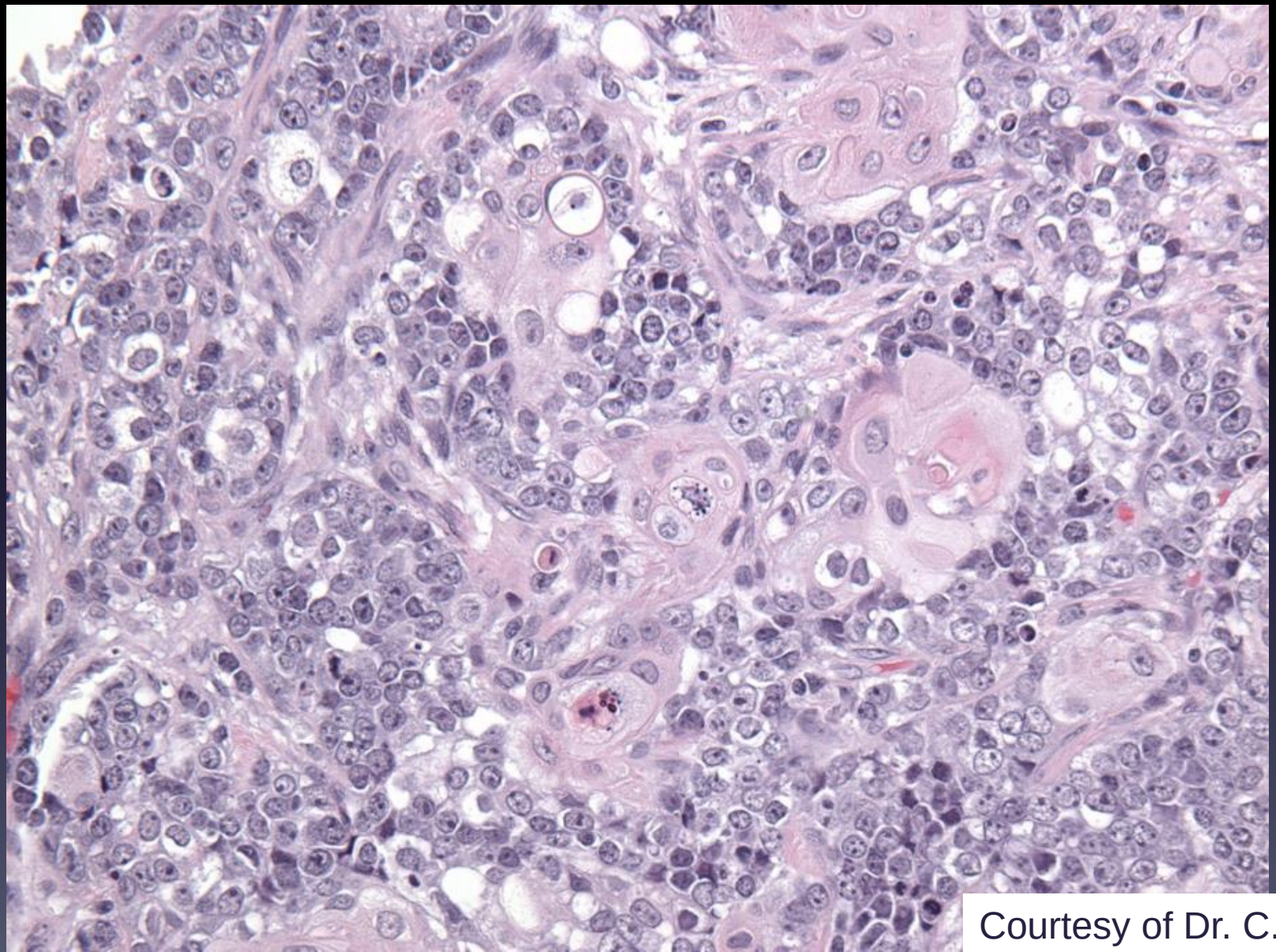


Basaloid SCC

- Poorly differentiated variant
- Aggressive
- Especially common in the head and neck region
- Basaloid appearance also common with HPV-associated SCC, but prognosis differs

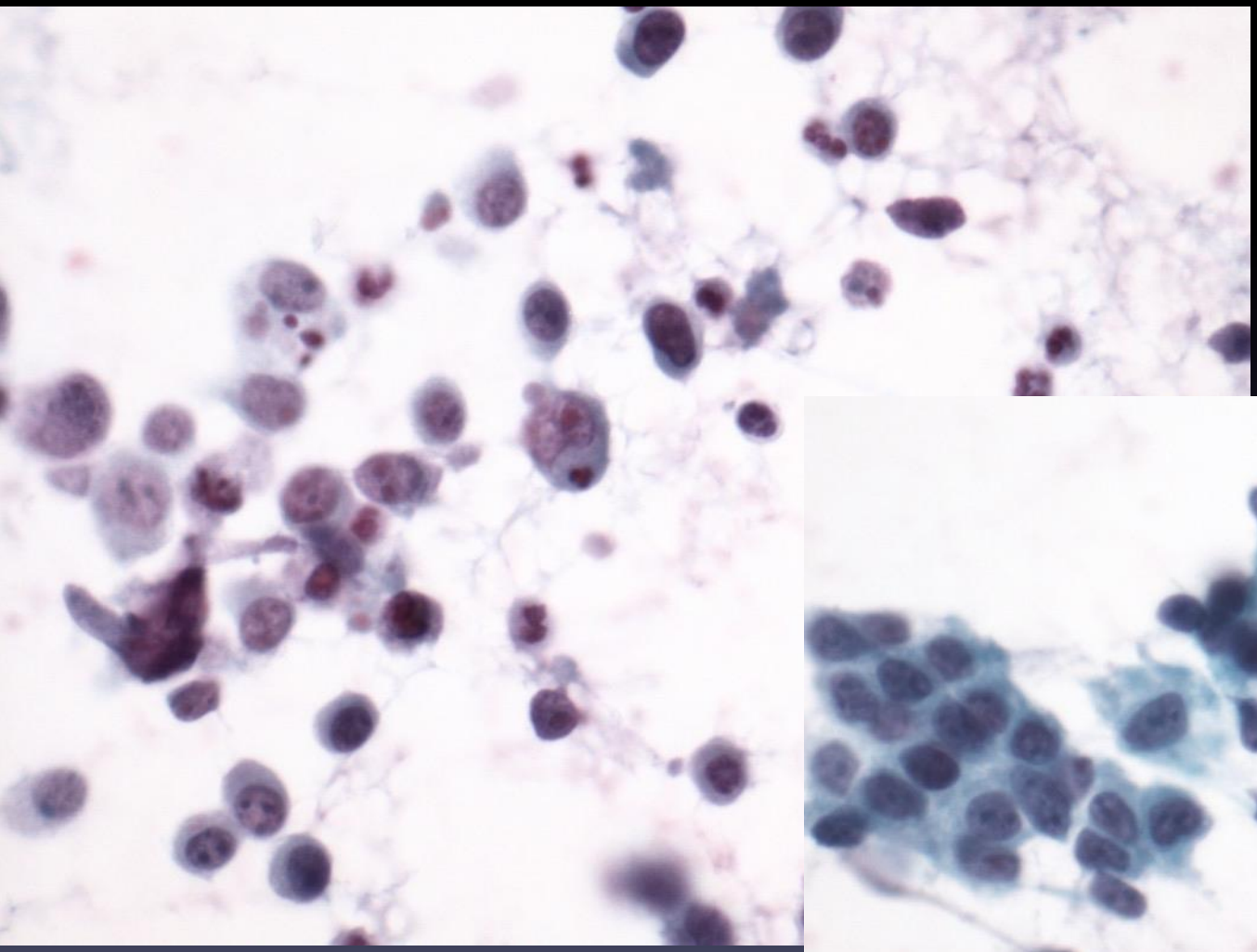


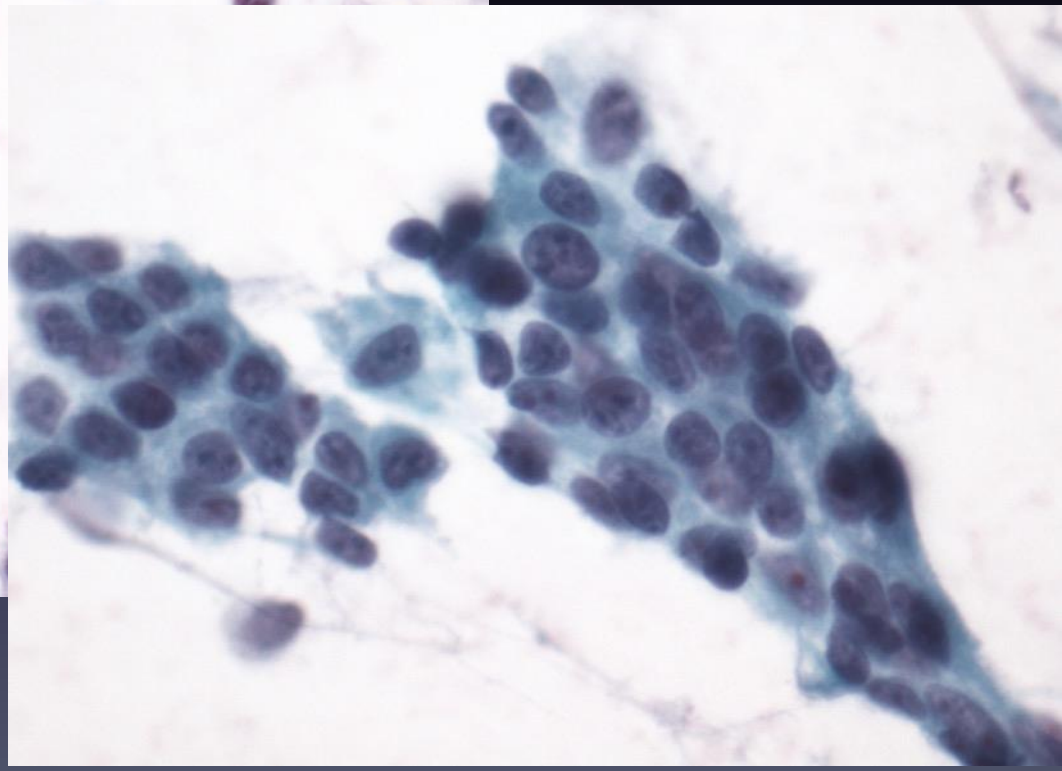
NUT-Midline Carcinoma



Courtesy of Dr. C. French

NUT-Midline Carcinoma

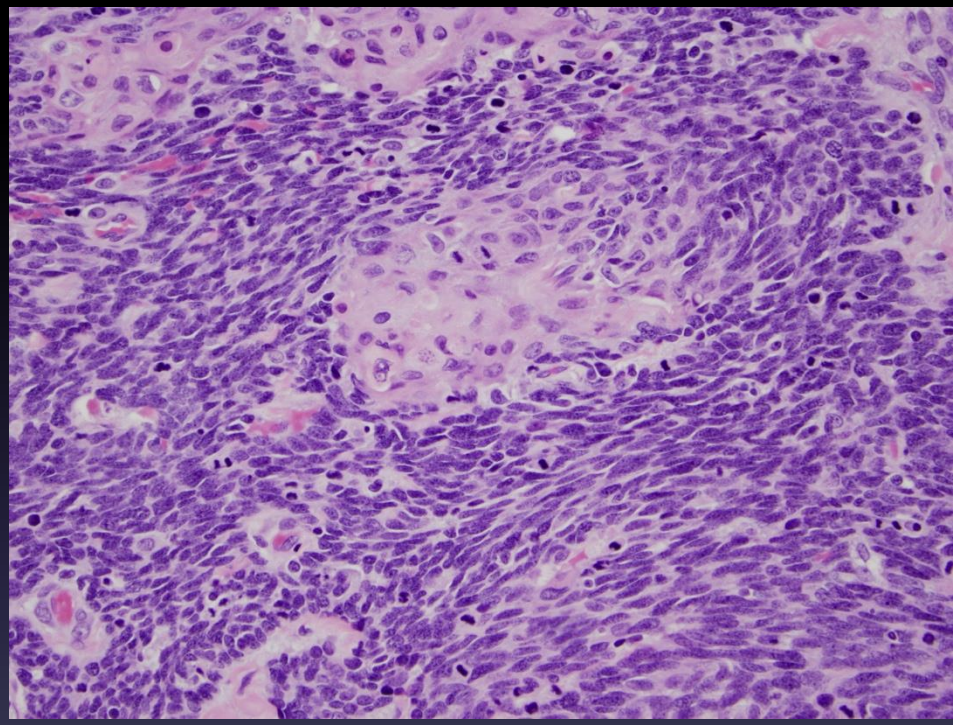




Courtesy of Dr. E. Stelow

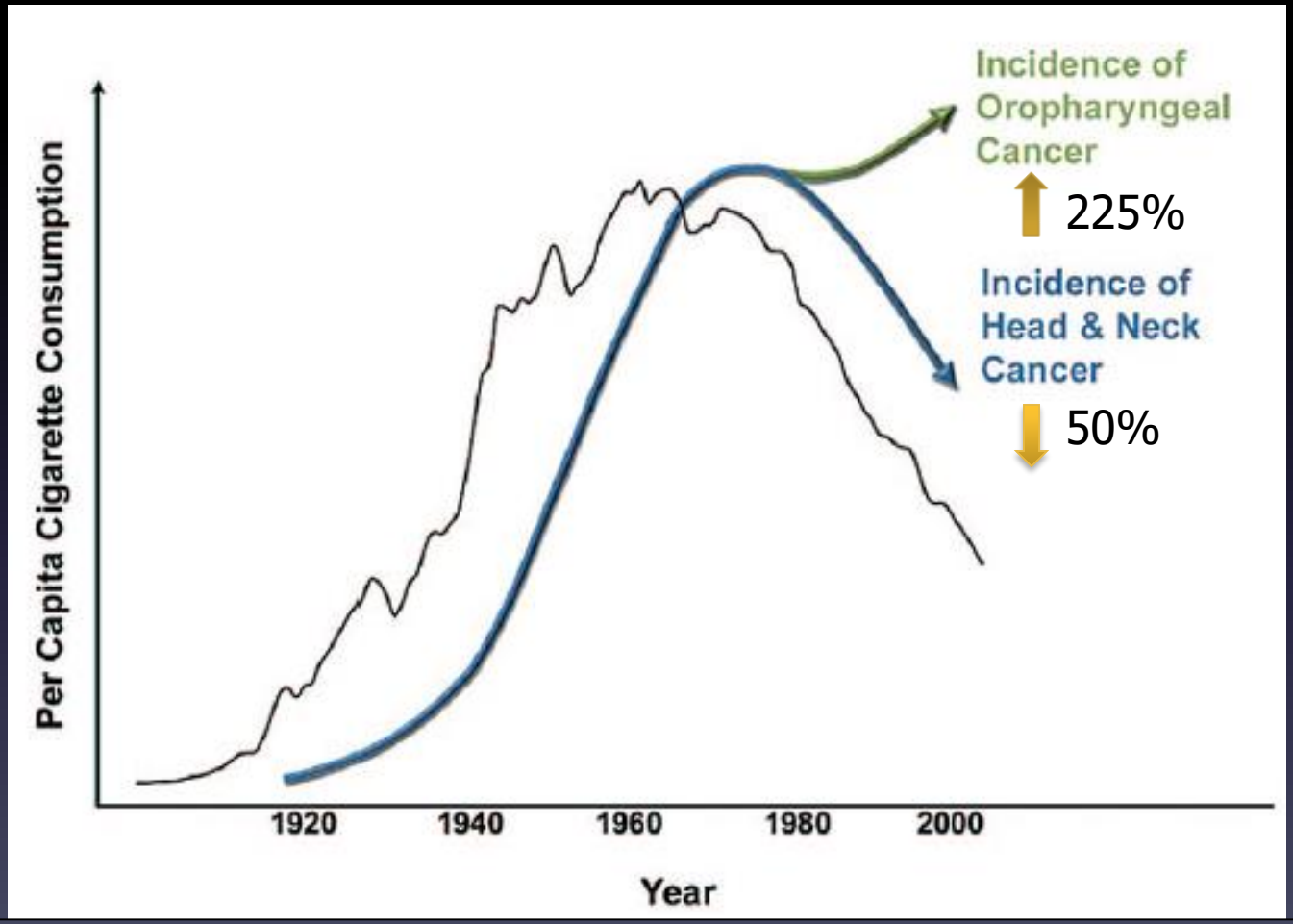
HPV-associated SCC

- 20-25% of all HNSCC are HPV+
- Oropharynx
  - 70% HPV+
  - ~90% HPV 16
- Molecular profiles differ



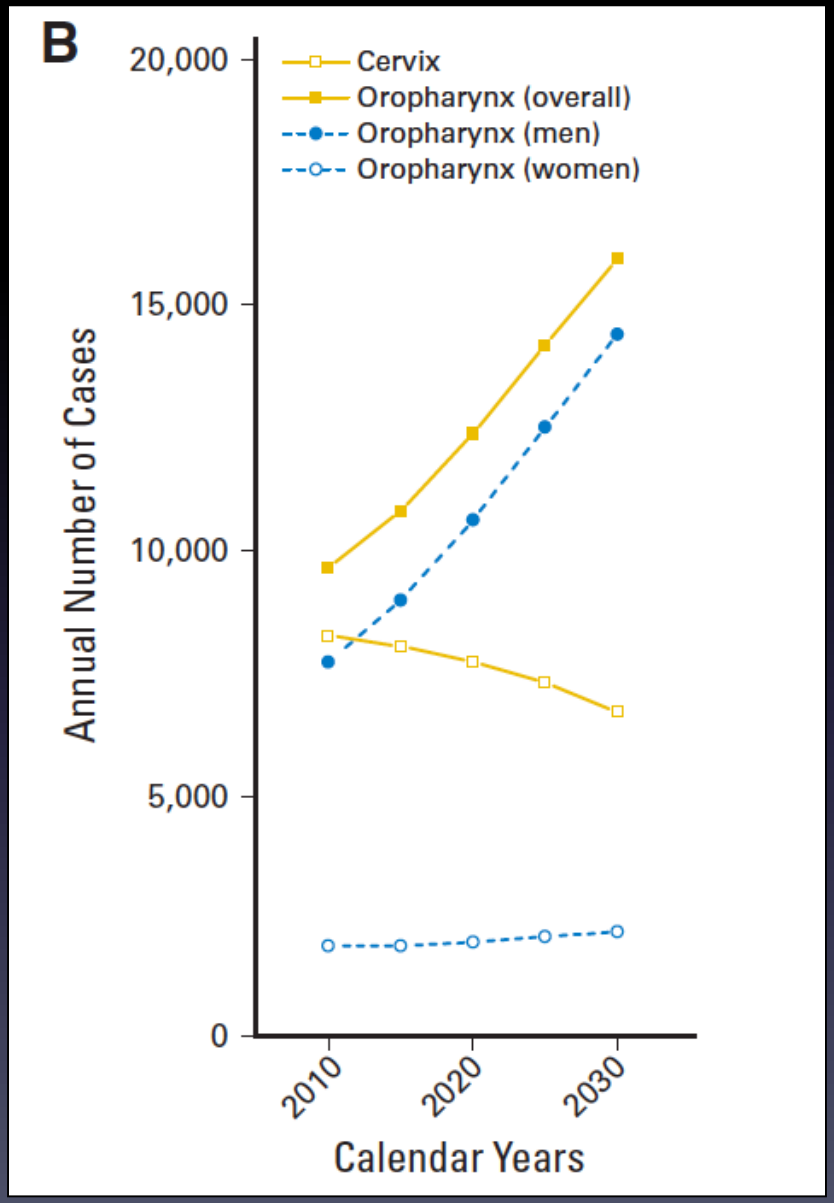
	Rb	p16	p53
HPV+	Decreased	Increased	WT
HPV-	Increased	Decreased	Mutated

HNSCC and Smoking Trends



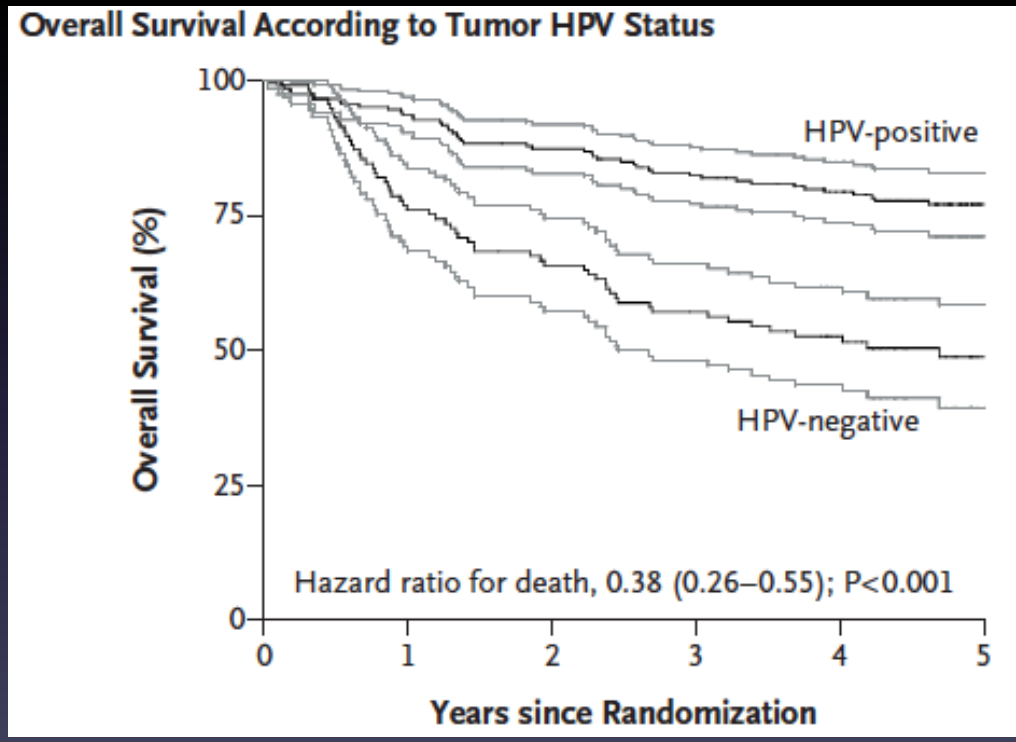
Oropharynx vs cervix

- US incidence in oropharynx > cervix
- M:F – at least 3:1
- Sexual transmission
  - Oral-oral
  - Oral-genital



What is the Value of Knowing HPV Status?

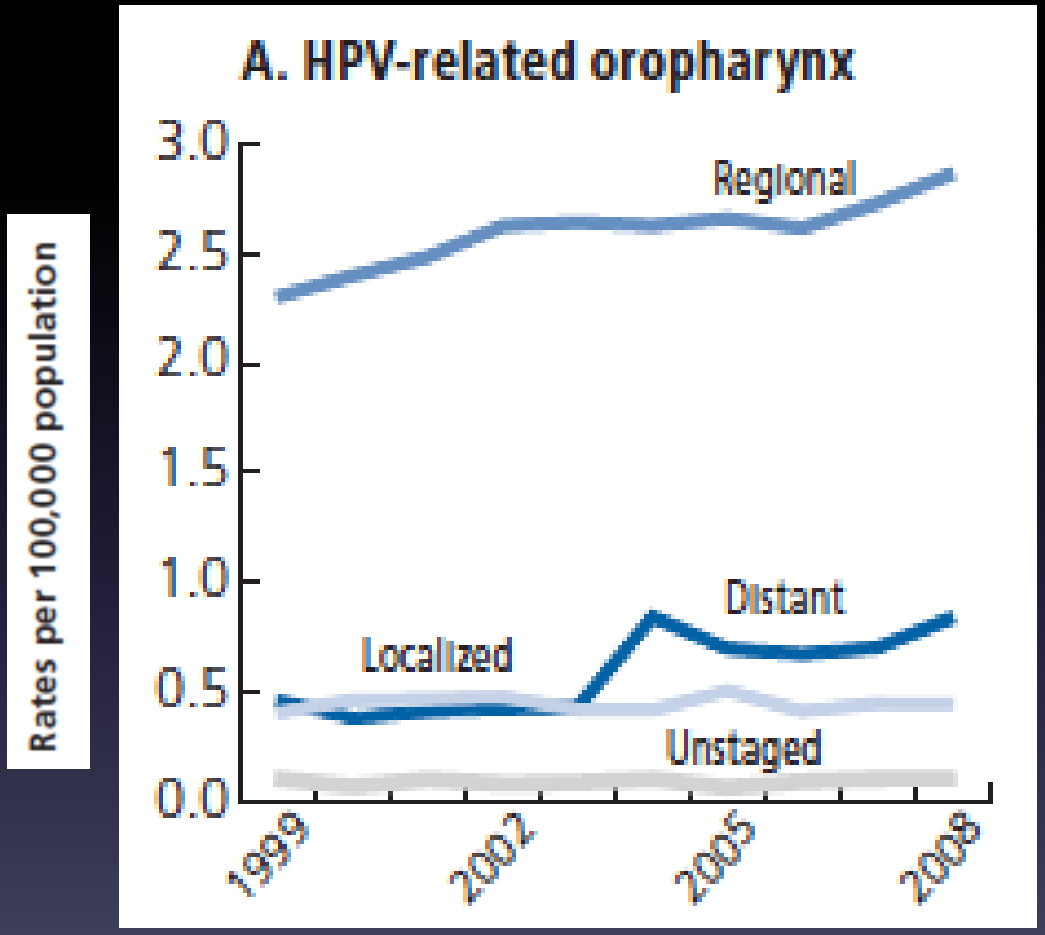
- Improved survival for HPV+ HNSCC
- Overall 3 yr survival
  - 82% HPV+
  - 57% HPV-



Ang et al *NEJM* 2010

Incidence Rates by Stage

- Low T stage
- High N stage
- Most present with nodal neck metastases



American Cancer Society. *Cancer Facts & Figures 2012.*

AJCC Staging Update

- HPV status of all oropharyngeal tumors
- Stage groupings substantially revised to reflect favorable prognosis
  - 2.1 cm primary with a single positive node 3.1 cm
    - 7th ed [or HPV-]: pT2 N2 (stage IVA)
    - 8th ed: pT2 N1 (stage I)

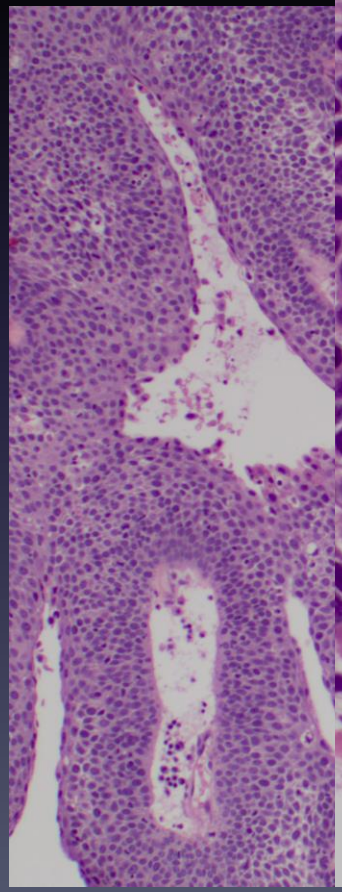
Morphologic variants of HPV associated SCC

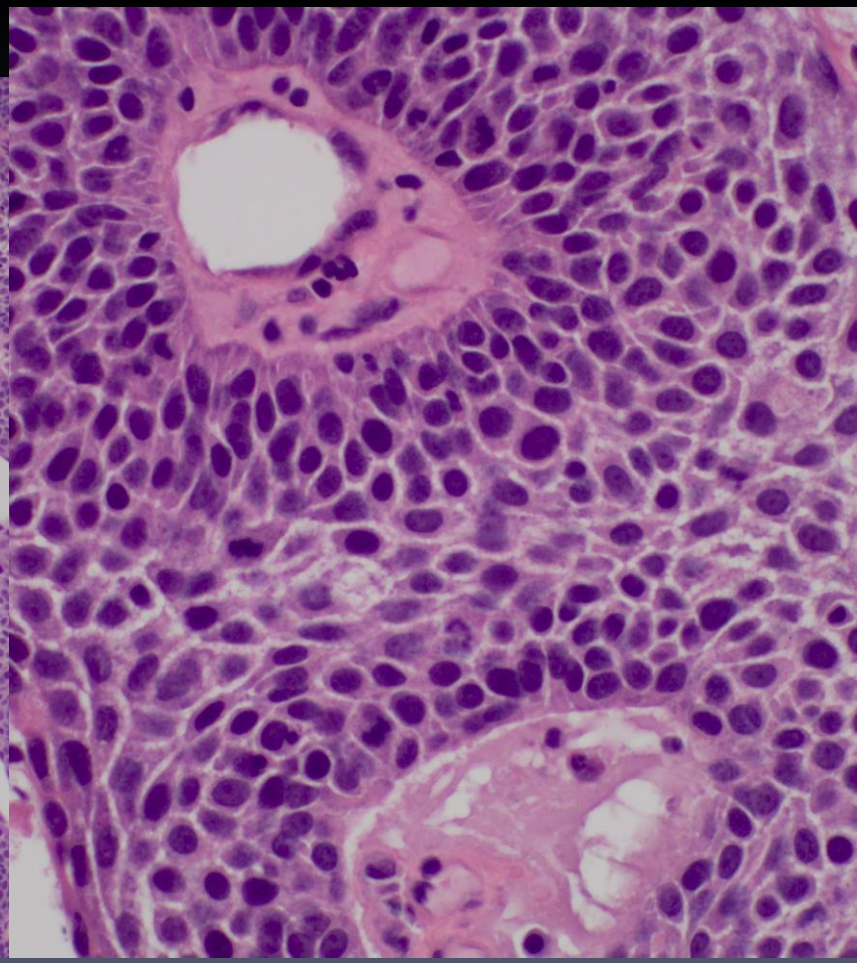
- Basaloid
- Papillary
- Undifferentiated (lymphoepithelial-like)
- Keratinizing

- All share a similar favorable prognosis

Morphologic variants: Papillary SCC

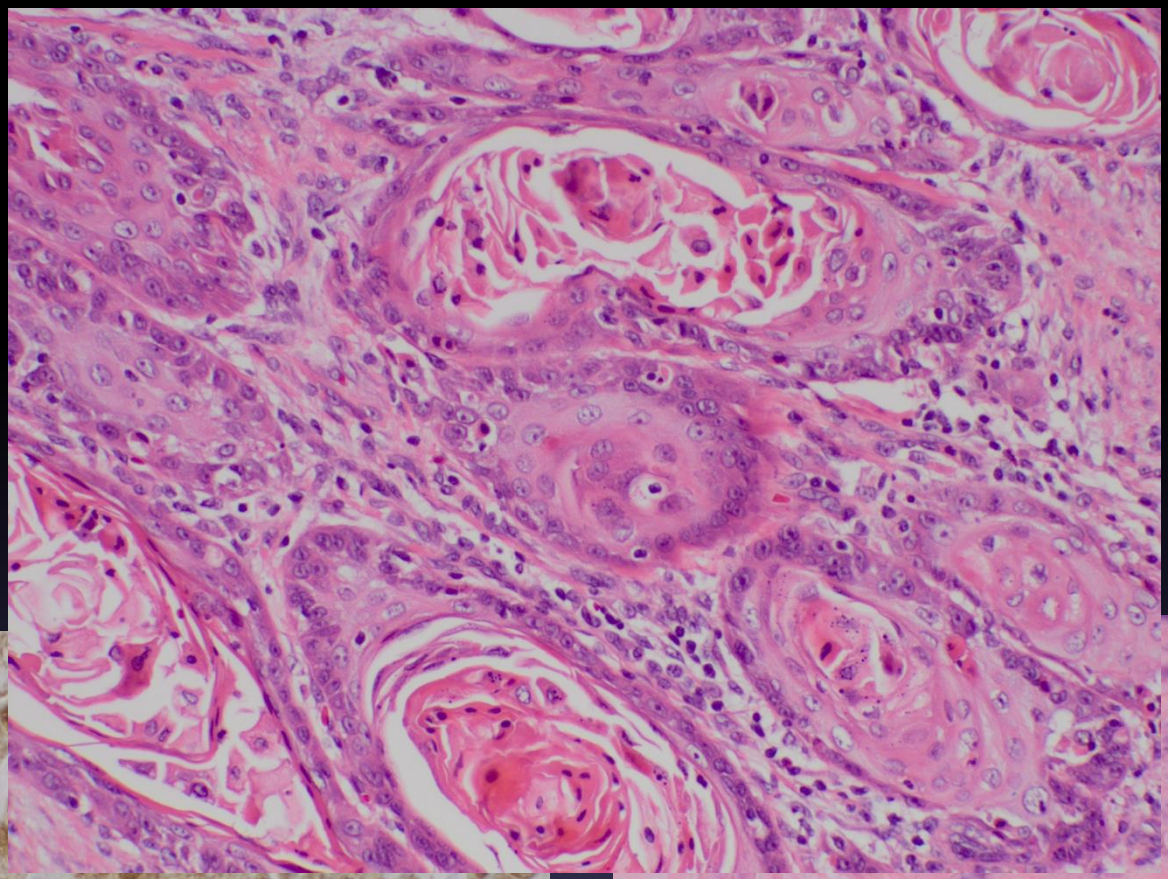
- Difficult to assess invasion
- Highly HPV associated
- Most common in oropharynx

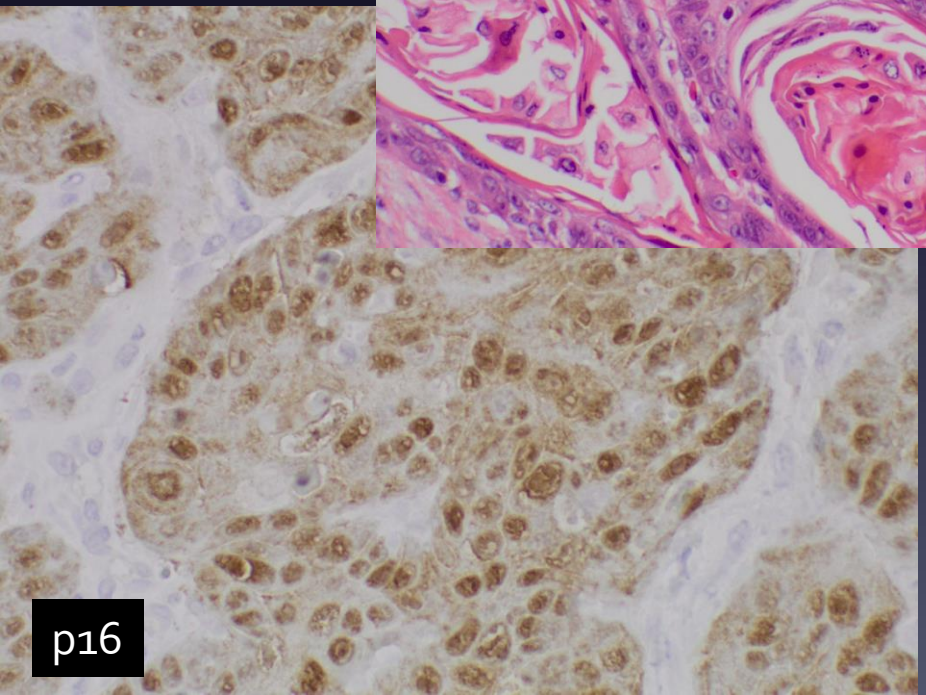


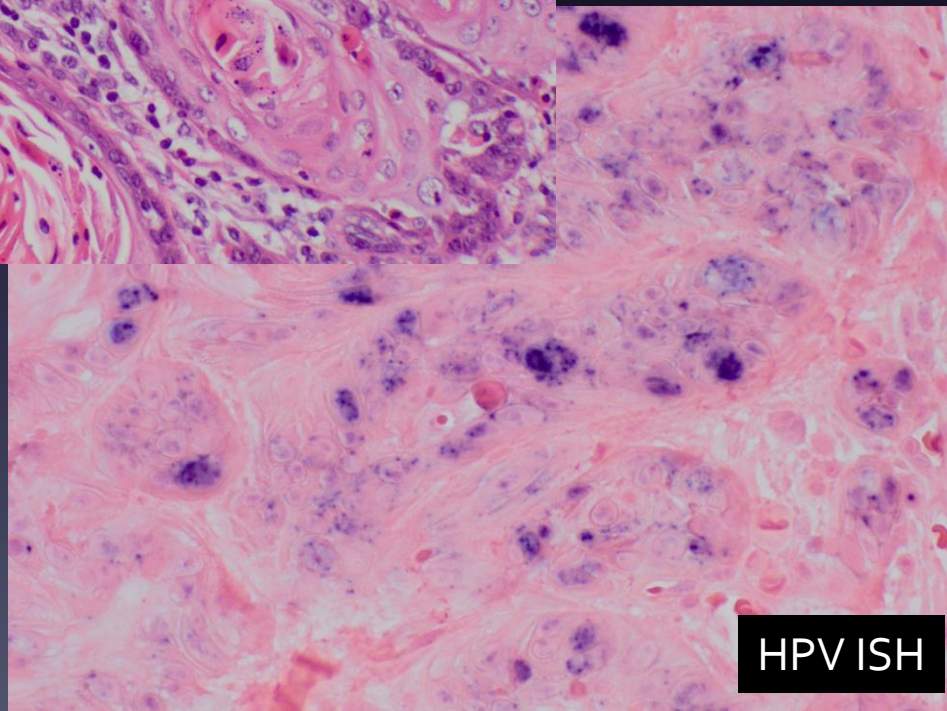


Jo et al *Am J Surg Pathol* 2009

Morphologic variants: Keratinizing

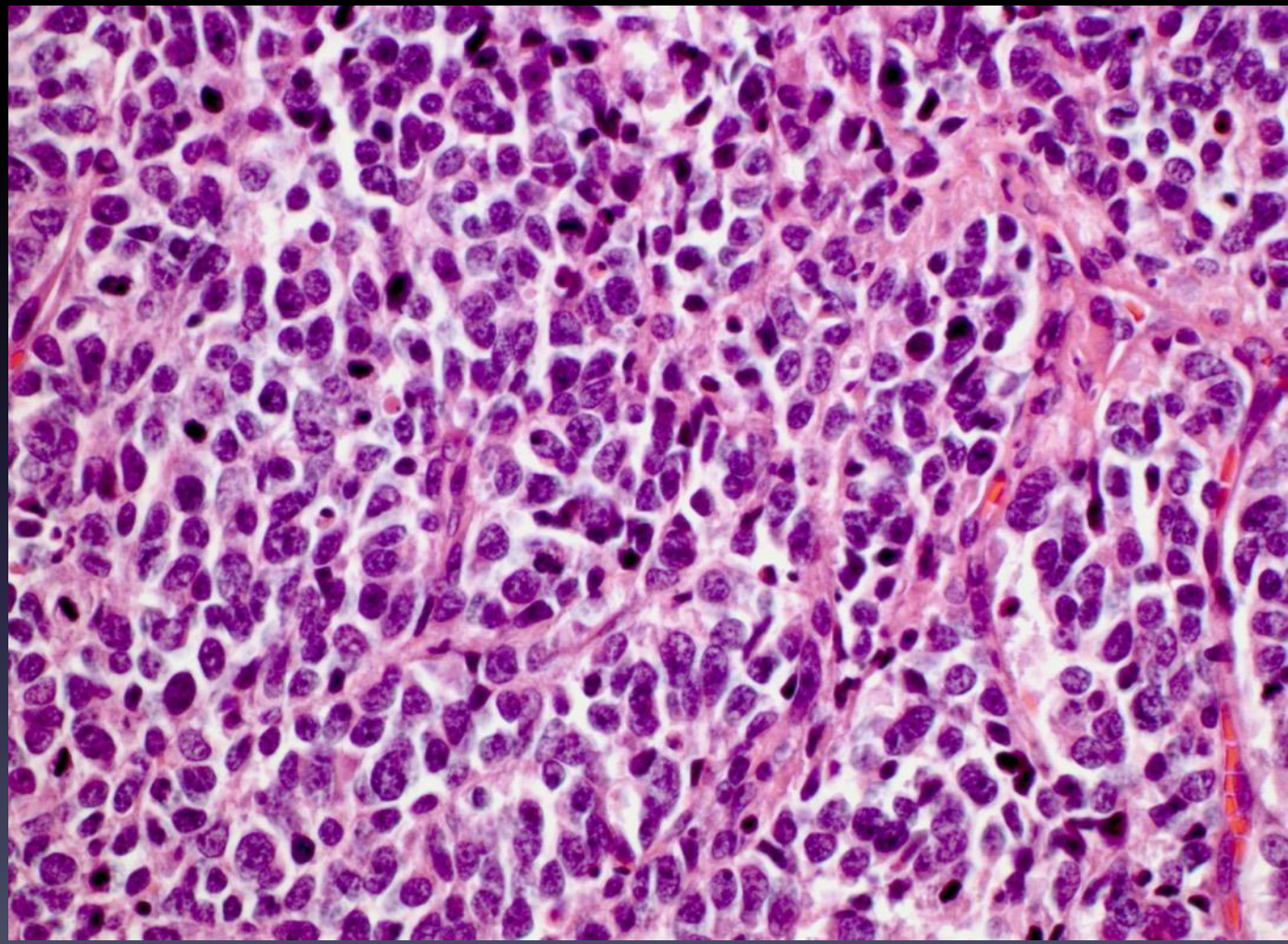






HPV+ Oropharyngeal Small Cell Carcinoma

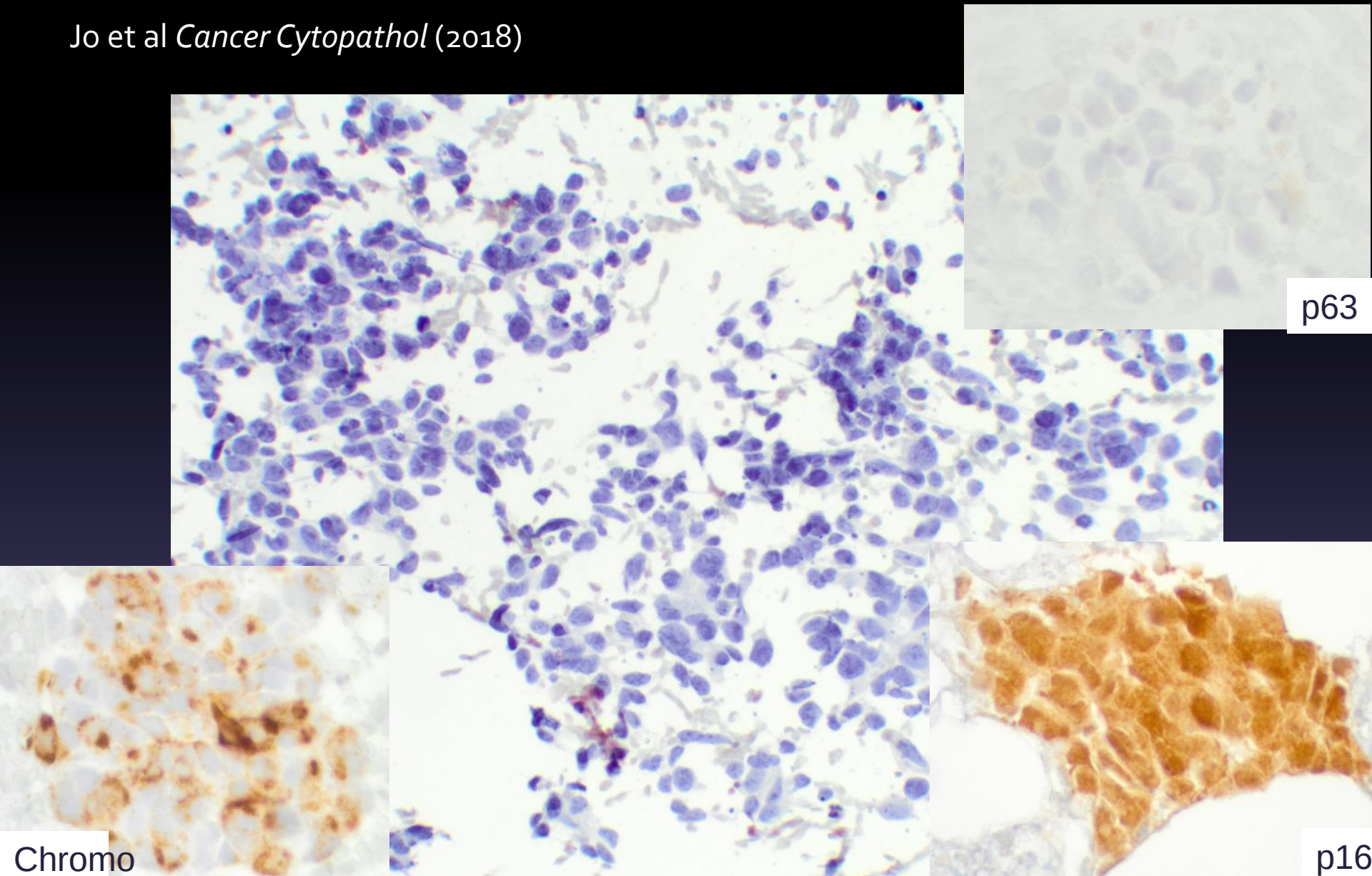
- Rare, aggressive variant



Bishop and Westra *Am J Surg Pathol* (2012); Kraft, Faquin, and Krane *Am J Surg Pathol* (2012)

HPV+ Oropharyngeal Small Cell Carcinoma

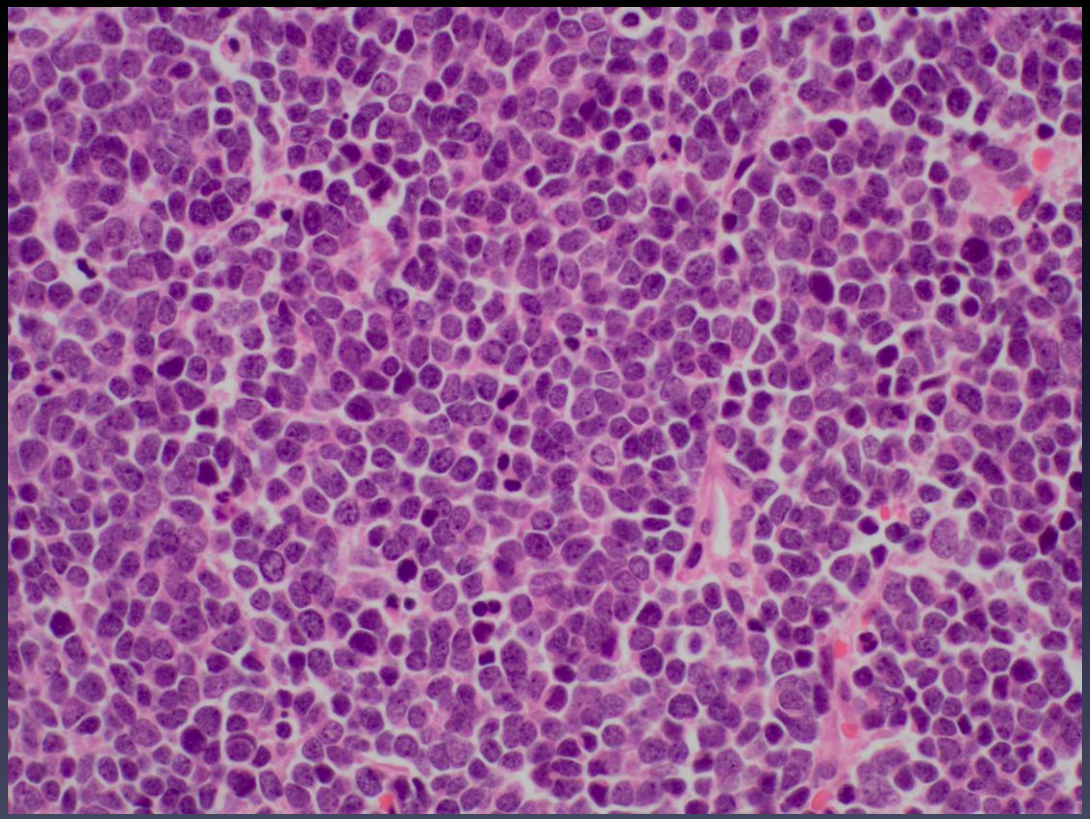
Jo et al *Cancer Cytopathol* (2018)



H&N Neuroendocrine Carcinomas

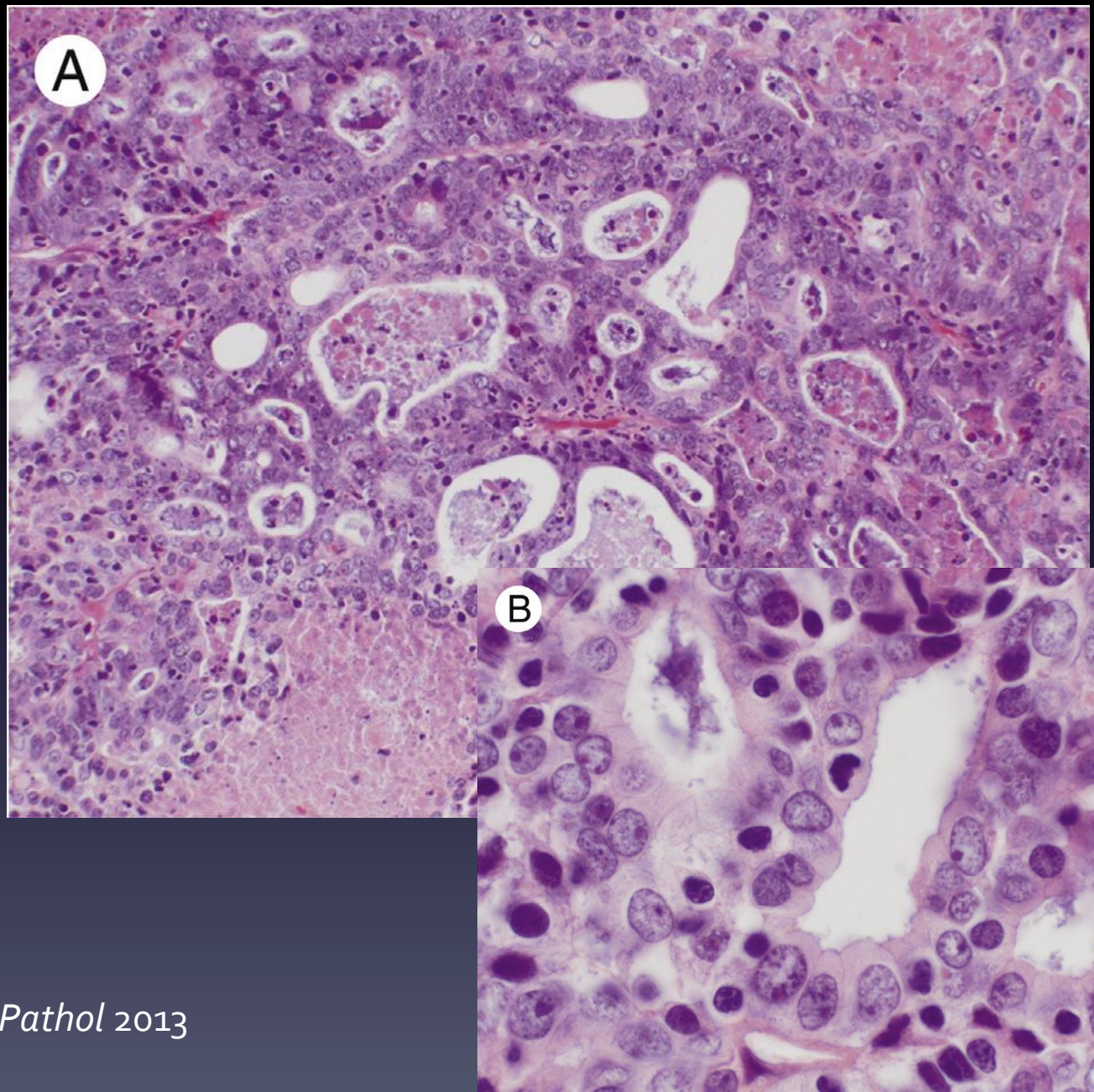
- Metastatic
  - Esp Merkel cell carcinoma
- Salivary gland
- Oropharynx

- P16 may be positive in all



HPV+ Oropharyngeal Adenocarcinoma

- Even rarer
  - Only 5 reported cases
  - 1 DOD, 1 metastatic



Hanna et al *Human Pathol* 2013

Cytology and HPV-associated HNSCC

- Screening?
- Diagnosis
- Determination of HPV status

Oropharyngeal Pap Test?

- Oral rinses
  - Not sensitive for detecting atypical cells
  - Can detect HPV (7% overall, 1% HPV16)
- Oral brushings
  - Can diagnose clinically apparent lesions
  - Does not detect precursor lesions
  - Inaccessible in base of tongue and tonsillar crypts

Fakhry et al *Cancer Prev Res* 2011
Gillison et al *JAMA* 2012

Cytology for Initial Diagnosis of HPV HNSCC

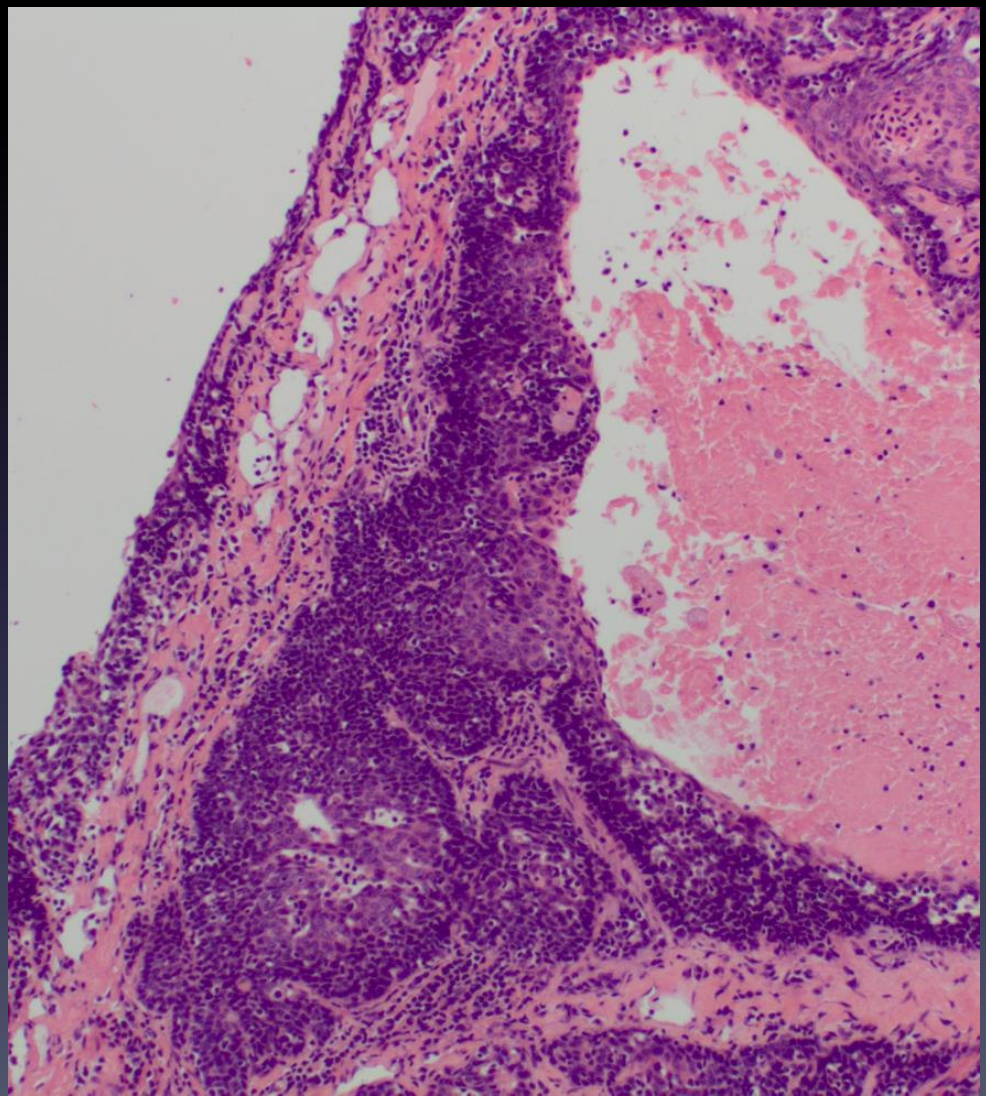
- Majority of oropharyngeal HPV-associated SCC patients present with a neck mass
- Essentially malignancy of unknown primary
- Cytology role
  - Confirm malignancy
  - Classify as SCC
  - Determine HPV status

Cytologic Patterns of HPV HNSCC

- Basaloid
- Cystic
- Undifferentiated

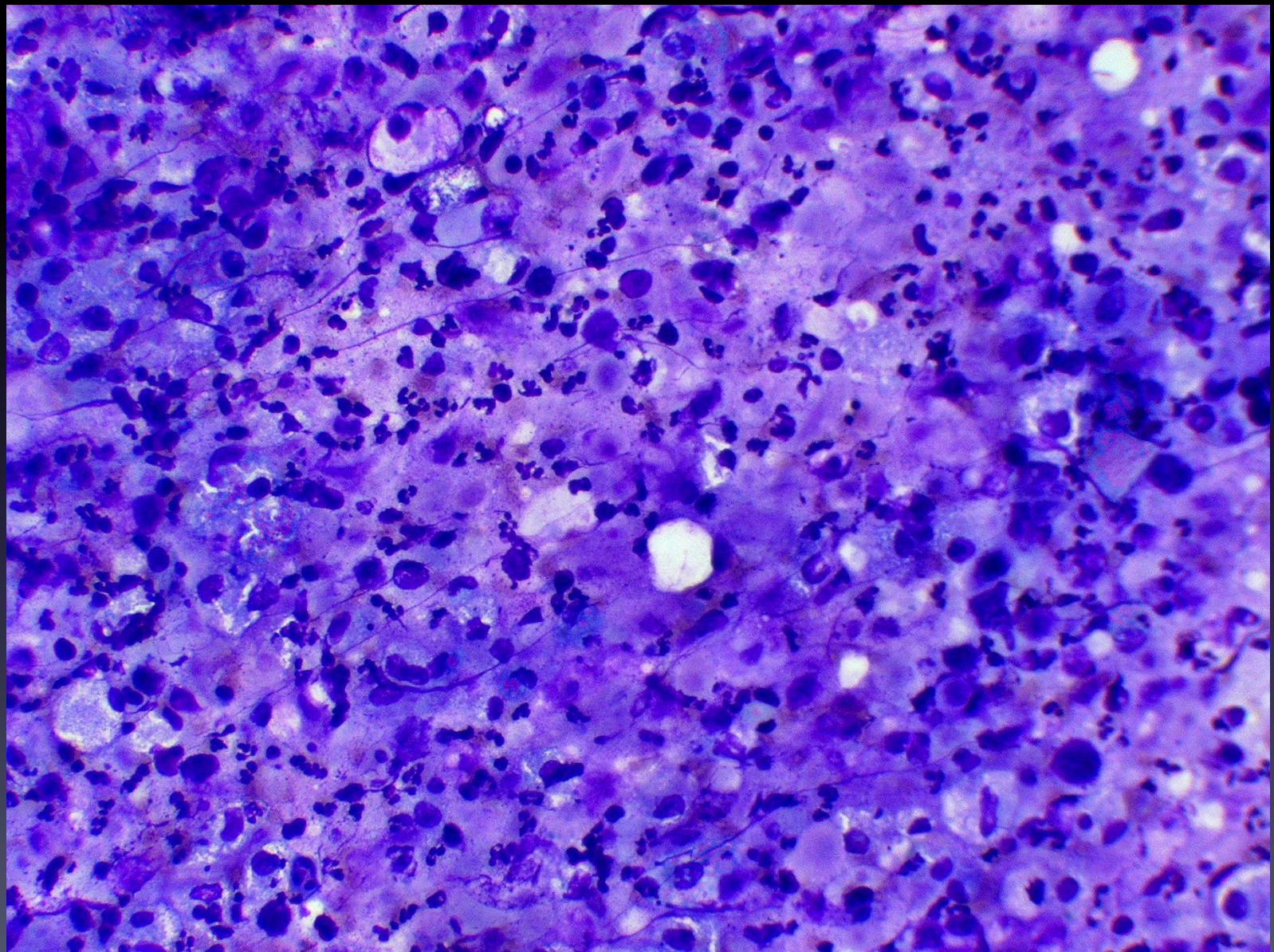
Cystic Metastatic Squamous Cell Carcinoma

- Metastasis from oropharyngeal primary
- HPV associated
- May be deceptively bland
- Raises question of carcinoma in a branchial cleft cyst
  - Does not occur!

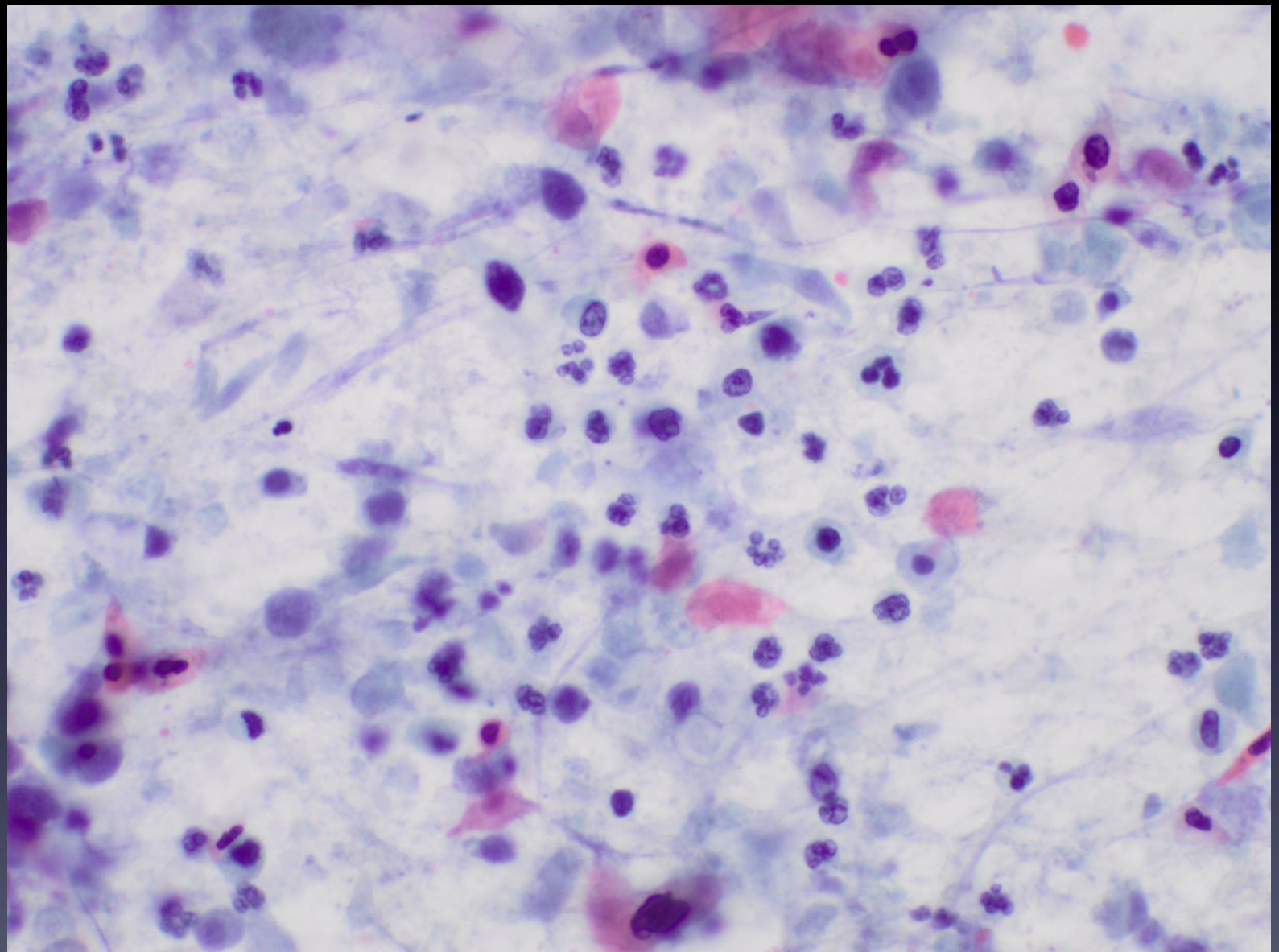


Goldenberg et al *Head and Neck* 2008

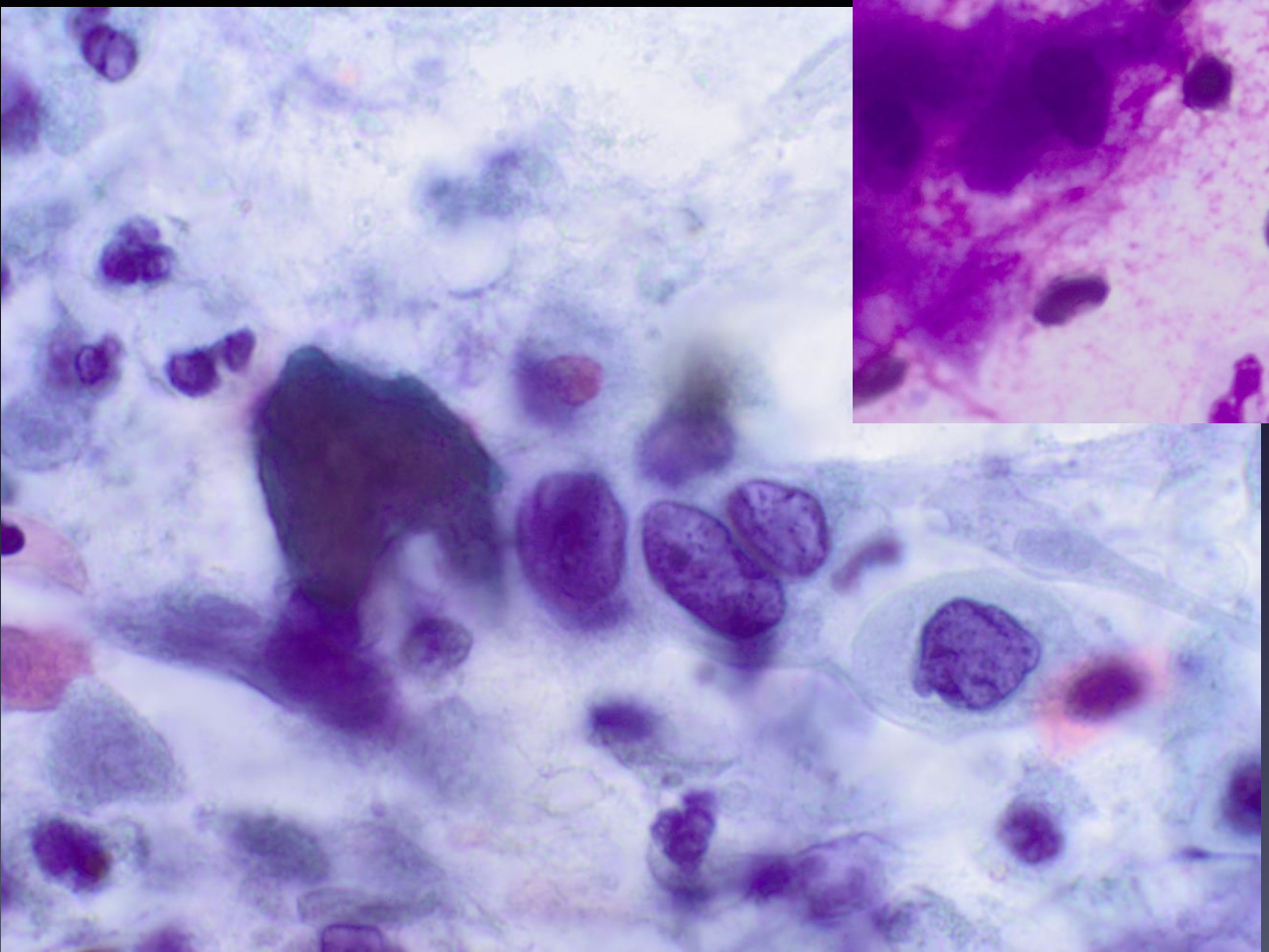
Cystic

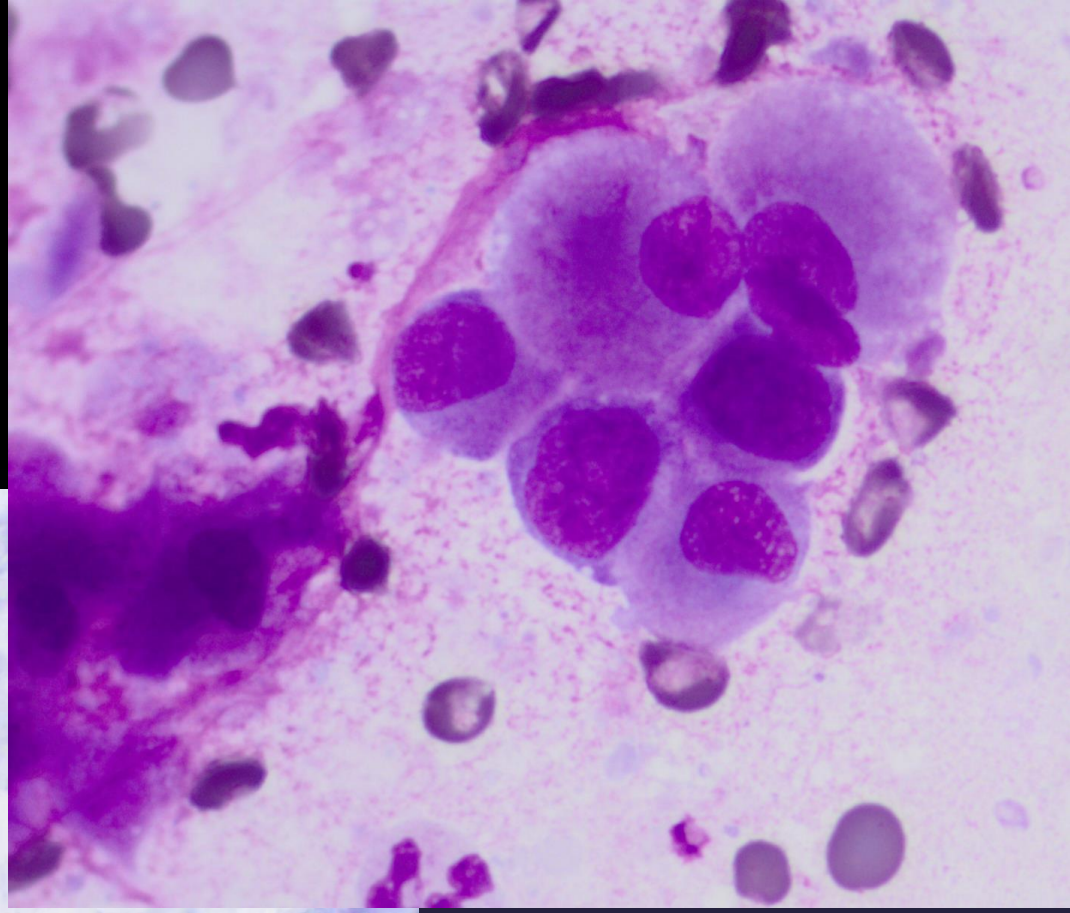


Cystic



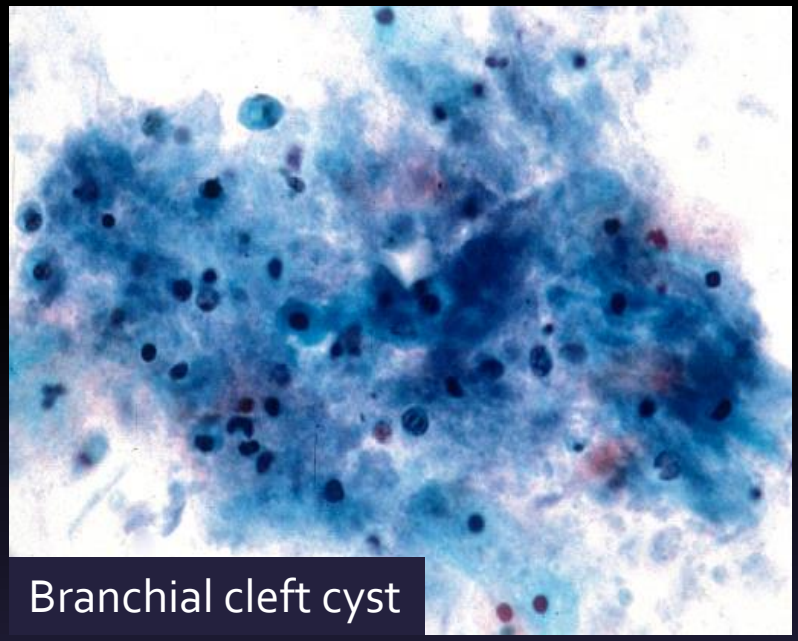
Cystic

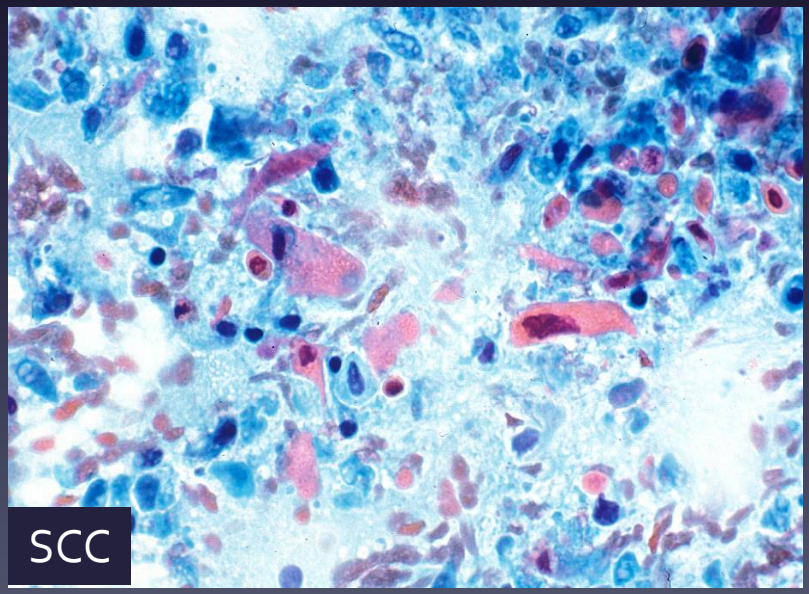




Cystic lesions

- Thorough examination of specimen is critical
- Age
- Low threshold for excision


Branchial cleft cyst


SCC

Importance of HPV Testing

- New diagnosis
  - HPV status may result in definitive treatment
  - Guide subsequent biopsies
  - If primary site is not identified (~5%), may help localize radiation therapy
  - Determine eligibility for clinical trials
  - Prognosis
- Known disease
  - Metastasis vs new primary

HPV Testing Options

- P16
- High-risk HPV DNA ISH
- High-risk HPV RNA ISH
- PCR
- Commercial tests developed for GYN:
  - Hybrid Capture II
  - Cervista
  - cobas
  - Aptima

CAP Guidelines for HPV testing of Head and Neck Cancers

- Lewis et al *Arch Pathol Lab Med* (2017)

CAP Guidelines Highlights
Surgical pathology

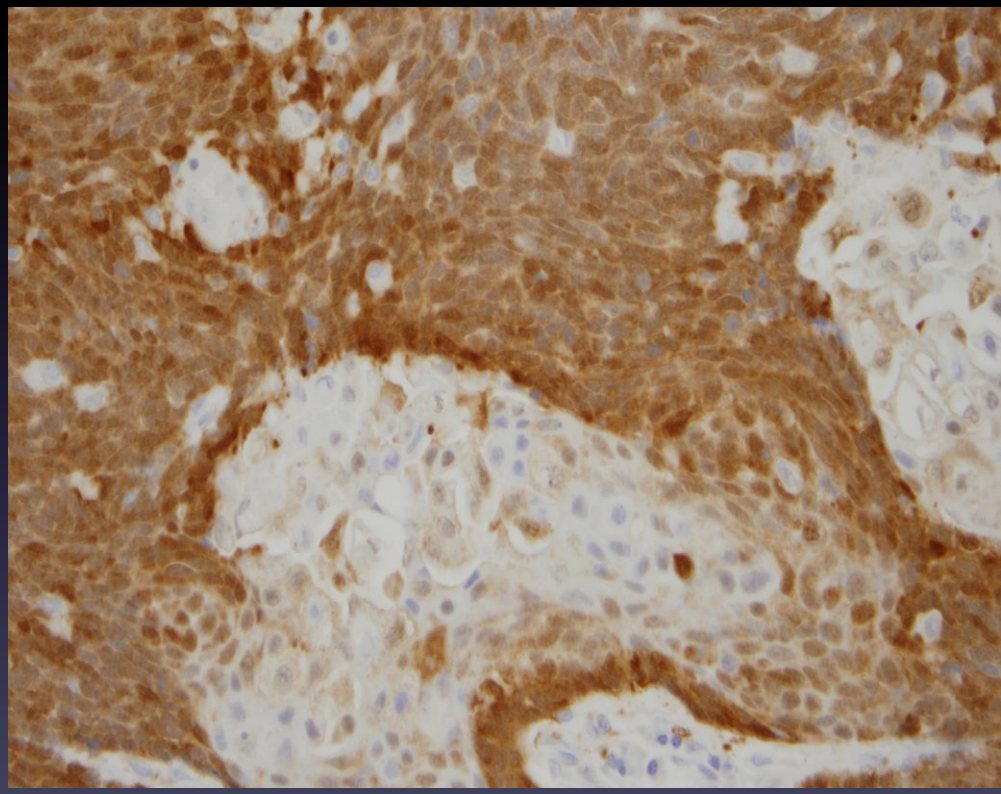
- Should HPV test new OPSCC
  - Either primary or met can be tested
- P16 IHC is preferred for OP specimens
- Should NOT routinely test non-OP SCC

CAP Guidelines Highlights Lymph nodes

- Should HPV test mets of unknown primary in upper and mid jugular LNs (levels II or III)
- P16 IHC is preferred
- Additional testing if outside levels II or III or if keratinizing morphology

CAP Guidelines Highlights

- P16+
  - At least 70% nuclear and cytoplasmic
  - Moderate or strong intensity



CAP Guidelines Highlights
FNA

- HR-HPV testing for:
  - OPSCC with no prior HPV testing
  - Suspected OPSCC
  - SCC of unknown primary
- No consensus at present regarding methodology
- Tests need validation in individual laboratories, particularly cutoff for a P16+ result
- If HPV testing is negative, it should be repeated on tissue if it becomes available

Heterogeneity of p16 Immunohistochemistry and Increased Sensitivity of RNA In Situ Hybridization in Cytology Specimens of HPV-Related Head and Neck Squamous Cell Carcinoma

Kristine S. Wong, MD[1]; Jeffrey F. Krane, MD, PhD [2]; and Vickie Y. Jo, MD [1]

N=97 CB cases known to be HPV+

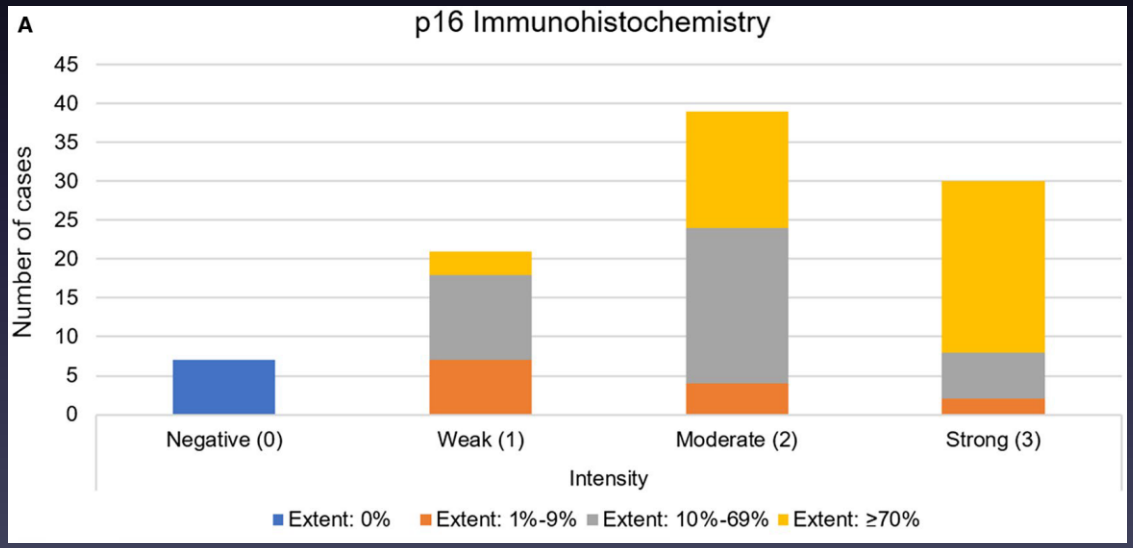


TABLE 3. Sensitivity of p16 IHC Based on Staining Intensity and Extent

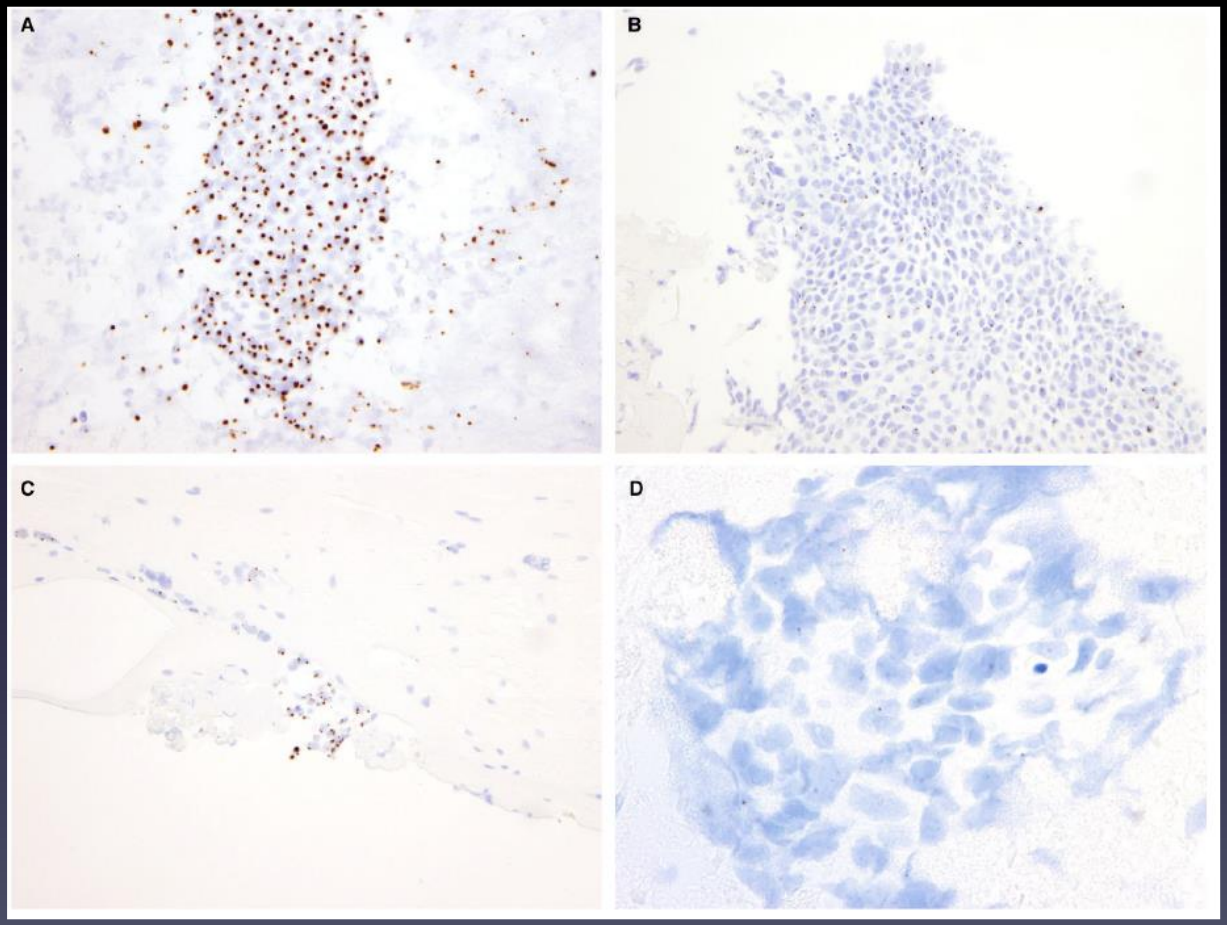
	Staining Intensity	
	Any	Moderate to Strong
p16 IHC extent		
≥1%	93%	86%
≥10%	79%	68%
≥70%	41%	38%

Abbreviation: IHC, Immunohistochemistry.

Wong et al *Cancer Cytopathol* (2019)

RNA ISH may be the solution

- RNA ISH positive in 97% of the same cases



Wong et al *Cancer Cytopathol* (2019)

Follow-up

- Specimen sent for HPV testing: HPV 16 positive.
- The patient subsequently underwent biopsies; however, a primary site was never identified. He underwent chemotherapy and radiation.
- His wife also had HPV 16 positive metastatic squamous cell carcinoma with a tonsillar primary later identified.
- Partial DNA sequence analysis revealed identical HPV 16 viral isolates.
- Interestingly, the wife had a hysterectomy in the 1950s for cervical dysplasia. Significance???

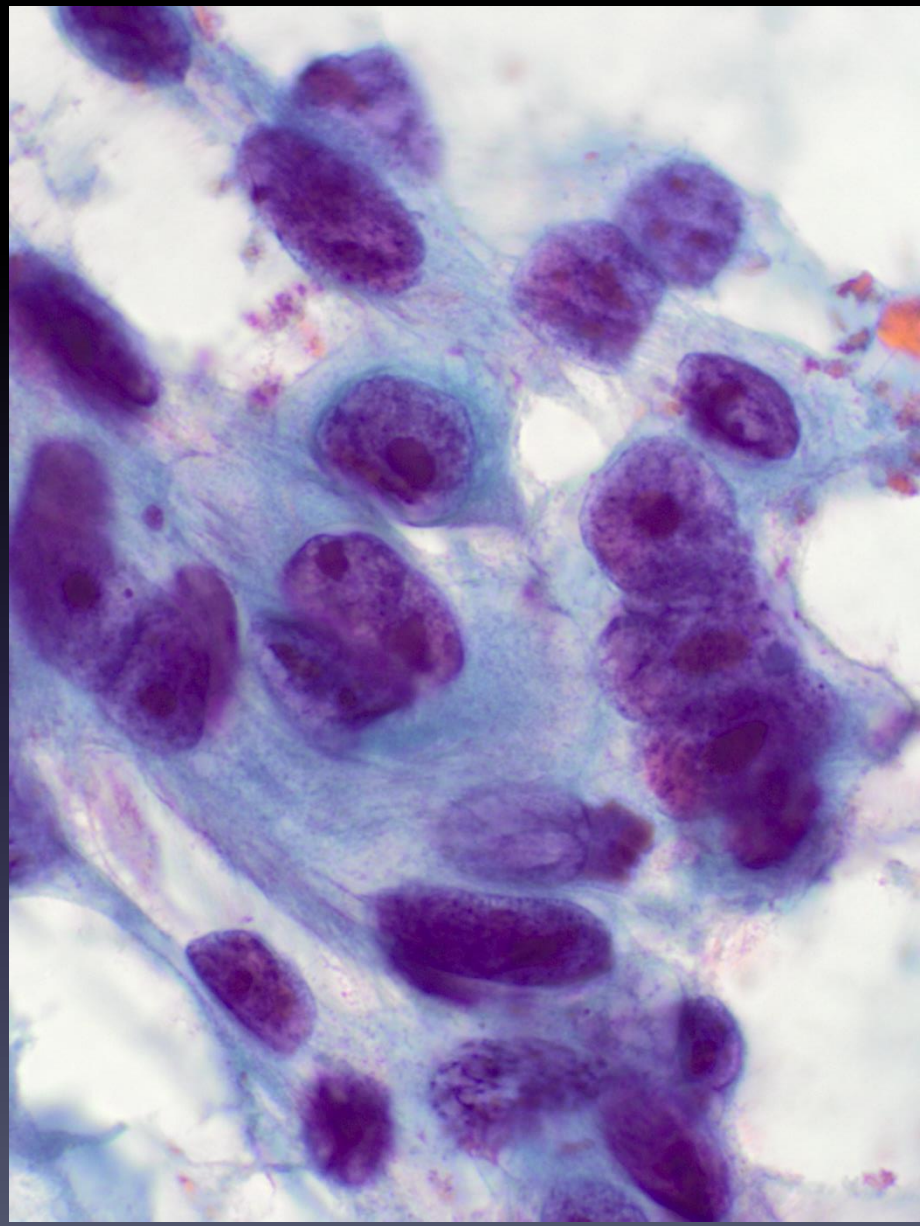
Haddad et al Oral Oncol 2008

Case 3: Final diagnosis

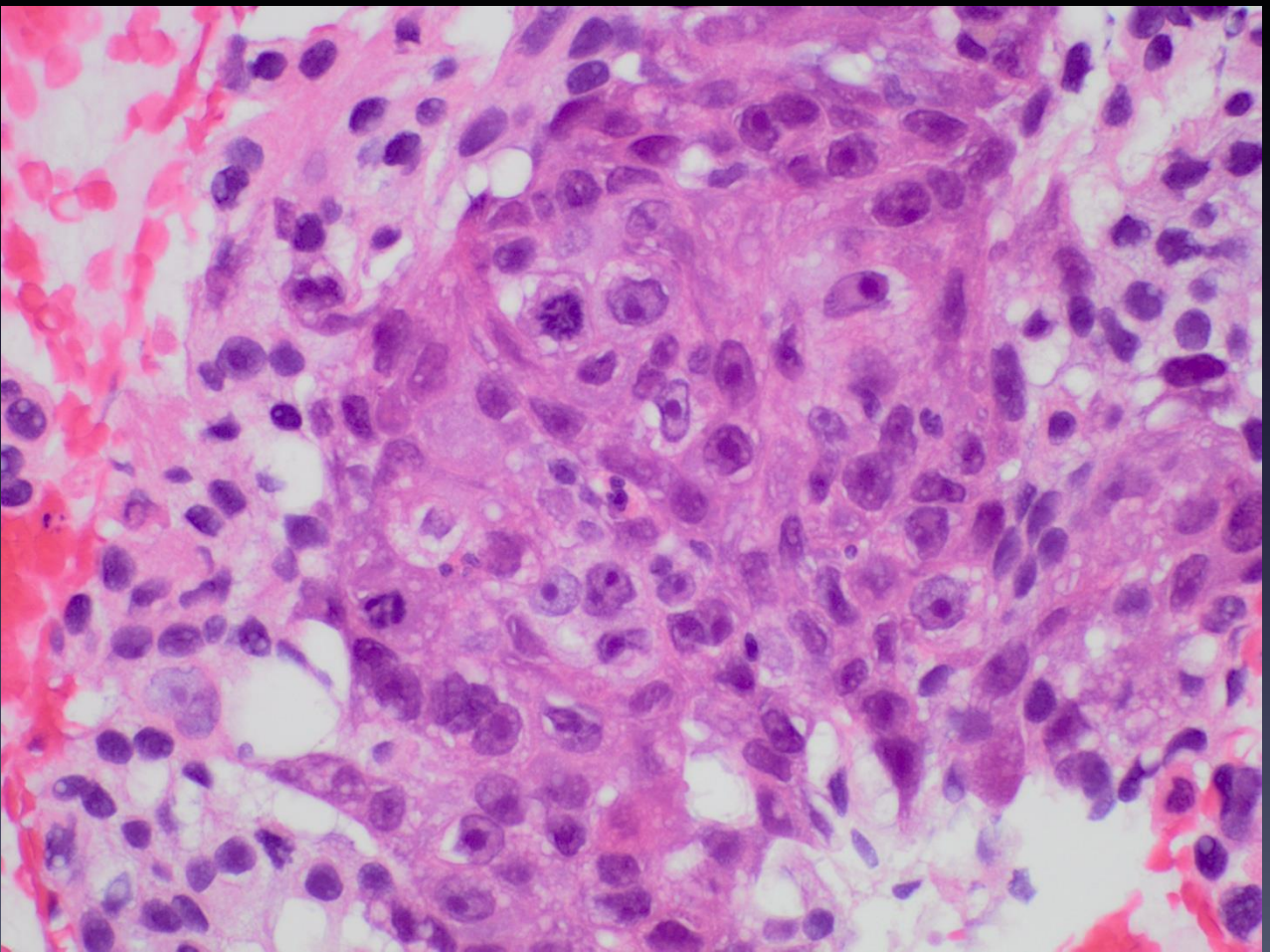
Metastatic HPV-associated Oropharyngeal SCC

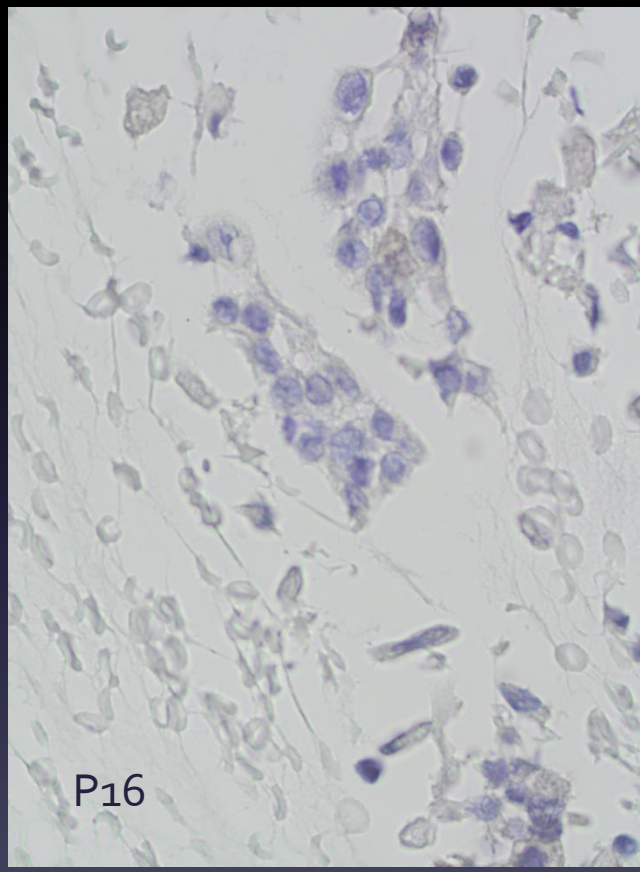
What about primary site for Case 2?

- Poorly differentiated SCC
- H/O tongue base SCC (HPV16+)
- H/O scalp SCC



Case 2





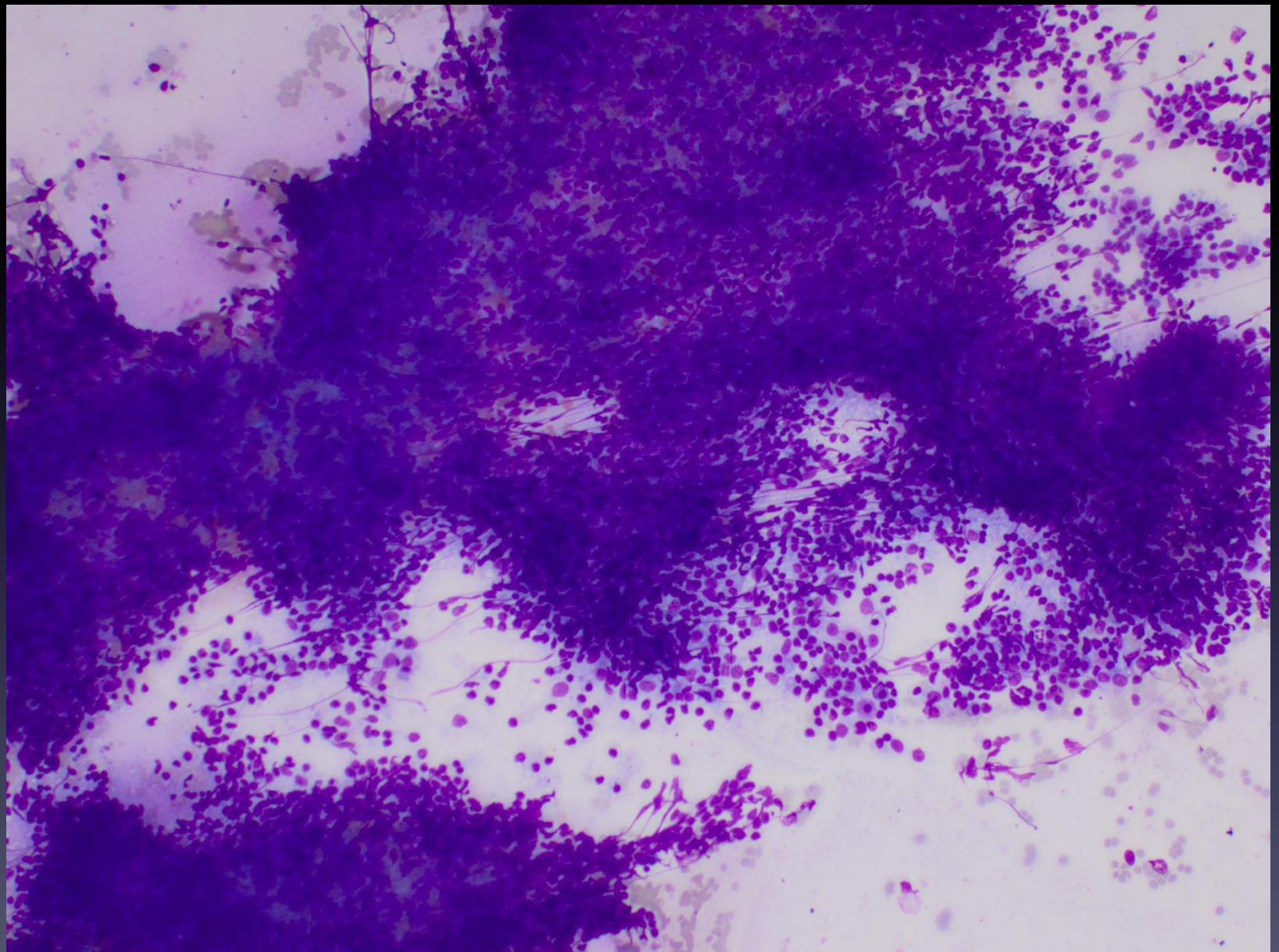
Case 2: Final diagnosis

Poorly differentiated SCC, most consistent with metastasis from patient's known scalp primary

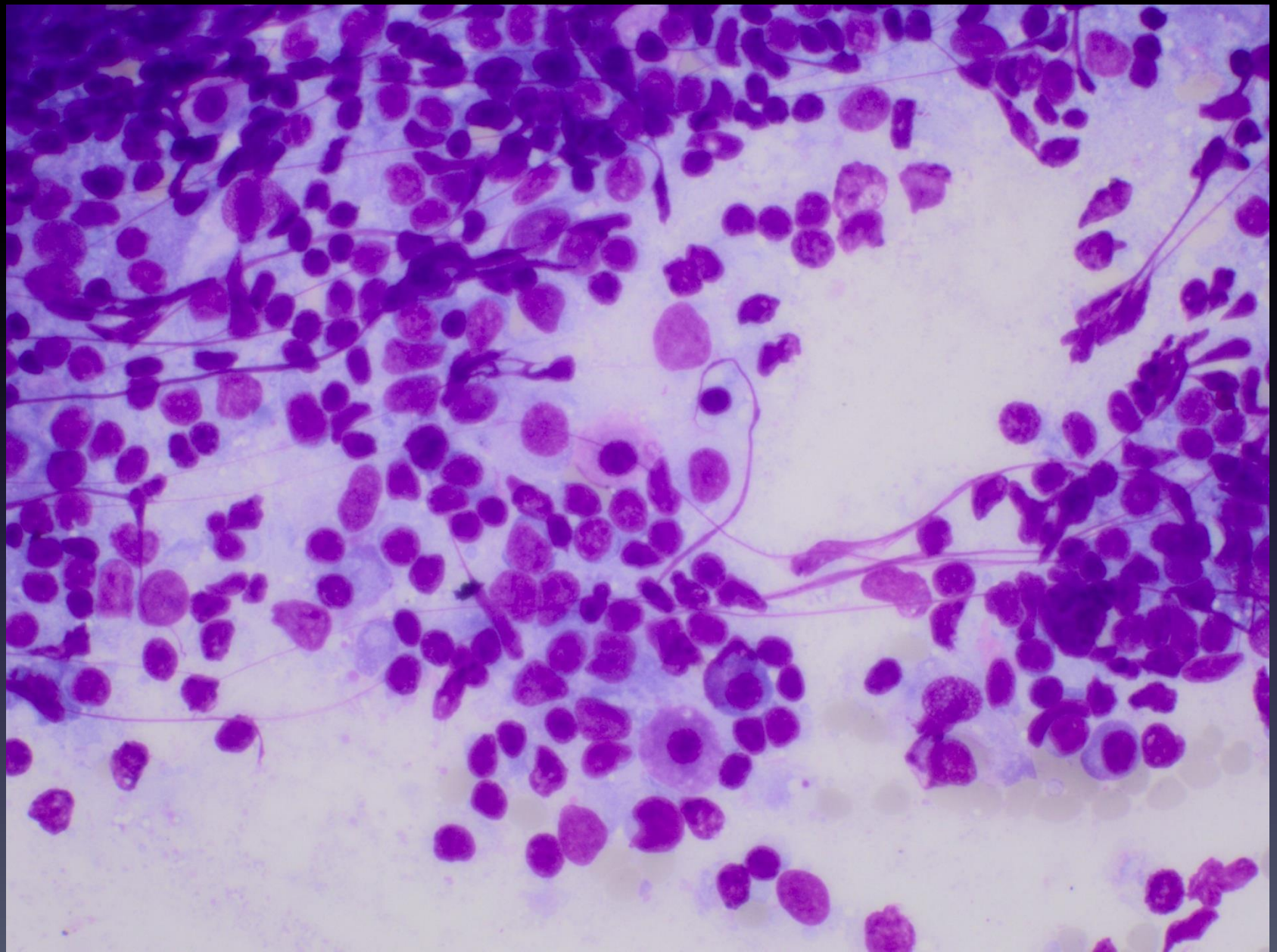
Case 4

A 59 year old man with a fibrosarcomatous DFSP of the right neck 10 years ago, now presents with a left neck mass

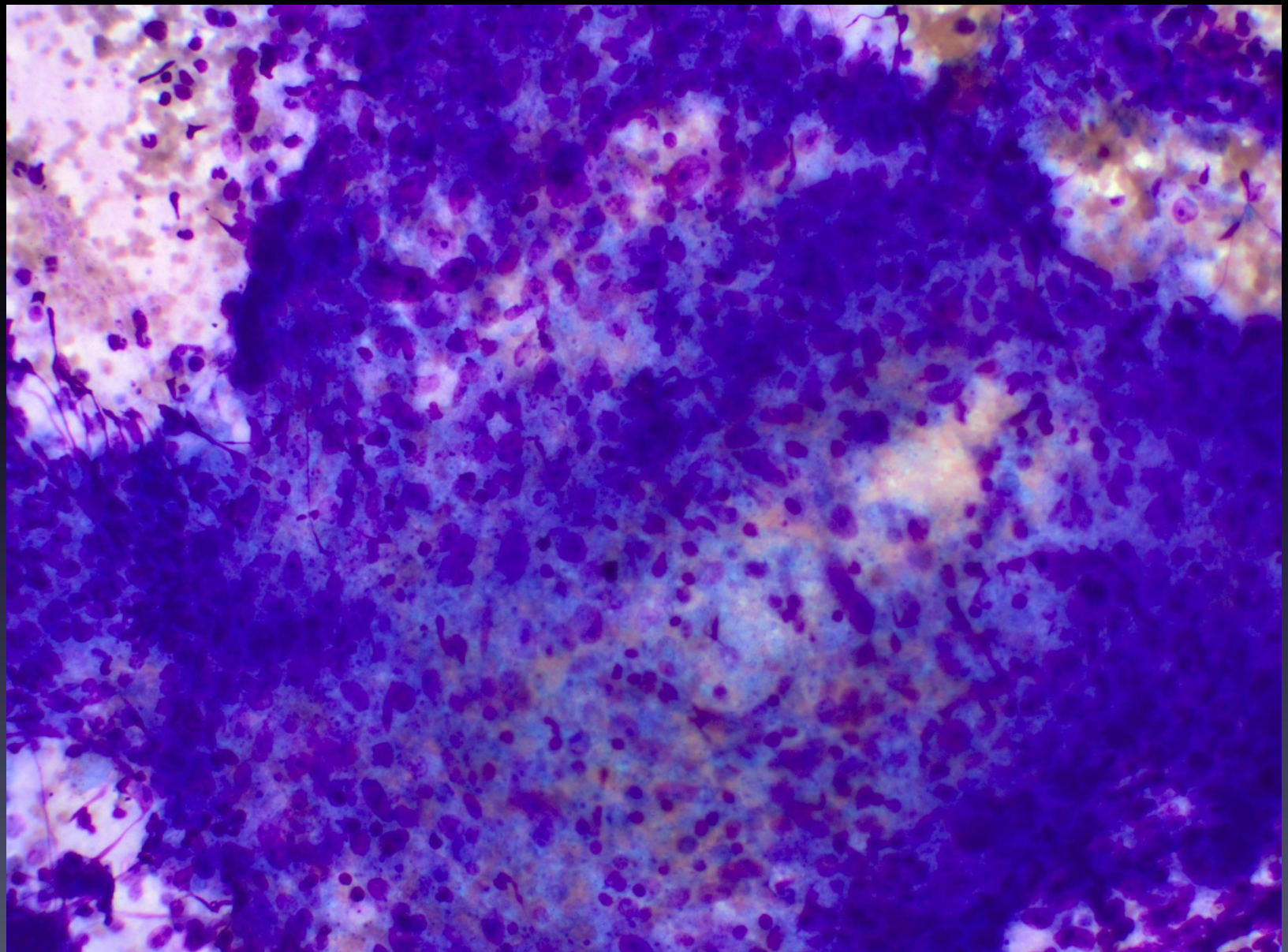
Case 4



Case 4



Case 4



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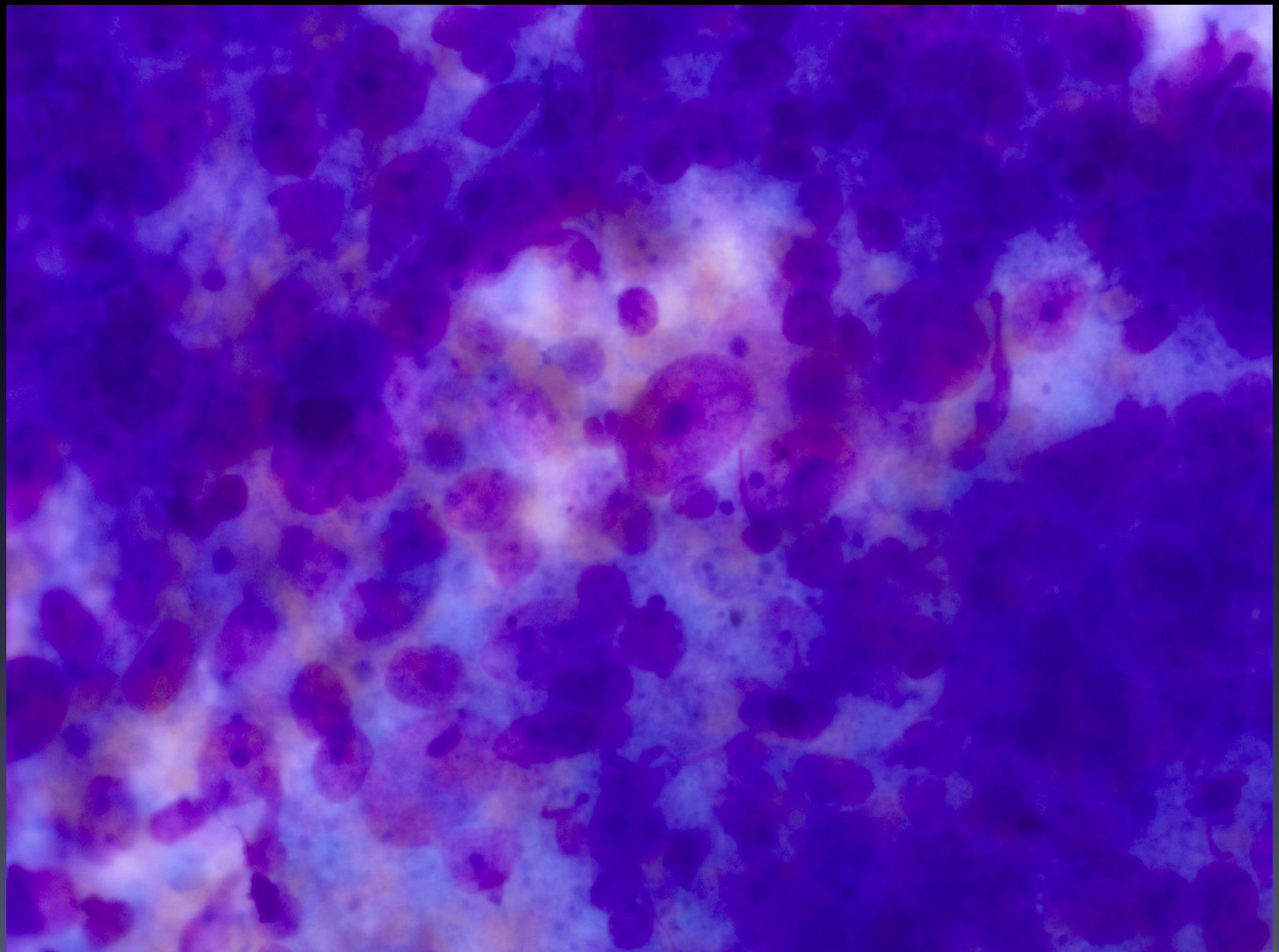

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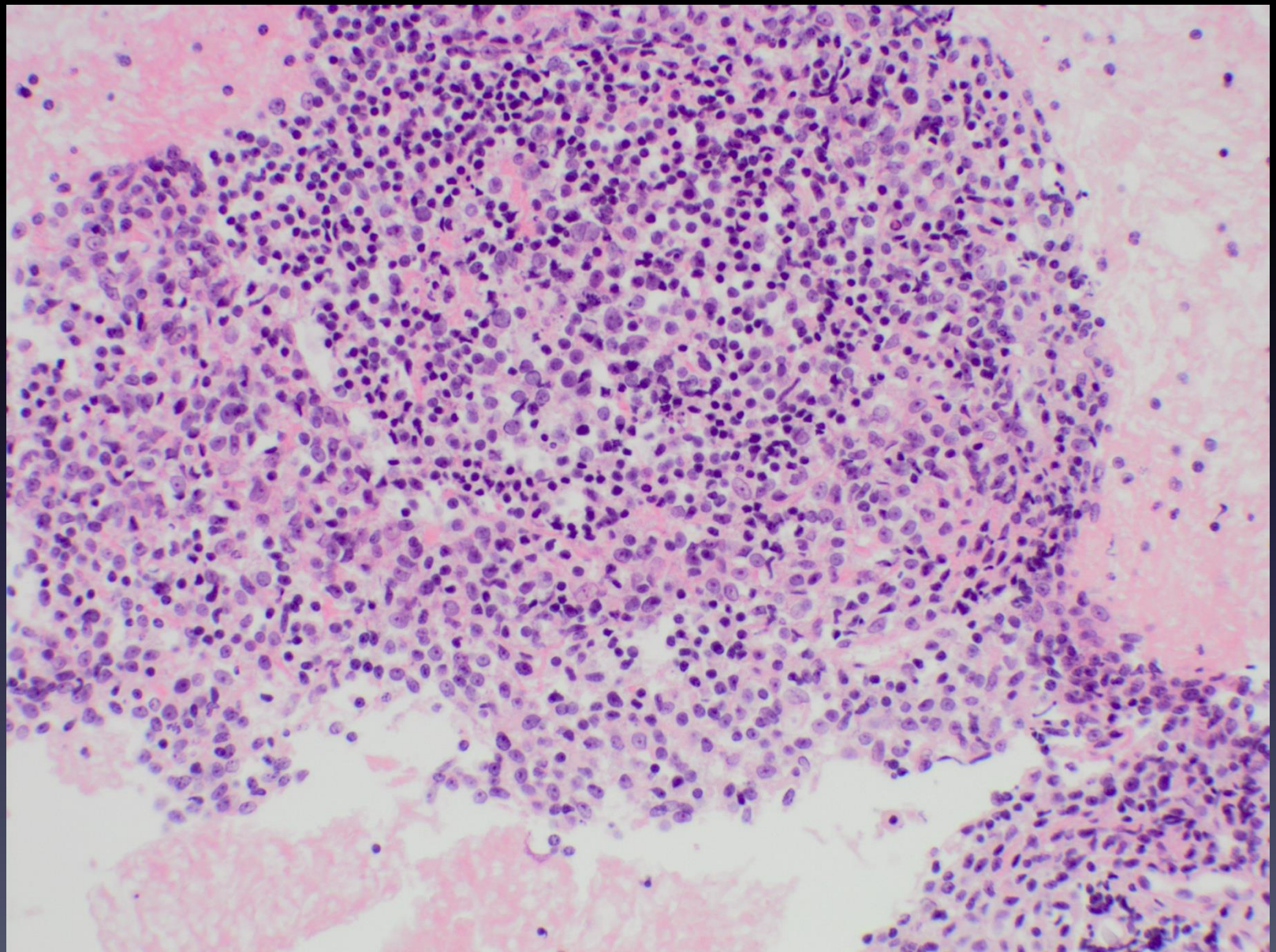
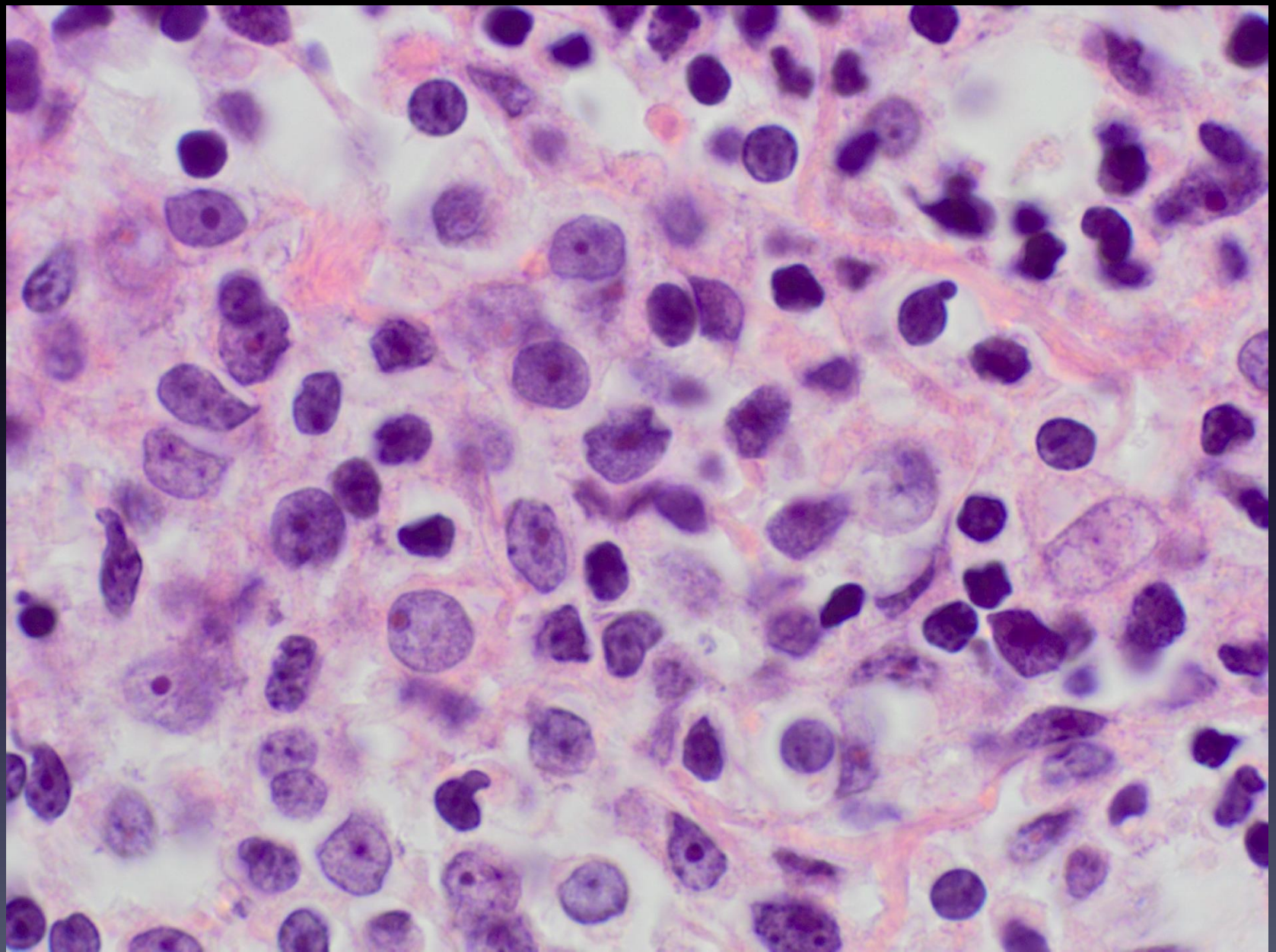


Case 4



Case 4: Diagnosis?

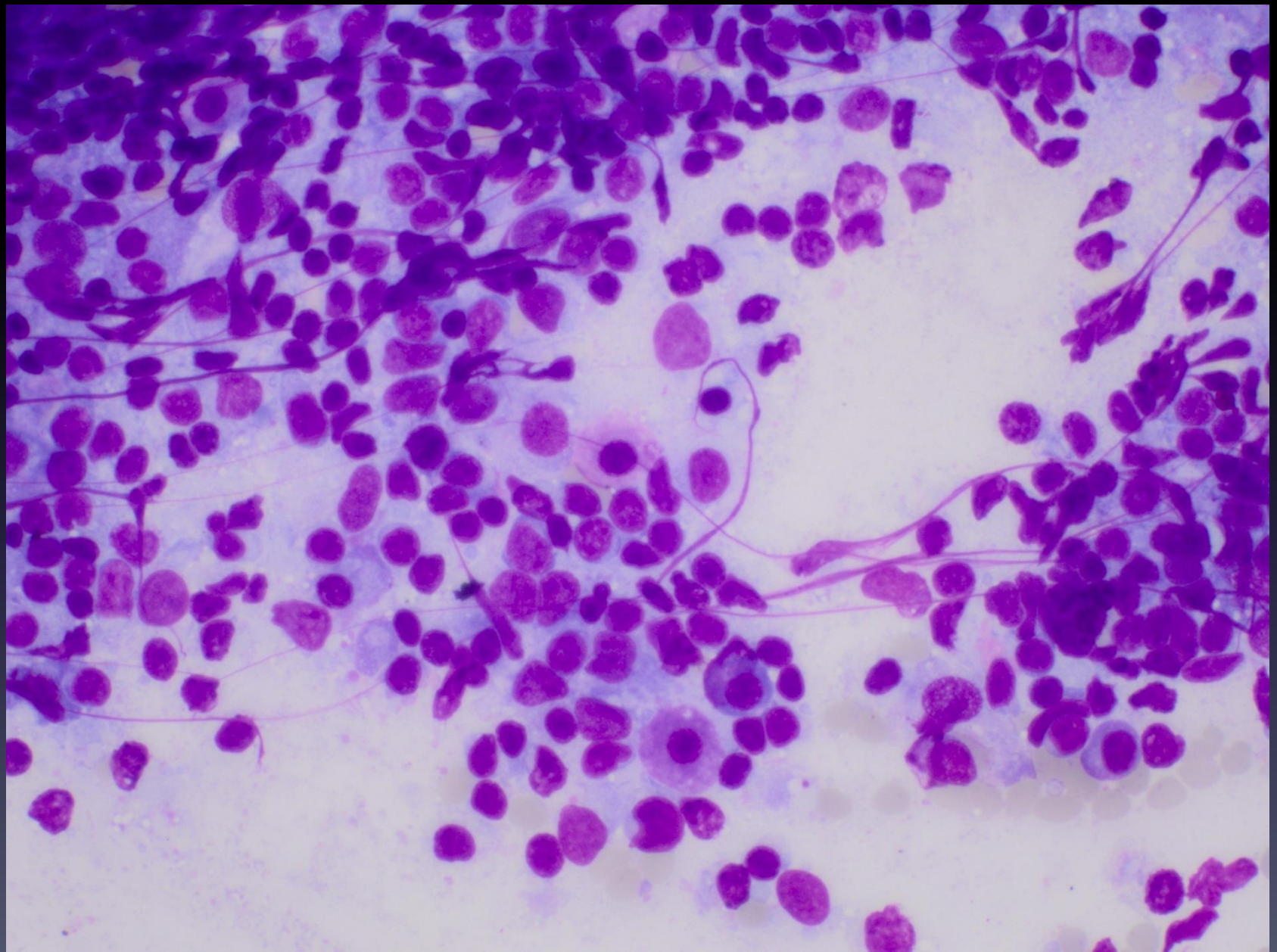
A. Large cell lymphoma

B. Hodgkin lymphoma

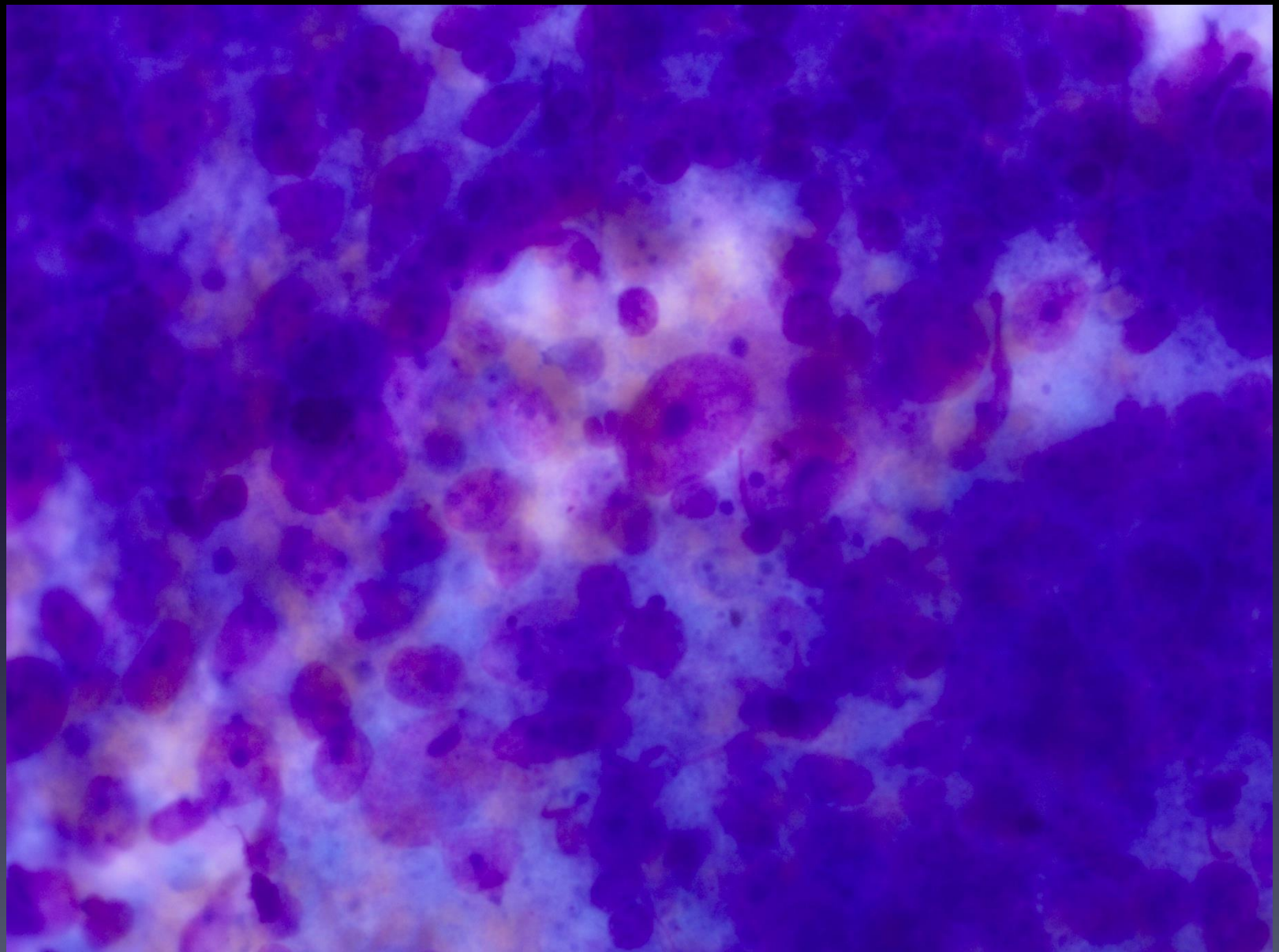
C. Nasopharyngeal carcinoma, undifferentiated type

D. Squamous cell carcinoma

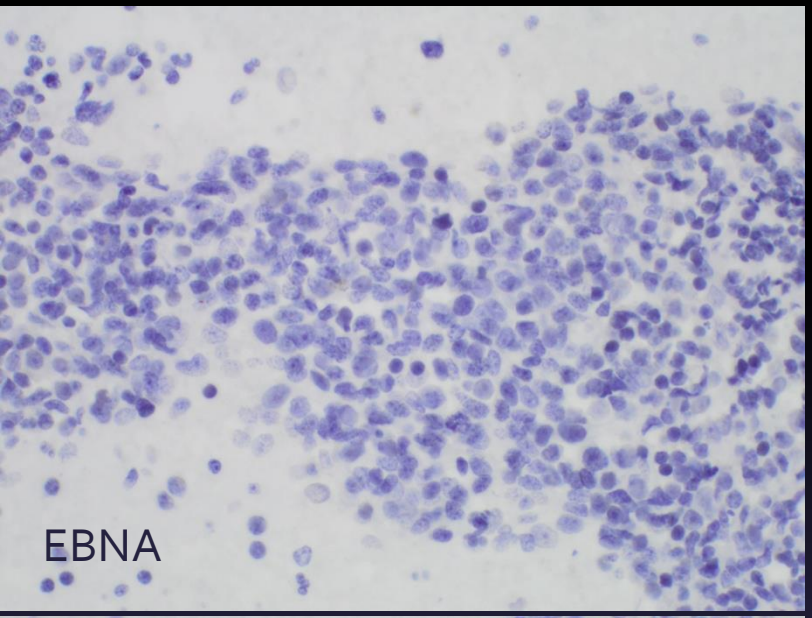
Case 4

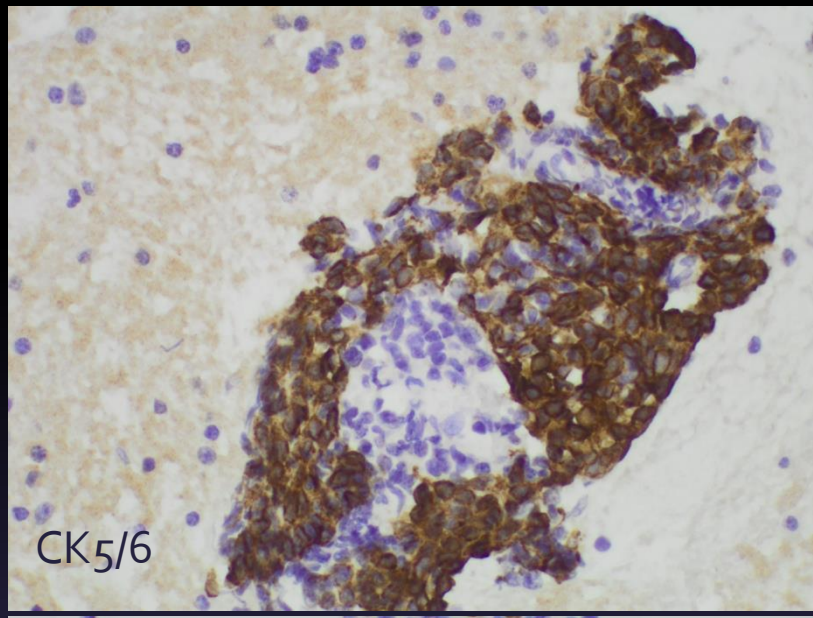


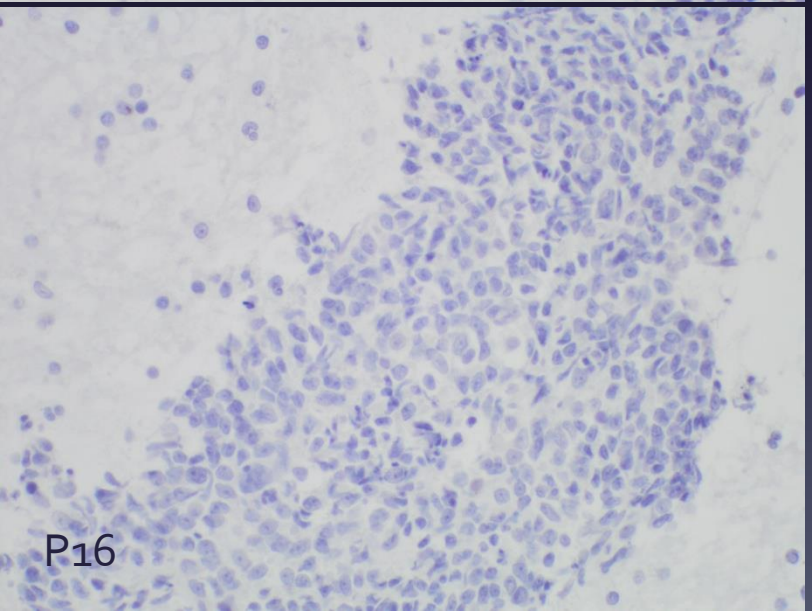
Case 4

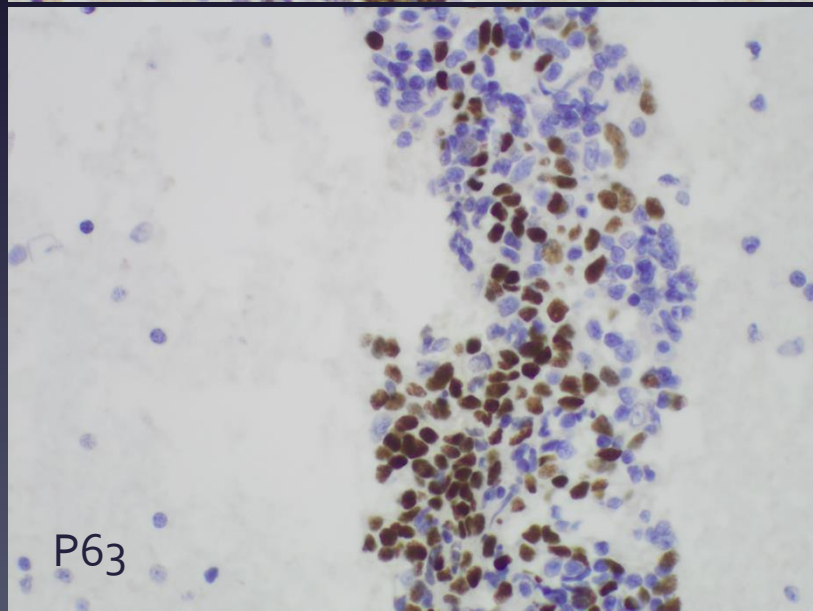


Case 4

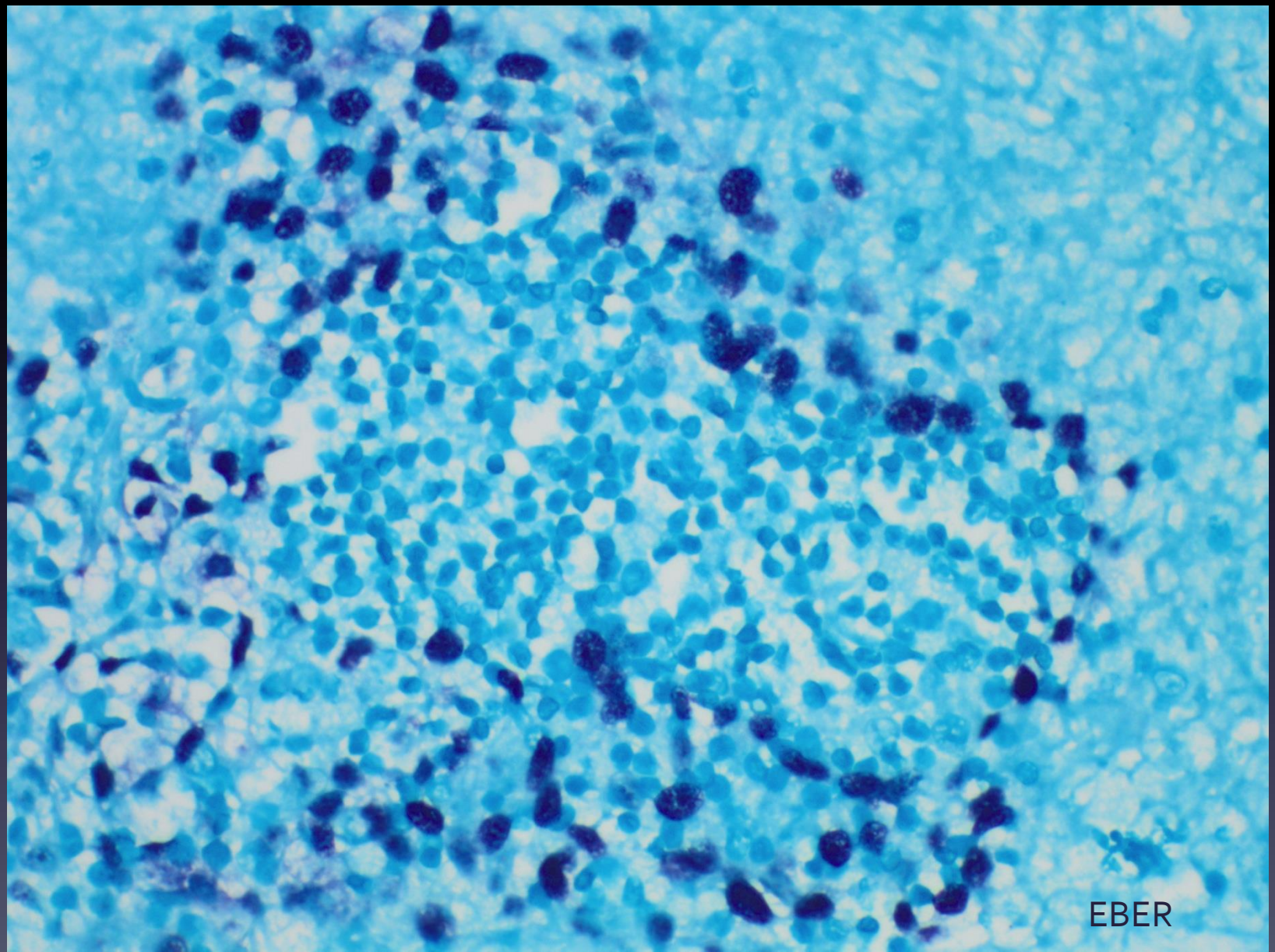








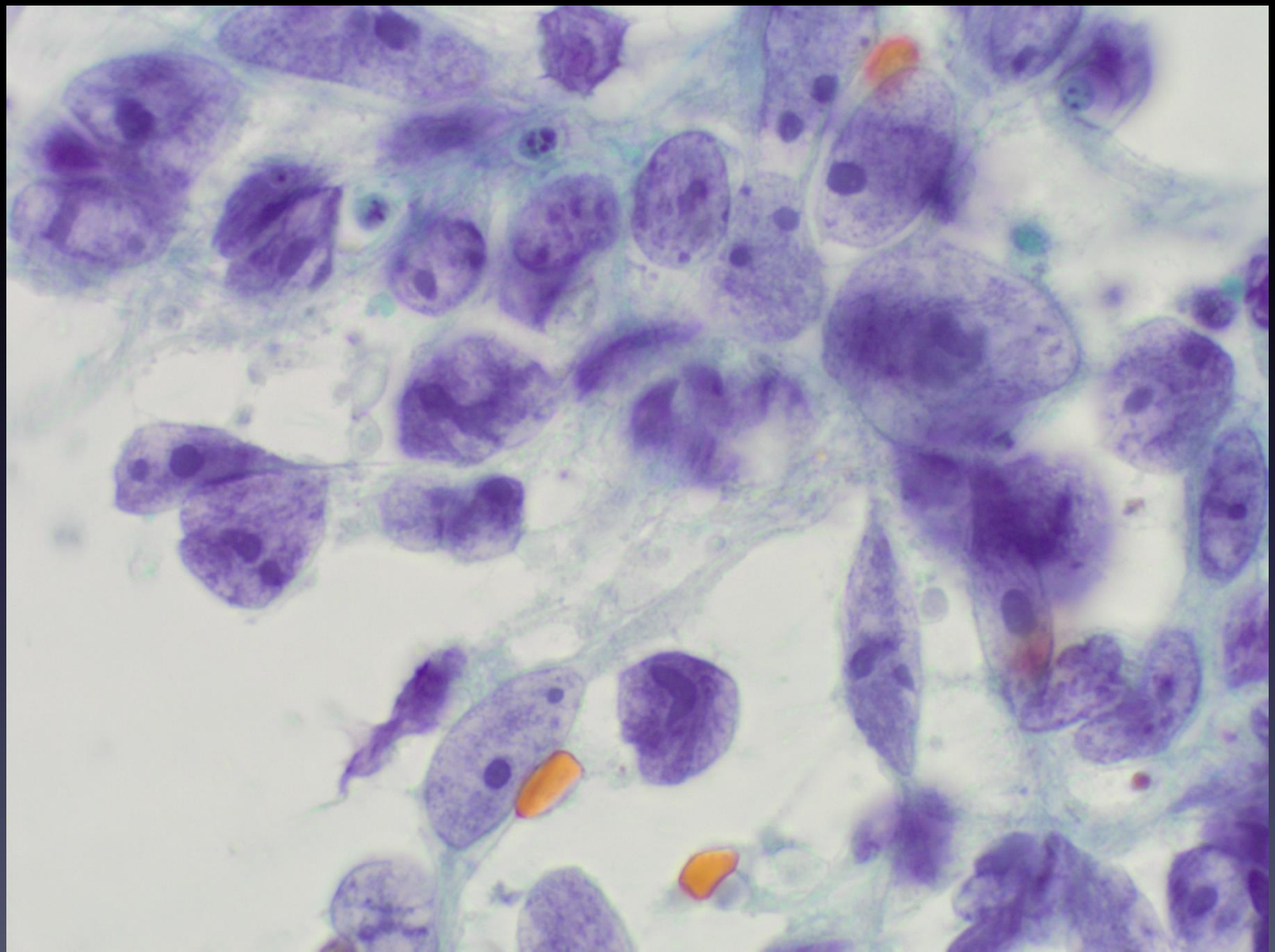
Case 4



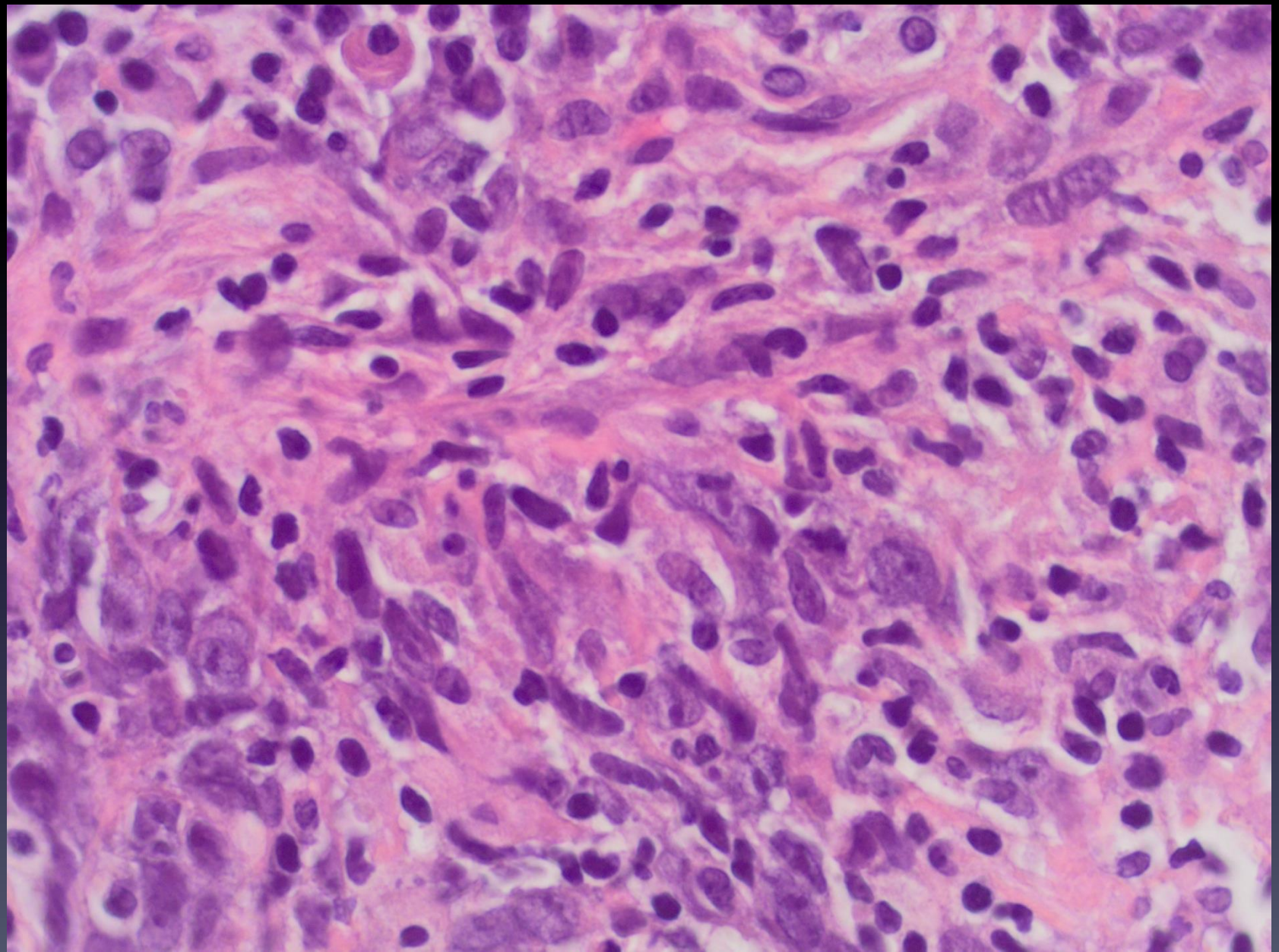
Case 4: Diagnosis

Metastatic nasopharyngeal carcinoma, non-keratinizing undifferentiated type (lymphoepithelial carcinoma; lymphoepithelioma)

NPC

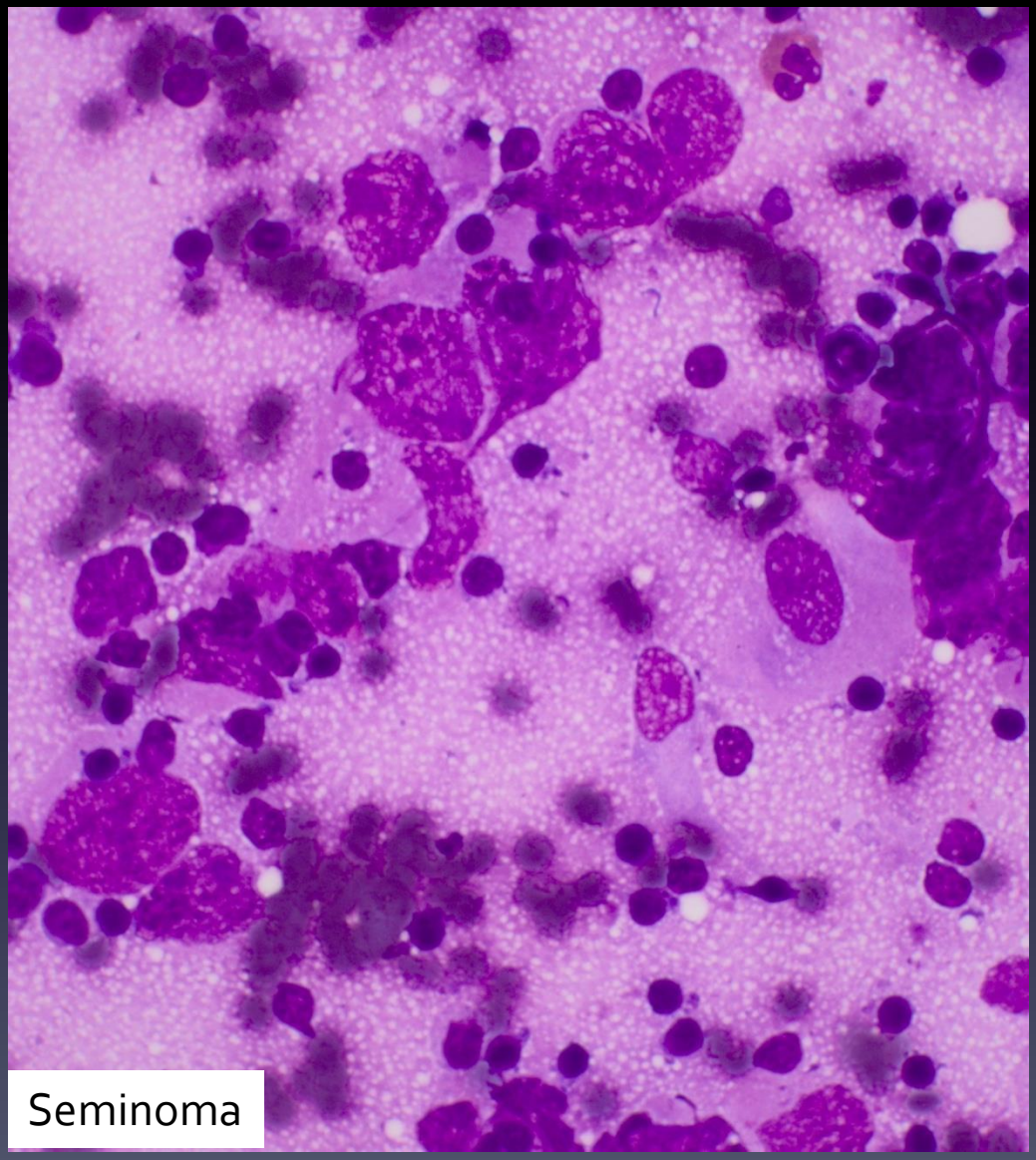


NPC



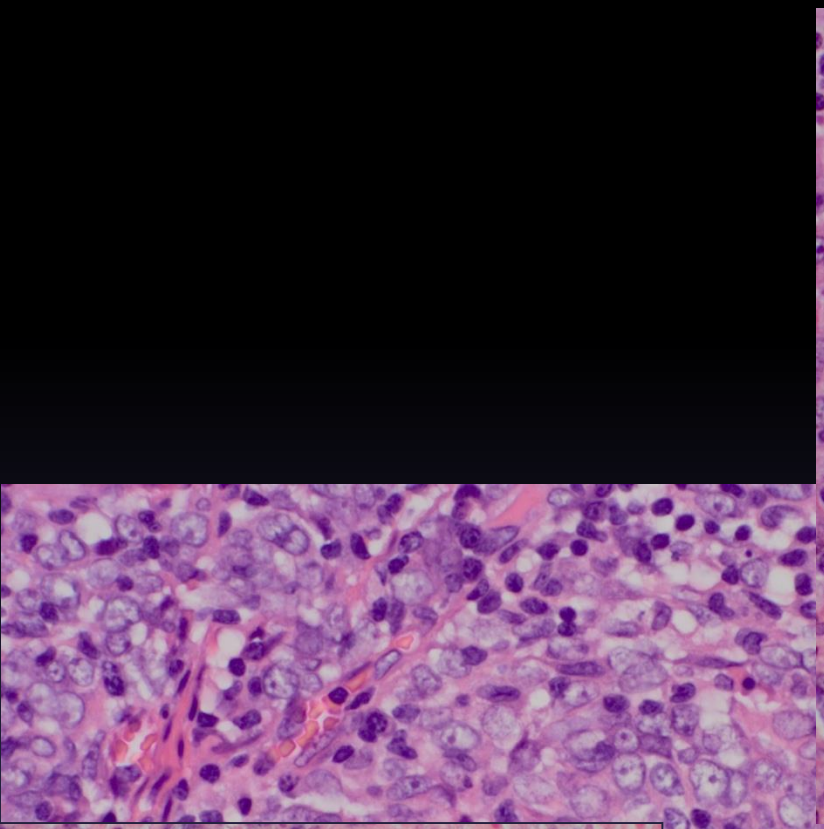
Large cells with small lymphocytes

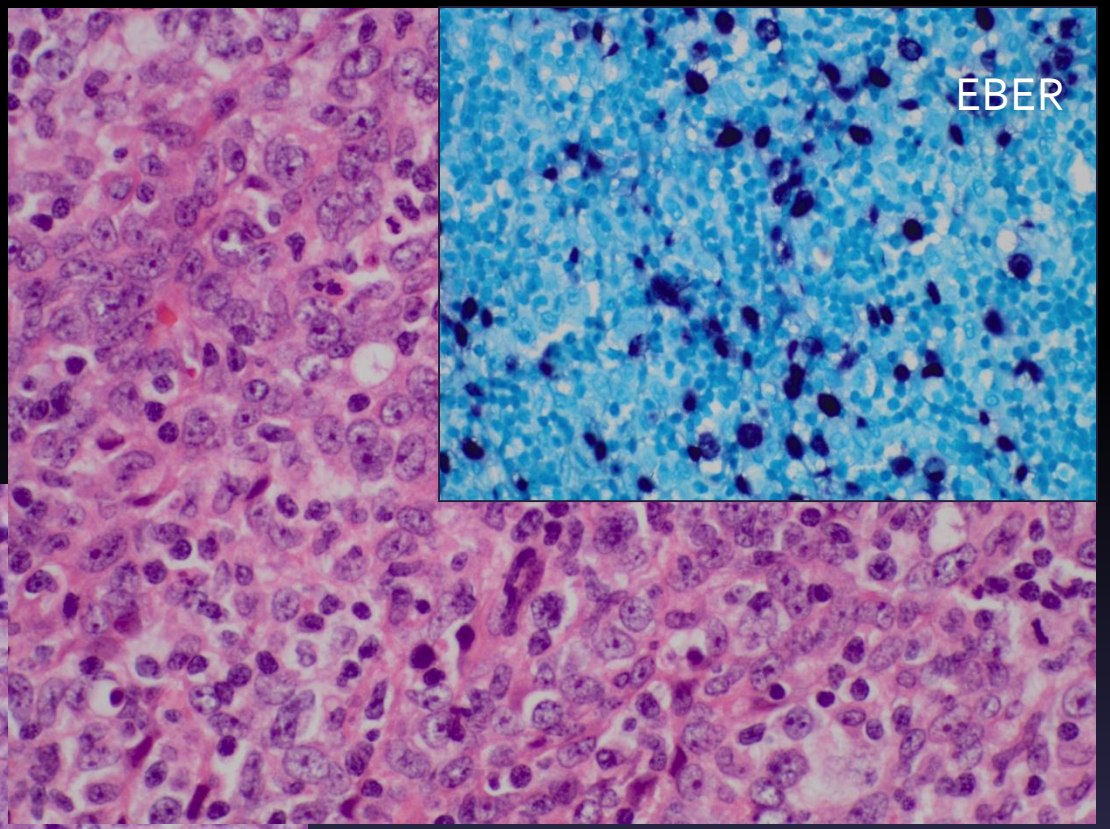
- Large cell lymphoma
- Hodgkin Disease
- Seminoma
- NPC
- Thymoma
- FDC sarcoma

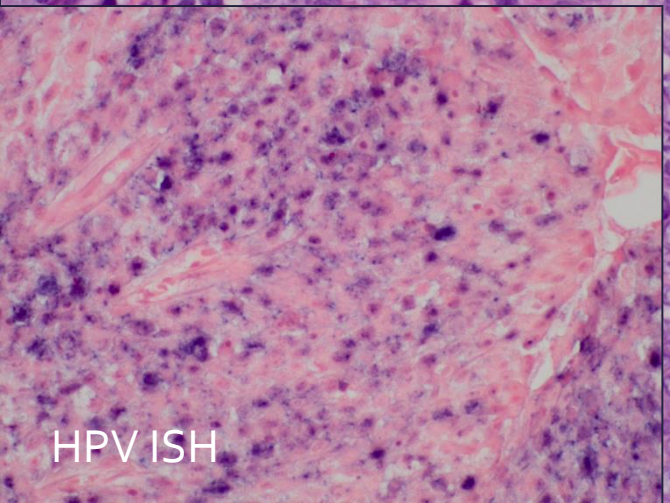


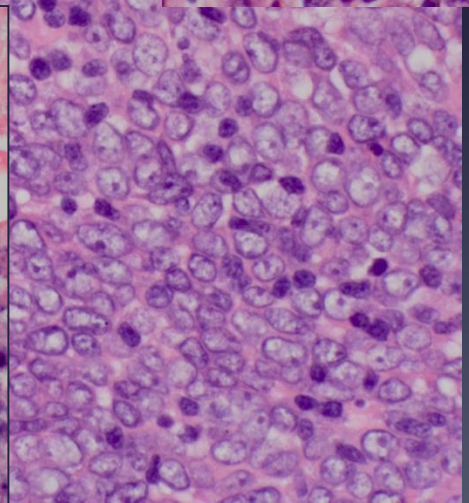
Seminoma

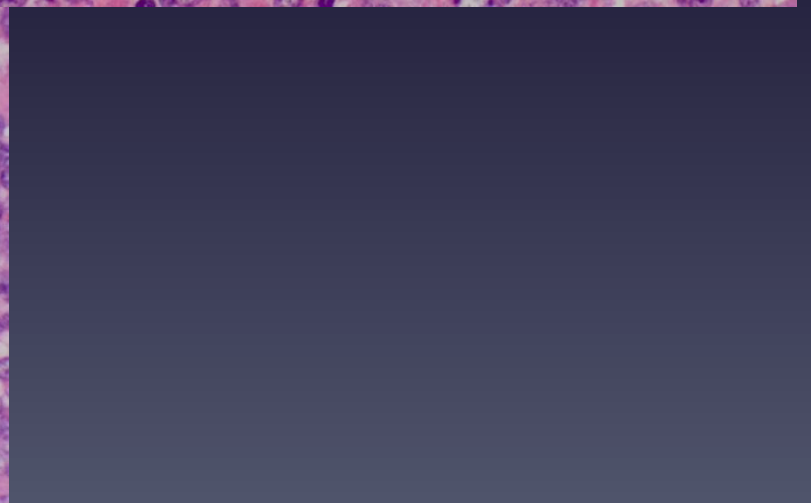
Morphologic variants: Undifferentiated (lymphoepithelioma-like)











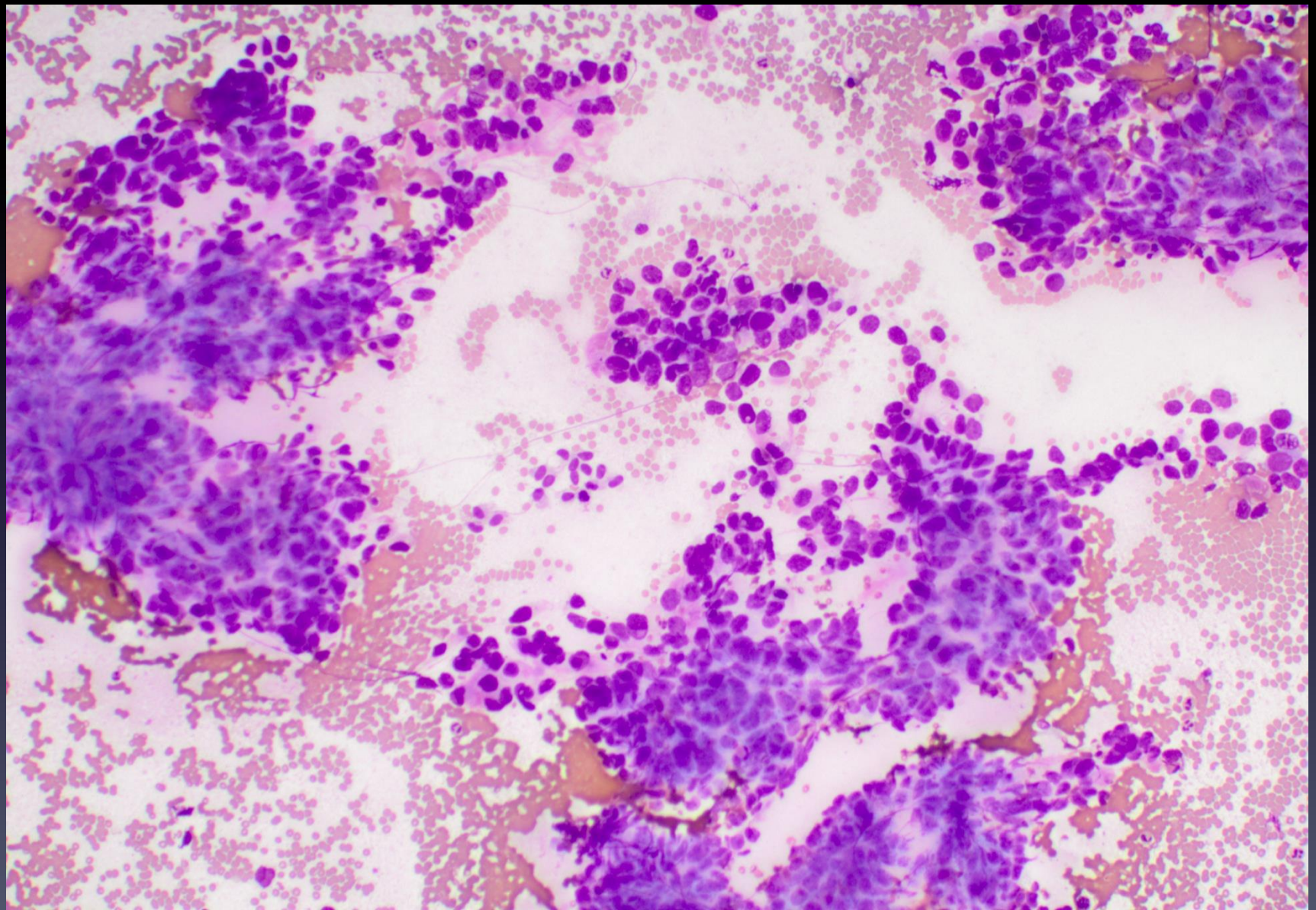
HNSCC of unknown primary

- Basaloid, cystic
  - HPV for oropharynx
- Undifferentiated
  - EBV for nasopharynx
  - Also consider HPV and oropharynx

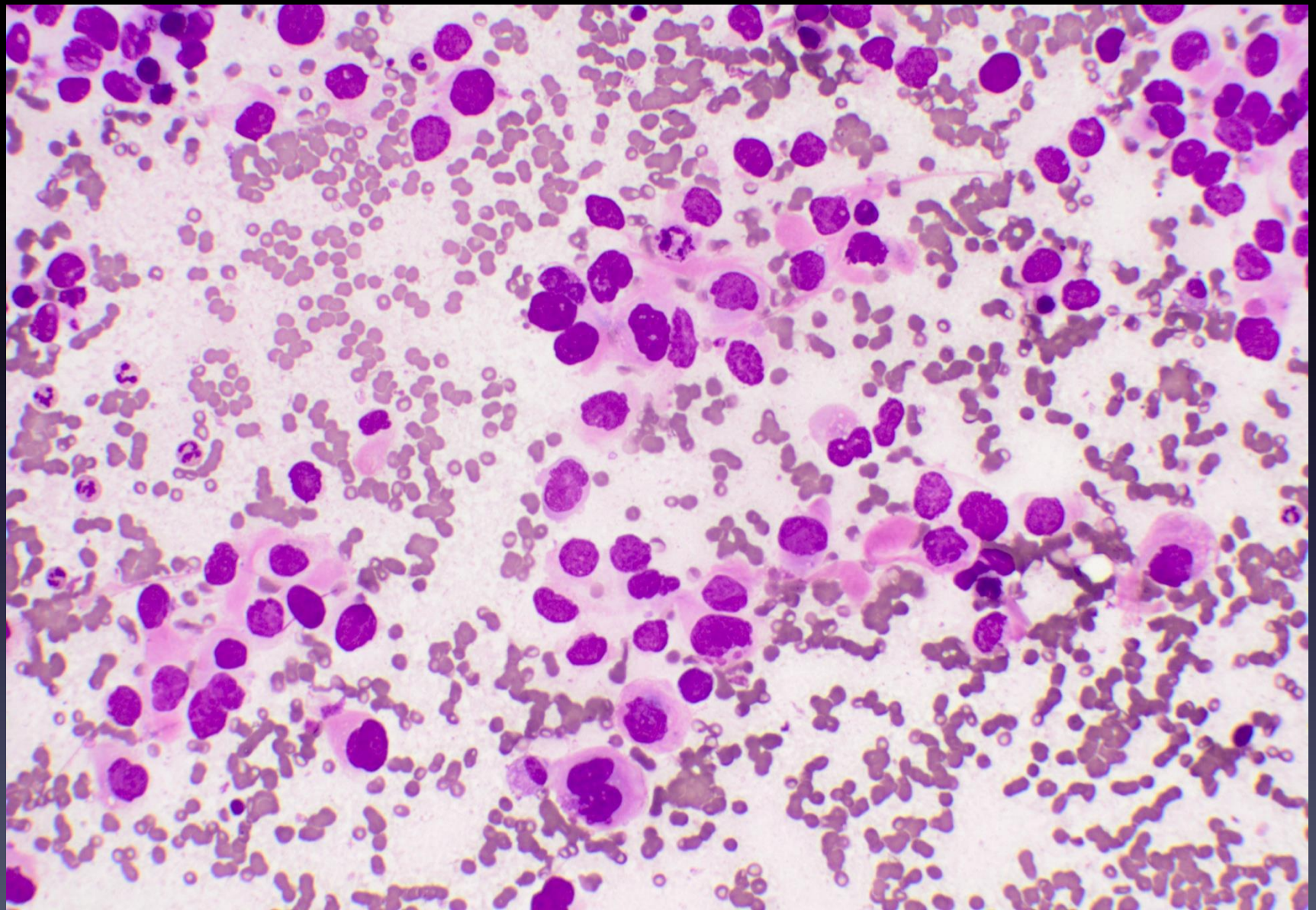
Case 5

A 28 year old man presents with a maxillary sinus and right neck mass.

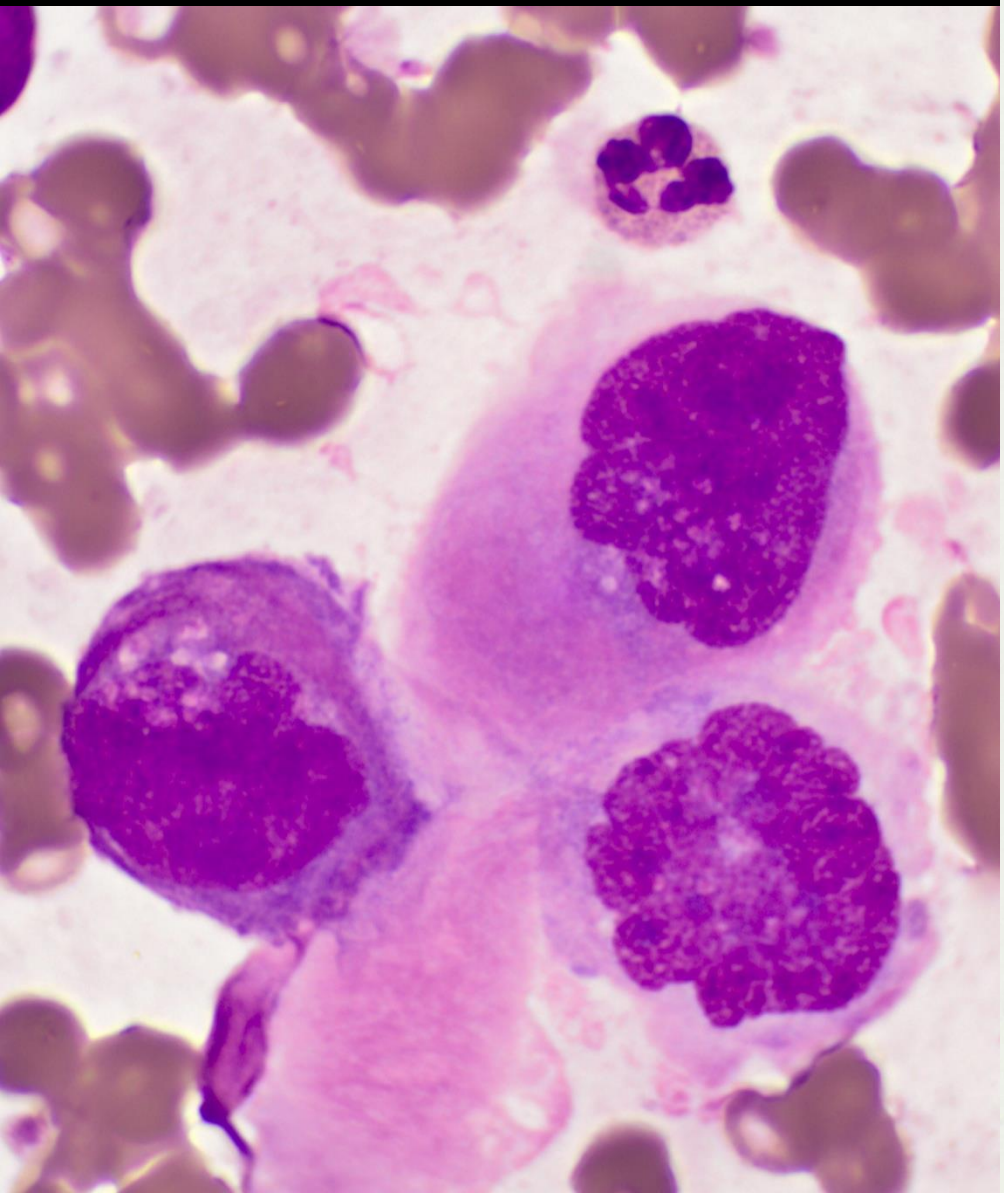
Case 5

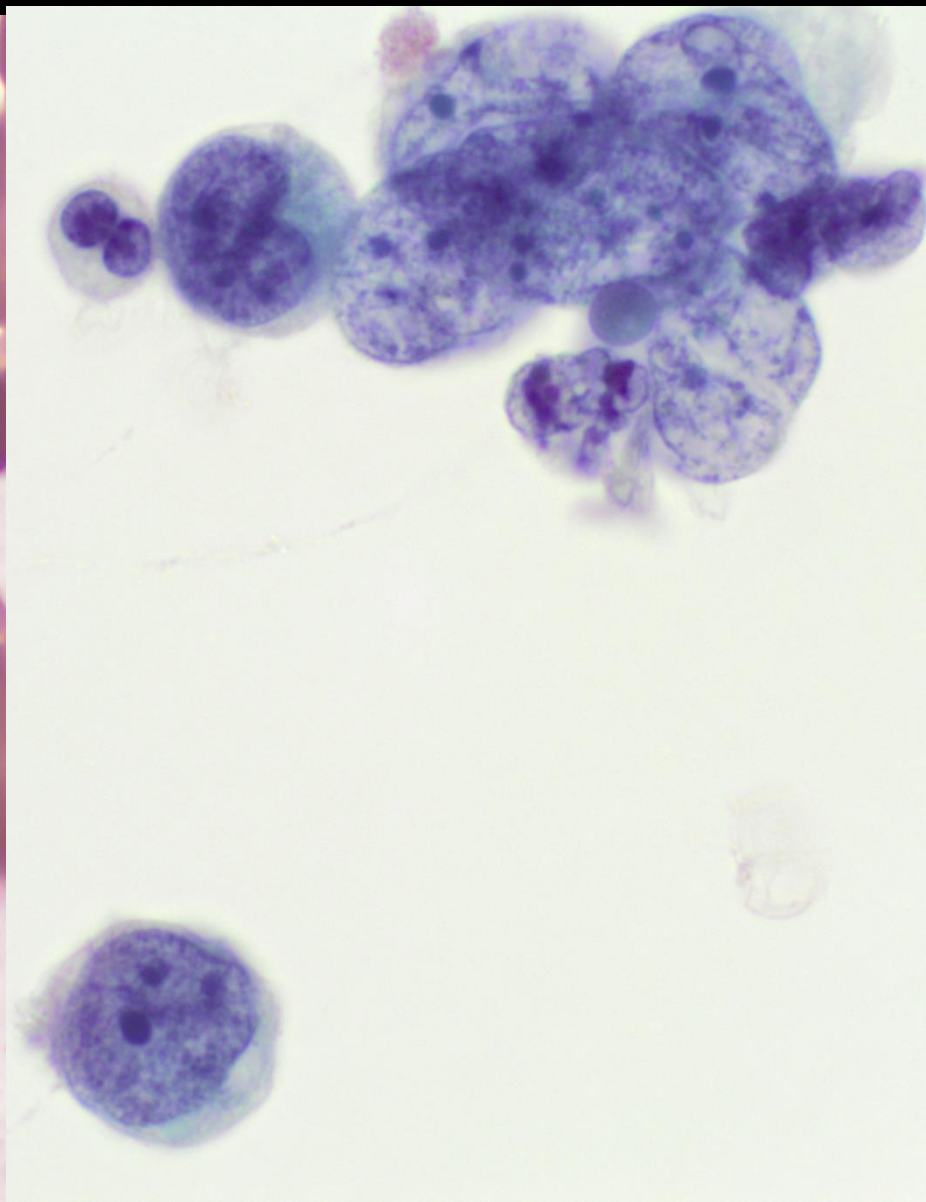


Case 5

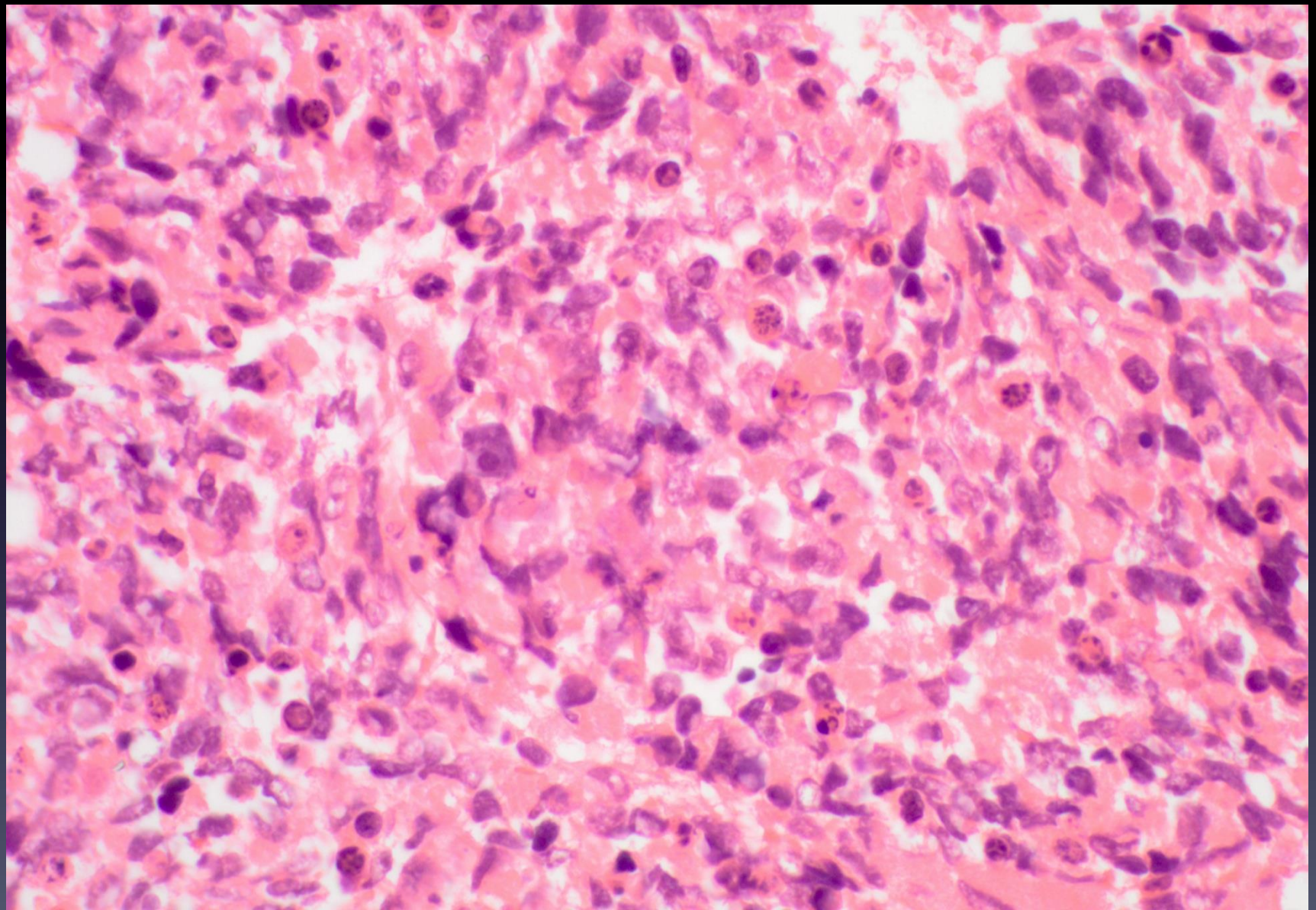


Case 5





Case 5



Case 5: Diagnosis?

A. Alveolar rhabdomyosarcoma

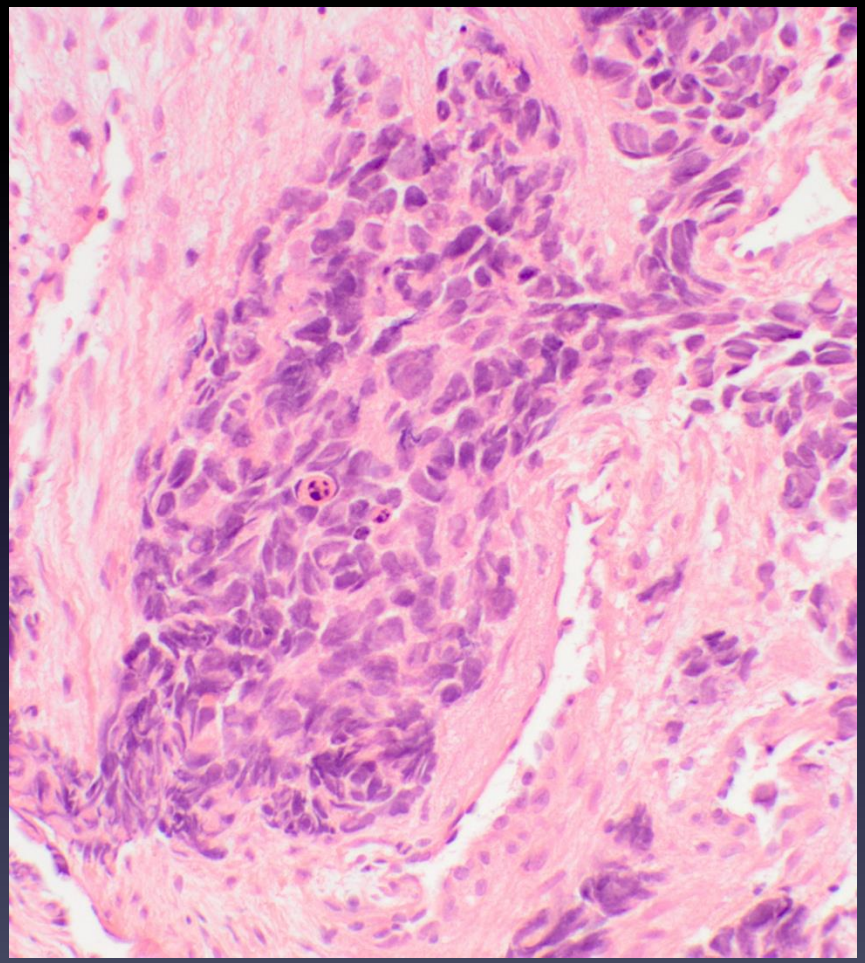
B. Poorly differentiated synovial sarcoma

C. Poorly differentiated carcinoma

D. Large cell lymphoma

Case 5

- Desmin+
- MyoD1 (Myf-4)+
- t(2;13)
- Absent
  - Rhabdomyoblasts
  - Wreath-like giant cells



Case 5: Diagnosis

Alveolar rhabdomyosarcoma

Rhabdomyosarcoma

- 35-45% in head and neck
- Mostly children, but also adults to age 50
- Metastasizes to lymph nodes

Small round cell neoplasms

- Lymphoma
- Small cell carcinoma
- Ewing sarcoma
- Rhabdomyosarcoma
- Synovial sarcoma, poorly differentiated

Conclusions

- Diagnosis of basaloid neoplasms is challenging
- Synthesize
  - History
  - Cytologic pattern recognition and potential subtle non-basaloid findings
  - Ancillary studies
    - IHC
    - ISH
    - Cytogenetics
- Classification not always possible on FNA
- Do not be afraid to give a differential diagnosis