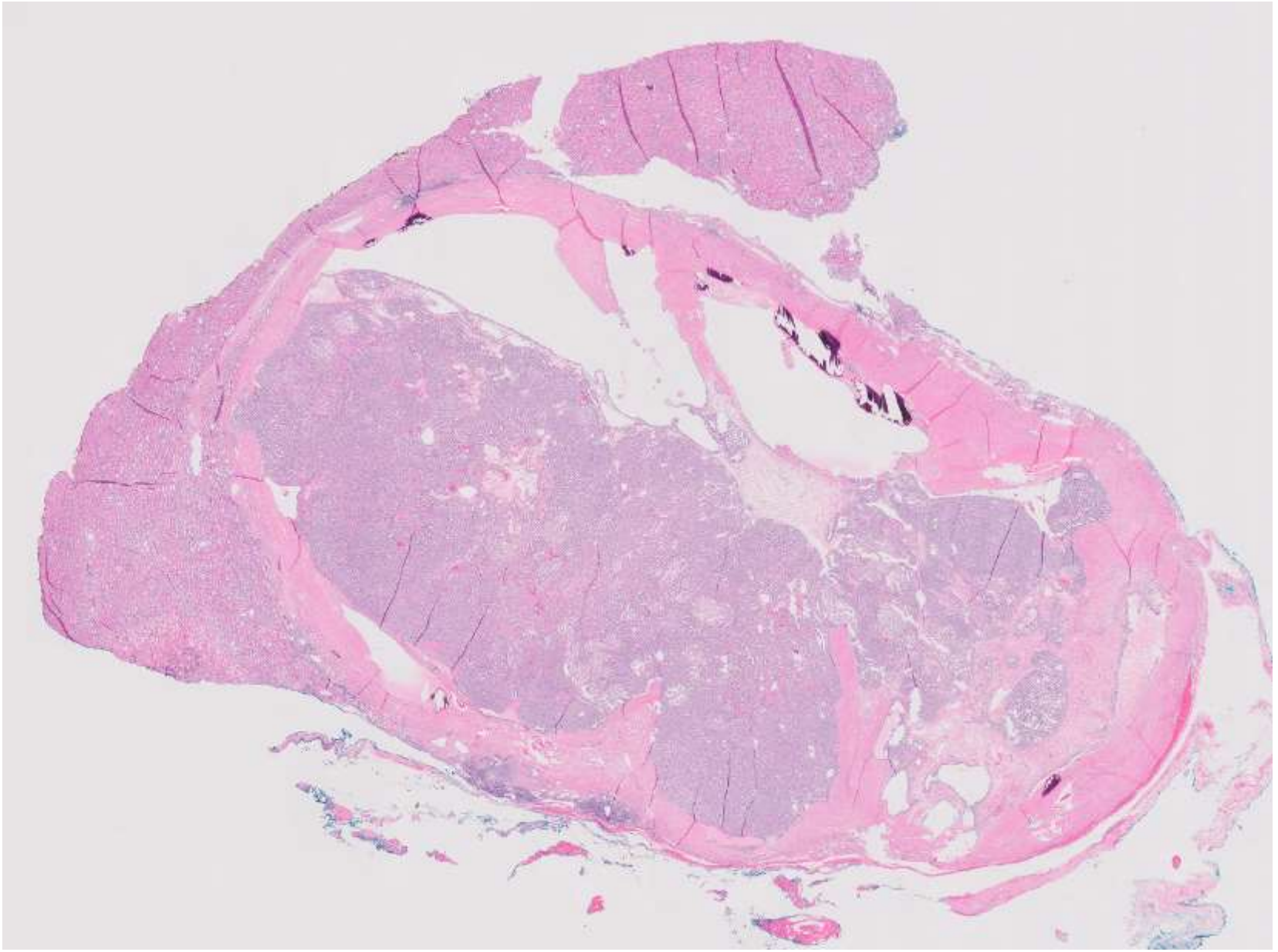
FEB 2022 DIAGNOSIS LIST

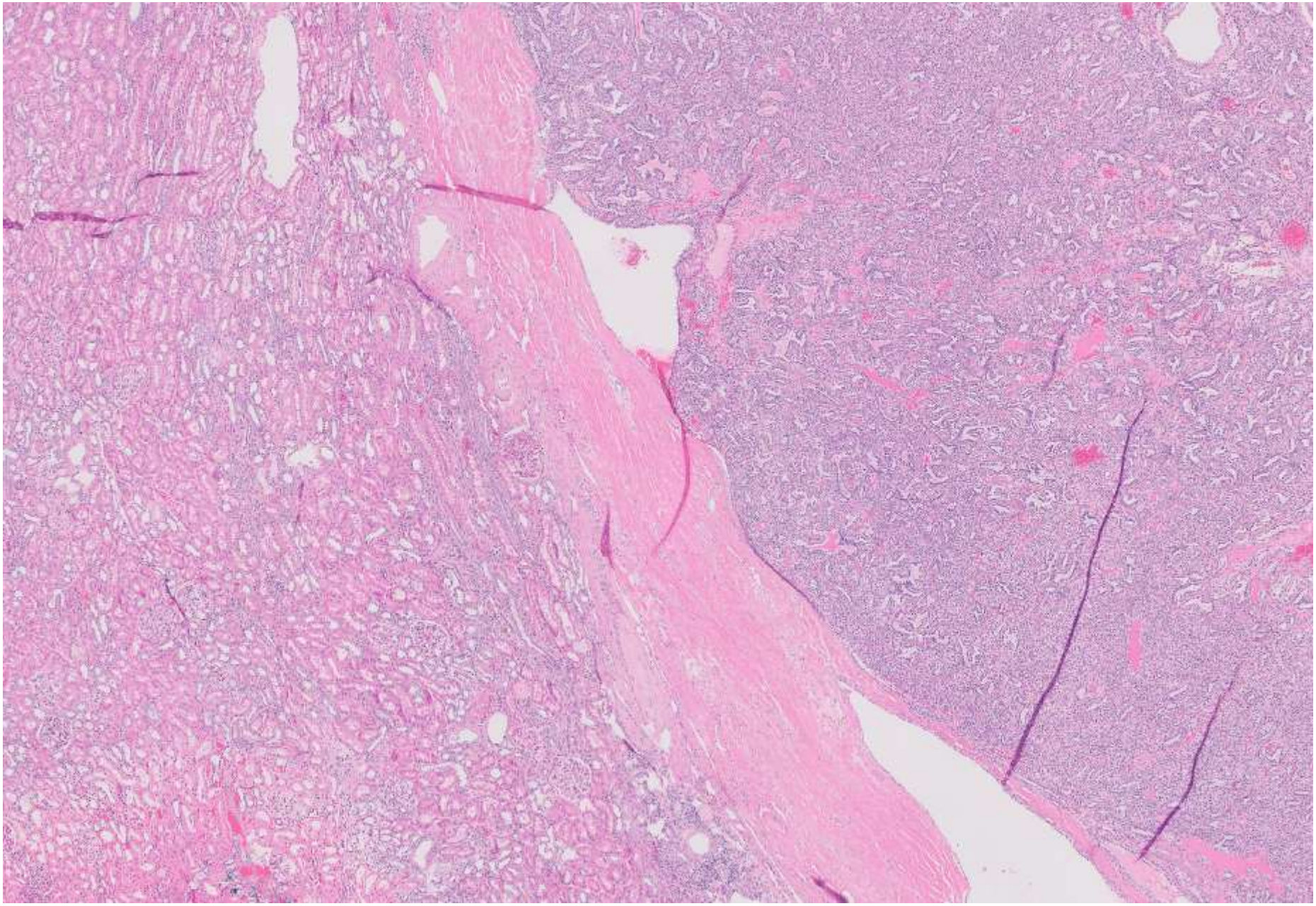
22-0201: clear cell papillary renal cell carcinoma (kidney; GU path)
22-0202: invasive ductal carcinoma with paraneoplastic syndrome (breast; breast path)
22-0203: endocrine mucin producing sweat gland carcinoma (skin; derm path)
22-0204: juvenile psammomatoid ossifying fibroma (skull base; BST path)
22-0205: high grade urothelial carcinoma invading lamina propria within diverticulum (no pT2) (bladder; GU path)
22-0206: mixed small cell neuroendocrine carcinoma/urothelial carcinoma (bladder; GU path)
22-0207: acute osteomyelitis with intraosseous pseudocarcinomatous squamous hyperplasia (bone; BST path)

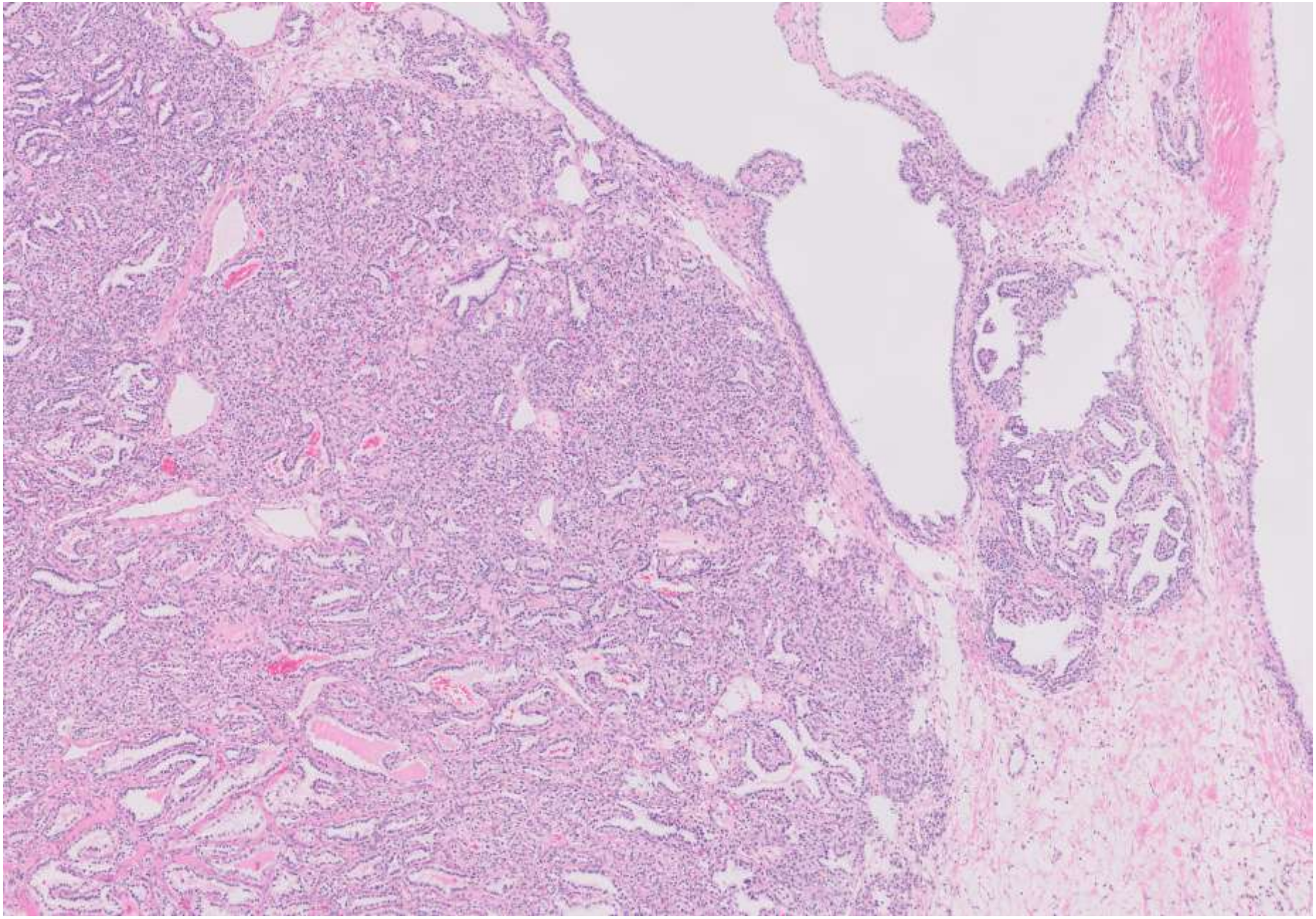
22-0201

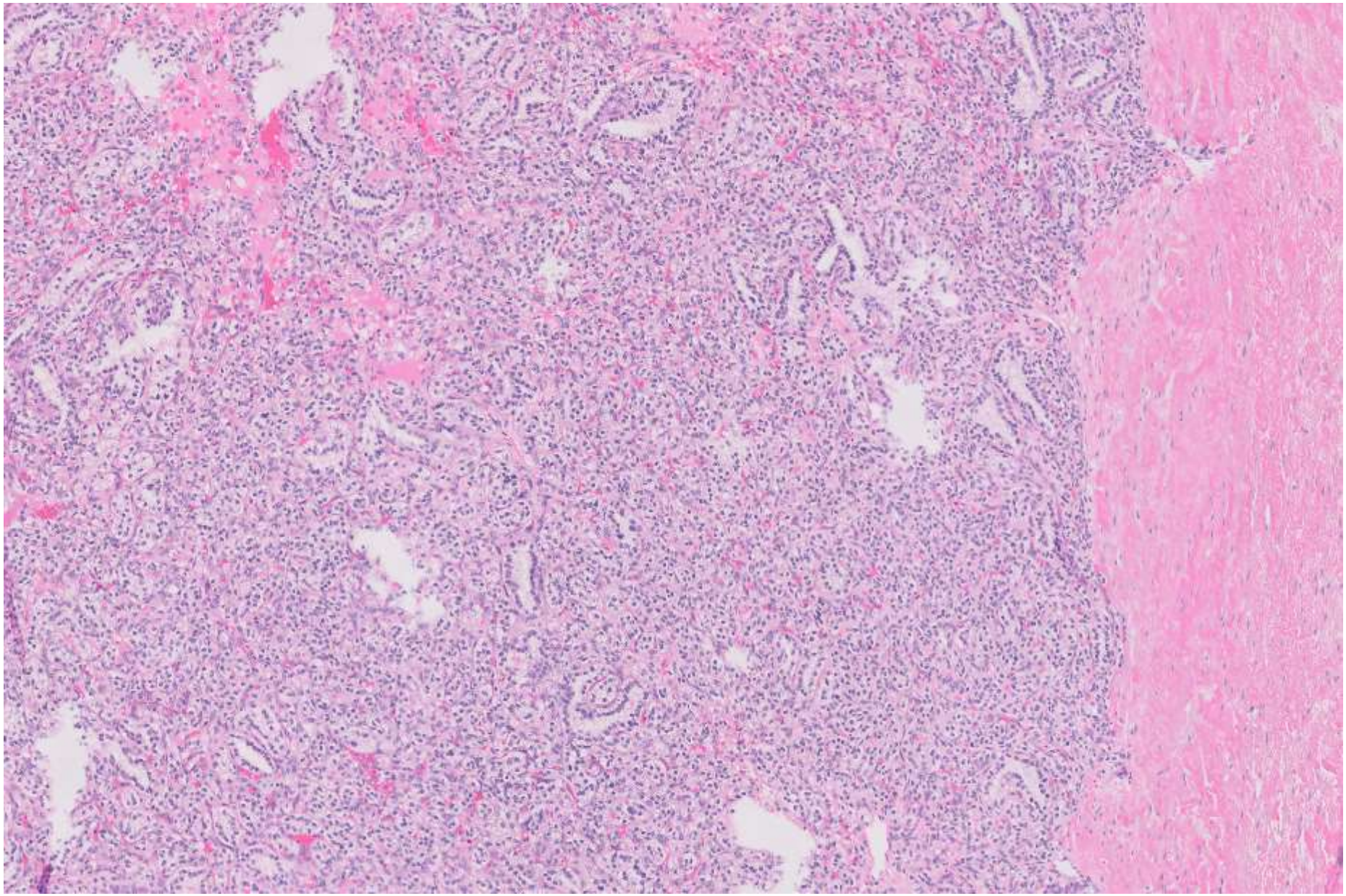
Emily Chan; UCSF

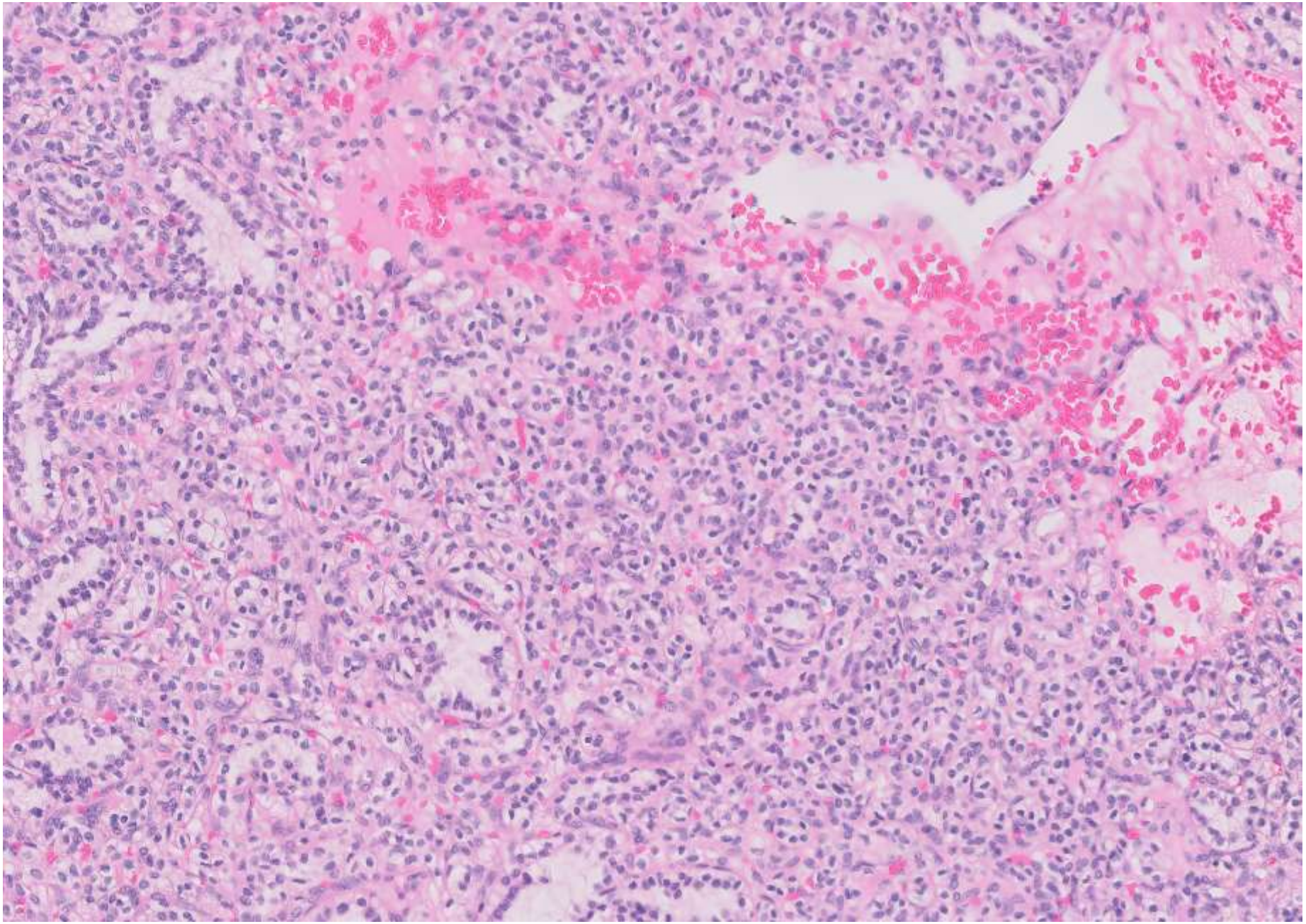
60ish F with 2.5cm left renal mass.

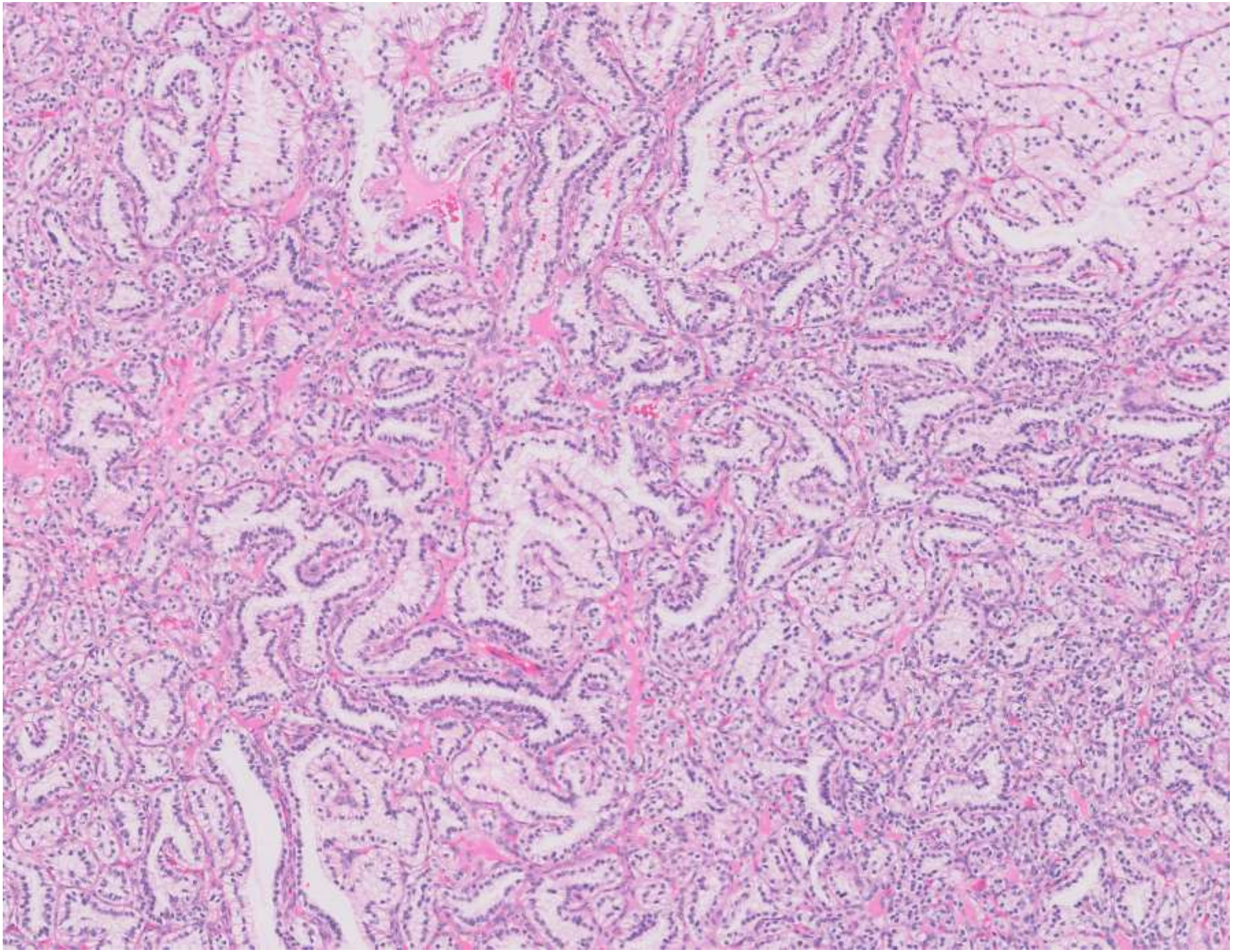


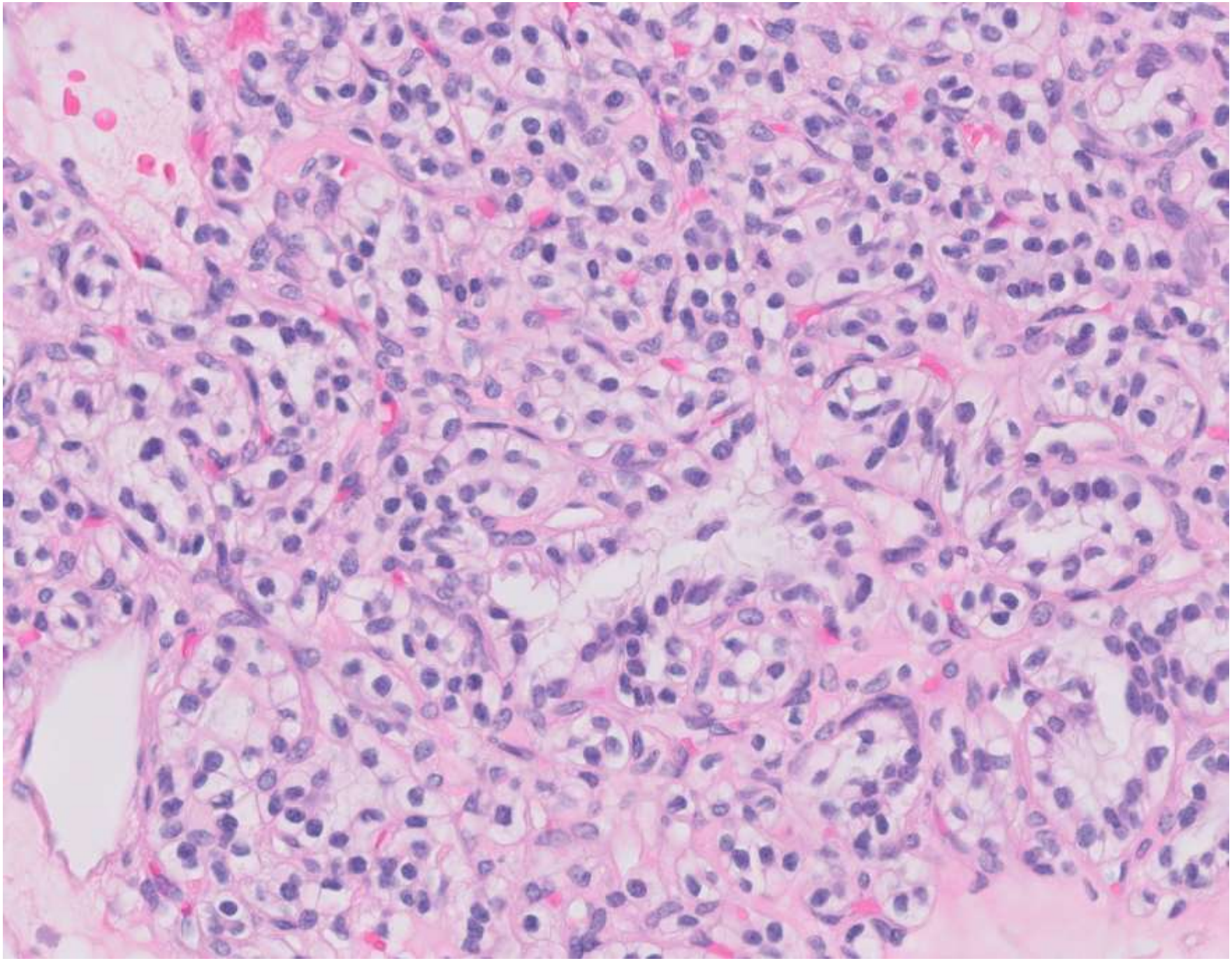




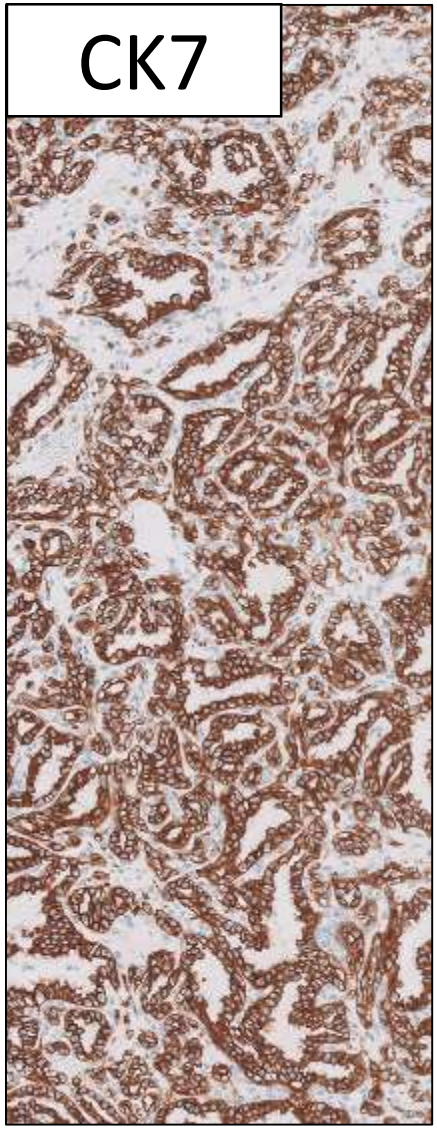


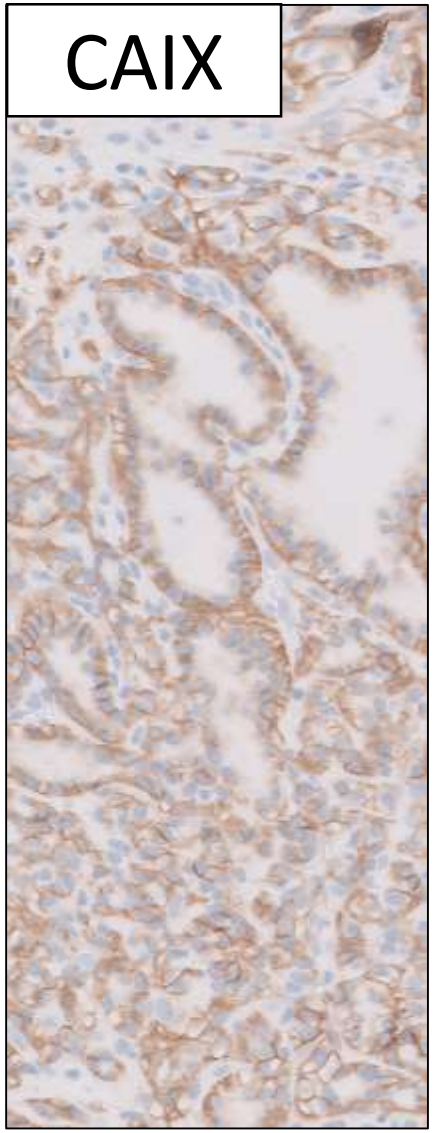


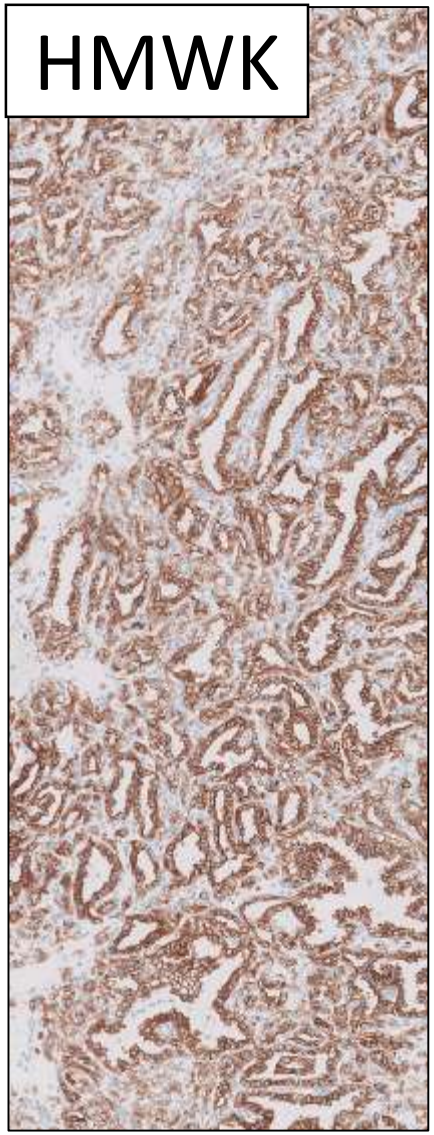


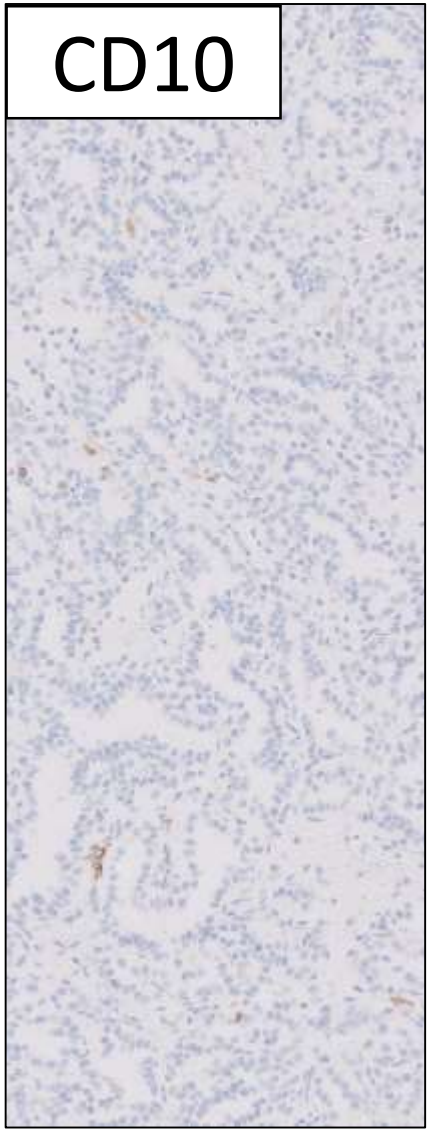


IHC









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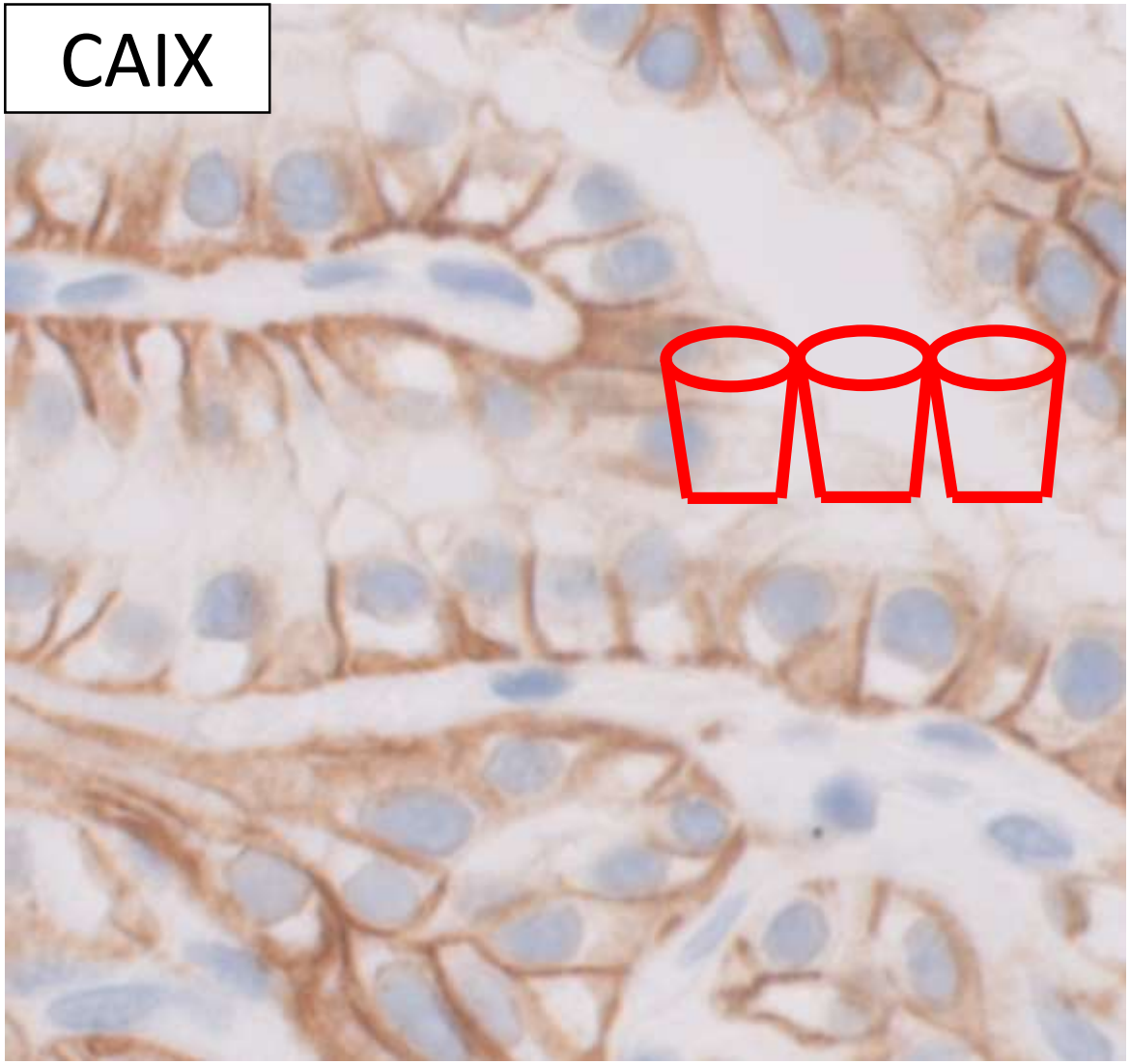


Diagnosis: Clear cell papillary renal cell carcinoma (ccpRCC)

- Papillae and tubules lined by clear cells with bland nuclei oriented apically
  - “Clear cell tubulopapillary RCC” in 2016 WHO
- Positive markers: CK7, CAIX “cup-like”, HMWK
- Negative markers: CD10, RCC
- Molecular: None for certain (importantly no VHL alterations or alterations associated with other established entities)

Some history…

- First described in the setting of end-stage renal disease but also occurs sporadically
- Recognized as distinct epithelial tumor entity by ISUP in 2013 and incorporated into 2016 WHO
- But then….

Do Clear Cell Papillary Renal Cell Carcinomas Have Malignant Potential?

Mairo L. Diolombi, MD, Liang Cheng, MD,†‡ Pedram Argani, MD,* and Jonathan I. Epstein, MD*§‖*

Abstract: There have been no recurrences or metastases of clear cell papillary renal cell carcinoma (CCPRCC) in 268 reported cases with follow-up in the English-language literature. We identified all our cases of CCPRCC (1990 to 2013), reviewing all cases that preceded the formal designation of the entity. Immunohistochemical stains were performed on 32 cases during their initial workup. In addition, stains for carbonic anhydrase IX and cytokeratin 7 were performed on 2 cases, one with atypical follow-up and the other with a more compact morphology, although not performed initially. An extended panel with AMACR, CD10, and renal cell carcinoma (RCC) was added to the case with atypical follow-up. Fluorescence in situ hybridization for chromosomes 3p, 7, and 17 was performed on the latter case and on another clinically presumed metastatic tumor. In classic cases, immunohistochemical staining was not performed. Fifty-eight patients (31 women; 27 men) with follow-up data were included in our study; 39 cases were from our consult service. The patients' ages ranged from 36 to 83 years, multiple partial nephrectomies. Metastatic disease to the lung was clinically presumed in 1 patient in whom a higher-grade lesion may have been missed during sampling of the predominantly cystic pT1b tumor and tissue confirmation of the metastases was not obtained. Another case presented with multiple skeletal and pulmonary metastases 8 months after resection of pT3 sarcomatoid CCPRCC. The patient with the sarcomatoid RCC died of multifocal skeletal and pulmonary metastatic disease 13 months after resection of the renal tumor.

Our study, the largest to date with follow-up, along with others, suggests that pure CCPRCC is an indolent tumor and should be renamed "clear cell papillary neoplasm of low malignant potential" to reflect their biology.

Key Words: clear cell papillary renal cell carcinoma, follow-up, prognosis, benign, malignant, aggressive, partial nephrectomy, radical nephrectomy

(*Am J Surg Pathol* 2015;39:1621–1634)

Modern Pathology (2021) 34:1392–1424
https://doi.org/10.1038/s41379-021-00779-w

ARTICLE

New developments in existing WHO entities and evolving molecular concepts: The Genitourinary Pathology Society (GUPS) update on renal neoplasia

Kiril Trpkov[1] · Ondrej Hes[2] · Sean R. Williamson[3] · Adebowale J. Adeniran[4] · Abbas Agaimy[5] · Reza Alaghehbandan[6] · Mahul B. Amin[7] · Pedram Argani[8] · Ying-Bei Chen[9] · Liang Cheng[10] · Jonathan I. Epstein[11] · John C. Cheville[12] · Eva Comperat[13] · Isabela Werneck da Cunha[14] · Jennifer B. Gordetsky[15] · Sounak Gupta[12] · Huiying He[16] · Michelle S. Hirsch[17] · Peter A. Humphrey[4] · Payal Kapur[18] · Fumiyoshi Kojima[19] · Jose I. Lopez[20] · Fiona Maclean[21,22] · Cristina Magi-Galluzzi[23] · Jesse K. McKenney[3] · Rohit Mehra[24] · Santosh Menon[25] · George J. Netto[23] · Christopher G. Przybycin[3] · Priya Rao[26] · Qiu Rao[27] · Victor E. Reuter[9] · Rola M. Saleeb[28] · Rajal B. Shah[29] · Steven C. Smith[30] · Satish Tickoo[9] · Maria S. Tretiakova[31] · Lawrence True[31] · Virginie Verkarre[32] · Sara E. Wobker[33] · Ming Zhou[34] · Anthony J. Gill[35,36,37]

- Diagnosis of clear cell papillary RCC requires use of strict morphologic and immunohistochemical criteria, particularly on biopsy.
- Currently, there is a lacks of strong evidence of aggressive behavior for clear cell papillary RCC, which may be a candidate for reclassification as a tumor of "low malignant potential", as more experience is gained.

Some history…

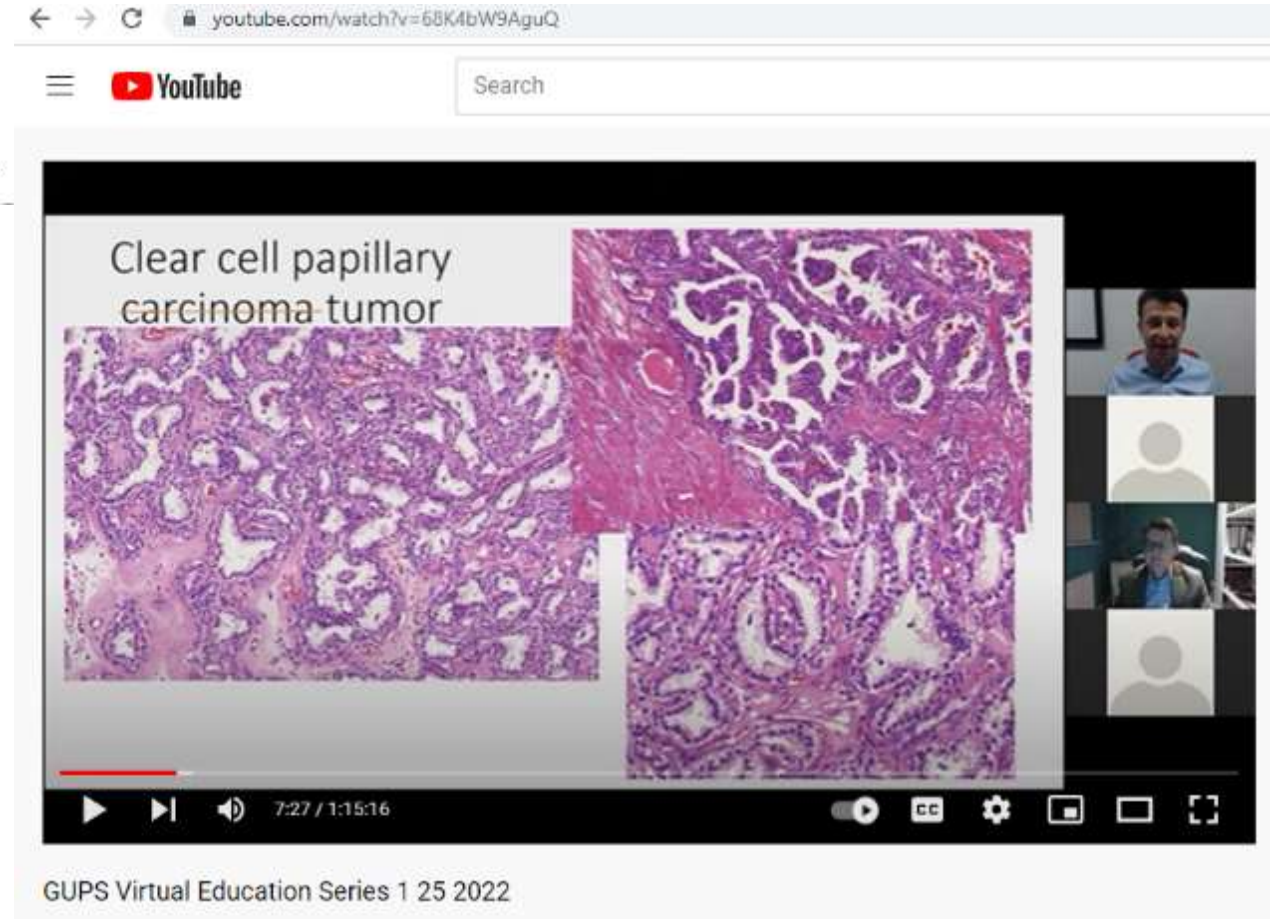
- First described in the setting of end-stage renal disease but also occurs sporadically
- Recognized as distinct epithelial tumor entity by ISUP in 2013 and incorporated into 2016 WHO
- Candidate for reclassification as a tumor of low malignant potential

GUPS
Genitourinary Pathology Society

GUPS EDUCATIONAL VIDEOS

EDUCATIONAL VIDEOS

GUPS Virtual Education Series event
Genitourinary Pathology: WHO Updates
The Latest on Renal, Urothelial, & Testicular Tumors



Given “benign” implications, it is important to…

- Use strict criteria
- Consider the differential diagnosis:
  - Clear cell renal cell carcinoma (ccRCC)
  - Papillary renal cell carcinoma with clear cell features
  - MiTF family translocation associated renal cell carcinoma
  - RCC with angioleiomyomatous stroma (AKA smooth muscle stroma, fibromyomatous stroma etc….)
    - Typically TCEB1, TSC, or MTOR mutated

Some history…

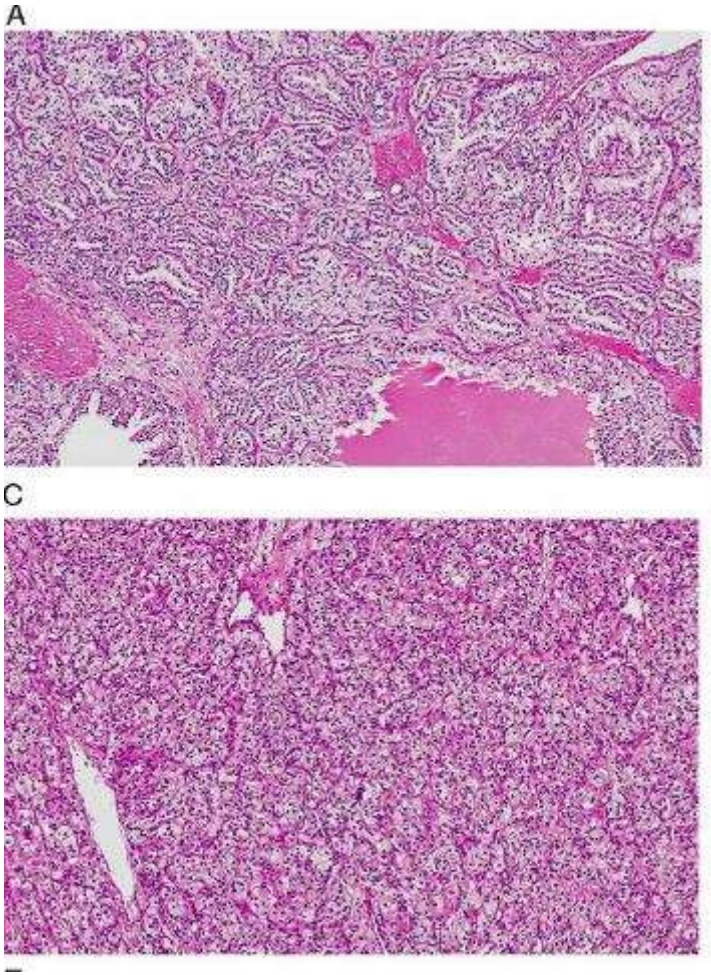
- First described in the setting of end-stage renal disease but also occurs sporadically
- Recognized as distinct epithelial tumor entity by ISUP in 2013 and incorporated into 2016 WHO
- Candidate for reclassification as a tumor of low malignant potential
- Previous reported “malignant” cases likely misclassified

Renal Neoplasms With Overlapping Features of Clear Cell Renal Cell Carcinoma and Clear Cell Papillary Renal Cell Carcinoma

A Clinicopathologic Study of 37 Cases From a Single Institution

Hari P. Dhakal, MD, PhD, Jesse K. McKenney, MD, Li Yan Khor, MD, Jordan P. Reynolds, MD, Cristina Magi-Galluzzi, MD, PhD, and Christopher G. Przybycin, MD

- ccRCC can have clear cell papillary-like areas and overall behave like ccRCC
- Caution in diagnosing ccpRCC on limited sampling
- Whole tumor needs to look like ccpRCC for diagnosis



AJSP 2016

A misleading recent case report…

Defining clear cell papillary renal cell carcinoma in routine clinical practice

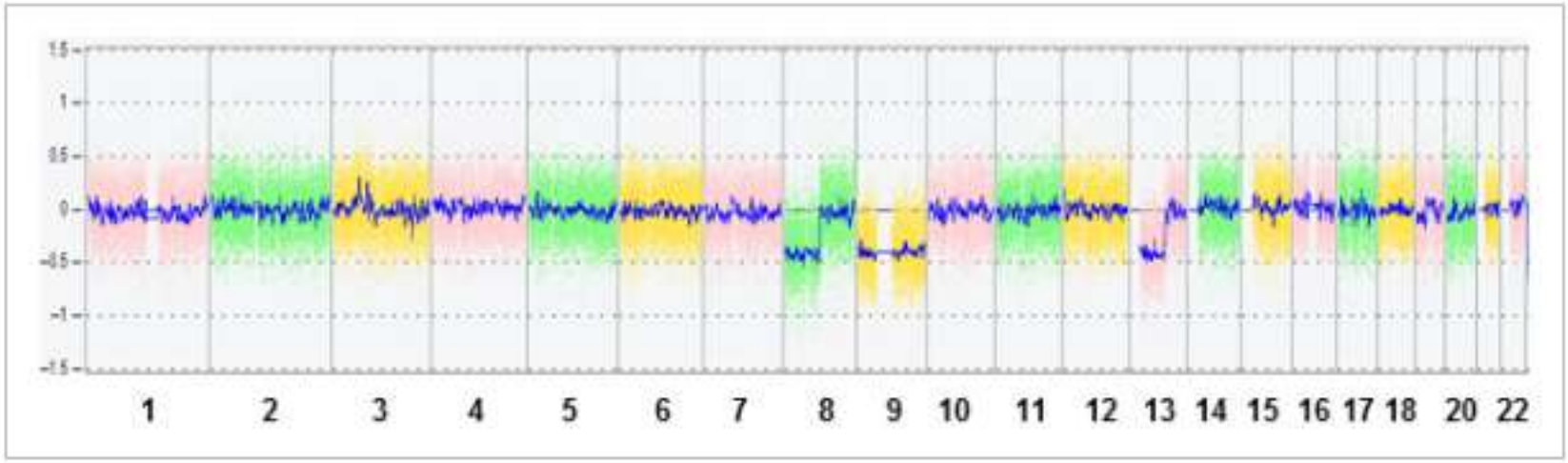
Histopathology

Correspondence | Full Access

Sounak Gupta, Carrie Y Inwards, Daniel L Van Dyke, Rafael E Jimenez, John C Cheville

First published: 27 January 2020 | https://doi.org/10.1111/his.14071 | Citations: 8

In summary, we highlight a case of a metastatic renal tumour that may be a metastatic CC-PRCC on the basis of morphological/immunophenotypic features and targeted molecular profiling. Limitations of our study include an absence of evaluation of the primary tumour, evaluation of *VHL* promoter hypermethylation status, and comprehensive molecular characterisation, including genes such as *TCEB1*.[6] Although these limitations prevent an



??? TCEB1 TSC1 ???

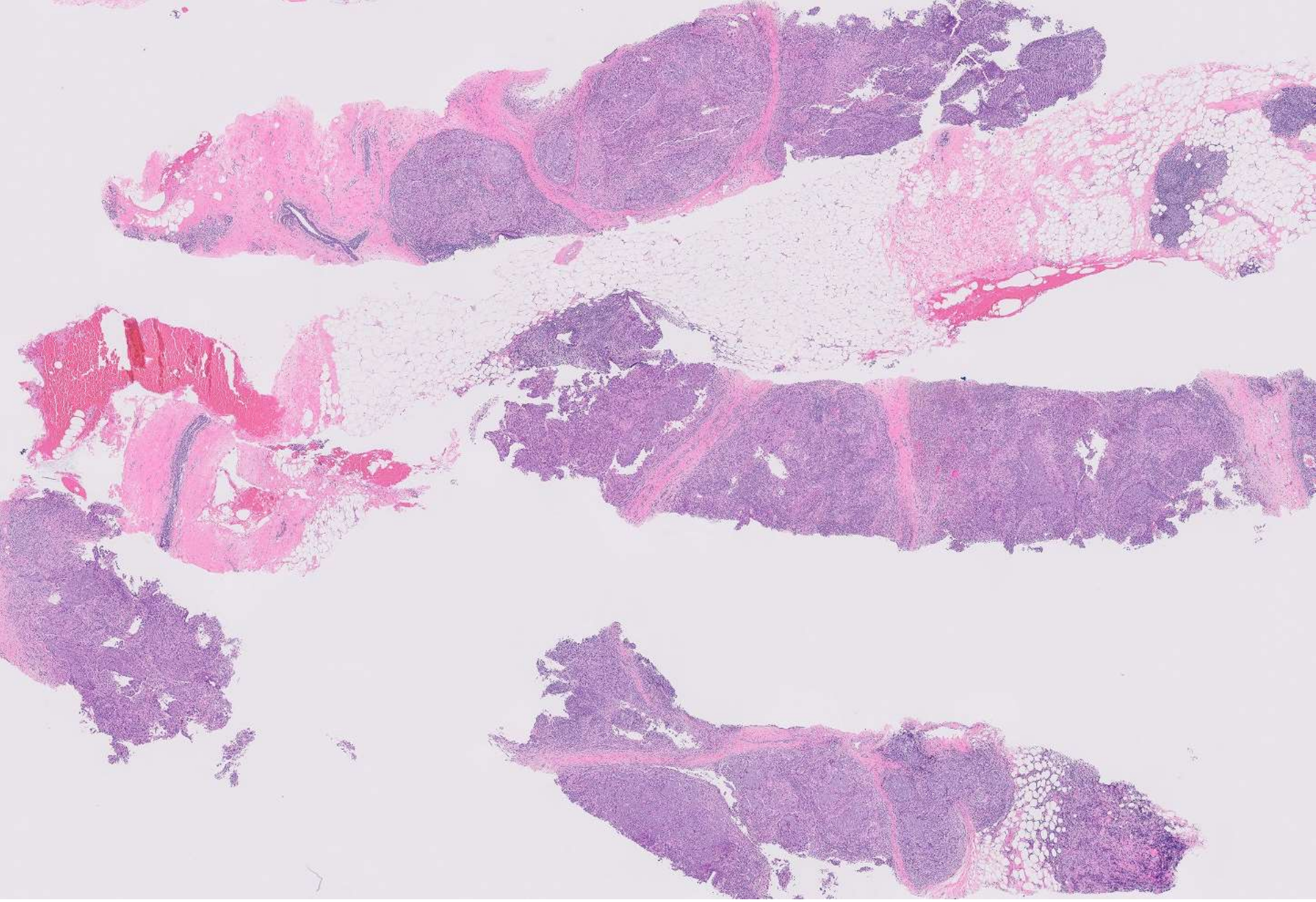
Summary: clear cell papillary ~~RCC~~/tumor

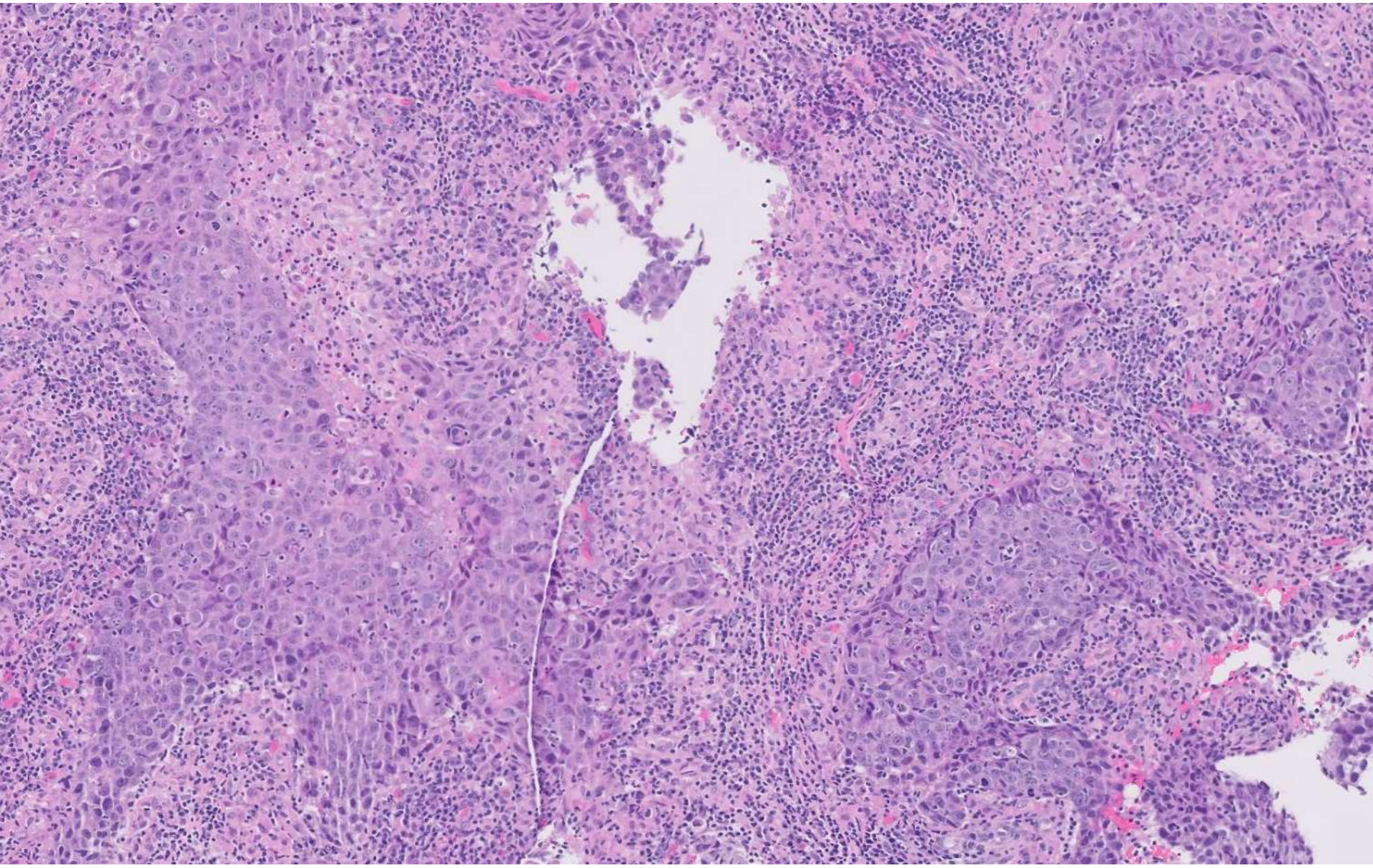
- Extremely indolent tumor, stay tuned for a potential name change in next WHO
- Use strict criteria for diagnosis:
  - Entire tumor should have classic ccpRCC morphology
  - Use IHC: CK7, CAIX cup-like, HMWK positive
- Exclude potential mimics which are all malignant
- Diagnose with caution on biopsy

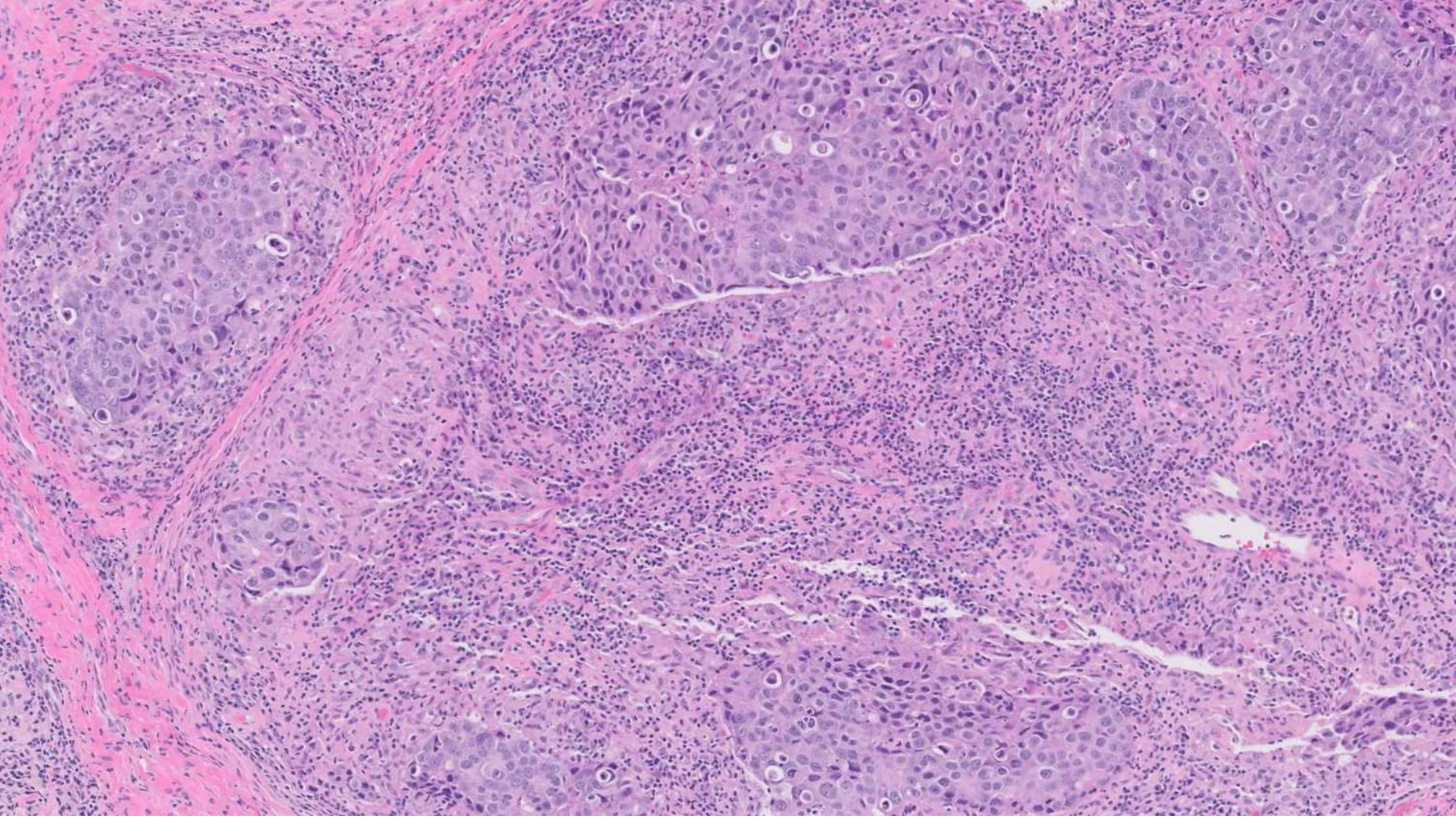
22-0202

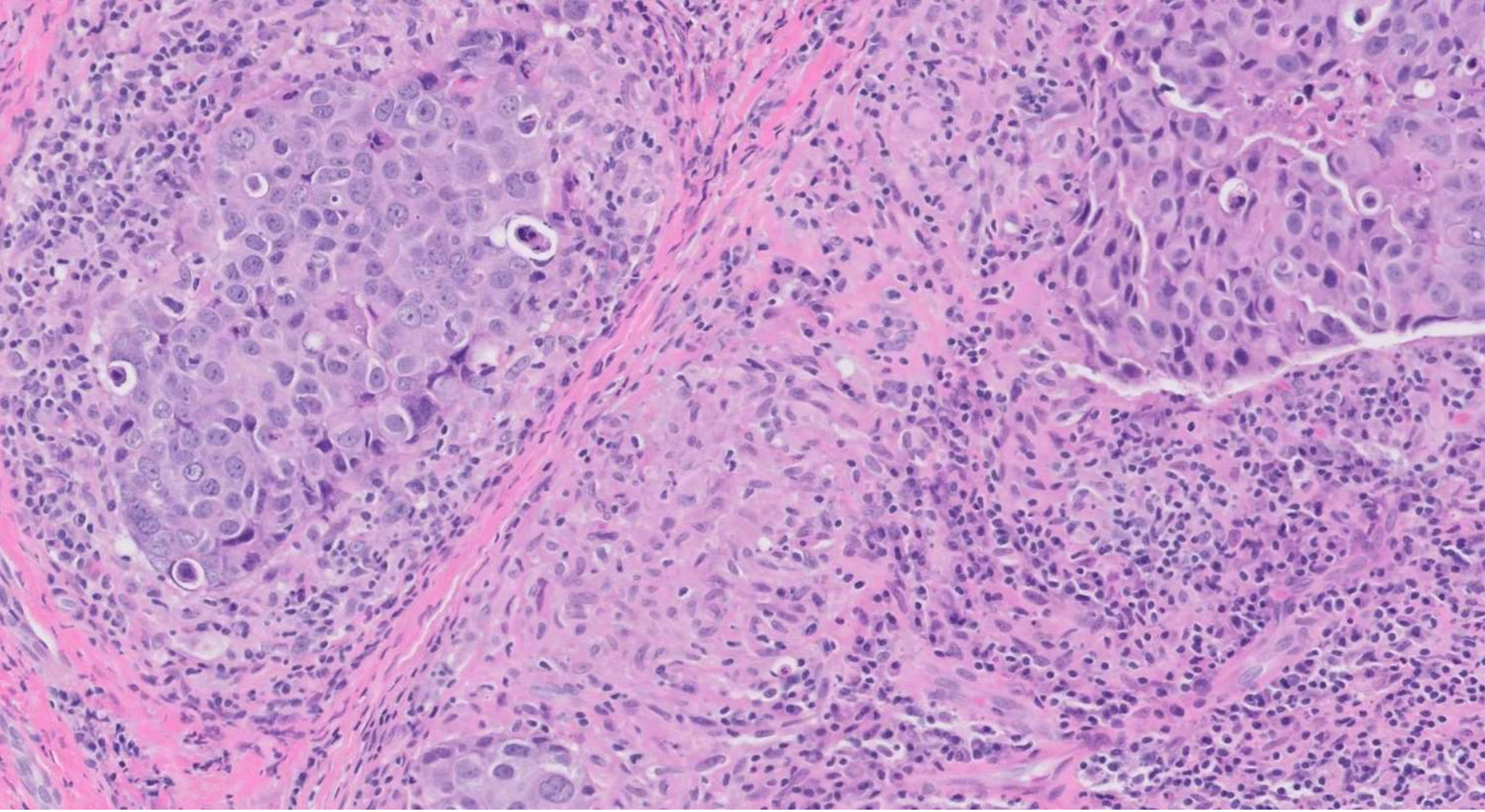
Megan Troxell; Stanford

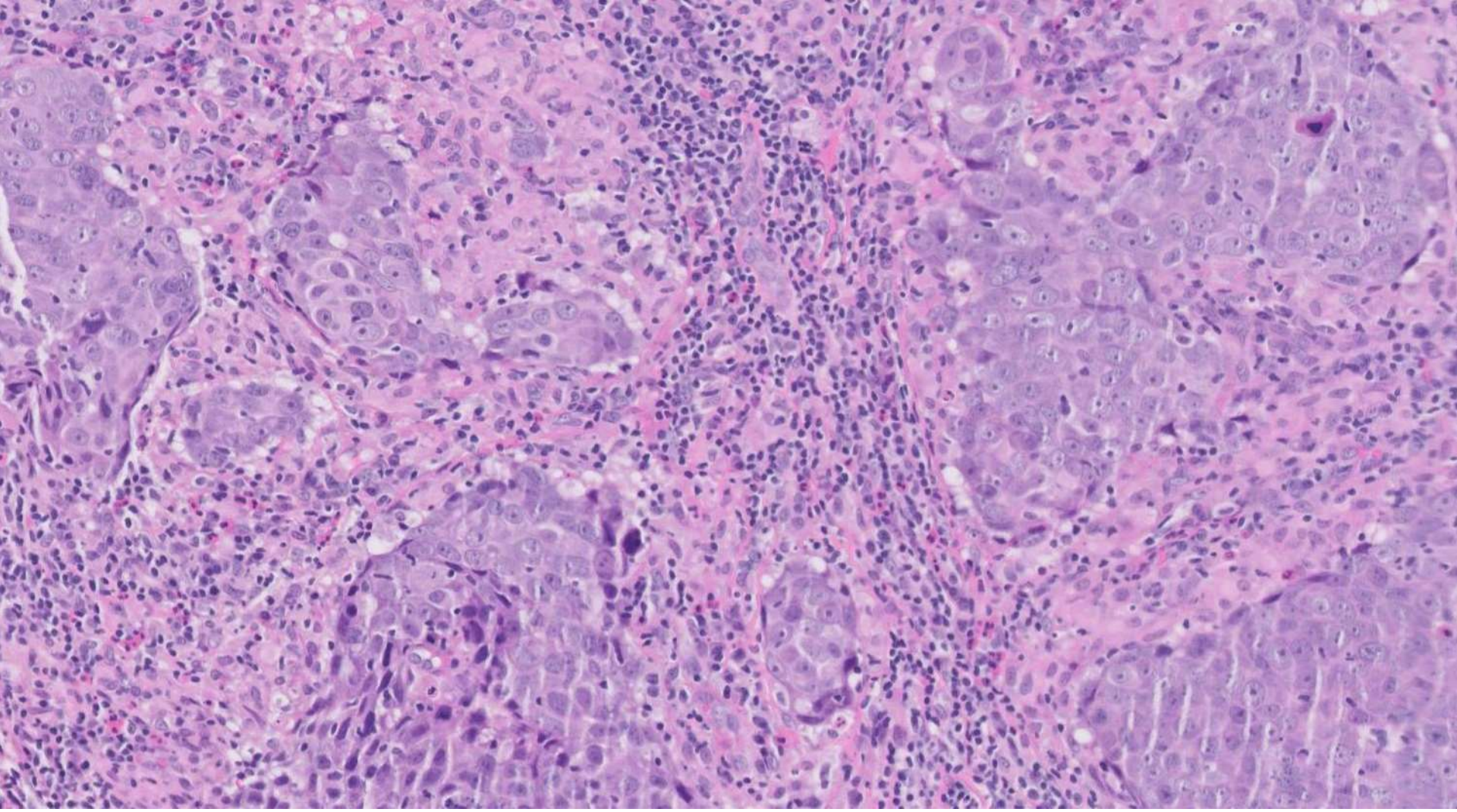
50ish F with double vision, difficulty with balance and walking. Breast pain; breast imaging shows fibroglandular density and and enlarged right axillary lymph node. Right breast (and axillary) biopsy performed.

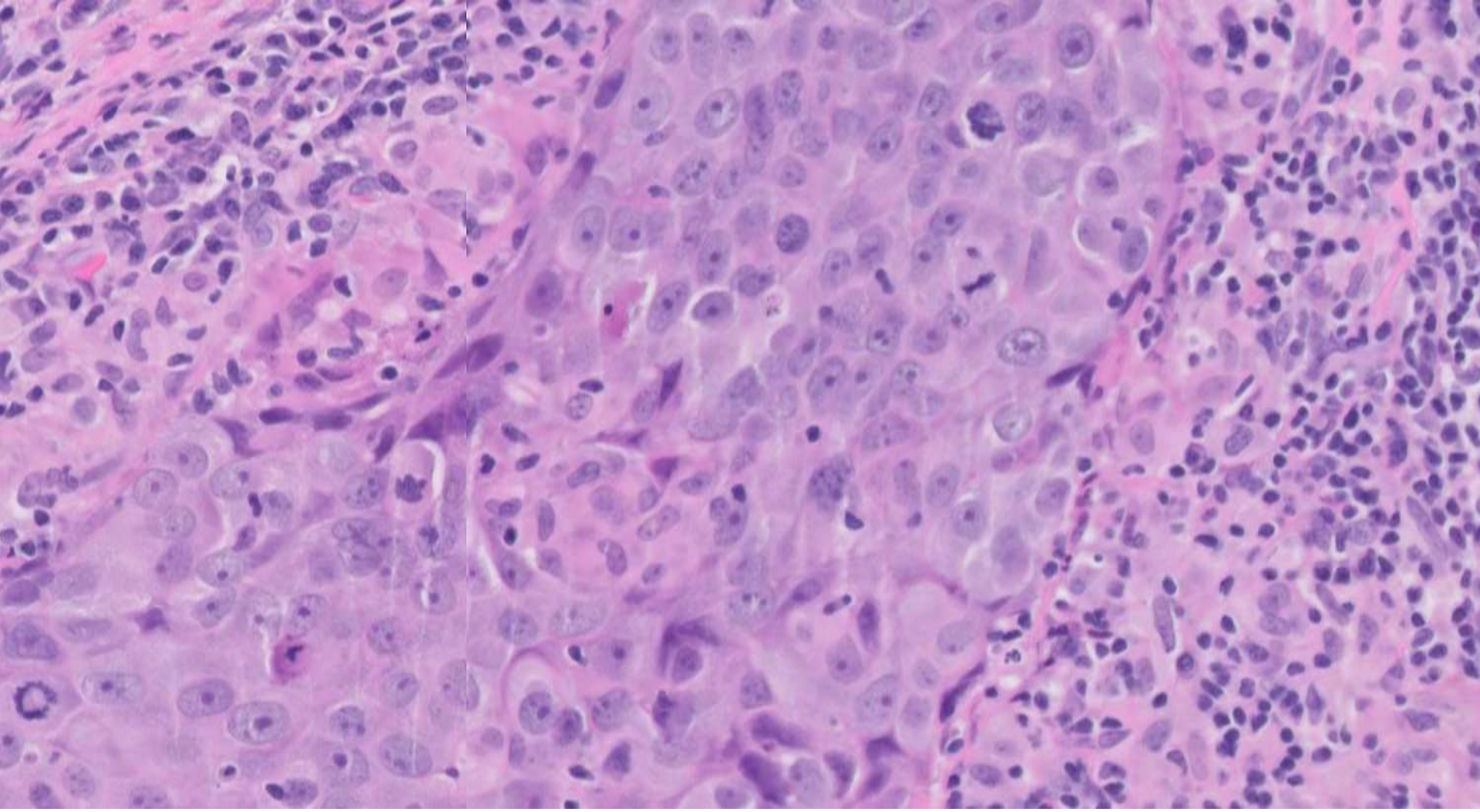






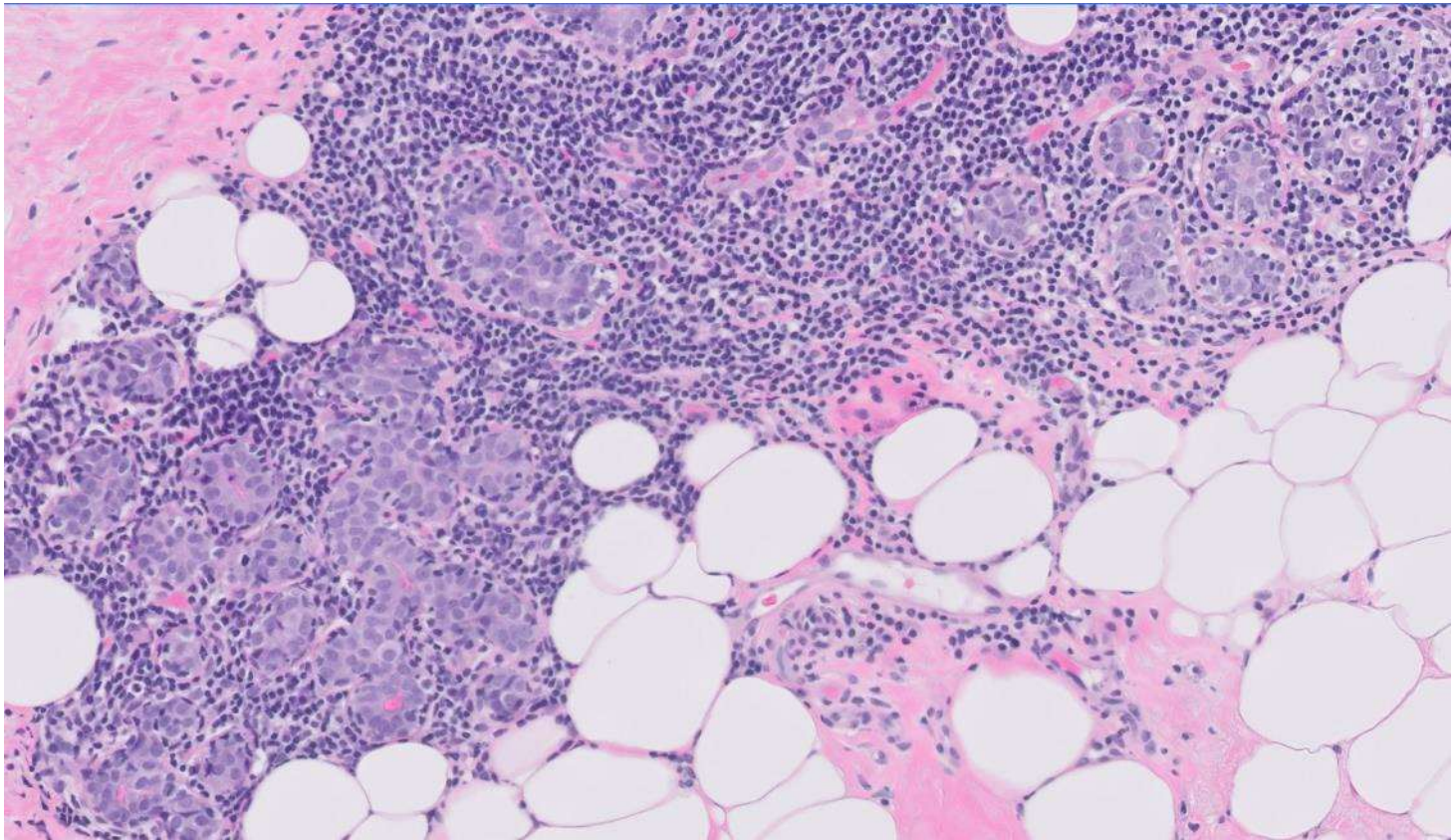




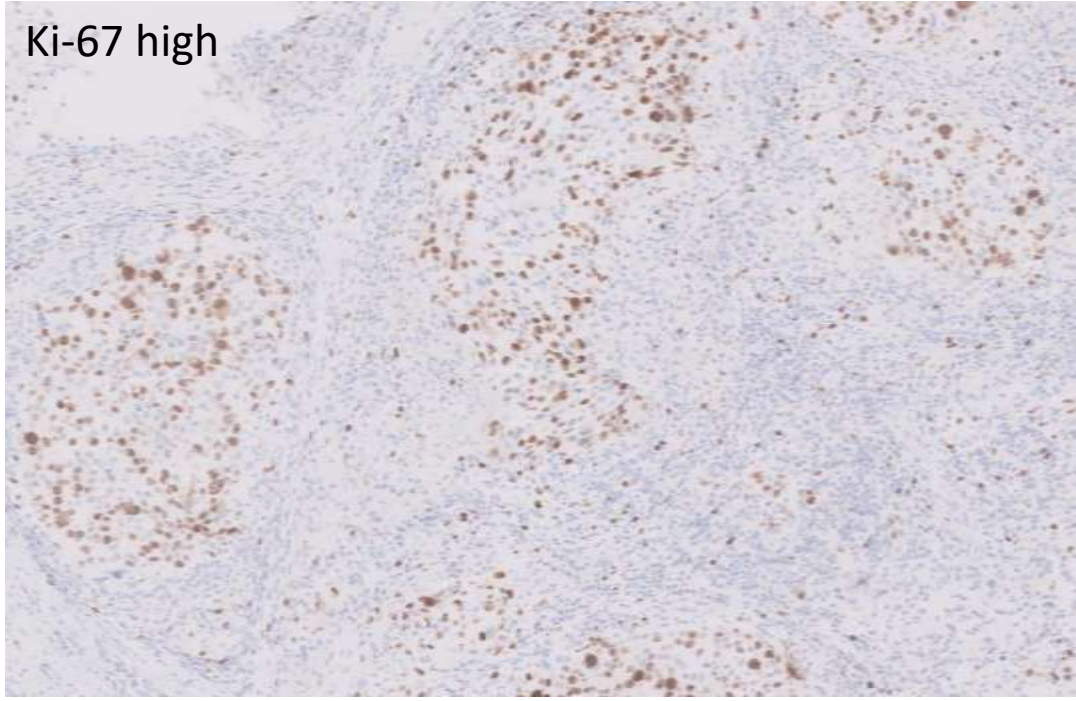


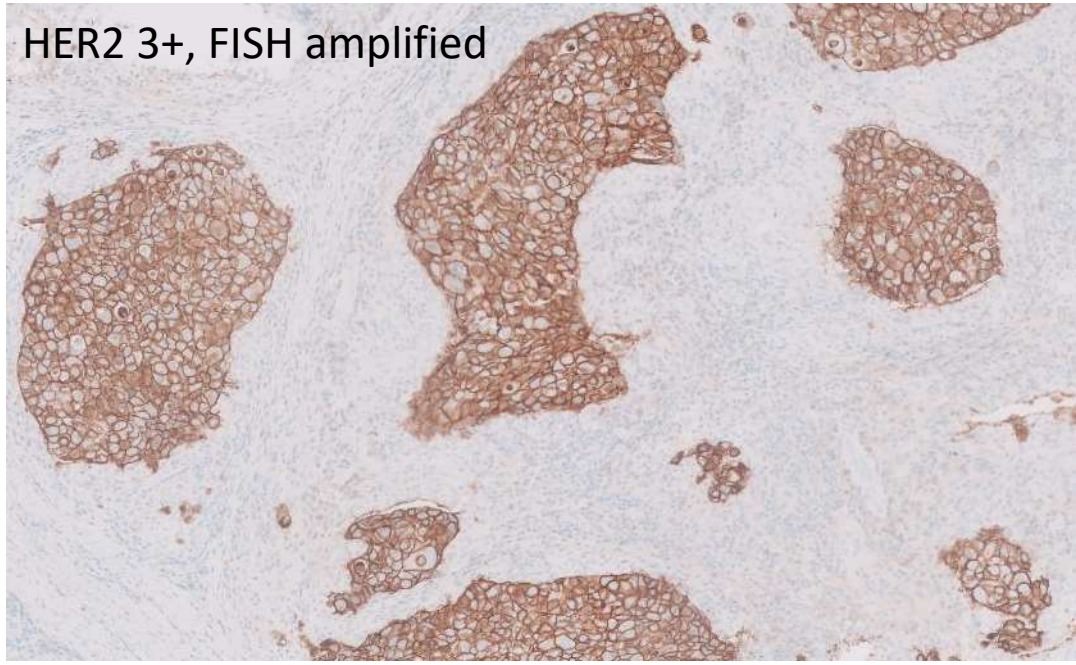
Diagnosis

- Invasive ductal carcinoma, Grade 3
- Paraneoplastic Cerebellar Degeneration, Anti-Yo Ab



ER, PR negative





Paraneoplastic Cerebellar Degeneration

- Cerebellar ataxia
- Neurologic disorders due to tumor induced autoimmunity vs cerebellar antigens.
  - 30 different antigens; Most common: anti-Yo (50%)
    - anti-Purkinje cell cytoplasmic antibody 1 (PCA-1) to CDR2
  - Associated cancers: gyn, breast (lung)
    - 2% with cancer have antibody; 10% with antibody have symptoms
- PCD→ consider Neuro Ddx→ cerebellar antibody panel→imaging search for cancer
- Cerebellar immune infiltrate, gliosis, later Purkinjie cell loss
- Treatment of tumor w/ immunosuppression (PLEX, IVIg steroid) often ineffective

Venkatraman & Opal. Ann Clin Transl Neurol . 2016;3:655-63.

22-0203

Yue Peng; VA San Francisco

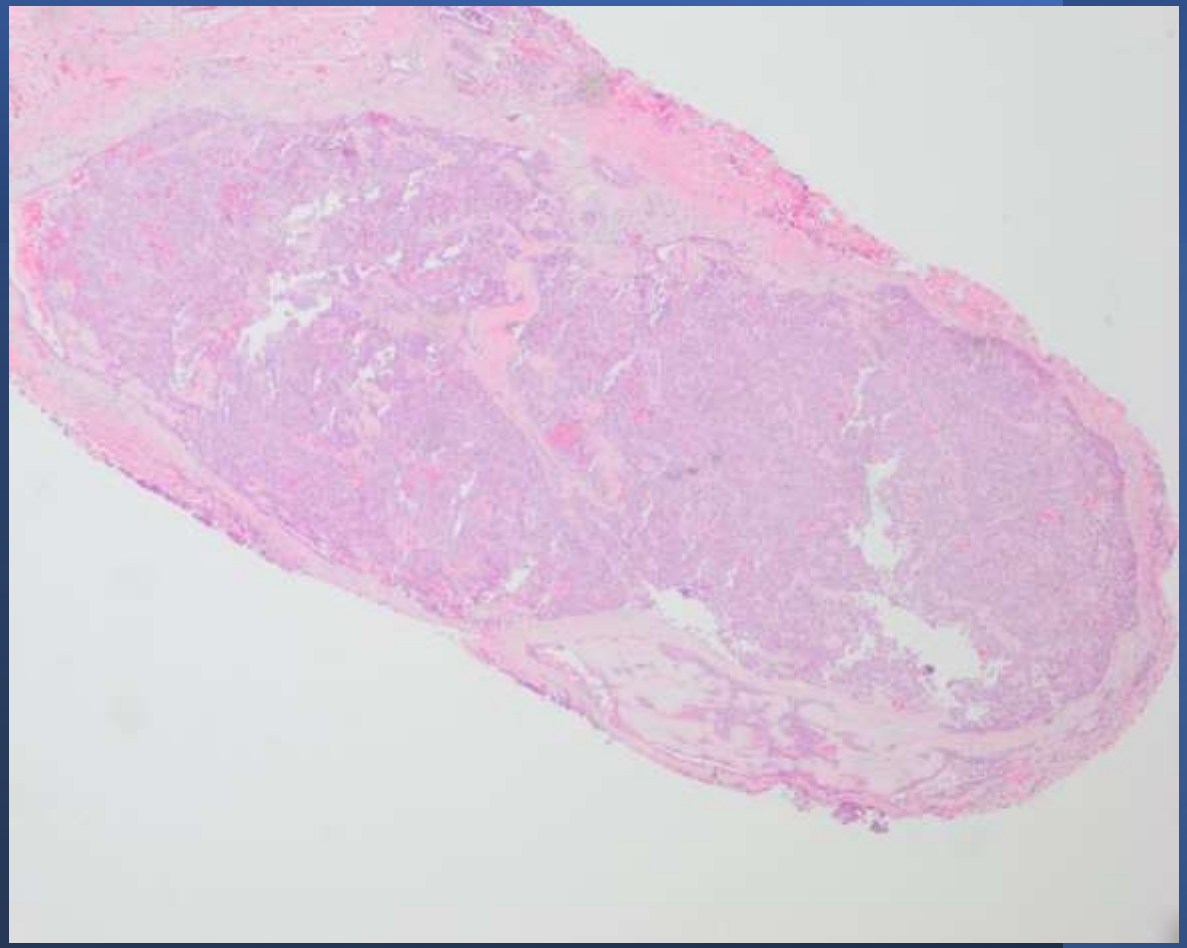
90ish M with left lower eyelid slow-growing cystic lesion. He underwent excisional biopsy.

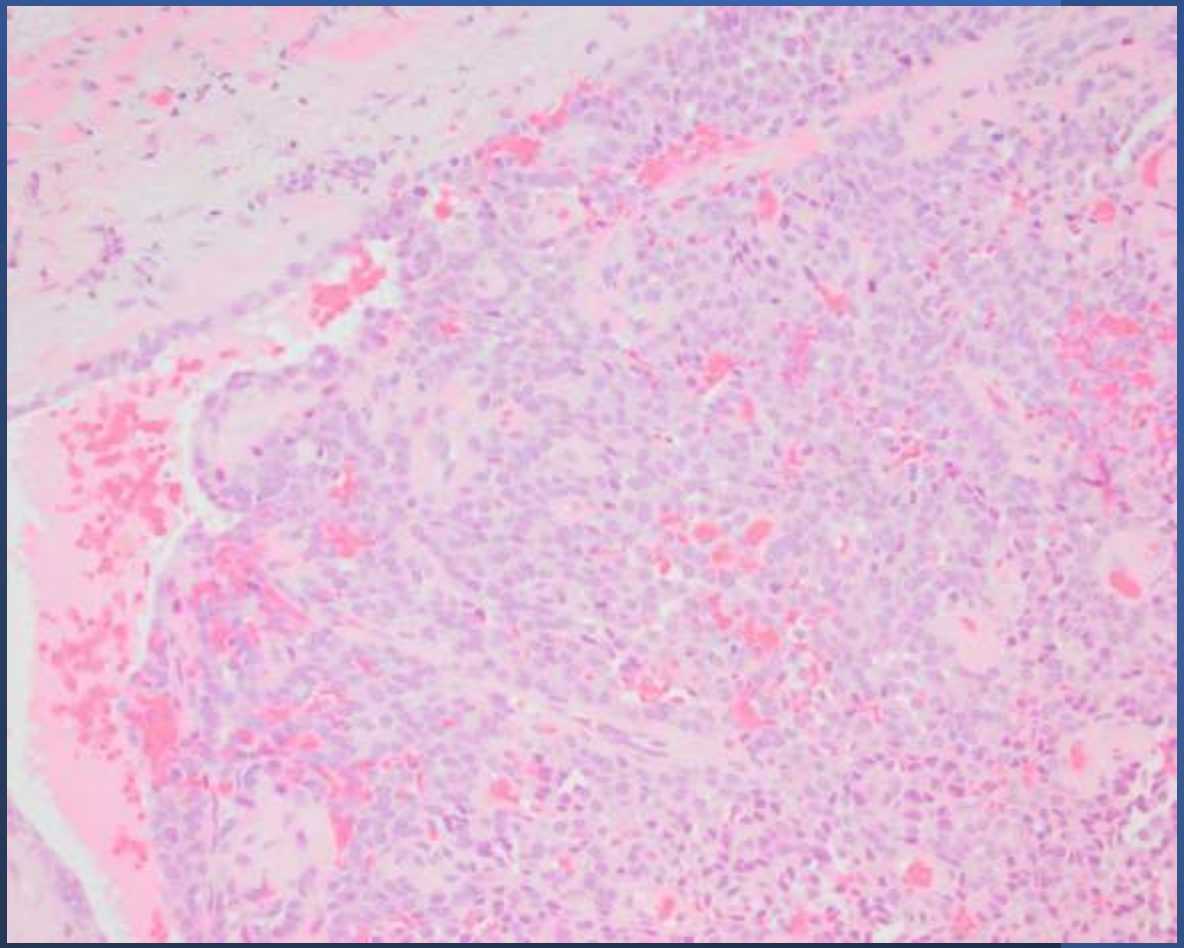
South Bay Pathology Society Meeting

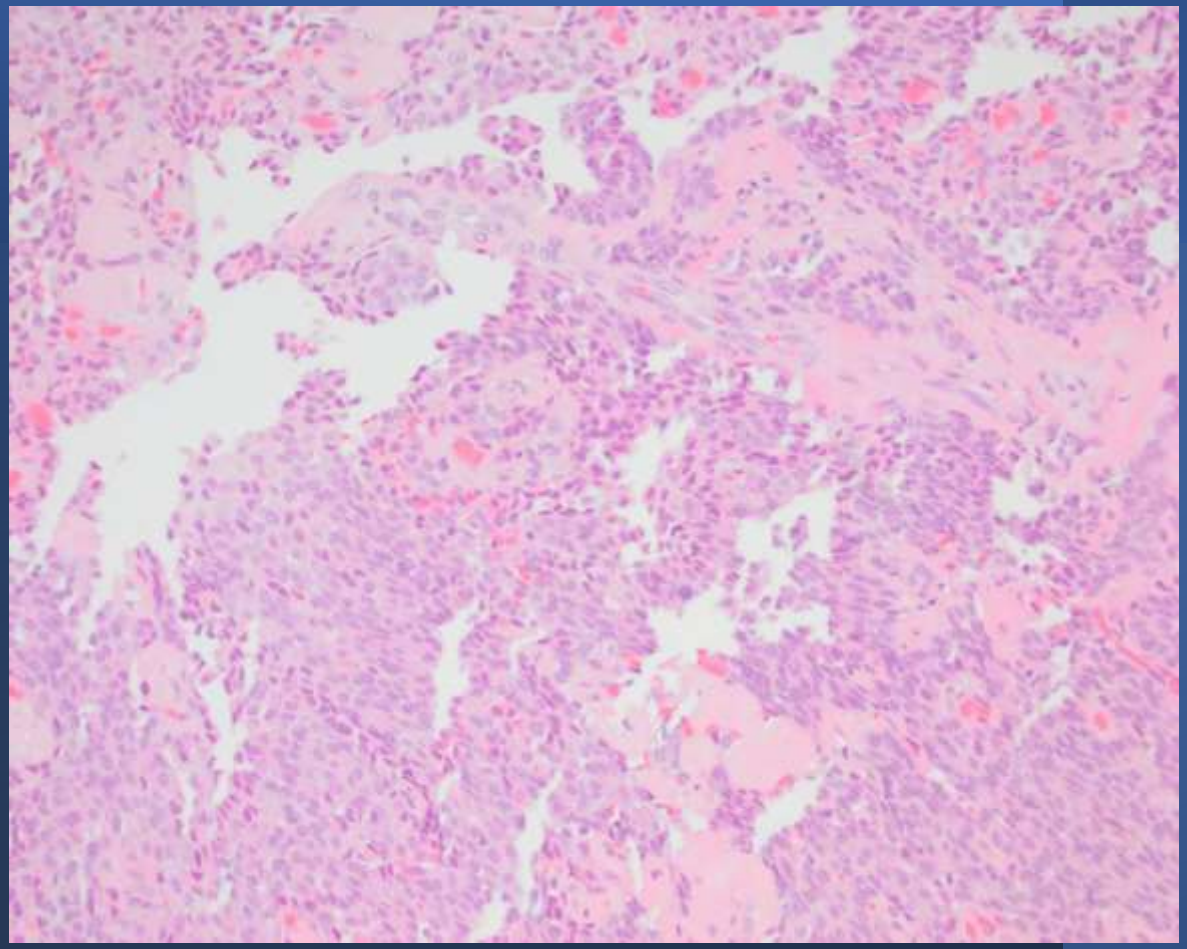
90ish male with a left lower eyelid slow-growing cystic lesion. He undergoes excisional biopsy.

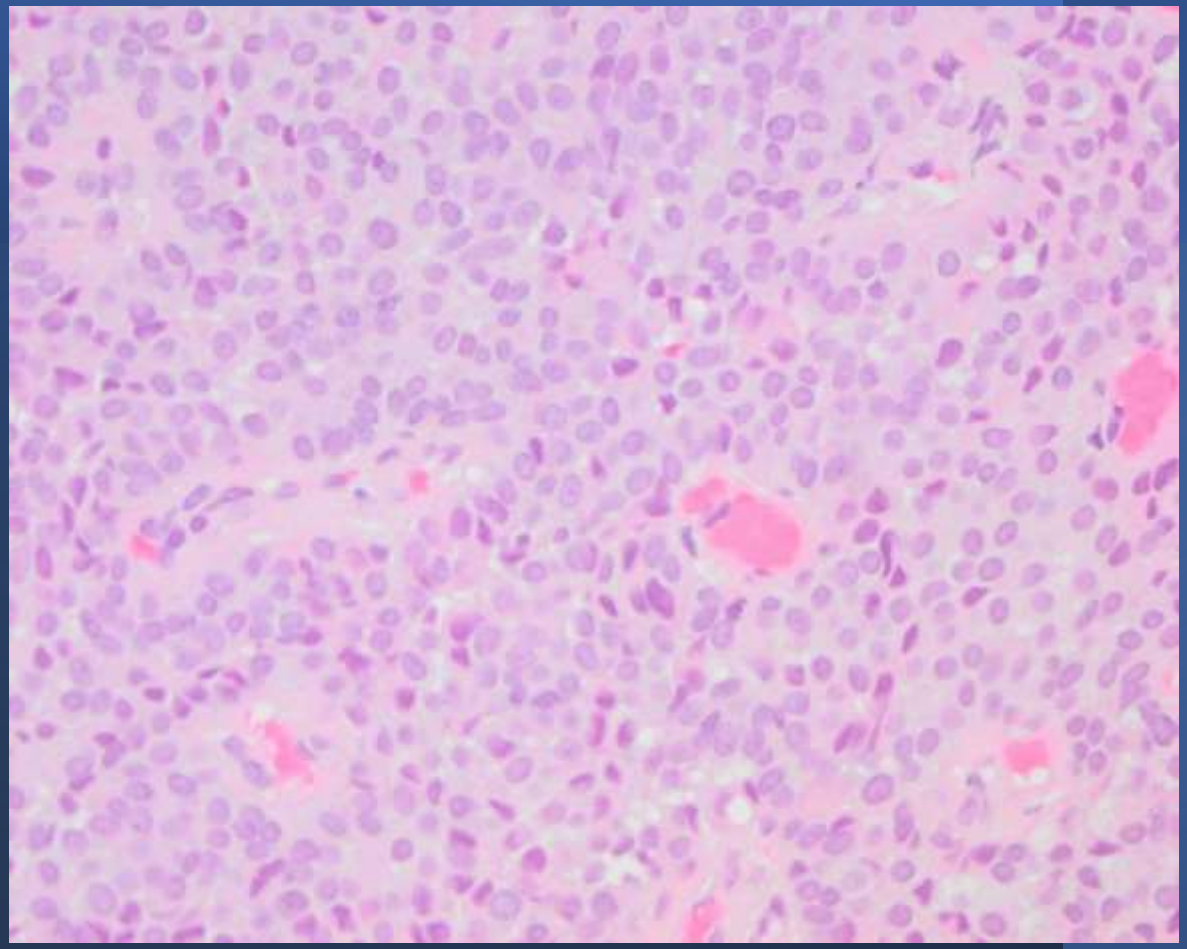
Yue Peng, Jeffrey North

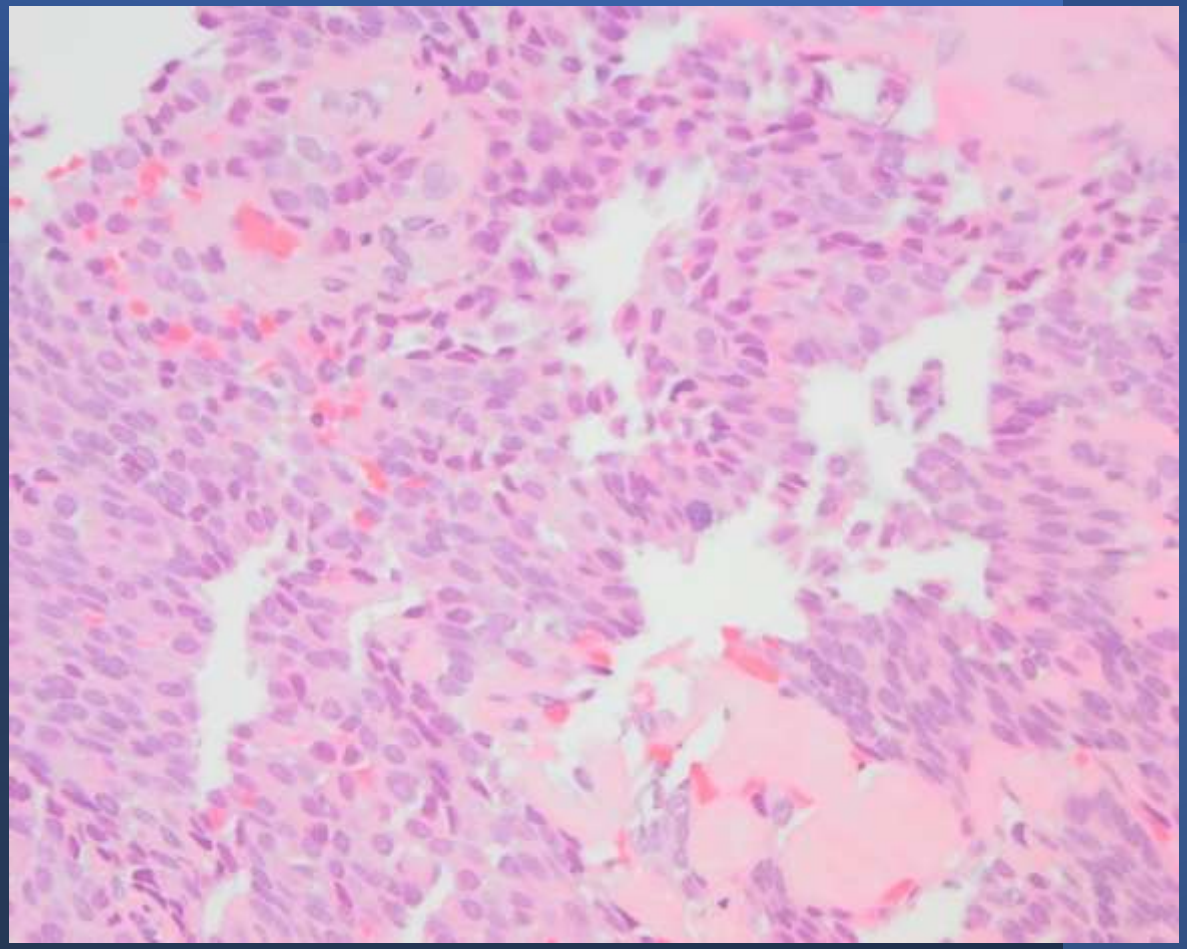
SFVA/UCSF

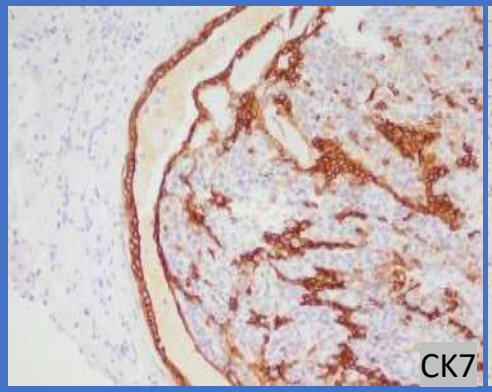


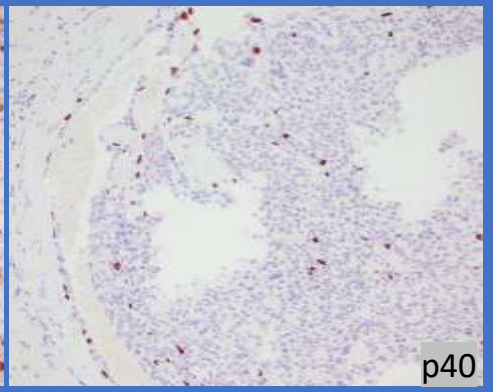









CK7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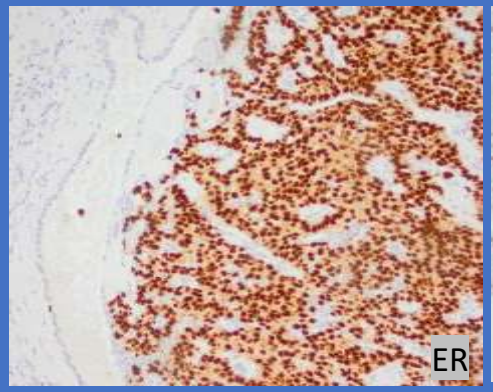
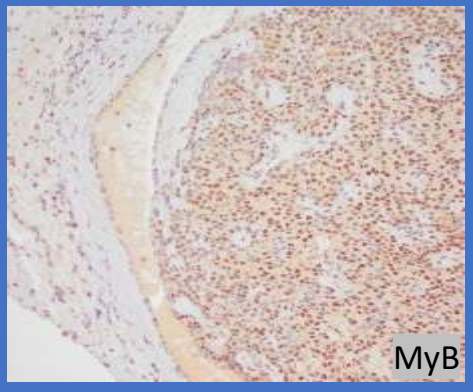
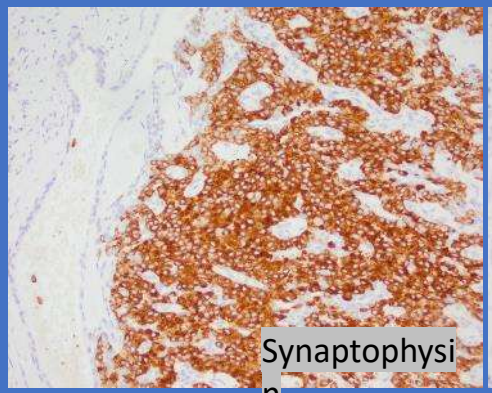
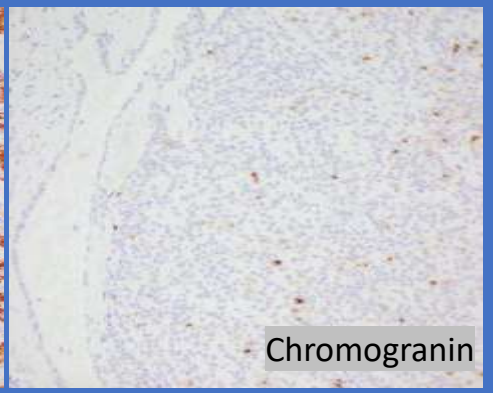
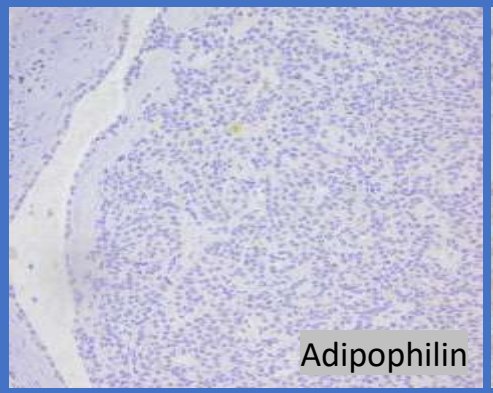
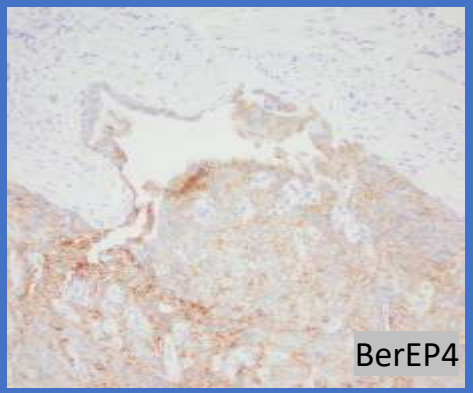

ER

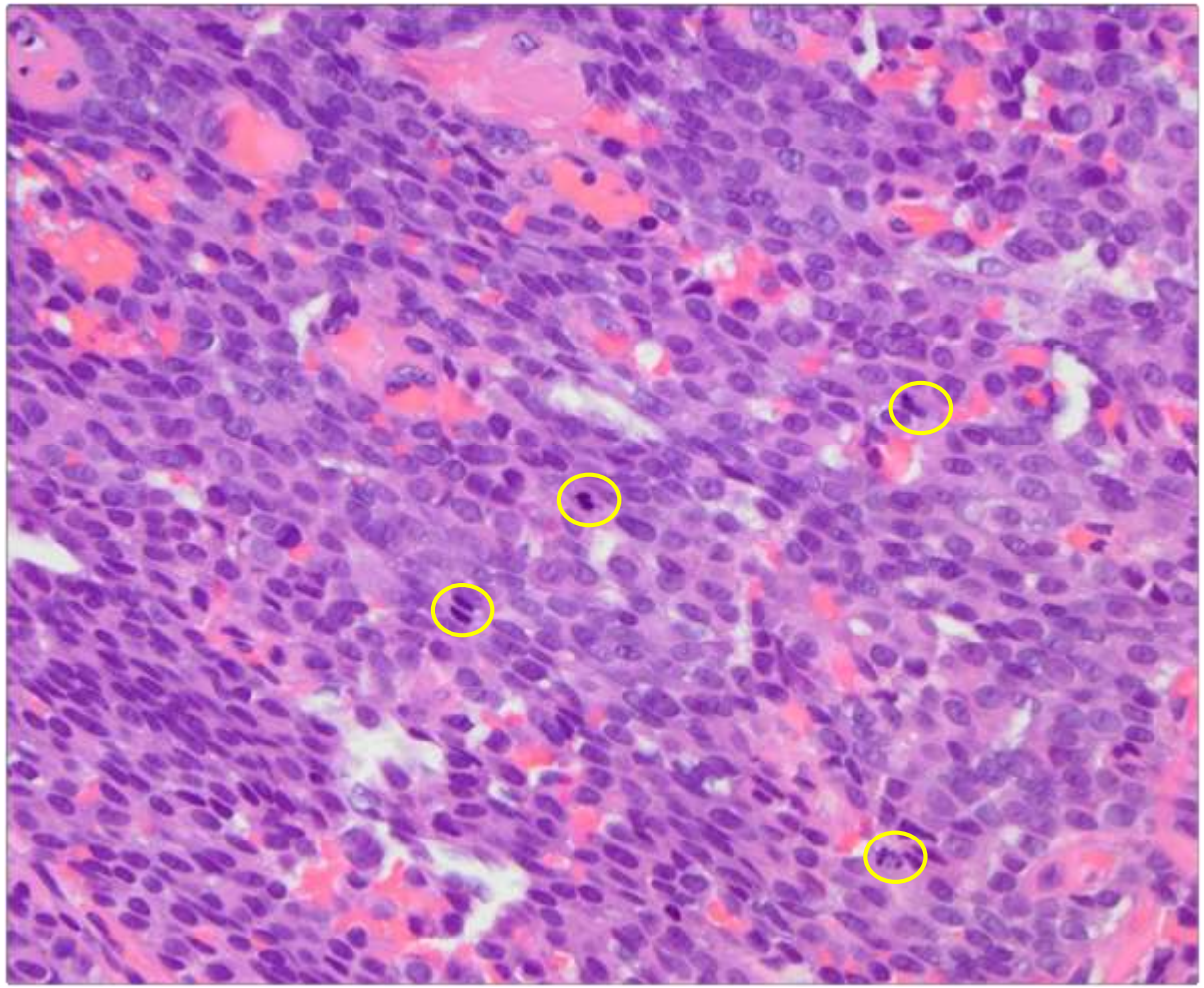

MyB

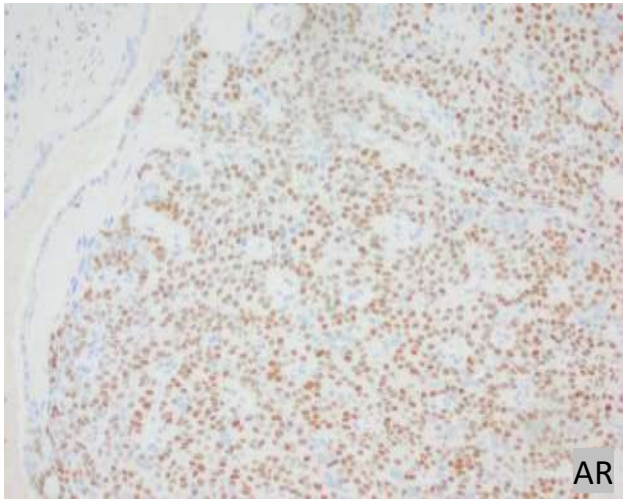

Synaptophysin


Chromogranin


Adipophilin


BerEP4

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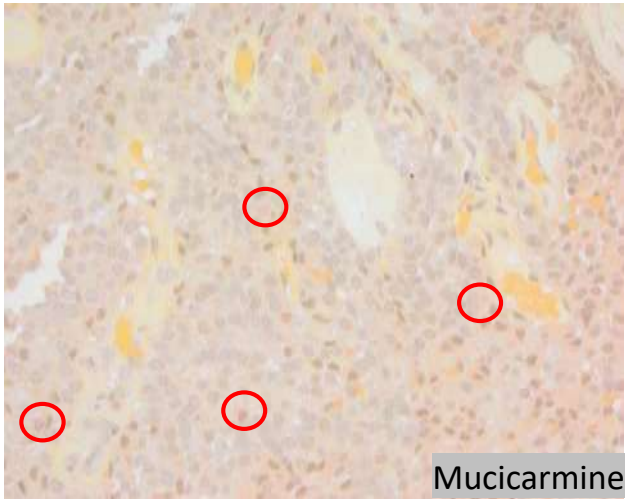
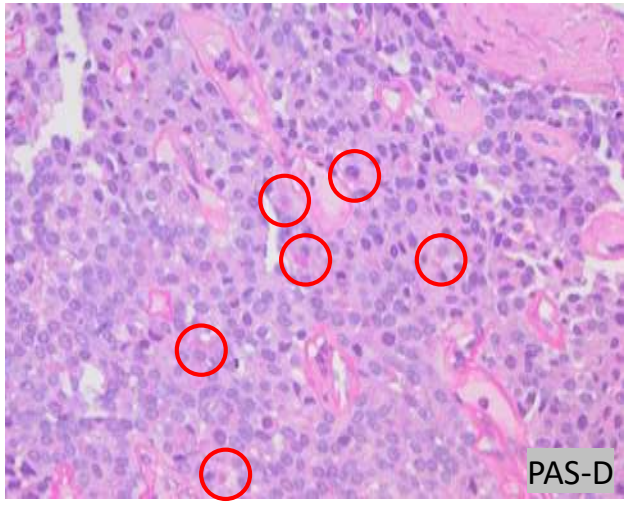

Mucicarmine


PAS-D

Summary of IHCs:

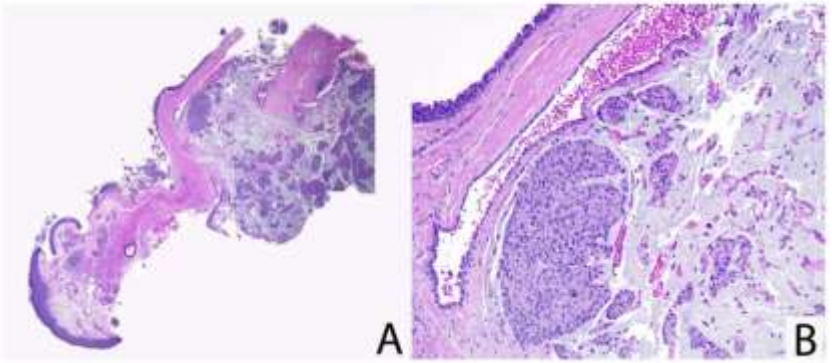
Positive	Negative
CK7	Adipophilin
P40, scattered in myoepithelial cells	
ER, strong and diffuse	
AR, moderate and diffuse	
Synaptophysin, diffuse	
Chromogranin, scattered	
BerEP4	
MyB	
EMA	

Differential Diagnoses:

- Nodular hidradenoma
- Hidrocystoma
- Basal cell carcinoma
- Sebaceous carcinoma
- Adenoid cystic carcinoma
- Merkel cell carcinoma
- Metastasis (e.g. breast, GI)
- Endocrine mucin-producing sweat gland carcinoma

Endocrine mucin producing sweat gland carcinoma (EMPSGC) – Definition:

- First introduced by Flieder et. al . Am J Surg Pathol. 1997.
- Low-grade adnexal carcinoma with endocrine/neuroendocrine differentiation
- Closely related (often precursor) to neuroendocrine-type primary cutaneous mucinous carcinoma (in 33.3% of cases)
- Shows strong resemblance to solid papillary carcinomas of breast



Meghana Agni *et. al*. Am J Surg Pathol. 2020

Endocrine mucin producing sweat gland carcinoma (EMPSGC) – Clinical features:

- Very rare tumors, in older adults, more frequent in women (~ 2/3 of cases)
- Typically occur on eyelids - Lower eyelid more common than upper
- Papular to nodular cystic dermal tumor
- Treatment
  - Complete excision with clear margins
  - Mohs surgery is likely optimal therapy
- Prognosis
  - Good in most cases
  - Local recurrences common (21%, Agni M. 2020); only rare metastasis reported

Histologic and cytologic features:

- Dermal-based adnexal tumor composed of nodules and glandular/cystic areas
- Ductal/glandular lumina are usually conspicuous
- Papillary and cribriforming areas often present
- Cystic areas may be present in some cases and can mimic hidrocystoma
- Stromal mucin is not prominent as in mucinous carcinomas
- Tumoral cells are small, basophilic, bland-appearing epithelioid cells with round to oval nuclei and inconspicuous nucleoli
  - Cytologic atypia is usually not prominent
  - Mitotic figures not numerous or atypical

Ancillary tests:

- Epithelial and neuroendocrine markers are usually positive
  - Pancytokeratins, CK7, CK5/6, and p40/p63 are typically positive
  - Endocrine/neuroendocrine markers, including ER, PR, chromogranin, synaptophysin, and INSM1, are usually positive
- Nuclear MYB expression typically seen, especially in mucin-poor cases
  - Evangelista MT, North JP. J Cutan Pathol. 2017; Held L. et. al. J Cutan Pathol. 2018
  - Negative for translocation or amplification of MYB gene by FISH (Held et. Al. 2018)
- Molecular pathology findings
  - Recent next-generation sequencing study (MSKIMPACT, 368 genes) identified 12 single-nucleotide-variants and one in-frame deletion in three cases, each with DNA damage response/repair (BRD4, PPP4R2, RTEL1) and tumor-suppressor pathway (BRD4, TP53, TSC1, LATS2) mutations. No microsatellite instability, copy number alterations, and structural alterations were identified. DNA damage repair and tumor-suppressor pathways may be implicated in multistep pathogenesis of EMPSGC.
  - This tumor might harbor different molecular profiles from solid papillary carcinoma of the breast that have expressed mutations in PIK3CA and AKT1.

Endocrine mucin producing sweat gland carcinoma (EMPSGC) – Key points

- EMPSGC should be considered in nodular lesions of elderly patients that occur in the face and particularly in eyelid locations.
- Microscopically, it resembles mammary solid papillary carcinoma.
- Key feature is neuroendocrine expression; the presence of myoepithelial layer is helpful to confirm primary cutaneous origin and exclude metastatic adenocarcinoma.
- Some cases have contiguous primary cutaneous mucinous carcinoma.

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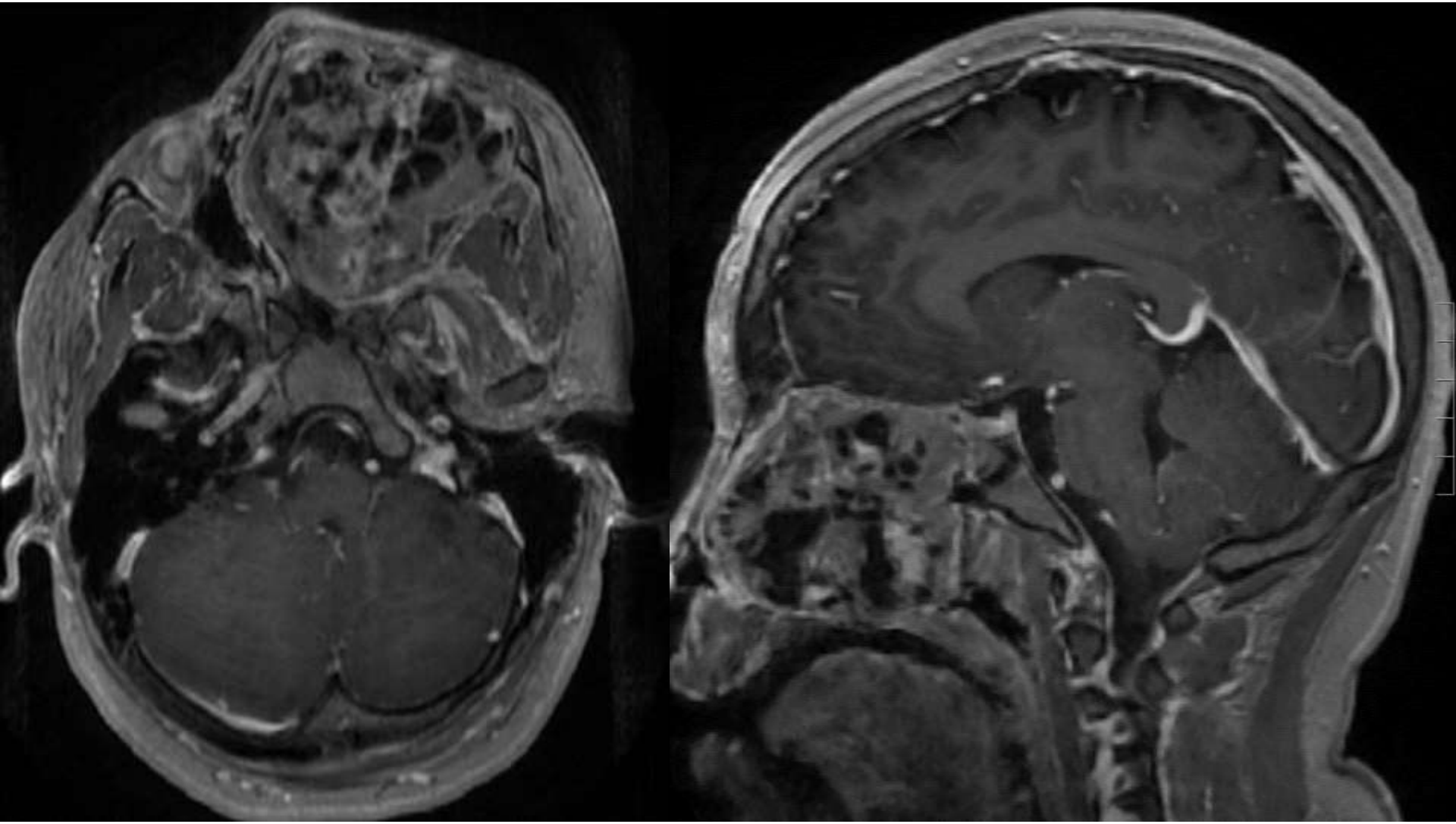
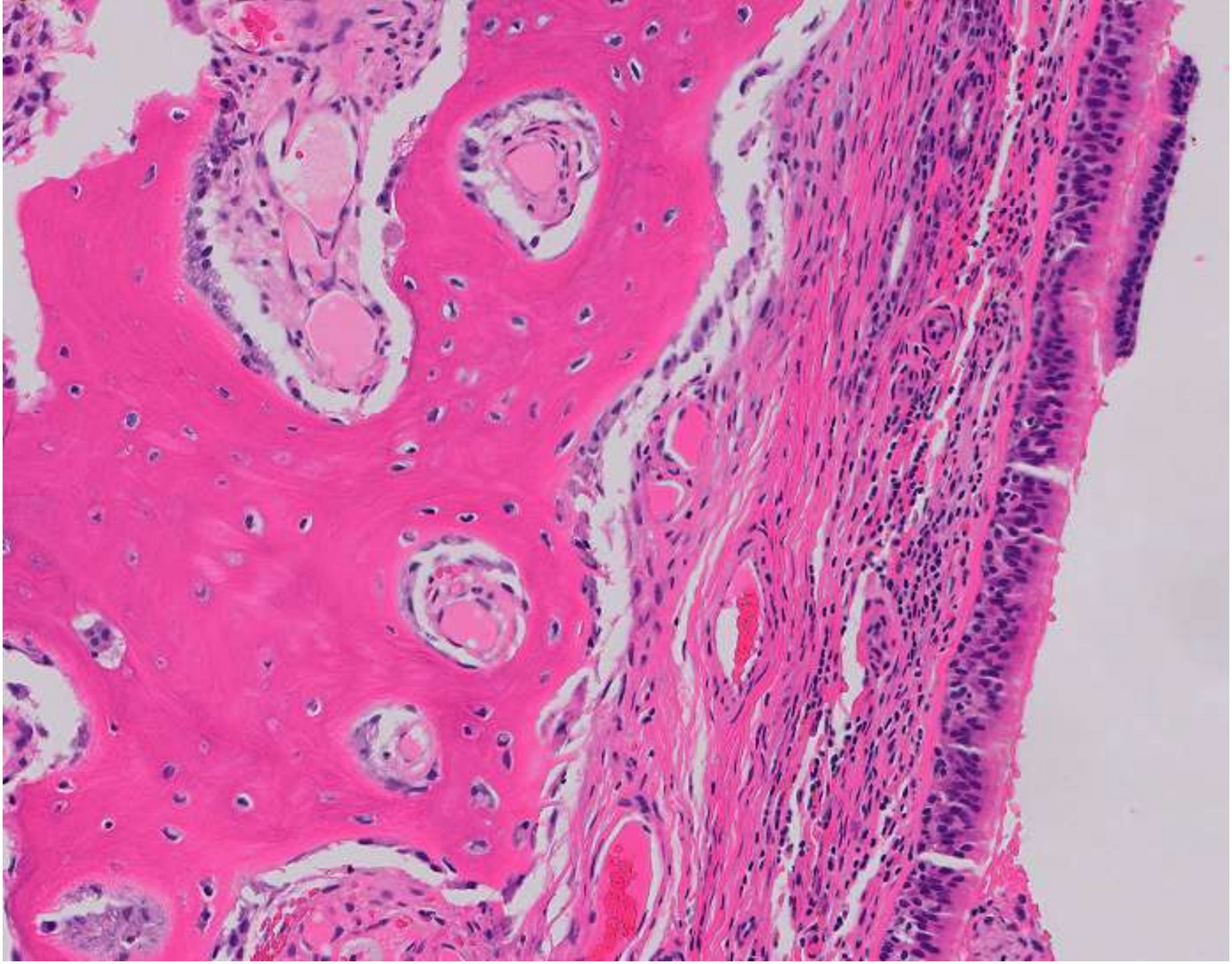
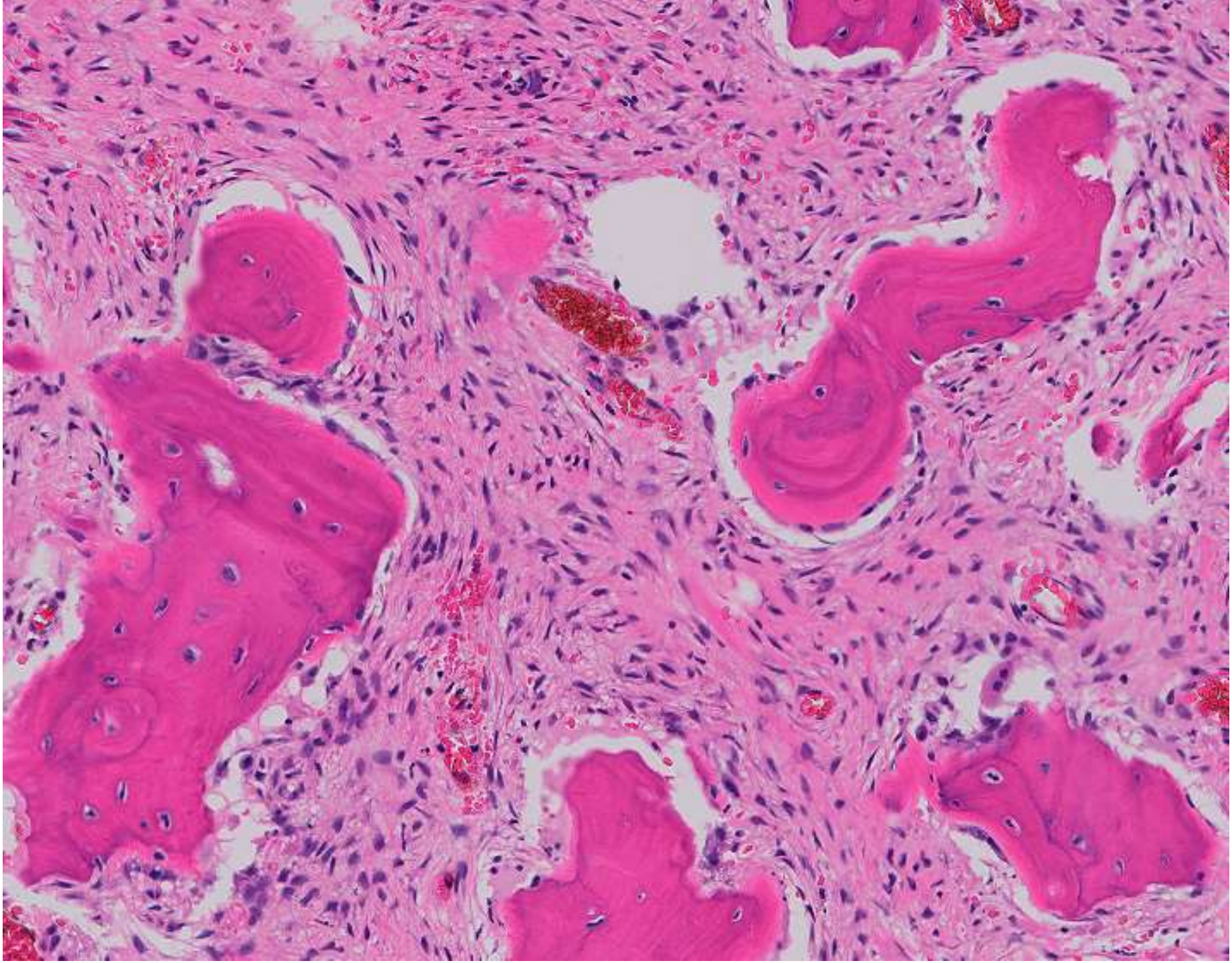
22-0204

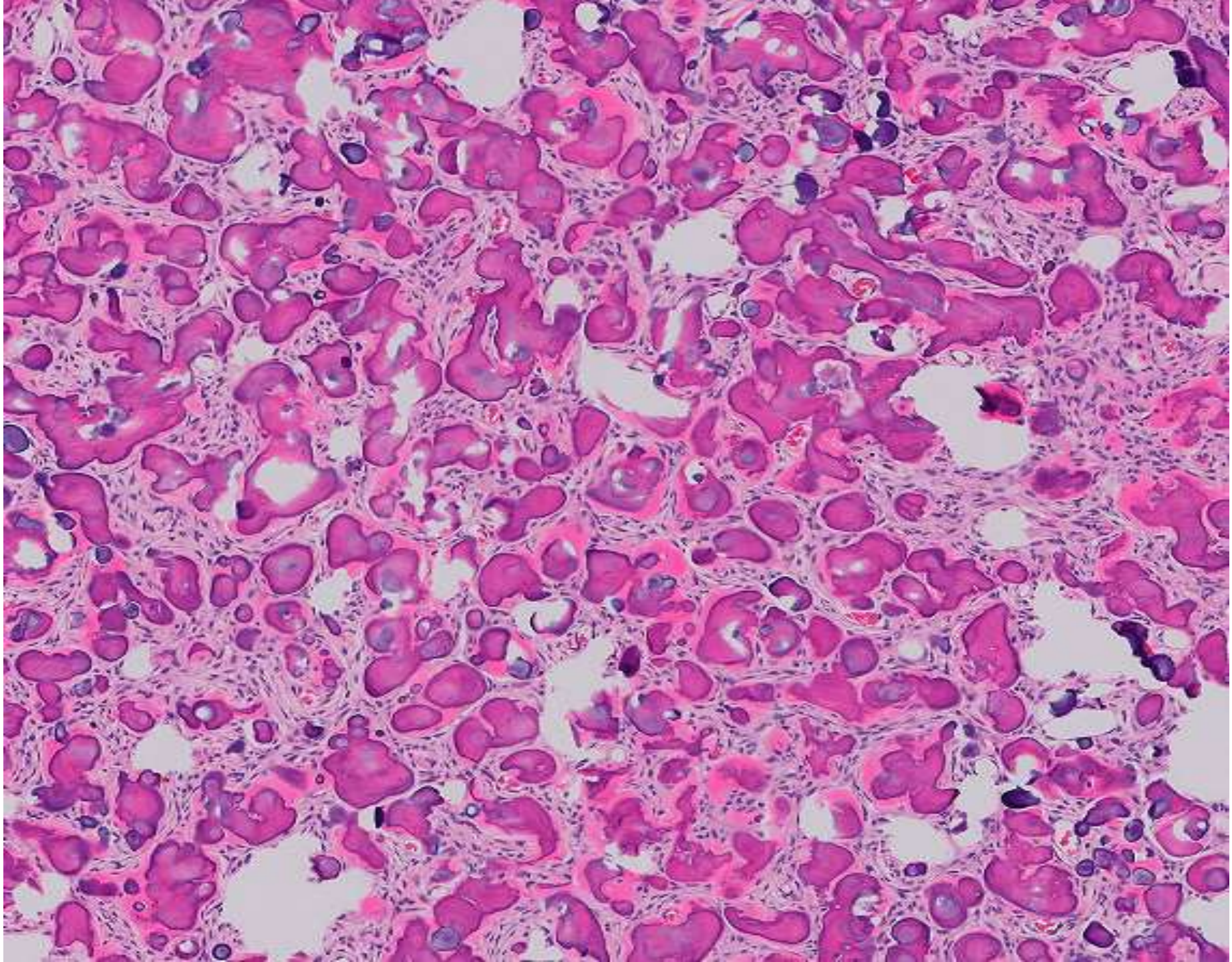
Angus Toland/Hannes Vogel; Stanford

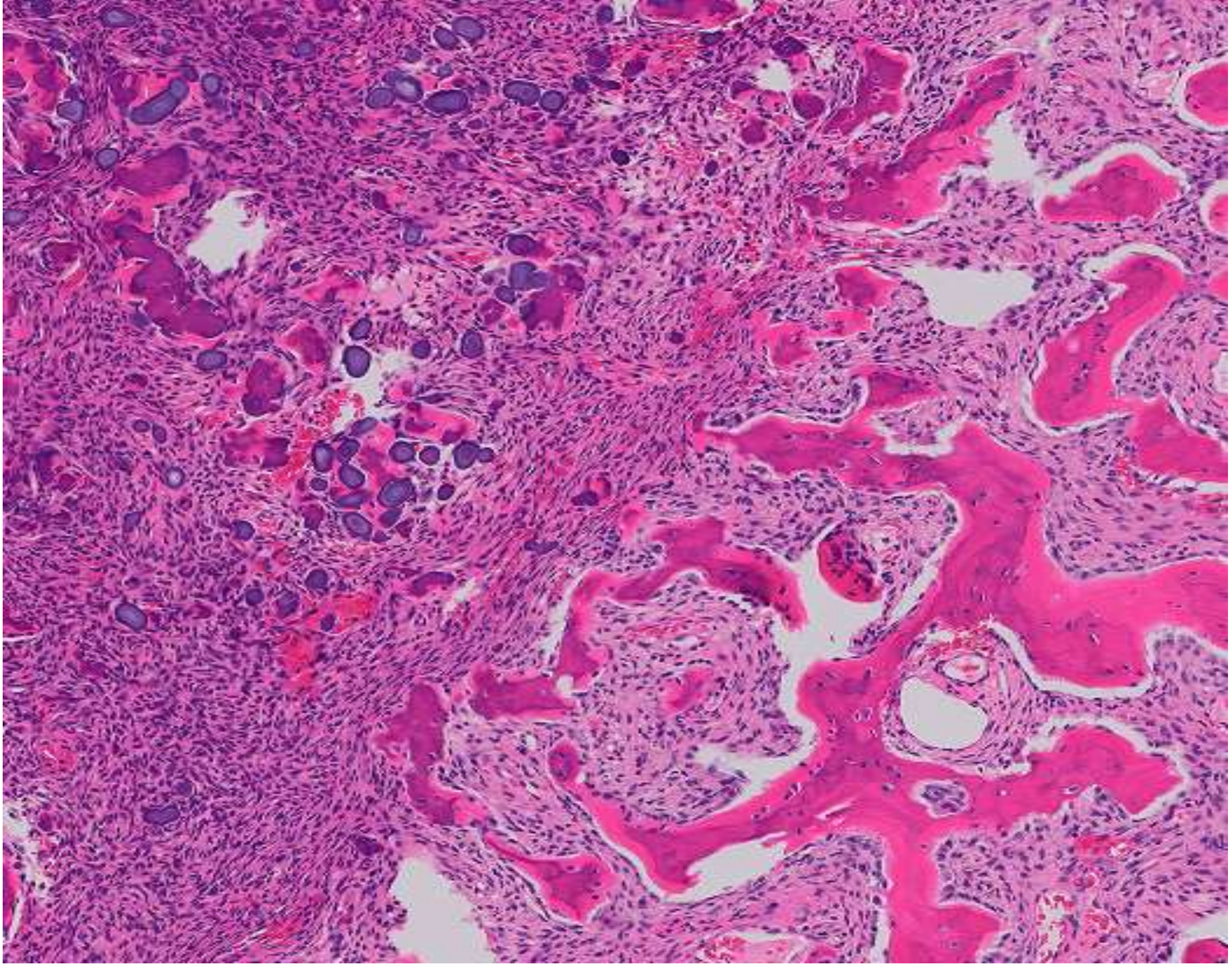
Teenage boy presented with facial swelling (began 5 years prior to presentation), left eye proptosis, and severe epistaxis. Imaging demonstrated a large, sclerotic, heterogenous skull base mass involving the ethmoid and maxillary region.

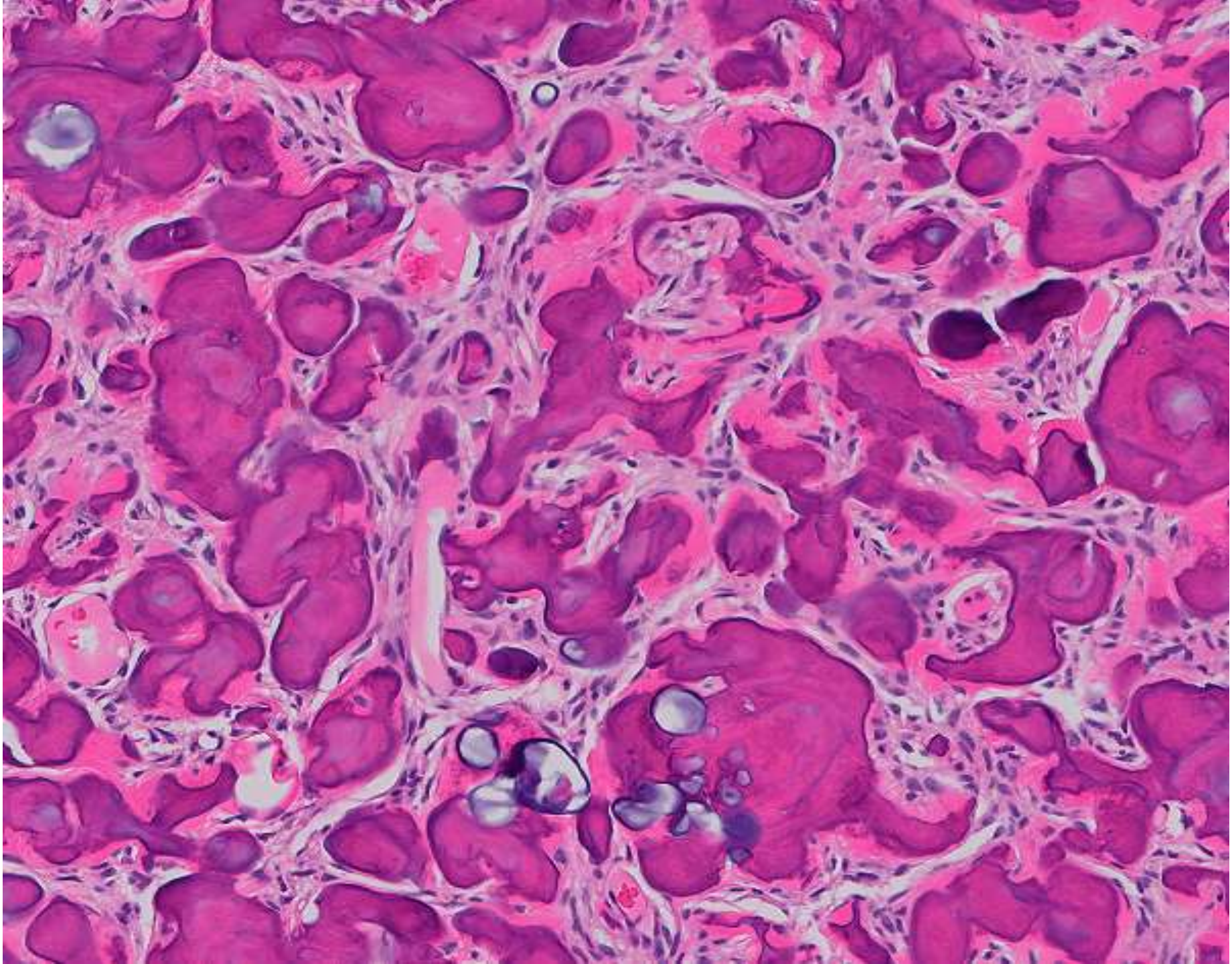


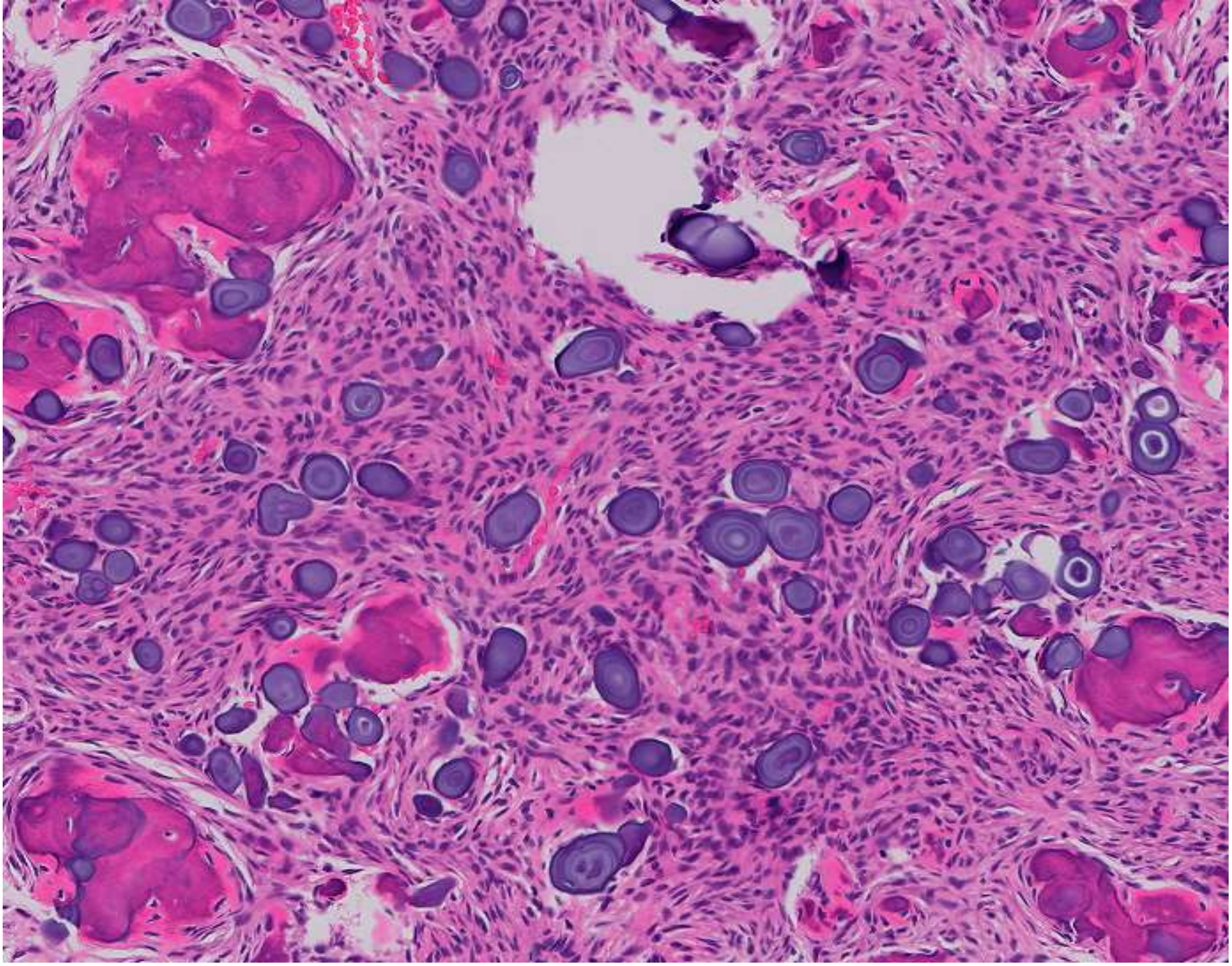


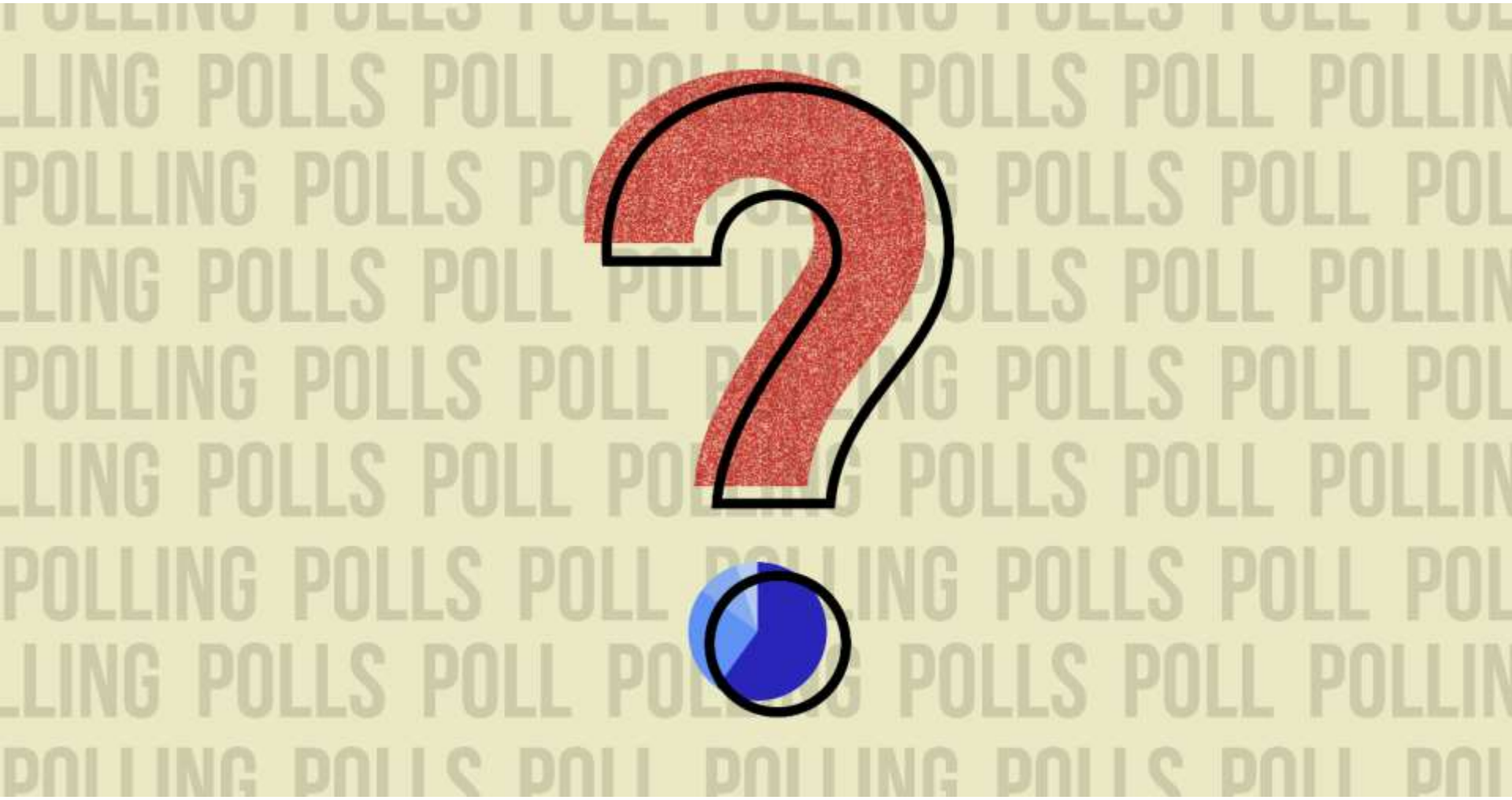










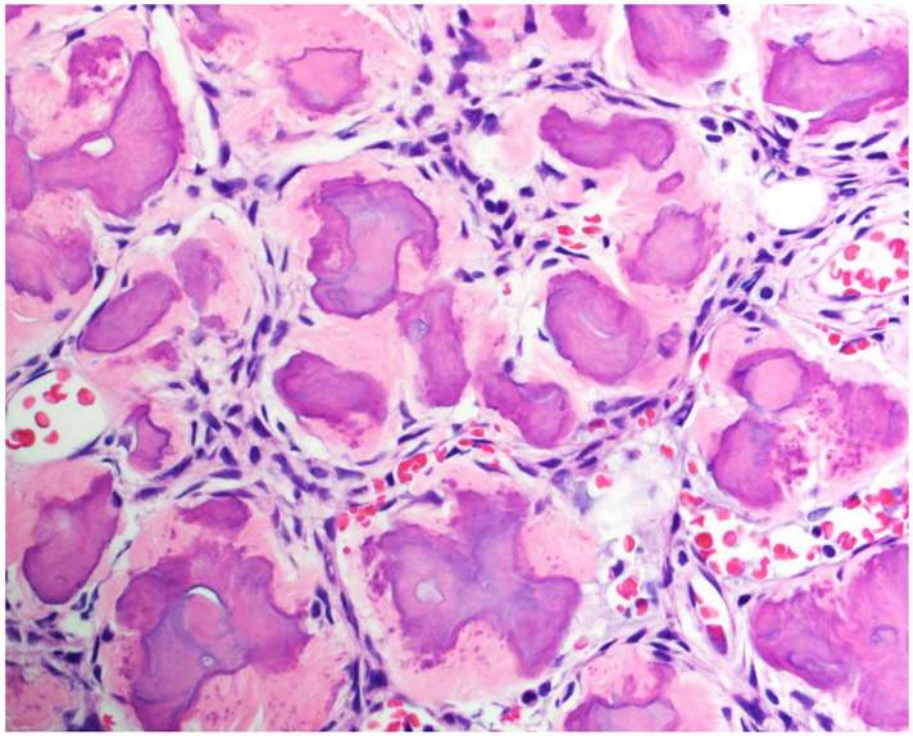

POLLING POLLS POLL

Juvenile Psammomatoid Ossifying Fibroma (JPOF)

- Benign variant of ossifying fibroma typically arising in non-odontogenic locations (paranasal sinuses, orbital bones, and skull base).
- Wide age distribution of 3 months-72 years; usually occur in first or second decade
  - Equal female:male predilection (ossifying fibroma ~5:1 F:M)
- Patients present with nasal obstruction, hearing loss, headaches, and/or proptosis
  - Majority are slow growing and may be identified incidentally
- Familial cases show *CDC73* mutations in association with hyperparathyroidism-jaw tumor syndrome
- Imaging demonstrates a well-demarcated, unilocular mass with internal calcifications/bone
  - Imaging is frequently characteristic and lesions may be observed with a presumed diagnosis
- Locally aggressive. Resection is curative; recurrence with subtotal resection

Histology

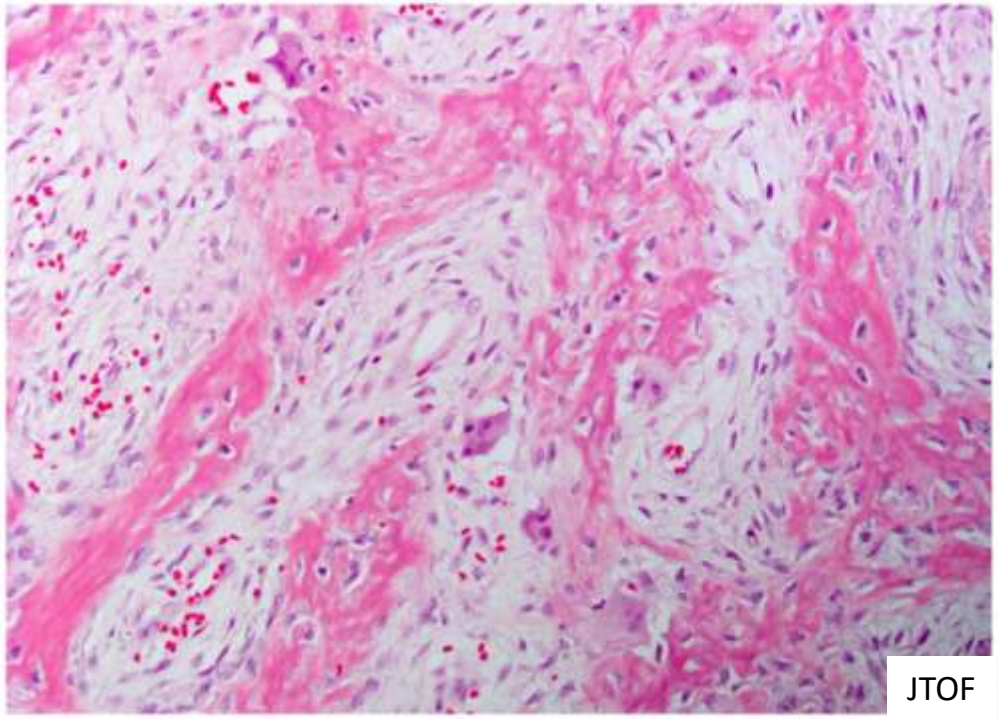
- Typical features of ossifying fibroma are present
  - Irregular woven and lamellar bone formation with osteoblastic rimming
  - Spindled and cytologically bland stromal cells; osteoclast giant cells frequent
  - JPOF shows high cellularity and innumerable psammomatoid calcifications (ossicles); mitotic activity may be higher than typical ossifying fibromas
  - Secondary aneurysmal bone cyst formation may occur
- Immunohistochemistry often not required/not helpful unless ruling out other fibro-osseous lesions
- ~70% show *MDM2* amplification; IHC shows no MDM2 overexpression



Nelson BL, Phillips BJ. Benign Fibro-Osseous Lesions of the Head and Neck. Head Neck Pathol. 2019

Differential

- Ossifying fibroma/cemento ossifying fibroma: typically distinct location (involves the mandible most frequently); fewer psammomatoid calcifications
- Juvenile trabecular ossifying fibroma (JTOF): More frequently arise in maxilla>mandible; characteristically shows “paintbrush stroke” cellular osteoid. Often lacks osteoblastic rimming
- Fibrous dysplasia: Typically lacks osteoblastic rimming, more infiltrative. No peripheral lamellar bone. Frequent *GNAS* mutations.
- Meningioma: Similar psammomatous calcifications, but pattern of ossification would be unusual (metaplastic meningioma shows more typical woven bone formation without osteoblastic rimming). Psammomatous variant more common in the spine. EMA and SSTR2A IHC positive



JTOF

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22-0205

Ankur Sangoi; El Camino Hospital

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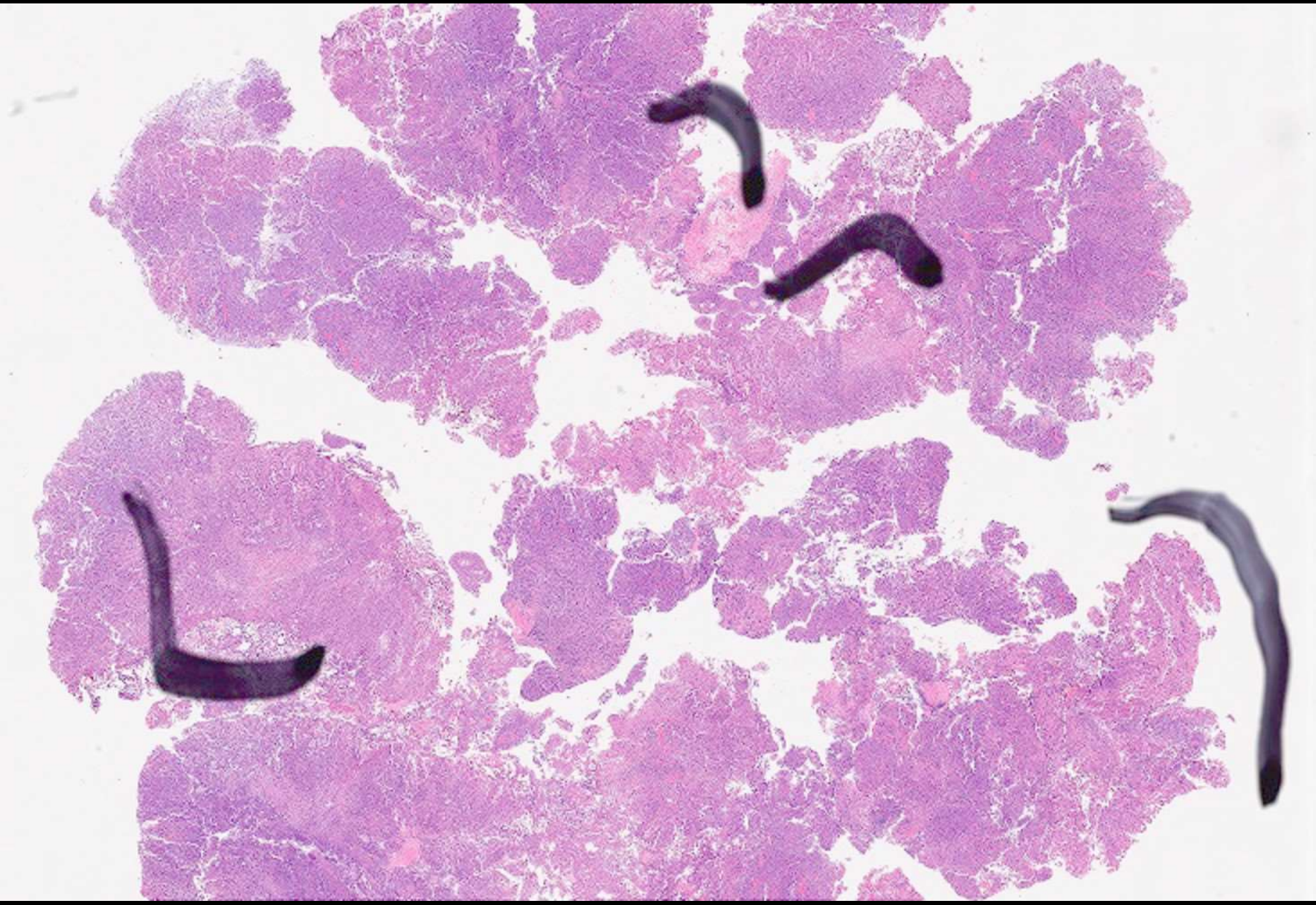
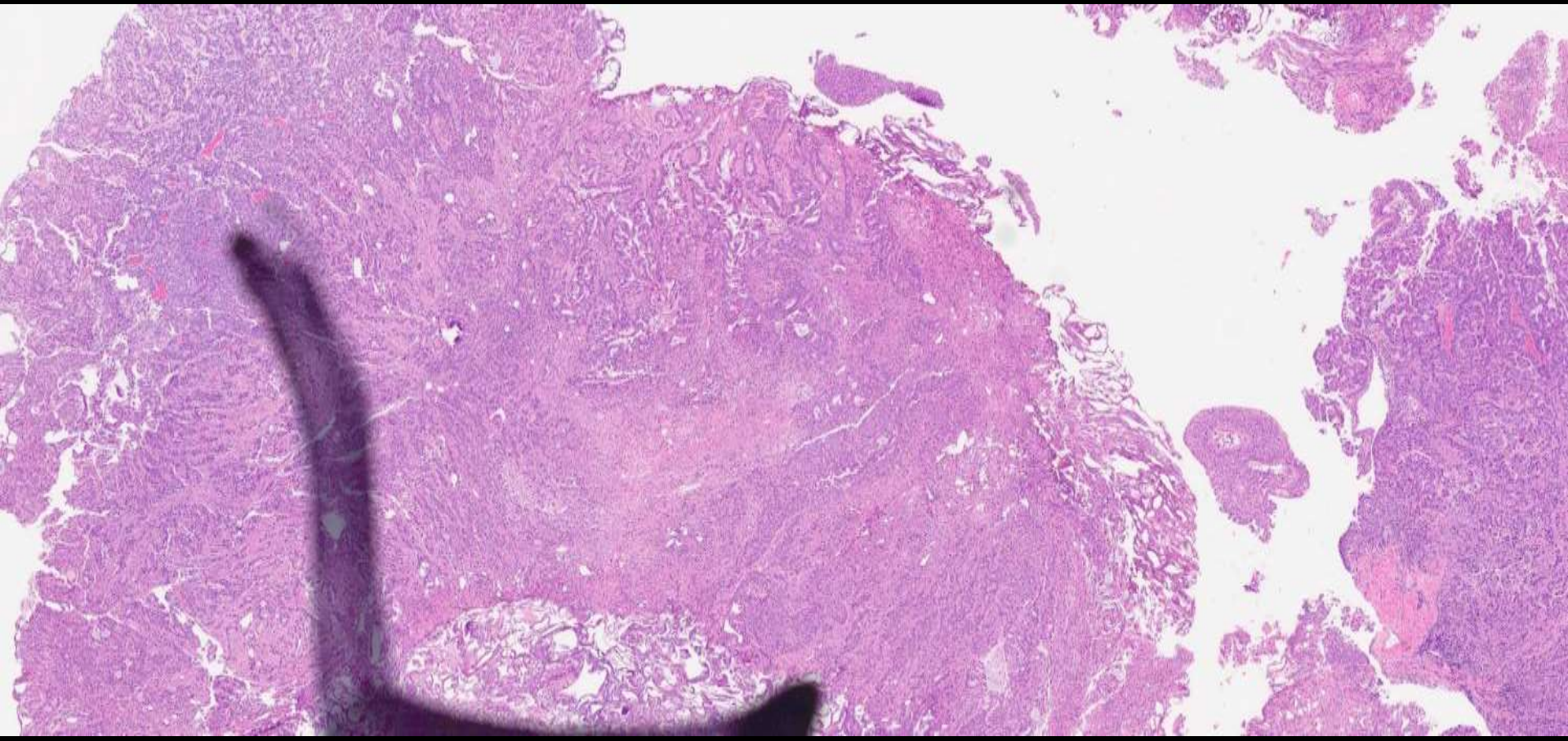
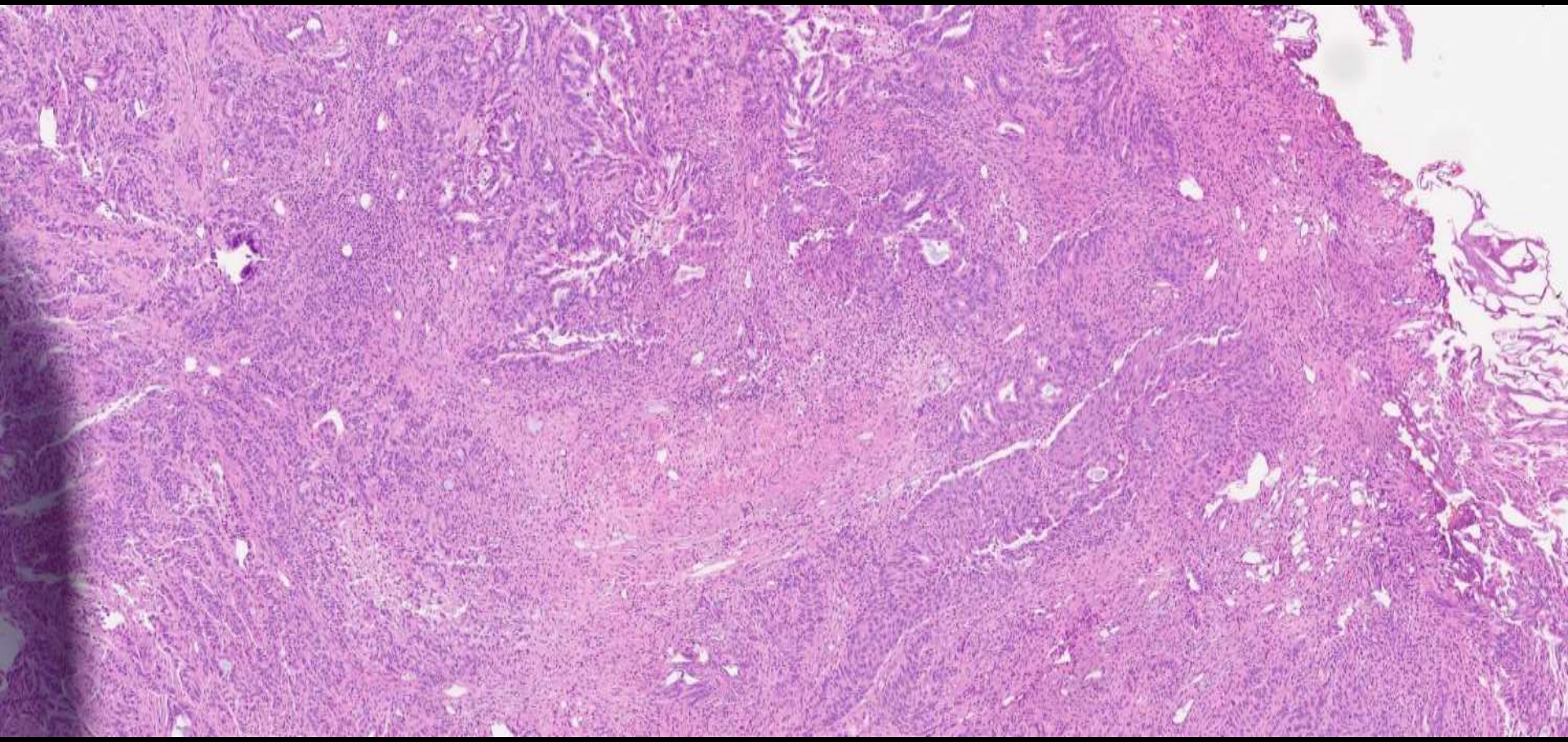
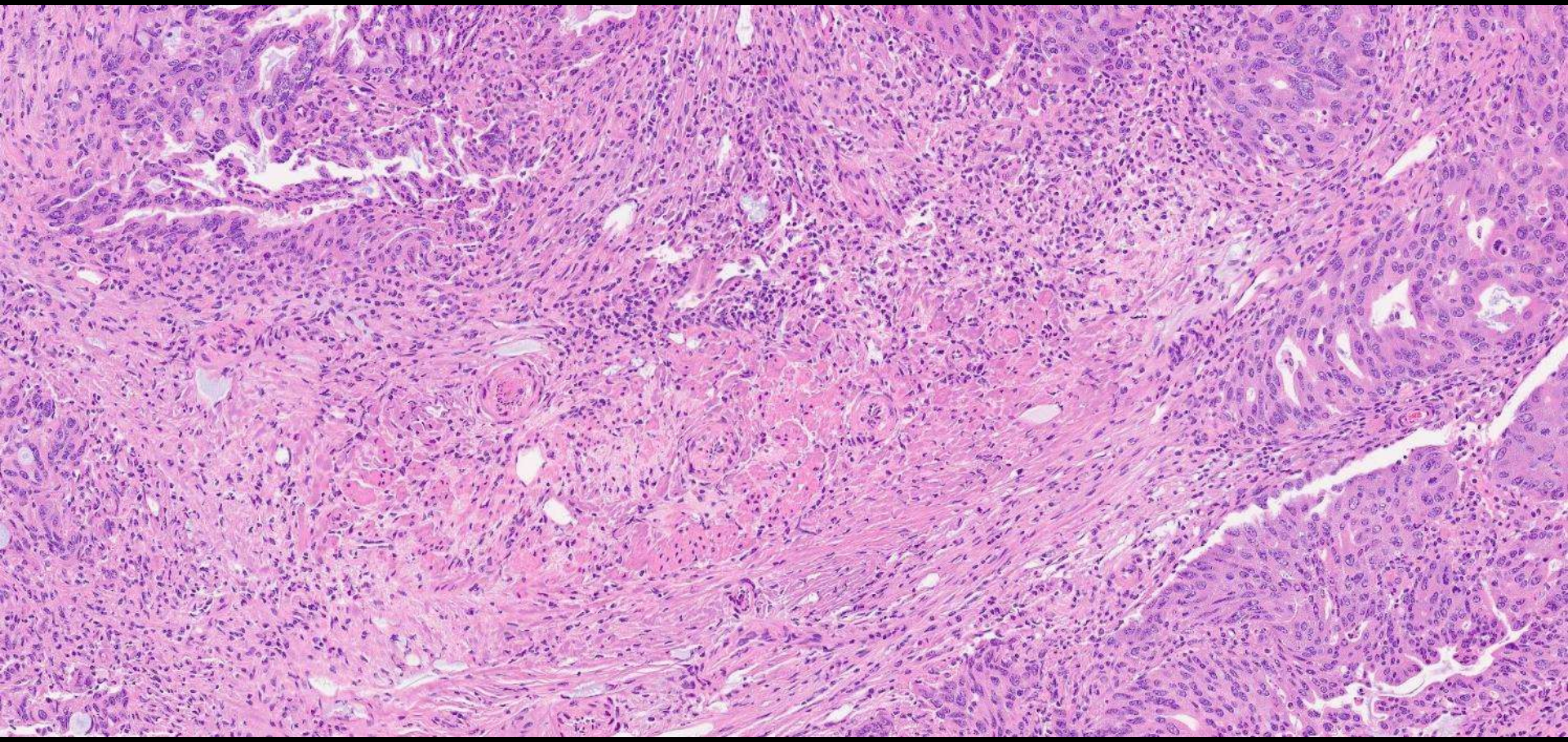
Elderly M presents with hematuria, TURBT performed.

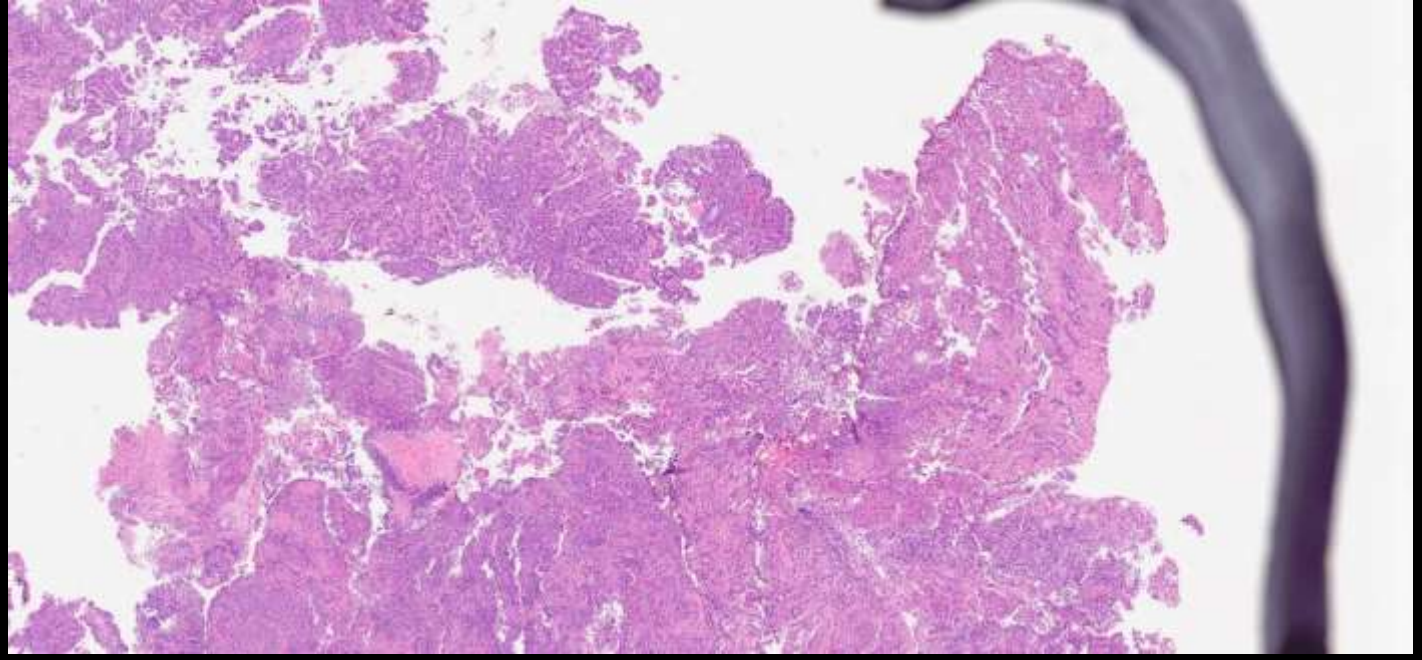
Stage?

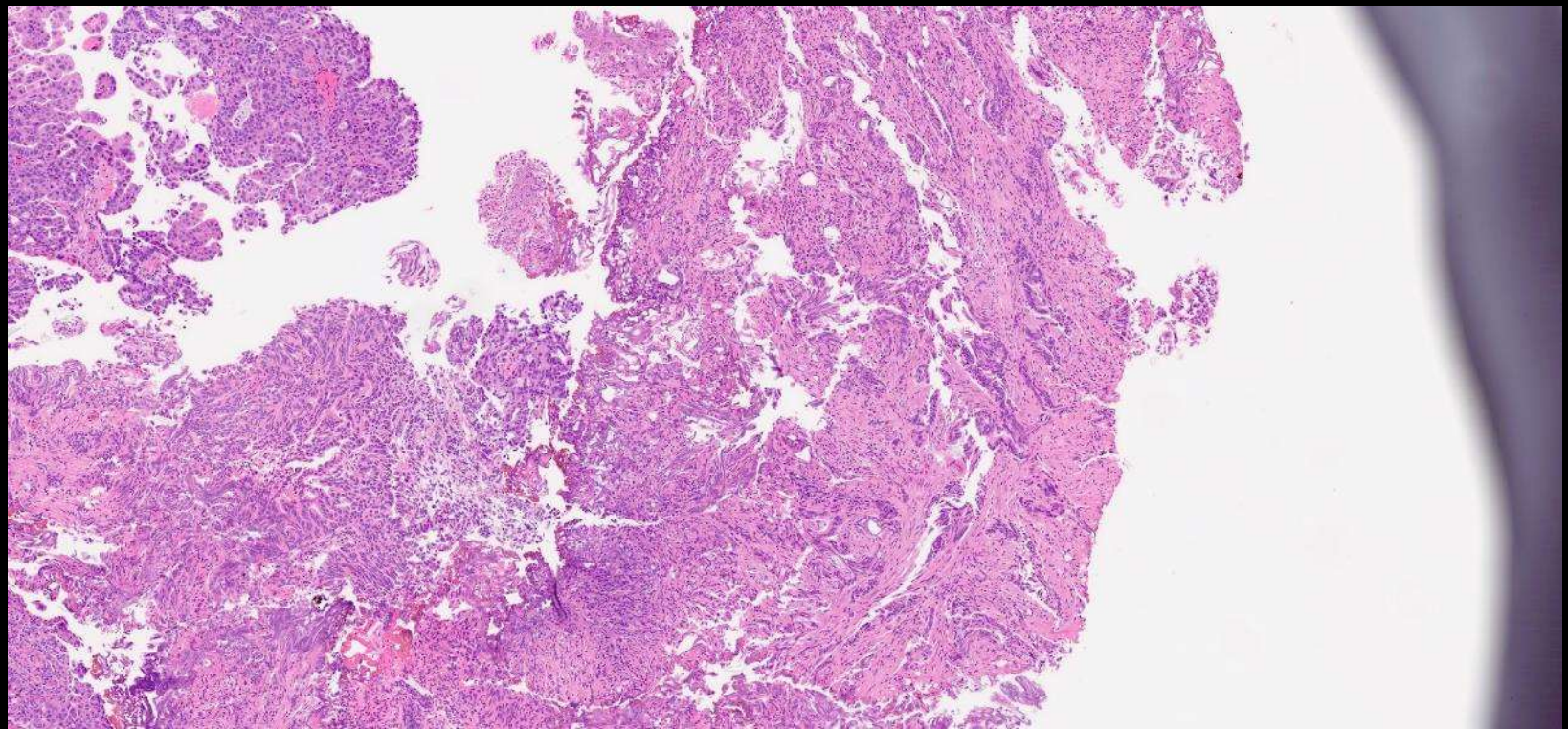


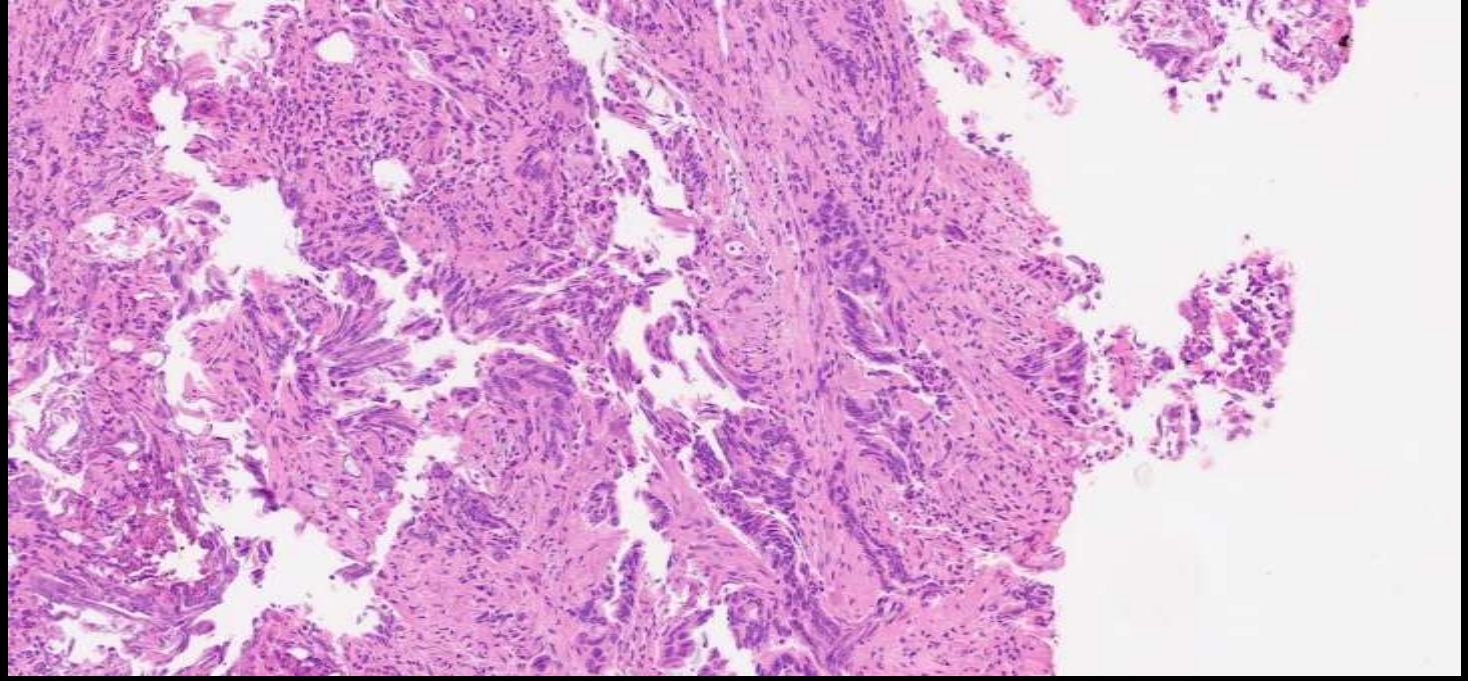


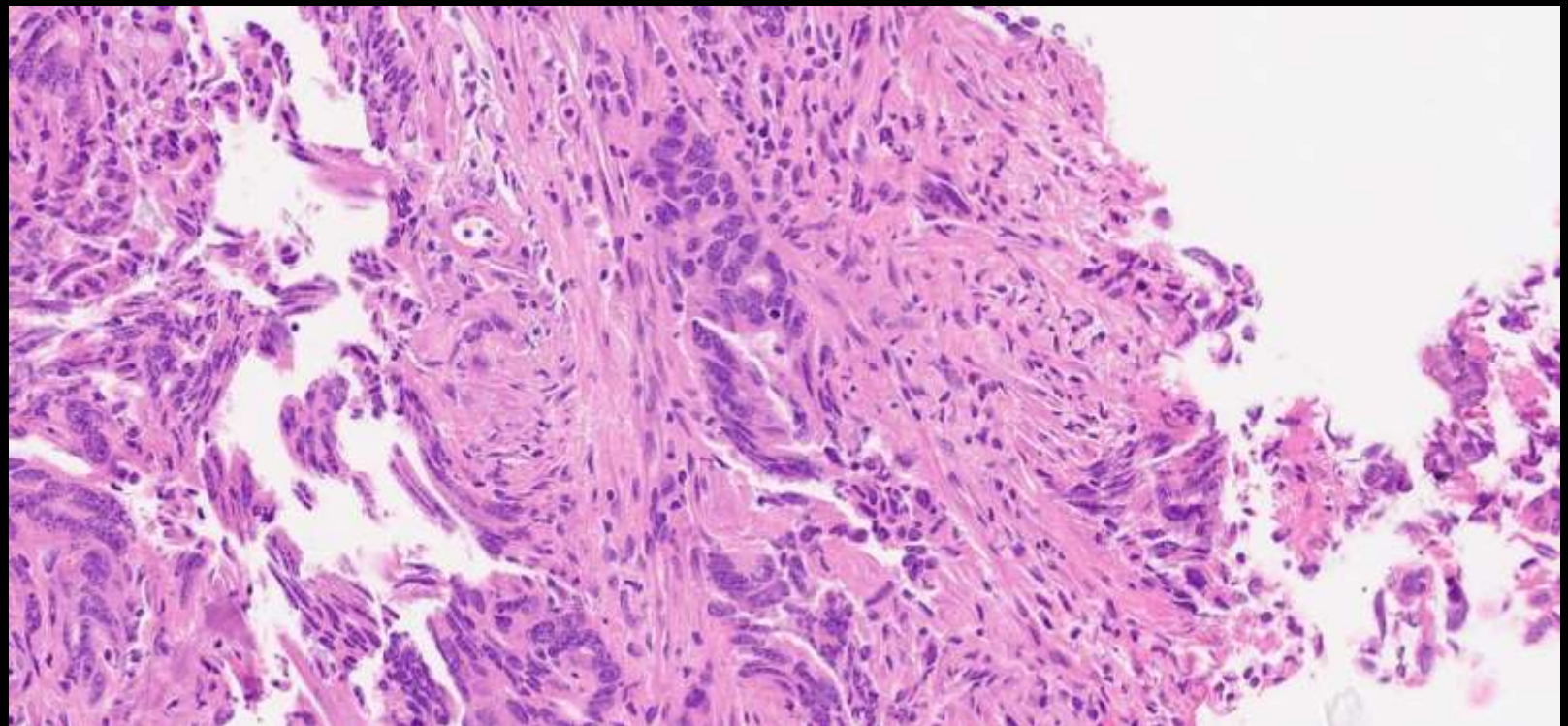


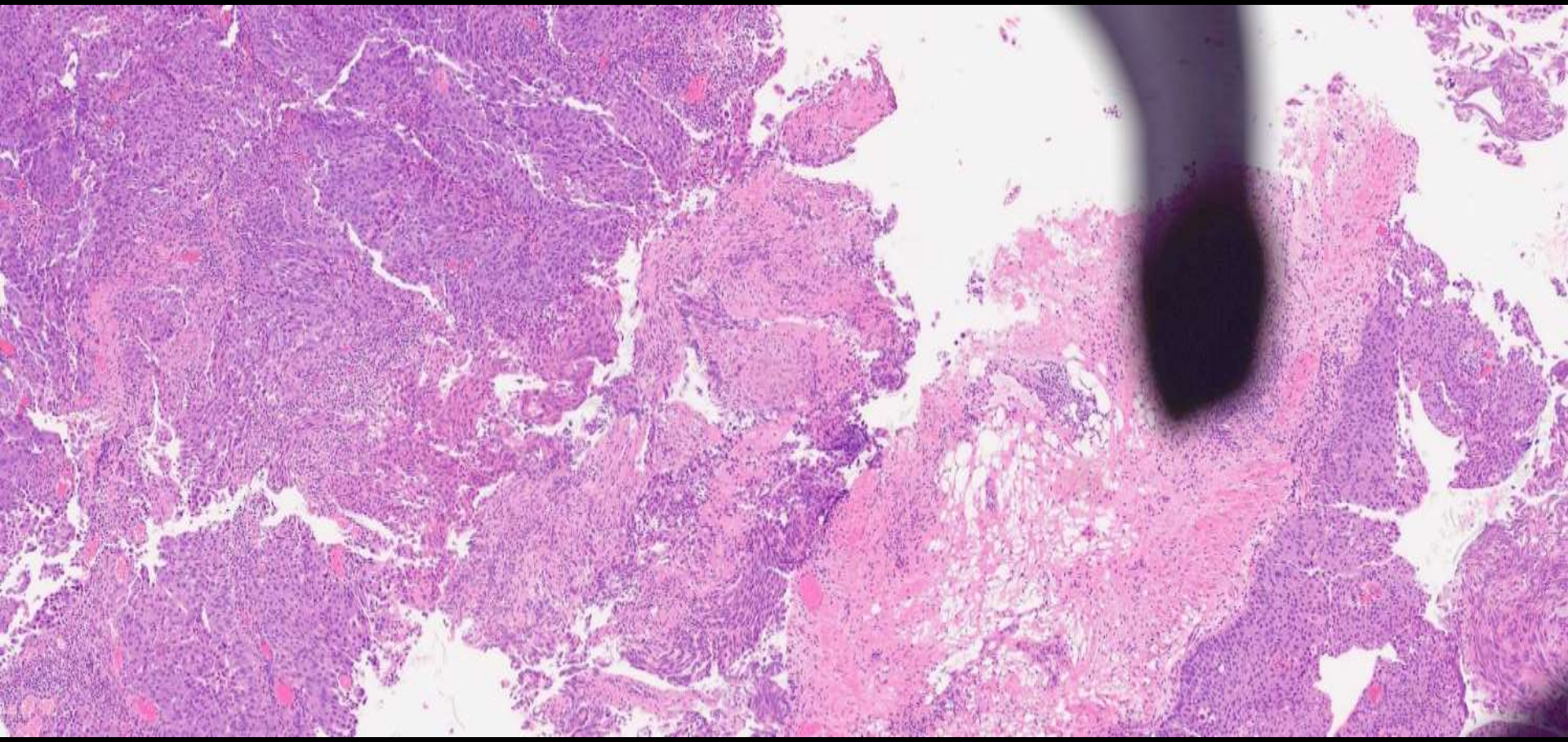


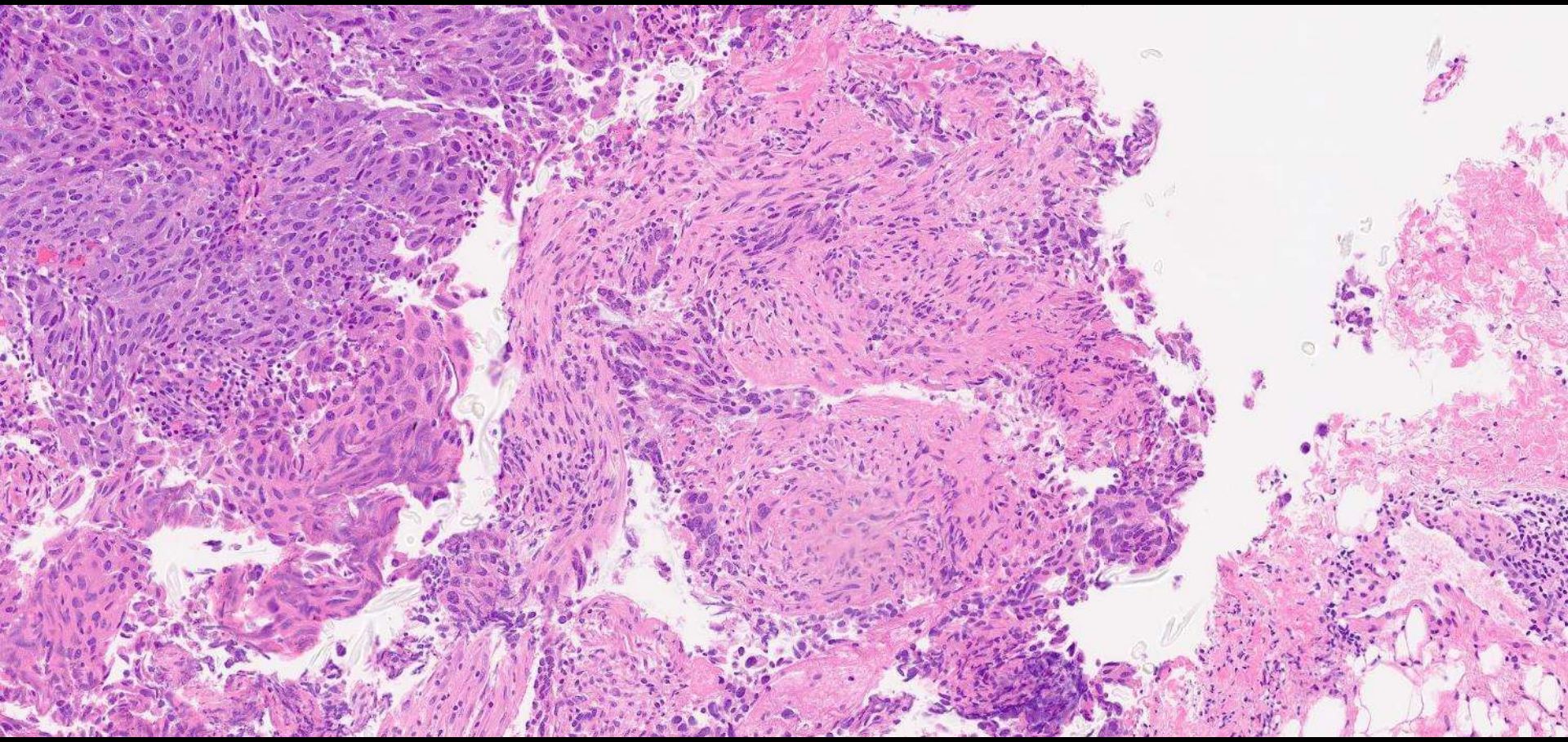












Stage?

- pTa
- pT1
- pT2
- pT3
- NEED MORE INFO!

Where in the bladder was TURBT taken from?

TURBT from bladder diverticulum

FINAL DX

- **High grade papillary urothelial carcinoma with glandular differentiation**
  - – Invading subepithelial connective tissue (pT1)

  COMMENT: since from diverticulum, muscularis propria assessment N/A

Table 3. Staging of urothelial carcinoma arising in a diverticulum

Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*: 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Not applicable
T3	Tumour invades perivesical tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostatic stroma, uterus, vagina
T4b	Tumour invades pelvic wall, abdominal wall

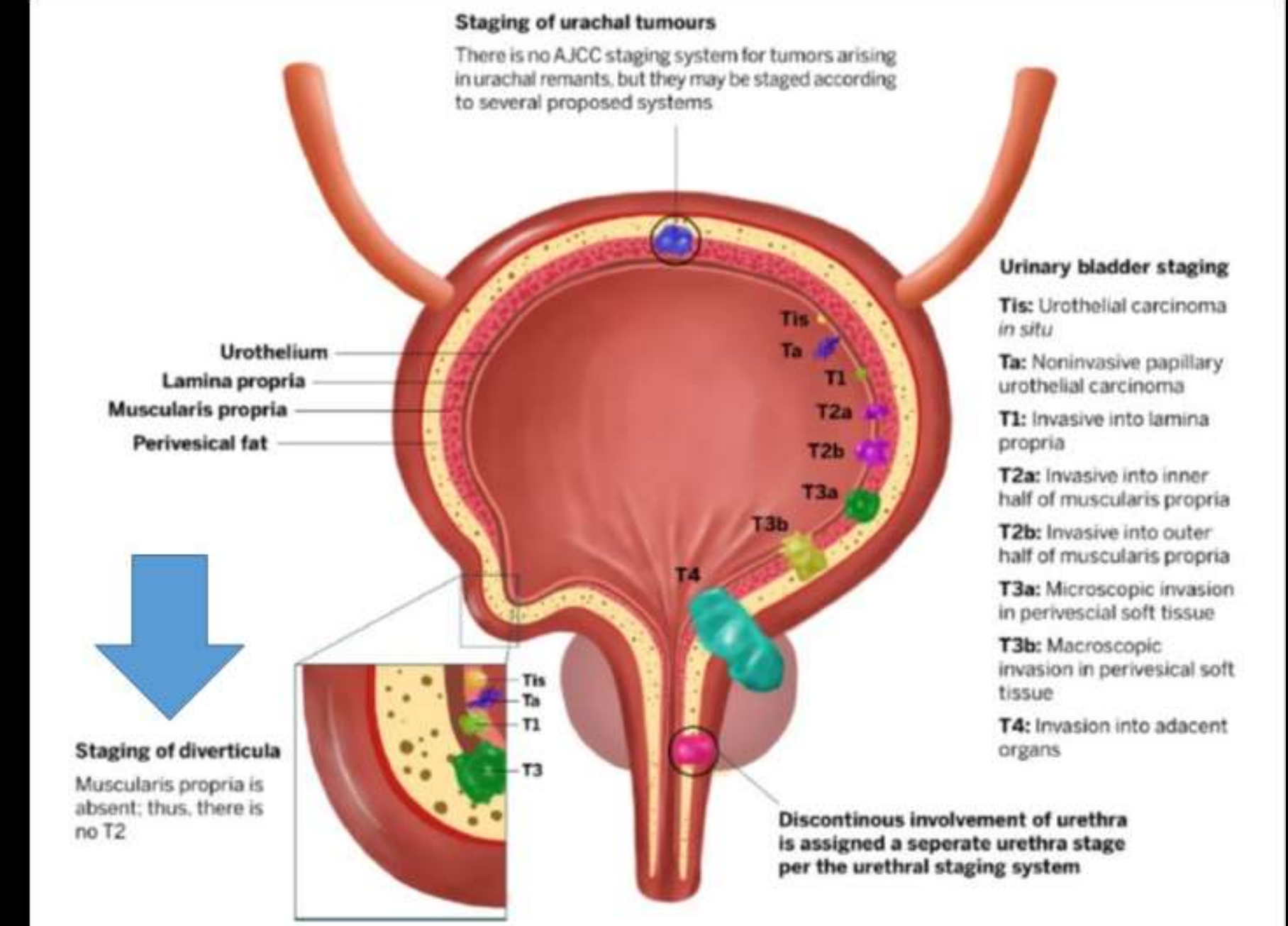


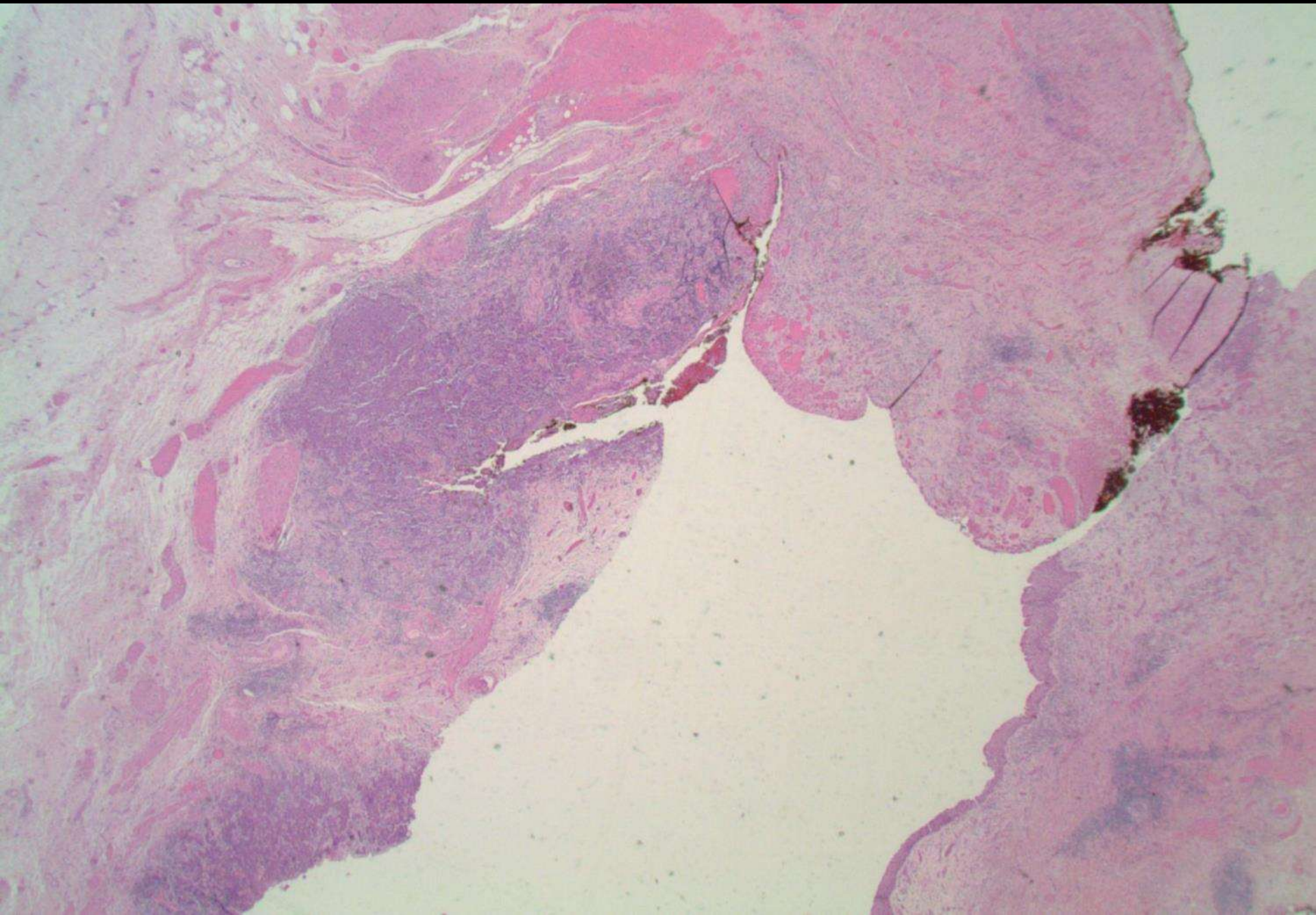
Figure 1. Overview of staging of tumours arising from the urinary bladder, diverticulum and urachal remnants.

 Histopathology, 74, 112–134.

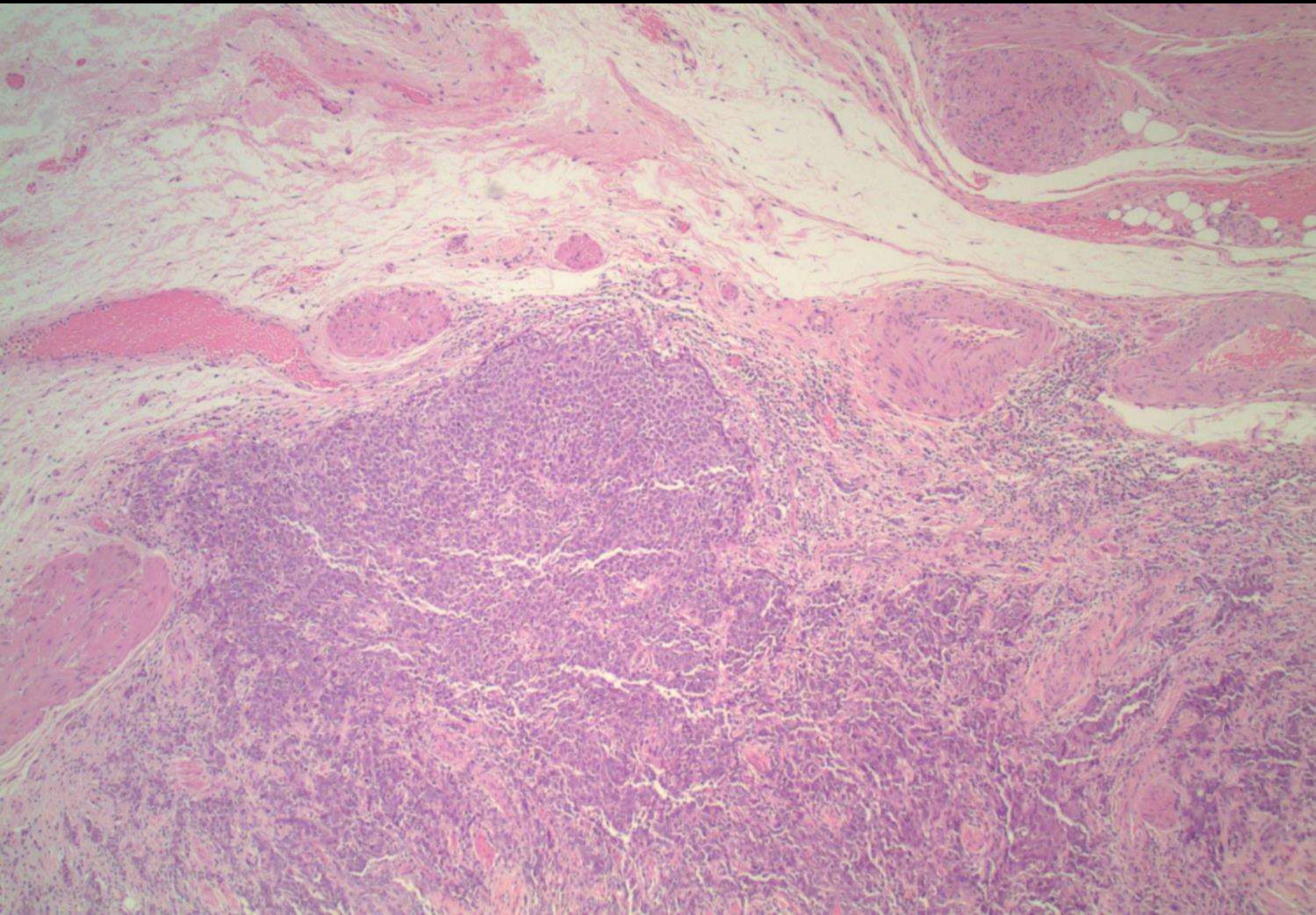
TABLE 4. Potential Pitfalls and Inaccuracies in pT Staging Related to Tumor Histology or Bladder Structural Features

Actual Stage	Urothelial Tumor	Potential Stage Misdiagnosis
pTa	Truncated high-grade PUC after therapy	pTis
	Flat "shoulder" of high-grade PUC in separate TUR fragment	pTis
	High-grade urothelial carcinoma with early papillary formation	pTis
	Inverted noninvasive high-grade PUC with inverted pattern mimicking invasion	pT1
pTis	CIS extending into von Brunn nests, cystitis cystica, or cystitis glandularis	pT1
	CIS along undulating mucosa or folds (pseudopapillae)	pTa
pT1	Urothelial carcinoma invading hyperplastic (or thick) MM	pT2
	Urothelial carcinoma involving LP adipose tissue in TUR	pT3
pT1 (diverticulum)	Urothelial carcinoma involving diverticular wall	pT2
pT2	MP fractured and dispersed by urothelial carcinoma	pT1
	Carcinoma infiltrating between, but not into, MP bundles	pT1
	MP involvement with lymphovascular invasion only in perivesical soft tissue	pT3a
pT2 (urethral staging)	Invasion of prostate parenchyma via intraurethral spread of bladder cancer	pT4a (bladder staging)
pT2b or pT3a	Carcinoma extension along irregular outer boundary of MP	pT3a or pT2b
pT3a (diverticulum)	Diverticular urothelial carcinoma with microscopic fat involvement	pT1
pT3a	Gross overestimation as extravesical mass due to florid reactive changes and fibrosis	pT3b
pT3b	Lack of gross documentation of macroscopic perivesical soft tissue invasion	pT3a
pT4a (bladder) or pT2 (urethral) with clinical correlation	Urothelial carcinoma involving prostatic chips in TUR only	pT2 (urethral) or pT4a (bladder)

DIFFERENT CASE: pT1 uro ca within bladder tic



DIFFERENT CASE: pT1 uro ca within bladder tic



22-0206

Ankur Sangoi; El Camino Hospital

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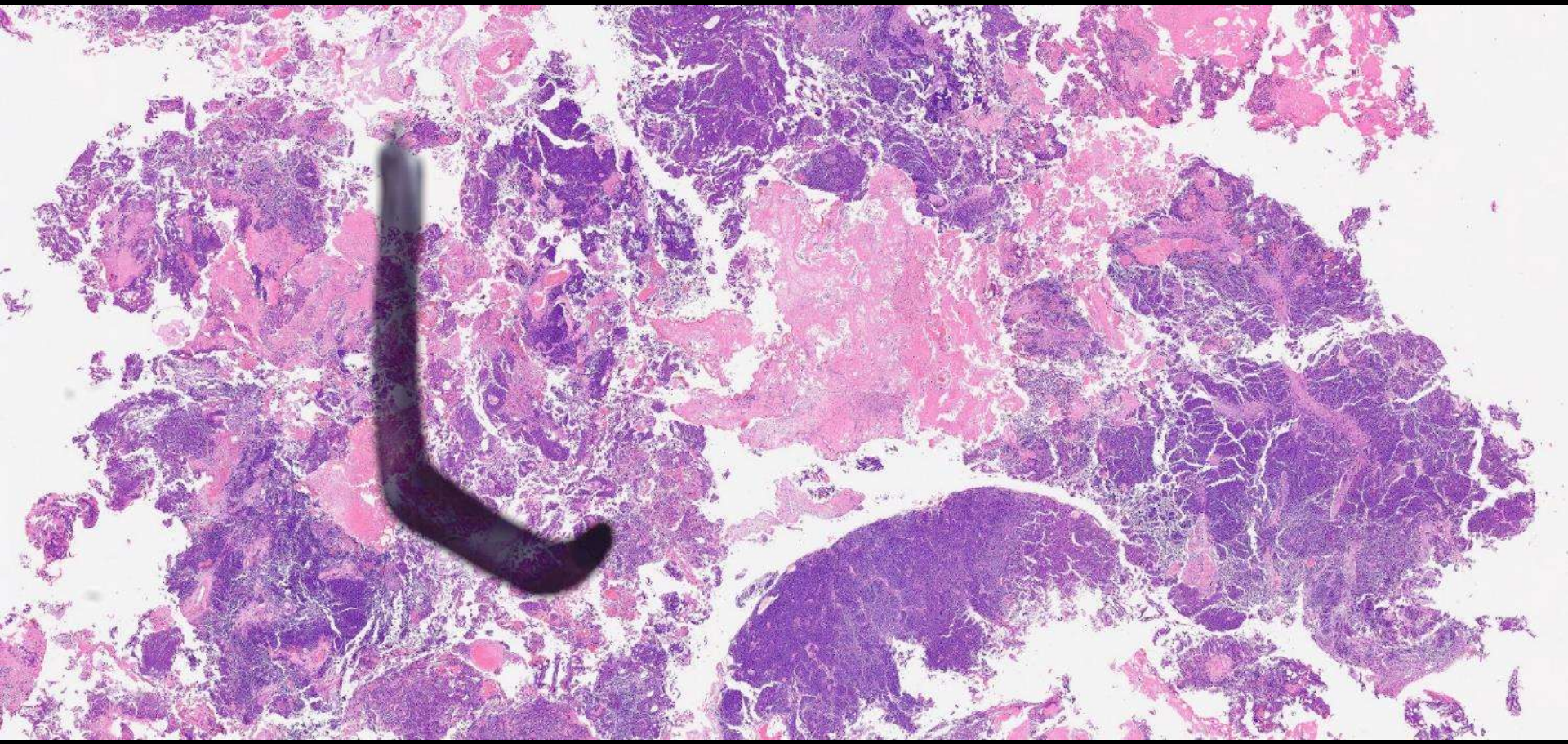
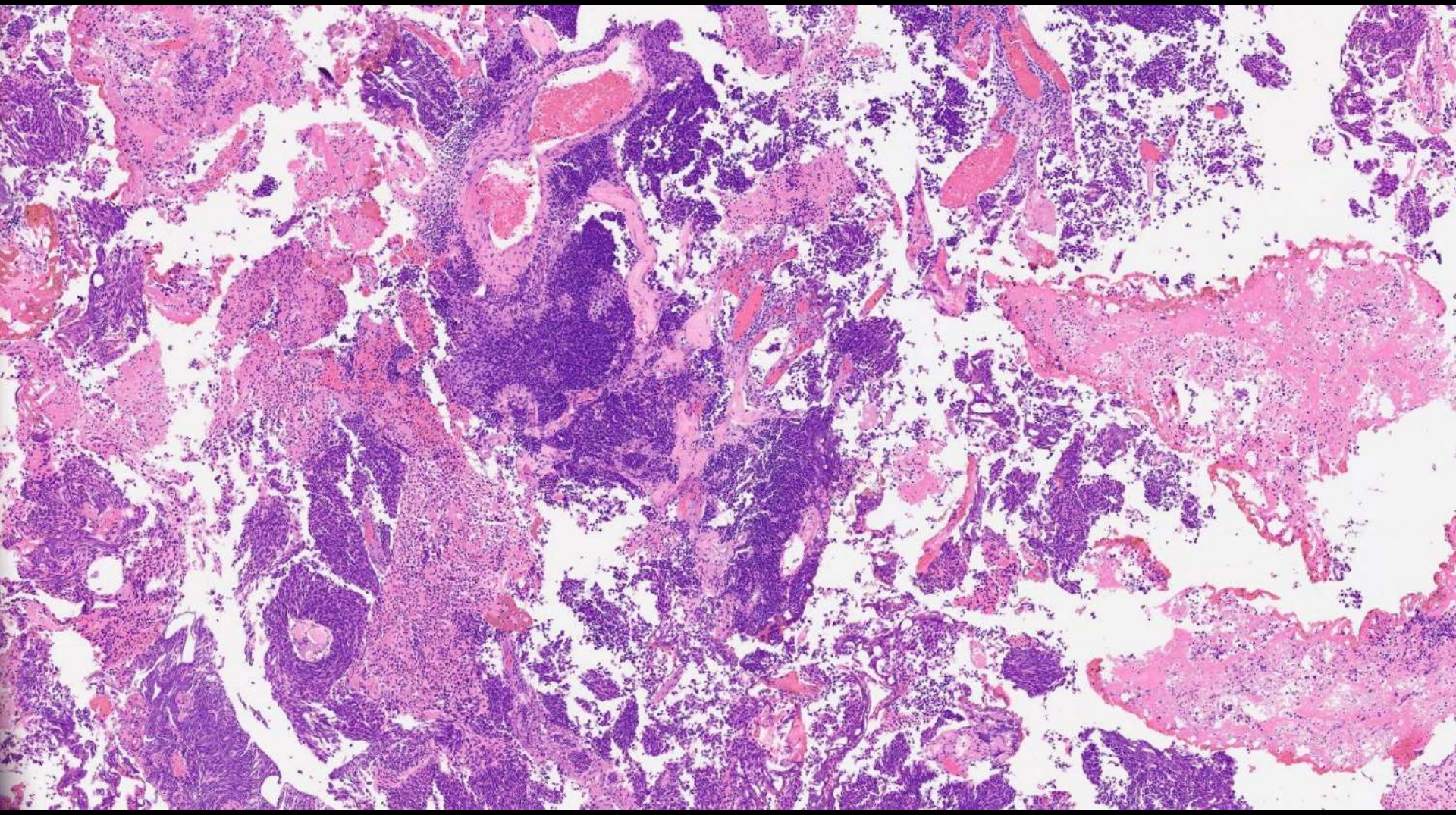
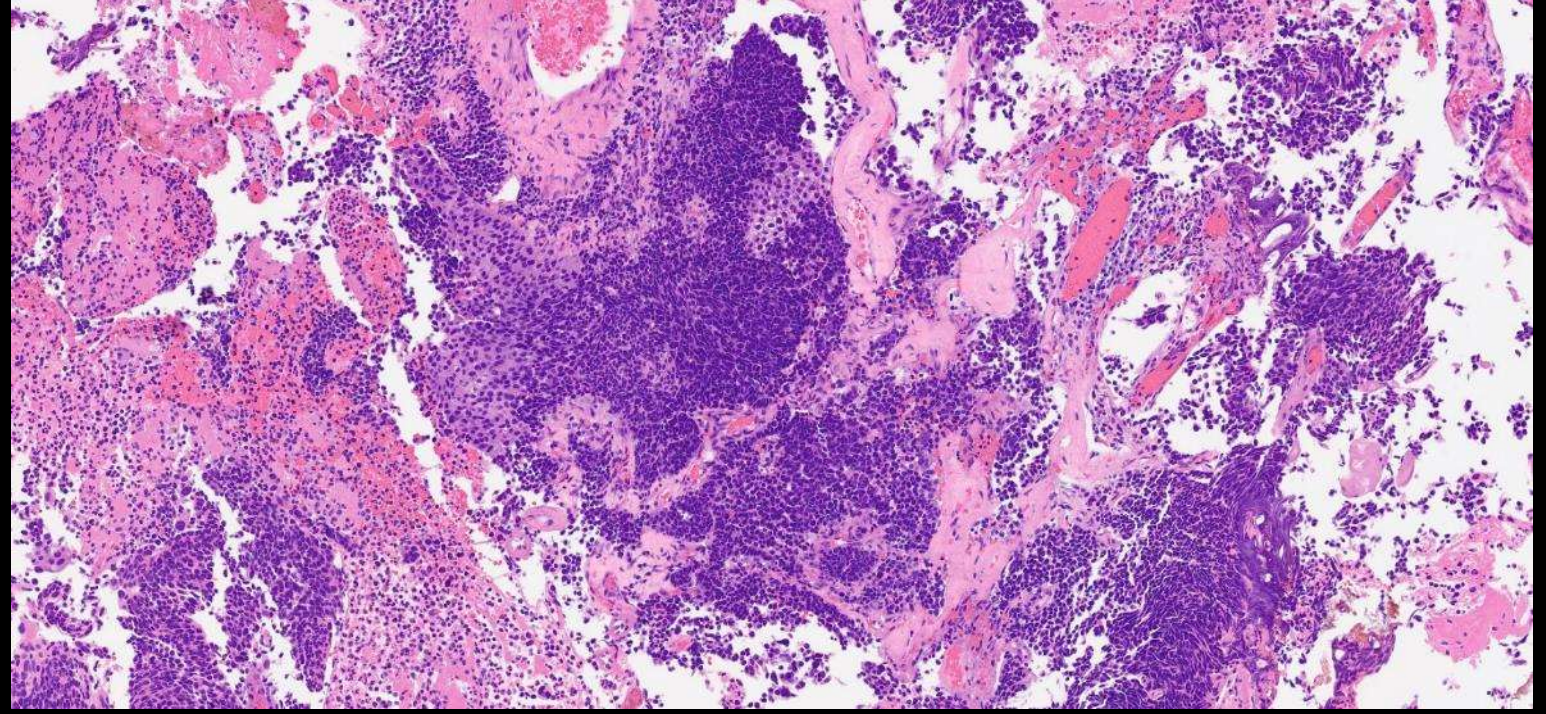
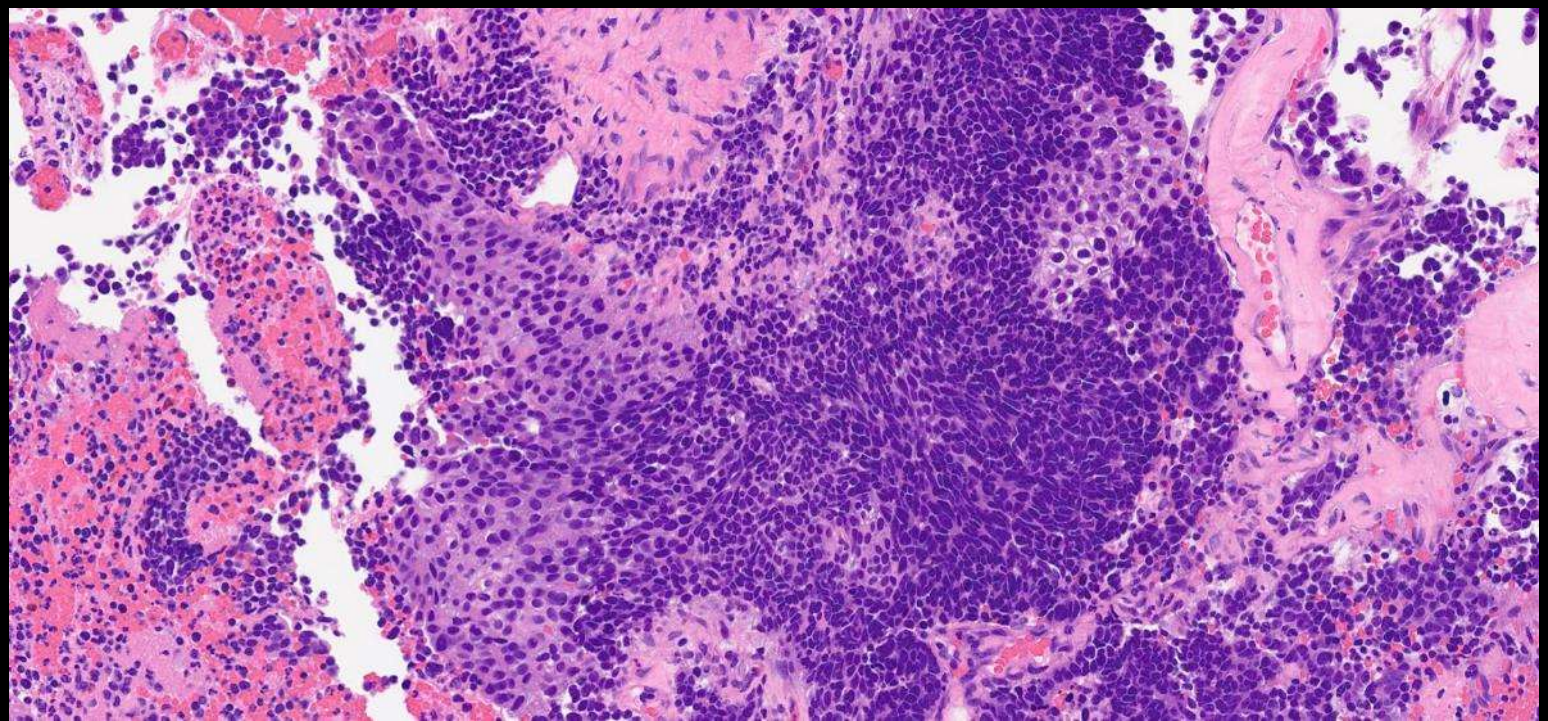
Middle-aged M presents with hematuria, TURBT performed.

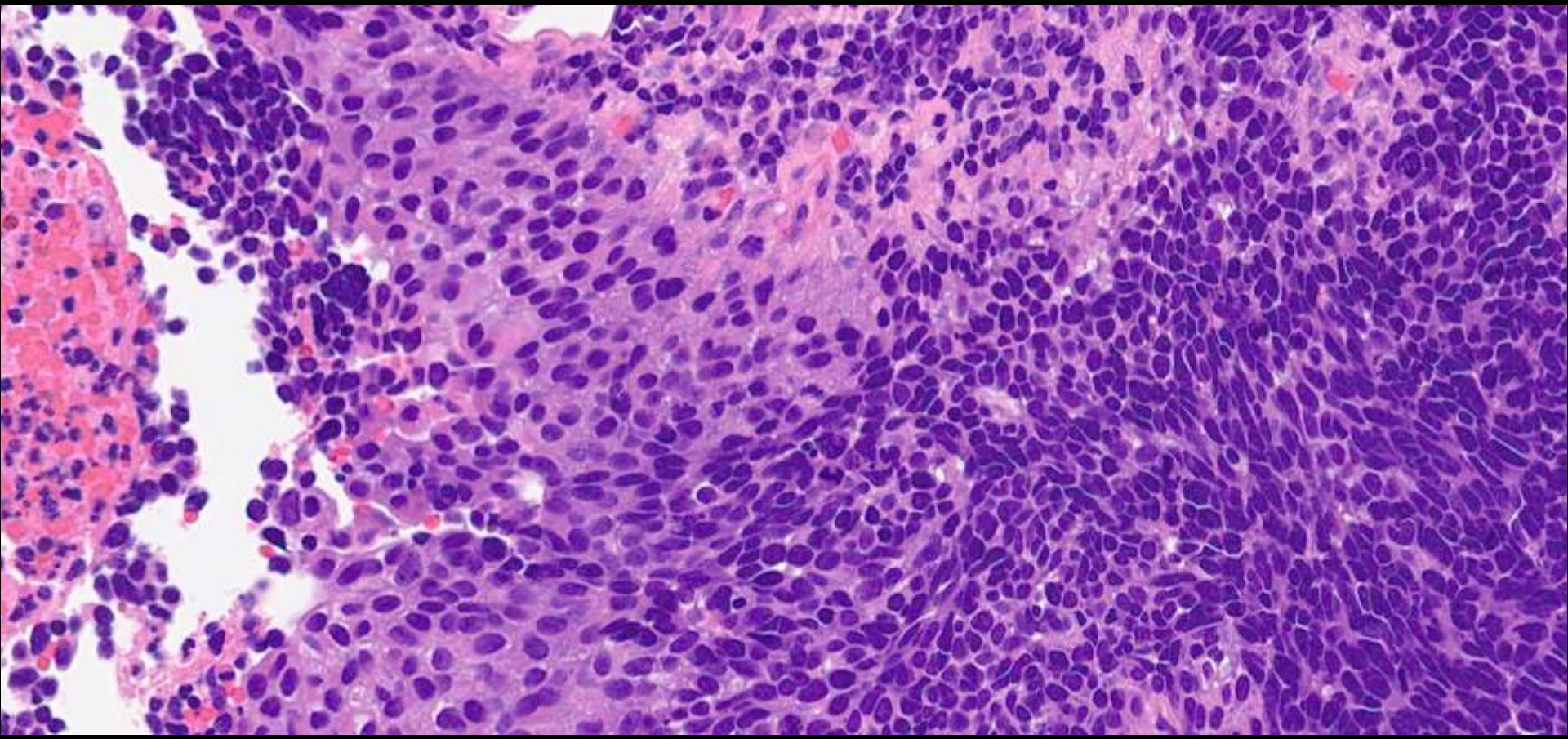
Dx?

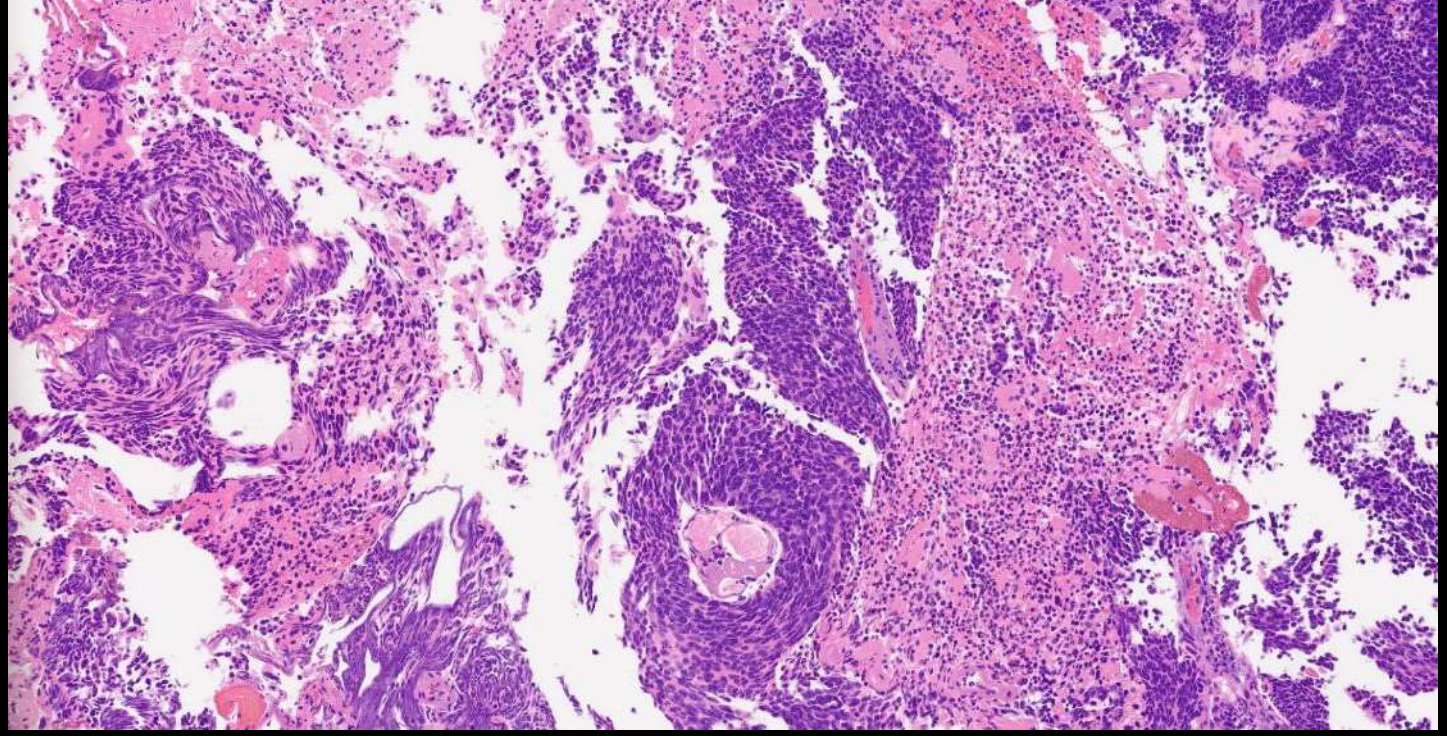


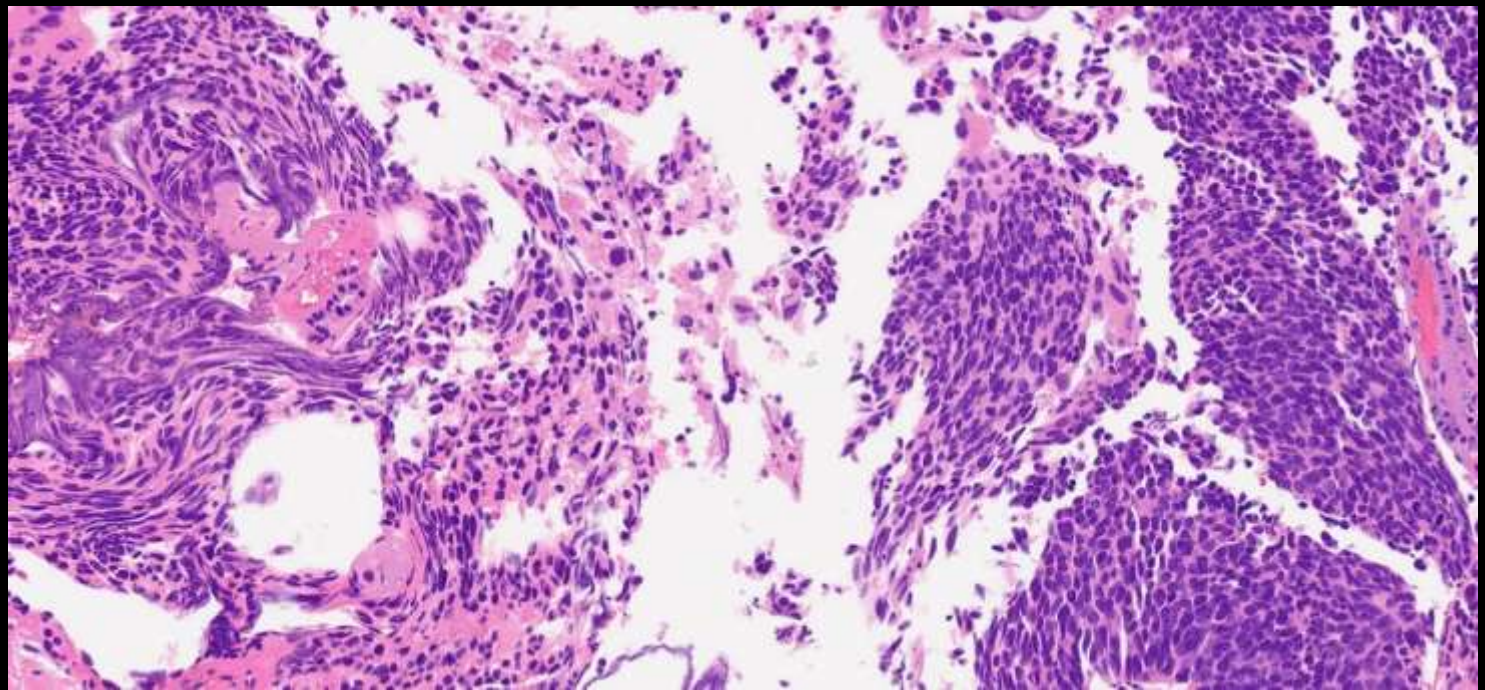


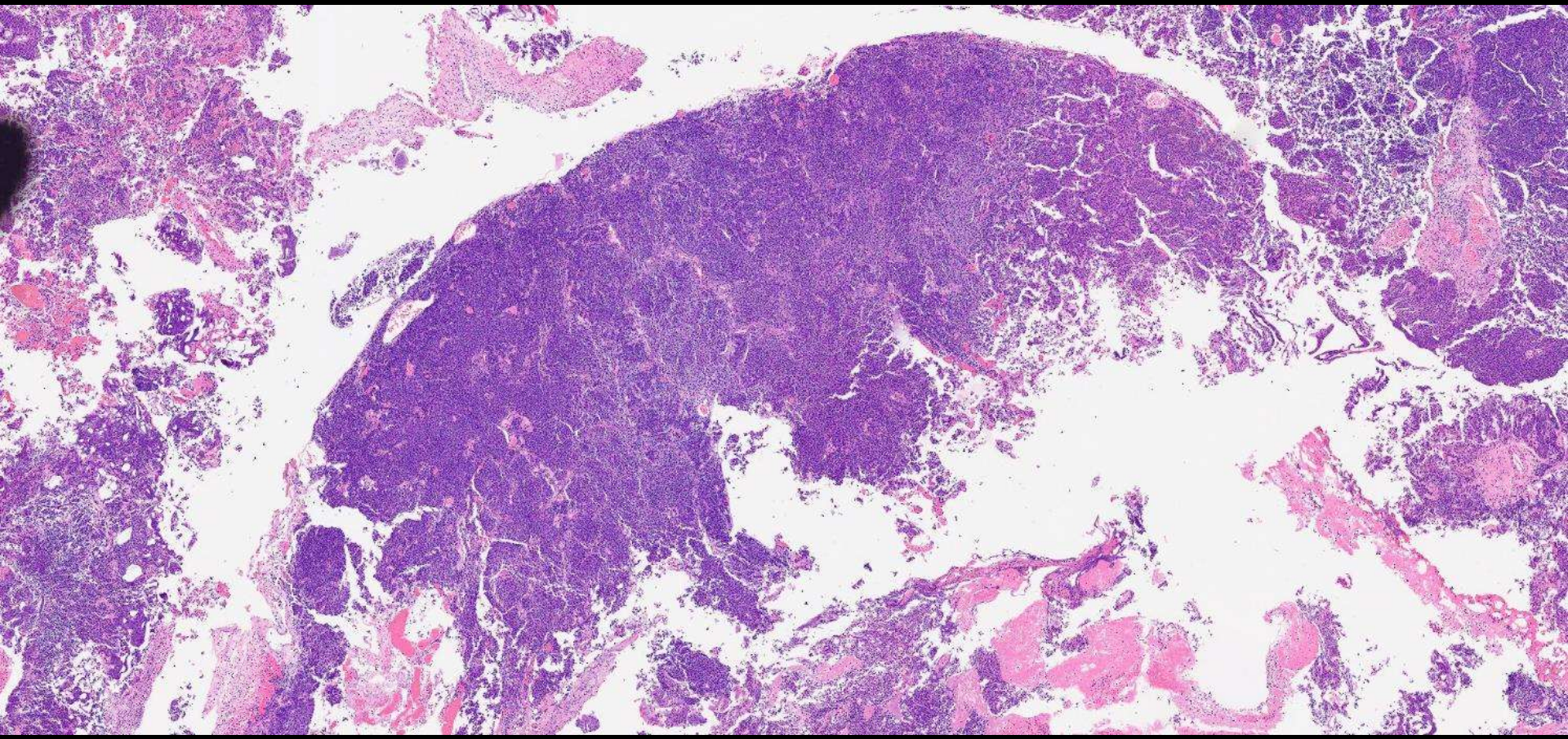


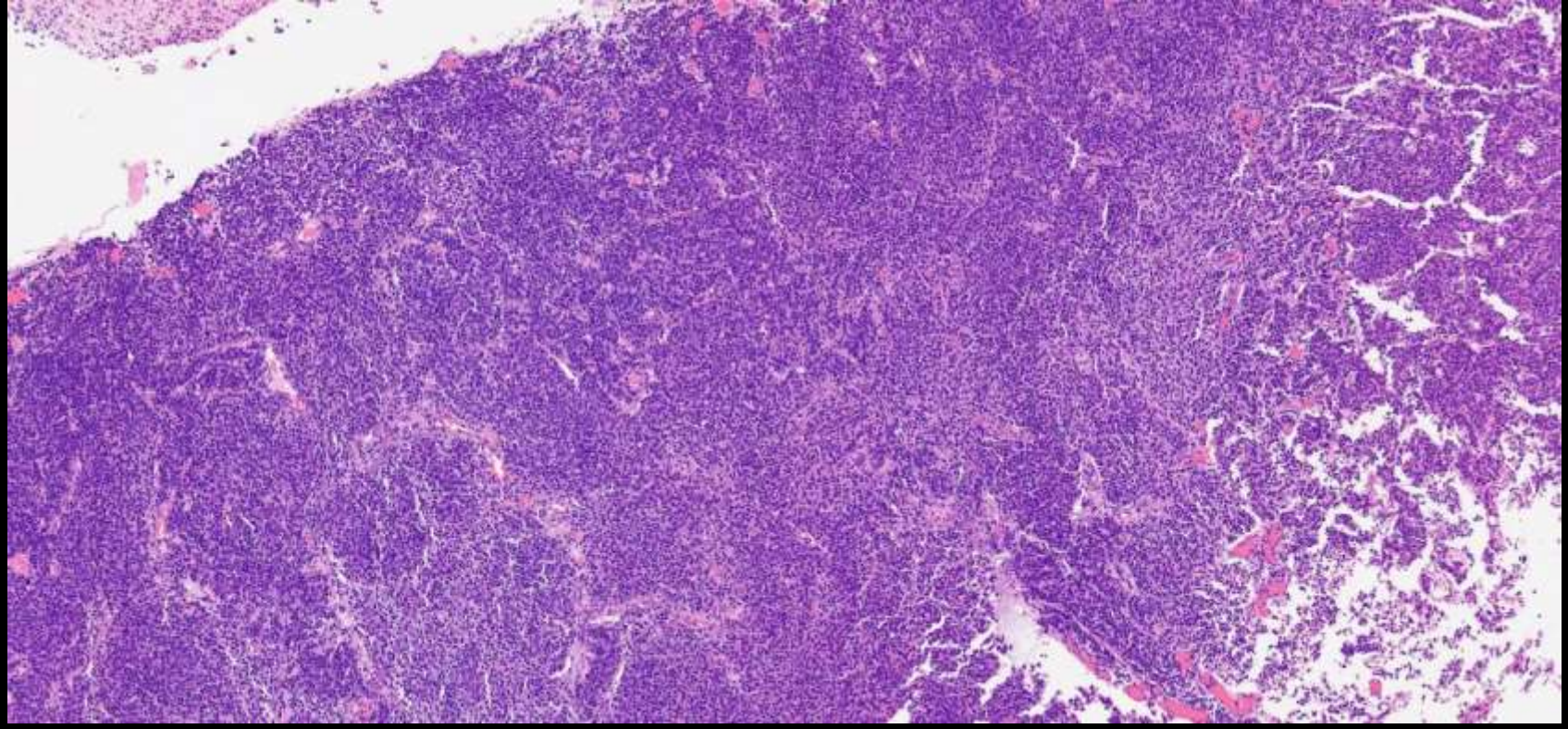


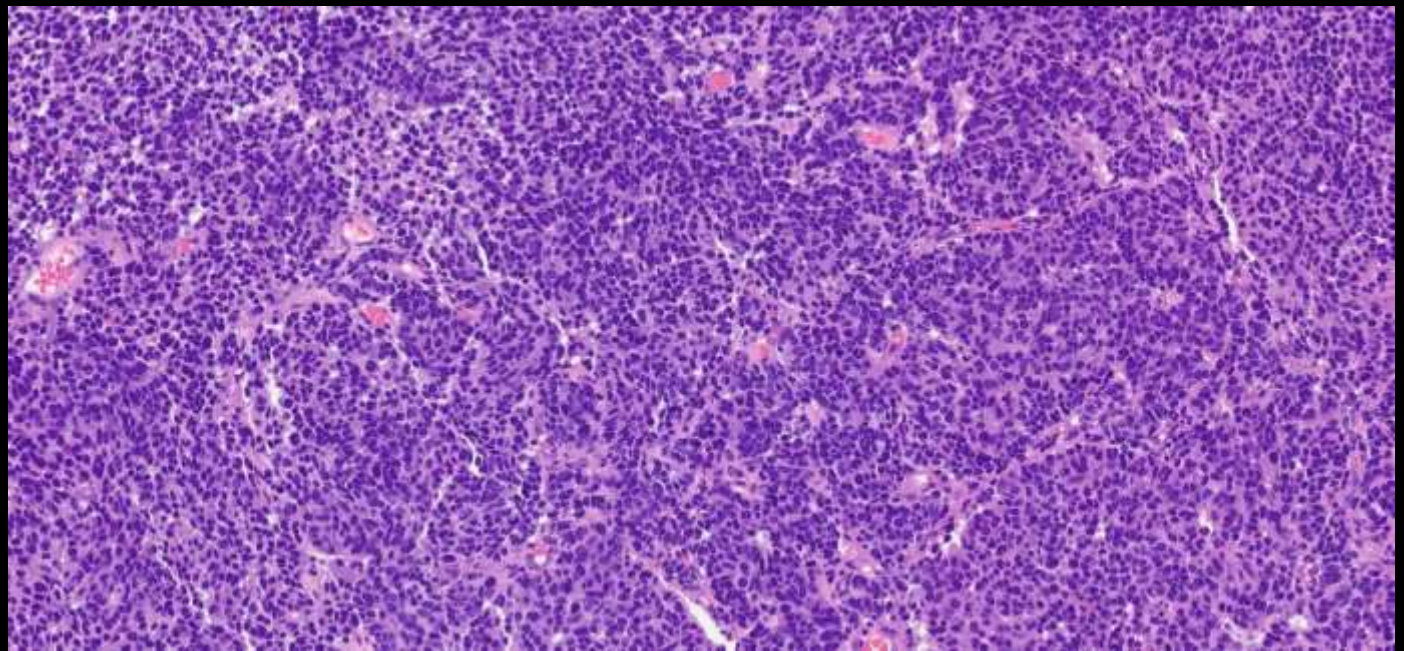


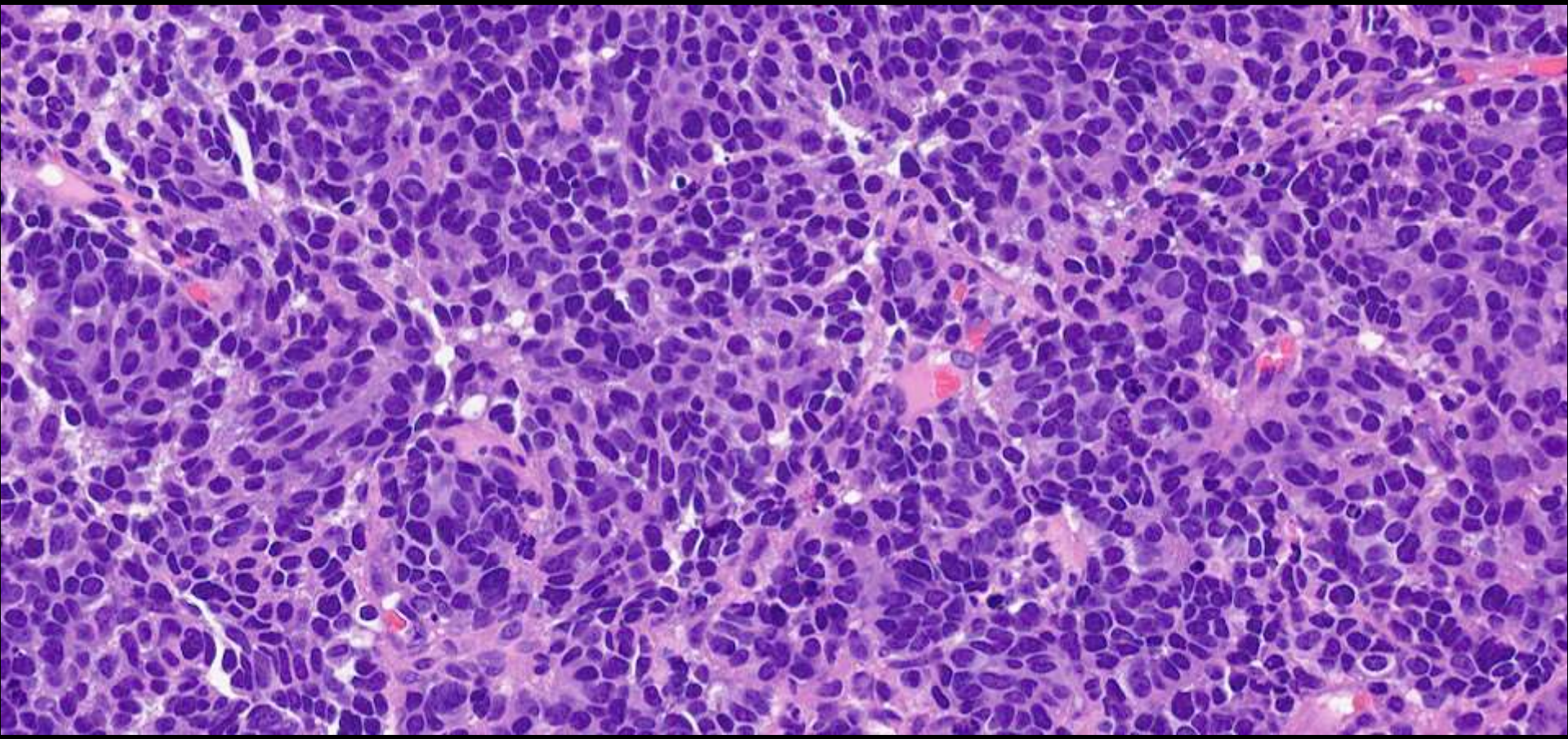


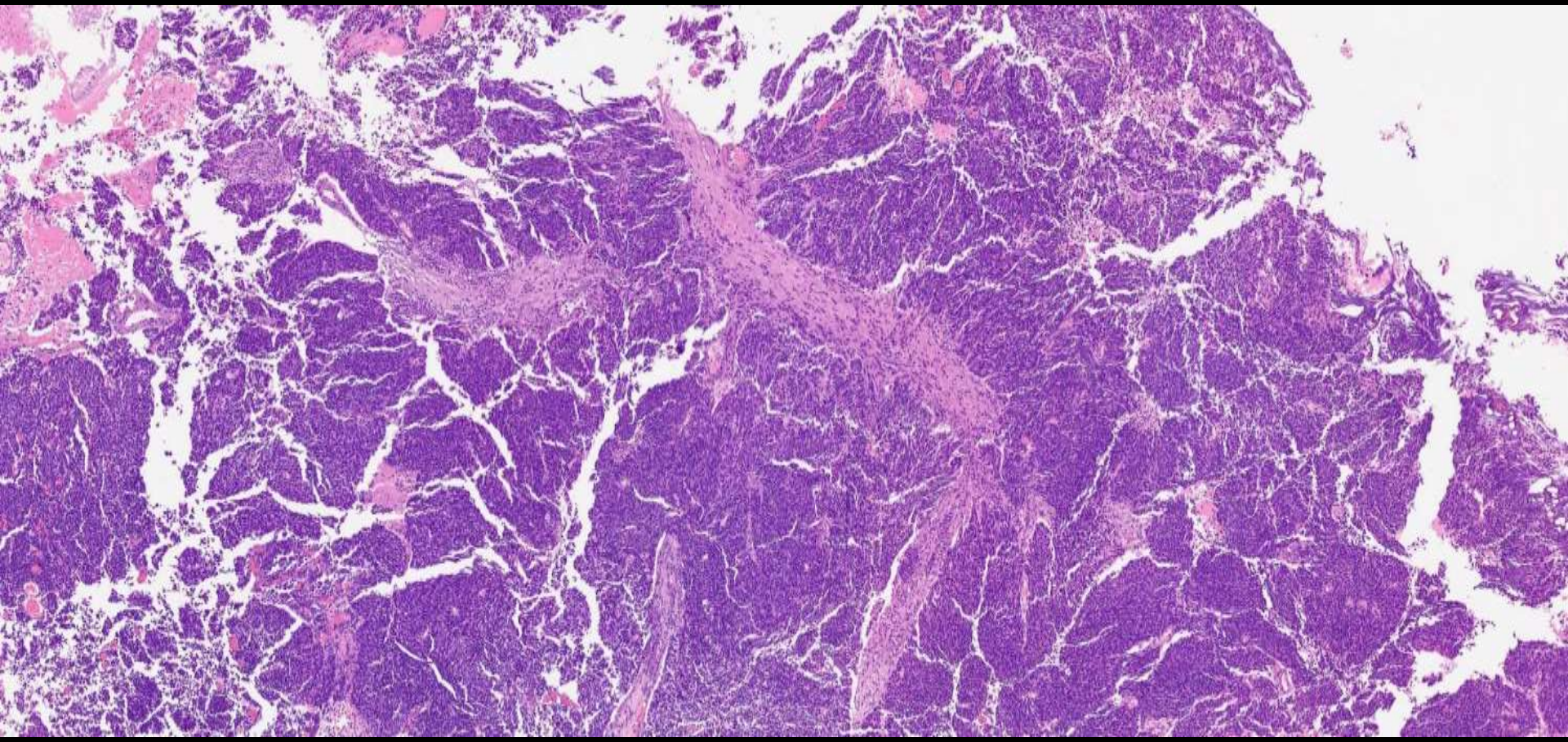


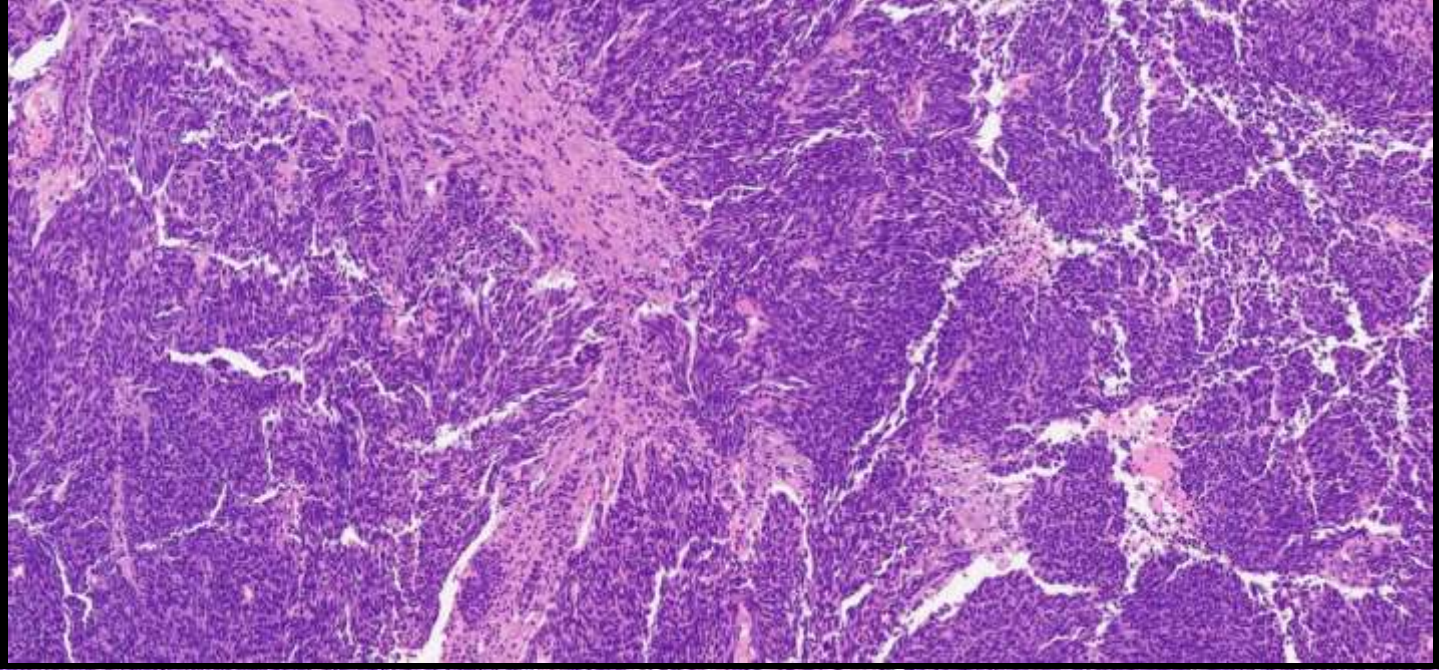


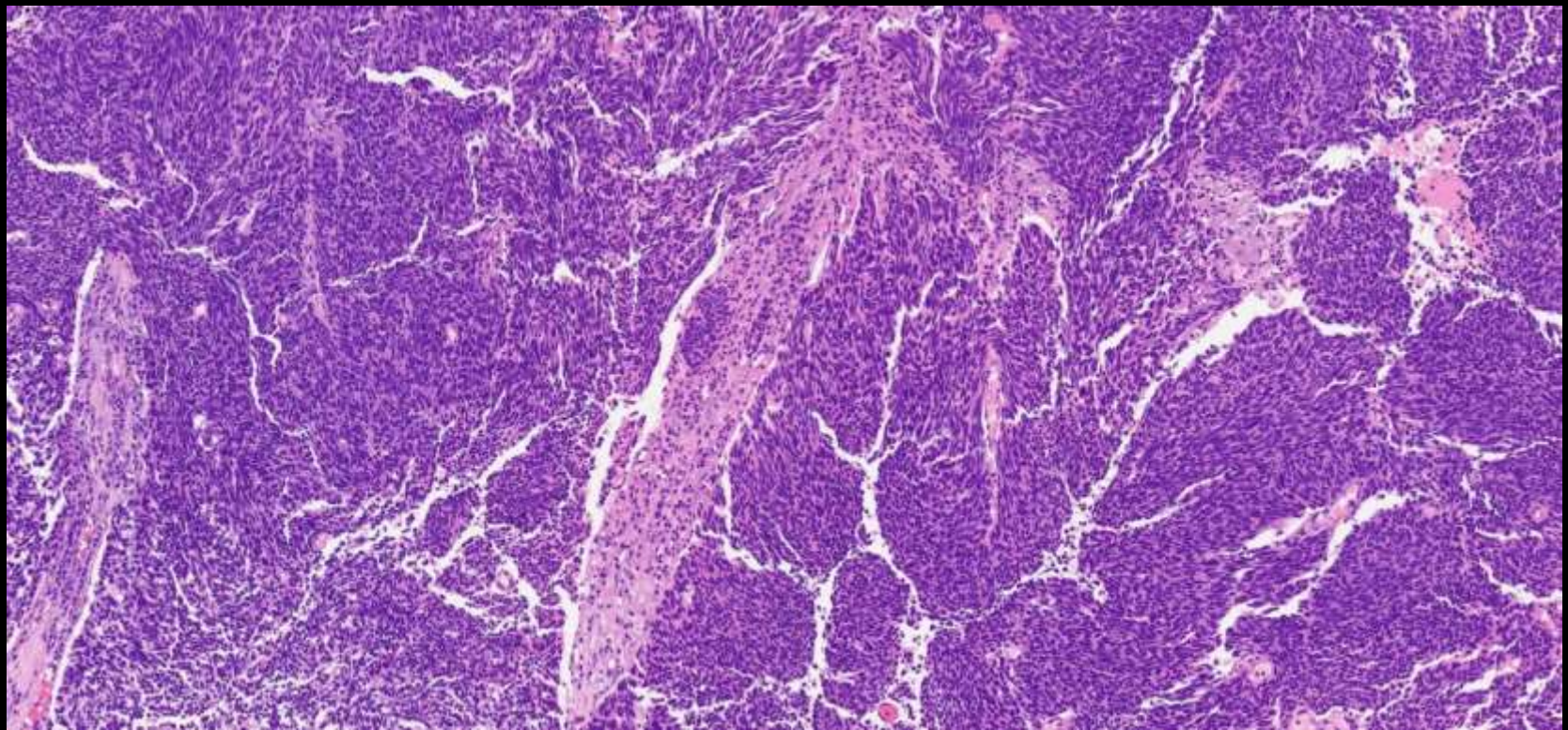


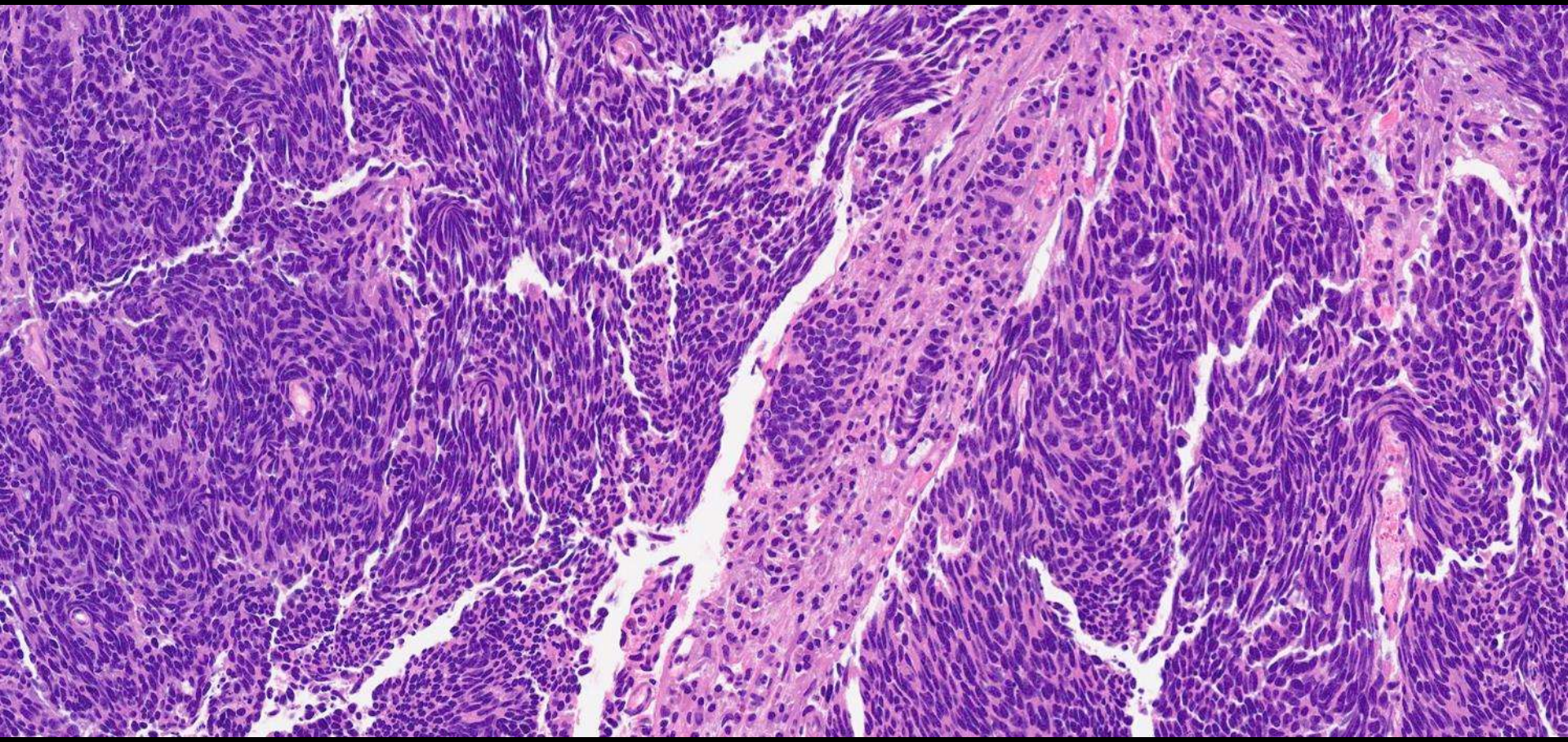






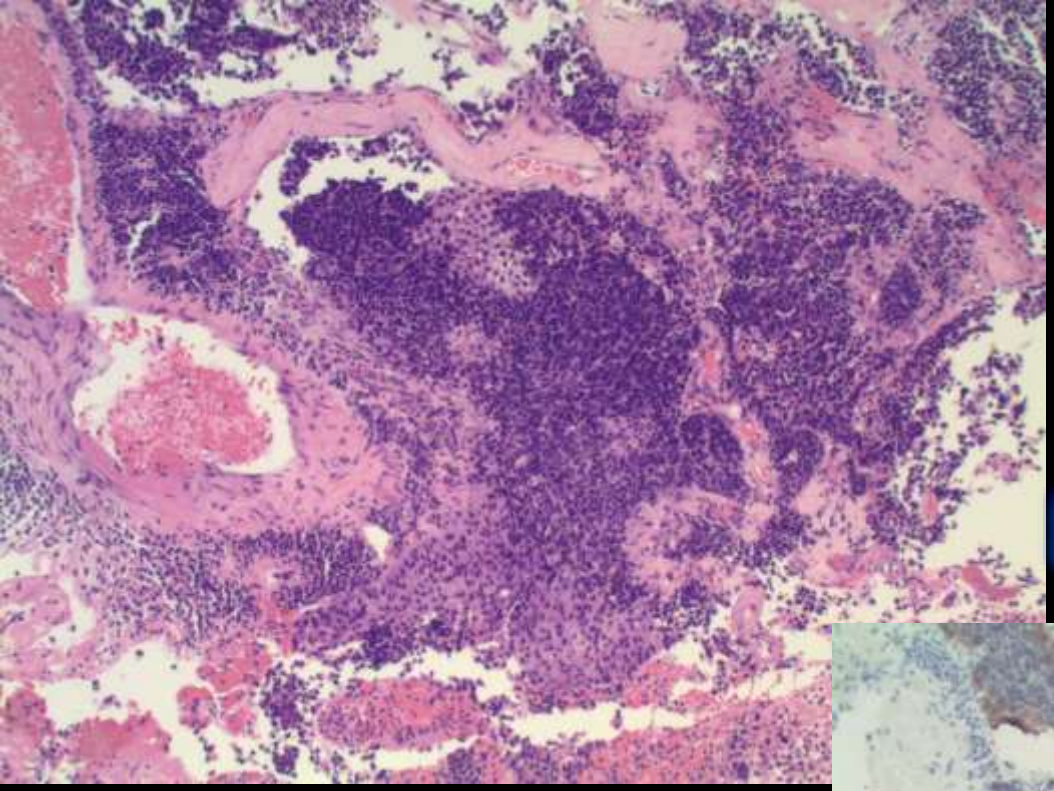






DDx

- Small cell carcinoma
- Mixed small cell carcinoma/urothelial carcinoma
- Poorly differentiated urothelial carcinoma
- Sarcomatoid urothelial carcinoma
- Lymphoma
- Rhabdomyosarcoma
- Ewing sarcoma
- Metastatic carcinoma



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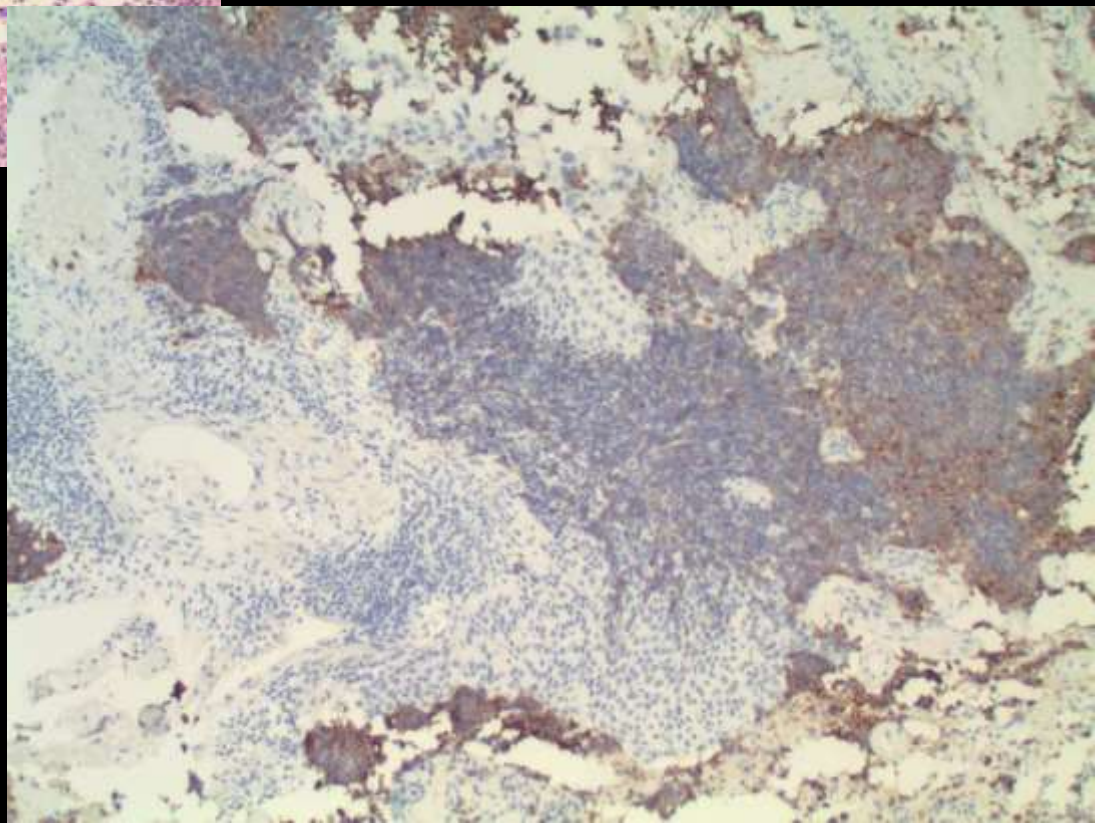
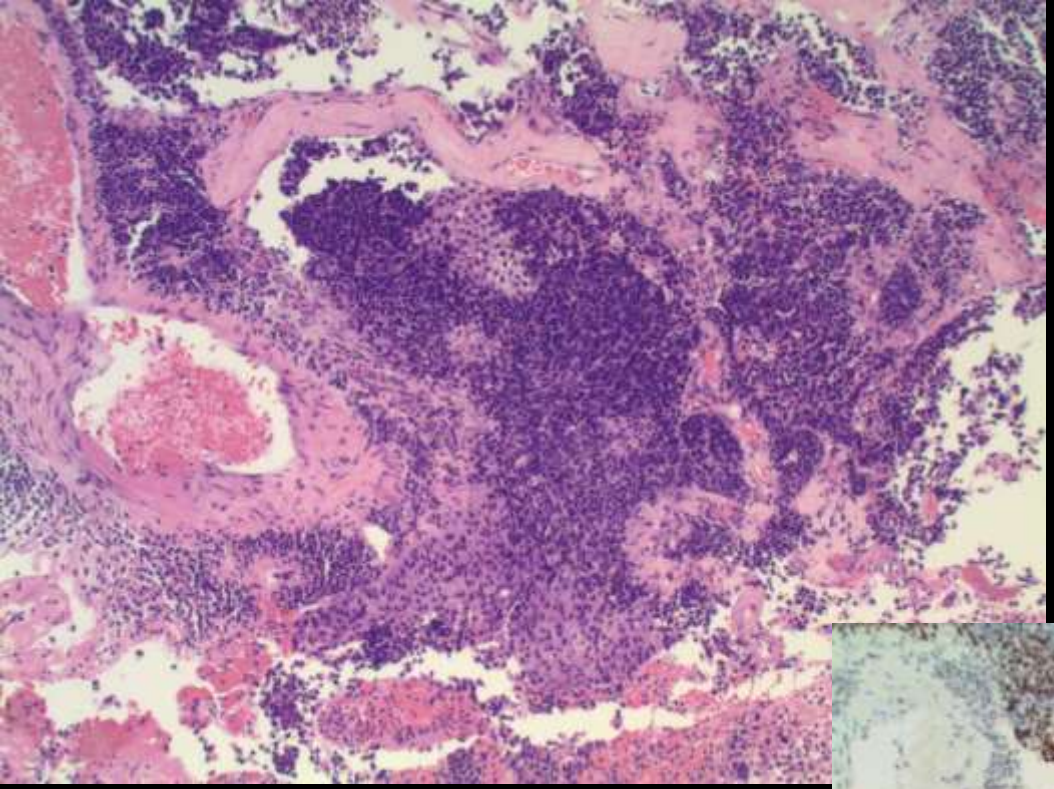
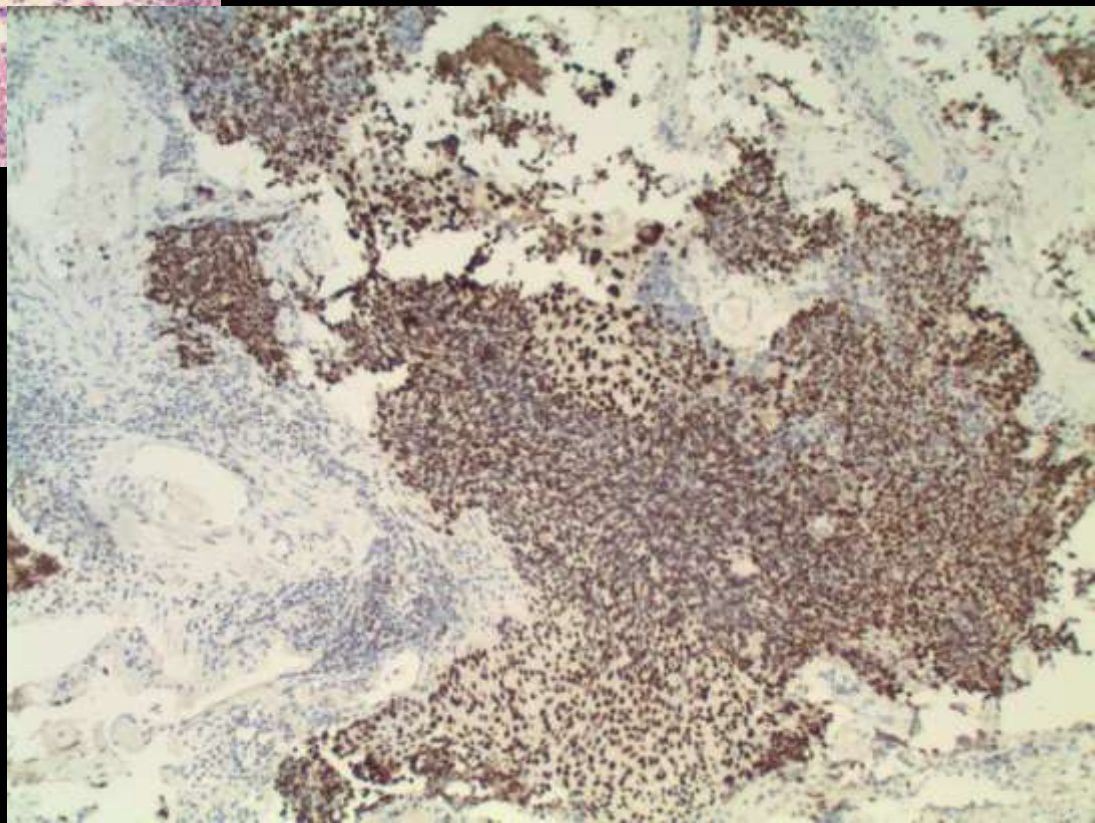
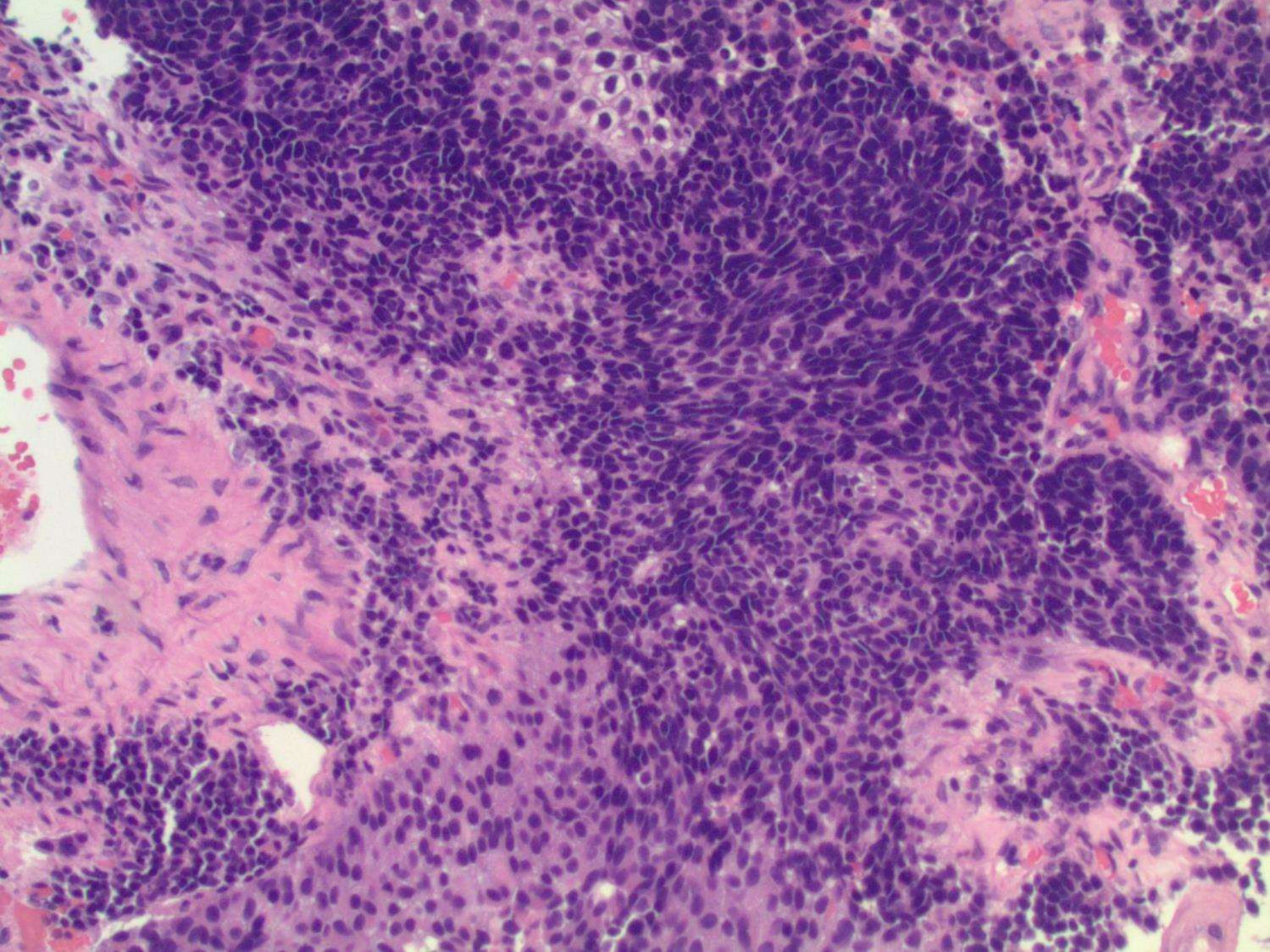
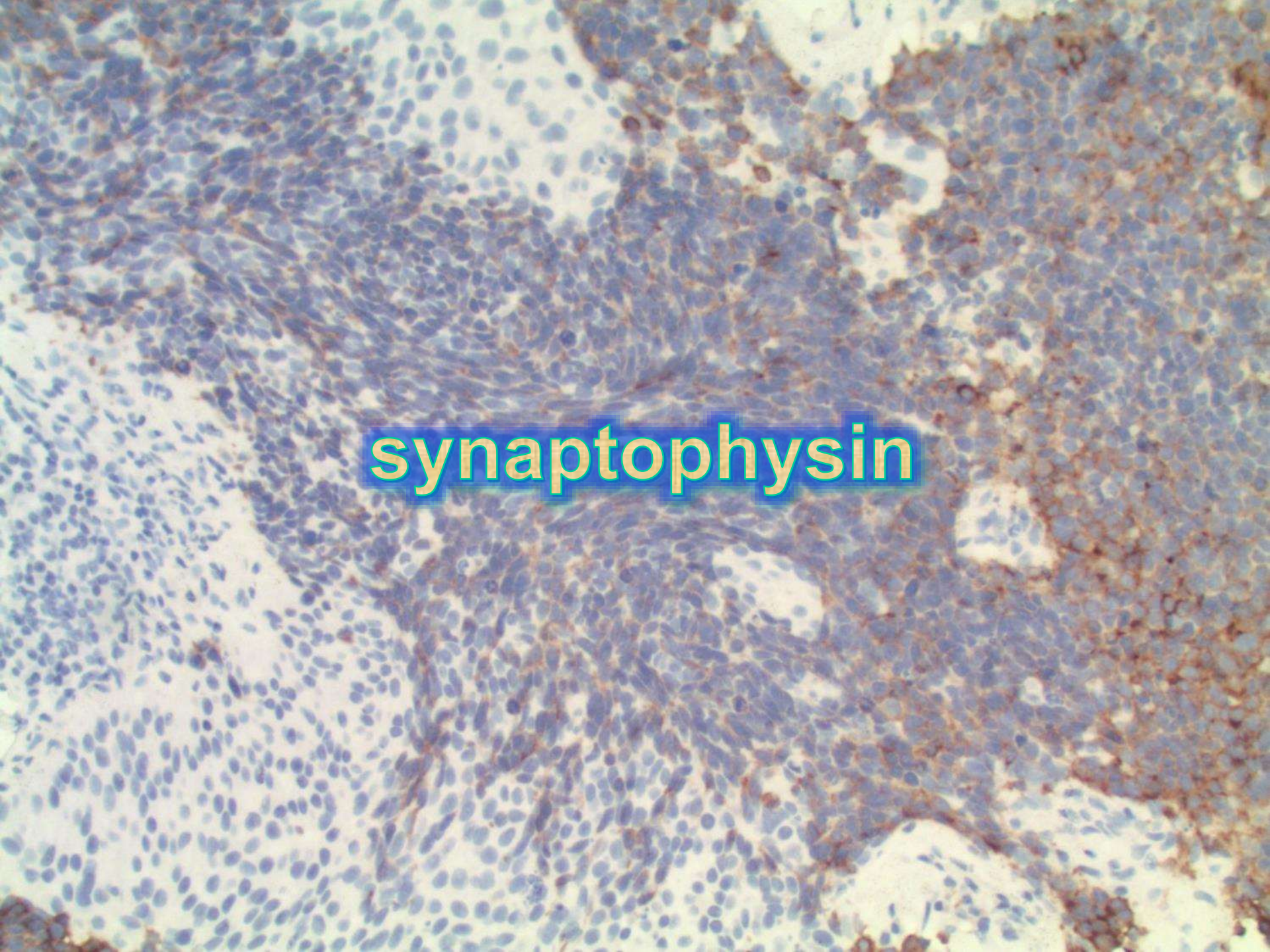




GATA3



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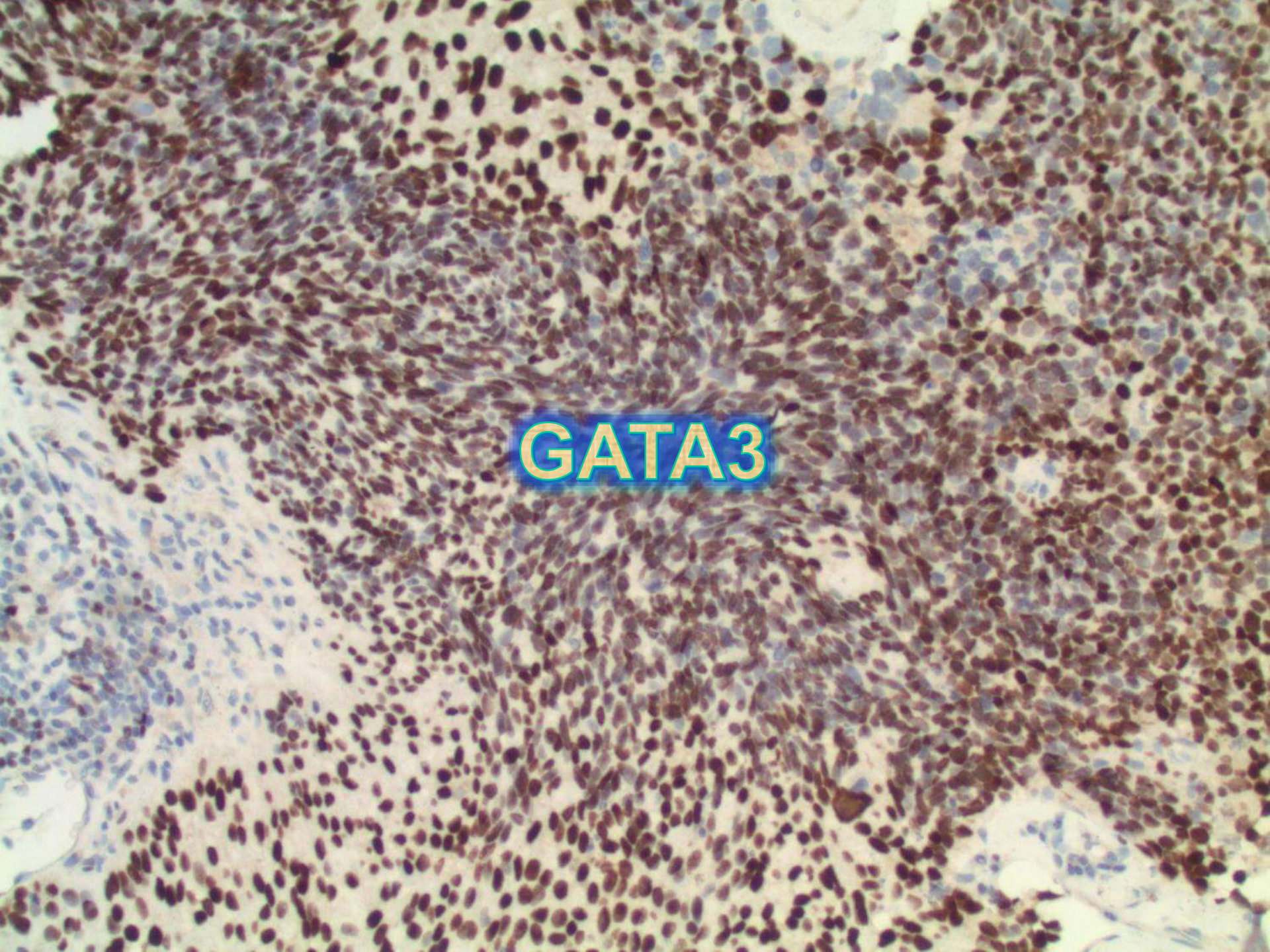
GATA3

Final Dx

- **Mixed small cell carcinoma (90%) and urothelial carcinoma (10%)**

  [pT2 in other areas]

Human Pathology (2018) 79, 57–65

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Original contribution

Small cell carcinoma of the urinary bladder: a clinicopathological and immunohistochemical analysis of 81 cases☆,☆☆

Gang Wang MD, PhD[a], Li Xiao MD[a], Miao Zhang MD, PhD[a], Ashish M. Kamat MD[b], Arlene Siefker-Radtke MD[c], Colin P. Dinney MD[b], Bogdan Czerniak MD, PhD[a], Charles C. Guo MD[a,*]

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Received 11 January 2018; revised 25 April 2018; accepted 4 May 2018

Keywords:
Bladder cancer;
Small cell carcinoma;
Urothelial carcinoma;
Neuroendocrine differentiation;
Immunohistochemistry;
Retinoblastoma gene

Summary Small cell carcinoma (SmCC) of the bladder is a rare disease. We retrospectively studied a large series of bladder SmCC from a single institution. The patients included 69 men and 12 women with a mean age of 68 years. Most bladder SmCCs were presented at advanced stage, with tumors invading the muscularis propria and beyond (n = 77). SmCC was pure in 27 cases and mixed with other histologic types in 54 cases, including urothelial carcinoma (UC) (n = 32), UC in situ (n = 26), glandular (n = 14), micropapillary (n = 4), sarcomatoid (n = 4), squamous (n = 3), and plasmacytoid (n = 1) features. Most SmCCs expressed neuroendocrine markers synaptophysin (41/56), chromogranin (26/55), and CD56 (39/41); however, they did not express UC luminal markers CK20 (0/17), GATA3 (1/30), and uroplakin II (1/22). Some SmCCs showed focal expression of CK5/6 (9/25), a marker for the basal molecular subtype. Furthermore, expression of the retinoblastoma 1 (*RB1*) gene protein was lost in most of the bladder SmCCs (2/23). The patients' survival was significantly associated with cancer stage but did not show a significant difference between mixed and pure SmCCs. Compared with conventional UC at similar stages, SmCC had a worse prognosis only when patients developed metastatic diseases. In conclusion, bladder SmCC is an aggressive disease that is frequently present at an advanced stage. A fraction of SmCCs show a basal molecular subtype, which may underlie its good response to chemotherapy. Inactivation of the *RB1* gene may be implicated in the oncogenesis of bladder SmCC.

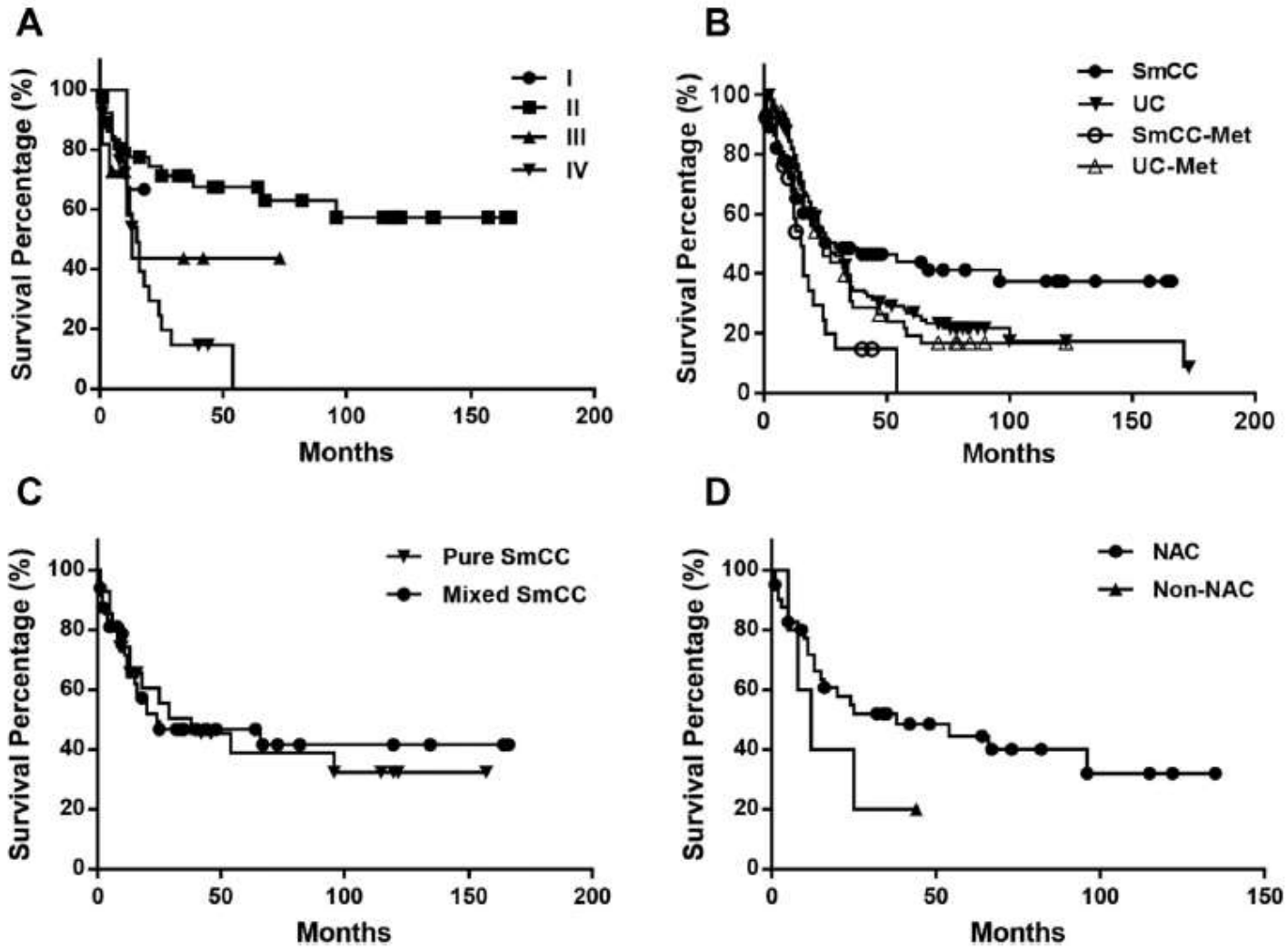
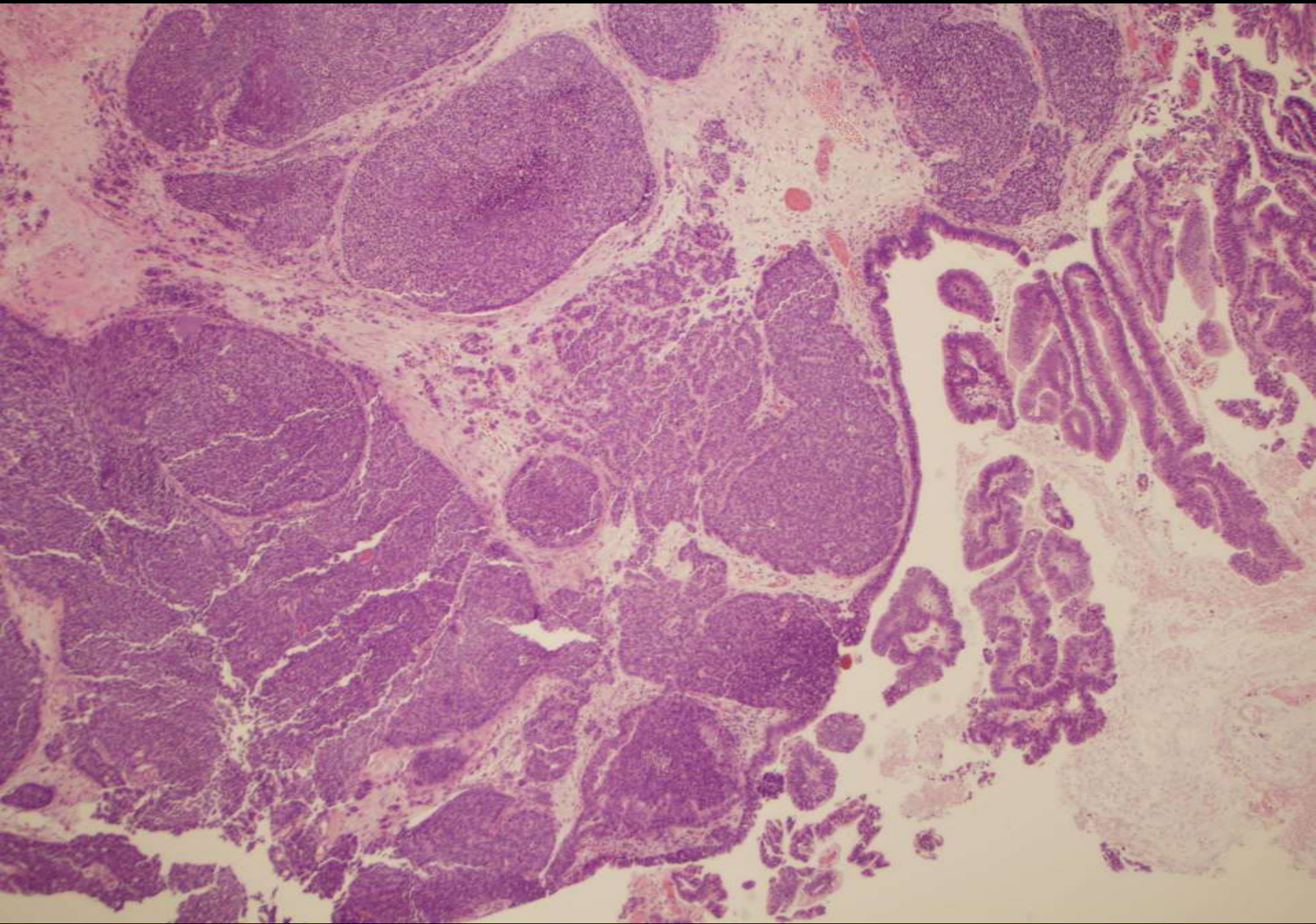
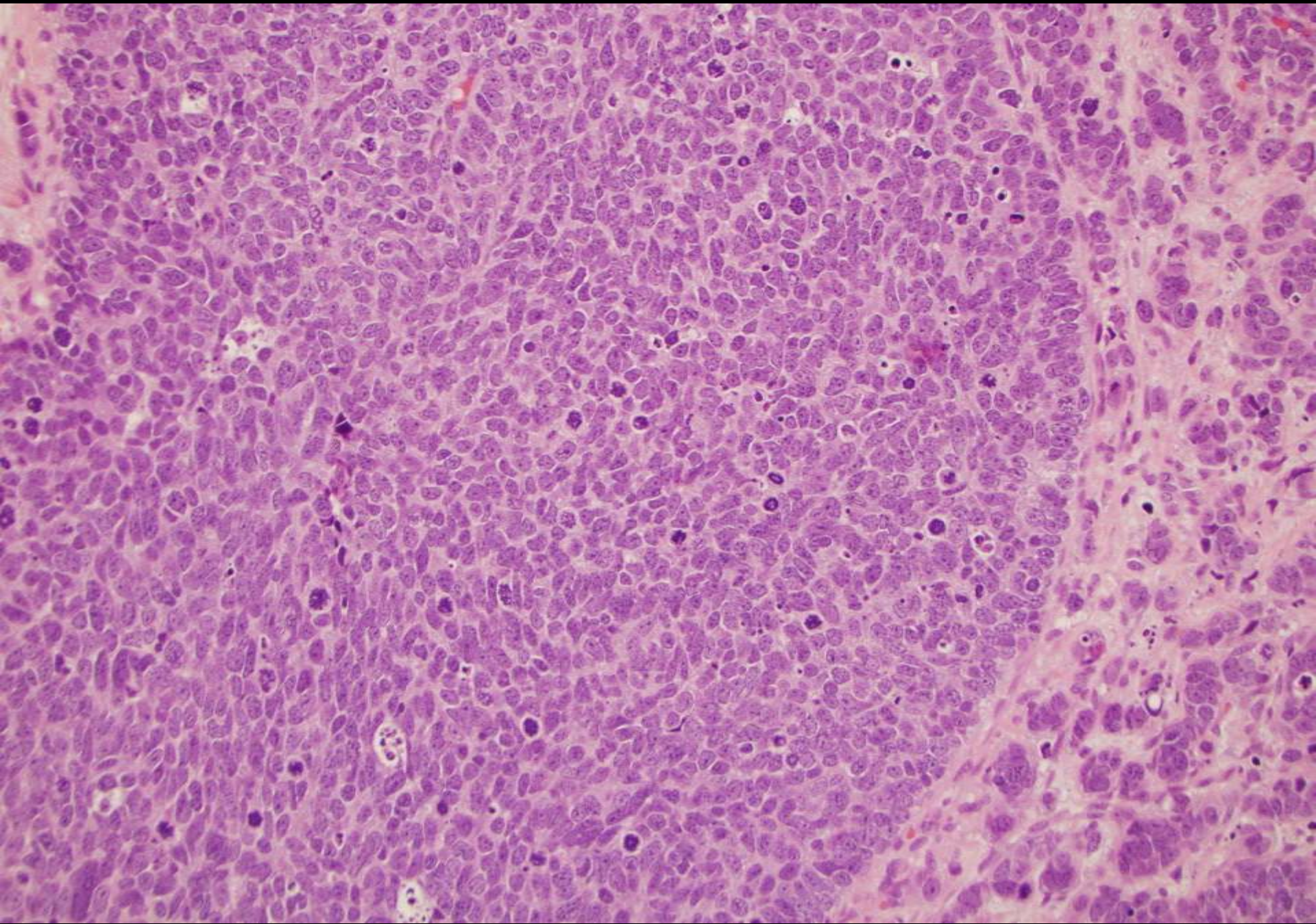


Fig. 5 Kaplan-Meier survival analyses of bladder SmCC. A, Cancer-specific survival is significantly associated with cancer stage. B, Survival is compared between SmCC and conventional UC. B, Cancer-specific survival for metastatic SmCC is significantly worse than that for metastatic UC, but there is no significant difference when the tumors are localized. C, Survival does not show a significant difference between mixed and pure SmCC. D, Neoadjuvant chemotherapy (NAC) significantly prolongs survival.

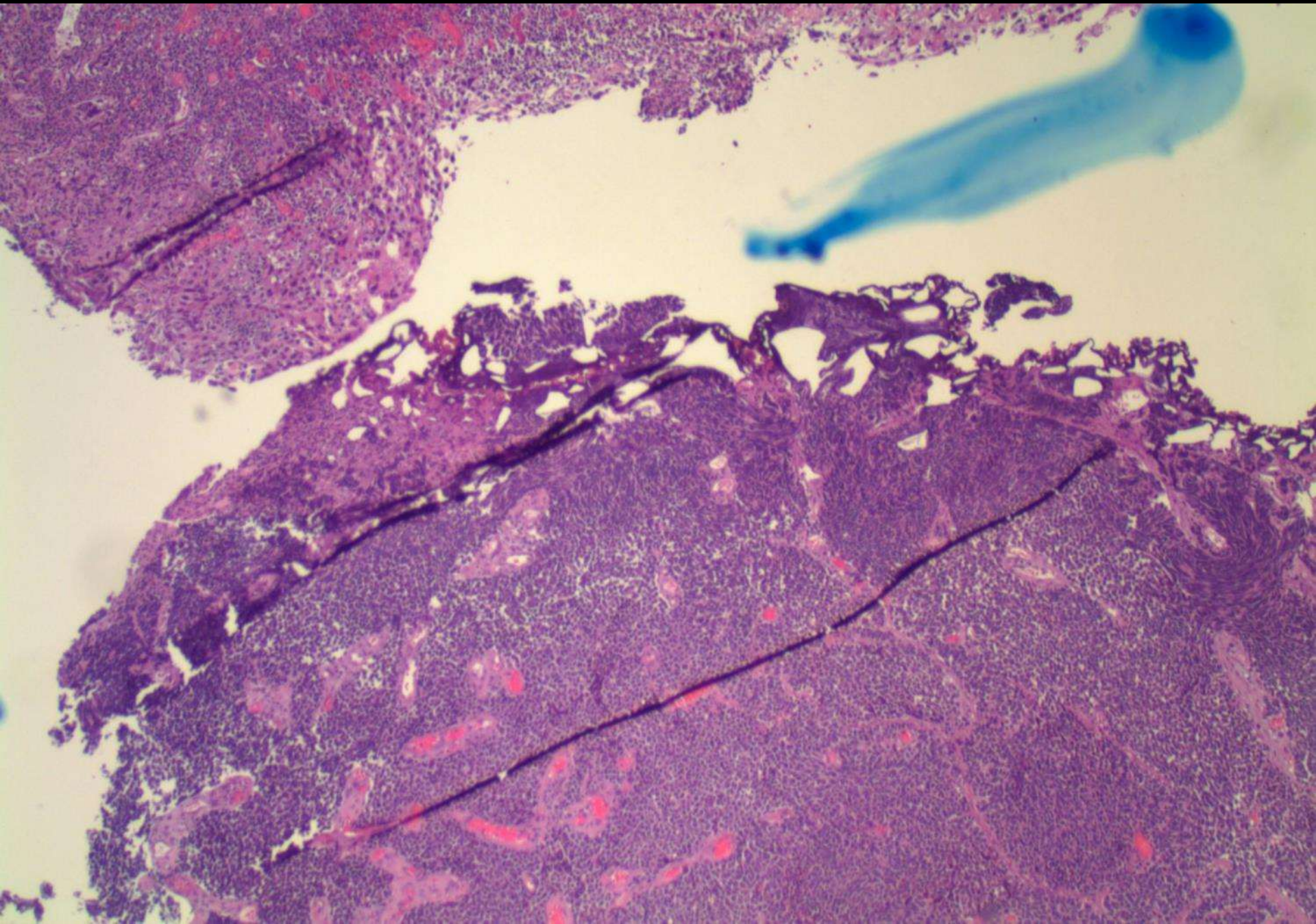
DIFFERENT CASE: mixed small cell ca/adenocarcinoma



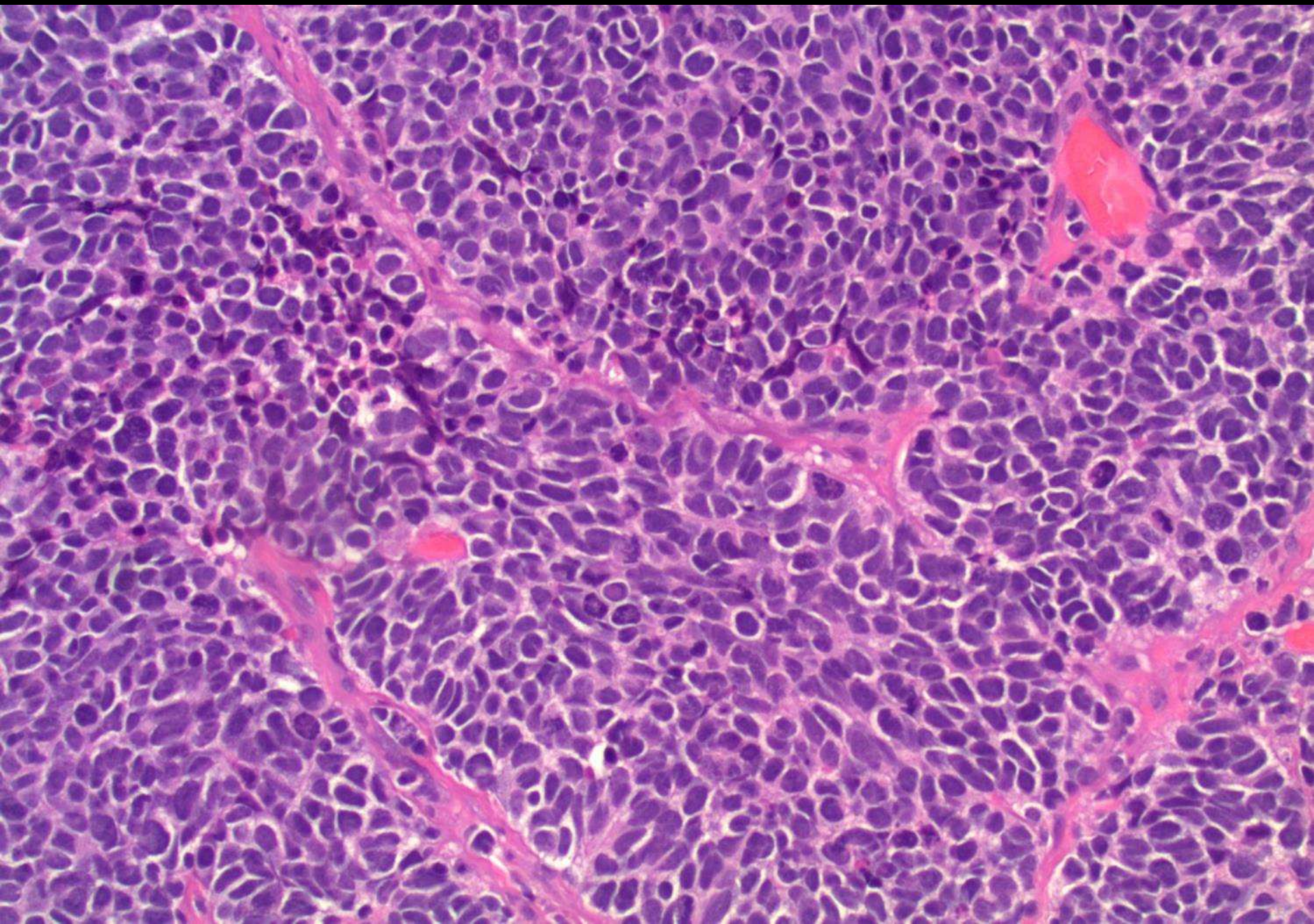
DIFFERENT CASE: mixed small cell ca/adenocarcinoma



DIFFERENT CASE: mixed small cell ca/urothelial ca



DIFFERENT CASE: mixed small cell ca/urothelial ca



Molecular Genetic Evidence for a Common Clonal Origin of Urinary Bladder Small Cell Carcinoma and Coexisting Urothelial Carcinoma

Liang Cheng,*† Timothy D. Jones,* Ryan P. McCarthy,* John N. Eble,* Mingsheng Wang,* Gregory T. MacLennan,‡ Antonio Lopez-Beltran,§ Ximing J. Yang,¶ Michael O. Koch,† Shaobo Zhang,* Chong-Xian Pan,‖ and Lee Ann Baldridge*

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In most cases, small-cell carcinoma of the urinary bladder is admixed with other histological types of bladder carcinoma. To understand the pathogenetic relationship between the two tumor types, we analyzed histologically distinct tumor cell populations from the same patient for loss of heterozygosity (LOH) and X chromosome inactivation (in female patients). We examined five polymorphic microsatellite markers located on chromosome 3p25-26 (D3S3050), chromosome 9p21 (IFNA and D9S171), chromosome 9q32-33 (D9S177), and chromosome 17p13 (TP53) in 20 patients with small-cell carcinoma of the urinary bladder and concurrent urothelial carcinoma. DNA samples were prepared from formalin-fixed, paraffin-embedded tissue sections using laser-assisted microdissection. A nearly identical pattern of allelic loss was observed in the two tumor types in all cases, with an overall frequency of allelic loss of 90% (18 of 20 cases). Three patients showed different allelic loss patterns in the two tumor types at a single locus; however, the LOH patterns at the remaining loci were identical. Similarly, the same pattern of nonrandom X chromosome inactivation was present in both carcinoma components in the four cases analyzed. Concordant genetic alterations and X chromosome inactivation between small-cell carcinoma and coexisting urothelial carcinoma suggest that both tumor components originate from the same cells in the urothelium.
(Am J Pathol 2005, 166:1533–1539)

Small-cell carcinoma of the urinary bladder histologically resembles that occurring in the lung and has been reported with an increasing frequency in recent years.[1–10] It has been estimated to represent 0.5% of bladder malignancies and develops more frequently in older men, with hematuria as the most common presenting symptom.[8] Small-cell carcinoma of the urinary bladder behaves aggressively, often with locally advanced or metastatic disease at the time of presentation.[11]

Over the years, three principal theories have been proposed to account for the development of small-cell carcinoma in the urinary bladder. The first theory is that small-cell carcinomas originate from multipotential, undifferentiated cells or stem cells in the urothelium.[5,8,12,13] The frequent association of this tumor with coexisting urothelial carcinoma supports this theory. The second theory is that these tumors arise from neuroendocrine cells within normal or metaplastic urothelium.[14] The third theory is that small-cell carcinomas are derived from an undefined population of submucosal neuroendocrine cells.[1] In this study, we investigated the clonal relationships between small-cell carcinoma and coexisting urothelial carcinoma using loss of heterozygosity (LOH) and X chromosome inactivation analysis.

Materials and Methods

Patients

Twenty patients with small-cell carcinoma of the urinary bladder and concurrent urothelial carcinoma were included in our study. Archival materials from the 20 cases

Accepted for publication January 13, 2005.

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Human Pathology (2014) 45, 1682–1687

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Original contribution

GATA3 expression in small cell carcinoma of bladder and prostate and its potential role in determining primary tumor origin☆

Stephania Martins Bezerra MD[a], Tamara Levin Lotan MD[a,b], Sheila Friedrich Faraj MD[a], Sarah Karram MD[a], Rajni Sharma PhD[a], Mark Schoenberg MD[b,c], Trinity J. Bivalacqua MD, PhD[b,c], George Jabboure Netto MD[a,b,c,*]

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Keywords:
Small cell carcinoma;
Bladder;
Prostate;
Lung;
GATA3
immunohistochemistry

Summary GATA3 is a sensitive marker for urothelial carcinoma. We here evaluate, for the first time, GATA3 expression in small cell carcinoma of bladder and prostate and assess its utility in the differential diagnosis with small cell carcinoma of lung primary. Archival tissues from 60 small cell carcinomas (12 bladder, 15 lung, and 33 prostate primary cases) were used to build 2 tissue microarrays. We also assessed whole slide sections from 10 additional primary small cell carcinomas of bladder. GATA3 nuclear expression was evaluated using standard immunohistochemistry. Intensity (weak, moderate, and strong) and extent of expression were assessed in each tissue microarray spot. Extent positivity was categorized as focal (1%-25%), multifocal (>25%), and diffuse (>75%). Nuclear GATA3 expression was encountered in 7 bladder (7/22, 32%) and 2 lung (2/15, 13%) small cell carcinomas. All 33 primary prostate small cell carcinomas were negative. Among bladder tumors, strong and diffuse (>75%) GATA3 labeling was seen in 3 cases (3/22, 14%); focal positivity was observed in the 4 remaining cases (4/22, 18%). Both positive lung cases had only focal positivity. Our study is the first to reveal GATA3 expression in the small subset of lung small cell carcinoma that should be taken into consideration in assigning site of origin in advanced small cell carcinoma cases. Our novel finding of GATA3 positivity in one-third of bladder small cell carcinoma is of potential value in differentiating small cell carcinomas of prostate origin from those of bladder origin.

Table 2 Presence of GATA3 nuclear expression in small cell carcinoma of bladder, prostate, and lung origin

Tumor site	GATA3 positive (any positivity)	GATA3 negative	*P*
Bladder	7/22 (32%)	15/22 (68%)	.003
Prostate	0/33 (0%)	33/33 (100%)	
Lung	2/15 (13%)	13/15 (87%)	

Table 5 Performance characteristics of presence of positive of GATA3 expression for the diagnosis of bladder small cell carcinoma

Site of origin	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Bladder *vs* other sites (prostate or lung)	31.8	96	77.7	76.1
Bladder *vs* prostate	31.8	100	100	68.7
Bladder *vs* lung	31.8	88	77.7	50

Human Pathology (2014) **45**, 1682–1687

Human Pathology (2013) 44, 2227–2233

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Original contribution

Frequent *TMPRSS2-ERG* rearrangement in prostatic small cell carcinoma detected by fluorescence in situ hybridization: the superiority of fluorescence in situ hybridization over ERG immunohistochemistry

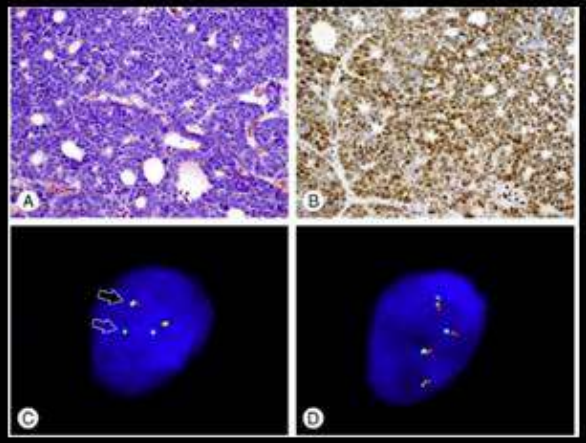
Lindsay A. Schelling MD[a,1], Sean R. Williamson MD[a,1], Shaobo Zhang MD[a], Jorge L. Yao MD[b], Mingsheng Wang MD[a], Jiaoti Huang MD[c], Rodolfo Montironi MD[d], Antonio Lopez-Beltran MD[e], Robert E. Emerson MD[a], Muhammad T. Idrees MD[a], Adeboye O. Osunkoya MD[f], Yan-Gao Man MD[g], Gregory T. MacLennan MD[h], Lee Ann Baldridge BA, HT(AJCP)[a], Eva Compérat MD[i], Liang Cheng MD[a,j,*]

Summary Small cell carcinoma of the prostate is both morphologically and immunohistochemically similar to small cell carcinoma of other organs such as the urinary bladder or lung. *TMPRSS2-ERG* gene fusion appears to be a highly specific alteration in prostatic carcinoma that is frequently shared by small cell carcinoma. In adenocarcinoma, immunohistochemistry for the ERG protein product has been reported to correlate well with the presence of the gene fusion, although in prostatic small cell carcinoma, this relationship is not completely understood. We evaluated 54 cases of small cell carcinoma of the prostate and compared *TMPRSS2-ERG* gene fusion status by fluorescence in situ hybridization (FISH) to immunohistochemical staining with antibody to ERG. Of 54 cases of prostatic small cell carcinoma, 26 (48%) were positive for *TMPRSS2-ERG* gene fusion by FISH and 12 (22%) showed overexpression of ERG protein by immunohistochemistry. Of the 26 cases positive by FISH, 11 were also positive for ERG protein by immunohistochemistry. One tumor was positive by immunohistochemistry but negative by FISH. Urinary bladder small cell carcinoma (n = 25) showed negative results by both methods; however, 2 of 14 small cell carcinomas of other organs (lung, head, and neck) showed positive immunohistochemistry but negative FISH. Positive staining for ERG by immunohistochemistry is present in a subset of prostatic small cell carcinomas and correlates with the presence of *TMPRSS2-ERG* gene fusion. Therefore, it may be useful in confirming prostatic origin when molecular testing is not accessible. However, sensitivity and specificity of ERG immunohistochemistry in small cell carcinoma are decreased compared to FISH.

Table Comparison of immunohistochemical expression of ERG protein to *TMPRSS2-ERG* gene fusion by FISH in prostatic small cell carcinoma

	TMPRSS2-ERG FISH+	*TMPRSS2-ERG* FISH−	Total
ERG IHC+	11	1	12
ERG IHC−	15	27	42
Total	26	28	

NOTE. When compared to FISH, ERG protein immunohistochemistry (IHC) yielded a sensitivity of only 42% but a specificity of 96%.
Abbreviations: +, positive; −, negative.



TAKE HOME POINTS ON BLADDER SMALL CELL CA

- **Can mimic poorly diff/cauterized urothelial ca**
  - Not all always all that “small” !
- **May express GATA3**
  - Usually + for other typical NE markers
- **Can occur in pure or mixed forms**
  - When mixed: may still be helpful to include %
- **Findings admixed traditional urothelial carcinoma helpful to r/o metastasis/direct invasion**

22-0207

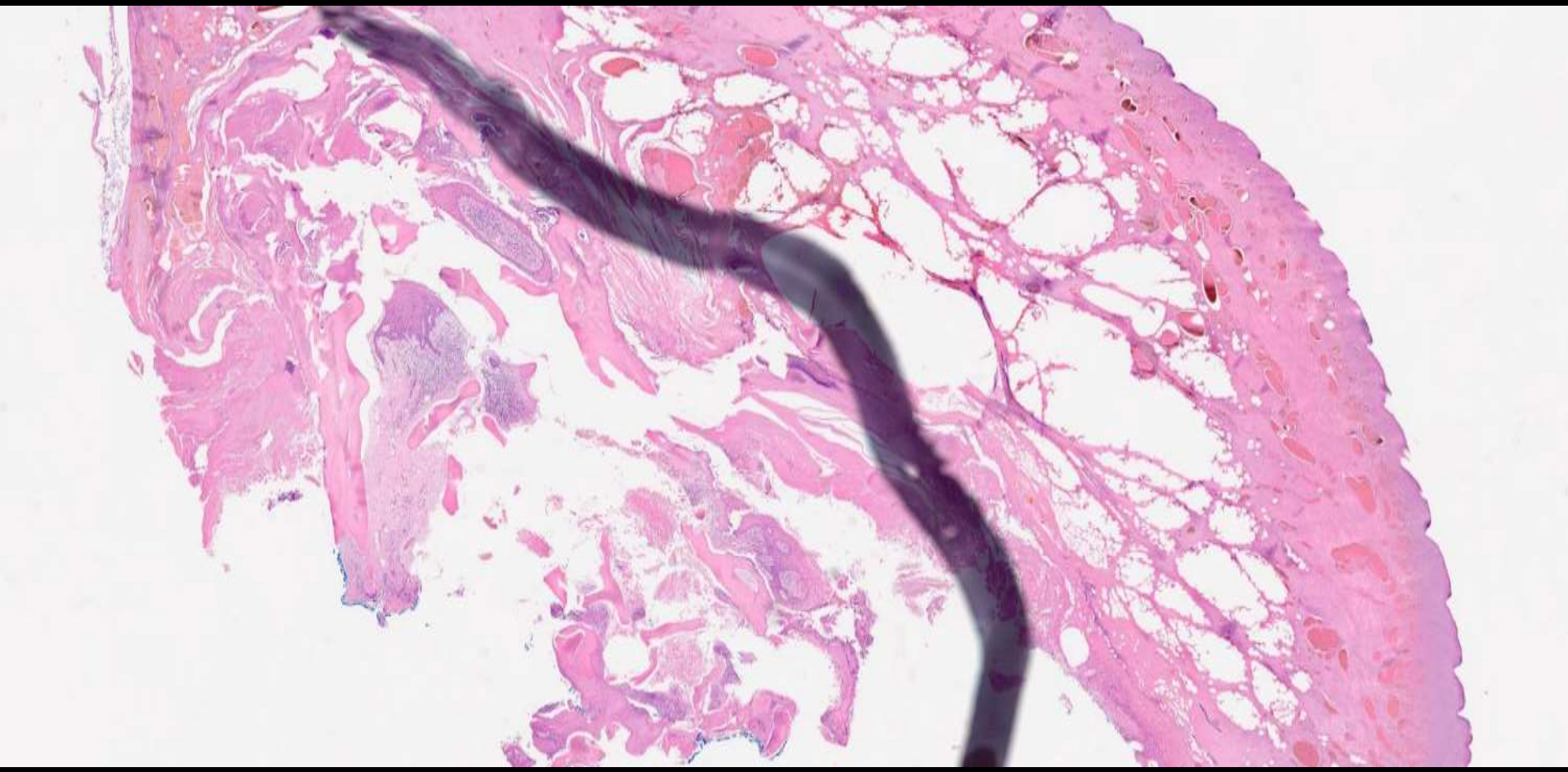
Ankur Sangoi; El Camino Hospital

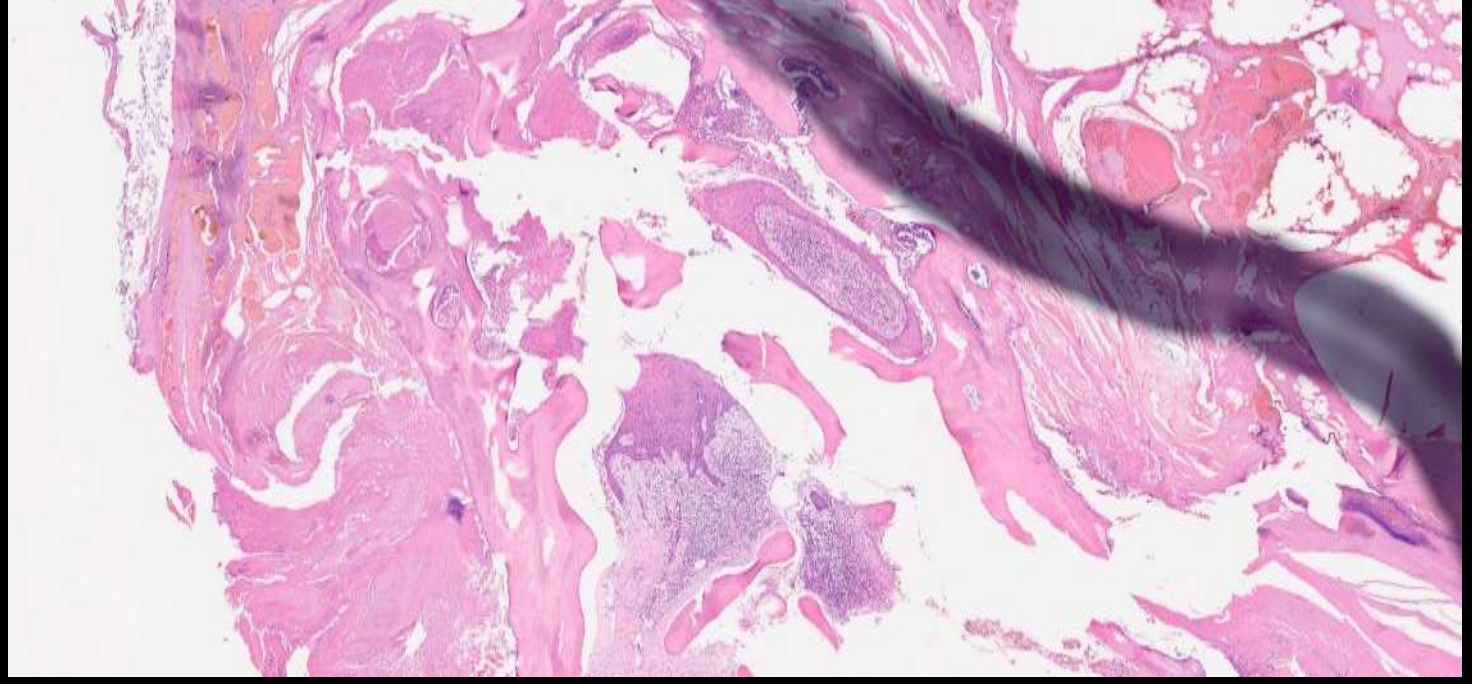
Direct links to scanned slides:

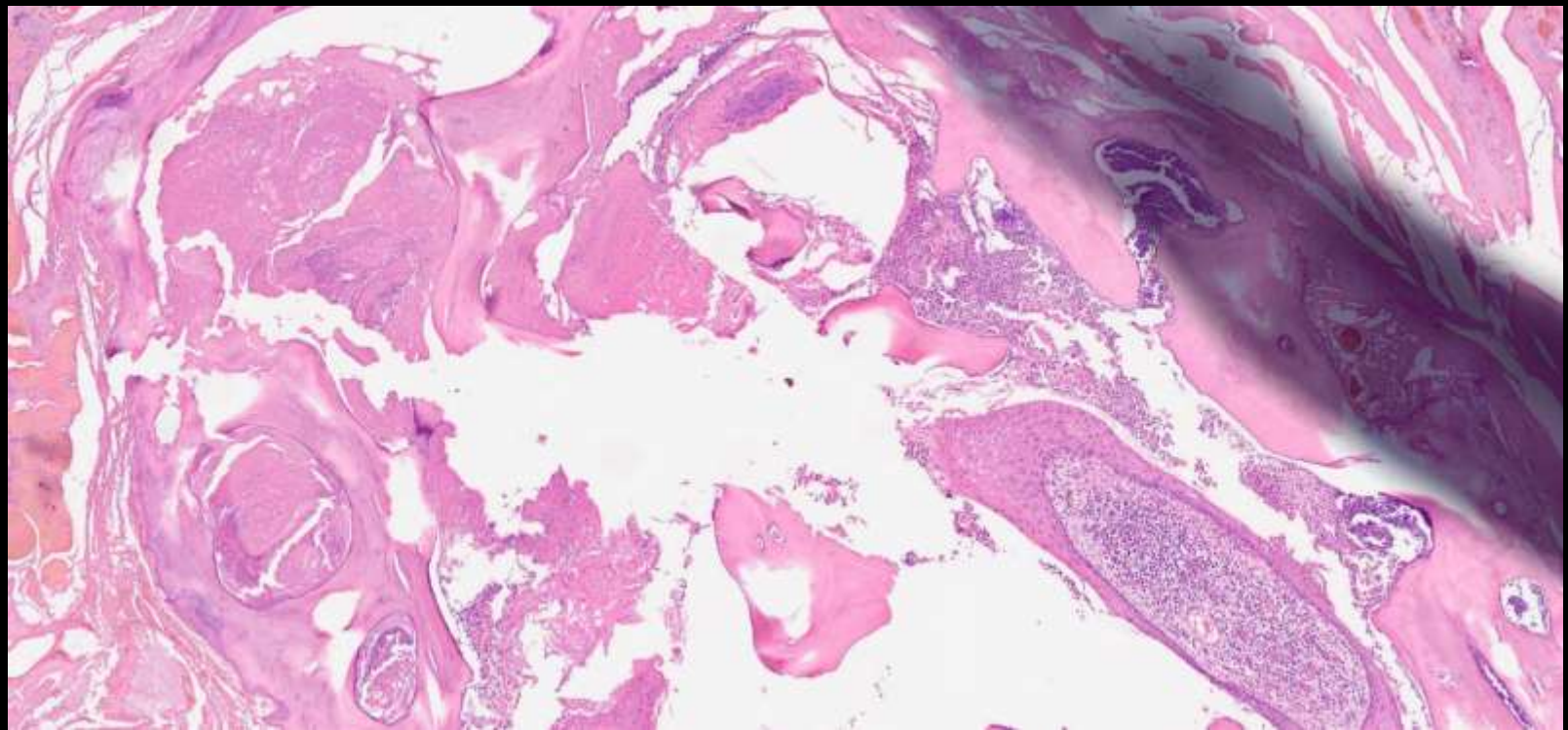
Finger → https://pathpresenter.net/#/public/display?token=2af15c0f

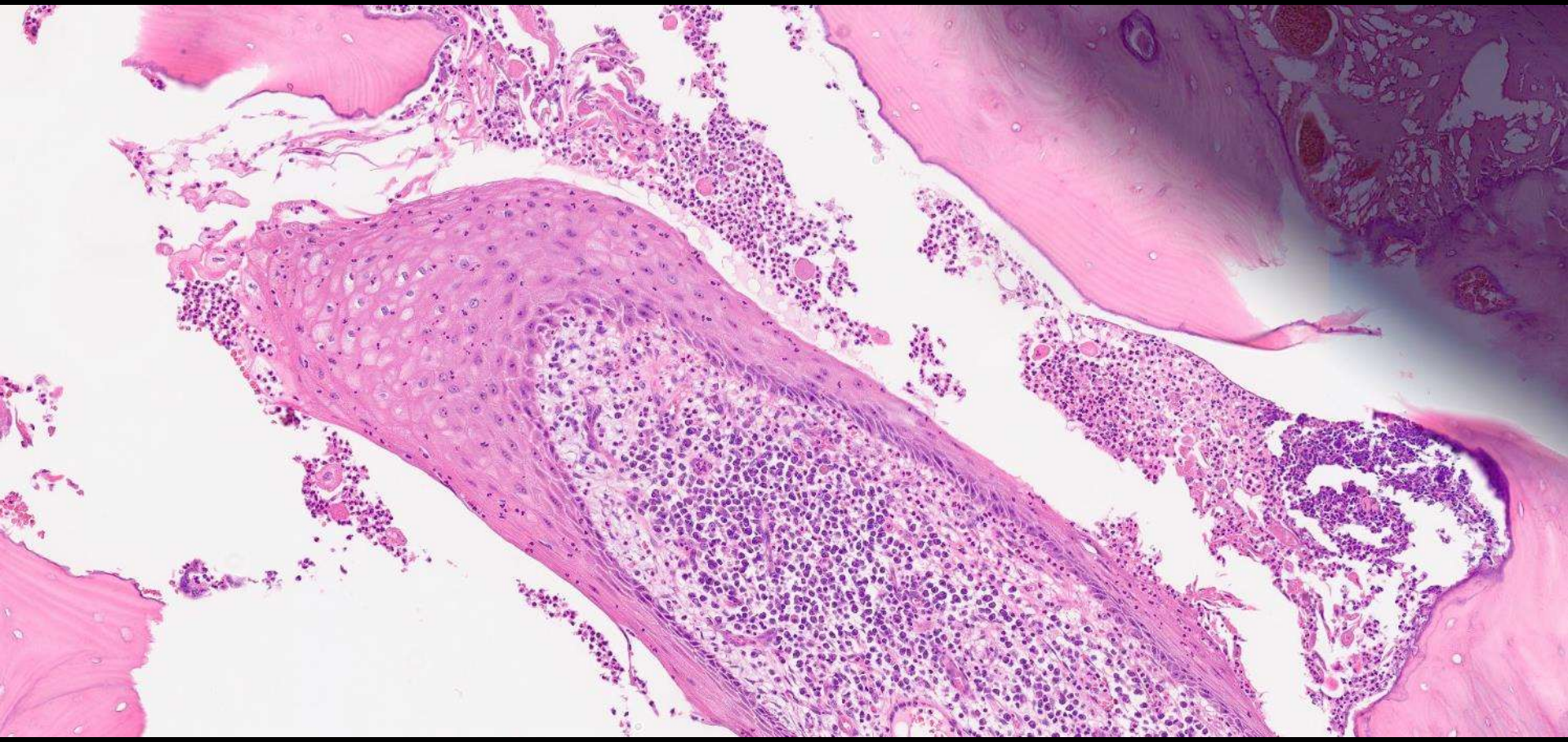
Toe → https://pathpresenter.net/#/public/display?token=5b48b317

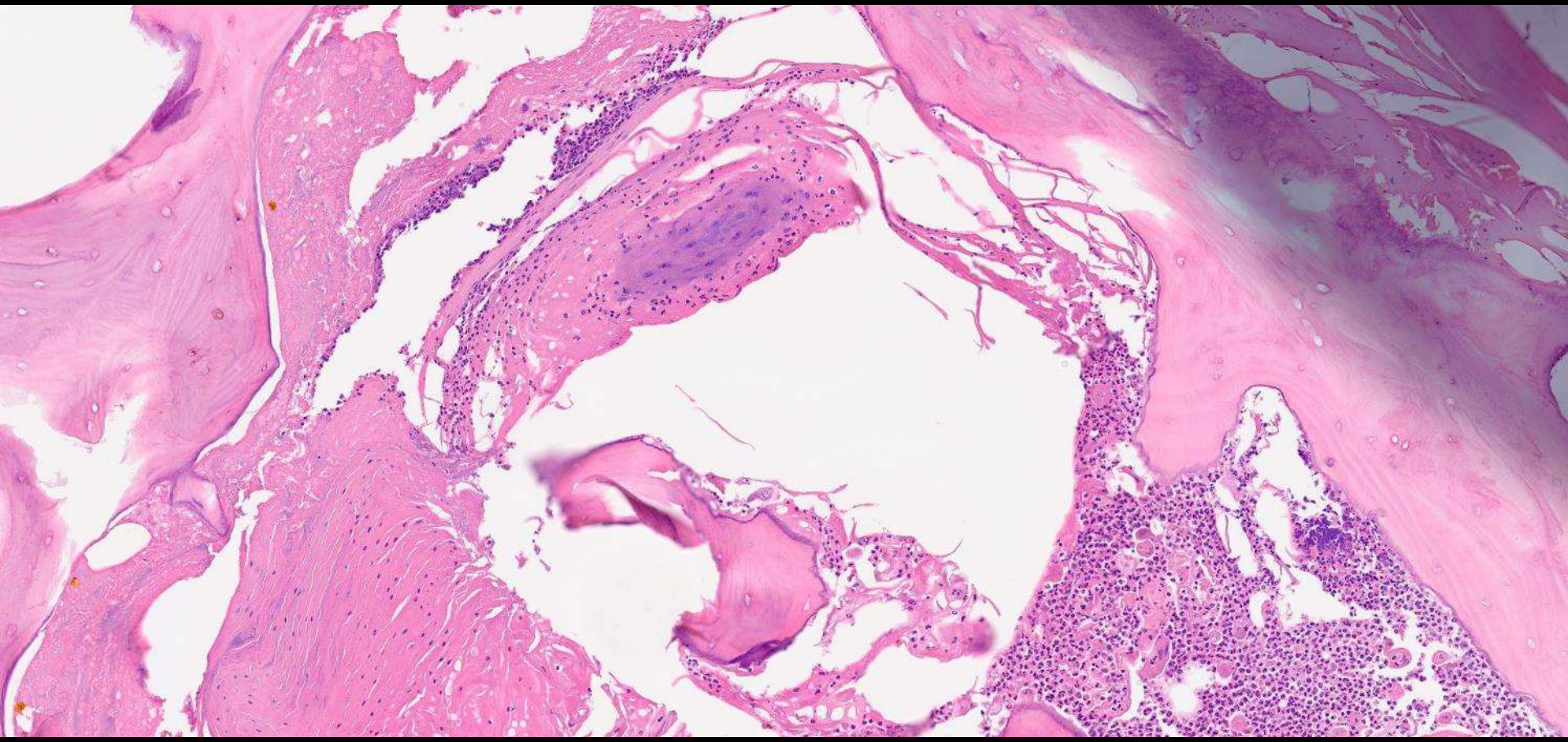
Elderly F with chronic ulcers of left finger and right toe. Amputation of both digits performed. Dx?

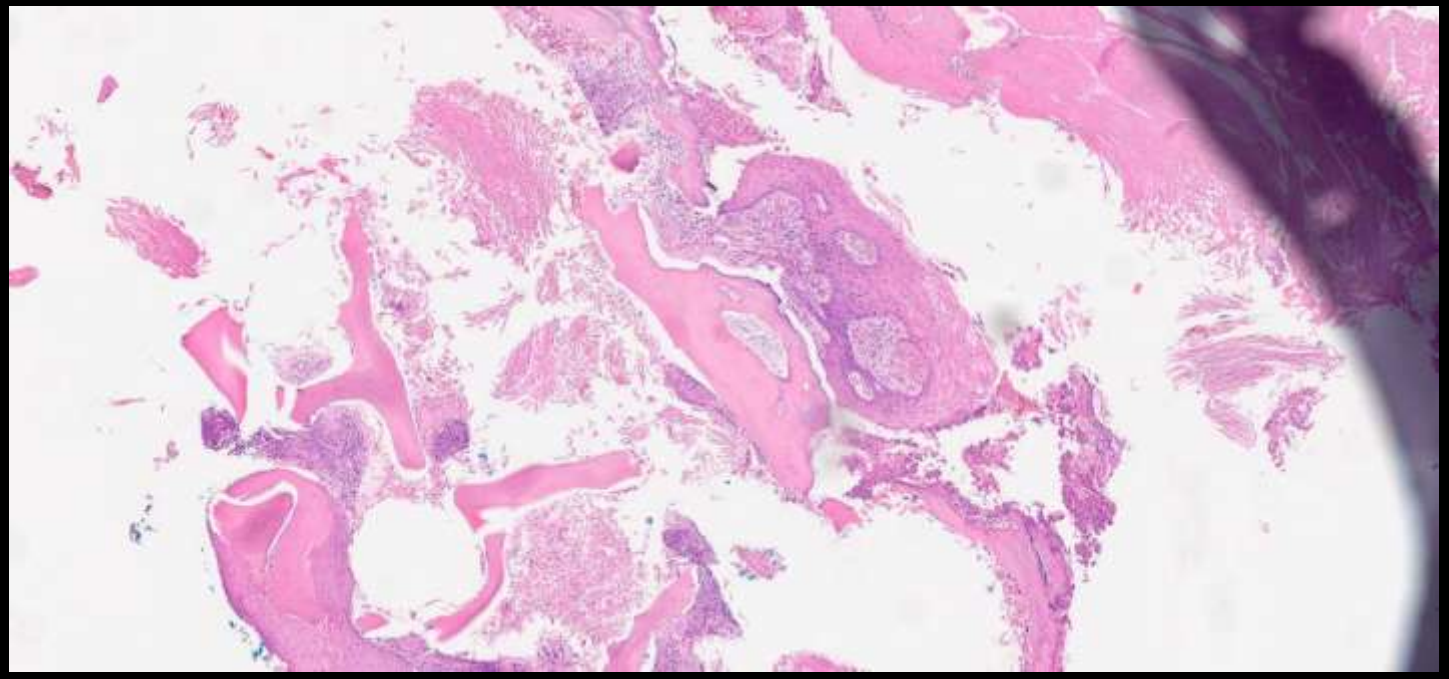


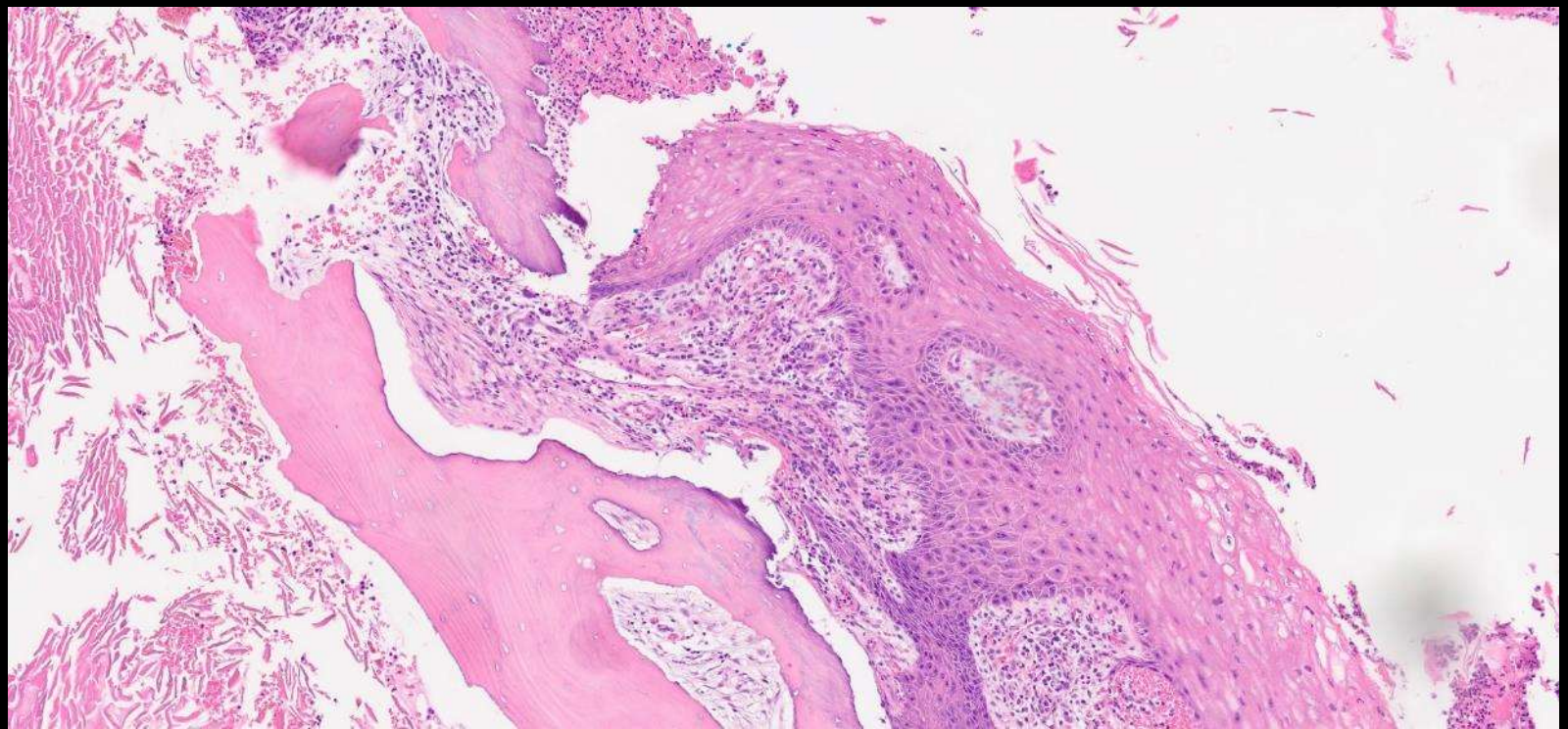


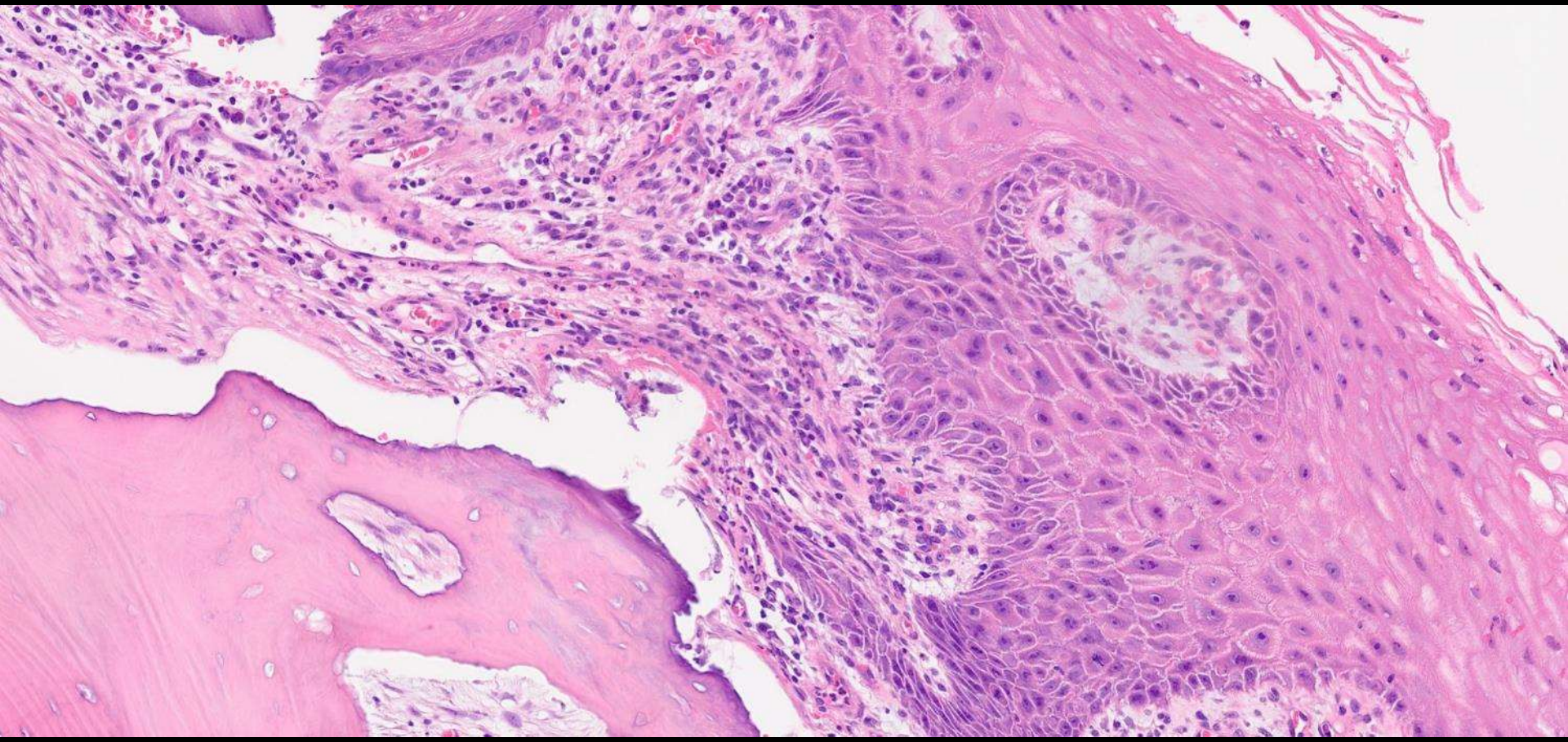


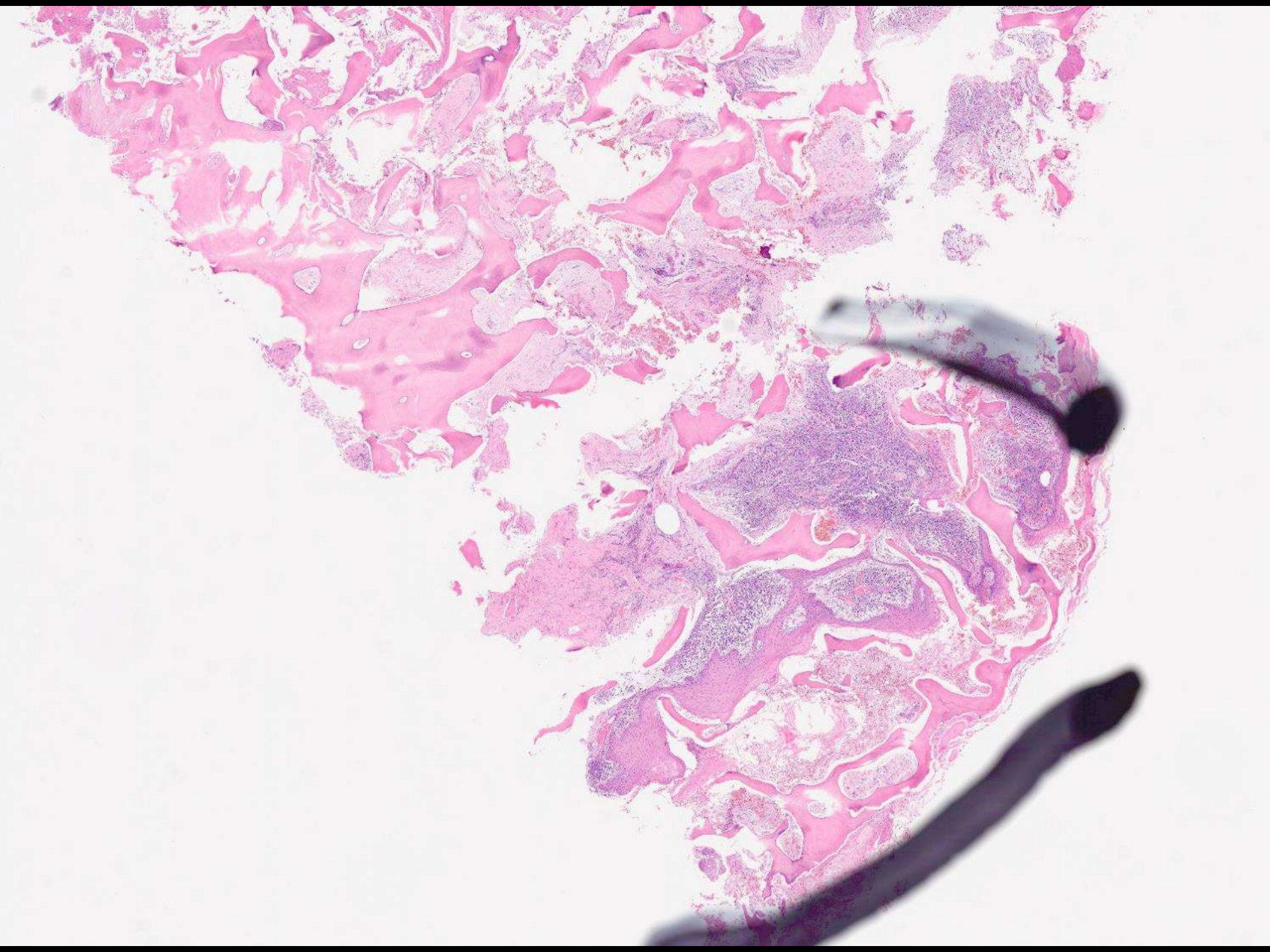


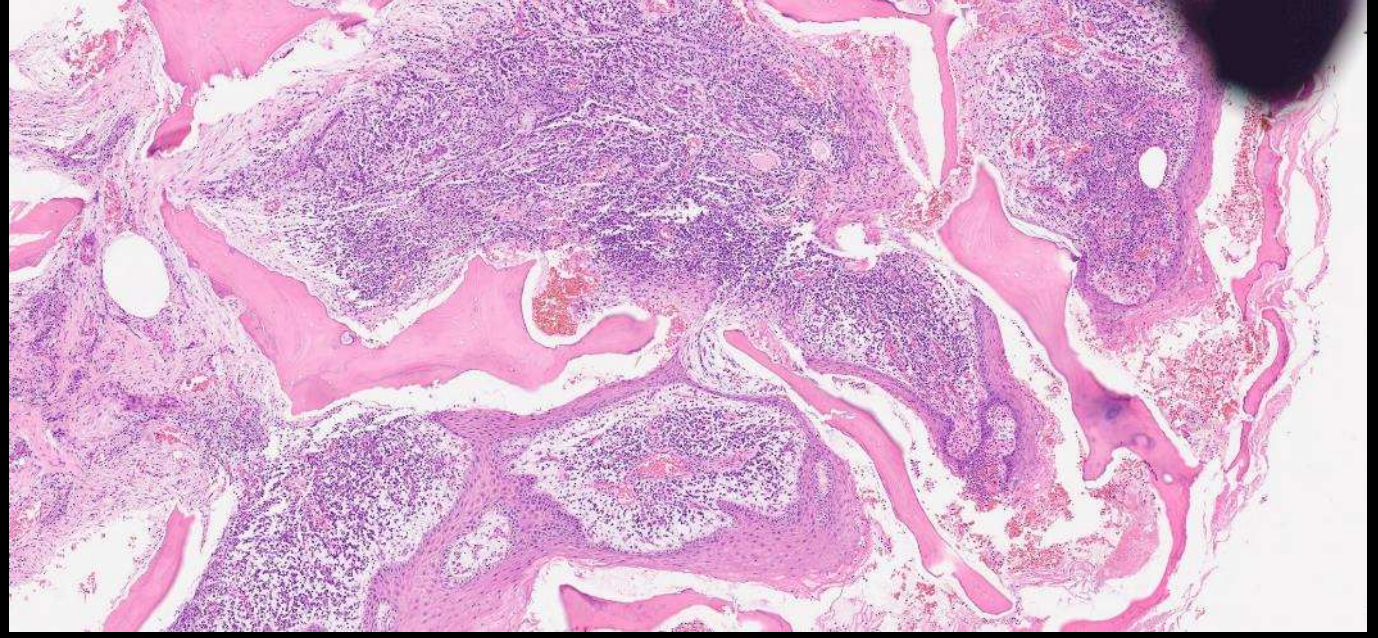


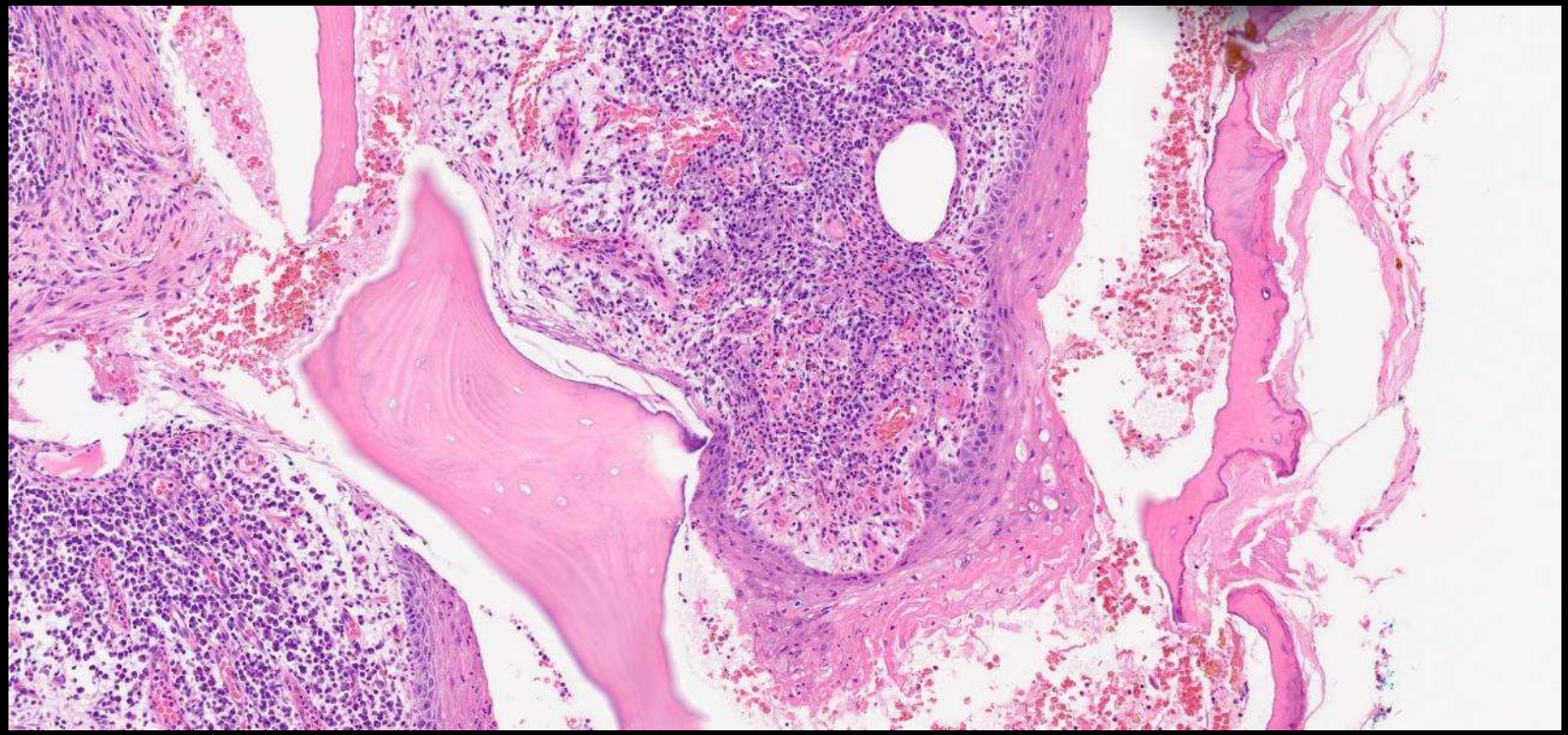


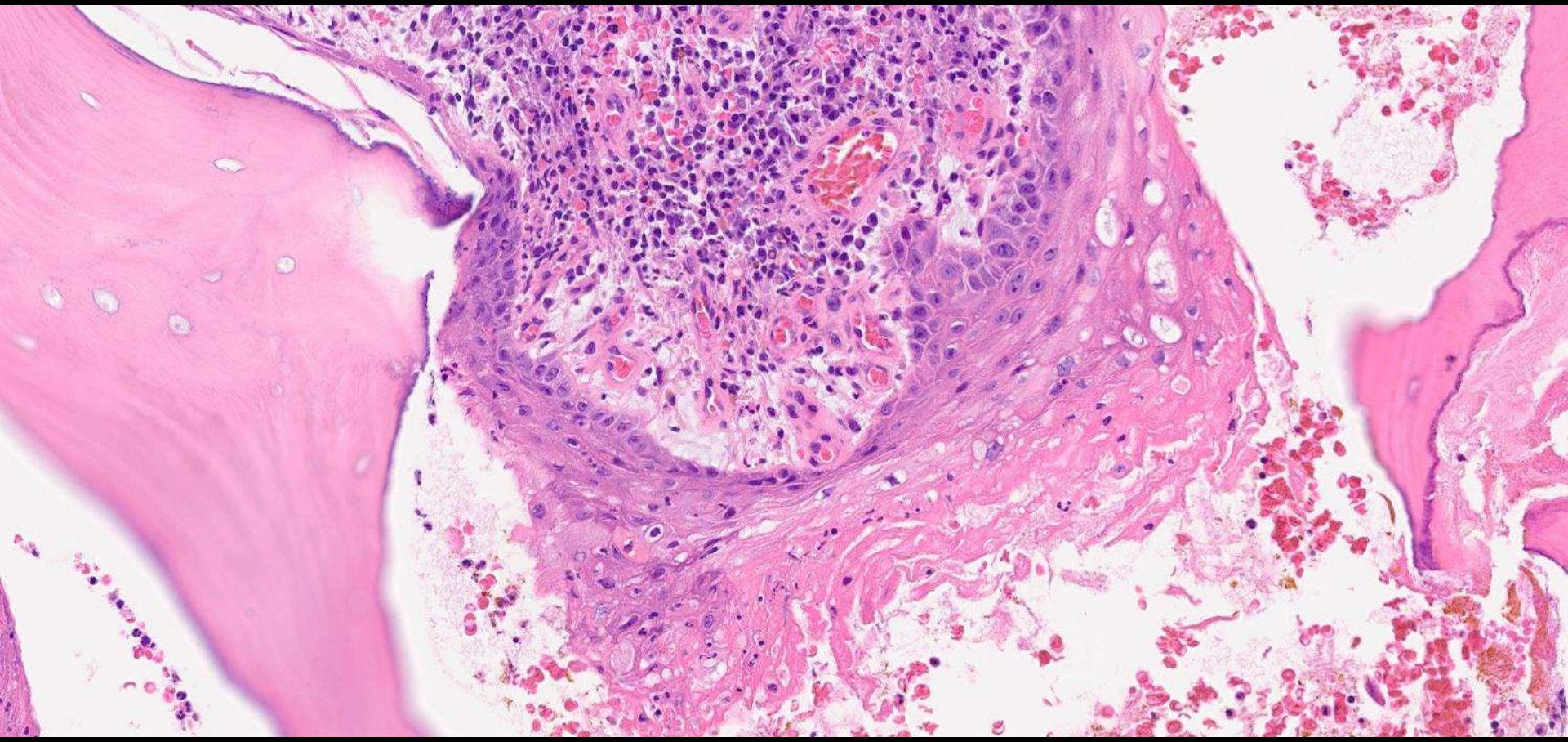


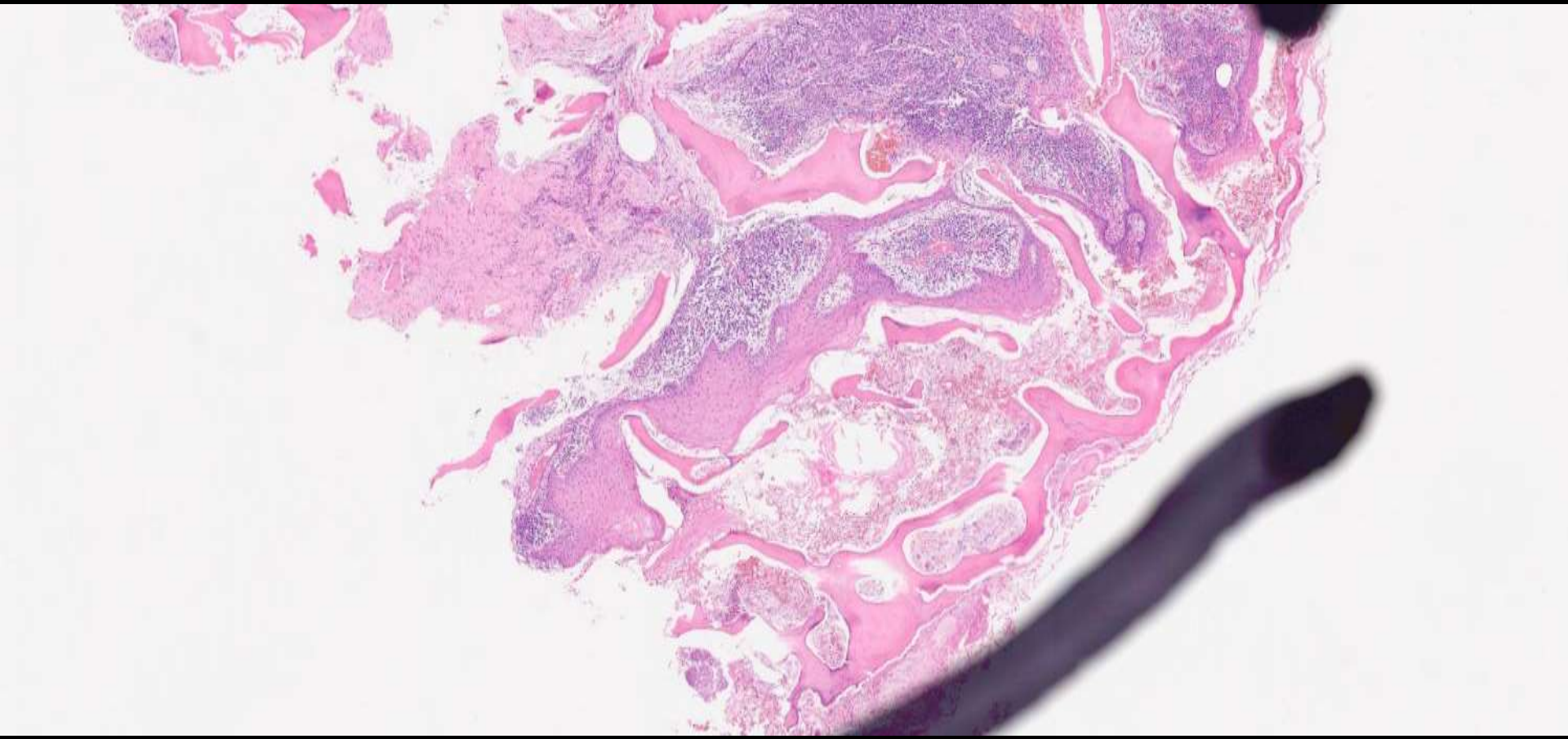


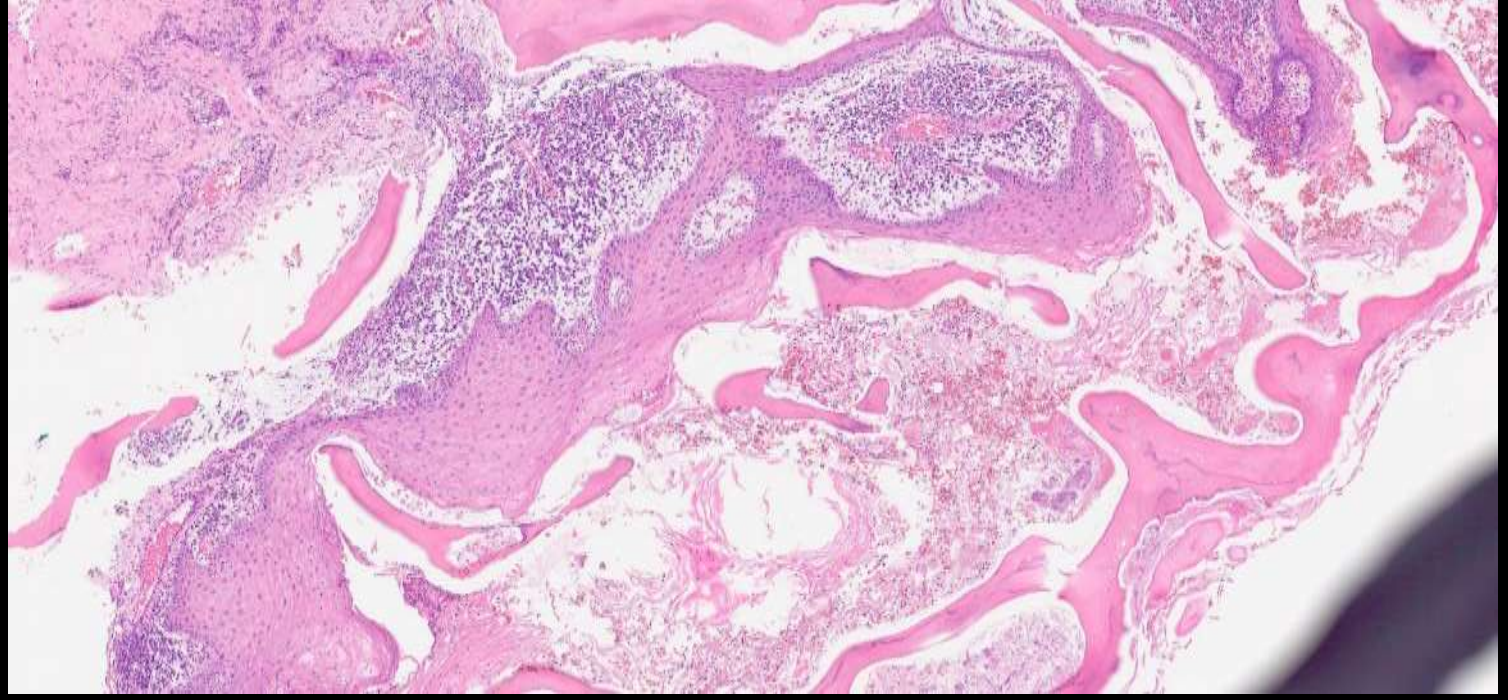


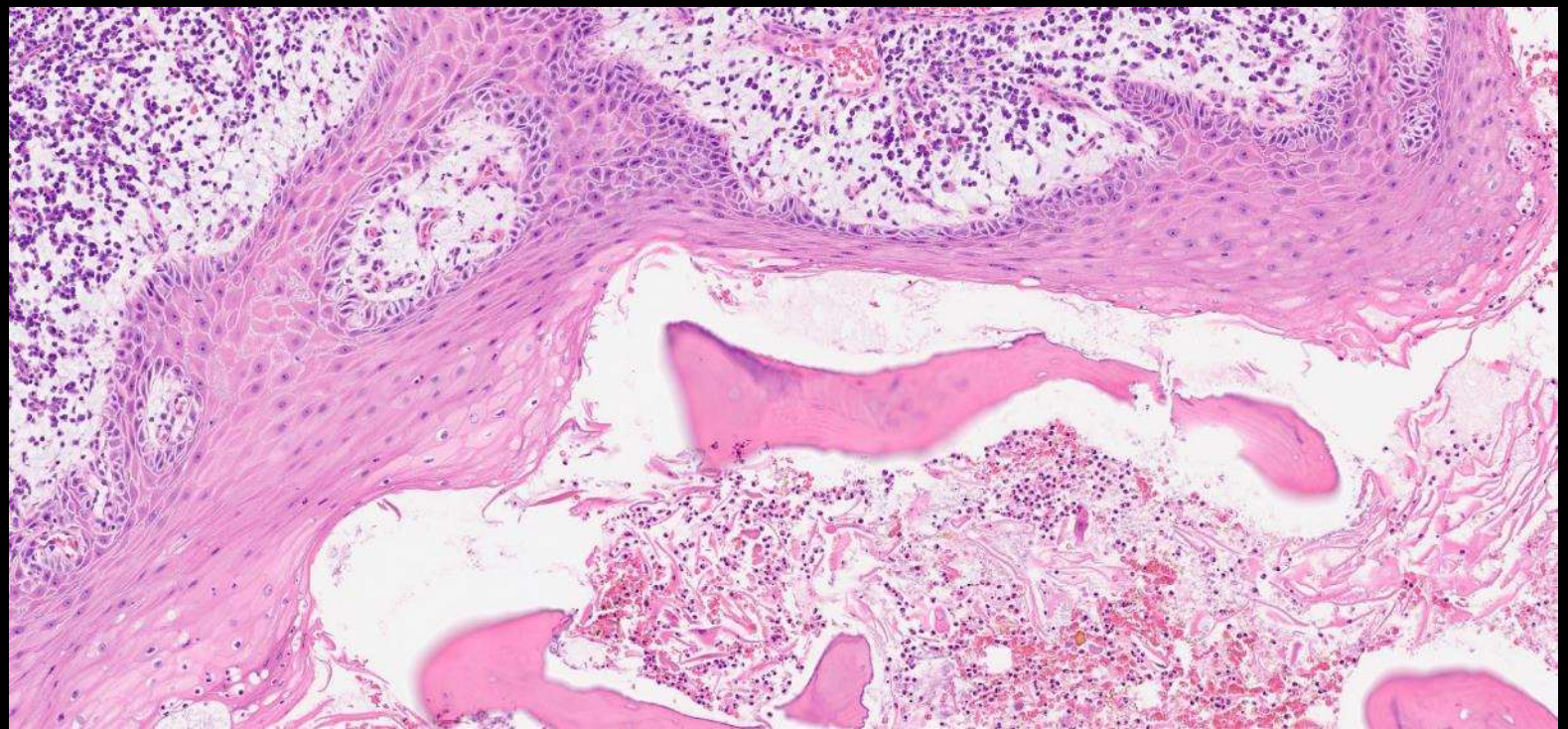


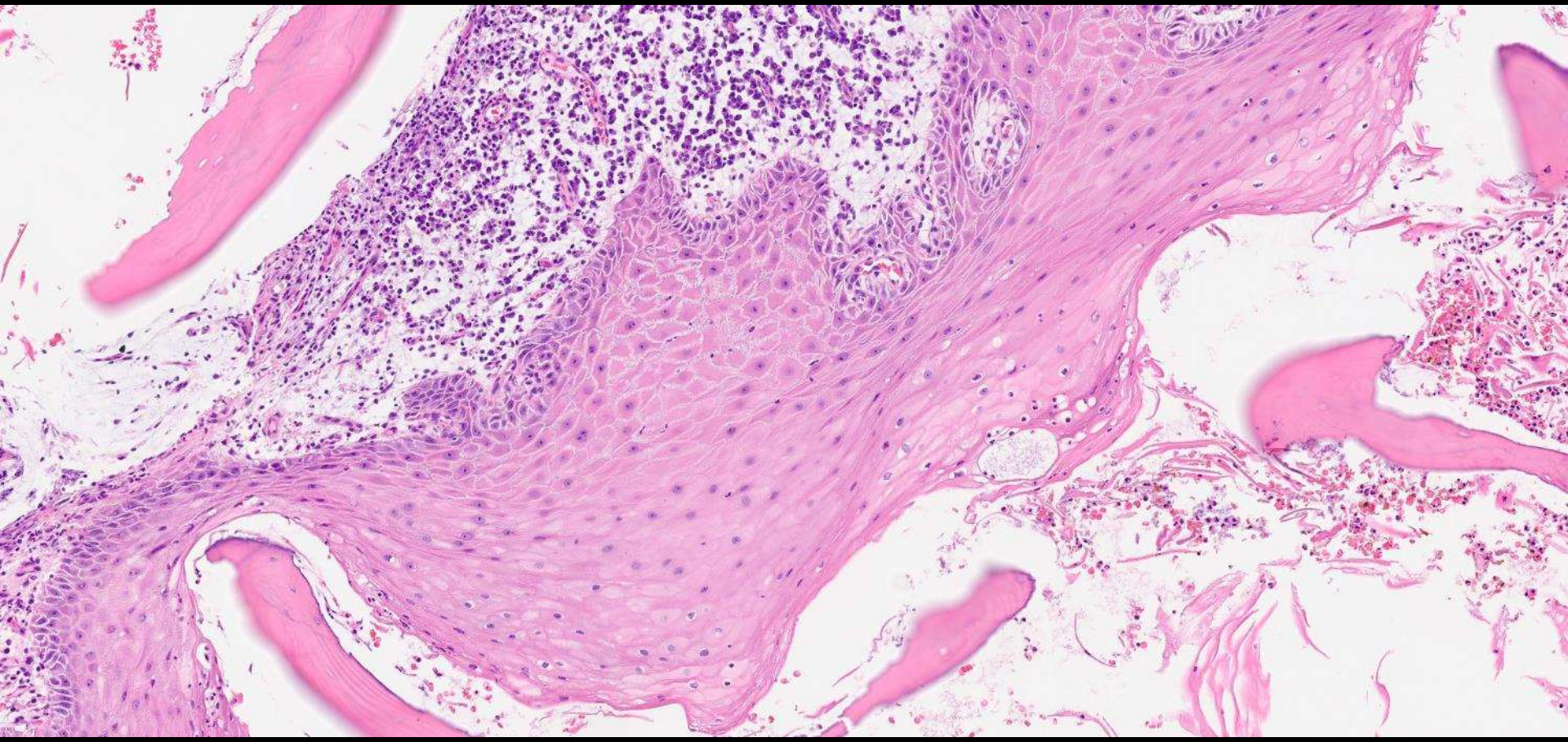












DDx

Pseudocarcinomatous Squamous Hyperplasia Involving Bone

A Diagnostic Pitfall Mimicking Squamous Cell Carcinoma

Smiljana Spasić, MD, Oleksandr N. Kryvenko, MD,*†‡ Darcy A. Kerr, MD,§‖ Gunnlaugur P. Nielsen, MD,¶ Carmen Gomez-Fernandez, MD,*‡ and Andrew E. Rosenberg, MD*‡*

Background: Pseudocarcinomatous squamous hyperplasia (PSH) within the bone is uncommon and closely mimics well-differentiated squamous cell carcinoma (SCC). It arises from cutaneous or mucosal surfaces and grows directly into the bone. This study analyzes a large series of PSH and discusses the clinicopathologic features that facilitate its distinction from SCC.

Design: Cases were identified from the surgical pathology files between 1985 and 2020.

Results: The 31 cases included 21 males, 9 females, 1 unknown sex; who were 20 to 87 years old (average: 59 y). Sites included mandible—17, maxilla—5, toes—4, and 1 case from finger, femur, tibia, ischium, and unknown. Fourteen patients had a history of SCC, 13 treated with resection and chemoradiation and developed infected osteoradionecrosis, 4—medication-related osteonecrosis, 3—peripheral vascular disease, and diabetes mellitus, 3—trauma, 3—osteomyelitis, 3—unknown, and 1—hematologic malignancy. All cases exhibited severe osteomyelitis and nests of reactive keratinizing squamous epithelium that matured towards the bone surface, lacked significant atypia, or mitotic activity but permeated the medullary cavity. Patients with previous SCC developed PSH after 2 months to 8 years (average: 4 y). Nineteen of 30 patients had follow-up (2 to 48 mo, average: 17 mo); 6 patients experienced repeated debridements over 2 months to 1 year; no patient developed SCC.

Conclusions: PSH involving bone is infrequent, complicates severe osteomyelitis, and is often therapy related. The clinical findings are usually not concerning for malignancy, however, the histologic findings are an important diagnostic pitfall because they mimic SCC.

Key Words: osteomyelitis, squamous epithelium, squamous cell carcinoma

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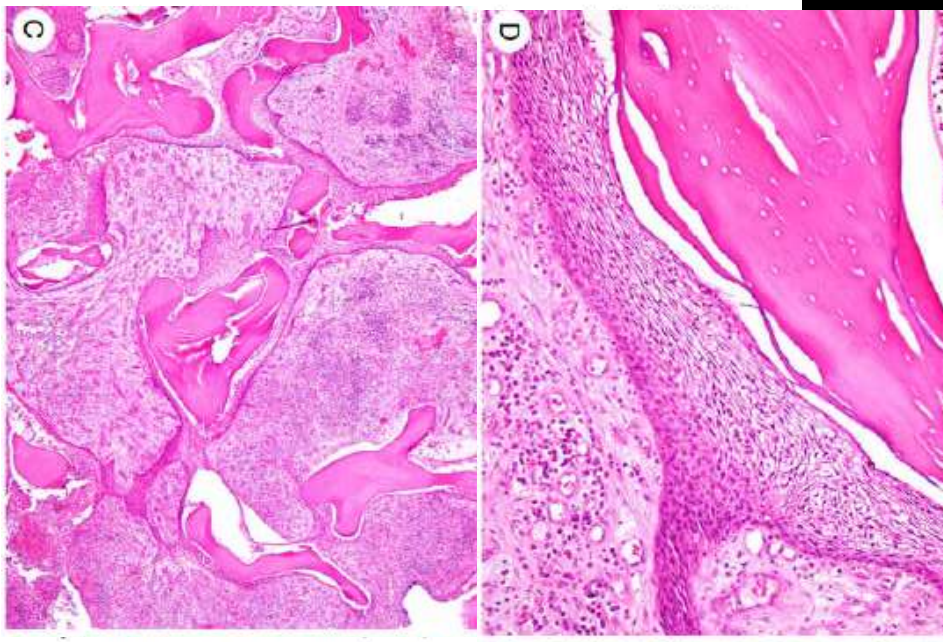

TABLE 1. Clinical Findings and Follow-up

Case No.	Age (y)	Sex	Site	PMH	Clinical Findings	Imaging	Follow-up
1	21	Male	Finger	Trauma	NA	NA	NEC (2 y)
2	37	Male	Femur	Osteomyelitis	NA	NA	NEC (4 y)
3	87	Female	Mandible	MRONJ	NA	NA	NEC (2 mo)
4	48	Female	Mandible	SCC of the tongue, s/p CRT	ORN	None	NEC (3 y)
5	81	Male	Mandible	SCC of the floor of mouth, s/p resection	Osteomyelitis	None	NEC (4 y)
6	65	Male	Tibia	Osteomyelitis	NA	NA	NEC (2 mo)
7	56	Male	Mandible	SCC of the tongue, s/p CRT	Osteomyelitis	ORN	UNK
8	66	Male	Maxilla	DM			NEC (1 y)
9	49	Male	Mandible	SCC of the tonsil, s/p CRT	Osteomyelitis and ORN	None	Recurrent metastatic SCC to the neck LN
10	87	Female	Mandible	SCC of the face, s/p CRT	Osteomyelitis and ORN	Osteolytic lesion	NEC (1 y)
11	66	Female	Mandible	SCC of the tonsil, s/p CRT	ORN	ORN	NEC (1 y)
12	57	Female	Toe	DM	NA	NA	NEC (1 y)
13	45	Female	Toe	BLL	NA	NA	NEC (2 y)
14	20	Male	Mandible	Osteomyelitis	NA	NA	UNK
15	53	Male	Toe	DM	NA	NA	NEC (11 mo)
16	62	Male	Mandible	SCC of the tongue, s/p CRT	Osteomyelitis	ORN	NEC (8 mo)
17	46	Male	Mandible	SCC of the tonsil, s/p CRT	Osteomyelitis	ORN	UNK
18	35	Male	Maxilla	Trauma	NA	NA	NEC (1 y, 3 mo)
19	72	Male	Mandible	SCC of the tongue, s/p CRT	Osteomyelitis and ORN	None	NEC (1 y, 8 mo)
20	74	Female	Maxilla	MRONJ	NA	NA	UNK
21	71	Male	Mandible	MRONJ	NA	NA	UNK
22	56	Male	Maxilla	MRONJ	NA	NA	UNK
23	74	Male	Mandible	SCC of the tongue, s/p CRT	Osteomyelitis and ORN	None	NEC (2 mo)
24	66	Male	Mandible	SCC of the floor of mouth, s/p CRT	ORN; rule out neoplasia	ORN	NEC (8 mo)
25	49	Male	Mandible	SCC of the buccal mucosa, s/p CRT	Osteomyelitis imaging cannot exclude neoplasia	ORN	NEC (1 y, 6 mo)
26	68	Male	Mandible	SCC of the oropharynx, s/p CRT	ORN	ORN	UNK
27	67	Male	Maxilla	SCC of the oropharynx, s/p CRT	ORN	None	NEC (2 mo)
28	64	Female	Mandible	Osteomyelitis	NA	NA	UNK
29	64	Male	Ischium	UNK	UNK	UNK	UNK
30	UNK	Female	Toe	UNK	UNK	UNK	UNK
31	UNK	UNK	UNK	UNK	UNK	UNK	UNK

Pseudocarcinomatous squamous hyperplasia (of bone)

Sometimes also called:

“pseudoepitheliomatous hyperplasia, invasive acanthosis, verrucoid epidermal hyperplasia, and carcinomatoid hyperplasia”

Pseudocarcinomatous squamous hyperplasia (of bone)

- relatively common complication associated with osteomyelitis
- predisposing factors are often related to the anatomic site
- underreported in the literature

Pseudocarcinomatous squamous hyperplasia (of bone)

- **Most commonly occurs in jaw**
  - squamous mucosa inclose proximity to underlying bone
  - ulceration with osteomyelitis exposes the medullary cavity & facilitates reepithelializing squamous mucosa to grow into the bone interior
- **Can occur at other sites!**

TABLE 2. Differential Features Between PSH and WD-SCC

Features	PSH	WD-SCC
Microscopic		
	Infiltrative growth pattern; no "pushing" margins	Large islands of squamous epithelium
	Small nests and thin, linear, interconnecting strips of squamous epithelium	Layer of reactive fibrous tissue surrounding leading edge of epithelial nests with pushing borders
	No squamous pearls	
	No invasion of nerves or vessels	Presence of keratin pearls
	No precursor lesion (dysplasia)	Presence of perineural and/or vascular invasion
Clinical		
	Presenting as infection and/or osteonecrosis	Presenting as a destructive mass