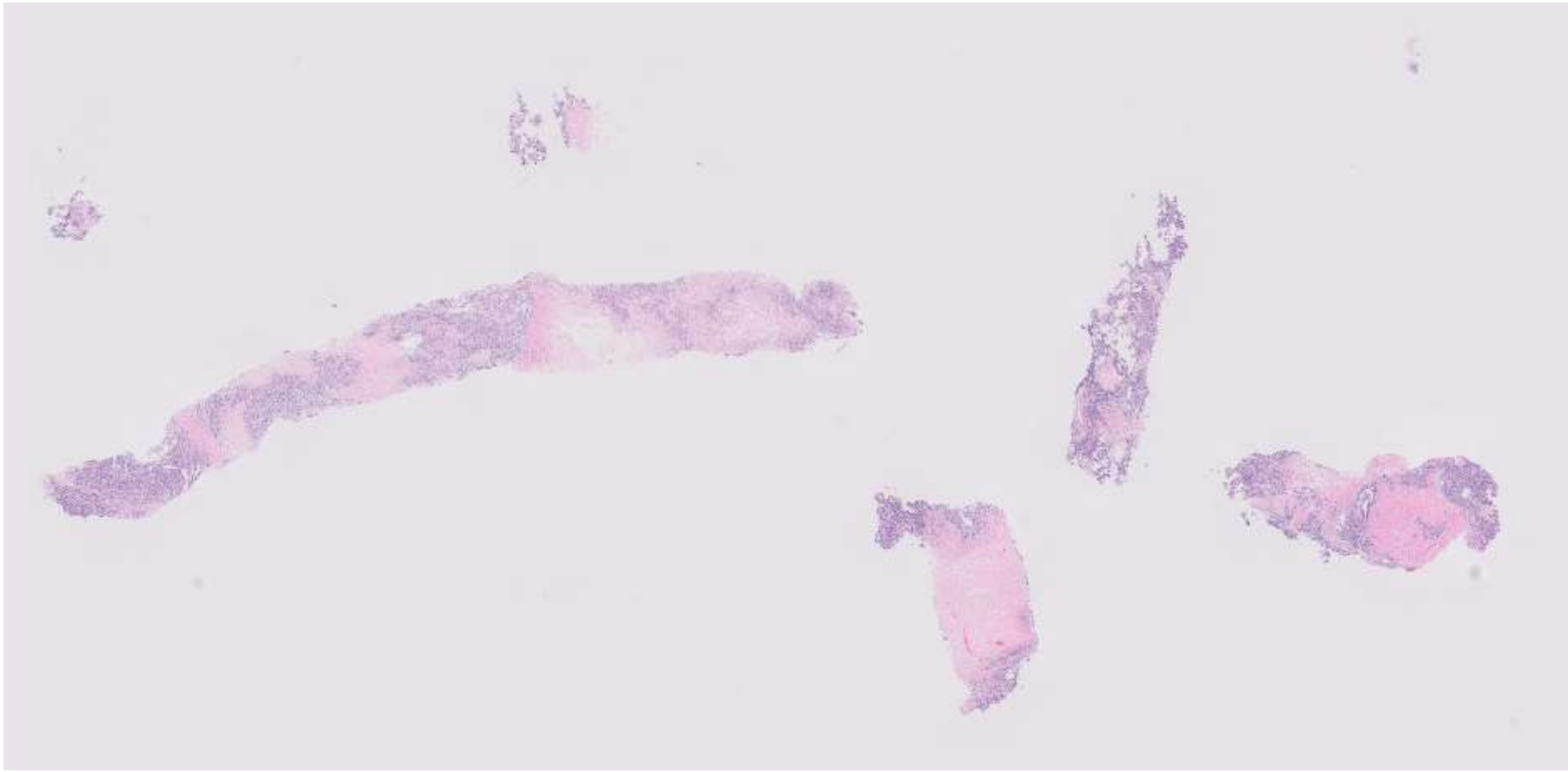
JUNE 2022 DIAGNOSIS LIST

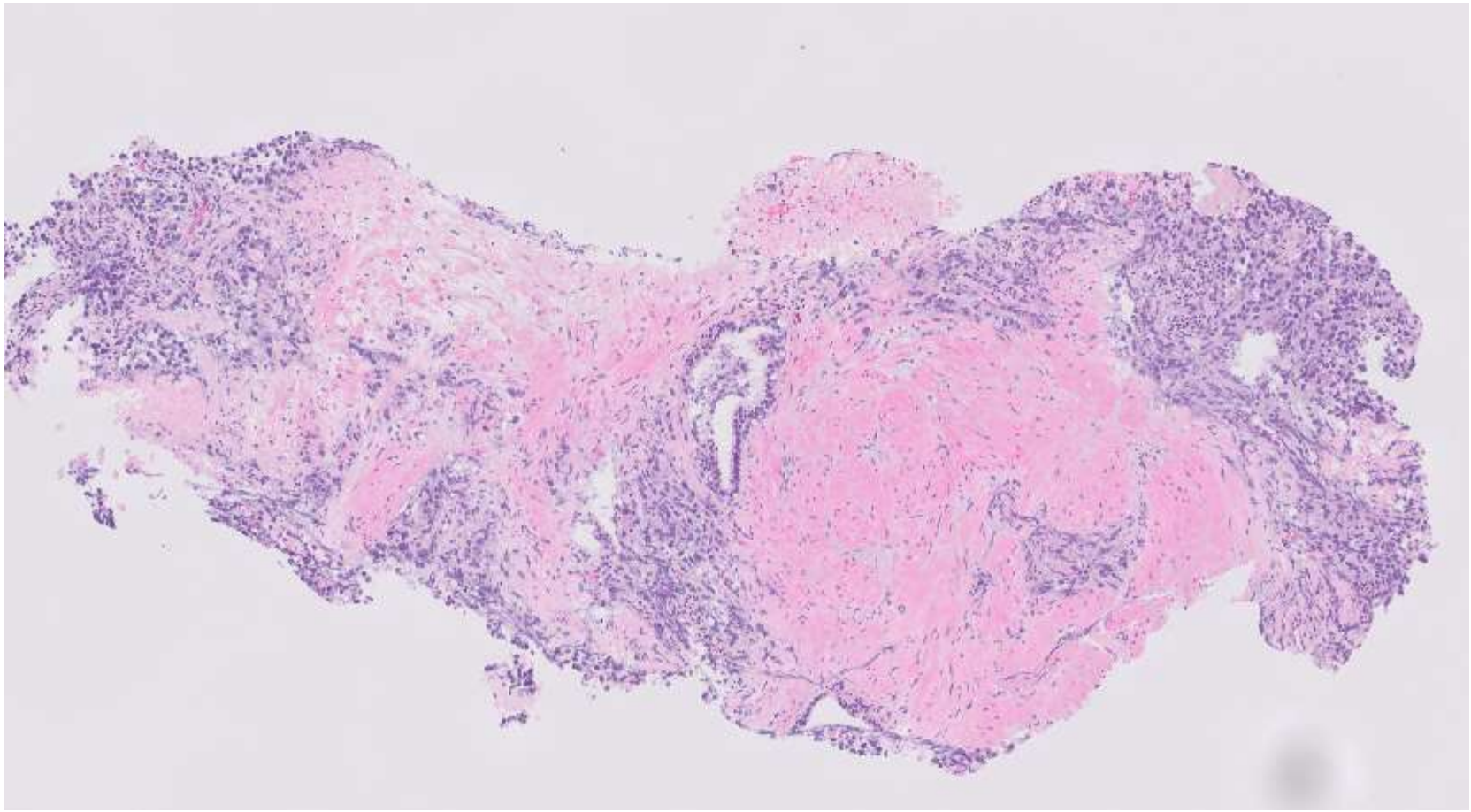
22-0601: seminoma (prostate; GU path)
22-0602: lymphoplasmacyte rich meningioma (brain; neuropath)
22-0603: small cell carcinoma hypercalcemic type (ovary; GYN path)
22-0604: Strongyloides (duodenum; GI path and ID path)
22-0605: Strongyloides (colon; GI path and ID path)
22-0606: subcutaneous panniculitis-like T-cell lymphoma and B-lymphoblastic leukemia/lymphoma (bone marrow; heme path)
22-0607: null pattern p53 urothelial CIS (bladder; GU path)
22-0608: cytoplasmic pattern p53 endometrial serous carcinoma (uterus; GU path)
22-0609: hydrogel pleural sealant (lung; lung path)
22-6010: benign nuclear atypia of epididymis (epididymis; GU path)

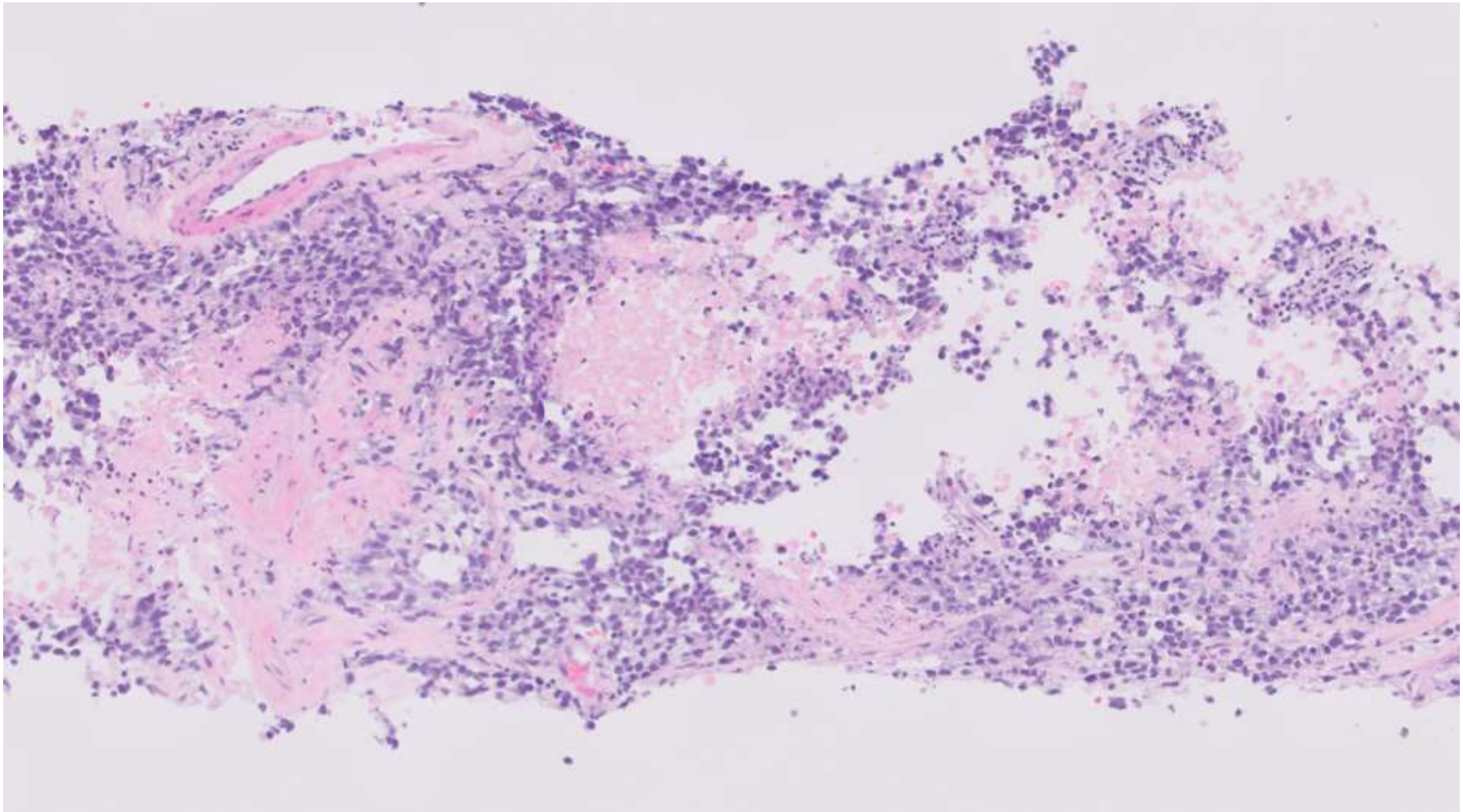
22-0601

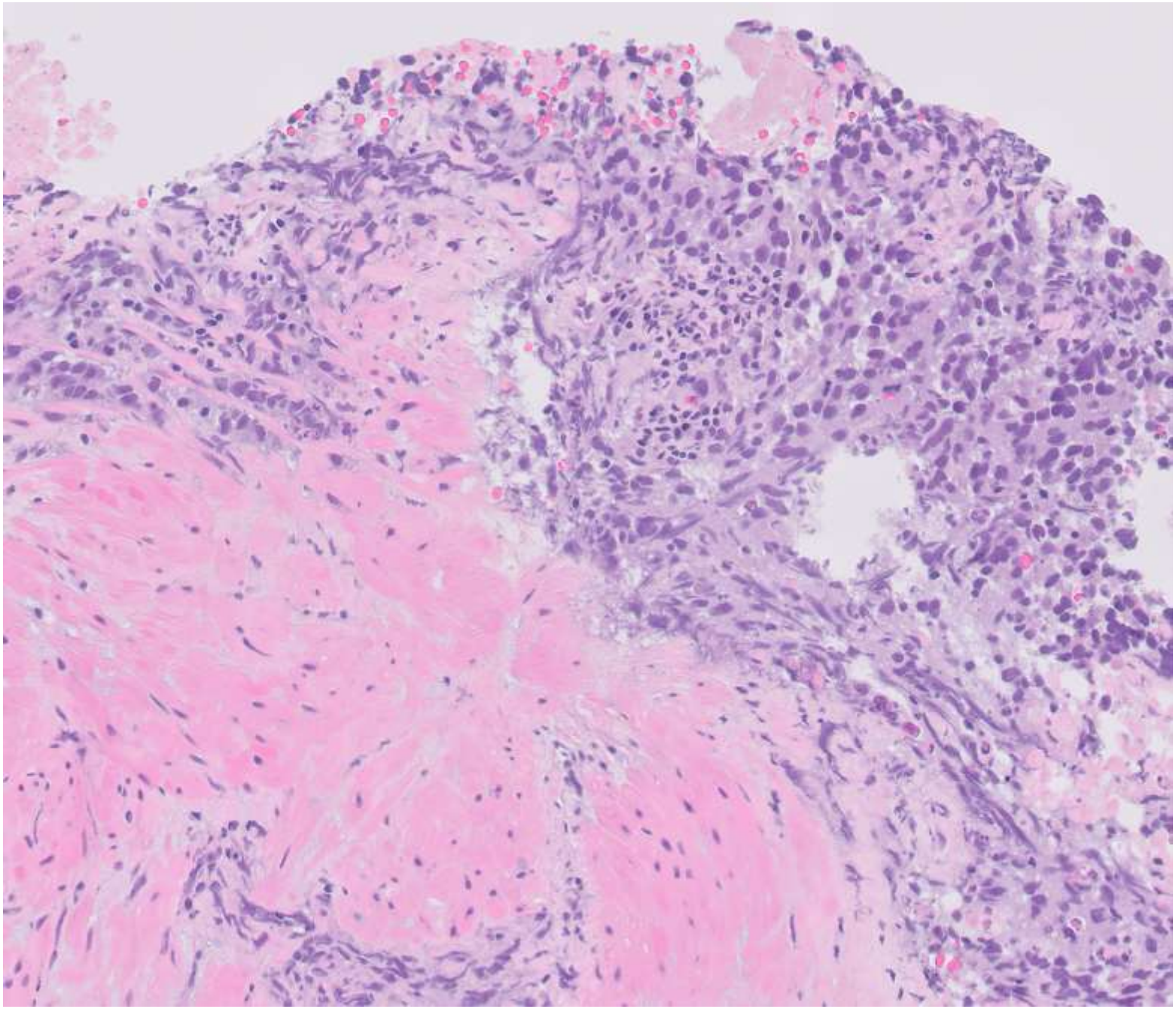
22-0401 – Emily Chan; UCSF

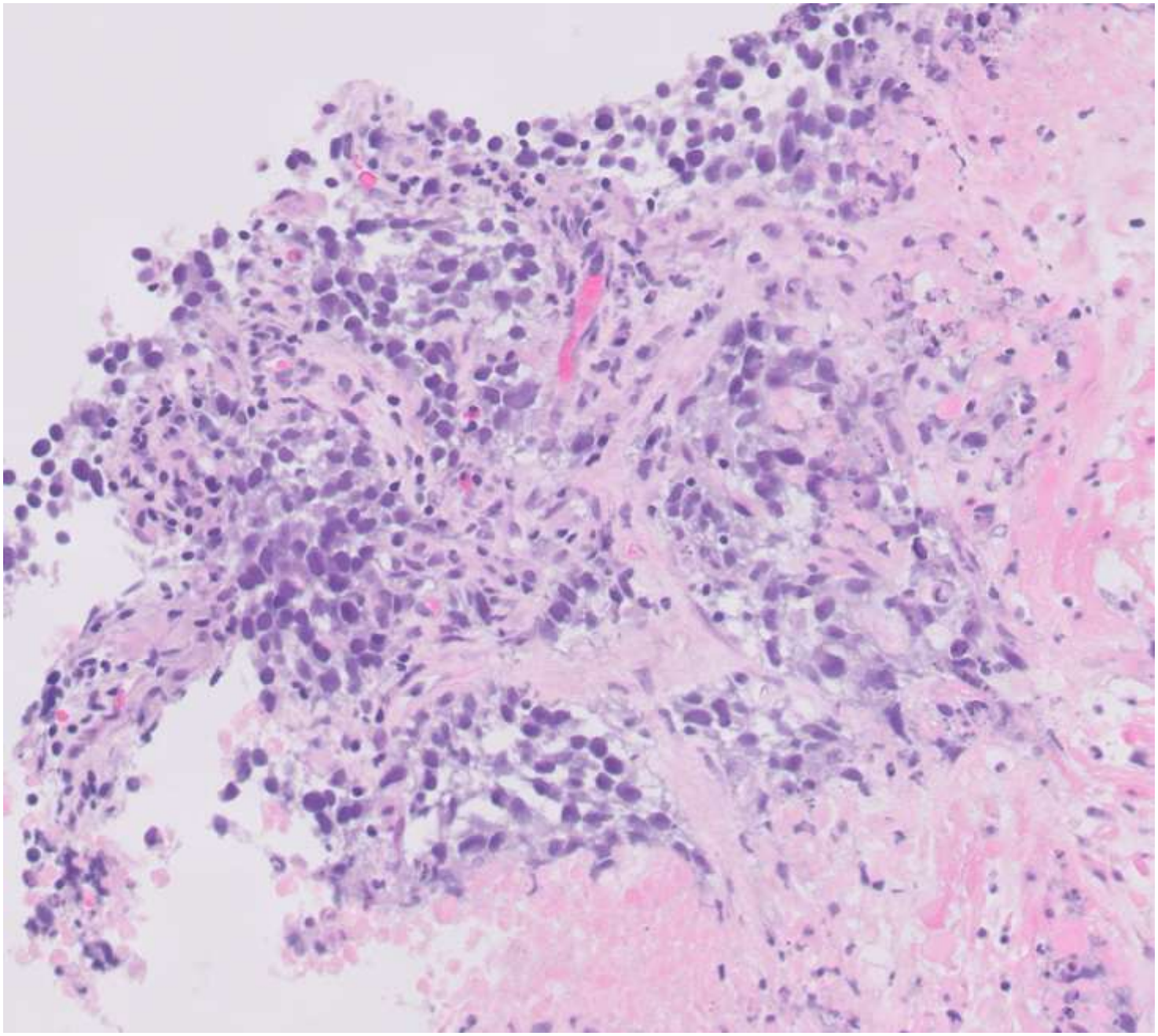
40ish M with urinary retention and enlarged prostate, PSA=2. Standard 12-cor prostate biopsies all showed similar findings.

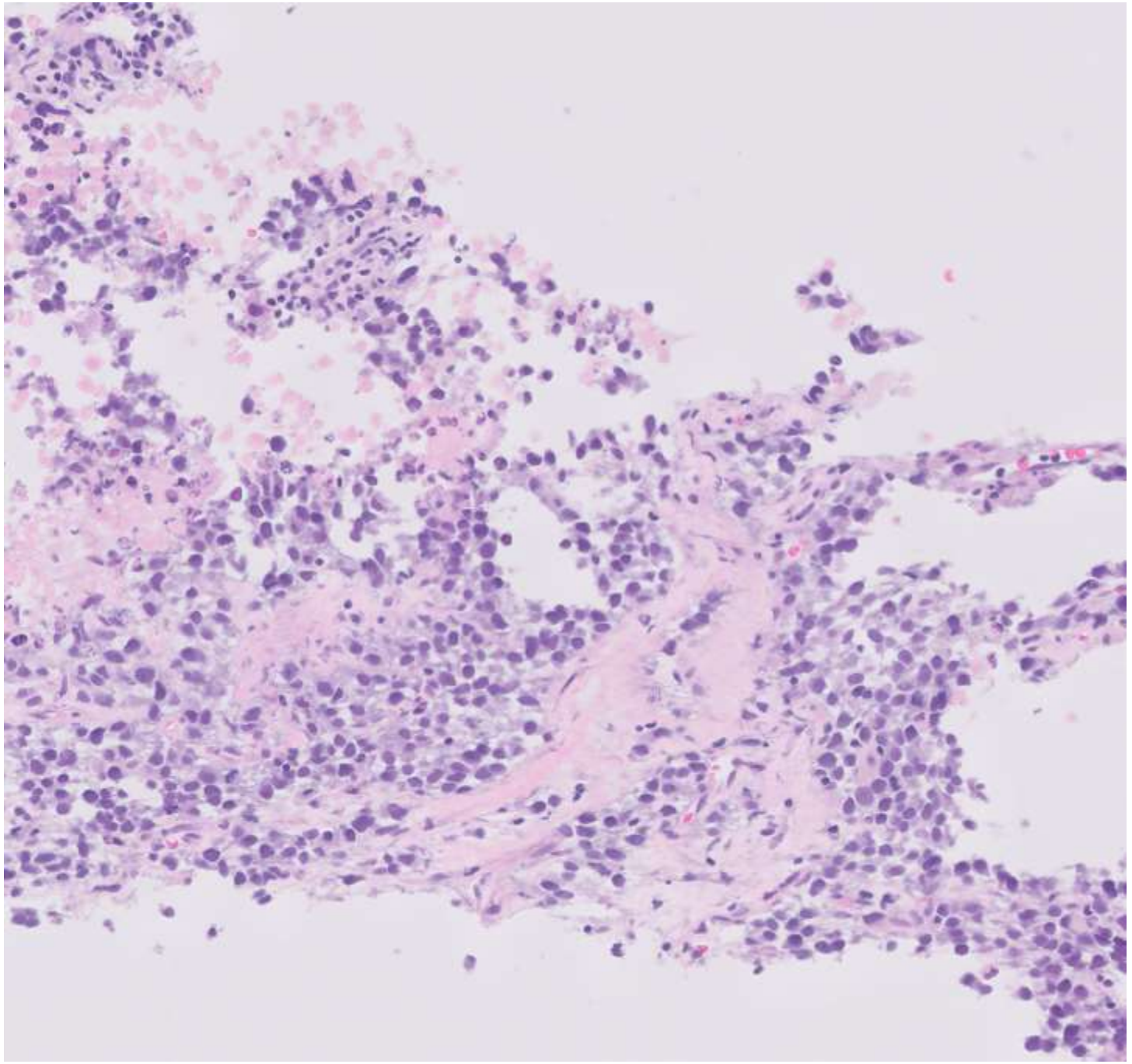


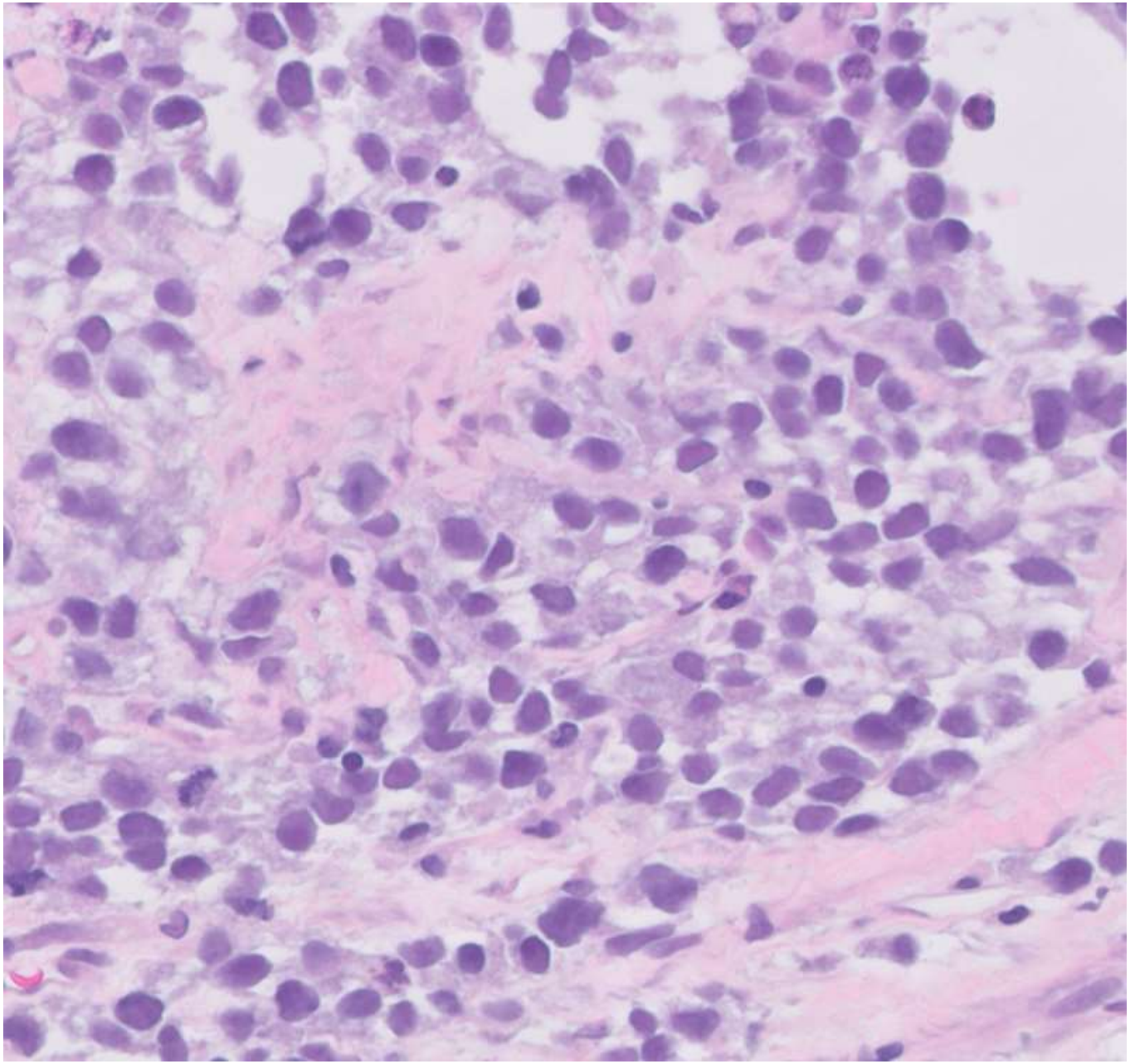


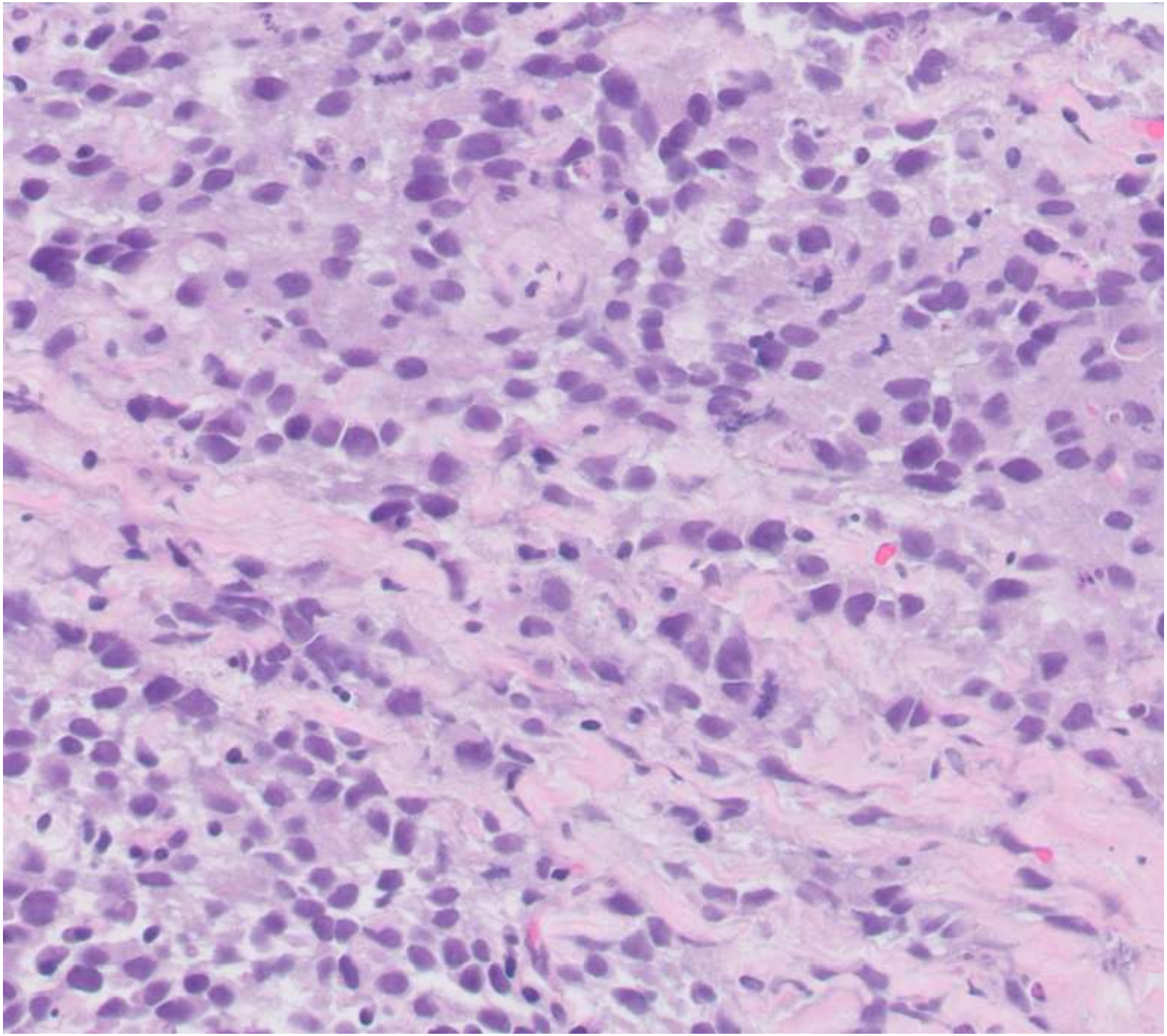












40-ish man with urinary retention and enlarged prostate. PSA 2. Standard 12 core prostate biopsies all showed similar findings.

Emily Chan

UCSF

South Bay Pathology Society Monthly Meeting

June 6, 2022

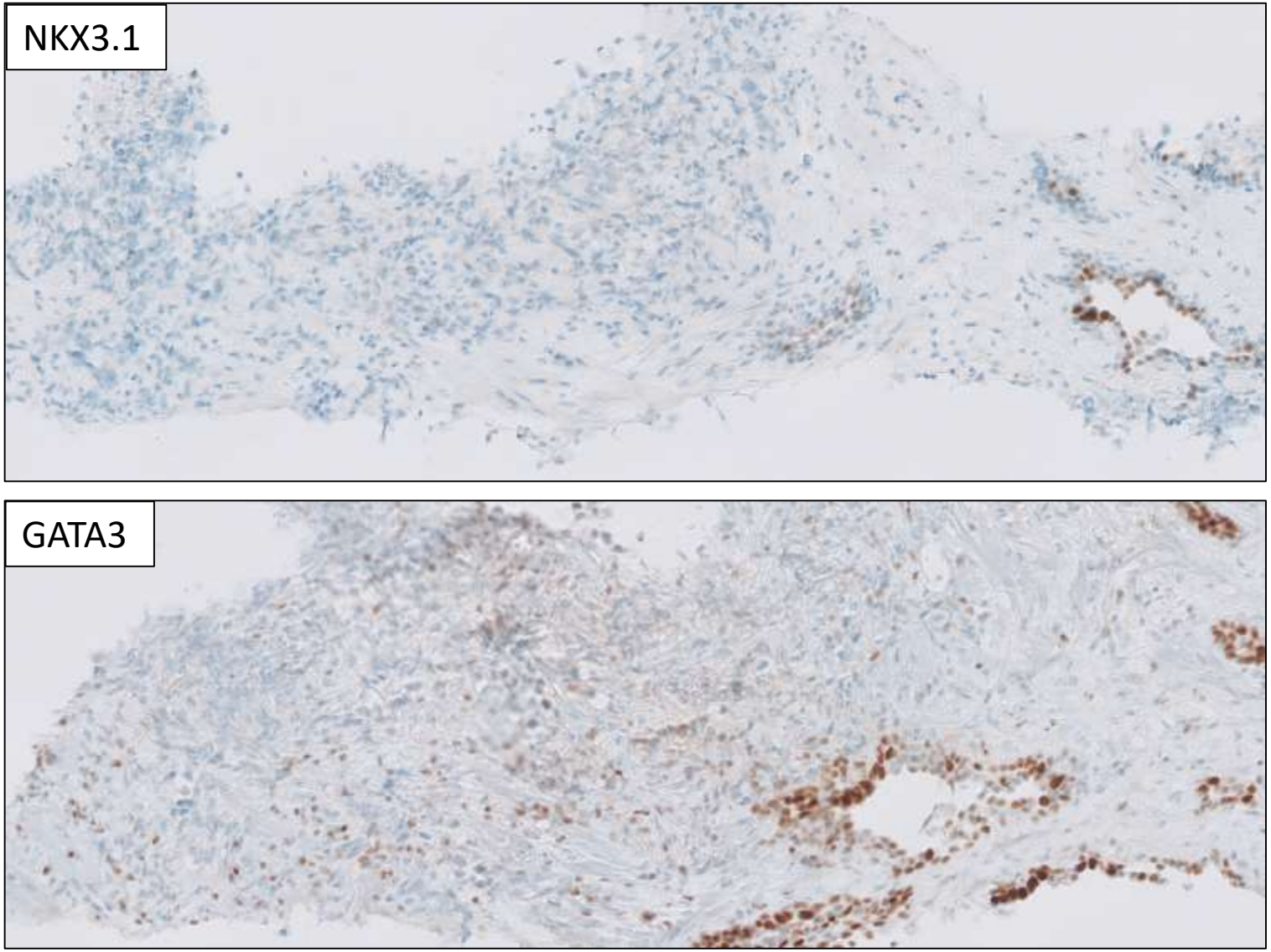
Acknowledgements:

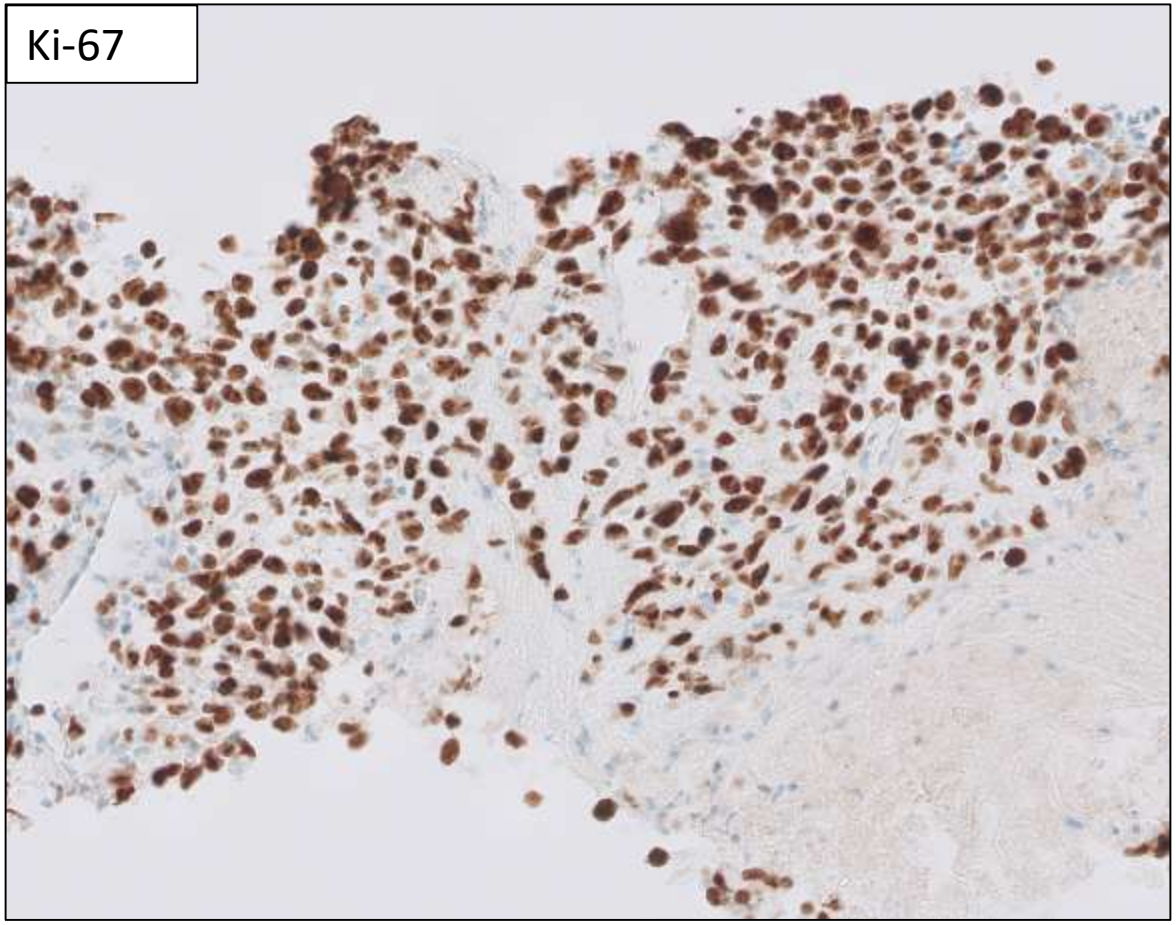
- Andrew Horvai for sharing the case from his personal consult service
- Those who send us consults!

Differential diagnosis

- Prostatic adenocarcinoma, Gleason score 5+5=10
- Urothelial carcinoma
- Neuroendocrine carcinoma
- Metastasis from…???

IHC Round 1




Ki-67

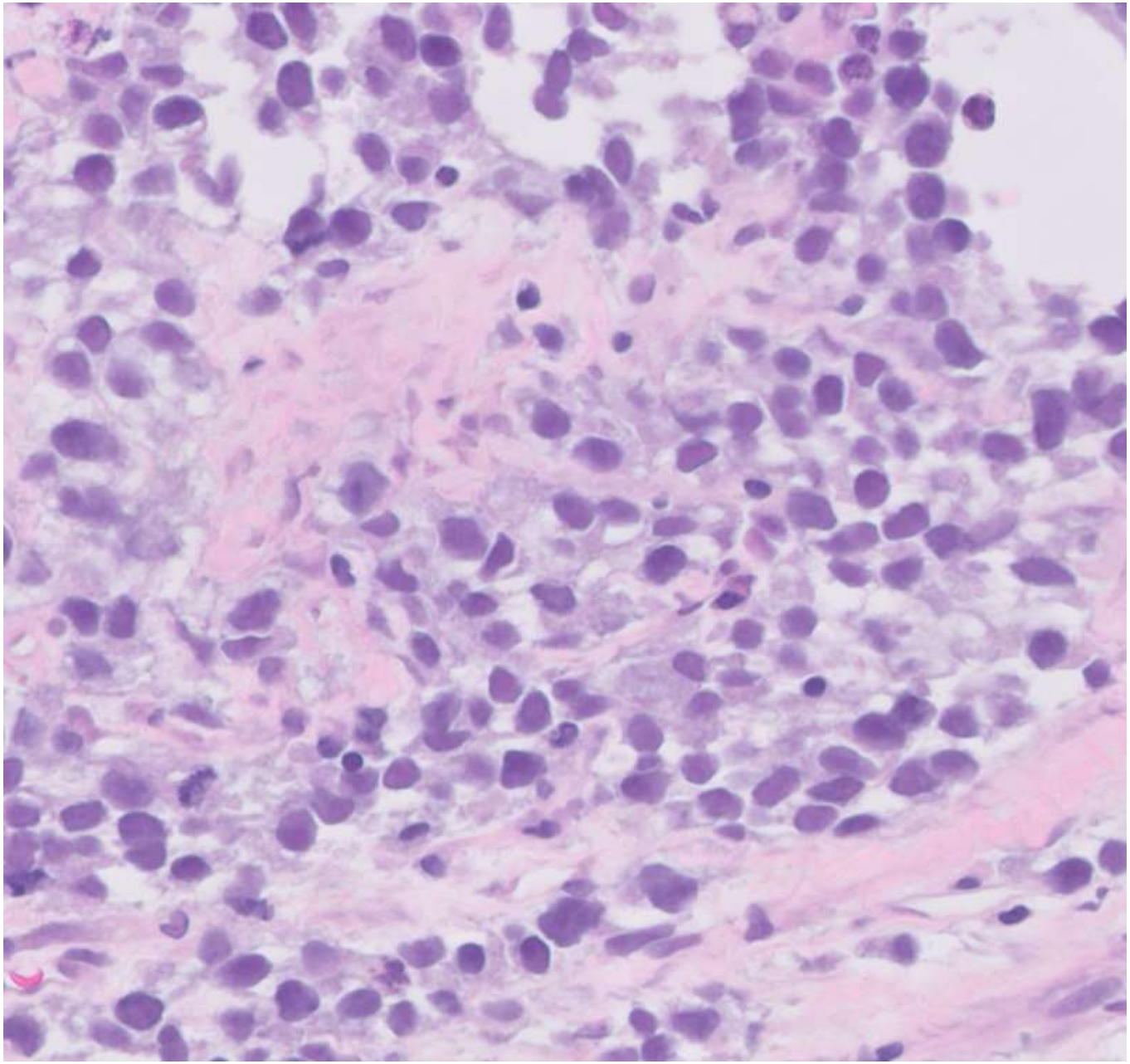
Other negative IHC

- Pankeratin
- CK7
- CK20
- P40
- PSA
- Synaptophysin, chromogranin, INSM1

Low PSA: ?mesenchymal tumor, lymphoma, other small round blue cell tumor??

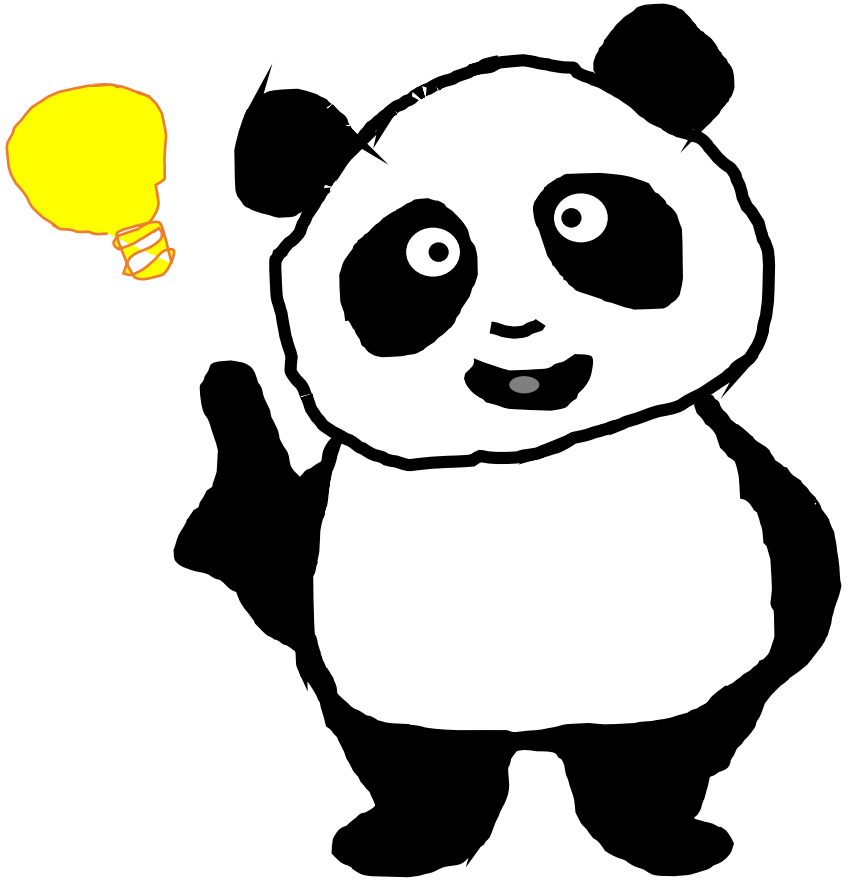
Additional negative stains:

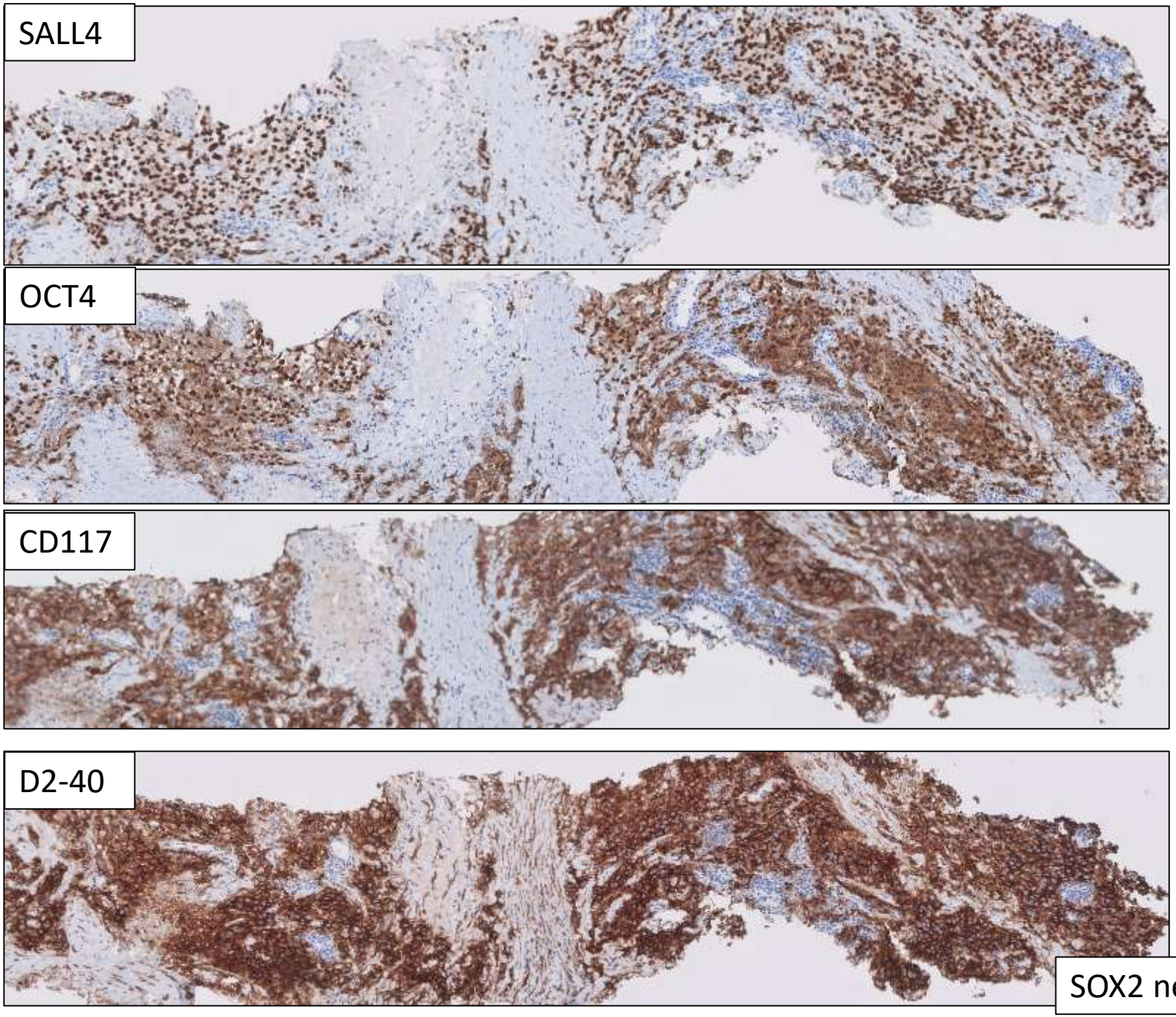
- Desmin, myoD, myogenin
- S100, SOX10
- ERG
- CD99
- CD45



What about a germ cell tumor??

- Young patient
- Male
- Low PSA
- Keratin negative
- Clear-ish cytoplasm




SALL4
OCT4
CD117
D2-40
SOX2 negative

Diagnosis: Malignant Germ Cell Tumor Consistent with Seminoma

Seminoma in the prostate

- Can be primary or metastatic, both very rare
  - Primary thought to arise from germ cells sequestered in prostate during migration from yolk sac to gonadal ridge
    - Less likely: Transformation of pluripotent stem cells within the prostate
  - Metastatic via retrograde migration through lymphatics from primary testicular GCT
    - Check the testis
- Serum markers to r/o mixed germ cell tumor

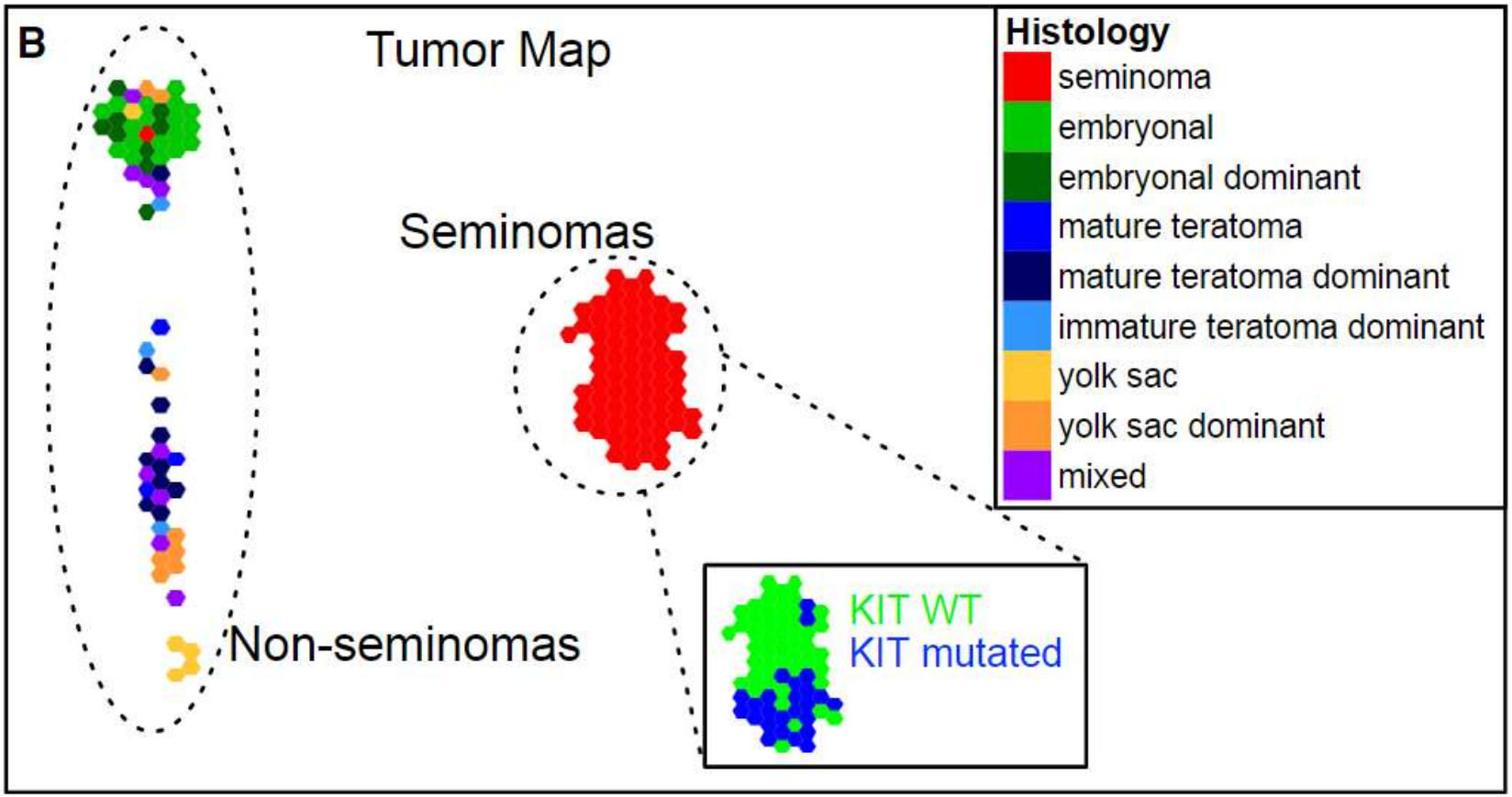
Patient follow up:

- AFP 4.5, HCG 1
- Scrotal US: 0.3 cm nonspecific nodule in right testis and inguinal canal lymphadenopathy, largest 1.5 cm)
- Started BEP with improved urinary obstructive symptoms after two cycles
- NGS sequencing of tumor revealed a *KIT* mutation

Integrated Molecular Characterization of Testicular Germ Cell Tumors

Cell Reports 2018

Hui Shen,[1,32] Juliann Shih,[2,3,4,32] Daniel P. Hollern,[5,32] Linghua Wang,[6,7,32] Reanne Bowlby,[8,32] Satish K. Tickoo,[9,32] Vésteinn Thorsson,[10] Andrew J. Mungall,[8] Yulia Newton,[11] Apurva M. Hegde,[12] Joshua Armenia,[13] Francisco Sánchez-Vega,[13] John Pluta,[14] Louise C. Pyle,[14,15] Rohit Mehra,[16] Victor E. Reuter,[9] Guilherme Godoy,[17]

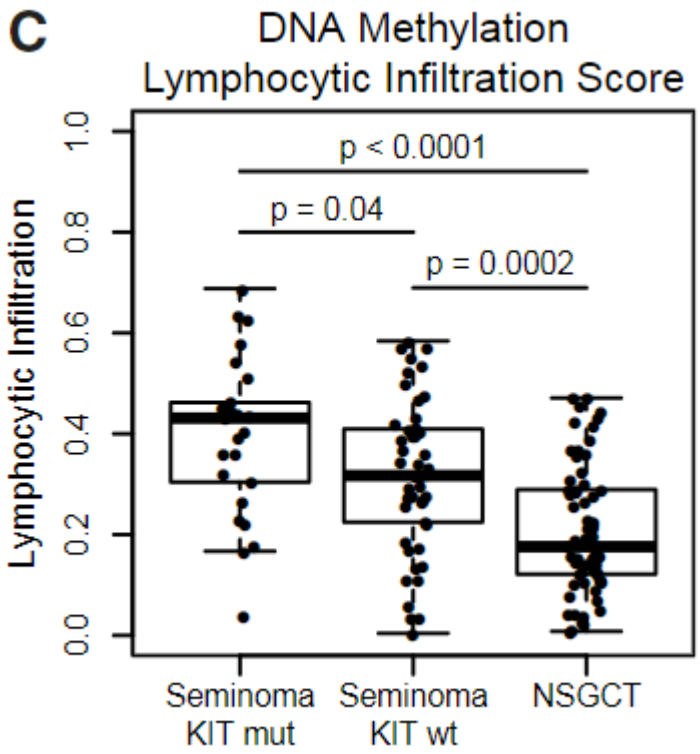


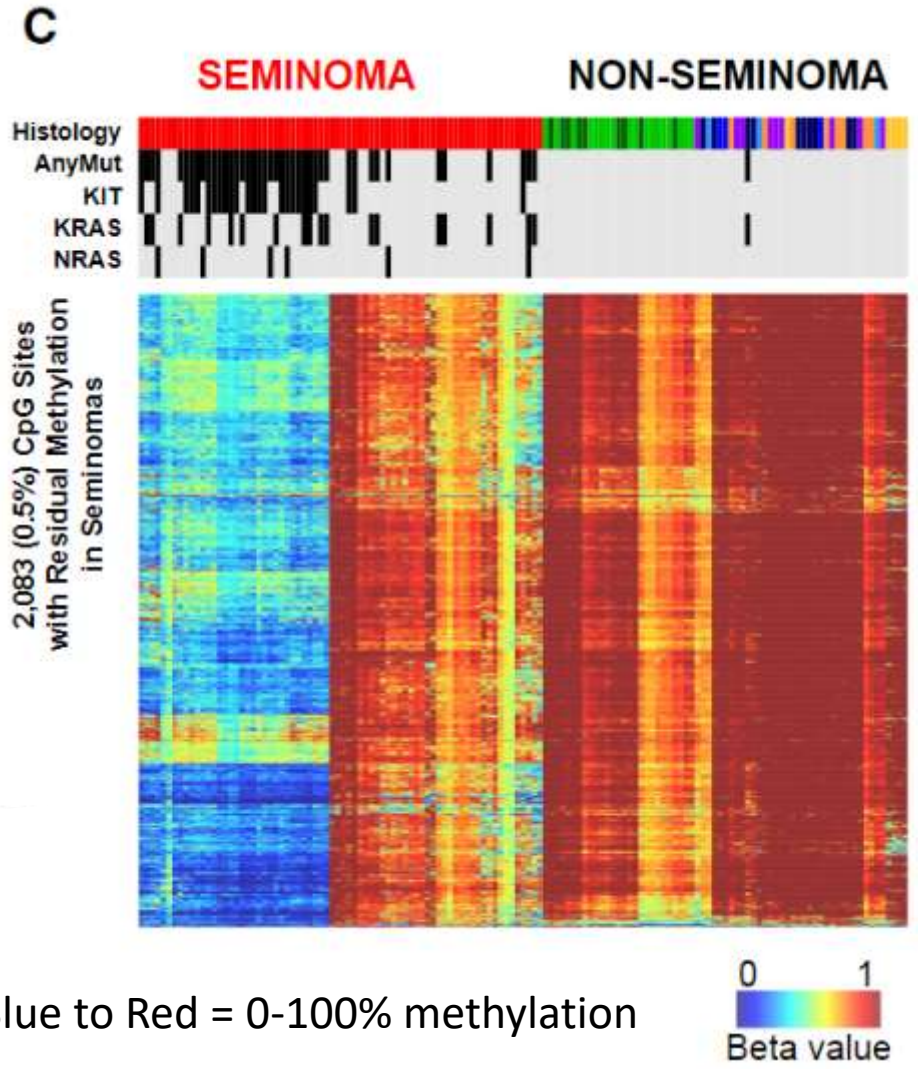
Subset of pure seminomas (35%) defined by *KIT* mutation

KIT-mutated Seminomas

- KIT signaling mediates proliferation/apoptotic pathways required for spermatogenesis
- KIT mutations enriched in and exclusive to seminomas amongst GCT
  - Possibly locks seminoma cells into a primordial germ cell-like state

KIT-mutated tumors show more extensive lymphocytic infiltration and lack of DNA methylation





Blue to Red = 0-100% methylation

Take home points:

- Always stain your Gleason score 5+5 prostate cancers and consider other possibilities
- Consider seminoma in younger patients, low PSA
- Prostatic seminomas are rare and should recommend evaluation for primary vs metastatic and serum markers for pure seminoma vs mixed GCT

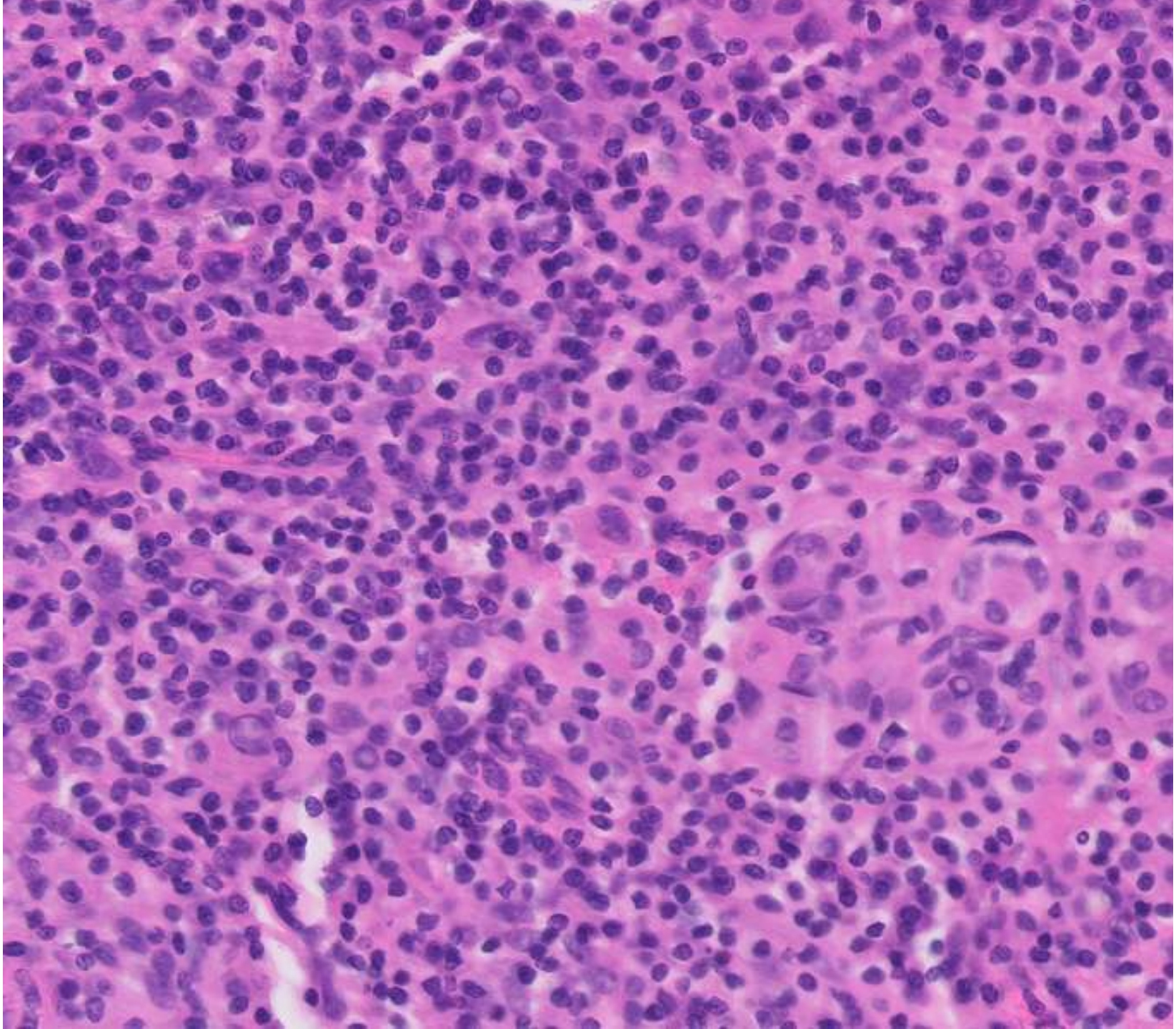
22-0602

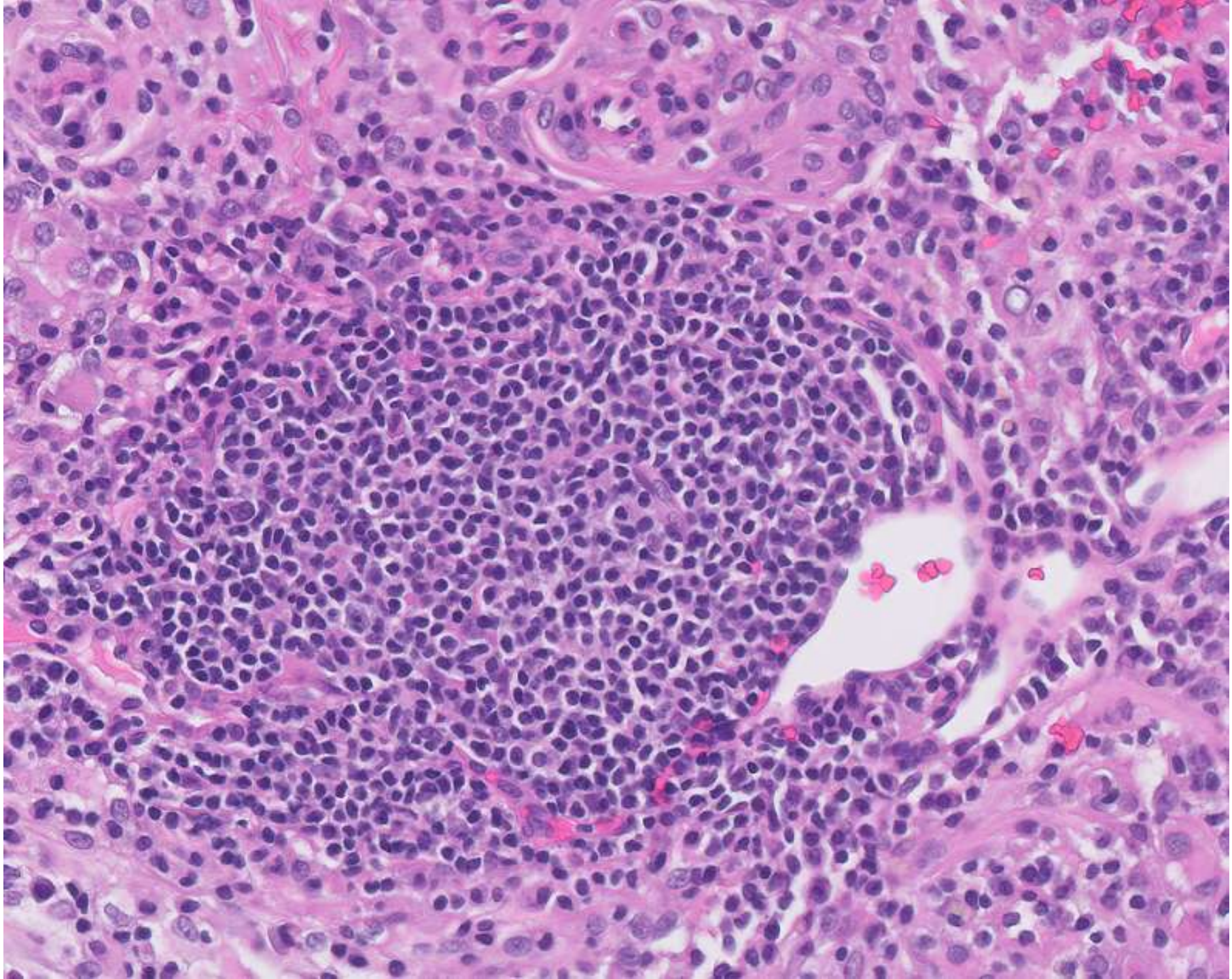
Angus Toland/Inma Cobos; Stanford

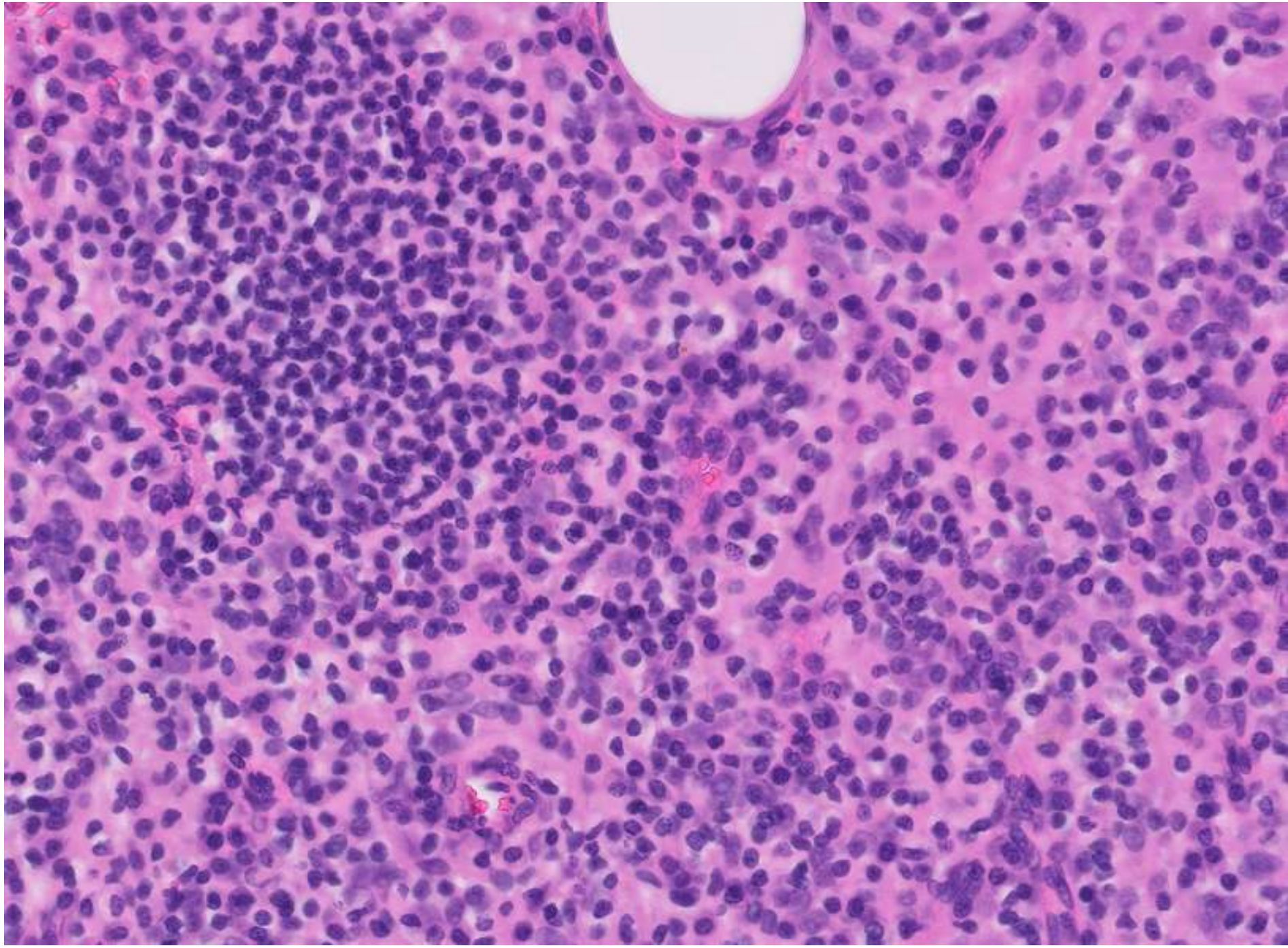
40ish F with right parieto-occipital dural-based mass. Resection submitted.

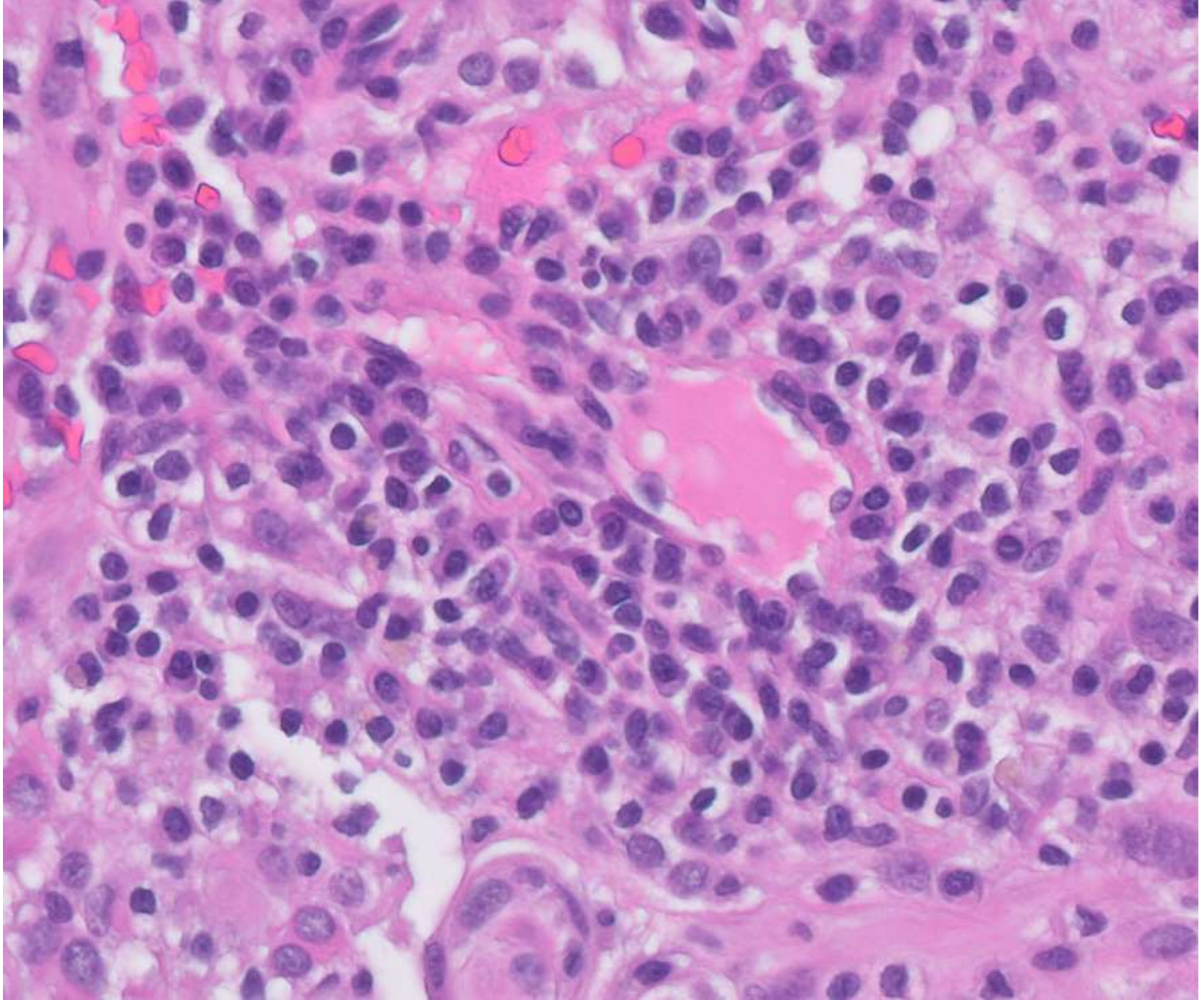
History

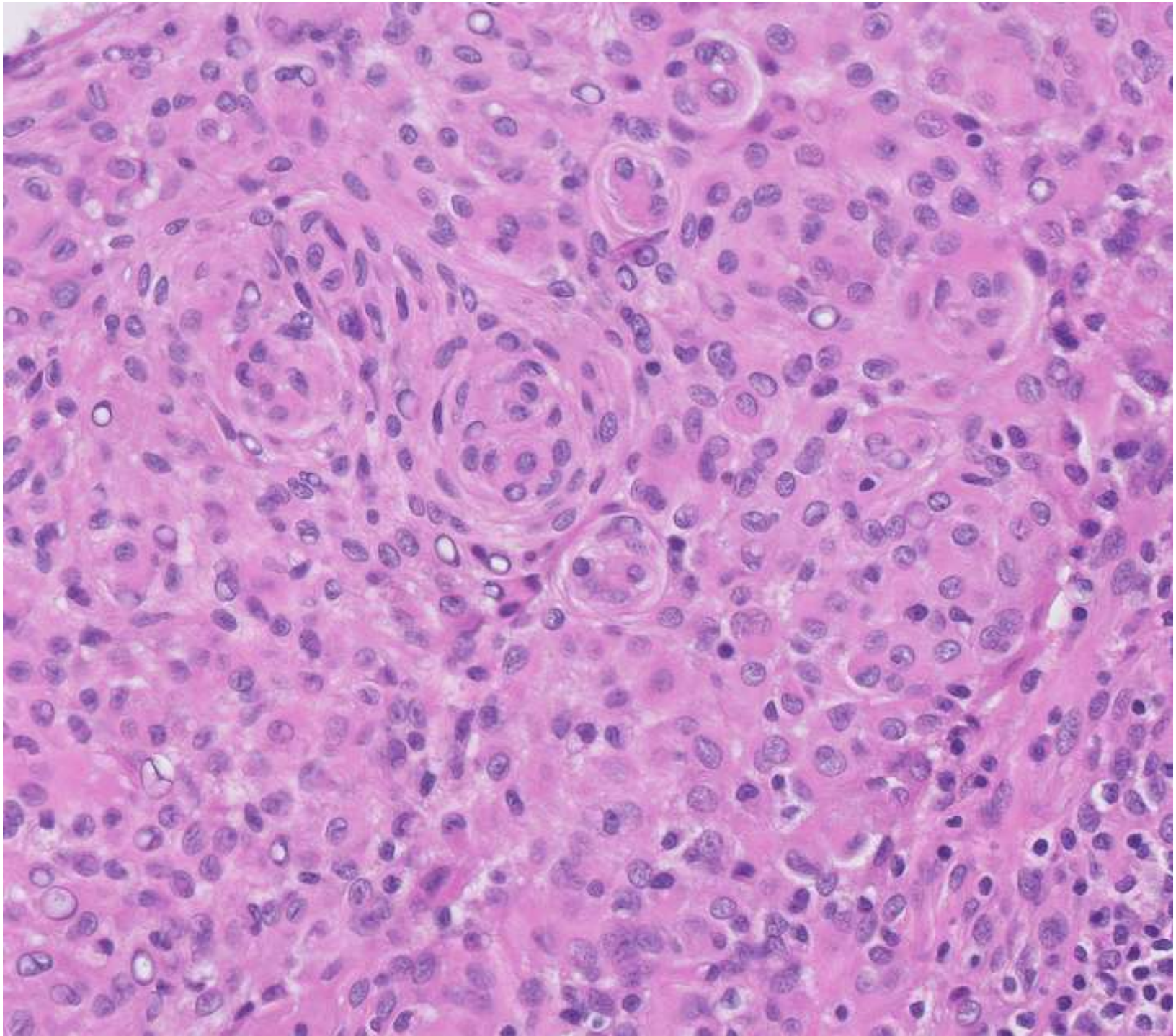
- 45-year-old woman with a right parieto-occipital dural-based mass (consult case; no imaging)

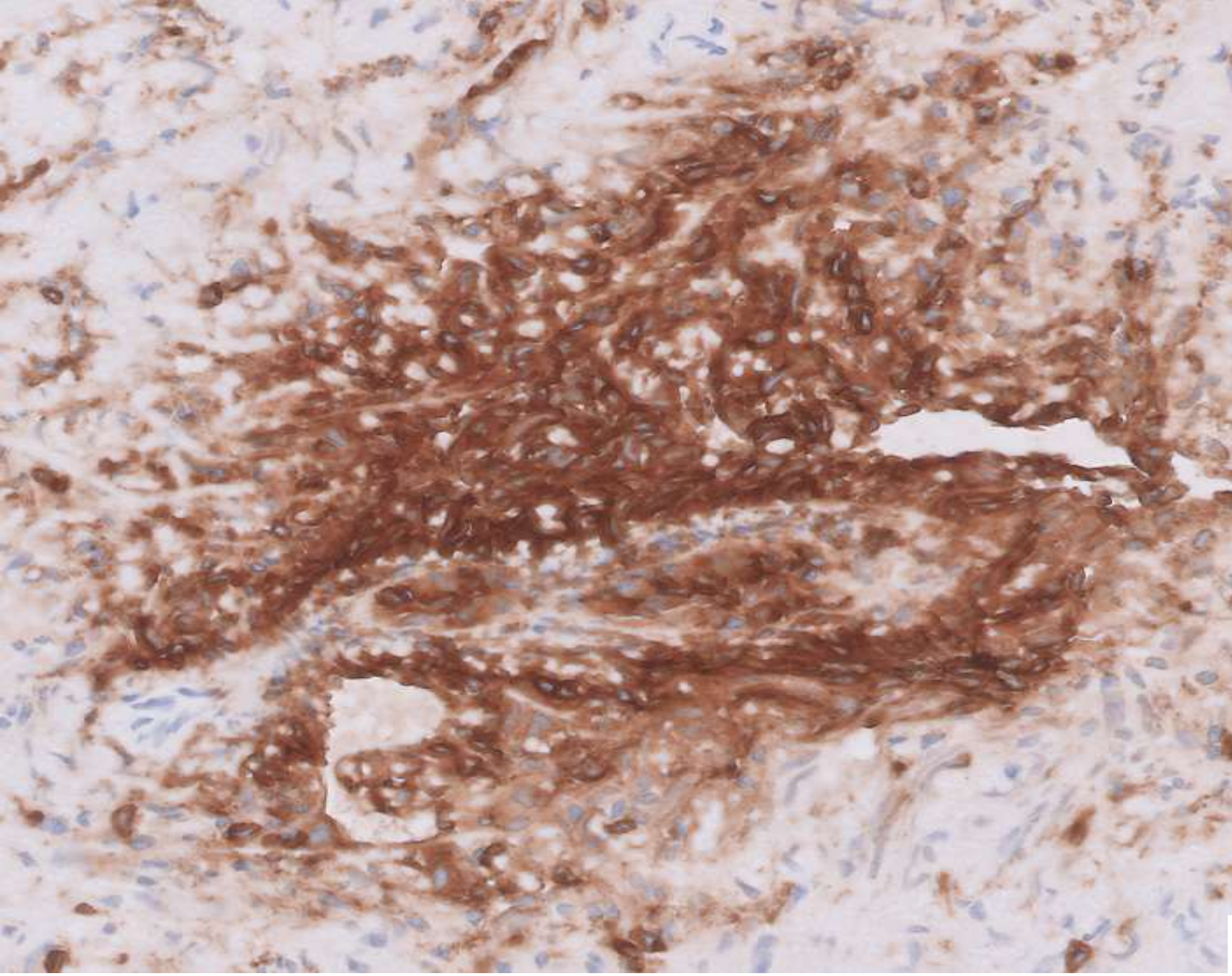




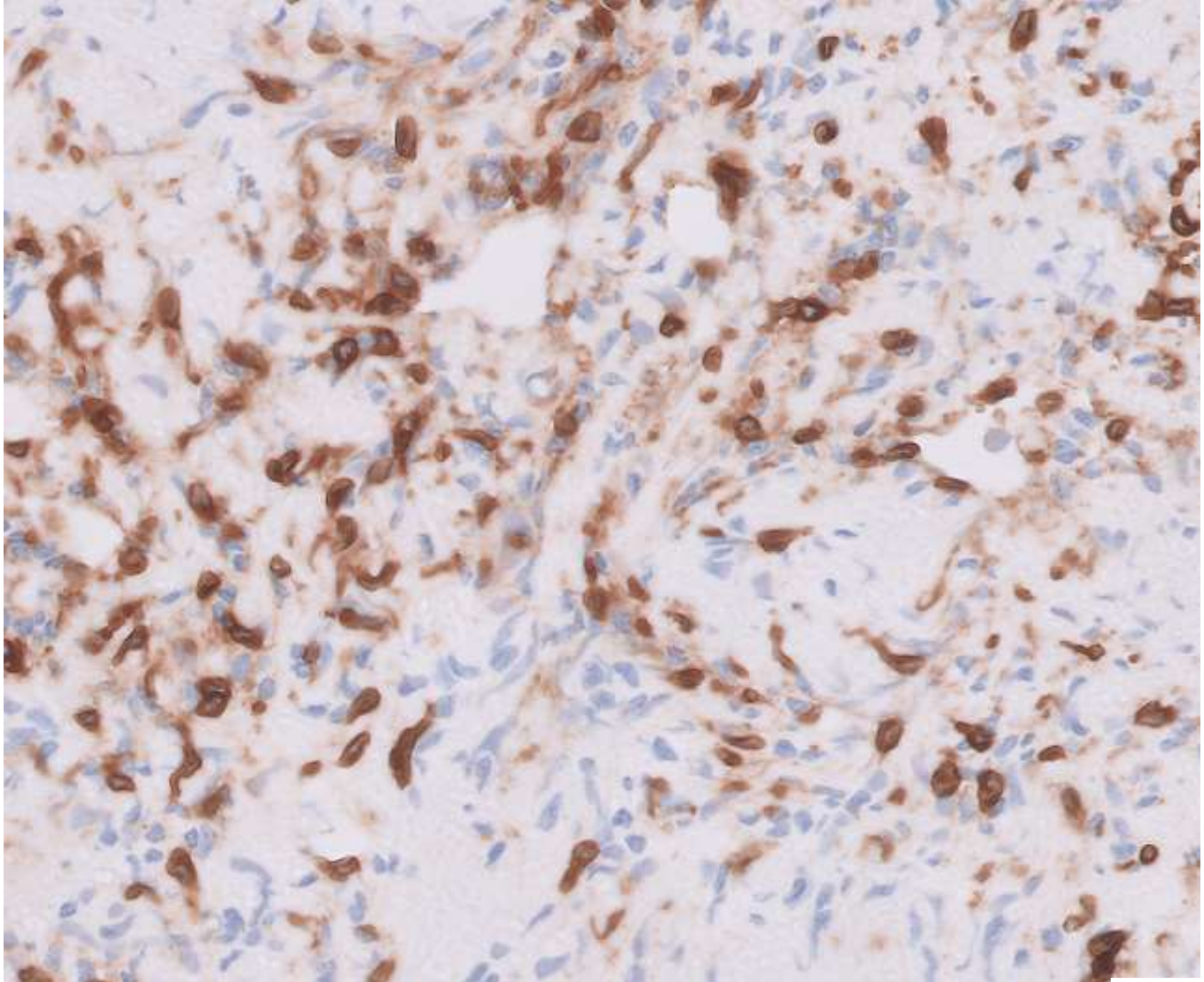




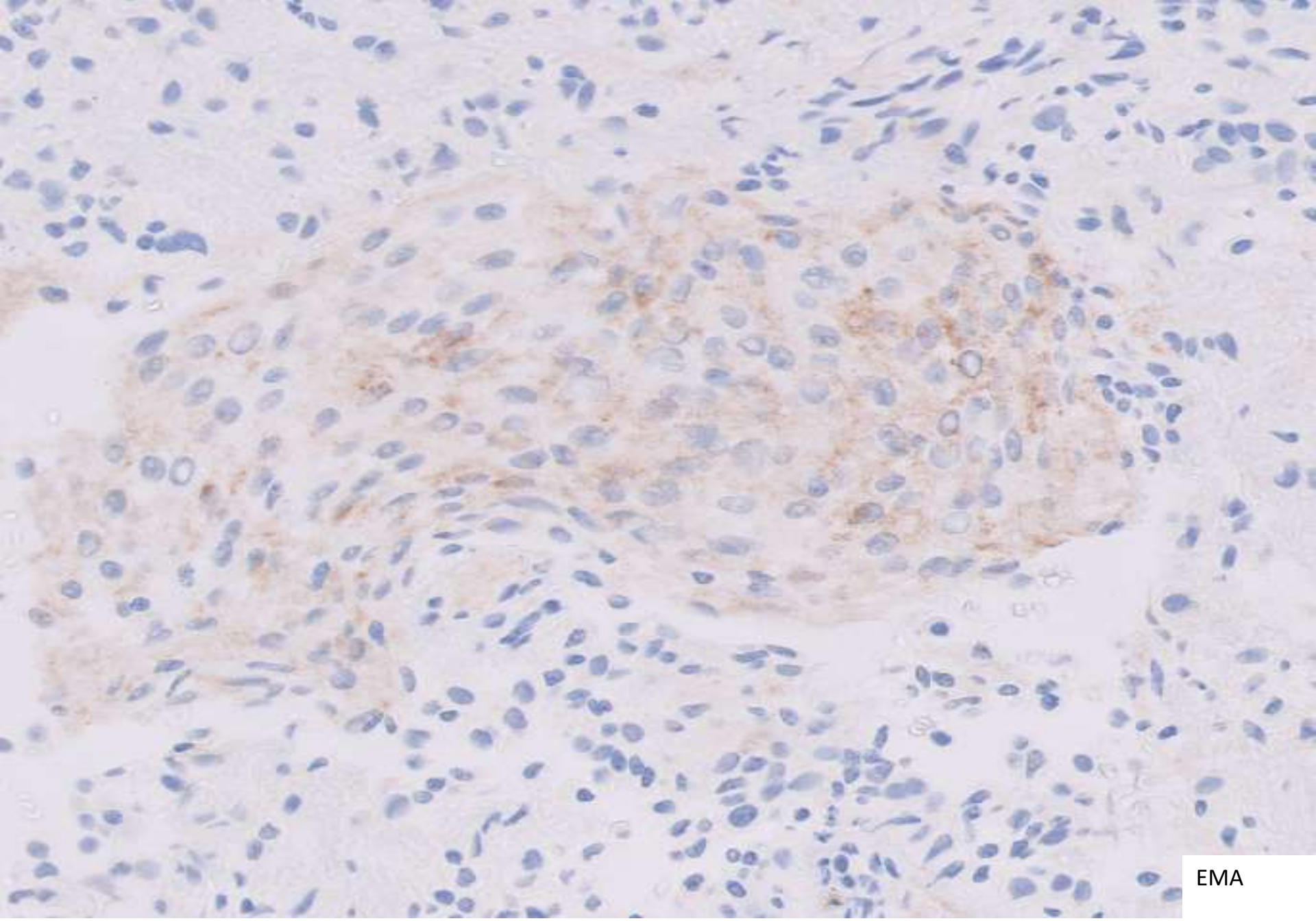




CD20



CD3

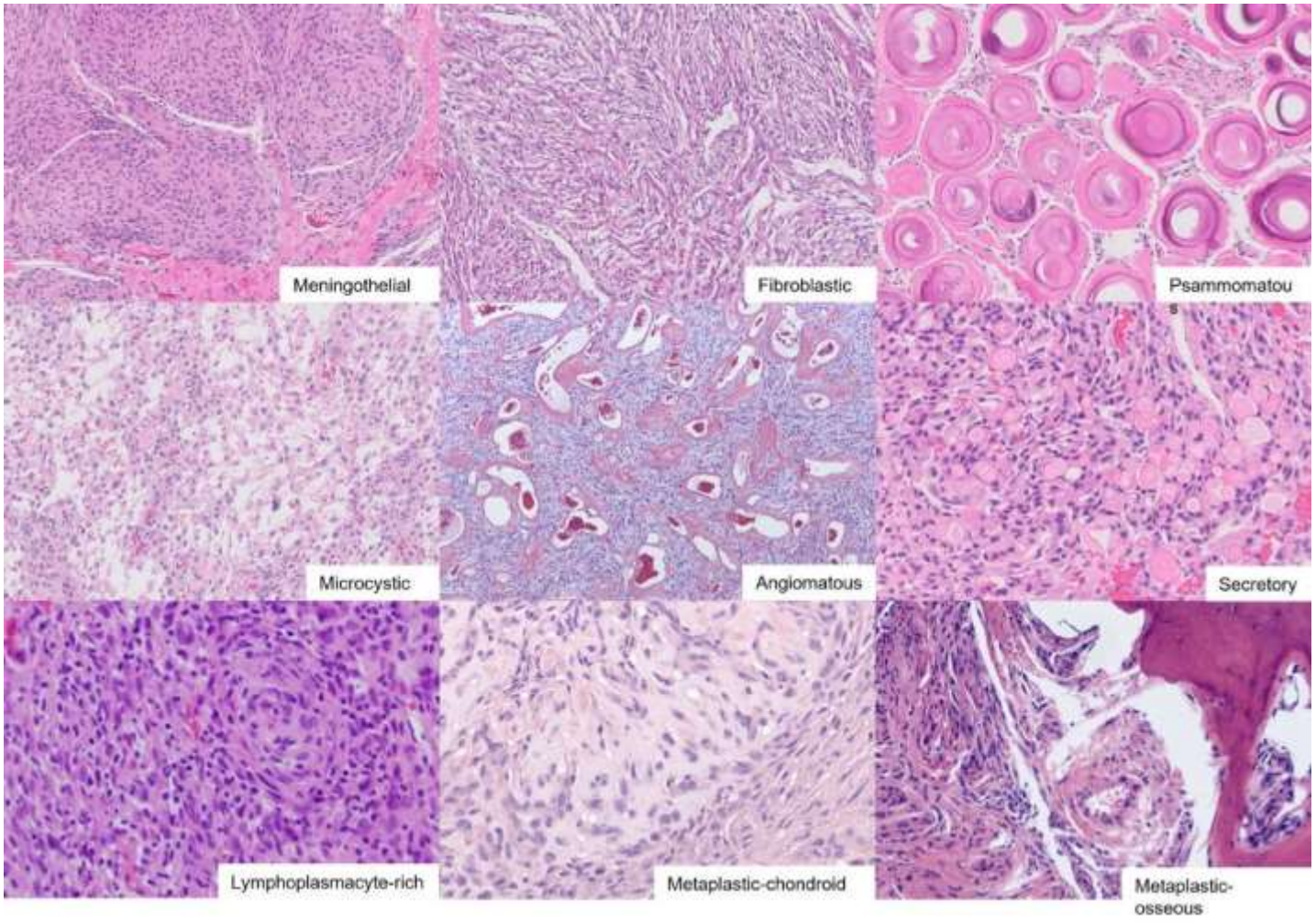


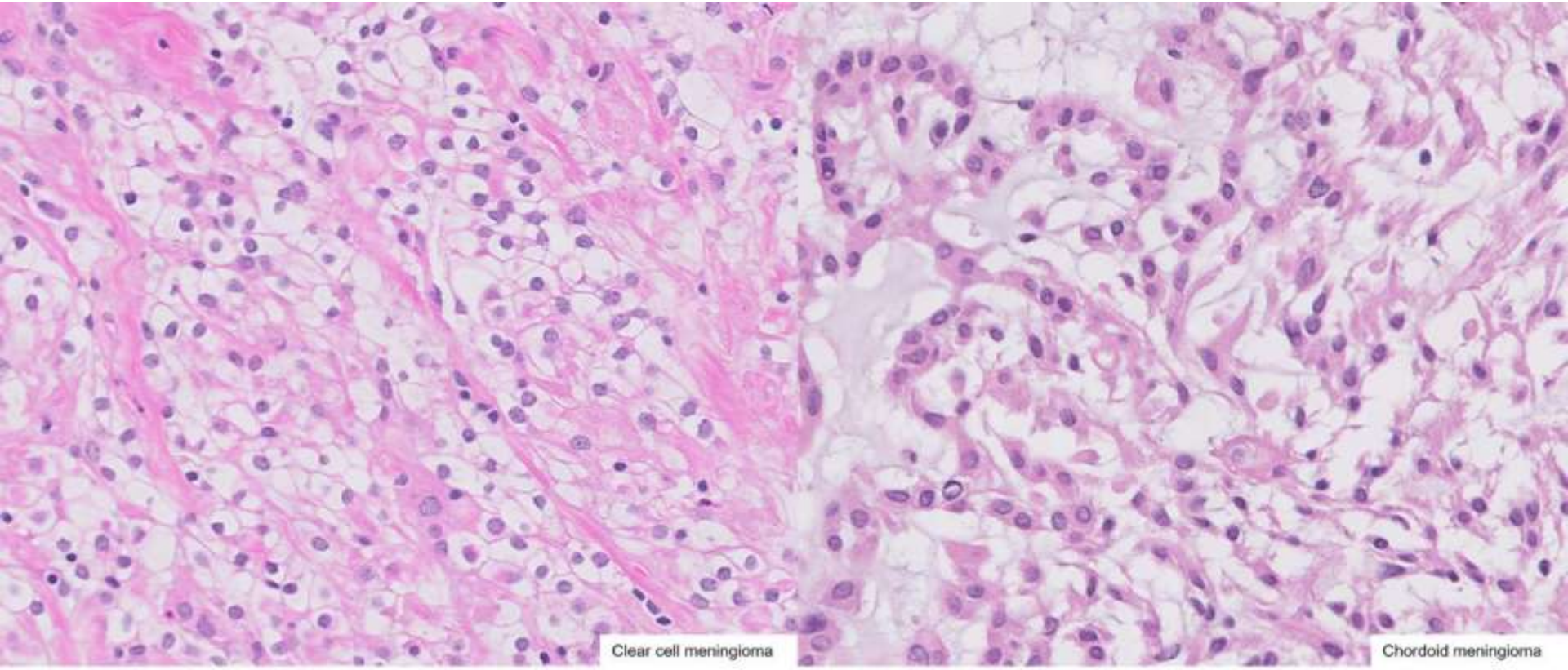
EMA

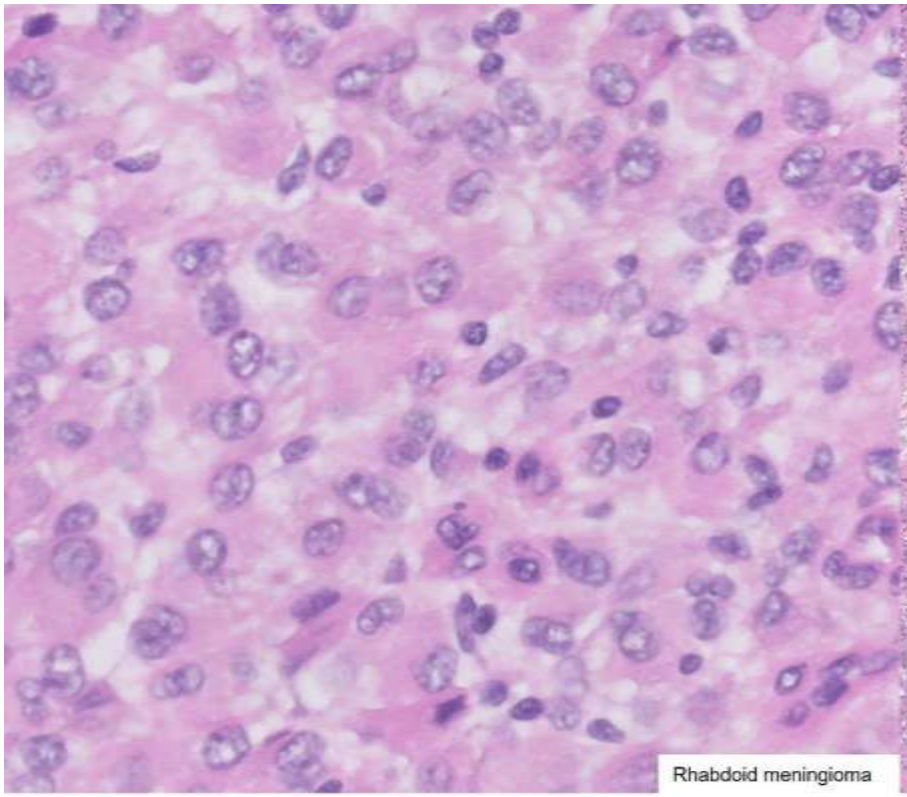
Meningioma

- Most common primary intracranial neoplasm in adults
- Increased incidence in females (2.3:1 F:M)
- Median age of diagnosis=66 years
- *NF2* gene mutations present in 40-60% of cases
  - Syndromic patients present earlier in life
- Prior radiation increases risk of development
- 13 histologic subtypes, 4 with grading implications
  - Mitotic activity, brain invasion, and additional "soft" histologic features
  - New molecular criteria: *CDKN2A/B* homozygous deletion OR *TERT* promoter mutation=grade 3

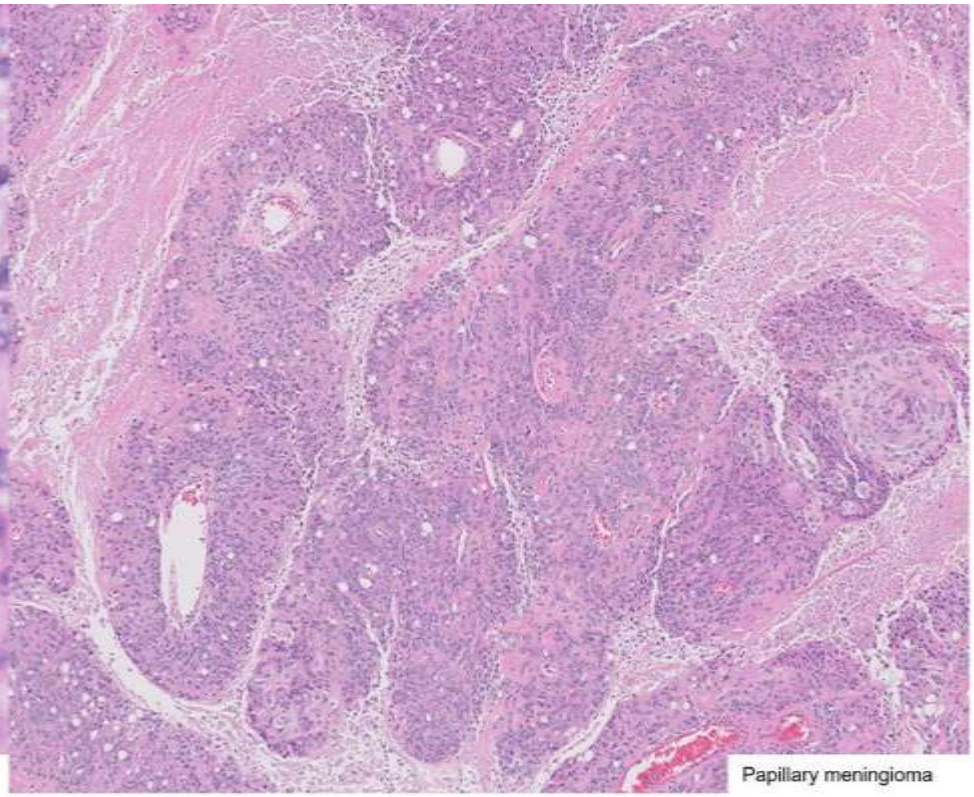
<table>
<tr><th colspan="3">WHO GRADE I</th></tr>
<tr><td>Meningothelial
Fibrous
Transitional
Psammomatous
Angiomatous</td><td colspan="2">Microcystic
Secretory
Metaplastic
Lymphoplasmacyte-rich</td></tr>
<tr><td colspan="3">WHO GRADE II</td></tr>
<tr><td><u>HISTOLOGIC FEATURES</u>
≥4 and ≤19 mitoses in 10 HPF
Brain parenchyma invasion
At least 3 of 5:
Sheeting architecture
Small cell change
Hypercellularity
Spontaneous necrosis
Prominent nucleoli</td><td colspan="2"><u>HISTOLOGIC SUBTYPES</u>
Clear Cell
Chordoid</td></tr>
<tr><td colspan="3">WHO GRADE III</td></tr>
<tr><td><u>HISTOLOGIC FEATURES</u>
≥20 mitoses in 10 HPF
Frank malignant (sarcoma, carcinoma, or melanoma) histology</td><td><u>HISTOLOGIC SUBTYPES</u>
Rhabdoid
Papillary</td><td><u>MOLECULAR</u>
TERT promoter mutation
CDKN2A/B homozygous deletion</td></tr>
</table>


Meningothelial
Fibroblastic
Psammomatous
Microcystic
Angiomatous
Secretory
Lymphoplasmacyte-rich
Metaplastic-chondroid
Metaplastic-osseous


Clear cell meningioma
Chordoid meningioma



Rhabdoid meningioma



Papillary meningioma

Lymphoplasmacyte-rich meningioma

- Rare histologic subtype with no specific grading implications
  - Significance of inflammation is unknown
- F:M~1:1, mean age ~40-45
- Meningioma and histologic features may be difficult to identify
  - Histologic grading criteria still apply
- Inflammation is mixed lymphocytes and plasma cells (often abundant macrophages as well)
  - Increased IgG4+ cells may be present
- Meningothelial cells EMA and SSTR2A+
- Differential may include lymphoproliferative disease, plasmacytoma, IgG4-related disease, Rosai-Dorfman disease, pachymeningitis, and infectious
  - Inflammatory conditions may induce meningothelial hyperplasia

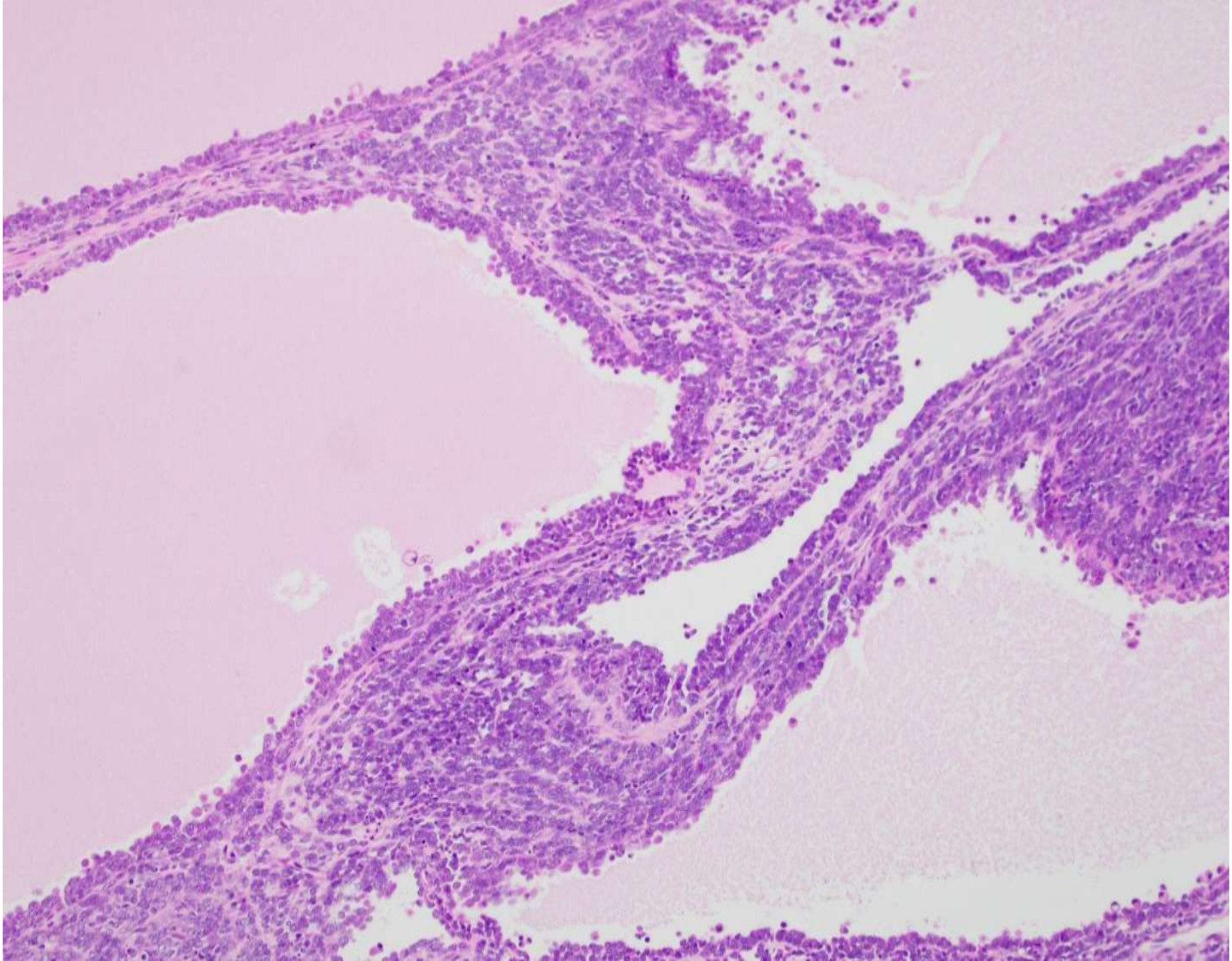
References

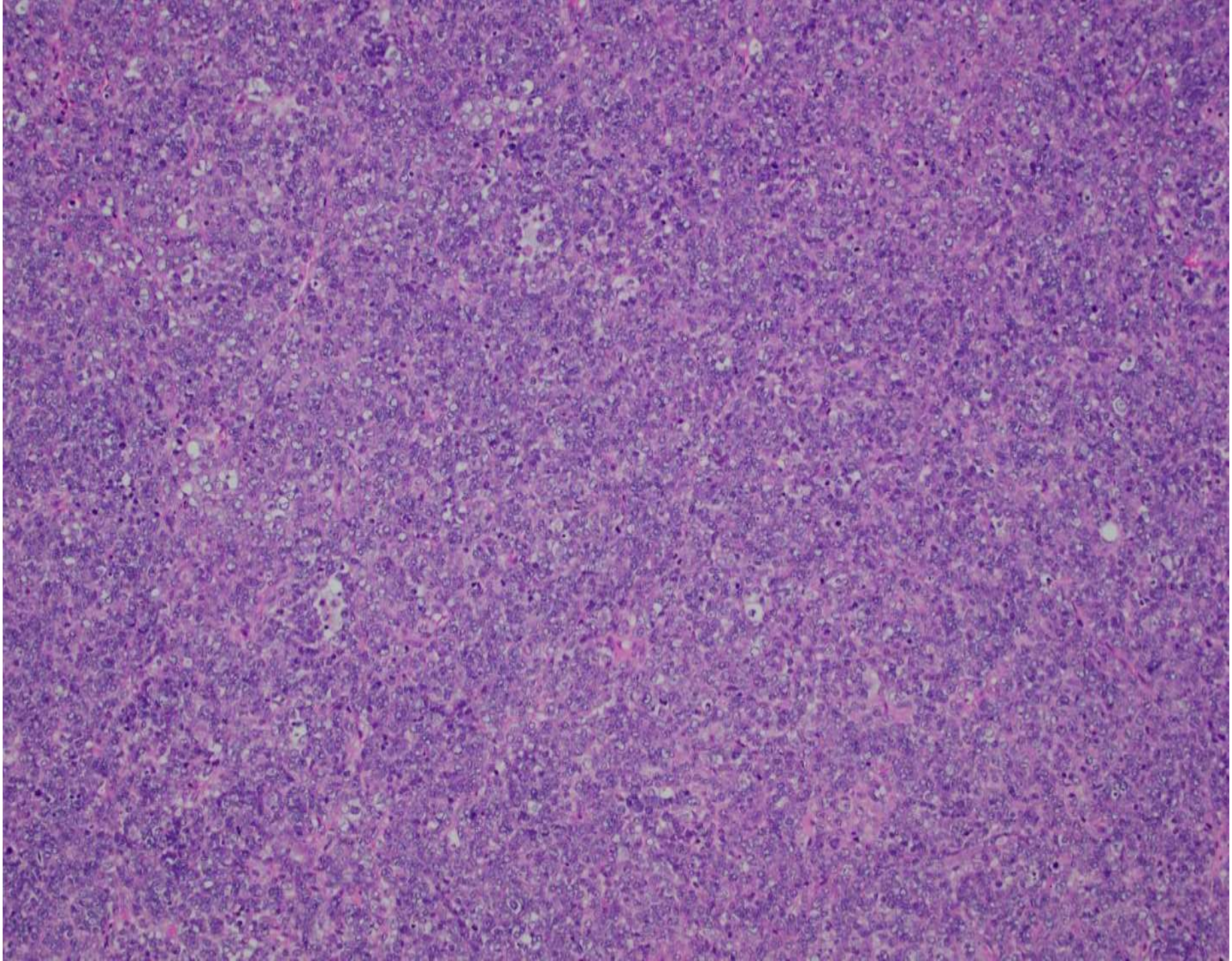
- Son HJ, Yu IK, Kim SM. Lymphoplasmacyte-Rich Meningioma With Atypical Angiomatous Feature and an Increased Deposition of IgG4-Positive Plasma Cells: An Unusual Case Report. Int J Surg Pathol. 2018 Feb;26(1):93-97.
- Tao X, Wang K, et. al. Clinical, Radiologic, and Pathologic Features of 56 Cases of Intracranial Lymphoplasmacyte-Rich Meningioma. World Neurosurg. 2017 Oct;106:152-164.

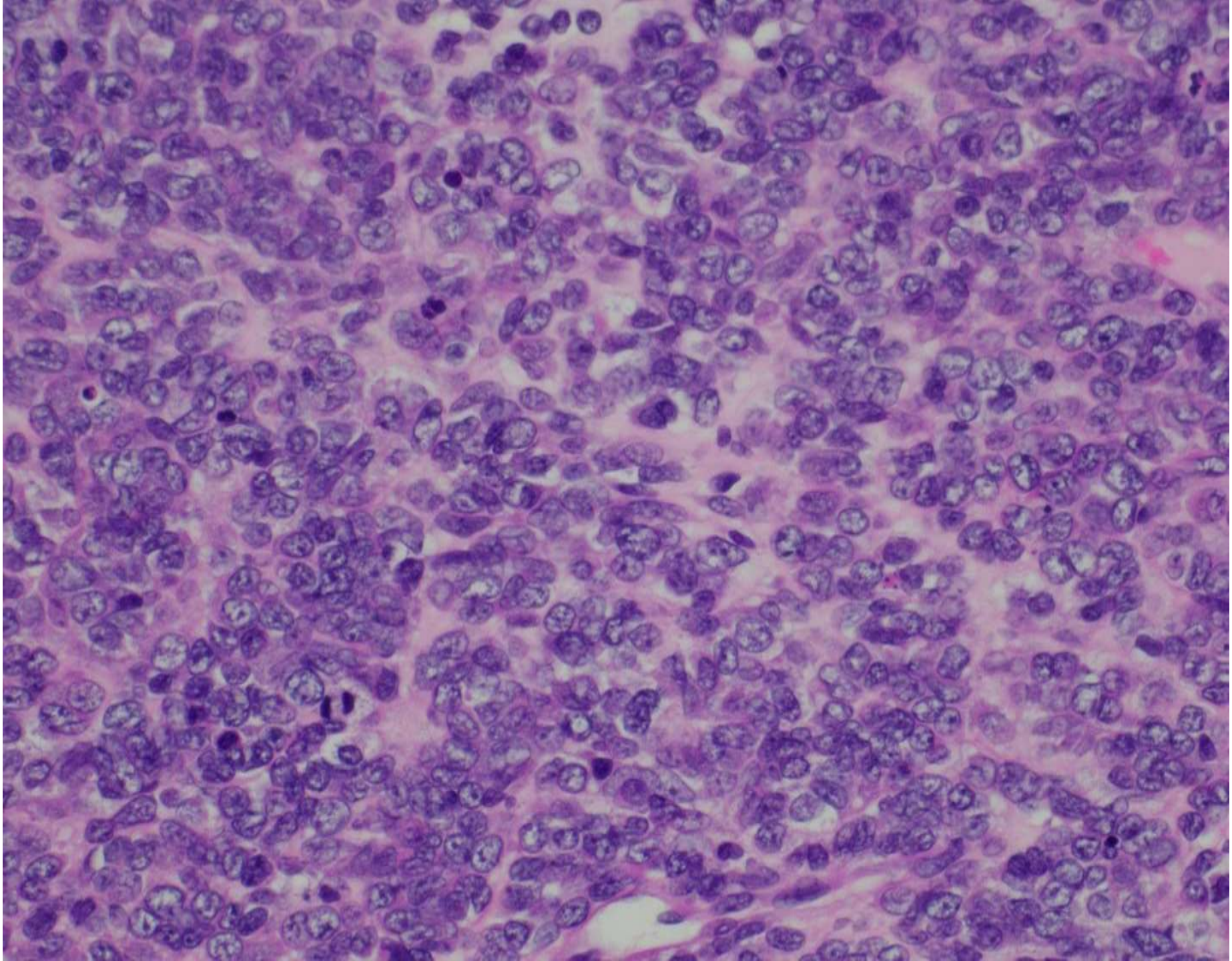
22-0603

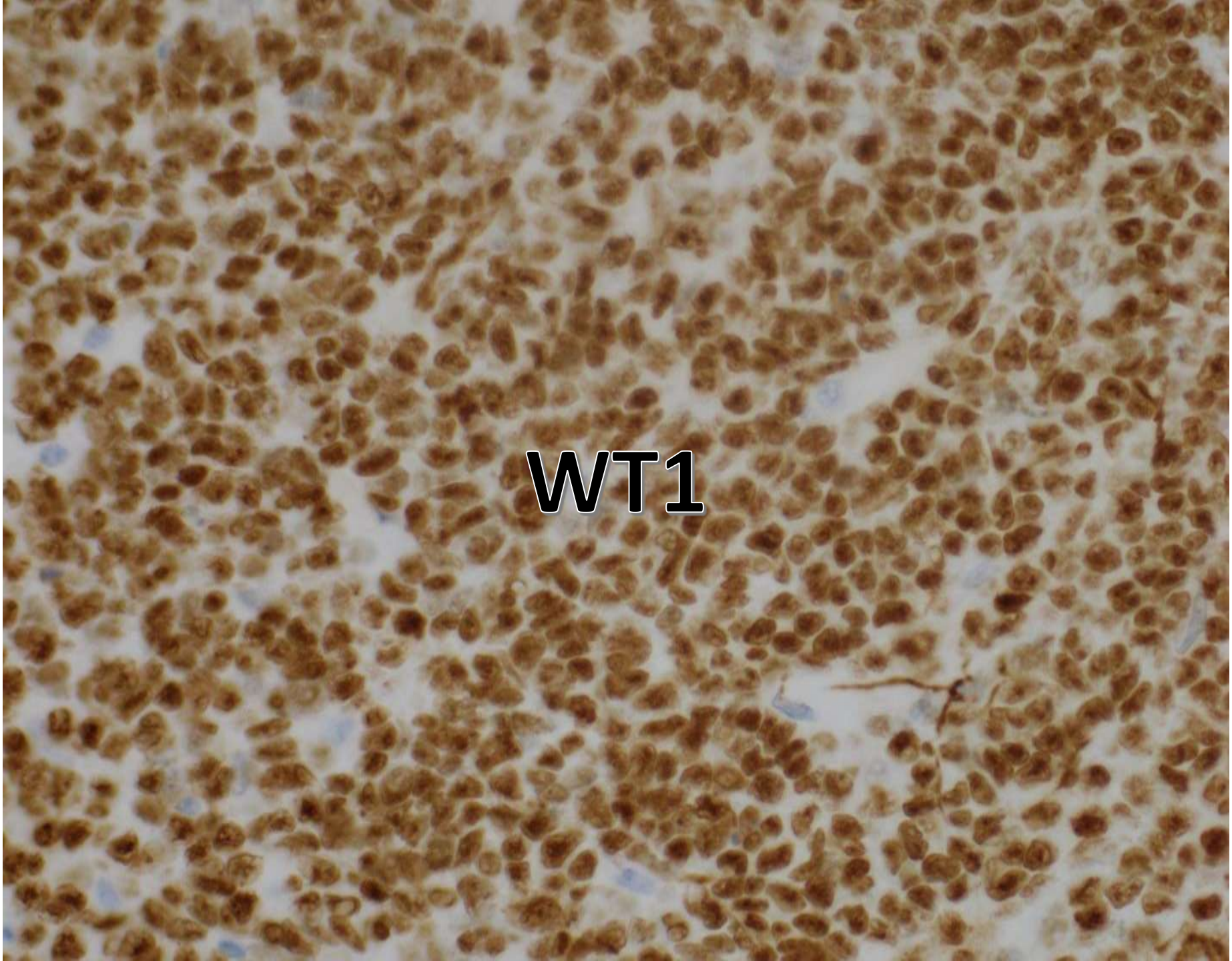
Caroline Temmins; Santa Clara Valley Medical Center

30ish G0P000 who presented with abdominal pain, nausea, vomiting and poor PO intake was found to have 13cm heterogenous adnexal mass. Right ovary submitted.



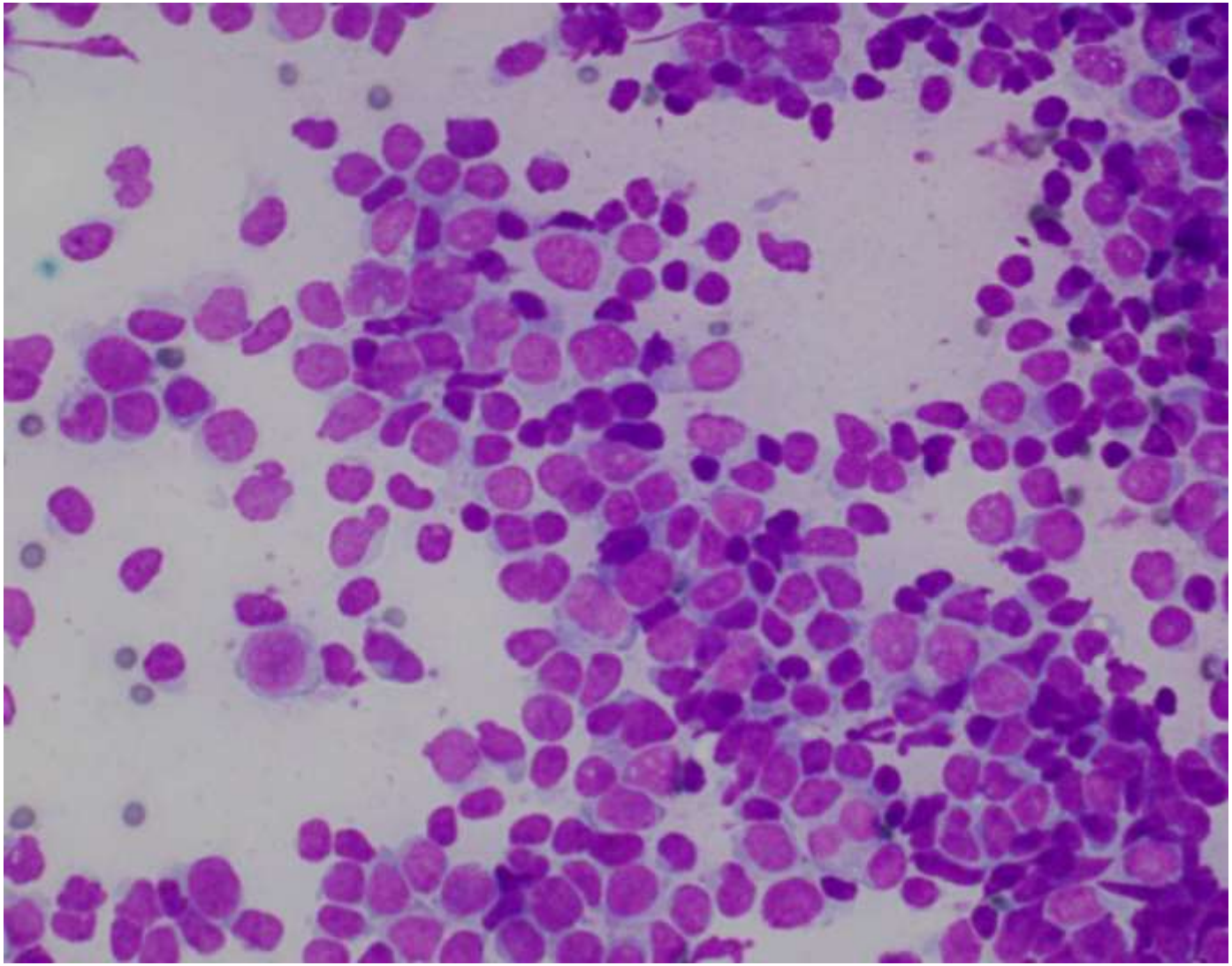


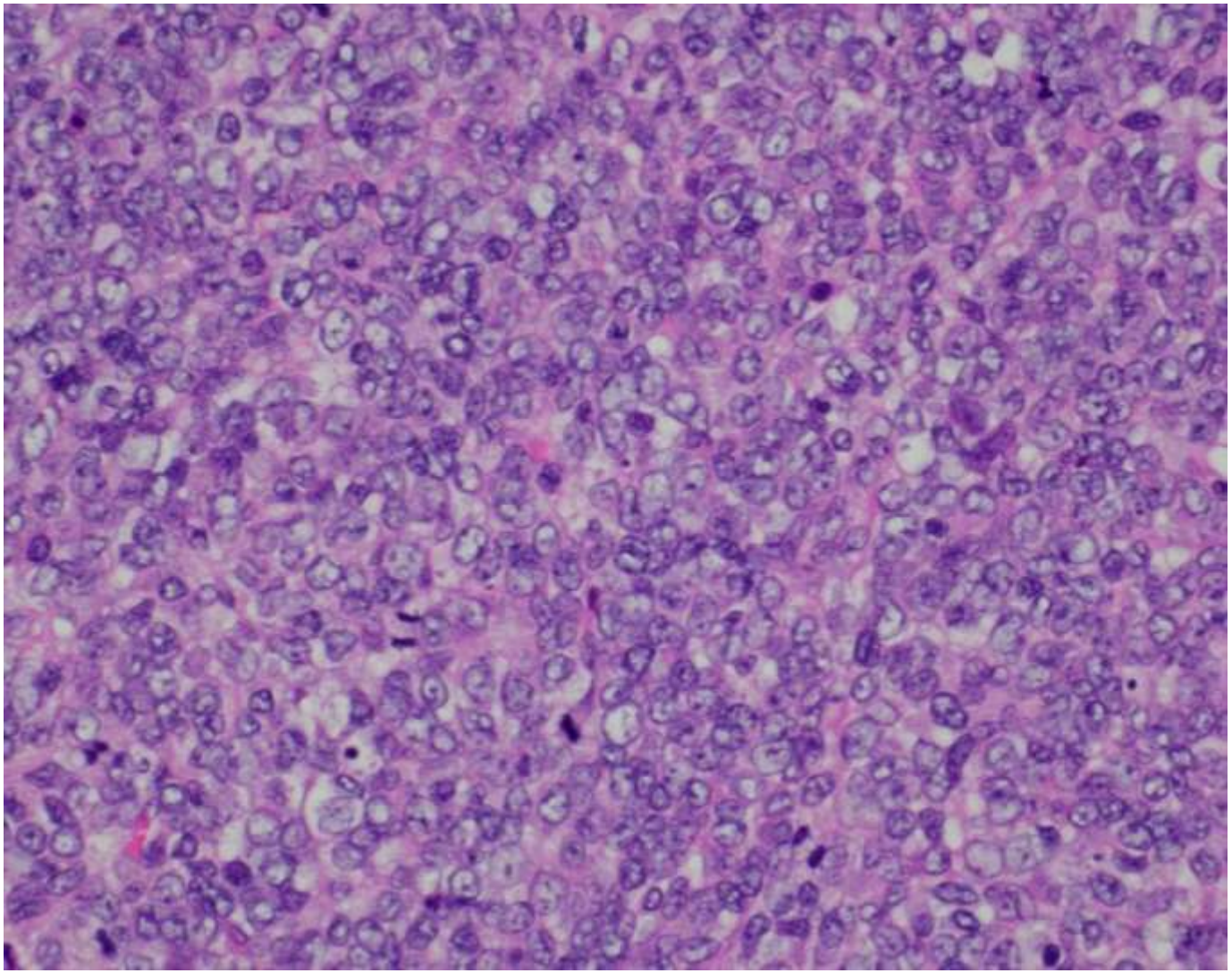


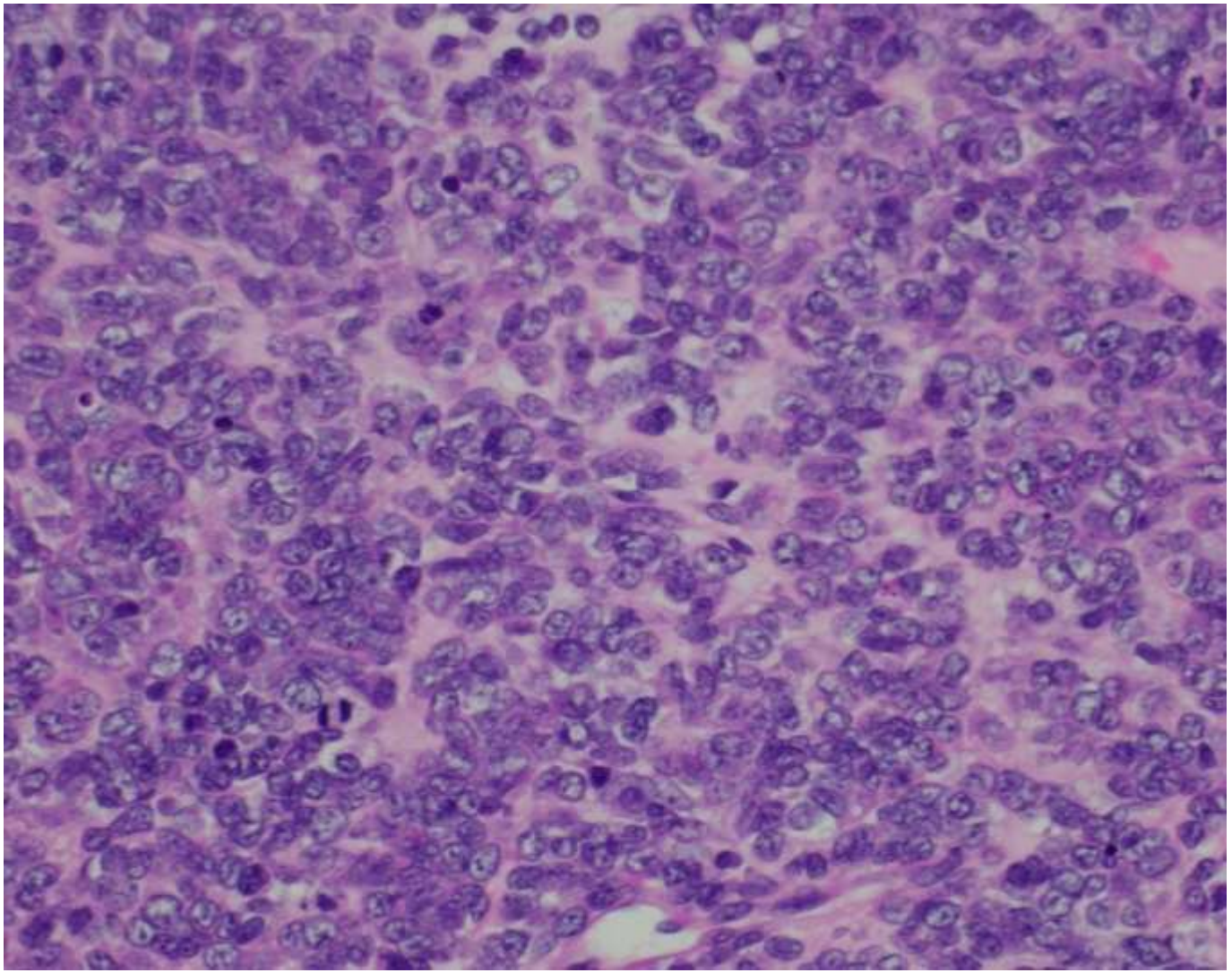

WT1

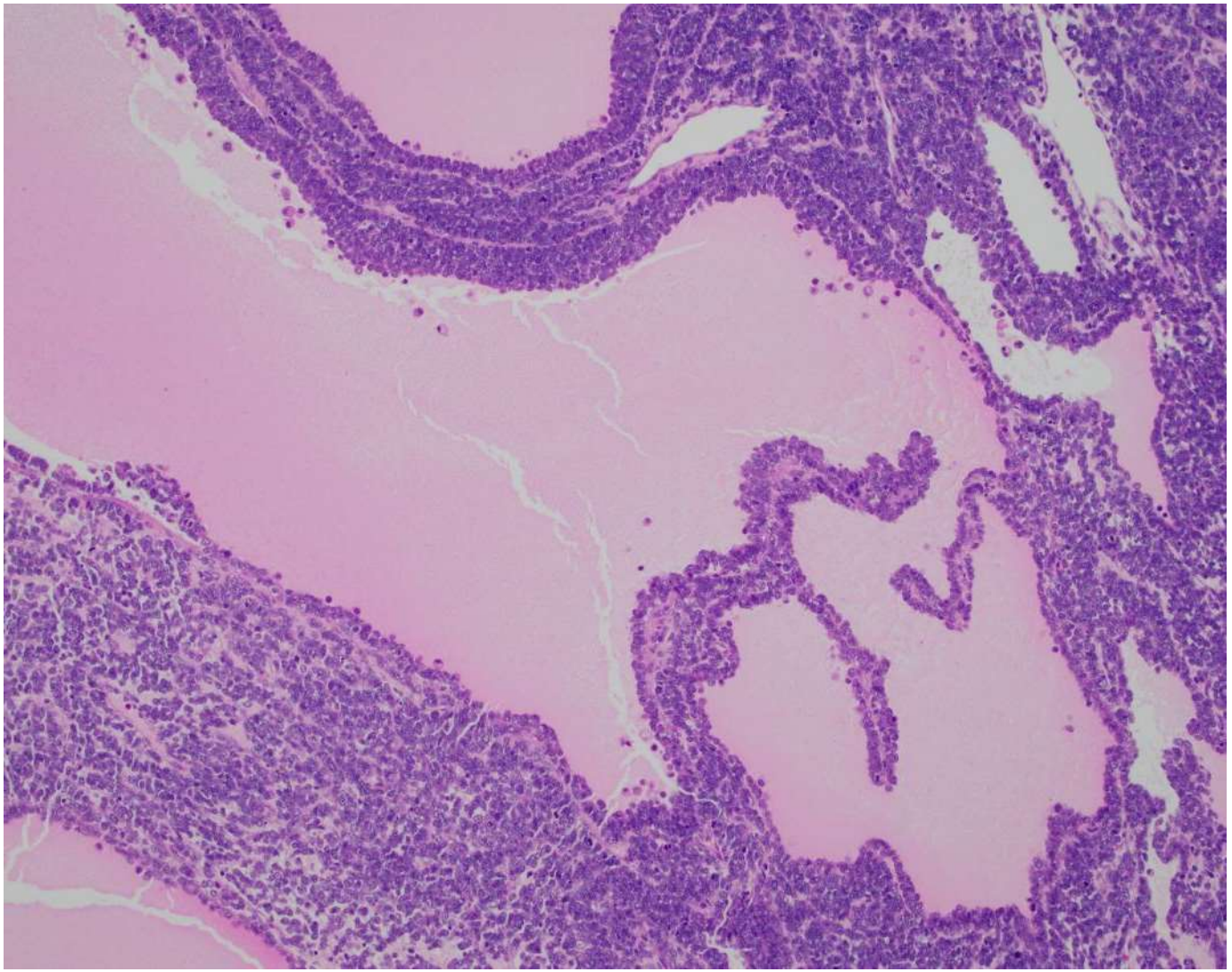
Clinical history

- 30(ish) year old G0P0000 who presented with abdominal pain, nausea, vomiting, and poor PO intake, admitted to medicine service for management of severe hypercalcemia and a large heterogeneous adnexal mass.
- Transferred to gyn onc service, taken to OR 2/8/22.



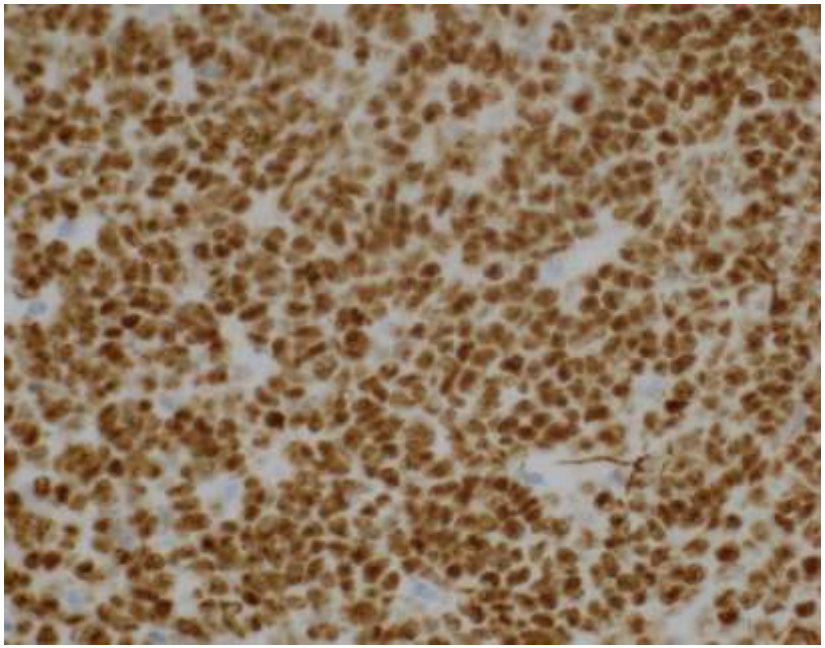


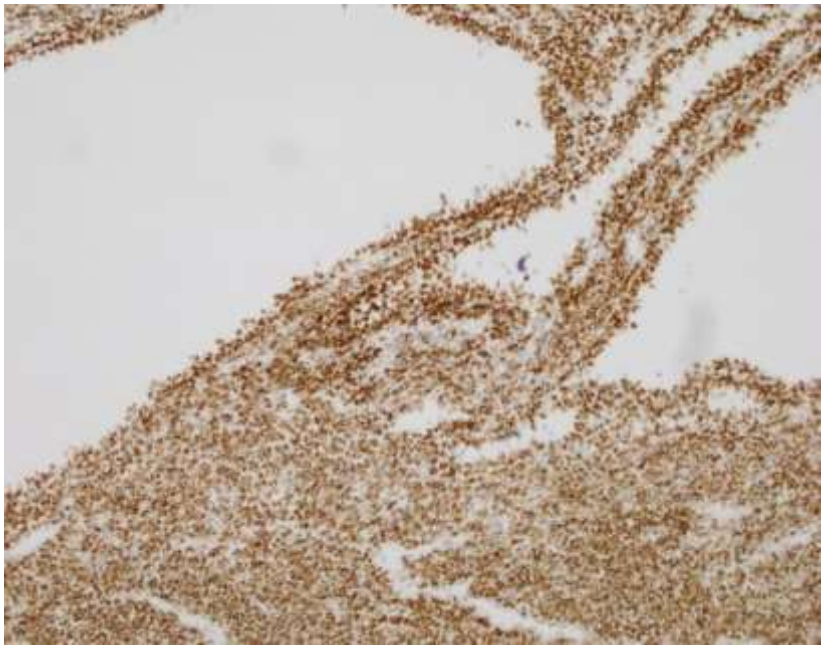




- Small round blue cell tumor.
- Differential:
  - Small cell carcinoma, hypercalcemic type
  - Lymphoma
  - Granulosa cell tumor

WT1 immunohistochemistry





Additional stains

- Synaptophysin: rare, dot like positivity
- Chromogranin: negative
- P53: patchy, wild-type
- CD45: negative
- CD10: negative
- CKAE1/AE3: rare positive cells
- EMA: negative
- Inhibin: negative
- S100: negative
- CAM5.2: negative
- BRG1(SMARCA4): complete loss of expression

Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT)

- Initially described by Dr. Robert Scully 1982
- Rare: represents less than 0.01% of all ovarian malignancies
- Two distinct clinical features:
  - First, SCCOHT patients are young. In the large cohort of Young et al., the patients ranged from 9 to 43 (average 23.9) years of age.
  - Second, preoperative calcium levels are elevated in about 62% patients. Thus, the term "hypercalcemic type" has been applied to distinguish it from ovarian small cell carcinoma of the pulmonary type (SCCOPT), a high grade neuroendocrine carcinoma
- Genetic inactivation of members of the SWI/SNF complex, including BRG-1(SMARCA4) or more rarely INI-1(SMARCB1) is the defining molecular event.
- 50% of patients with SCCOHT found to have germline mutations, even without prior family history of disease.

Clinical behavior and treatment

- SCCOHT is a *highly aggressive* tumor.
- Extraovarian spread is seen in approximately half of the cases. Lymph node metastasis is present in 19/34 (55.8%) cases.
- **Tumor stage** remains the mainstay in the assessment of prognosis.
  - Young et al. reported that one third patients (14/42) at FIGO (International Federation of Gynecology and Obstetrics) stage Ia survived free of disease 1-13 years after surgery whereas almost all patients at an advanced stage died of disease.

Clinical behavior and treatment

- The rarity of SCCOHT limits the implementation of randomized clinical trial.
- no consensus of the standard treatment
- Recent data have indicated that a multi-modality treatment approach consisting of surgery, high dose multi-agent chemotherapy with possible stem cell transplantation and radiotherapy is an attractive treatment option for the SCCOHT patients

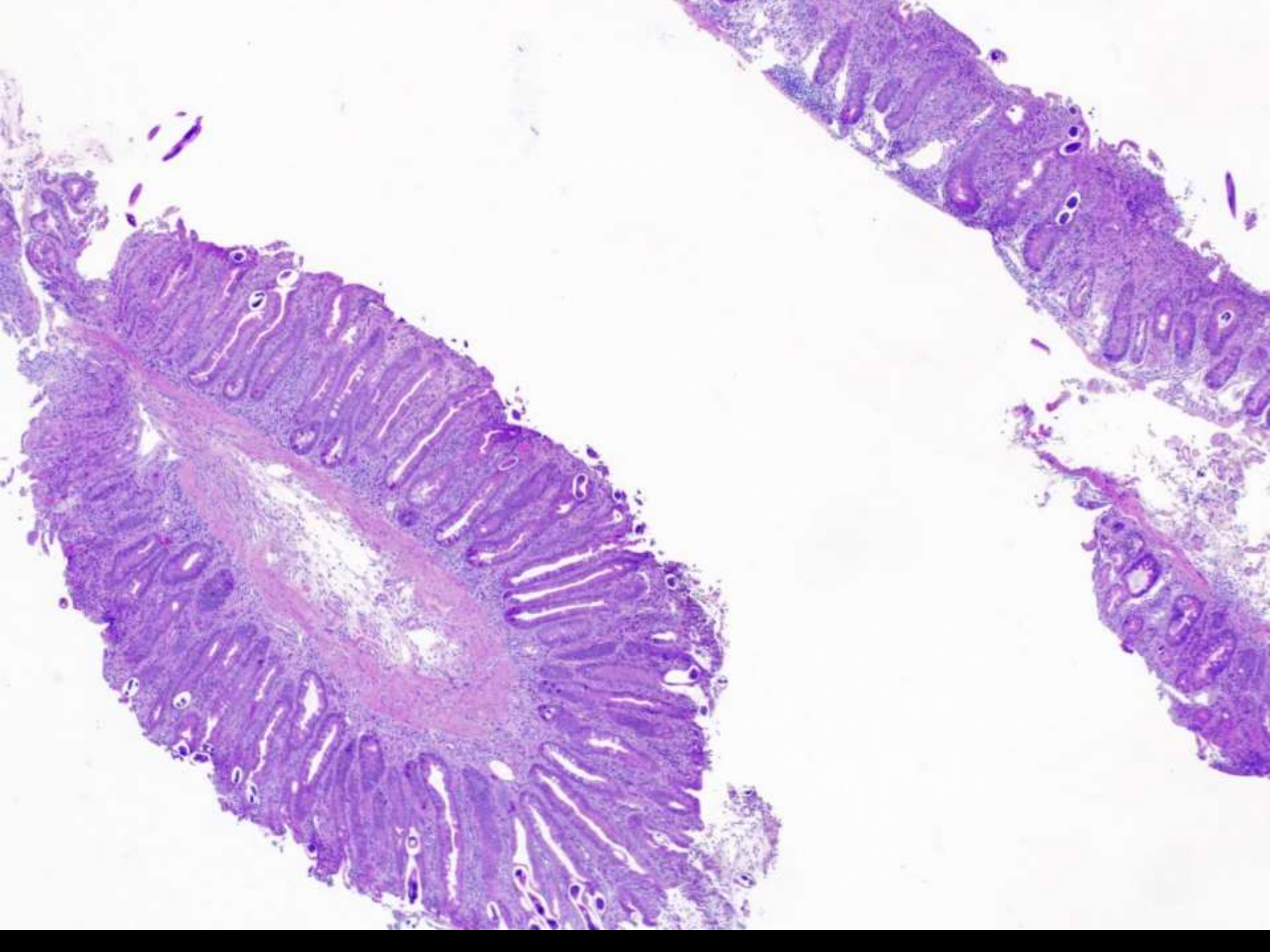
References

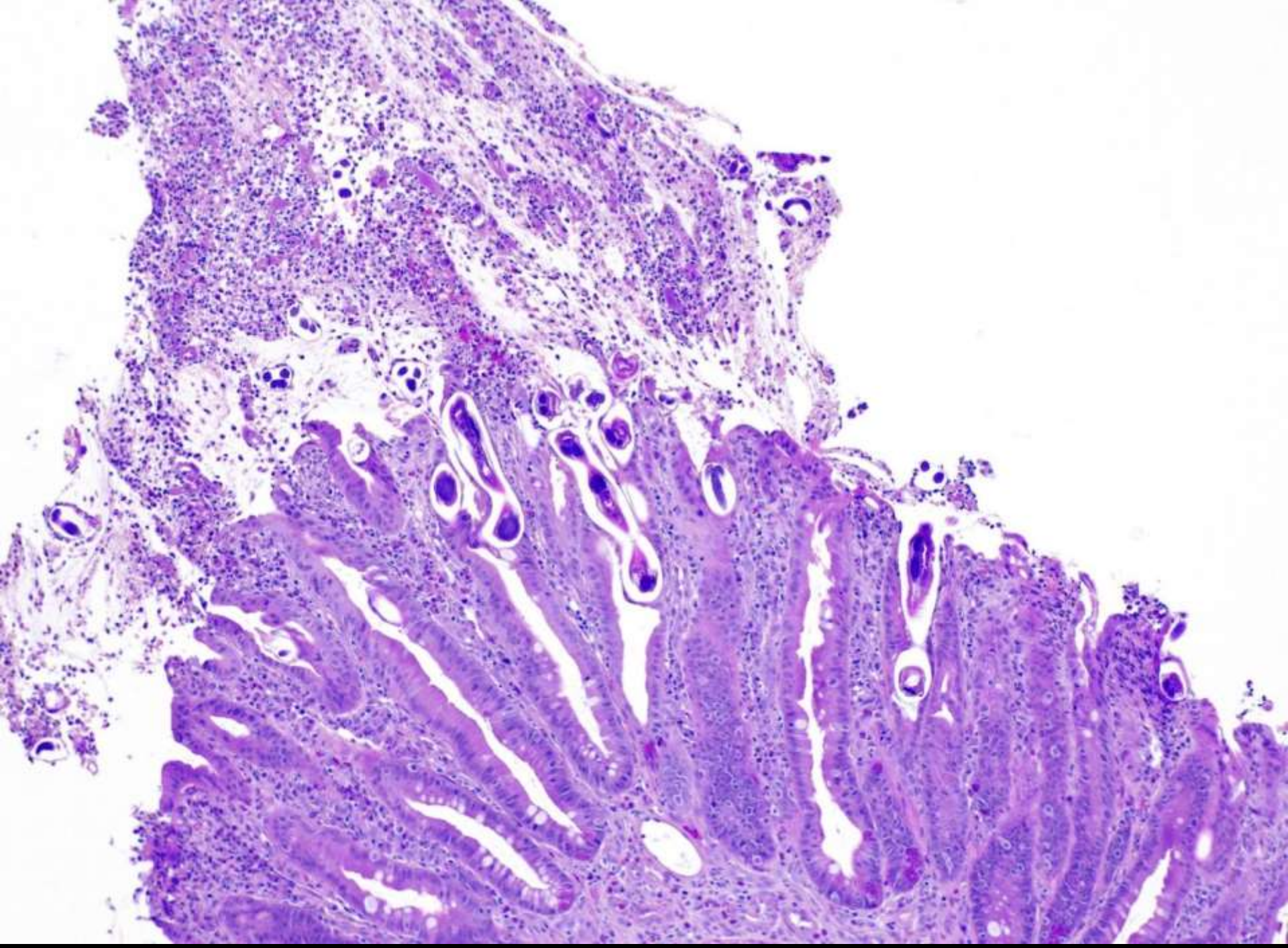
- 1. Dickersin GR, Kline IW, Scully RE. **Small cell carcinoma of the ovary with hypercalcemia, a report of eleven cases**. *Cancer.* 1982;**49**:188-97
- 2. Young RH, Oliva E, Scully RE. **Small cell carcinoma of the ovary.; hypercalcemic type. A clinicopathological analysis of 150 cases**. *Am J Surg Pathol.* 1994;**18**:1102-16

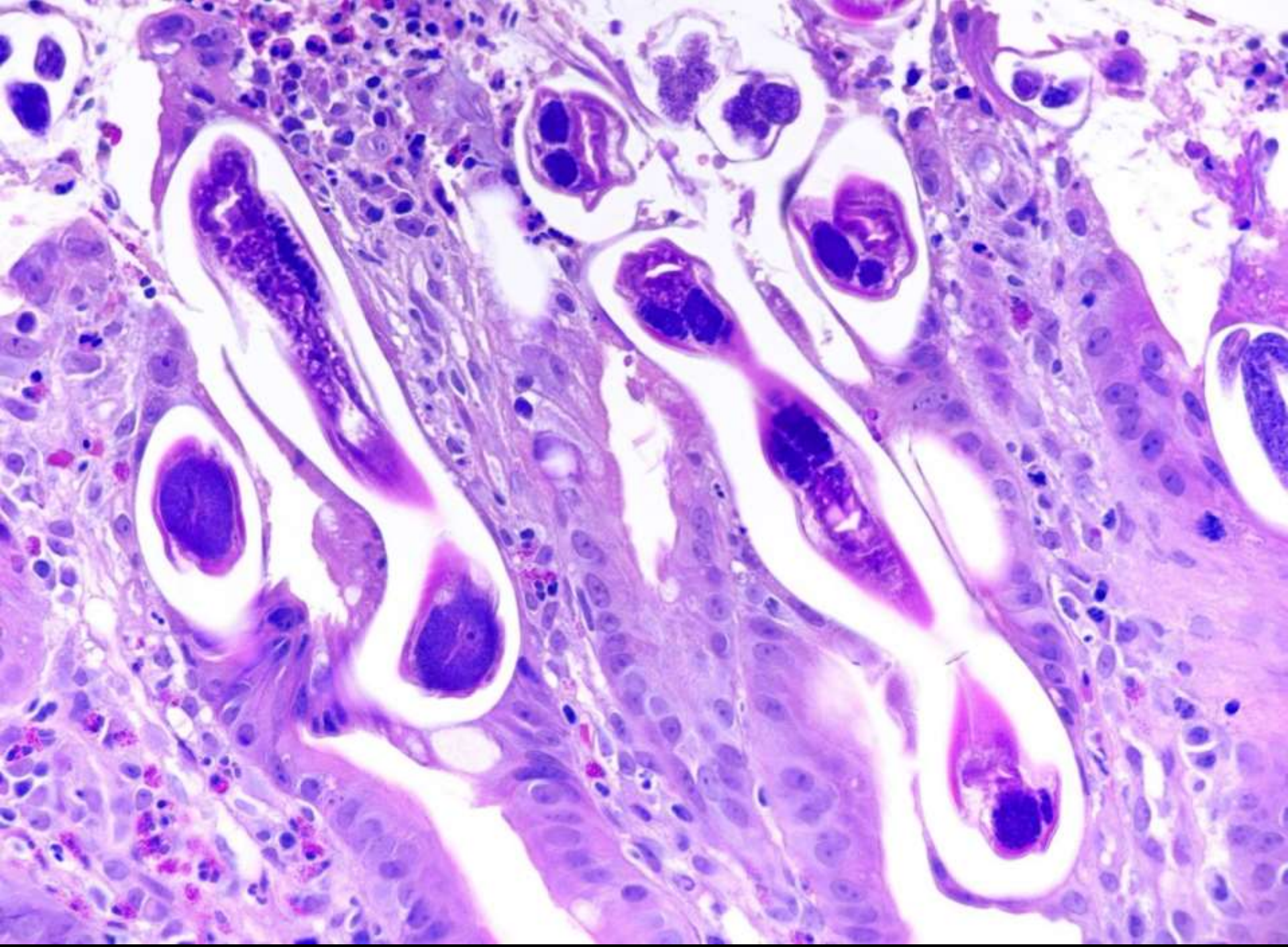
22-0604

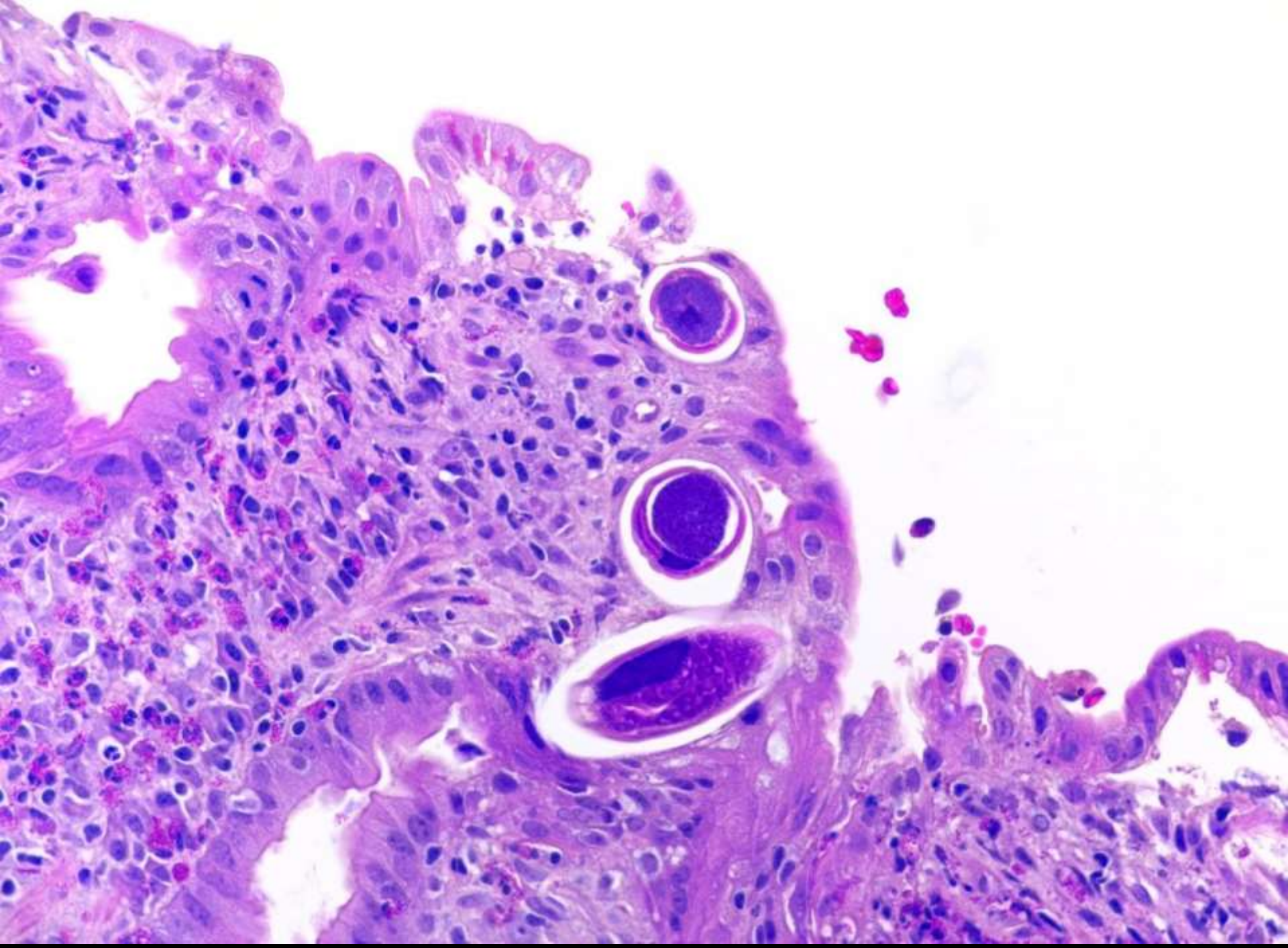
John Higgins; Stanford

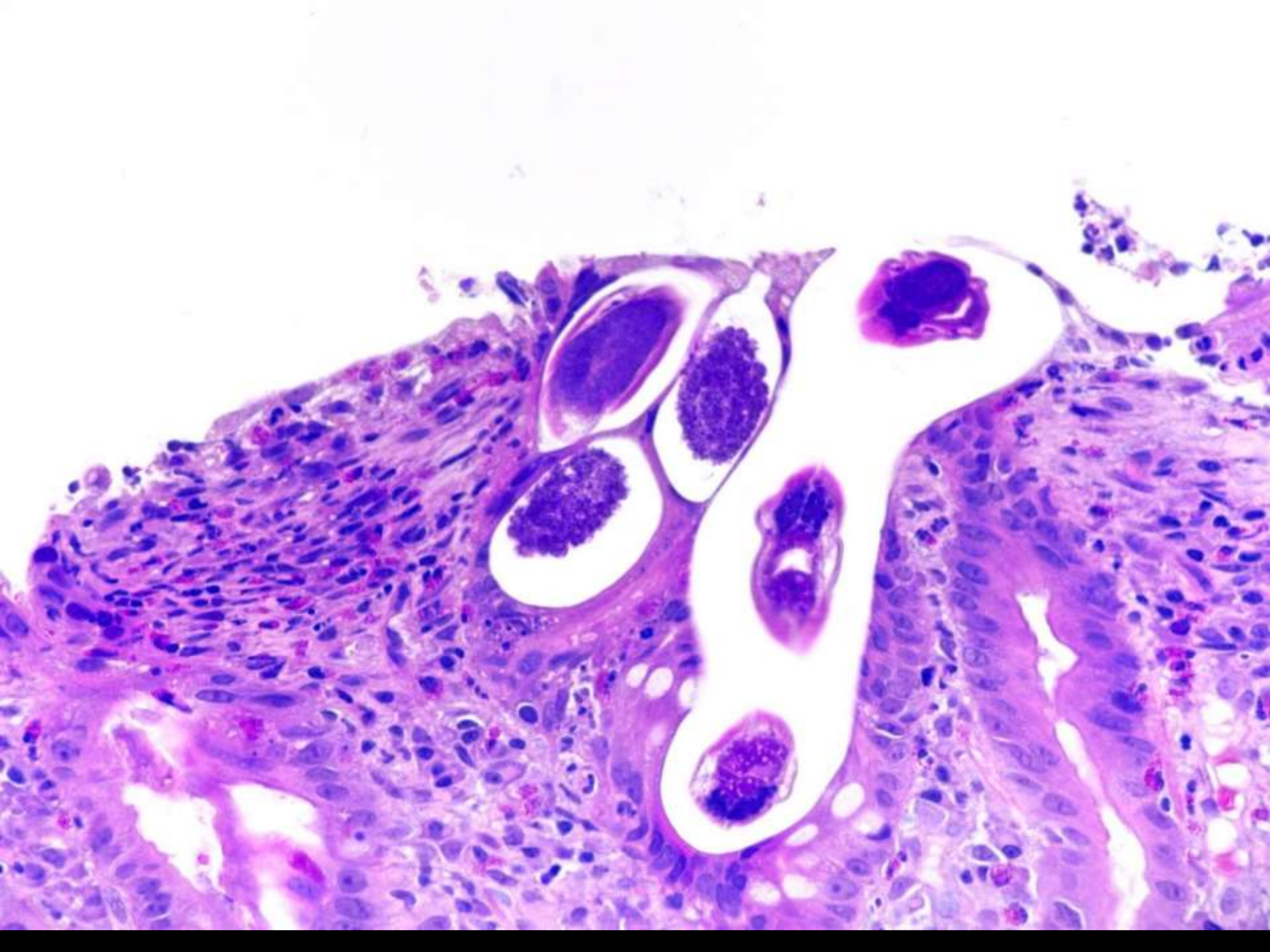
60ish M who underwent liver transplant 1 year ago. He now presents with dysphagia and abdominal pain. He was found to have duodenitis. Duodenal bx submitted.

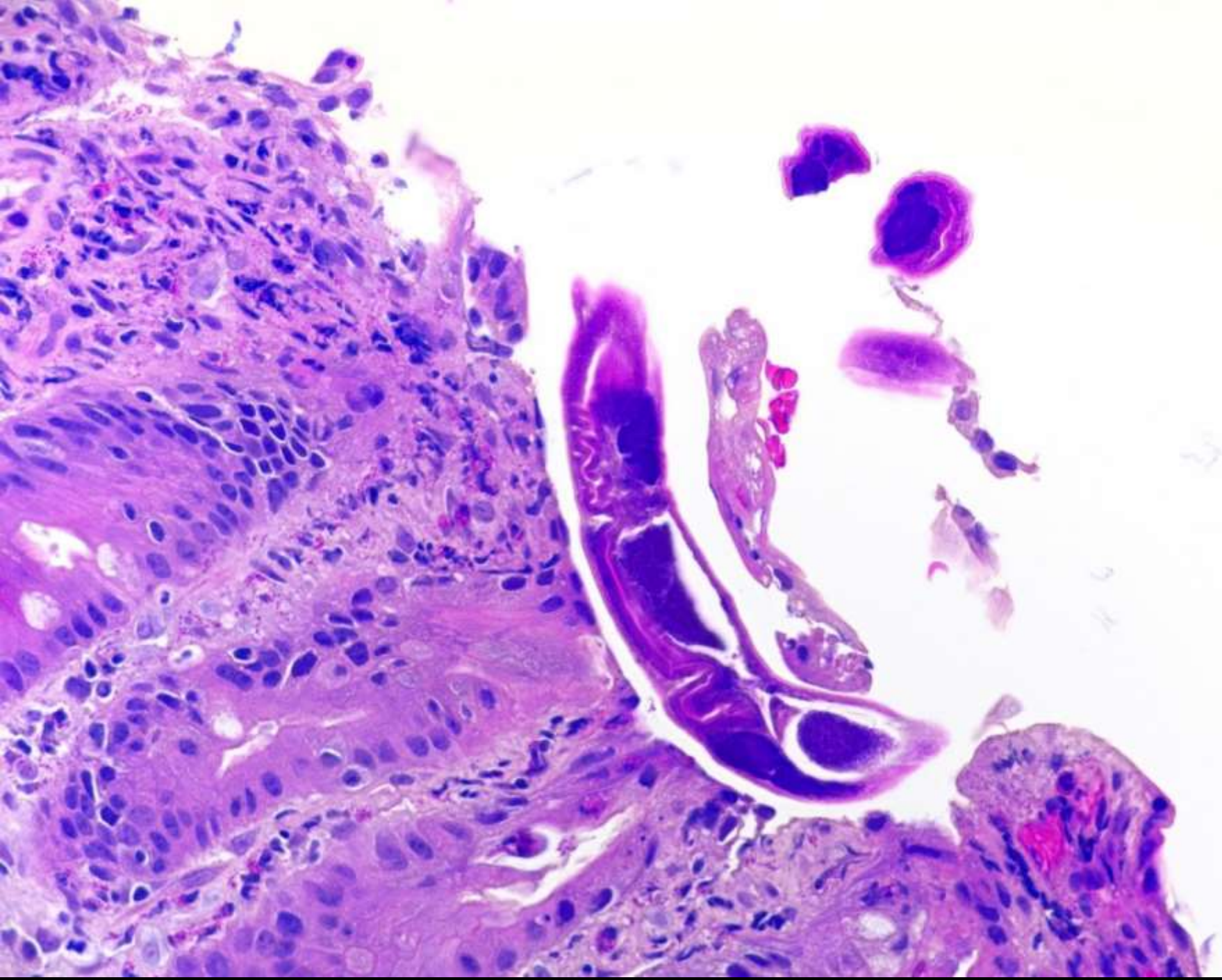




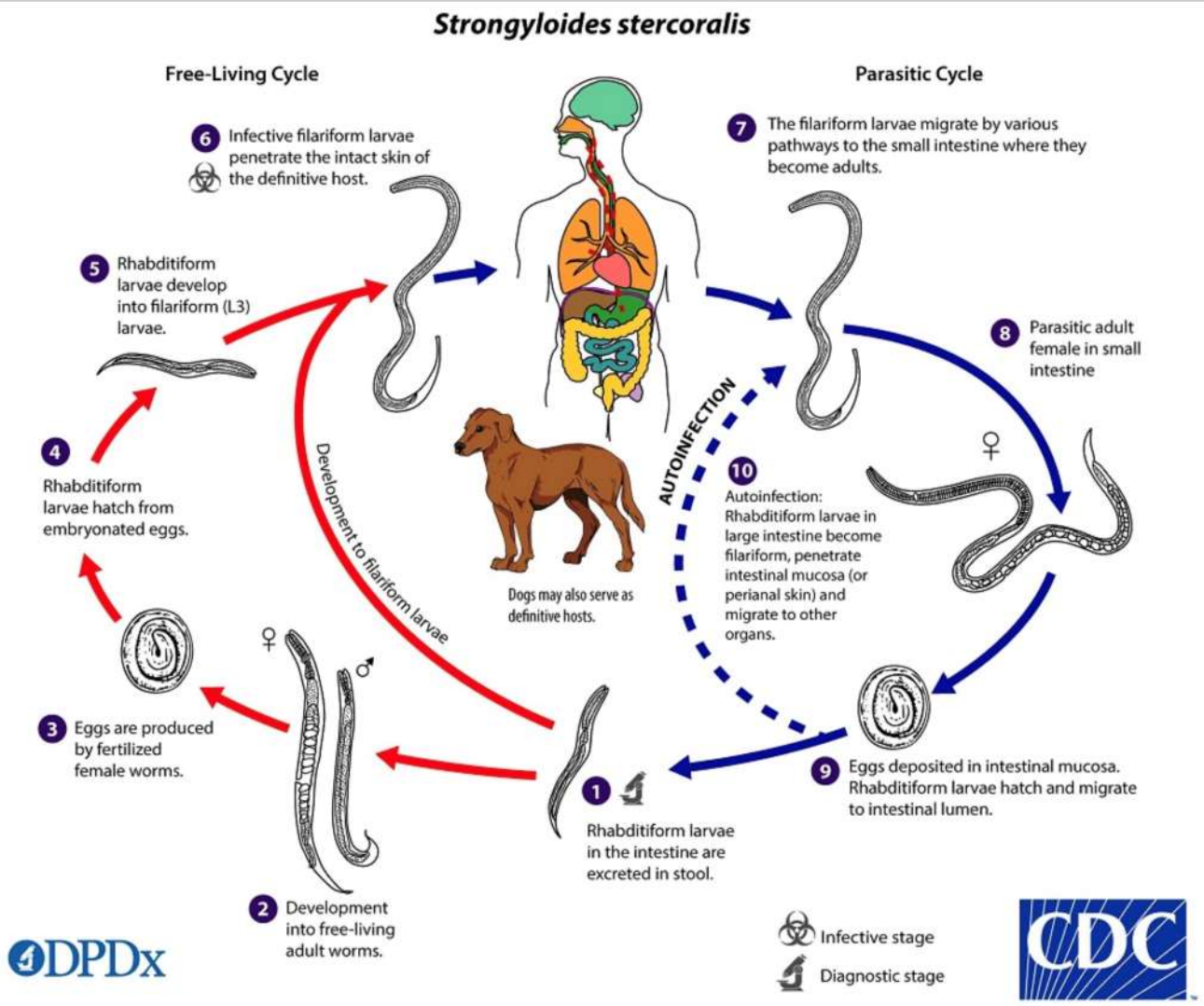








Diagnosis:
Strongyloides stercoralis


Strongyloides stercoralis
Free-Living Cycle
Parasitic Cycle
6 Infective filariform larvae penetrate the intact skin of the definitive host.
7 The filariform larvae migrate by various pathways to the small intestine where they become adults.
5 Rhabditiform larvae develop into filariform (L3) larvae.
8 Parasitic adult female in small intestine
4 Rhabditiform larvae hatch from embryonated eggs.
Development to filariform larvae
AUTOINFECTION
10 Autoinfection: Rhabditiform larvae in large intestine become filariform, penetrate intestinal mucosa (or perianal skin) and migrate to other organs.
Dogs may also serve as definitive hosts.
3 Eggs are produced by fertilized female worms.
9 Eggs deposited in intestinal mucosa. Rhabditiform larvae hatch and migrate to intestinal lumen.
1 Rhabditiform larvae in the intestine are excreted in stool.
2 Development into free-living adult worms.
DPDx
Infective stage
Diagnostic stage
CDC

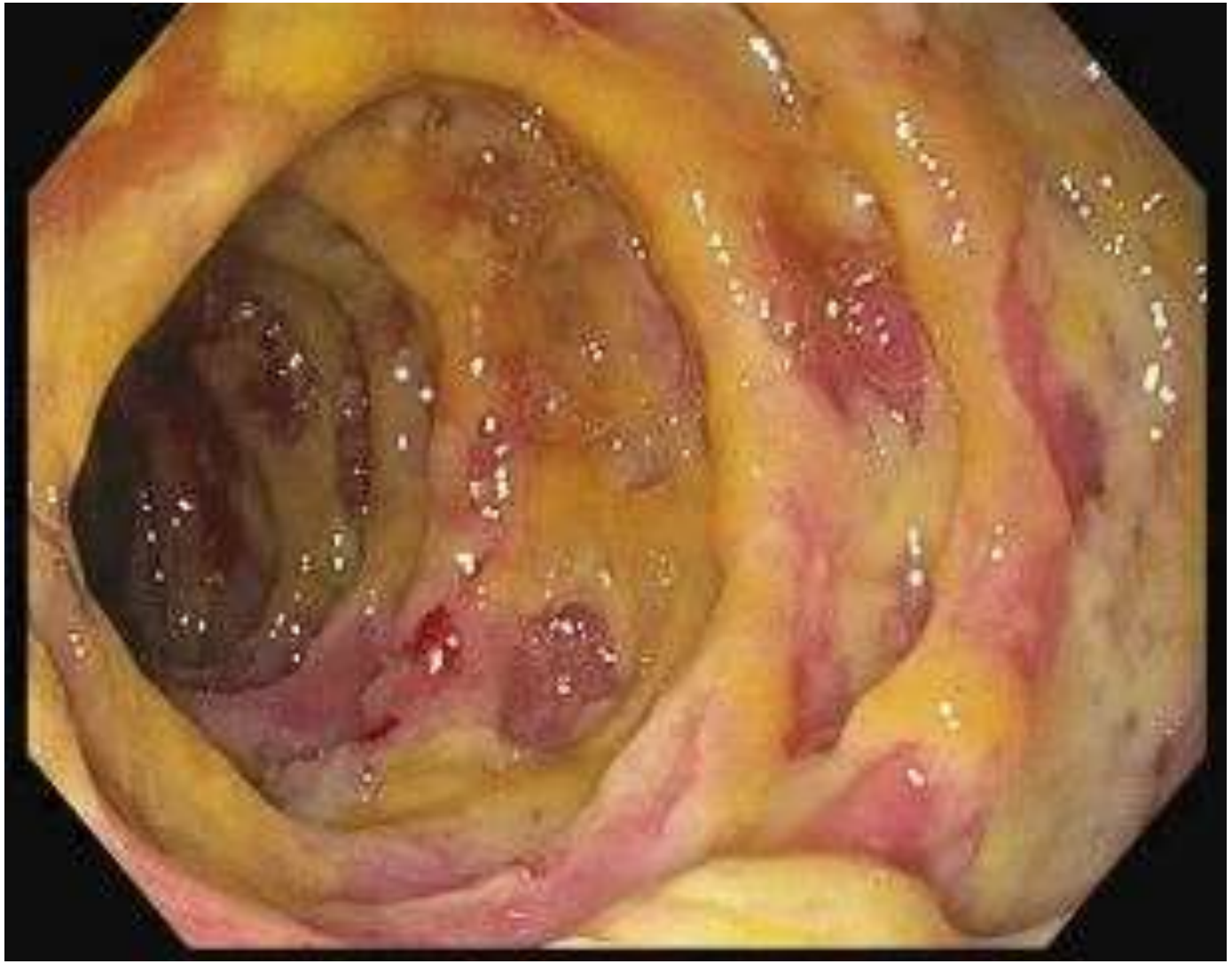
Intestinal Strongyloidiasis
Recognition, Management, and Determinants of Outcome

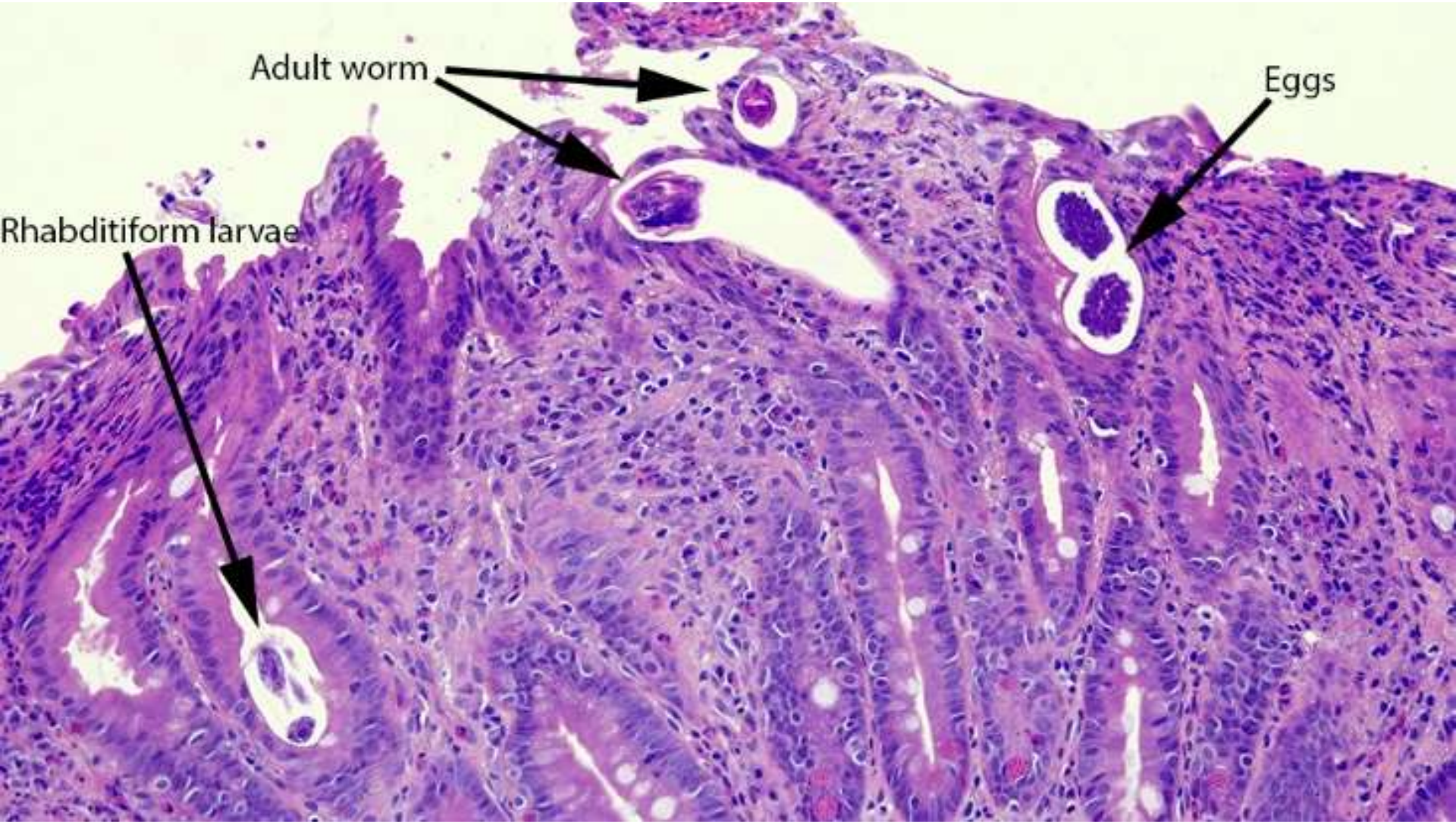
Concha, Ronald MD*; Harrington, William Jr MD†; Rogers, Arvey I MD, FACP‡

TABLE 1. Strongyloidiasis: Classification and Definition of Syndromes

Intestinal strongyloidiasis: Strongylodiasis infection with presence of the adult parasite in the intestinal tract. The ability to establish an autoinfection cycle may lead to chronic infection (carrier).
Hyperinfection syndrome: Increase in parasite burden due to acceleration of autinfection cycle without an accompanying spread of larvae outside the usual migration pattern. Severe gastrointestinal tract and pulmonary symptoms are commonly seen.
Disseminated strongyloidiasis: Systemic spread of invasive filariform larvae to sites outside their normal migration pattern with extensive invasion to virtually every organ. While dissemination implies coexisting hyperinfection, hyperinfection can occur without dissemination.

J Clin Gastroenterol 2005;39:203–211

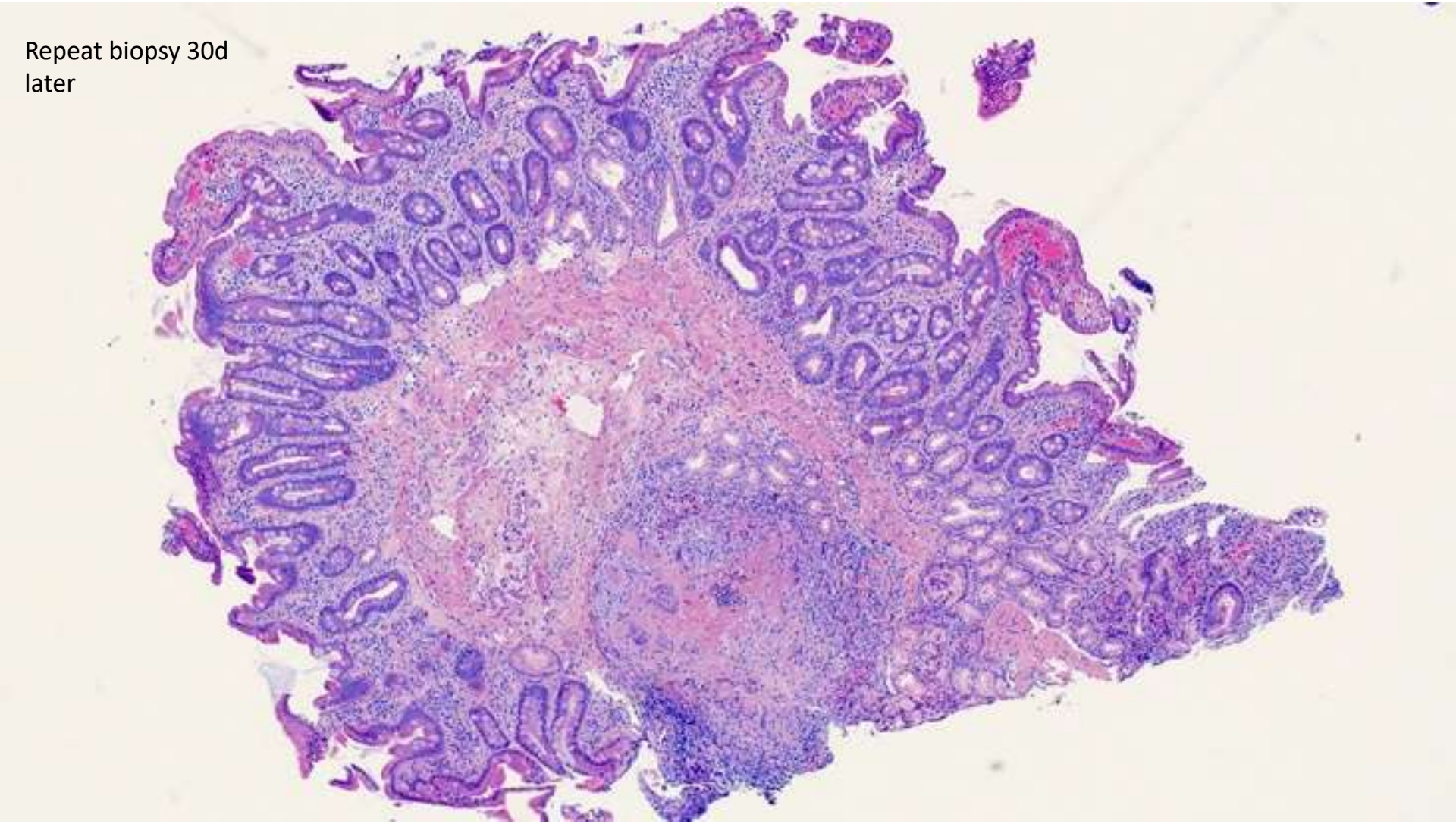



Adult worm
Eggs
Rhabditiform larvae

Additional clinical history

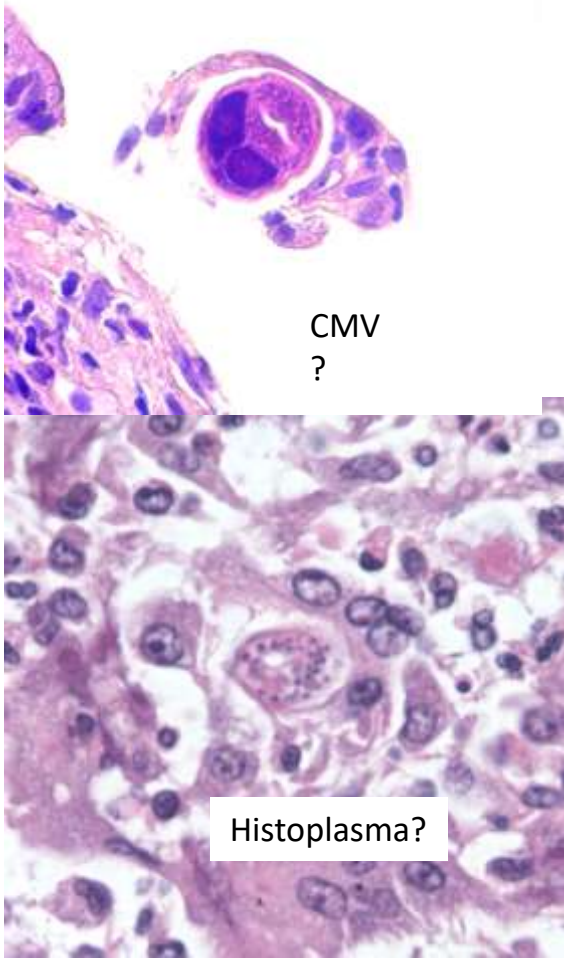
- Born in Mexico but lived in US x 30 years. Visits Mexico annually but mostly stays in the city
- Hx Quantiferon positive. No evid at that time for active TB. Had three culture-negative induced sputums, then started on INH/B6.
- Developed biliary cast syndrome, strictures s/p OLT. Multiple stents placed.
- Latent syphilis of unknown duration treated Nov/Dec 2020 with 4 doses of pen G
- Strongyloides stercoralis Antibody IgG NEGATIVE (in 2019 at time of transplant)
- No history of eosinophilia
- Treatment
  - Ivermectin 12 mg/day
  - Albendazole 400mg PO BID
    - Anticipate 14 day course of therapy from time of negative strongy stool cultures
- Additional evaluation after biopsy result
  - Stool culture – positive for S. stercoralis
  - Stool Helminthic ova and larvae – positive for S. stercoralis
  - Strongyloides IgG antibody – positive
  - HTLV-1 antibody – result unknown

Repeat biopsy 30d later



Differential diagnosis

- Viral infection – intense basophilia of ovary may mimic a viral inclusion
- Histoplasma capsulatum – transverse section of filariform larva may mimic macrophage with intracellular H. capsulatum organisms
- Eosinophilic gastroenteritis – always look for Strongyloides before making this diagnosis
- Chronic inflammatory bowel disease
  - large number of eos, LP neutrophils without cryptitits
  - High penalty misdiagnosis – 40% mortality
- Capillaria philippinensis – looks like Stronglyoides but acquired from eating undercooked seafood but probably will respond to same therapy



Diagnosis

- No role for endoscopy in diagnosis
- Serum testing by ELISA
- Stool O&P
  - Low sensitivity with 25-50% false negative rate
  - 7 or more samples to yield 90% sensitivity
- Duodenal fluid aspirate – most accurate

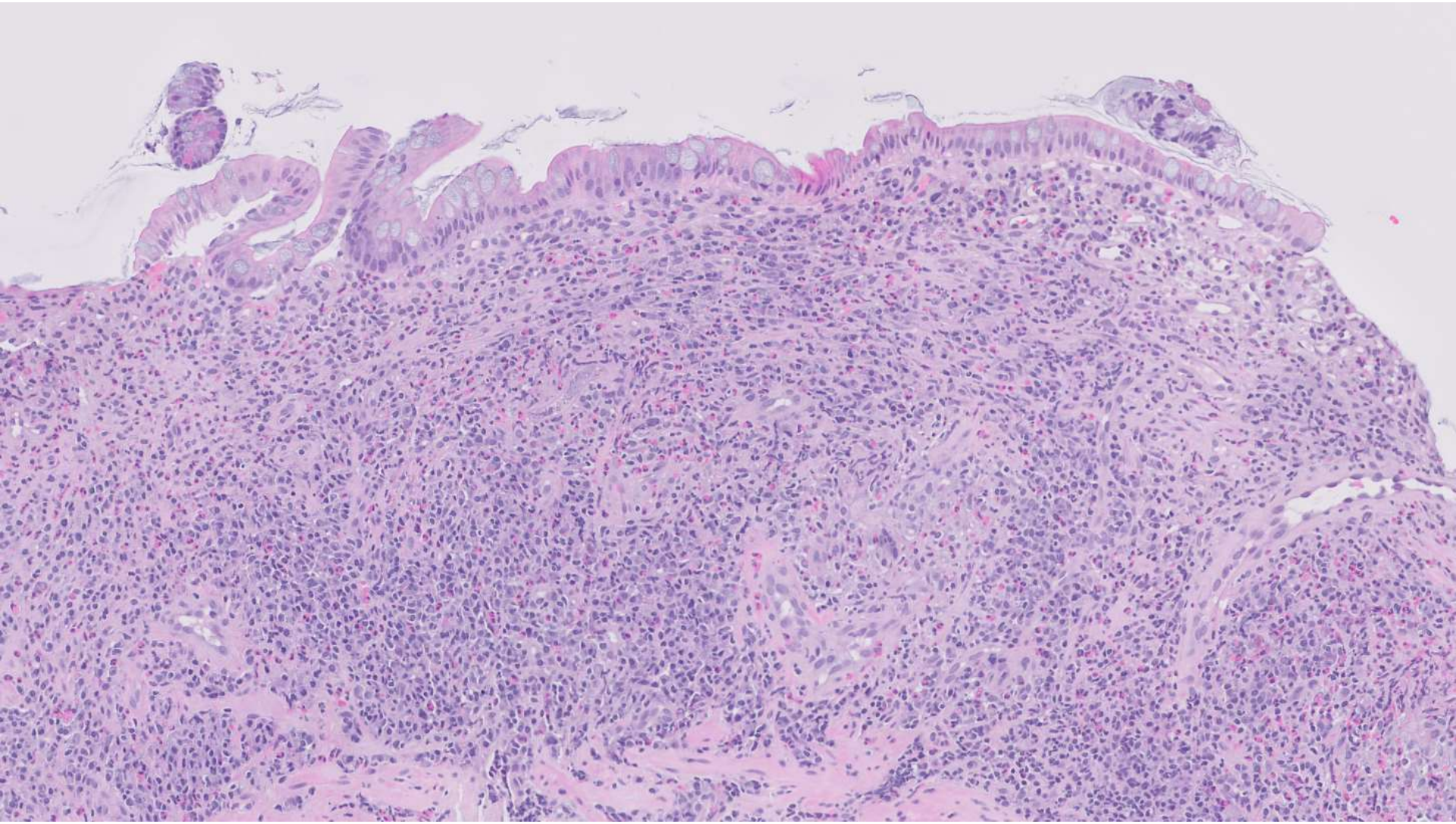
Take home points

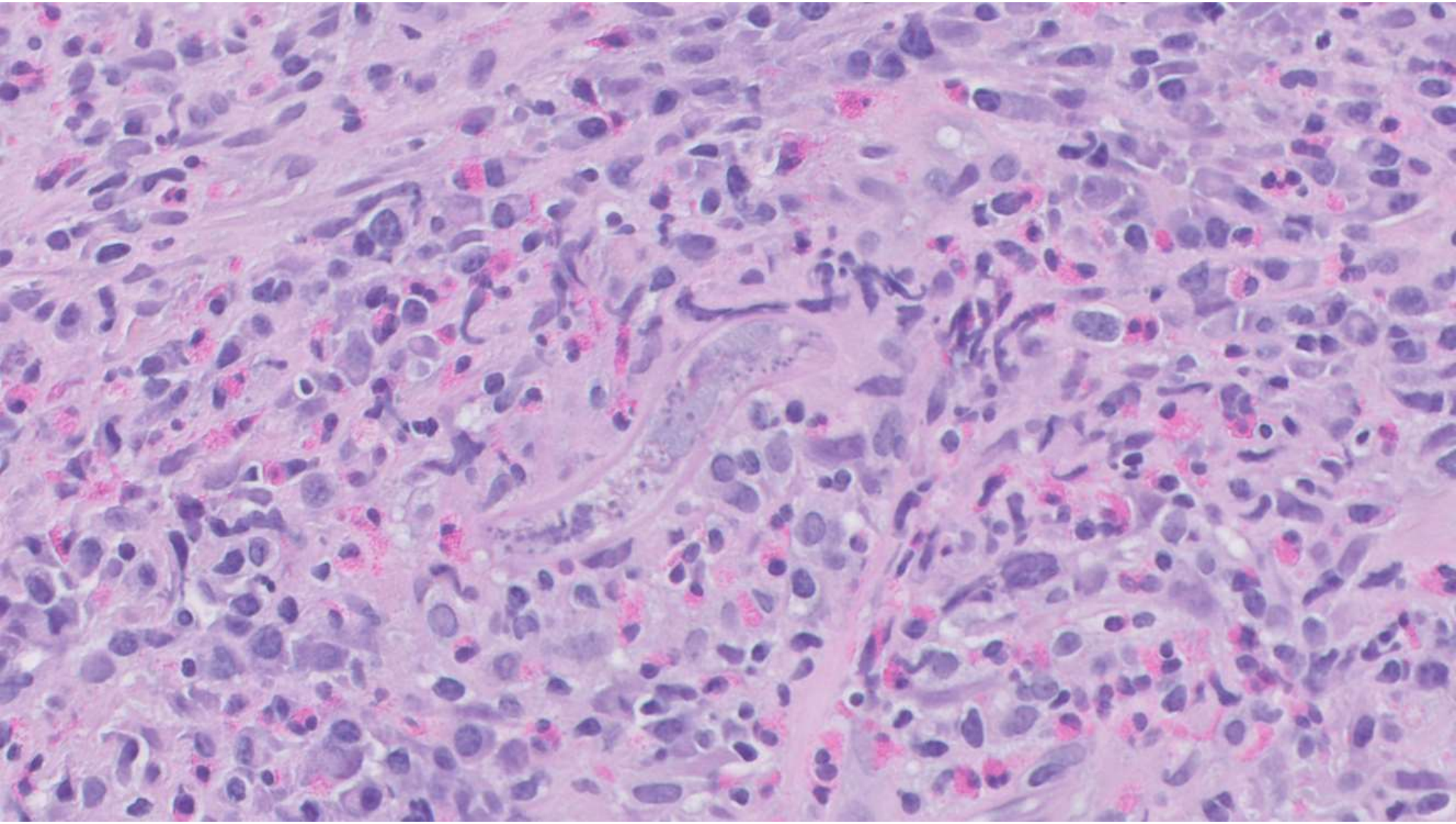
- Infection occurs from skin exposure to soil contaminated with feces (human or dog), e.g. in tropics or southeastern US
- Adult worms, larvae and eggs may all be seen in tissue
- Hyperinfection occurs with immunosuppression and may be overwhelming but autoinfection also occurs in asymptomatic patients in whom the disease may persist for decades after residence in an endemic area

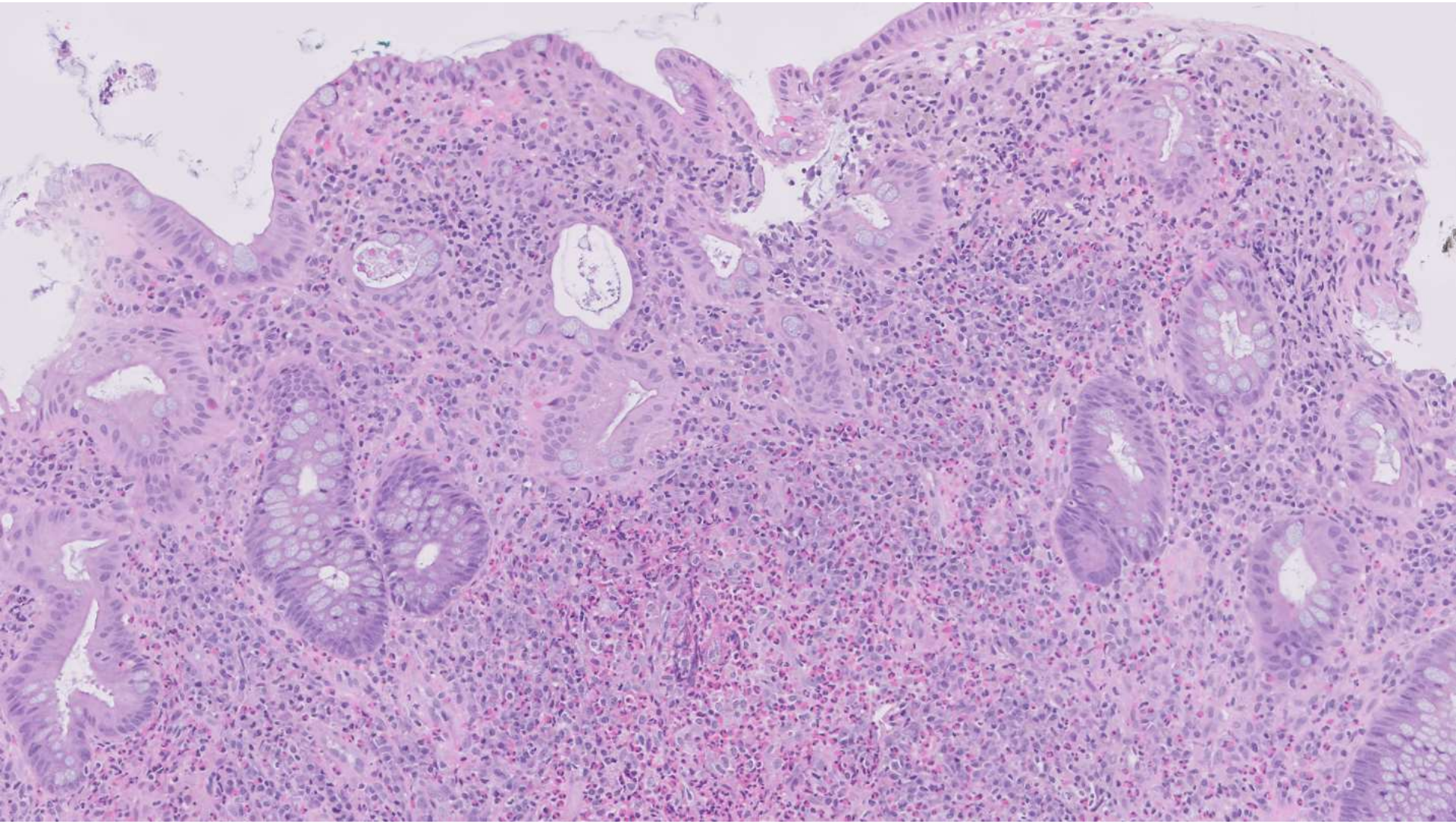
22-0605

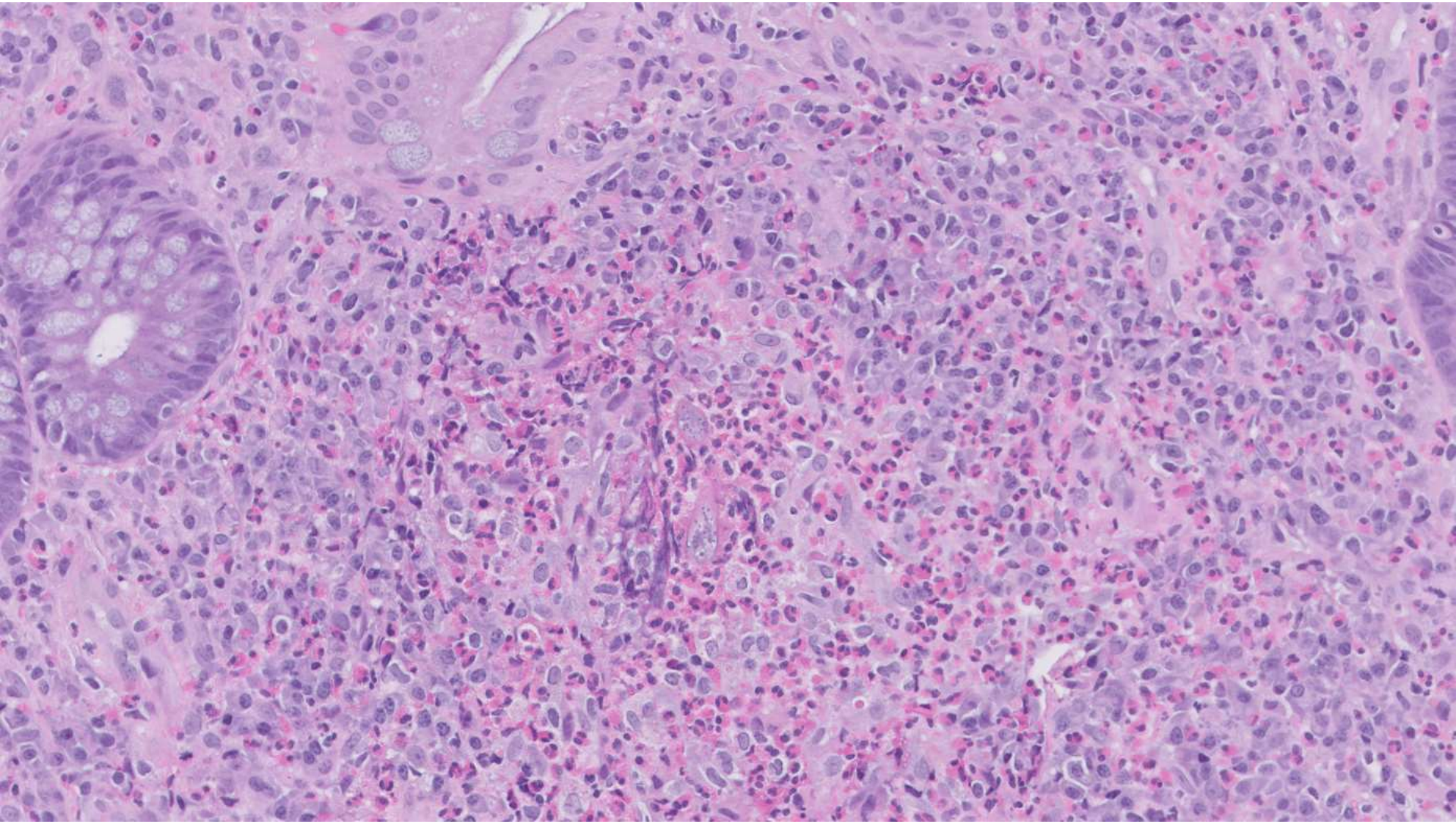
Cindy Wang/John Higgins; Stanford

70ish M with anemia. Colon bx submitted.









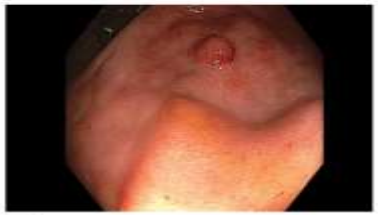
22-0605

Cindy Wang/John Higgins; Stanford

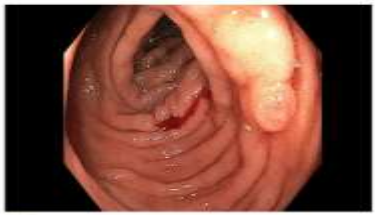
https://pathpresenter.net/public/presentation/display?token=567ef177

Colonoscopy Findings

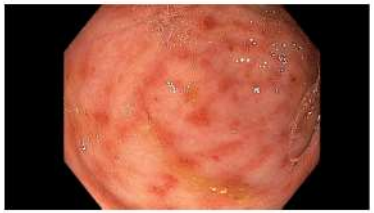
- Diffuse moderate inflammation was found in the entire examined colon secondary to colitis.
- Many polyps in the entire colon.
- Severe diverticulosis in the sigmoid colon.



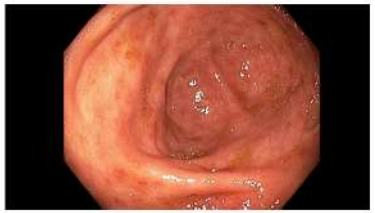
8 Transverse Colon : Multiple Polyps



9 Transverse Colon : *Inflammation, Single Polyp



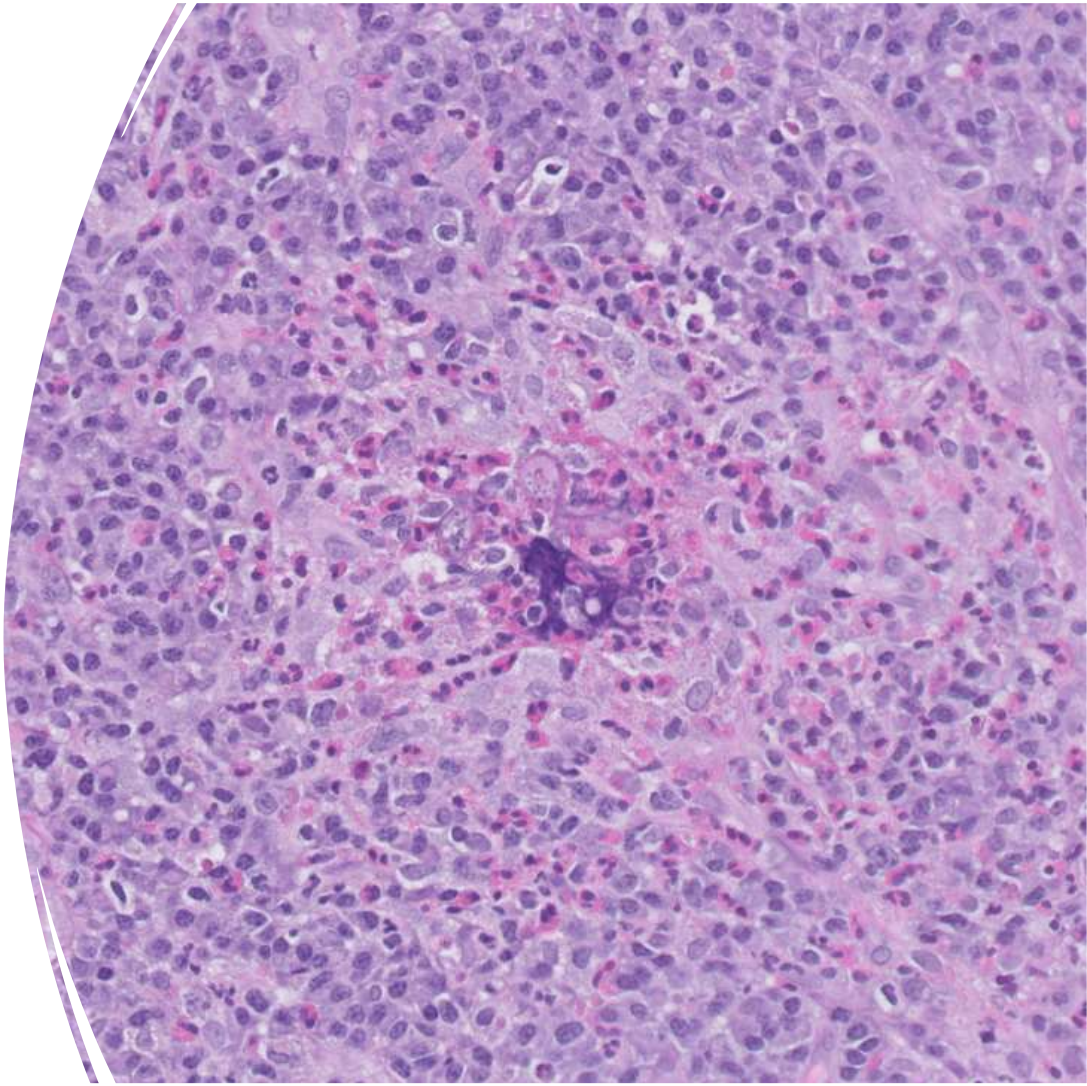
4 Sigmoid Colon : *Inflammation



5 Descending Colon : *Inflammation

Strongyloides filariform larvae

- Invades into mucosa → elicit an eosinophil-rich inflammatory response
- Localized eosinophilic infiltrates → larvae commonly found in eosinophilic abscesses
- Severe disease may progress to ulceration and perforation



***Strongyloides* colitis is a lethal mimic of ulcerative colitis: the key morphologic differential diagnosis**

Zhenhong Qu MD, PhD*, Uma R. Kundu MD[1], Rania A. Abadeer MD[1], Audrey Wanger PhD

Strongyloides colitis

- Literature review of 25 cases of Strongyloides colitis cases revealed a 52% misdiagnosis rate and a 39% mortality rate in the setting of misdiagnosis
- Ulcerative colitis was the diagnosis rendered in 38.5% of the misdiagnosed cases
- Crohn's disease accounts for 7.7% of misdiagnoses

Table 1 Summary of clinical and pathologic features

	Incidence (%)[a]	Reference
Clinical features		
Male/female	2.1:1.0	
Median/mean age (y)	61/59.9 ± 10.6	
Age range (y)	38-83	
Peripheral eosinophilia	12/19 (63.2%)	[8,15-19,21,22,28-31]
Steroid therapy	17/23 (73.9%)	[13,15-18,20-22, 28-30,32,33]
Initial misdiagnosis[b]	13/25 (52.0%)	[15-17,19,21,28,31-33]
UC as initial diagnosis	5/13 (38.5%)	[15,17,21,31]
Mortality rate	9/23 (39.1%)	[15-17,21,28,32,33]
Morphologic features		
Right colon	7/18 (38.9%)	[8,15,18-20]
Left colon	1/18 (5.5%)	[17]
Pancolitis	10/19 (52.6%)	[13-15,22,29-31,33]
Mucosal ulcer	17/25 (68.0%)	[8,13,14,16,19,20,22, 29-32]
Eosinophilic microabscess	7/23 (30.4%)	[8,14-16,22]
"Granulomas" described	11/25 (44.0%)	[8,13,15,21,32,33]
Larvae in tissue	24/24 (100%)	
Larvae/ova in stool	10/19 (52.6%)	[8,13-16,18,20,22,29,31]

NOTE. Right colon includes cecum, ascending, and proximal transverse colon; left colon, segments distal to the transverse colon.

[a] The denominator represents only the number of cases with available information.

[b] Initial diagnoses other than *Strongyloides* colitis.

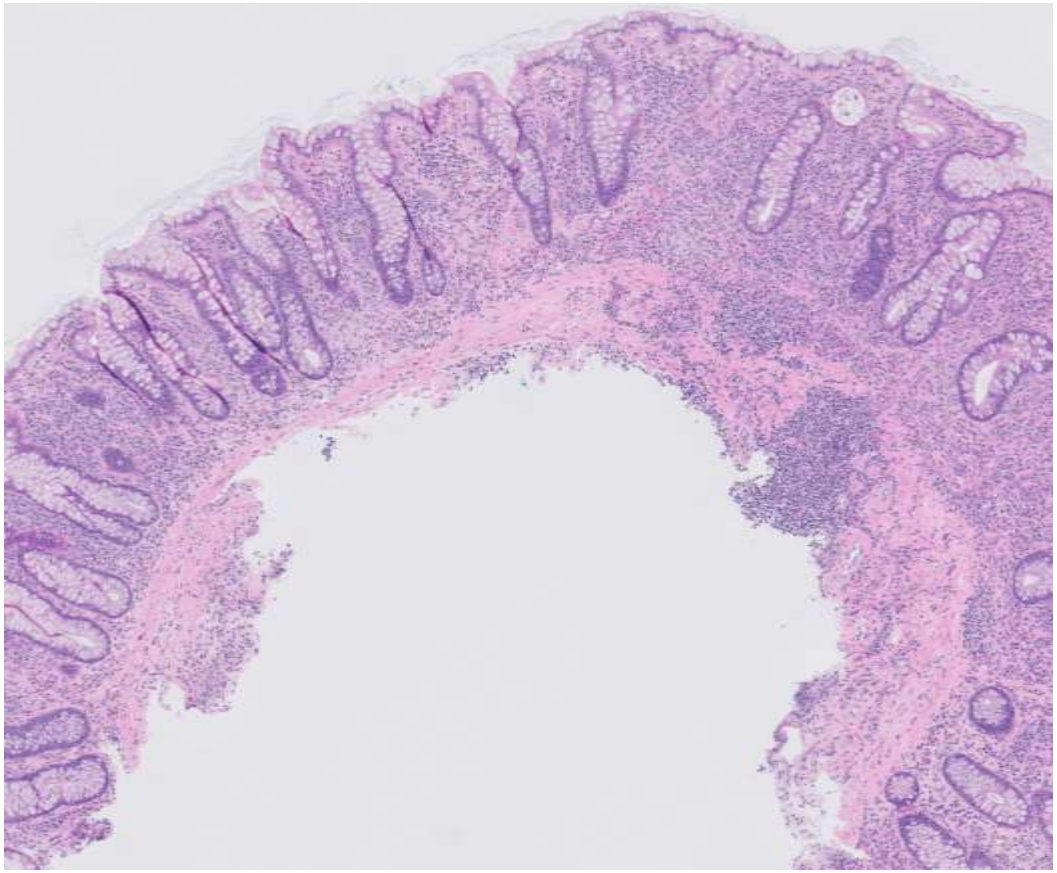
Human Pathology (2009) **40**, 572–577

Strongyloides colitis as mimic of IBD

- Clues pointing towards strongyloides colitis
  - Skip lesions
  - magnitude of crypt architecture distortion is milder
  - Histological changes attenuates distally (reverse of UC)
  - inflammation commonly extends into the submucosa and can be transmural
  - microabscesses tend to form in the lamina propria instead of crypts
  - eosinophil-rich inflammation with eosinophilic microabscesses or eosinophilic granulomas
- Treatment is effective → antiparasitic and removal of immunosuppressants (ie. Steroids)
- IBD is treated with corticosteroids, which has been proven to be the leading risk factor for the most severe forms of strongyloidiasis

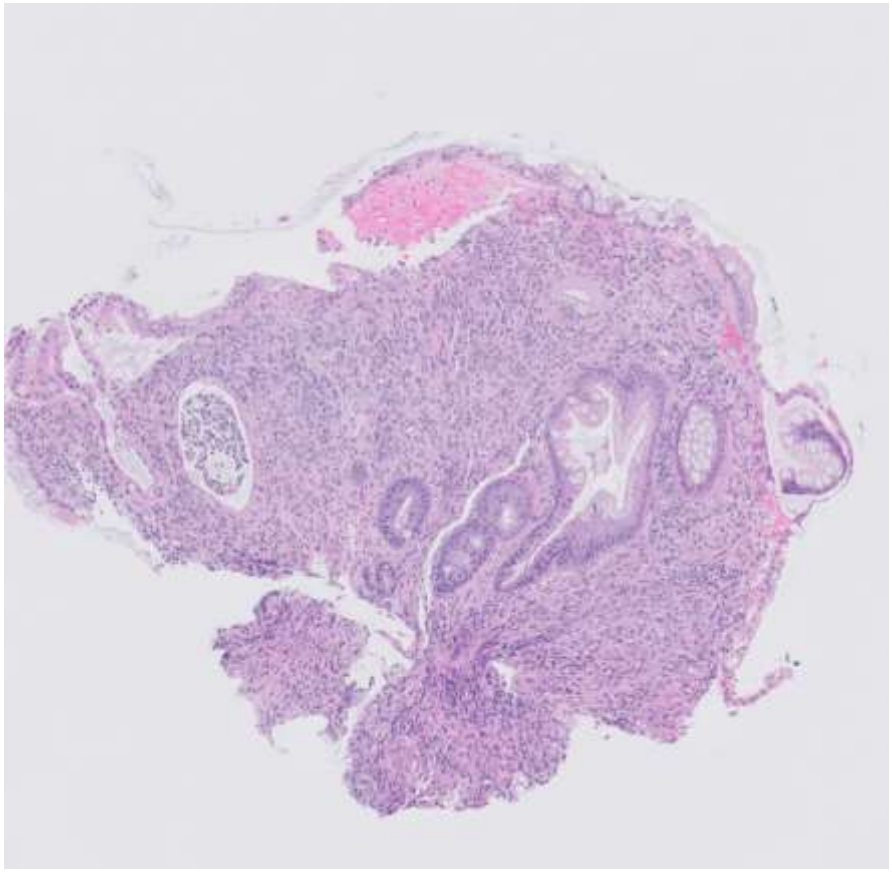
Review of Our Case

- Endoscopic diffuse inflammation with pseudopolyps
- Histologic changes of chronic colitis



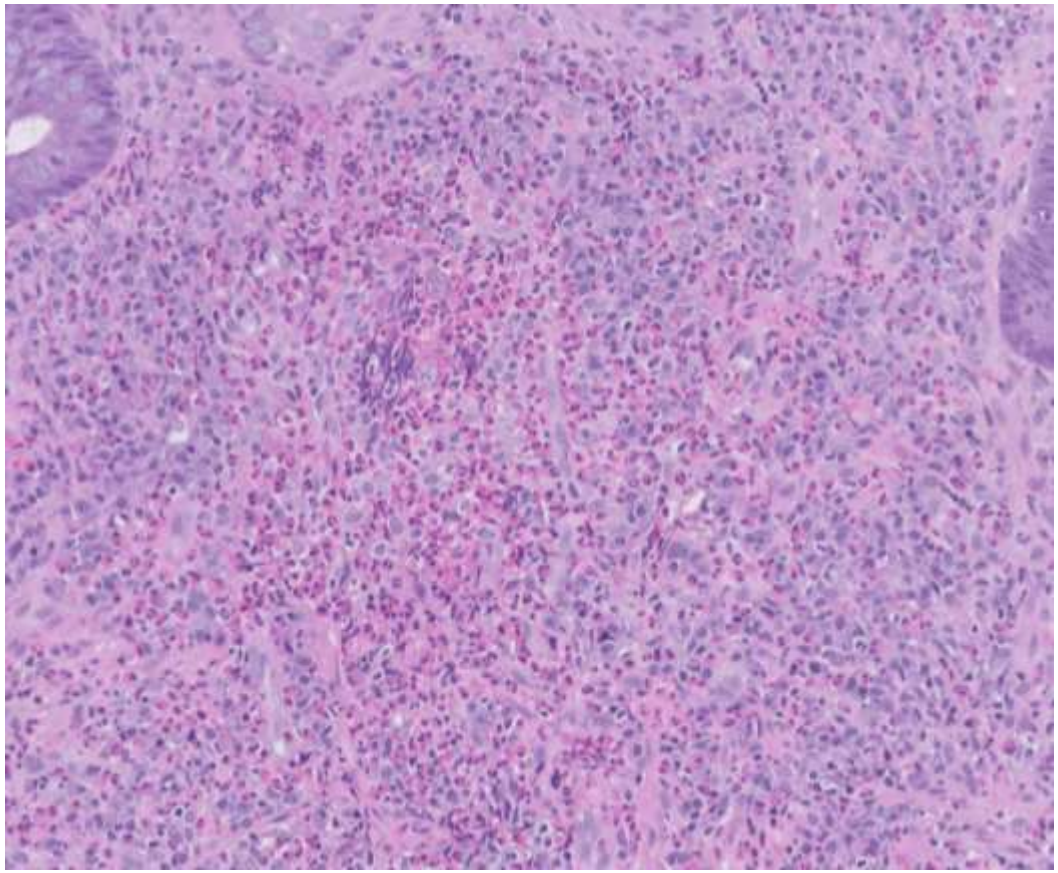
Review of Our Case

- Endoscopic diffuse inflammation with pseudopolyps
- Histologic changes of chronic colitis and pseudopolyps



Review of Our Case

- Endoscopic diffuse inflammation with pseudopolyps
- Histologic changes of chronic colitis and pseudopolyps
- Eosinophil rich with eosinophilic microabscess
- Larvae usually found in eosinophilic microabscess

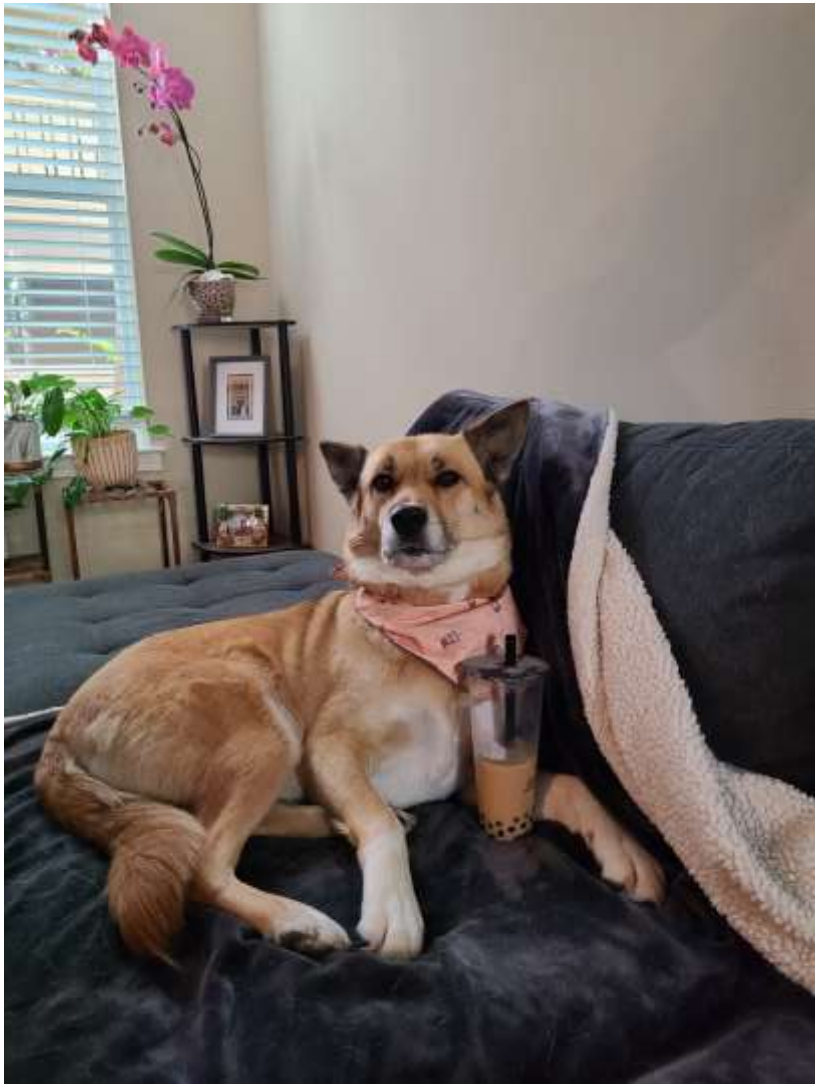


Strongyloides colitis as mimic of IBD

- Treatment is effective → antiparasitic and removal of immunosuppressants (ie. Steroids)
- IBD is treated with steroids → leading risk factor for the most severe forms of strongyloidiasis

Thank You!

Questions



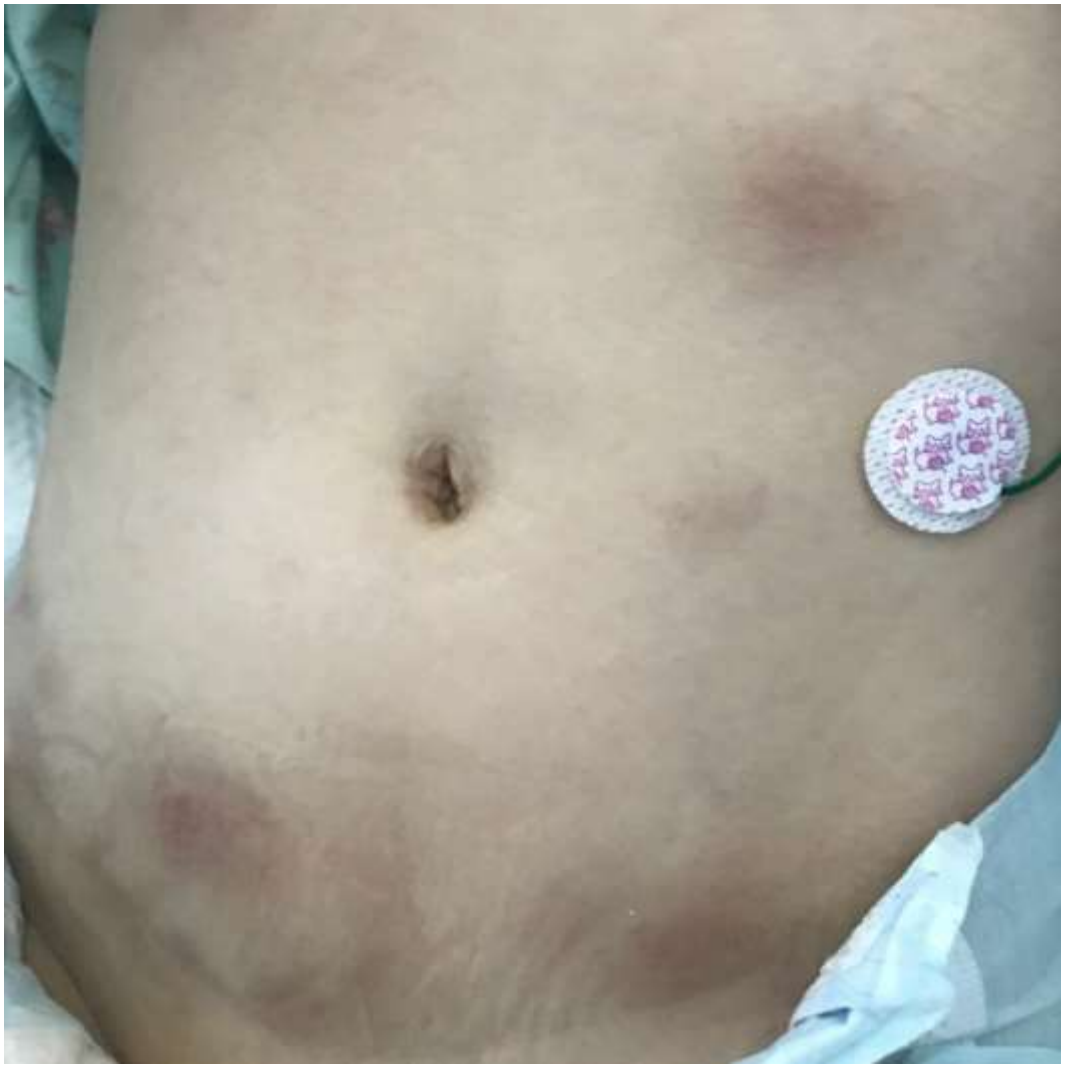
References

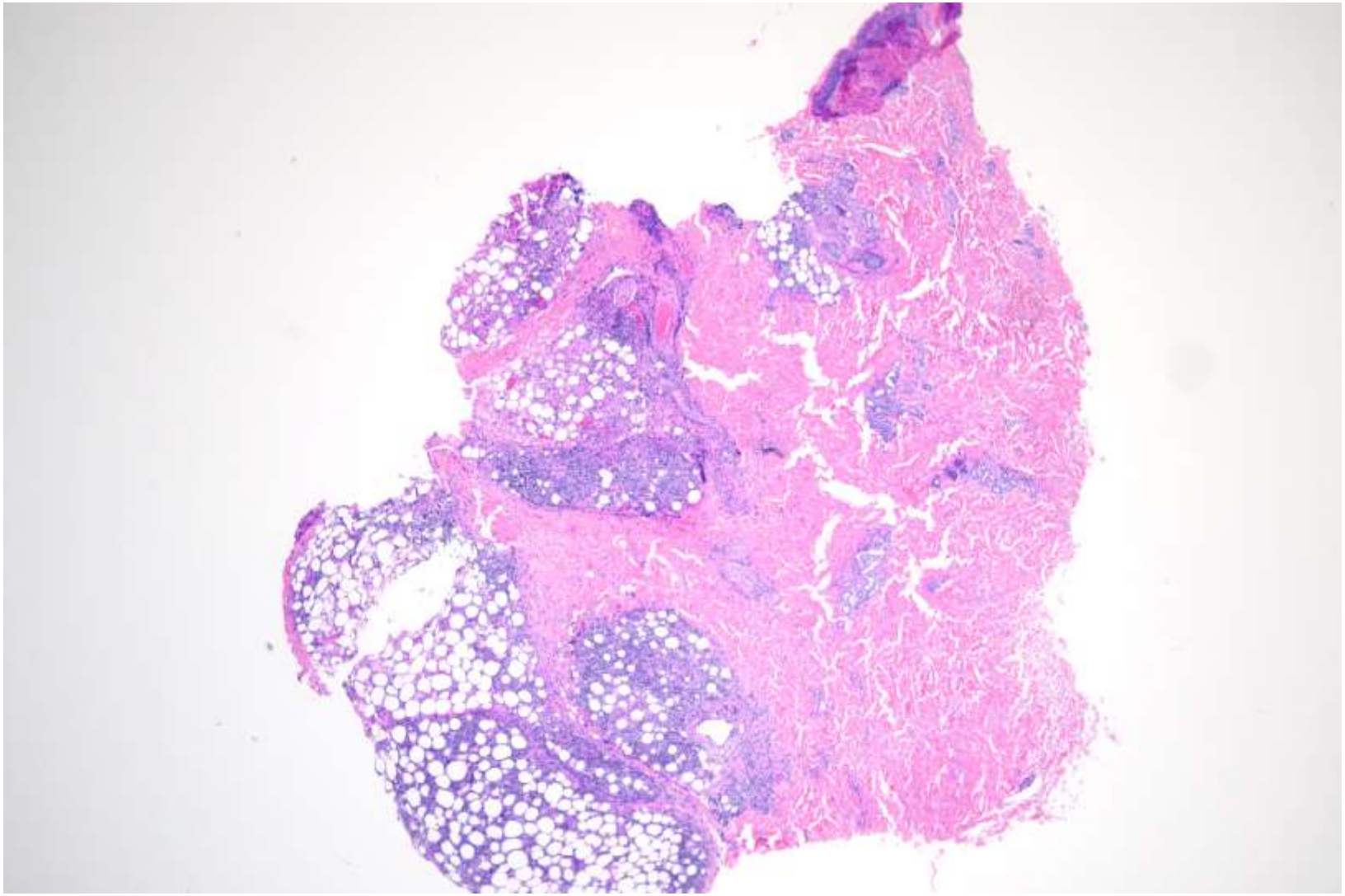
- Yantiss RK. Eosinophils in the GI tract: how many is too many and what do they mean?. Modern pathology. 2015 Jan;28(1):S7-21.
- Tesfaye B, Badurdeen D, Arhinful J, Mekasha G. StrongyloidesColitis: A Lethal Mimic of Ulcerative Colitis: 1364. Official journal of the American College of Gastroenterology| ACG. 2014 Oct 1;109:S402.
- Poveda J, El-Sharkawy F, Arosemena LR, Garcia-Buitrago MT, Rojas CP. Strongyloides colitis as a harmful mimicker of inflammatory bowel disease. Case Reports in Pathology. 2017 May 7;2017.

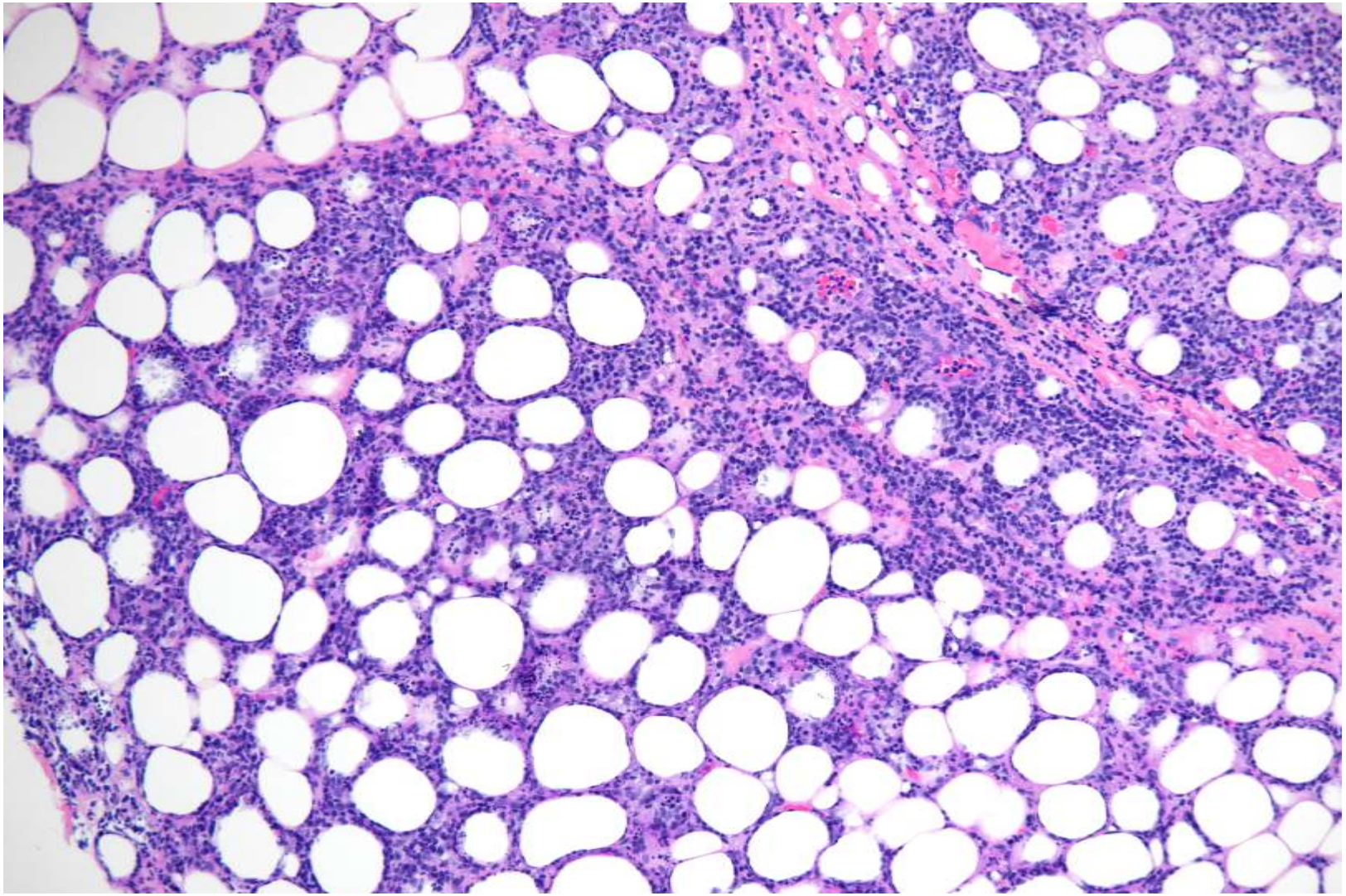
22-0606

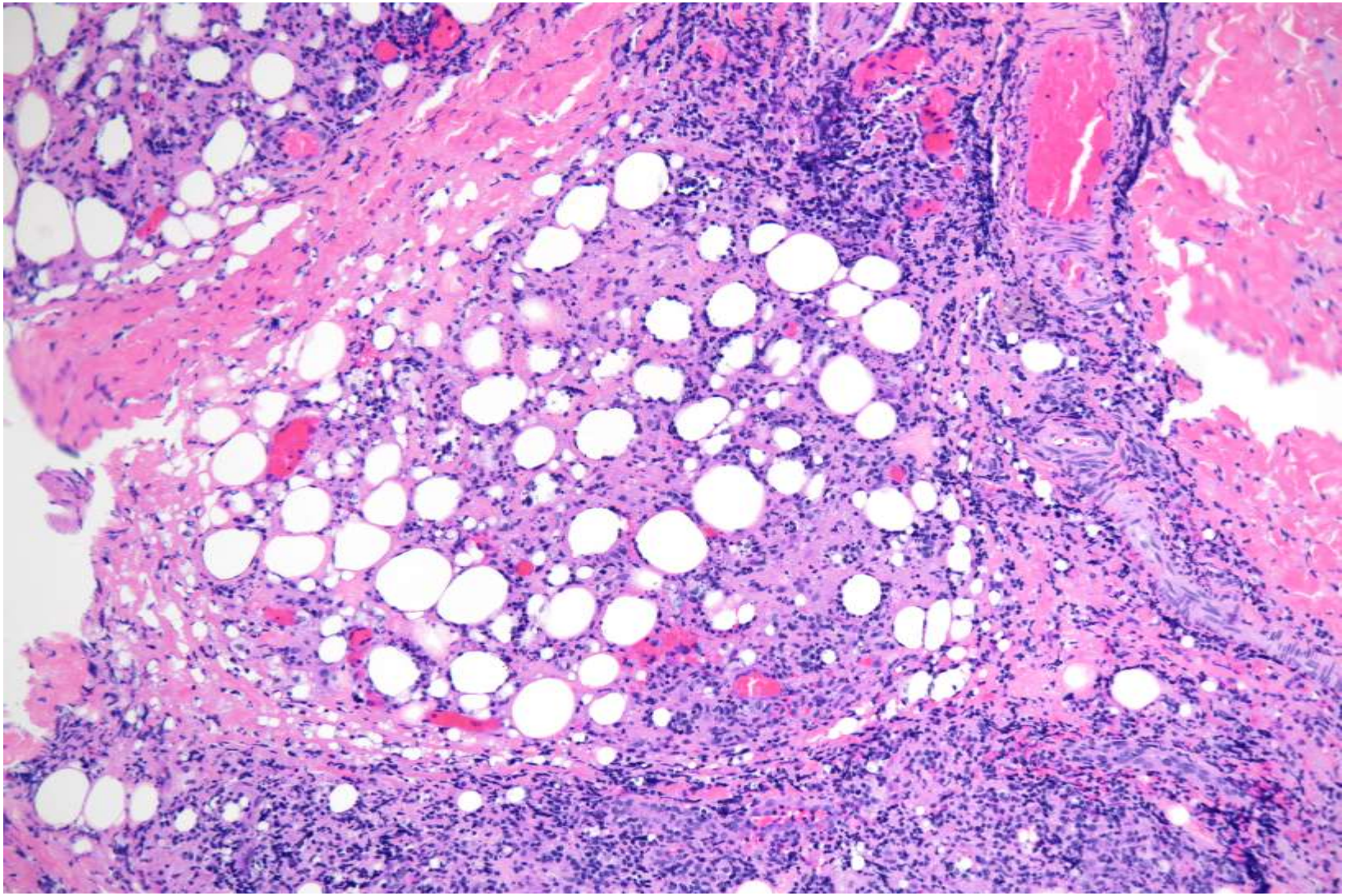
Ruobin Wu/Linlin Wang; UCSF

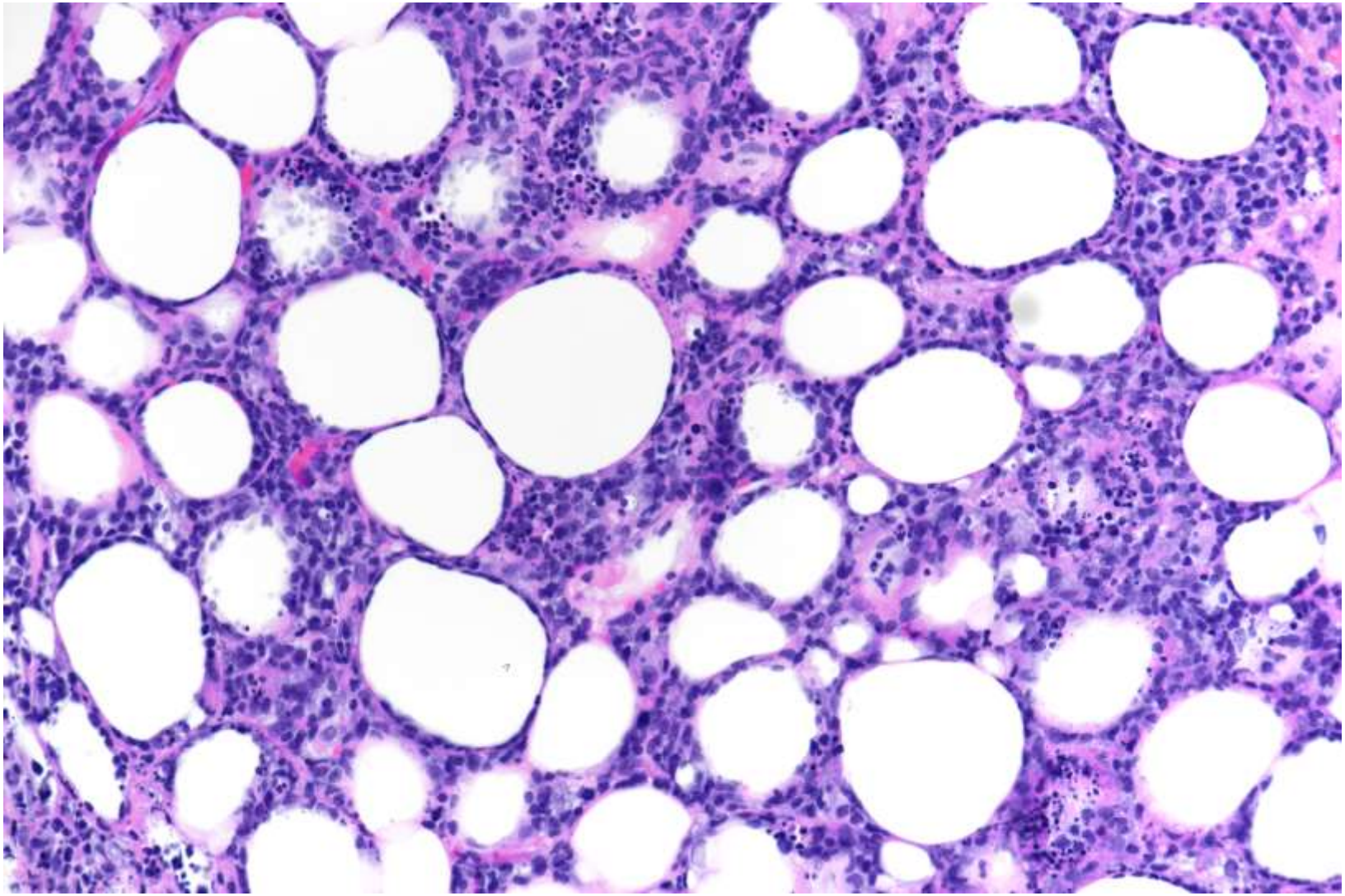
Previously-healthy young girl presents with firm subcutaneous nodules on neck, torso and legs. During workup, found to have pancytopenia (WBC 3.5/Hgb 9.8/Plt 68).

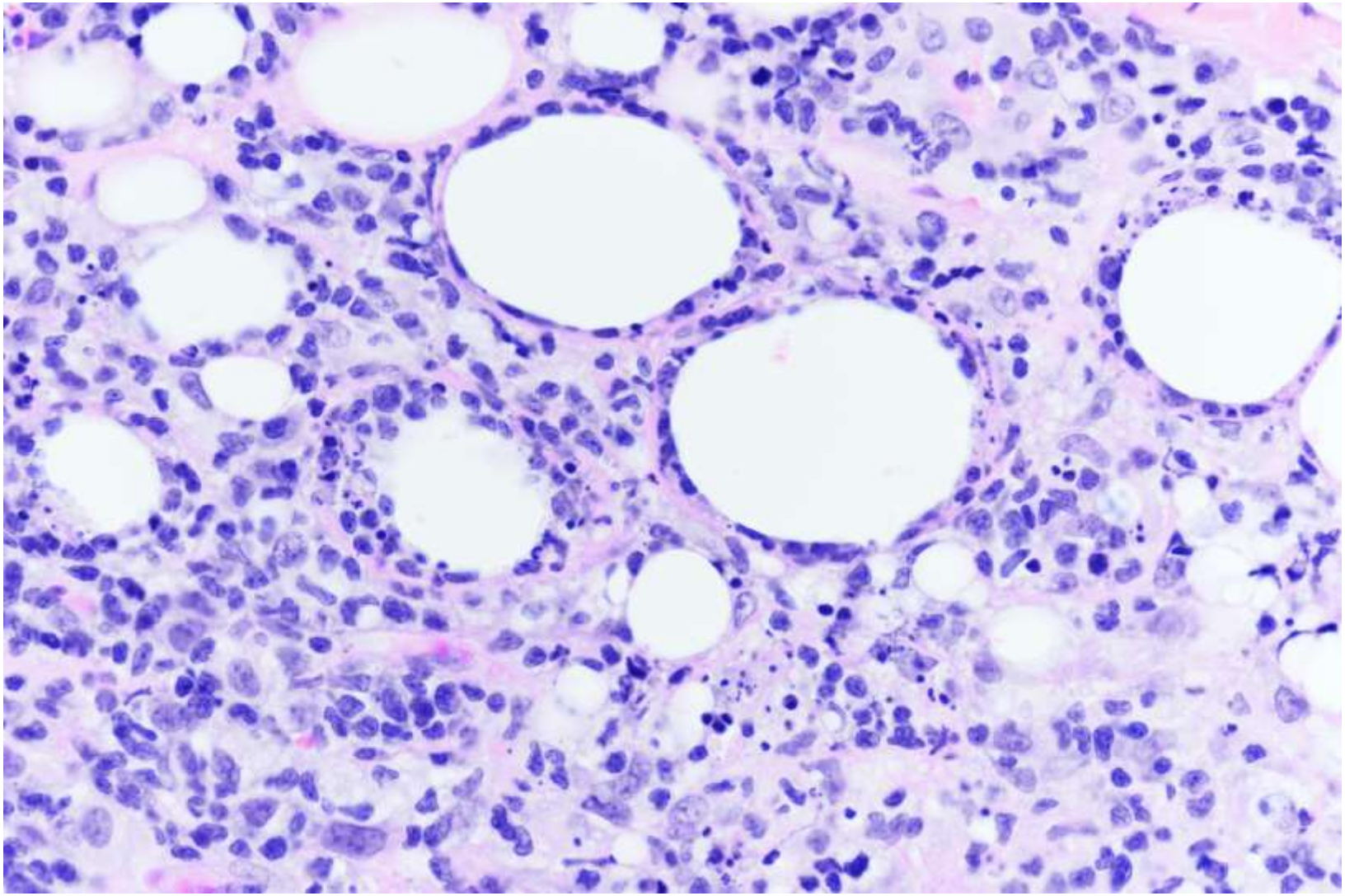


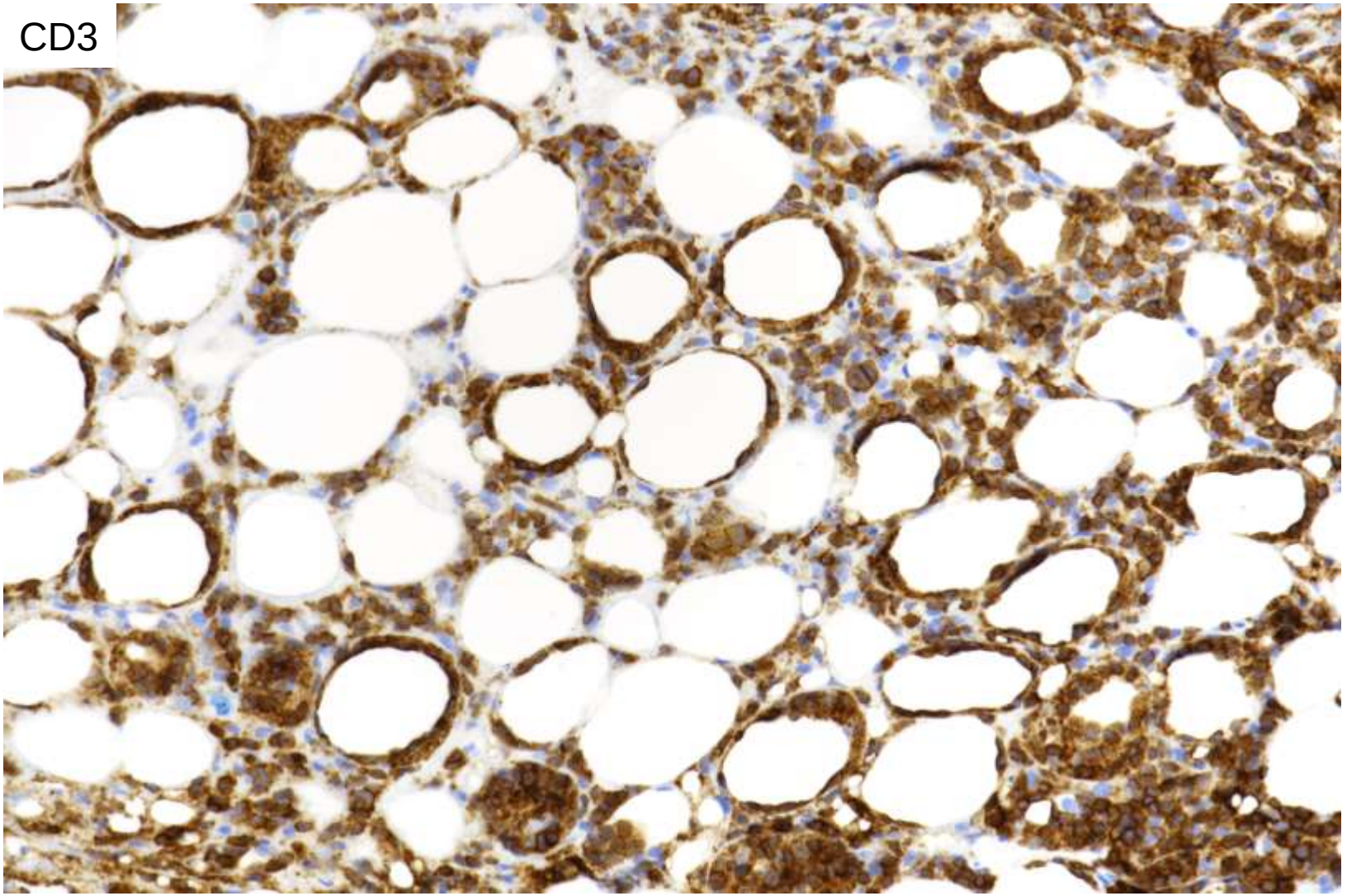




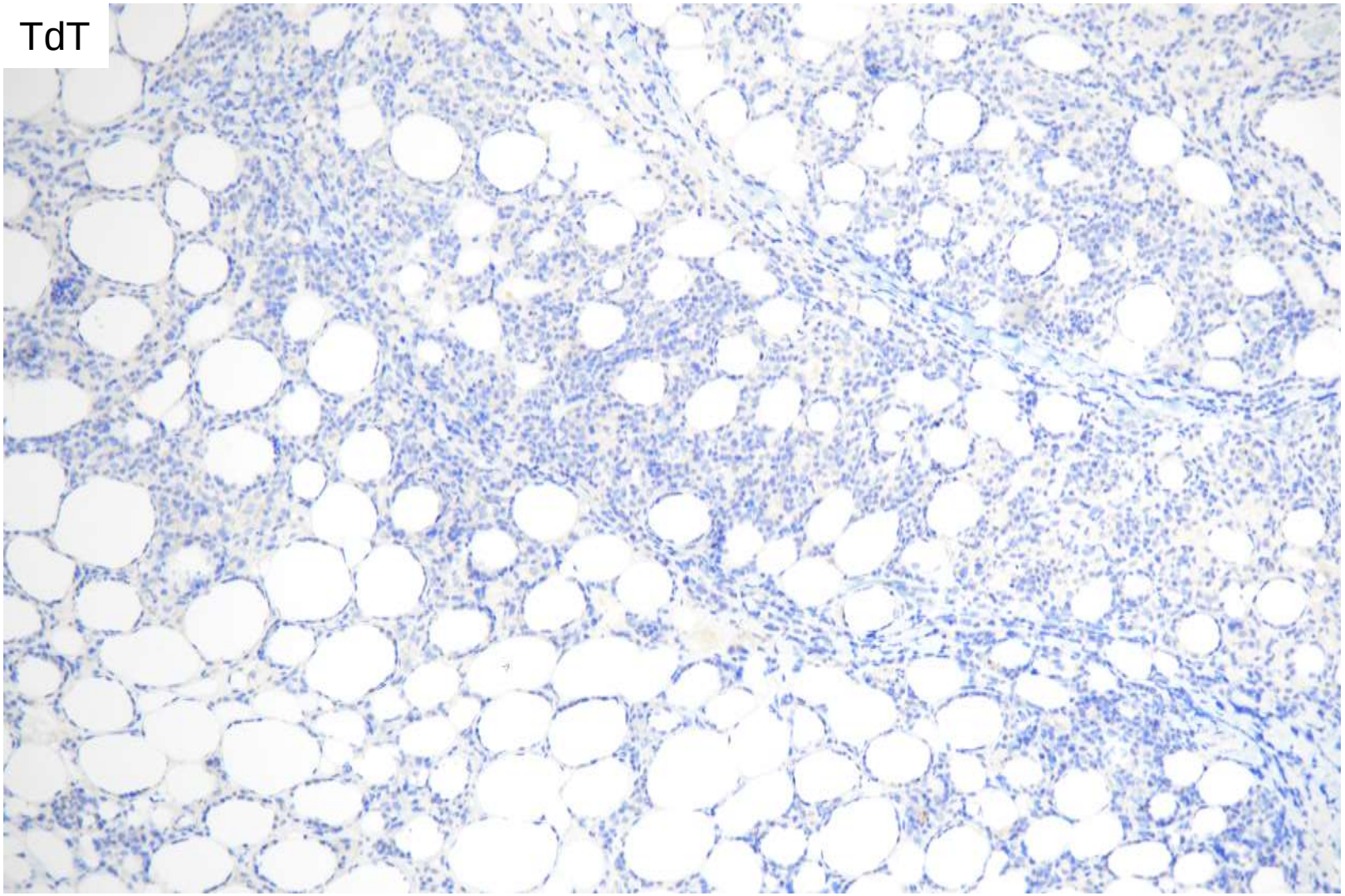


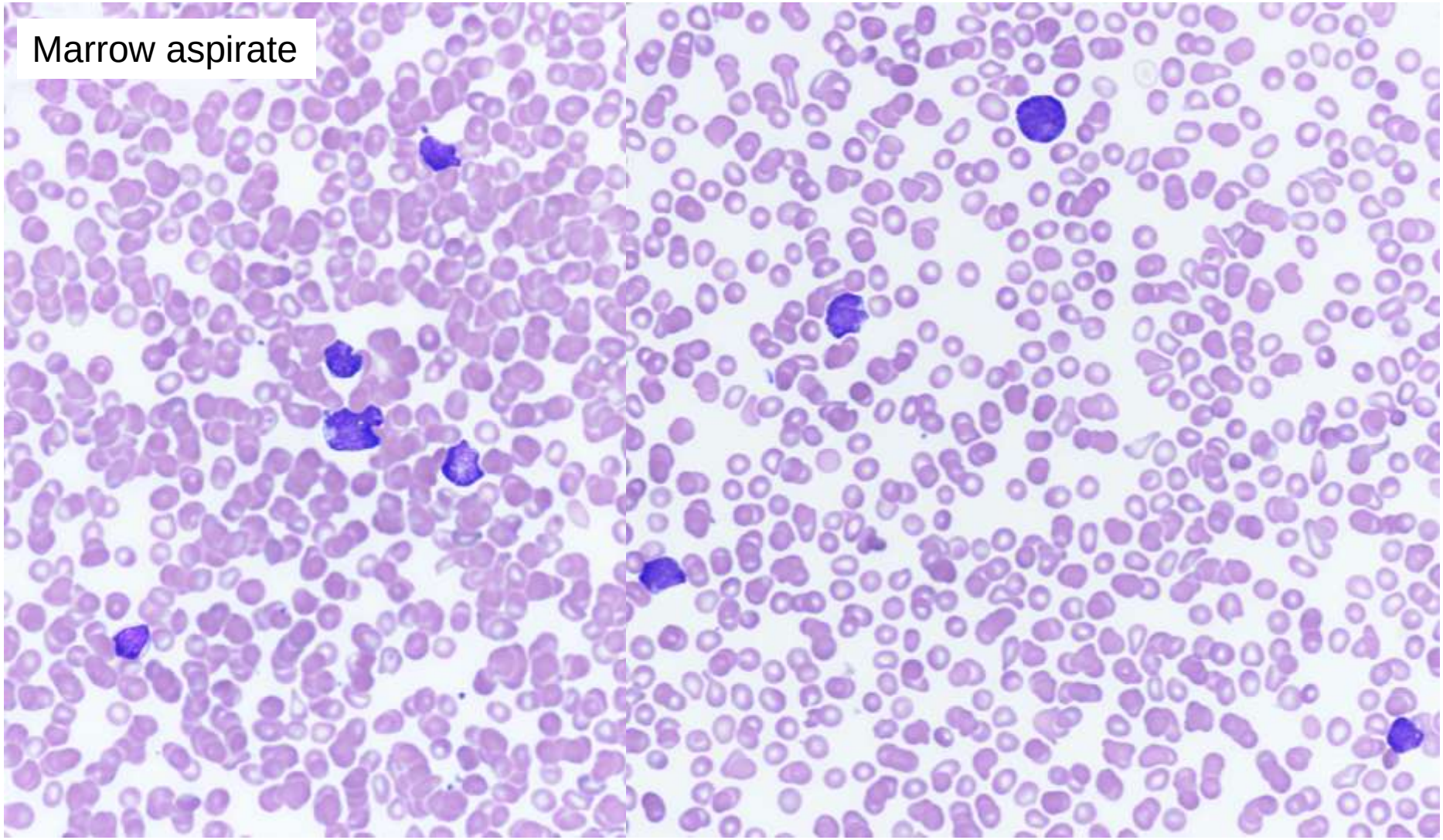


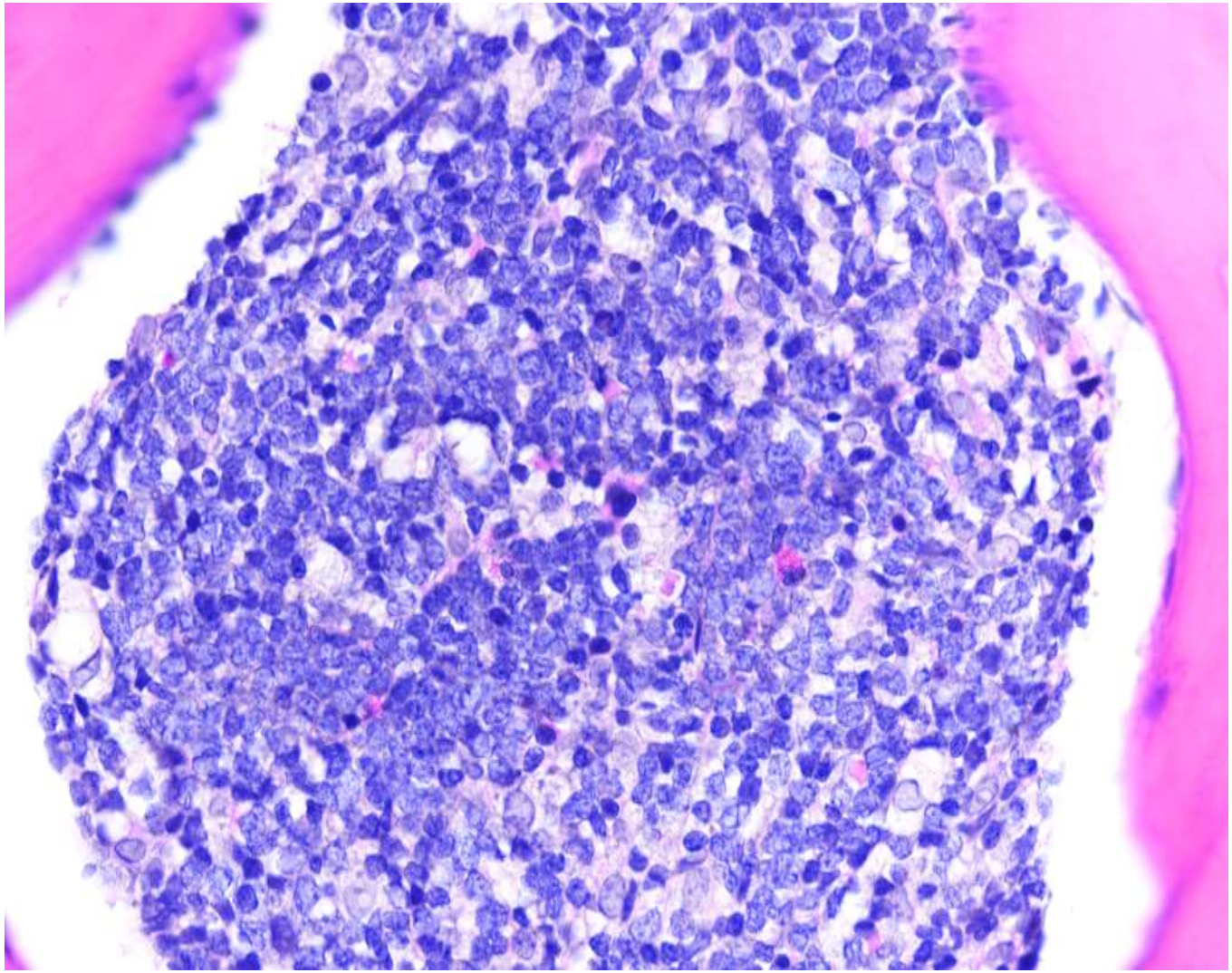


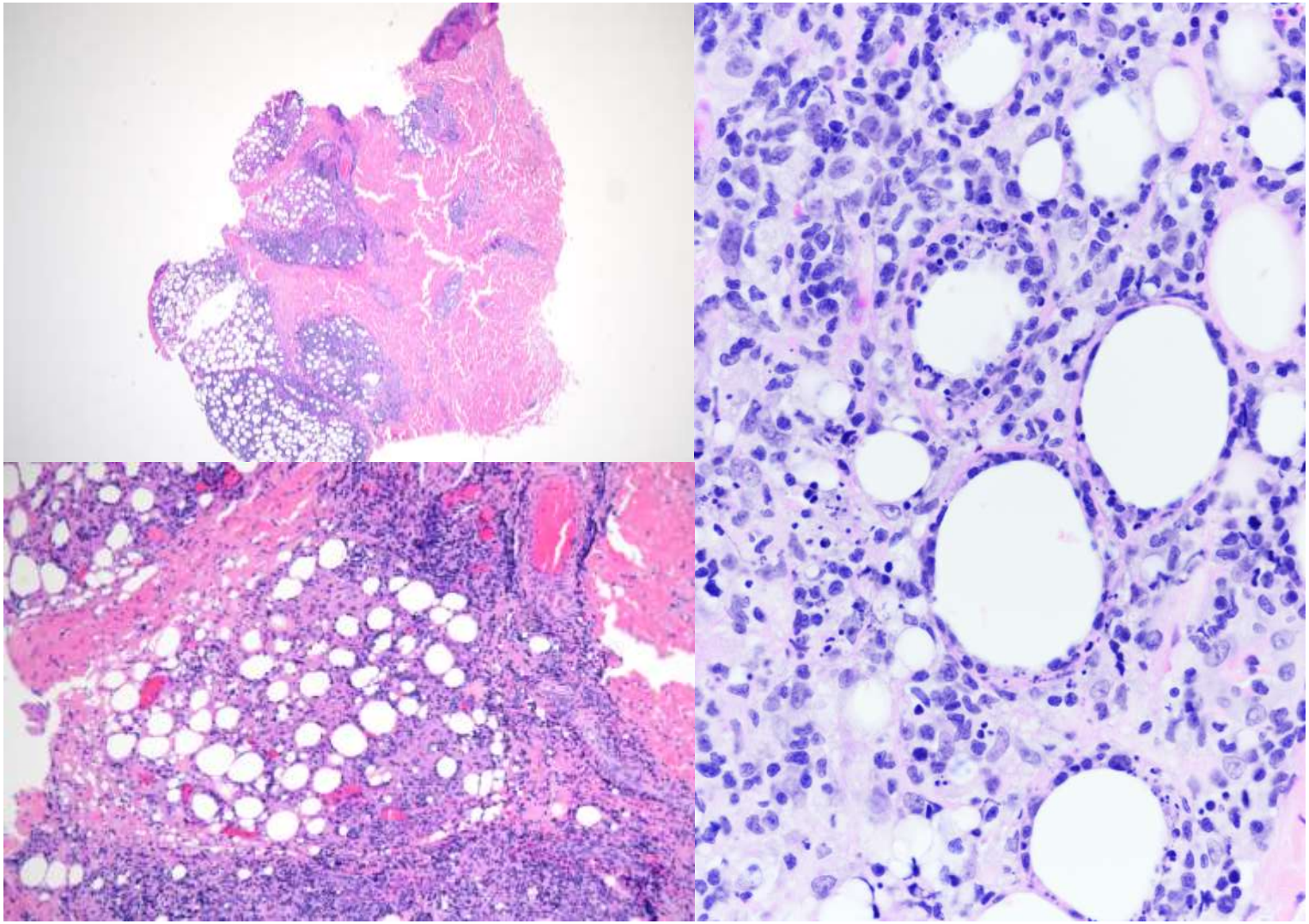

CD3

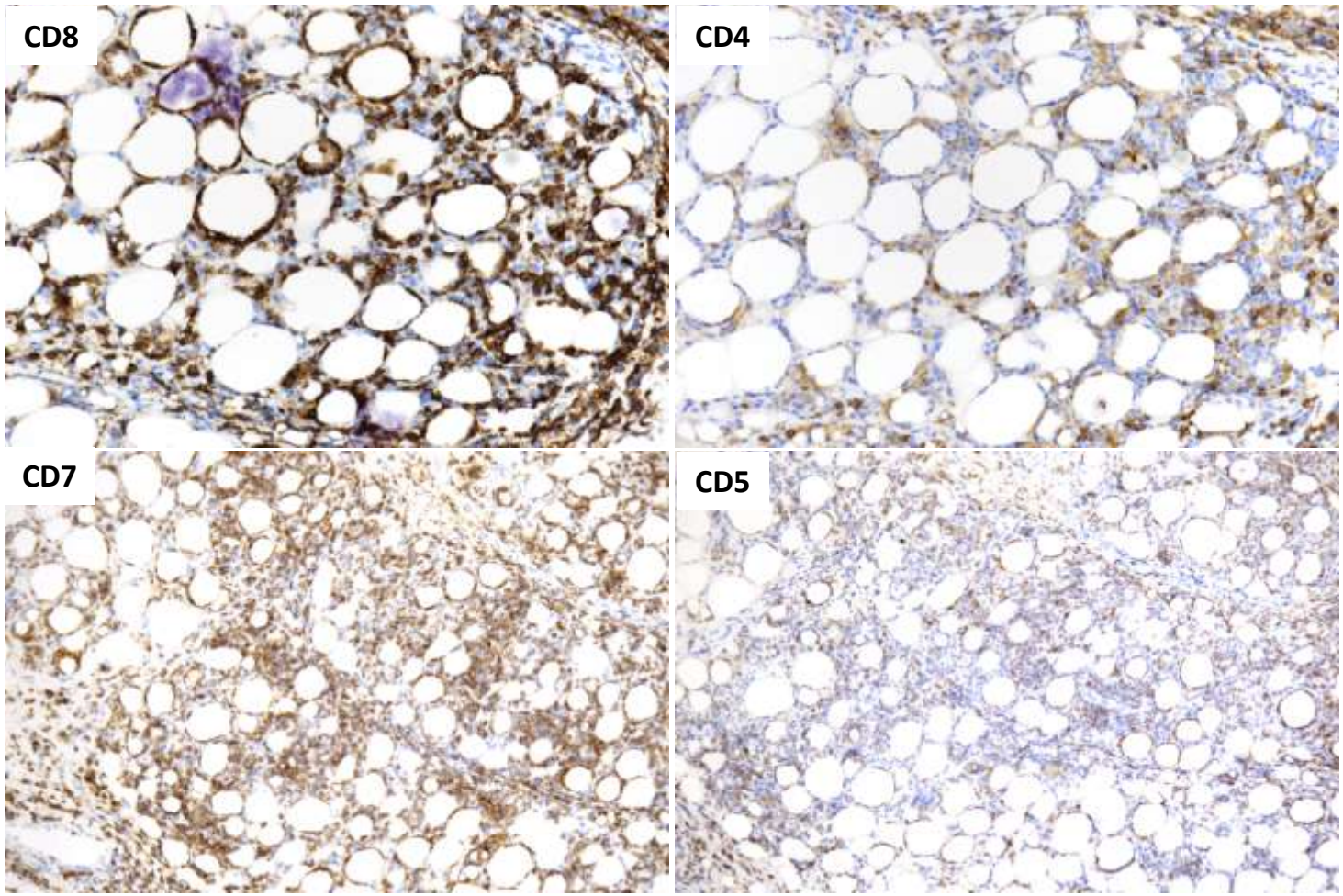
TdT

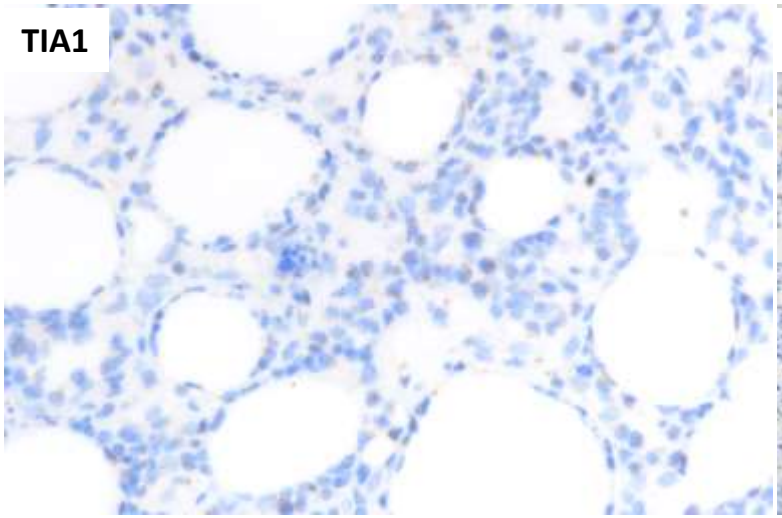


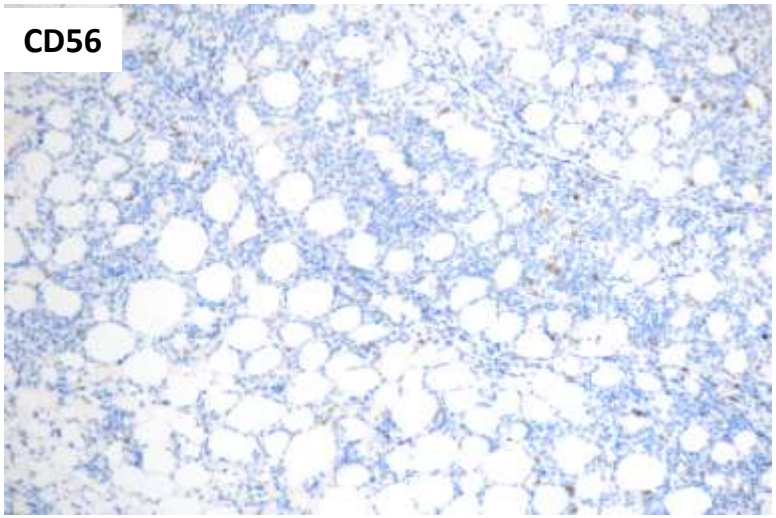

Marrow aspirate

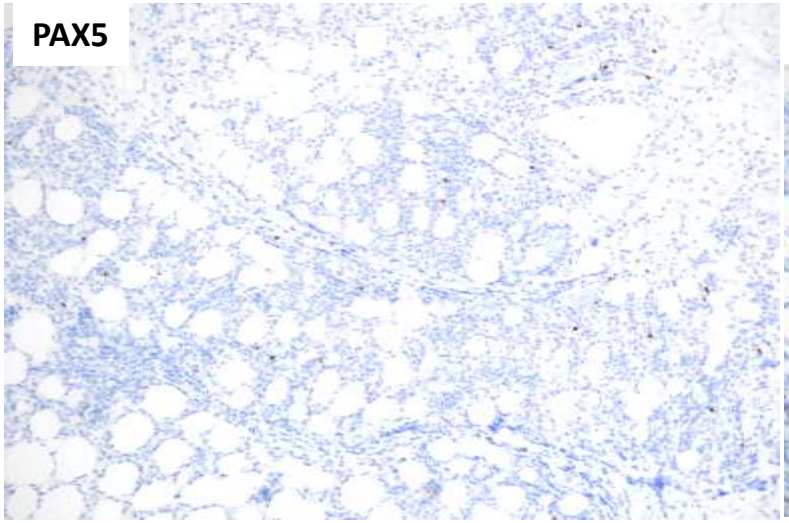


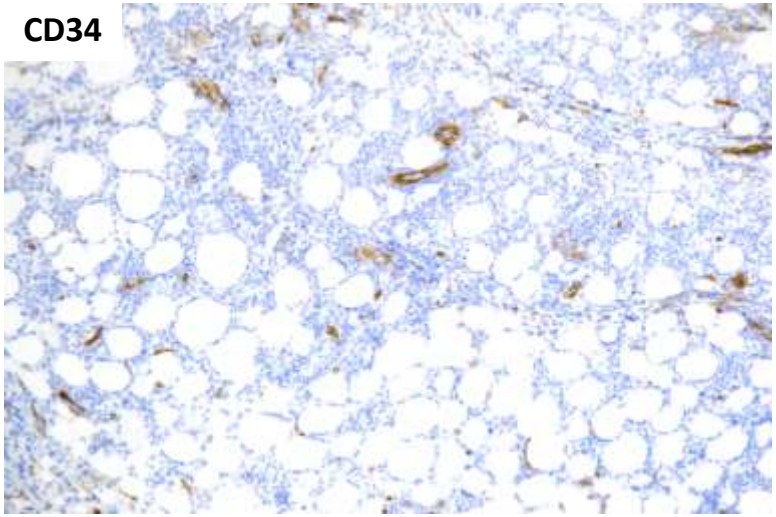



CD8
CD4
CD7
CD5


TIA1


CD56


PAX5


CD34

Ancillary studies

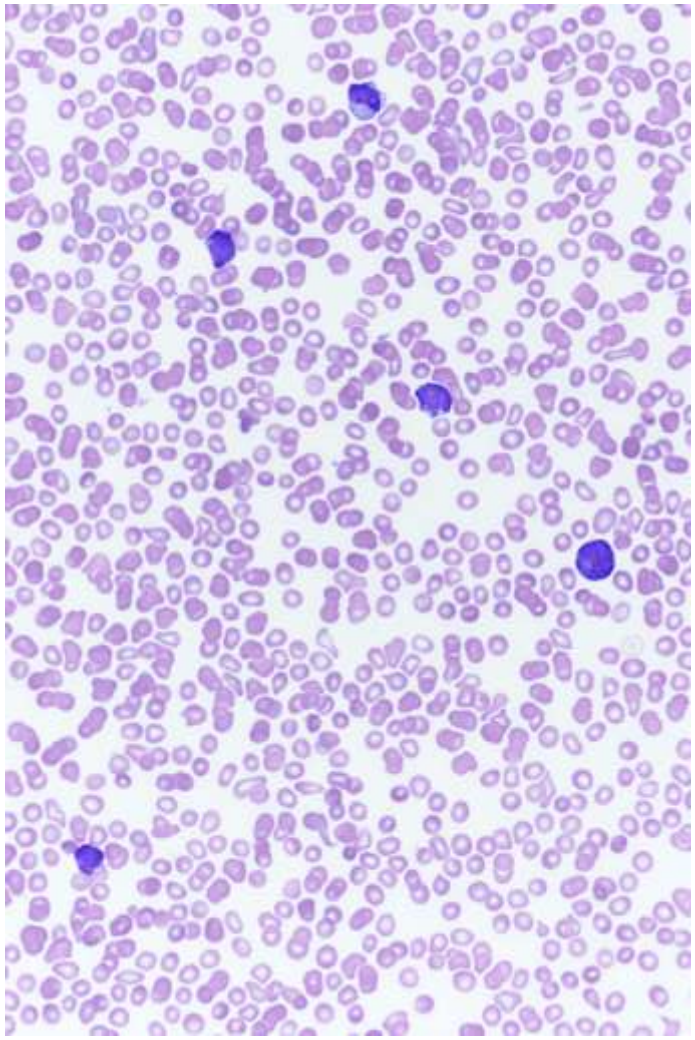
- **Flow cytometry (skin):** No immunophenotypically abnormal cell population and no immature B-cell population identified in a limited viability sample (1% viability).

- **T-cell receptor gene rearrangement:** Positive

Flow cytometry (BM)

- B lymphoblastic leukemia/lymphoma
- No abnormal T-cell population

Comment: B lymphoid blasts accounted for 22% of total events and expressed CD10, CD19, weak CD22, CD38, and variable HLA-DR with cytoplasmic expression of variable CD22, CD79a, and TdT and without co-expression of surface Ig, CD20, MPO, other myeloid antigens, or T-cell antigens. A small subset of blasts expressed CD34 (8% of blasts).



Diagnosis

- Subcutaneous panniculitis-like T-cell lymphoma
- B- lymphoblastic leukemia/lymphoma

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)

- Rare, cytotoxic T-cell lymphoma expressing alpha/beta TCR phenotype.
- Most common in young adults, can occur at a wide age range.
- Multiple subcutaneous lesions and may also have systemic symptoms and/or laboratory abnormalities such as cytopenias.
- The overall 5-year median survival is approximately 80%, although the prognosis is poor if associated with a hemophagocytic syndrome.
- Histology: Subcutaneous involvement, fat rimming, karyorrhexis, necrosis, CD8+, TIA1/Granzyme B/Perforin+, Beta F1+, CD56-
- Differential: Primary cutaneous gamma delta T-cell lymphomas;

  Lupus panniculitis

Pediatr Blood Cancer 2013;60:1165–1170

Subcutaneous Panniculitis-Like T-Cell Lymphoma in the Pediatric Age Group: A Lymphoma of Low Malignant Potential

Alison R. Huppmann, MD, Liqiang Xi, MD, Mark Raffeld, MD, Stefania Pittaluga, MD, PhD, and Elaine S. Jaffe, MD*

Background. Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare neoplasm of mature αβ cytotoxic T-cells. Most commonly occurring in young adults, few reports are described in children. A separate analysis of a significant cohort of pediatric patients has not previously been performed. ***Procedure.*** We analyzed the pathology including molecular results as well as available clinical data from 16 pediatric patients (age 5 months to 21 years) who had a total of 19 biopsies submitted to the National Cancer Institute from 1999 to 2011. This included 6 males and 10 females. ***Results.*** Most patients (10/16, 62.5%) had multiple skin lesions at the time of biopsy. Histologic features included rimming of adipocytes by atypical lymphocytes, fat necrosis, and karyorrhectic debris. Four biopsies showed only partial involvement by lymphoma; and plasma cells were identified in 14/19 (74%) cases, including three in which they were focally prominent. The neoplastic cells in general were positive for CD3, CD8, TIA-1, and βF1 and were negative for CD4 and CD56. CD5 expression was weak to negative in 5/8 cases (63%). A clonal T-cell receptor gene rearrangement was demonstrated in 11/17 (65%). Patients were treated with a variety of agents. While 5/9 (56%) patients had evidence of recurrent skin lesions, no deaths were attributed to disease for the seven patients with follow-up information. ***Conclusions.*** Pediatric SPTCL shares many clinical and pathologic features with adult SPTCL. The presence of partial involvement or admixed plasma cells makes the differential diagnosis with reactive conditions challenging in some cases. Pediatr Blood Cancer 2013;60:1165–1170.

Key words: lupus panniculitis; pediatric; subcutaneous panniculitis-like T-cell lymphoma

Next Generation Sequencing (UCSF500)

Bone marrow

Pathogenic or Likely Pathogenic SOMATIC ALTERATIONS				
VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
KRAS p.A146V	NM_004985	Pathogenic	552	23%

Skin

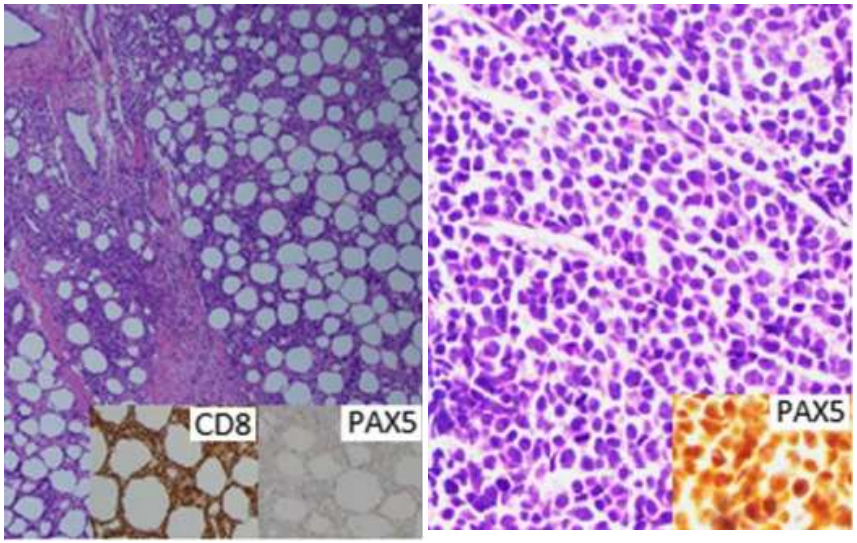
Pathogenic or Likely Pathogenic SOMATIC ALTERATIONS				
VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
No pathogenic or likely pathogenic alterations identified.				

Buccal swab

Pathogenic or Likely Pathogenic GERMLINE ALTERATIONS*				
VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS (Normal/Tumor)	MUTANT ALLELE FREQUENCY (Normal/Tumor)
No pathogenic or likely pathogenic alterations identified.				

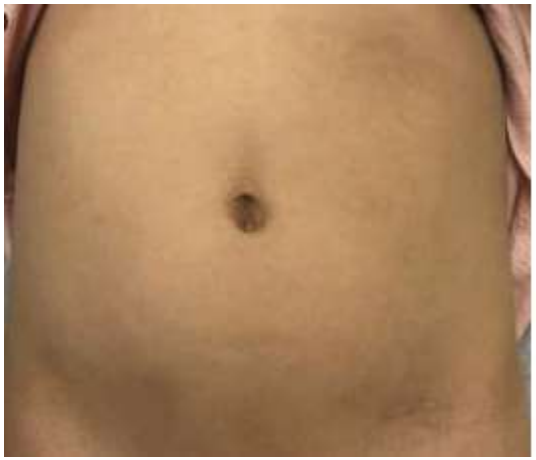
Concurrent Subcutaneous Panniculitis-like T-Cell Lymphoma and B-Cell Acute Lymphoblastic Leukemia in 2 Pediatric Patients

Geoffrey A. Smith, MD, PhD, Anya L. Levinson, MD,*
Robert T. Galvin, MD,† Leah E. Lalor, MD,‡ Timothy McCalmont, MD,‡§
Linlin Wang, MD, PhD,‖ Michael C. Geis, MD,¶ Karah Odegaard, MD,¶
Meghan Hupp, MD,# Sheilagh Maguiness, MD,**
Lucie M. Turcotte, MD, MPH,†† Kelly M. Cordoro, MD,‡
and Michelle L. Hermiston, MD, PhD**



What happened to the patient?

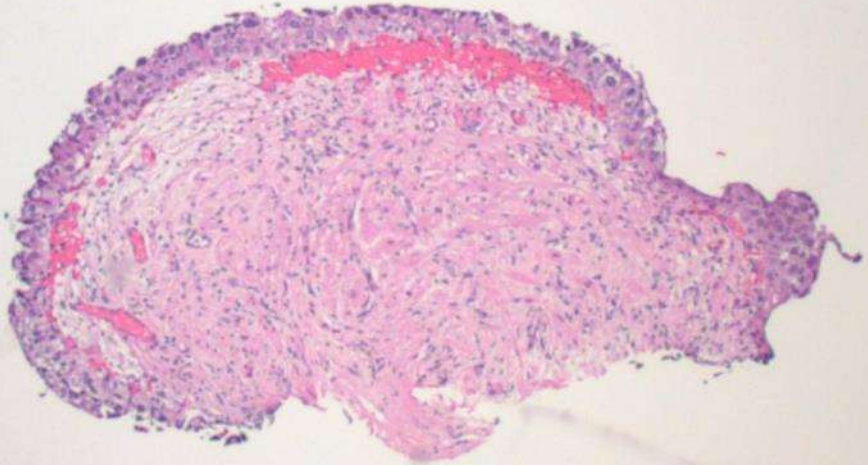
- Initiated on B-ALL regimen, AALL0932 protocol (5/2018-7/2020)
- In remission for B-ALL
- Skin lesion not present
- 22 month off therapy now

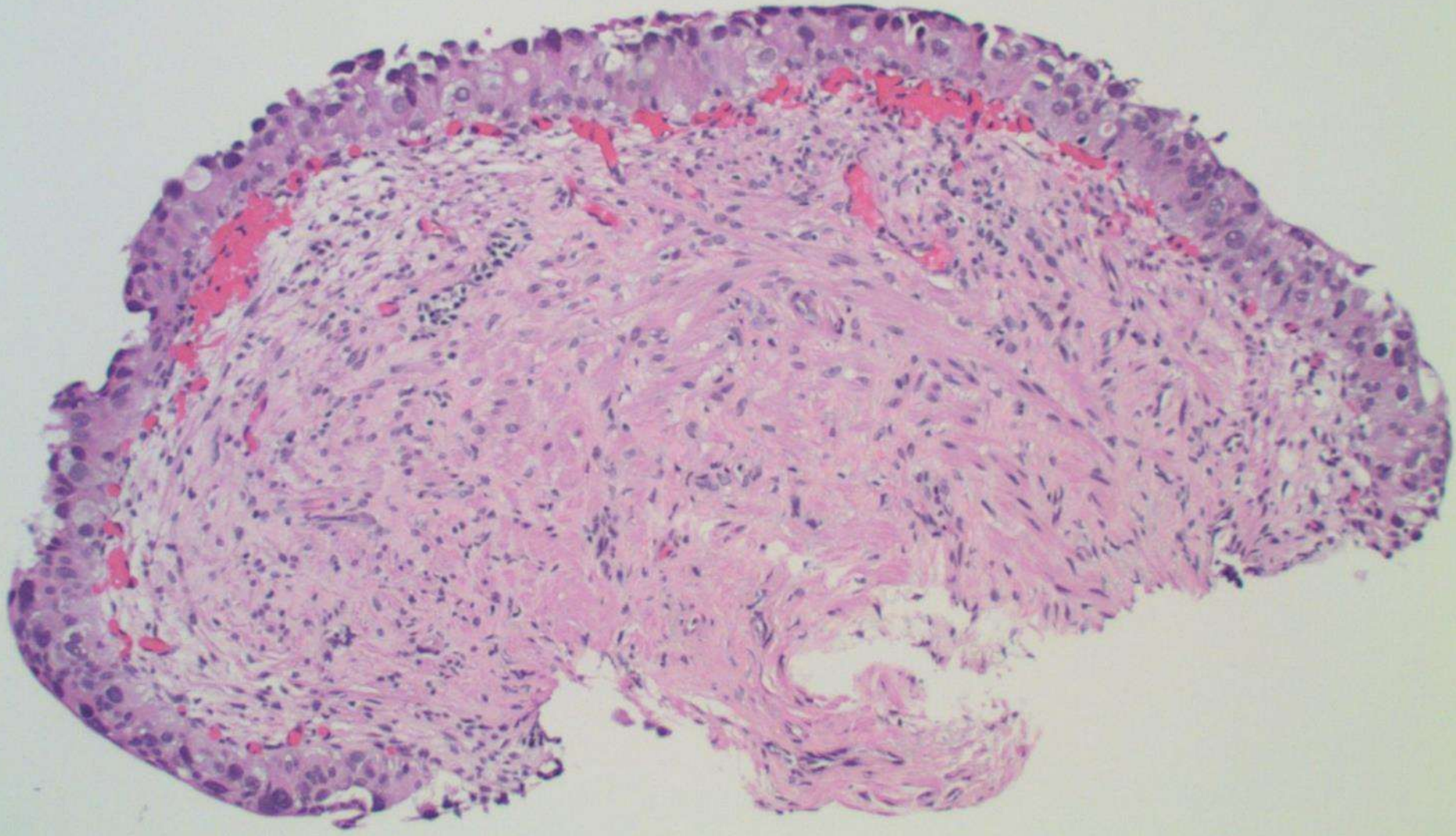


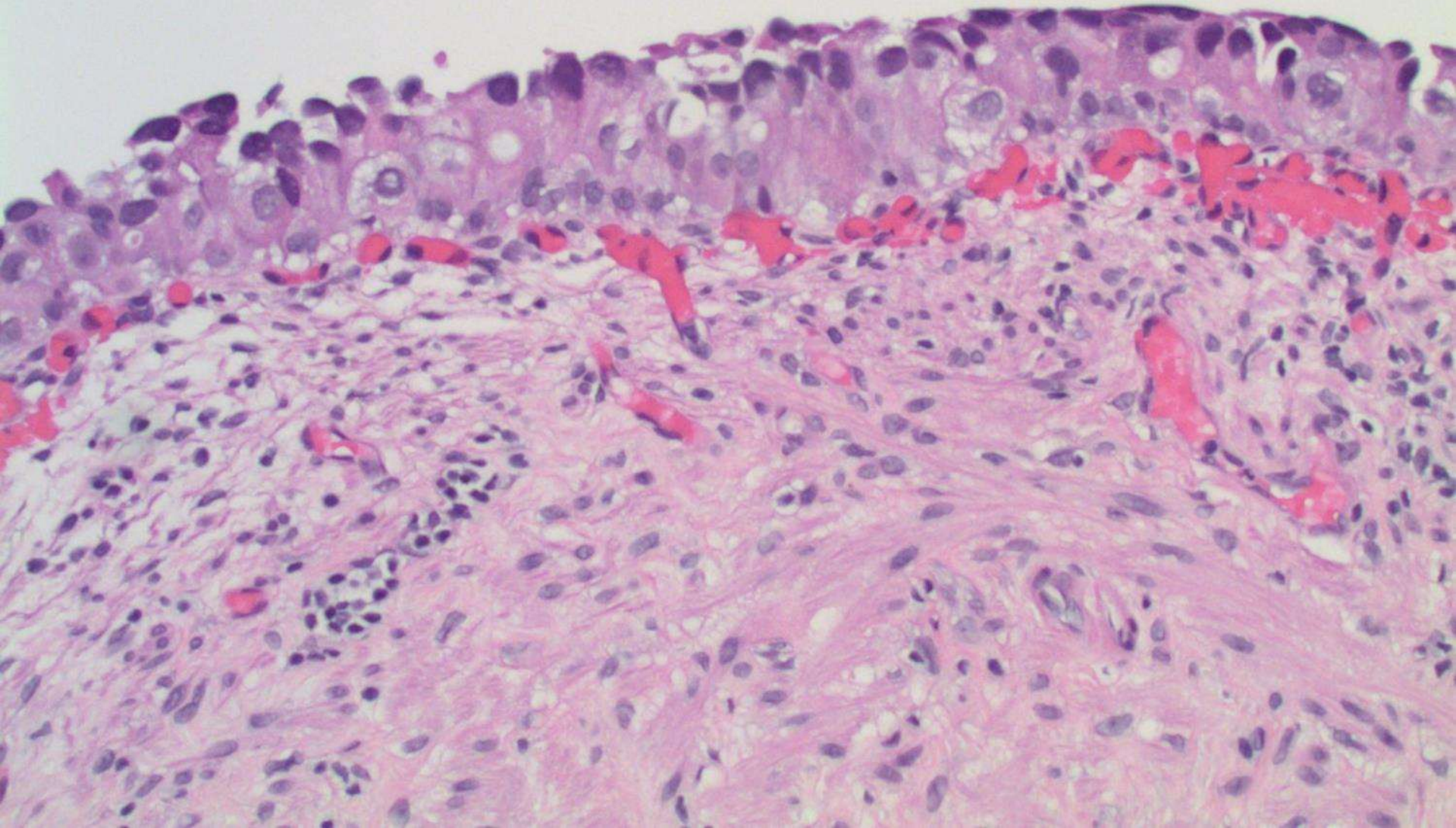
22-0607

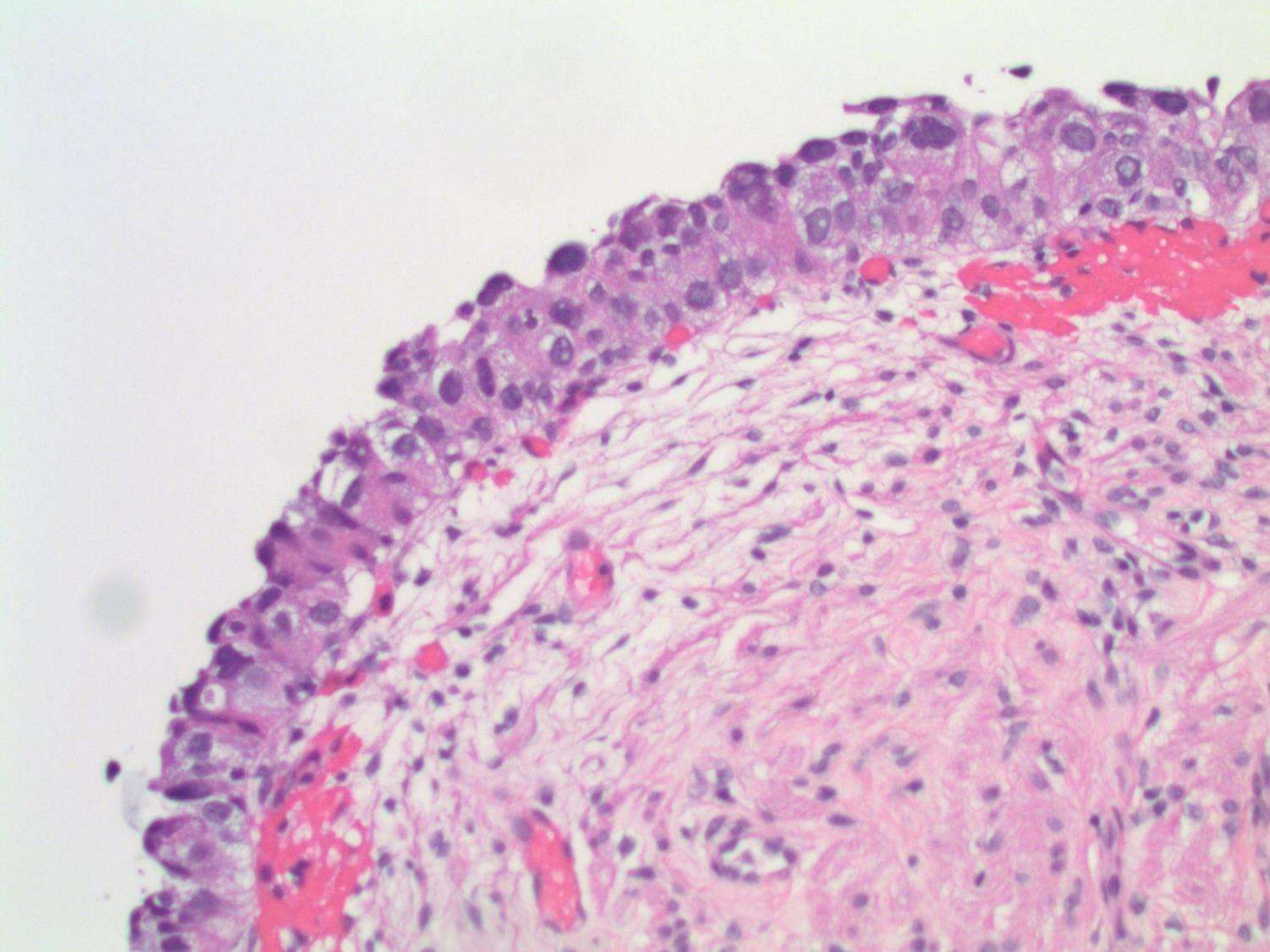
Ankur Sangoi; El Camino Hospital

Middle-aged M presents with hematuria. Cystoscopy showed blue light positive bladder lesions, bx submitted.

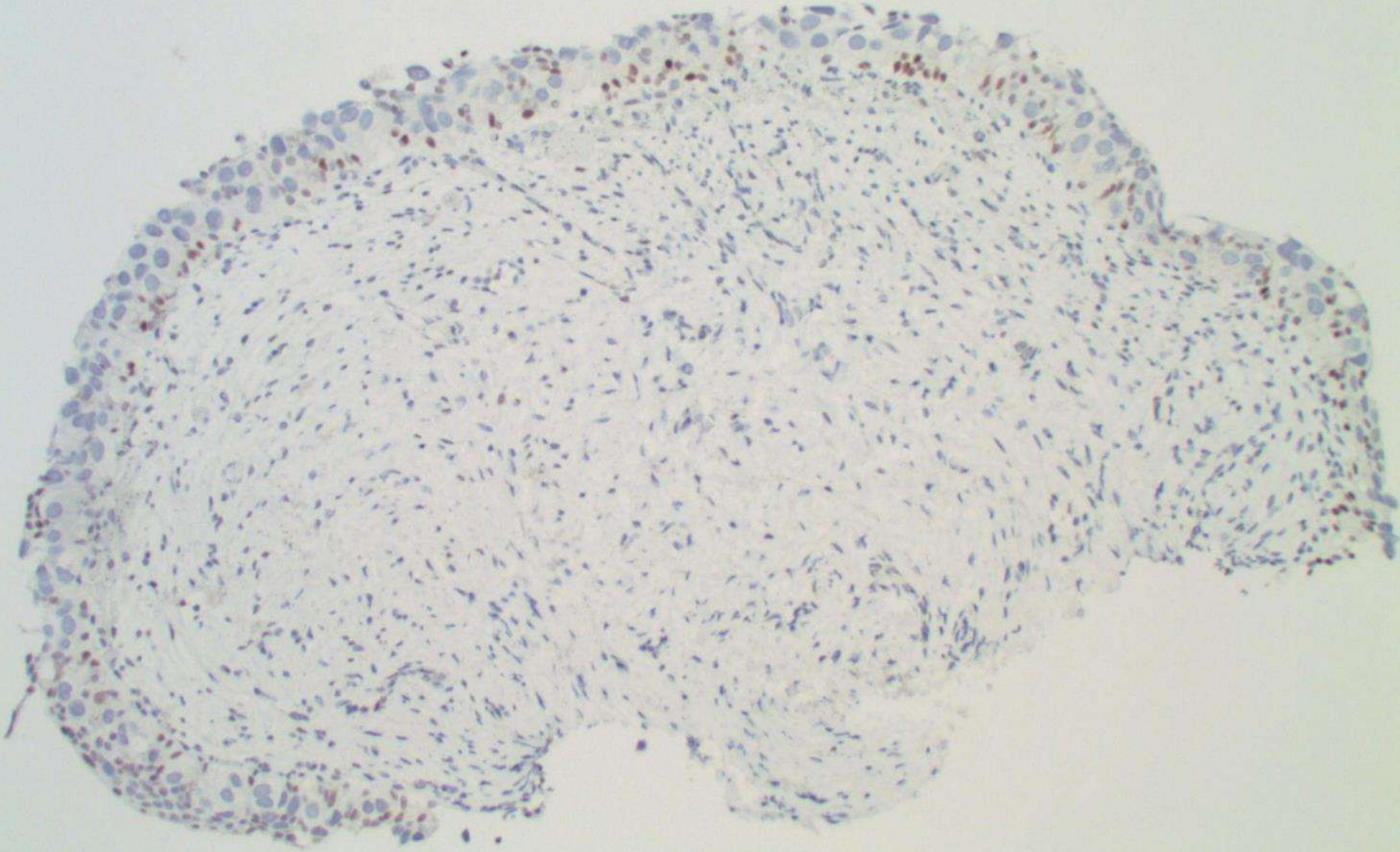






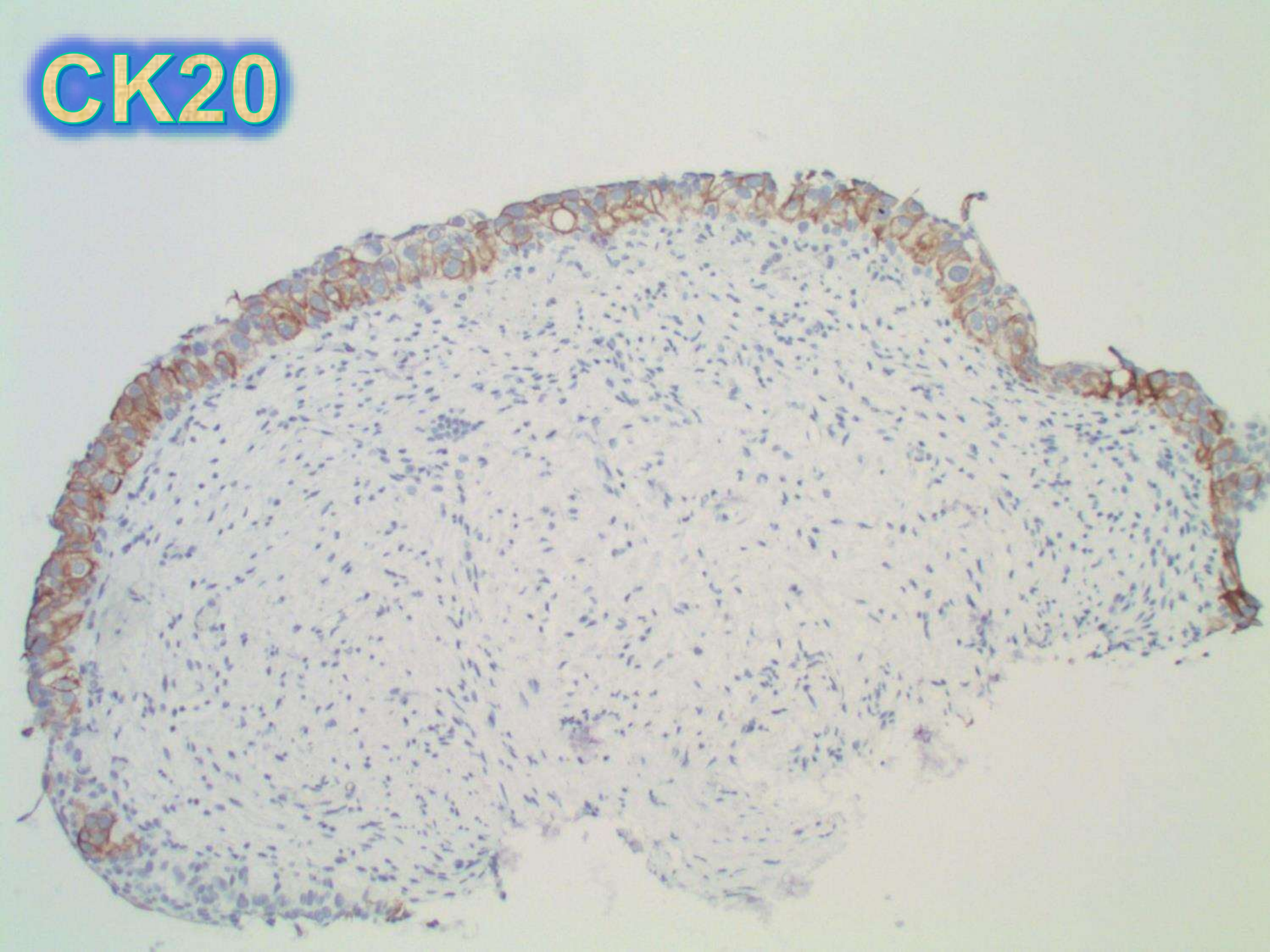


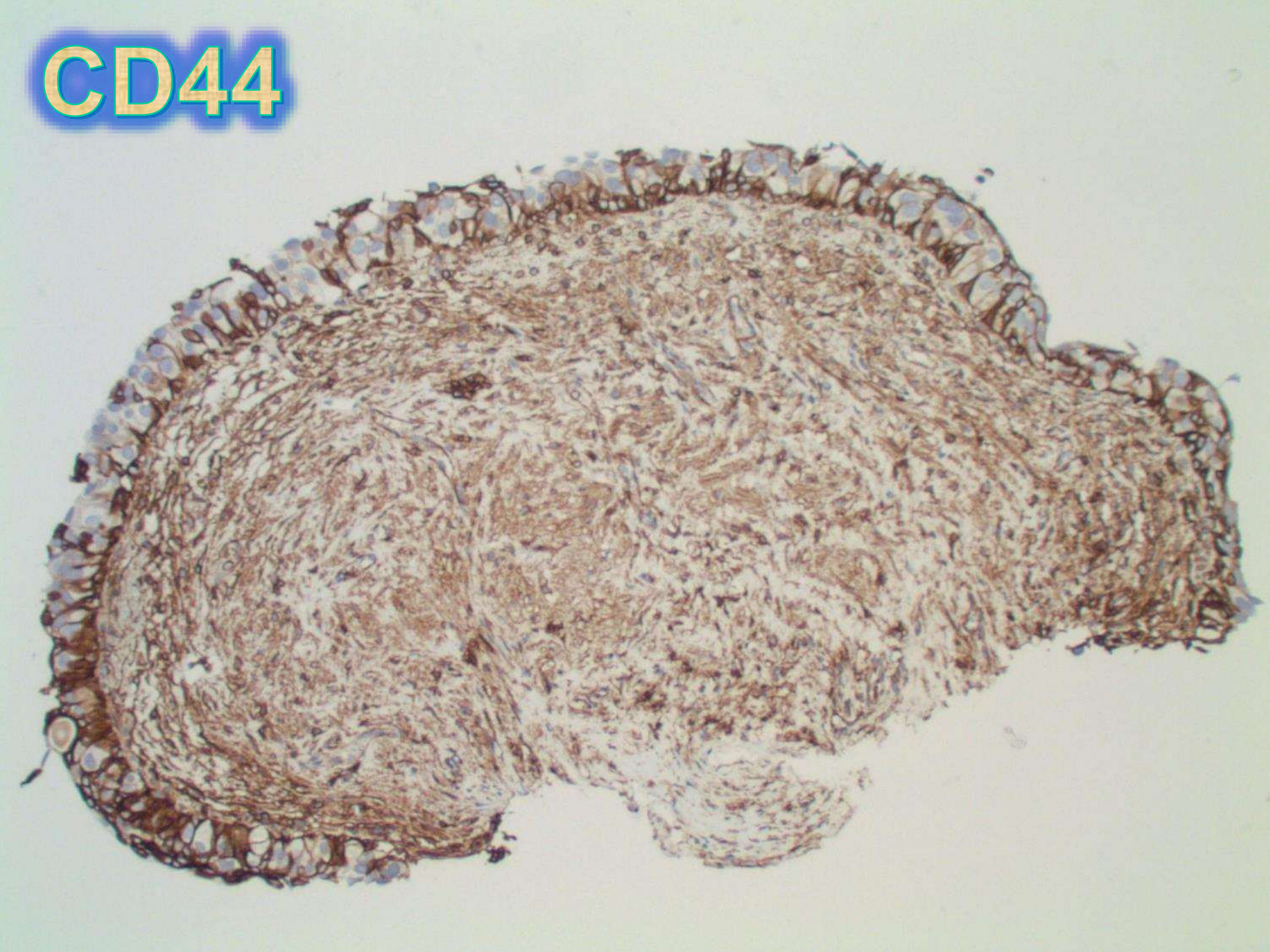
p53



DDx

- Urothelial carcinoma in situ
- Urothelial dysplasia
- Reactive urothelial atypia
- Radiation/chemotherapy effect
- BCG/mitomycin-associated atypia
- BK viral cytopathic atypia


CK20


CD44

FINAL DX

Urothelial carcinoma in situ

<u>IHC:</u>

CK20 positive

p53 aberrant (“null phenotype”)

CD44 negative

Discriminatory Immunohistochemical Staining of Urothelial Carcinoma in Situ and Non-neoplastic Urothelium

An Analysis of Cytokeratin 20, p53, and CD44 Antigens

Jesse K. McKenney, M.D., Sangeeta Desai, M.D., Cynthia Cohen, M.D., and Mahul B. Amin, M.D.

Distinction of urothelial carcinoma in situ (CIS) from reactive atypia on the basis of morphology alone may be difficult in some cases. Because this distinction is therapeutically and prognostically critical, we attempted to determine if an immunohistochemical panel would help in this differential diagnosis. The immunoprofile of 21 cases of CIS and 25 non-neoplastic urothelia (15 urothelial biopsies with reactive atypia from patients without a history of bladder cancer and 10 normal ureter sections from nephrectomies performed for renal cell carcinoma) was determined using antibodies against cytokeratin 20 (CK20), p53, and CD44 (standard isoform). In the normal urothelium CK20 showed patchy cytoplasmic immunoreactivity in only the superficial umbrella cell layer and CD44 stained only the basal cells. Nuclear immunoreactivity to p53 varied from negative to weak and patchy. Reactive urothelium also showed CK20 immunoreactivity in only the umbrella cell layer in all 15 cases, and p53 nuclear staining was predominantly negative with occasional weak positivity in the basal and parabasal intermediate cells. CD44 was overexpressed in the entire reactive urothelium in 9 cases (60%) or focally positive in intermediate cells in 6 cases (40%). In contrast, CIS showed intense CK20 and p53 positivity (81% and 57%, respectively) in the majority (>50%) of malignant cells. CD44 staining revealed residual basal cells with membranous reactivity in 44% of the cases of CIS; however, the neoplastic cells were immunonegative in all cases. At least one positive immunomarker (CK20 or p53) was abnormally expressed in all cases of CIS. Abnormal expression of CK20 (increased), p53 (increased), and CD44 (decreased) in urothelial CIS, and increased expression of CD44 in reactive atypia allows more confident distinction of urothelial CIS from non-neoplastic urothelial atypias. From a differential diagnosis perspective, use of a panel of all three antibodies with morphologic correlation would be essential.

Key Words: Urinary bladder—Carcinoma in situ—Reactive atypia—Intraepithelial lesions—Cytokeratin 20—p53—CD44—Immunohistochemistry.

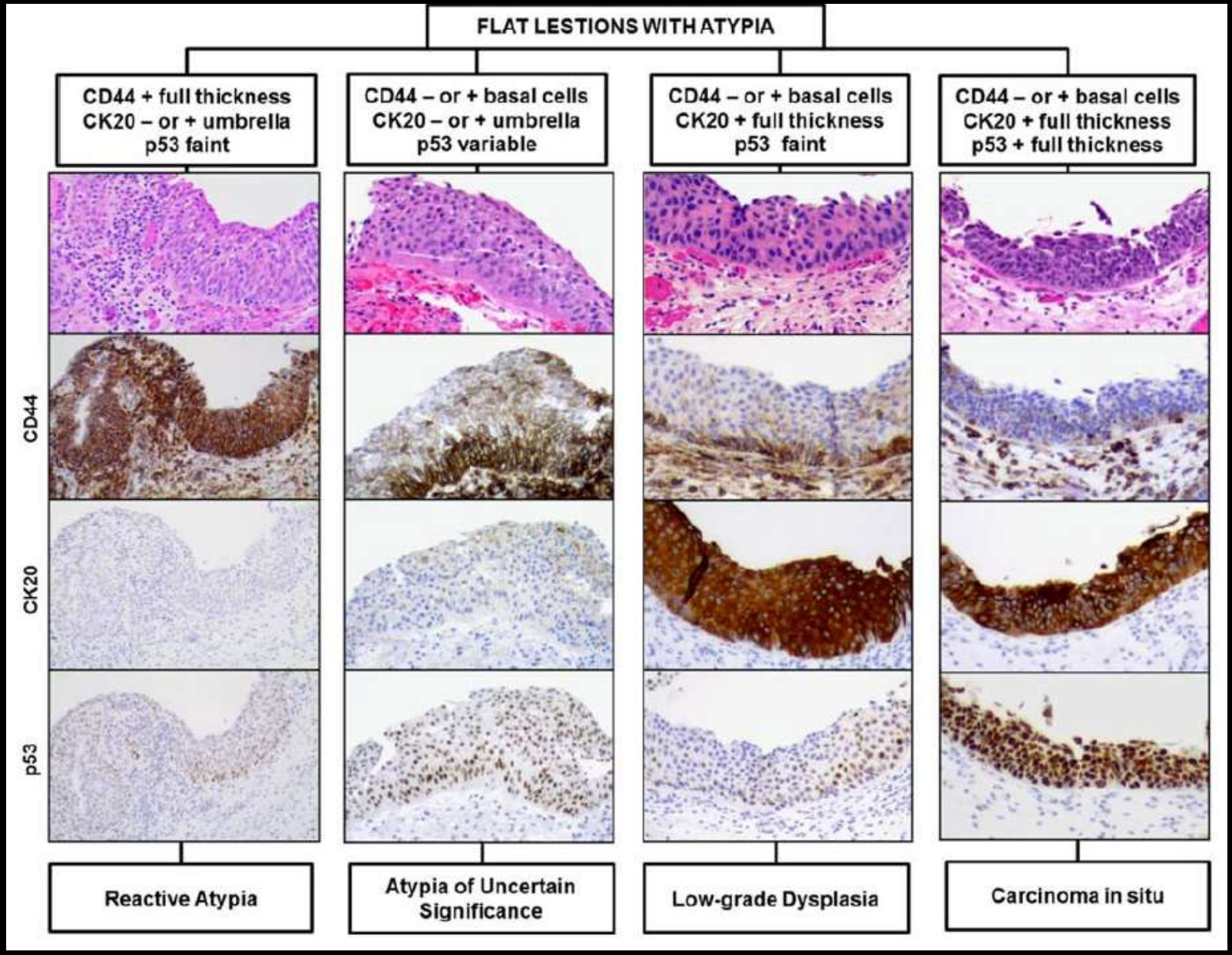
Am J Surg Pathol 25(8): 1074–1078, 2001.

In the spectrum of flat intraurothelial lesions with atypia, urothelial carcinoma in situ (CIS) is an aggressive disease.[12] Patients with CIS are at significant risk for the development of invasive urothelial carcinoma.[4,10,13] The presence of CIS in a patient with a coexisting noninvasive papillary urothelial carcinoma has a significant negative influence on clinical outcome.[10] The recognition of CIS in bladder biopsy specimens is thus crucial because it not only alters prognosis but often alters the subsequent therapy as well.

The morphology of urothelial CIS may overlap with that of reactive urothelial atypia resulting in diagnostic difficulty when interpreting bladder biopsies of patients on surveillance for urothelial neoplasia. A recent column in *CAP Today* emphasized the difficulty and importance of distinguishing CIS from benign atypias by highlighting malpractice cases involving the failure to recognize CIS.[35] In general, reactive atypia lacks irregular chroma-

TABLE 2. *Reactivity patterns for CIS**

Case no.	CK20	p53	CD44
1	4(+)	2	0
2	4(+)	4(+)	0
3	4(+)	2	0
4	4(+)	4(+)	0
5	1	4(+)	0
6	2	4(+)	0
7	4(+)	4(+)	0
8	4(+)	2	0
9	4(+)	2	0
10	4(+)	2	0
11	4(+)	4(+)	0
12	4(+)	4(+)	0
13	4(+)	2	0
14	4(+)	2	0
15	4(+)	2	0
16	1	4(+)	0
17	4(+)	4(+)	0
18	3(+)	4(+)	0
19	4(+)	4(+)	0
20	1	4(+)	0
21	4(+)	2	0



(*Appl Immunohistochem Mol Morphol* 2018;26:180–185)

Human Pathology (2020) 98, 81–88

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

Immunohistochemical staining patterns of Ki-67 and p53 in florid reactive urothelial atypia and urothelial carcinoma in situ demonstrate significant overlap☆,☆☆

Jane K. Nguyen MD, PhD[a], Christopher G. Przybycin MD[a], Jesse K. McKenney MD[a], Cristina Magi-Galluzzi MD, PhD[b,*]

[a] *Robert J. Tomsich Pathology and Laboratory Medicine Institute, Anatomic Pathology, Cleveland Clinic, Cleveland, OH, 44195, USA*

[b] *Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, 35249, USA*

Received 20 December 2019; revised 12 February 2020; accepted 23 February 2020
Available online 3 March 2020

Keywords:
Urothelial carcinoma in situ;
Reactive urothelial atypia;
p53;
Ki-67;
CK20;
CD44

Summary Flat urothelial lesions with atypia may pose significant diagnostic challenges. Given frequent increased proliferation rates in florid reactive urothelial atypia and limited studies on the interpretation of p53 stains in the urothelium (following current standard guidelines for correlation with P53 mutation status), we sought to further study the discriminatory value of Ki-67 and p53 for florid reactive urothelial atypia versus urothelial carcinoma in situ (CIS). Bladder specimens diagnosed as reactive urothelial atypia (n = 40) and CIS (n = 40) were assessed by immunohistochemical staining with antibodies for Ki-67, p53, CD44, and CK20. Immunoreactivity was scored based on percent cells positive for Ki-67 and pattern of reactivity with p53 (aberrant: diffuse strong positive or negative; normal: patchy/wild type). CD44 and CK20 reactivity patterns served as adjunctive internal validation controls for reactive urothelial atypia and CIS, as previously described. In reactive urothelial atypia, Ki-67 ranged from 0% to 90% (mean, 34% ± 26) with 30 cases (75%) having >10%. In CIS, Ki-67 ranged from 5% to 95% (mean, 50% ± 25) with 17 cases (43%) having >50%. In all 40 cases (100%) of reactive urothelial atypia, p53 expression had a wild-type pattern. In CIS, aberrant p53 expression was identified in 15 cases (37%): 3 cases (7%) were p53 negative (i.e. null phenotype) and 12 cases (30%) showed strong and diffuse nuclear reactivity (in >85% of cells). The remaining 25 cases (63%) of CIS had a p53 wild-type pattern of expression. Cytoplasmic CK20 immunoreactivity in umbrella cells was seen in 34 cases (85%) of reactive urothelial atypia, and 6 cases (15%) were negative. In addition, 35 cases (88%) of reactive urothelial atypia demonstrated full-thickness CD44 expression, while 5 cases (12%) had expression confined to the basal/parabasal layers of the urothelium. Strong and diffuse CK20 positivity was present in 39 cases (98%) of CIS, and patchy positivity was detected in 1 case (2%). None of the CIS cases overexpressed CD44: 16 cases (40%) showed focal expression in the nonneoplastic basal cell

Best Practices Recommendations in the Application of Immunohistochemistry in the Bladder Lesions

Report From the International Society of Urologic Pathology Consensus Conference

Mahul B. Amin, MD, Kiril Trpkov, MD,† Antonio Lopez-Beltran, MD,‡ David Grignon, MD,§ and Members of the ISUP Immunohistochemistry in Diagnostic Urologic Pathology Group*

Abstract: The bladder working group of the 2013 International Society of Urologic Pathology (ISUP) Conference on Best Practices Recommendation in the Application of Immunohistochemistry (IHC) in Urologic Pathology discussed 5 settings in which IHC is commonly used in clinical practice. With regard to markers for urothelial differentiation, the committee found that there is no ideal marker or established panel to confirm urothelial differentiation. On the basis of the differential diagnostic consideration, positivity for GATA3, CK20, p63, and either high–molecular weight cytokeratin (HMWCK) or cytokeratin (CK)5/6 is of value in proving urothelial differentiation in the appropriate morphologic and clinical context. With regard to the role of IHC in the distinction of reactive atypia from urothelial carcinoma in situ, the committee recommended that morphology remains the gold standard in this differential diagnosis and that, at best, the IHC panel of CK20/p53/CD44(s) has potential utility but is variably used and has limitations. The immunostaining pattern must be interpreted with strict morphologic correlation, because overreliance on IHC may be misleading, particularly in the posttreatment setting. IHC has no role in the distinction of dysplasia versus carcinoma in situ and in the grading of papillary urothelial carcinoma. IHC may have a limited but distinct role in staging of bladder cancer. In a subset of cases, depending on the clinical and histologic context, broad-spectrum cytokeratins (to identify early or obscured invasion) and desmin (distinction of muscle from desmoplasia and to highlight muscle contours for subclassification) may be helpful. Limited experience and conflicting data preclude smoothelin or vimentin to be recommended routinely for subclassifying muscle type at this time. In the workup of a spindled cell proliferation of the bladder and in limited specimens, we recommend an immunohistochemical panel of 6 markers including ALK1, SMA, desmin, cytokeratin (AE1/AE3), and p63 with either of HMWCK or CK5/6. Currently, there are no prognostic immunohistochemical or molecular studies that are recommended to be routinely performed on biopsy or resection specimens.

Key Words: urinary bladder, immunohistochemistry, best practices, consensus

(*Am J Surg Pathol* 2014;38:e20–e34)

In the bladder session of the conference, the role of the IHC in the following settings was discussed: (a) confirmation of urothelial differentiation at a metastatic site or in a bladder primary in a tumor with unusual histology including variants; (b) distinction of reactive atypia from carcinoma in situ (CIS); (c) role of IHC in staging of

TABLE 1. Typical Immunoreactivity for Commonly Used Markers in Flat Urothelial Lesions

	Normal Urothelium	Reactive Atypia	CIS
CK20	Limited to umbrella cells	Limited to umbrella cells	Aberrant expression through all cell layers. May be full thickness
CD44(s)	Limited to basal cells	Increased reactivity in all cell layers	Absent in atypical cells
p53	Absent	Absent	Strong and intense positivity in atypical cells

Am J Surg Pathol • Volume 38, Number 8, August 2014

p53 null phenotype is a "positive result" in urothelial carcinoma in situ

Ankur R. Sangoi[1]✉, Emily Chan[2], Eman Abdulfatah[3], Bradley A. Stohr[2], Jane Nguyen[4], Kiril Trpkov[5], Farshid Siadat[5], Michelle Hirsch[6], Sara Falzarano[7], Aaron M. Udager[3,8,9,10] and L. Priya Kunju[3,8,9,10]

The concept of a "p53 null phenotype" (complete loss of staining) is well-recognized in the gynecologic pathology literature, implicitly reflecting that this staining pattern represents a *TP53* mutation. However, in the genitourinary pathology literature, a p53 null phenotype has only been addressed regarding the prognosis of invasive urothelial carcinoma, and not as a diagnostic biomarker for urothelial carcinoma in situ (CIS). Herein, 25 cases of urothelial carcinoma in situ [diagnoses made on hematoxylin and eosin (H&E) stained sections] showing null pattern p53 staining were retrieved from 22 different patients (16 males and 6 females, age range 52–85 years; average 69.6 years), most commonly showing large cell pleomorphic pattern morphology. One representative tissue block per case was selected for next-generation DNA sequencing (NGS). All 21 cases (100%) passing quality control for NGS showed at least 1 *TP53* mutation (majority nonsense or frameshift mutations), including 3 cases with 2 mutations and 3 cases with 3 mutations. Three patients with multiple available samples harbored 1 or more shared *TP53* mutations at 2 different time points, indicating clonality of the temporally distinct lesions. Additionally, 2 patients had an additional unique *TP53* mutation at a later time point, suggesting intratumoral heterogeneity and/or temporal clonal evolution. While urothelial CIS remains an H&E diagnosis in most cases, a p53 immunostain may be useful in a subset of challenging cases. This study demonstrates that a p53 null phenotype represents an aberrant result in urothelial CIS with supportive molecular analysis showing a previously unknown level of complexity for *TP53* mutations among these noninvasive lesions. Adequate recognition of the p53 null phenotype as a "biologically supportive result", similar to strong and diffuse staining with p53, is important and may warrant a formal consensus statement for recommended p53 reporting (i.e., "wild type" versus "aberrant or mutant").

Modern Pathology; https://doi.org/10.1038/s41379-022-01062-2

Table 1. Clinicopathologic features of p53 null urothelial carcinoma in situ (CIS) cases.

CASE	specimen type	Age	Sex	Stage	Pattern of CIS	p53 staining pattern (clone/vendor)	p53 mutation
1	cystoprostatectomy	76	M	pT4aN2	large cell pleomorphic	null phenotype (DO-7/Leica)	p.P47fs
2	bladder biopsy	65	F	pT1	large cell nonpleomorphic	null phenotype (DO-7/Leica)	p.(Q192X);(C238Y)
3	bladder biopsy	65	F	pT1	large cell pleomorphic	null phenotype (DO-7/Leica)	p.(Q192X);(C238Y);(Q354X)
4*	bladder biopsy	75	M	pTis	large cell pleomorphic, clinging	null phenotype (DO-7/Leica)	p.R213X
5*	bladder biopsy	75	M	pTis	large cell pleomorphic	null phenotype (DO-7/Leica)	p.(R213X);(C238Y)
6#	bladder biopsy	70	M	pTis	large cell pleomorphic, pagetoid	null phenotype (DO-7/Leica)	p.Q104X
7	bladder biopsy	80	M	pTis	pagetoid	null phenotype (DO-7/Leica)	p.(C238Y);(R290S)
8	nephro-ureterectomy	85	F	pT3	large cell pleomorphic	null phenotype (DO-7/Leica)	p.C141fs
9	TURBT	64	M	pTis	large cell pleomorphic	null phenotype (DO-7/Leica)	p.[(p.S90F;S94X)];(Q192X)
10#	bladder biopsy	70	M	pTis	large cell pleomorphic	null phenotype (DO-7/Leica)	n/a
11^	bladder biopsy	71	M	pTis	large cell pleomorphic	null phenotype (DO-7/Ventana)	p.E198X
12^	bladder biopsy	71	M	pTis	large cell, pleomorphic	null phenotype (DO-7/Ventana)	p.E198X
13	cystectomy	70	F	ypT1N0	large cell pleomorphic, clinging	null phenotype (DO-7/Leica)	p.R213X
14	cystoprostatectomy	73	M	pT3aN0	large cell pleomorphic	null phenotype (DO-7/Leica)	p.Q255X
15	cystoprostatectomy	74	M	ypT3aN0	large cell pleomorphic	null phenotype (DO-7/Leica)	splice site (c.96 + 1 G > C)
16	bladder biopsy	64	M	pTis	large cell pleomorphic	null phenotype (DO-7/Leica)	p.E68X
17	ureterectomy	61	F	ypTis	pagetoid	null phenotype (DO-7/Leica)	p.L111fs
18	TURP	77	M	pT2	large cell nonpleomorphic	null phenotype (DO-7/Ventana)	p.V143fs
19	bladder biopsy	52	F	pTis	large cell pleomorphic	null phenotype (DO-7/Dako)	p.E62X
20	bladder biopsy	80	M	pTis	large cell pleomorphic	null phenotype (DO-7/Dako)	p.Q192X
21	bladder biopsy	81	M	pTis	large cell pleomorphic	null phenotype (DO-7/Dako)	p.G154fs
22	bladder biopsy	60	M	pTis	large cell pleomorphic	null phenotype (DO-7/Dako)	p.(Q192X);([C238Y;G245C])
23	cystoprostatectomy	71	M	pTis	pagetoid	null phenotype (DO-7/Agilent)	NGS failed QC
24	bladder biopsy	57	M	pTis	plasmacytoid	null phenotype (DO-7/Agilent)	NGS failed QC
25	cystoprostatectomy	53	M	pT4N2	pagetoid	null phenotype (DO-7/Agilent)	NGS failed QC

TAKE HOME POINTS

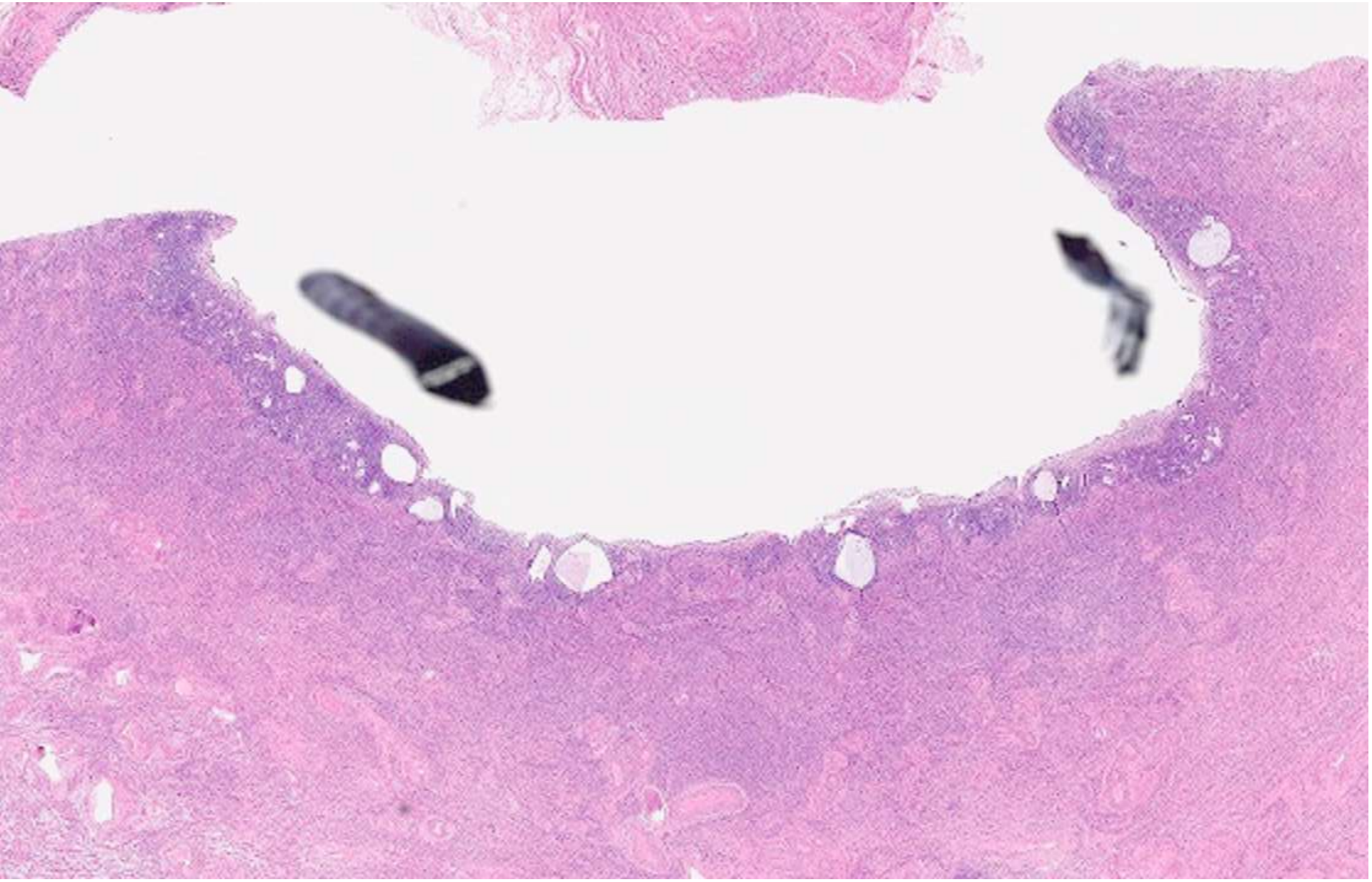
- **Use IHC for flat lesions cautiously when morphology is problematic**
- **CK20 & p53 probably best; CD44 optional**
  - CIS PATTERN: CK20+, p53+ or null, CD44-

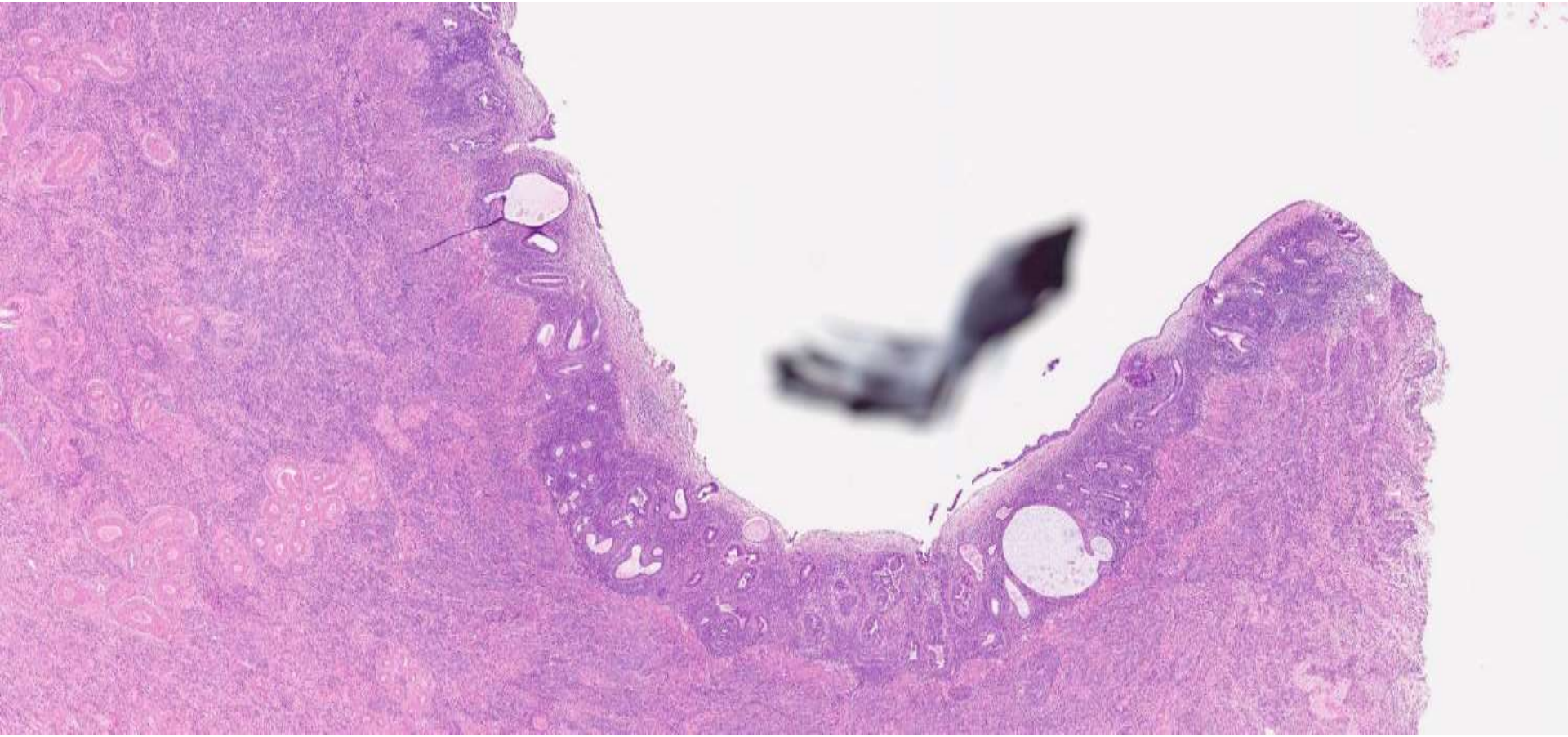
  described pattern of p53 ~GYNpath cases!
- **Check h/o prior chemo**
  - Can induce p53 IHC changes

22-0608

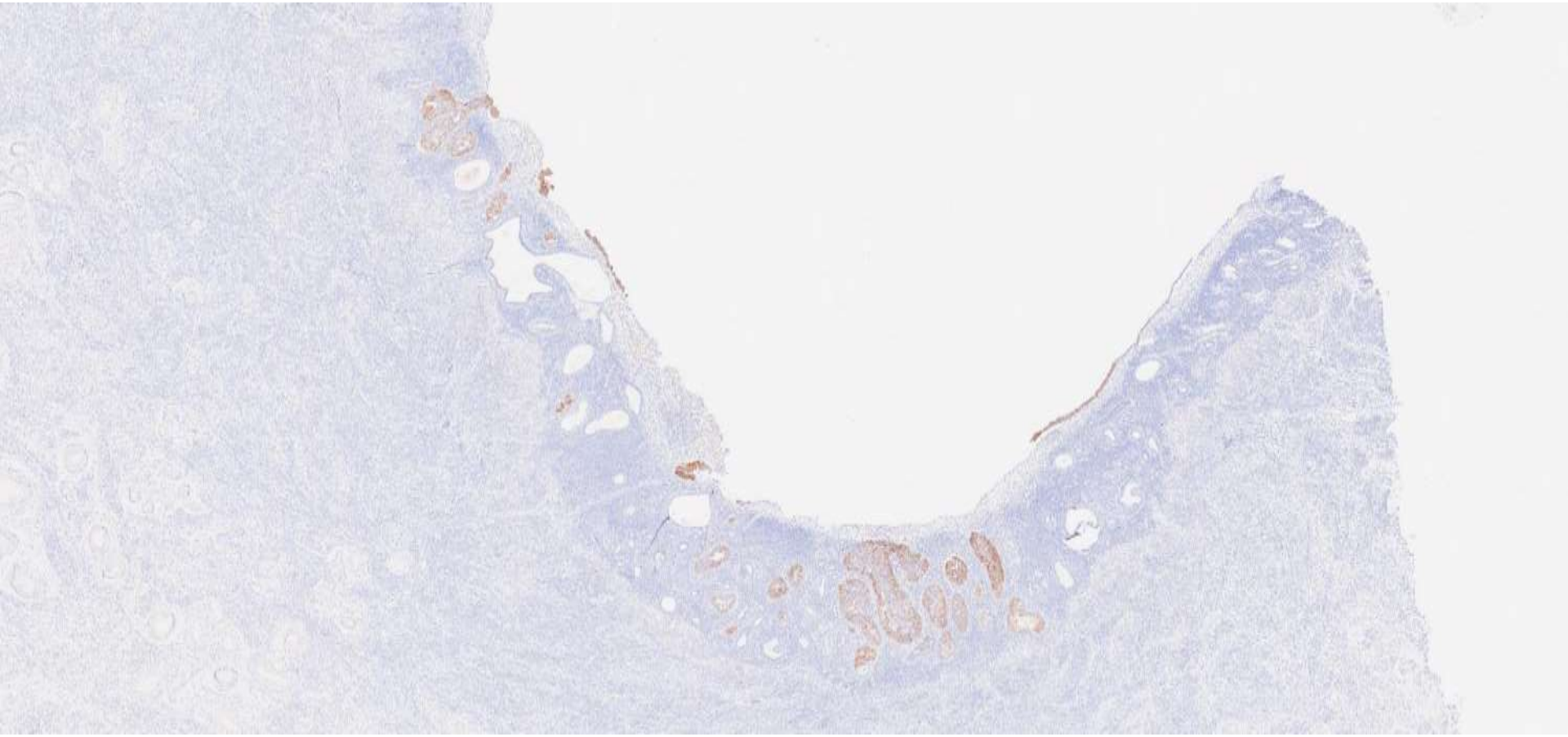
Ankur Sangoi; El Camino Hospital

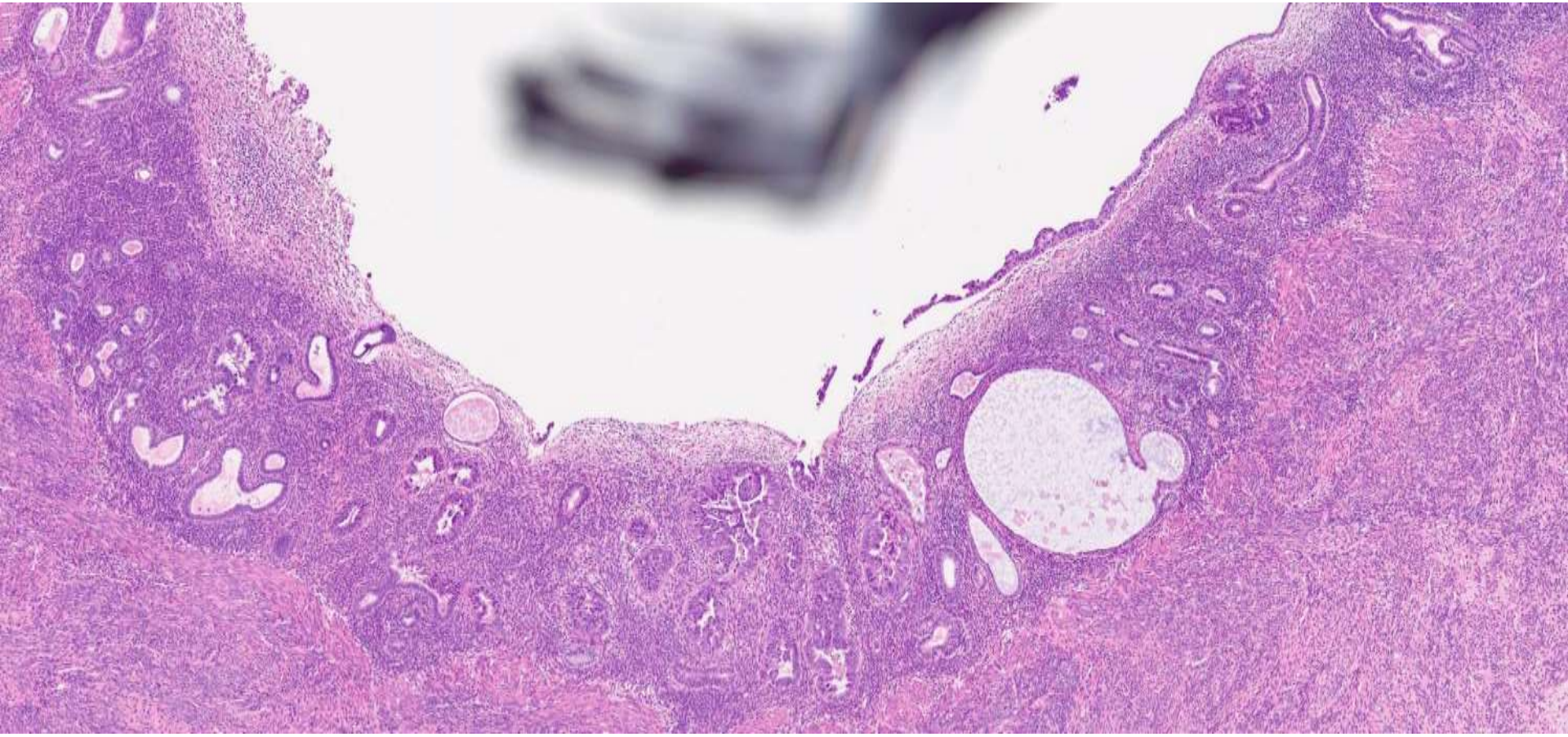
Older F presents with bleeding. Endometrial bx showed rare atypical cells. TAH/BSO performed. Section of endometrial polyp submitted.



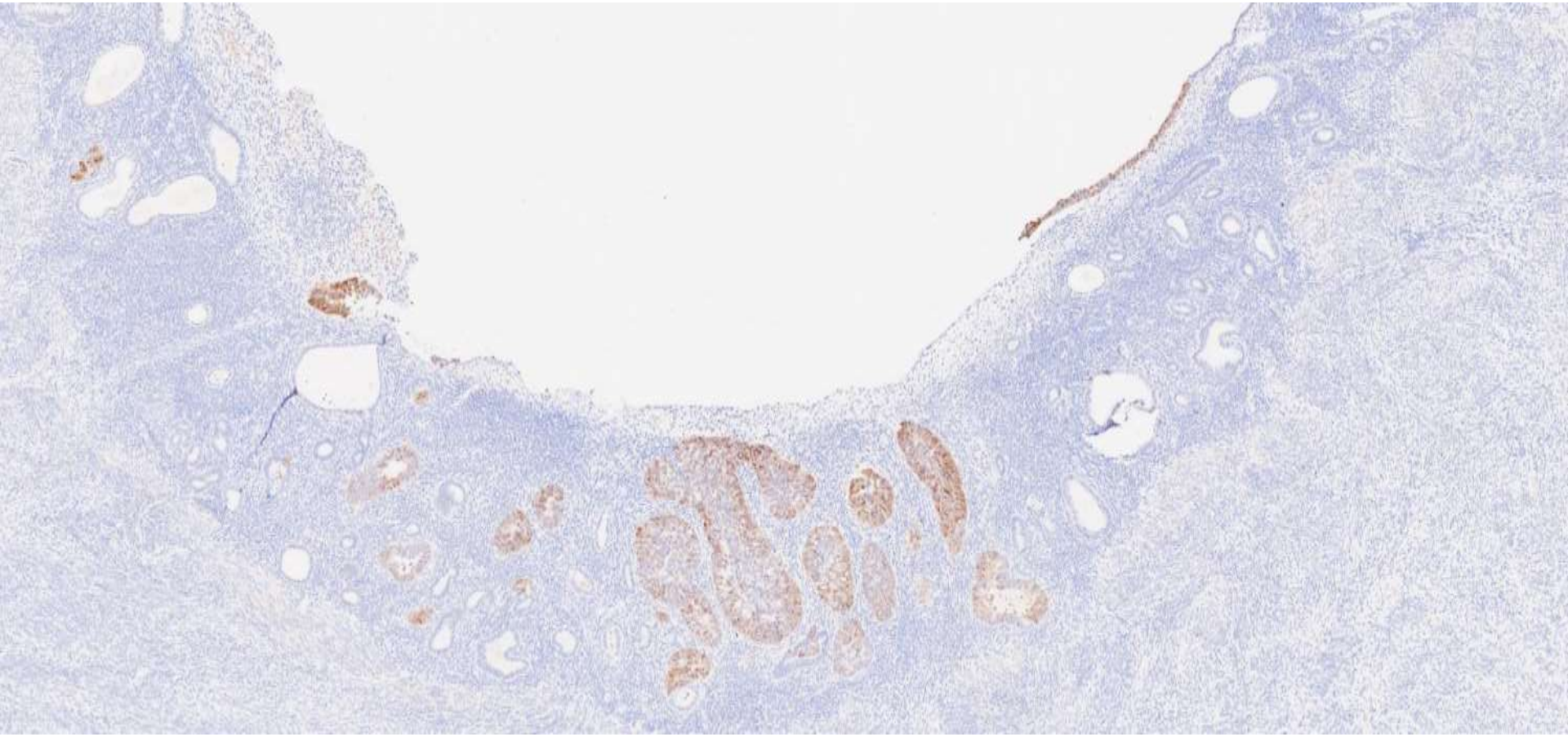


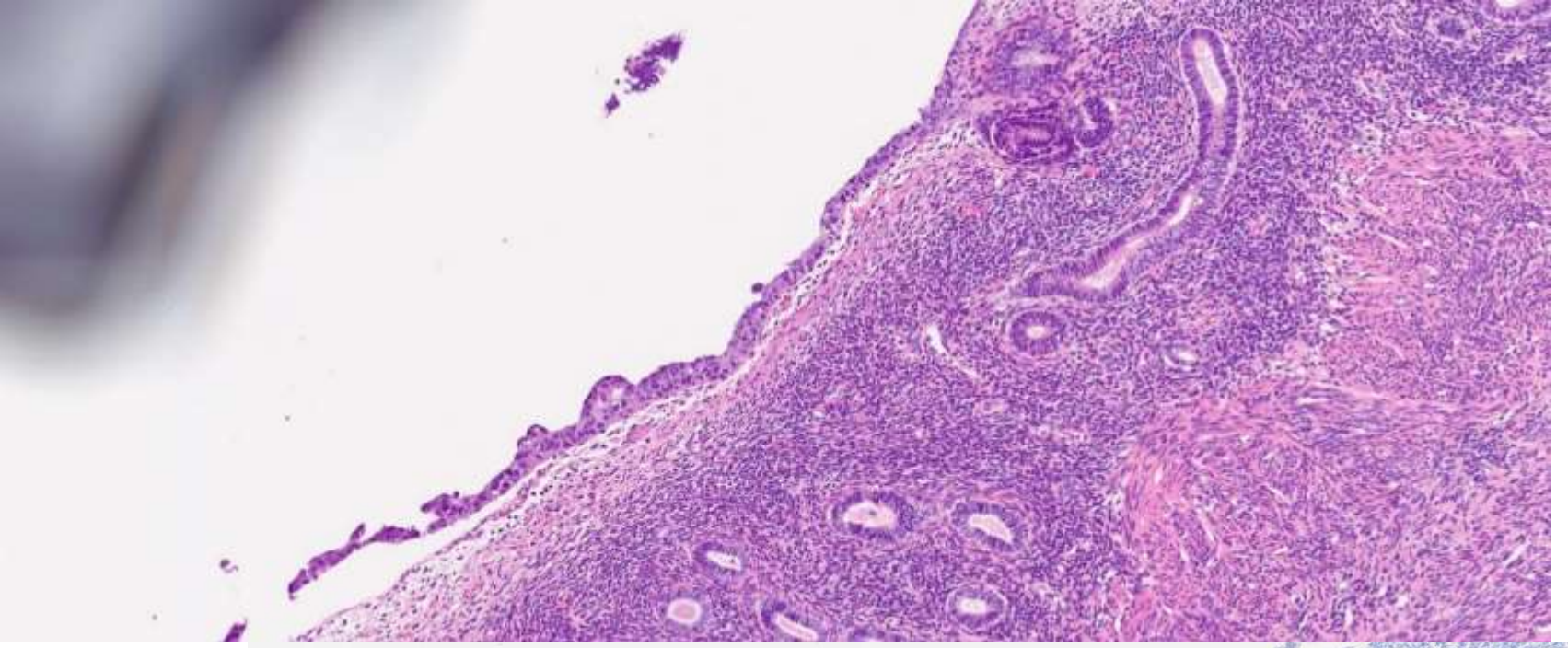
p53

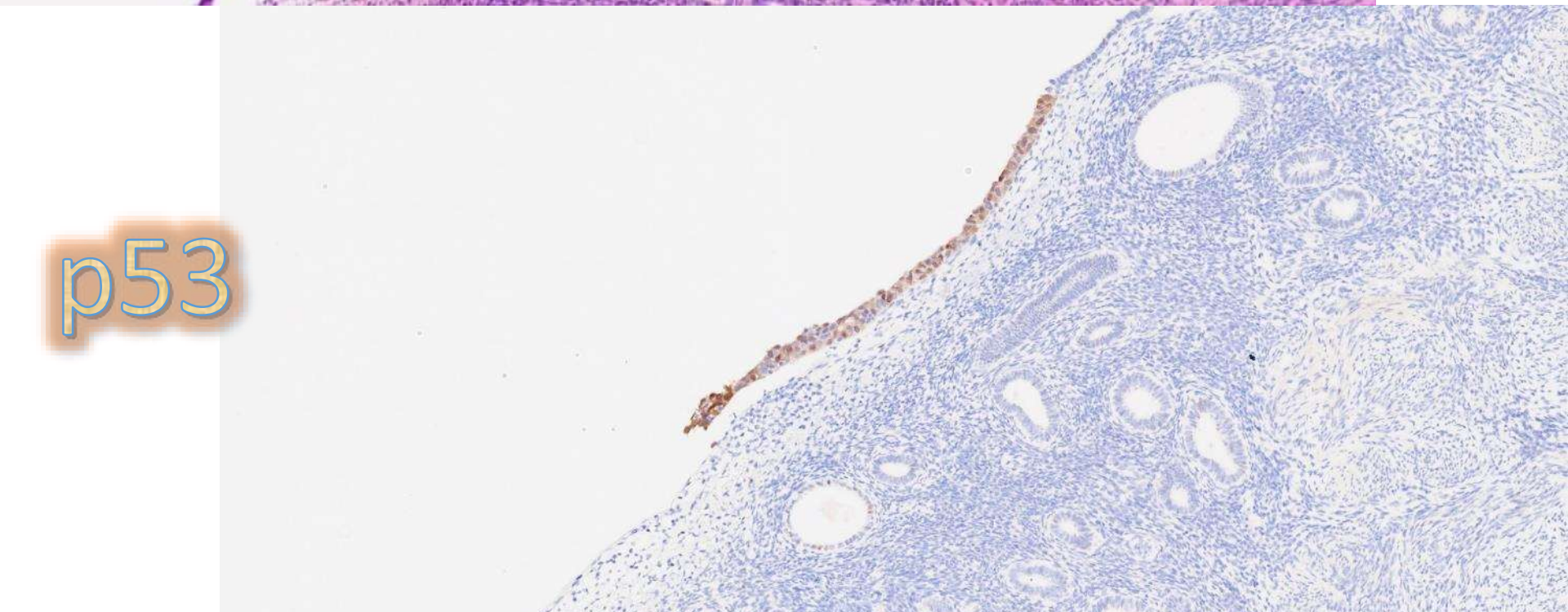


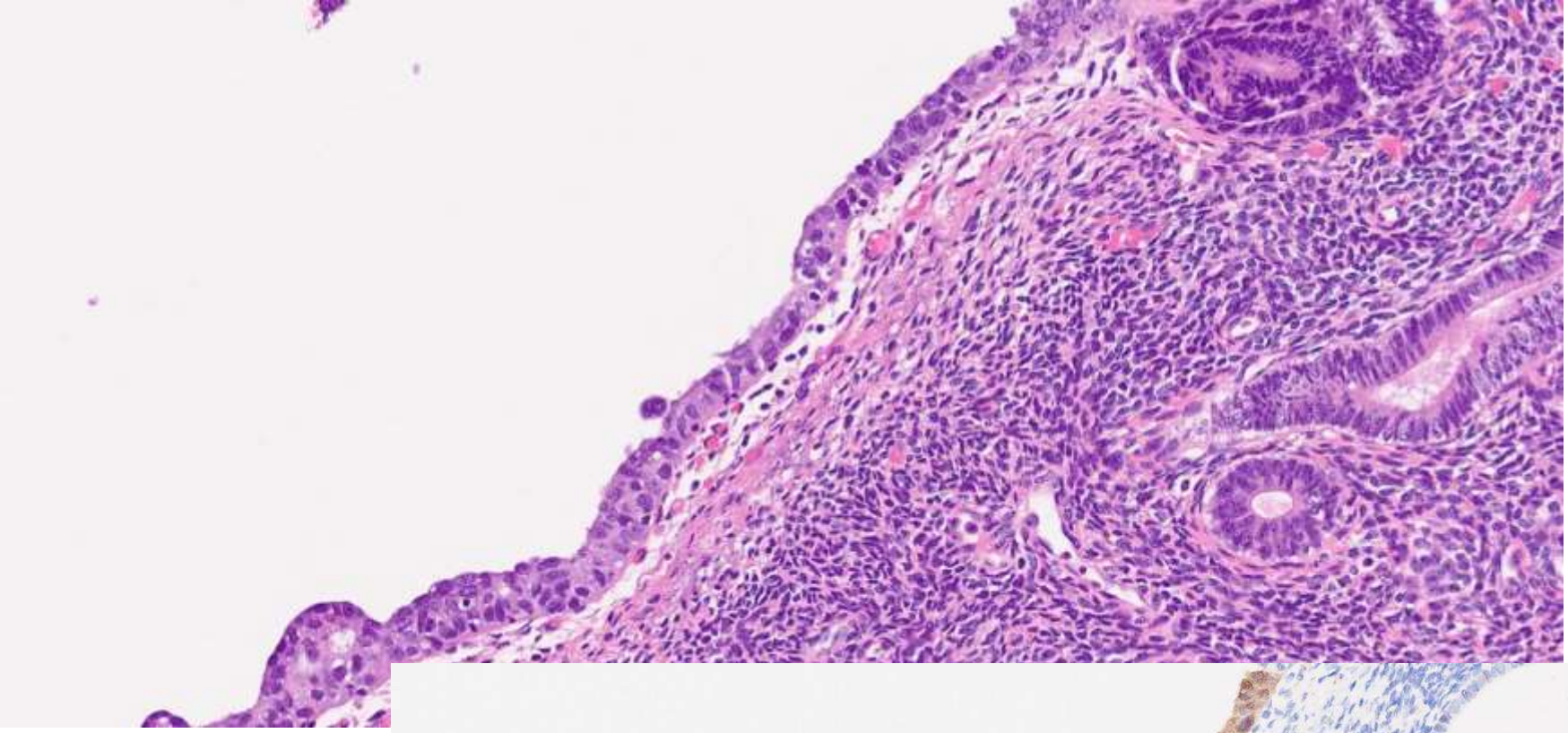


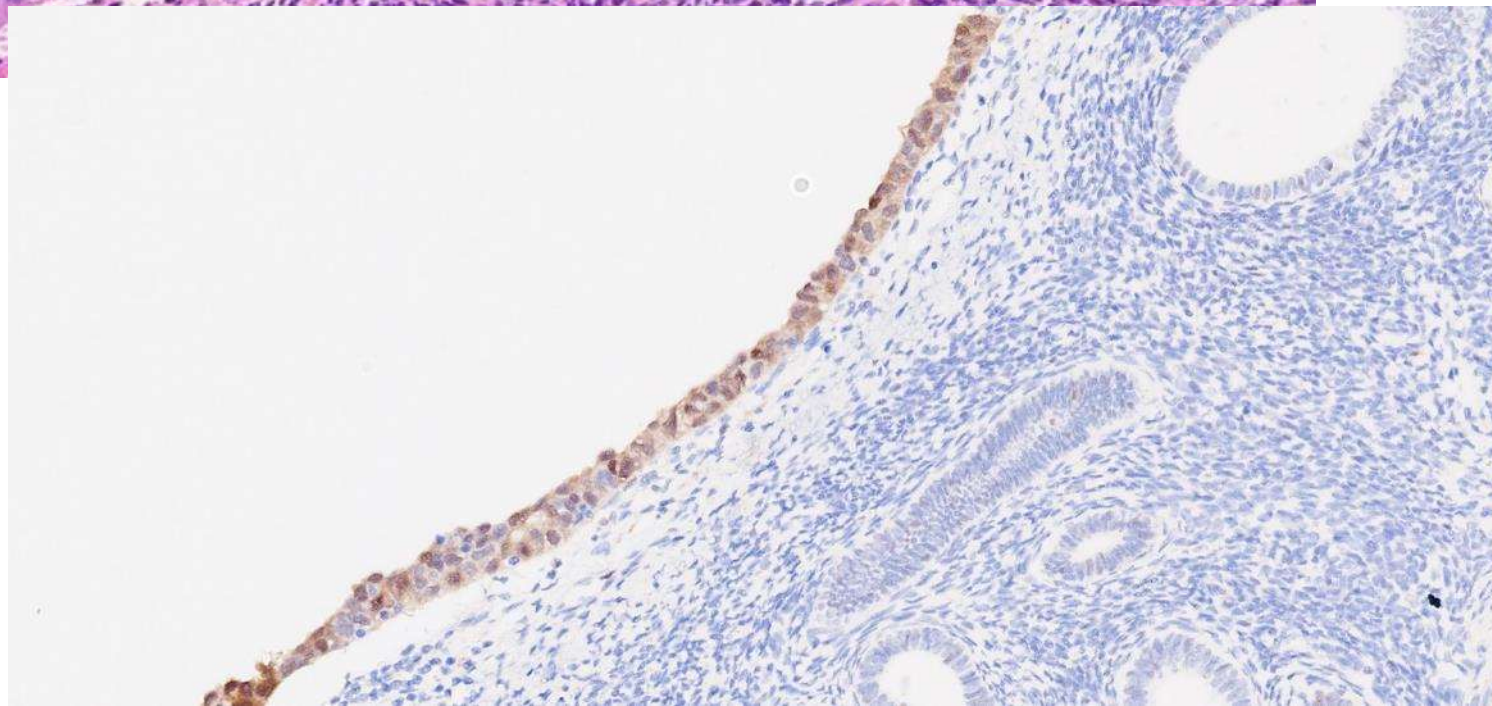
p53



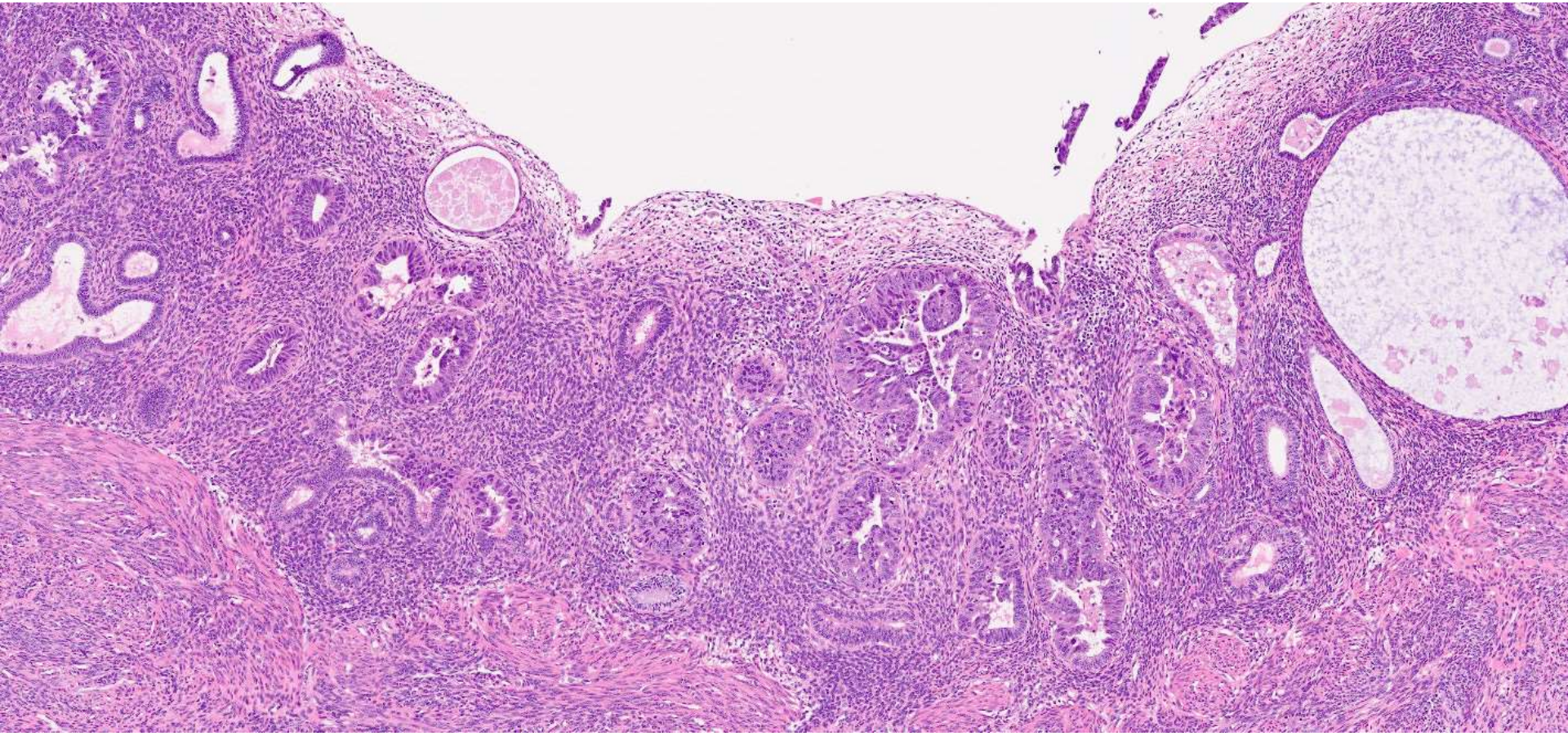



p53

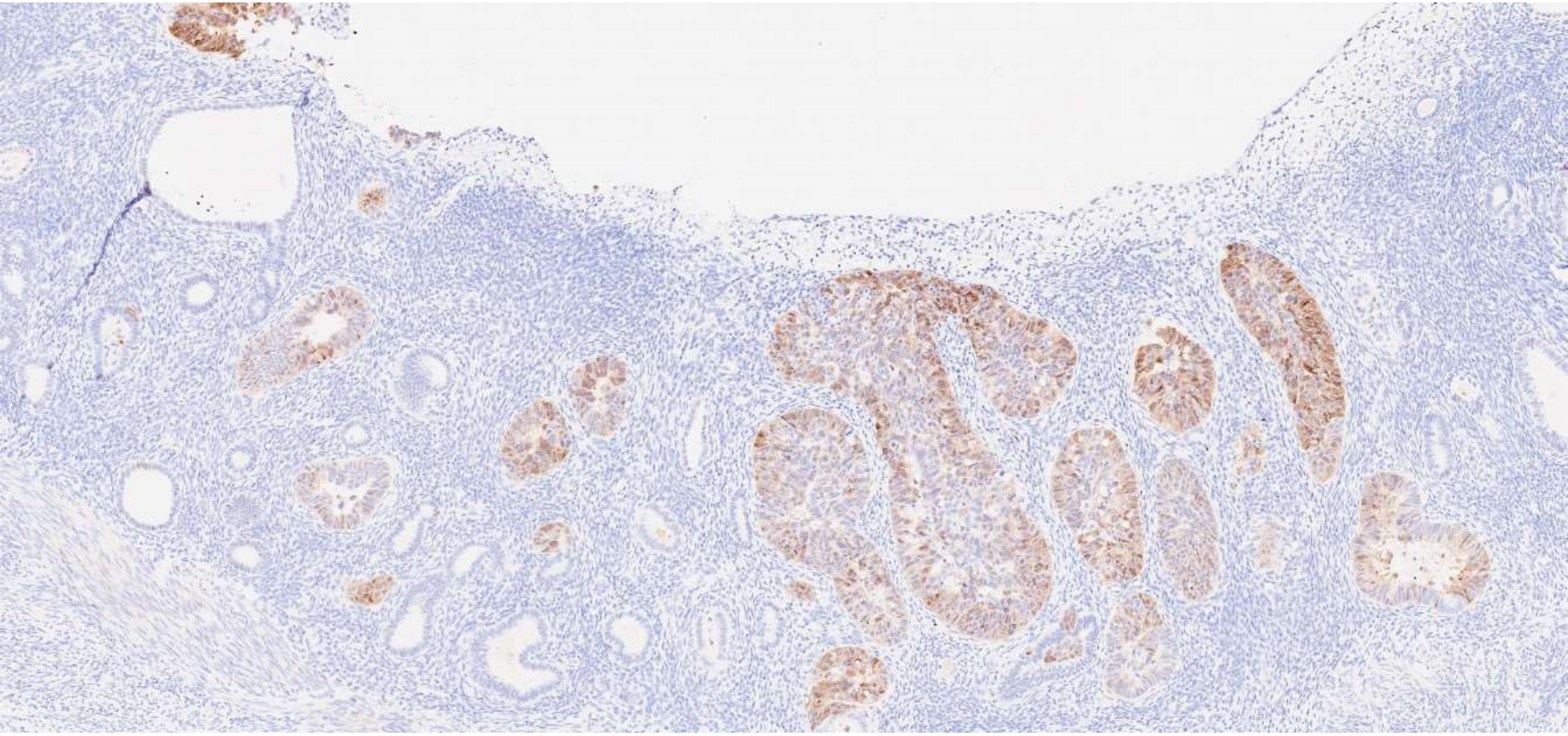


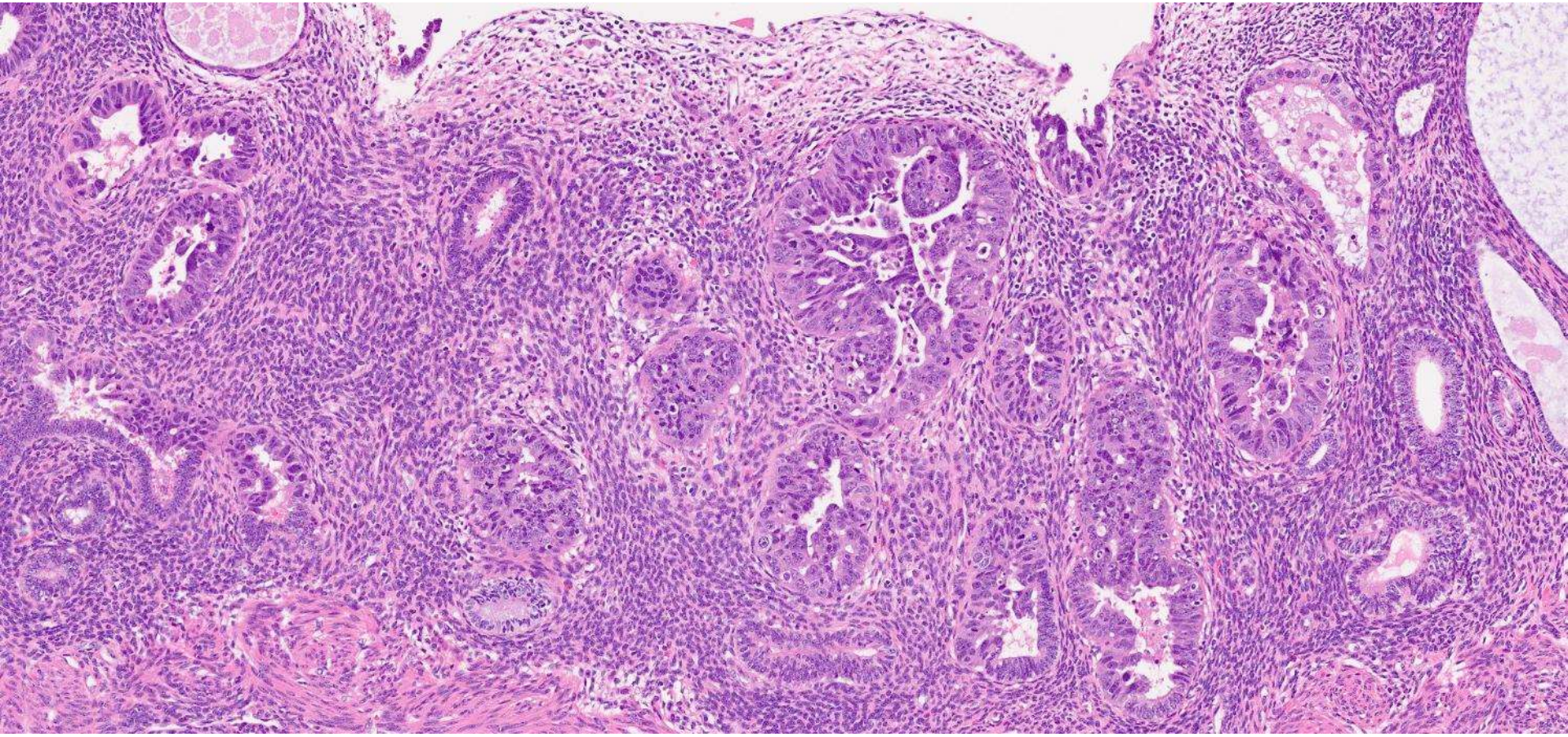


p53

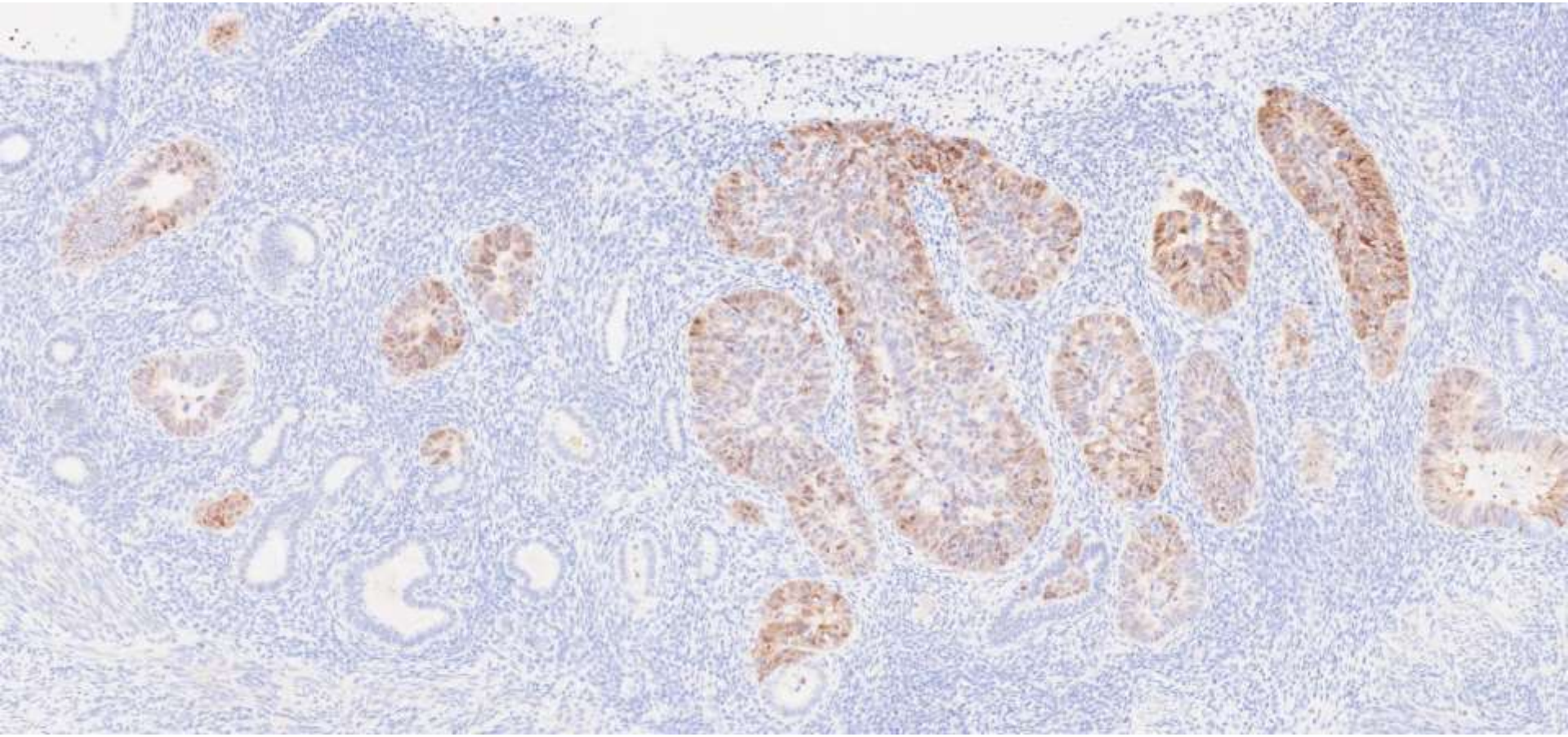


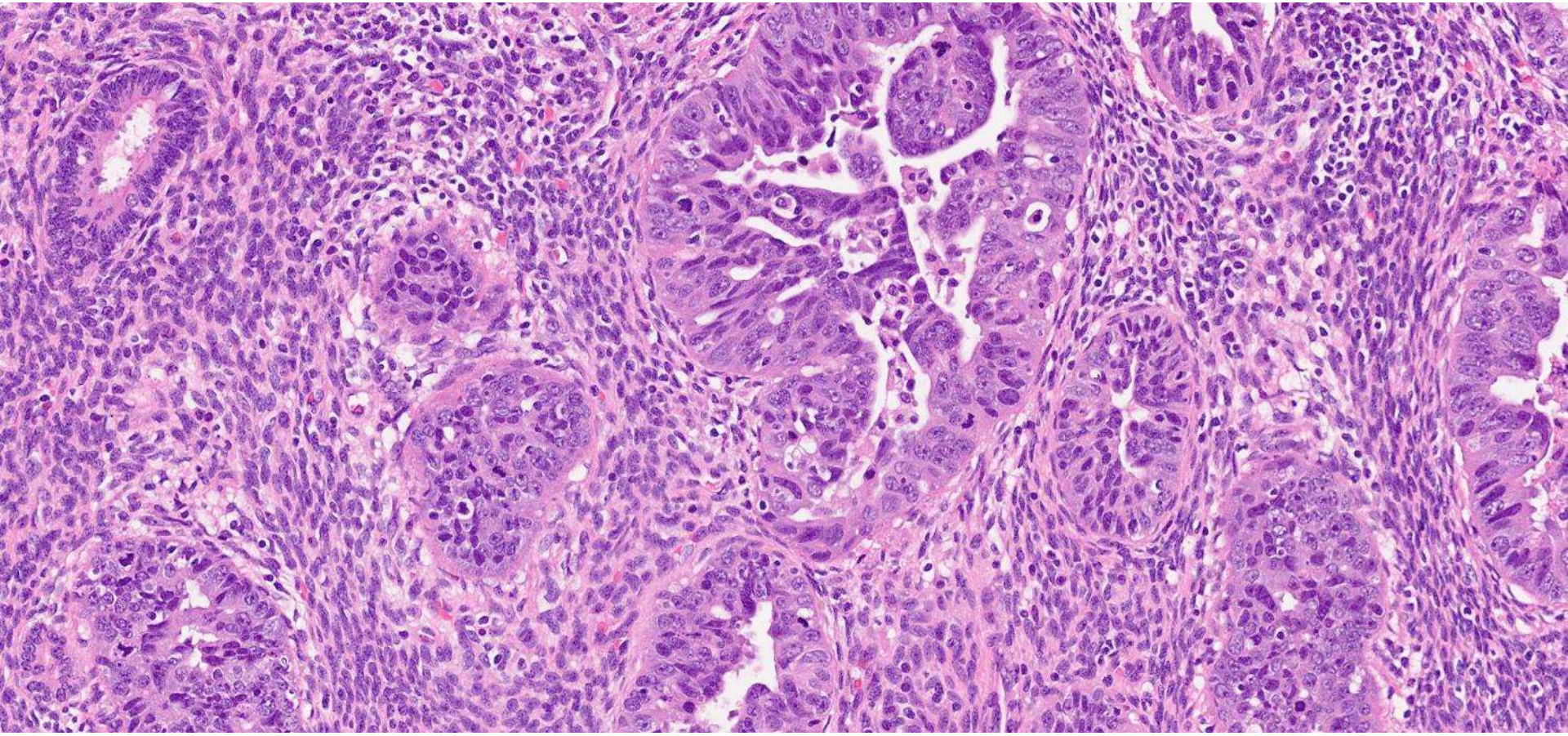
p53



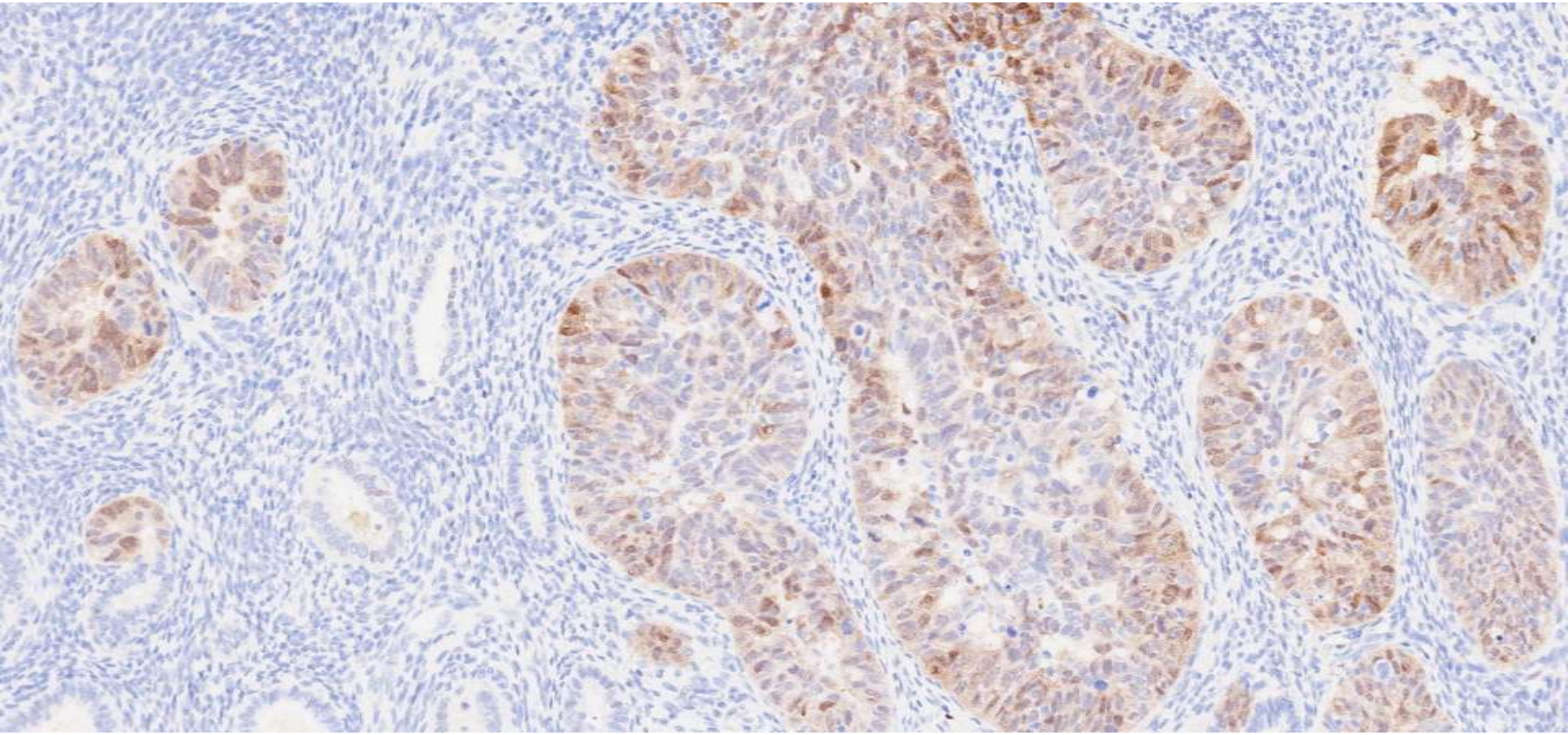


p53





p53



DDx

- Endometrial polyp with by serous carcinoma
- Endometrial polyp with complex atypical hyperplasia
- Endometrial polyp with reactive atypia

ADD'L IHC NOT SHOWN

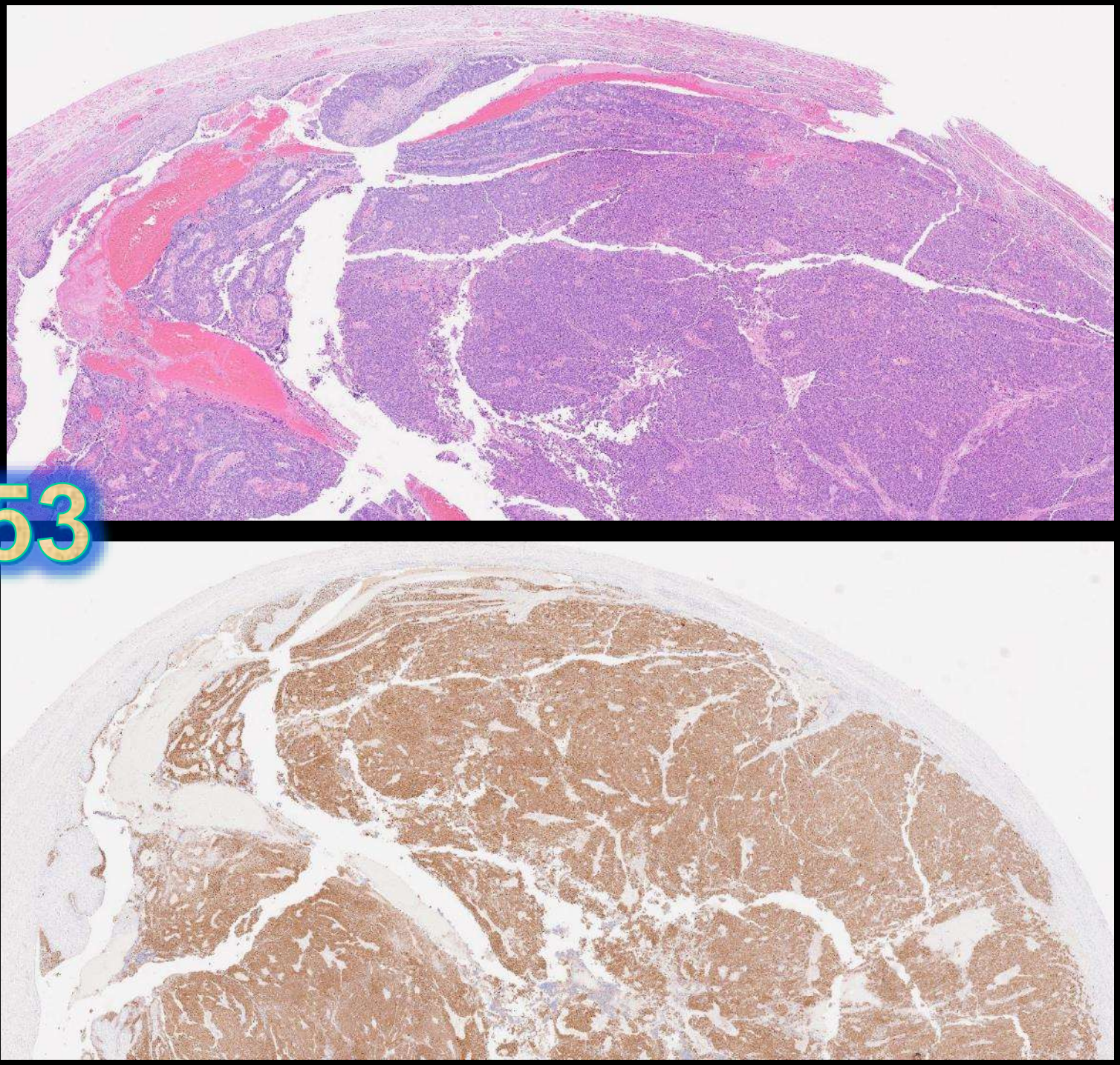
Lesional cells:

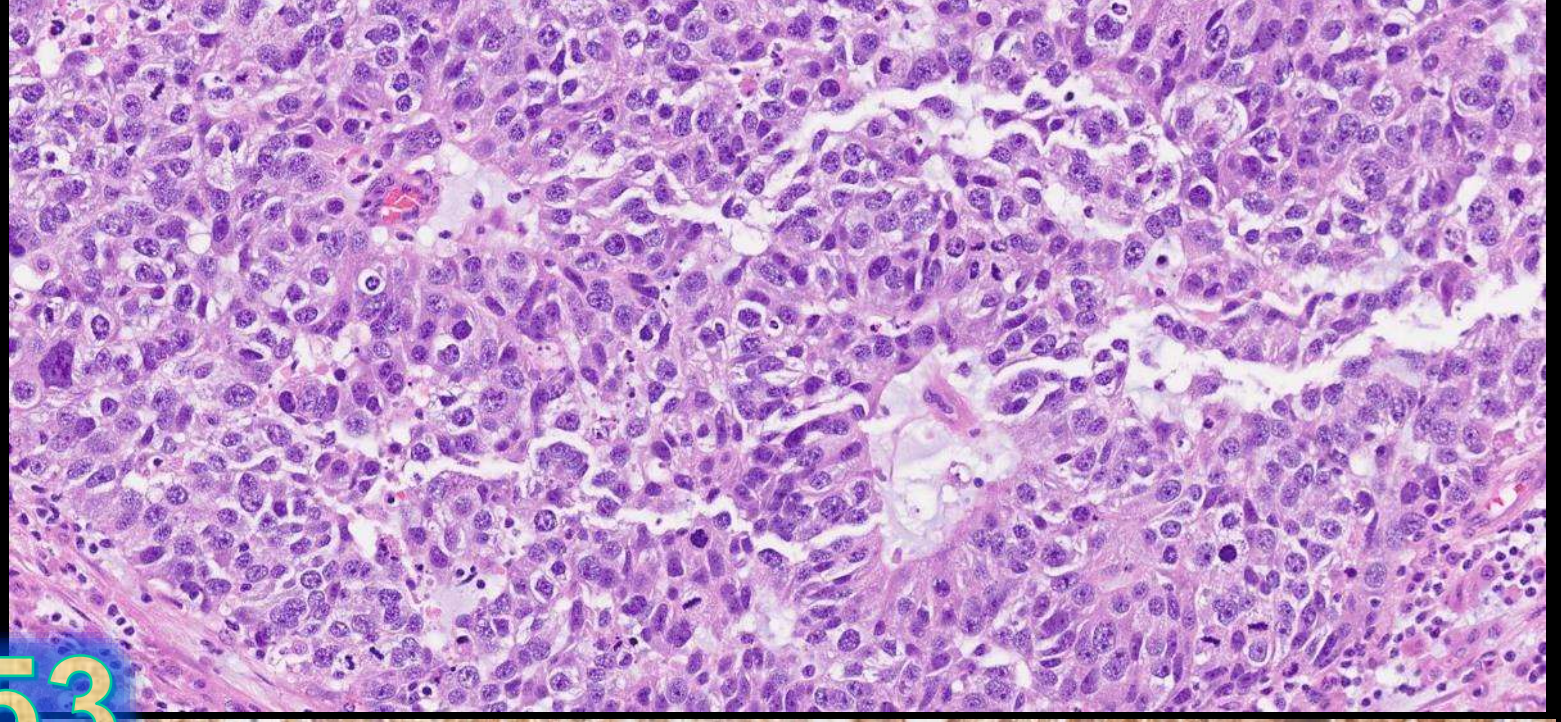
p16+

ER-

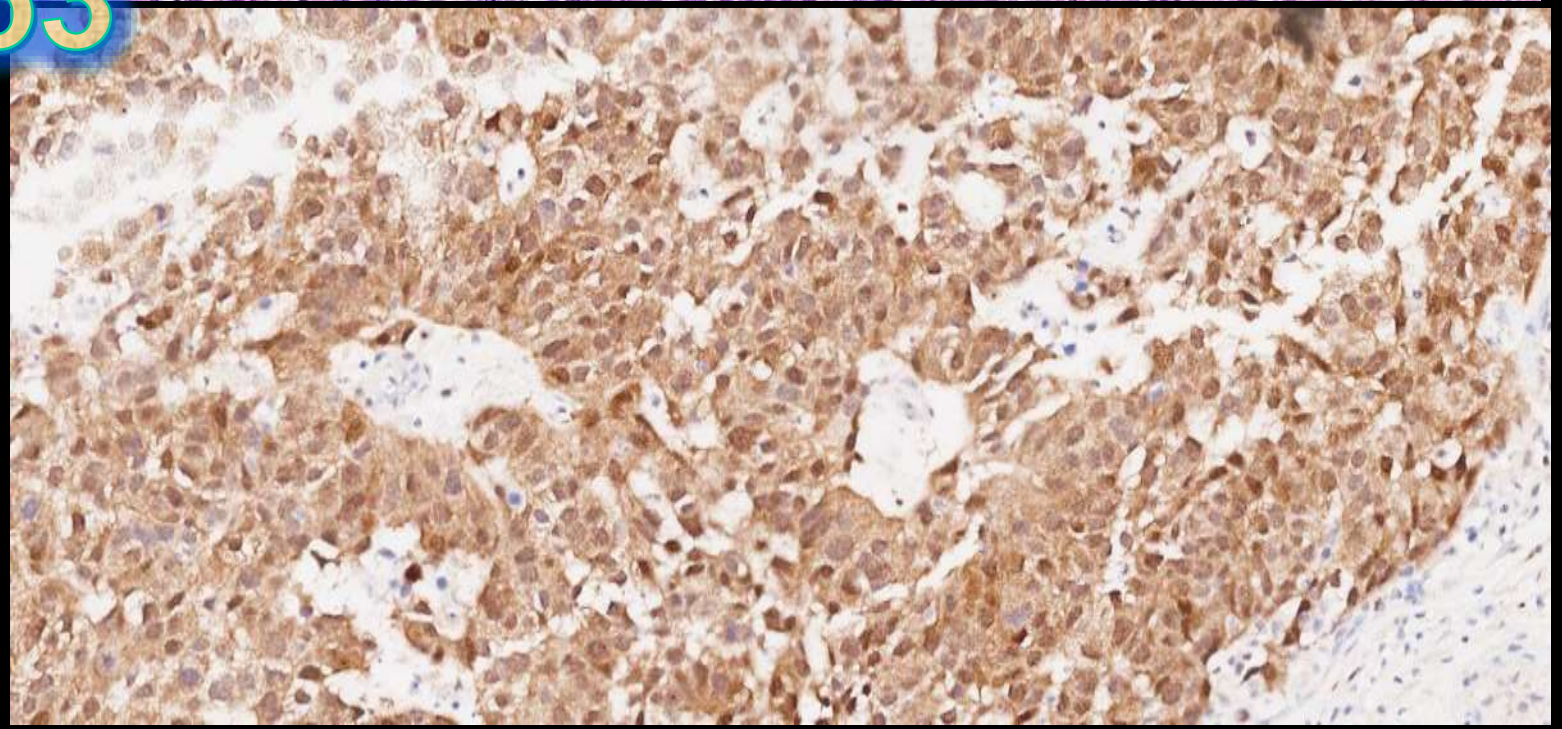
WT-

PTEN retained


p53



p53



Final Dx

- **High grade serous carcinoma**
  - Arising from endometrial polyp

  (p53 aberrant → diffuse cytoplasmic)

p53 overexpression in morphologically ambiguous endometrial carcinomas correlates with adverse clinical outcomes

Karuna Garg[1], Mario M Leitao Jr[2], Christine A Wynveen[1], Gabriel L Sica[1], Jinru Shia[1], Weiji Shi[3] and Robert A Soslow*[,1]

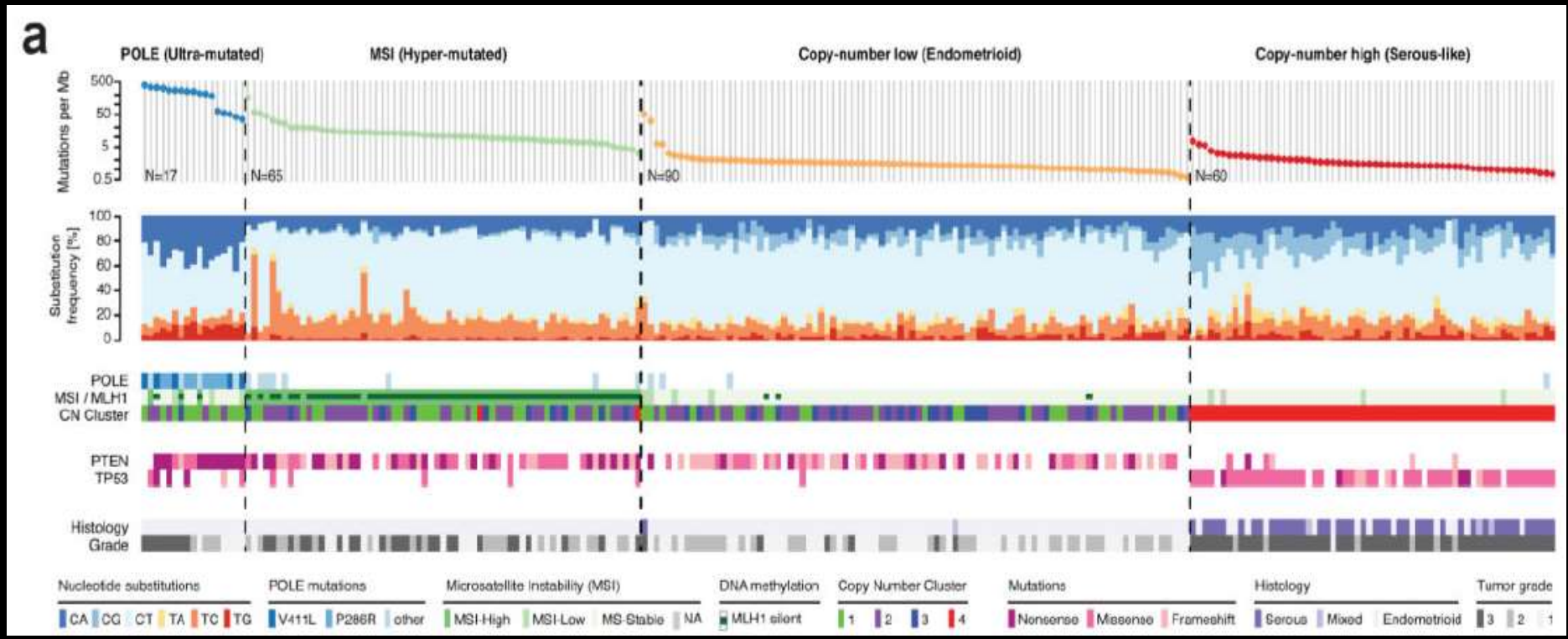
[1]*Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [2]*Department of Surgery, Gynecology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA and* [3]*Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA*

The distinction between uterine serous and endometrioid carcinomas can usually be achieved by morphologic examination alone. However, there are occasional 'morphologically ambiguous endometrial carcinomas' that show overlapping serous and endometrioid features and defy histologic classification. The primary aim of this study was to assess the clinical significance of p53 overexpression using immunohistochemistry in such tumors. Related aims included (1) assessing interobserver diagnostic concordance for histologic subclassification of these tumors using a panel of pathologists with and without gynecologic pathology expertise and (2) elucidating the histologic features that correlate with p53 status. Thirty-five such cases were identified during the study period. p53 overexpression was seen in 17 of 35 cases. Tumors with p53 overexpression were associated with a significantly inferior progression-free survival and disease-specific survival compared with those that lacked p53 overexpression (3-year progression-free survival and disease-specific survival were 94 and 100% in patients with no p53 overexpression, and 52 and 54% in patients with p53 overexpression; $P=0.02$ and 0.003, respectively). The consensus diagnosis rendered by gynecologic pathologists was predictive of disease-specific survival ($P=0.002$), but not progression-free survival ($P=0.11$). Although the interobserver diagnostic concordance (kappa = 0.70) was substantial for gynecologic pathologists, and highly associated with p53 status (77% of 'favor serous' cases showed p53 overexpression, whereas only 25% of 'favor endometrioid' cases showed p53 overexpression; $P=0.005$), the concordance between the consensus diagnosis of the two specialized pathologists *versus* each of three non-specialized pathologists was poor (kappa = 0.13–0.25). The histologic feature that correlated most with p53 overexpression was the presence of diffuse high nuclear grade. p53 immunohistochemistry assays in morphologically ambiguous endometrial carcinomas are roughly as clinically informative as gynecologic pathology consultation and can be helpful for prognostic assessment and therapeutic decision making in difficult endometrial carcinomas.

Modern Pathology (2010) **23**, 80–92; doi:10.1038/modpathol.2009.153; published online 23 October 2009

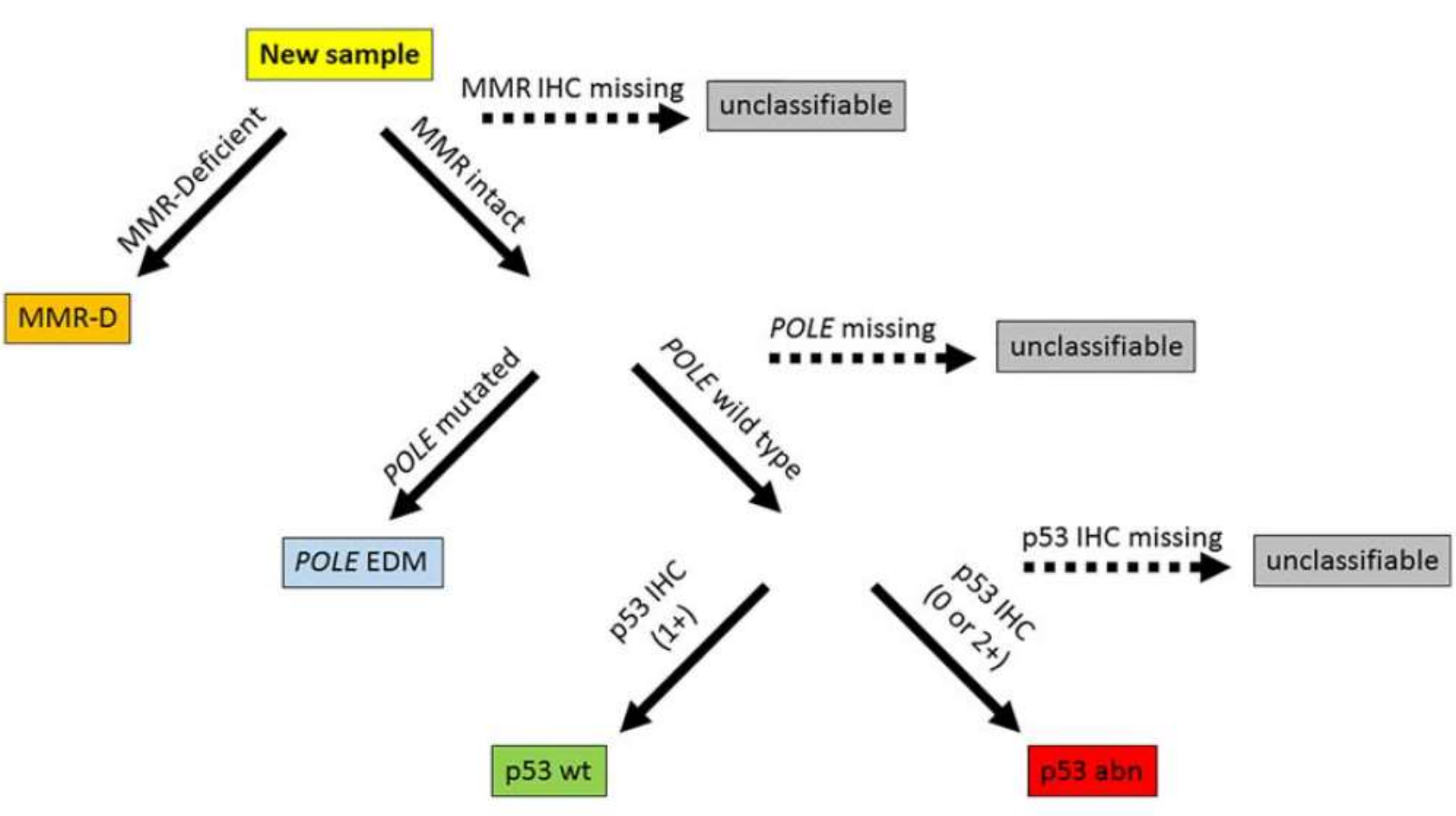
Keywords: p53; endometrial carcinoma; outcome

TCGA Integrated Genomic Analysis of Endometrial Carcinoma



Nature. 2013 May 2; 497(7447): 67–73.

Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE)



Cancer 2017;123:802-13.

International Journal of Gynecological Pathology
38:S123–S131, Lippincott Williams & Wilkins, Baltimore

OPEN

Interpretation of P53 Immunohistochemistry in Endometrial Carcinomas: Toward Increased Reproducibility

Martin Köbel, M.D., Brigitte M. Ronnett, M.D., Naveena Singh, M.D., Robert A. Soslow, M.D., C. Blake Gilks, M.D., and W. Glenn McCluggage, M.D.

Summary: P53 immunohistochemistry has evolved into an accurate surrogate reflecting the underlying *TP53* mutation status of a tumor, and has utility in the diagnostic workup of endometrial carcinomas. Recent work predominantly carried out in tubo-ovarian high-grade serous carcinoma has revealed 4 main patterns of p53 staining (normal/wild-type, complete absence, overexpression, and cytoplasmic); the latter 3 patterns are variably termed abnormal/aberrant/mutation-type and are strongly predictive of an underlying *TP53* mutation. The aim of this review is to provide practical advice to pathologists regarding various aspects of p53 immunohistochemical staining. These include laboratory methods to optimize staining, a description of the different patterns of staining, advice regarding the interpretation, and reporting of p53 staining and practical uses of p53 staining in endometrial carcinoma diagnosis. Illustrations are provided to aid in the interpretational problems. **Key Words:** Endometrial carcinoma—p53—*TP53*—Immunohistochemistry—Interpretation.

TABLE 1. *p53 immunohistochemical staining patterns observed in tubo-ovarian high-grade serous carcinoma*

Staining pattern	*TP53* status	P53 IHC interpretation	% in tubo-ovarian high-grade serous carcinoma
TP53 mutation absent			
Wild-type	No mutation	Normal/wild-type	0
TP53 mutation present			
Overexpression	Nonsynonymous missense mutation	Abnormal/aberrant/mutation-type	66
Complete absence	Loss of function mutation	Abnormal/aberrant/mutation-type	25
Cytoplasmic	Loss of function mutation disrupting nuclear localization domain	Abnormal/aberrant/mutation-type	4
Wild-type	Truncating mutation	Normal/wild-type	5

IHC indicates immunohistochemistry.

Histopathology 2011, 59, 786–803

Correspondence

Patterns of p53 immunoreactivity in endometrial carcinomas: 'all or nothing' staining is of importance

DOI: 10.1111/j.1365-2559.2011.03907.x

Sir: We read with interest the recent item of correspondence from Kaye *et al.*[1] regarding p53 staining as a tool with which to identify dysplasia in Barrett's oesophagus. The authors point out that both diffuse intense nuclear staining and totally absent staining are aberrant patterns of p53 immunoreactivity, and may be found in dysplastic Barrett's epithelium. This contrasts with the focal weak immunoreactivity that is common in normal tissues and in some cases of dysplastic Barrett's epithelium (possibly those unassociated with *TP53* mutation) and is referred to as 'wild-type' pattern staining.[1]

Cytoplasmic Pattern p53 Immunoexpression in Pelvic and Endometrial Carcinomas With *TP53* Mutation Involving Nuclear Localization Domains

An Uncommon But Potential Diagnostic Pitfall With Clinical Implications

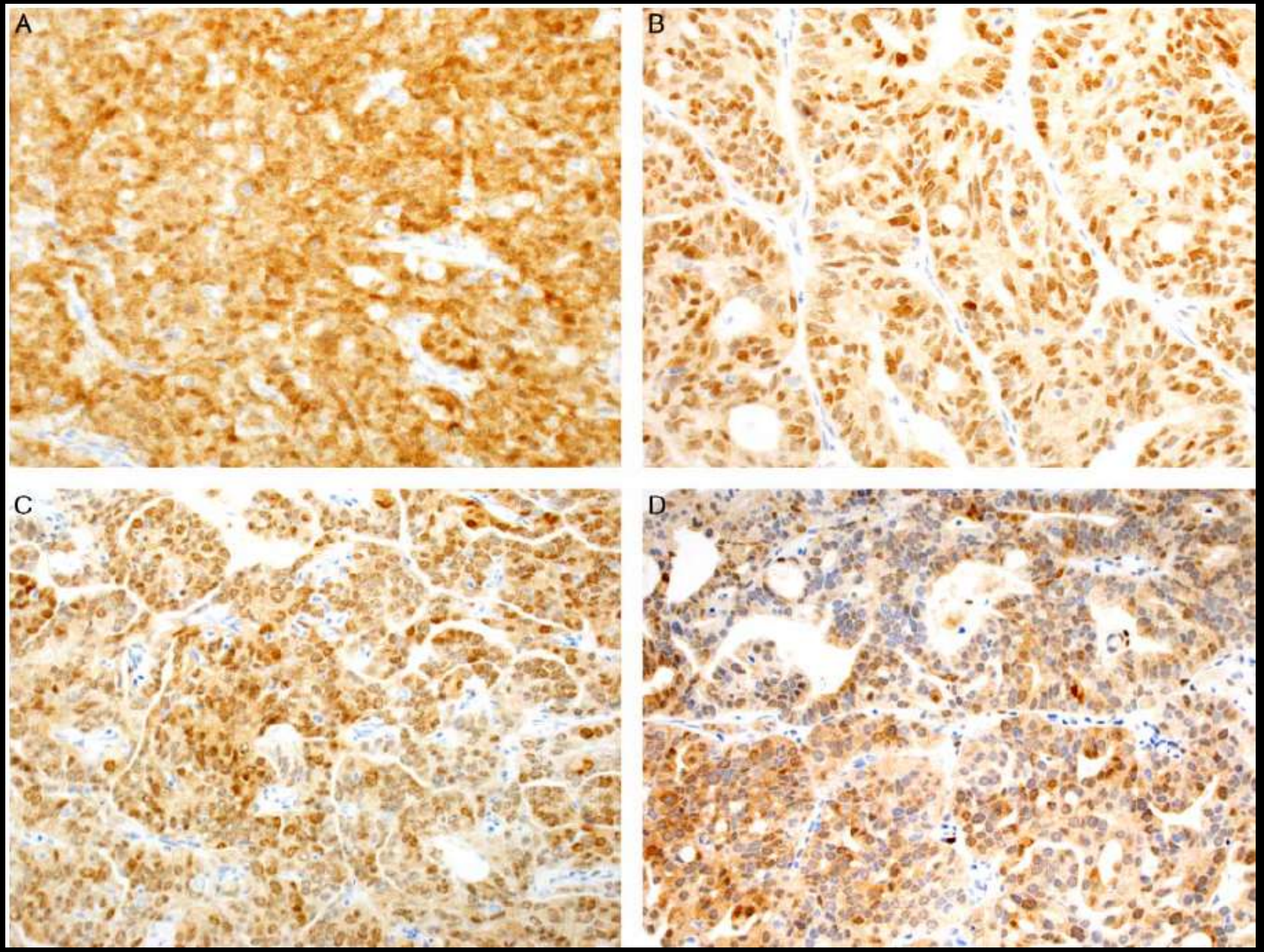
Joseph T. Rabban, MD, MPH, Karuna Garg, MD, Nicholas R. Ladwig, MD, Charles J. Zaloudek, MD, and W. Patrick Devine, MD, PhD

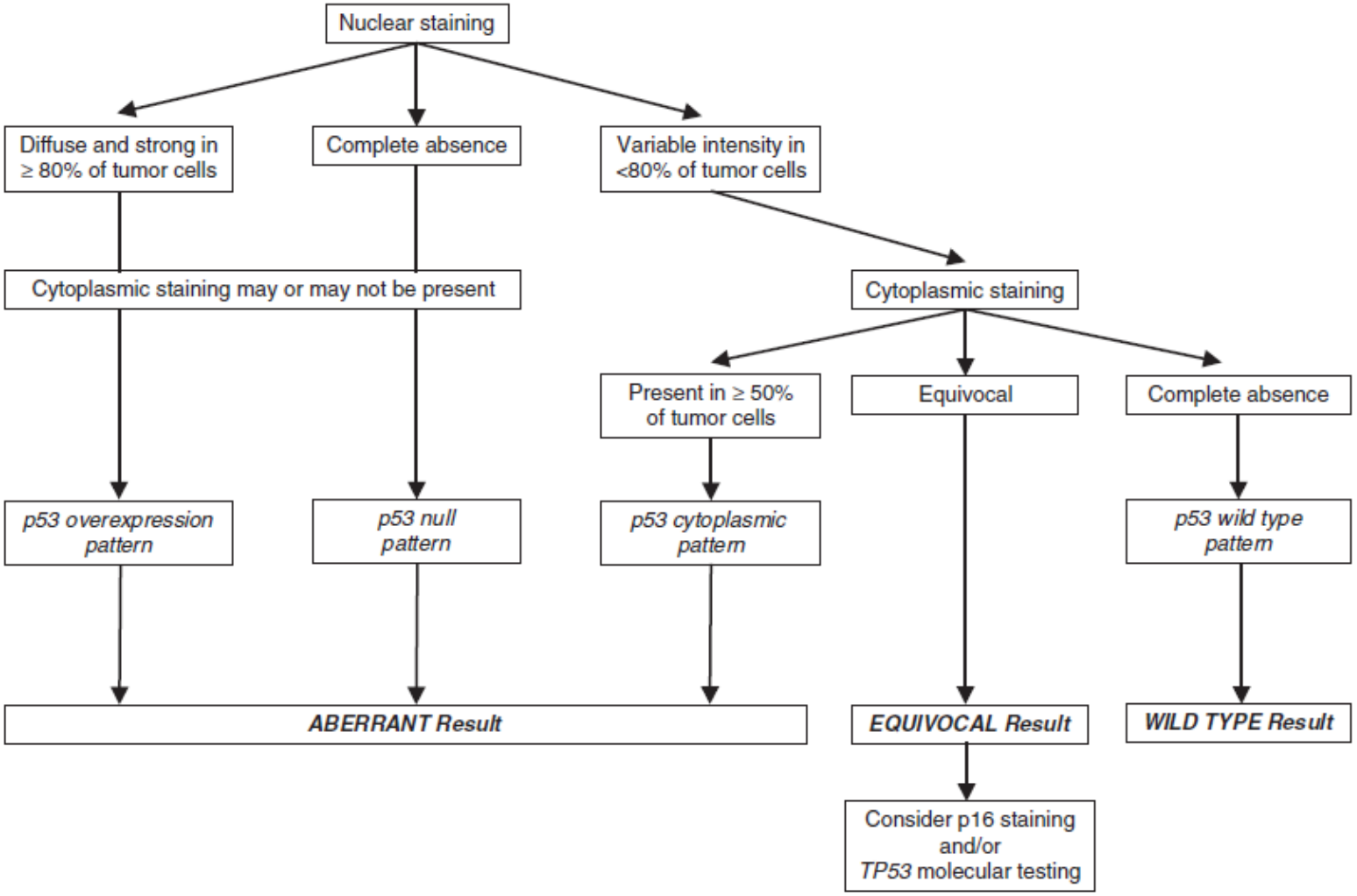
Abstract: A cytoplasmic pattern of p53 immunohistochemical expression has recently been reported in a rare subset of pelvic and endometrial cancers with a *TP53* mutation involving domains affecting nuclear localization. This study reports the clinicopathologic features of 31 cases with a *TP53* mutation involving nuclear localization, the largest study to date, emphasizing practical strategies for recognizing this uncommon variant and distinguishing it from the p53 wild-type pattern. The study also evaluates the prognostic significance of *TP53* mutation involving nuclear localization in the ovarian high-grade serous carcinoma (HGSC) cohort of The Cancer Genome Atlas database. Most of the 31 tumors were advanced stage pelvic or endometrial HGSC. All *TP53* mutations were predicted to result in loss of function. The p53 overexpression pattern was present in 6 tumors; the p53 null pattern in 3 and the p53 cytoplasmic pattern in 22 tumors. The p53 cytoplasmic pattern predominantly consisted of weak to moderate cytoplasmic staining in >95% of tumor cells as well as variable intensity nuclear staining involving a range of just a few cells to just under 80% of tumor cells. The p53 cytoplasmic pattern was observed in 100% of tumors with *TP53* mutation in the nuclear localization domain and in 33% to 44% of tumors with a mutation in the adjacent tetramerization domain or nuclear exclusion sequence ($P<0.01$). p16 immunoexpression was present in 74% of tumors. In The Cancer Genome Atlas ovarian HGSC cohort, 9% of 471 nonredundant *TP53*-mutant cases had a nuclear localization domain, tetramerization domain, or nuclear exclusion sequence mutation but there was no significant difference in survival when compared to cases with *TP53* mutation outside those domains ($P>0.05$). p53 cytoplasmic staining merits classification as an aberrant result despite coexisting nuclear staining that in some cases may resemble the p53 wild-type pattern. While positive p16 immunostaining may be of value to confirm diagnostically challenging cases of p53 cytoplasmic staining, a negative result is noninformative and molecular testing for *TP53* mutation should be considered, if available.

Key Words: p53, immunohistochemistry, ovarian cancer, endometrial cancer, molecular diagnostic testing

(*Am J Surg Pathol* 2021;45:1441–1451)

p53 immunohistochemistry (IHC) is widely used as a surrogate for *TP53* mutation testing in diagnostic gynecologic pathology, particularly for evaluating epithelial neoplasms and their mimics. The most common application in the ovary is to distinguish pelvic high-grade serous carcinoma (HGSC) from other high-grade tumor types and from pelvic low-grade serous carcinoma[1–3]; in the endometrium, to distinguish endometrial serous carcinoma from its benign and malignant mimics[4,5]; in the fallopian tube to distinguish serous tubal intraepithelial carcinoma (STIC) from its benign and malignant mimics[6]; and in the vulva to distinguish p53-mediated human papillomavirus (HPV)-independent vulvar squamous cell neoplasia from benign and malignant


A
B
C
D


Nuclear staining
Diffuse and strong in ≥ 80% of tumor cells
Complete absence
Variable intensity in <80% of tumor cells
Cytoplasmic staining may or may not be present
Cytoplasmic staining
Present in ≥ 50% of tumor cells
Equivocal
Complete absence
p53 overexpression pattern
p53 null pattern
p53 cytoplasmic pattern
p53 wild type pattern
ABERRANT Result
EQUIVOCAL Result
WILD TYPE Result
Consider p16 staining and/or TP53 molecular testing

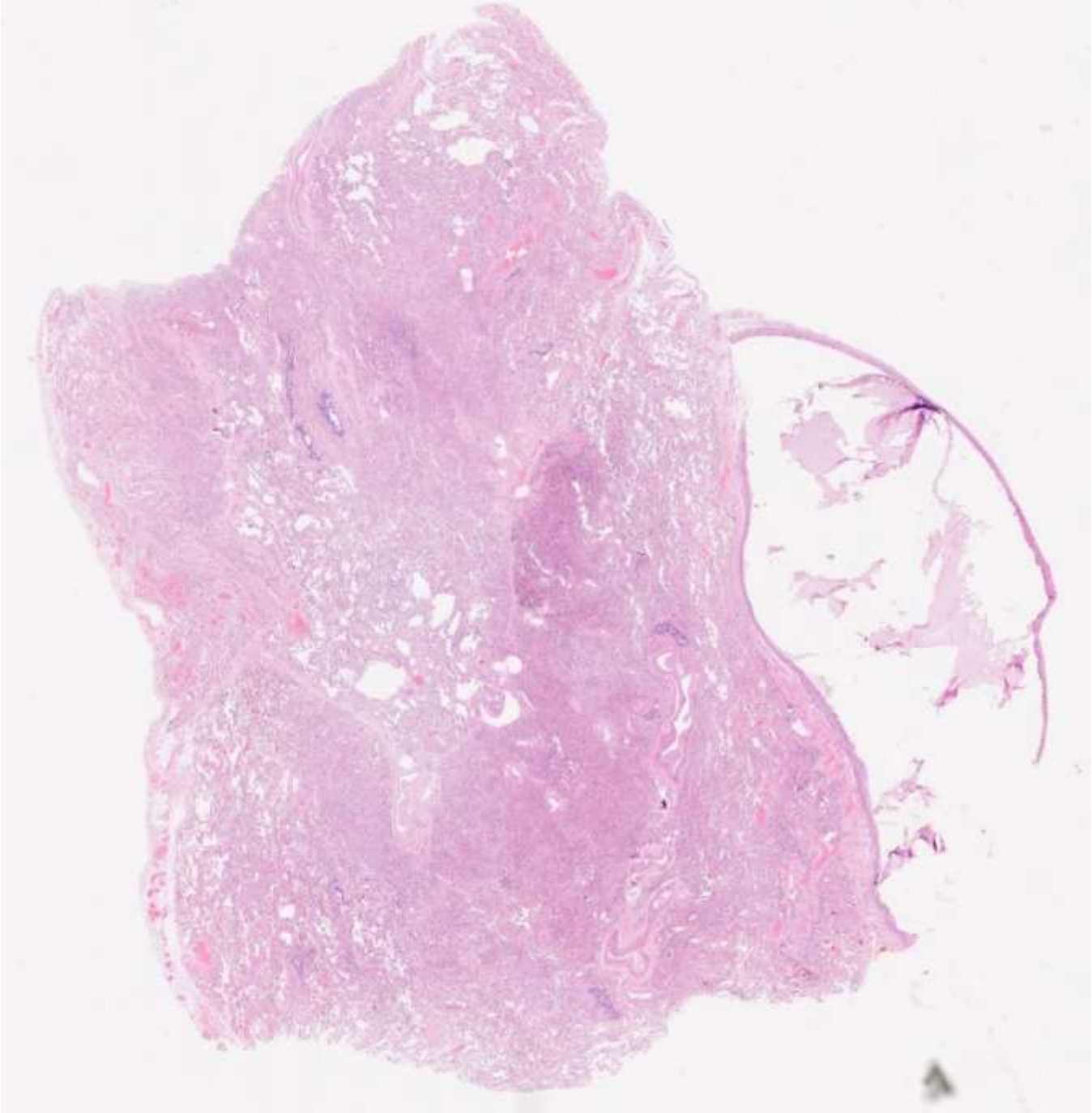
TAKE HOME POINTS

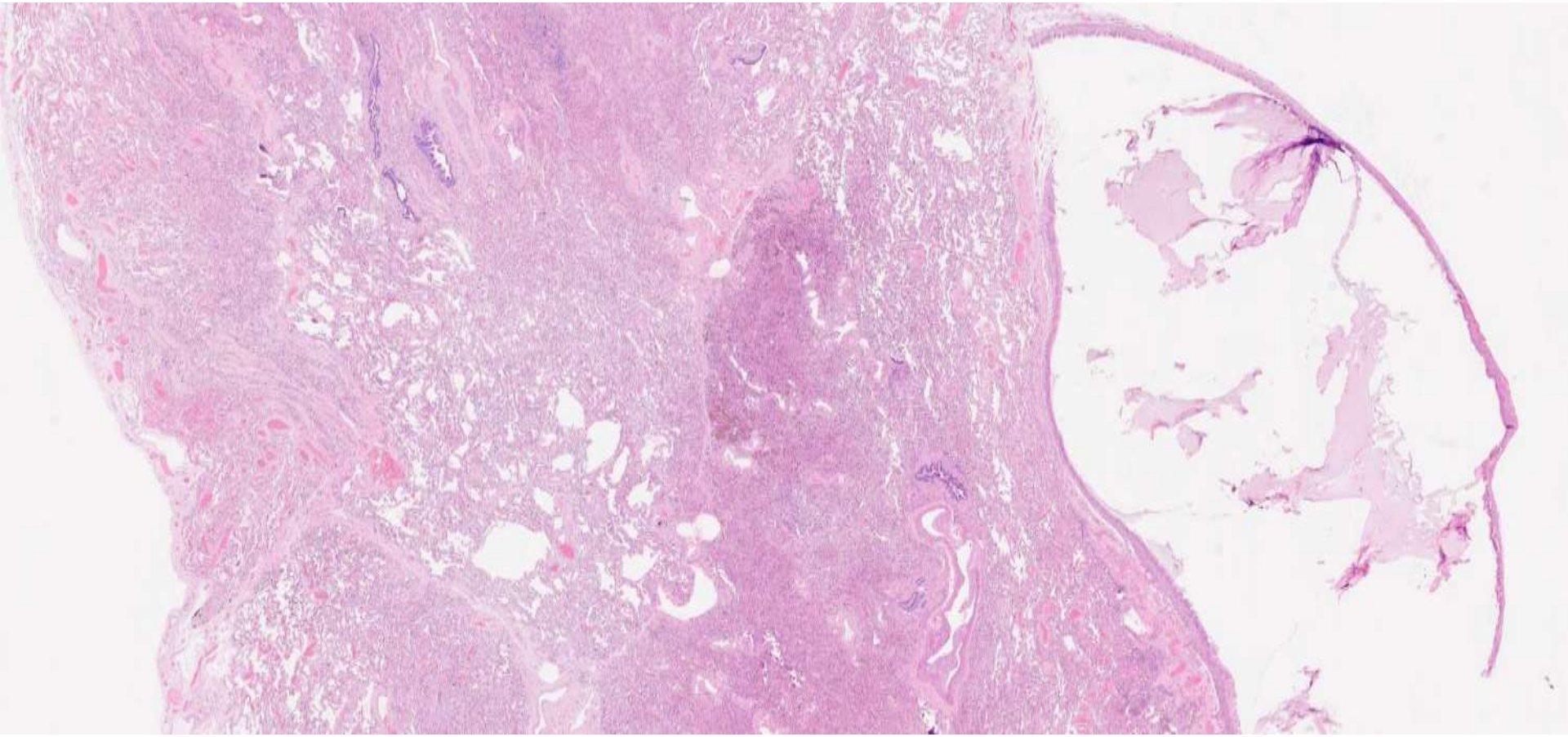
- **When employing p53 IHC in assessment of GYN carcinoma:**
  - Important to specify staining pattern beyond just “positive” or “negative”
  - Consider using “abnormal” or “aberrant’ or “mutant”
    - Further clarify p53 IHC pattern as: overexpression, null, cytoplasmic

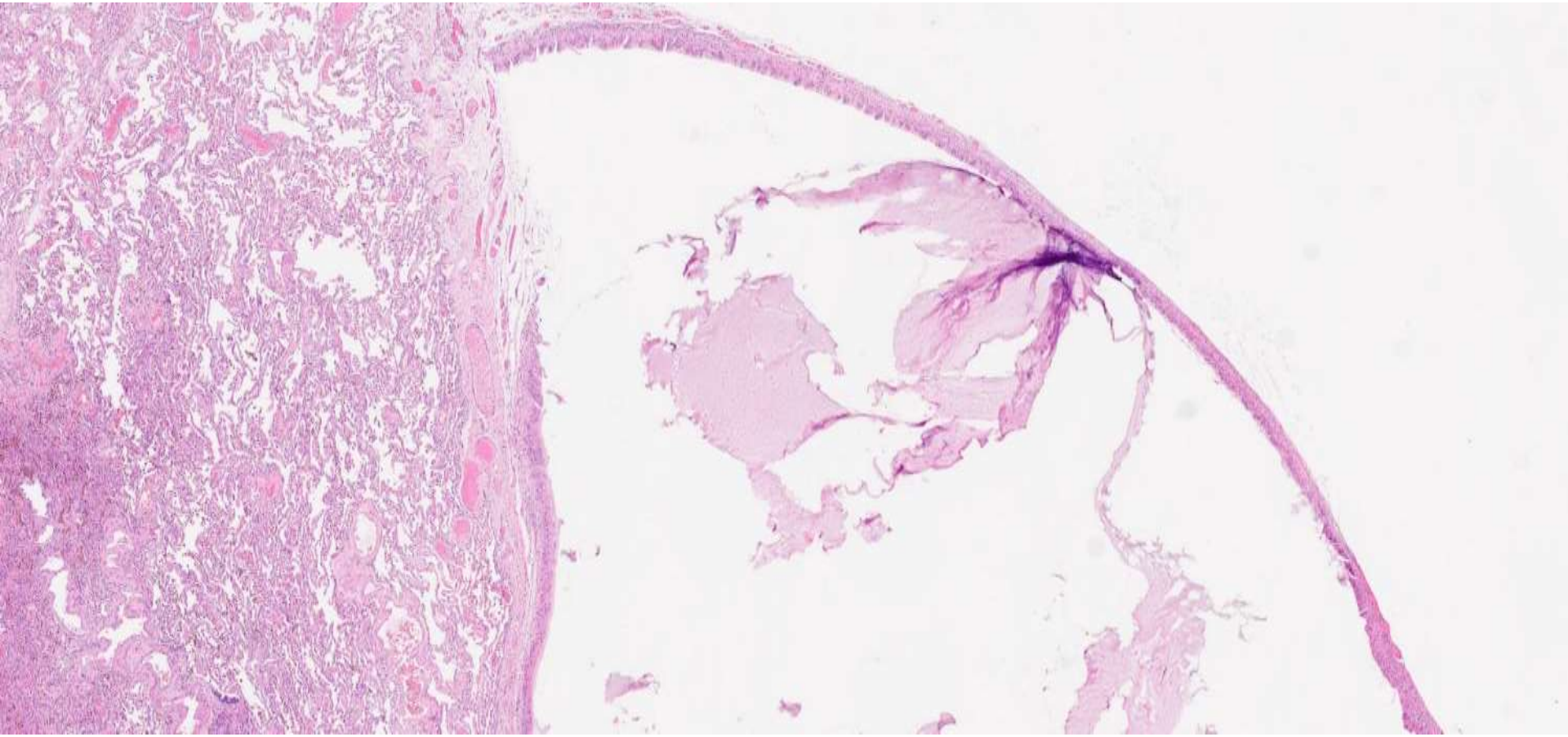
22-0609
Direct links to scanned slides:

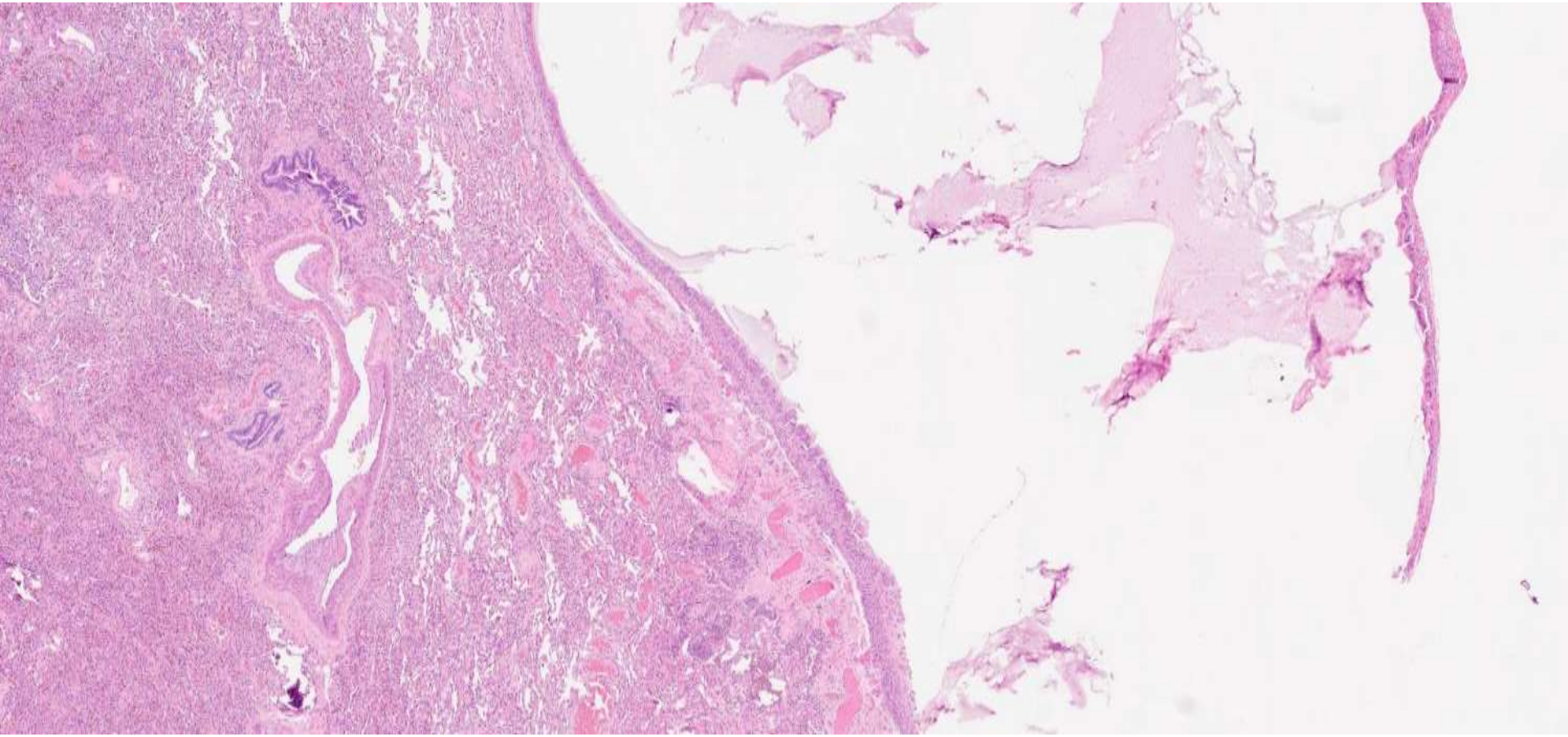
Ankur Sangoi; El Camino Hospital

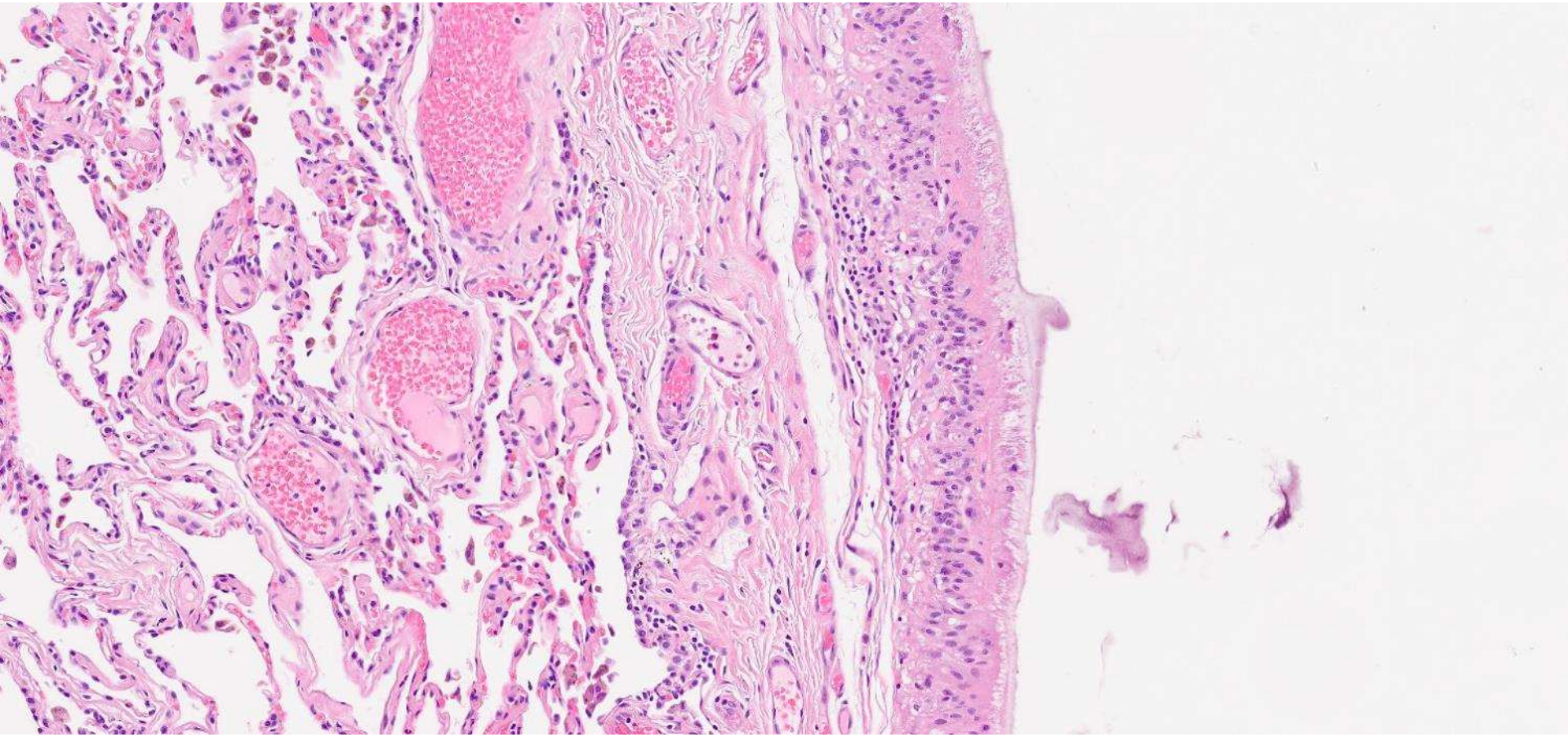
Middle aged F presents with 2.5cm right middle lobe lung mass. Prior attempted FNA non-diagnostic. Lobectomy performed. Sections of grossly found 1cm tubular structure near pleural somewhat away from tumor.

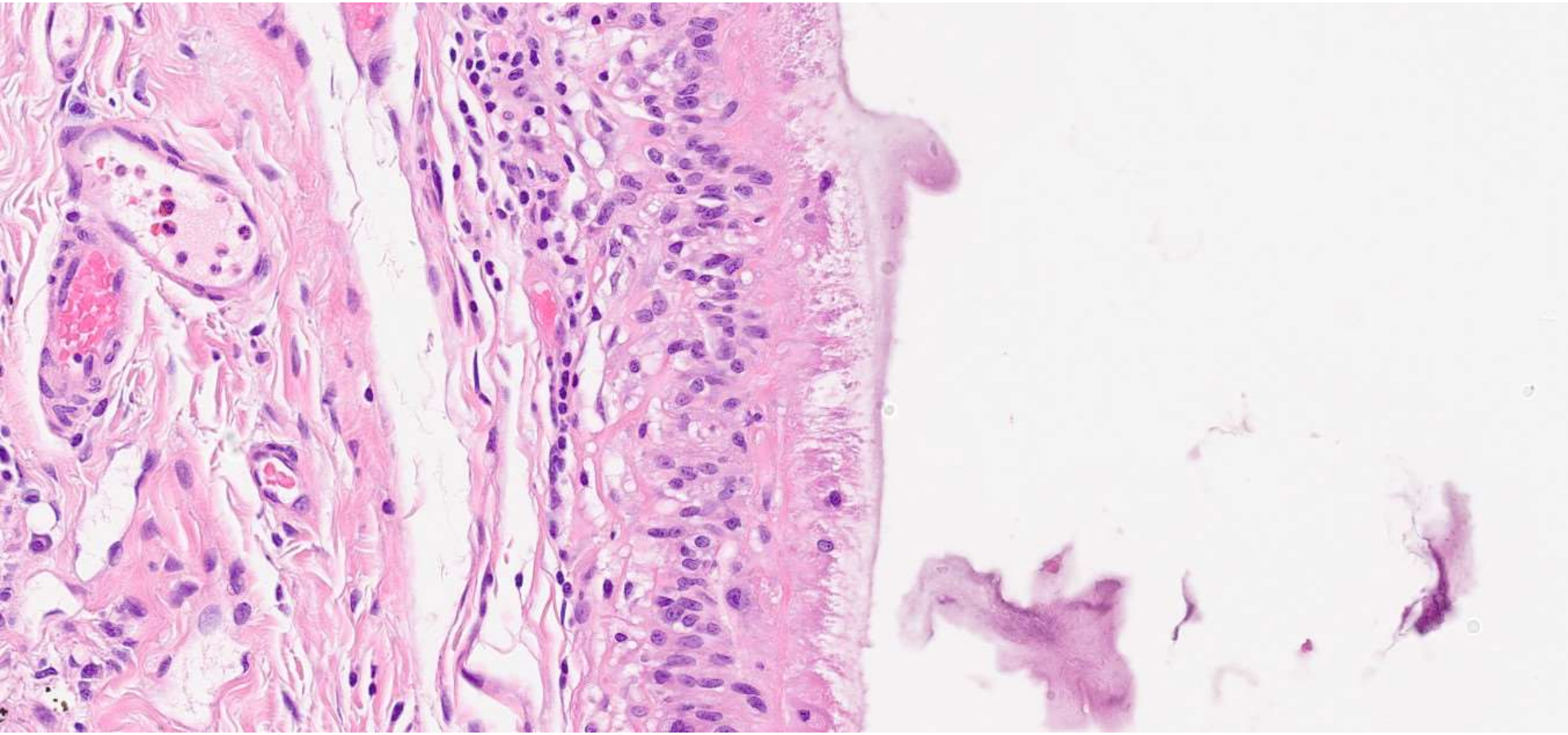


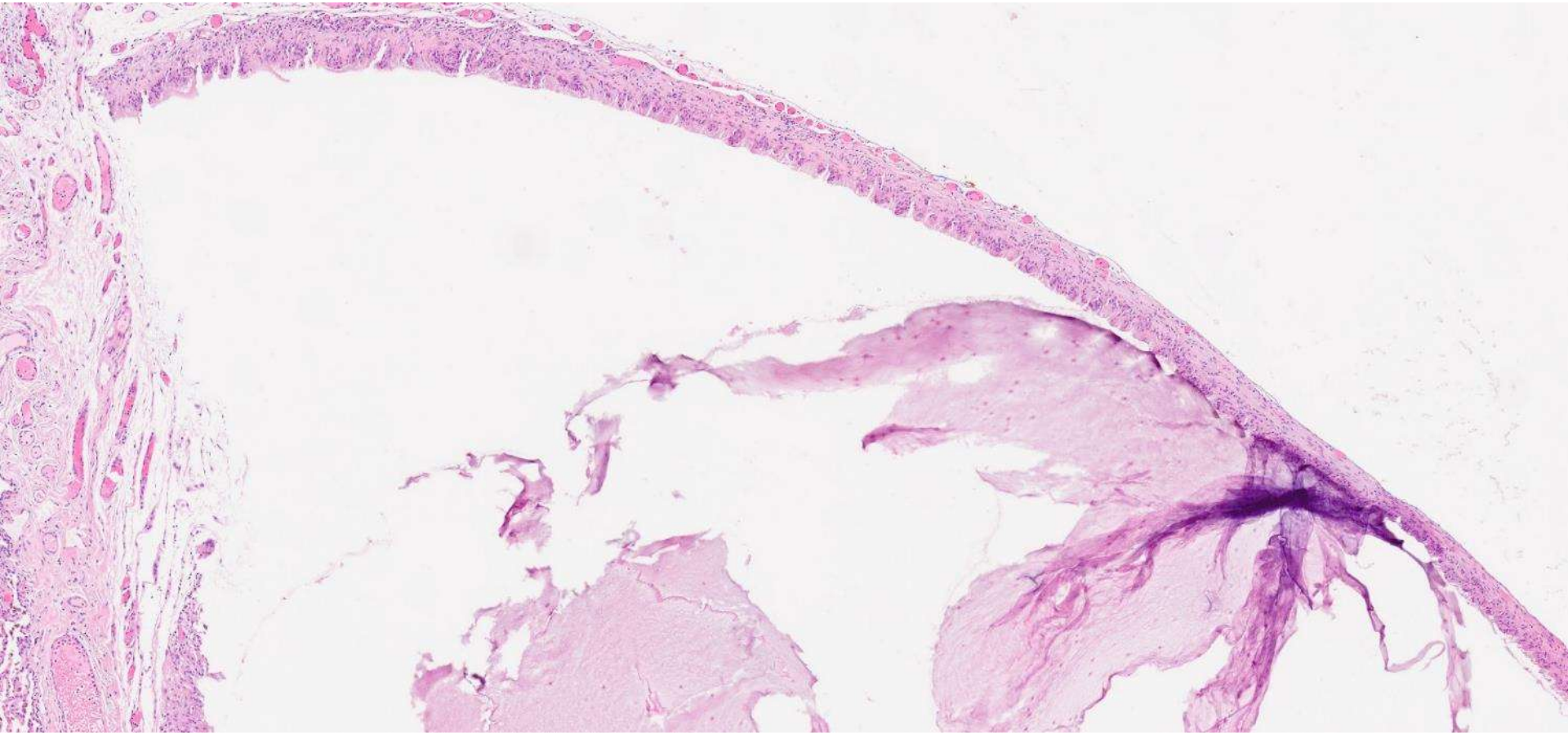


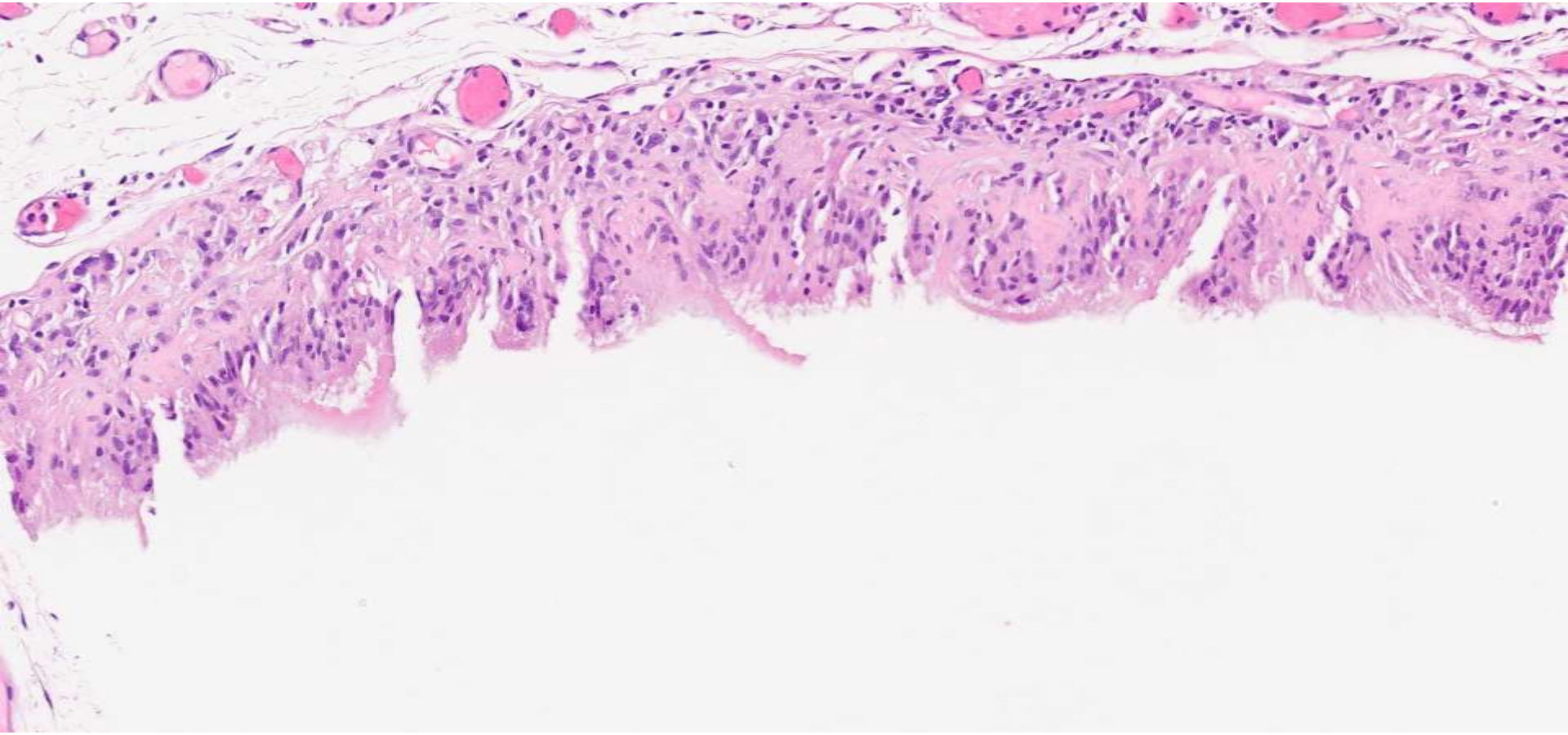


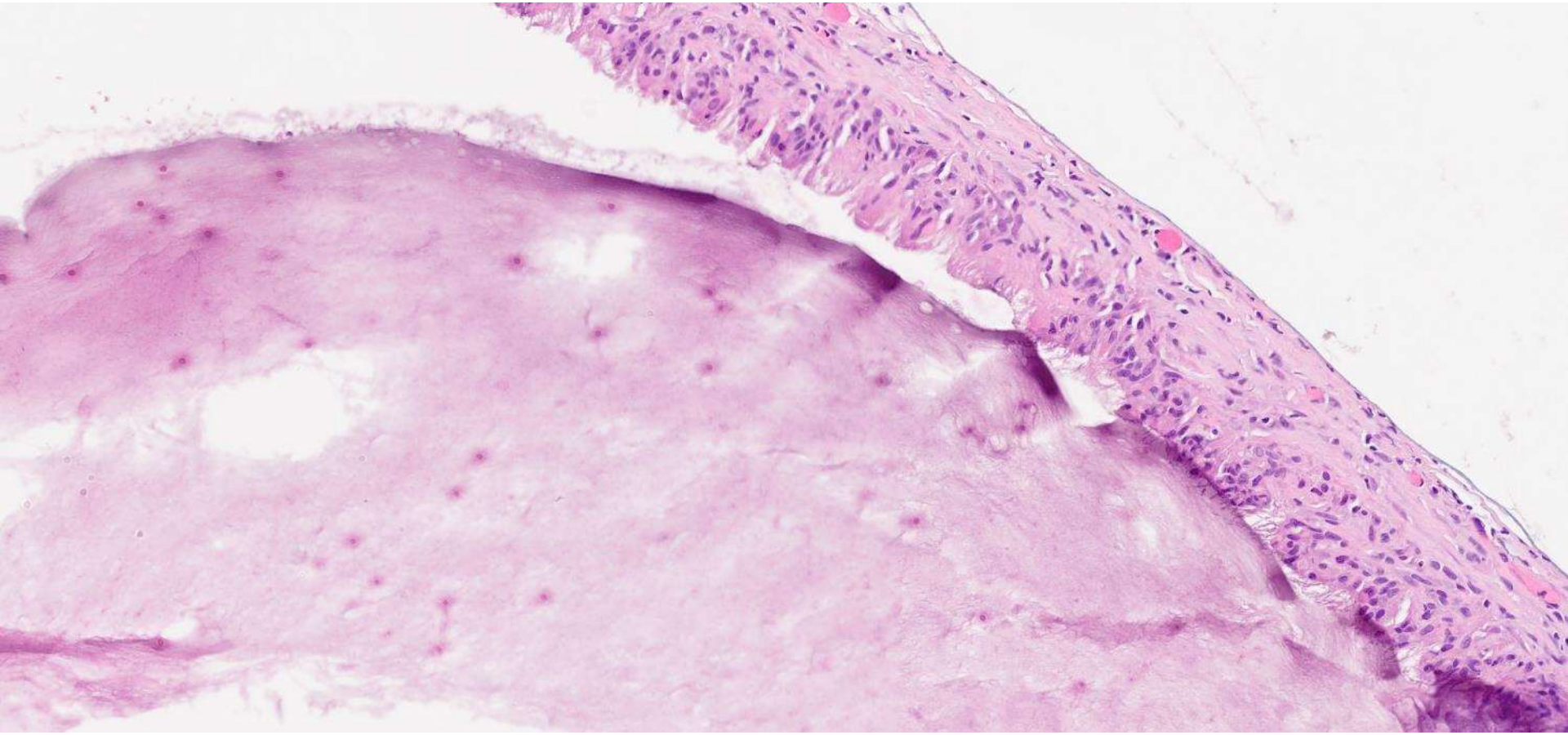






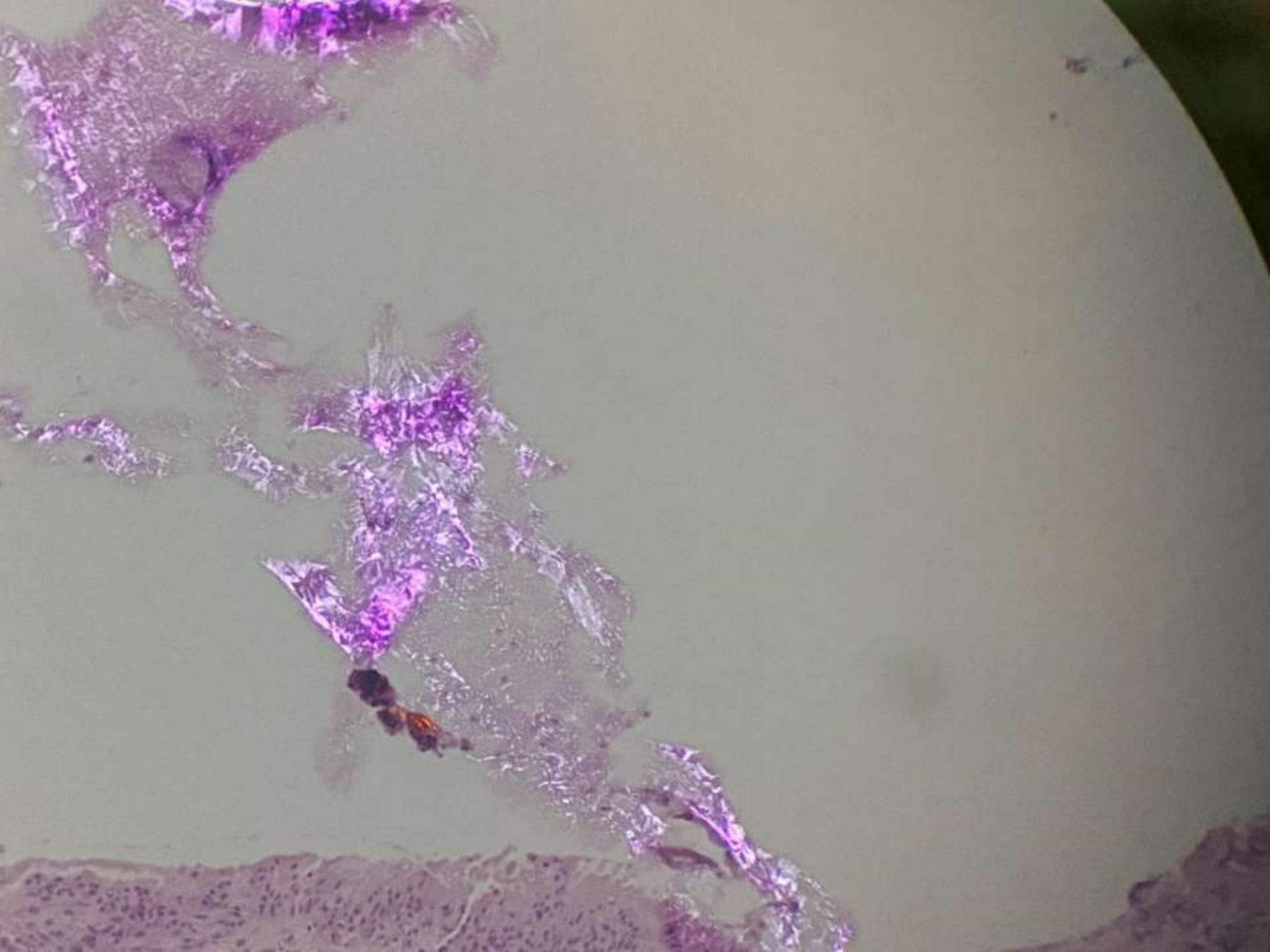


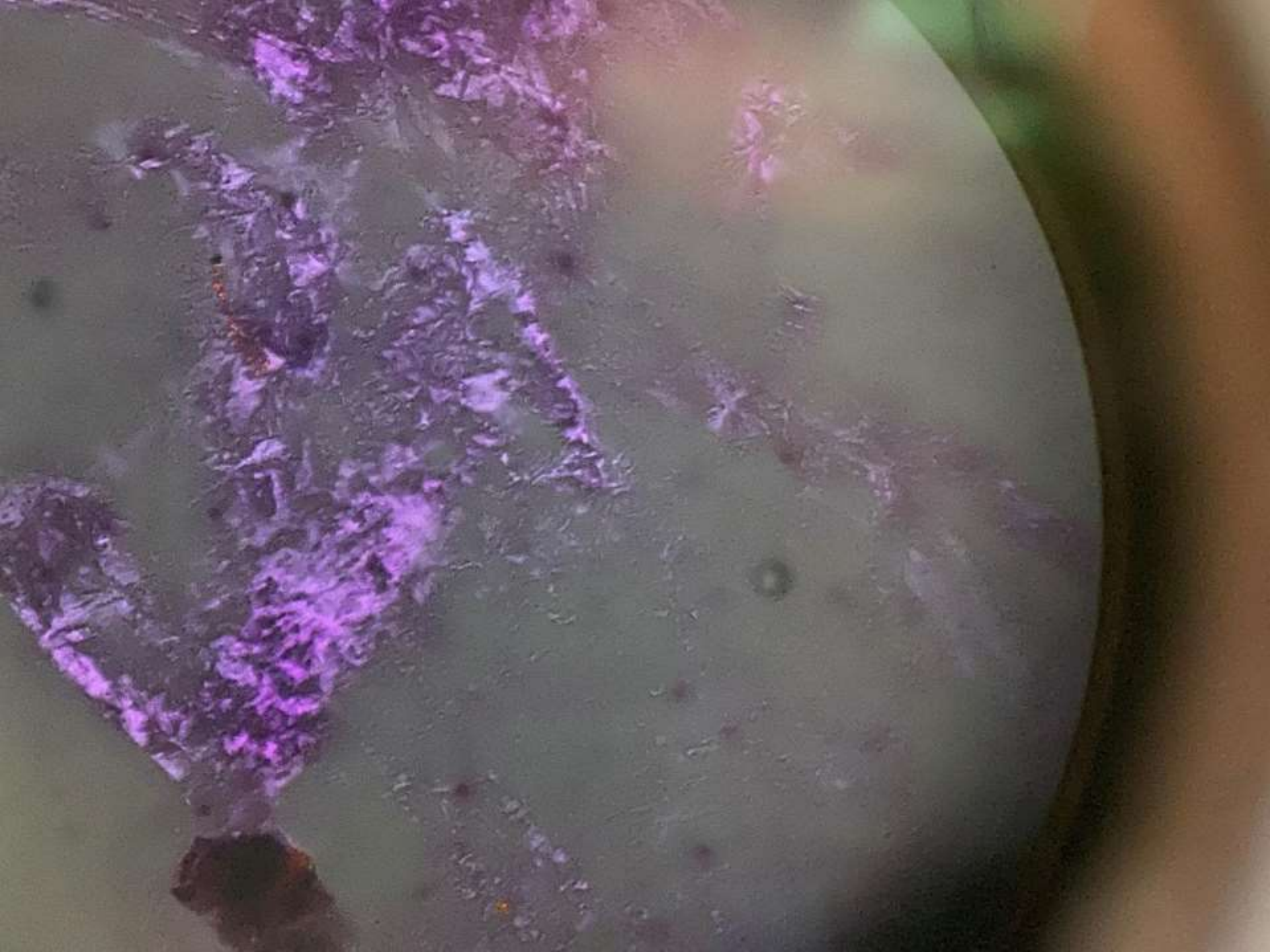




DDx

- Parasitic lung infection
- Cystic granulomatous tuberculosis
- Autoimmune-related granulomas
- Extracellular mucin
- Bullous emphysema
- Biopsy site change



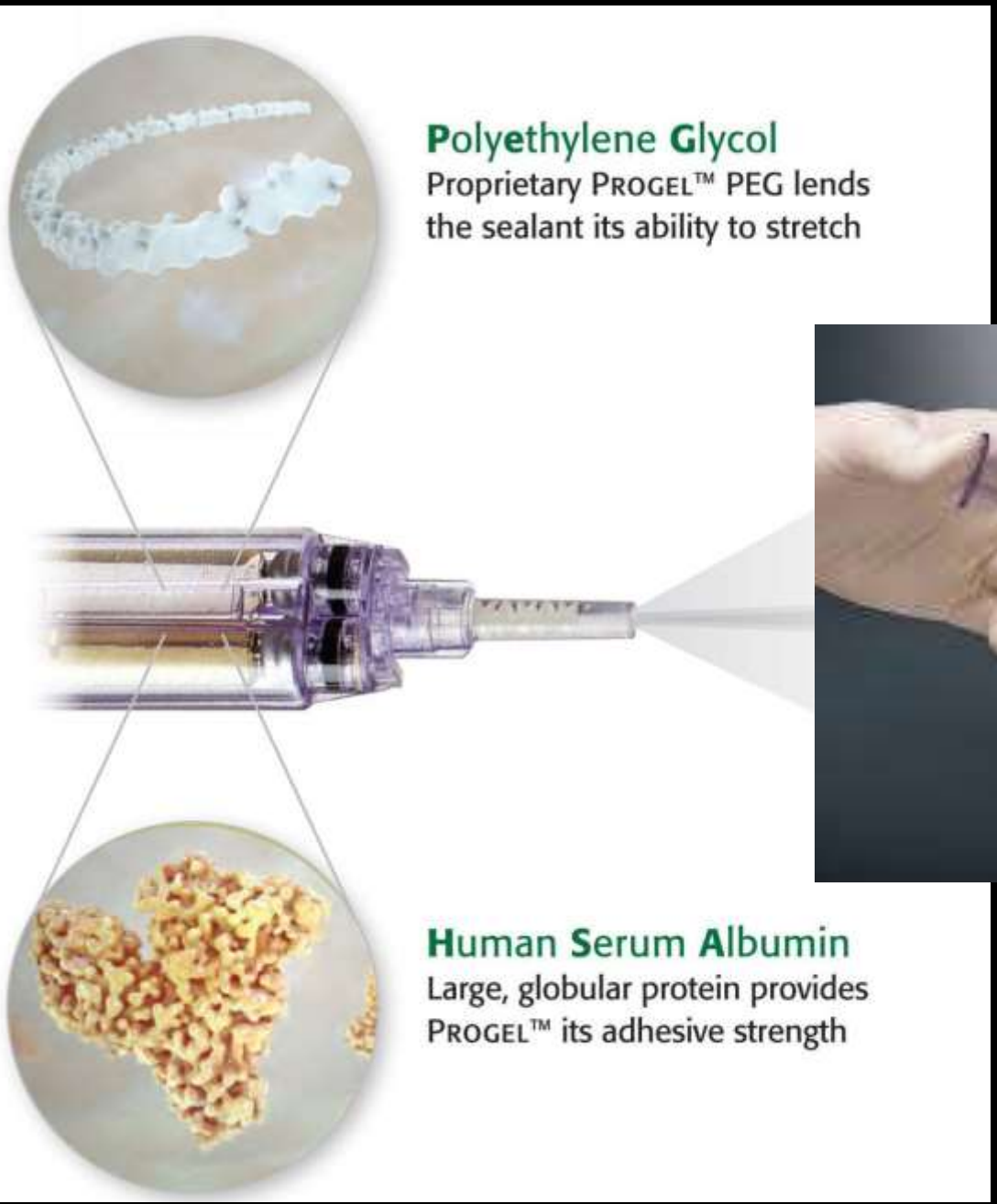


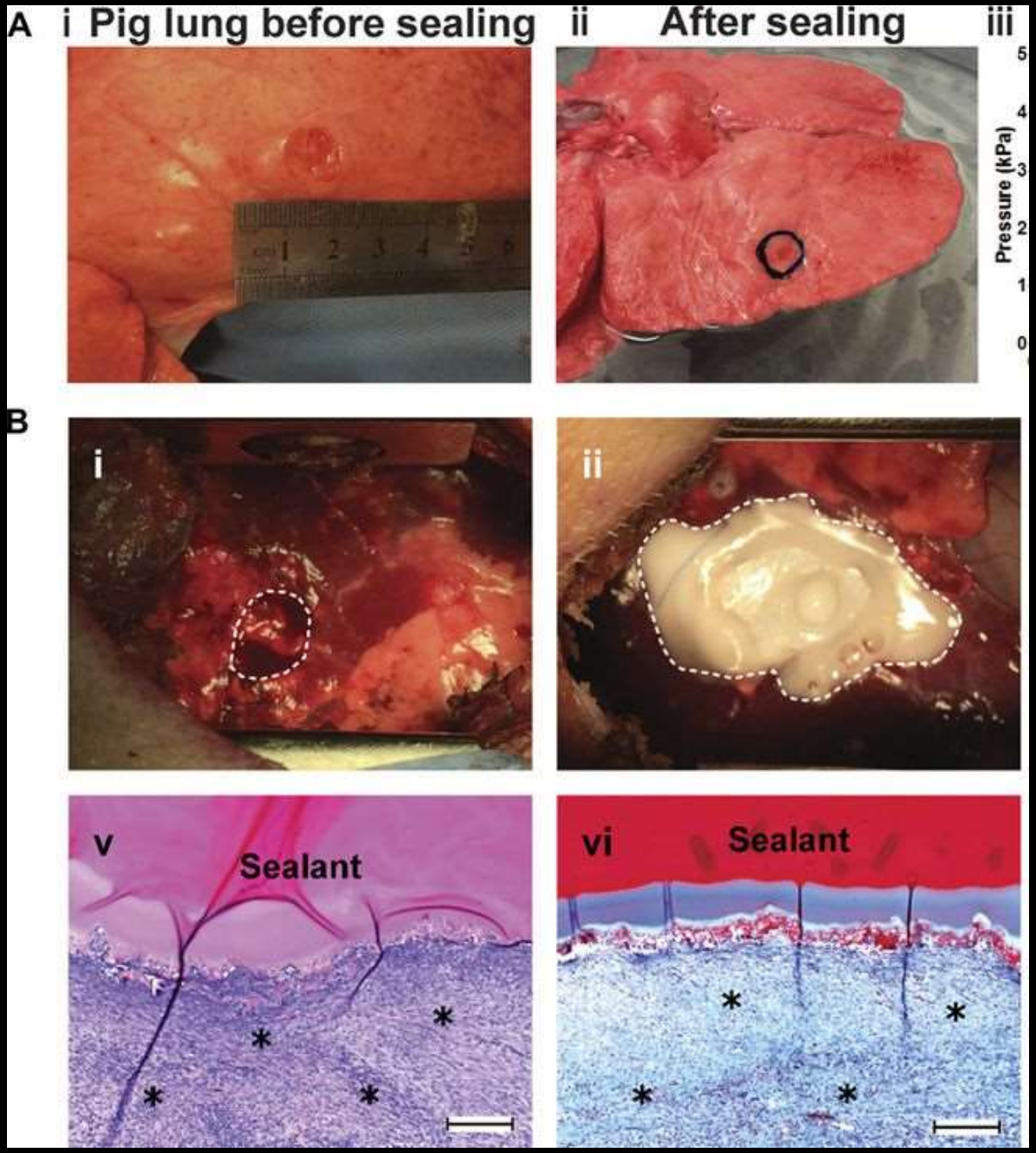
DDx

- Parasitic lung infection
- Cystic granulomatous tuberculosis
- Autoimmune-related granulomas
- Extracellular mucin
- Bullous emphysema
- **Biopsy site change**
  - Talc pleurodesis?
  - Pleural filler?

FINAL DX

- **Pleural changes consistent with pleural sealant used during prior bx**


Polyethylene Glycol
Proprietary PROGEL™ PEG lends the sealant its ability to stretch
Human Serum Albumin
Large, globular protein provides PROGEL™ its adhesive strength



Annabi N et al. Engineering a highly elastic human protein-based sealant for surgical applications. Sci Transl Med. 2017 Oct 4;9(410):eaai7466.

Human Pathology (2019) 89, 40–43

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

Pulmonary pathologic alterations associated with biopsy inserted hydrogel plugs☆

Samuel A. Yousem MD [a,*], Rajnikant M. Amin MD [a], Ryan Levy MD [b], Nicholas Baker MD [b], Paul Lee MD [c]

[a] *Department of Pathology, University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA 15213-2582*
[b] *Department of Radiology, University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA 15213-2582*
[c] *Department of Cardiothoracic Surgery, University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA 15213-2582*

Received 28 January 2019; revised 17 April 2019; accepted 20 April 2019

Keywords:
Hydrogel plug;
Pneumothorax;
Lung biopsy

Summary The prevention of pneumothorax after percutaneous lung biopsy is a major patient safety concern. The insertion of hydrogel plugs into biopsy sites to mitigate this complication is a new intervention. The histology of the plug has not been previously reported, and in this study the histologic reaction is reported in 13 cases. The hydrogel plug forms a spherical basophilic matrix pool with an adjacent foreign body giant cell reaction and patchy eosinophilia. No extension to the pleural surface is present. The potential diagnostic errors related to the presence of the plug are discussed.

Impact of Histopathologic Changes Induced by Polyethylene Glycol Hydrogel Pleural Sealants Used During Transthoracic Biopsy on Lung Cancer Resection Specimen Staging

Kelly J. Butnor, MD, Adina A. Bodolan, MD, Britni R.E. Bryant, MD, and Alan Schned, MD

Abstract: Patients undergoing transthoracic needle core lung biopsy (TTNB) are at risk for biopsy-related pneumothorax. Instilling pleural sealant at the pleural puncture site reduces this risk. The impact of histologic changes associated with pleural sealant on assessing the histologic type and pathologic stage in lung cancer resection specimens has not been previously evaluated. All lung cancer resection specimens from 2015 to 2018 in which polyethylene glycol hydrogel pleural sealant was instilled during TTNB were reviewed. Thirty-three cases were identified. TTNB preceded lobectomy by an average of 35 days. Amphophilic, weakly polarizable, crinkled pleural sealant material was associated with tumor in 11 cases (33%), including 8 adenocarcinomas, 2 squamous cell carcinomas, and 1 pleomorphic carcinoma that averaged 1.7 cm in greatest dimension. Surrounding the sealant material was a 0.25 to 1.0 cm in greatest dimension pseudocystic space with a thin granulomatous rim of macrophages and multinucleated giant cells that occupied on average 17% of the tumoral area. Pleural sealant could have impaired assessment of pathologic stage in 1 case by obscuring the visceral pleural elastic layer, but definitive visceral pleural invasion was present nearby. Although hydrogel pleural sealant instilled during TTNB has the potential to obscure important histologic features, in practice, it appears to have little or no adverse impact on the assessment of histologic type and pathologic stage in subsequent lung cancer resection specimens. Recognition of the histologic appearance of hydrogel pleural sealant and its associated tissue response is important for avoiding diagnostic misinterpretation.

Key Words: pleural sealant, polyethylene glycol hydrogel plug, transthoracic lung biopsy, lung cancer resection staging

(*Am J Surg Pathol* 2020;44:490–494)

Percutaneous computed tomographic–guided transthoracic needle biopsy (TTNB) is a useful modality for determining the nature of peripheral lung lesions. Pneumothorax complicates TTNB in about 20% of cases.[1] The instillation of a self-expanding polyethylene glycol hydrogel plug at the pleural puncture site is a relatively novel technique for reducing this risk.[2] The histopathologic changes induced by hydrogel plug-type pleural sealant have been described only recently.[3] It is not known how often pleural sealant becomes embedded in the lung lesion that is being biopsied and the range of diagnostic difficulties this may cause. This study explores the histologic differential diagnosis of hydrogel pleural sealant and examines how frequently pleural sealants used during TTNB are in continuity with lung carcinoma in subsequent resection specimens and the impact this has on assessing histologic type and tumor stage.

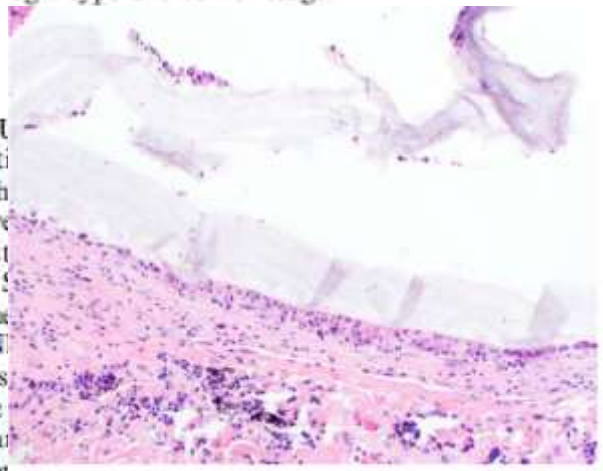


TABLE 1. Clinicopathologic Findings in Lung Carcinoma Resection Specimens Containing Hydrogel Pleural Sealant

Case No.	Days Between Biopsy and Resection	Pleural Sealant Location	Tumor Type	Tumor Size (cm)	Tumoral Area Occupied by Sealant and Tissue Reaction (%)	Histologic Features of Sealant Reaction	Visceral Pleural Invasion	Tumor Stage	Histologic Assessment Impacted by Pleural Sealant?
1	34	Intratumoral	Squamous	1.3	4	Pseudocyst with granulomatous rim and eosinophils	No	pT1b	N
2	72	Intratumoral	Adenocarcinoma, solid predominant	1.4	18	Pseudocyst with granulomatous rim and eosinophils	Yes	pT2a	N
3	35	Intratumoral	Adenocarcinoma, acinar predominant	1.4	32	Pseudocyst with granulomatous rim and eosinophils	No	pT1b	N
4	41	Intratumoral	Adenocarcinoma, solid predominant	2.5	4	Pseudocyst with fibrin, neutrophils, and xanthogranulomatous rim	No	pT1c	N
5	28	Intratumoral	Adenocarcinoma, mixed mucinous and nonmucinous	1.2	6	Pseudocyst with granulomatous rim and eosinophils	No	pT1b	N
6	34	Tumor periphery	Adenocarcinoma, acinar (cribriform) predominant	0.9	NA	Pseudocyst with granulomatous rim and eosinophils	Yes	pT2a	Potentially*
7	22	Lung parenchyma	Adenocarcinoma, invasive mucinous	2.4	NA	Pseudocyst with granulomatous rim and eosinophils	Yes	pT2a	N
8	66	Lung parenchyma	Adenocarcinoma, solid predominant	2.0	NA	Pseudocyst with granulomatous rim and eosinophils	No	pT1b	N
9	29	Intratumoral	Pleomorphic	1.8	31	Pseudocyst with granulomatous rim and eosinophils	No	pT1b	N
10	32	Intratumoral	Adenocarcinoma, papillary predominant	1.9	28	Pseudocyst with granulomatous rim and eosinophils	Yes	pT2a	N
11	44	Intratumoral	Adenocarcinoma, papillary predominant	2.1	4	Pseudocyst with granulomatous rim and eosinophils	Yes	pT2a	N
12	41	Intratumoral	Adenocarcinoma, solid predominant	1.5	36	Pseudocyst with granulomatous rim and eosinophils	No	pT1b	N
13	38	Intratumoral	Squamous	2.5	8	Pseudocyst with granulomatous rim	Yes	pT2a	N

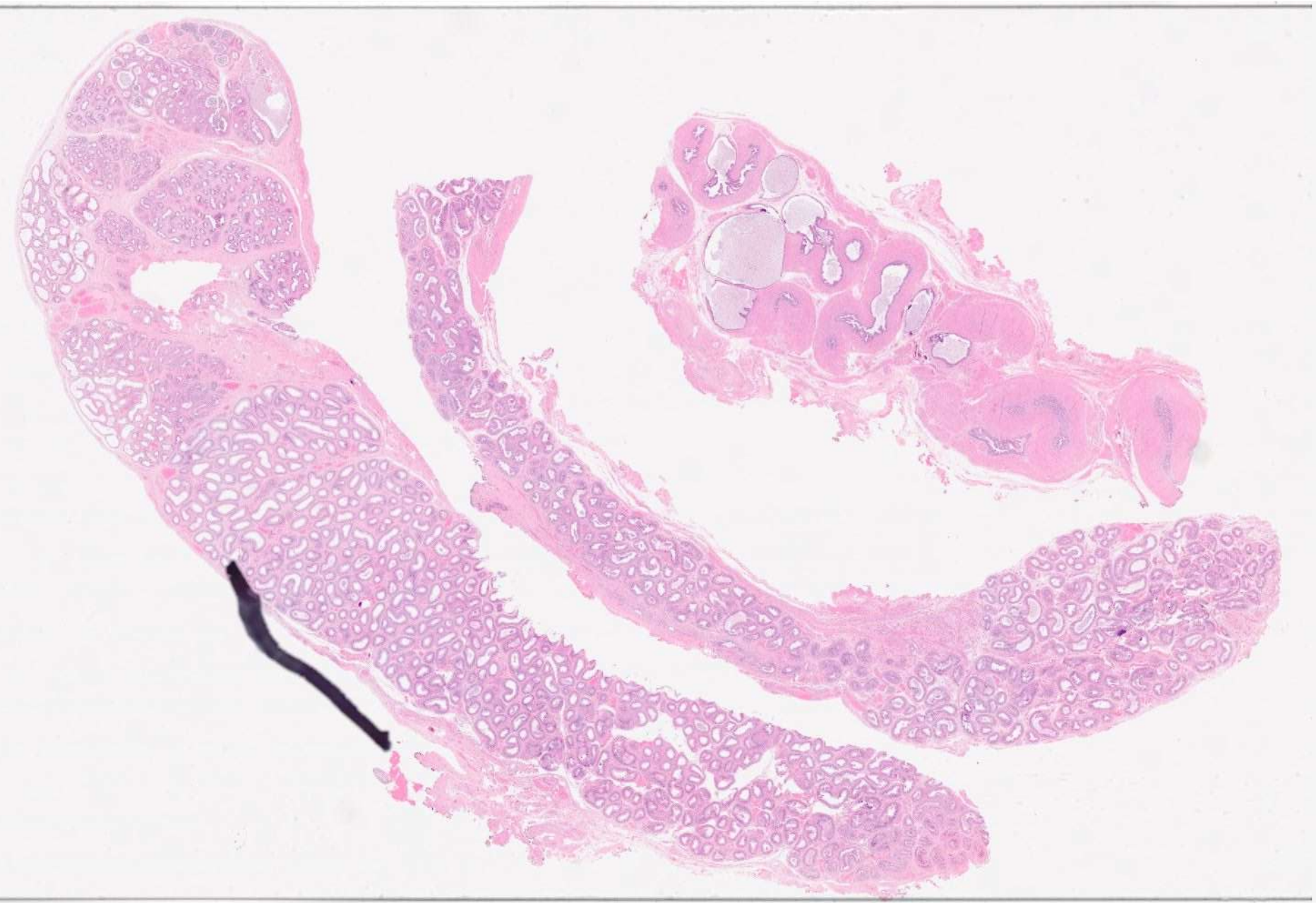
TAKE HOME POINTS

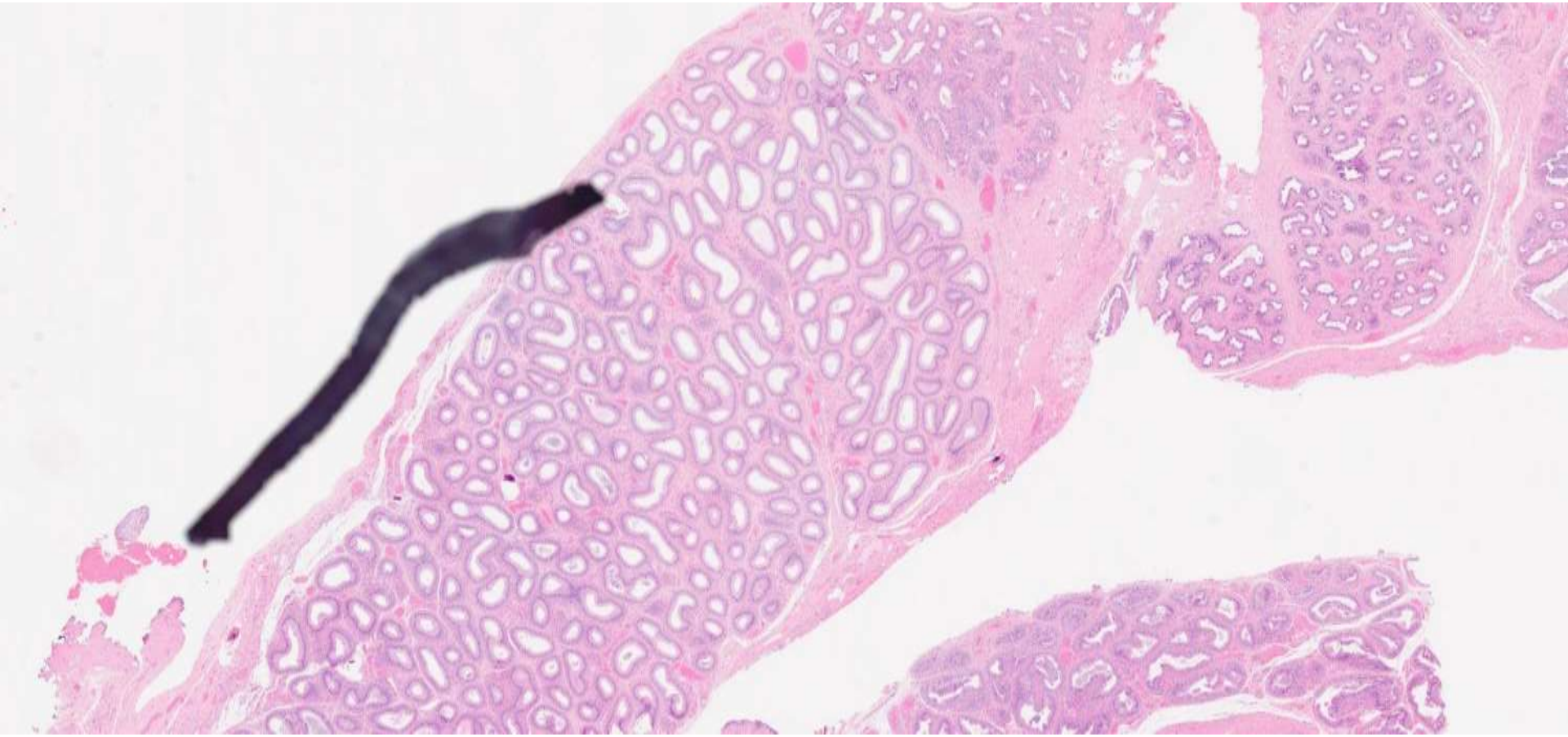
- **In cases with funny pseudocysts (intra/peri-tumoral or pleural) with luminal wispy basophilic webs**
  - Consider pleural sealant (“pleural plug”) from prior bx
    - Done to prevent pneumothorax (up to 20% of transthoracic needle biopsy)
  - occasionally but infrequently can affect staging

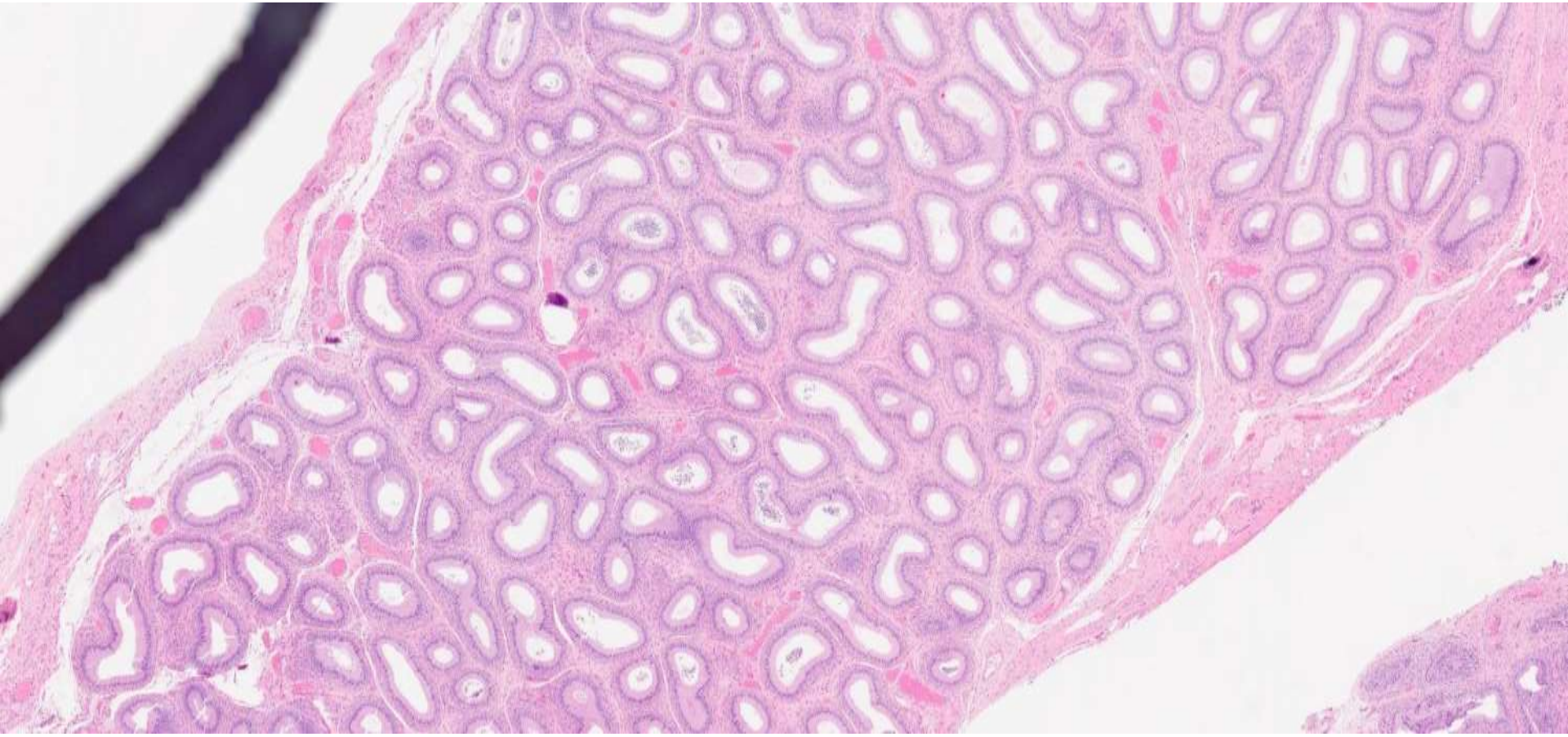
22-0610
Direct links to scanned slides:

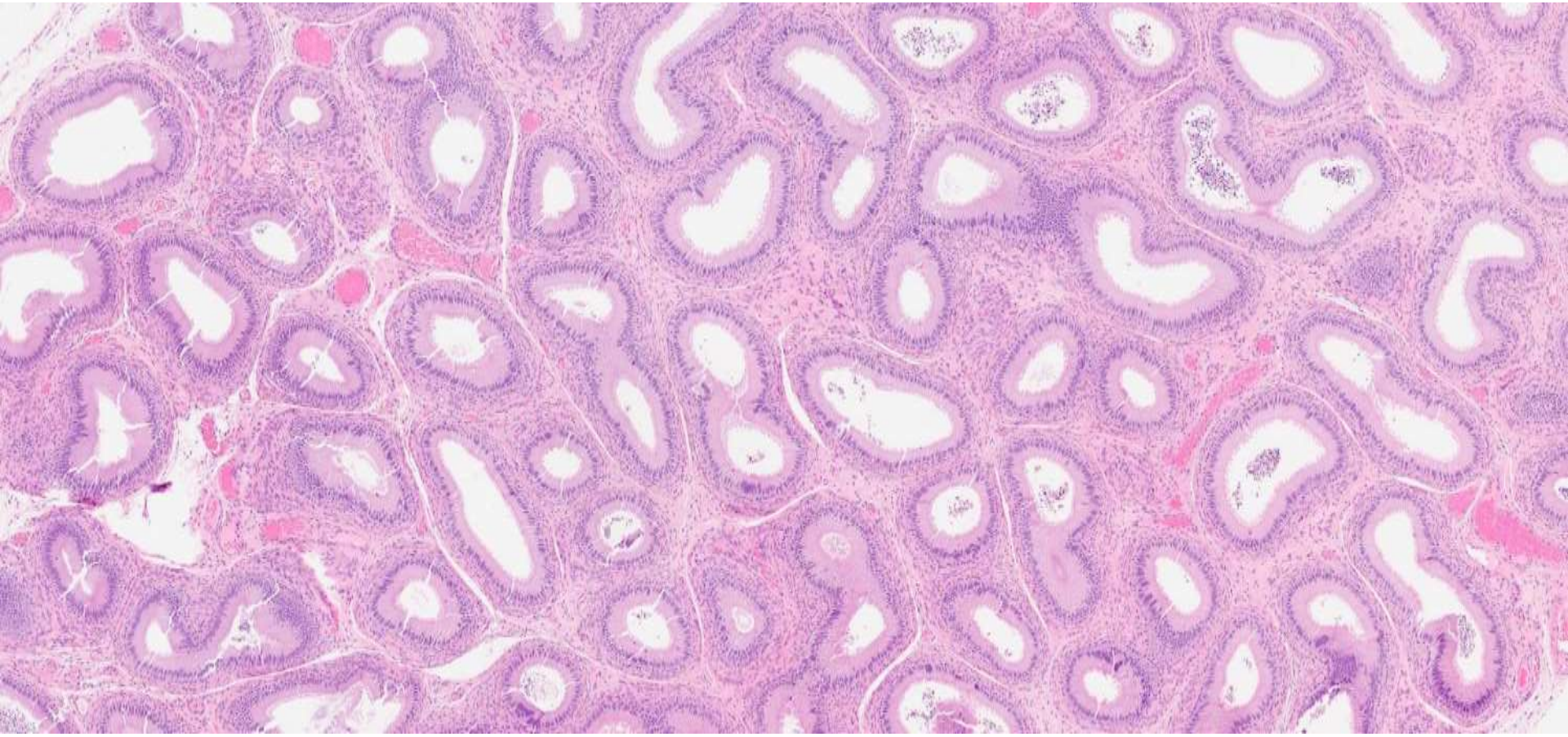
Ankur Sangoi; El Camino Hospital

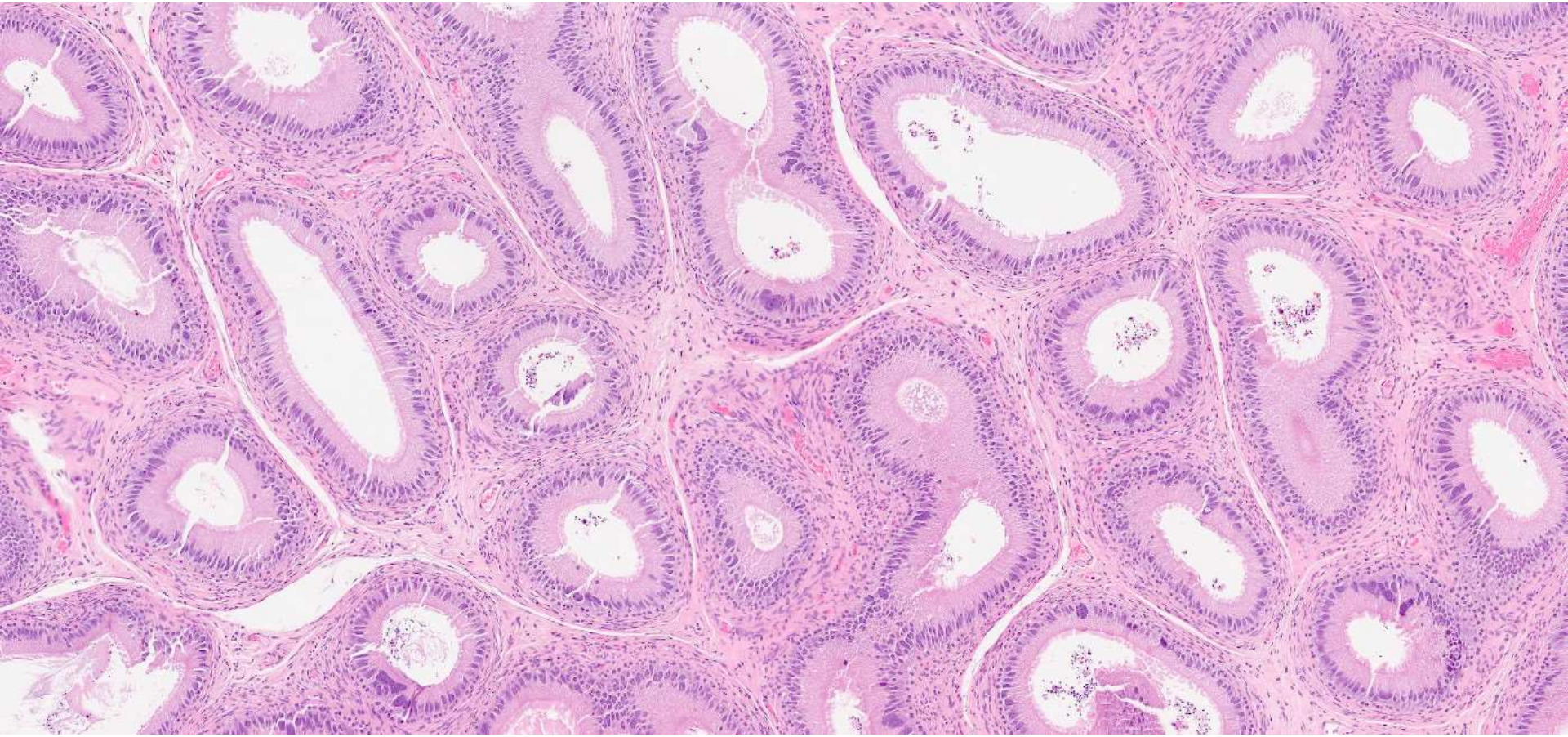
Middle aged M presents with epididymitis. Epididymis excision submitted.

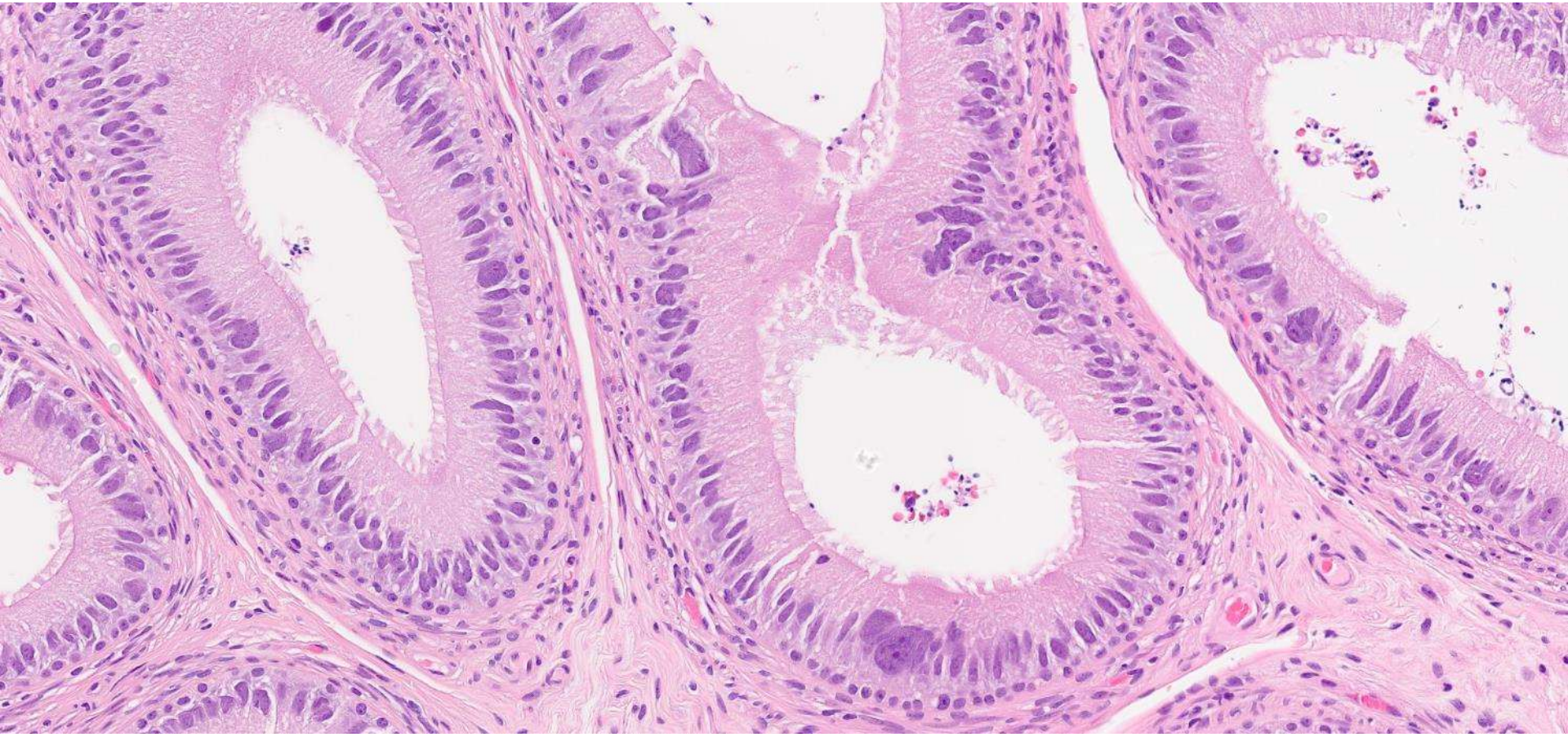


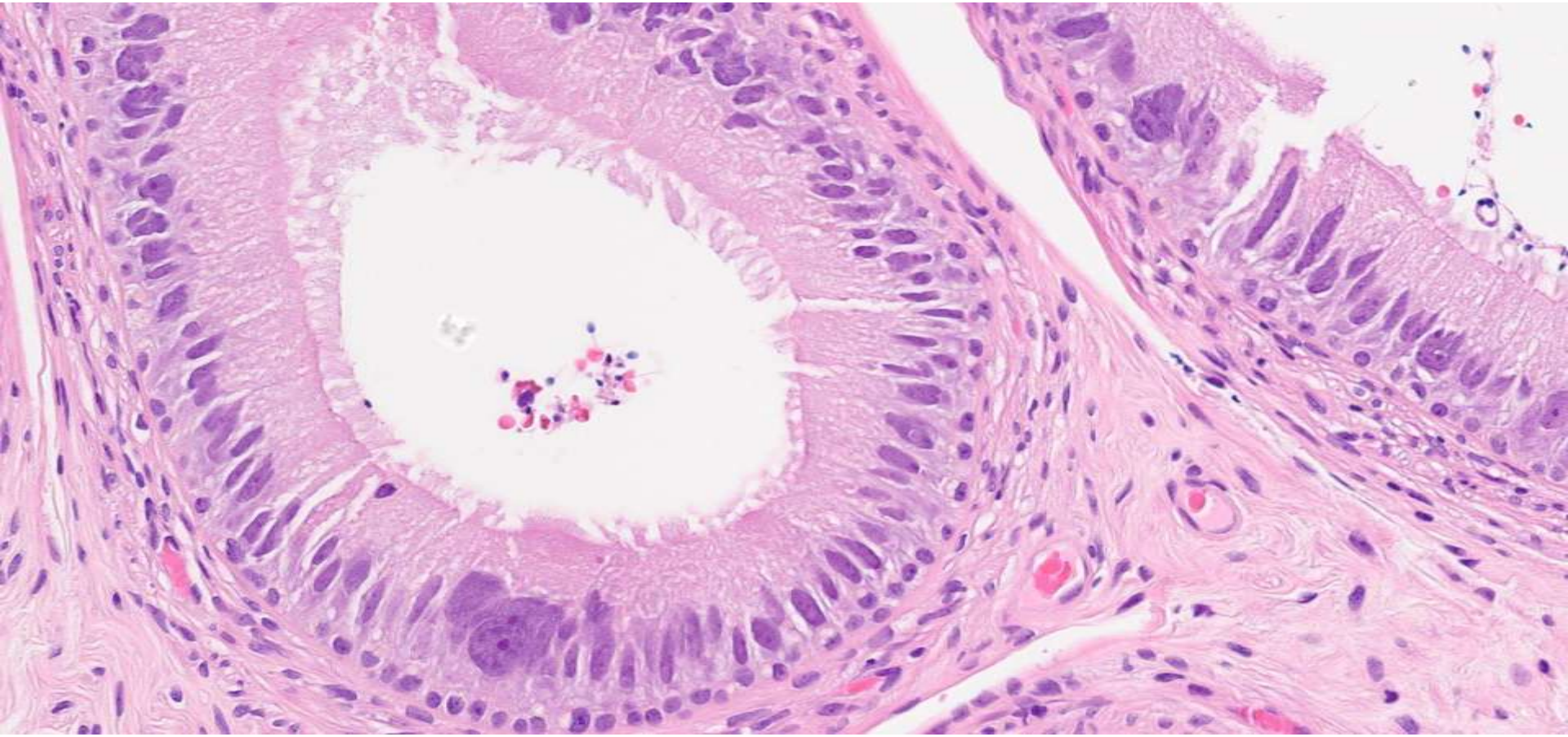


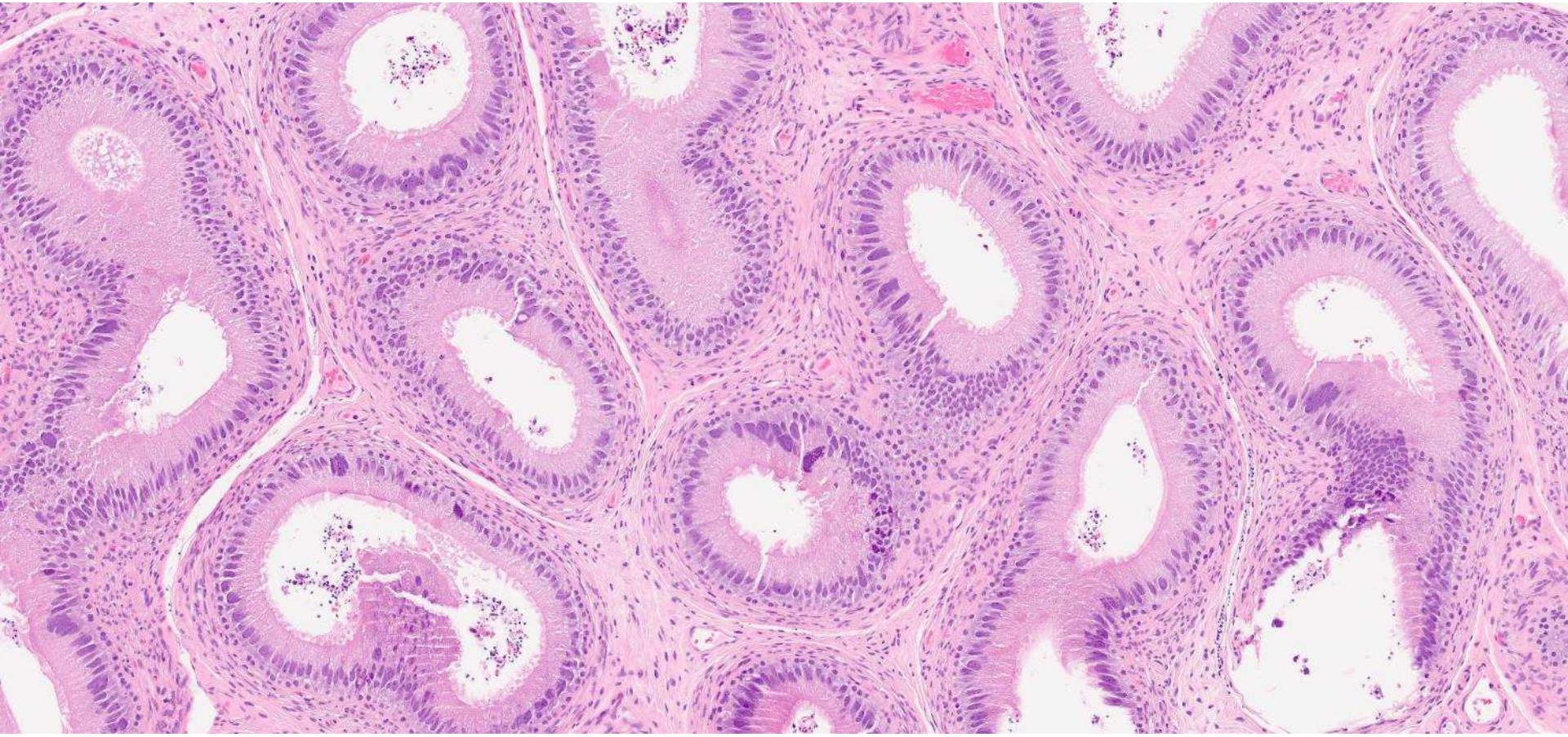


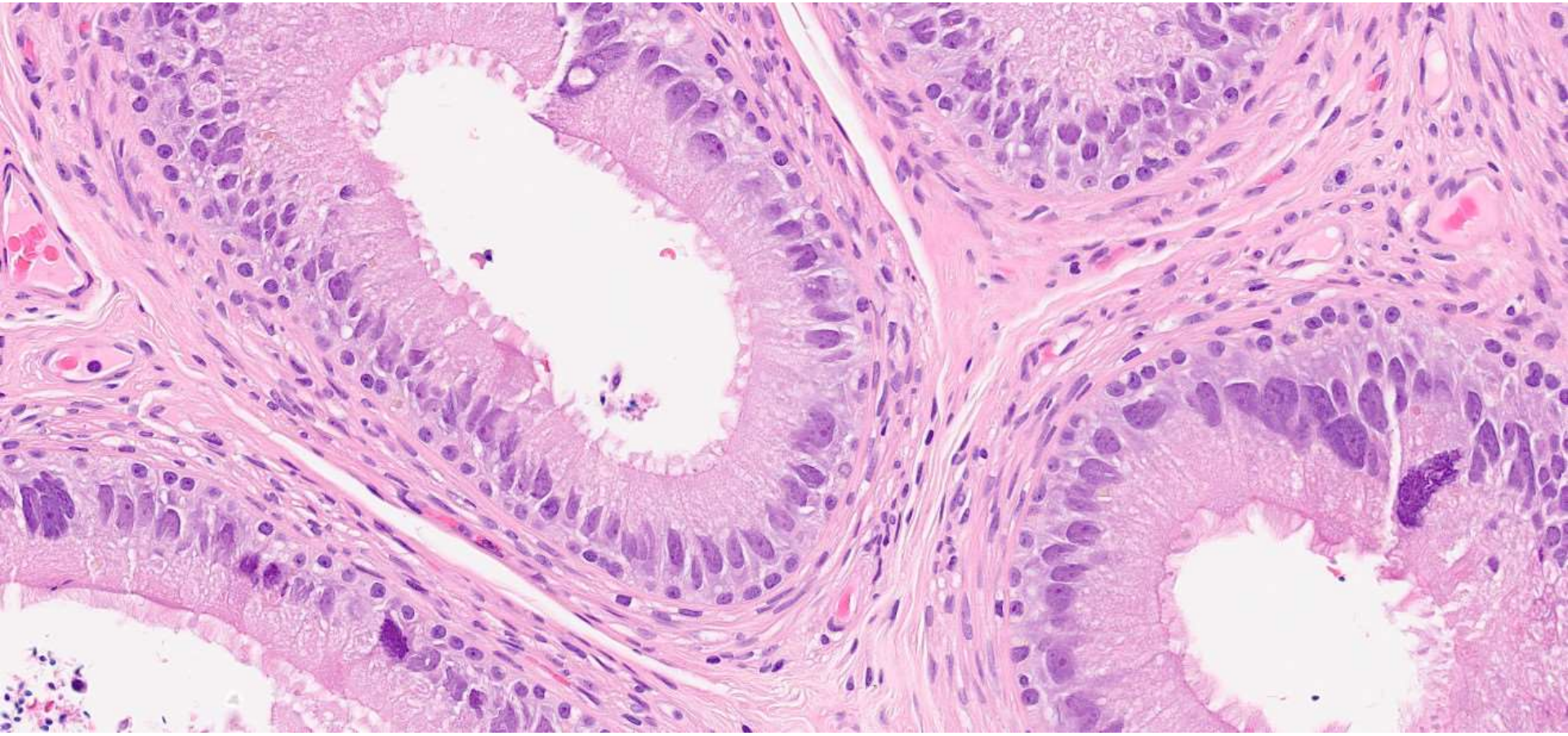


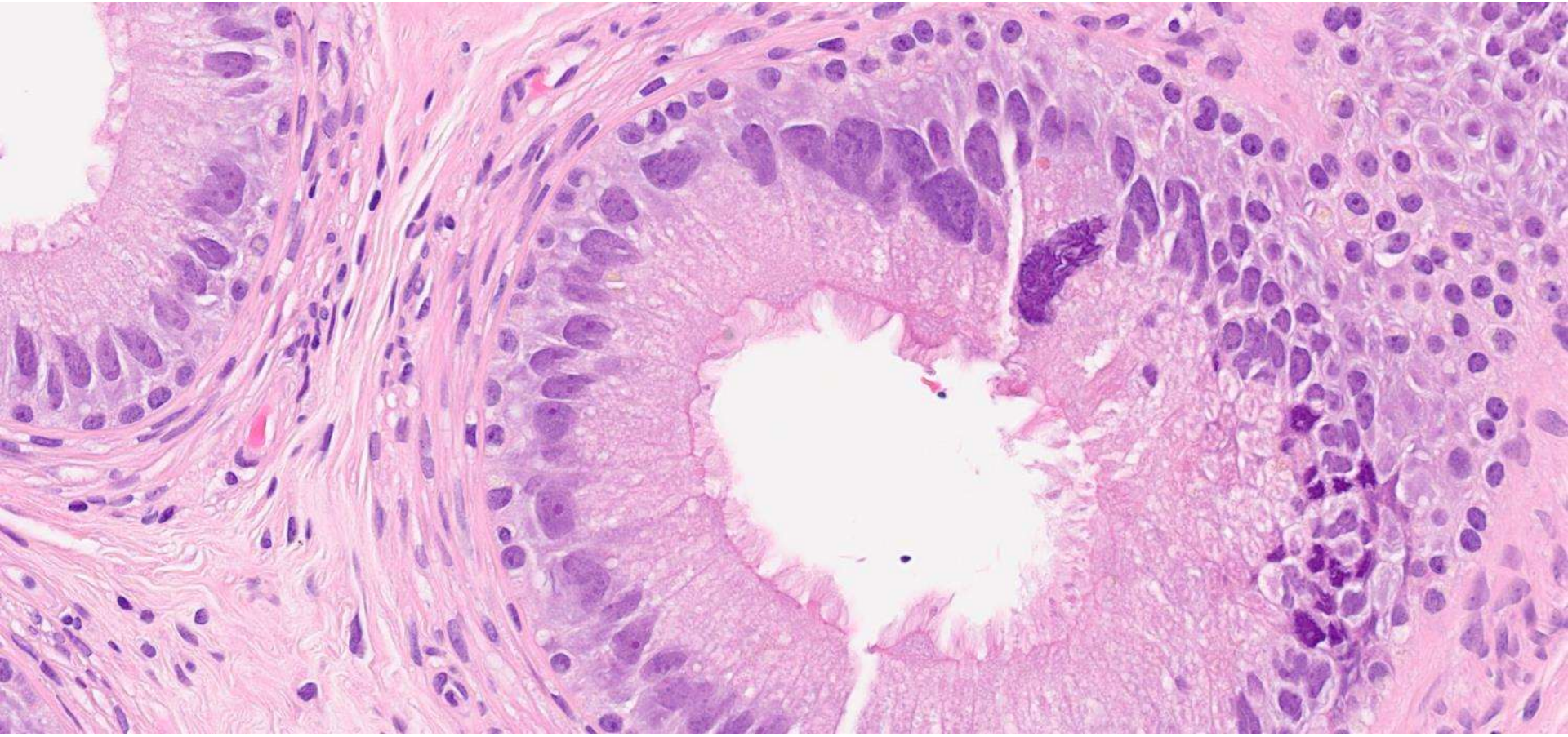












DDx

- **BENIGN**
  - Prior chemo/XRT?
  - Normal variant histology for epididymis?

- **MALIGNANT**
  - GCNIS colonizing epididymis?
  - Urothelial CIS colonizing epididymis?
  - Metastasis?

Histologic Variations in the Epididymis

Findings in 167 Orchiectomy Specimens

Varsha I. Shah, M.R.C.Path., Jae Y. Ro, M.D., Mahul B. Amin, M.D., Seema Mullick, M.D., Tipu Nazeer, M.D., and Alberto G. Ayala, M.D.

Nonpathologic morphologic variations in the epididymal histology in 167 orchiectomy specimens were analyzed to assess and document the nature, frequency, and possible relation to patient age and underlying testicular pathology. Variations in histology included intranuclear eosinophilic inclusions, lipofuscin pigment, cribriform hyperplasia, Paneth cell-like metaplasia, and nuclear atypia. Intranuclear eosinophilic inclusions were observed in 72.5% of patients, and they appeared to occur at an older age than cribriform hyperplasia and Paneth cell-like metaplasia. Lipofuscin pigment was found in 32.9% of patients; this change was observed predominantly in ductuli efferentes and was more commonly associated with obstructive changes. Cribriform hyperplasia was seen in 41.9% of patients, and it occurred in 1 normal testis and in 33 testes with diverse pathologic alterations. Paneth cell-like metaplasia characterized by bright eosinophilic intracytoplasmic hyaline-like granules and globules, was present in 8.3% of patients and was accompanied by changes of obstruction in almost all instances. The globules were strongly periodic acid-Schiff positive, both before and after diastase digestion, and were negative for chromogranin A, KP-1, and MAC387 immunostains. Nuclear atypia, similar to that seen in seminal vesicles, was focally present in 13.8% of patients and tended to occur at an older age. The authors conclude that variations in epididymal morphology are fairly common and, therefore, surgical pathologists should be aware of these changes. Although exuberant in some patients, in no cases did these variations cause serious diagnostic problems.

Key Words: Epididymis—Intranuclear eosinophilic inclusions—Lipofuscin pigment—Cribriform hyperplasia—Paneth cell-like metaplasia—Nuclear atypia—Immunohistochemistry.

Am J Surg Pathol 22(8): 990–996, 1998.

the initial portion of t
regions are characterize
thelia, and contractile el
the ductuli efferentes is
cells, some with cilia, o
of the ductus epididymis
with small basal cells, cl
cells with stereocilia, th
toplasmic clear vacuoles
have often observed var
morphology, and these in
inclusions, lipofuscin pig
Paneth cell-like metaplasia
intranuclear eosinophilic i
ment have been document
texts,[8] we found very limit
hyperplasia, Paneth cell-l
atypia. Furthermore, there i
whether these morphologic
nificant or correlate with pa

Because of the relatively
the subject and because the
orchiectomy specimens, we a
tology in 167 cases to assess
of histologic variations in t
cribriform hyperplasia and P
and their relation, if any, to
testicular disease. The potentia

TABLE 2. *Incidence of histologic variations in cases of testicular atrophy*

Histologic variation	No. of cases (%)
Intranuclear eosinophilic inclusions	67 (65.0)
Lipofuscin pigment	48 (46.6)
Cribriform hyperplasia	34 (33.0)
Paneth cell-like metaplasia	12 (11.7)
Nuclear atypia	20 (19.4)

Am J Surg Pathol, Vol. 22, No. 8, 1998

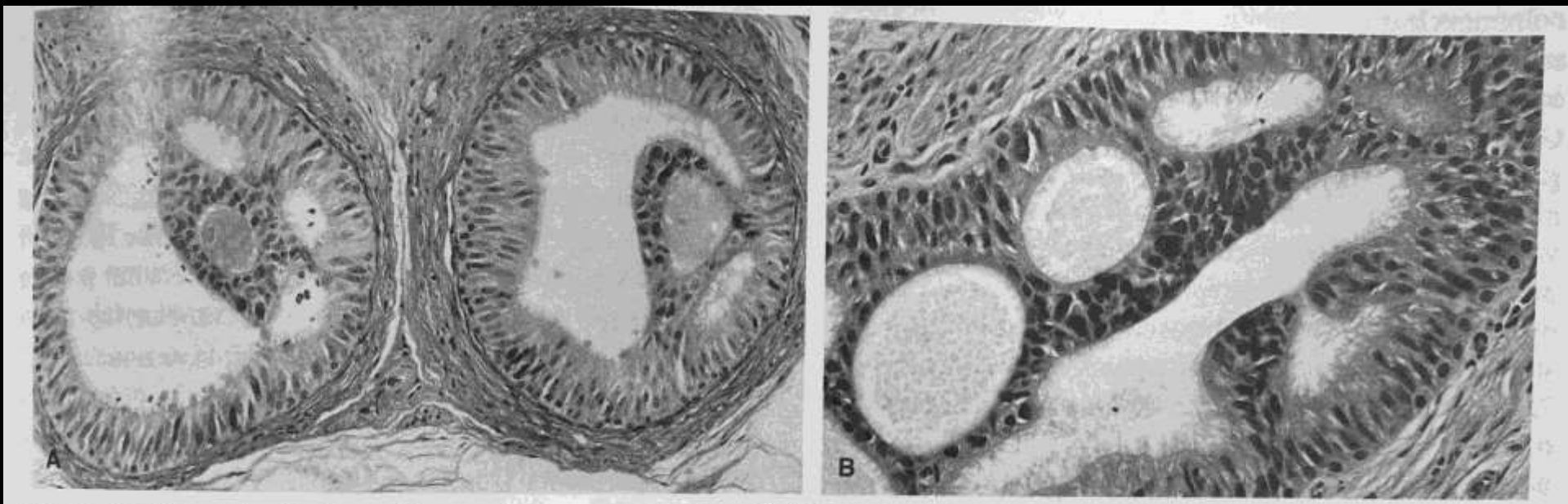


FIG. 3. Epididymal cribriform hyperplasia with rigid epithelial bridges, nuclear crowding, hyperchromasia, and focal anisonucleosis. **(A)** Low power. **(B)** High power.

TAKE HOME POINTS

- **Variations in epididymal morphology common**
  - Be aware of nuclear atypia!