

# Disclosures

## July 8, 2019

Dr. Ankur Sangoi has disclosed a financial relationship with Google (consultant). Dr. Dennis Adams has disclosed financial relationships with Portola Pharmaceuticals, Aurinia Pharmaceuticals, and Global Blood Therapeutics (shareholder). Dr. Keith Duncan has disclosed a financial relationship with Abbvie (consultant). South Bay Pathology Society has determined that these relationships are not relevant to the clinical cases being presented.

The following planners and faculty had no financial relationships with commercial interests to disclose:

### **Presenters:**

Mahendra Ranchod, MD  
Balaram Puligandla, MD  
Megan Troxell, MD, PhD  
Charles Lombard, MD  
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Dita Gratzinger, MD, PhD  
Nicholas Ladwig, MD  
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Gerry Berry, MD  
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### **Activity Planners/Moderator:**

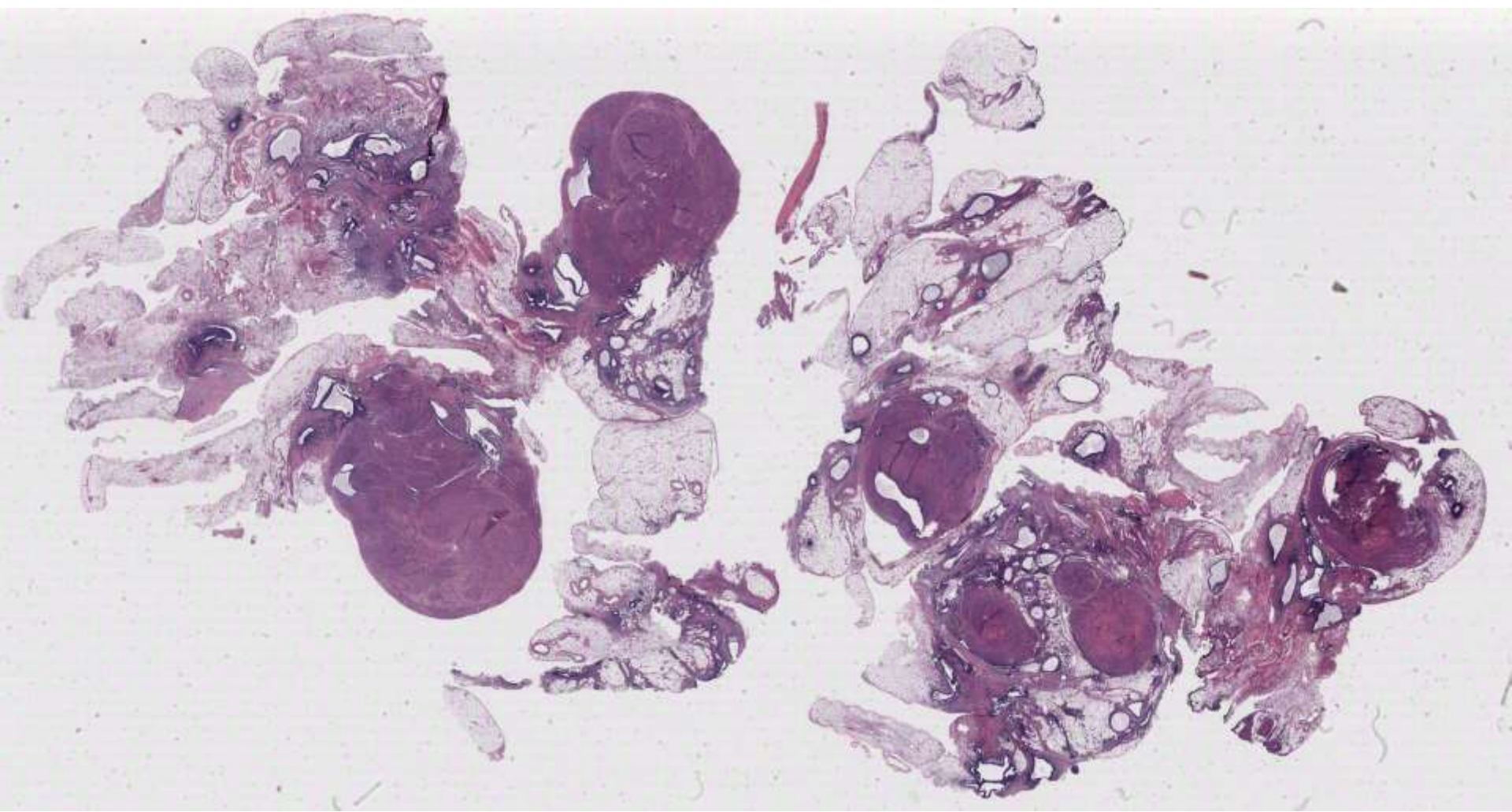
Kristin Jensen, MD  
Megan Troxell, MD, PhD

# 19-0701

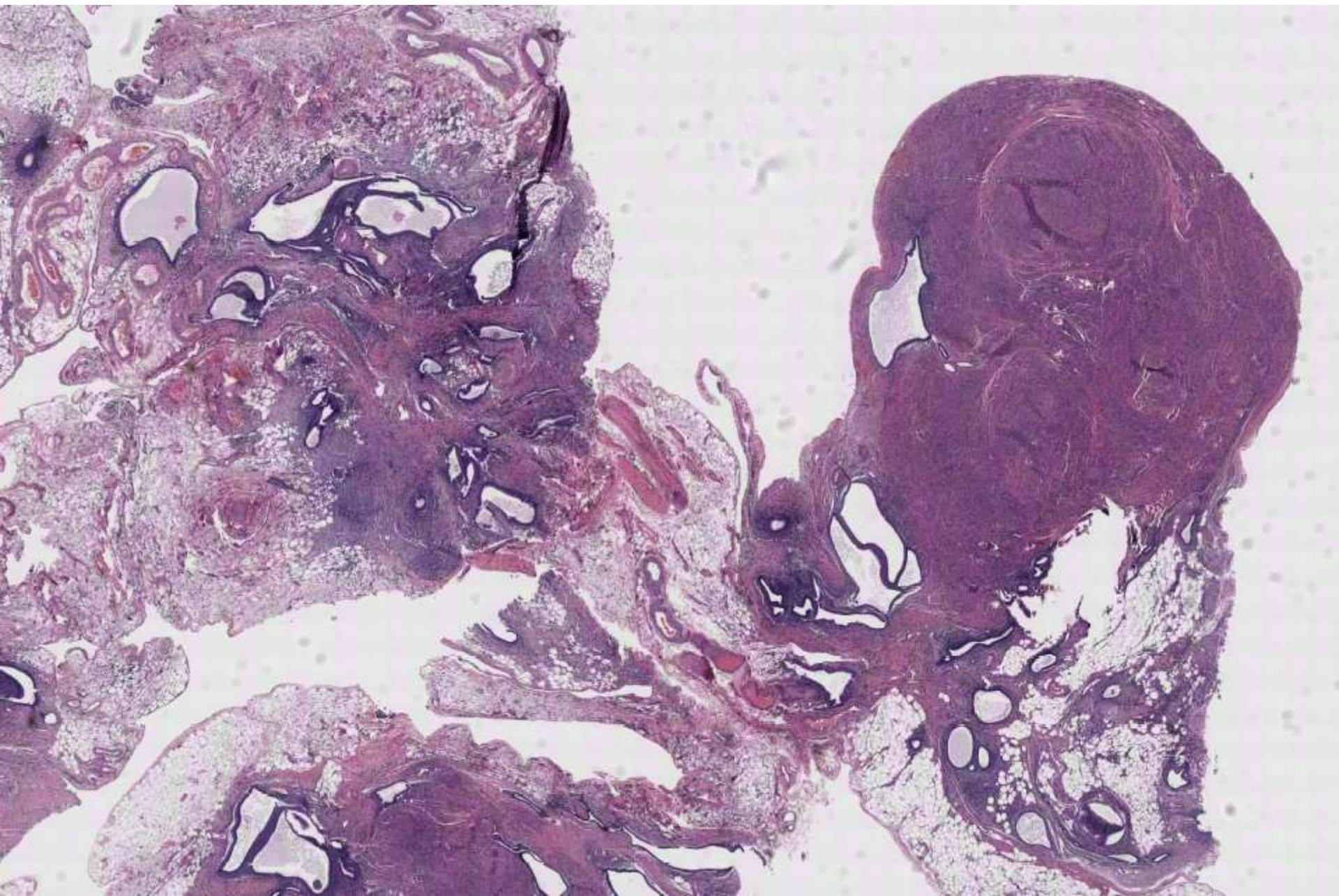
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**Mahendra Ranchod; Good  
Samaritan Hospital**

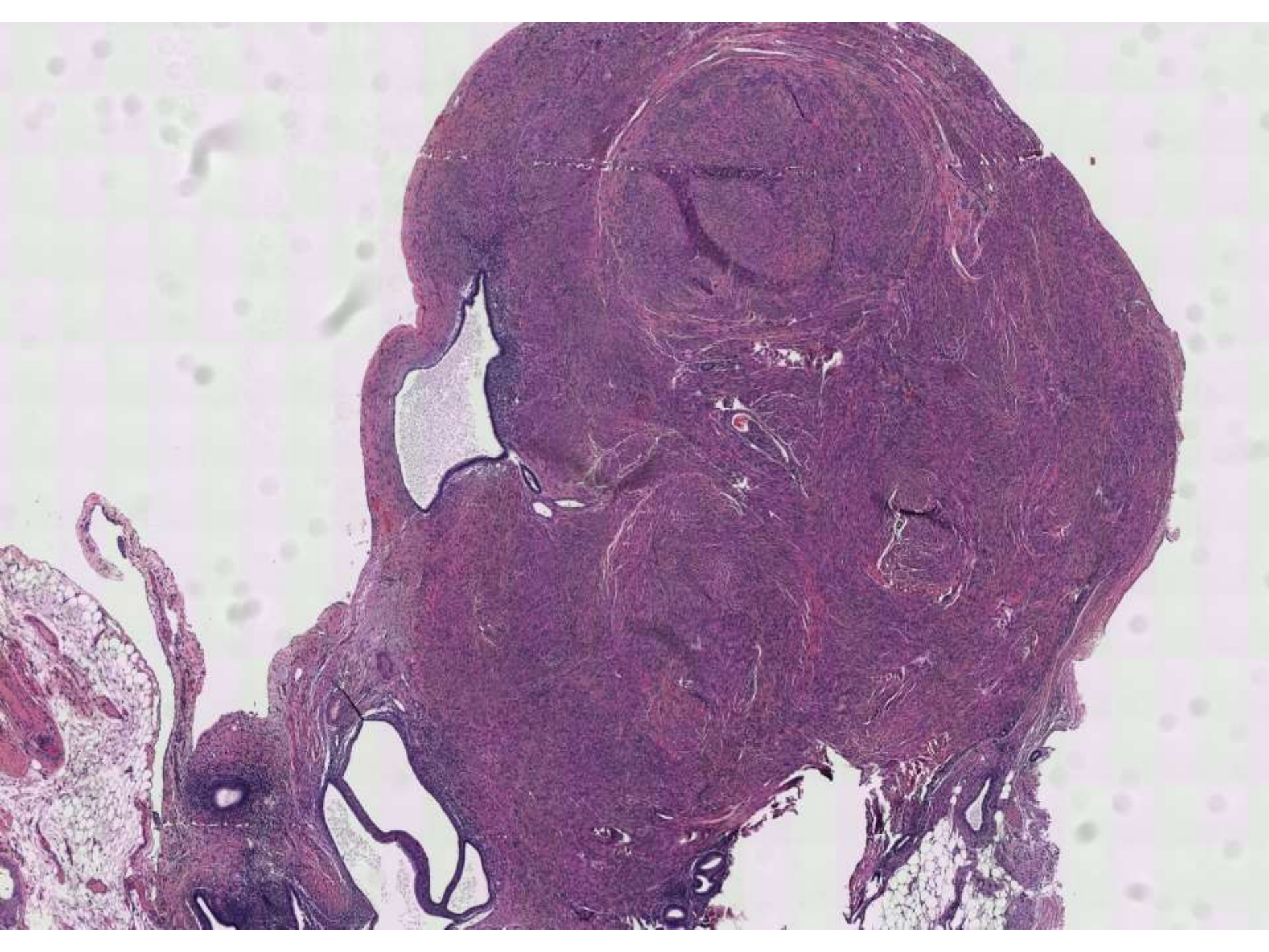
37-year-old woman with endometriosis was found to have 3 firm nodules in the omentum, largest 8mm in maximum dimension.



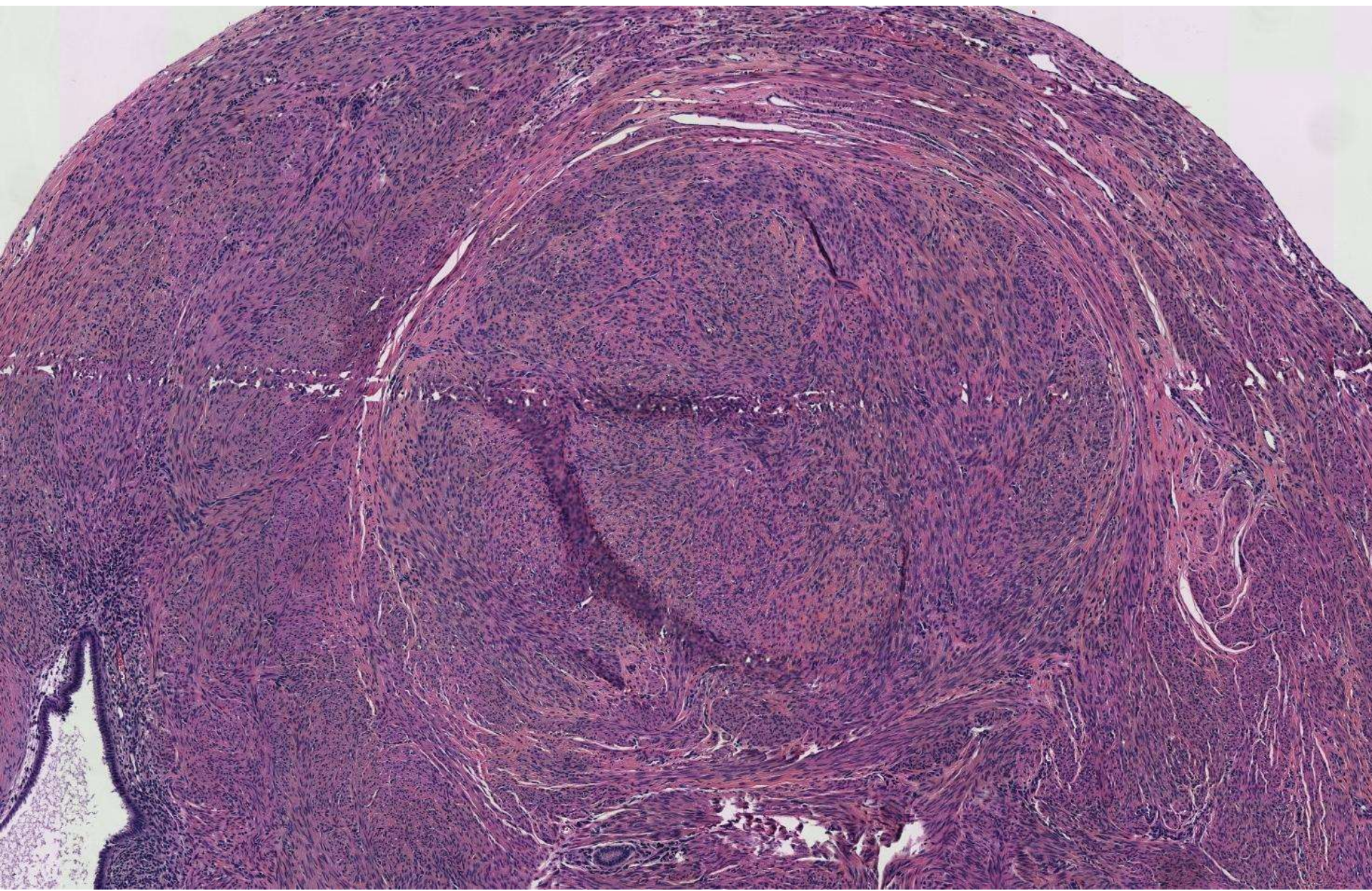




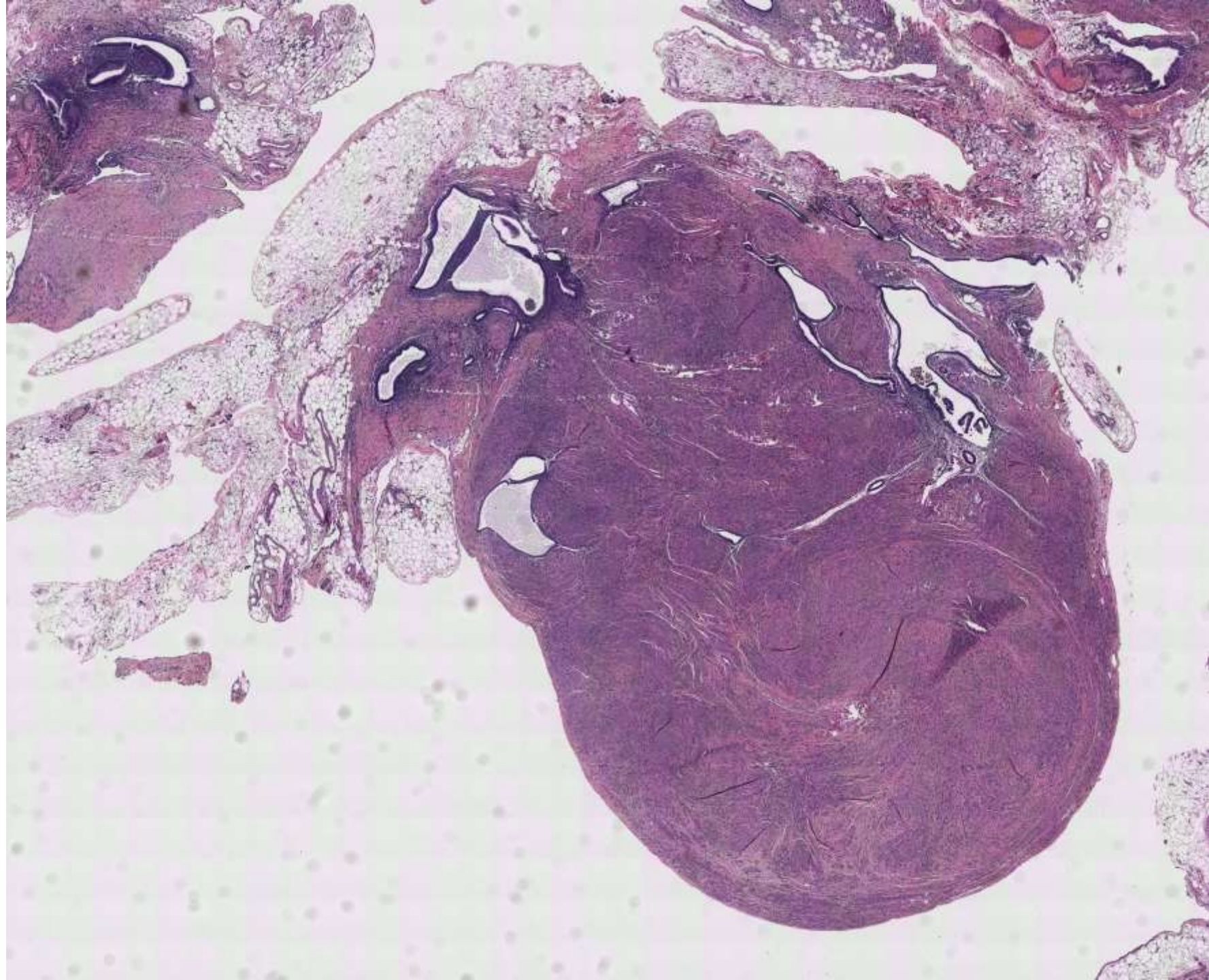




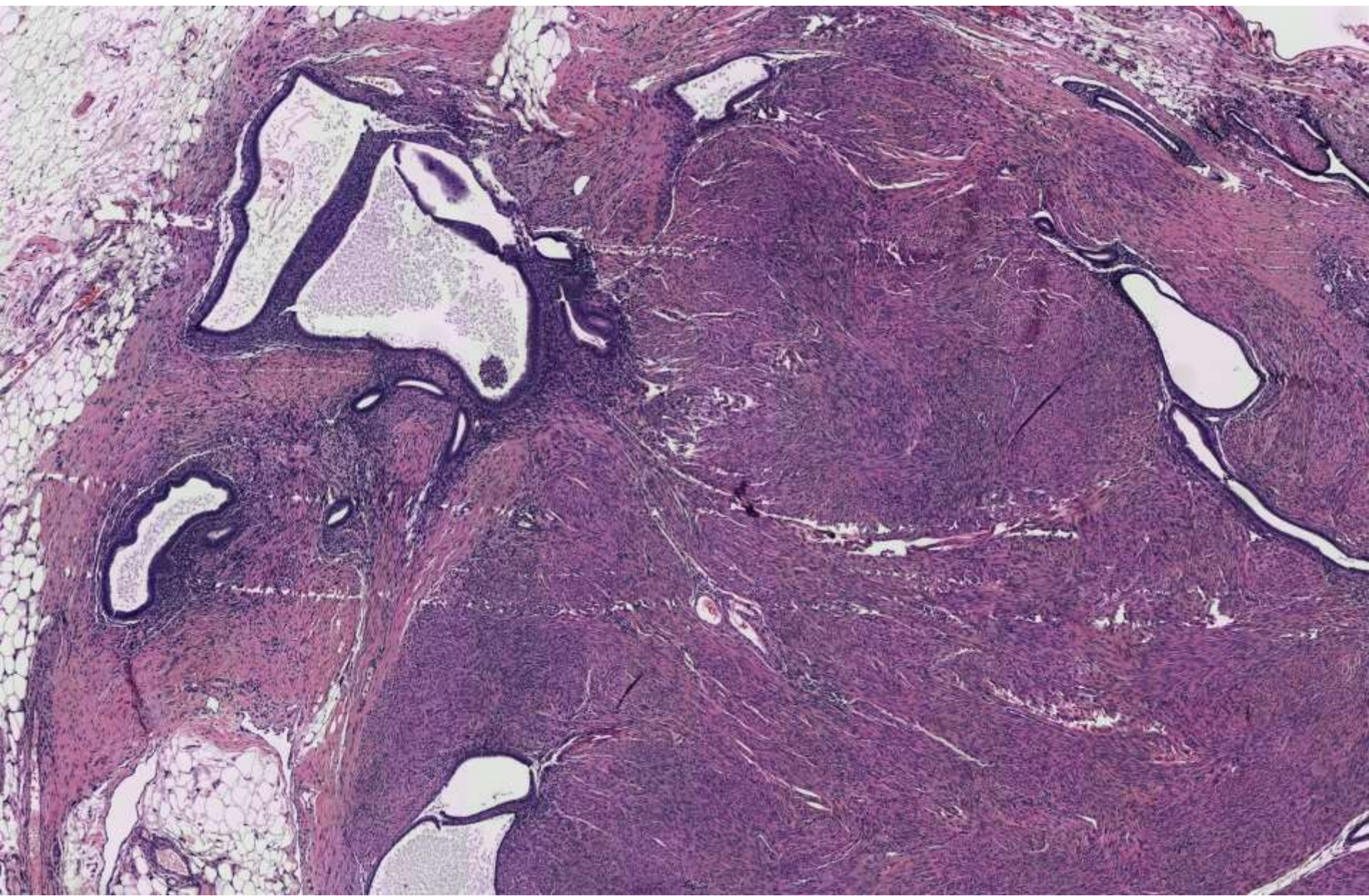




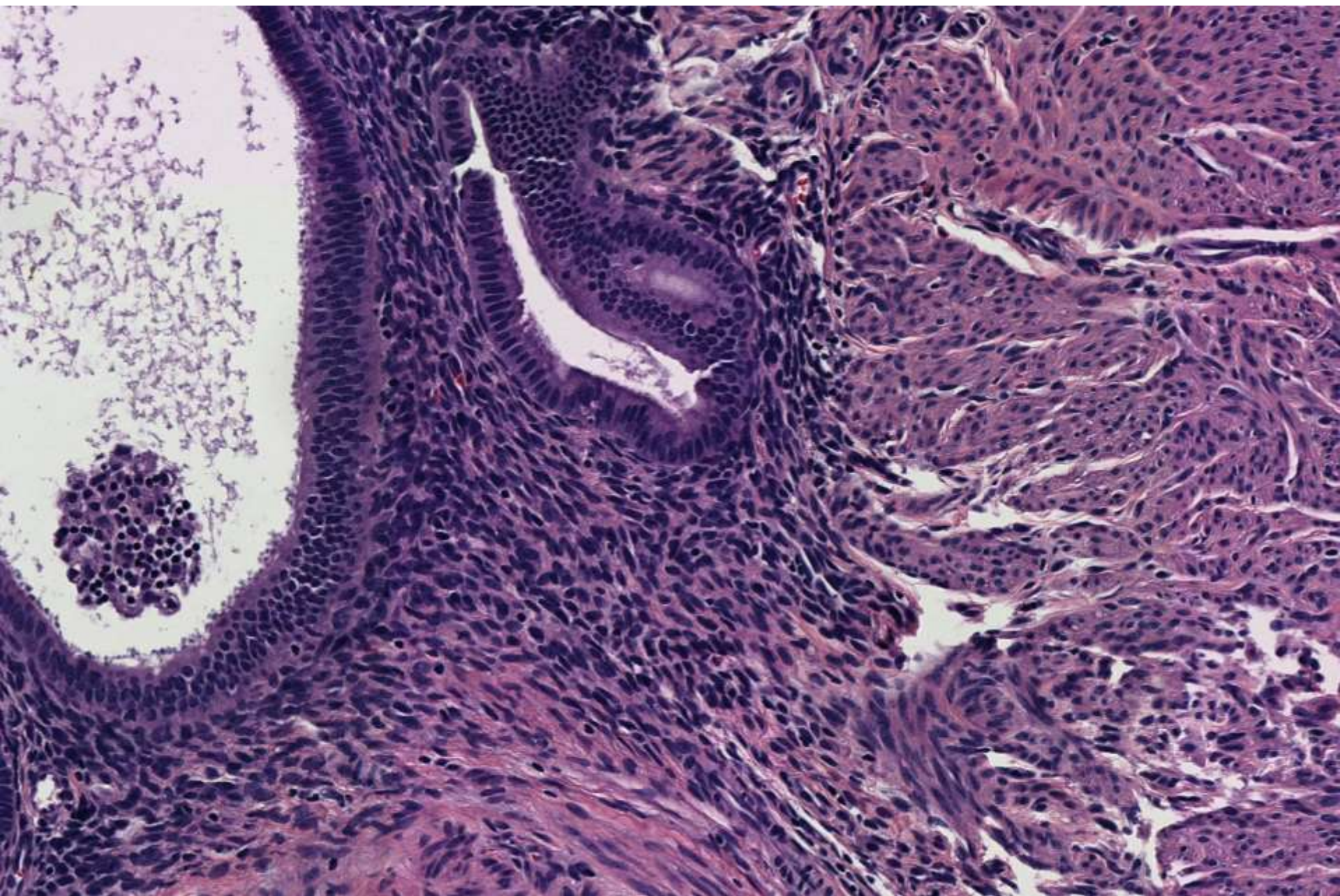




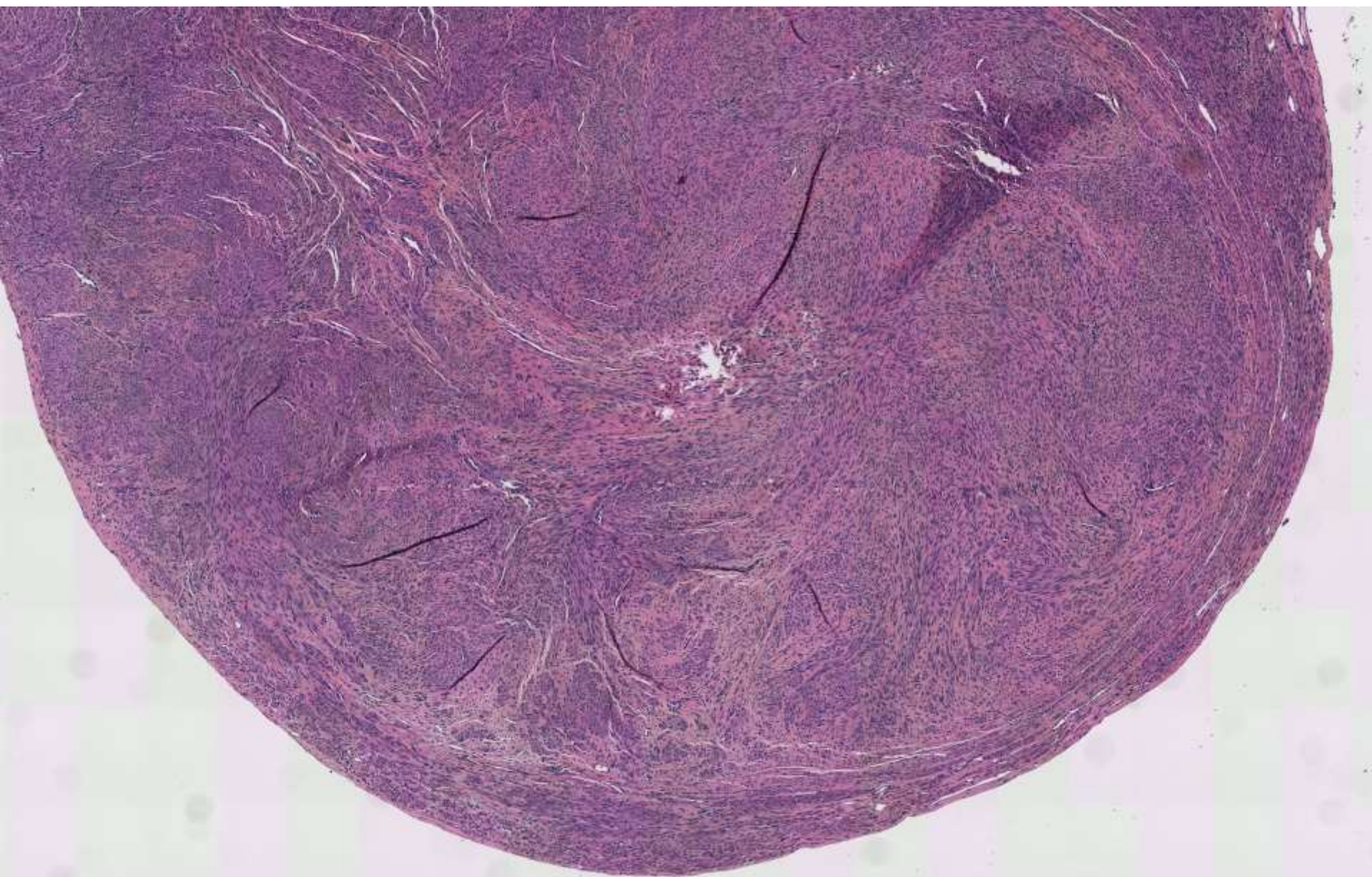




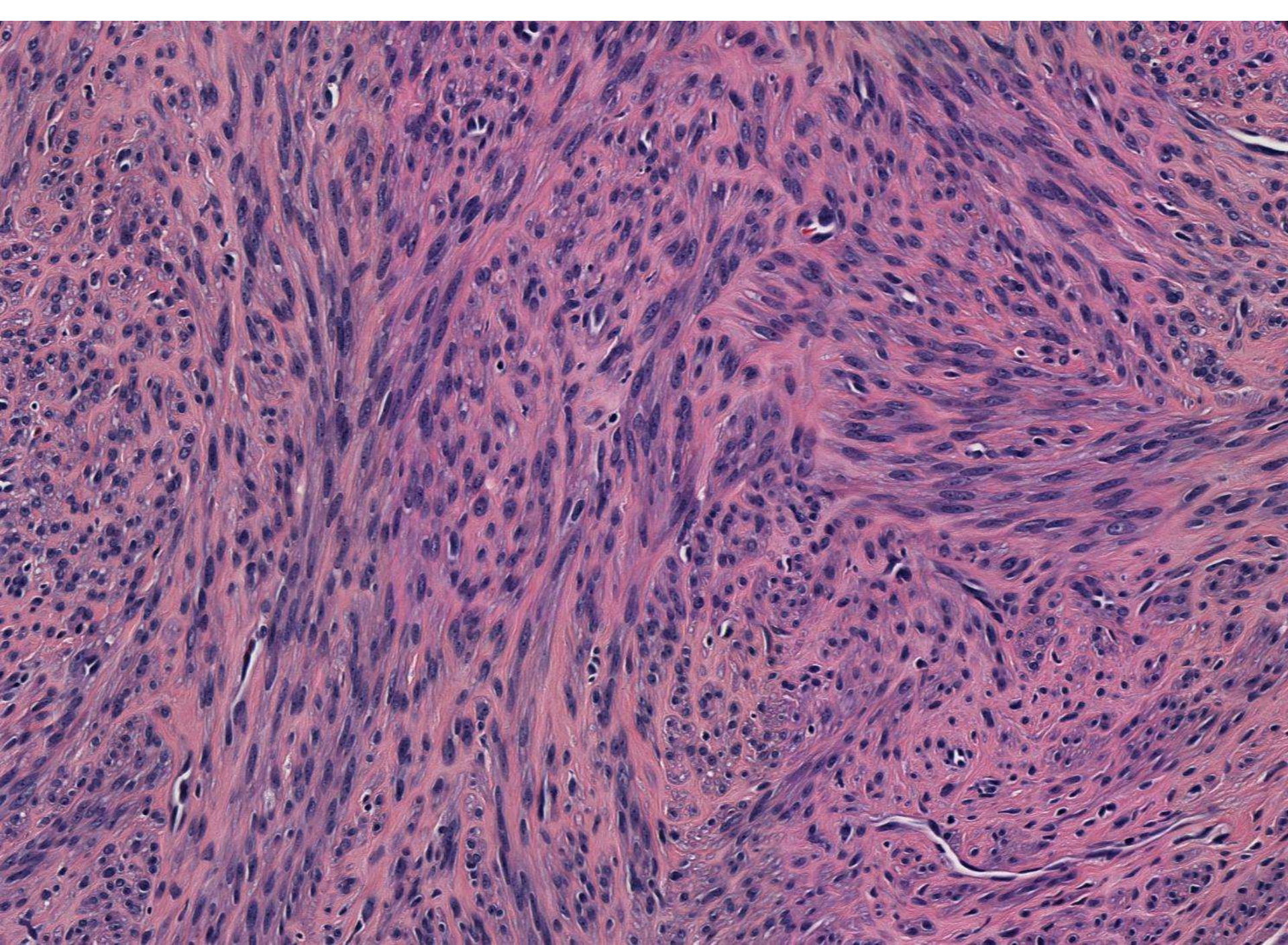














# DIAGNOSIS?







# **Endometriosis and smooth muscle**

- **SM hyperplasia in hollow muscular organs**
  - **Uterus with adenomyosis**
  - **Colon and appendix**
- **SM metaplasia of endometrioid stromal cells**
  - **Endometrial adenomyomatous polyp**
  - **Pelvic peritoneum and other sites**
- **Nodular hyperplasia of SM**







# Tonight's case breaker theme: (thanks Hannes!)

**It's time again for the annual " Stella Awards"! For those unfamiliar with these awards, they are named after 81 y/o Stella Liebeck who spilled hot coffee on herself and successfully sued the McDonald's in New Mexico, where she purchased coffee (you remember, she took the lid off the coffee and put it between her knees while she was driving...Who would ever think one could get burned doing that, right?)**

That's right! these are awards for the most outlandish lawsuits and verdicts in the U.S. You know, the kinds of cases that make you scratch your head. So keep your head scratcher handy.

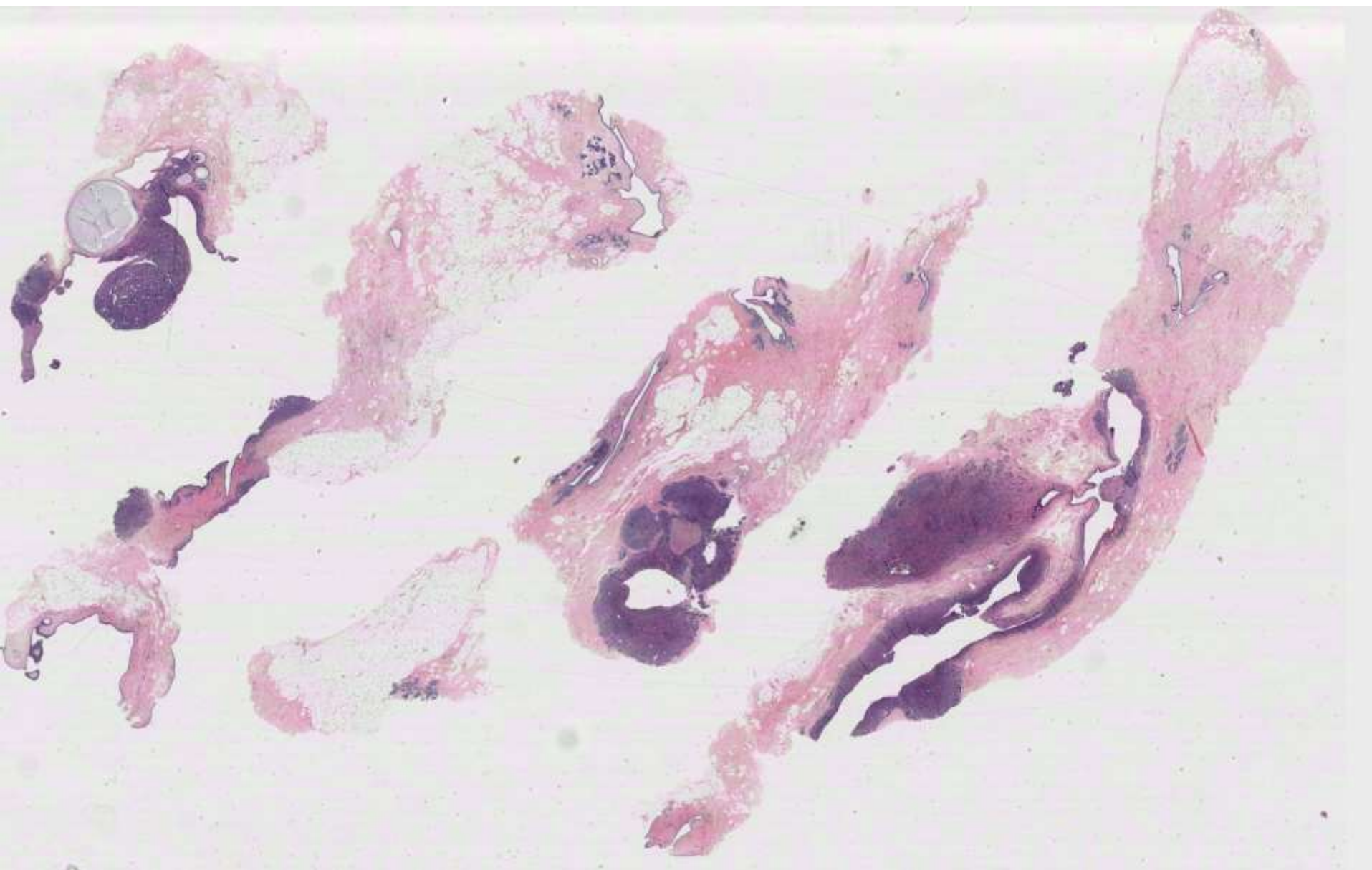
# 19-0702

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Megan Troxell; Stanford

46-year-old woman with h/o  
contralateral breast cancer. Now with  
left breast mass noted on MRI and  
ultrasound.

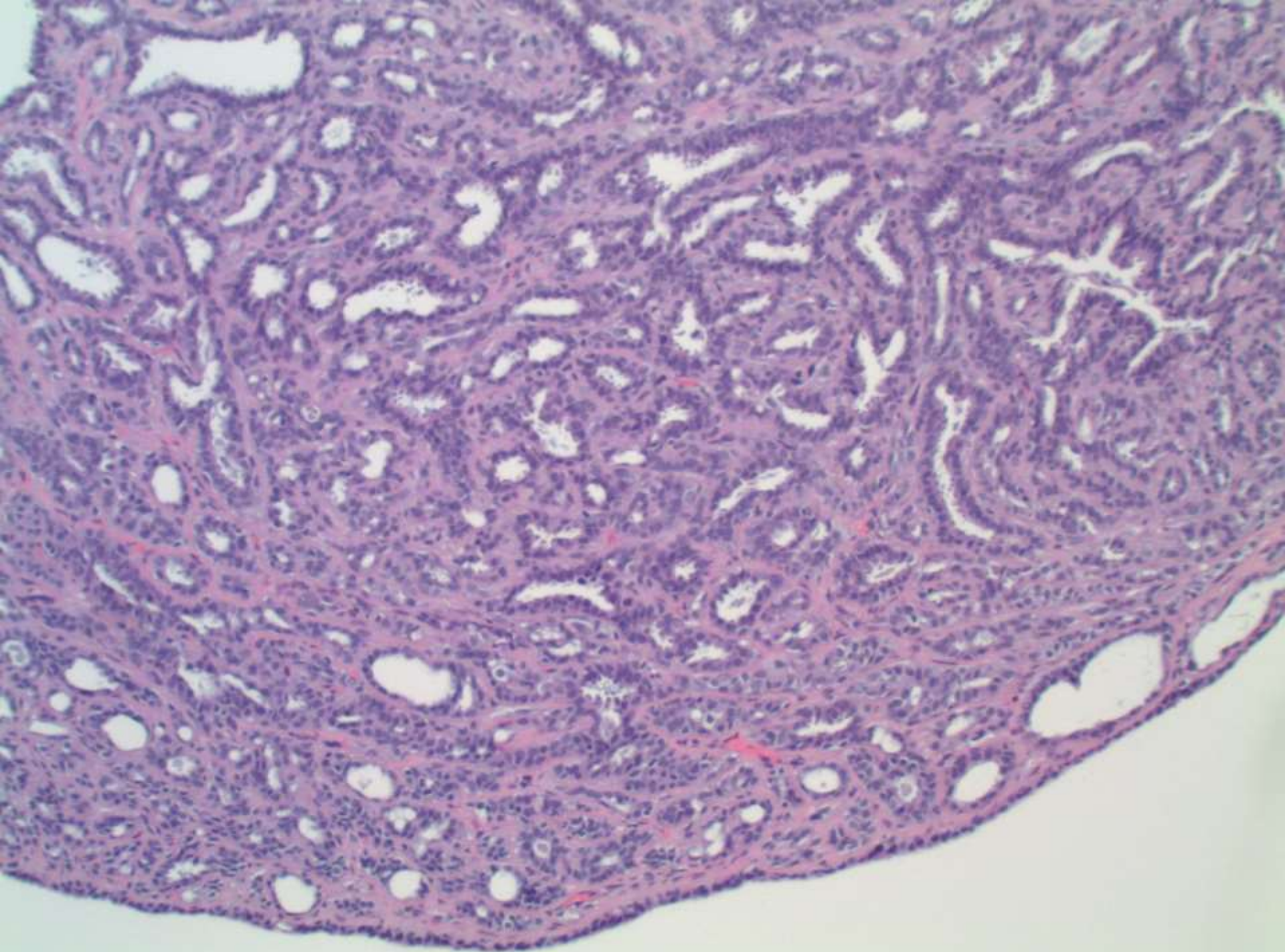




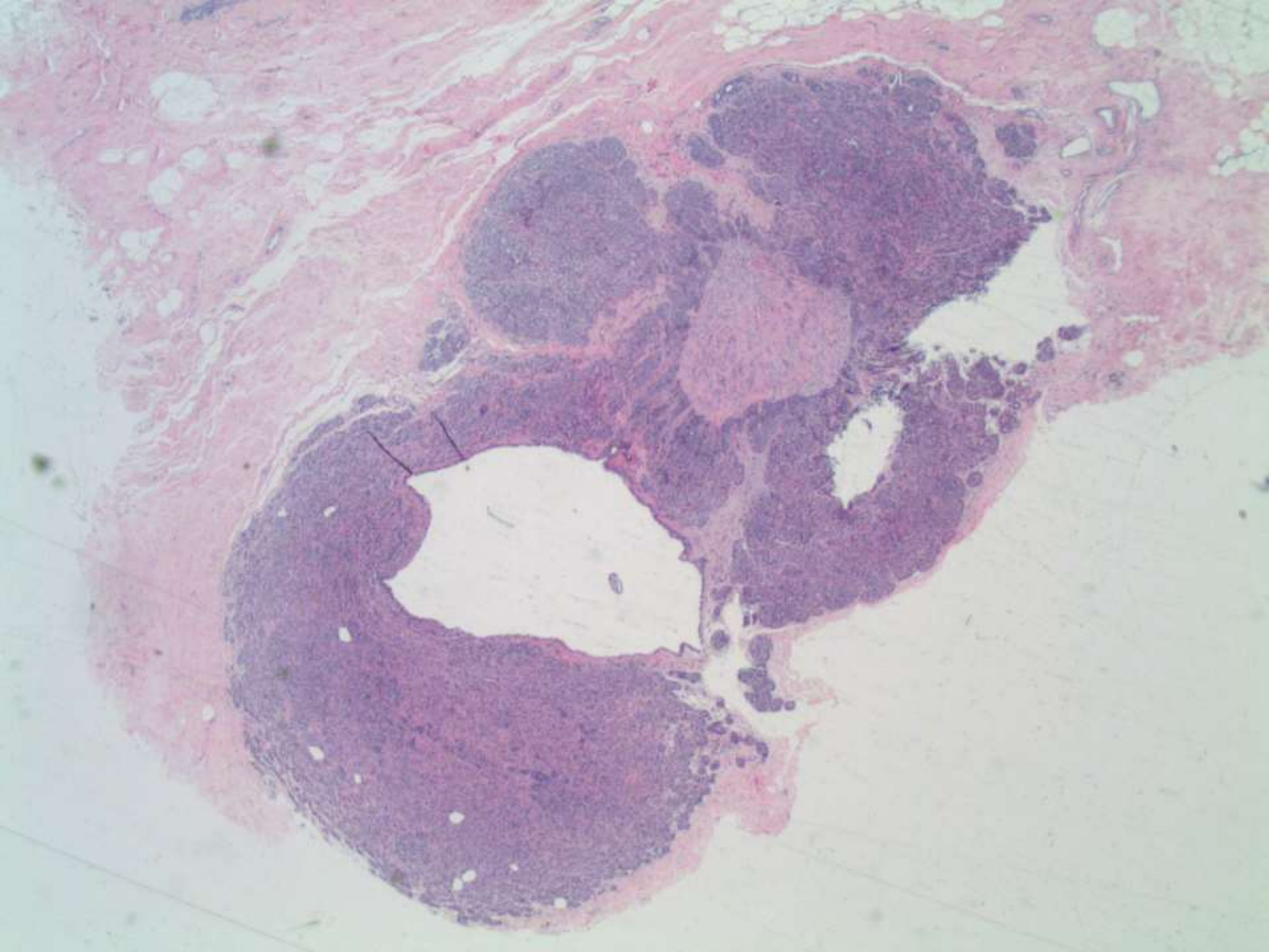




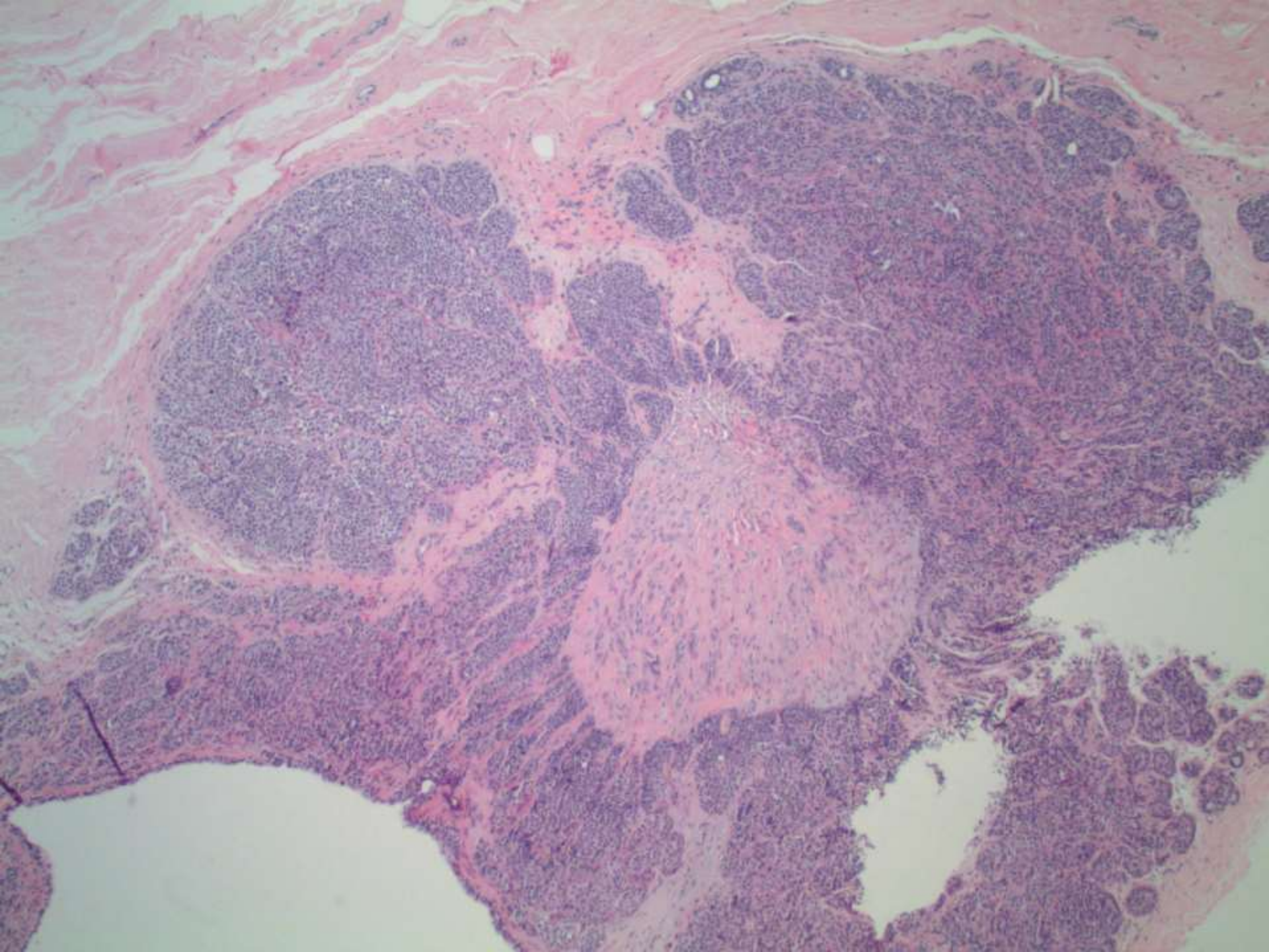




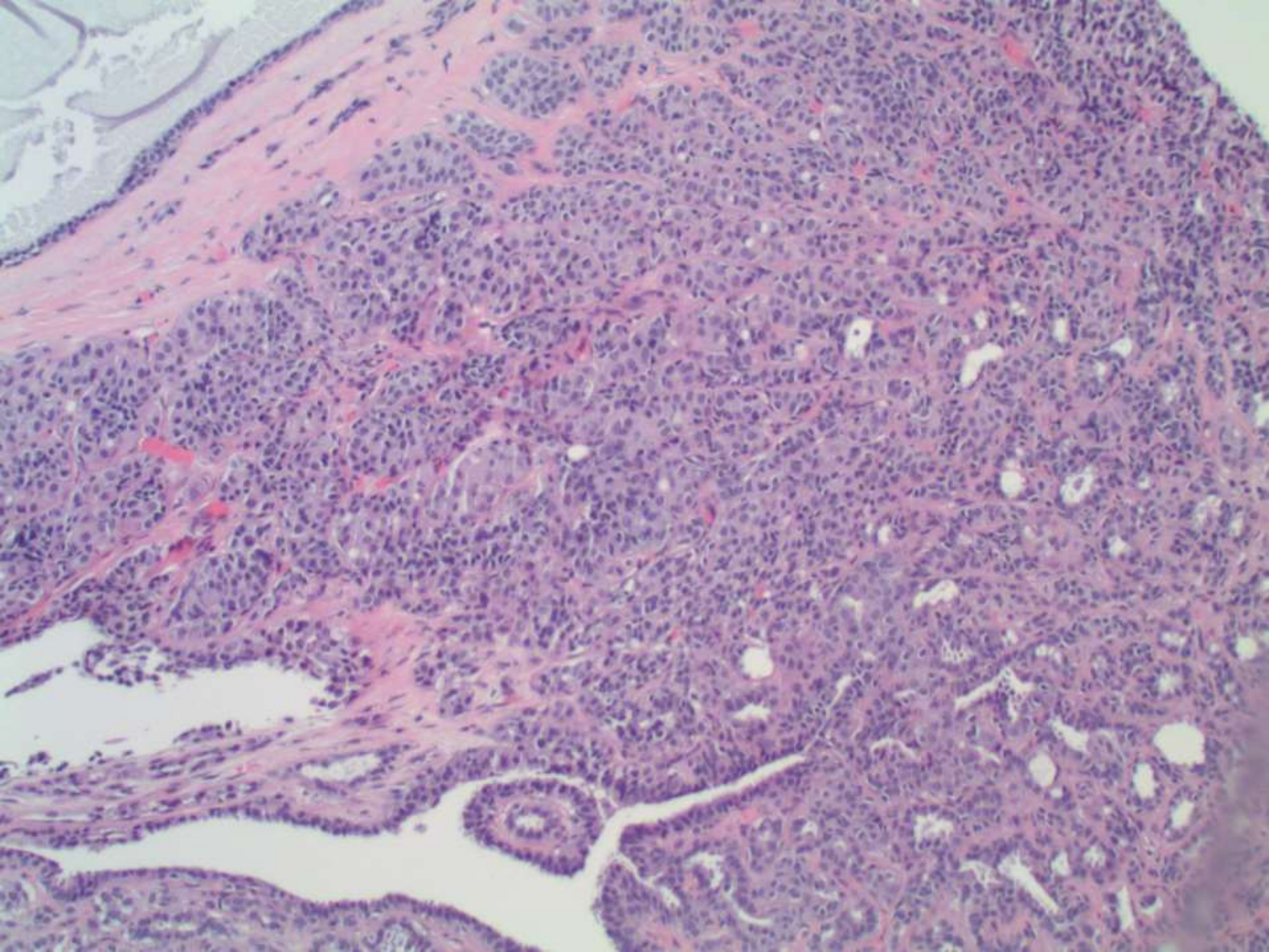




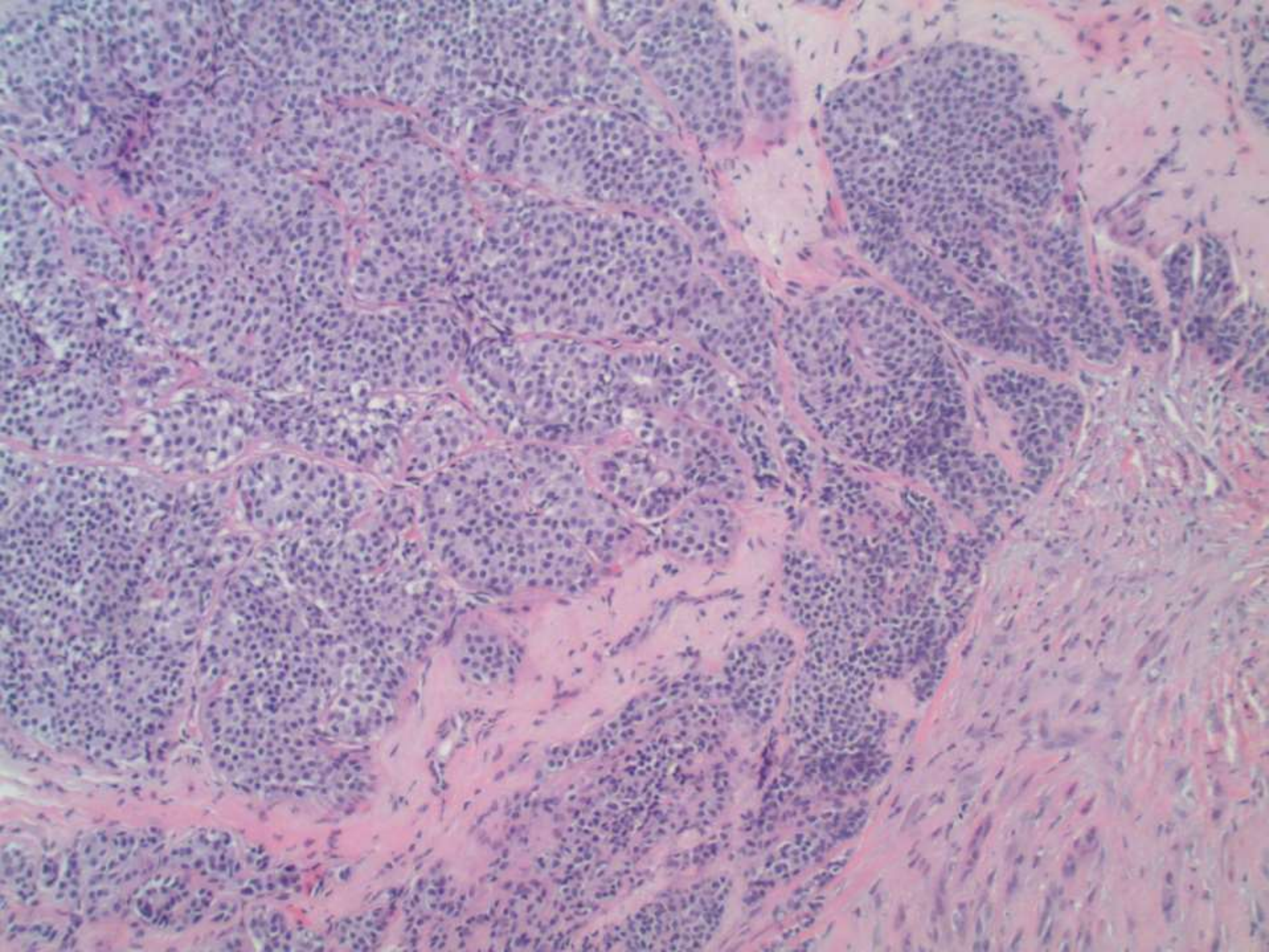




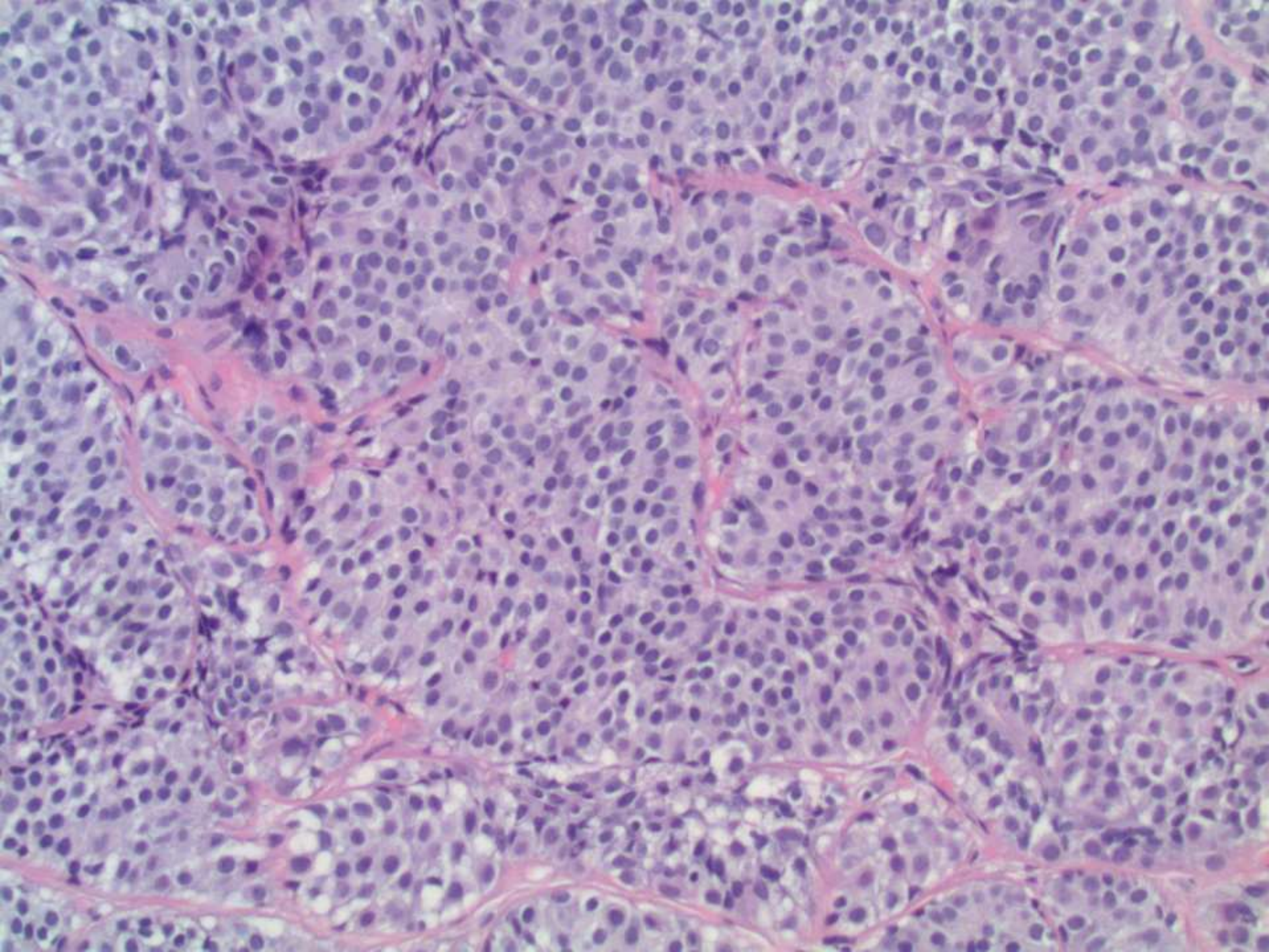




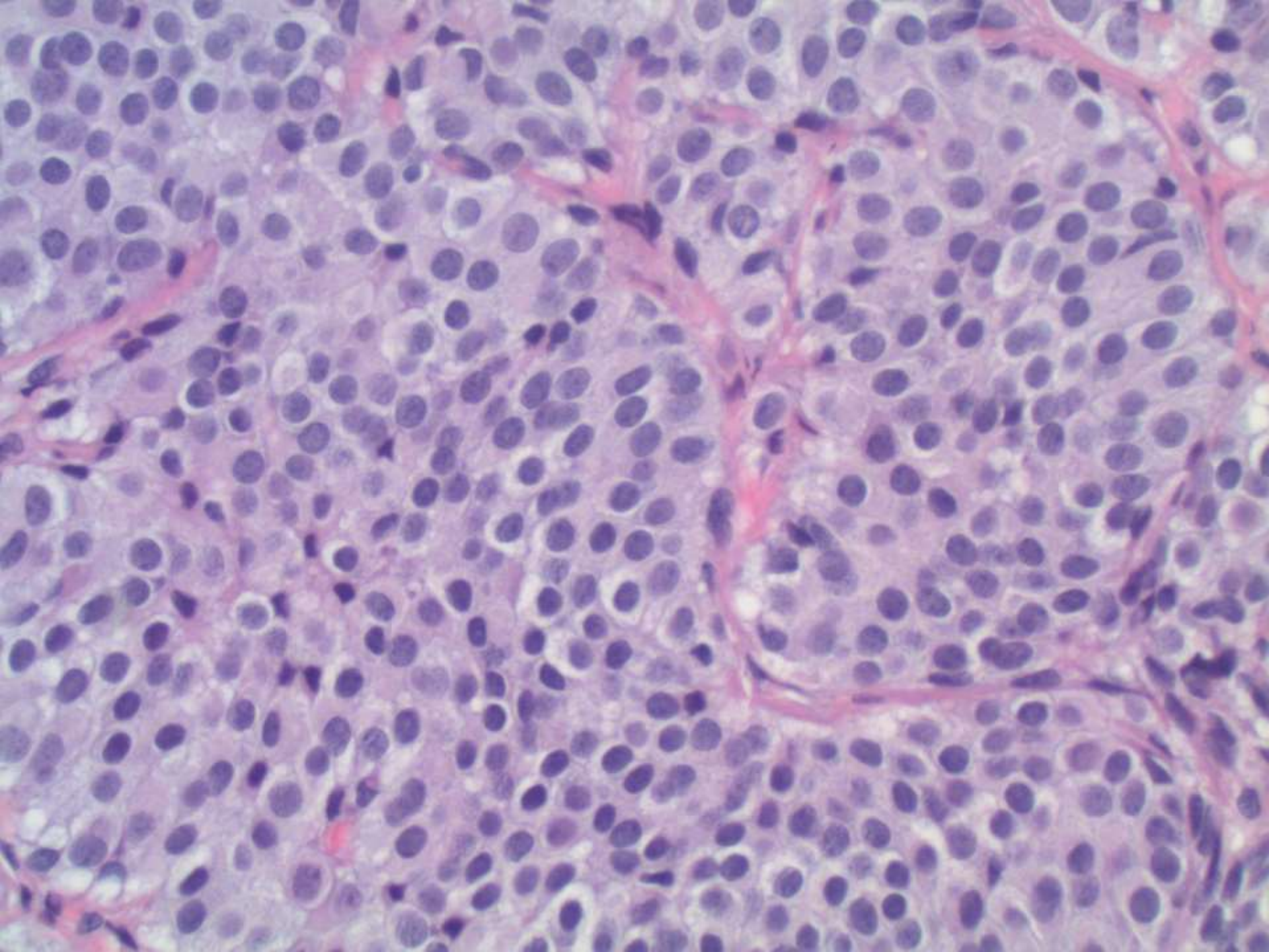




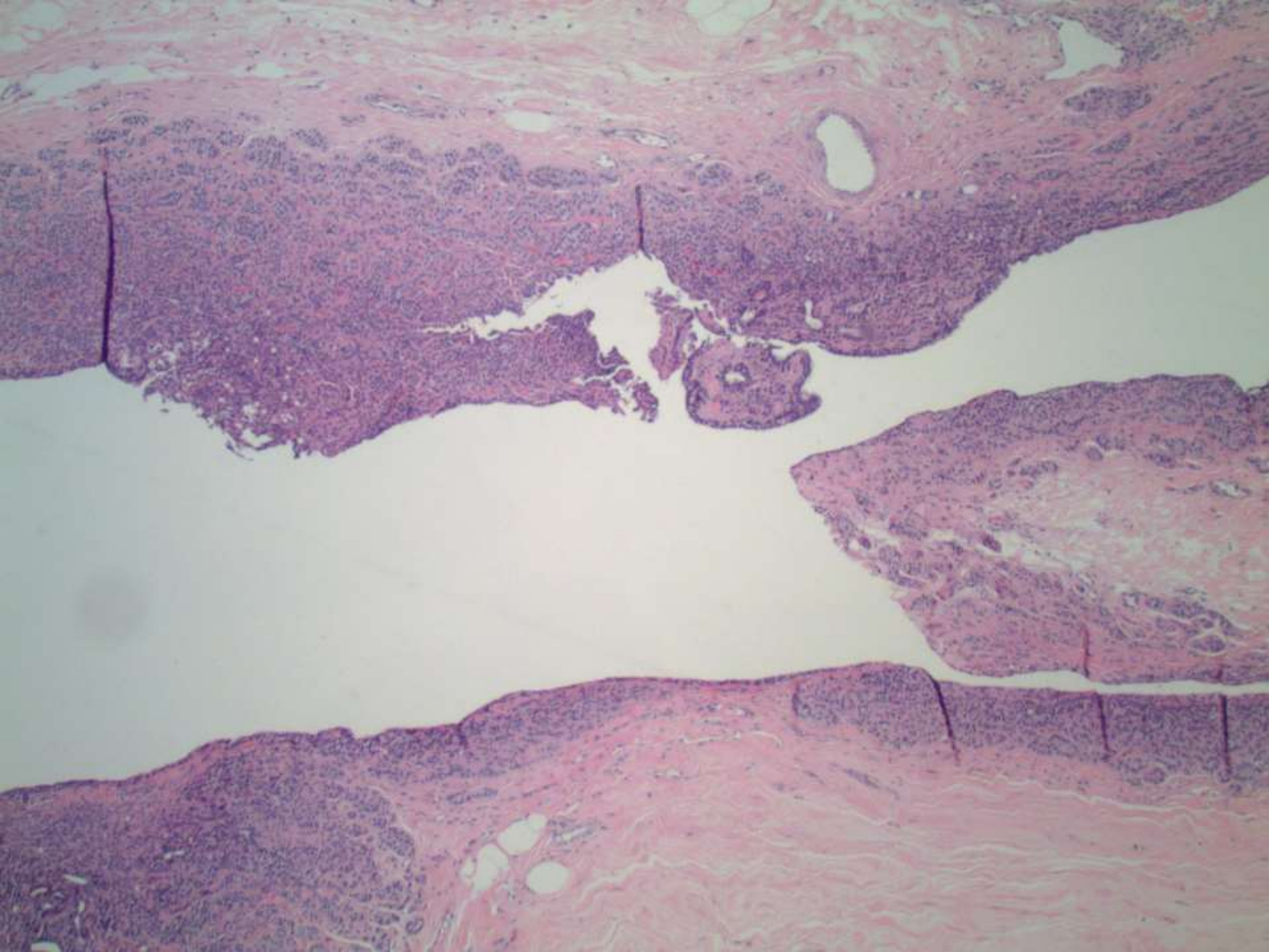




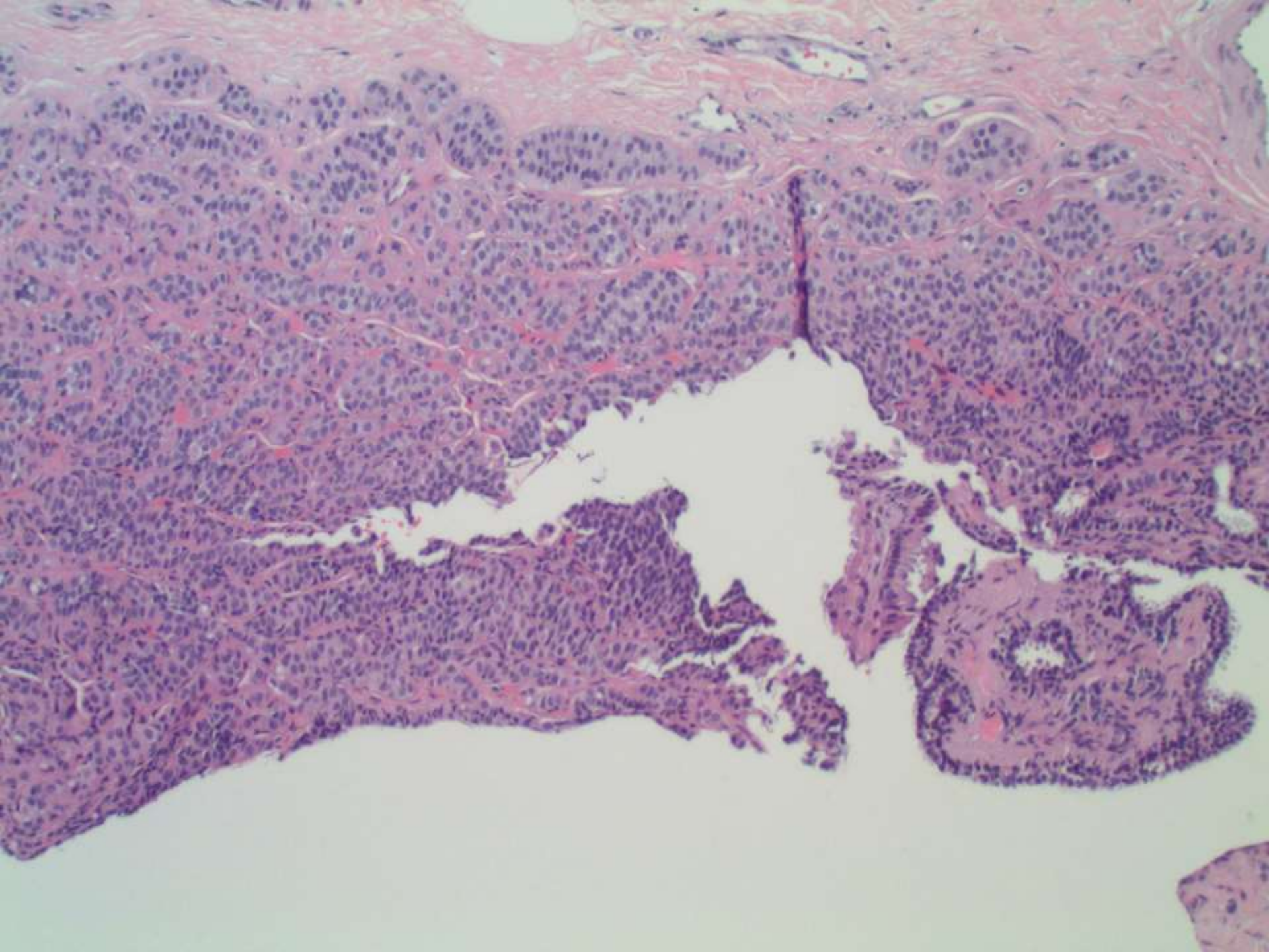




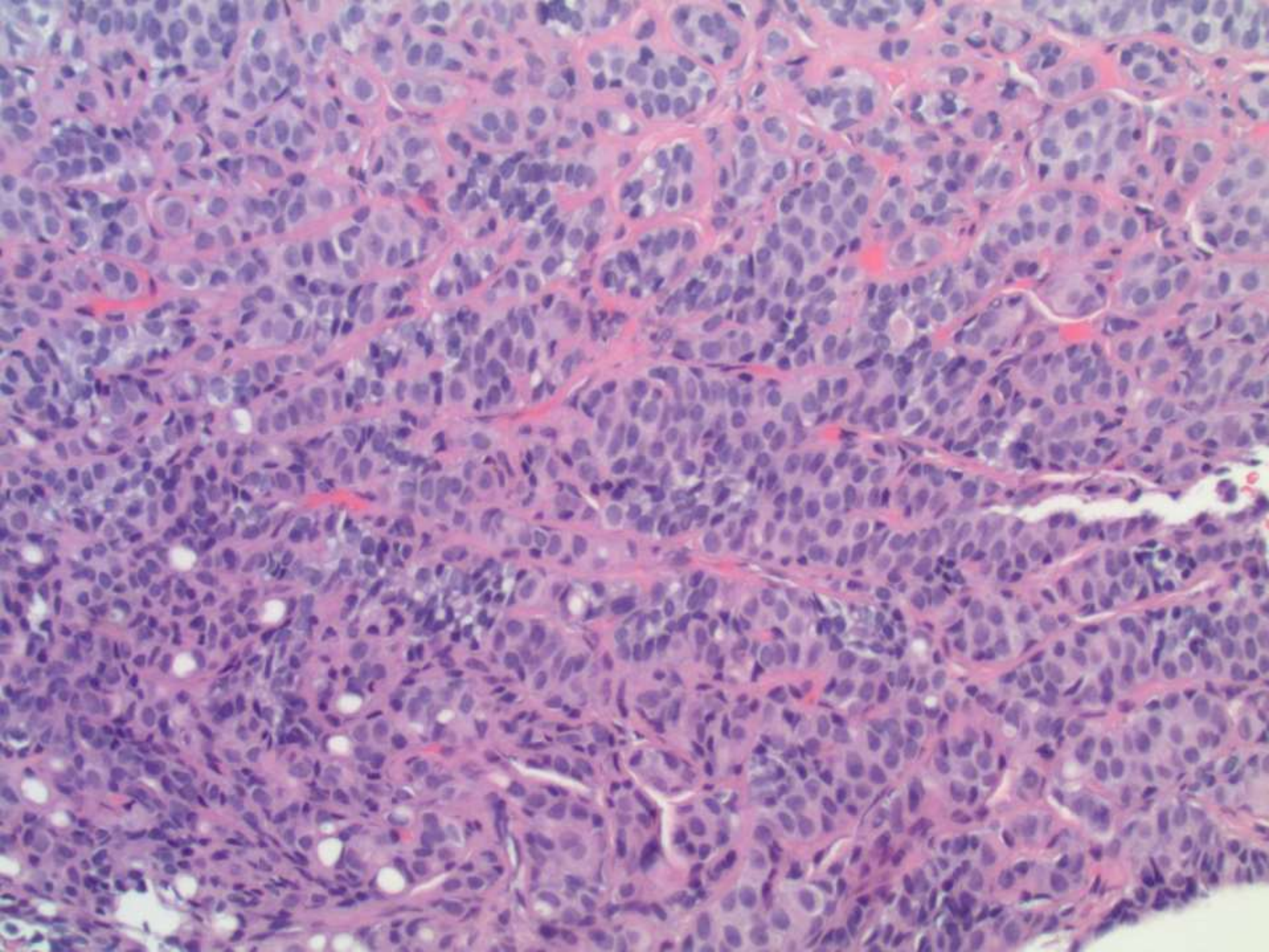




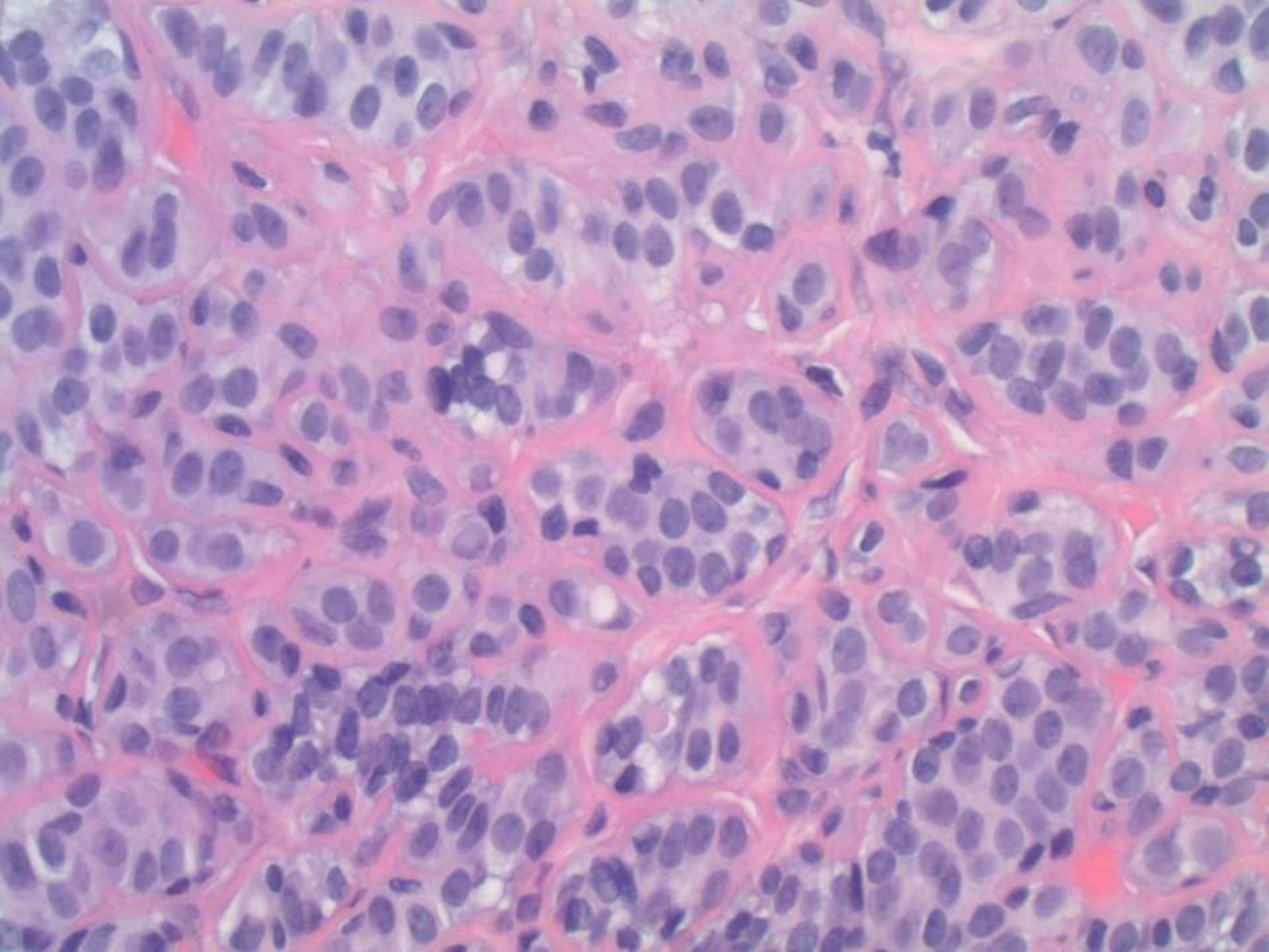




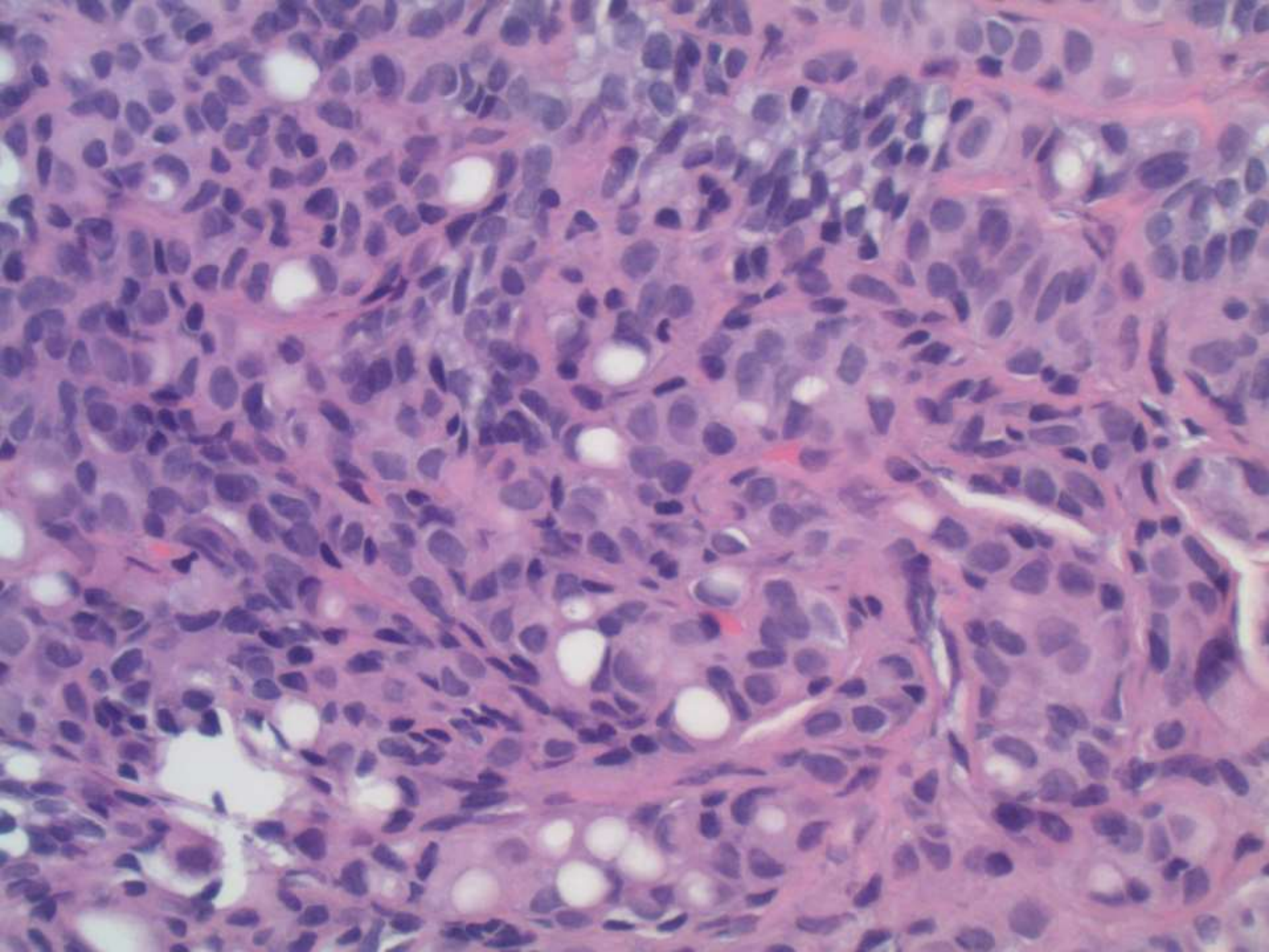




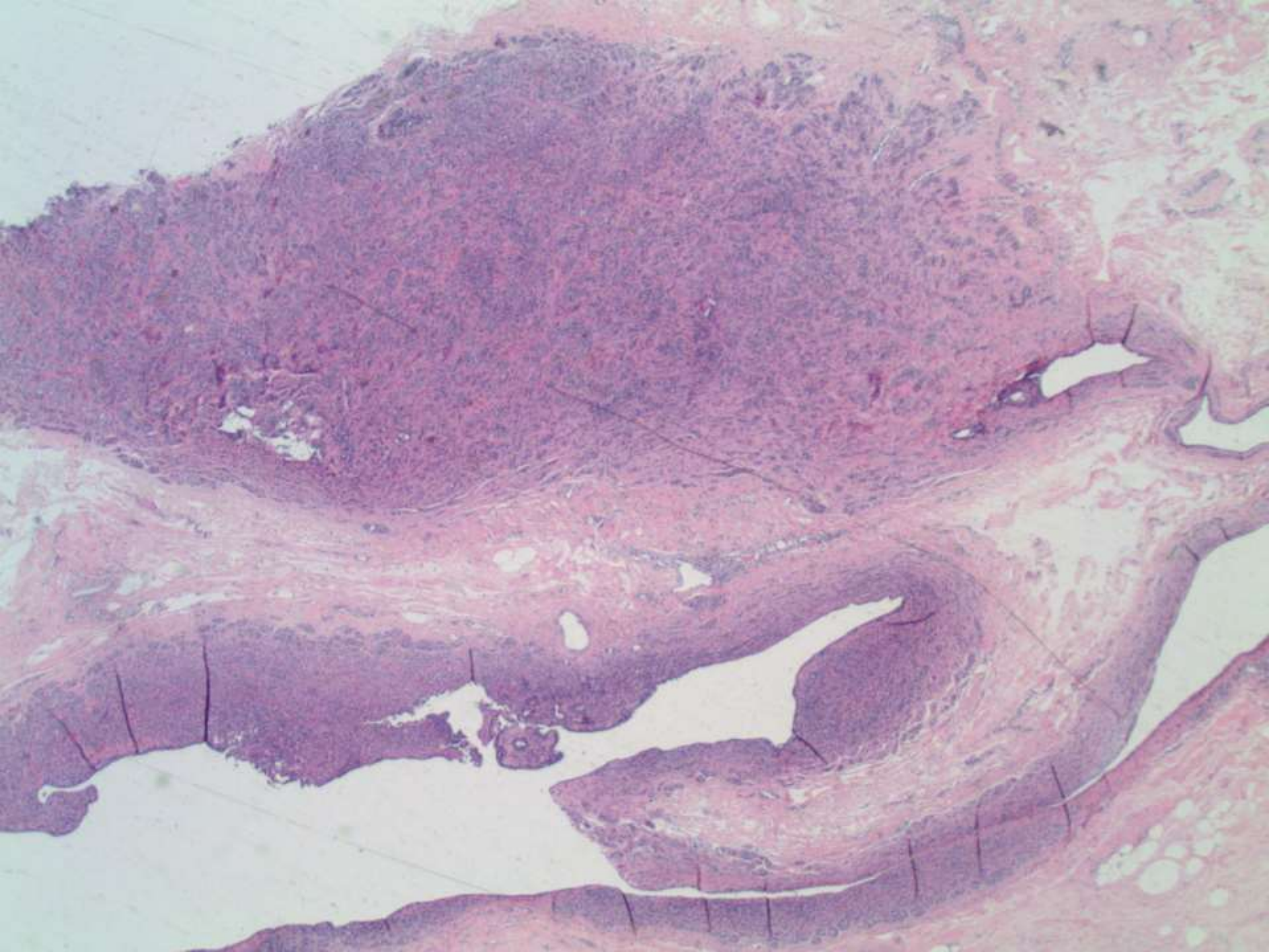




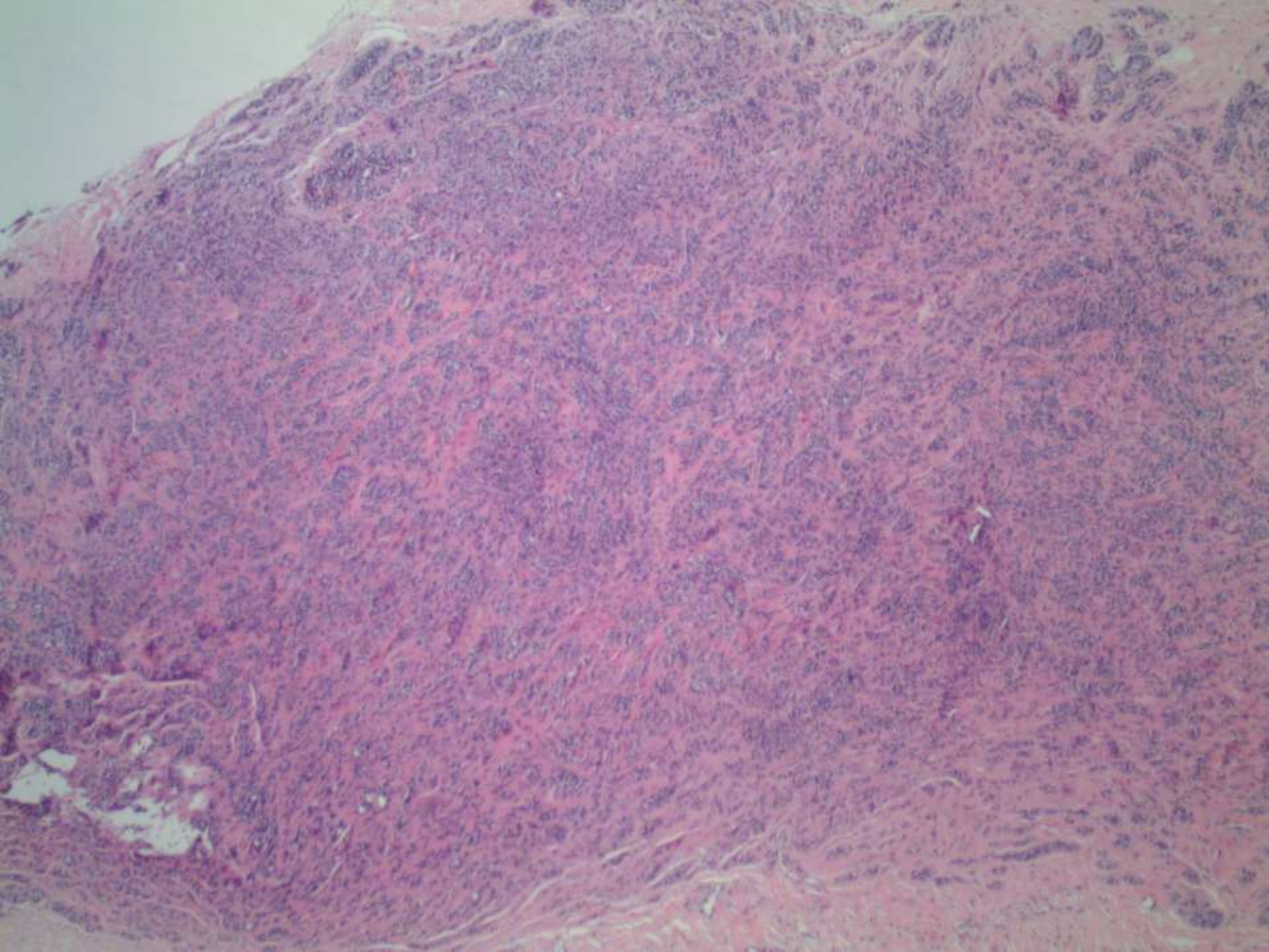




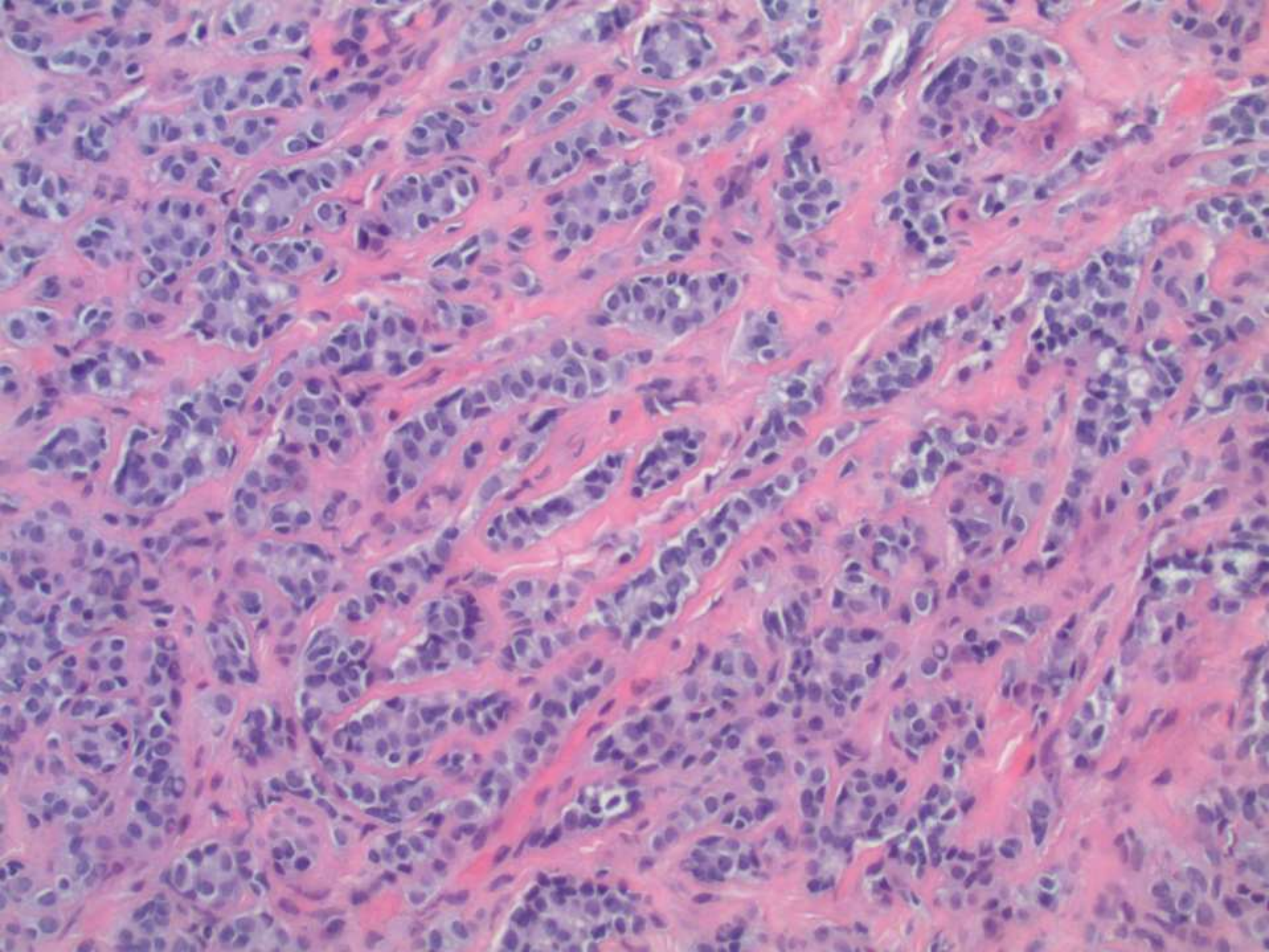




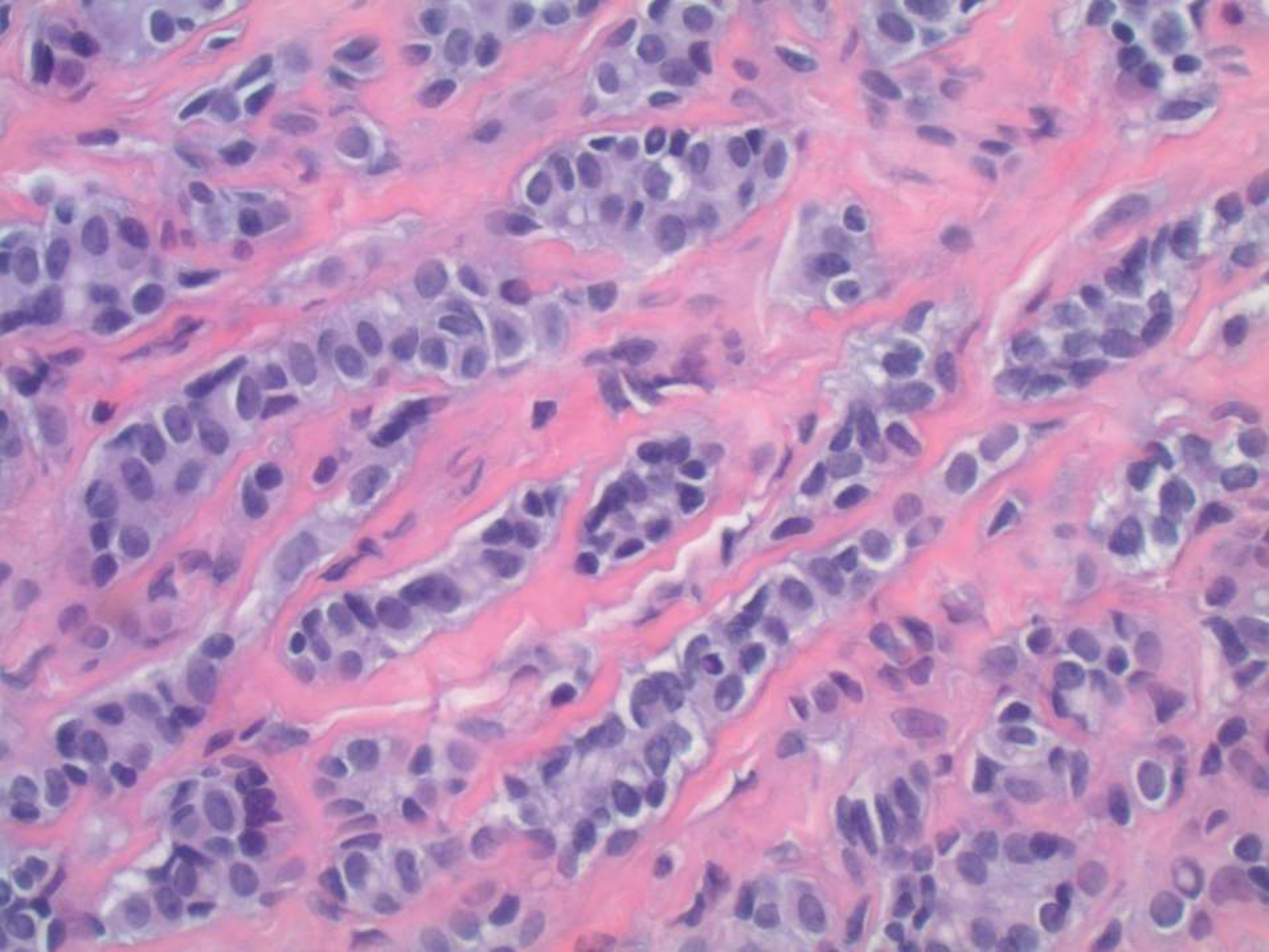














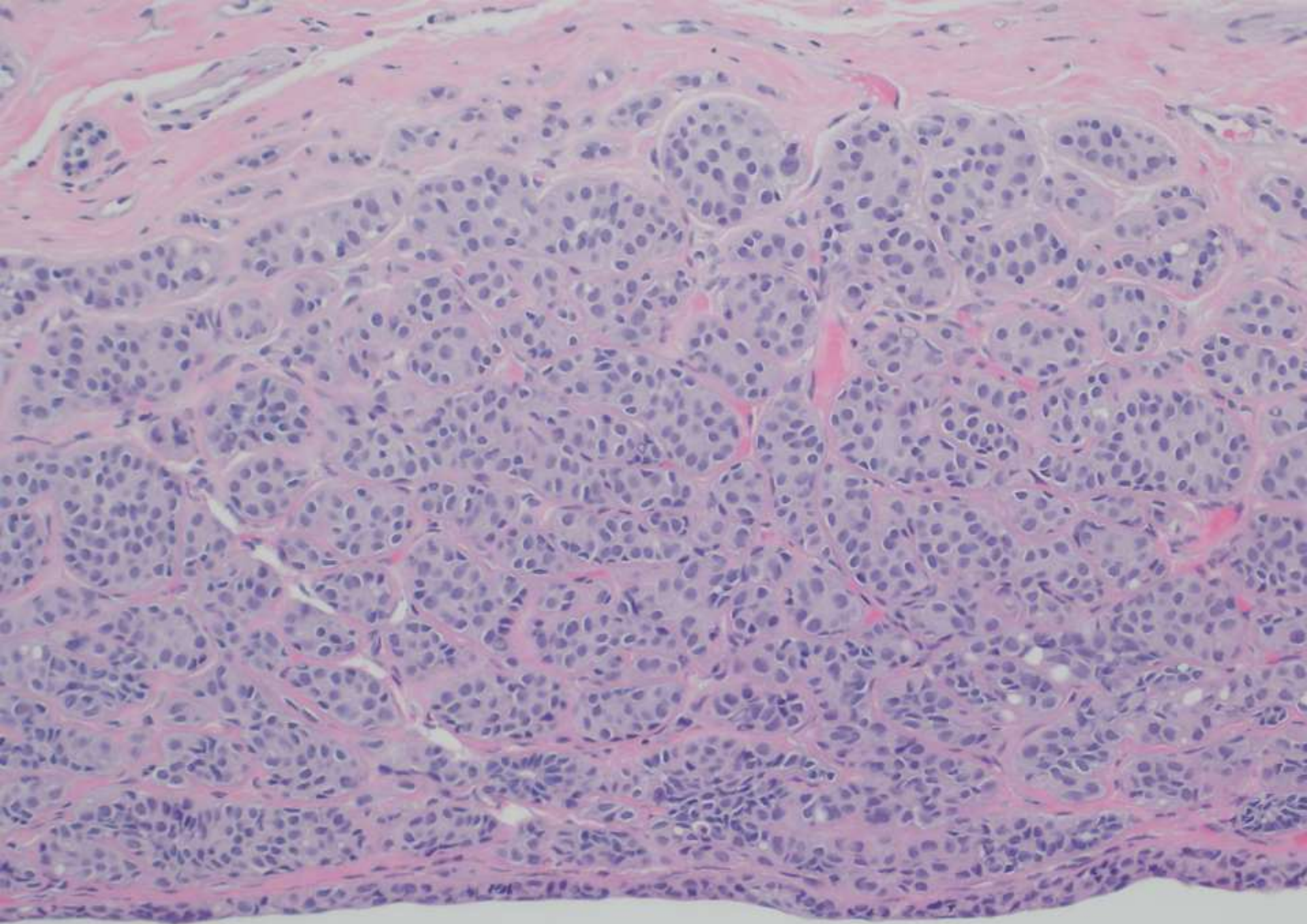
# DIAGNOSIS?



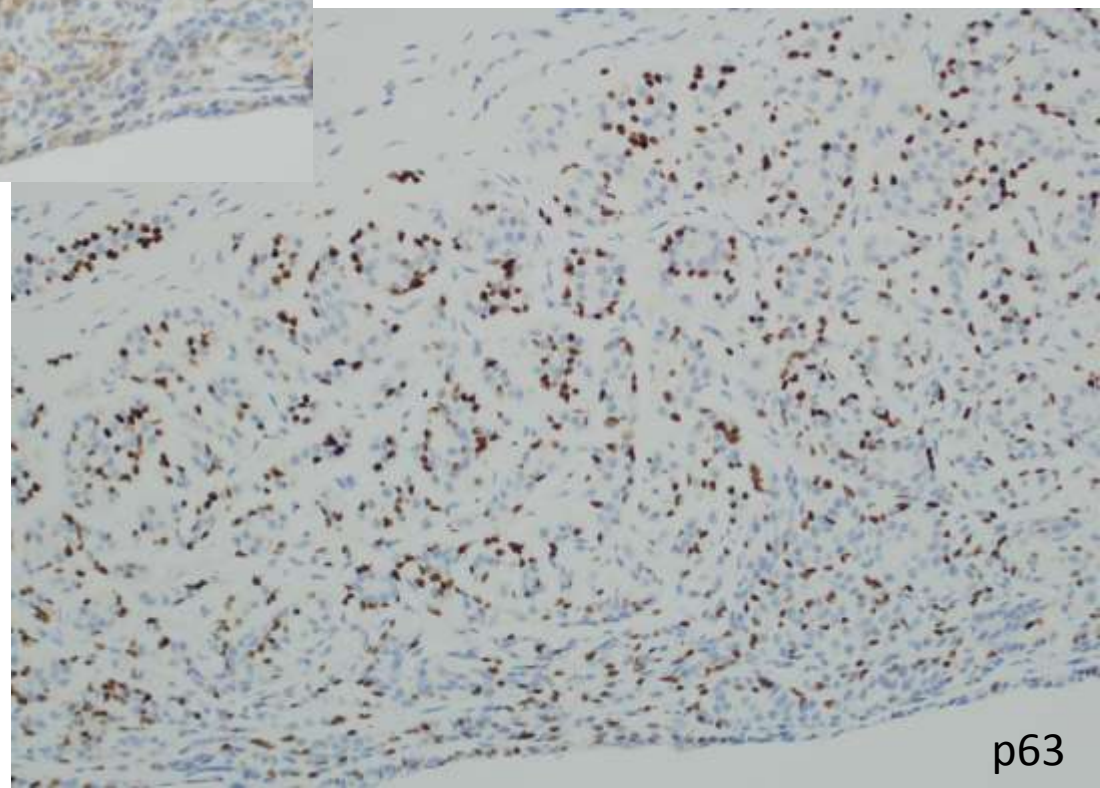
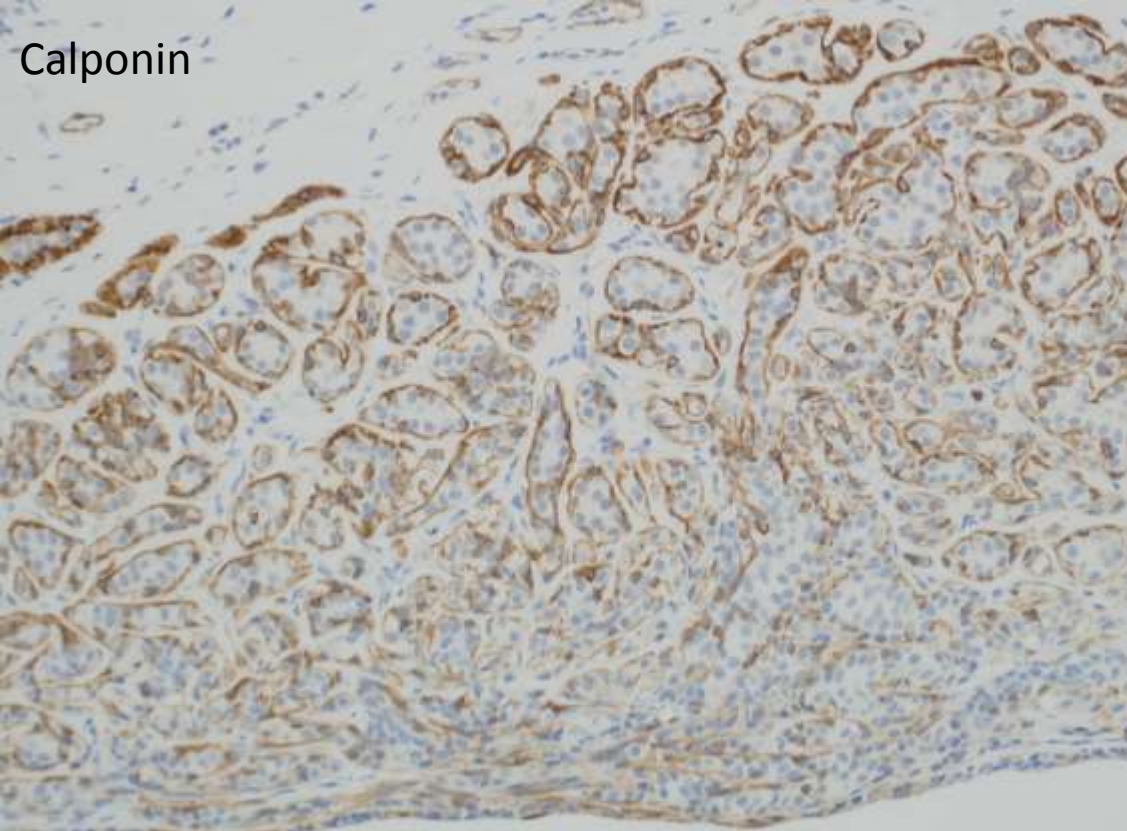




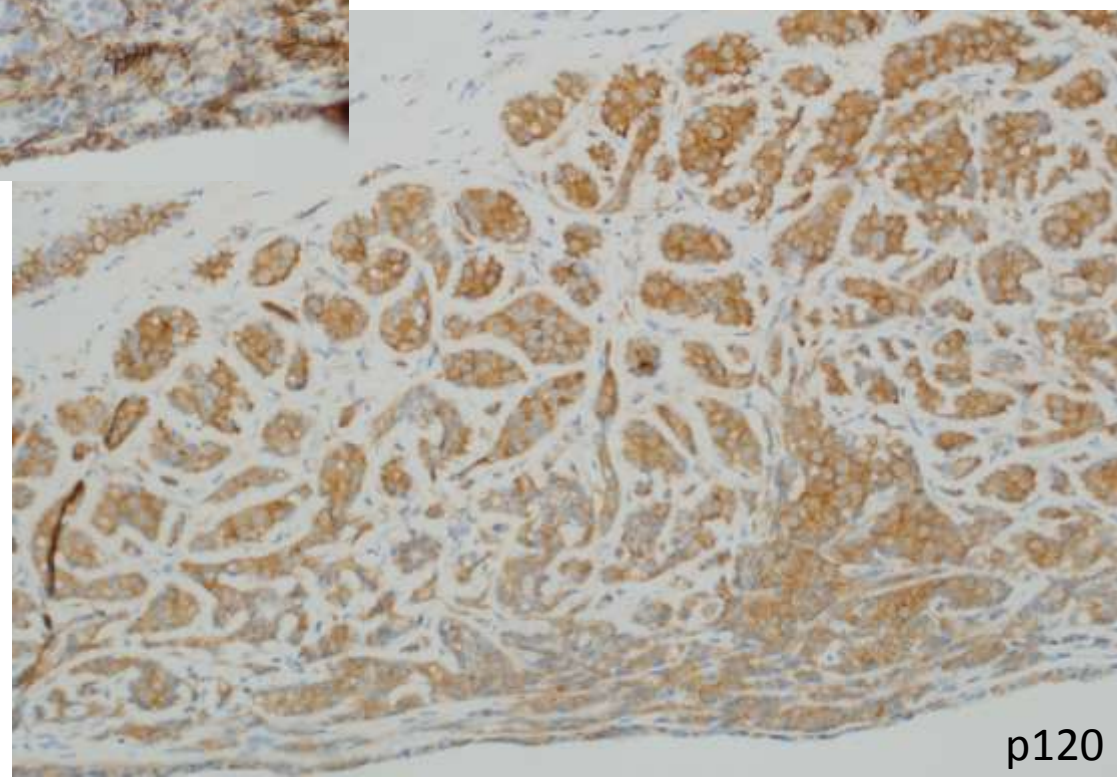
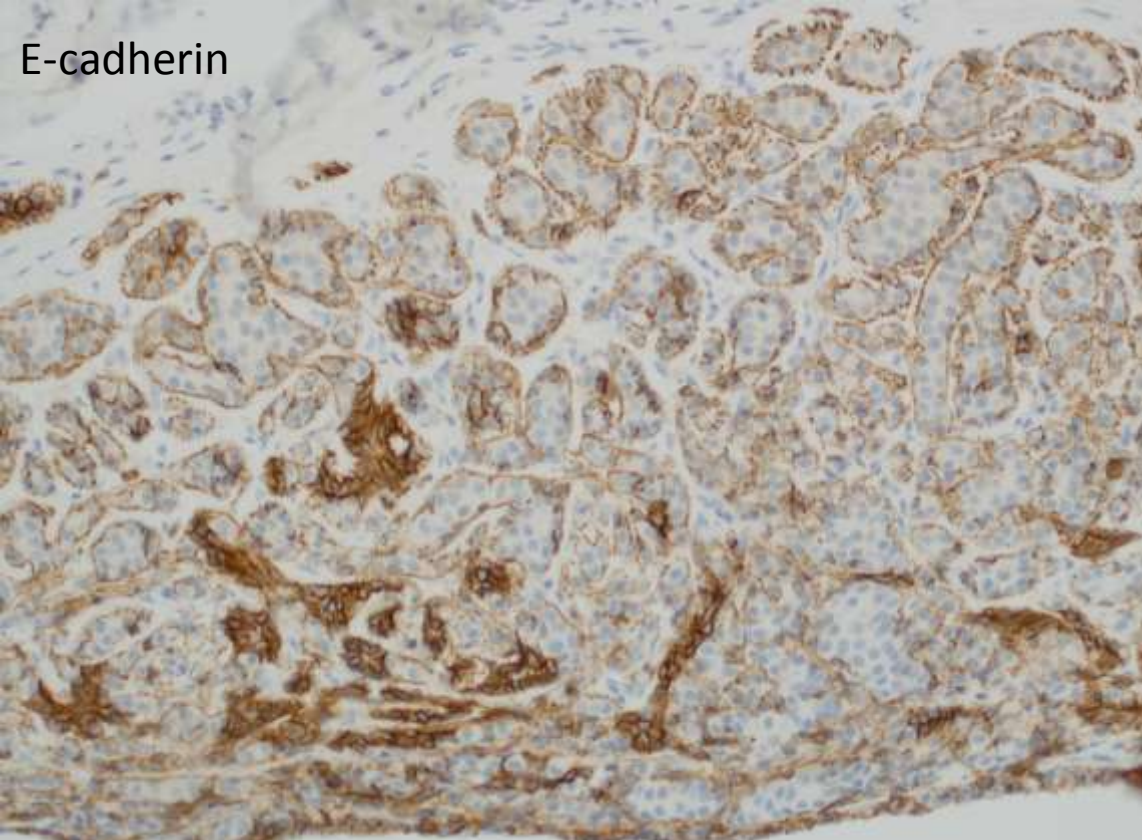




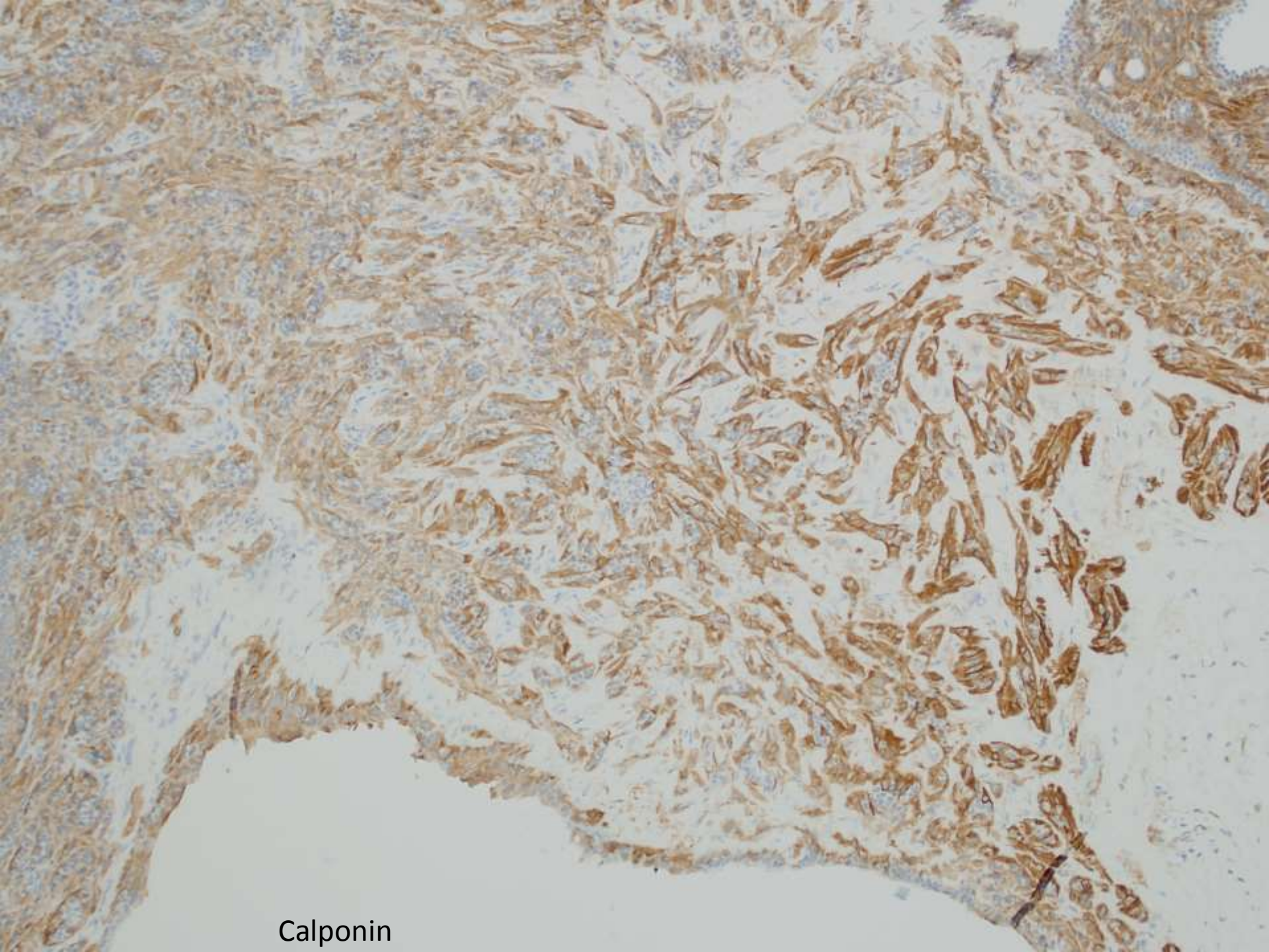






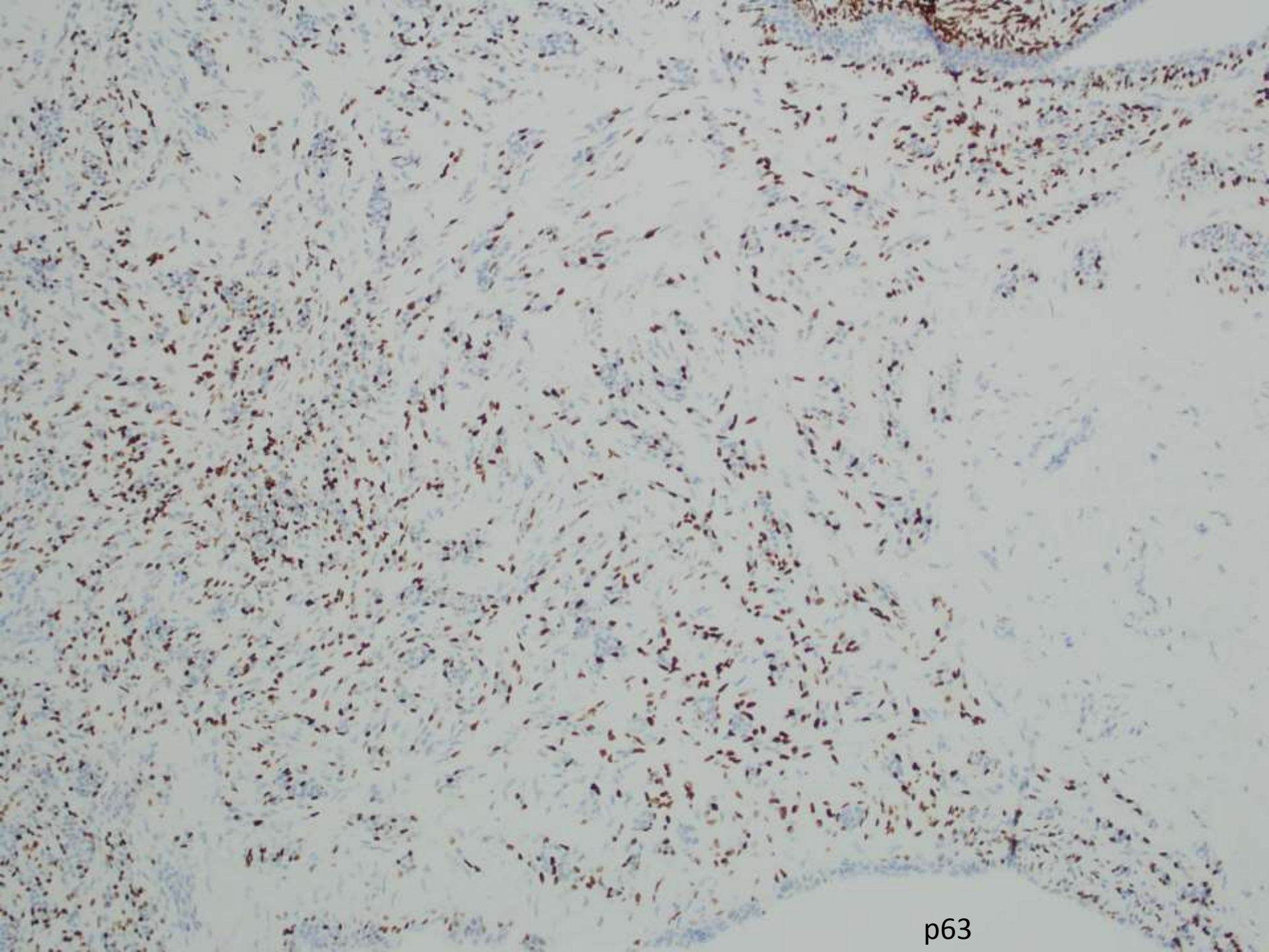






Calponin





p63



# Diagnosis

- Lobular neoplasia
  - LCIS/ALH entrapped in fibrosis/adenosis within & surrounding papillary lesion
- Atypical papillary lesion
- Subsequent resection
  - Extensive LCIS
  - Intraductal papilloma with UDH
  - No invasive carcinoma identified



# Lobular neoplasia in situ

- LCIS/ALH colonizing papilloma
  - DDx: hyperplastic myoepithelium, dimorphic papillary carcinoma, ADH/DCIS
- LCIS/ALH colonizing sclerosing adenosis
  - Usually background of sclerosing adenosis
  - Core bx can mimic invasive lesion

Yu et al.	SA + DCIS	SA + LCIS	SA + both
SA w/ CIS n=163	83%	12%	5%

Yu B-H, et al. J Clin Pathol 2018;71:546–553.

Koerner F, Maluf H. Uncommon morphologic patterns of lobular neoplasia.  
Ann Diagn Pathol. 1999;3:249-59



# SEVENTH PLACE

- Kathleen Robertson of Austin, Texas was awarded \$80,000 by a jury of her peers after breaking her ankle tripping over a toddler who was running inside a furniture store. The store owners were understandably surprised by the verdict, considering the running toddler was her own son.

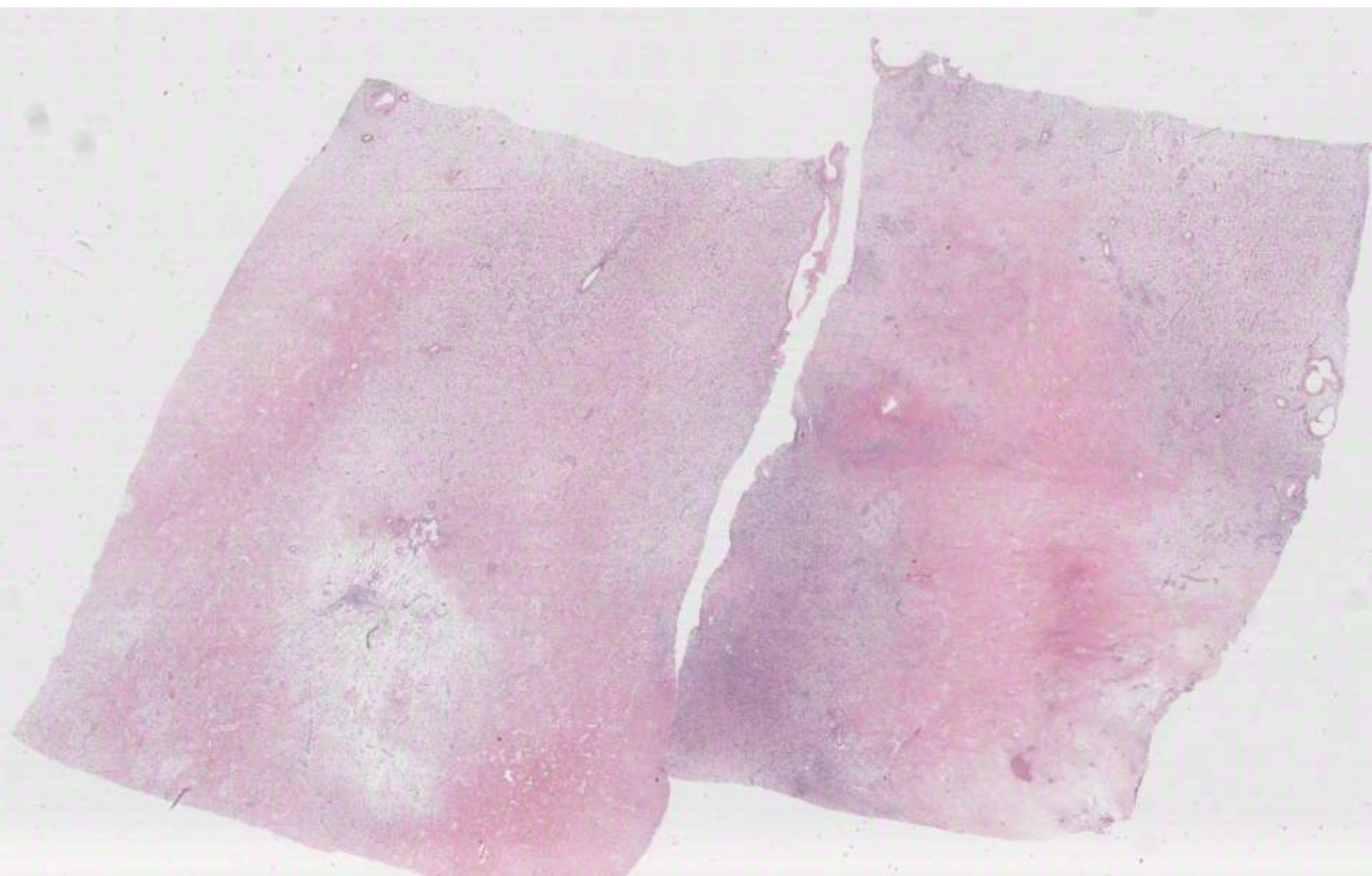
# 19-0703

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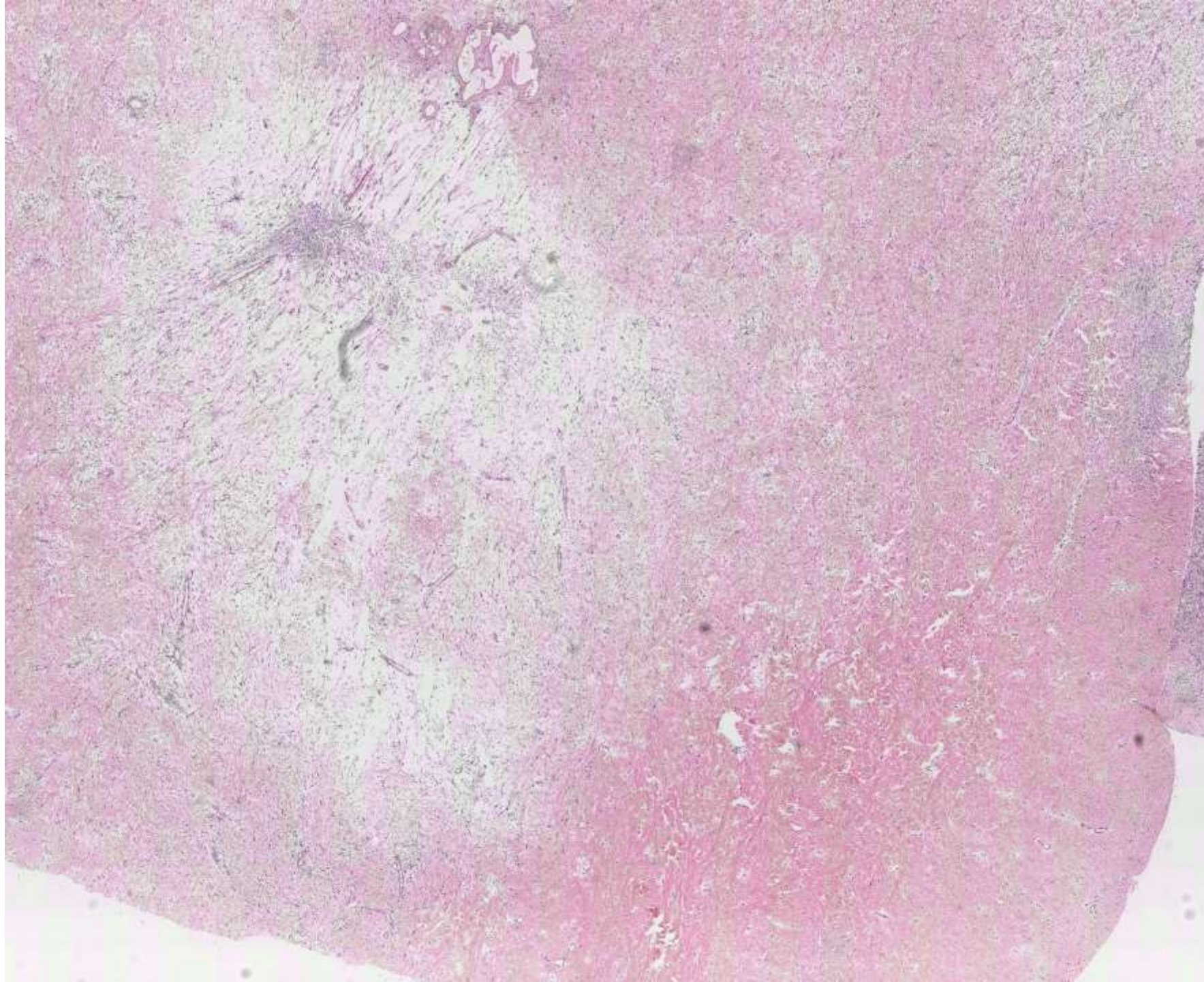
Balaram Puligandla; Kaiser Oakland

62-year-old woman with h/o breast cancer in 1994, s/p mastectomy, chemo/radiation now with a large left pleural/chest wall mass.

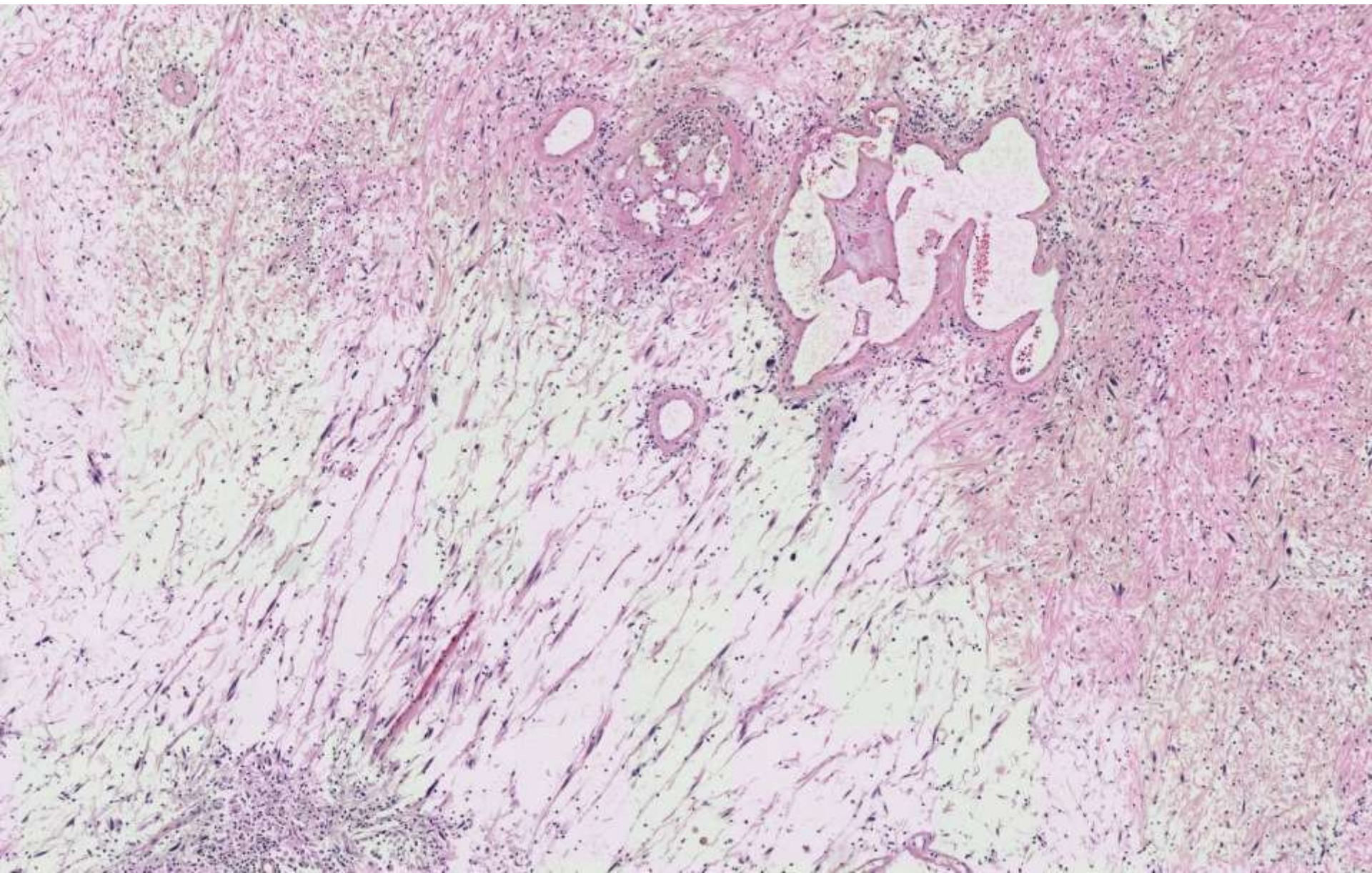




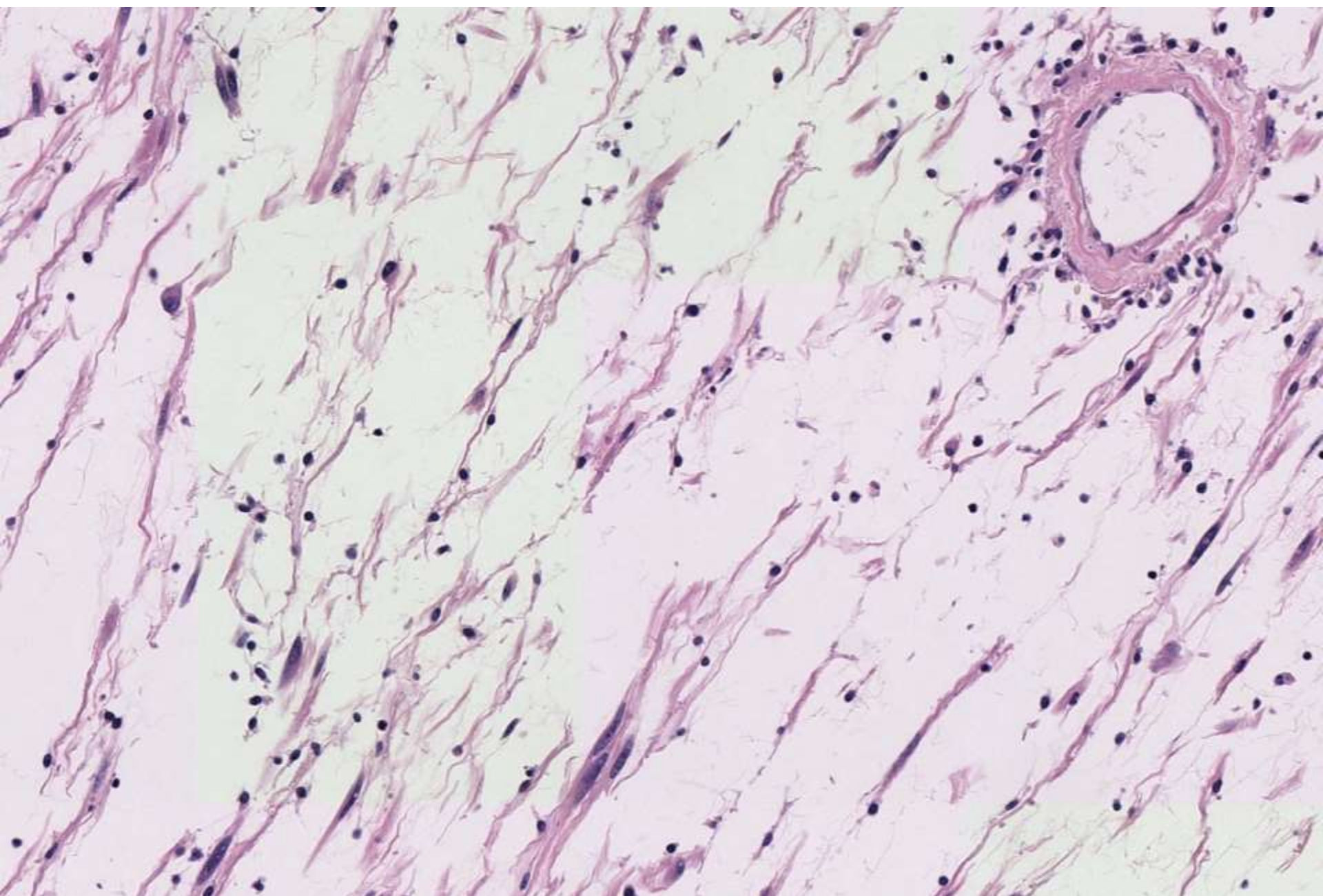




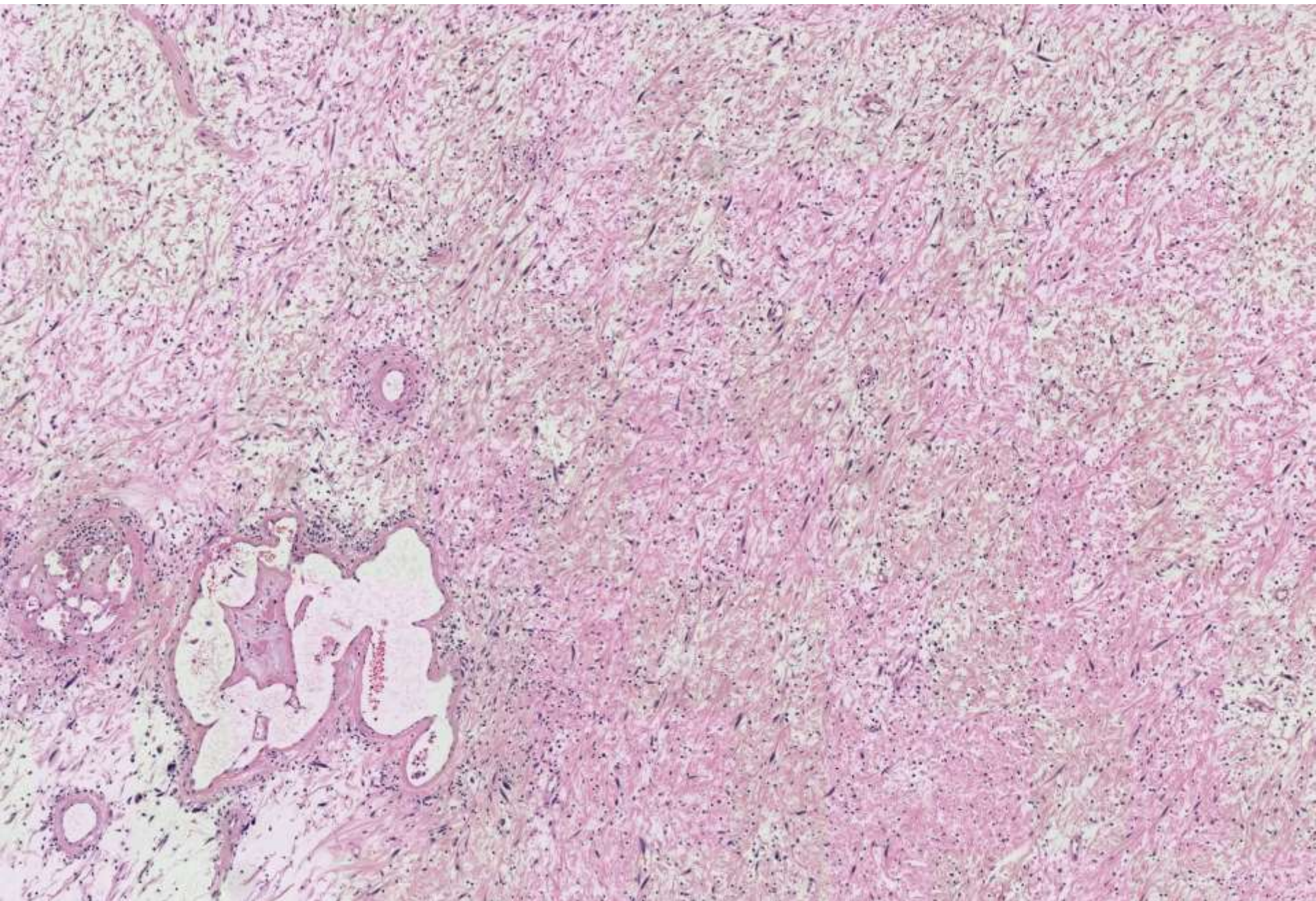




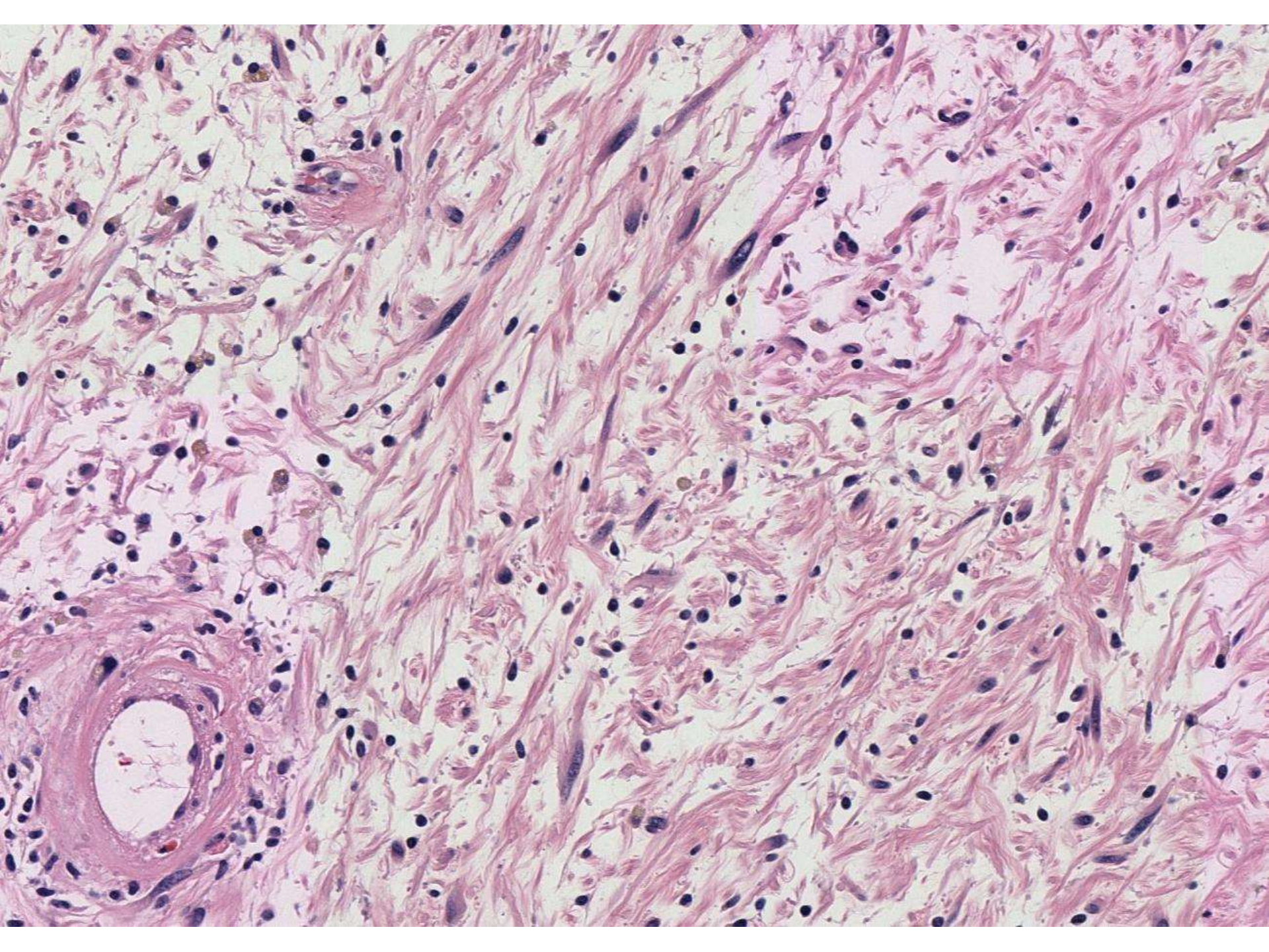




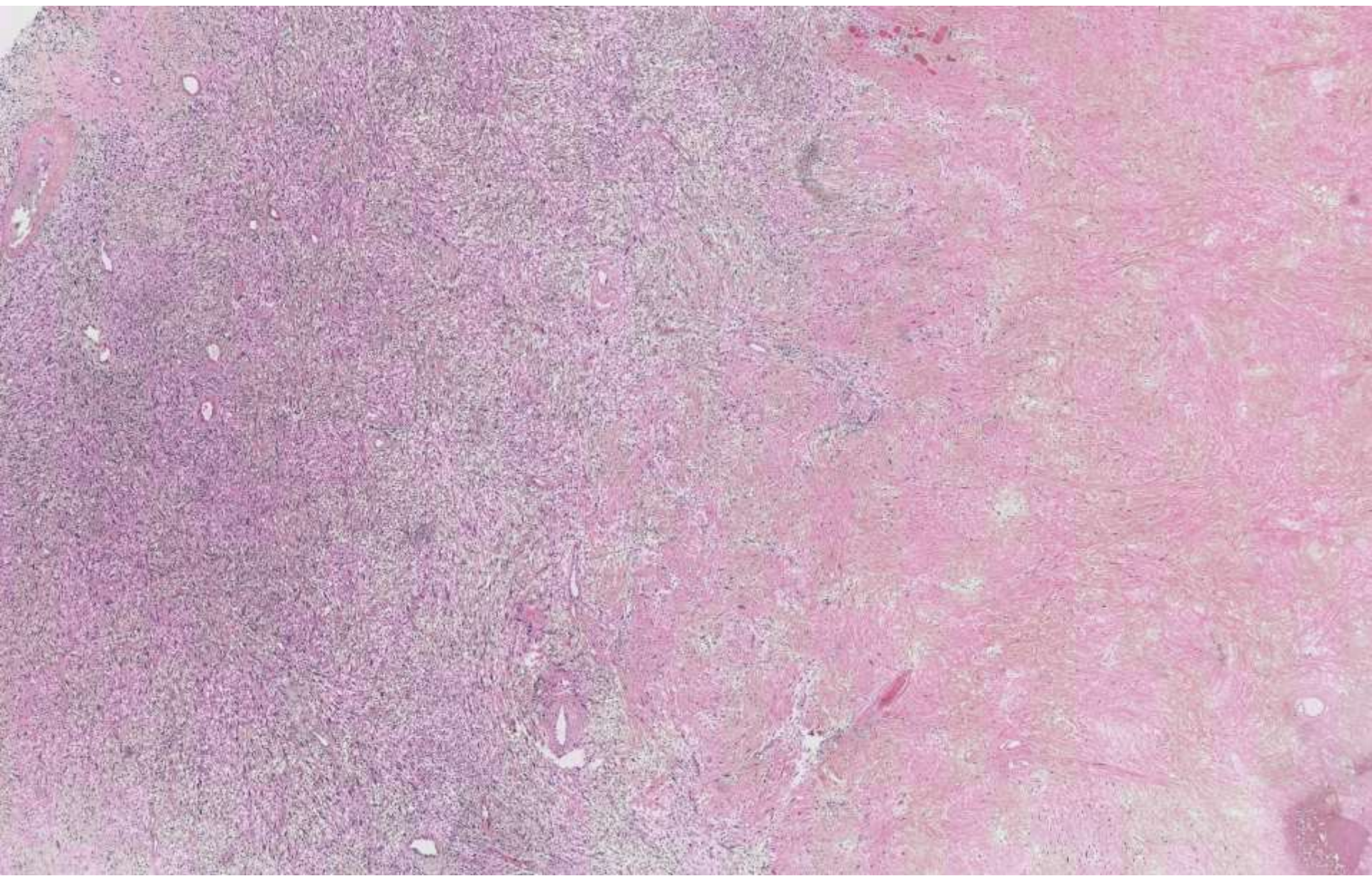




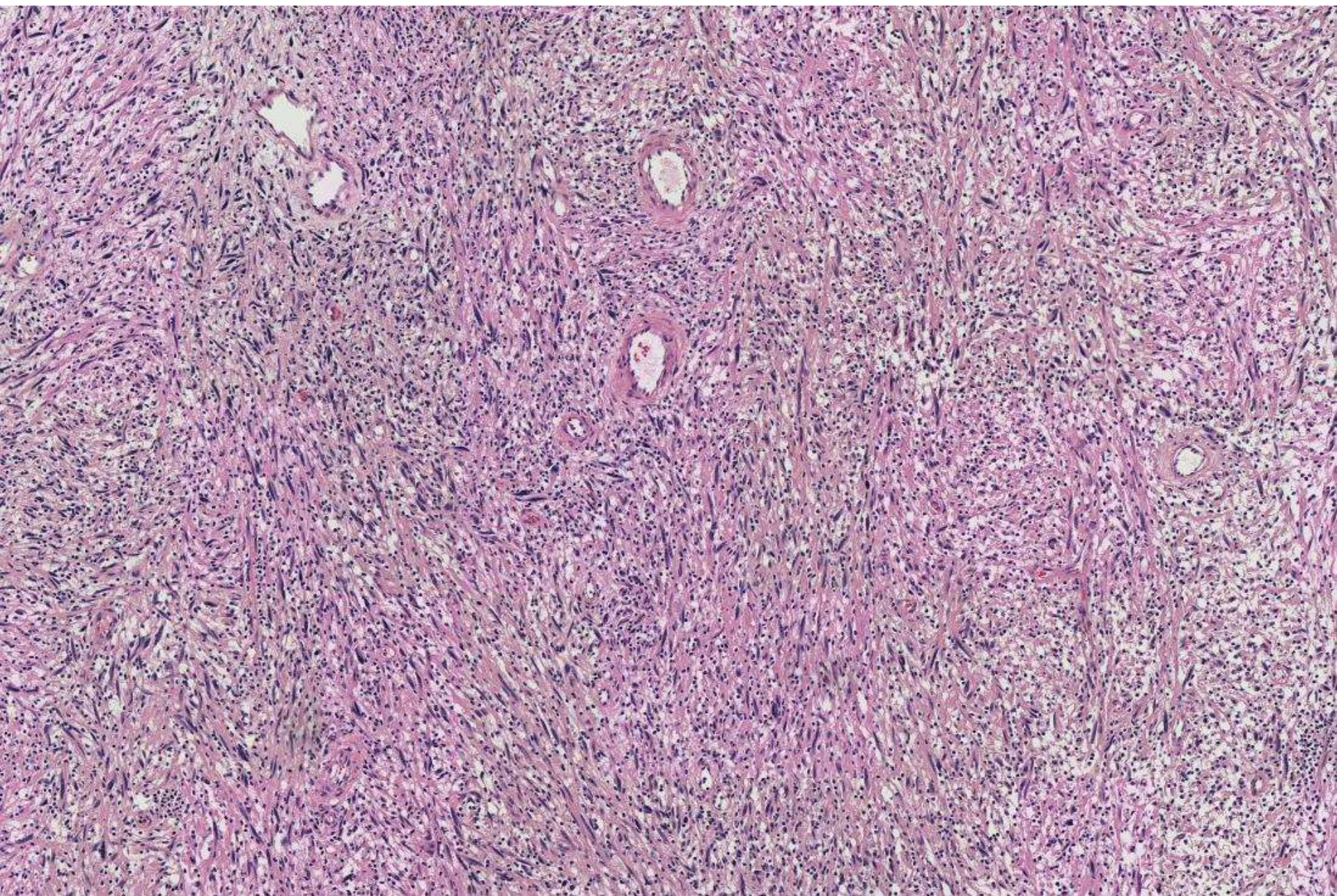




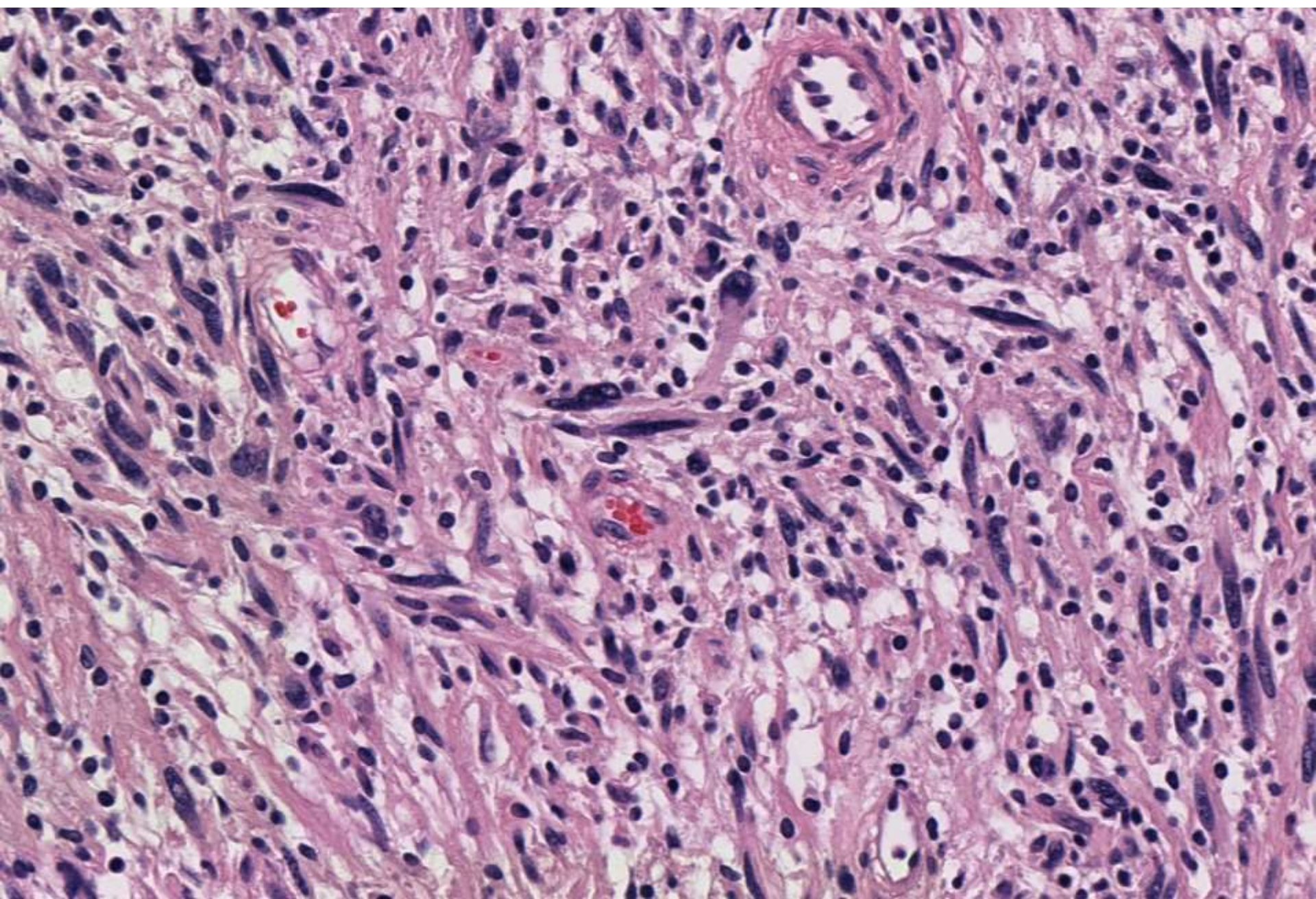




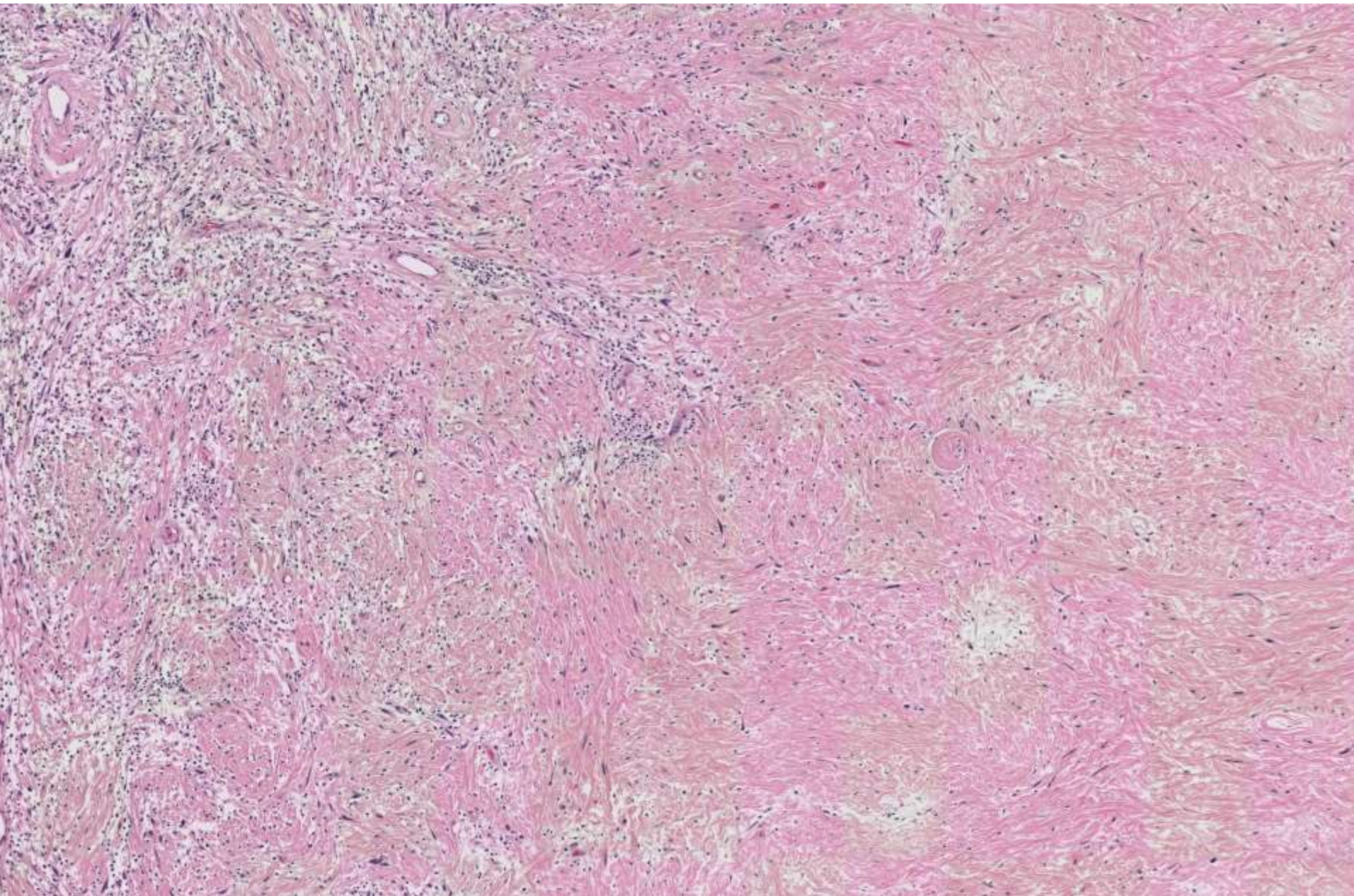




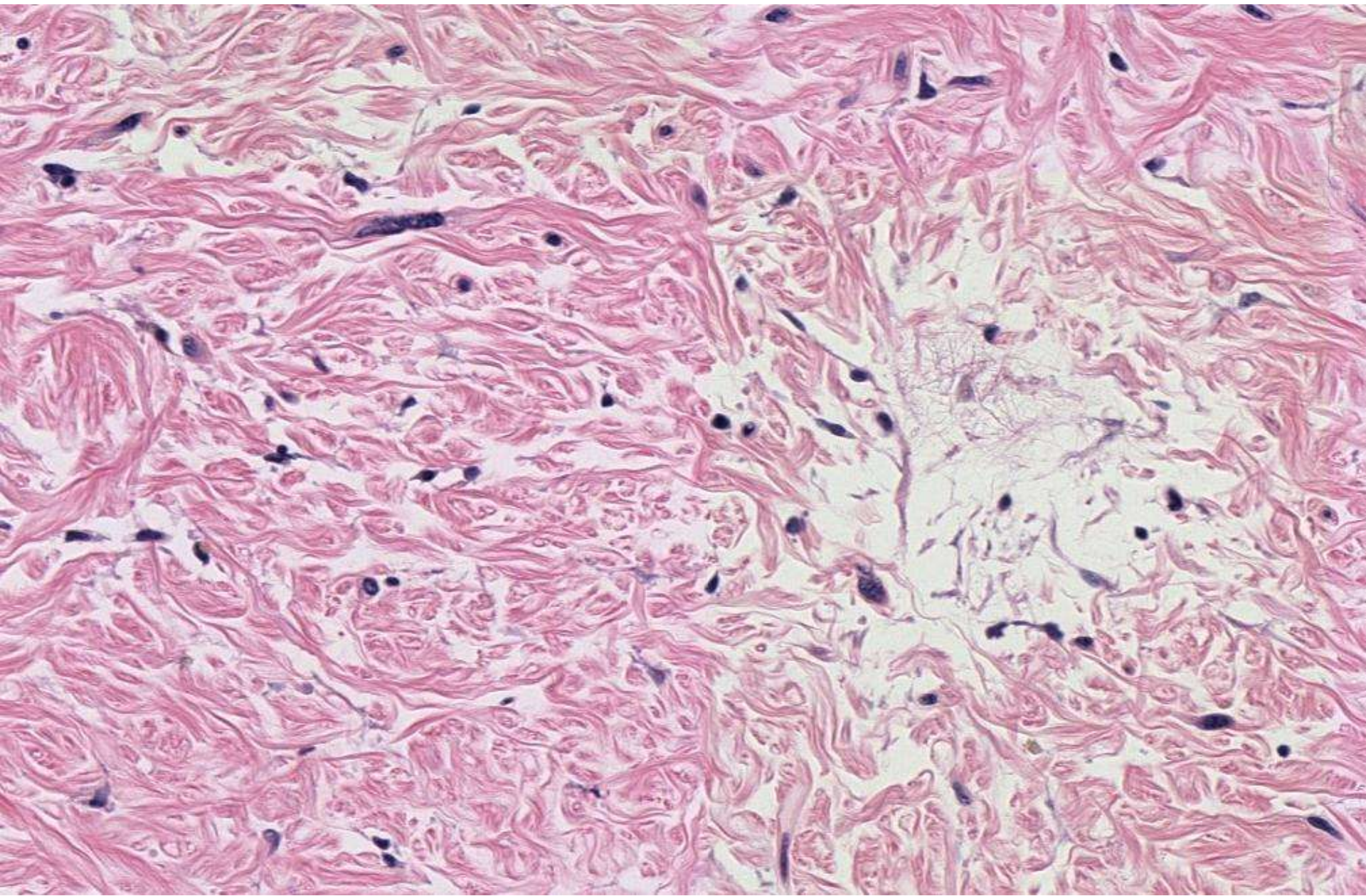




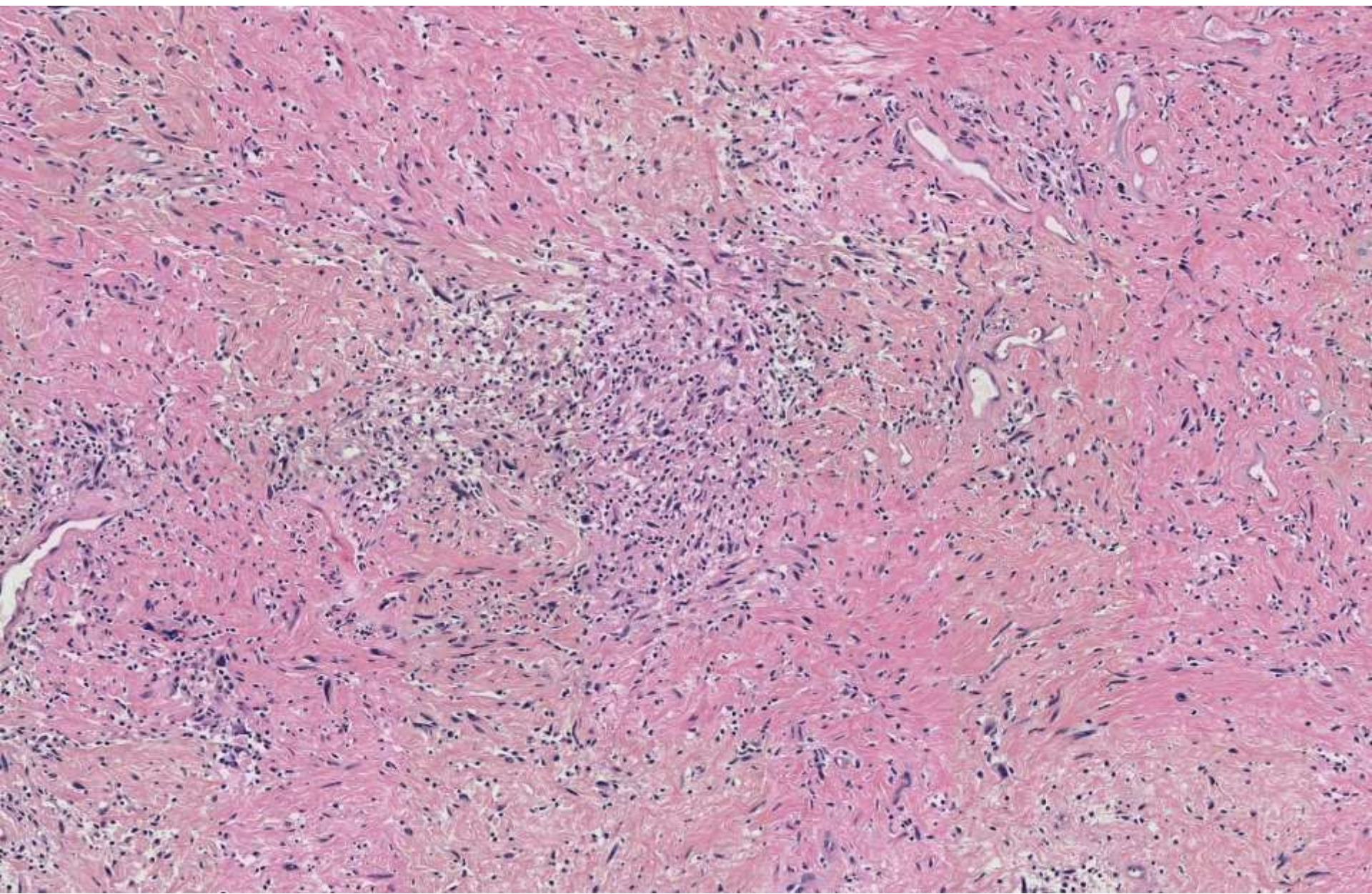














# DIAGNOSIS?





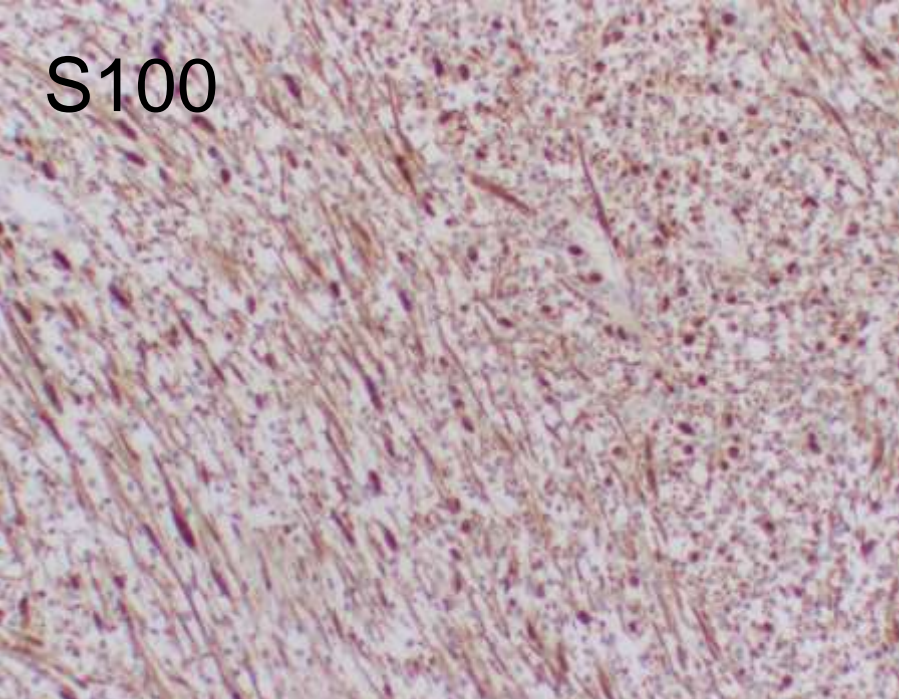
19-0703



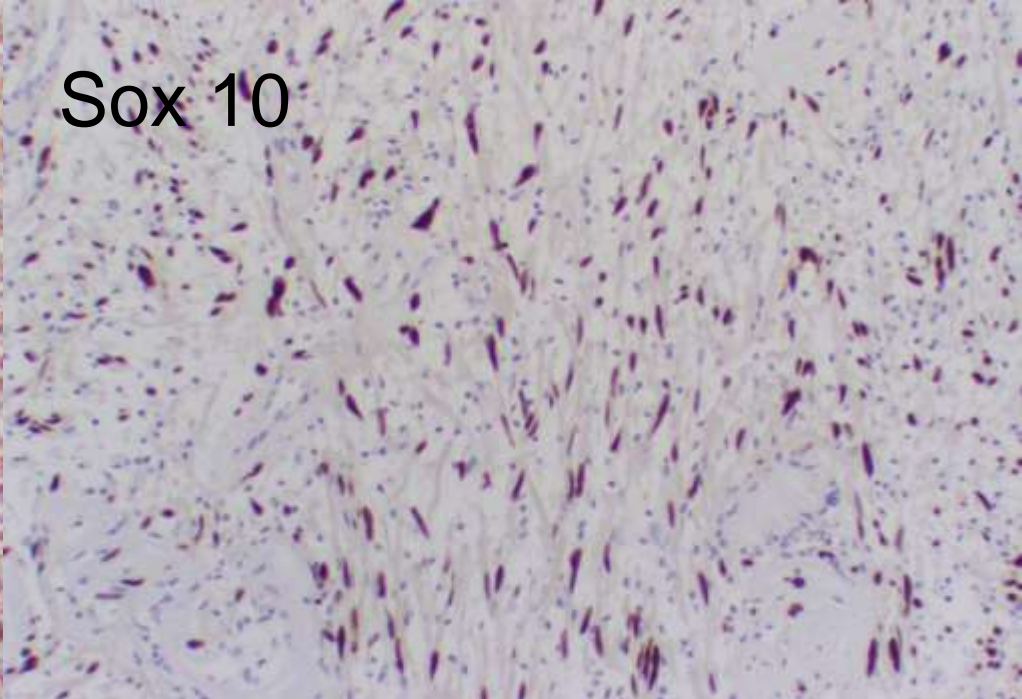
# Ancient Schwannoma



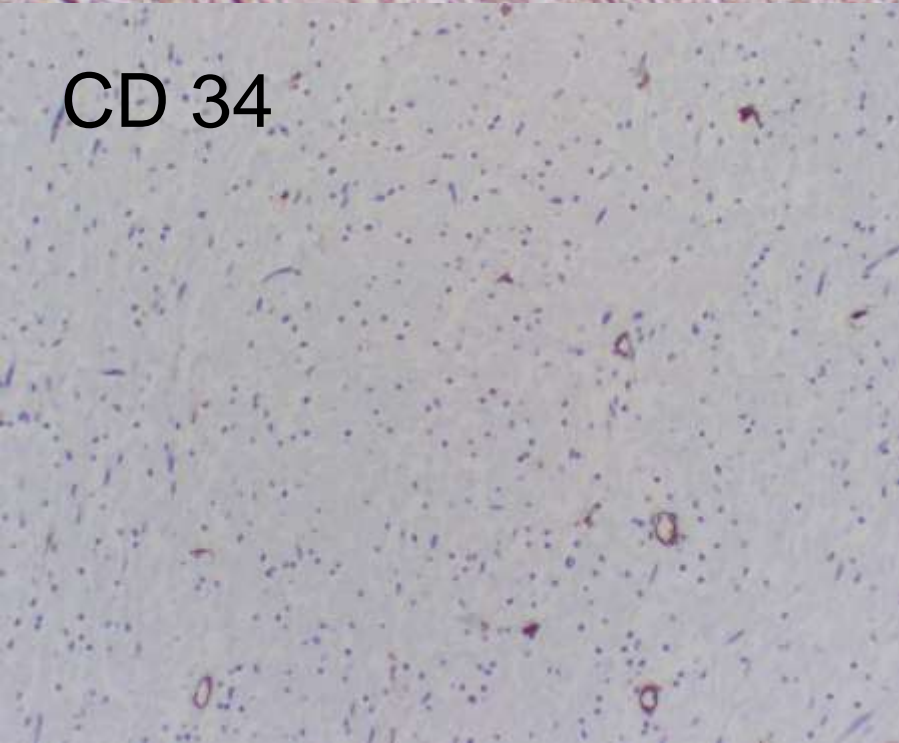
S100



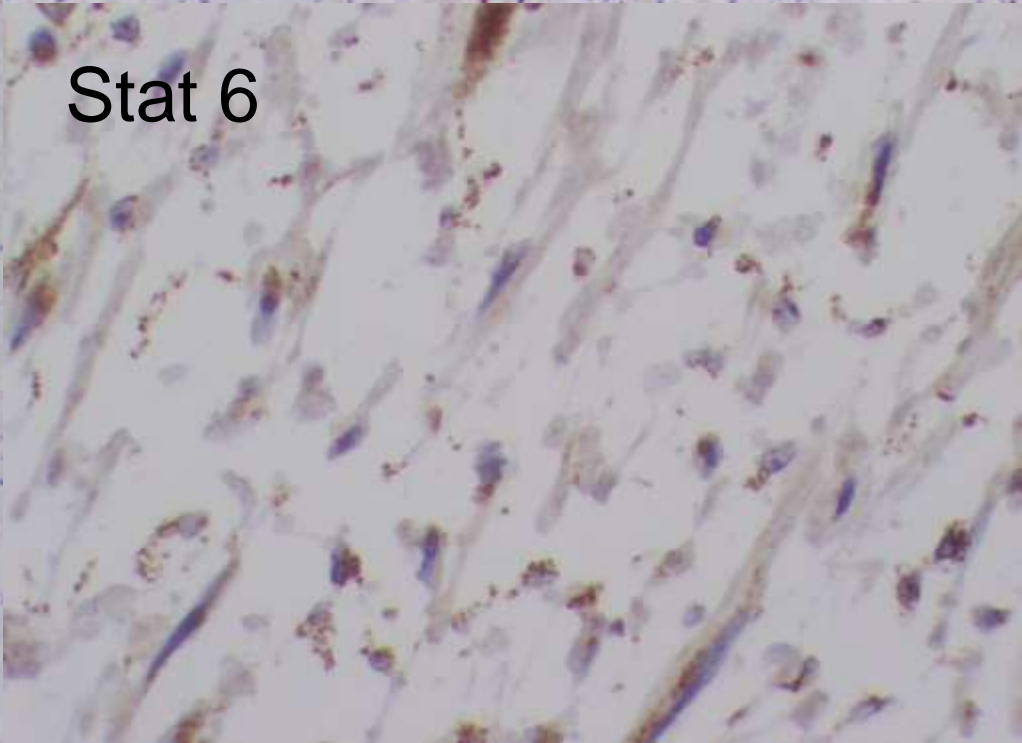
Sox 10



CD 34



Stat 6





- Primary pulmonary tumors of NS origin are rare: 32 Cases identified in a literature review published in 1965; 4 identified in a 13 year retrospective review (0.2%) of all pulmonary neoplasms published in 1983.
- 4 cases identified in a 20 year retrospective study from The Queen's University of Belfast in 1995.
- 1-Endobronchial, 2-parenchymal with no pleural involvement, 1-parenchymal with pleural involvement.
- 2 benign, 2 malignant

Histopathology 26: 247-254, 1995



- 2018 CT Report: Large rounded mass in the left superior lateral hemi-thorax with a somewhat benign appearance.
- 2018 Op Findings: L Pleural mass in the major fissure, well circumscribed and encapsulated and resected *en bloc* without violation of the mass or of the underlying lung.
- Patient presented in March 2019 with a cough and was found to have bilateral pulmonary nodules. A biopsy in April 2019 showed fibrous tissue with blood clot.
- Scheduled for a repeat scan and possible re-biopsy in August 2019.



# SIXTH PLACE

- Carl Truman, 19, of Los Angeles, California won \$74,000 plus medical expenses when his neighbor ran over his hand with a Honda Accord. Truman apparently didn't notice there was someone at the wheel of the car when he was trying to steal his neighbor's hubcaps.

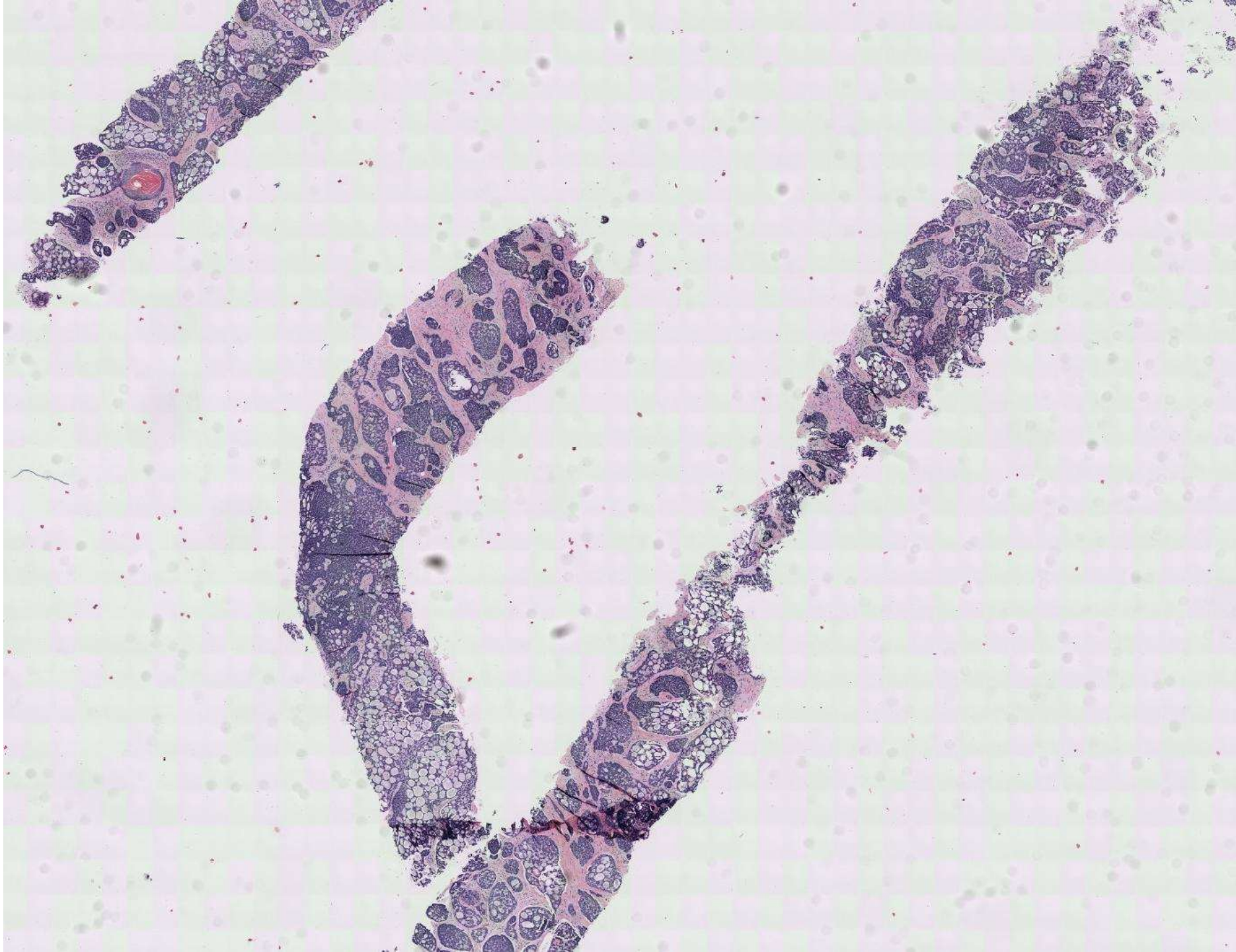


# 19-0704

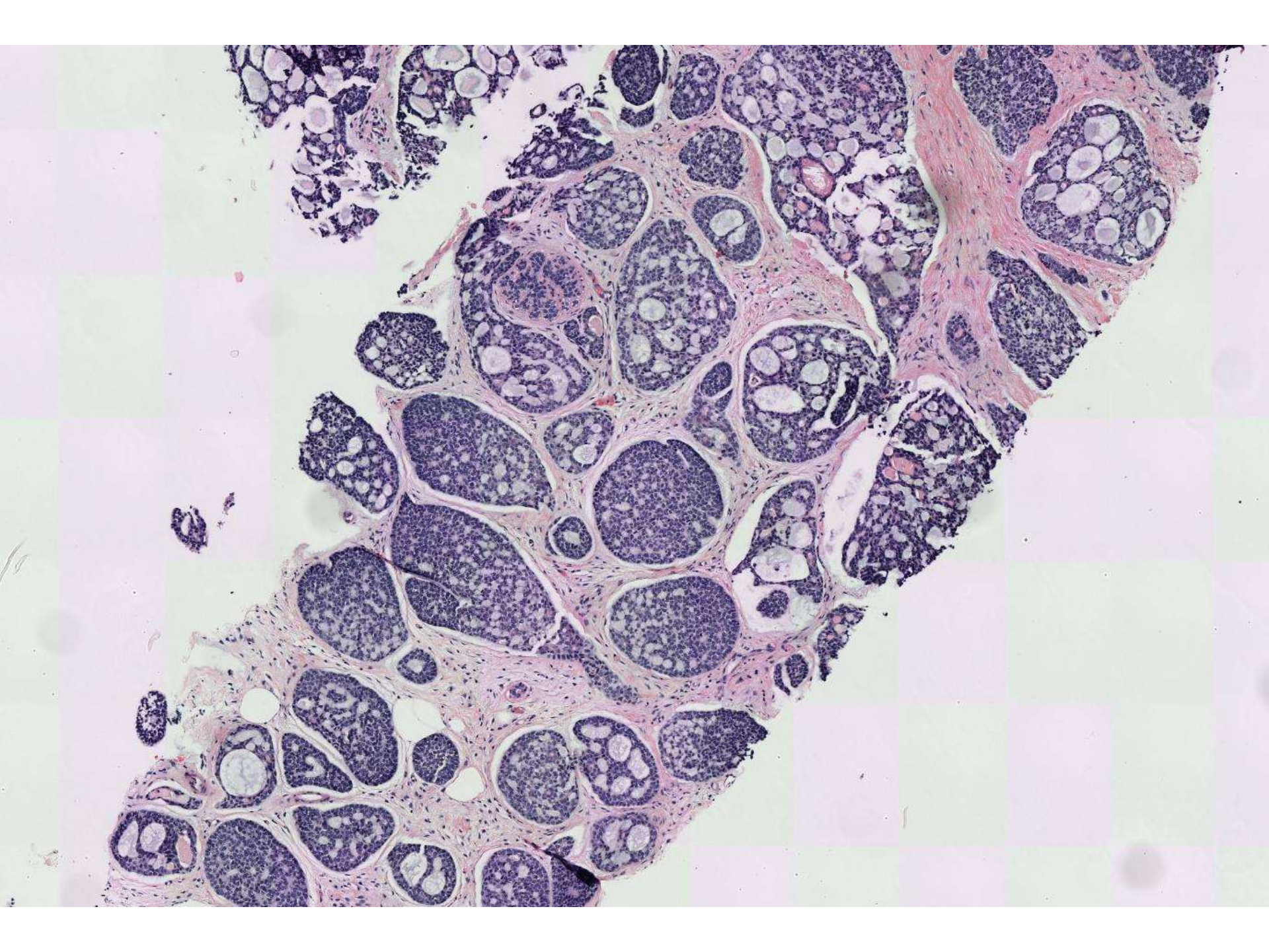
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Keith Duncan; Mills-Peninsula

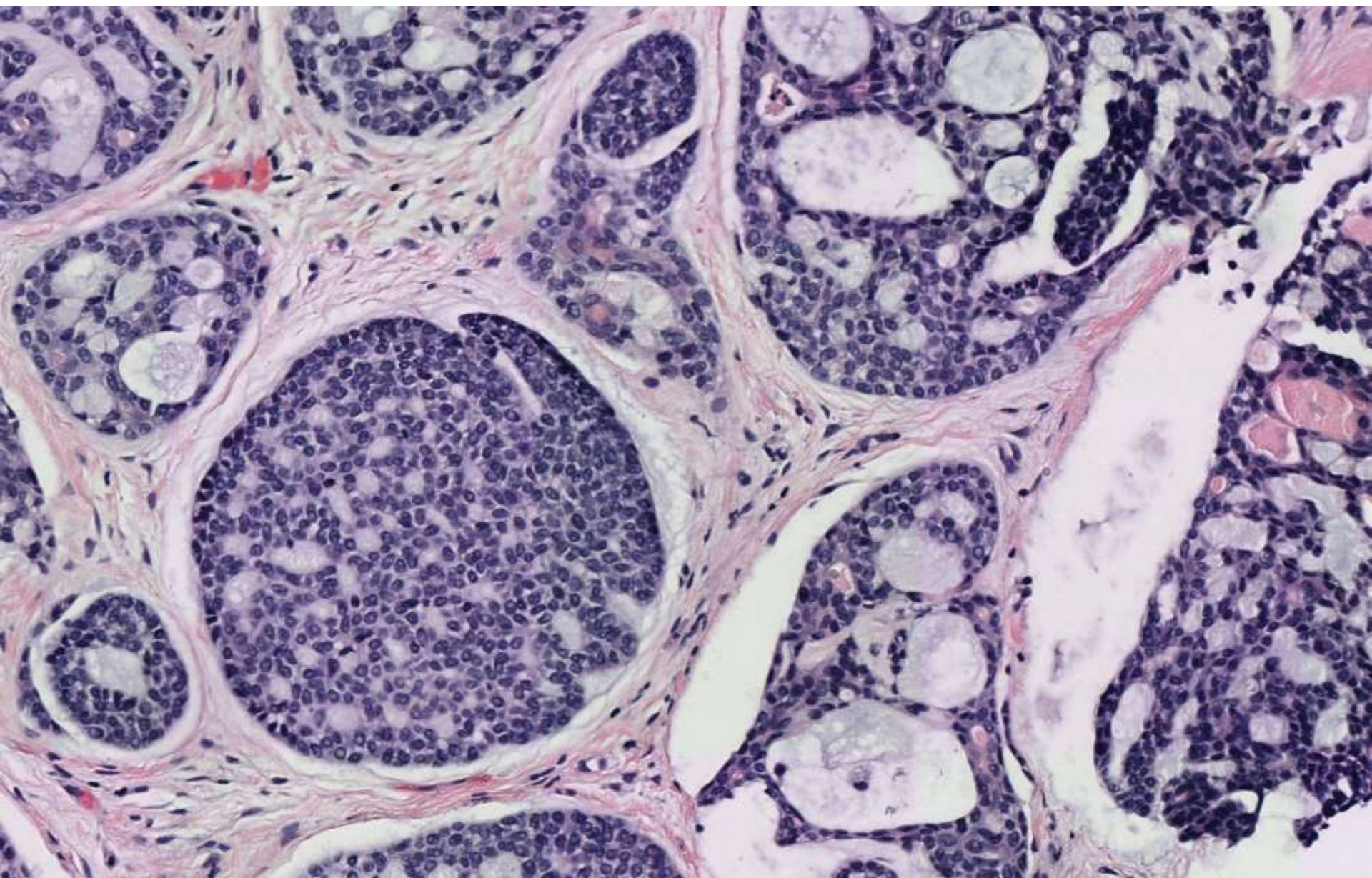
71-year-old female with solid breast  
mass, biopsied.



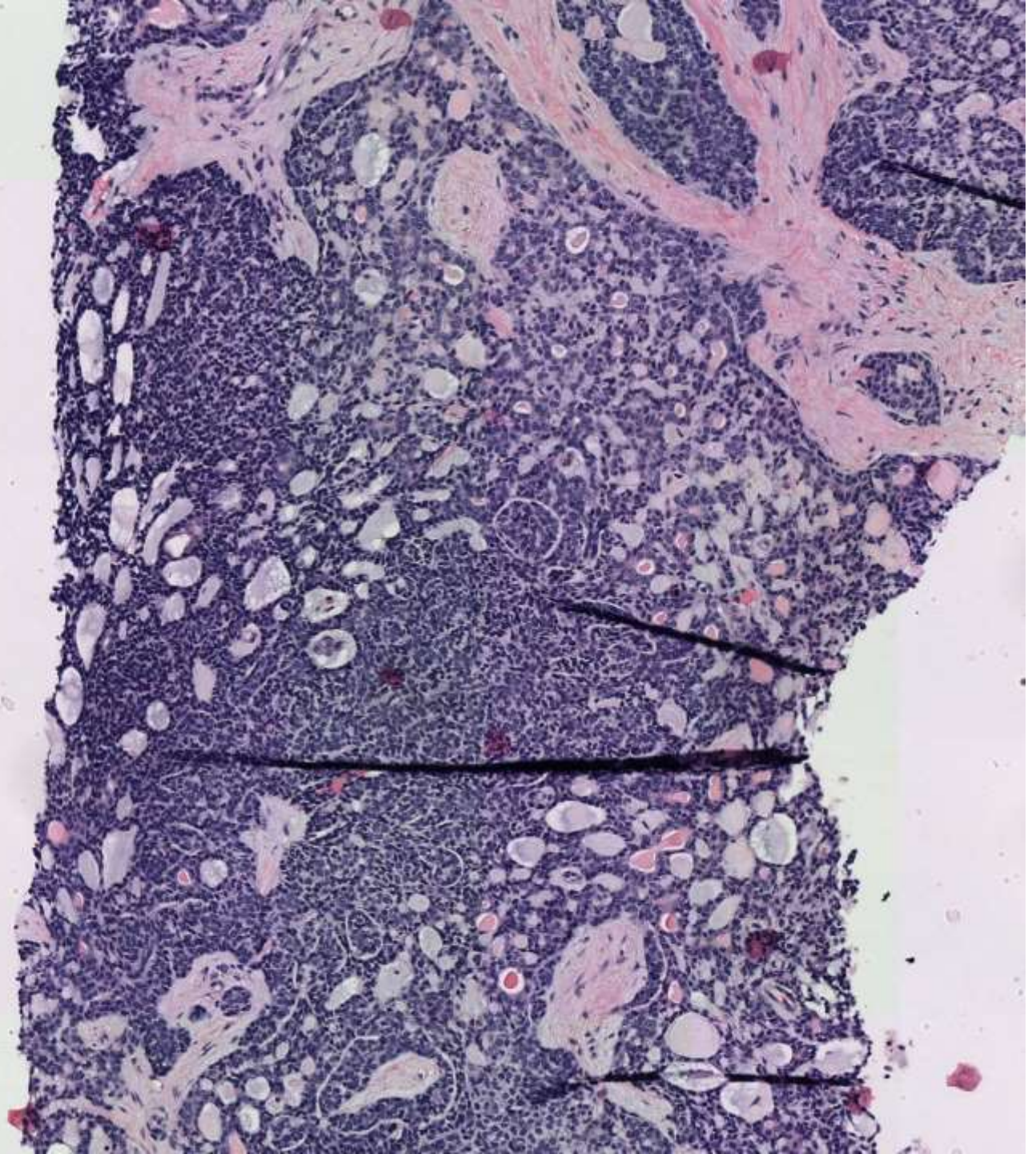




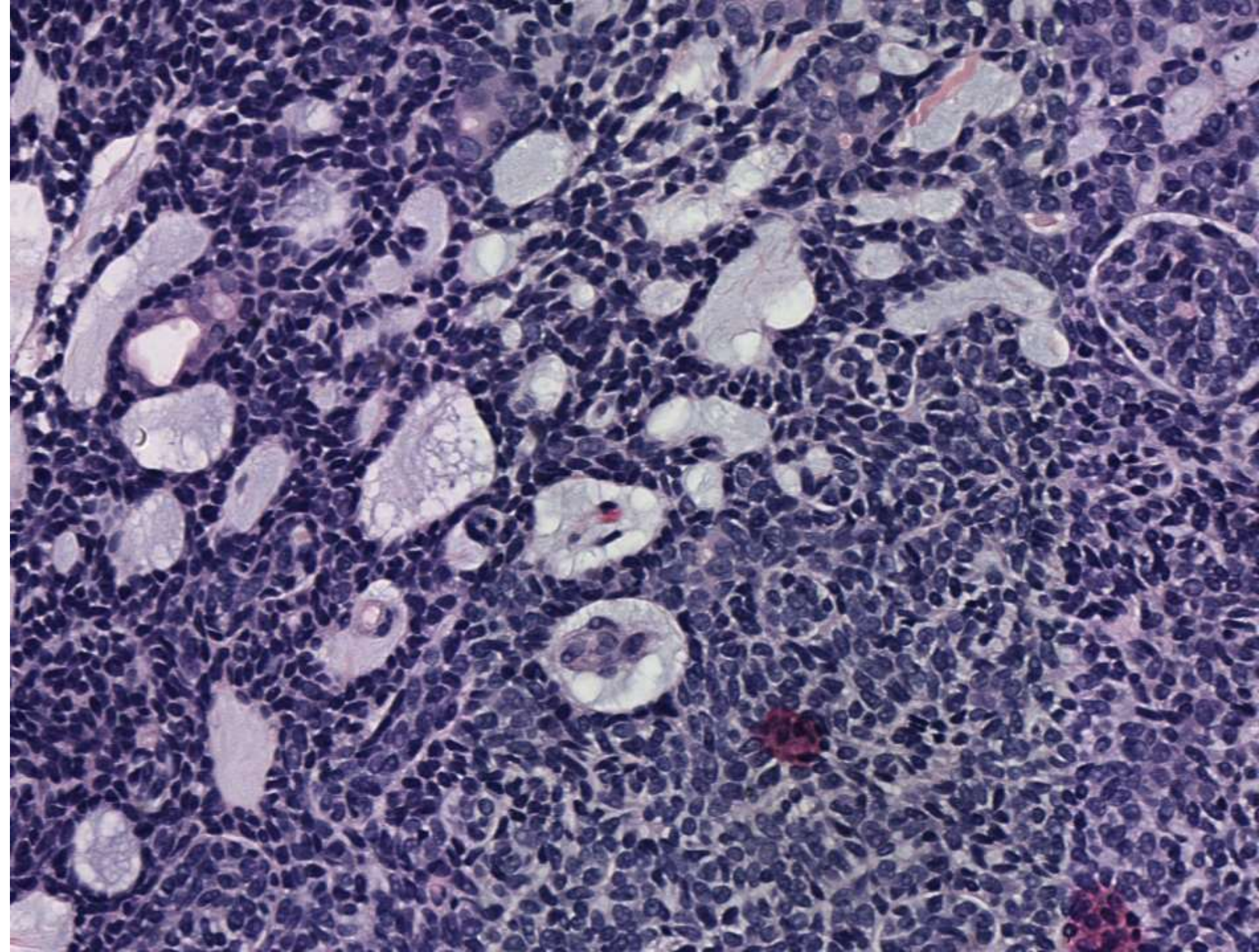




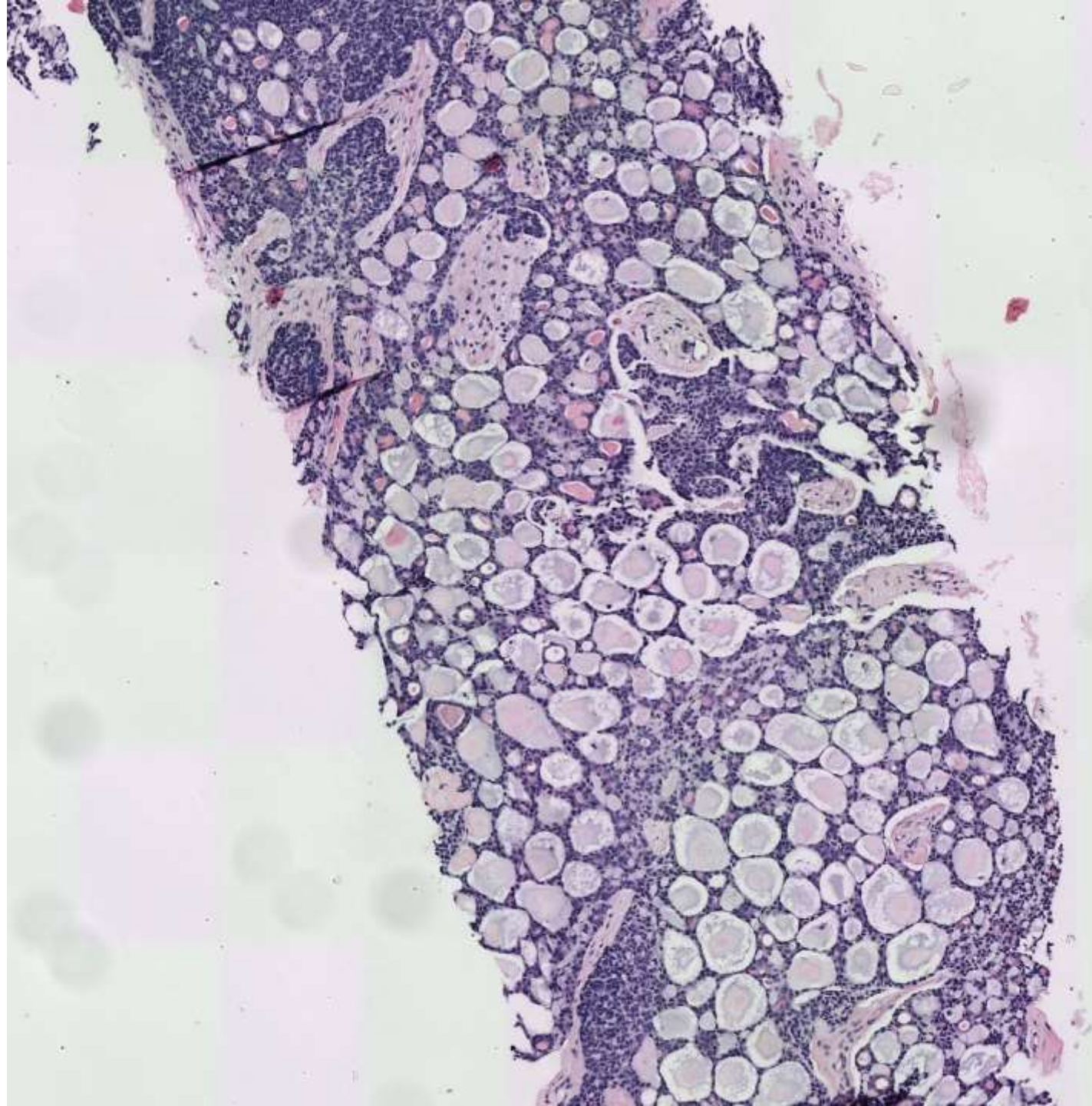




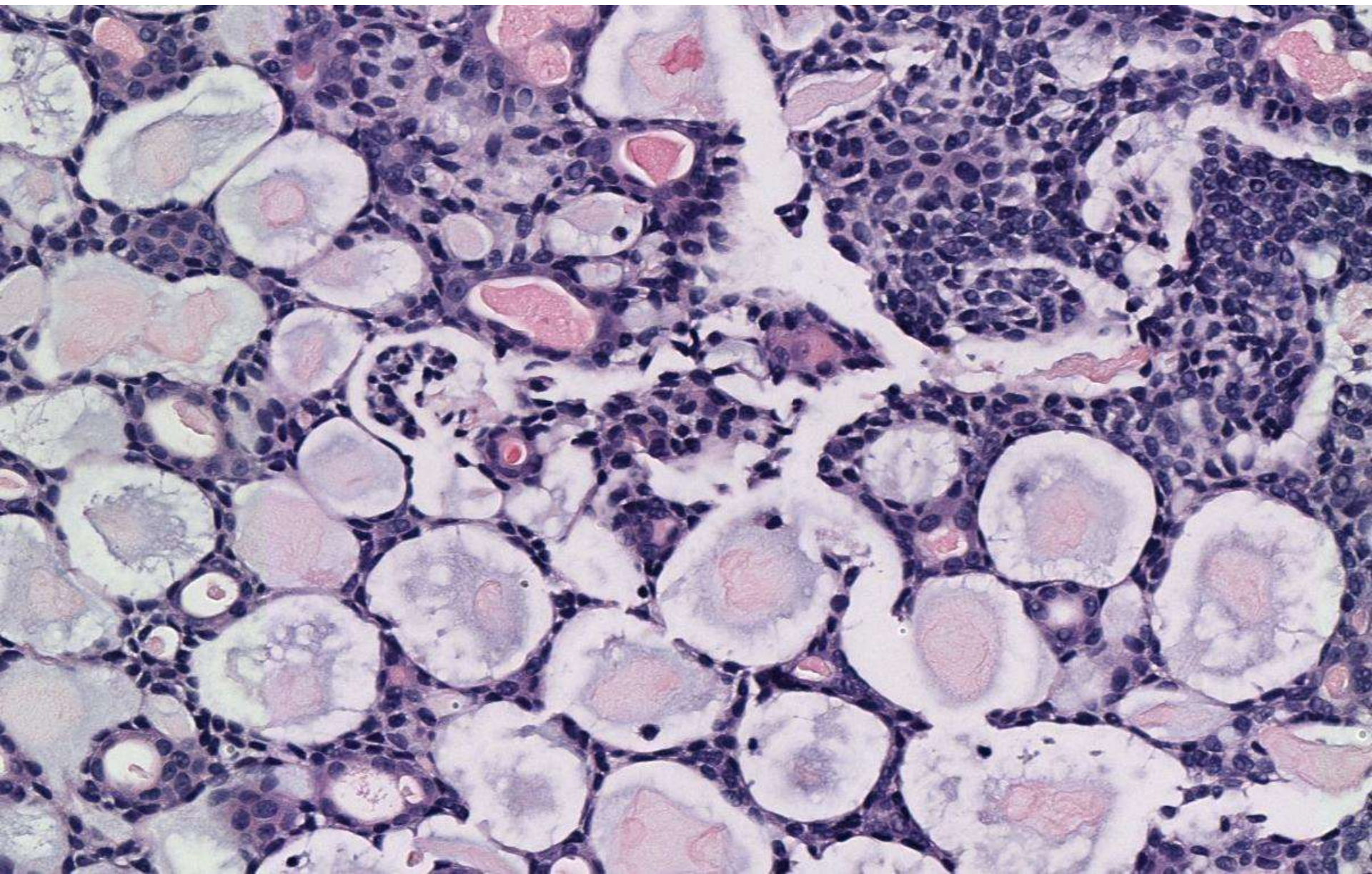














# DIAGNOSIS?







# Adenoid cystic carcinoma of the breast

- Identical to salivary gland counterpart:
- cribriform, solid, trabecular or basaloid patterns
- 2 types of cavities & 2 types of cells:
- (1) true glandular lumina lined by ductal epithelium and (2) eosinophilic "cylinders" with basement membrane material lined by basal / myoepithelial type cells
- May have sebaceous differentiation and be associated with microglandular adenosis



# Adenoid cystic carcinoma of the breast

## Treatment and prognosis:

- Good to excellent prognosis
- Recurs or metastasizes less than IDC
- High rates of positive margins
- Microscopic infiltration and perineural invasion are common
- Axillary LN metastases rare

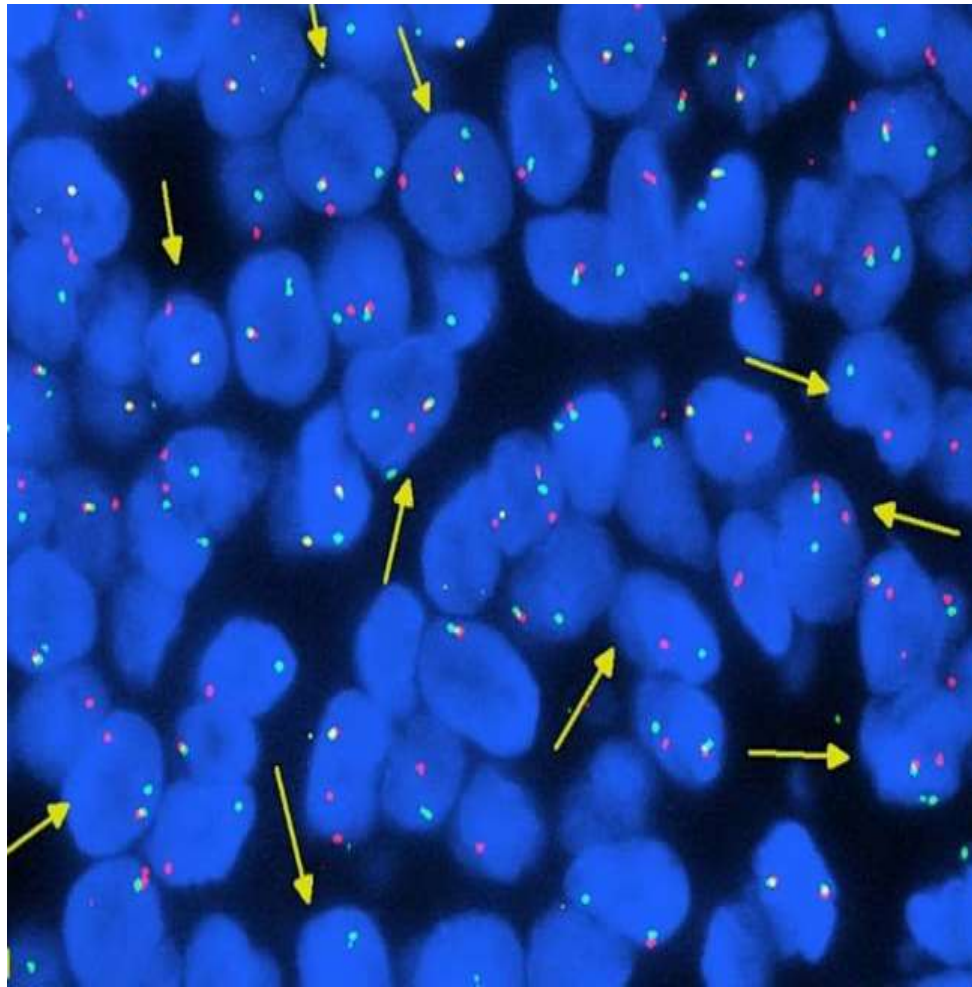
# Adenoid cystic carcinoma of the breast

- **Positive stains**
- Ductal epithelial cells:
  - [EMA](#)
  - [Keratin](#)
  - [CD117](#)
- Basaloid / myoepithelial-type cells:
  - [p63](#)
  - [S100](#)
  - [Smooth muscle actin](#)
- **Negative stains**
- [ER](#), [PR](#) (usually), [HER2](#)
- [Calponin](#) & Smooth muscle [myosin](#) heavy chain



# Adenoid cystic carcinoma of the breast

- Rare, 0.1% of breast carcinomas
- Mean age 50 - 63 years, range 25 - 80 years
- 50% are subperiareolar
- **Molecular / cytogenetics description**
- MYB-NFIB fusion gene (t(6;9)(q22-23;p23-24)) ([J Pathol 2012;226:84](#))
- Genomically distinct subgroup of triple negative breast cancer



- **MYB (6q23.3) Rearrangement by FISH:**
- Result is interpreted as **positive** for MYB gene rearrangement when the red and green probes are separated



# Differential diagnosis

- Collagenous spherulosis: 1 cell type, calponin+, smooth muscle myosin heavy chain+, CD117-
- Cribriform carcinoma: in situ or invasive, has 1 cell type, ER+, PR+, p63-, CD117-
- Adenoid cystic carcinoma: denser and tightly nodular material is rarely degenerated, stromal invasion, CD117+ luminal cells, calponin and smooth muscle myosin heavy chain negative

# FIFTH PLACE

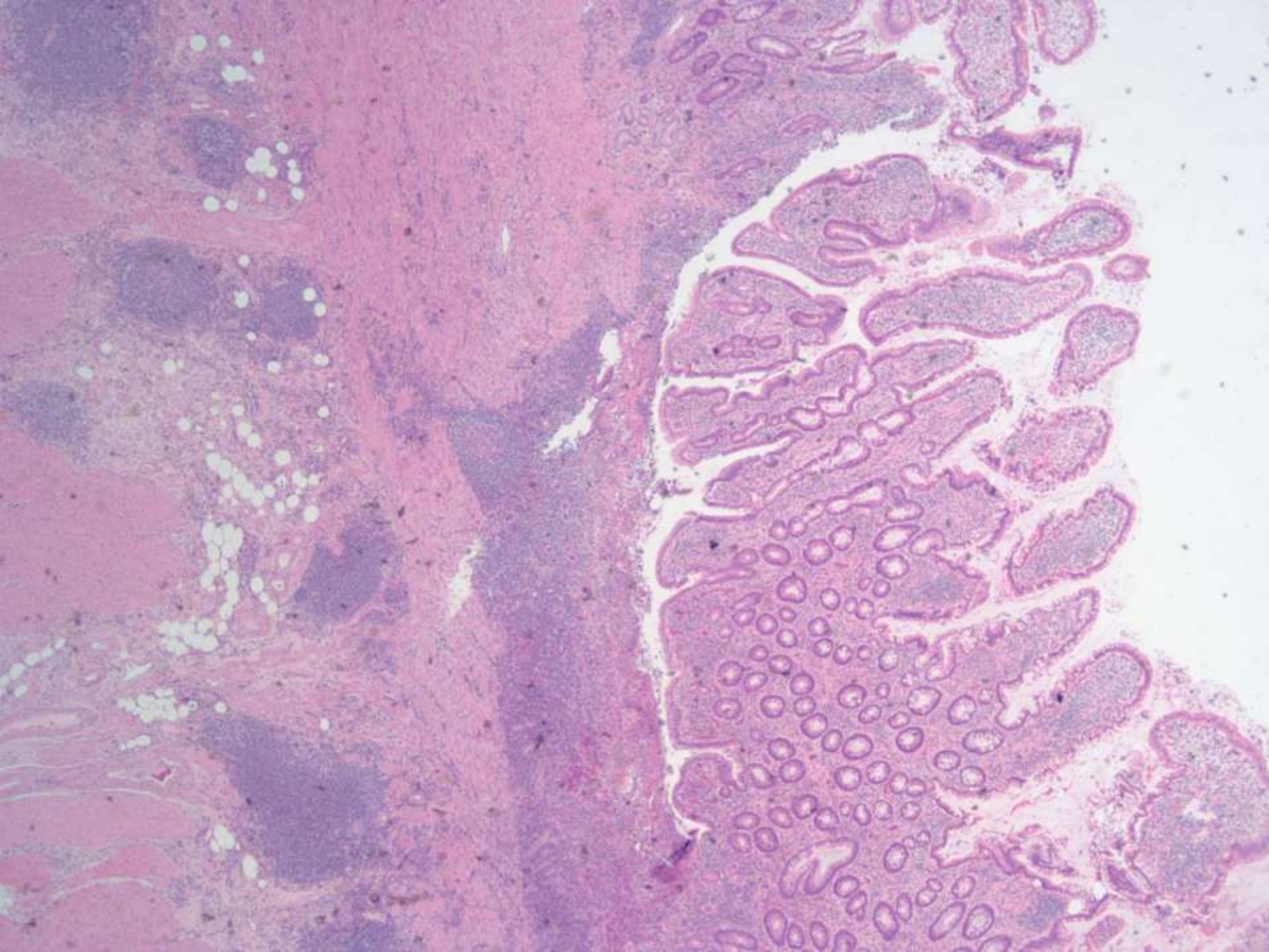
- Terrence Dickson, of Bristol, Pennsylvania, was leaving a house he had just burglarized by way of the garage. Unfortunately for Dickson, the automatic garage door opener malfunctioned and he could not get the garage door to open. Worse, he couldn't re-enter the house because the door connecting the garage to the house locked when Dickson pulled it shut. Forced to sit for eight, count 'em, EIGHT days and survive on a case of Pepsi and a large bag of dry dog food, he sued the homeowner's insurance company claiming undue mental Anguish. Amazingly, the jury said the insurance company must pay Dickson \$500,000 for his anguish.



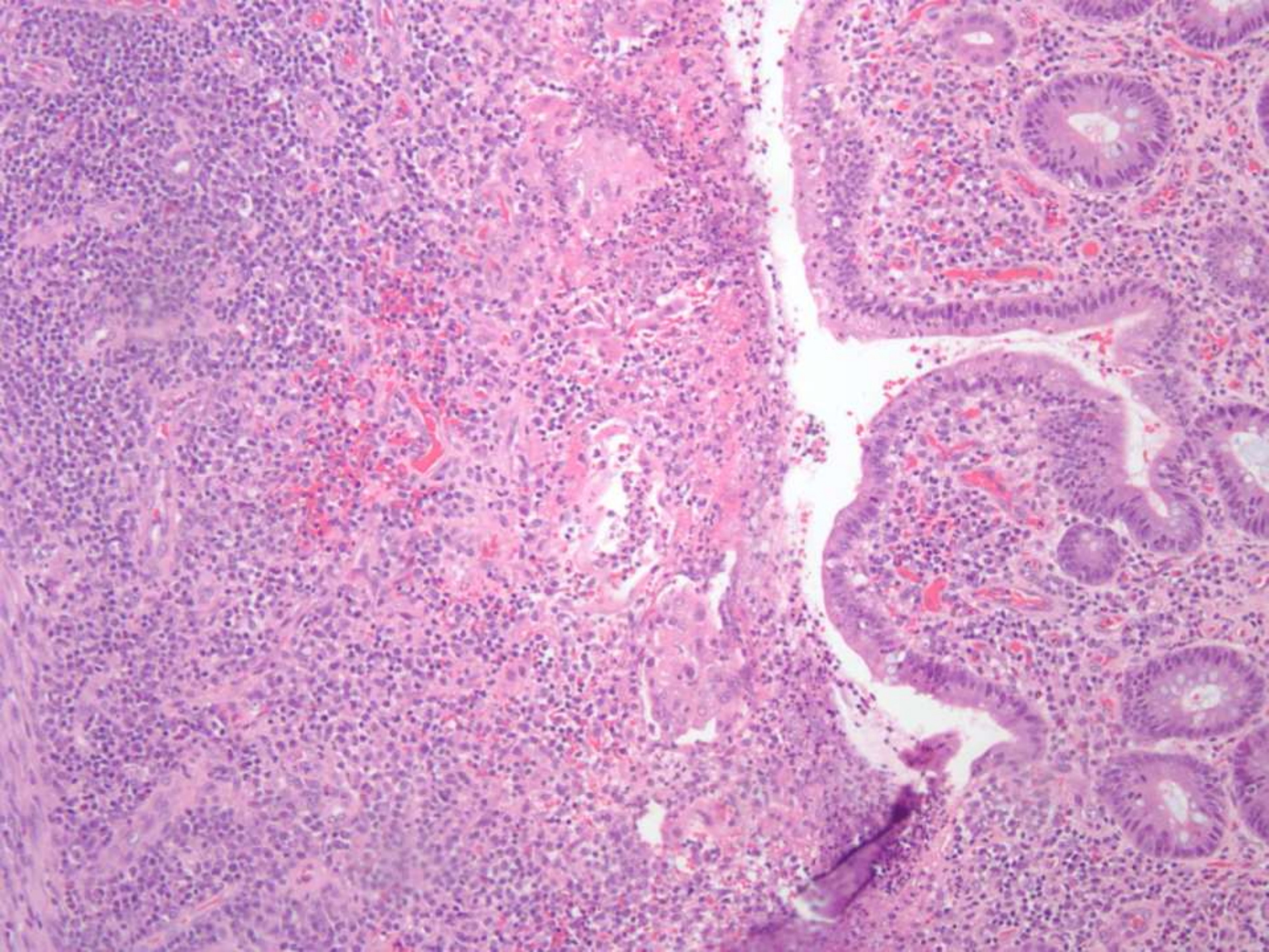
# 19-0705

Charles Lombard; El Camino Hospital

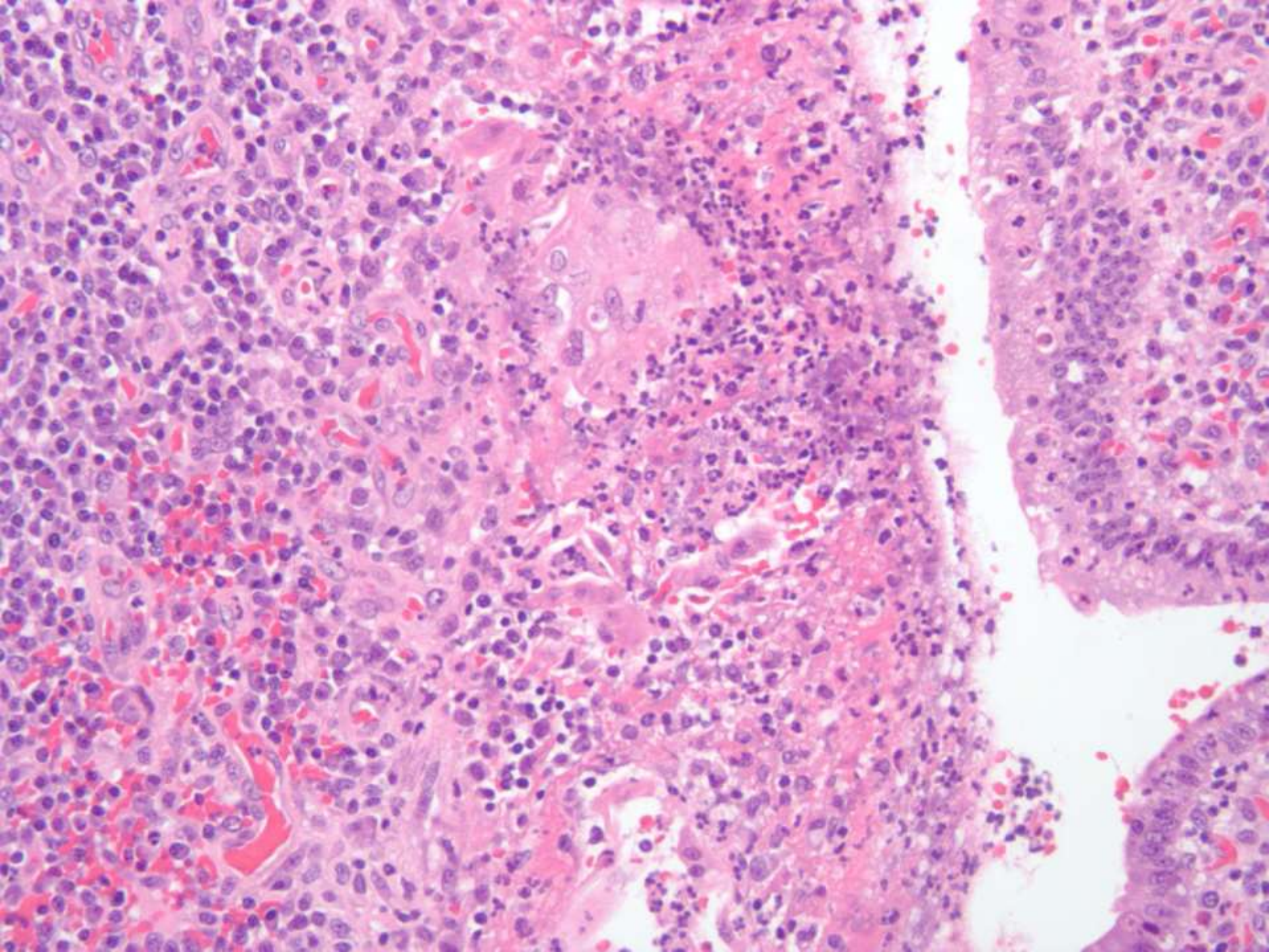
69-year-old woman undergoes  
ileocolonic resection for obstruction.



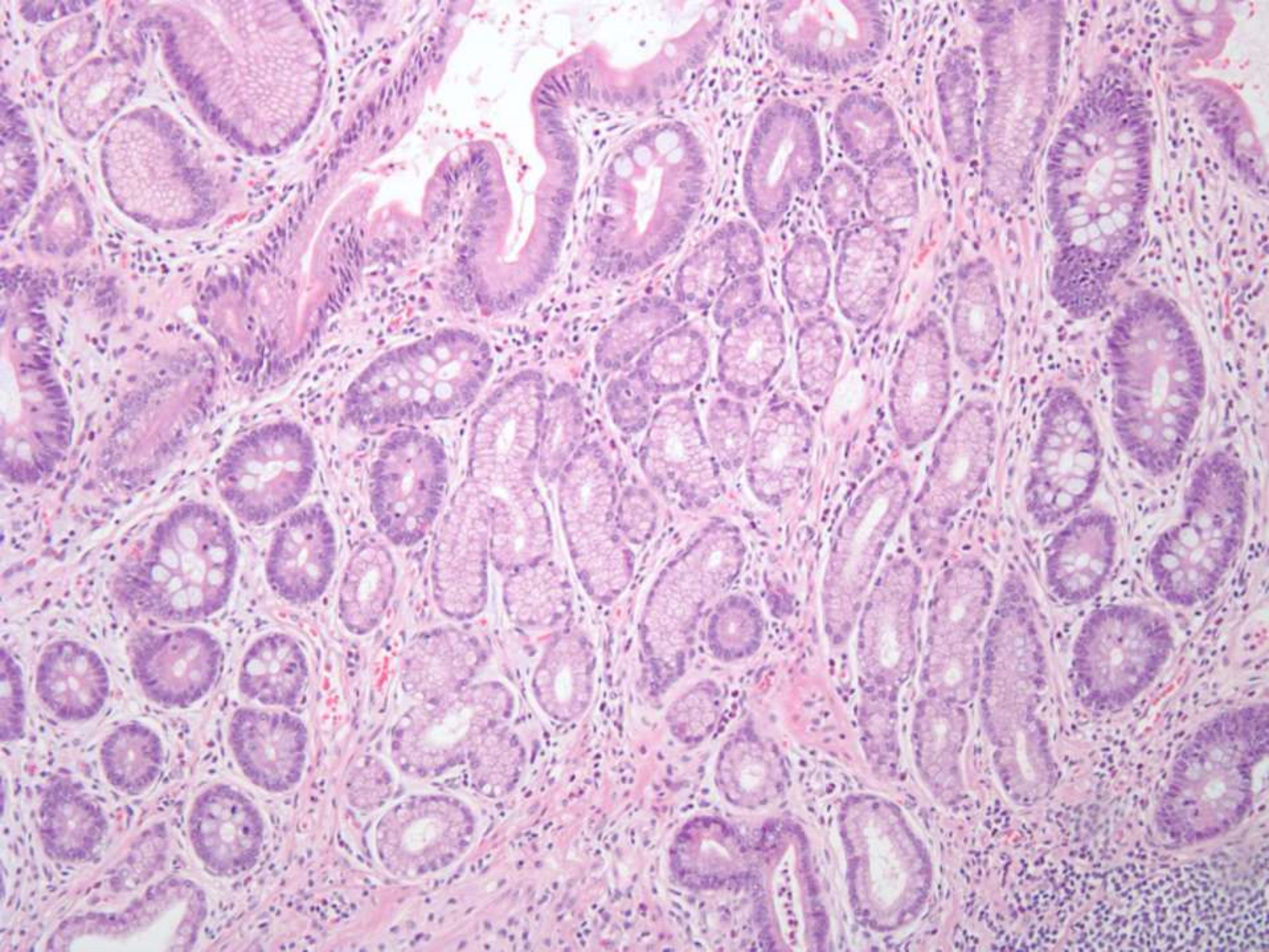




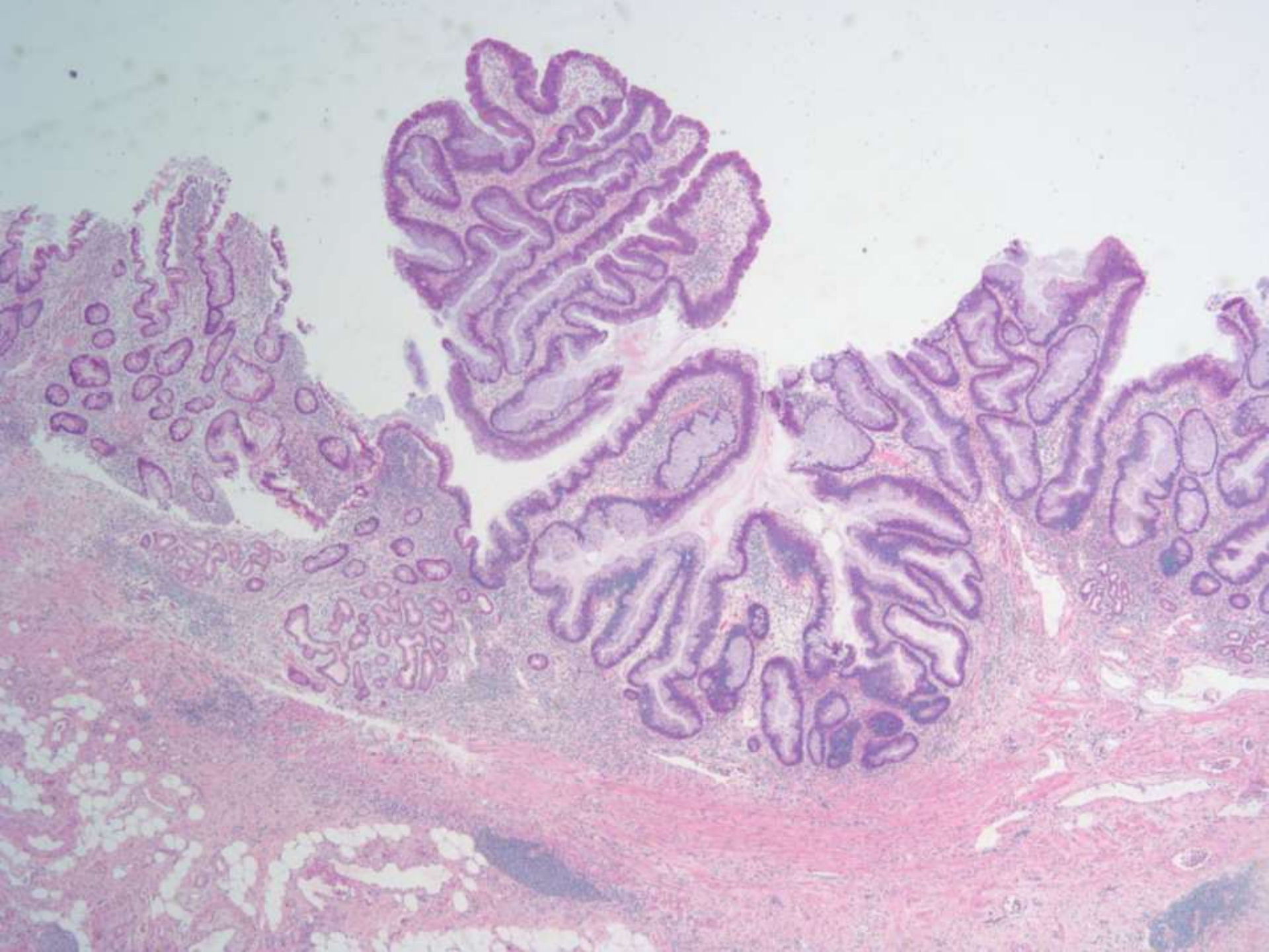




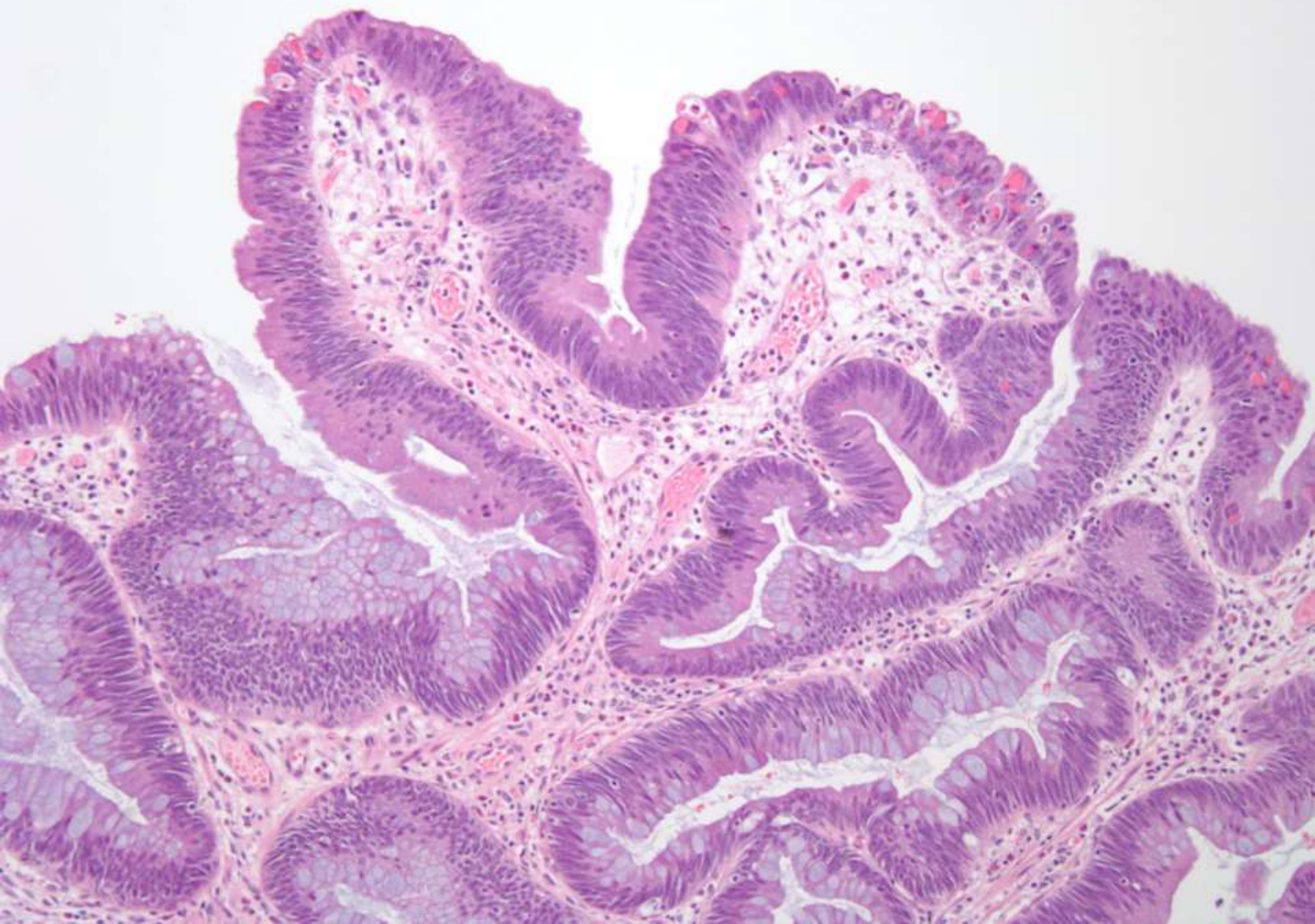




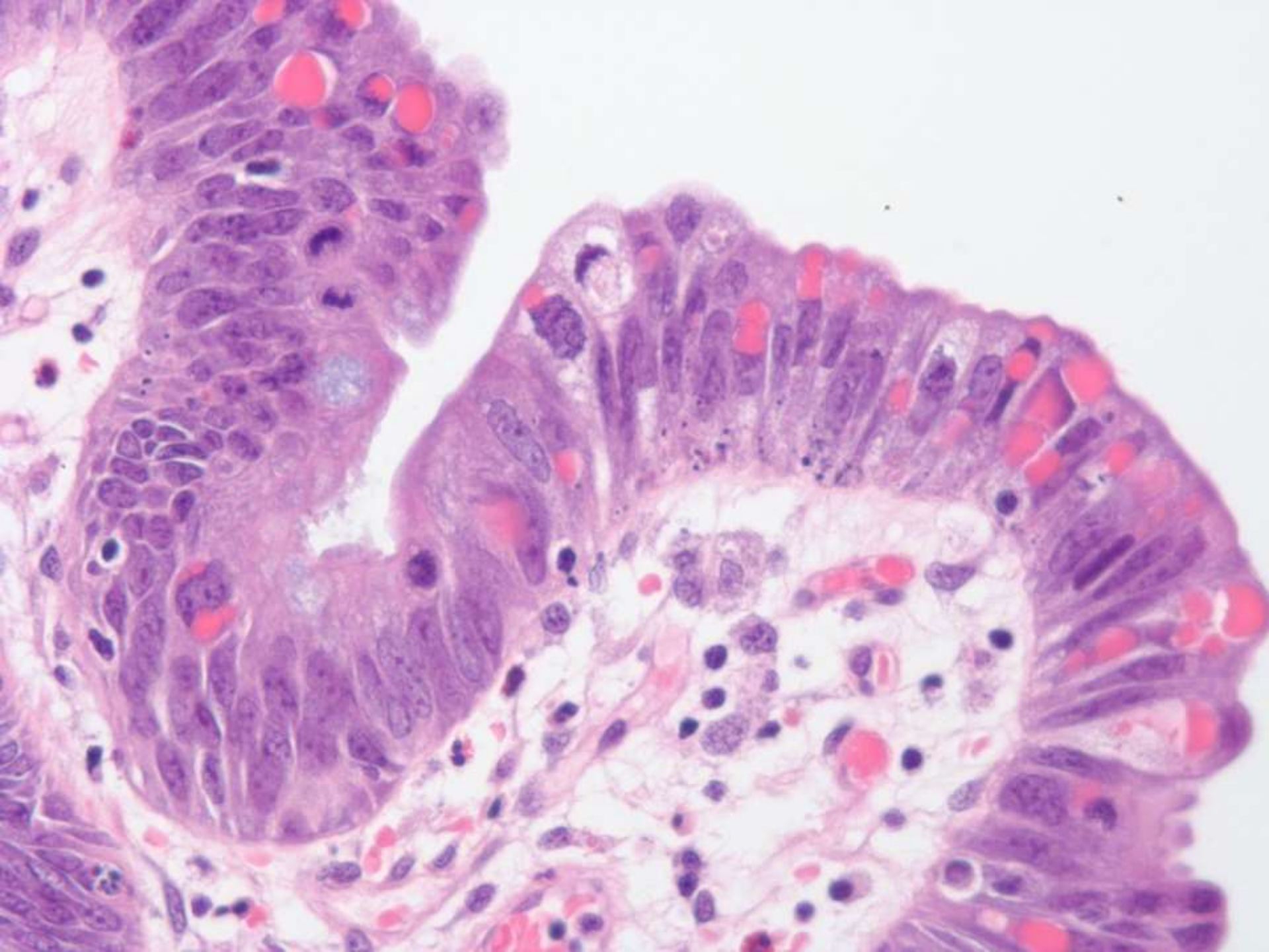




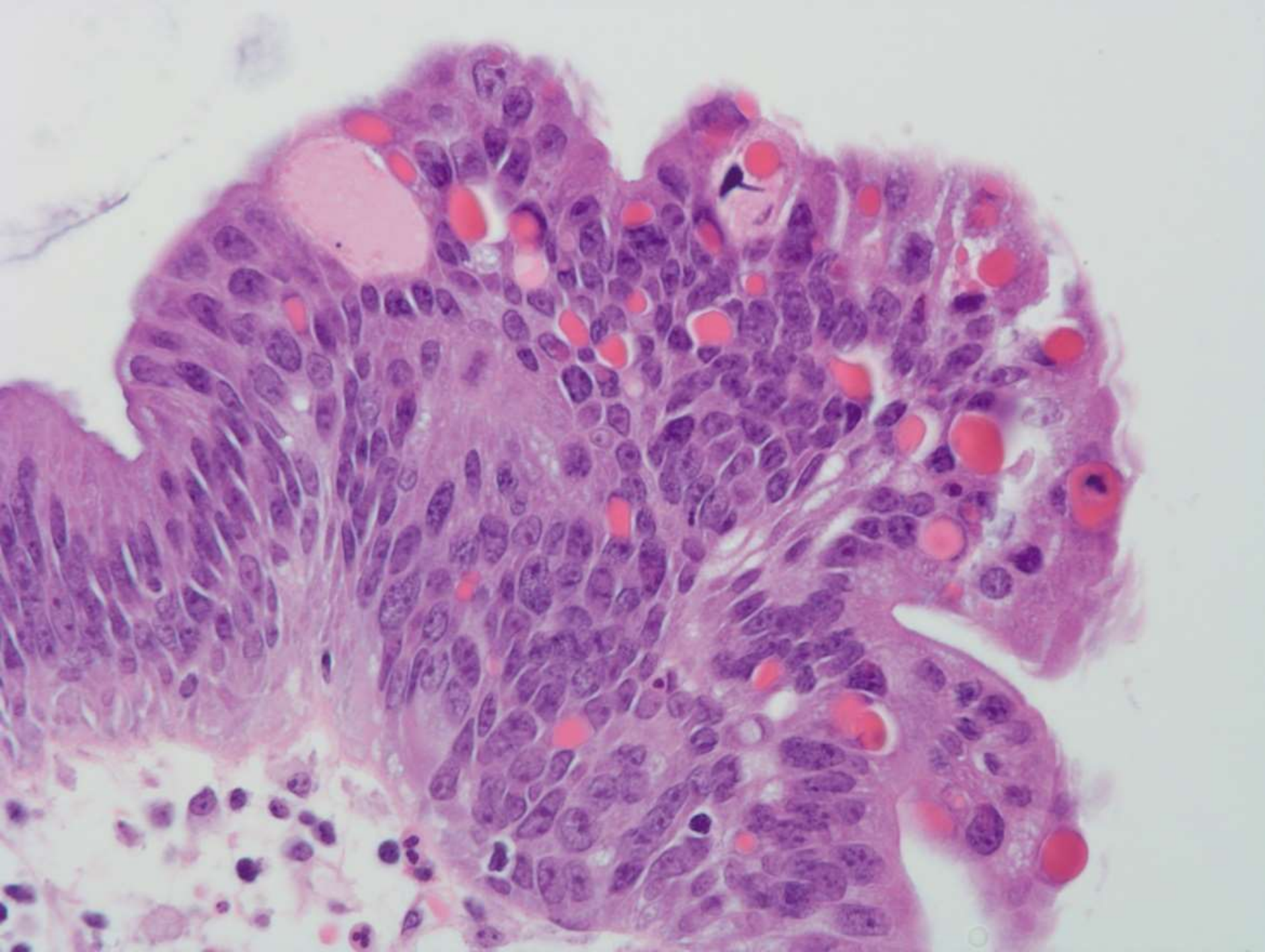






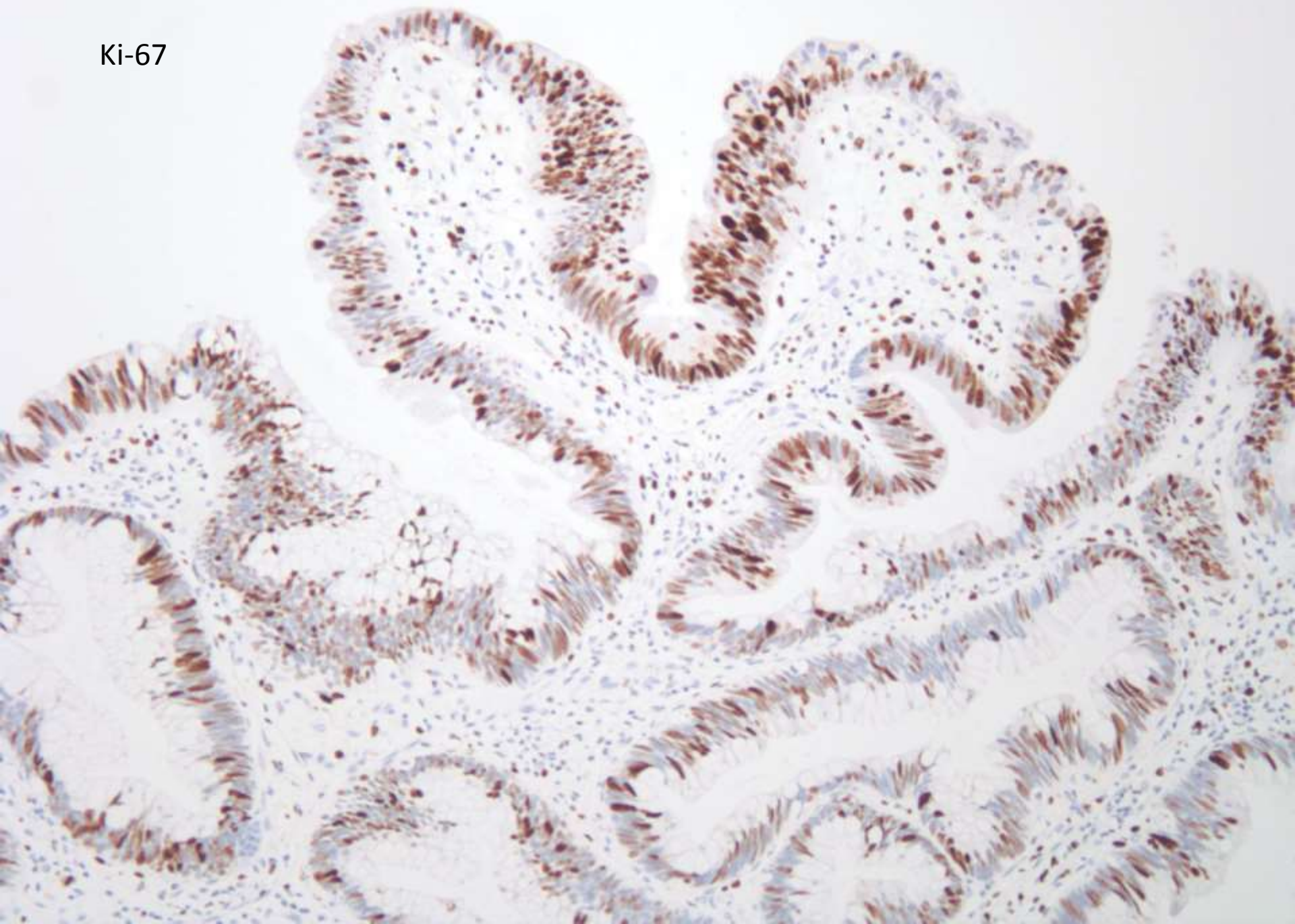








Ki-67





# DIAGNOSIS?







# Adenomatous polyp arising in the setting of long standing Crohn's disease

Thanatosomes

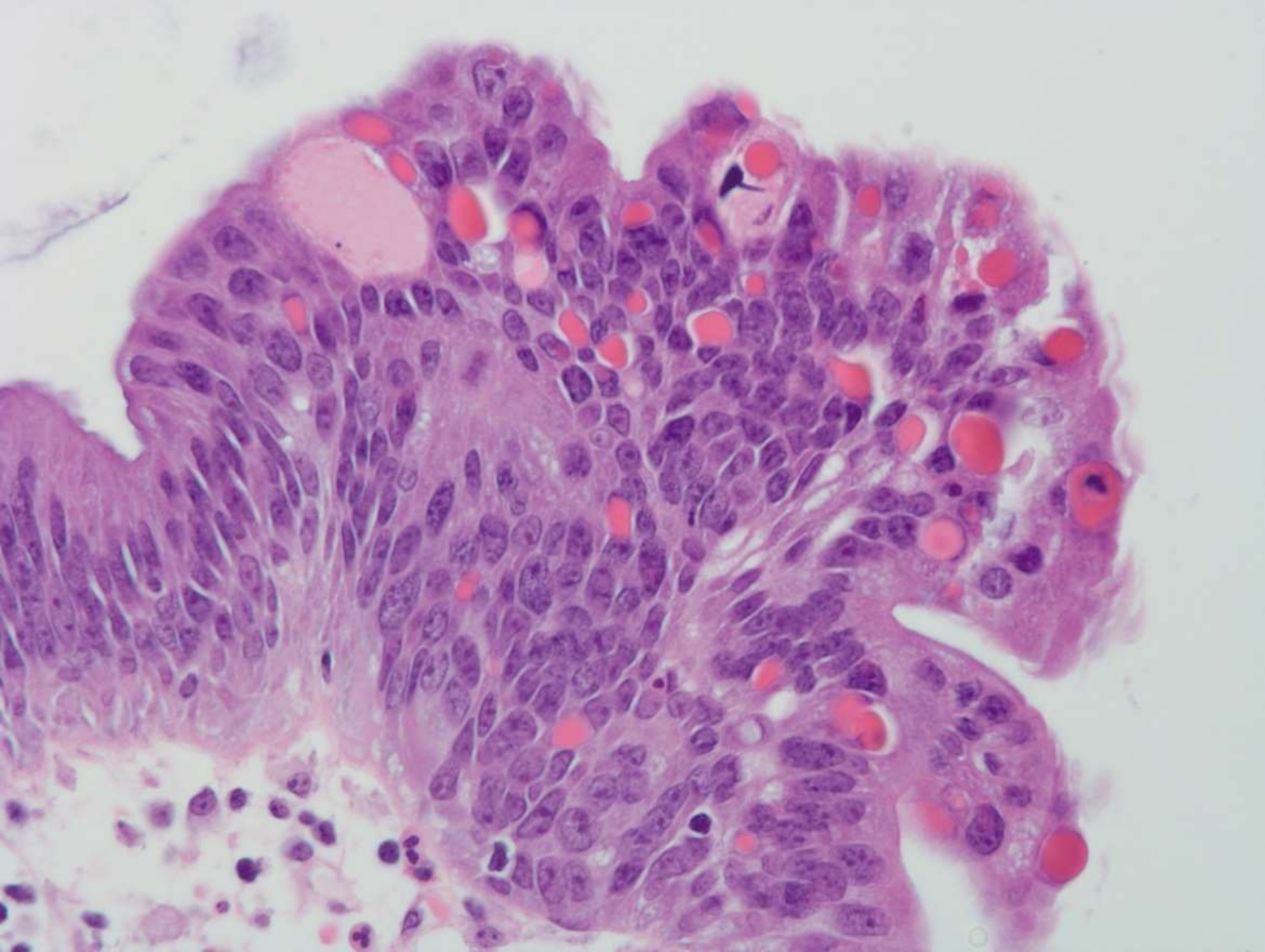
# Carcinoma in Crohn's Disease

- 2-16% patient with CD have dysplasia detected during the course of their illness
- Carcinoma when found typically occurs close to areas of dysplasia
  - 75% colon
  - 25% small intestineand
- Relative risk for carcinoma varies widely depending on the study (2.5 for colon cancer and 6-40 for small intestinal carcinoma)



# Small intestinal carcinoma in CD

- No effective screening programs
  - Recrudescence symptoms after long periods of quiescence
  - Obstruction refractory to medical therapy
- Symptoms are late with obstruction, nausea, vomiting and abdominal pain
  - Similar to exacerbations of CD
- Over 50% of carcinomas and resected Crohn's disease segments were unsuspected in one series
- 75% are located in the ileum

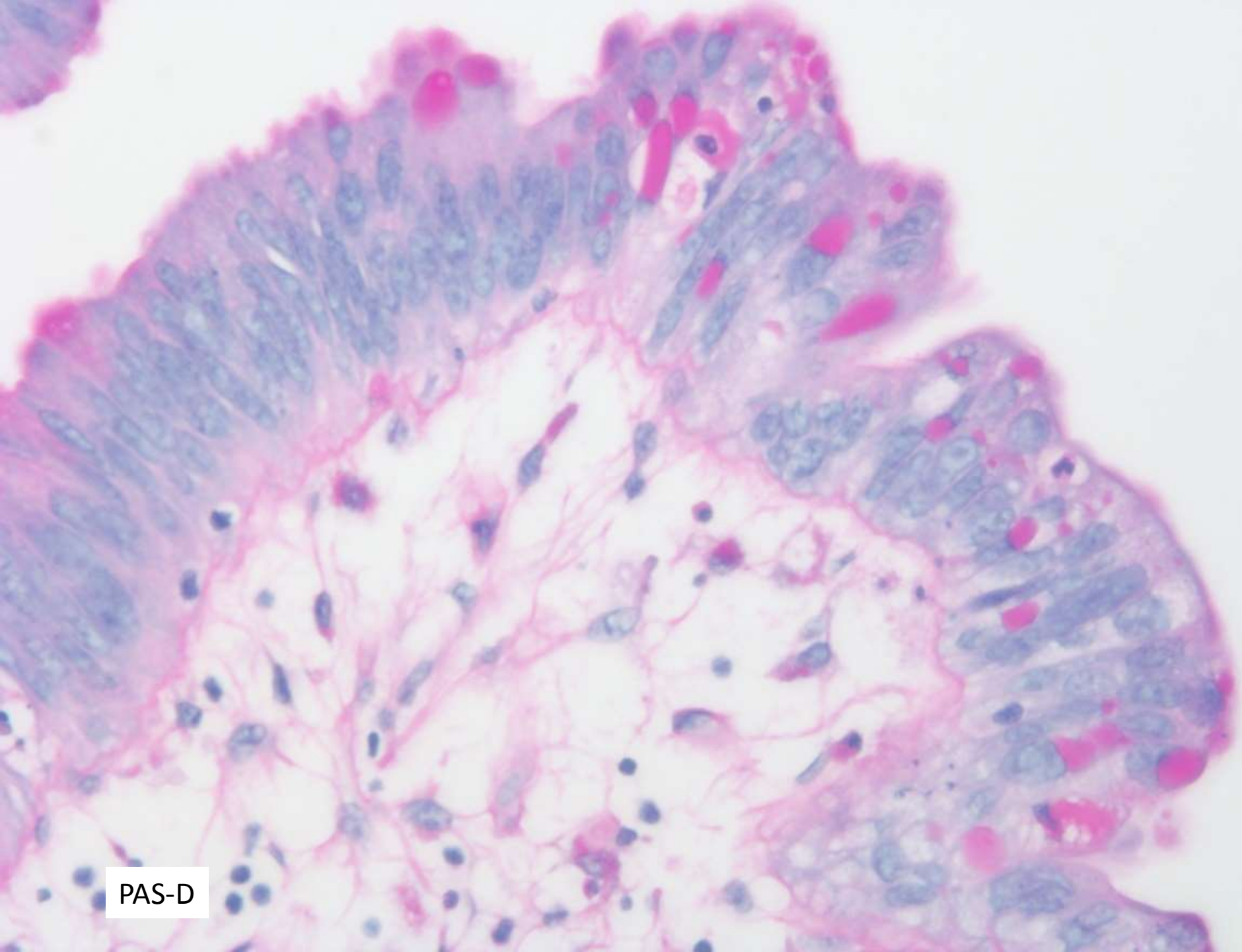




# Thanatosomes

Hyaline globules

- Concept of Thanatosomes introduced by Papadimitriou et al in 2000.
- Derived from Greek: Thanatos meaning death
- Seen in wide variety of benign and malignant conditions
- Perfectly round refractiles spheres to waxy dull ovoid structures
- Variably PAS positive



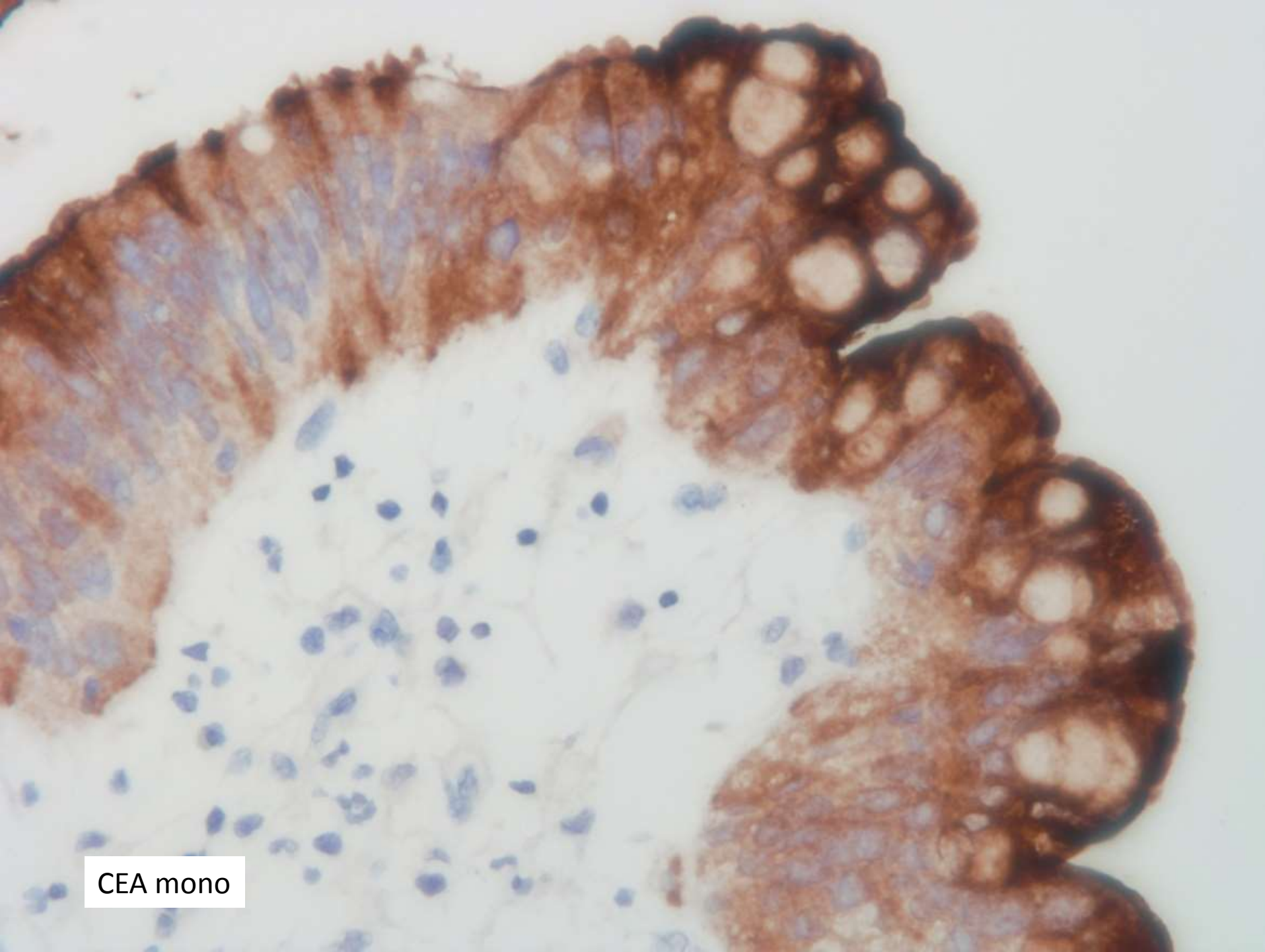
PAS-D



# Thanatosomes

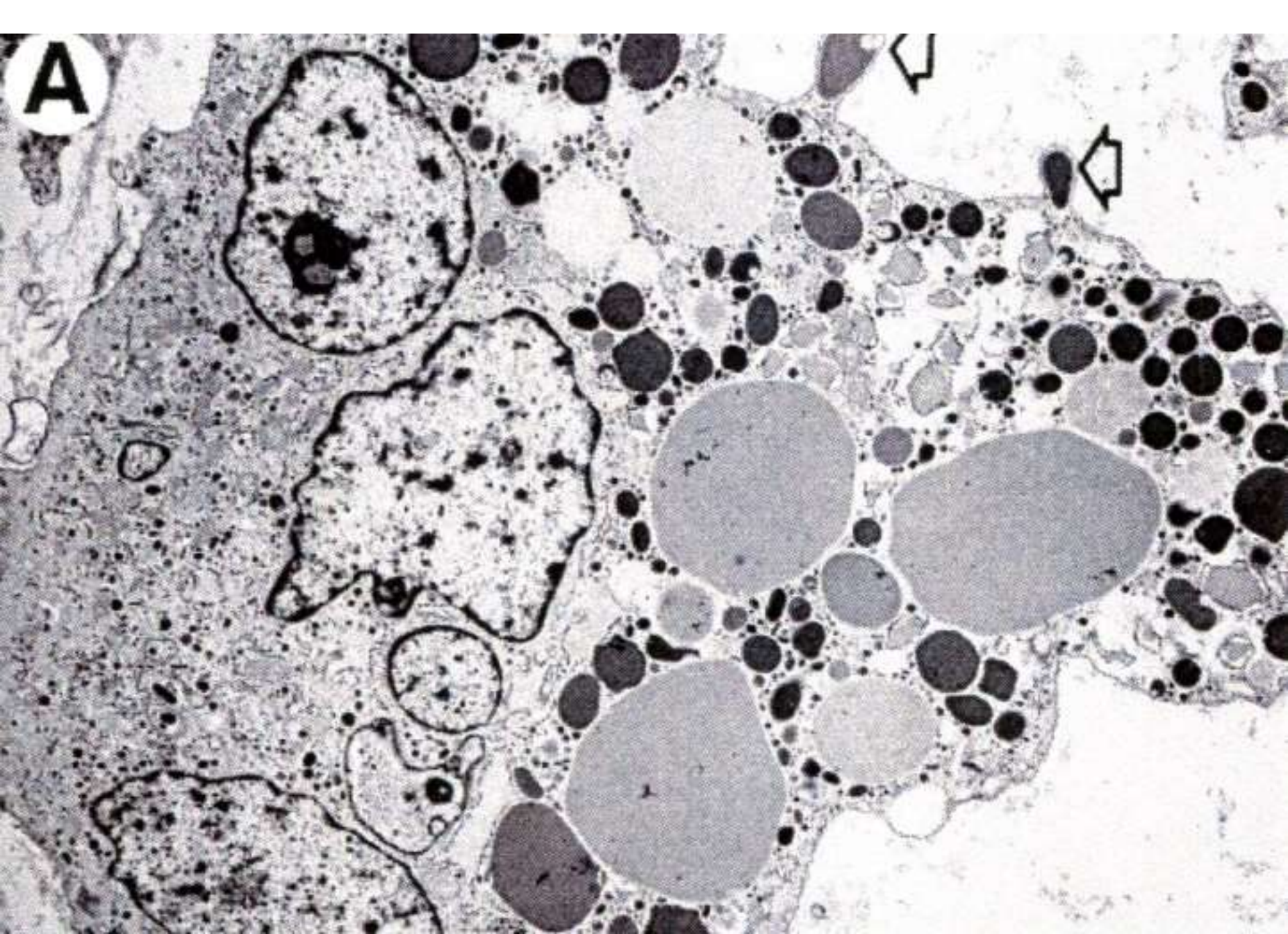
## IHC/EM

- Stain variably with a variety of proteins
  - A-1-AT, ferritin, C3, K/λ, IgG, and CEA
- EM: large osmophilic inclusions
  - Contain membrane, lipid and nuclear debris in varying stages of digestion
  - RER encircles some inclusions
  - Associated with intense cytoplasmic blebbing and interrupted plasma membranes
    - Suggesting extrusion from cells

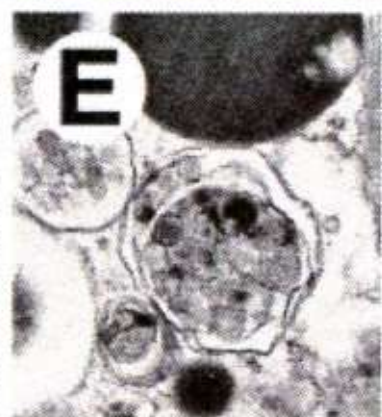
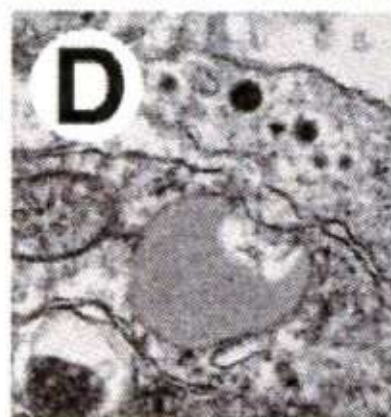
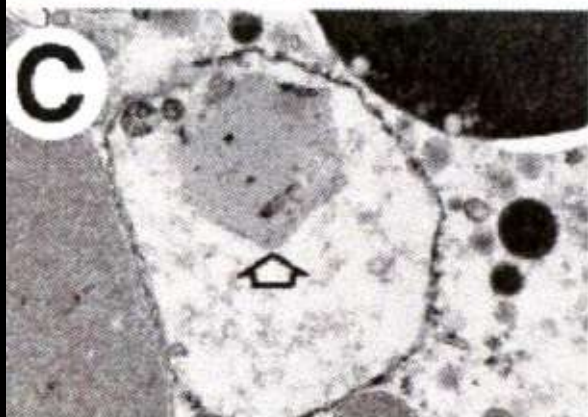
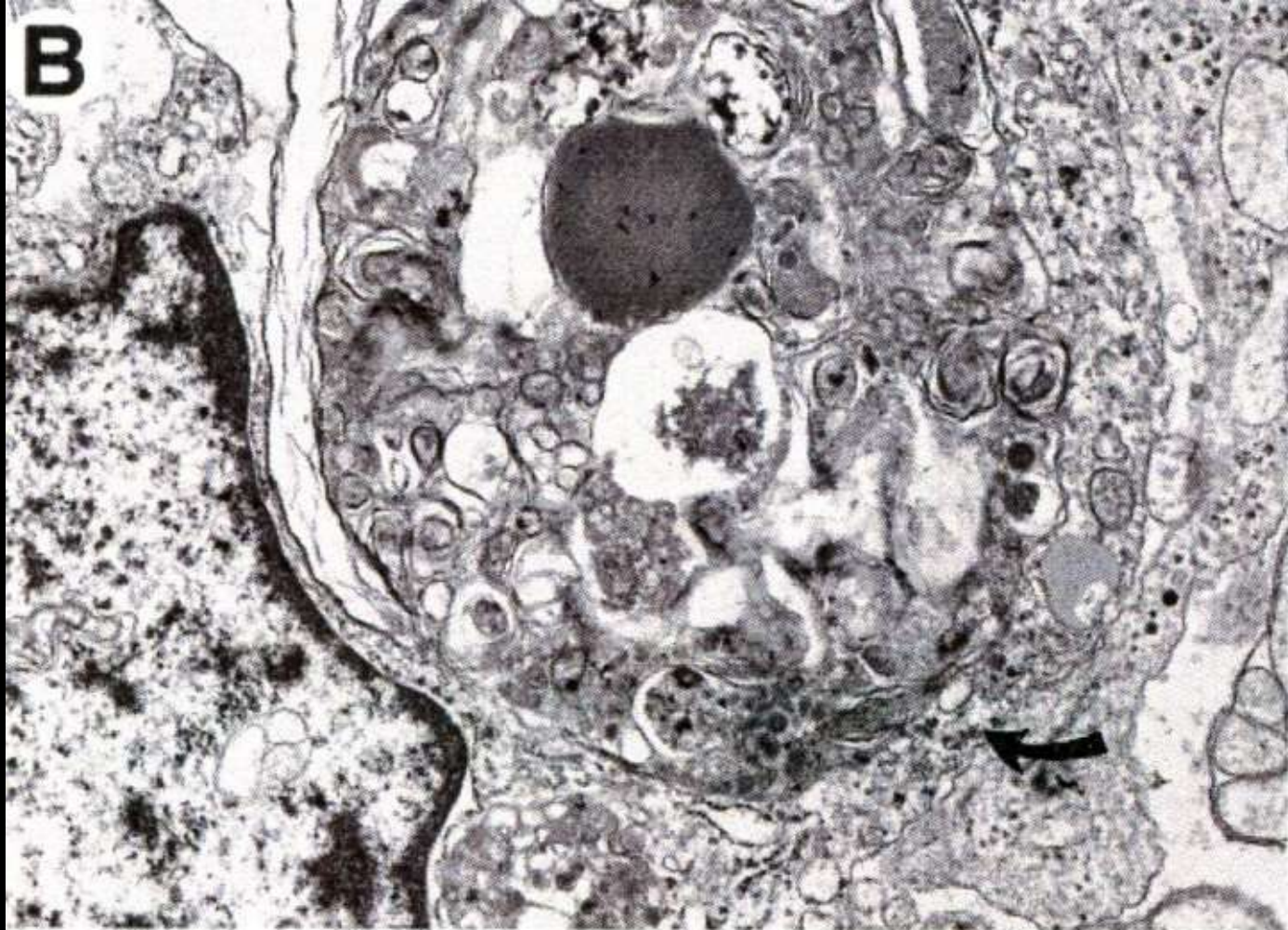


CEA mono











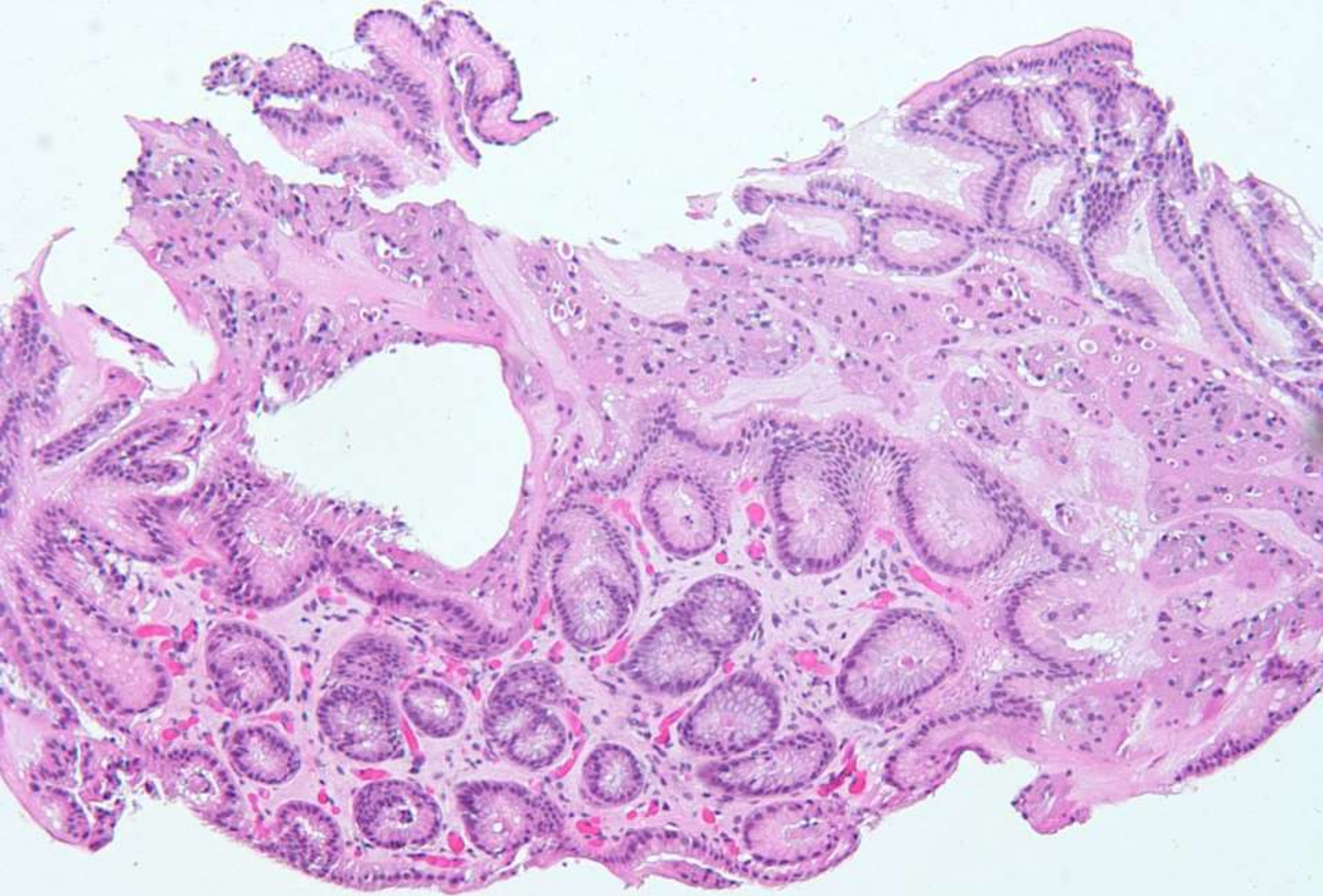
# Thanatosomes

- Thanatosomes are not specific to any tumor but represent a degenerative phenomena related to apoptosis, common to all cell types, benign or malignant. Thanatosomes result from cytoplasmic blebbing and nuclear fragmentation followed by phagocytosis by neighboring cells or auto phagocytosis, accompanied by increased membrane permeability to plasma proteins.
- Reference: Human pathology 31: 1455-65; 2000

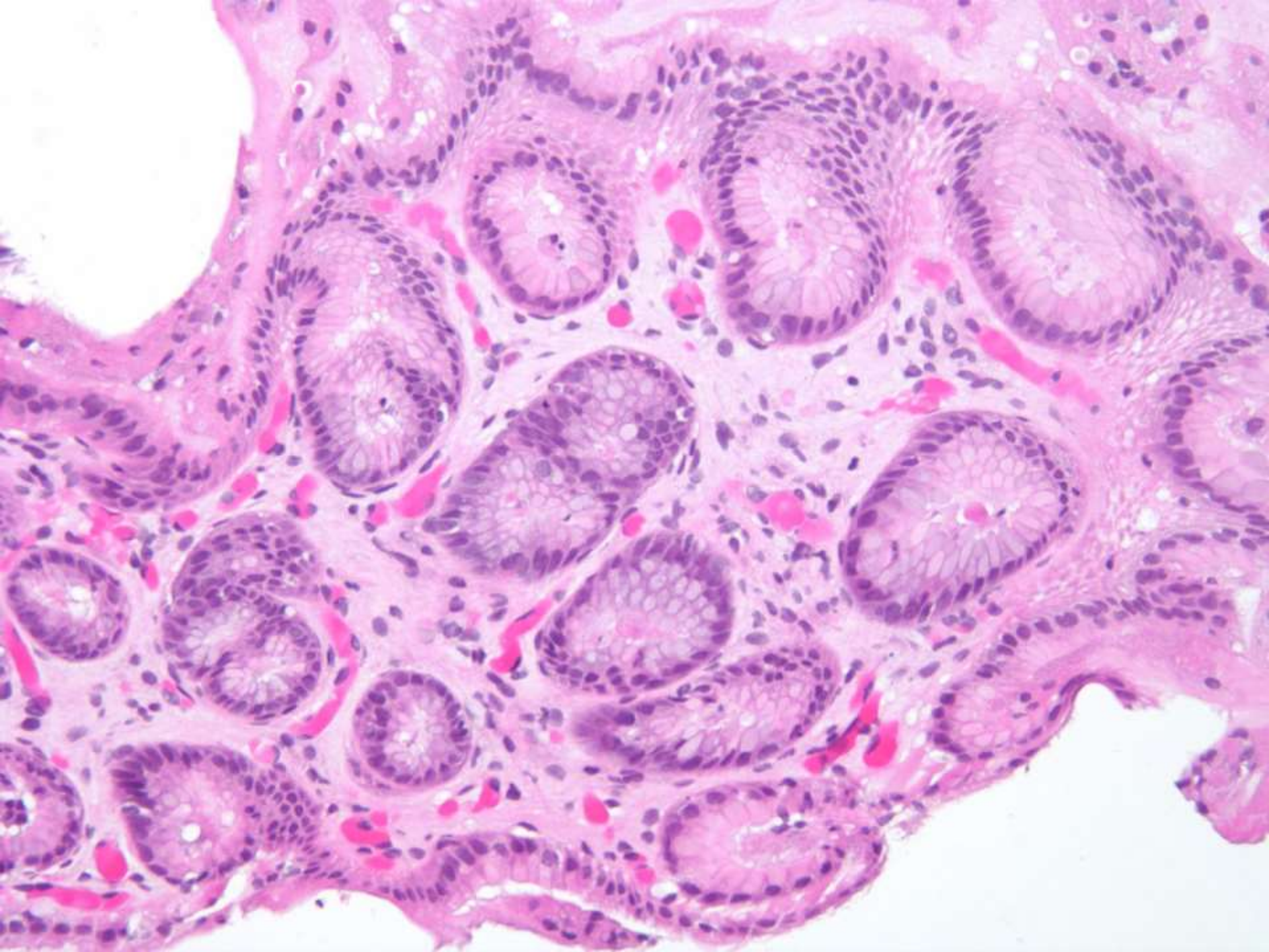
28 yo M

Biopsy of Gastric Antrum

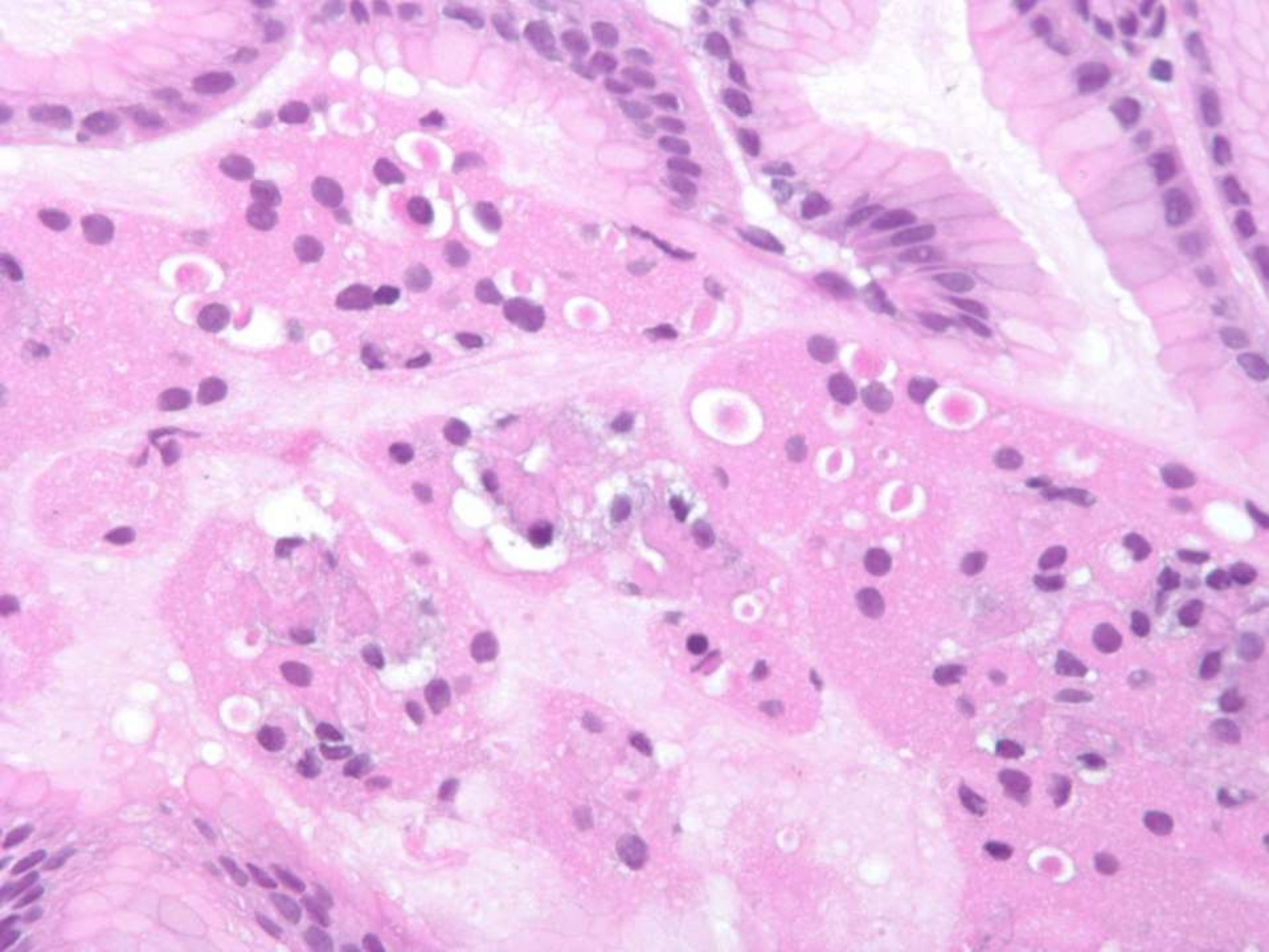












# Summary

- Scattered eosinophilic globules are identified associated with the gastric epithelium. These cytoplasmic structures have been called “thanatosomes” and are thought to represent a marker of enhanced epithelial cell turnover (regenerative epithelium) and ischemic injury.
  - May be demonstrated in otherwise normal, congested, hyperplastic, and regenerative epithelium.
  - Reported to be identified in 10 high than 30% of adenomatous polyps and adenocarcinoma.
- Dikov et al: “Hyalin globules (Thanatosomes) in gastrointestinal epithelium”. AJCP 2007; 127: 792-9.



Thanatosomes !!!

# FOURTH PLACE

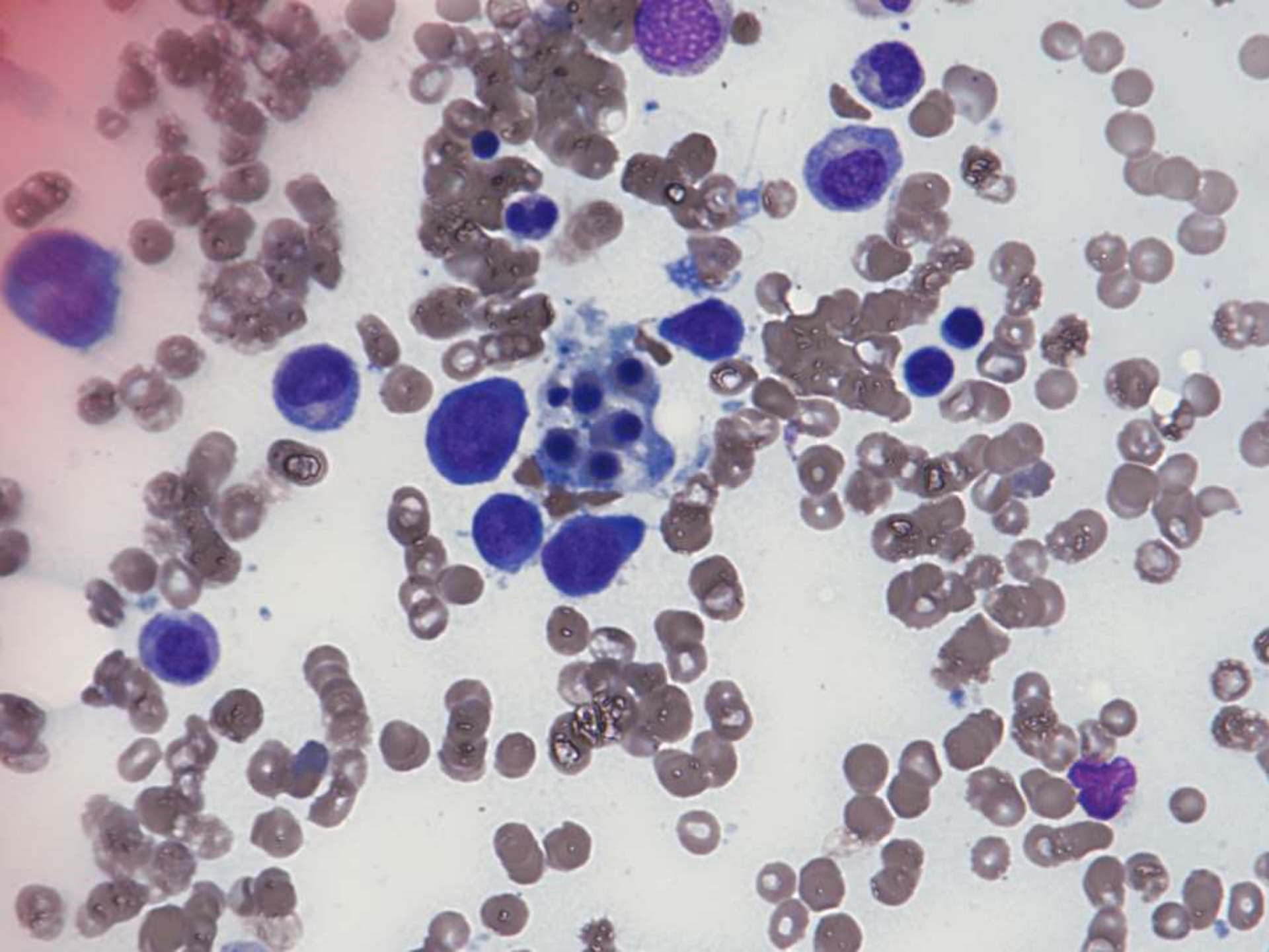
- Jerry Williams, of Little Rock, Arkansas, was awarded \$14,500 plus medical expenses after being bitten on the butt by his next door neighbor's beagle - even though the beagle was on a chain in its owner's fenced yard. Williams did not get as much as he asked for because the jury believed the beagle might have been provoked at the time of the butt bite because Williams had climbed over the fence into the yard and repeatedly shot the dog with a pellet gun



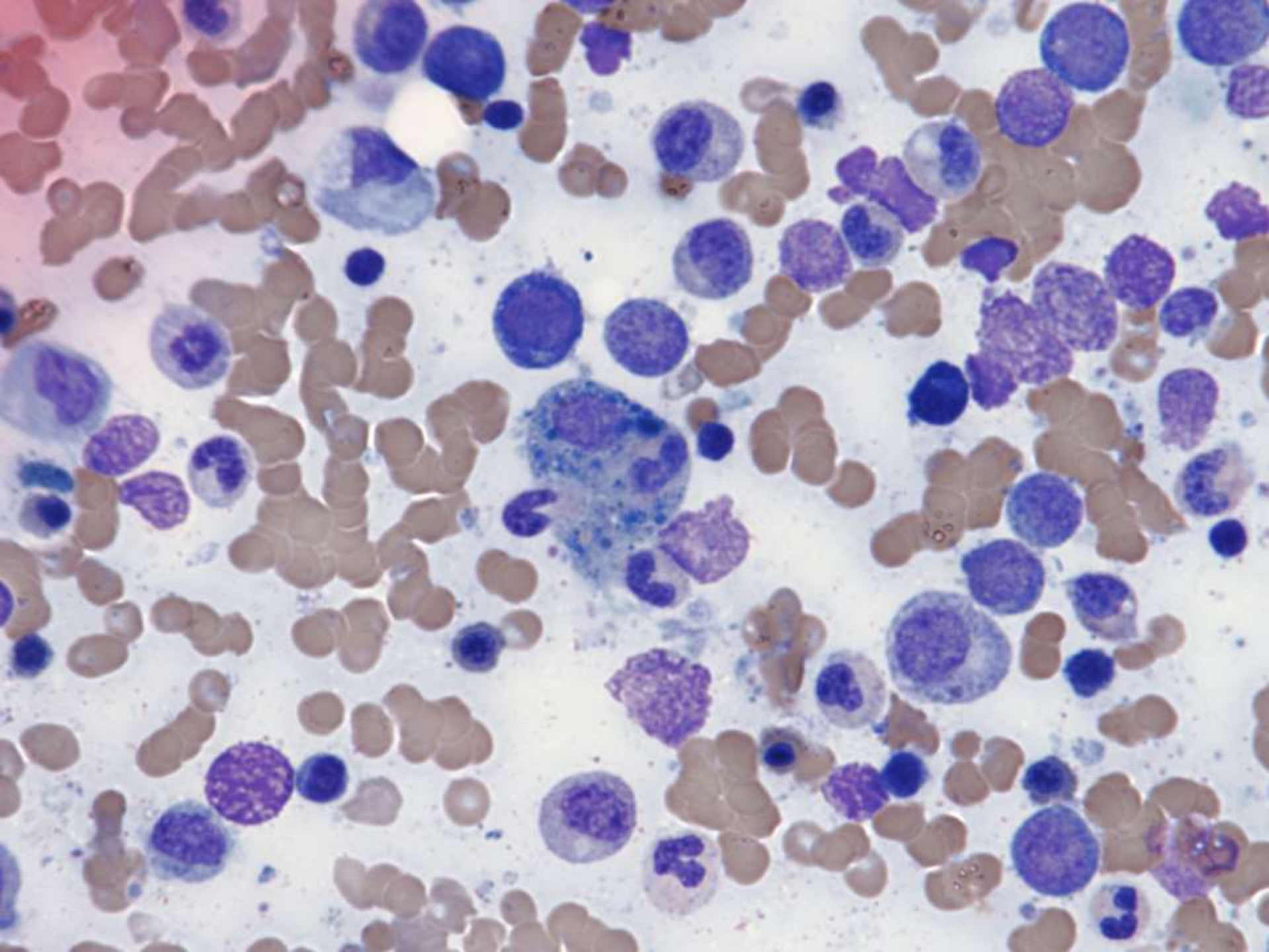
# 19-0706

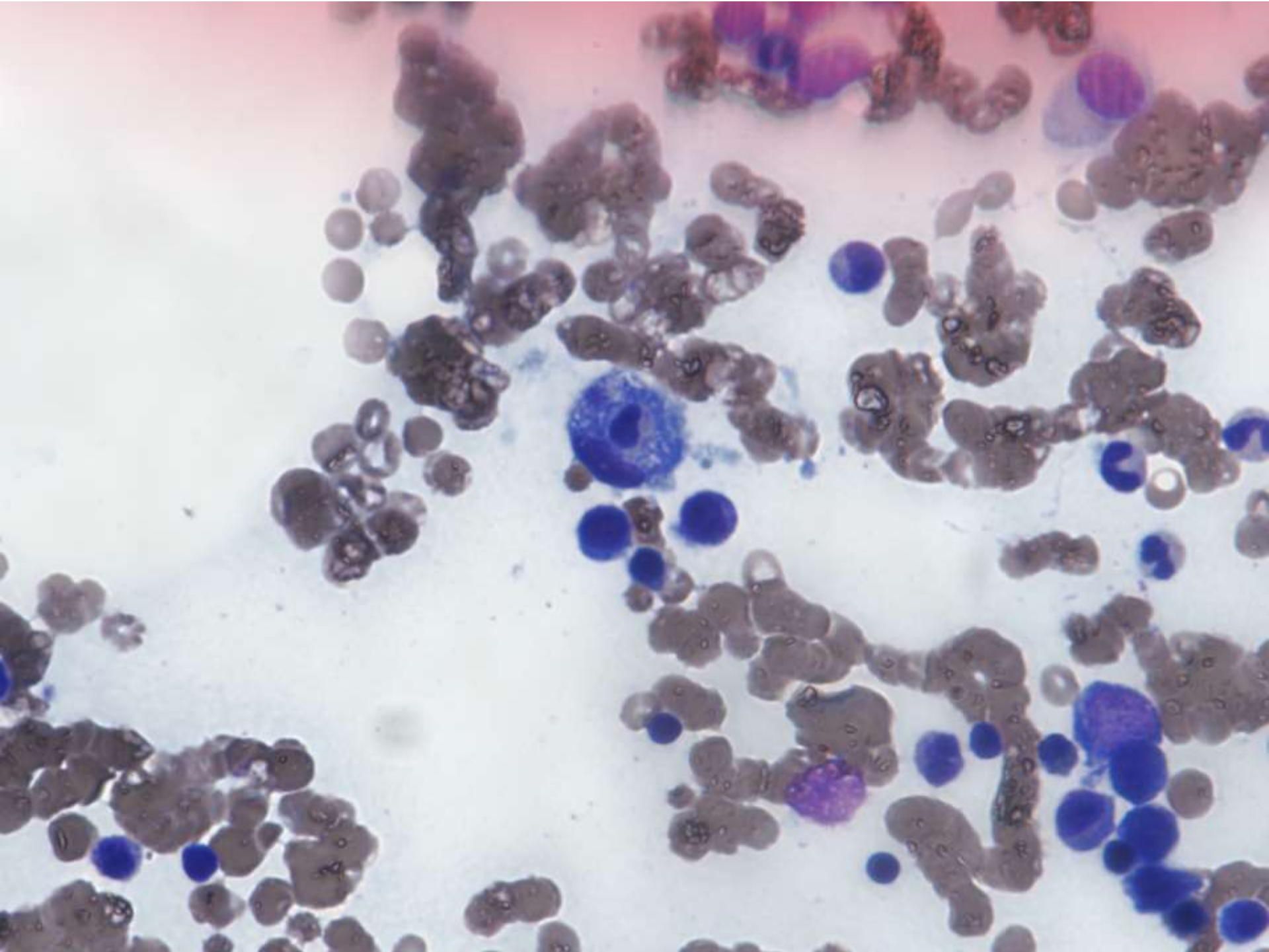
Sebastian Fernandez-Pol/Dita  
Gratzinger; Stanford

40-year-old man with no significant  
past medical history undergoes bone  
marrow biopsy.

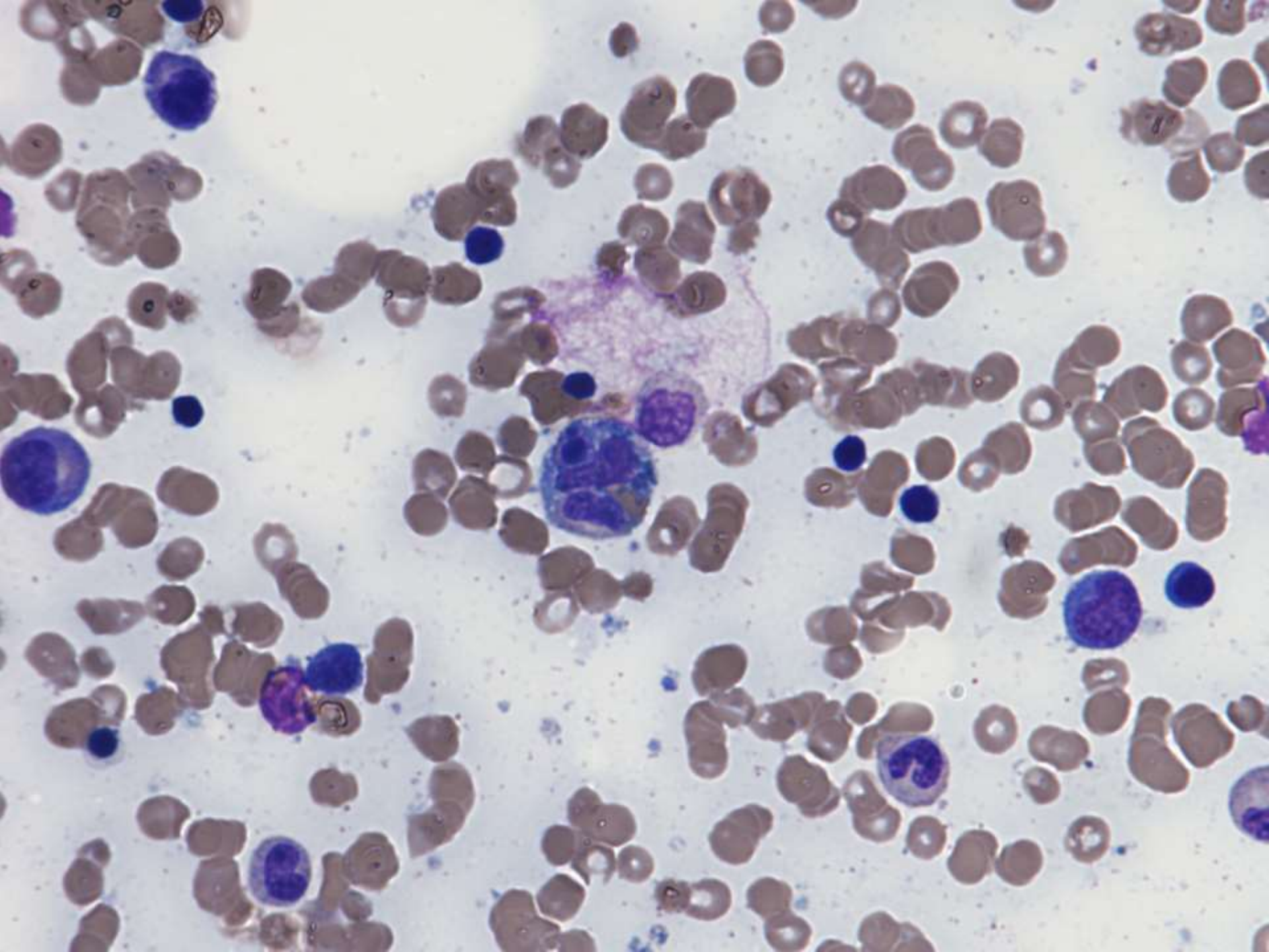


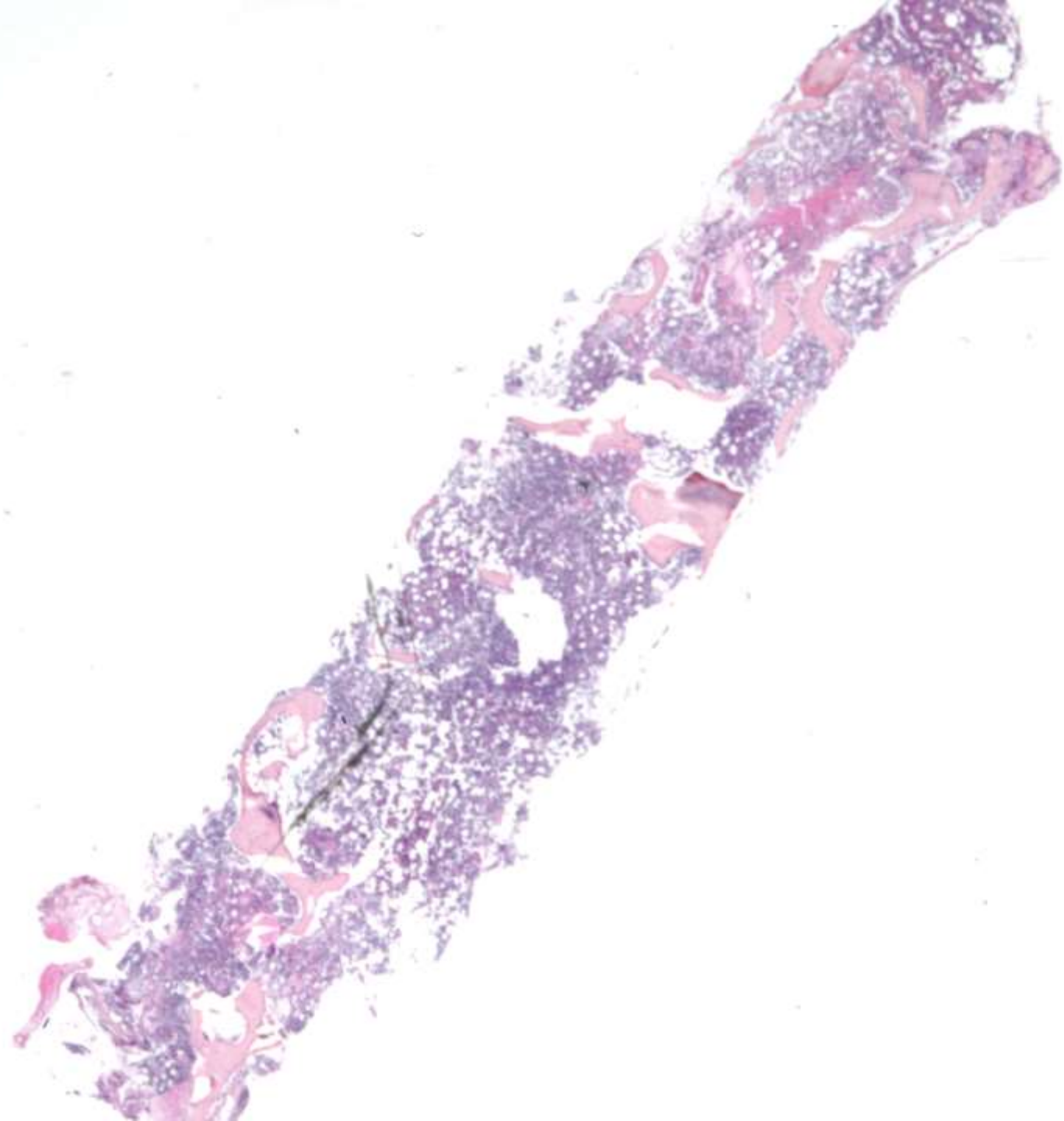




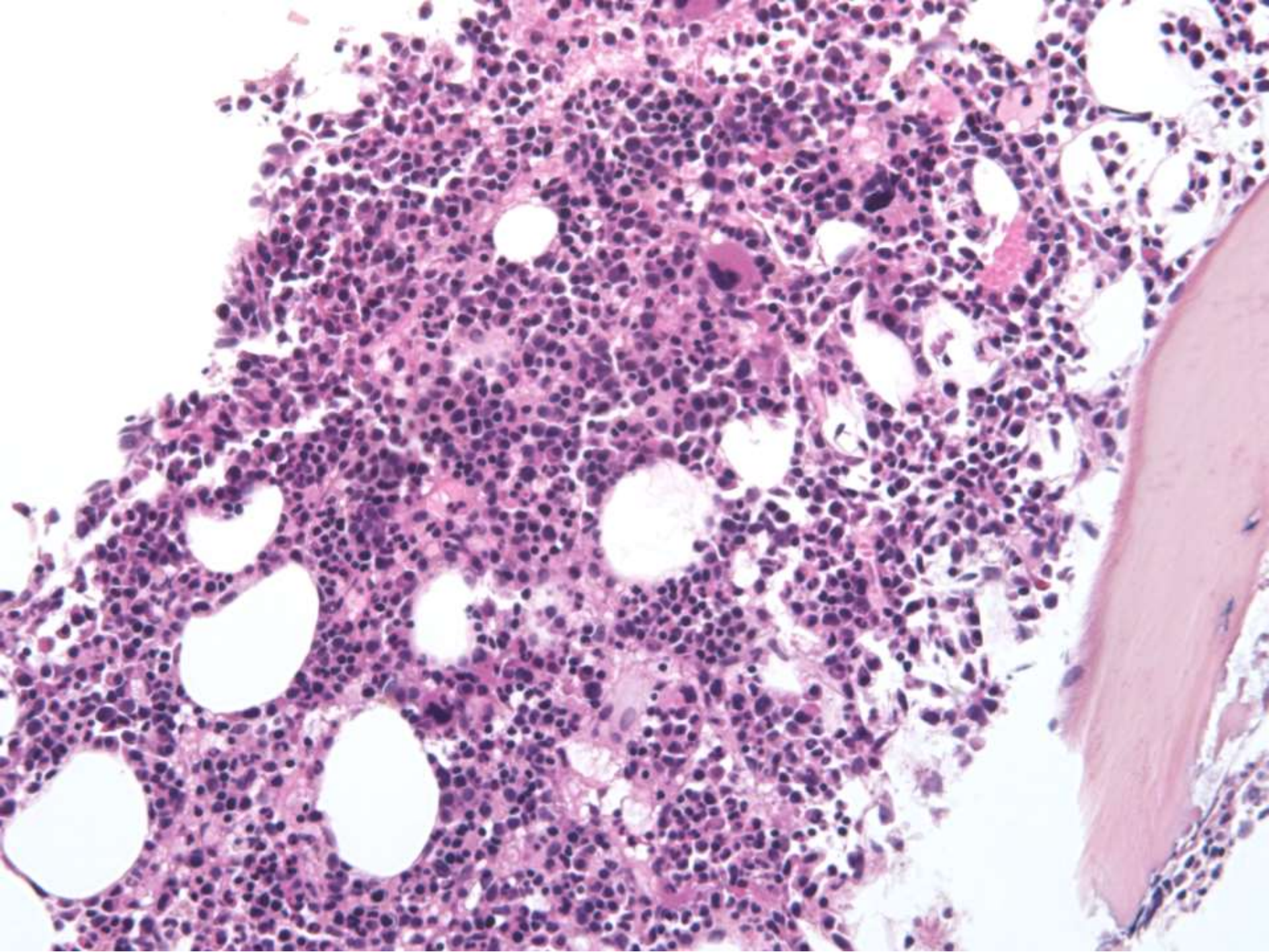




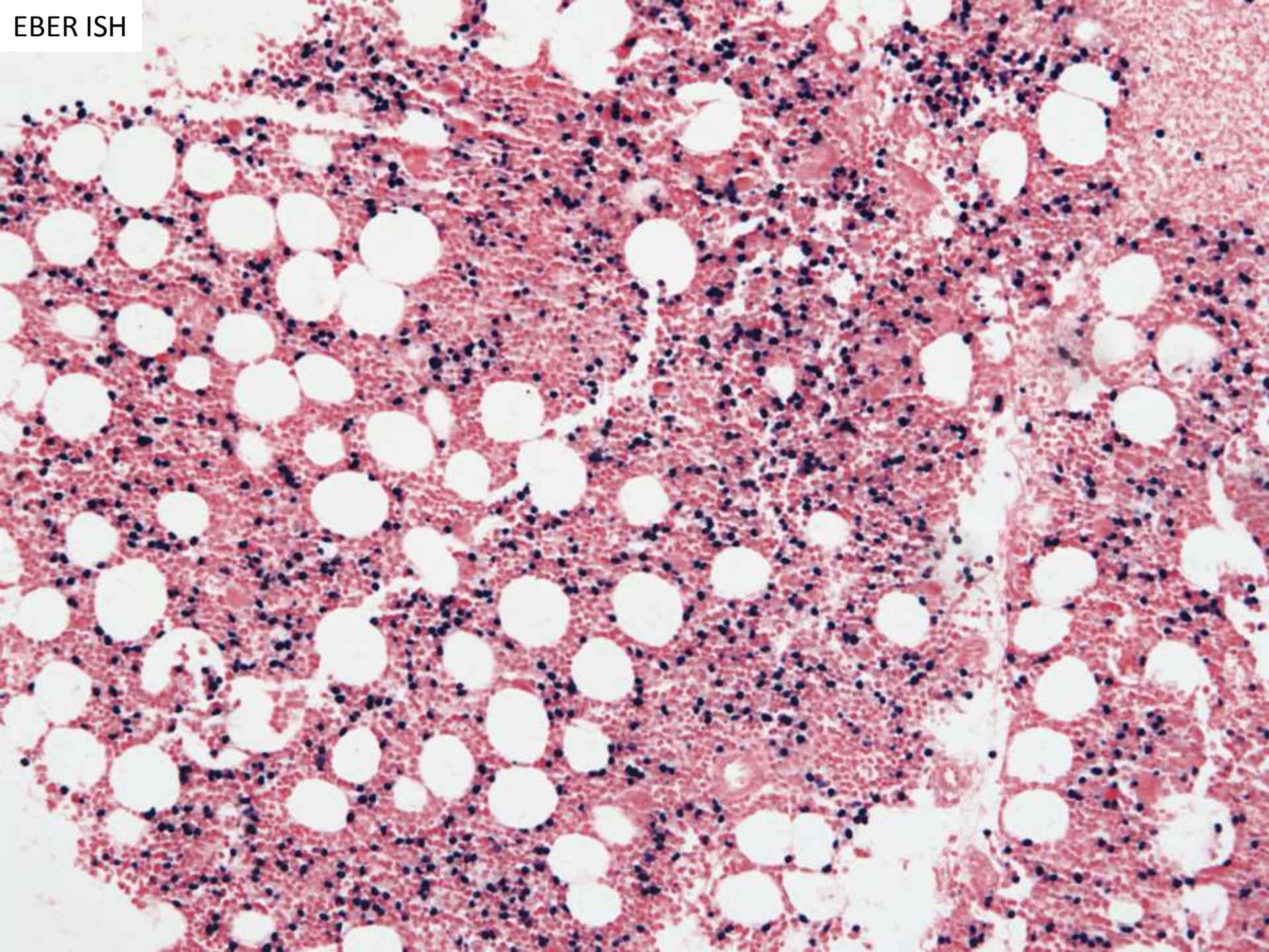








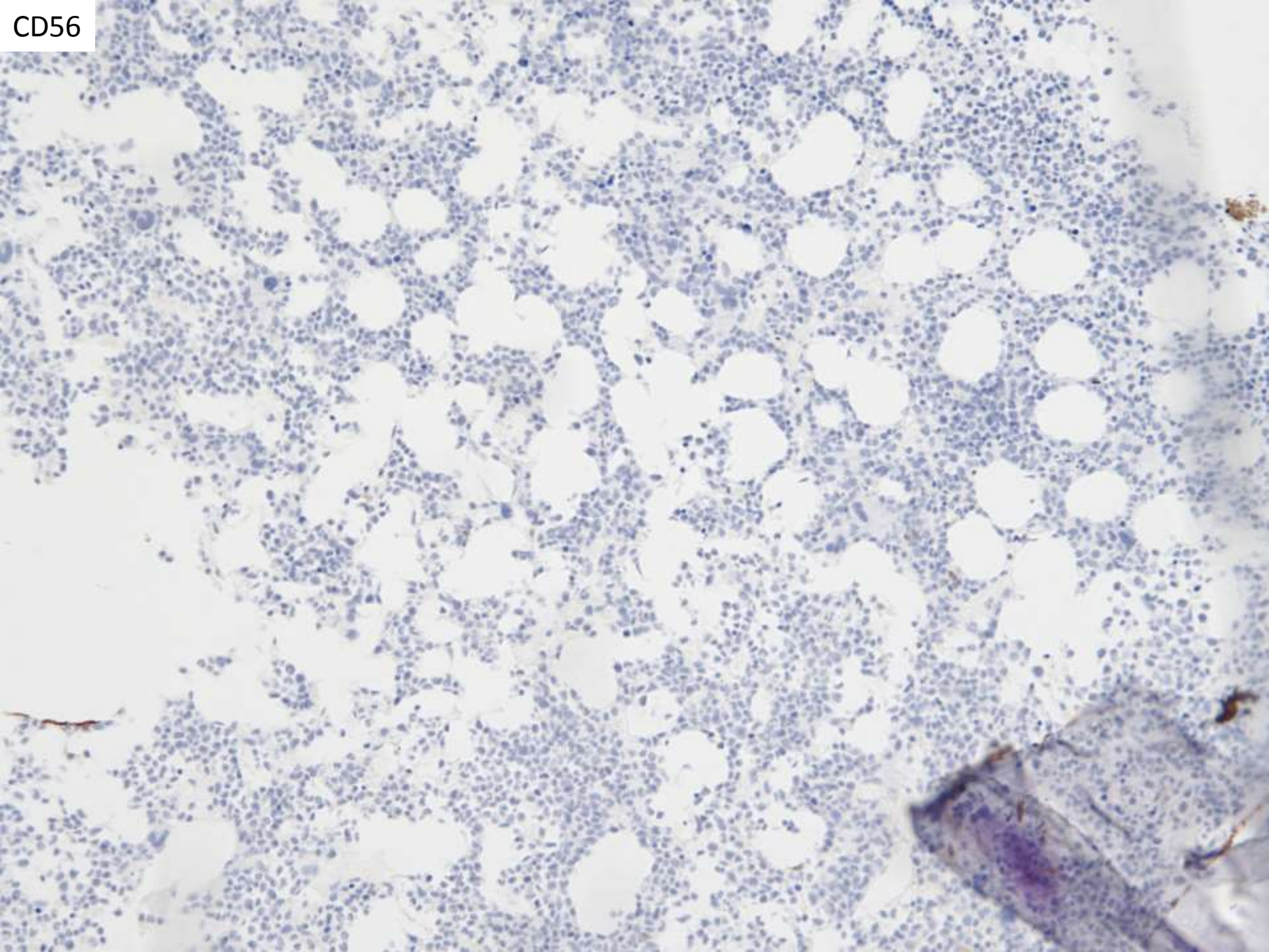




EBER ISH

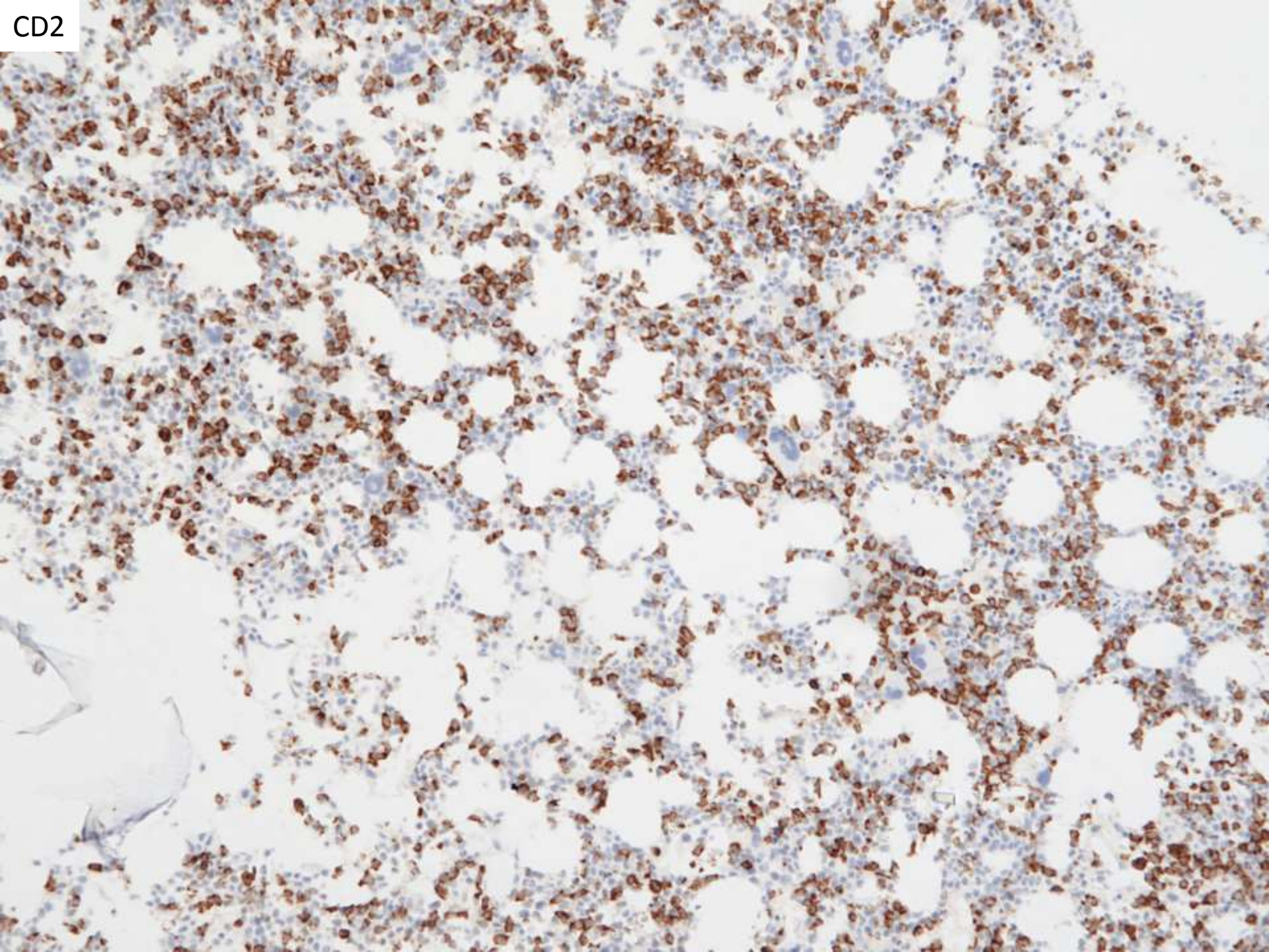


CD56

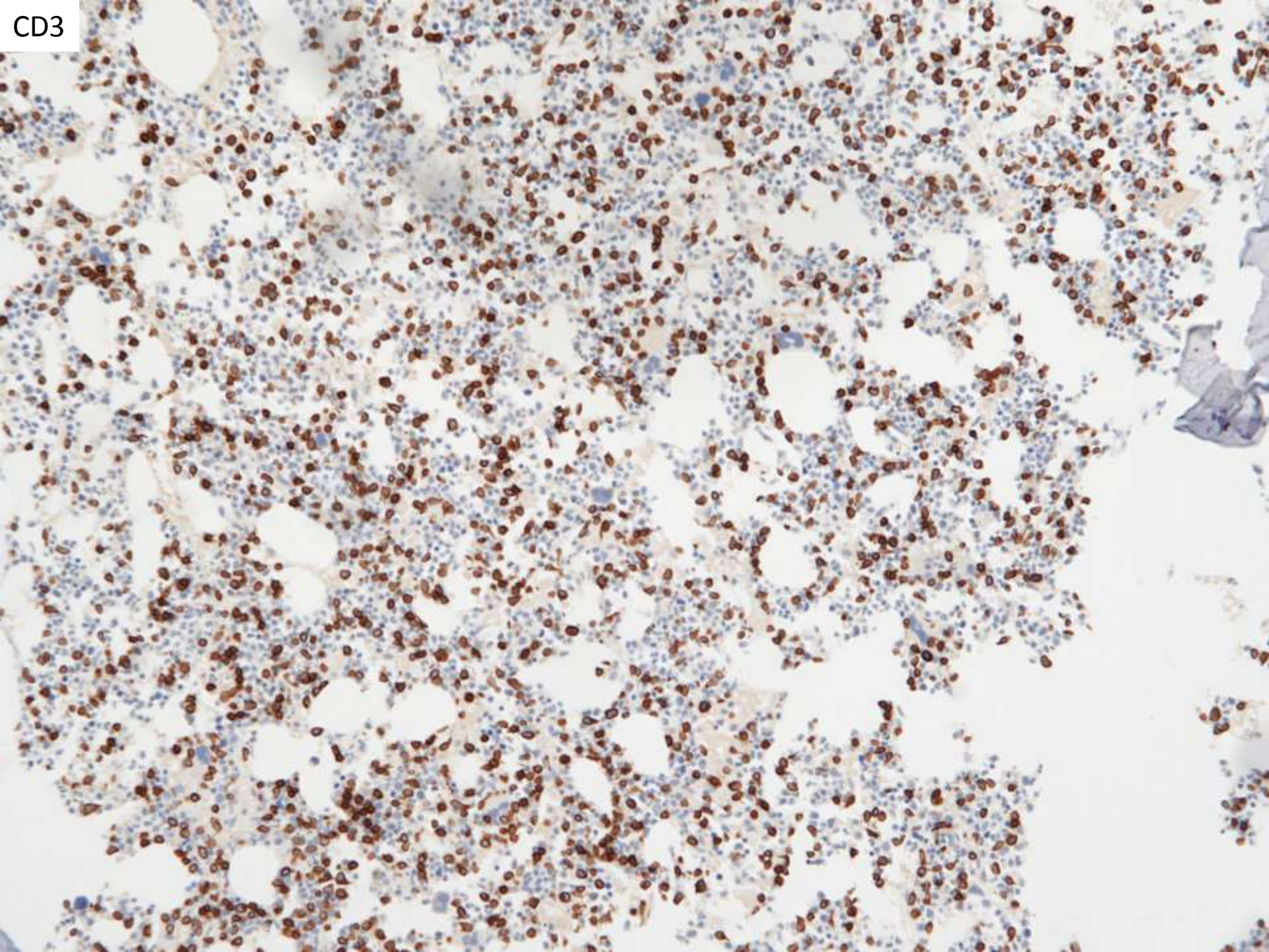




CD2

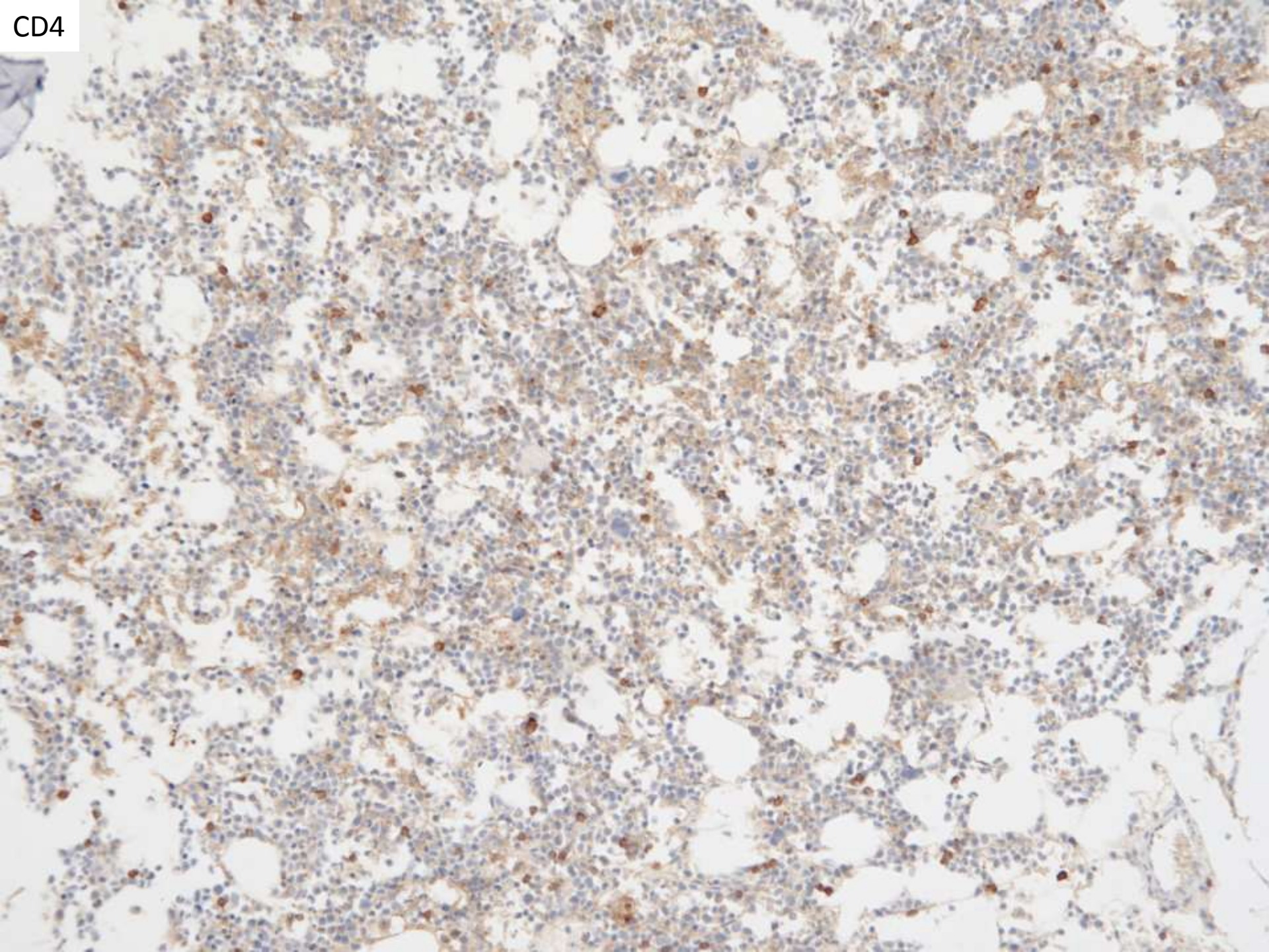






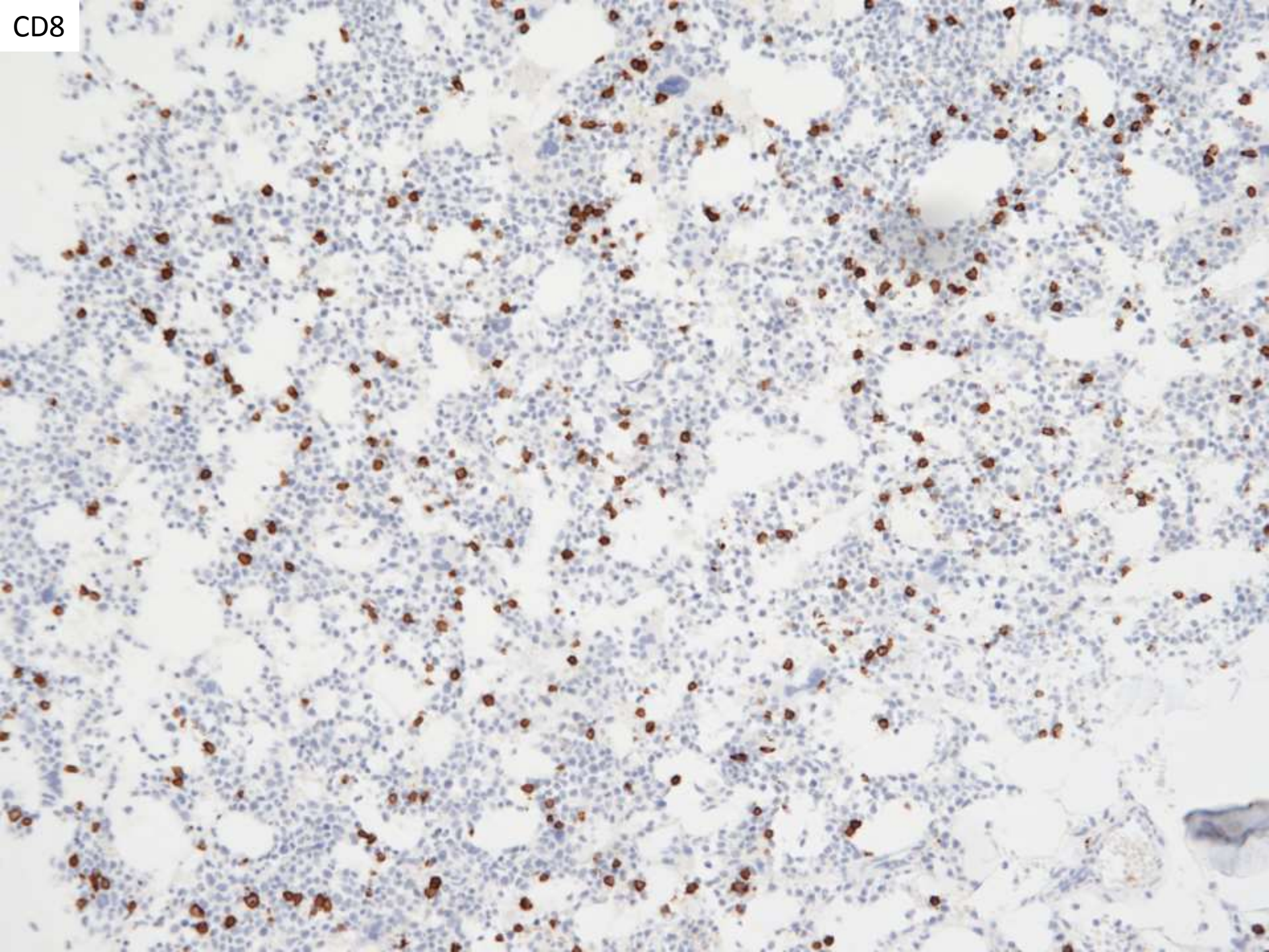


CD4

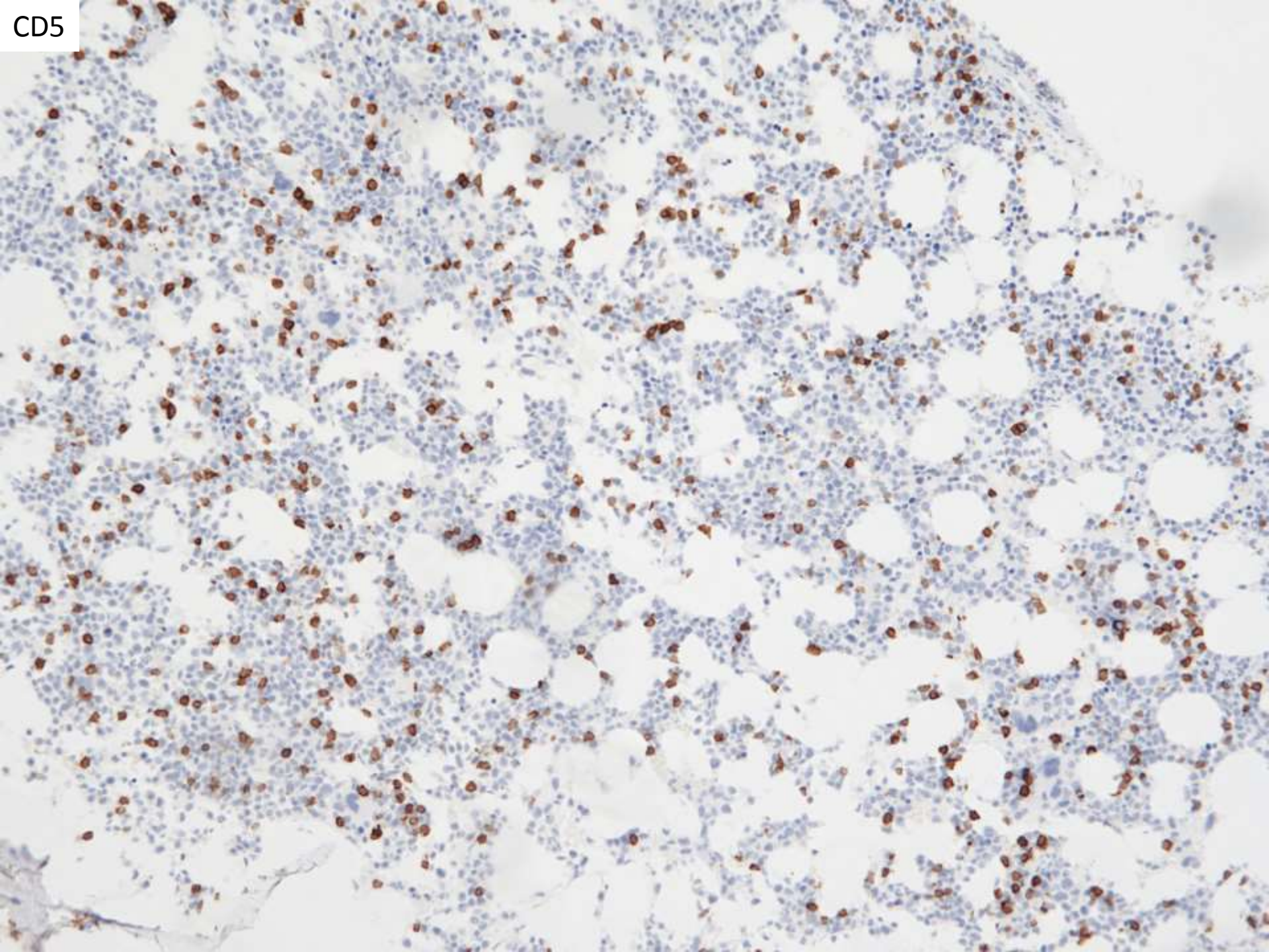




CD8

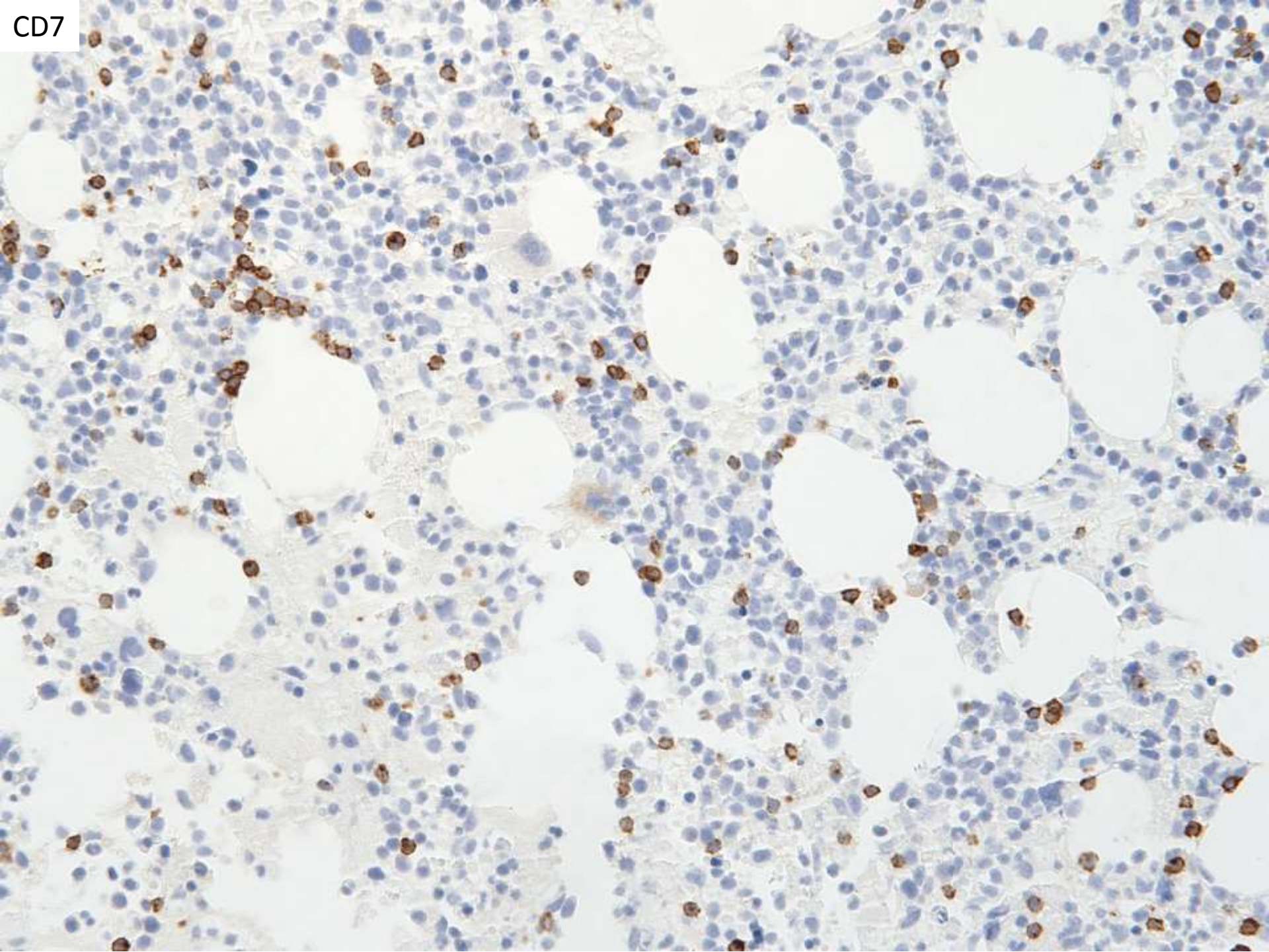






CD5

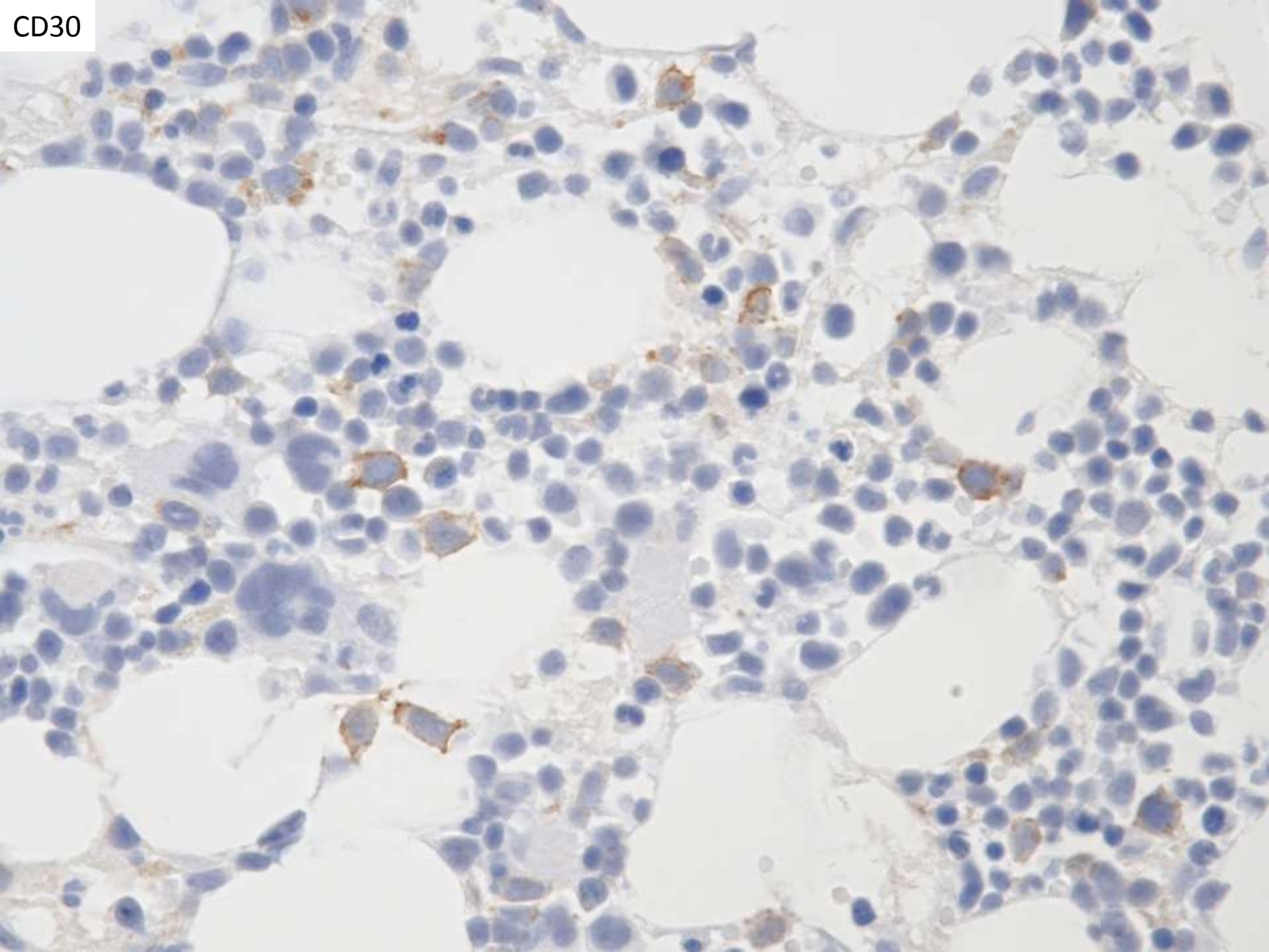




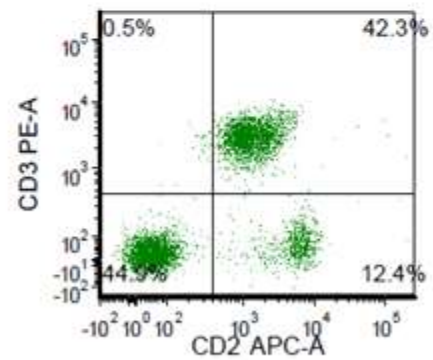
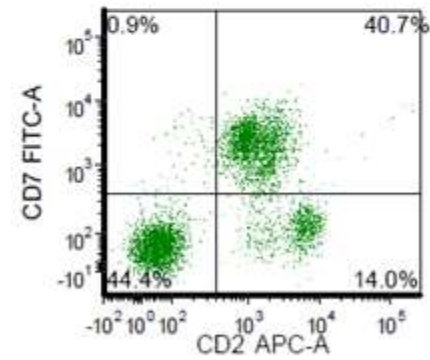
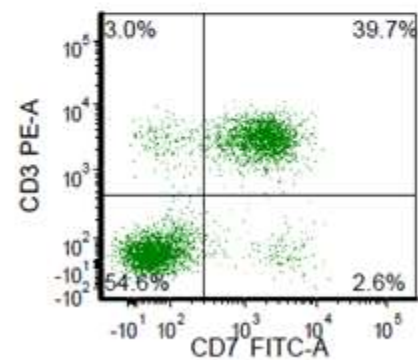
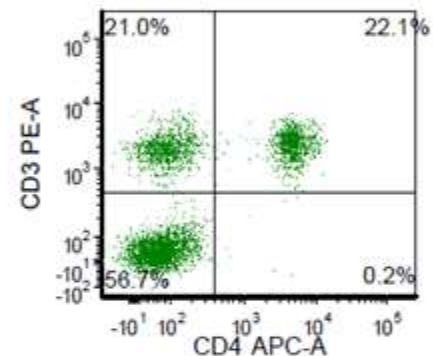
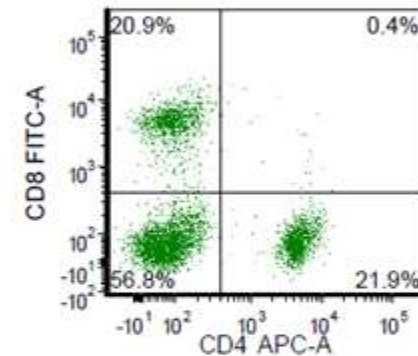
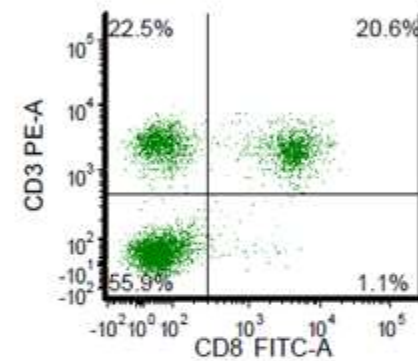
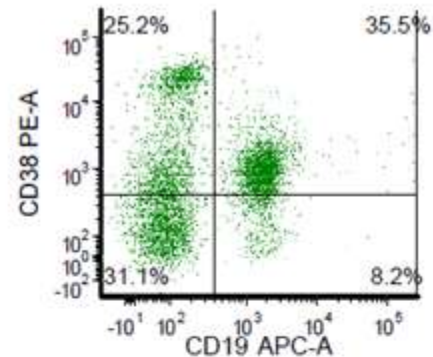
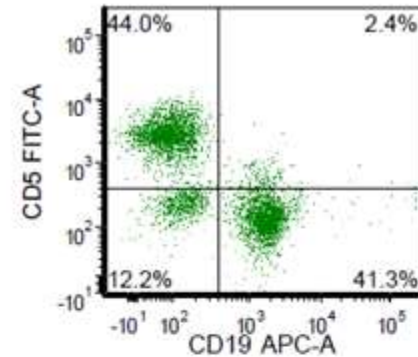
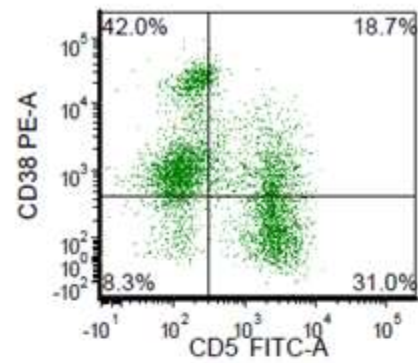
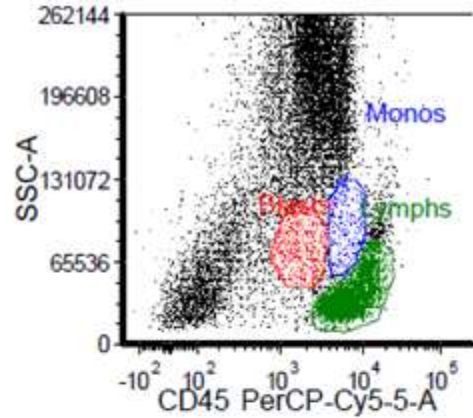
CD7

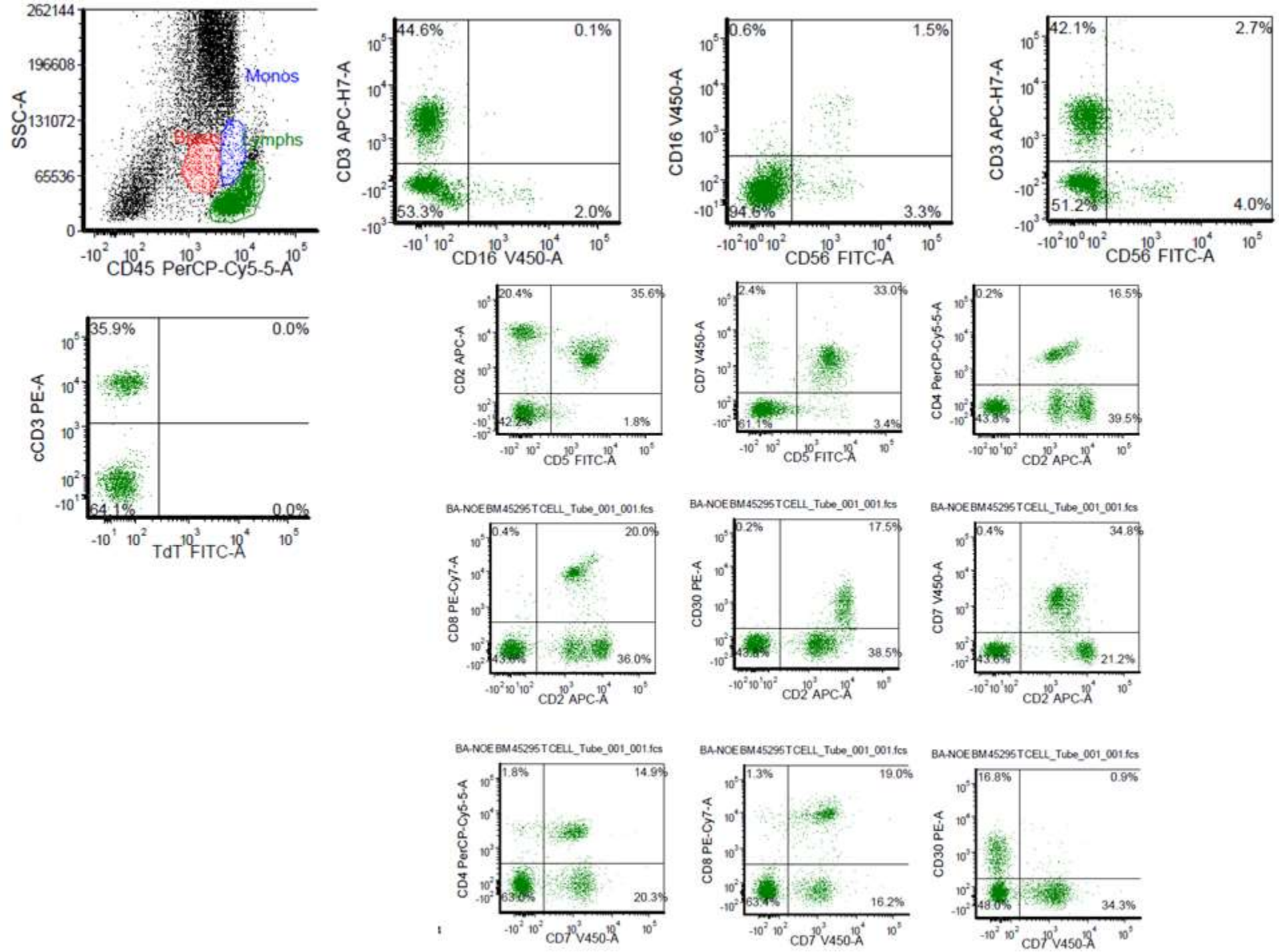


CD30

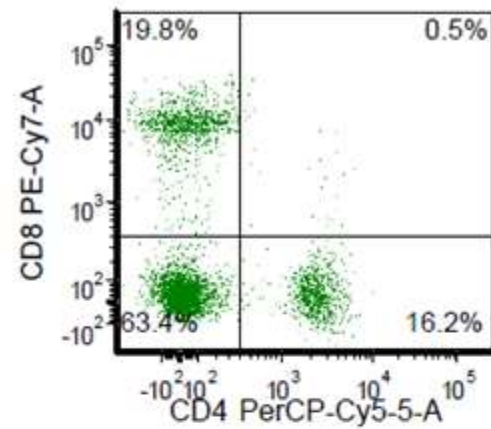
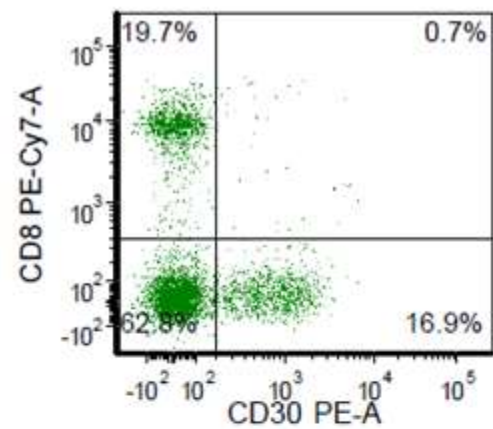
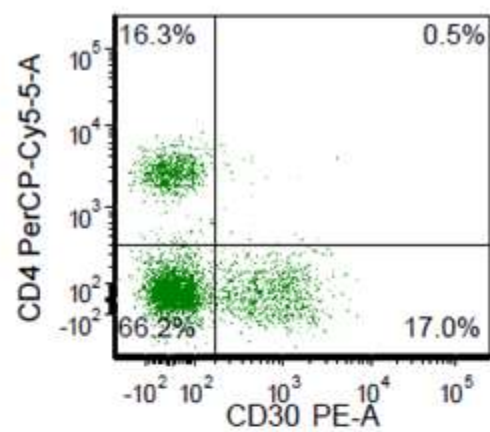












# DIAGNOSIS?







# Summary of findings

- 40 year old male with 1 month fever, HA, NV
- Hemophagocytosis
- Immunoprofile of abnormal population:
  - EBV+
  - CD3+
  - CD2+
  - CD5-
  - CD7-
  - CD4-
  - CD8-
  - CD56-
  - CD30 dim

## Differential diagnosis

- Systemic EBV-positive T-cell lymphoma of childhood
  - CD56-, **CD8+** or **CD4+**
- Chronic active EBV (CAEBV)
  - Need 3 months of mono-like symptoms
  - Usually CD4+, less often CD8+
- EBV-associated hemophagocytic lymphohistiocytosis (HLH)
- Aggressive NK-cell leukemia
  - **CD56+**



# Systemic EBV-positive T-cell lymphoma of childhood

- Aggressive with rapid progression, multiorgan failure, sepsis, and death usually in **days to weeks**
- Usually children
- Can occur shortly after primary acute EBV or in the setting of chronic active EBV infections (CAEBV)
  - Usually CD8+ if primary
  - Usually CD4+ when following CAEBV, but can be CD4+CD8+ or CD8+
- Clinical and pathologic overlap with aggressive NK-cell leukemia

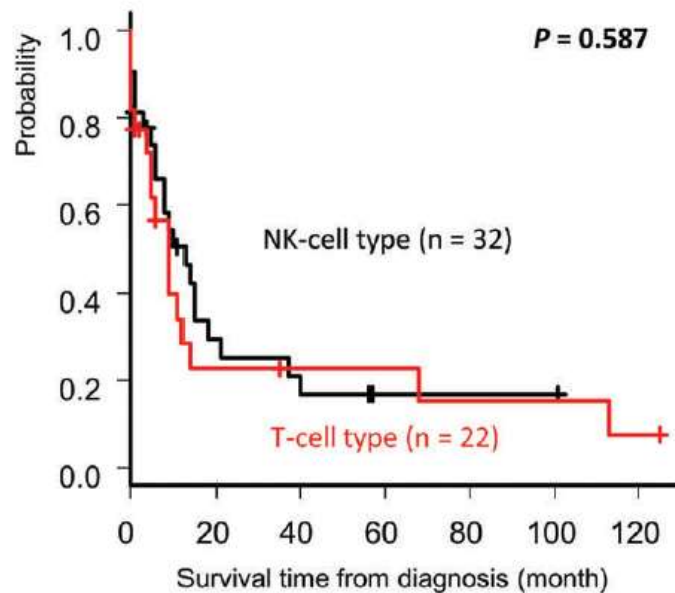
# Chronic active EBV (CAEBV) diagnostic criteria

- At least 3 months of intermittent or persistent infectious mononucleosis-like symptoms such as fever, lymphadenopathy, and hepatosplenomegaly
- High viral load in peripheral blood or tissues
- No known immunodeficiency
- Polyclonal, oligoclonal, or often monoclonal T-cell or NK-cells



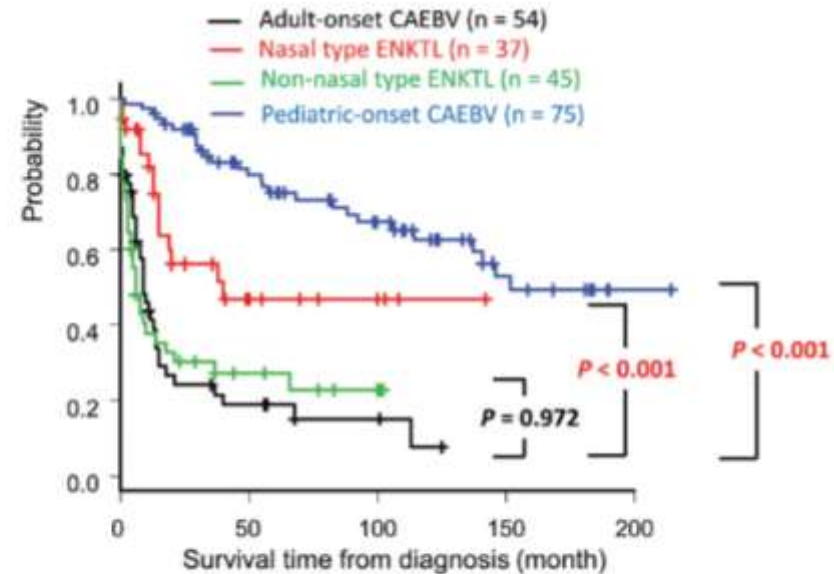
# Adult-onset chronic active EBV (CAEBV)

A



## Patient at risk

NK-cell type	32	7	5	2	1	1	0
T-cell type	22	4	3	3	2	2	1



## Patient at risk

Adult-onset CAEBV	54	7	3	0	0
Nasal type ENKTL	37	8	4	0	0
Non-nasal type ENKTL	45	7	3	0	0
Pediatric-onset CAEBV	75	49	32	15	6

# Clinical course

- 1 month of fever, chills, nausea vomiting
- Initial plasma EBV = 126,642 IU/mL
- Etoposide and CHOP
- Pulmonary and mediastinal Rhizopus infection
- Duodenal biopsy with intravascular involvement by EBV+ T-cell lymphoma
- Bone marrow biopsy ~3 months after initial diagnosis showed an atypical CD30+ population
  - Plasma EBV = 107,055 IU/mL
- Expired ~4 months after symptom onset



# Take home points

- This case highlights the challenge in diagnostic classification of EBV+ T-cell lymphoproliferative disorders and predicting outcomes
  - Systemic EBV+ T-cell lymphoma of “childhood”
  - Chronic active EBV
  - EBV-associated hemophagocytic lymphohistiocytosis (HLH)
- Have a low threshold for doing EBER stain in a patient with unexplained fevers

# THIRD PLACE

- Amber Carson of Lancaster, Pennsylvania because a jury ordered a Philadelphia restaurant to pay her \$113,500 after she slipped on a spilled soft drink and broke her tailbone
- The reason the soft drink was on the floor: Ms. Carson had thrown it at her boyfriend 30 seconds earlier during an argument.

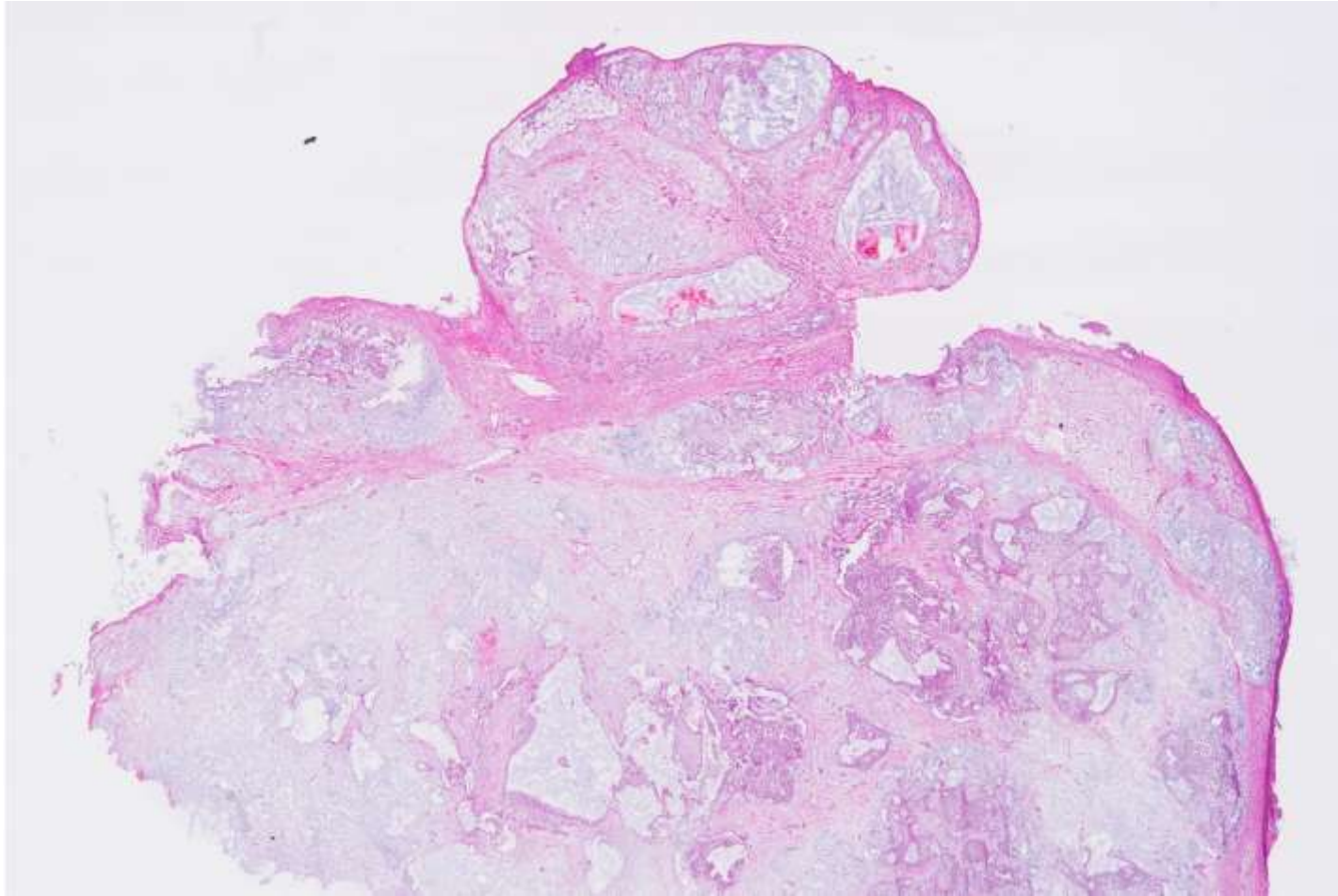


# 19-0707

Nicholas Ladwig/Charles Zaloudek;  
UCSF

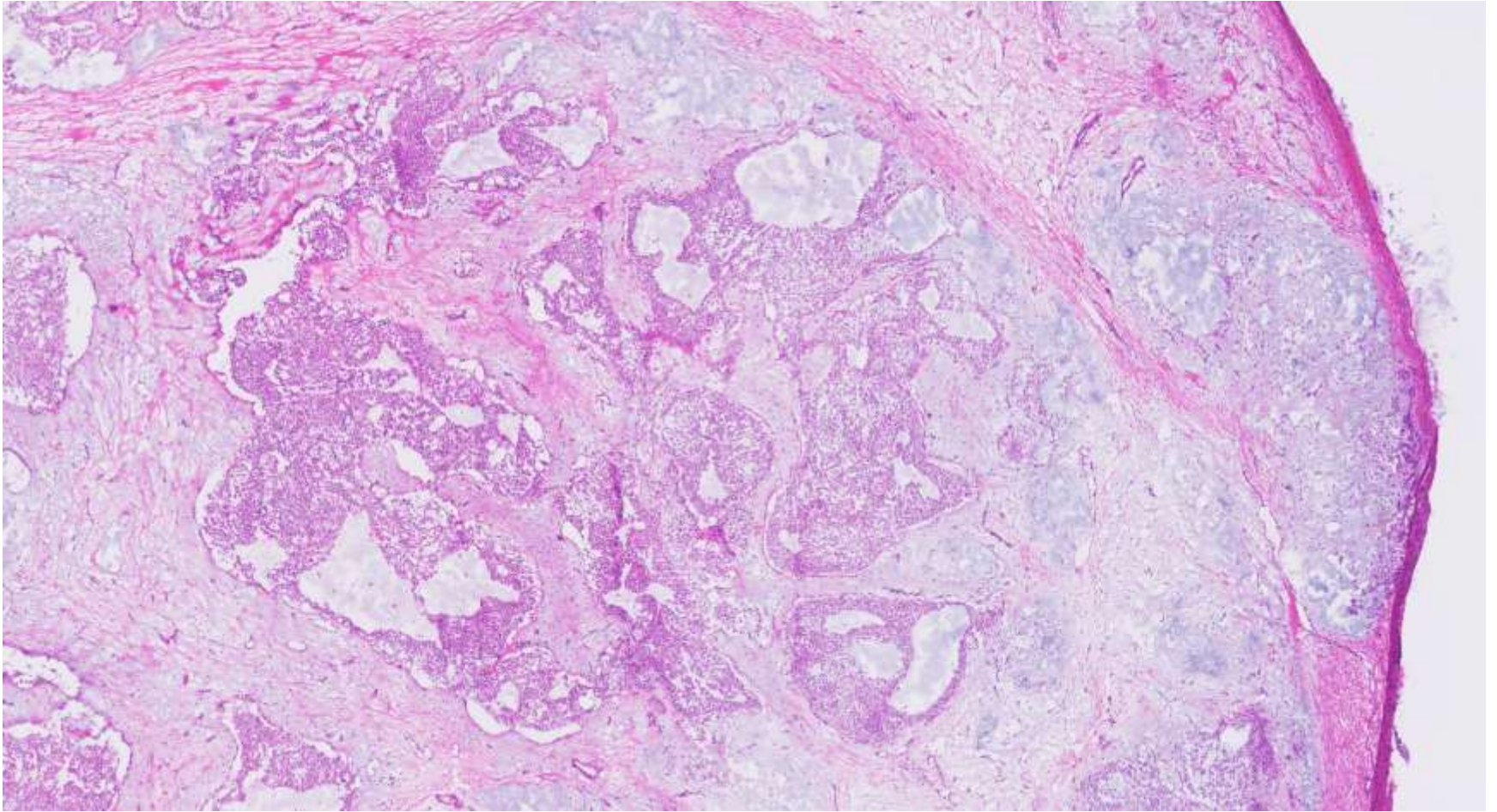
5-day-old newborn male undergoes orchiectomy for suspected testicular torsion. Intraoperative evaluation revealed 1.5cm testicular mass, specimen sent for frozen section. Labs sent at time of frozen section:  
AFP 15,418 ug/L, HCG 2IU/L.

1x



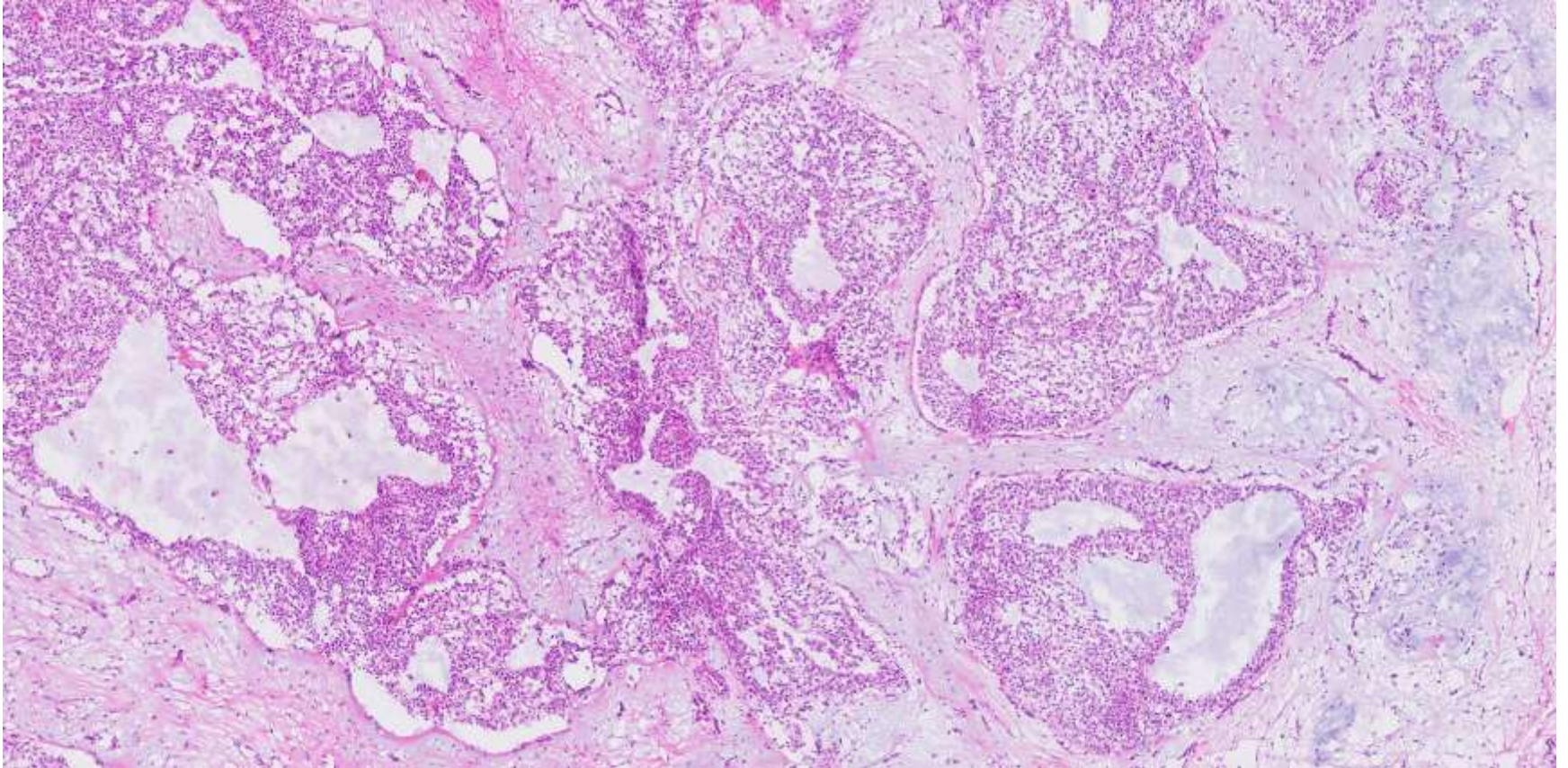


2x



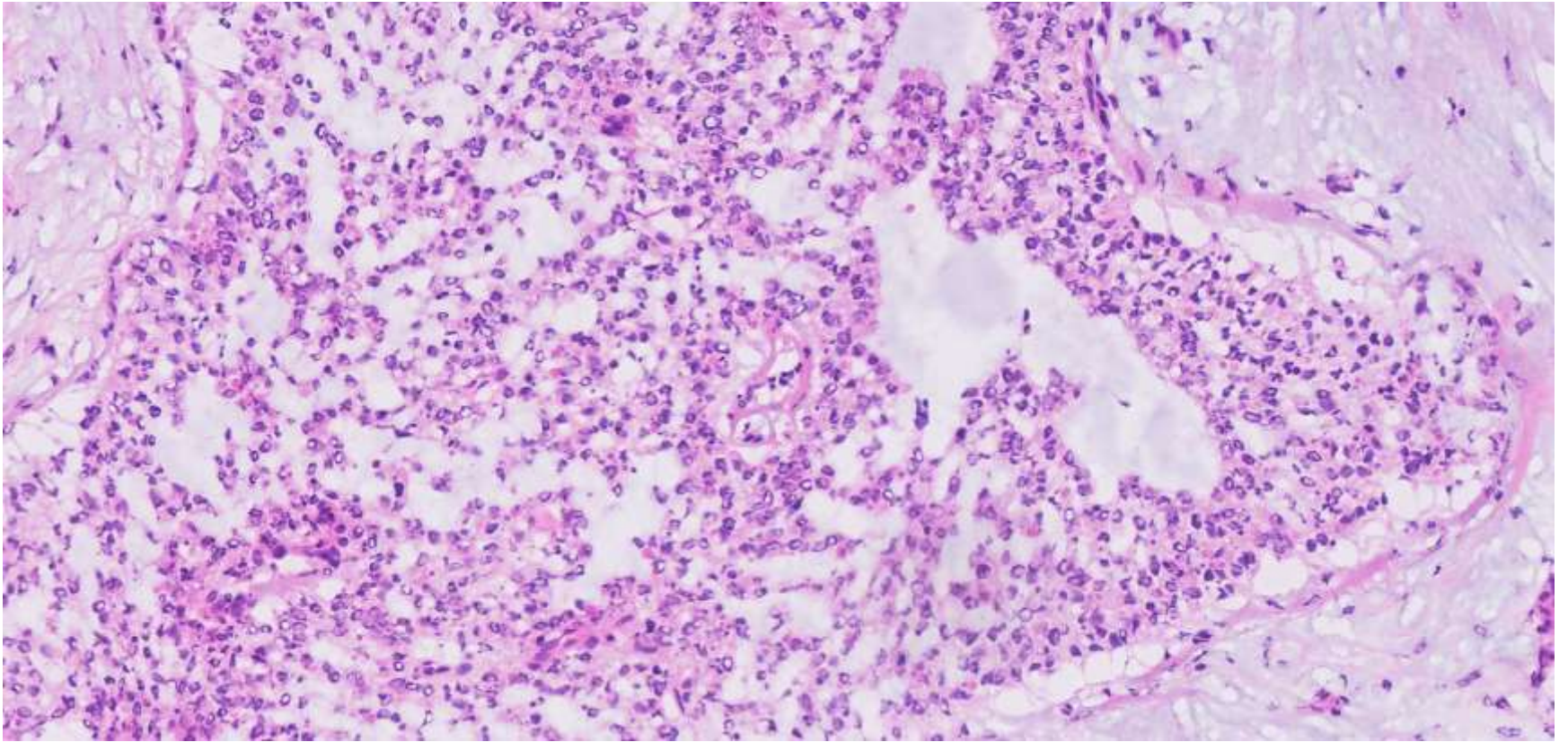


5x

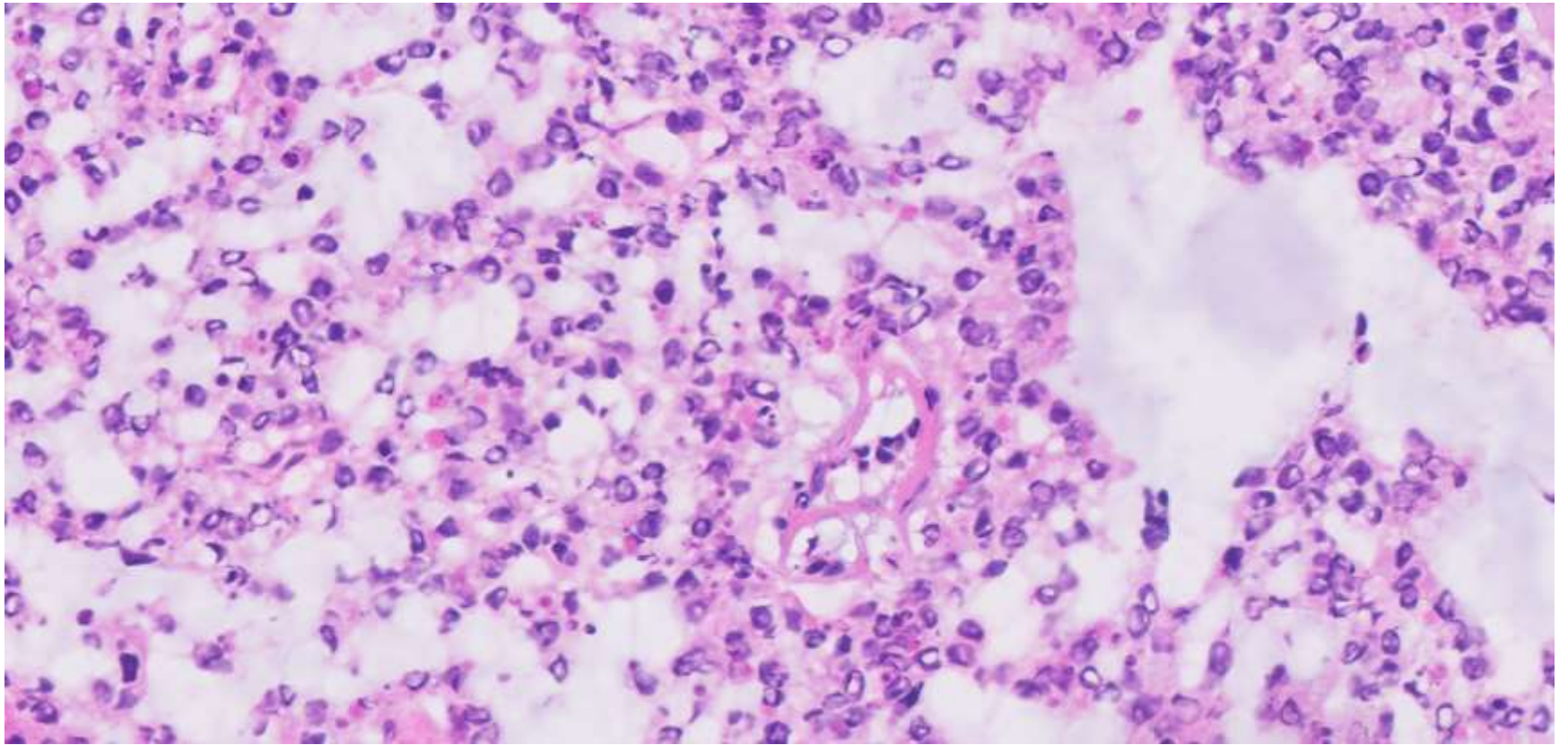




20x

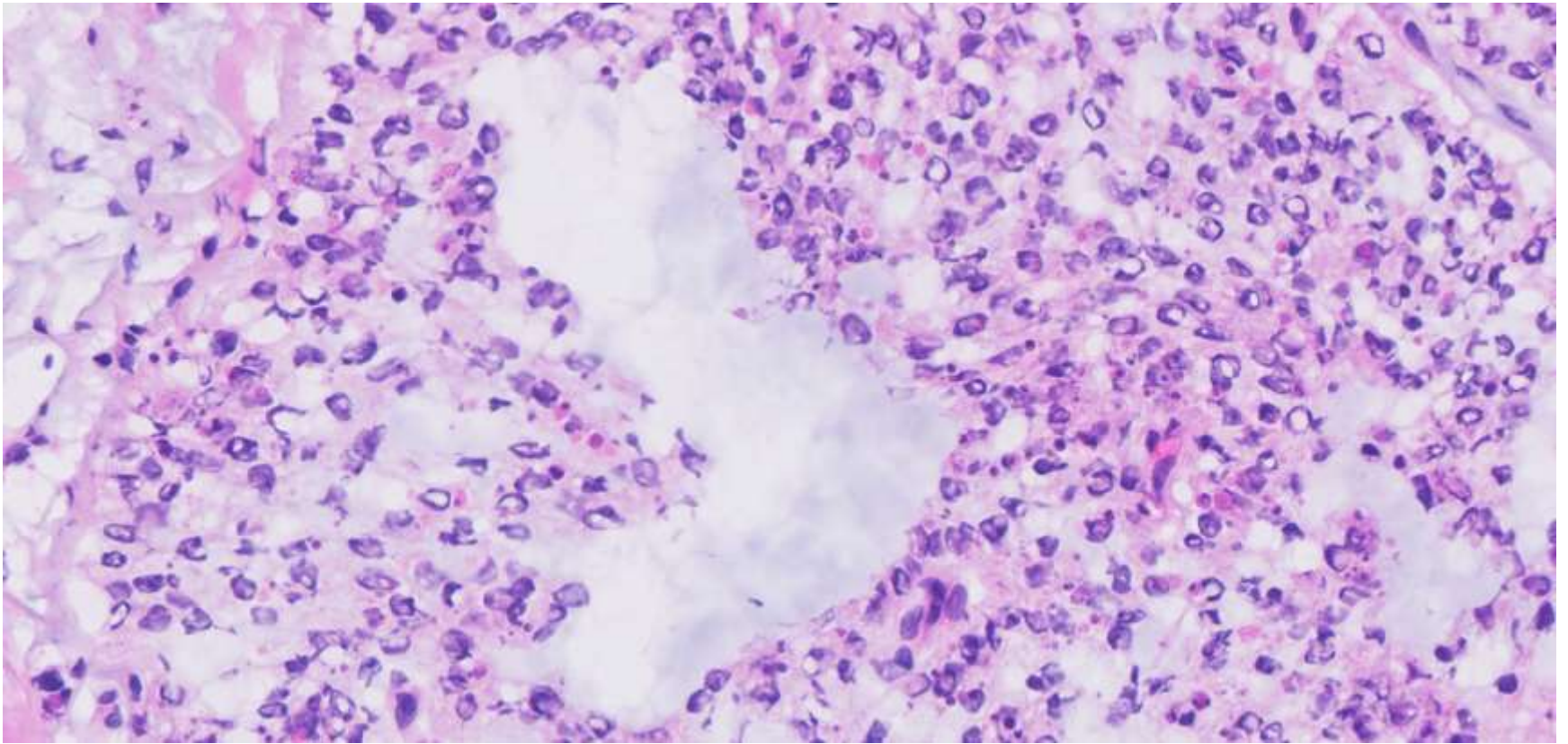


40x





40x #2



# DIAGNOSIS?





# South Bay Case Discussion

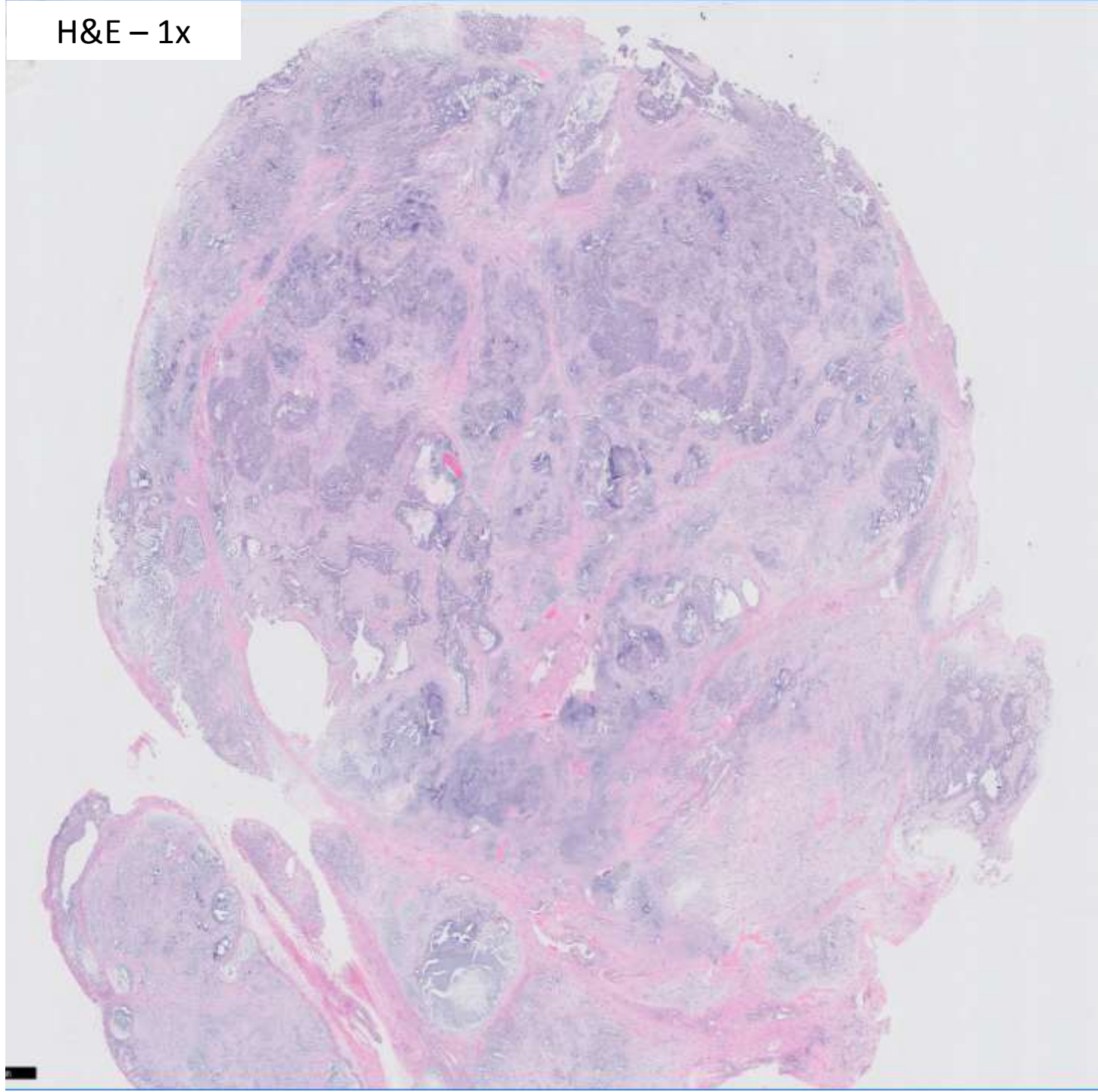
Nicholas Ladwig / Charles Zaloudek

July 8, 2019

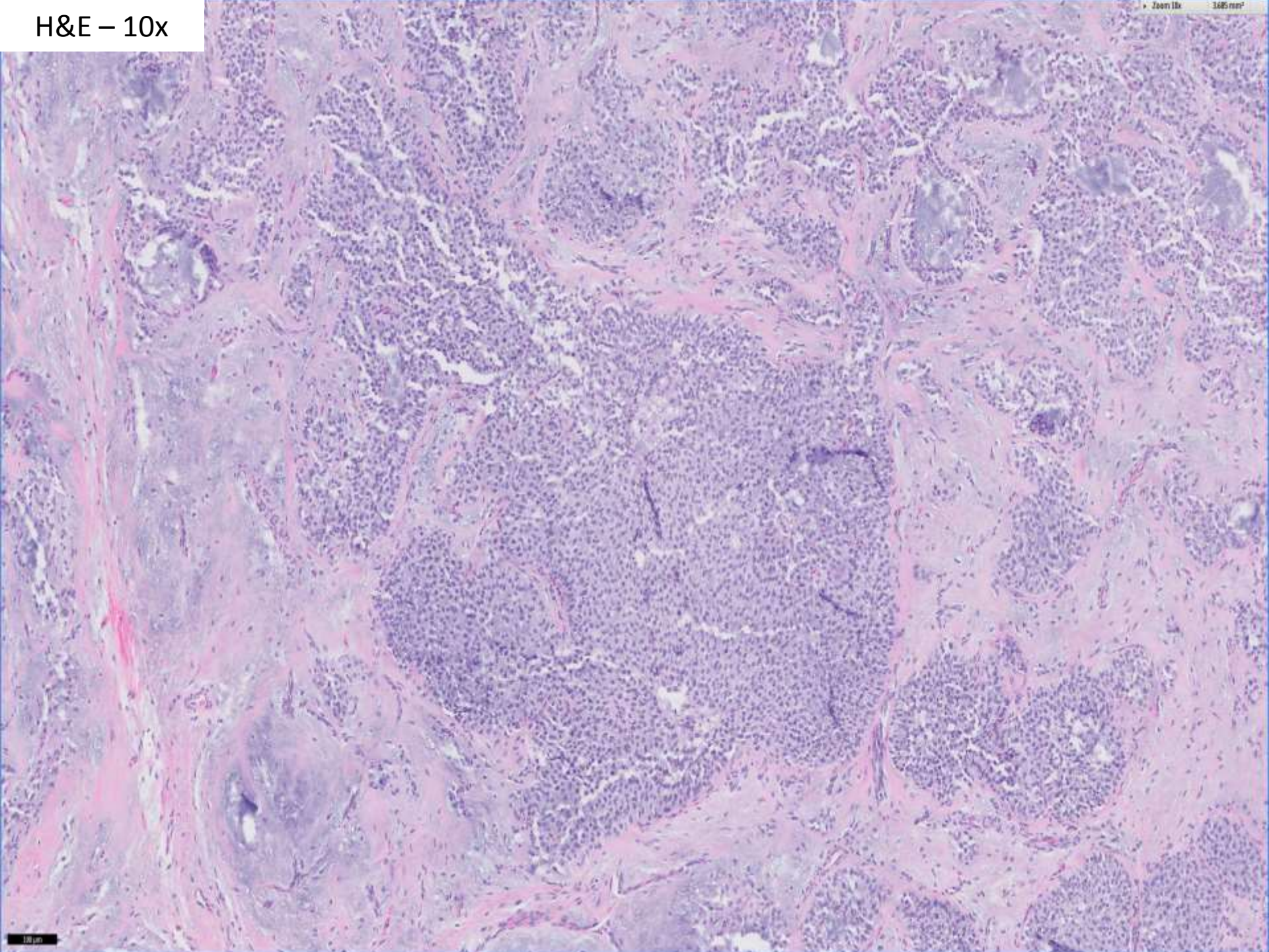




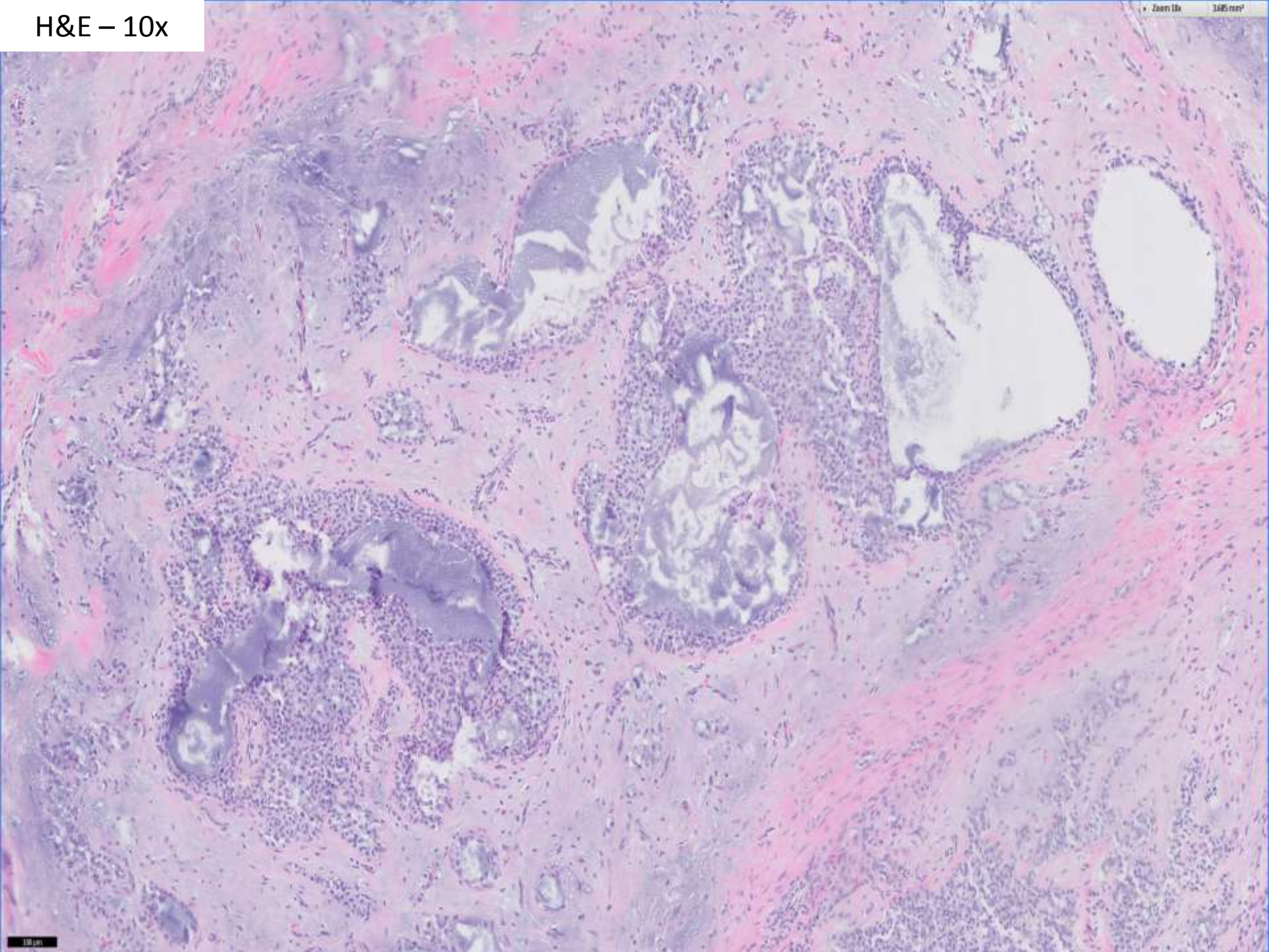
H&E – 1x



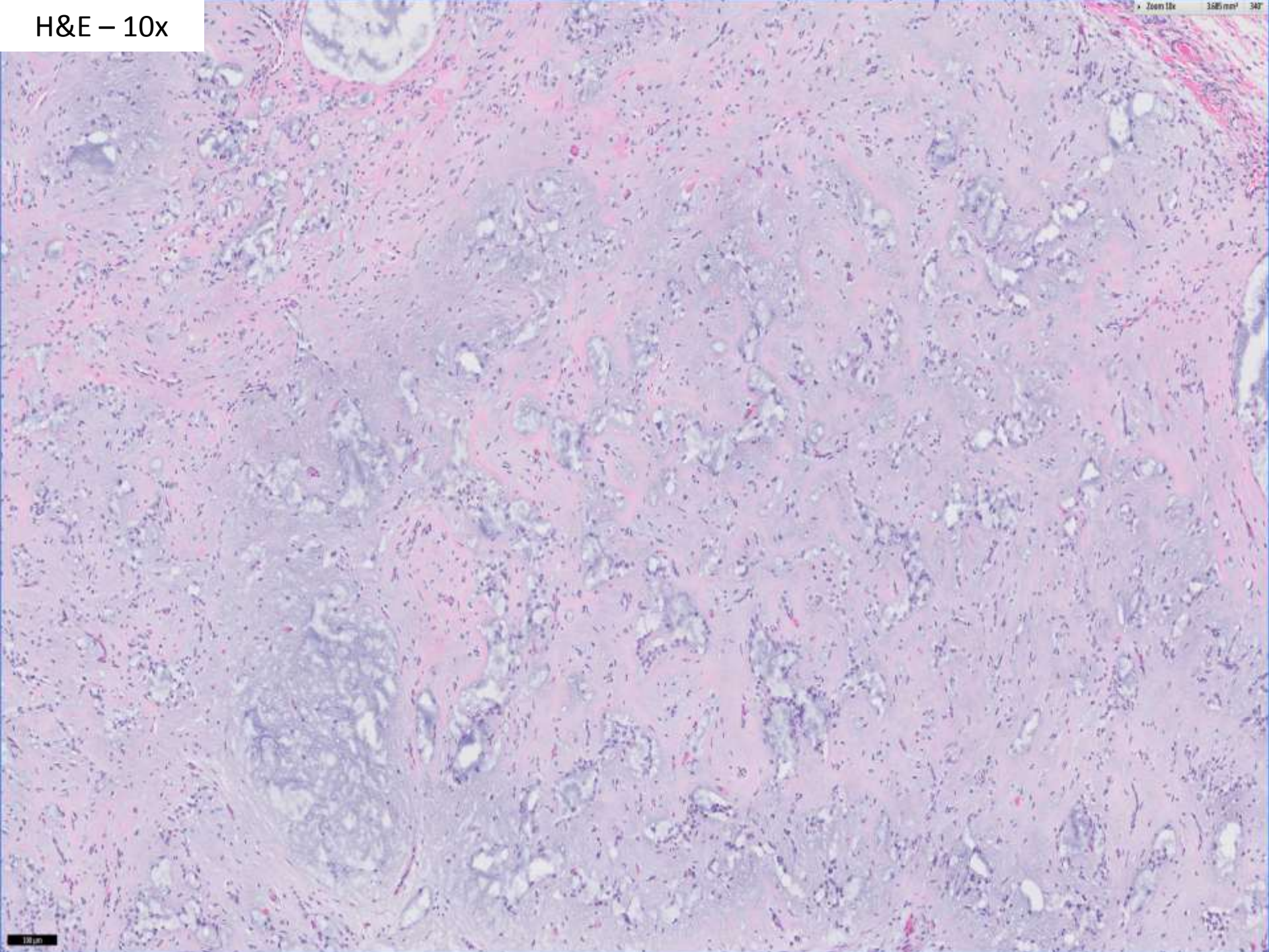






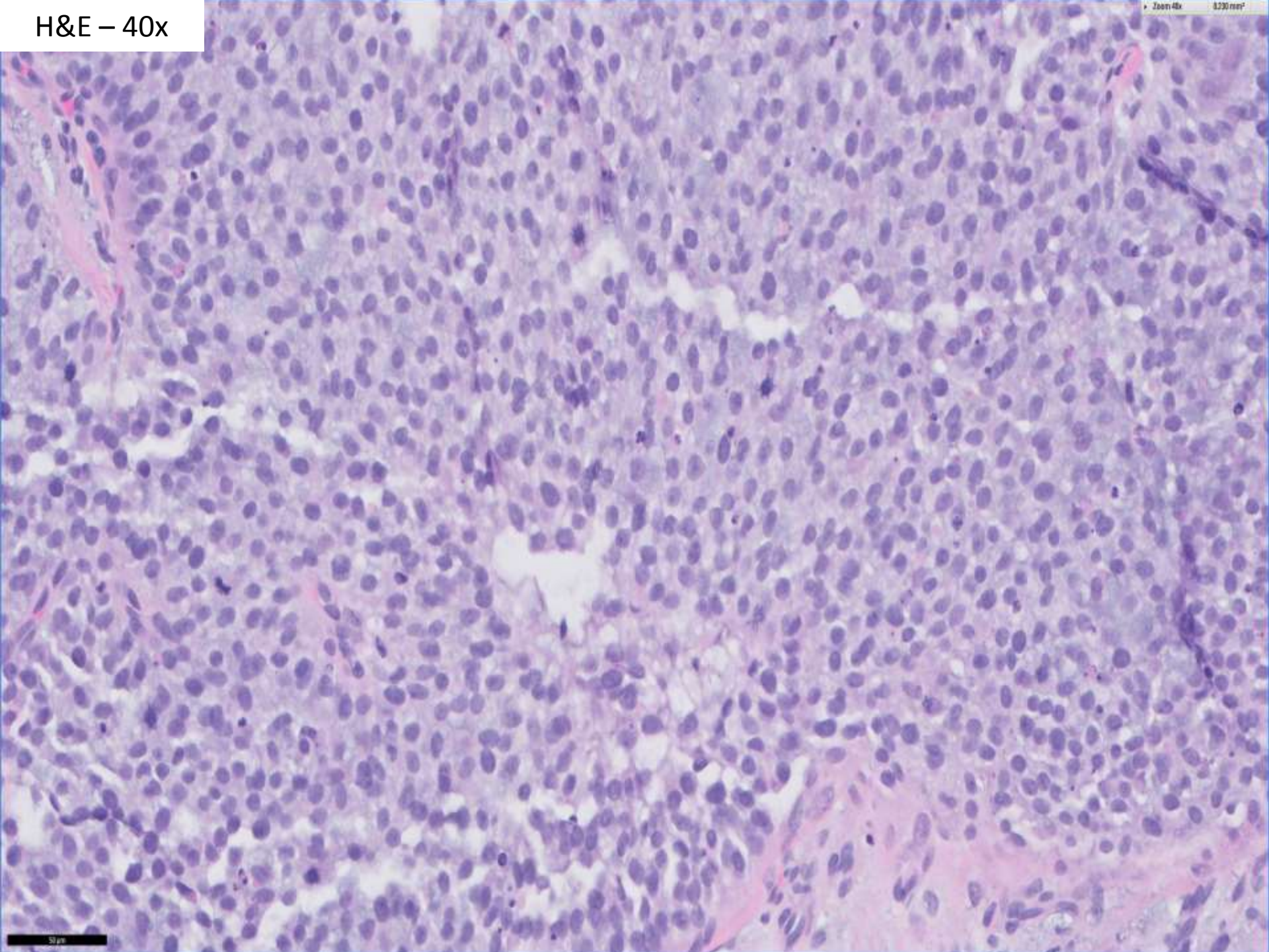






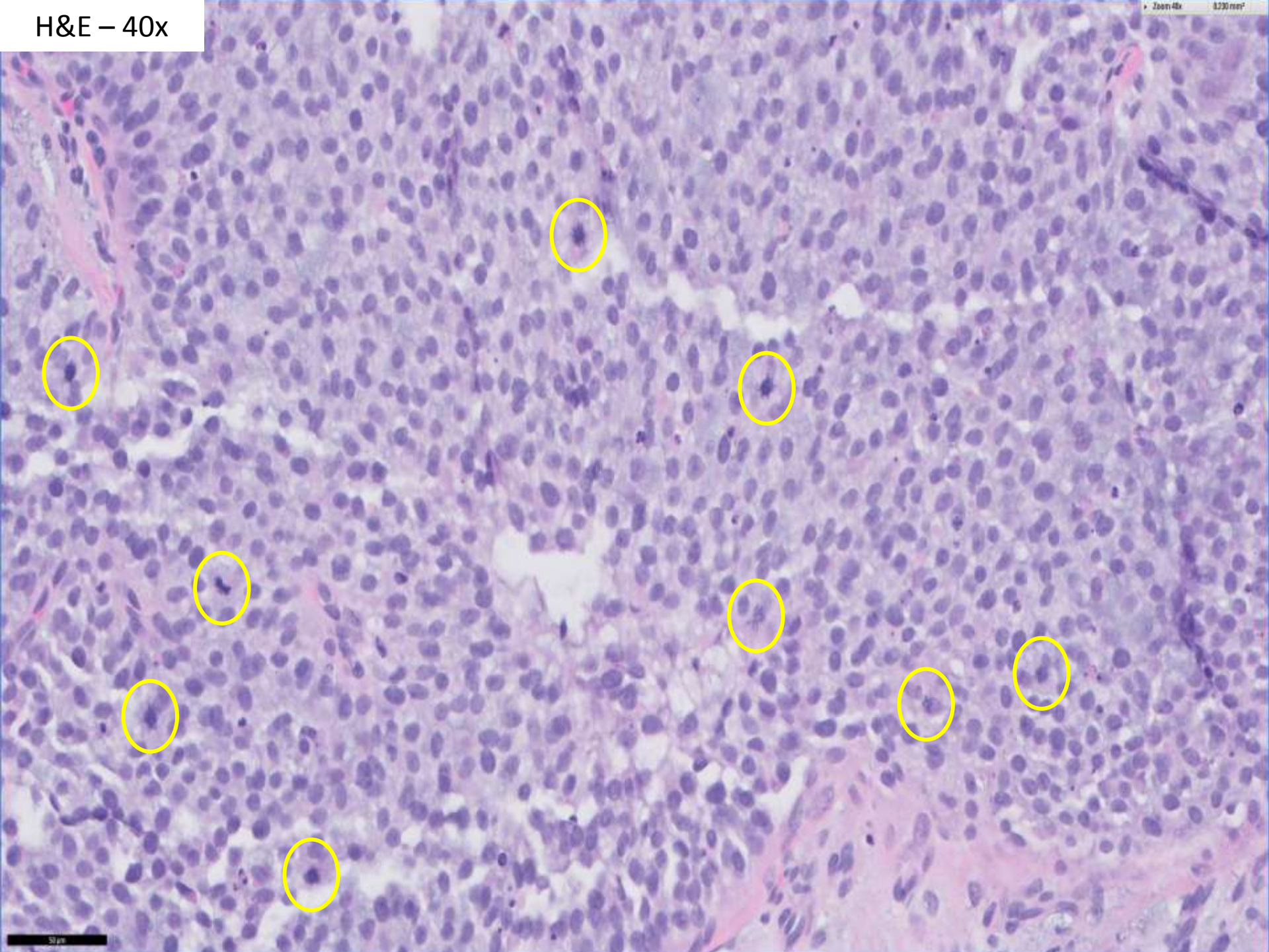


H&E - 40x



Zoom 40x 0.230 mm²

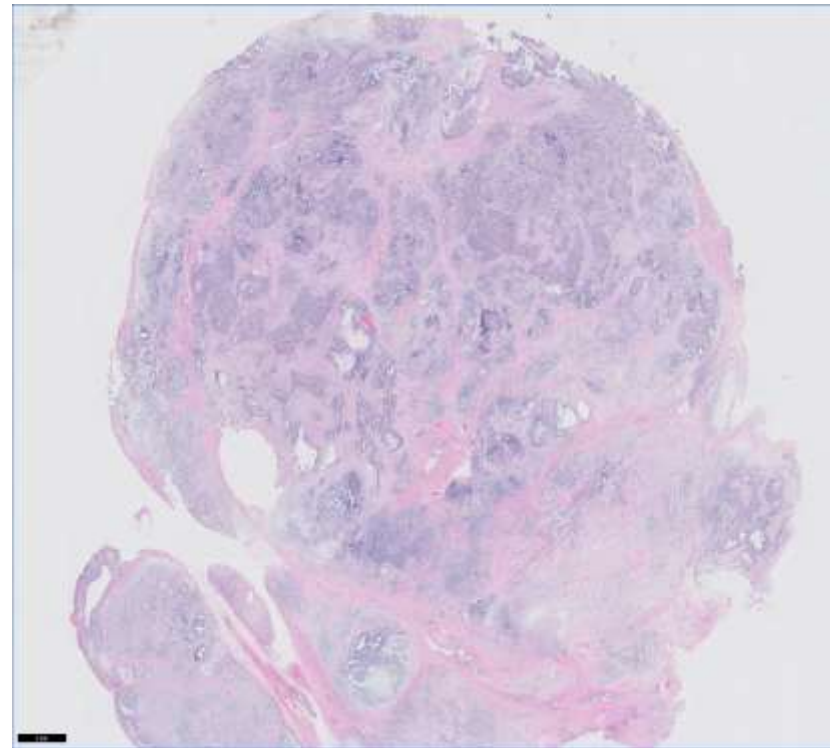




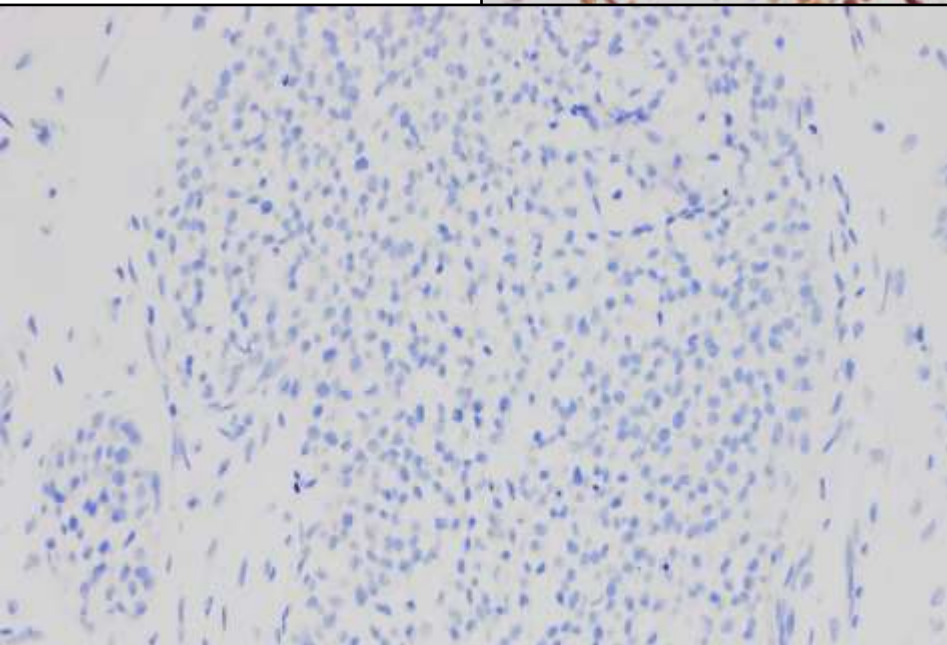
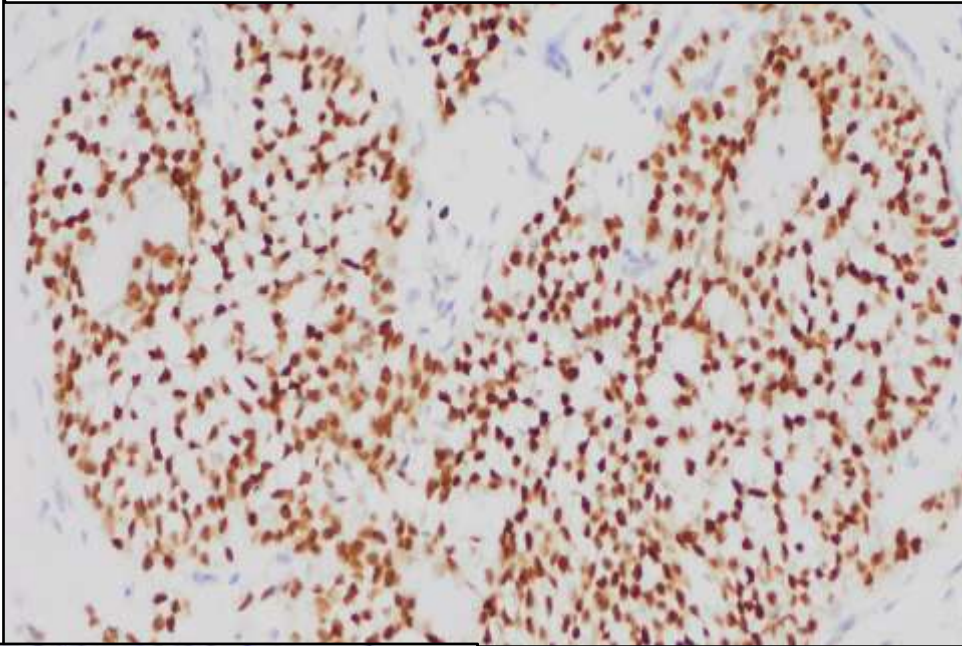


# Differential Diagnosis

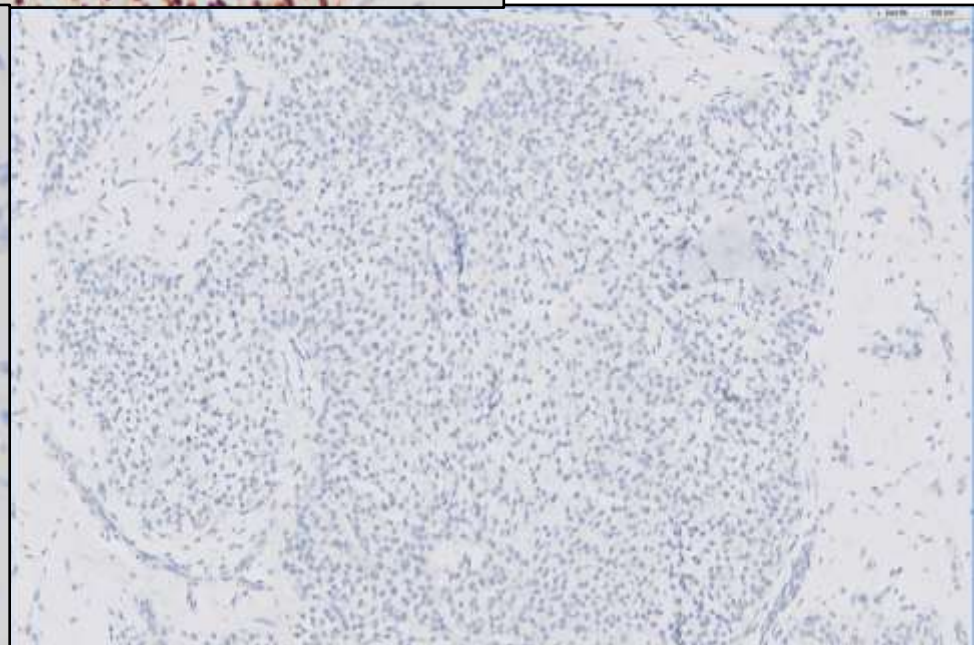
1. Germ cell tumors:
  1. Teratoma
  2. Yolk sac tumor
2. Sex cord stromal tumors
  1. Juvenile granulosa cell tumor
  2. Adult granulosa cell tumor
  3. Sertoli cell tumor
3. Paratesticular tumors
  1. Embryonal rhabdomyosarcoma



FOXL2



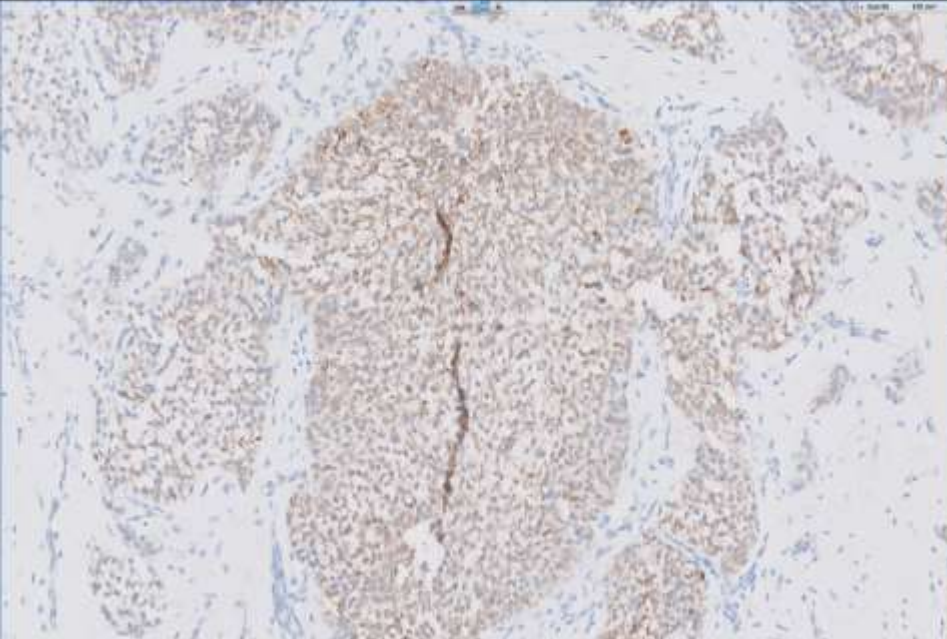
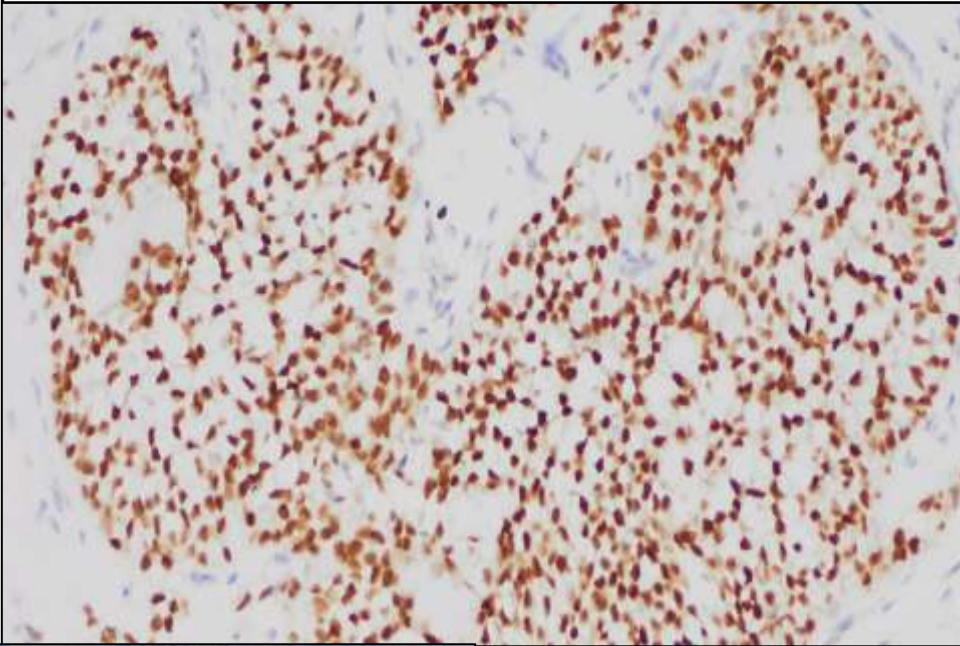
EMA



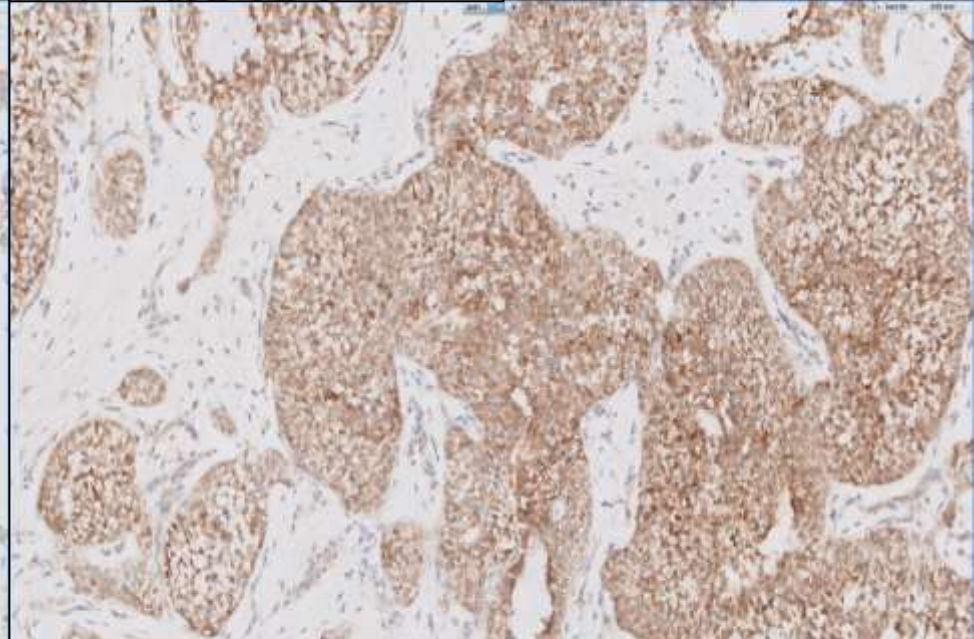
SALL4



FOXL2



Inhibin



Calretinin

Final Diagnosis:

Juvenile granulosa cell tumor of  
the testis



# Juvenile Granulosa Cell Tumors of the Testis

## *A Clinicopathologic Study of 70 Cases With Emphasis on Its Wide Morphologic Spectrum*


*Chia-Sui Kao, MD,\*† Kristine M. Cornejo, MD,\*† Thomas M. Ulbright, MD,‡  
and Robert H. Young, MD\*†*

# JGCT of Testis – Morphology

Morphologic Feature	% of Cases
Lobulated	100%
Mixed follicular / solid	79%
Fibrous stroma	50%
Fibromyxoid stroma	50%
Mitotic activity >10/10 HPF	37%
Apoptotic bodies >20/HPF	46%
Hyaline globules	1%




# JGCT of Testis – IHC



Antibody	% of Cases
FOXL2	100%
SF1	100%
Calretinin	89%
Inhibin	89%
WT1	86%
SALL4	0%
AFP	10%

# JGCT of Testis – Age at Presentation



Cultural and  
Linguistic  
Competency:

Testicular tumors in  
infants



# JGCT of Testis – Age at Presentation

Age Group	# of Cases	% of Cases
< 1 month	34	51%
1-2 months	8	12%
2-3 months	8	12%
3-4 months	4	6%
4-5 months	5	7%
5-6 months	1	1%

Age Group	# of Cases	% of Cases
< 6 months	60	90%
> 6 months	7	10%

TABLE 1. *Tumor types for primary testis tumors in boys younger than 12 years*

Tumor Type	No. Pts. (%)
Yolk sac	244 (62)
Teratoma	92 (23)
Unspecified stromal	16 (4)
Epidermoid cyst	13 (3)
Juvenile granulosa cell	11 (3)
Sertoli cell	10 (3)
Leydig cell	5 (1)
Gonadoblastoma	4 (1)

TABLE 2. *Patient age at presentation for different tumor types*

Tumor Type	No. Pts.	Median Mos. Age (range)
Yolk sac	244	16 (0–131)
Teratoma	92	13 (0–111)
Unspecified stromal	16	4 (0–111)
Juvenile granulosa	11	0.1 (0–6)
Sertoli cell	10	6 (4–121)
Leydig cell	5	66 (24–126)



Age	Juvenile Granulosa Cell Tumor	Yolk Sac Tumor
<6 months	90%	9%
6-12 months	4%	15%
>12 months	6%	76%

# Pitfall – “Elevated” AFP

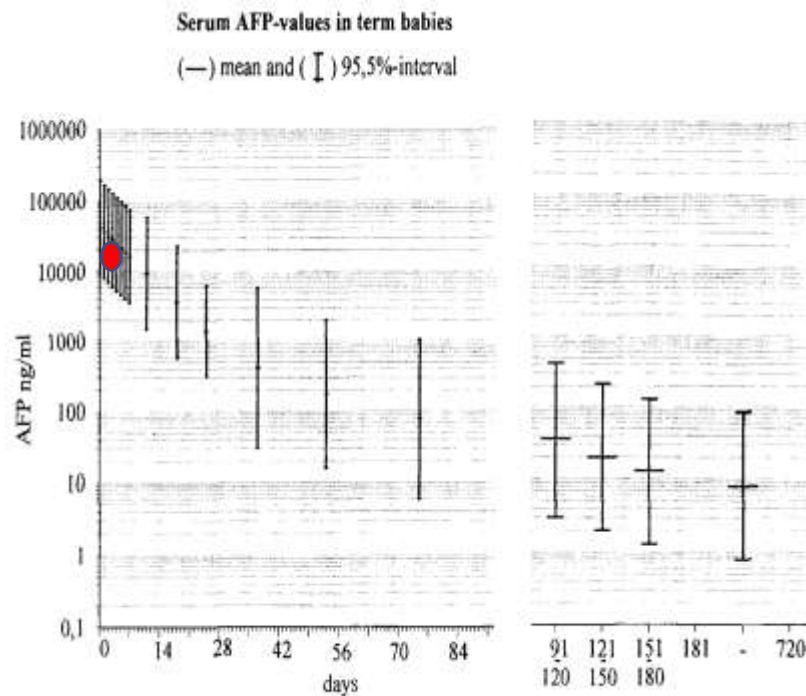


Figure 1. Serum AFP values in term babies: (—) mean and (I) 95.5% interval.

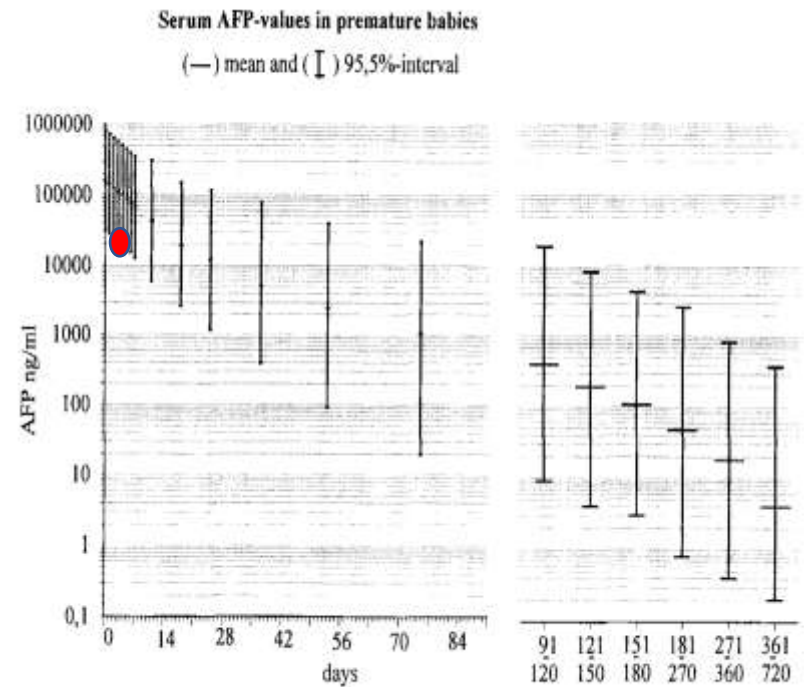


Figure 2. Serum AFP values in premature babies: (—) mean and (I) 95.5% interval



# Case Summary

- Final Diagnosis:
  - Juvenile granulosa cell tumor (JGCT) of the testis
- Take Home Points:
  - JGCT show a variety of morphologic patterns with considerable overlap with yolk sac tumor (YST)
    - JGCT most common in patients < 6 mo (often < 1 mo)
    - YST most common in patients > 1 yr
  - IHC (FOXL2, SALL4, etc) will resolve the differential diagnosis
  - JGCT of testis have benign clinical course, despite high mitotic activity
  - Serum AFP is physiologically elevated in newborns

# References

1. Blohm ME, Vesterling-Horner D, Calaminus G, et al. Alpha 1-fetoprotein (AFP) reference values in infants up to 2 years of age. *Pediatr Hematol Oncol*. 1998;15:135-142.
2. Cornejo KM, Frazier L, Lee RS, et al. Yolk Sac Tumor of the Testis in Infants and Children: A Clinicopathologic Analysis of 33 Cases. *Am J Surg Pathol*. 2015;39:1121-1131.
3. Fresneau B, Orbach D, Faure-Contier C, et al. Sex-Cord Stromal Tumors in Children and Teenagers: Results of the TGM-95 Study. *Pediatr Blood Cancer*. 2015;62:2114-2119.
4. Hofmann M, Schlegel PG, Hippert F, et al. Testicular sex cord stromal tumors: analysis of patients from the MAKEI study. *Pediatr Blood Cancer*. 2013;60:1651-1655.
5. Kao CS, Cornejo KM, Ulbright TM, et al. Juvenile granulosa cell tumors of the testis: a clinicopathologic study of 70 cases with emphasis on its wide morphologic spectrum. *Am J Surg Pathol*. 2015;39:1159-1169.
6. Ross JH, Rybicki L, Kay R. Clinical behavior and a contemporary management algorithm for prepubertal testis tumors: a summary of the Prepubertal Testis Tumor Registry. *J Urol*. 2002;168:1675-1678; discussion 1678-1679.
7. Ulbright TM, Young RH. Testicular and paratesticular tumors and tumor-like lesions in the first 2 decades. *Semin Diagn Pathol*. 2014;31:323-381.



## SECOND PLACE

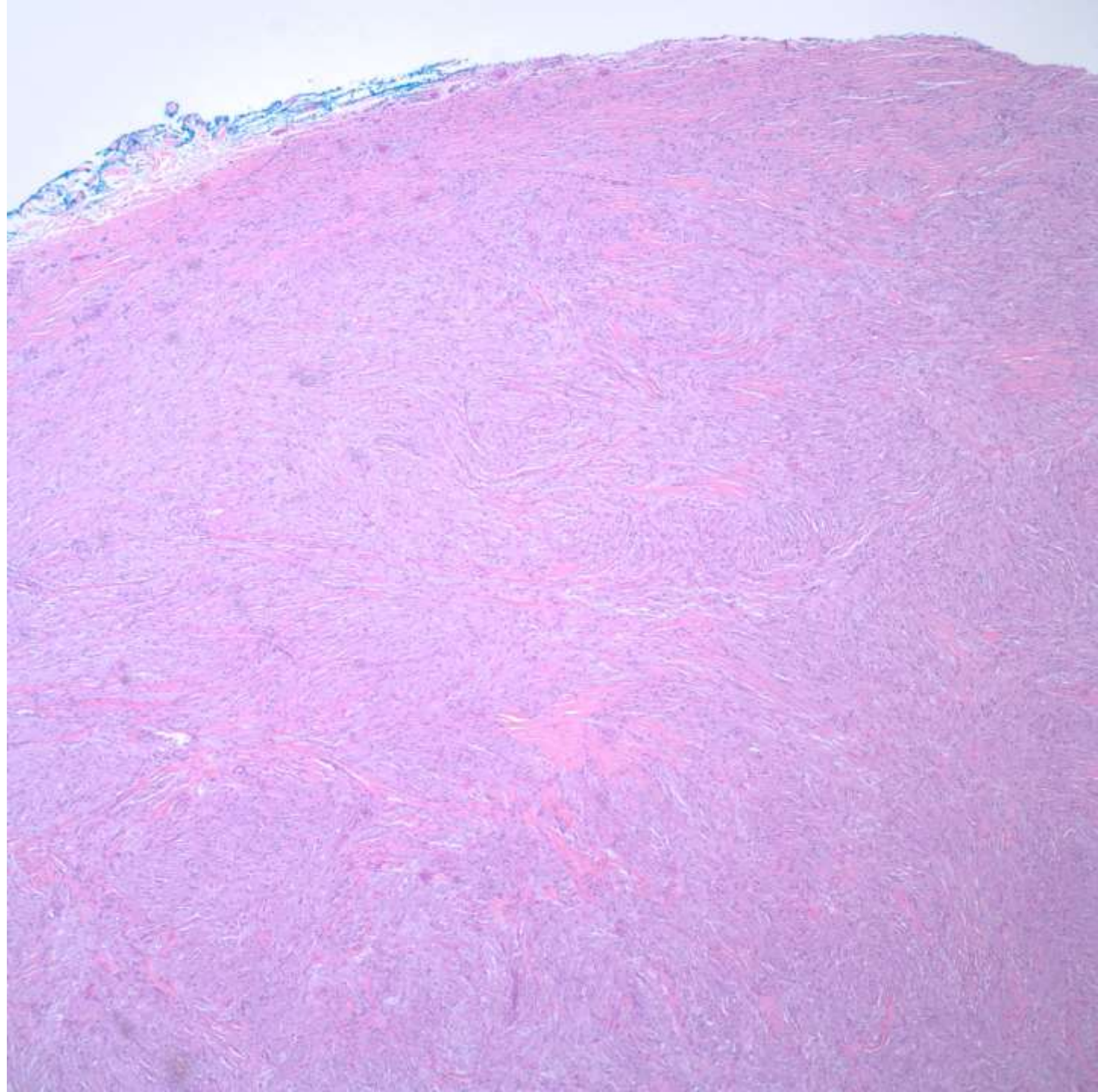
- Kara Walton, of Claymont, Delaware sued the owner of a night club in a nearby city because she fell from the bathroom window to the floor, knocking out her two front teeth. Even though Ms. Walton was trying to sneak through the ladies room window to avoid paying the \$3.50 cover charge, the jury said the night club had to pay her \$12,000....oh, yeah, plus dental expenses.

# 19-0708

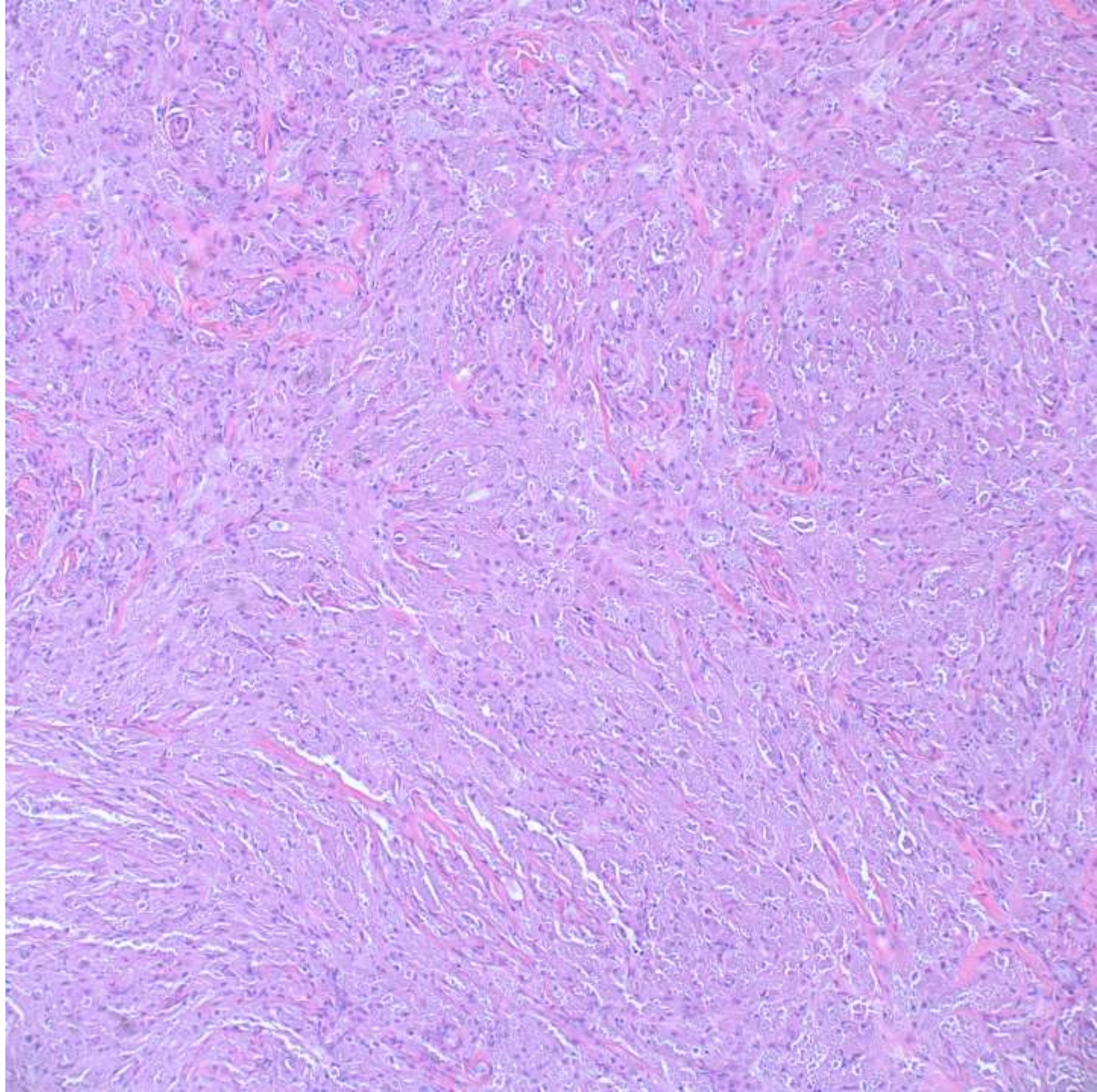
Dennis Adams/Brooke Howitt;  
Stanford

23-year-old woman with a left mid  
clavicle soft tissue mass excision.

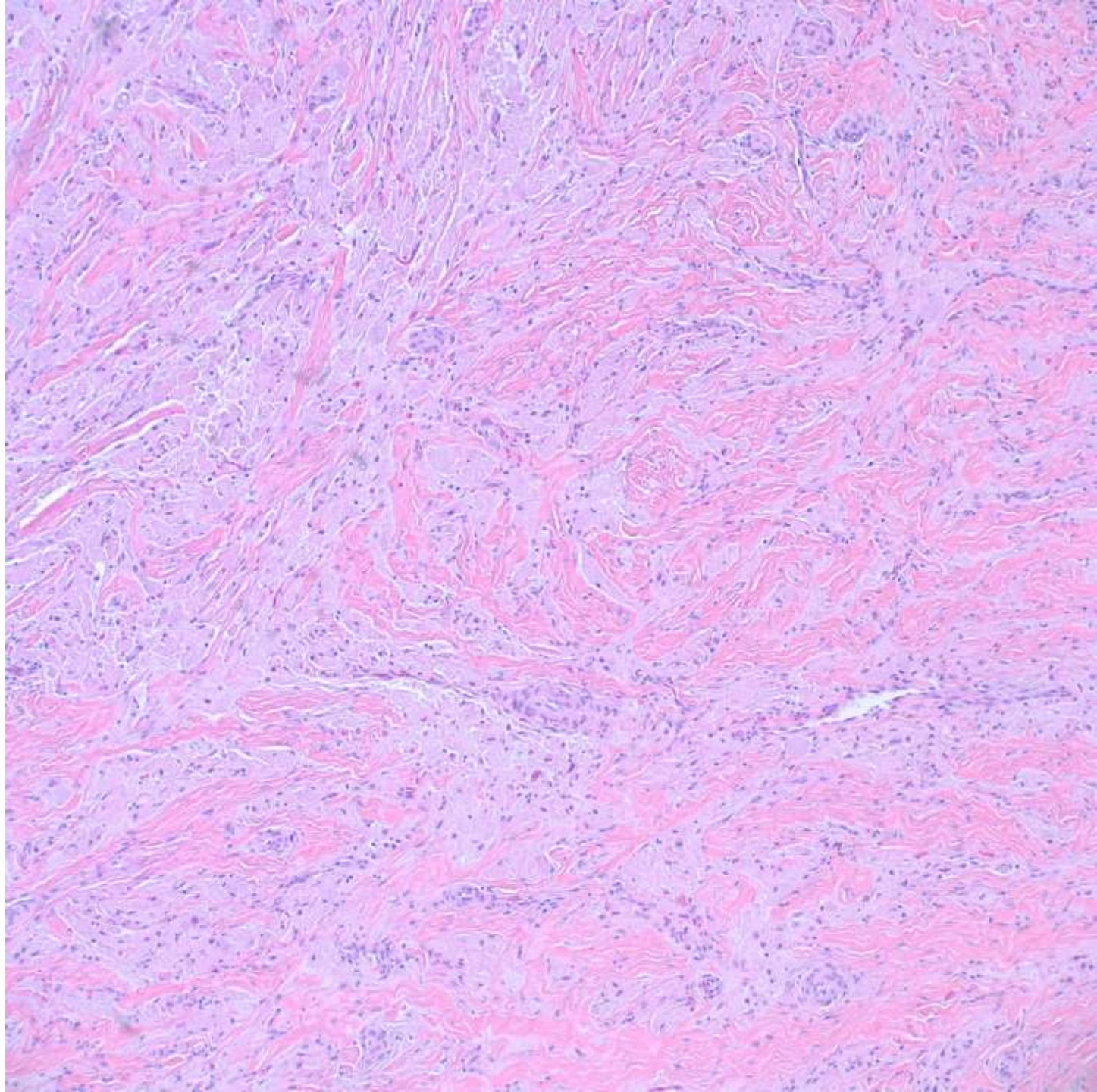




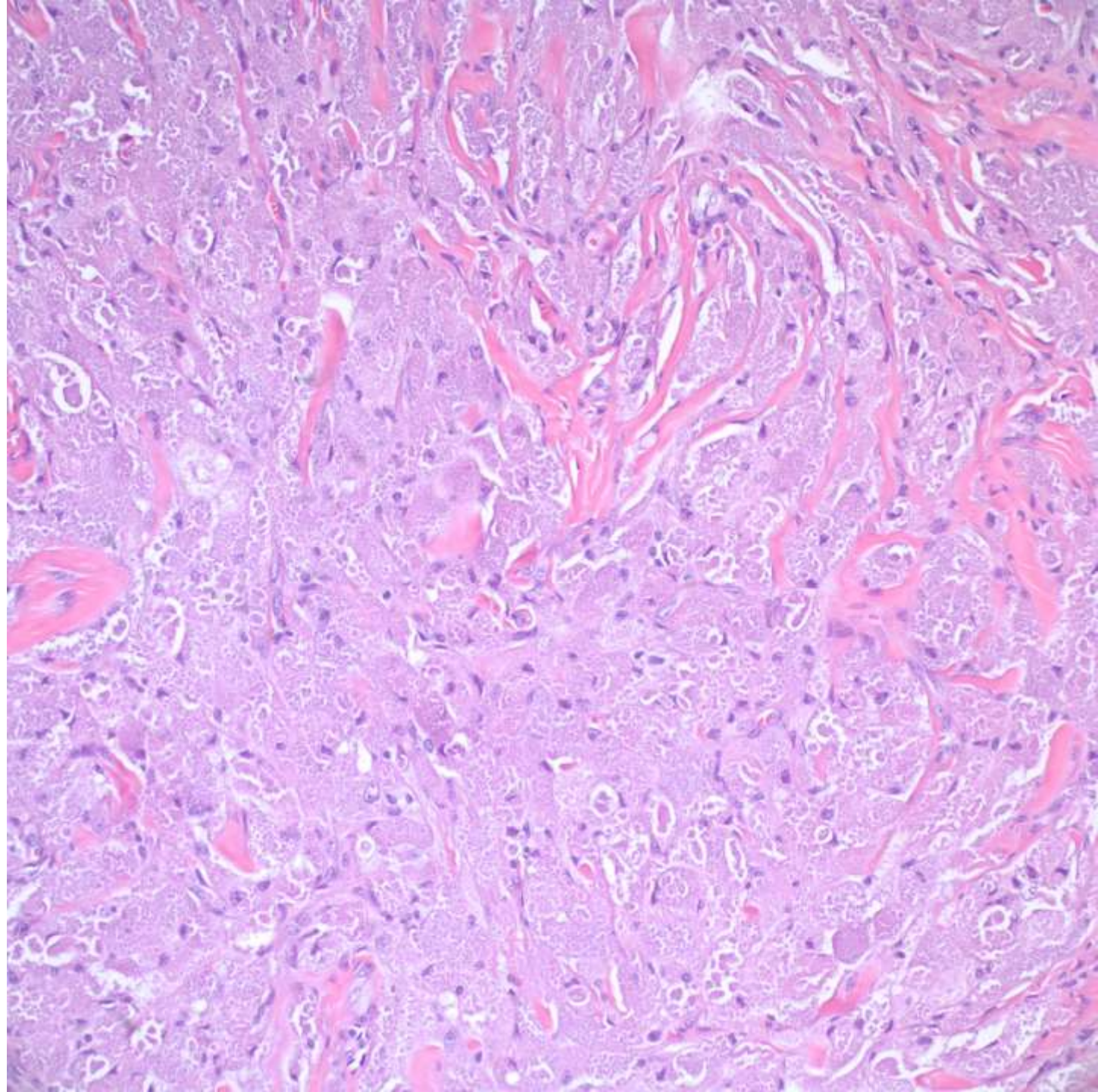




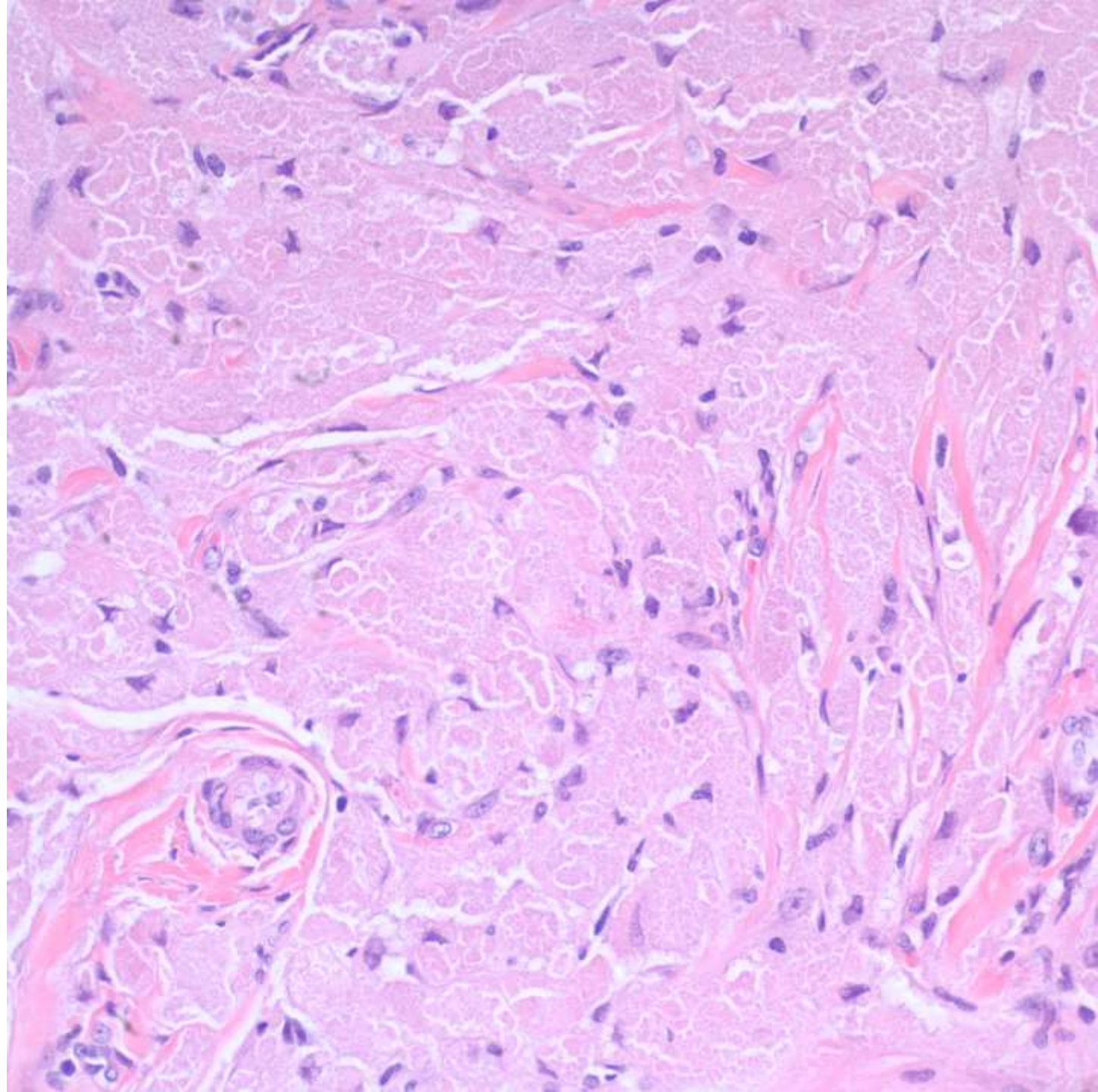




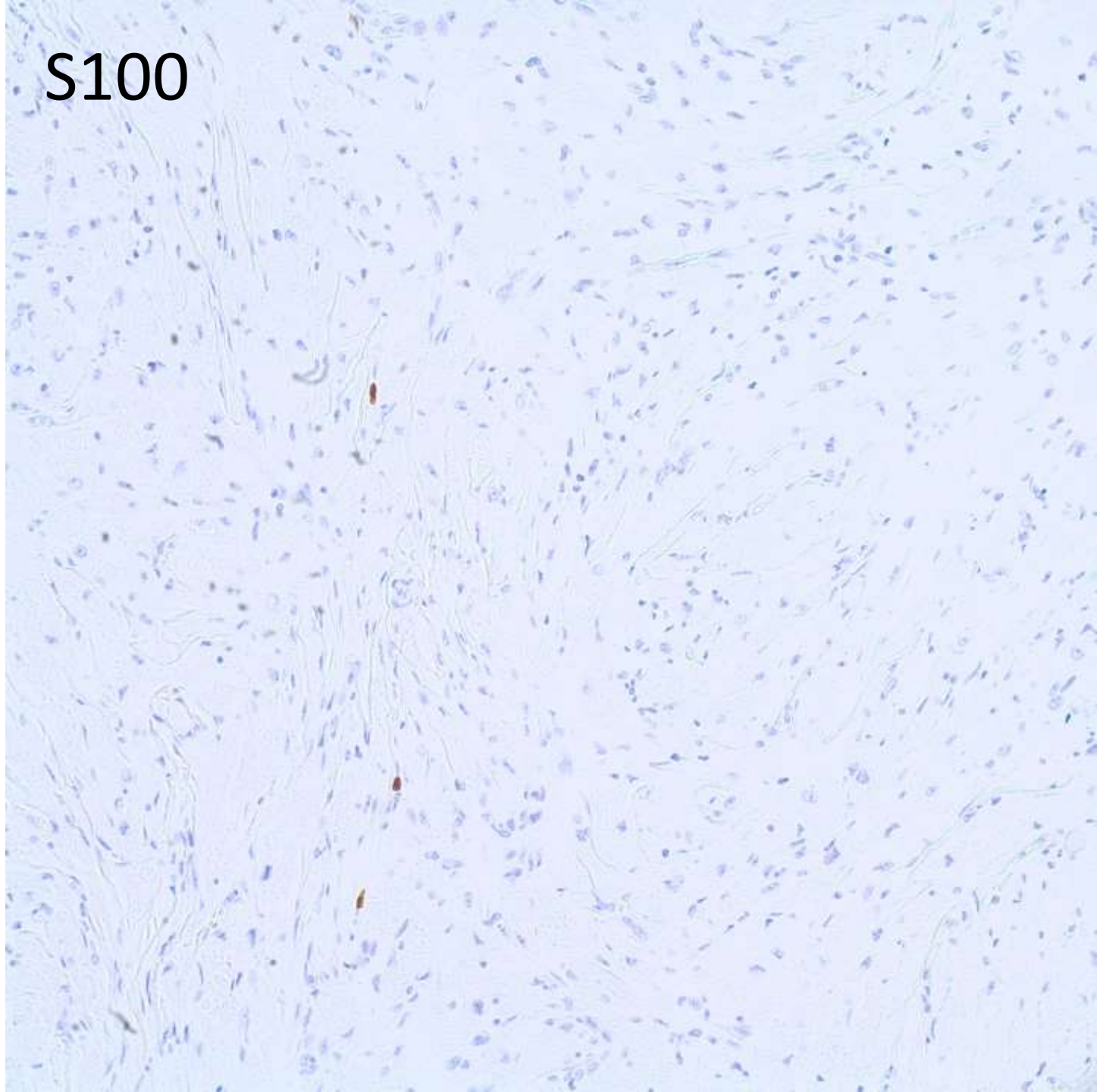








S100





# DIAGNOSIS?

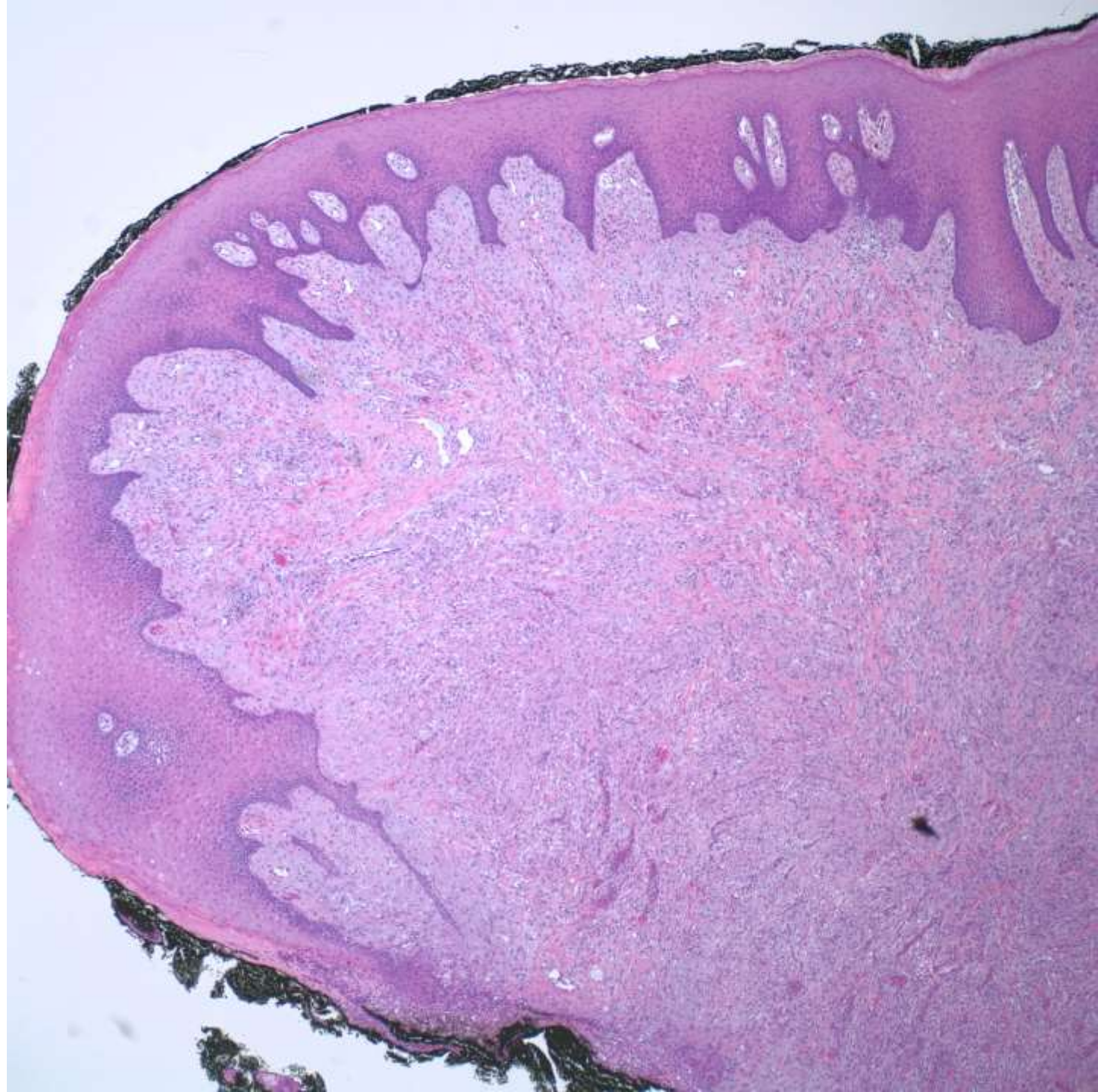


# 19-0709

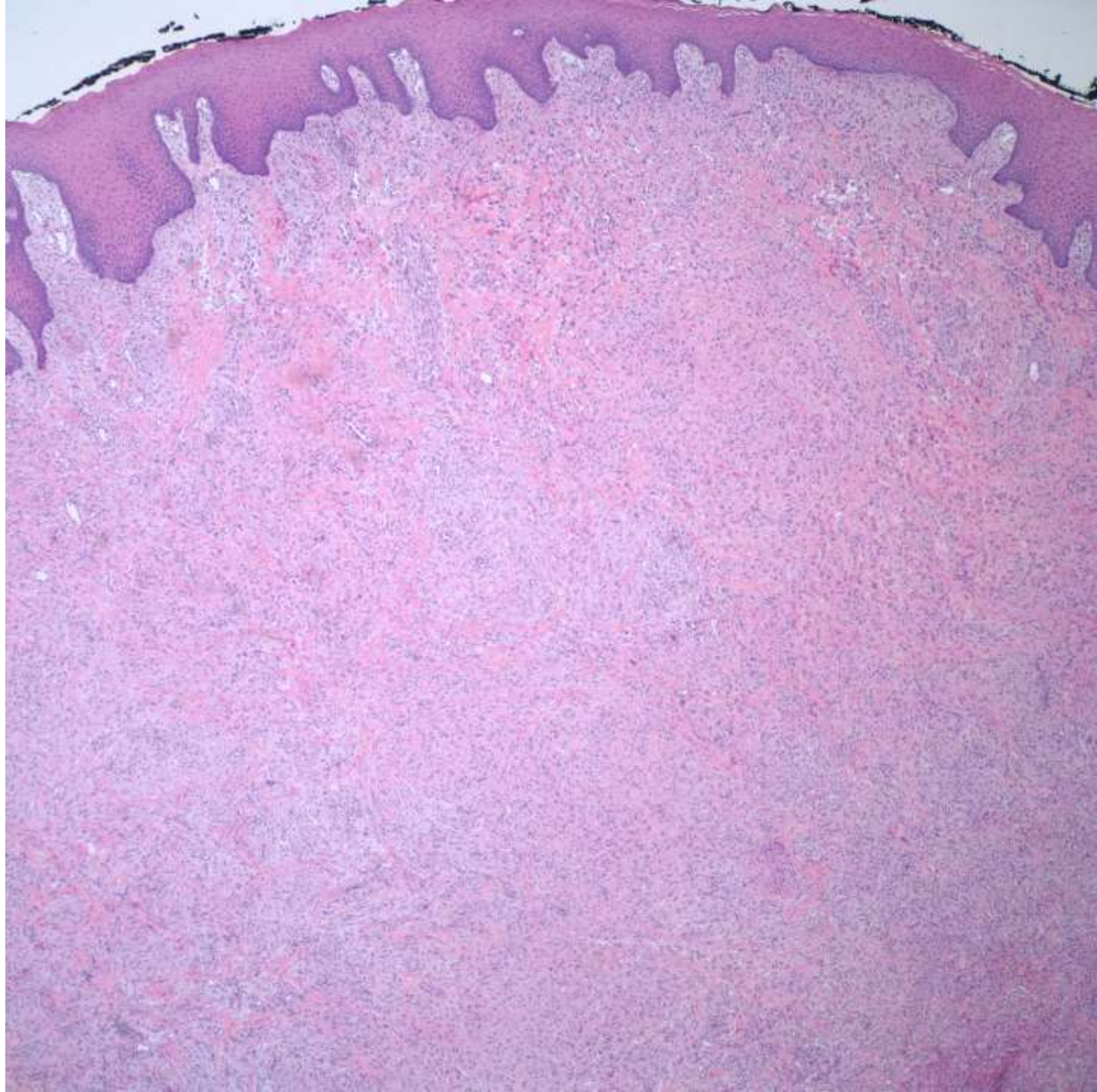
Dennis Adams/Gerald Berry;  
Stanford

16-month-old male with was  
incidentally found to have a tongue  
lesion of unknown duration.

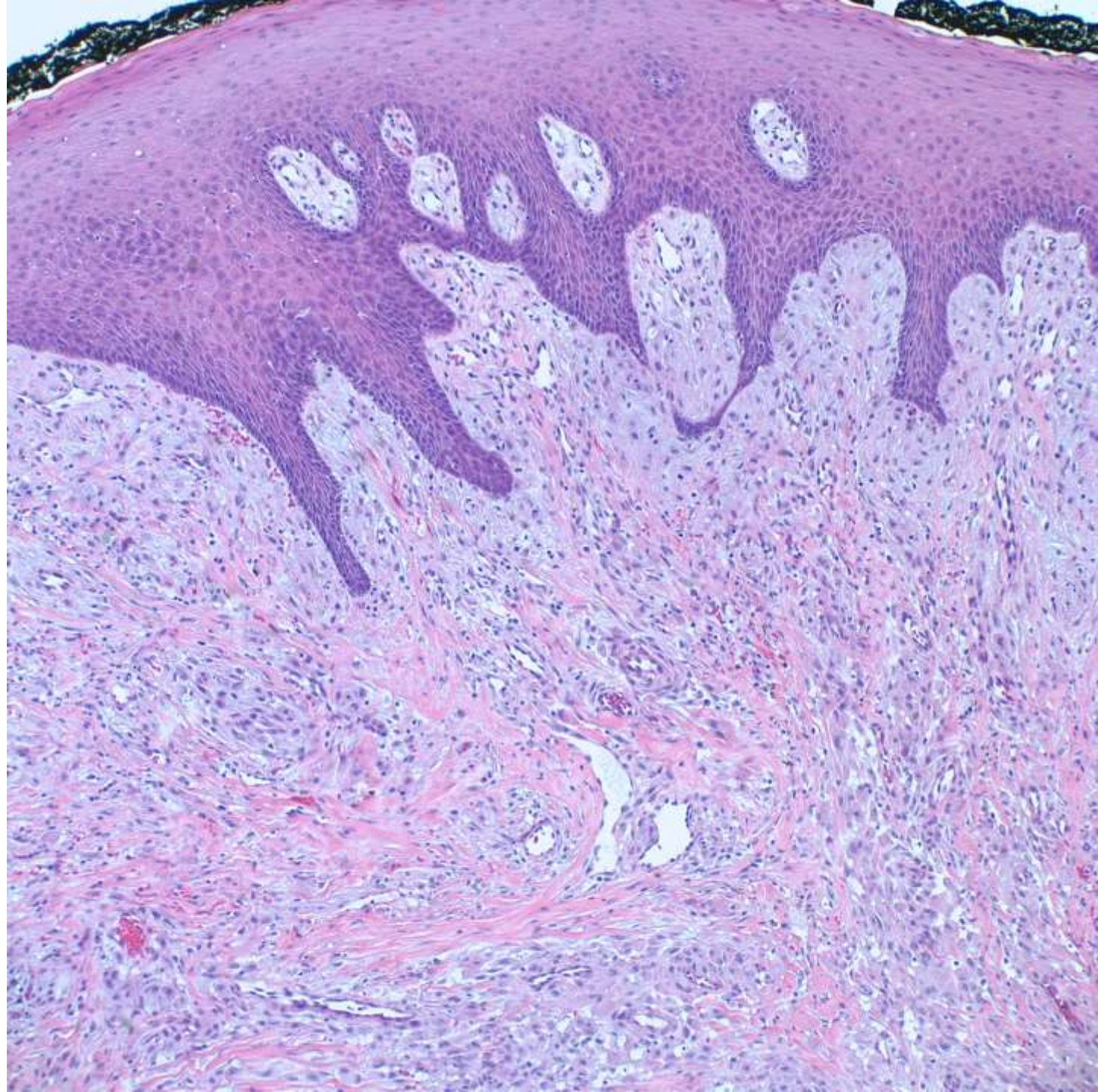




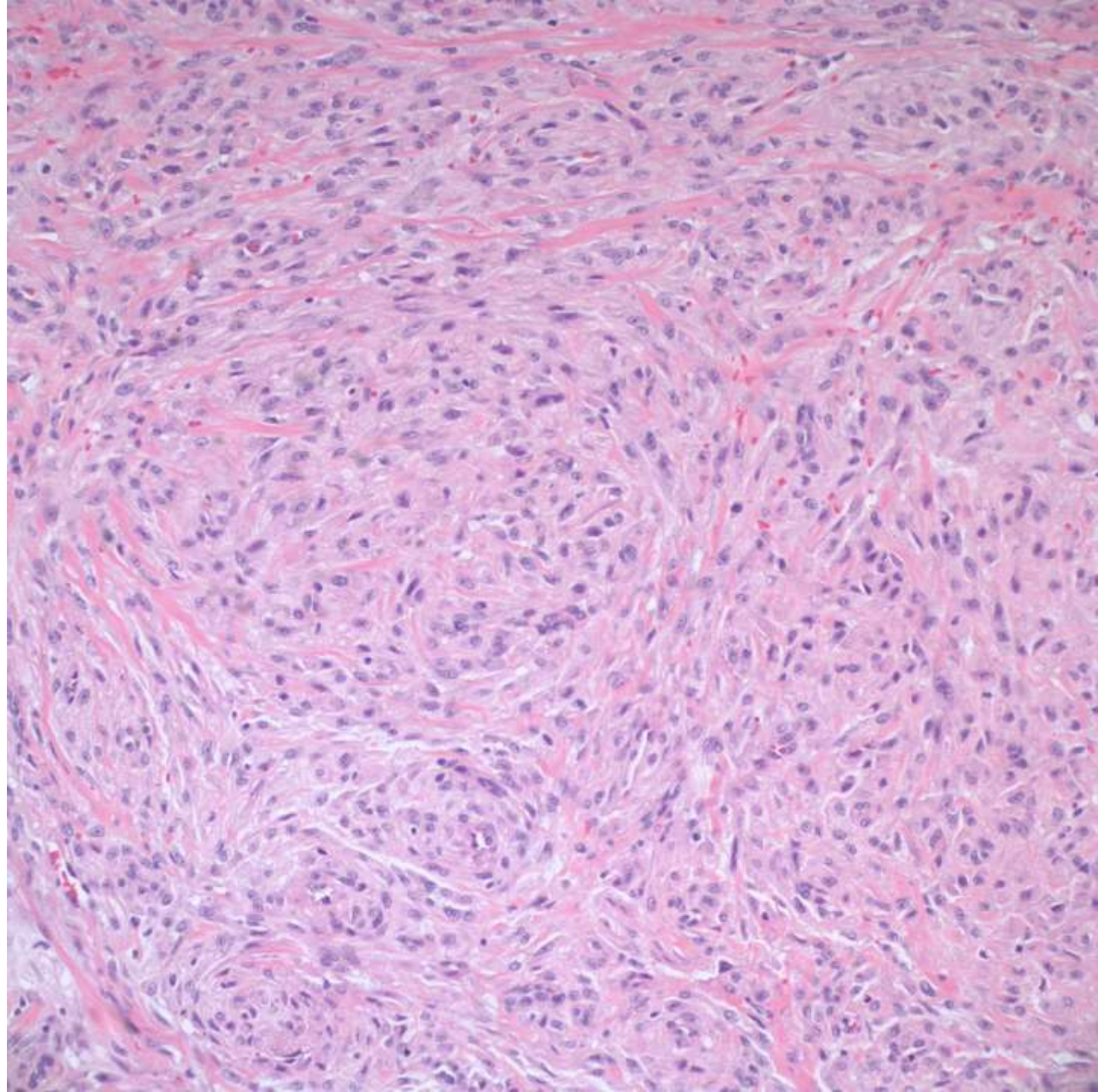




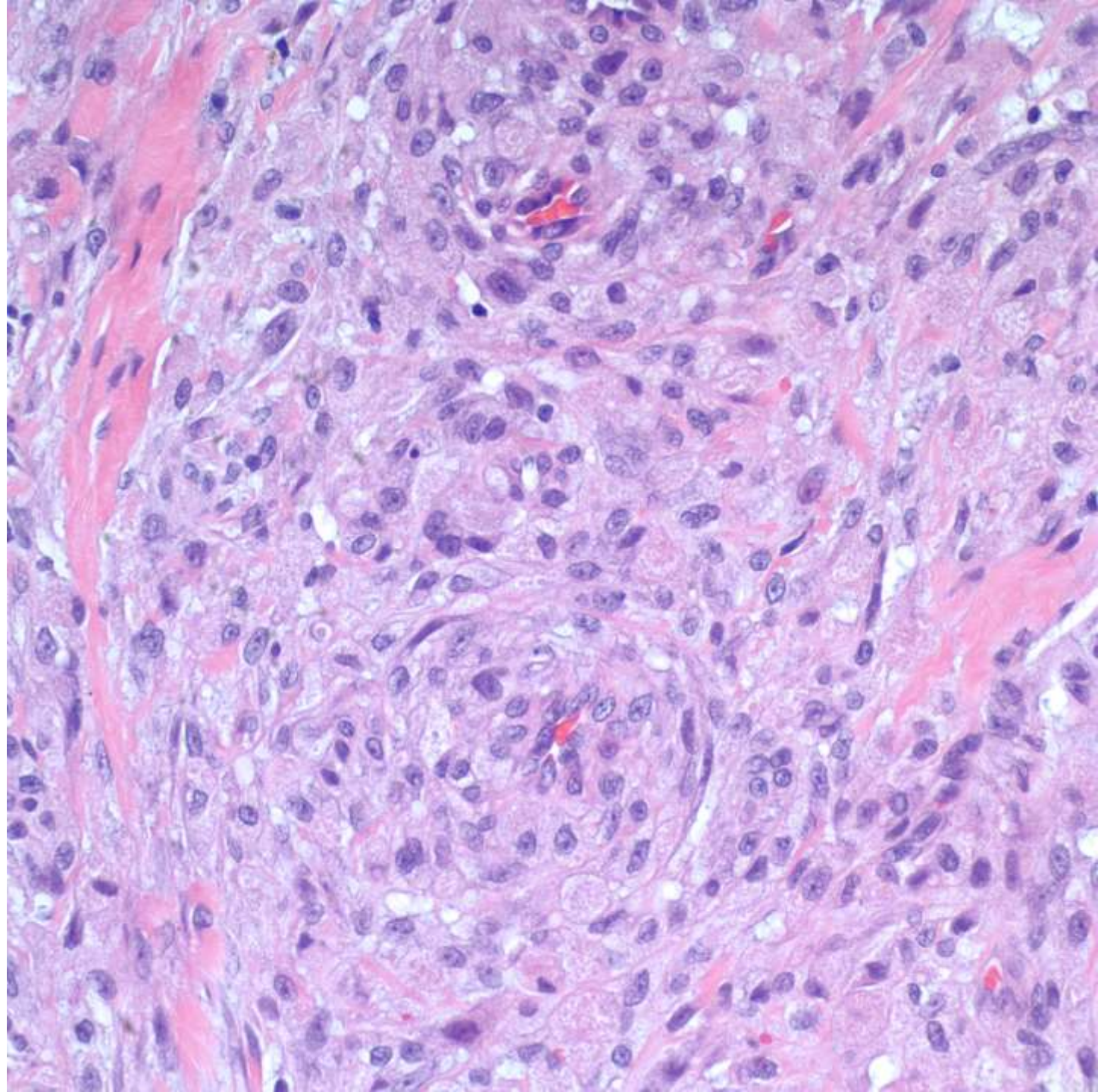












# DIAGNOSIS?





# DDx

- Granular cell tumor
- Congenital granular cell epulis
- Leiomyoma/leiomyosarcoma with granular cell features
- Melanocytic lesion with granular cell change
- PEComa
- Verruciform xanthoma
- Benign fibrous histiocyoma with granular cell change
- Cellular neurothekeoma
- Juvenile xanthogranuloma
- Epithelioid fibrous histiocyoma
- Langerhans cell histiocytosis
- Atypical fibroxanthoma

(19-0708)

NKI/C3

CD68

CD163

ALK



# Add'l IHC results (19-0708)

- Positive: inhibin (patchy blush)
- Negative: S100, SOX-10, CK-mix, EMA, CD34, Factor-13a, MITF, HMB45, calretinin, INI1 (retained)

# IHC results (19-0709)

- Positive: NKI/C3 (strong and diffuse), inhibin (weak)
- Negative: S100, SOX-10, CK-mix, CD68, CD163, SMA, desmin, ALK, GFAP, p63, CD45, Factor-13a, HMB45, calretinin, CD1a, langerin, INI1 (retained)
- GMS and PAS with fungal organisms consistent with *Candida* spp. in the squamous epithelium



# Diagnosis

- 19-0708
  - SOFT TISSUE, LEFT CLAVICLE, EXCISION
    - S100-NEGATIVE GRANULAR CELL TUMOR (SEE COMMENT)
- 19-0709
  - TONGUE, LEFT, BIOPSY
    - MOST COMPATIBLE WITH NON-NEURAL GRANULAR CELL TUMOR (SEE COMMENT)

# Non-neural granular cell tumor (NNGCT)

- Rare neoplasm composed of large, ovoid cells with granular cytoplasm
- Described in cutaneous sites (trunk, extremities, face) and oral cavity
  - Congenital granular cell epulis may be related to oral NNGCT
- S100 negative
  - NKI/C3+, CD68 +/-, NSE +/-, PGP9.5 -/+, F13a -/+
- Can exhibit nuclear atypia, increased mitoses
  - Pitfall: misdiagnosis of NNGCT as malignant granular cell tumor
- Behavior generally benign, with rare cases of nodal metastases



# Cohen et al., AJSP 2018

- A subset of cutaneous NNGCTs possess *ALK* gene fusions
  - 3/5 NNGCTs (60%)
  - One with *SQSTM1-ALK* fusion
  - Two with *DCTN1-ALK* fusions

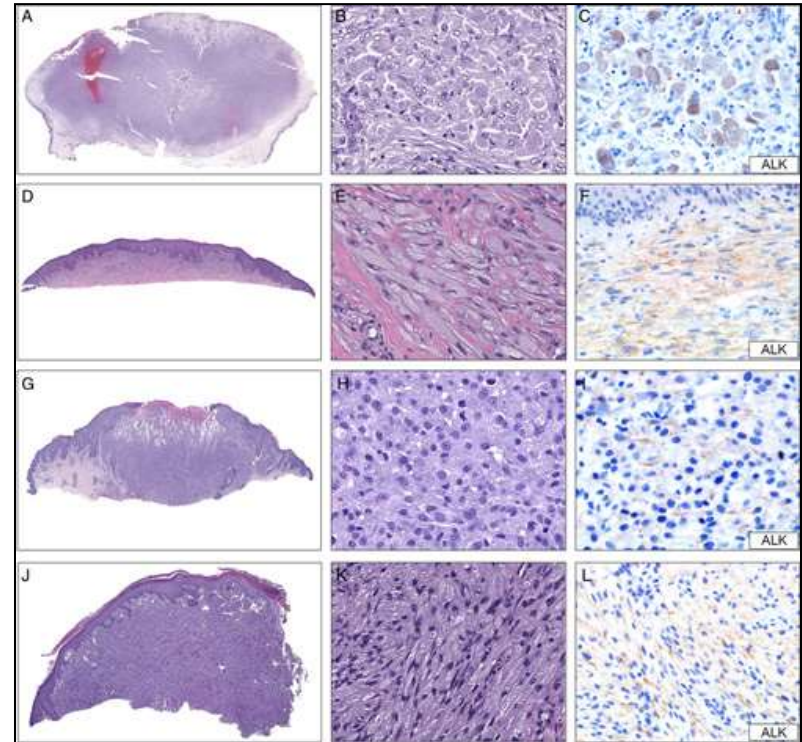


FIGURE 1 . NNGCT with positive ALK immunohistochemistry. Case 1 (A-C), case 2 (D-F), case 3 (G-I), and case 4 (J-L). The tumors had a polypoid or dome-shaped silhouette, and showed variability in morphology ranging from epithelioid to spindled/fascicular cells. ALK immunoreactivity was moderate (C) or weak (F, I, L).

**Cutaneous Non-Neural Granular Cell Tumors Harbor Recurrent ALK Gene Fusions.**  
Cohen, Jarish; MD, PhD; Yeh, Iwei; MD, PhD; Jordan, Richard; DDS, PhD; Wolsky, Rebecca; Horvai, Andrew; MD, PhD; McCalmont, Timothy; LeBoit, Philip

American Journal of Surgical Pathology. 42(9):1133-1142, September 2018.  
DOI: 10.1097/PAS.0000000000001122

# FIRST PLACE

- [Mrs. Merv Grazinski, of Oklahoma City](#), Oklahoma, who purchased a new 32-foot Winnebago motor home. On her first trip home, from an OU football game, having driven on to the freeway, she set the cruise control at 70 mph and calmly left the driver's seat to go to the back of the Winnebago to make herself a sandwich. Not surprisingly, the motor home left the freeway, crashed and overturned. Also not surprisingly, Mrs. Grazinski sued Winnebago for not putting in the owner's manual that she couldn't actually leave the driver's seat while the cruise control was set. The Oklahoma jury awarded her, are you sitting down?

\$1,750,000.

PLUS a new motor home. Winnebago actually changed their manuals as a result of this suit, just in case Mrs. Grazinski has any relatives who might also buy a motor home.

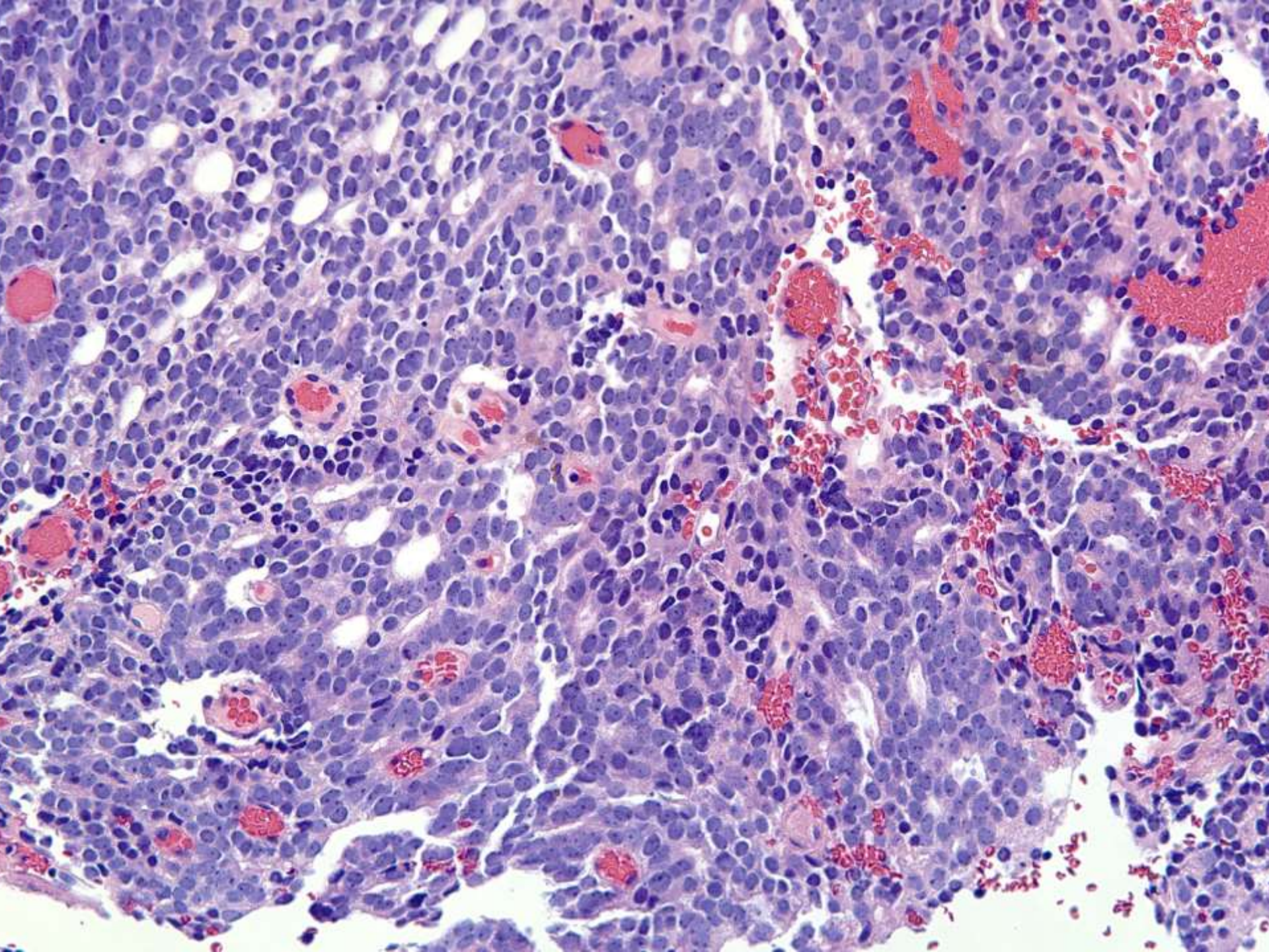


# 19-0710

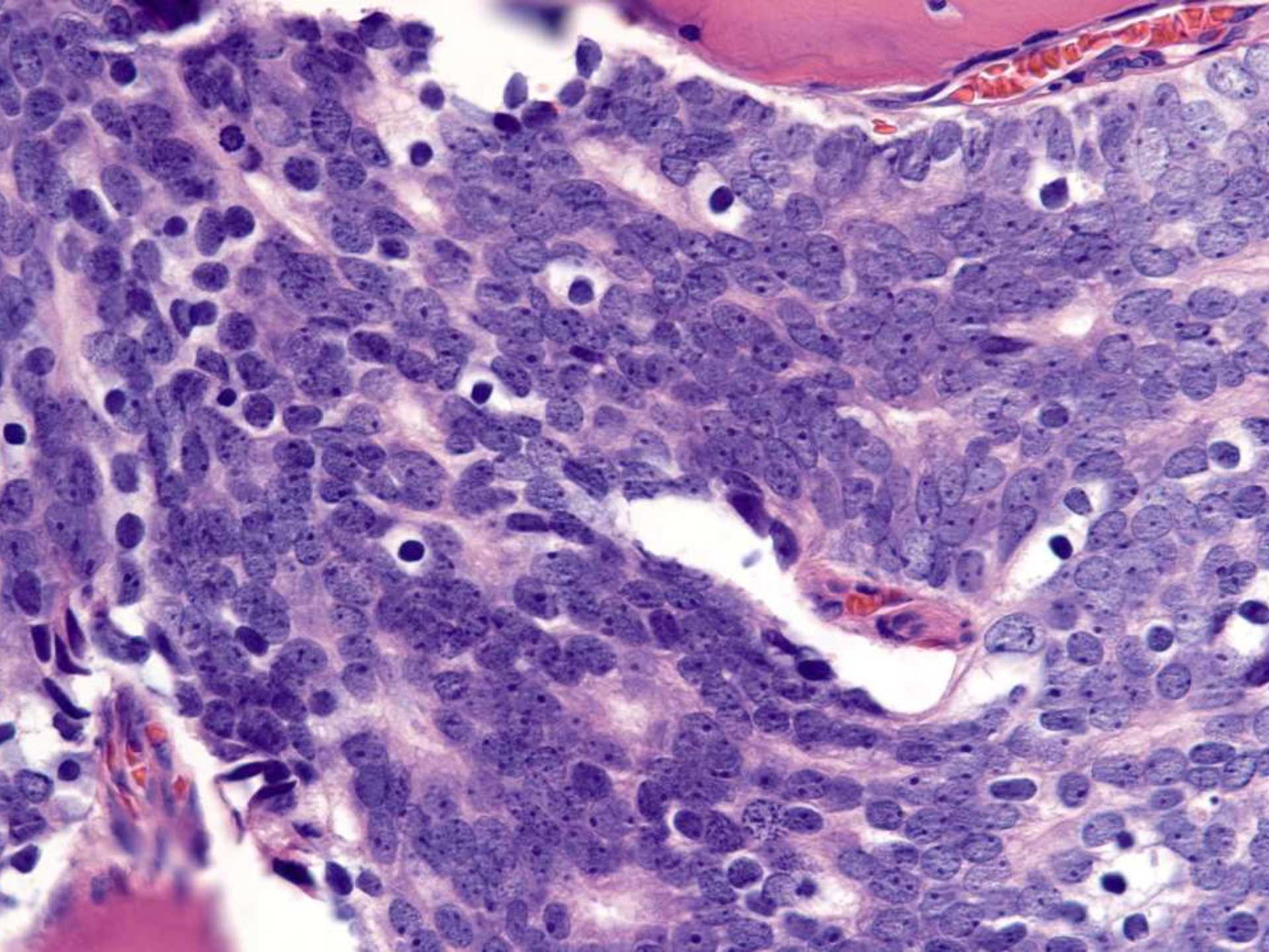
Romain Cayrol/Hannes Vogel;  
Stanford

64-year-old male with pituitary  
tumor.







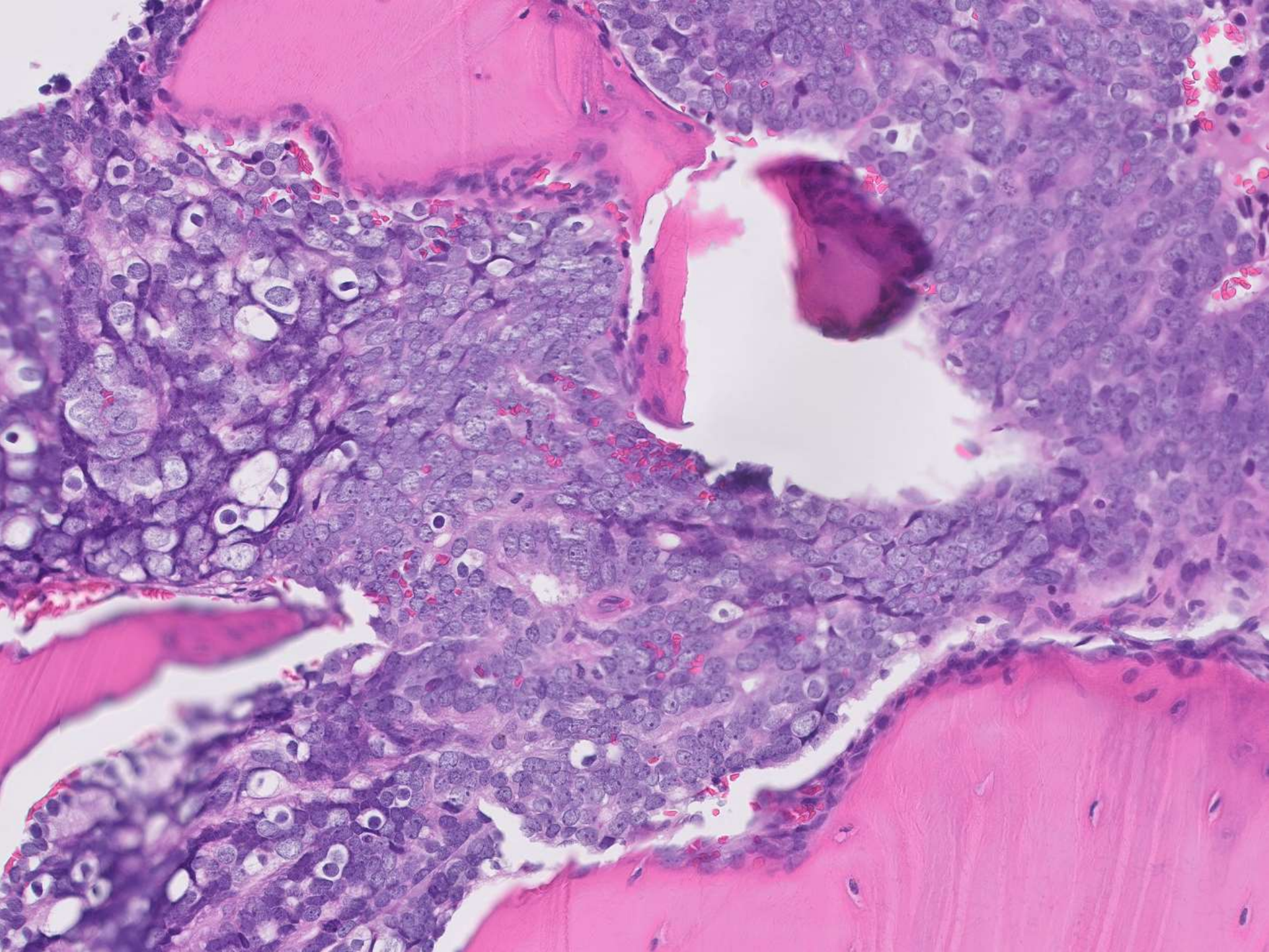




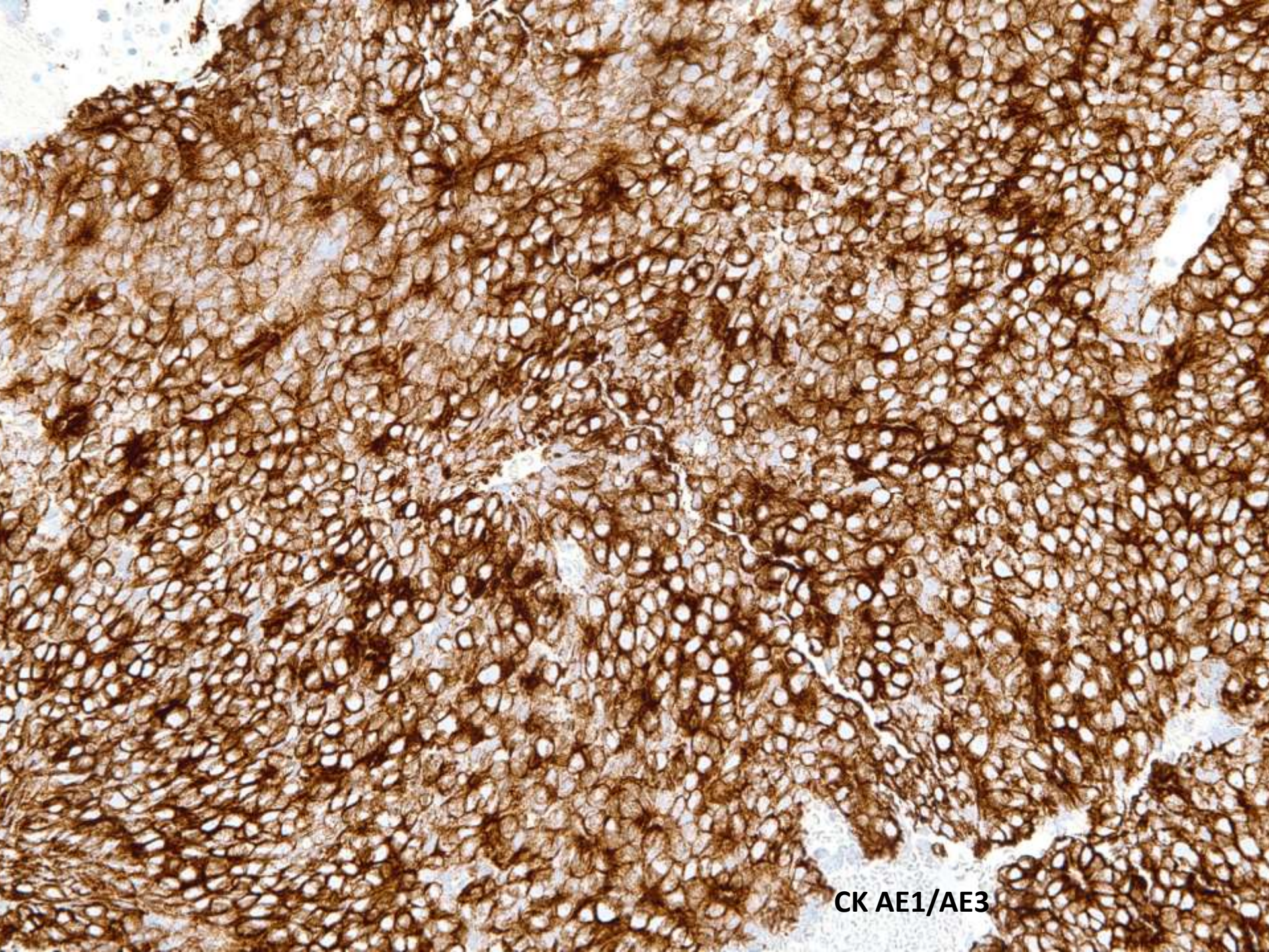
# DIAGNOSIS?





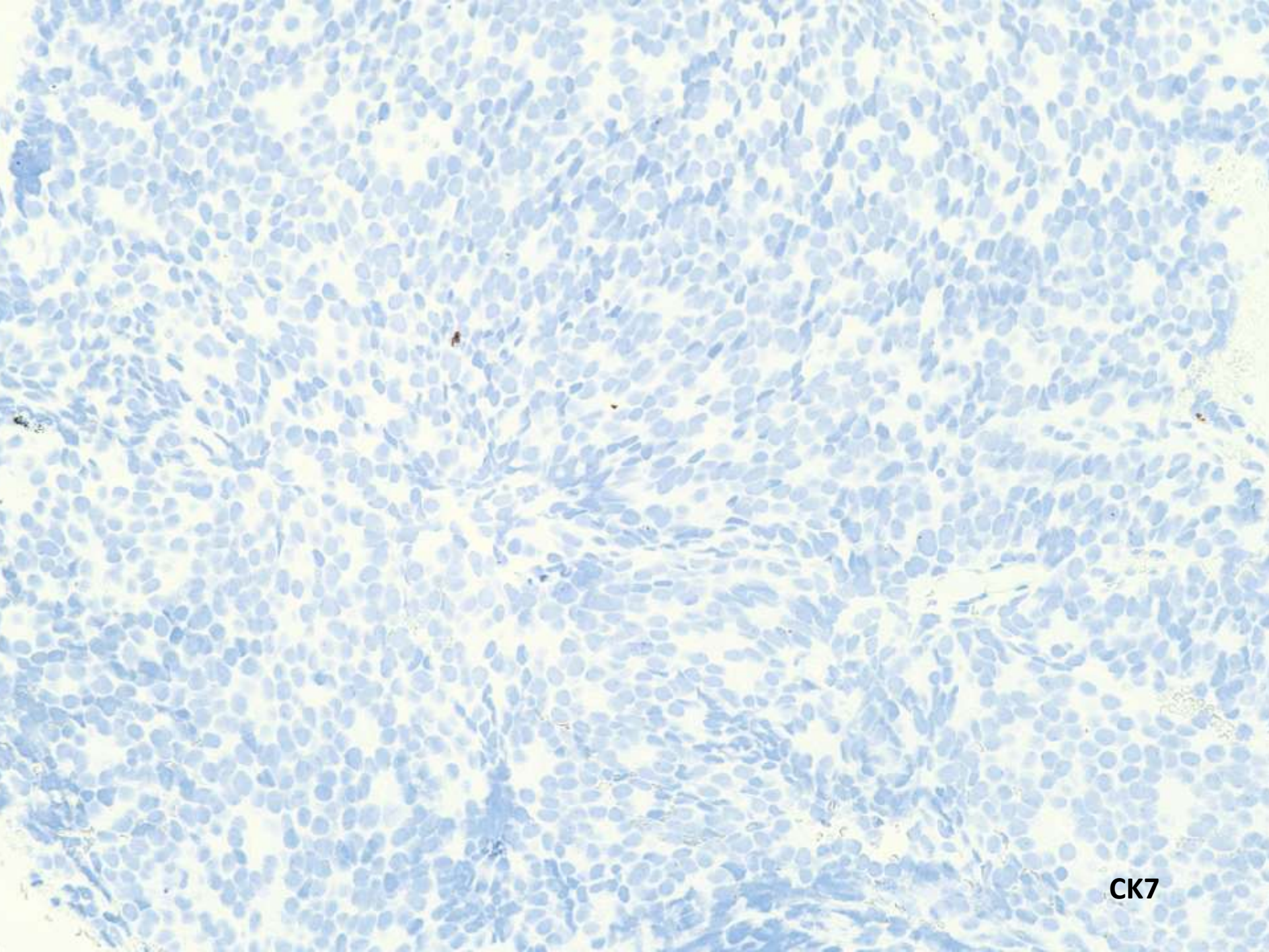






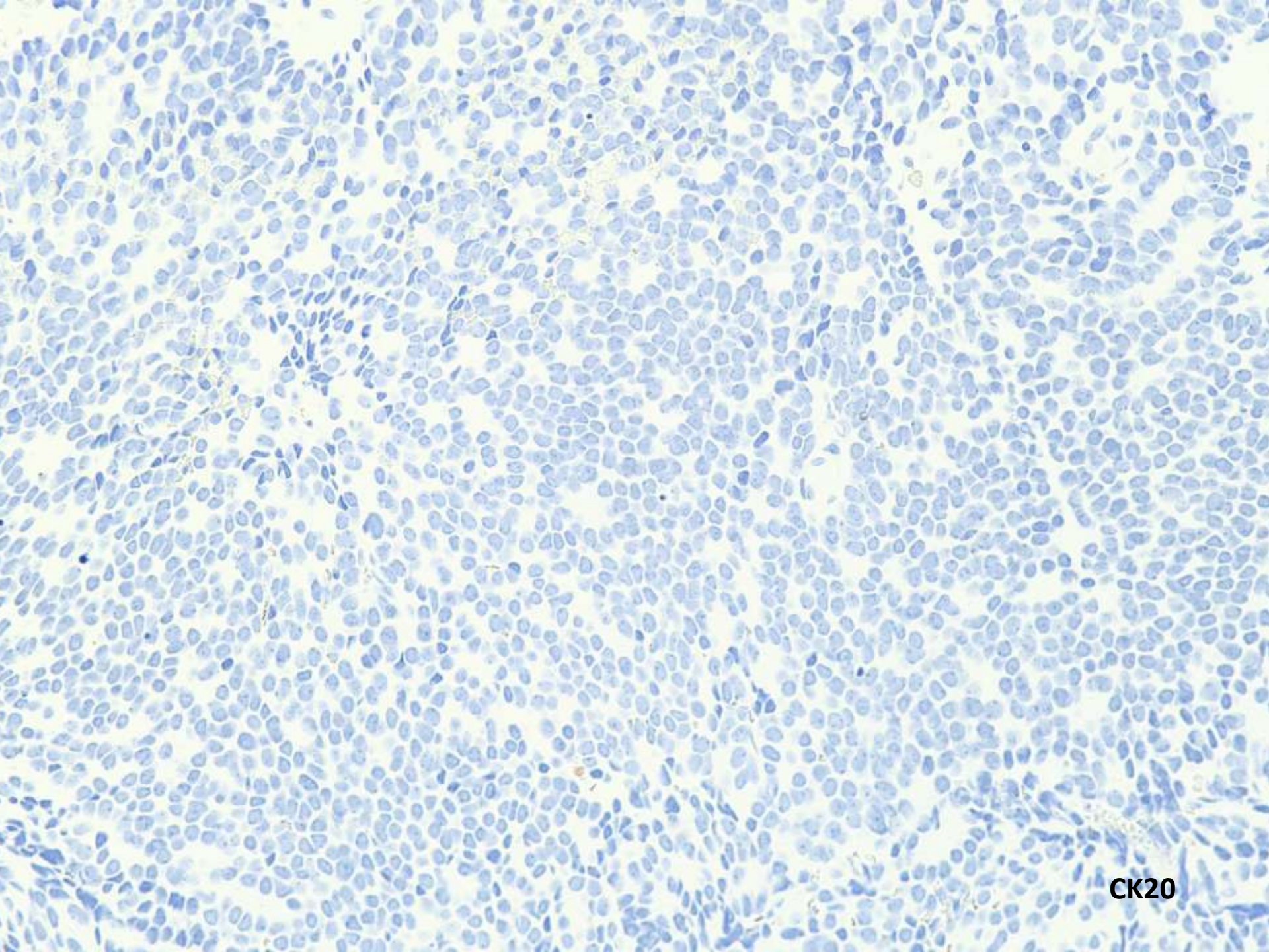
CK AE1/AE3





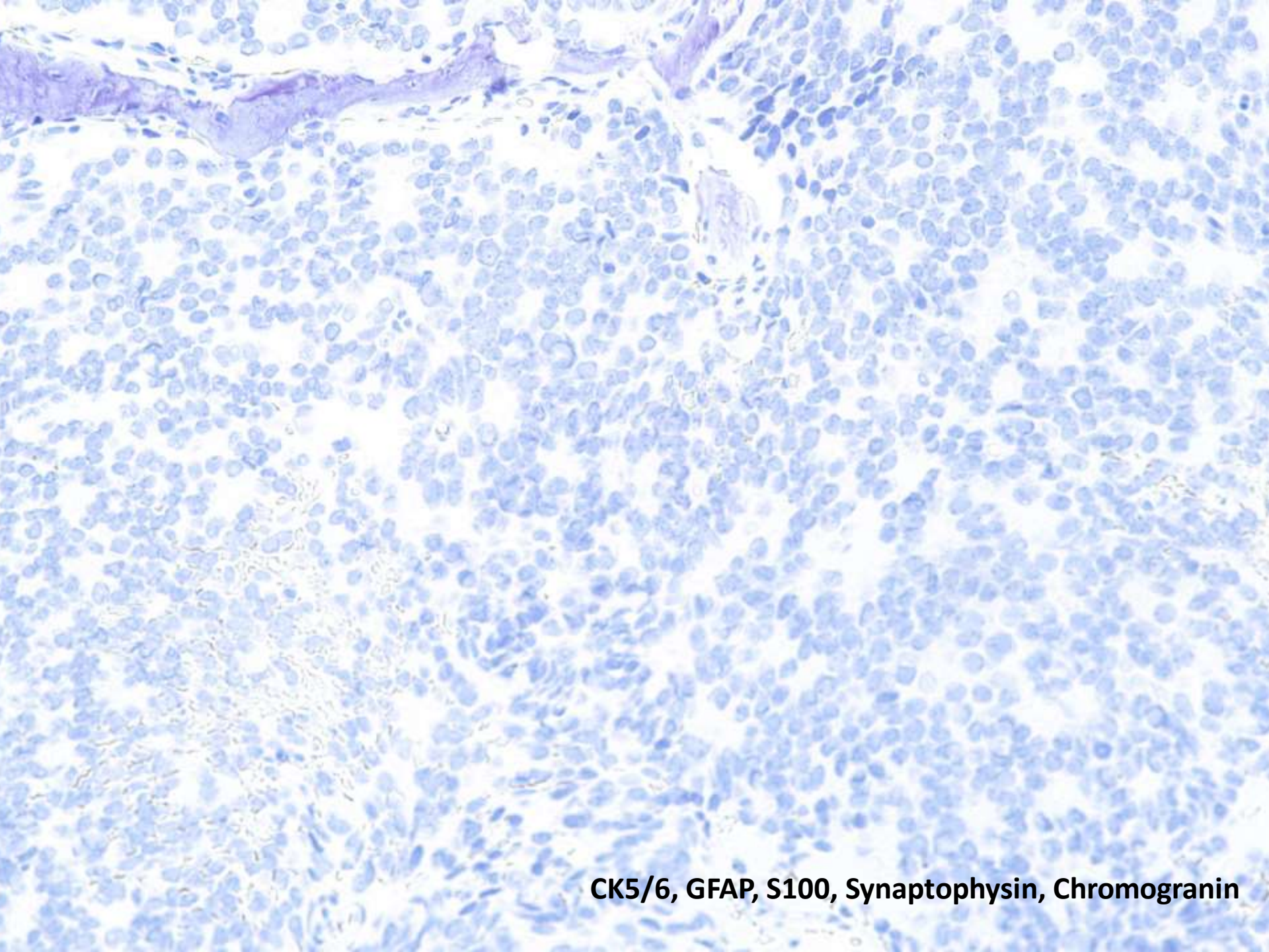
CK7





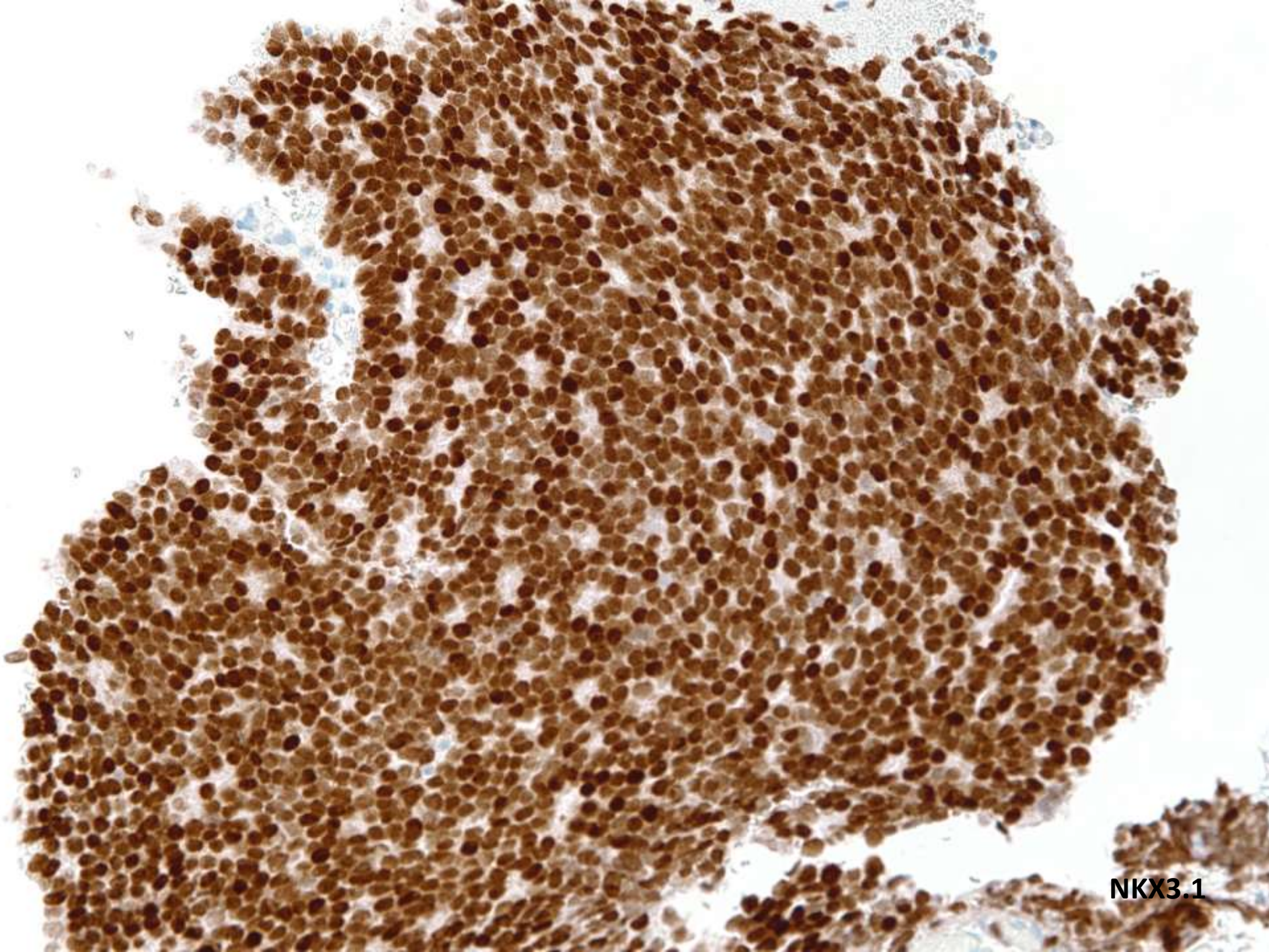
CK20





CK5/6, GFAP, S100, Synaptophysin, Chromogranin



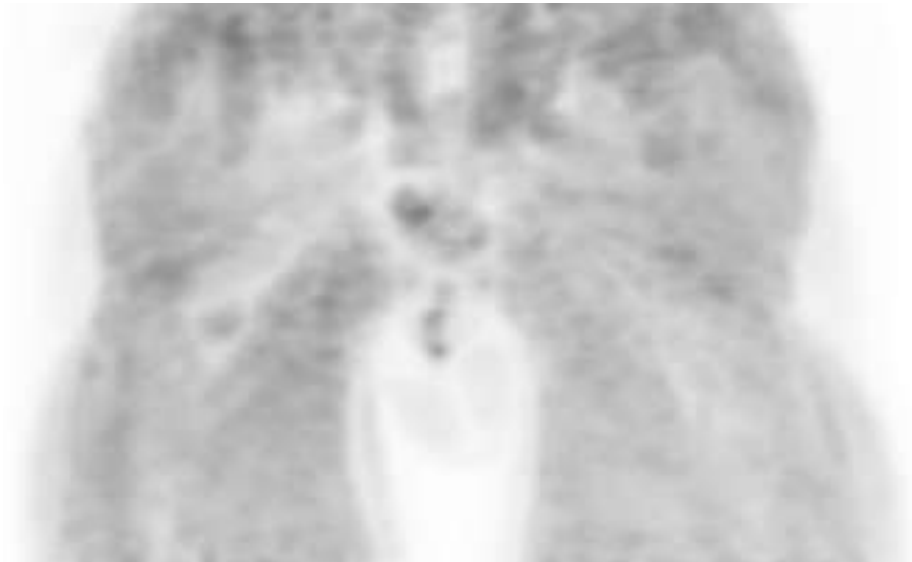
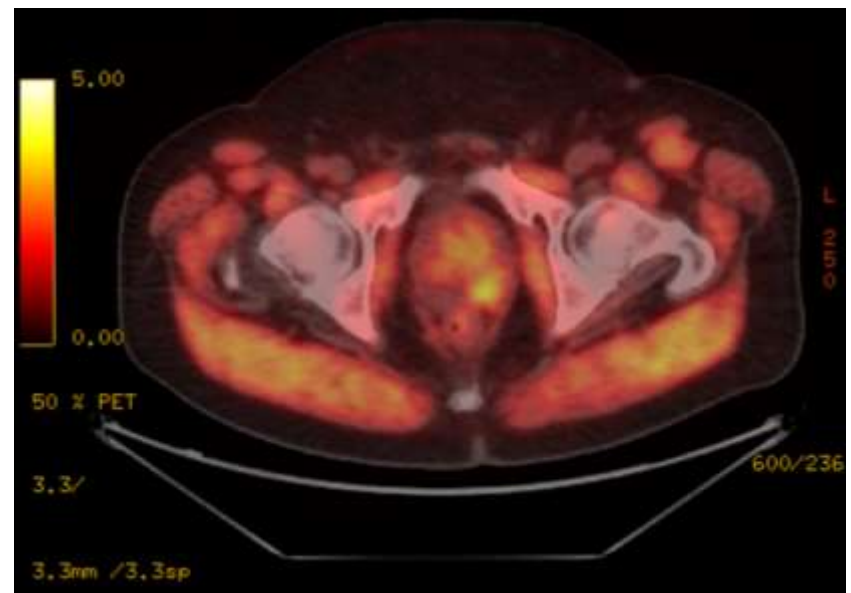
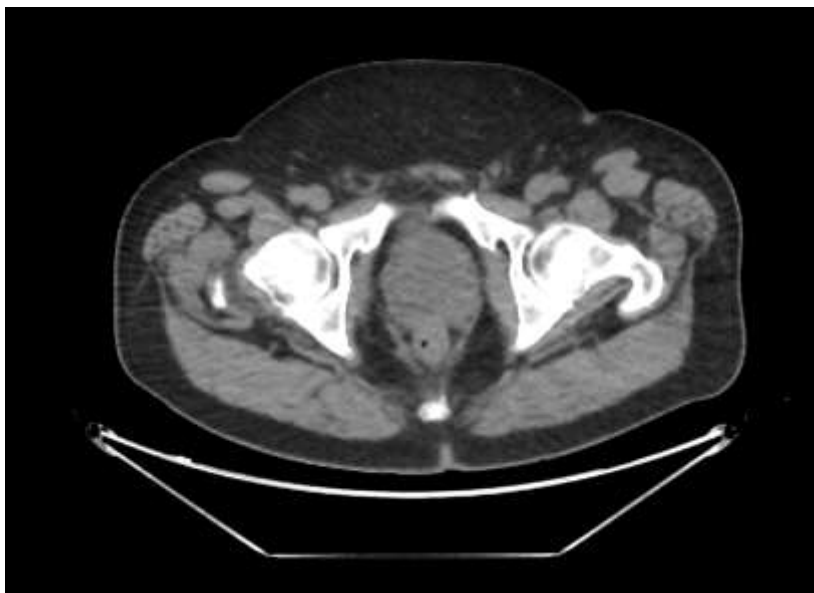


NKX3.1



# DIAGNOSIS

- BRAIN, SELLAR AND SUPRASELLAR TUMOR, RESECTION
  - METASTATIC PROSTATIC ADENOCARCINOMA
    - Ckmix +, NKX3.1+, PSA+
    - CK7/20-
    - Synaptophysin-, chromogranin-, S100-, GFAP-, CK5/6-



- Retrospectively a prior abdominal scan demonstrated a large nodular prostate with suspected involvement of the left seminal vesicle and sphenoid bone involvement
- A post-op PET-Scan confirms the suspicion



# Prostatic adenocarcinoma

- 2<sup>nd</sup> most common malignancy worldwide and the fifth most lethal in men
- Often detected after 60 years of age
- Dietary carcinogens, estrogens, oxidants, chronic inflammation
  - Red meat, animal fats
- Markers: PSA (and different isoforms), PCA3 RNA in urine, ETS gene fusions (TMPRSS2-ERG gene fusion seen in 40-60% of carcinomas)

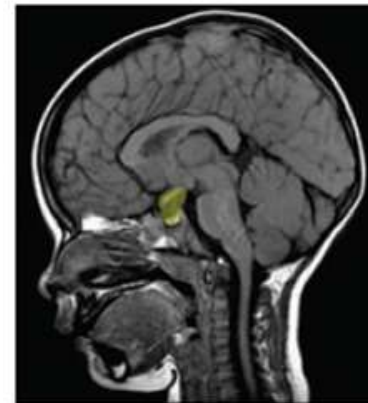
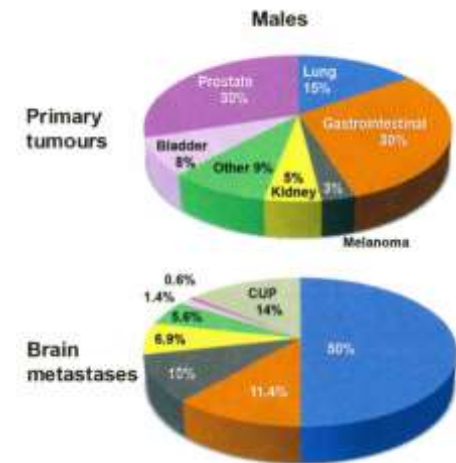
## • Tumor spread

- Local infiltration, lymphatics, blood vessels and nerves
- Metastasis:
  - Bone (85%)
  - Regional lymph nodes (iliac, pudental, presacral) and distant lymph nodes (11%)
  - Liver (10%)
  - Thorax (9%)
  - Brain (3%)

TNM	Stage	Description
Tumor (T)	Tx	Tumor cannot be assessed
	T0	No evidence of tumor
	T1	Clinically unapparent tumor not detected by physical exam (DRE) or visible by imaging
	T1a	Tumor found incidentally in tissue removed from prostate for other reasons, histologic finding in <5% of tissue resected
	T1b	Tumor found incidentally in tissue removed from prostate for other reasons, histologic finding in >5% of tissue resected
	T1c	Tumor identified by needle biopsy because of elevated PSA
	T2	Tumor confined within the prostate
	T2a	Tumor involves ≤50% of one lobe or less
	T2b	Tumor involves >50% of one lobe but not both lobes
	T2c	Tumor involves both lobes
	T3	Tumor extends outside the prostate capsule
	T3a	Extracapsular extension (unilateral or bilateral)
Regional lymph Nodes (N)	T3b	Tumor involves the seminal vesicles
	T4	Tumor invades nearby structures other than the seminal vesicles, such as the bladder or rectum
	Nx	Regional lymph nodes were not assessed
	N0	No spread to nearby lymph nodes
	N1	Metastasis in nearby lymph nodes
Distant Metastasis (M)	Mx	Distant metastases cannot be assessed (not evaluated)
	M0	No distant metastasis
	M1	Distant Metastasis
	M1a	Lymph node(s) outside of nearby area
	M1b	Bone(s)
Histopathologic Grade (G)	M1c	Other sites with or without bone disease
	Gx	Grade cannot be assessed
	G1	Gleason 2-4
	G2	Gleason 5-6
	G3-4	Gleason 7-10

# CNS metastatic tumors

- CNS metastases are the most common CNS neoplasms in adults (30% of all cancers)
- Prostatic carcinoma metastases are rare and often treated by radiotherapy without histological confirmation
- Retrospective study by Ormond et al, 2019
  - Epidural/dural tumors (16) and parenchymal metastases (5)
  - Often associated with other metastases (20/21)
  - 19/21 (90.5%) cases showed loss of ERG
  - ERG negative prostatic carcinoma are often androgen deprivation resistant and have a tendency for CNS metastasis
- Major prognostic factors are age, Karnofsky performance status, number of CNS brain metastasis and status of extracranial disease



Pediatric	Adult
Sellar/infundibular	
Craniopharyngioma	Pituitary adenoma
Langerhans cell histiocytosis	Meningioma
	Metastases
Suprasellar	
Pilocytic astrocytoma/optic glioma	Papillary craniopharyngioma
Germ cell tumors	
Craniopharyngioma	





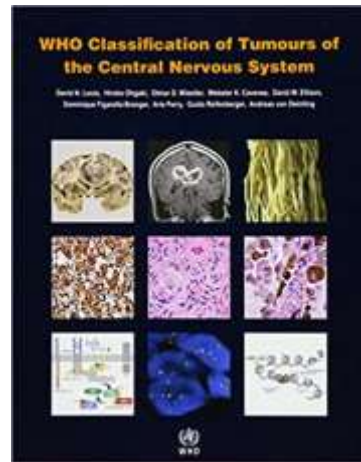
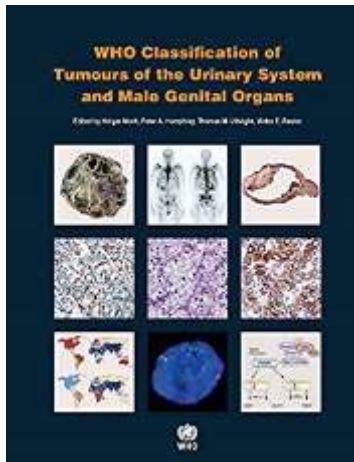
ERG

# Conclusions

- CNS metastases are the most common CNS neoplasms in adults
- Metastatic prostatic carcinoma to the CNS is rare
  - Dural/epidural, rarely parenchymal
  - Associated with other metastatic disease
  - ERG negative prostatic carcinoma
  - Androgen therapy resistant disease



# References



Journal of Neuro-Oncology (2019) 142:319–325  
<https://doi.org/10.1007/s11060-019-03099-x>

## CLINICAL STUDY



### Prostatic adenocarcinoma CNS parenchymal and dural metastases: alterations in ERG, CHD1 and MAP3K7 expression

D. Ryan Ormond<sup>1,5</sup> · B. K. Kleinschmidt-DeMasters<sup>1,2,3</sup> · Daniel Cavalcante<sup>1</sup> · Elizabeth E. Smith<sup>2</sup> · Scott D. Cramer<sup>4</sup> · M. Scott Lucia<sup>2</sup>

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