

# Disclosures

## April 3, 2017

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

**Presenters:**

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Don Born, MD  
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Balaram Puligandla, MD  
Sunny Kao, MD  
Yung Kang, MD  
Charles Zaloudek, MD  
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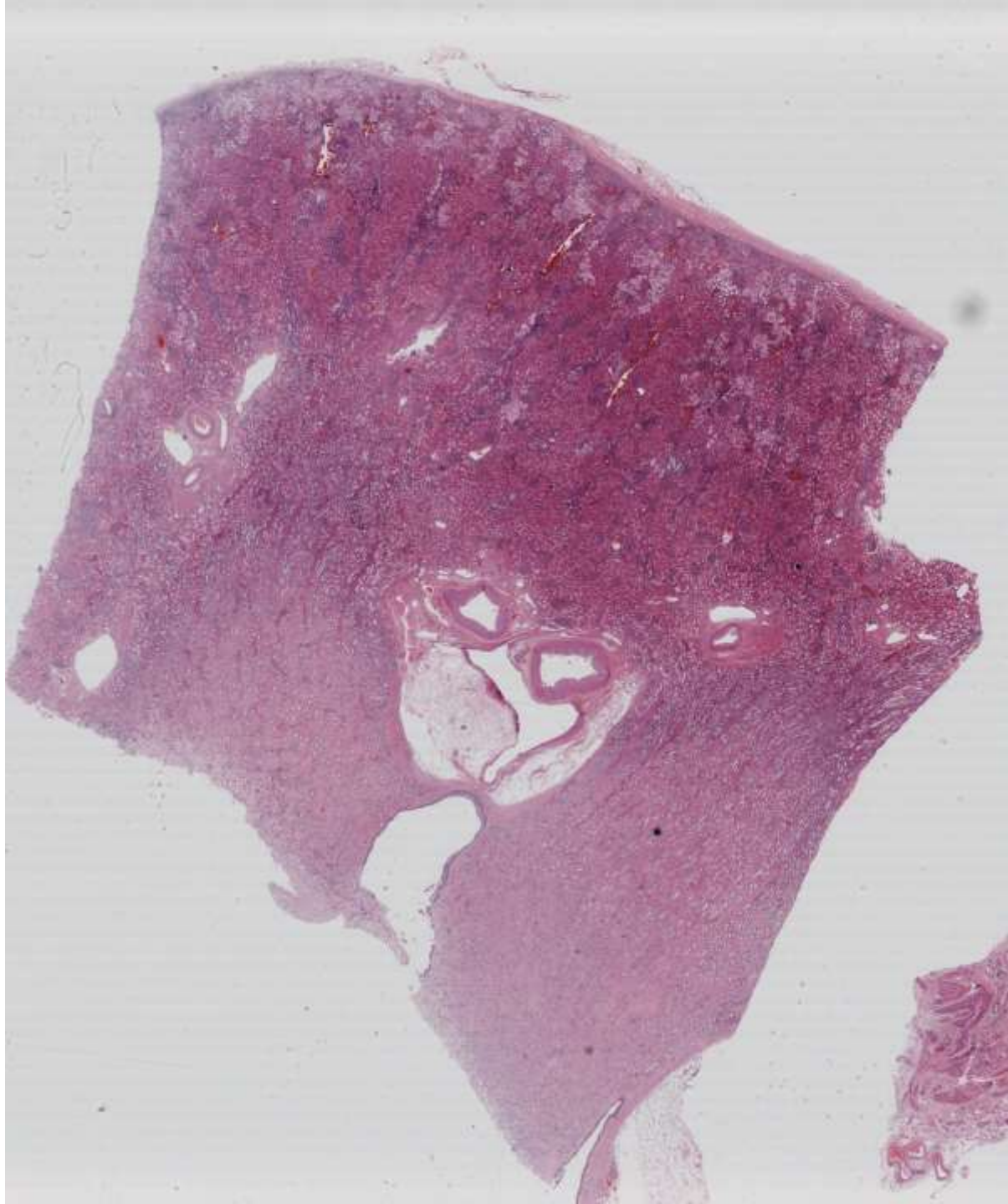
**Activity Planners/Moderator:**

Kristin Jensen, MD  
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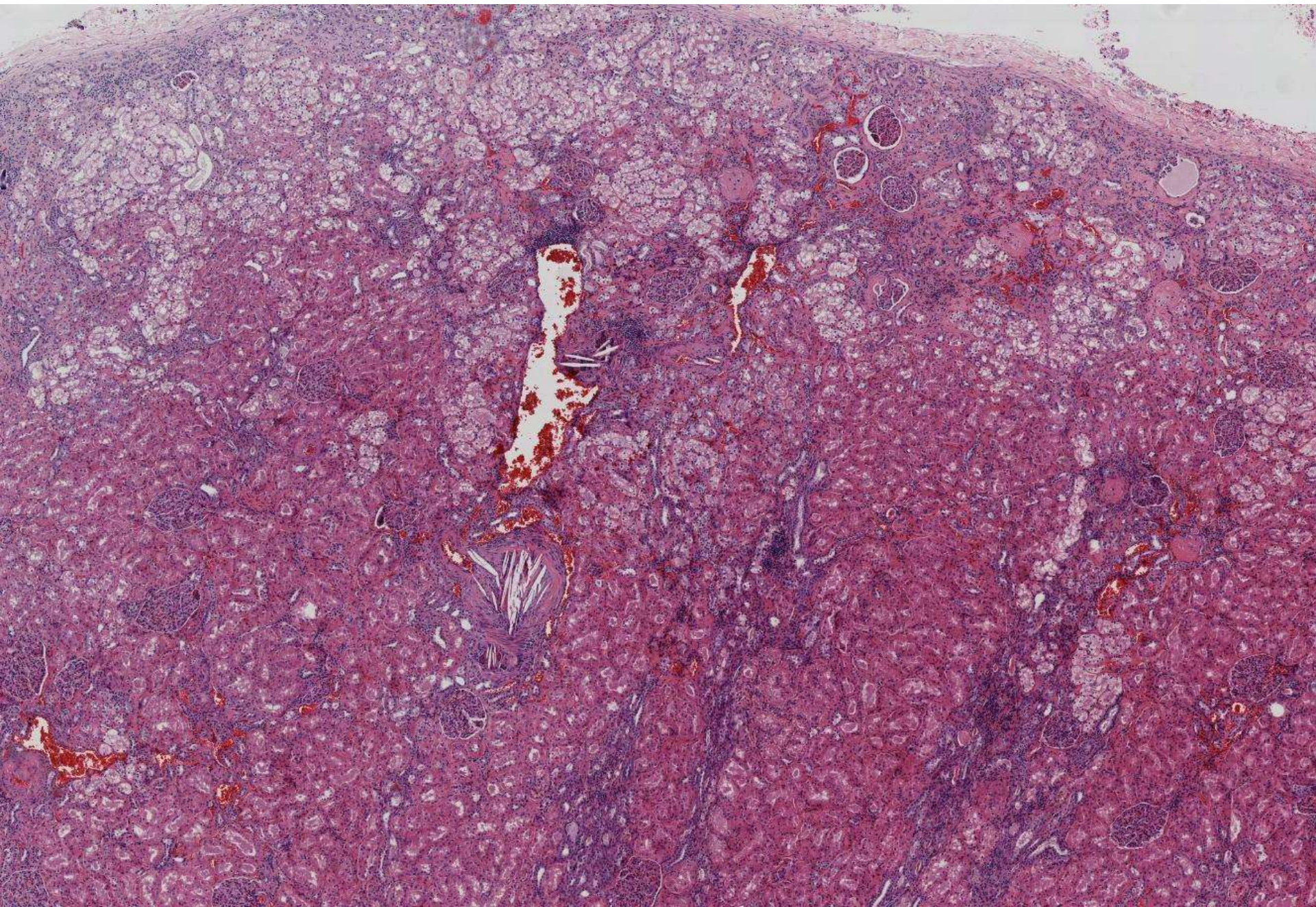
**SB 6151 (scanned slide available)**

**Greg Charville/Megan Troxell; Stanford**

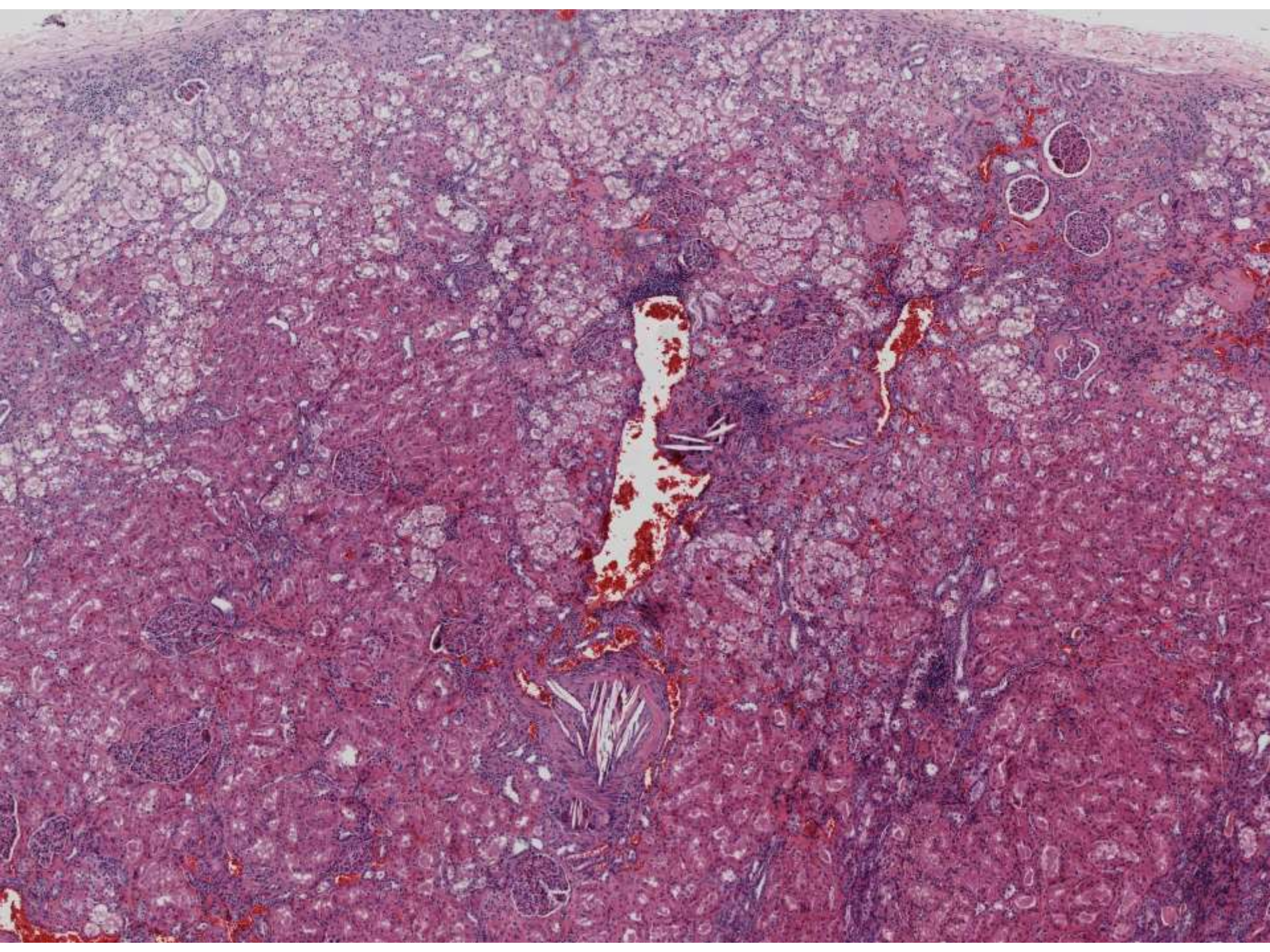
Elderly man undergoes nephrectomy  
for renal cell carcinoma. Non-neoplastic  
kidney section submitted.



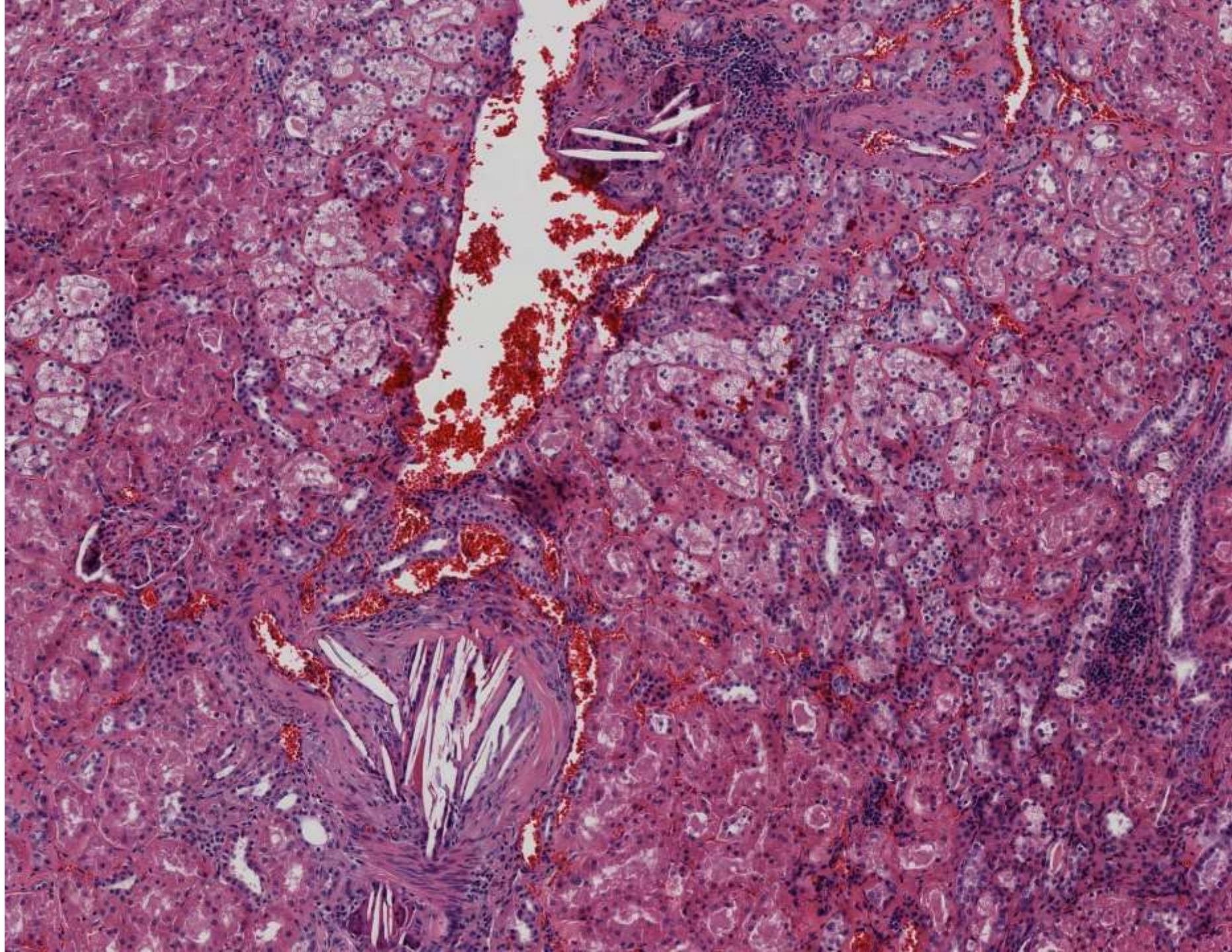




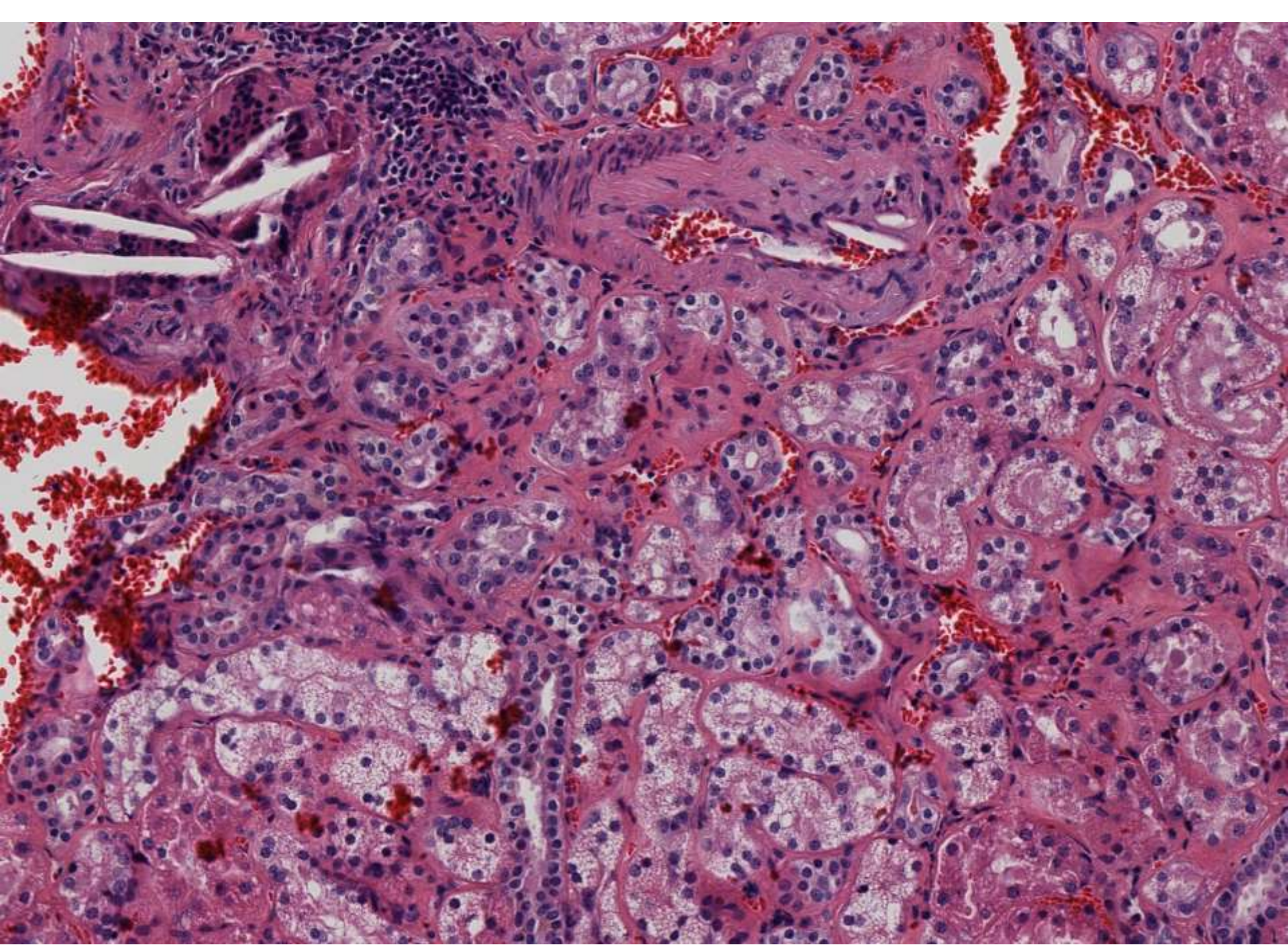




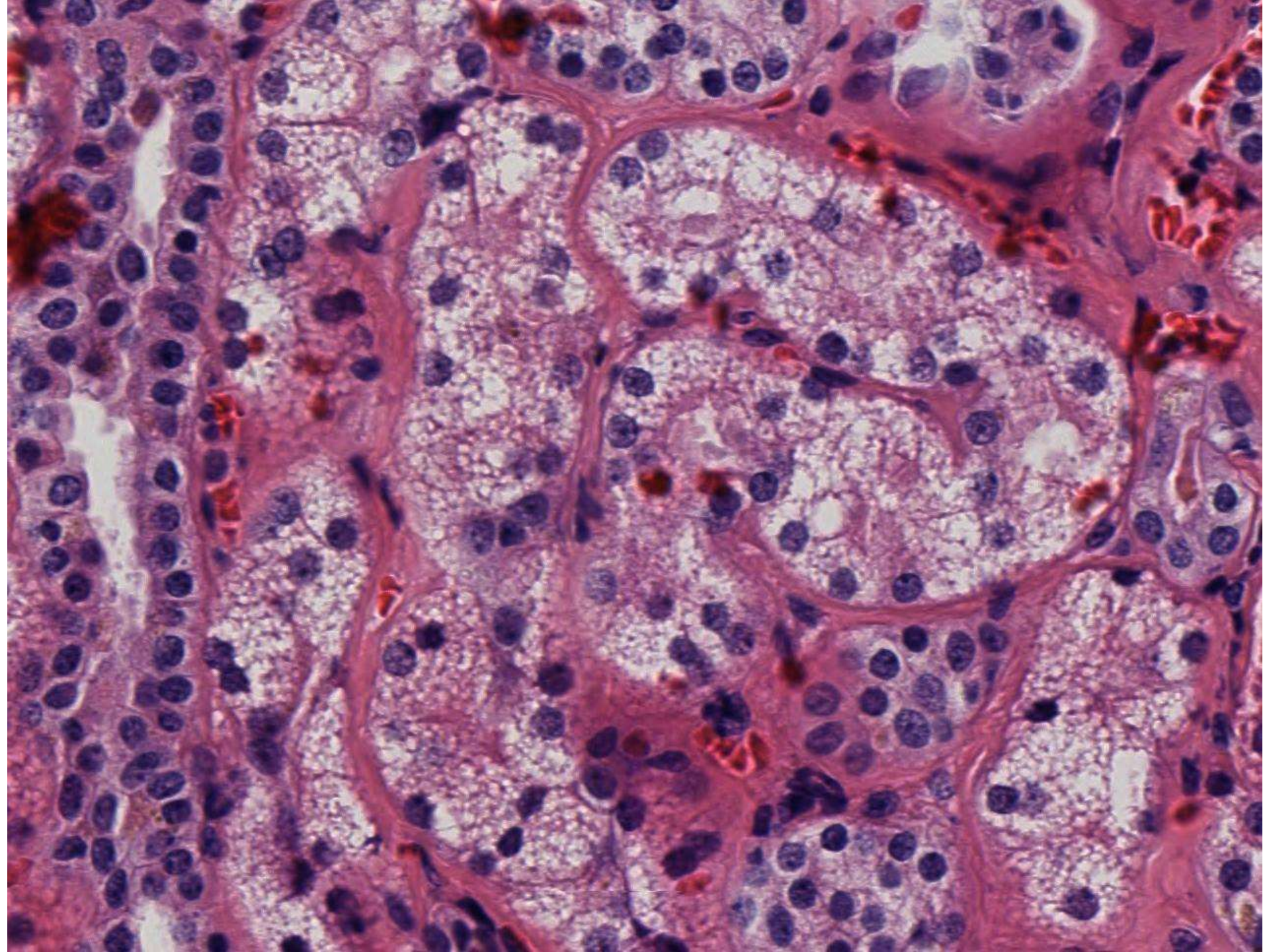




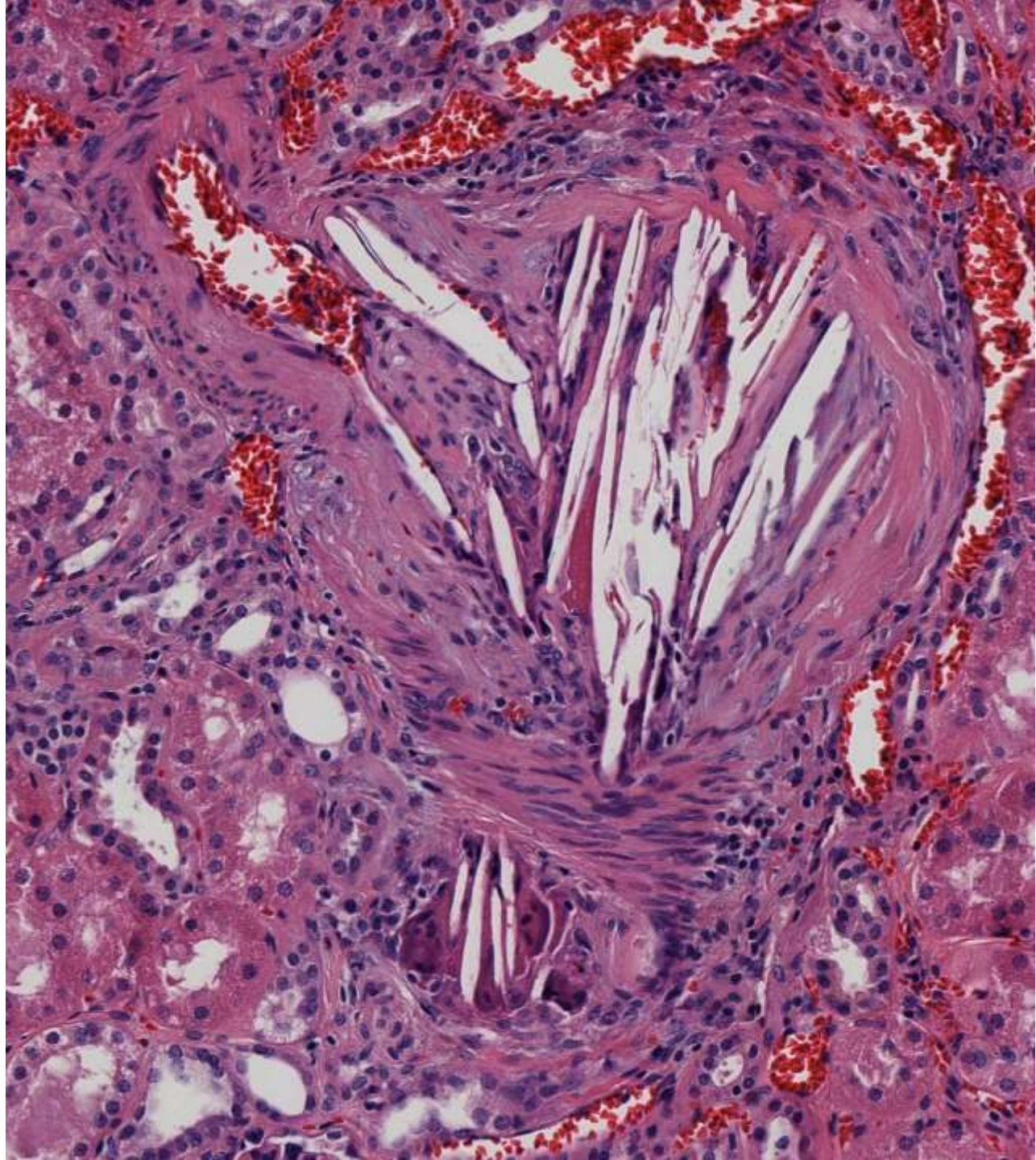




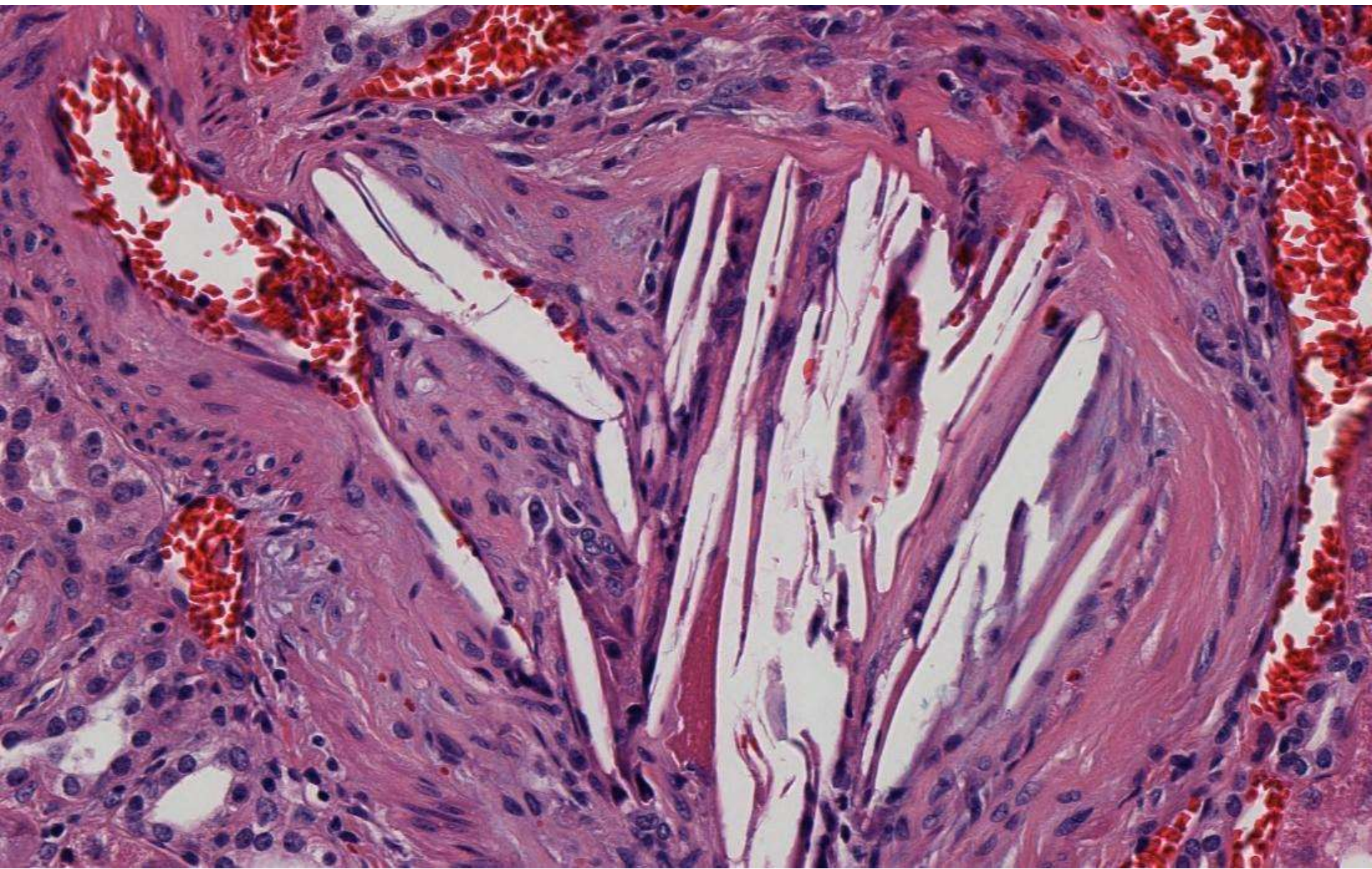














# DIAGNOSIS?

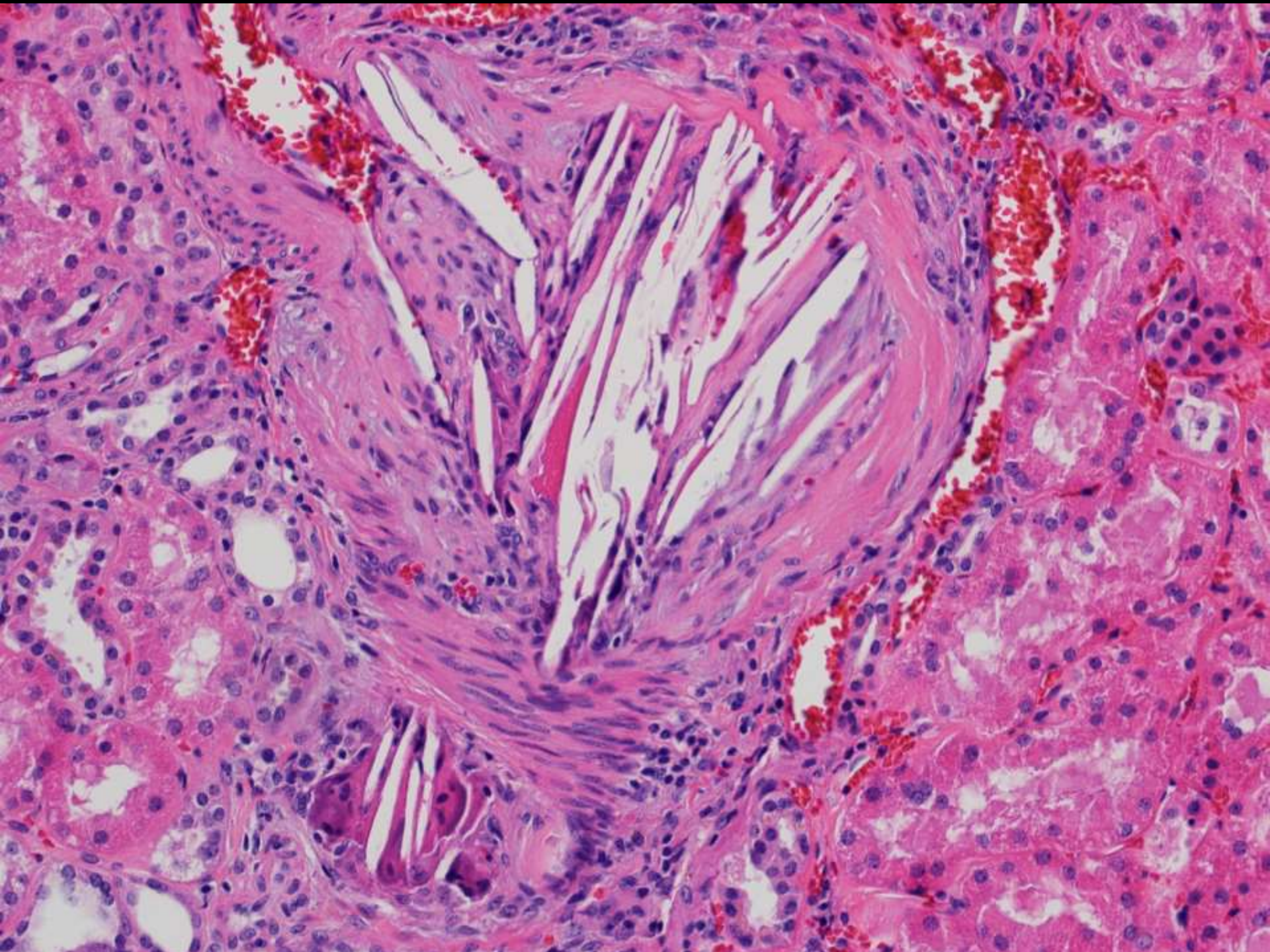






Elderly man undergoes nephrectomy for renal cell carcinoma. A single section of non-neoplastic kidney is examined.

Greg Charville and Megan Troxell  
*Stanford*





# Renal atheroembolic disease – causes

	n	Spontaneous AERD (%)	Iatrogenic AERD			
			All causes (%)	Angiography (%)	CV surgery (%)	Anticoagulation (%)
Fine <sup>4</sup>	221	153 (69%)	68 (31%)	39 (18%)	20 (9%)	30 (14%)
Lye <sup>5</sup>	129	50 (40%)	79 (60%)	55 (43%)	7 (5%)	17 (13%)
Thadhani <sup>8</sup>	52	0 (0%)	52 (100%)	50 (96%)	2 (41%)	19 (37%)
Belenfant <sup>10</sup>	67	3 (4%)	64 (96%)	57 (85%)	24 (36%)	51 (76%)
Scolari <sup>27</sup>	354	83 (24%)	271 (76%)	221 (81%)	69 (25%)	108 (40%)

AERD=atheroembolic renal disease. CV=cardiovascular.



# Renal atheroembolic disease – presentation

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## Kidney

- Acute, subacute, and chronic renal failure
- Severe uncontrolled hypertension
- Renal infarction

## Skin

- Livedo reticularis
- Blue toe syndrome
- Ulceration and gangrene
- Purpura

## Gastrointestinal system

- Abdominal pain
- Gastrointestinal bleeding
- Bowel ischaemia, infarction, and obstruction
- Pancreatitis, cholecystitis, and abnormal liver tests
- Splenic infarcts

## Heart

- Myocardial ischaemia
- Myocardial infarction

## Central nervous system

- Transient ischaemic attacks
- Amaurosis fugax
- Altered mental status
- Cerebral infarction
- Spinal cord infarction

## Eye

- Retinal emboli (Hollenhorst plaques)

## Systemic signs

- Fever
- Weight loss
- Malaise
- Myalgia
- Anorexia



# Renal atheroembolic disease – diagnosis

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## **1 Patient at risk**

- Men older than 60 years
- Longstanding hypertension
- Tobacco use
- Diffuse atherosclerotic disease

## **2 Presence of classic triad**

- Exposure to precipitating factor
- Acute or subacute renal failure
- Peripheral signs of embolisations (eg, blue toe syndrome)

## **3 Gastrointestinal or neurological effects and eosinophilia**

- Should raise the level of suspicion

## **4 Histological confirmation**

- Pathological specimens obtained from the kidney, skin, or muscle

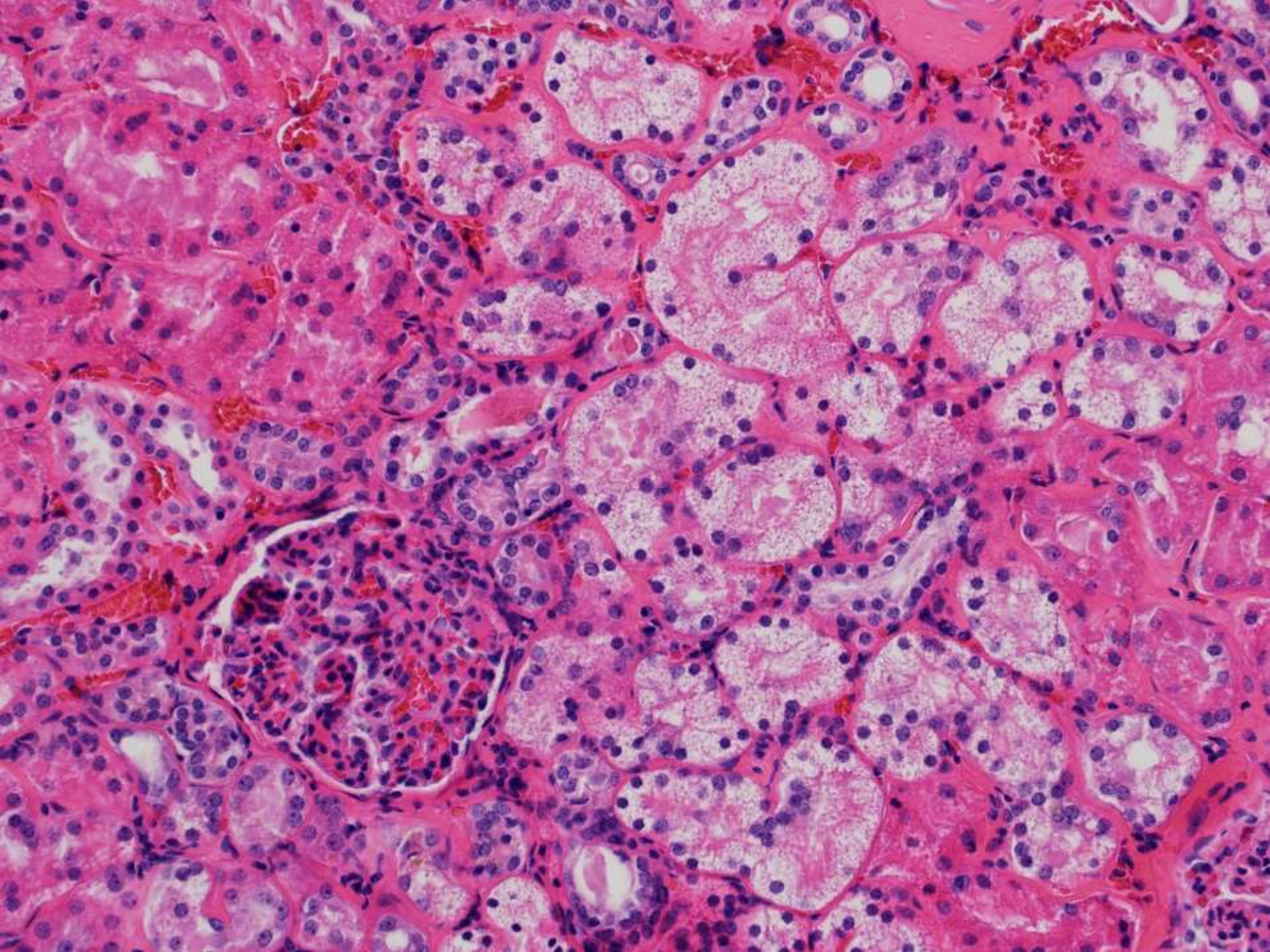


# Renal atheroembolic disease – outcomes

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	n	Renal failure needing dialysis	Recovery of dialysis- dependent renal failure	Maintenance dialysis (end of follow-up)	1-year mortality
Fine <sup>4</sup>	221	62 (28%)	13 (21%)	0	179 (81%)
Lye <sup>5</sup>	129	52 (40%)	13 (26%)	0	83 (64%)
Thadhani <sup>8</sup>	52	23 (44%)	7 (32%)	0	45 (87%)
Belenfant <sup>10</sup>	67	41 (61%)	16 (39%)	23 (35%)	9 (13%)
Scolari <sup>27</sup>	354	11 (33%)	33 (28%)	88 (25%)	60 (17%)







# Clear-cell change of renal tubular epithelium

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## Osmotic tubulopathy

- Isometric cytoplasmic vacuoles, nuclei basally displaced

## Nephrotic syndrome

- Interstitial clear cells, focal/basal vacuolization

## Ischemia

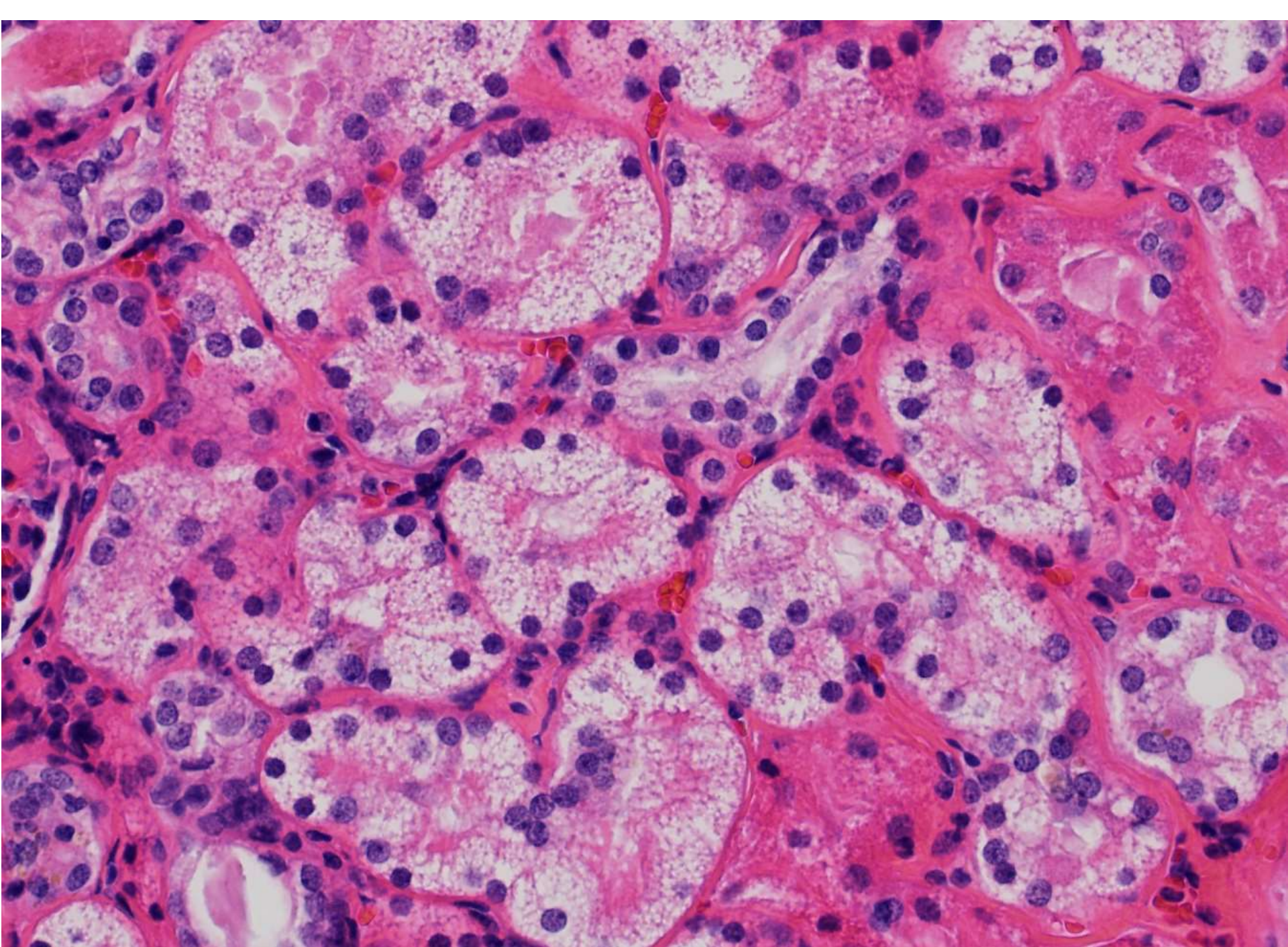
- Variably sized vacuoles, loss of brush border, regenerative changes, epithelial sloughing

## Hyperglycemic tubulopathy

- Outer medulla, PAS+ diastase-sensitive (glycogen)

## Calcineurin inhibitor

- Focal vacuolization, assoc. arteriolopathy





# Osmotic tubulopathy: histologic features

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- Diffuse or focal clear cell change with isometric vacuolization and luminal narrowing
- Proximal > Distal
- Vacuoles are apically biased
- Preserved brush border; no epithelial necrosis or sloughing
- Immunofluorescence: negative
- EM: Cytoplasmic vacuoles, intact brush border

# Agents causing osmotic nephrosis

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- Intravenous immune globulin
- Mannitol (decrease ICP)
- Dextrans (decrease thrombosis, volume replacement)
- Contrast agents



# Osmotic tubulopathy: clinical features

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- Acute deterioration in function with exposure
- Renal failure may come and go without clinical signs
- Typically oliguric
- Begins within days of infusion, reverses after cessation, usually within days to weeks
- Persistent impairment is rare
- Diagnosis by kidney biopsy

# Take home points

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- Osmotic tubulopathy and renal atheroemboli can both present secondary to intravascular imaging procedures
- Osmotic tubulopathy is diagnosed by biopsy, although rarely performed given typically self-limited course
- Differential diagnosis of osmotic tubulopathy is broad
- Renal atheroembolic disease frequently requires dialysis, although function can be regained



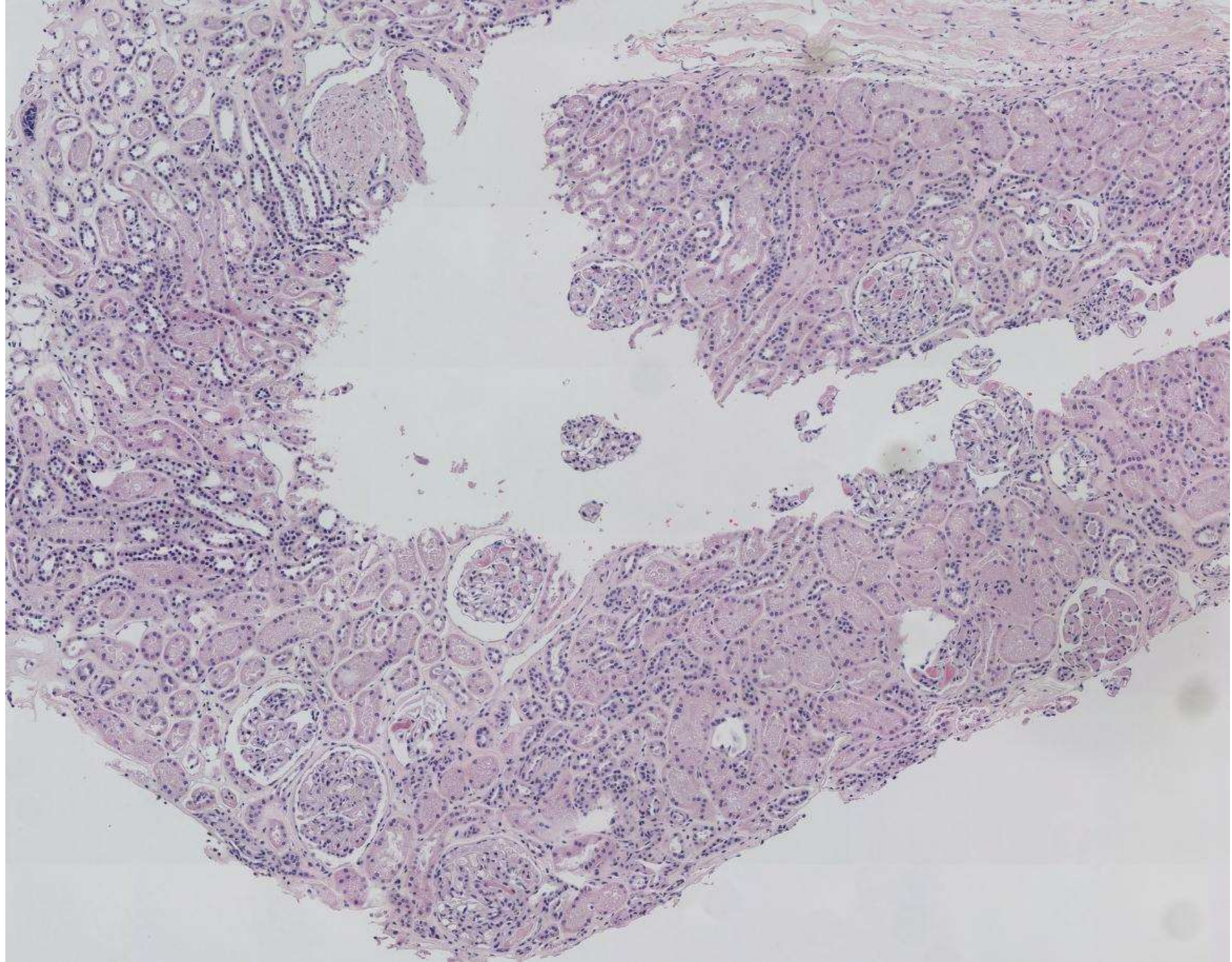
**SB 6152 (scanned slide available)**

**Megan Troxell; Stanford**

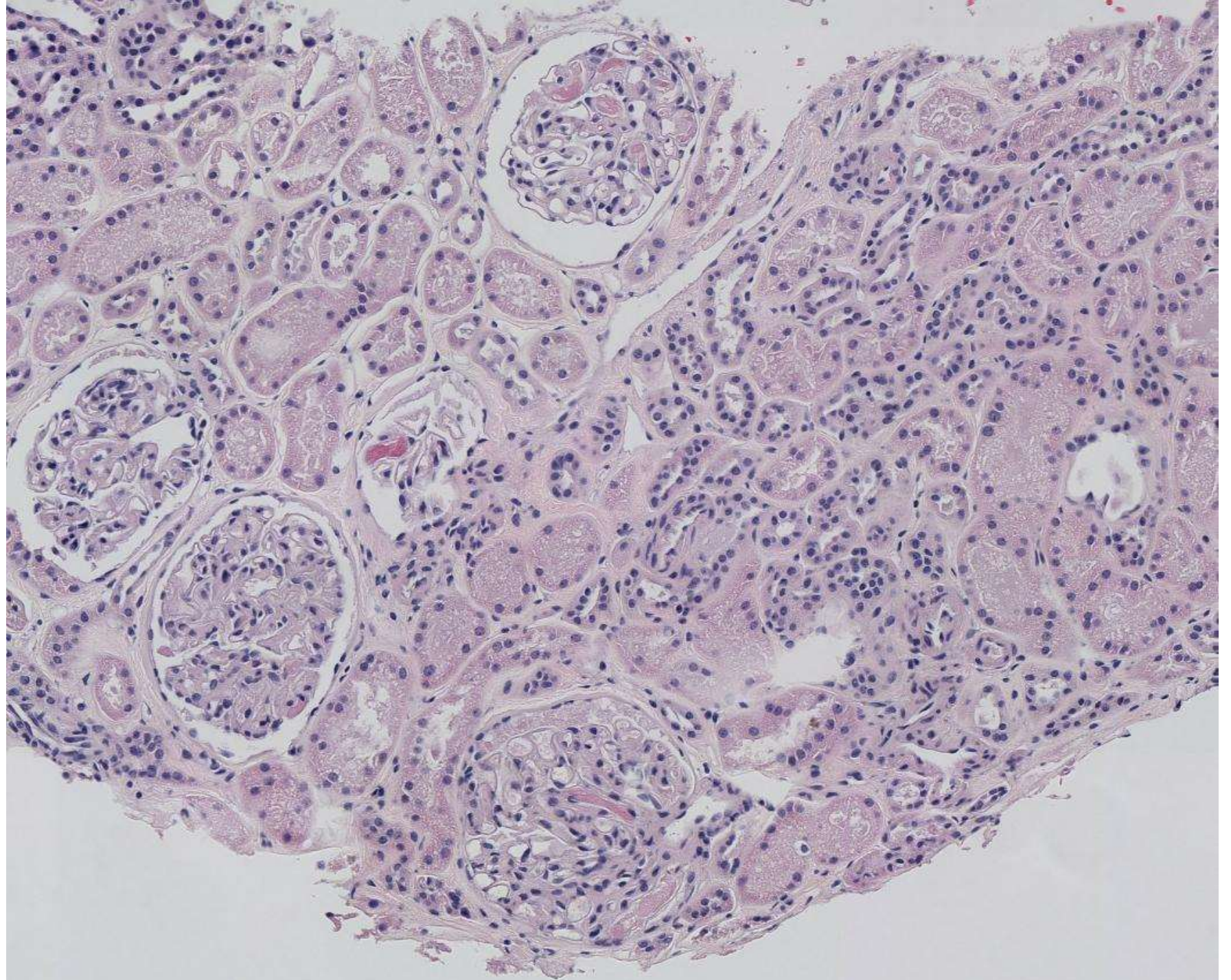
Needle biopsy of donor kidney  
submitted for frozen section  
(permanents of FS submitted).



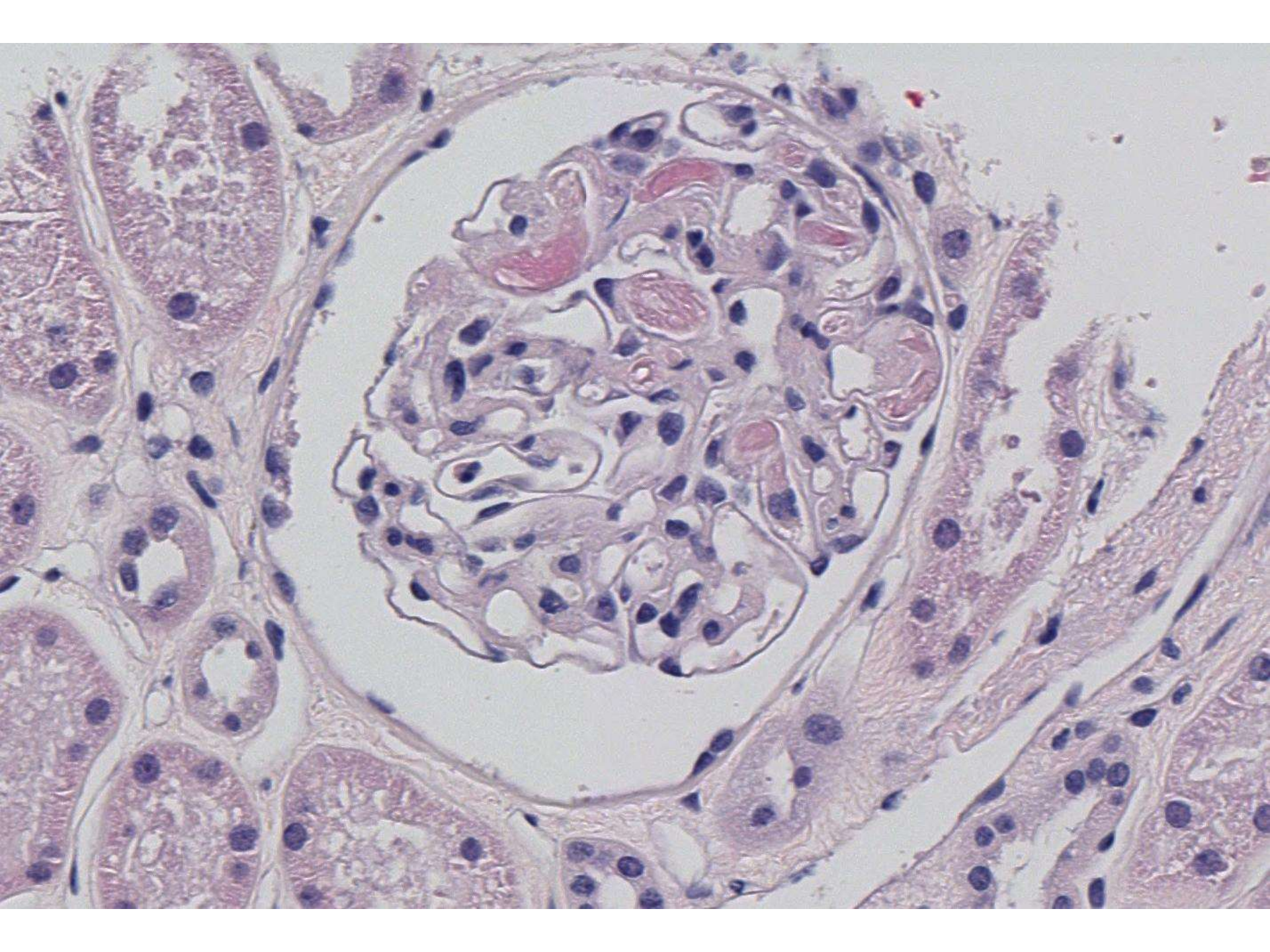




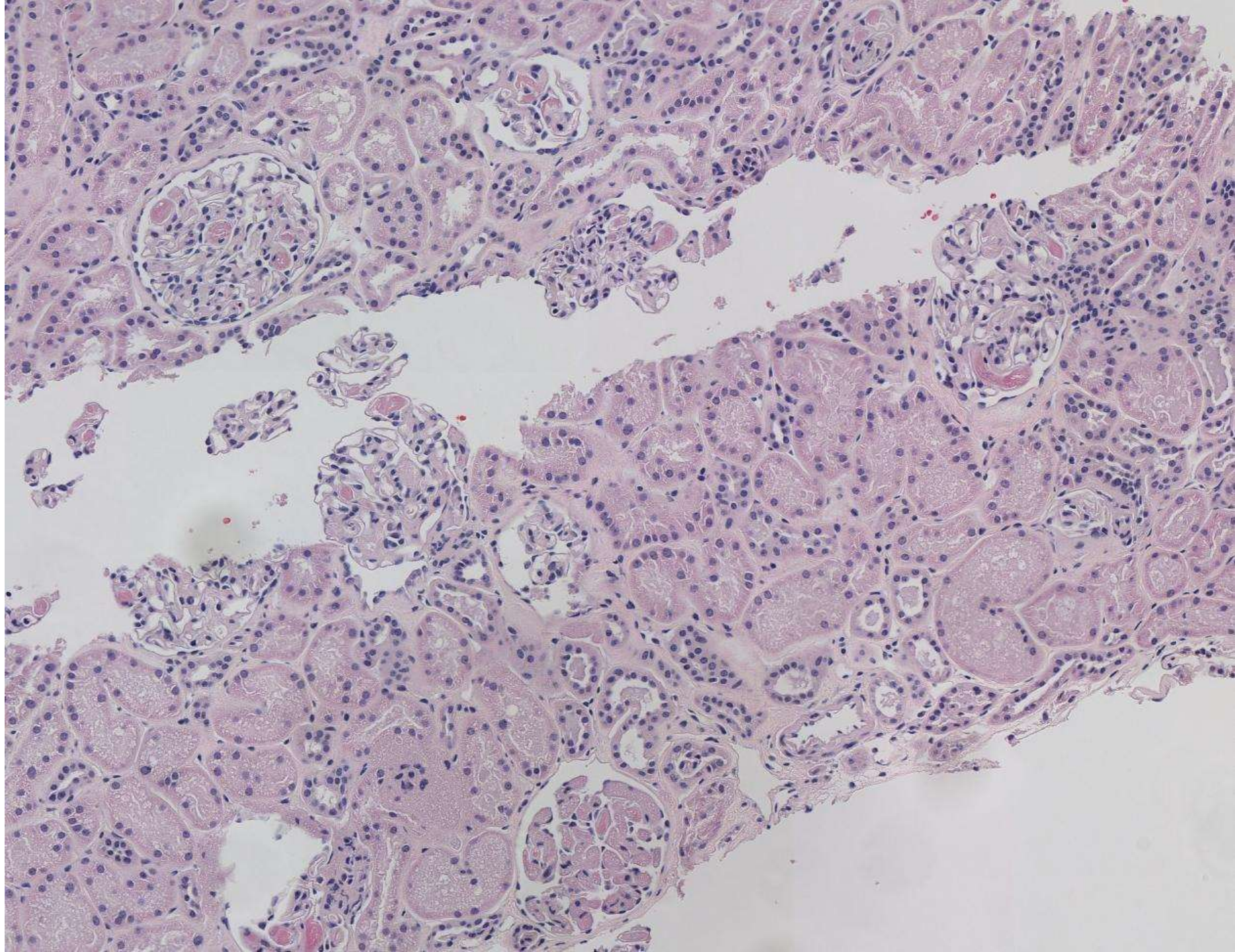




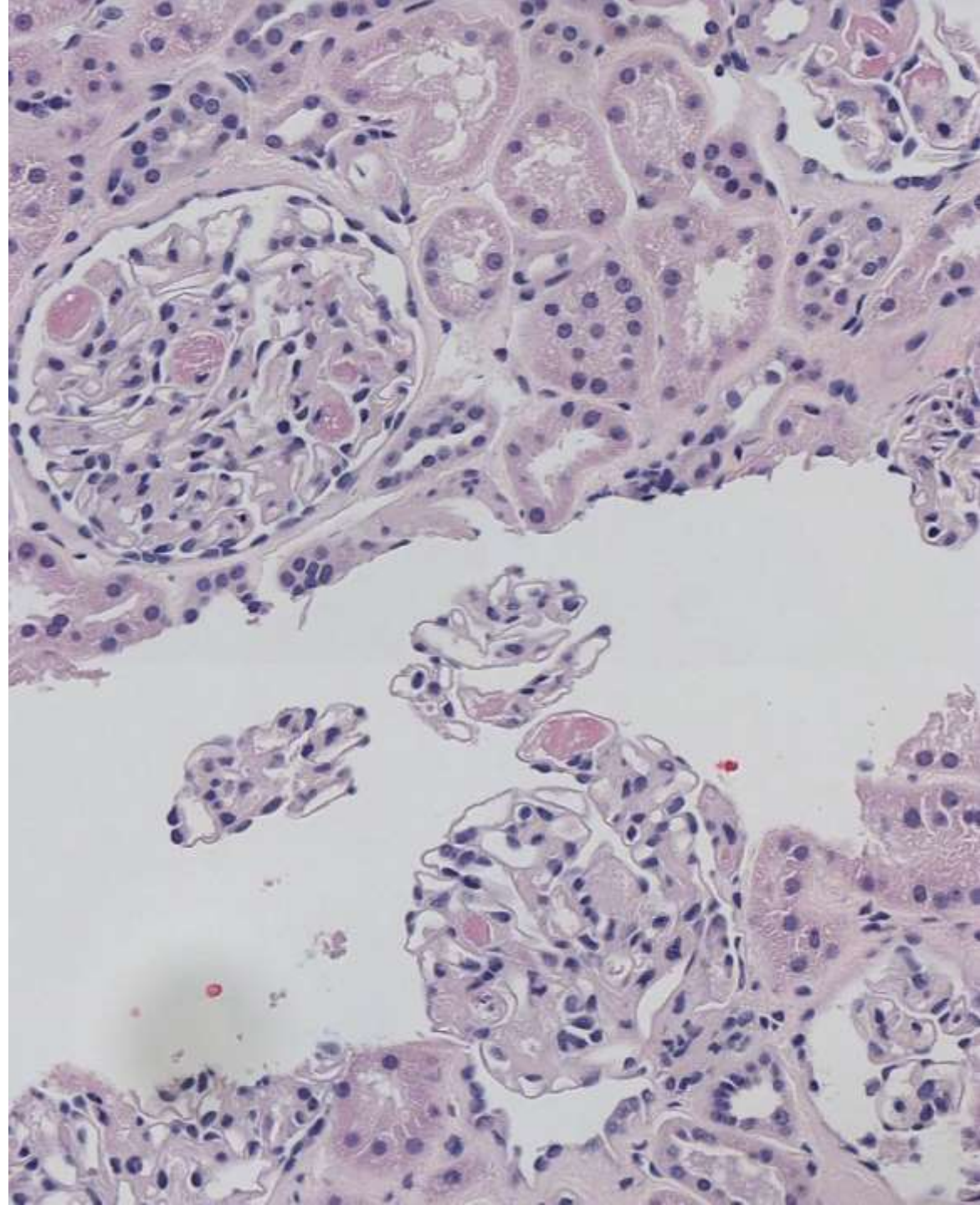


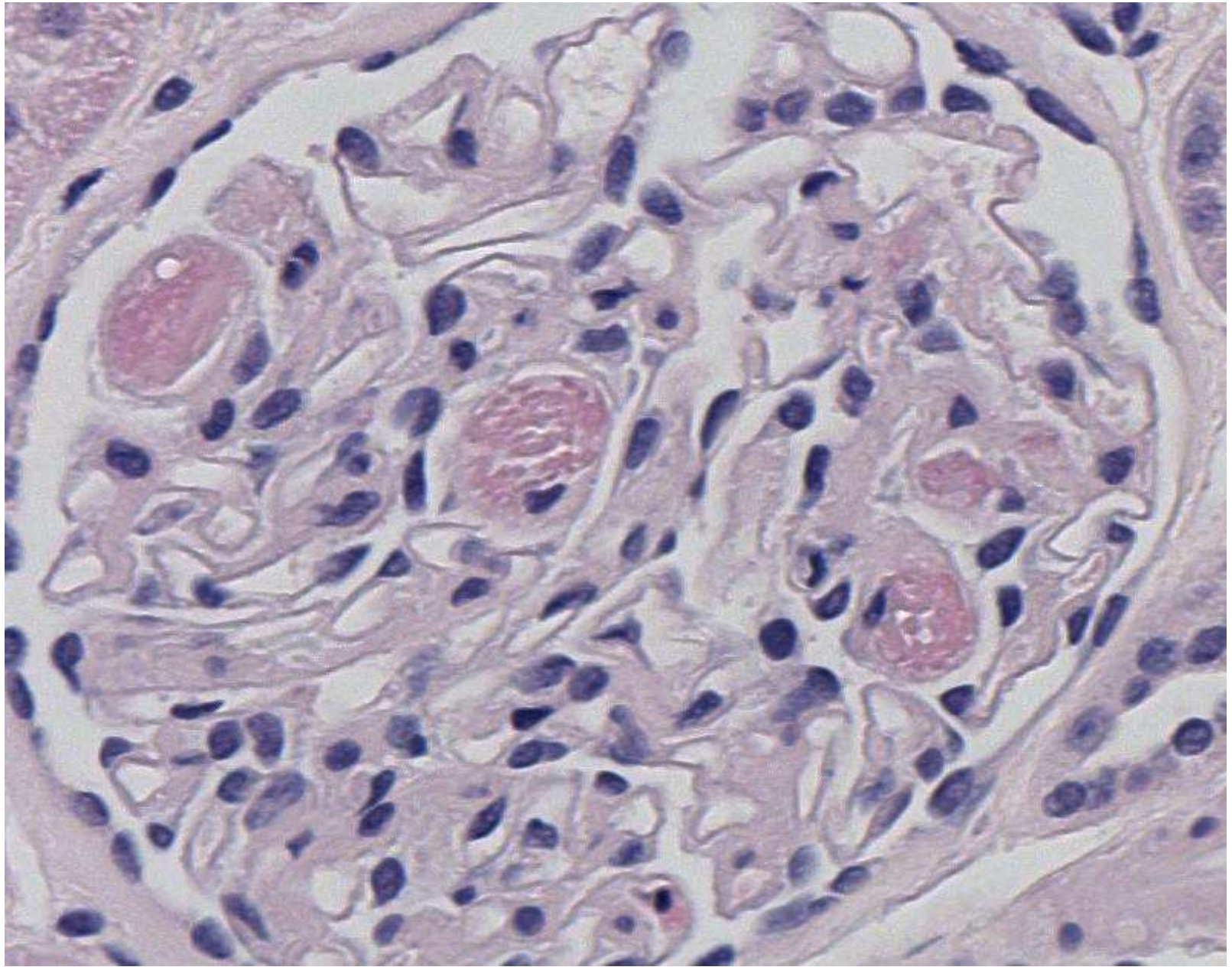














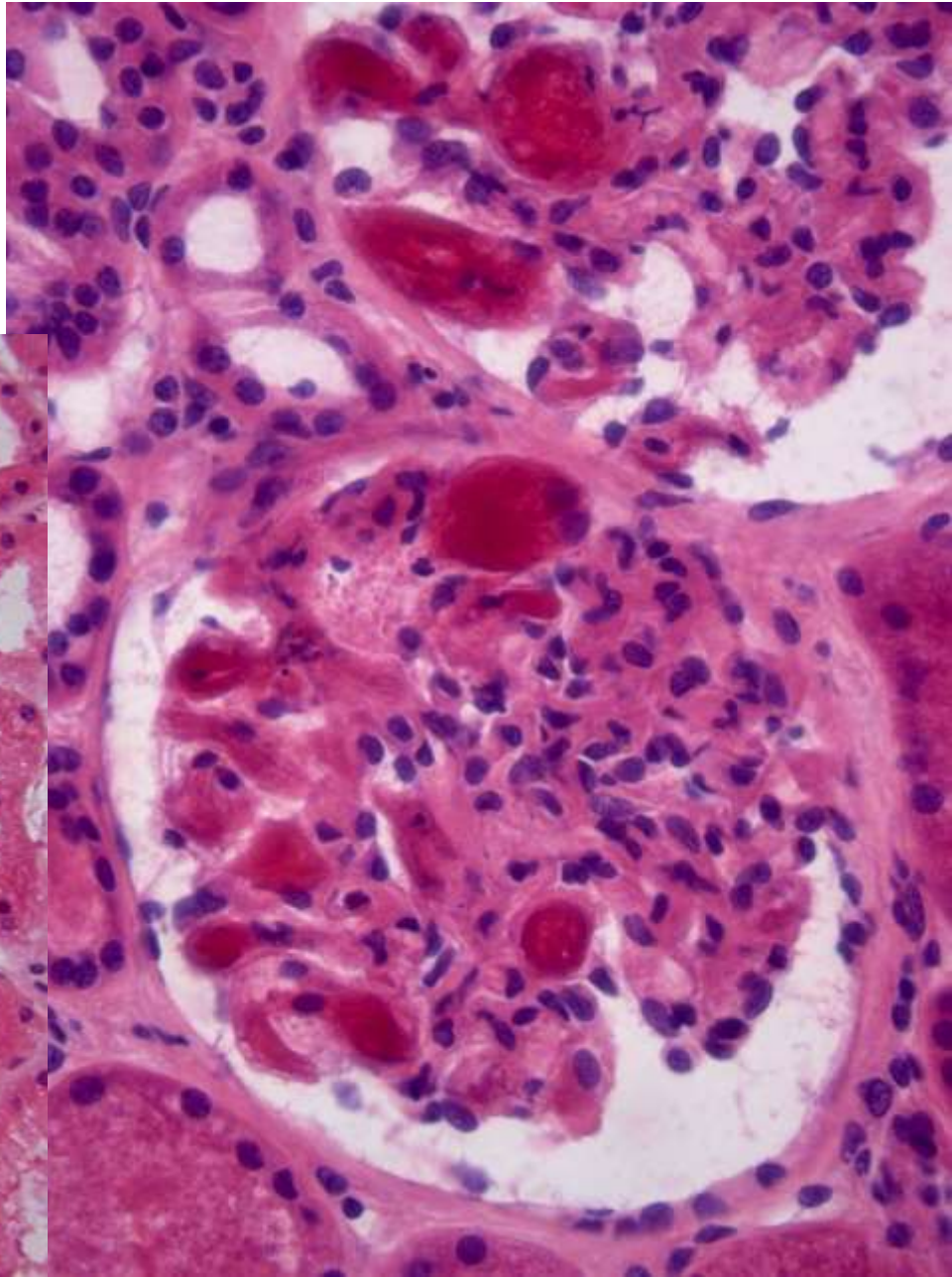
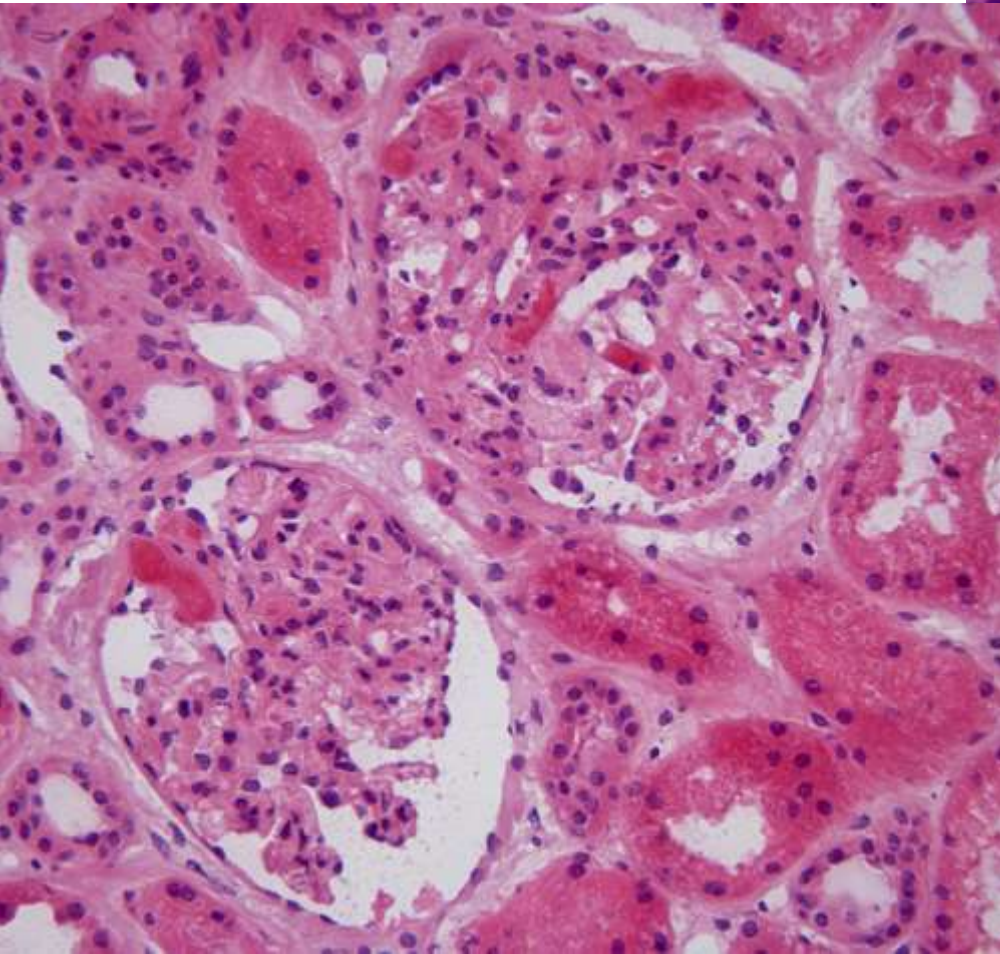
# DIAGNOSIS?



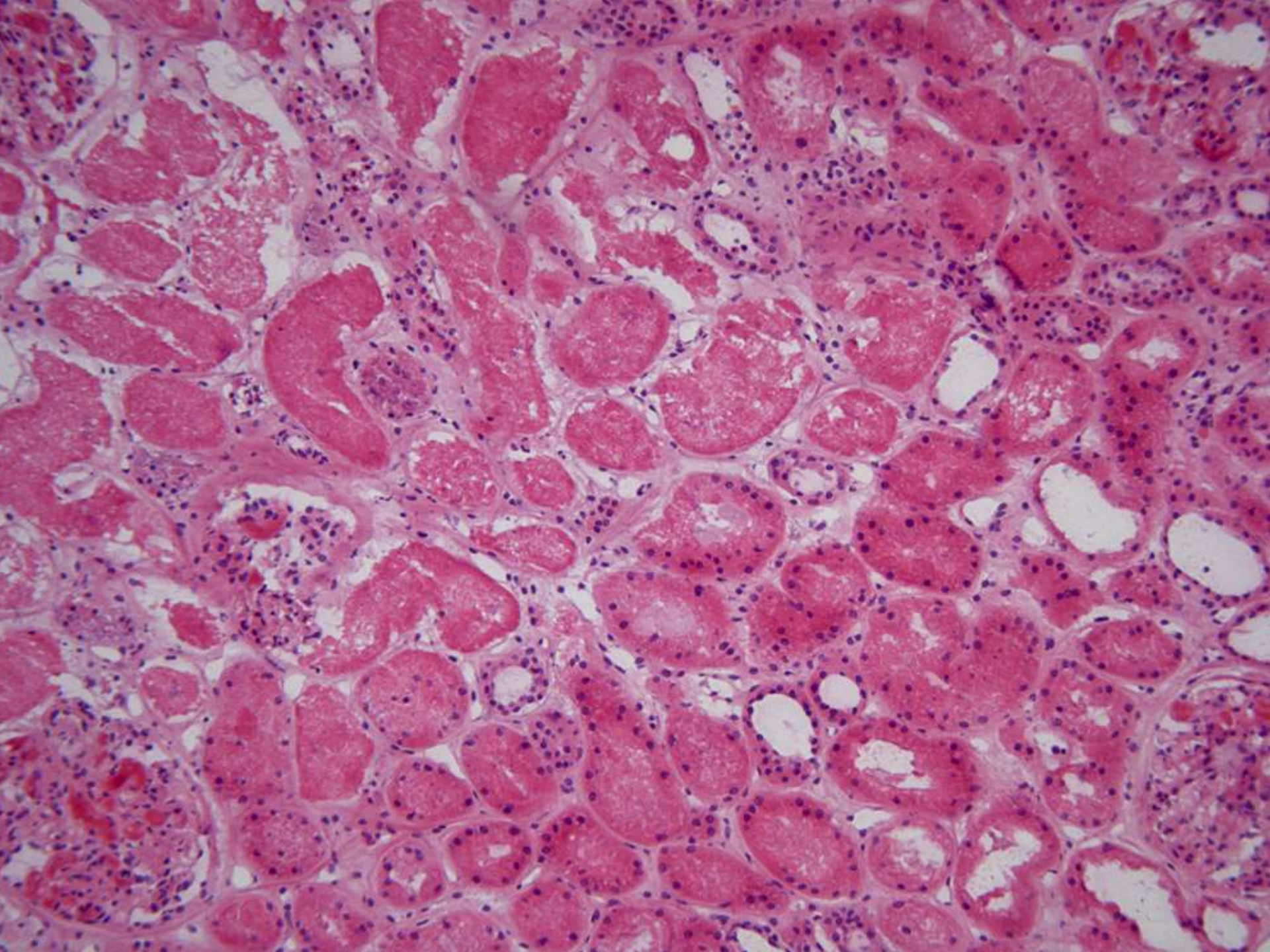




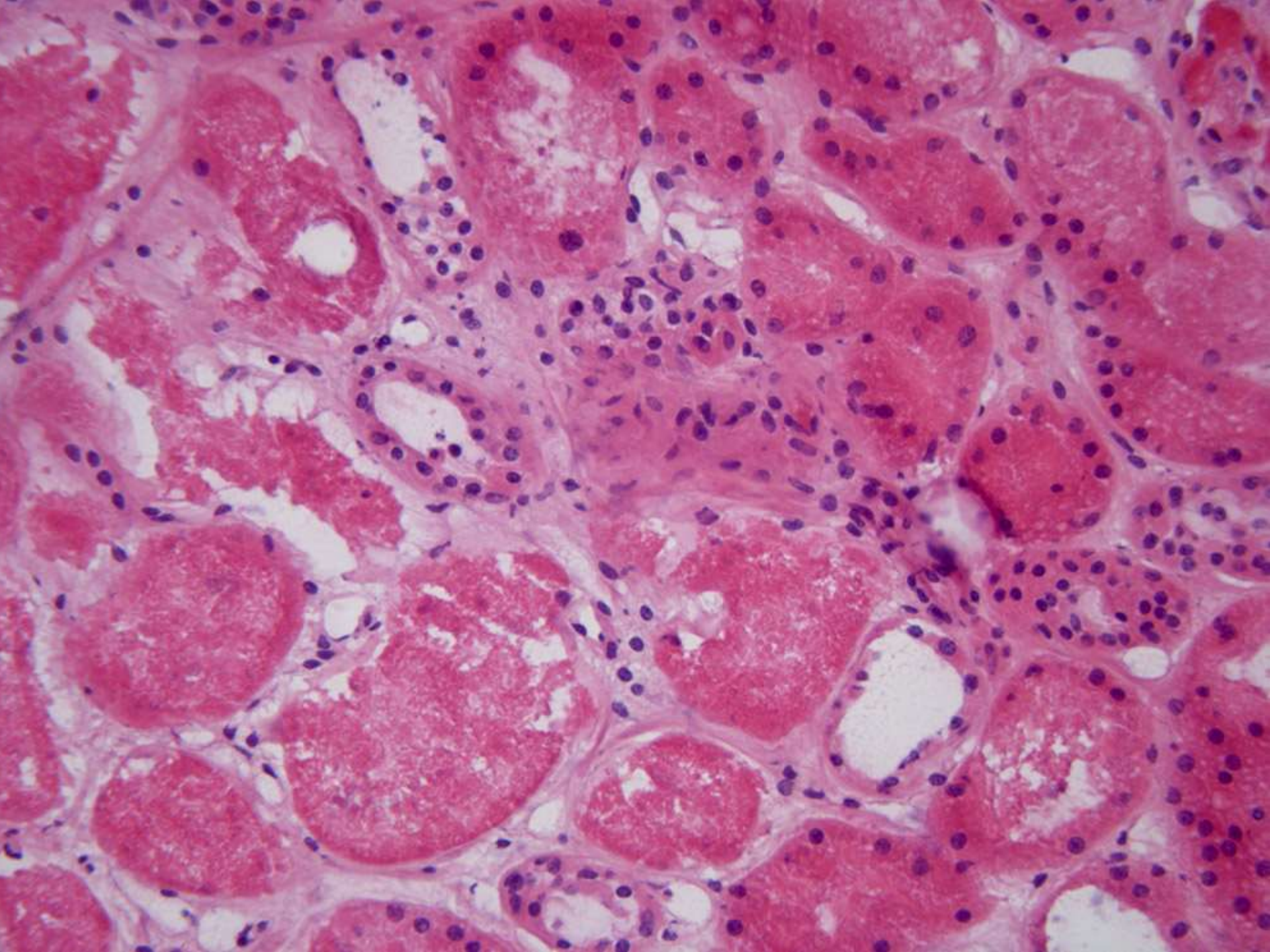
Actual FS  
different case





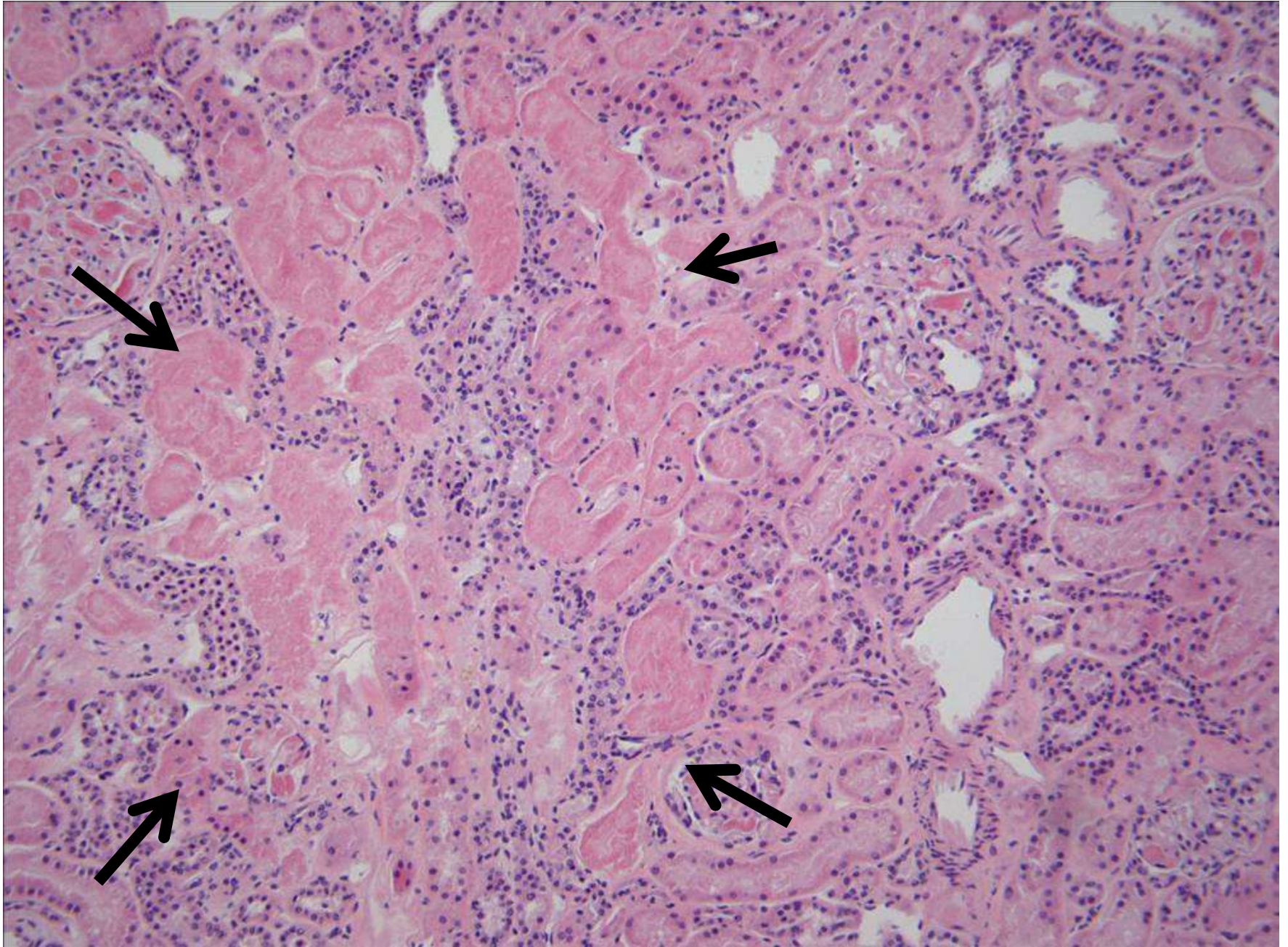








# Parenchymal necrosis (no nuclei)

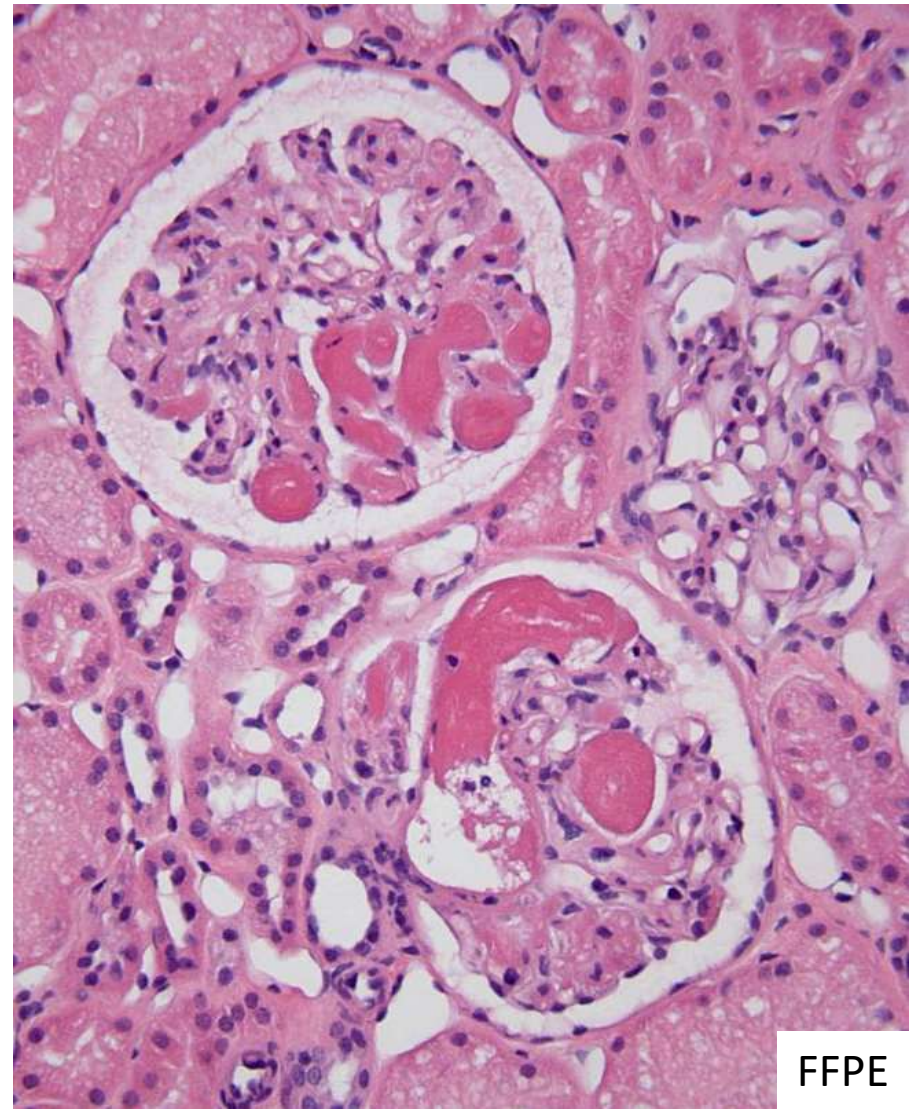




# Glomerular fibrin thrombi

## Anecdotal: paired kidneys

- Behaved ‘like DIC kidneys’ at transplant
- Kidney w/o tubular necrosis doing well
- Kidney w/ tubular necrosis
  - transplanted 1<sup>st</sup>, shorter cold ischemia time
  - Stagnant x 4 days, then doing better
- Long term outcome???



## Brief Communication

Batra et al. (Mayo Scottsdale)

# Rapid Resolution of Donor-Derived Glomerular Fibrin Thrombi After Deceased Donor Kidney Transplantation

**Table 2:** Clinical outcomes

	Focal-40 Diffuse-21	GFT group (n = 61)	Control group (n = 557)	p-value
DGF rate (%)		49	39	0.14
Creatinine, 1 month (mg/dL)		1.99 (0.14)	1.77 (0.05)	0.13
Creatinine, 4 months (mg/dL)		1.53 (0.10)	1.45 (0.03)	0.42
Creatinine, 1 year (mg/dL)		1.52 (0.15)	1.40 (0.05)	0.45
eGFR, 1 year (mL/min/1.73 m <sup>2</sup> )		59.8 (3.3)	58.6 (1.0)	0.73
Cumulative rejection rate at 1 year (%)		12	16	0.44*
IF/TA mod-severe at 1 yr	24%		30%	0.42

--Excluded >10% coagulative  
necrosis of tubular epithelium  
--2 GFT cases with early failure  
--primary non-function;  
nephrectomy at 6 wk=  
diffuse cortical necrosis  
--renal vein thrombosis at  
9 days  
--Bx at 1 month, 50/52 with  
complete resolution of GFT



Q: Could you share the local philosophy on transplantation of donor kidneys with GFT/microvascular thrombosis/donor DIC?

A: ...always a difficult decision

....kidneys can and do recover, but ....I suspect it [long term outcome] may be compromised

...very long waiting time to transplantation in the Bay Area.....try to transplant the best organ possible for the individual patient

....more circumspect about transplanting kidneys with glomerular injury [fibrin thrombi]

# References

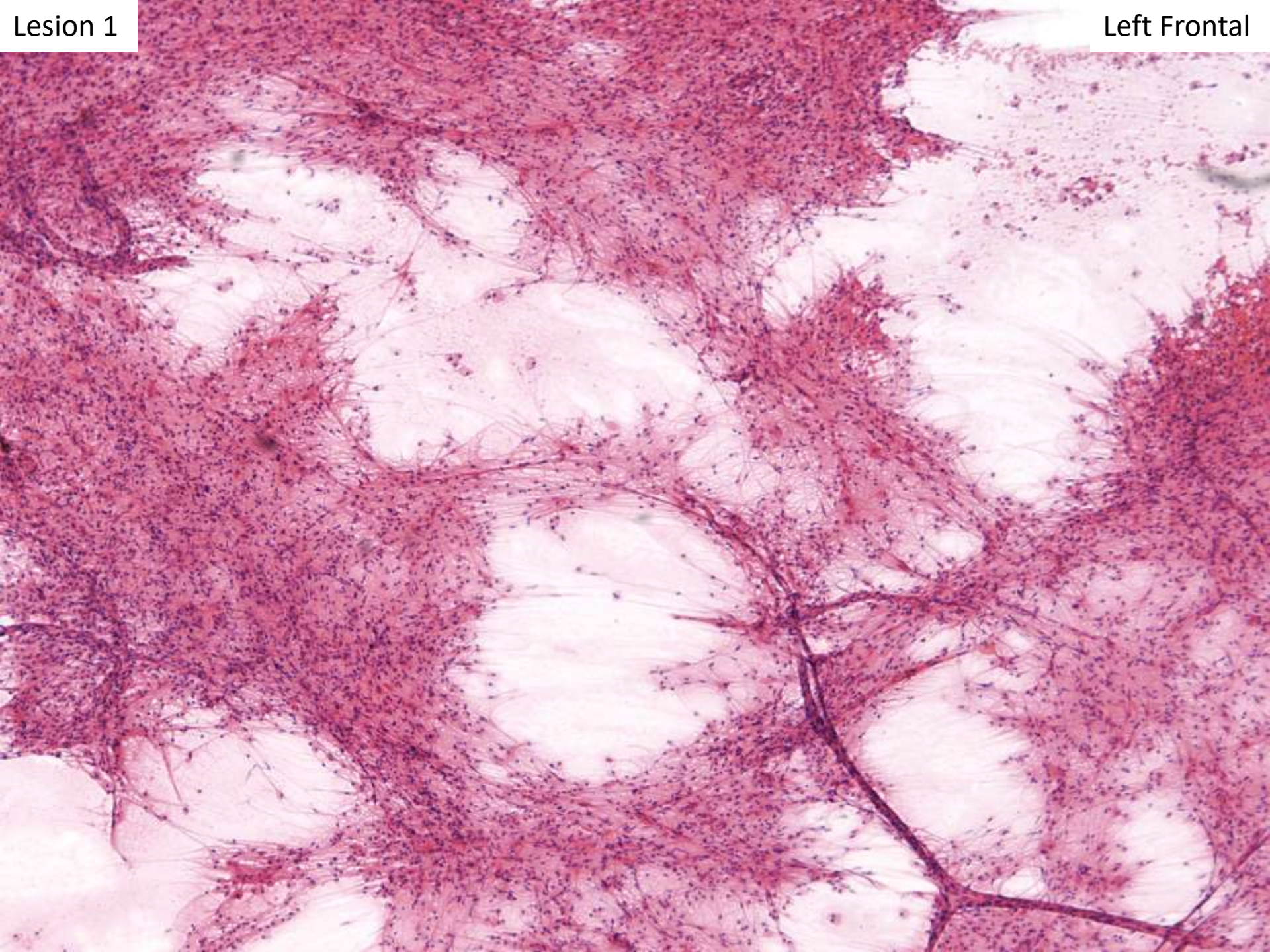
- Batra RK et al. Rapid Resolution of Donor-Derived Glomerular Fibrin Thrombi After Deceased Donor Kidney Transplantation. Am J Transplant. 2016;1015-20.
- Soares KC et al. Successful Renal Transplantation of Deceased Donor Kidneys With 100% Glomerular Fibrin Thrombi and Acute Renal Failure Due To Disseminated Intravascular Coagulation. Transplantation. 2016 Aug 3. [Epub ahead of print]



# SB 6153

**Peyman Samghabadi/Hannes Vogel/Donald Born; Stanford**

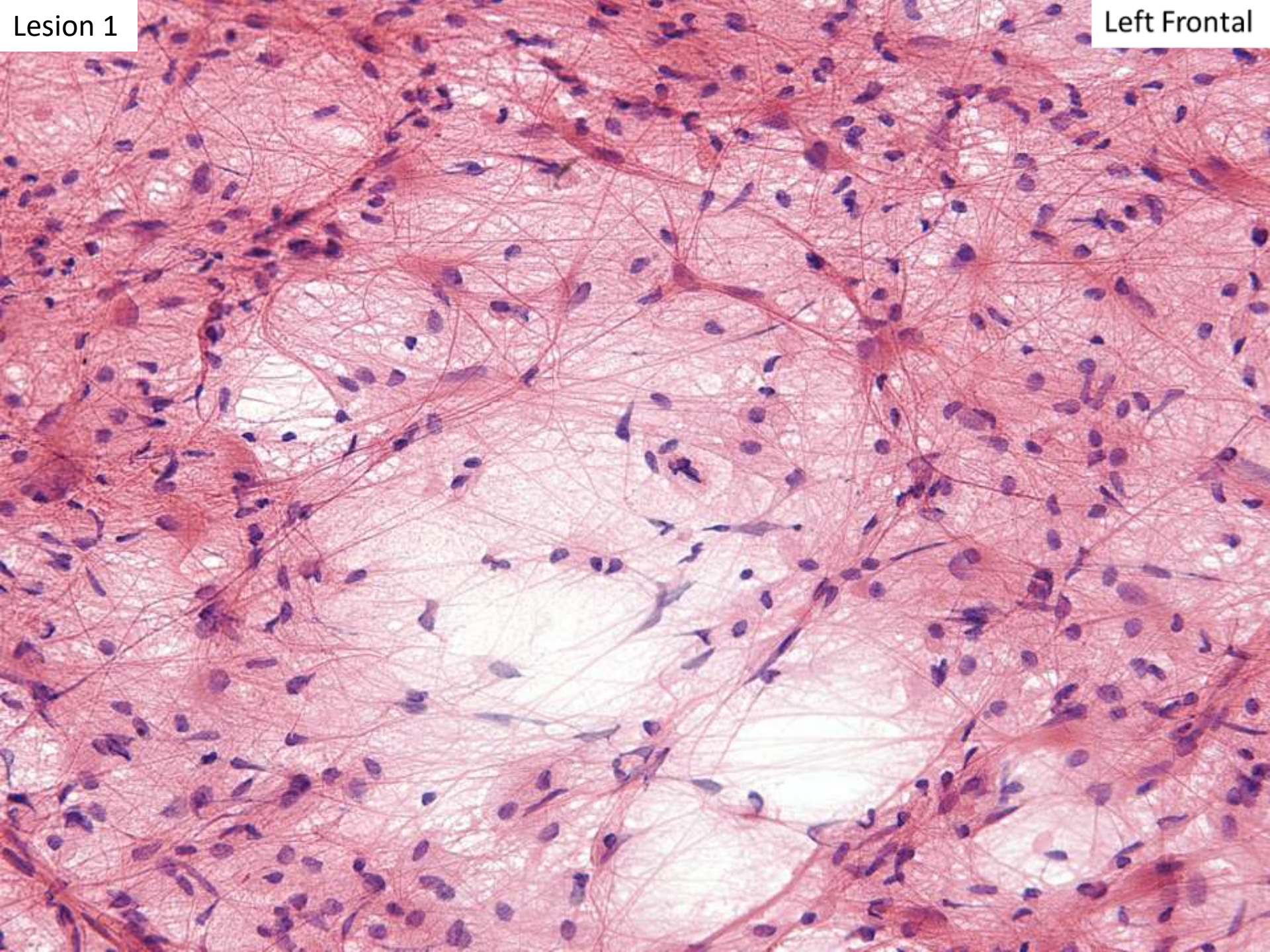
A 46-year-old white male presented with flu-like symptoms, cutaneous lesions and bilateral axillary lymphadenopathy. During metastatic evaluation brain MRI revealed an enhancing left caudate lesion. An axillary lymph node biopsy confirmed the diagnosis of melanoma. Repeat MRI showed new T2 hyperintensities with restricted diffusion in the corpus callosum and left frontal lobe adjacent to the left caudate lesion and in the right parietal lobe (presumed infarctions). The patient started pembrolizumab for treatment of metastatic melanoma. Two days later he presented with encephalopathy, paraparesis and bowel incontinence. Neuraxis MRI revealed enlargement of the callosal/left frontal and right parietal “infarcts,” enhancing intramedullary cord lesions and enhancement of the spinal nerve roots and cauda equina. Submitted biopsies were 1) left frontal target and 2) left caudate target.



Lesion 1

Left Frontal

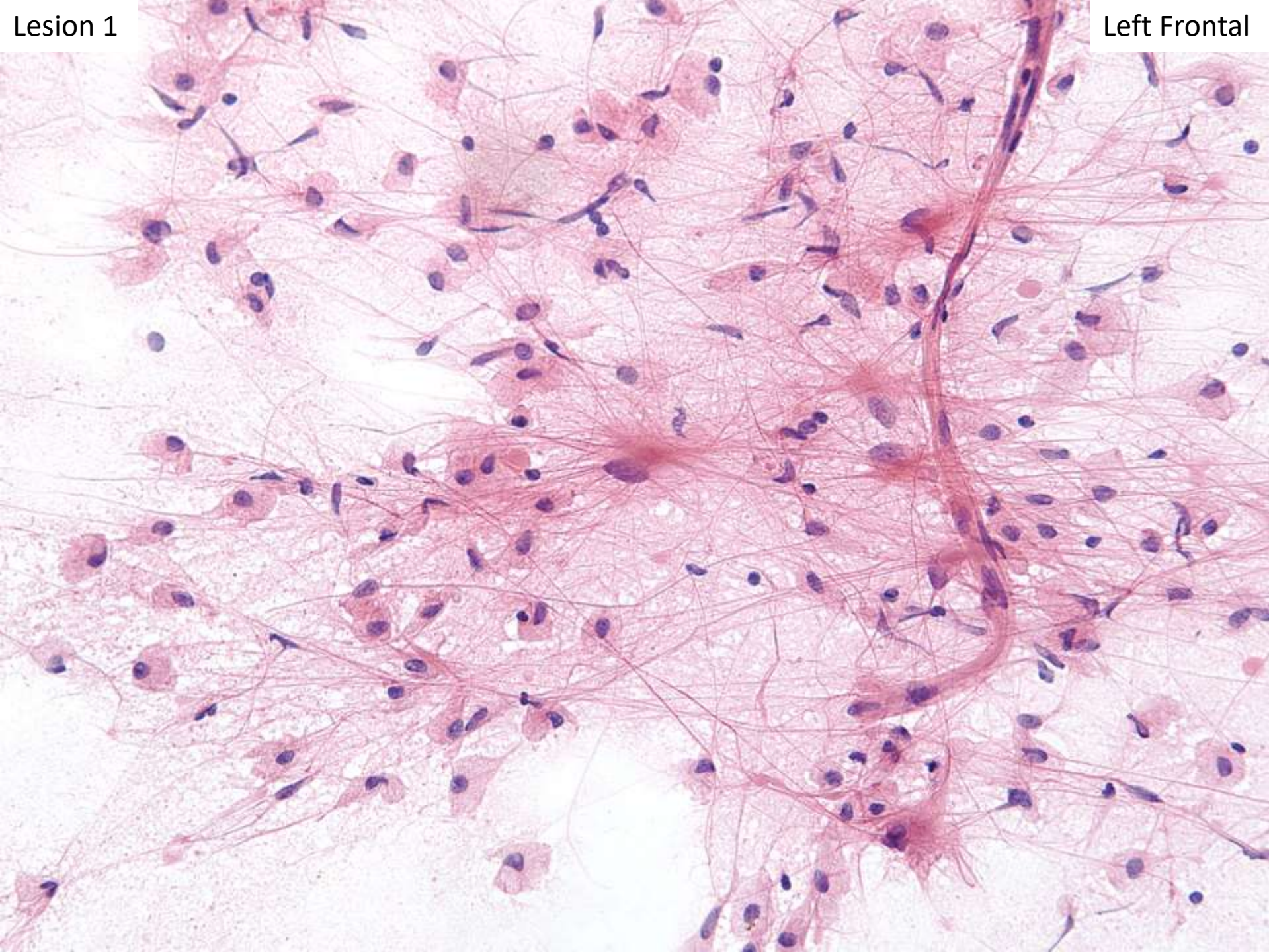




Lesion 1

Left Frontal





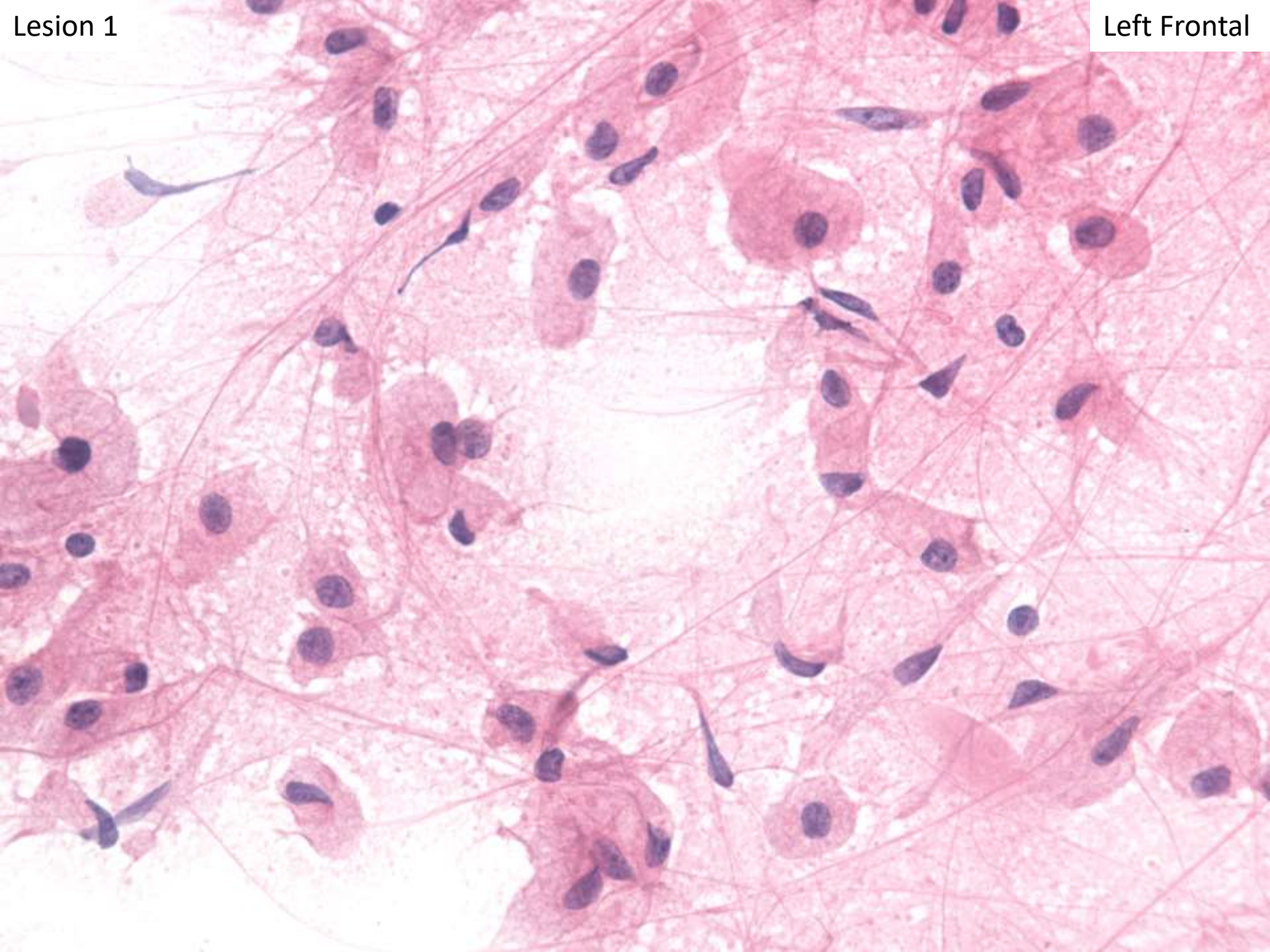
Lesion 1

Left Frontal

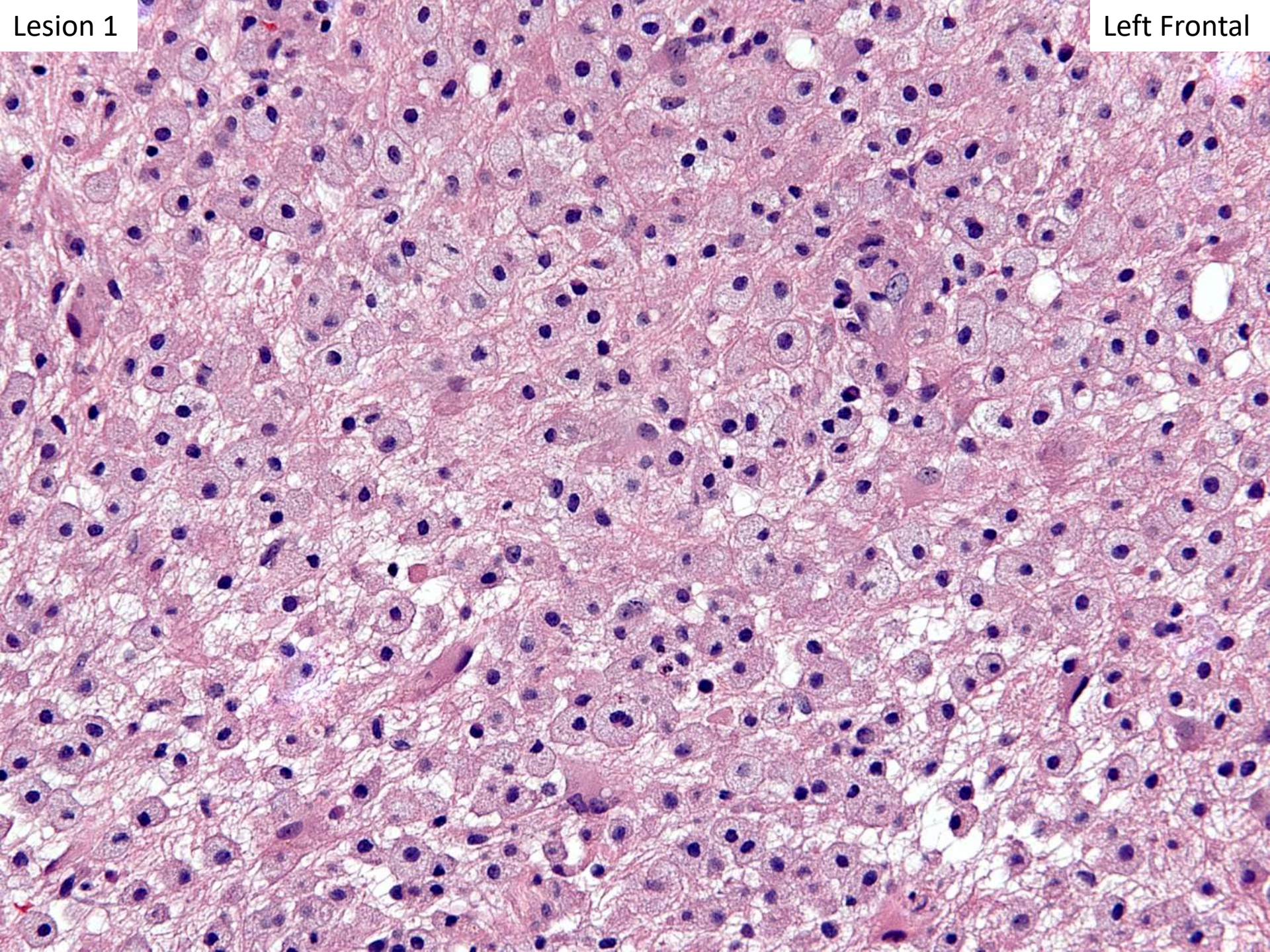


Lesion 1

Left Frontal



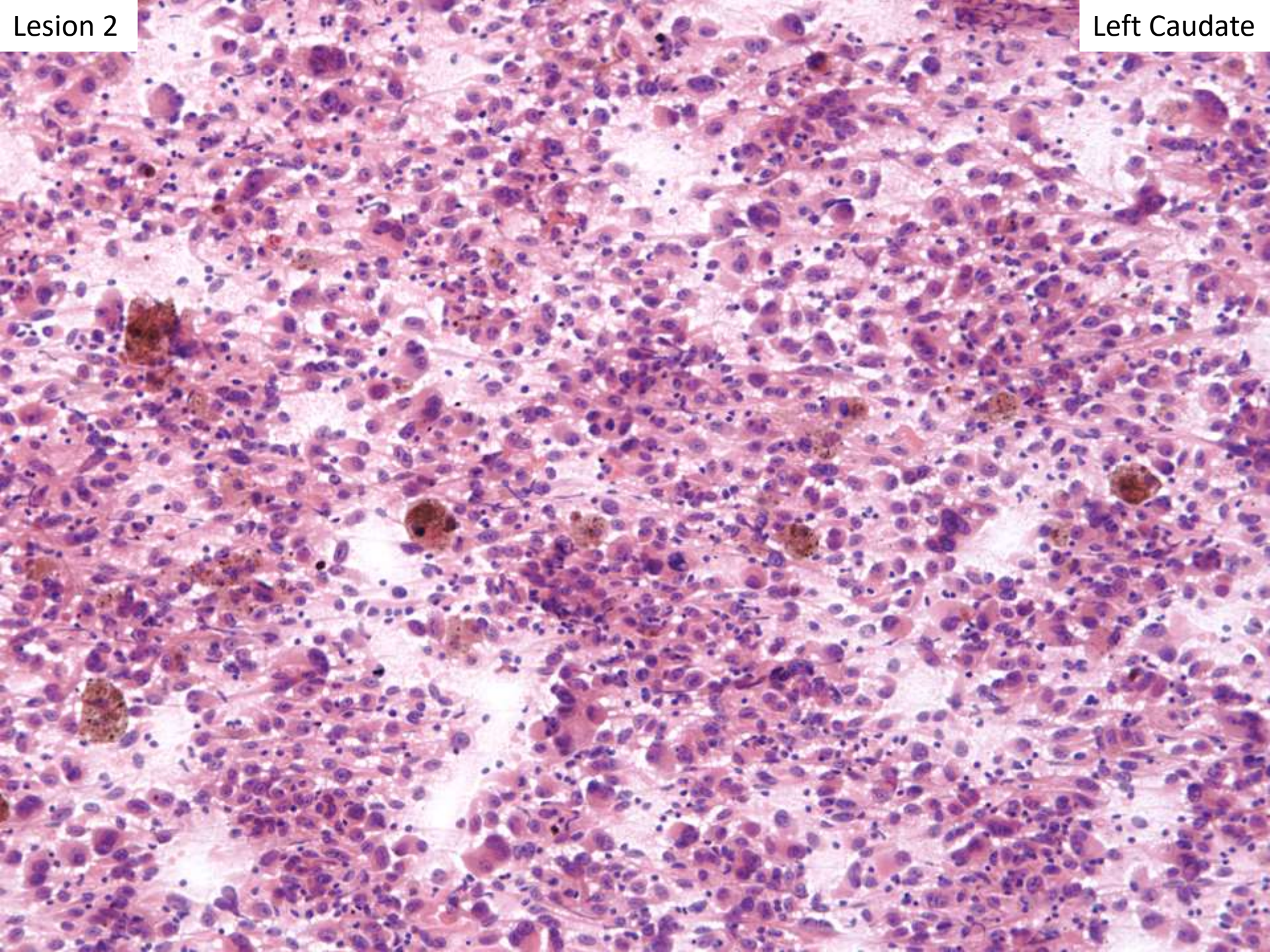




Lesion 1

Left Frontal

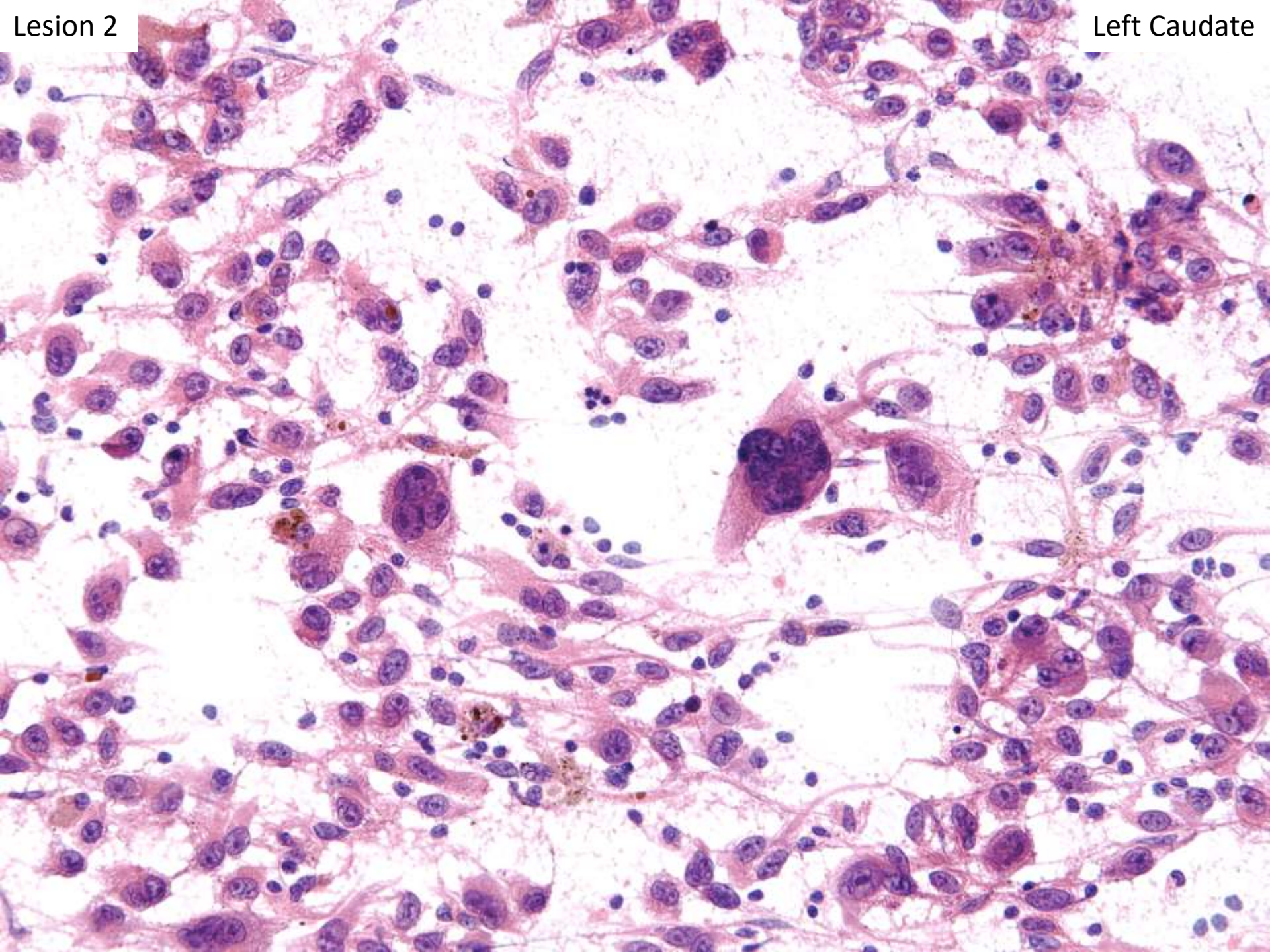
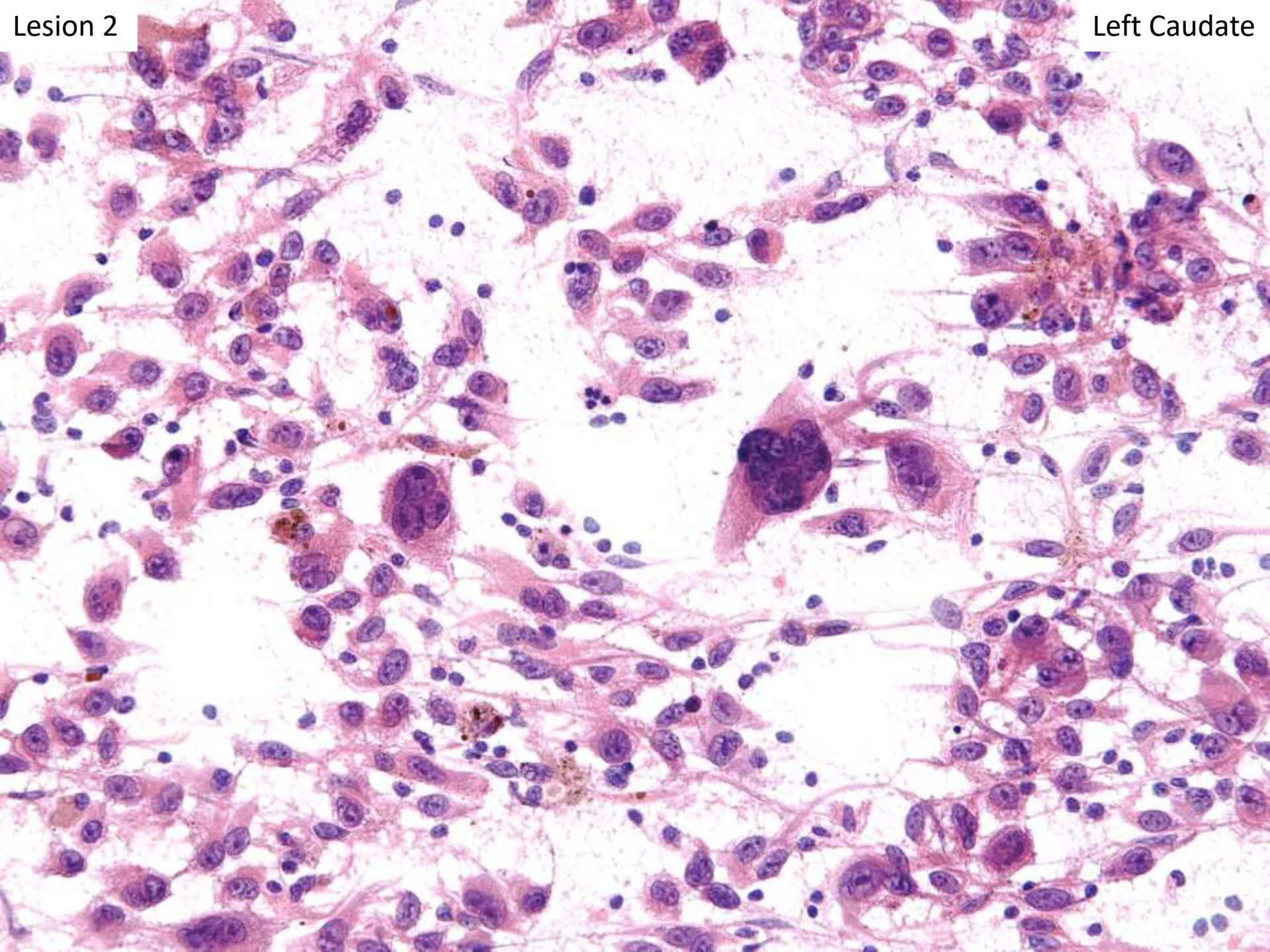




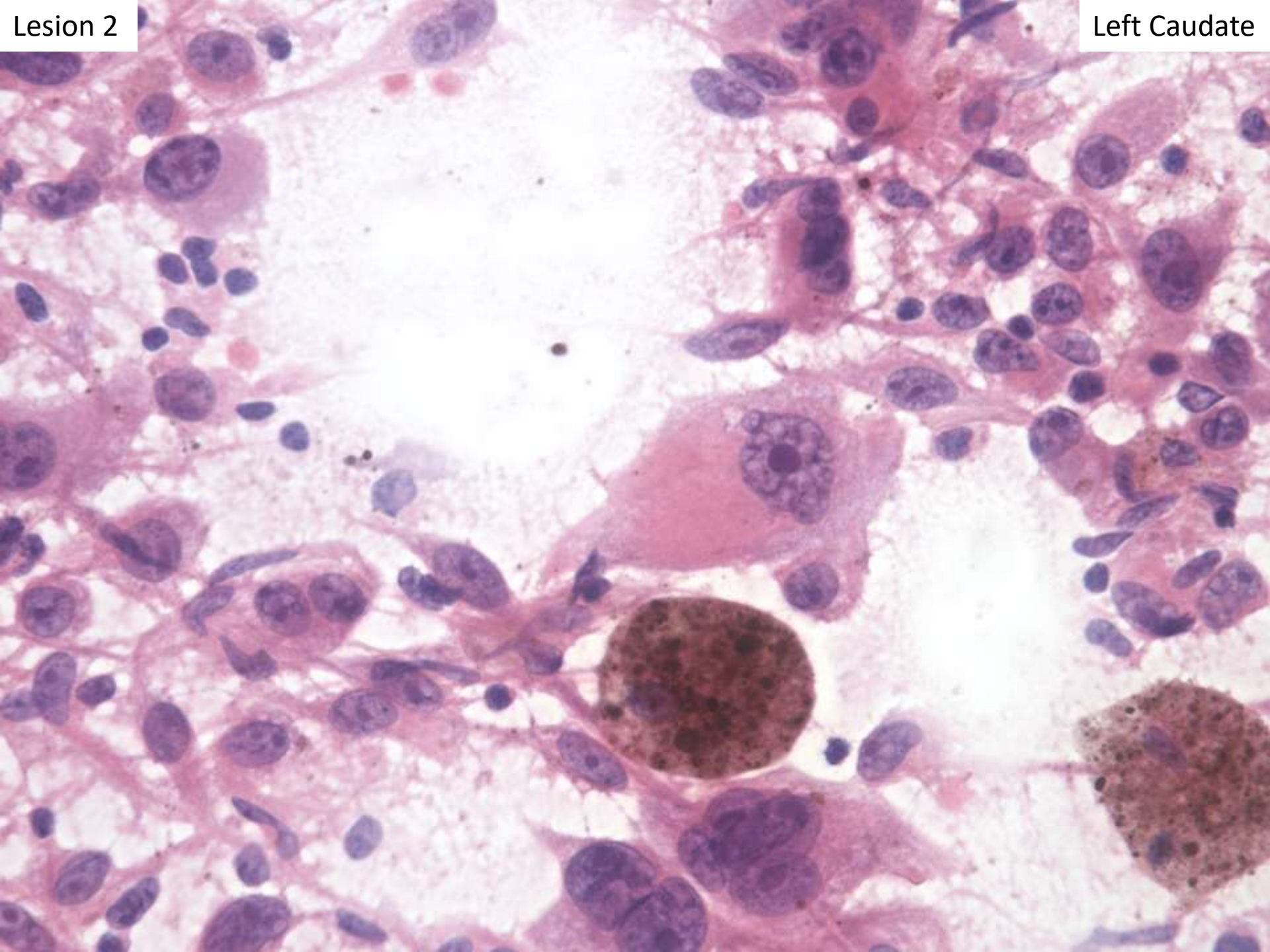
Lesion 2

Left Caudate





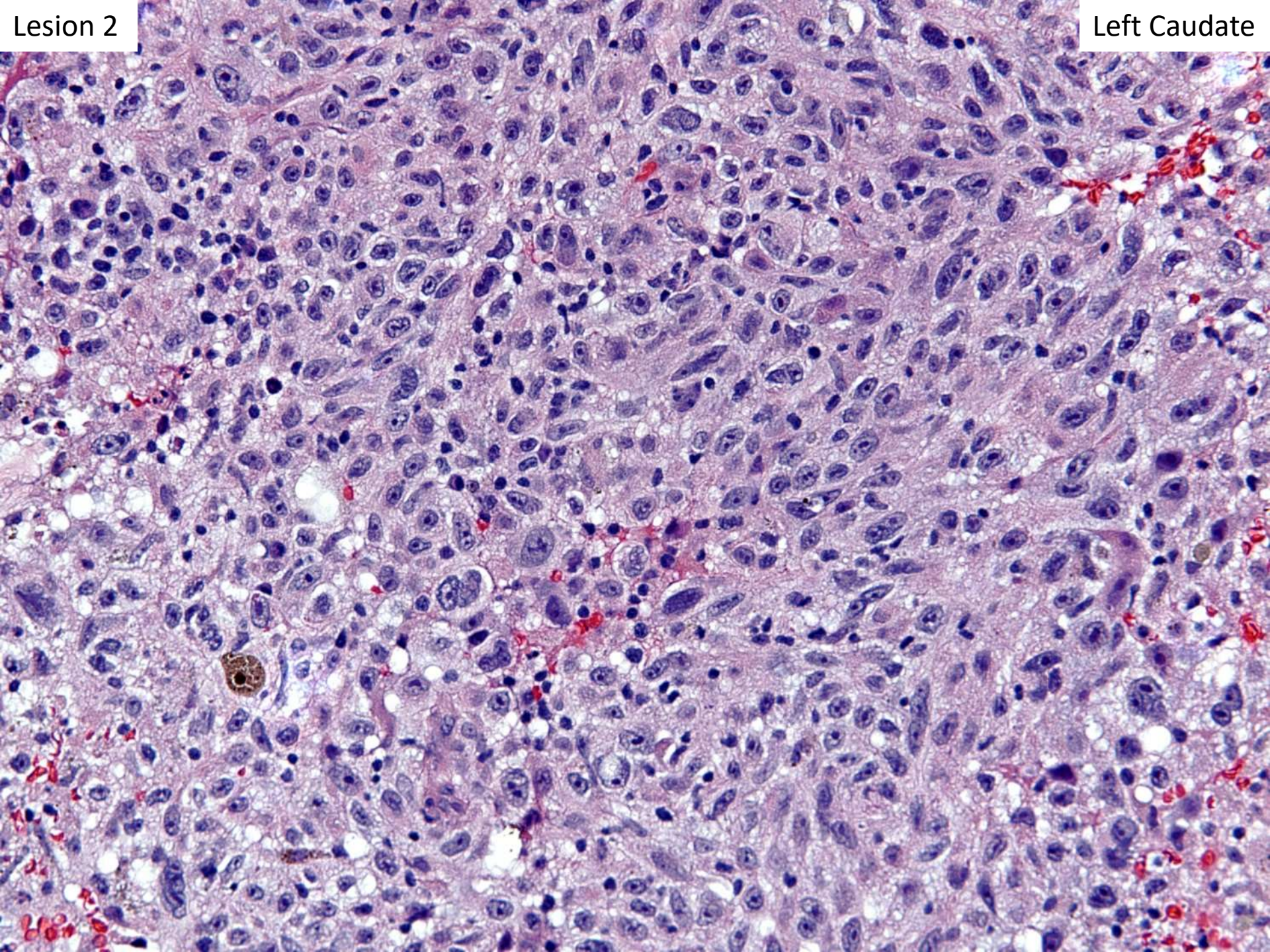




Lesion 2

Left Caudate





Lesion 2

Left Caudate



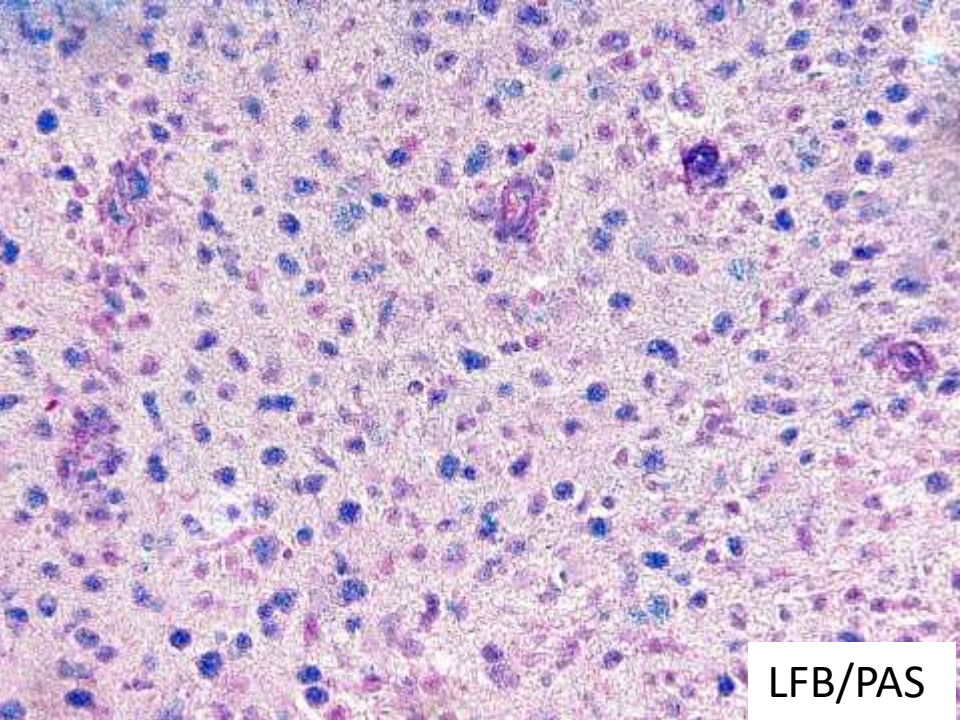
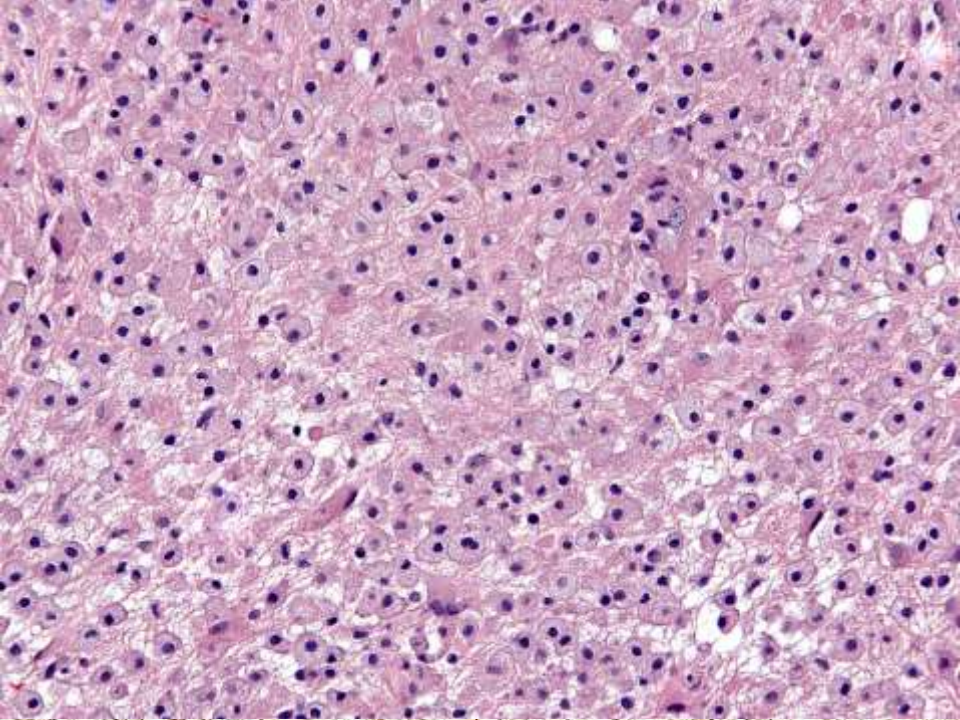
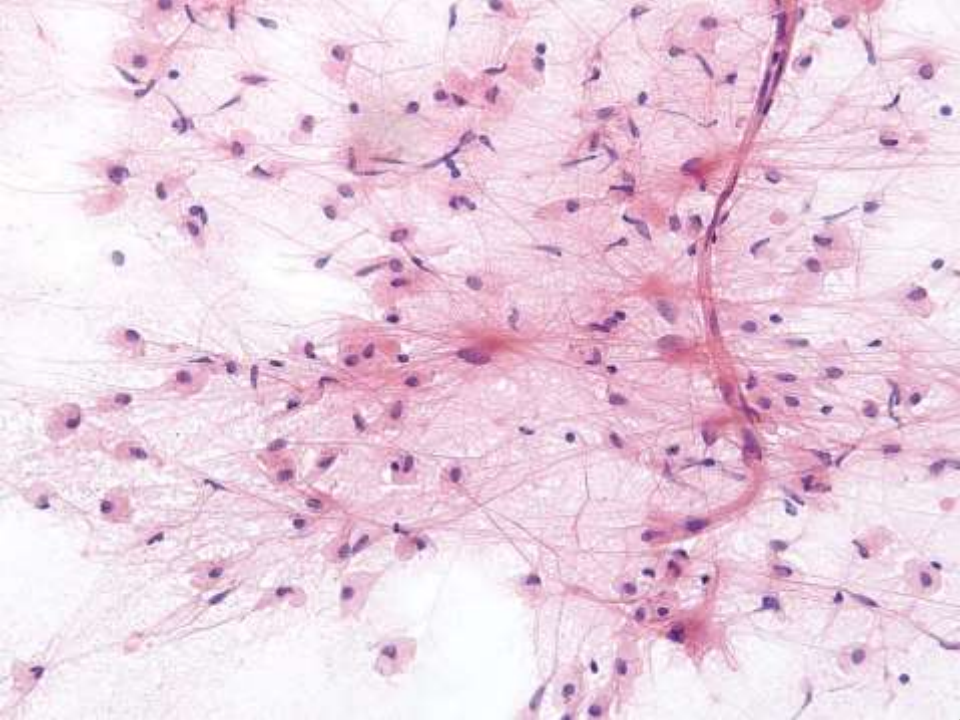
# DIAGNOSIS?









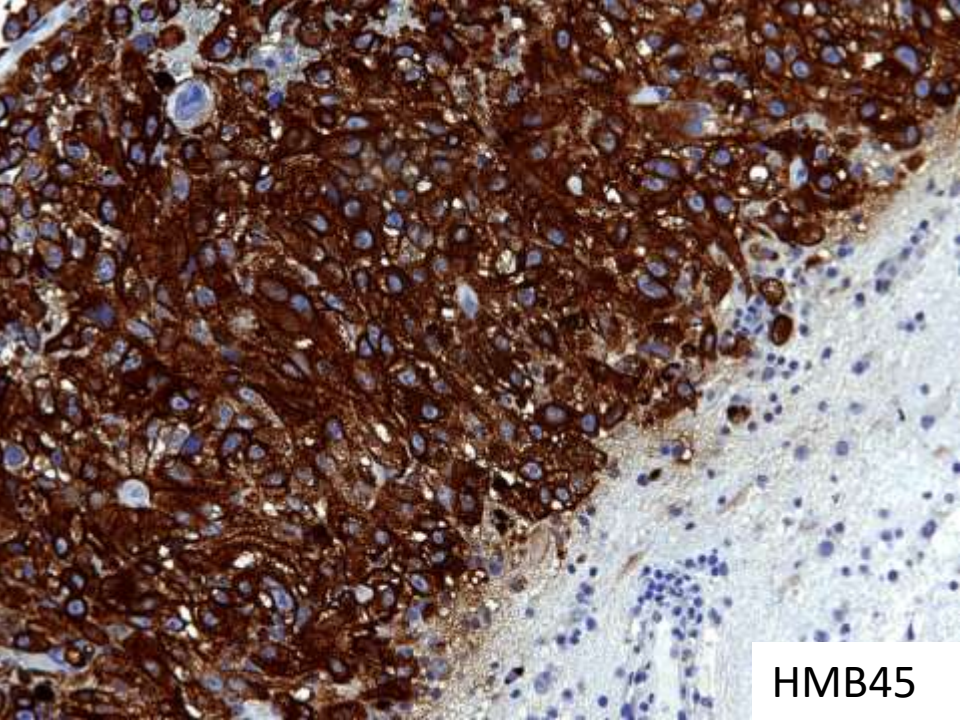
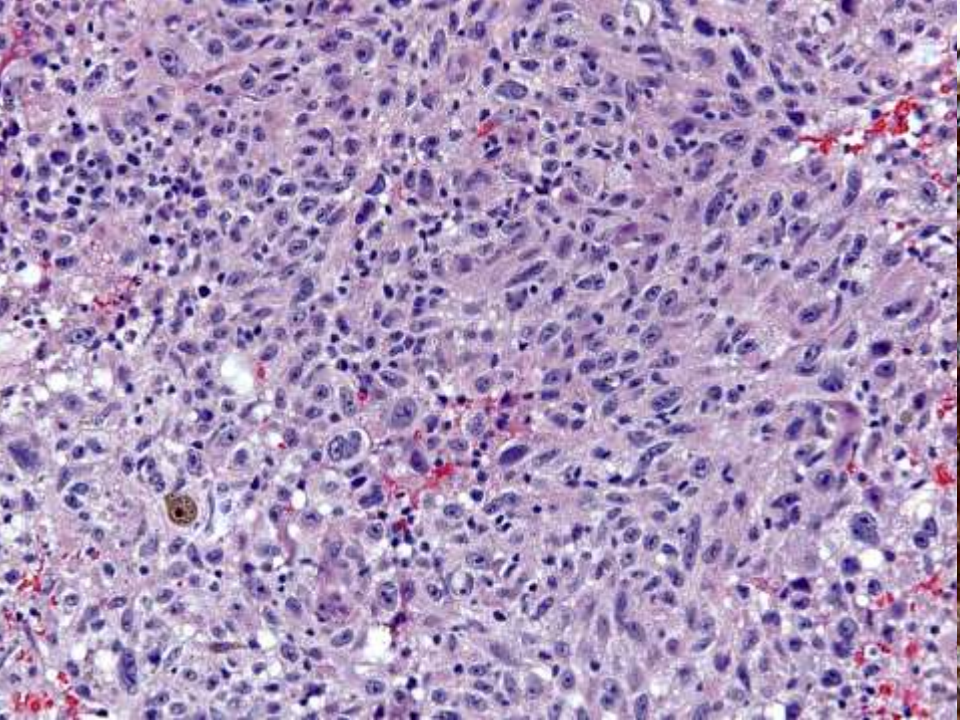
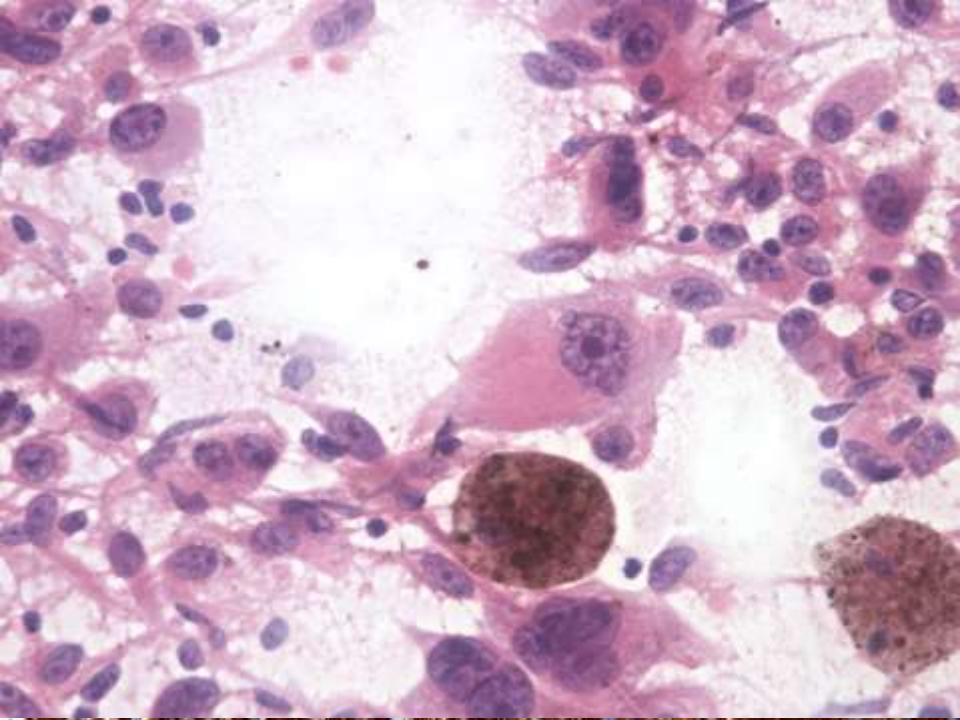
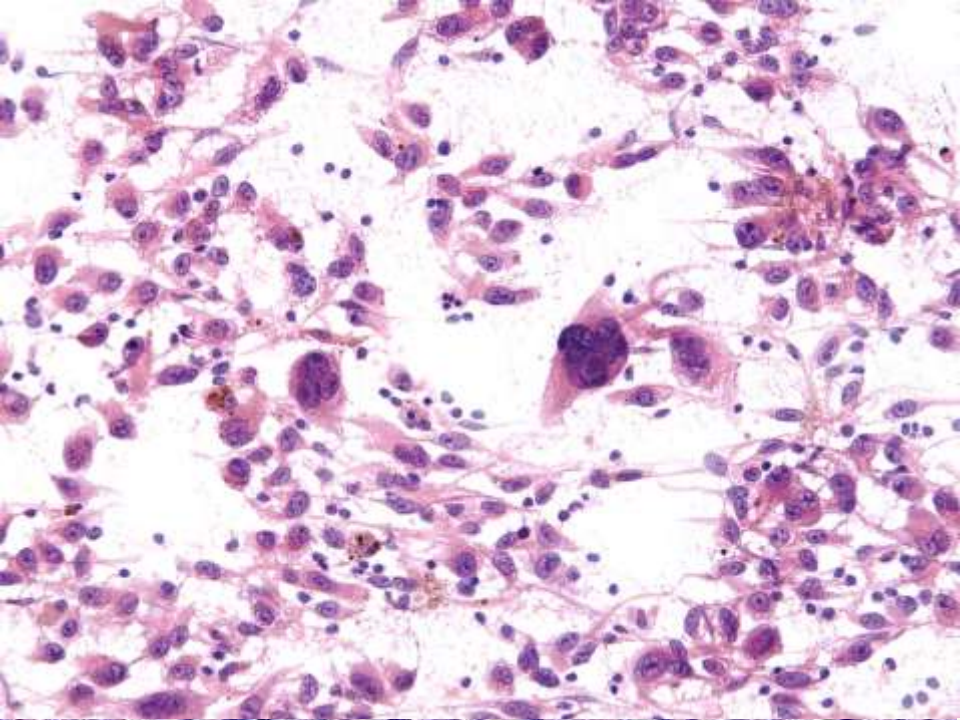


LFB/PAS



Bielschowsky





HMB45



LEFT FRONTAL, LESION #1

-- DEMYELINATING PROCESS

LEFT FRONTAL, LESION #2

-- METASTATIC MELANOMA

## Subacute CNS Demyelination after Treatment with Nivolumab for Melanoma

Catherine Maurice<sup>1</sup>, Raphael Schneider<sup>2</sup>, Tim-Rasmus Kiehl<sup>3,4</sup>, Prashant Bavi<sup>3,5</sup>, Michael H.A. Roehrl<sup>3,4,5</sup>, Warren P. Mason<sup>6</sup>, and David Hogg<sup>6</sup>

### Abstract

Immunotherapy with monoclonal antibodies targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4) or programmed cell death 1 (PD-1) has improved the survival of patients with metastatic melanoma. These agents carry a certain risk of adverse immune-related events. We present a patient with widely metastatic melanoma who was initially treated with ipilimumab and subsequently with nivolumab. After four infusions of nivolumab, he developed subacute multifocal central nervous system (CNS) demyelination. Nivolumab was discontinued and, despite immunosuppressive therapy, the largest lesion progressed significantly, whereas another lesion showed radiographic improvement. After further progression, the

patient succumbed. Autopsy revealed extensive perivascular necrosis. The demyelination was consistent with nivolumab. The severity of the CNS demyelination was consistent with comprehensive characterization of the potential CNS toxicity of immune checkpoint inhibitors.

Koelzer et al. *Journal for Immunotherapy of Cancer* (2016) 4:13  
DOI: 10.1186/s40425-016-0117-1

Journal for Immunotherapy  
of Cancer

### CASE REPORT

### Open Access



## Systemic inflammation in a melanoma patient treated with immune checkpoint inhibitors—an autopsy study

Viktor H. Koelzer<sup>1,2</sup>, Sacha I. Rothschild<sup>3</sup>, Deborah Zihler<sup>4</sup>, Andreas Wicki<sup>3</sup>, Berenika Willi<sup>5</sup>, Niels Willi<sup>1</sup>, Michèle Voegeli<sup>4</sup>, Gieri Cathomas<sup>1</sup>, Alfred Zippelius<sup>3</sup> and Kirsten D. Mertz<sup>1\*</sup>

### Abstract

**Background:** Immune checkpoint inhibitors targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) have been recently approved for treatment of patients with metastatic melanoma and non-small cell lung cancer (NSCLC). Despite important clinical benefits, these therapies are associated with a diverse spectrum of immune-related adverse events (irAEs) that are typically transient, but occasionally severe or even fatal.

**Case presentation:** This autopsy case illustrates that clinically overt irAEs may represent only a fraction of the total spectrum of immune-related organ pathology in patients treated with immune checkpoint inhibitors. We report a comprehensive analysis of systemic irAE pathology based on the autopsy of a 35-year-old female patient with metastatic melanoma treated first with ipilimumab and then nivolumab. The clinical course was characterized by a mixed tumor response with regression of skin and lung metastases and fatal progression of metastatic disease in the small bowel, peritoneum and brain. During therapy with ipilimumab, radiographic features of immune-related pneumonitis were noted. The autopsy examination established a sarcoid-like granulomatous reaction of the lung, pulmonary fibrosis and diffuse alveolar damage. Importantly, a clinically unapparent but histologically striking systemic inflammation involving the heart, central nervous system, liver and bone marrow was identified. Severe immune-related end-organ damage due to lymphocytic myocarditis was found.

**Conclusions:** Autopsy studies are an important measure of quality control and may identify clinically unapparent irAEs in patients treated with immunotherapy. Pathologists and clinicians need to be aware of the broad spectrum of irAEs for timely management of treatment-related morbidity.

**Keywords:** Melanoma, Immunotherapy, Immune checkpoint inhibitors, Antibody, Ipilimumab, Nivolumab, Autoimmunity, Autopsy, Anti-tumor T cell response



# Take home points...

- 1) CNS demyelination is important to be aware of:
  - Intraoperative: Foamy macrophages, reactive astrocytes, (variable perivascular lymphocytes)
  - FFPE: loss of myelin (LFB/PAS or MBP), relative preservation of axons (Biel or NF)
- 2) Immune checkpoint inhibitors are showing association with immune-related adverse events (irAEs) including CNS demyelination



**SB 6154 (scanned slide available)**

**Walden Browne; Kaiser Oakland**

65-year-old woman, right buccal  
mass (1cm), submitted as “fibroma”.

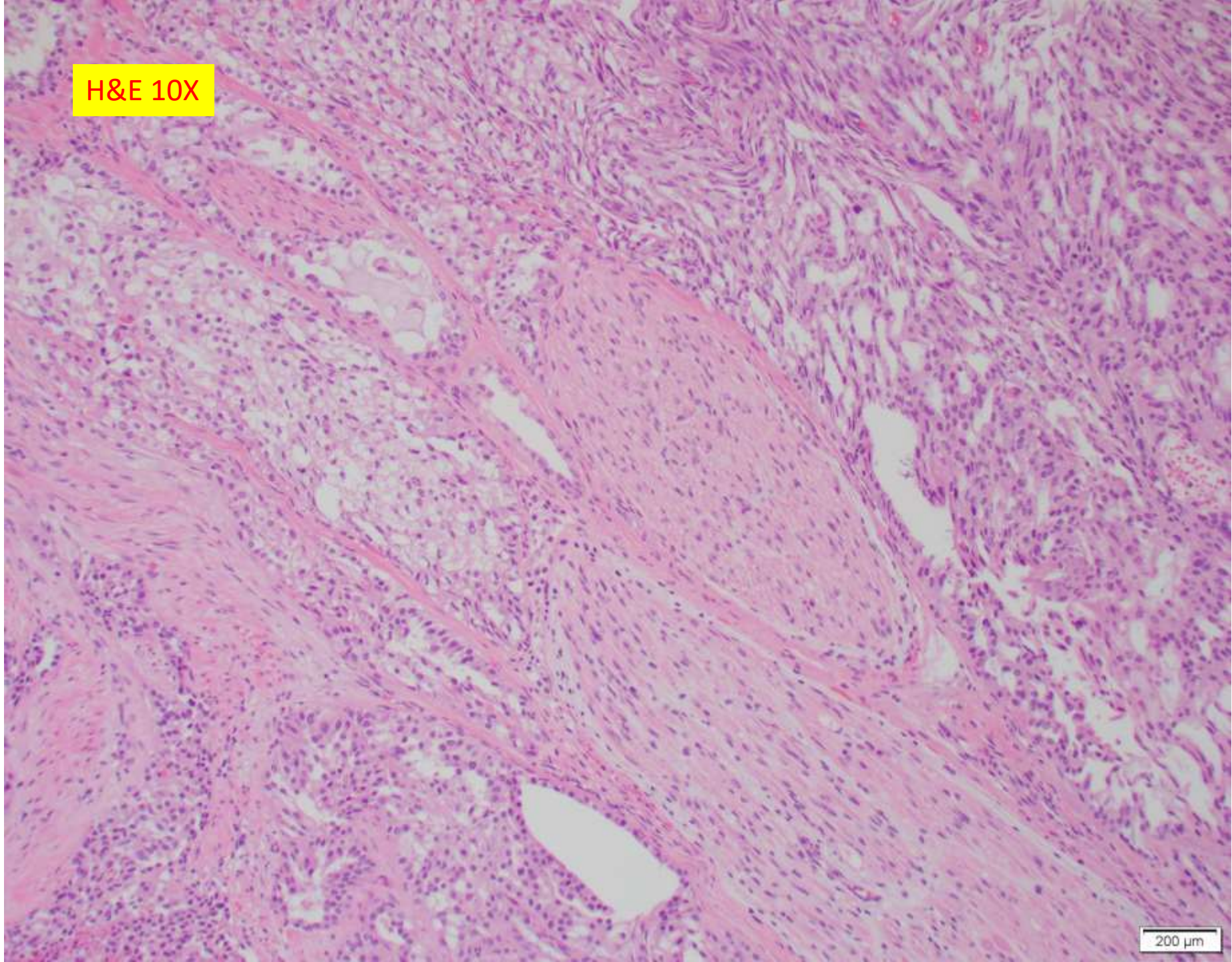
H&E 2X

200  $\mu$ m



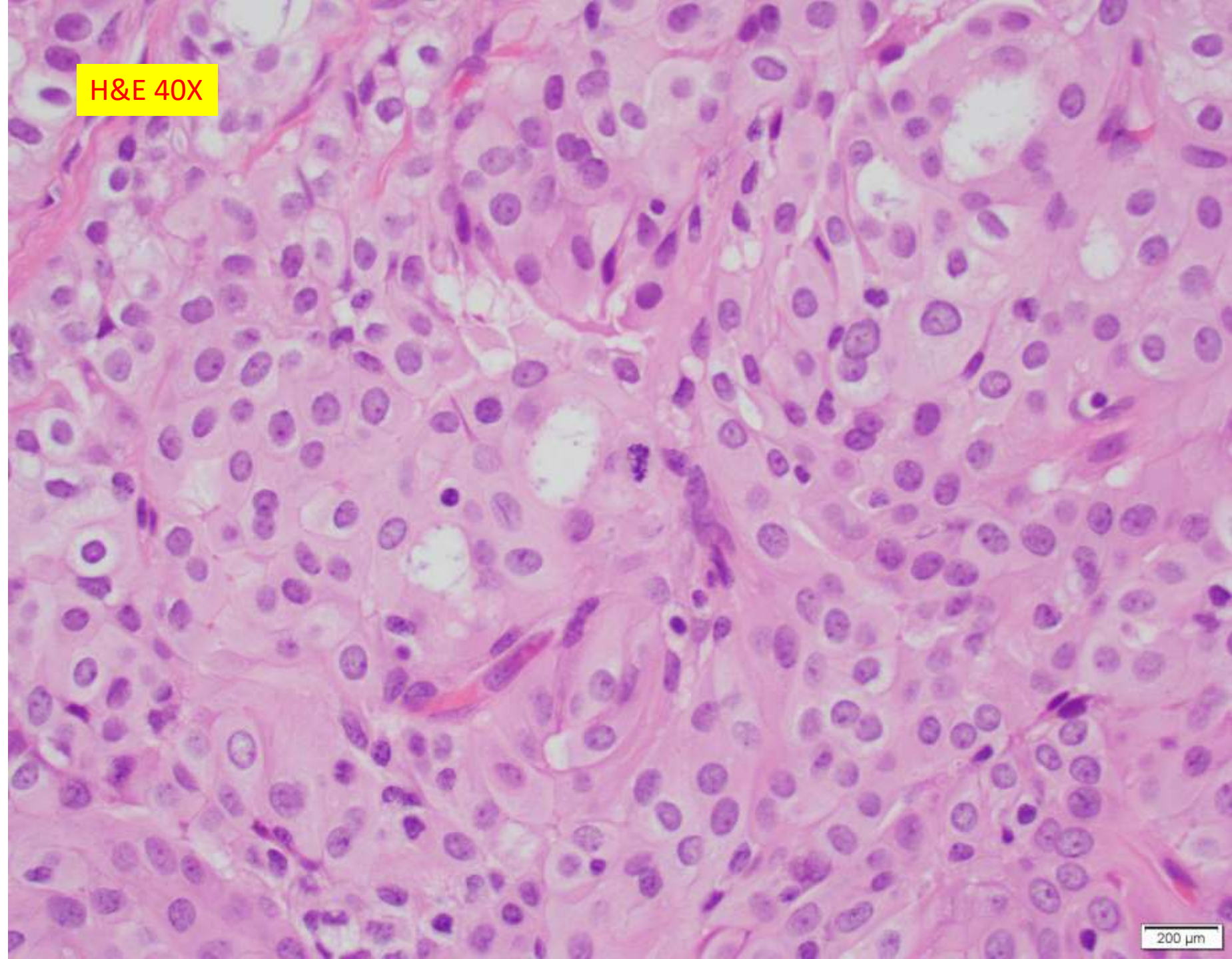
H&E 10X

200  $\mu$ m





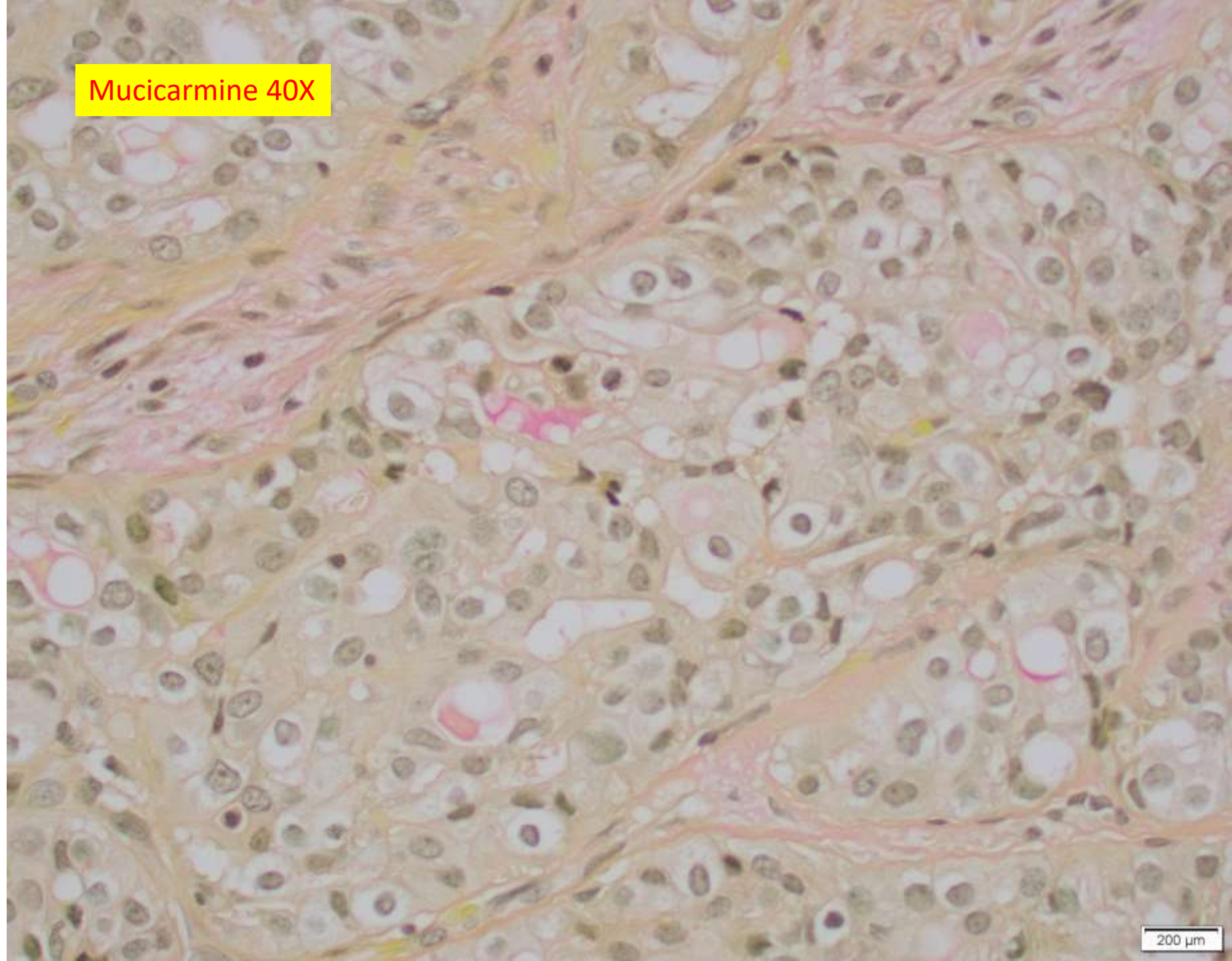
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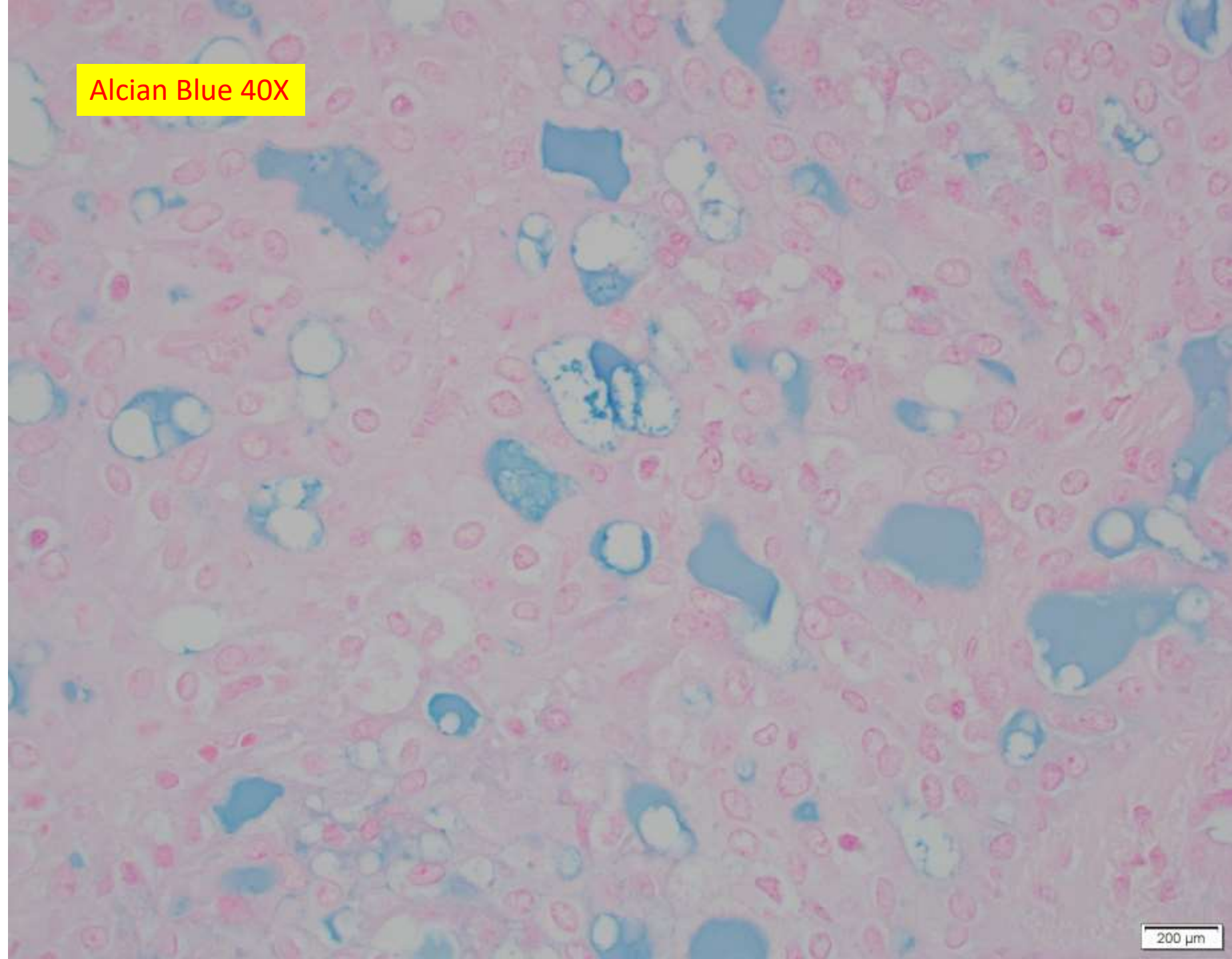


Mucicarmine 40X



200  $\mu$ m

Alcian Blue 40X



200  $\mu$ m



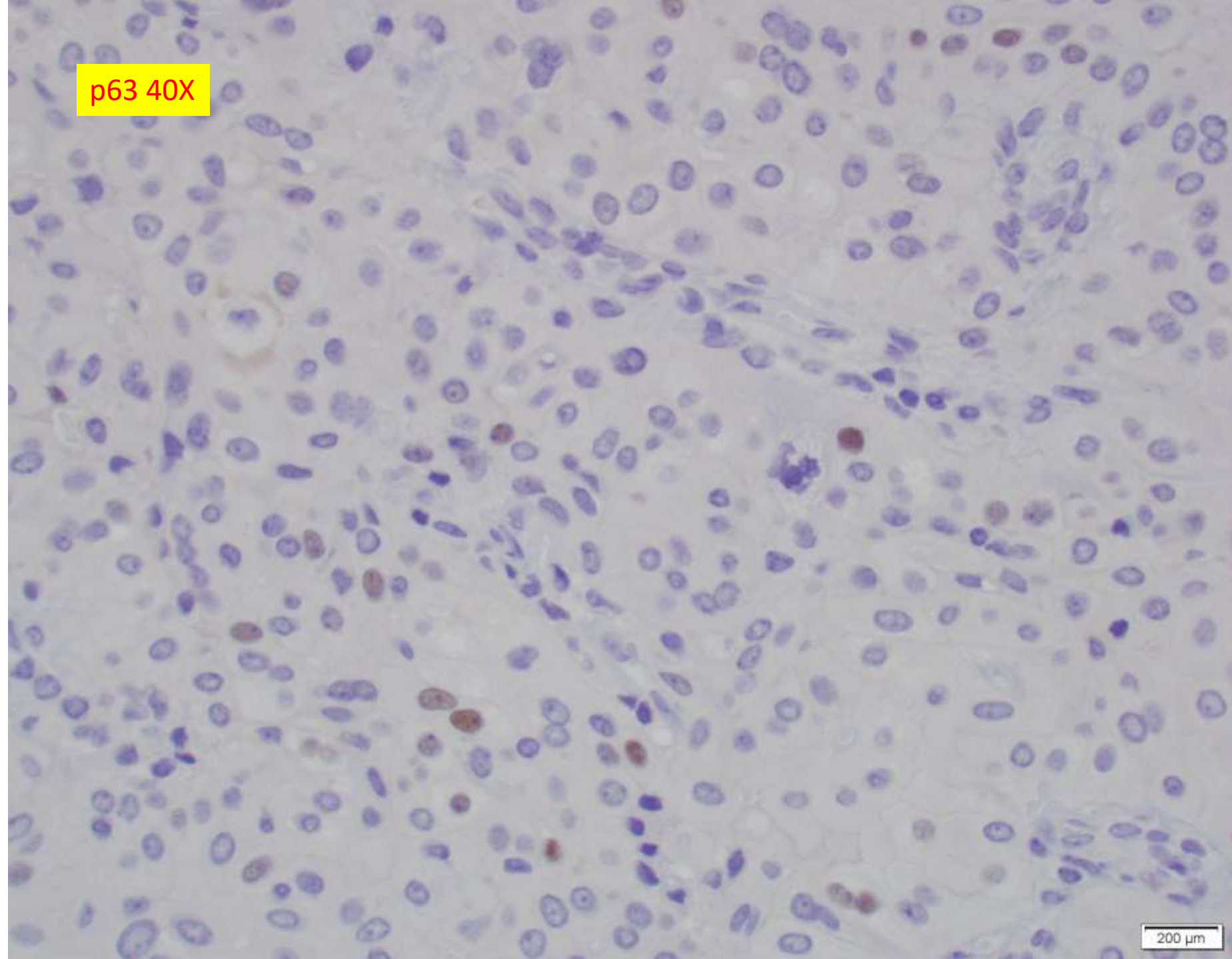
CK7 2X



200 μm



p63 40X

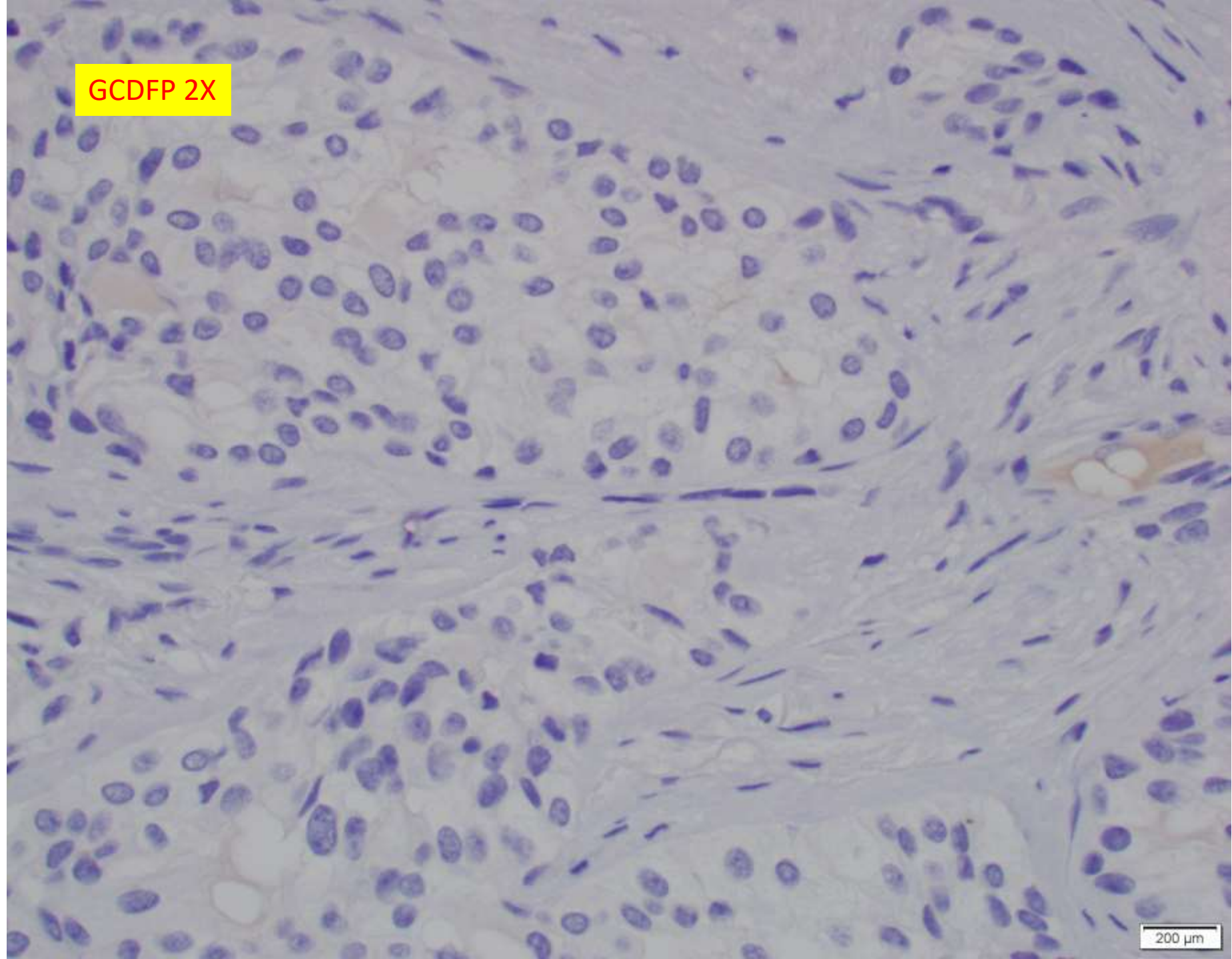


200 μm



GCDFP 2X

200  $\mu$ m



# DIAGNOSIS?





# Discussion of Walden Browne Case April 3, 2017



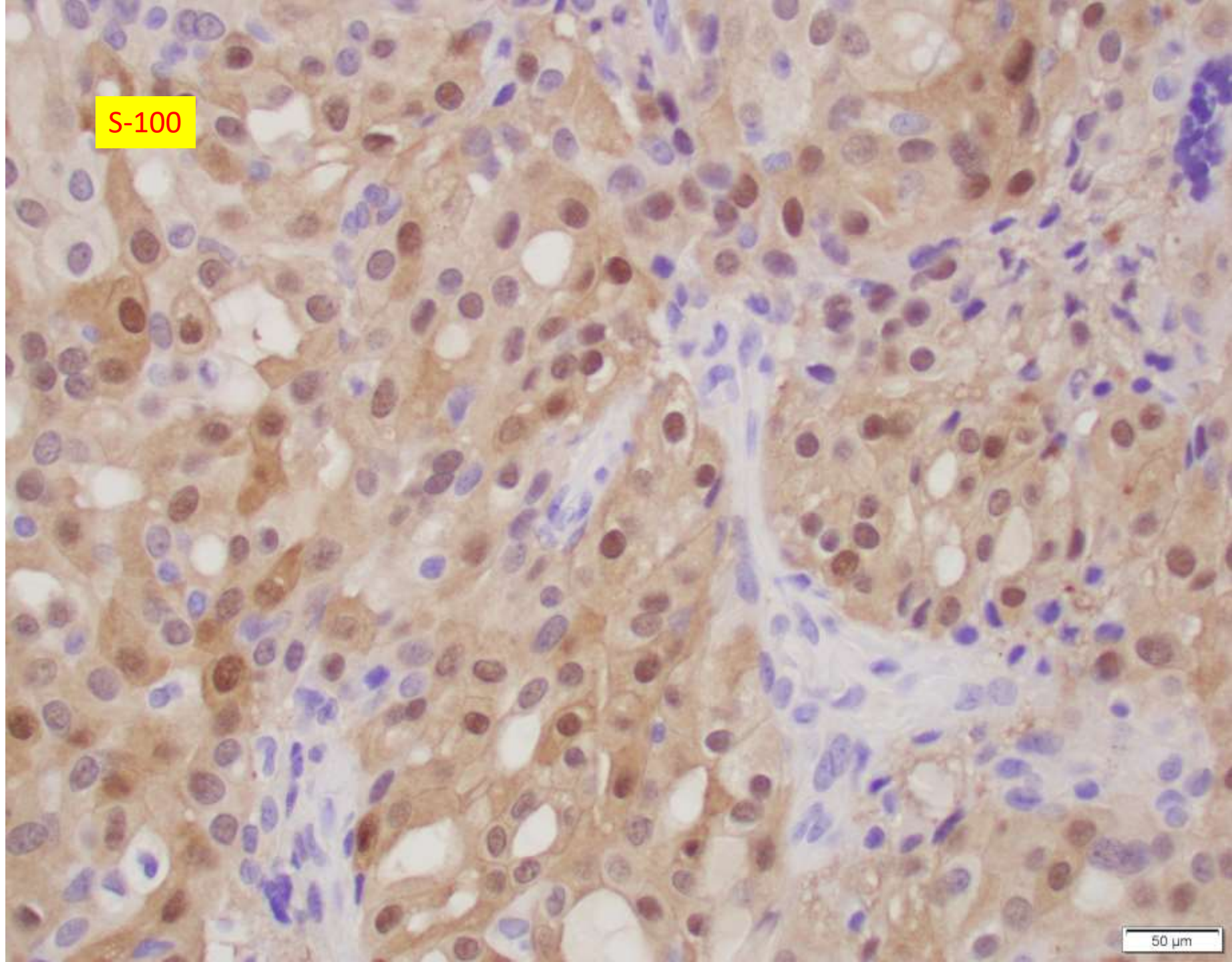


# DIFFERENTIAL DIAGNOSIS

	P63	S-100	GCDFP-15	Mammoglobin
ACINIC CELL CARCINOMA	-	+/-	-	-
MAMMARY ANALOGUE SECRETORY CARCINOMA	+/-	+	+	+
MUCOEPIDERMOID CARCINOMA	+	-	-	-
POLYMORPHOUS LOW- GRADE ADENOCARCINOMA	+	+	-	-

S-100

50  $\mu$ m





“Breast Mix”: GCDFP + Mammoglobin



50 μm



Mammaglobin

50  $\mu$ m



# Mammary Analogue Secretory Carcinoma

- Sent to Stanford University (Gerry Berry) for FISH confirmation: FISH positive for ETV6 Gene Rearrangement
- Perineural invasion unusual in MASC
- 10% occur in buccal mucosa
- GCDFP-15 is negative 15% of cases: Mammaglobin is better

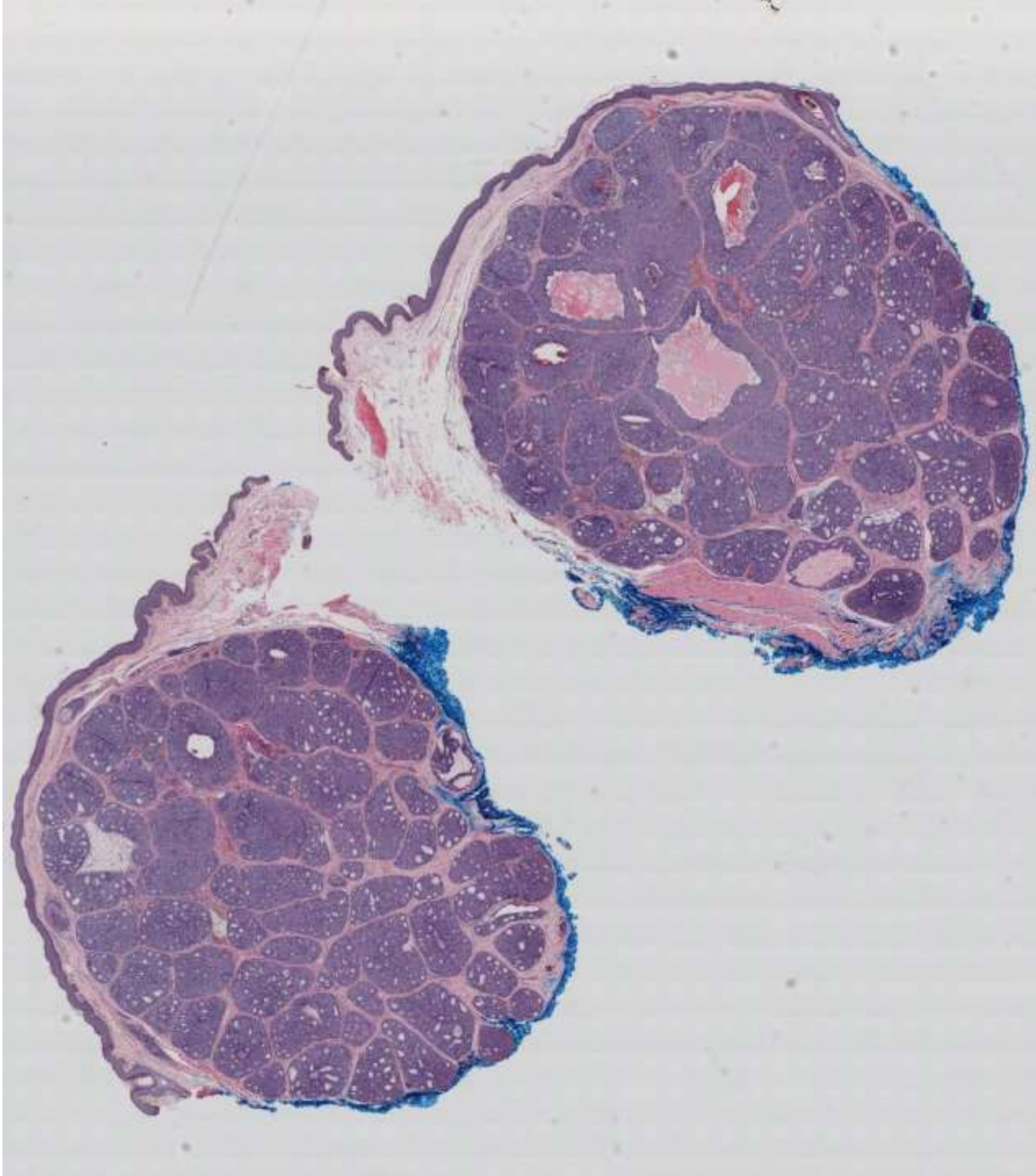
# Selected References

- Hellquist H, Skalova A. *Histopathology of the Salivary Glands*. (Heidelberg: Springer, 2014).
- Luk PP, Selinger CI, Eviston TJ, Lum T, Yu B, O'Toole SA, Clark JR, Gupta R. Mammary analogue secretory carcinoma: an evaluation of its clinicopathological and genetic characteristics. *Pathology*. 2015 Dec 1;47(7):659-66.
- Patel KR, Solomon IH, El-Mofty SK, Lewis JS, Chernock RD. Mammaglobin and S-100 immunoreactivity in salivary gland carcinomas other than mammary analogue secretory carcinoma. *Human pathology*. 2013 Nov 30;44(11):2501-8.

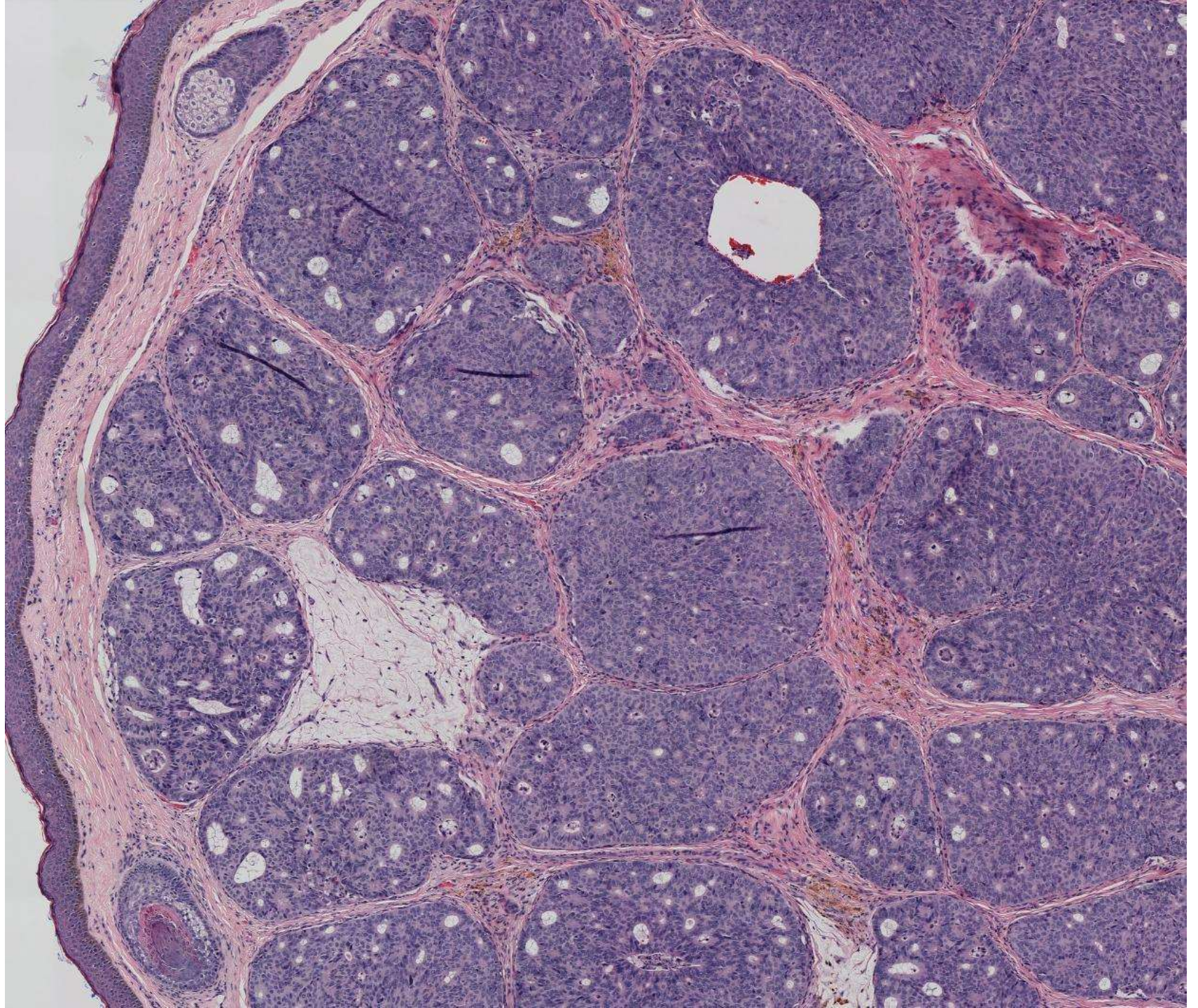


**SB 6155 (scanned slide available)**

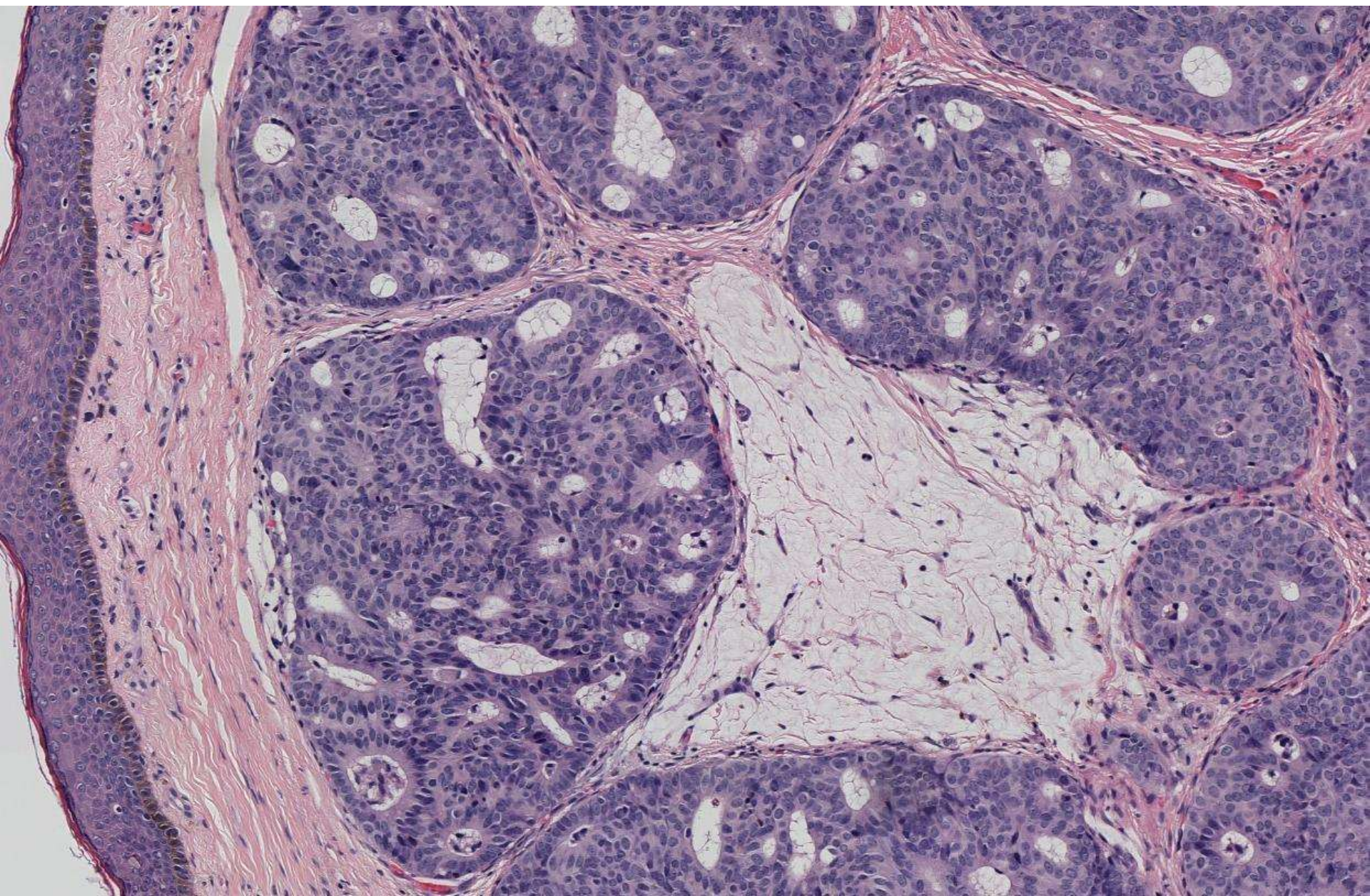
**Balaram Puligandla; Kaiser Oakland**  
66-year-old woman with right upper  
eyelid cyst, clinical DDx hidrocystoma.



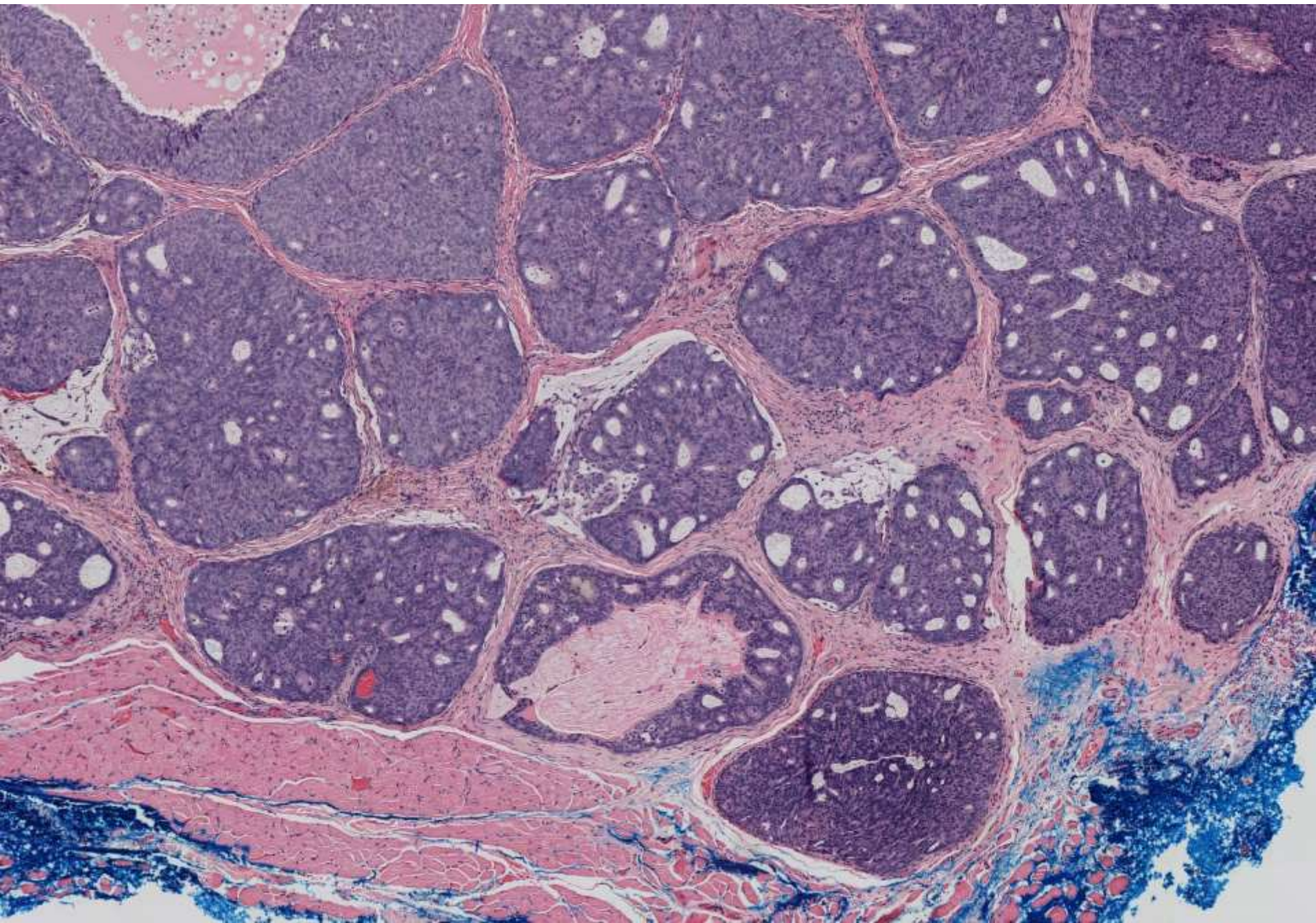




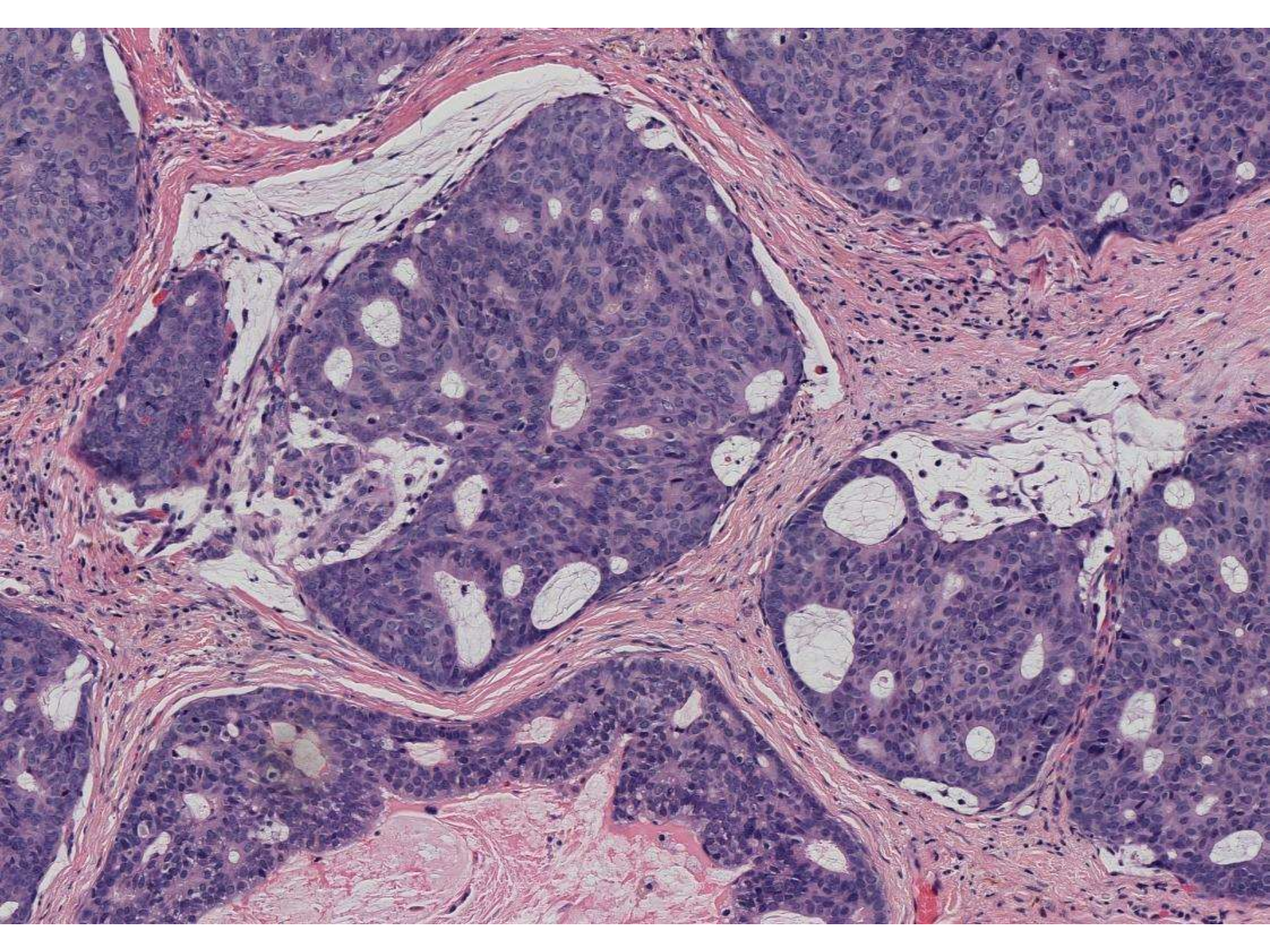




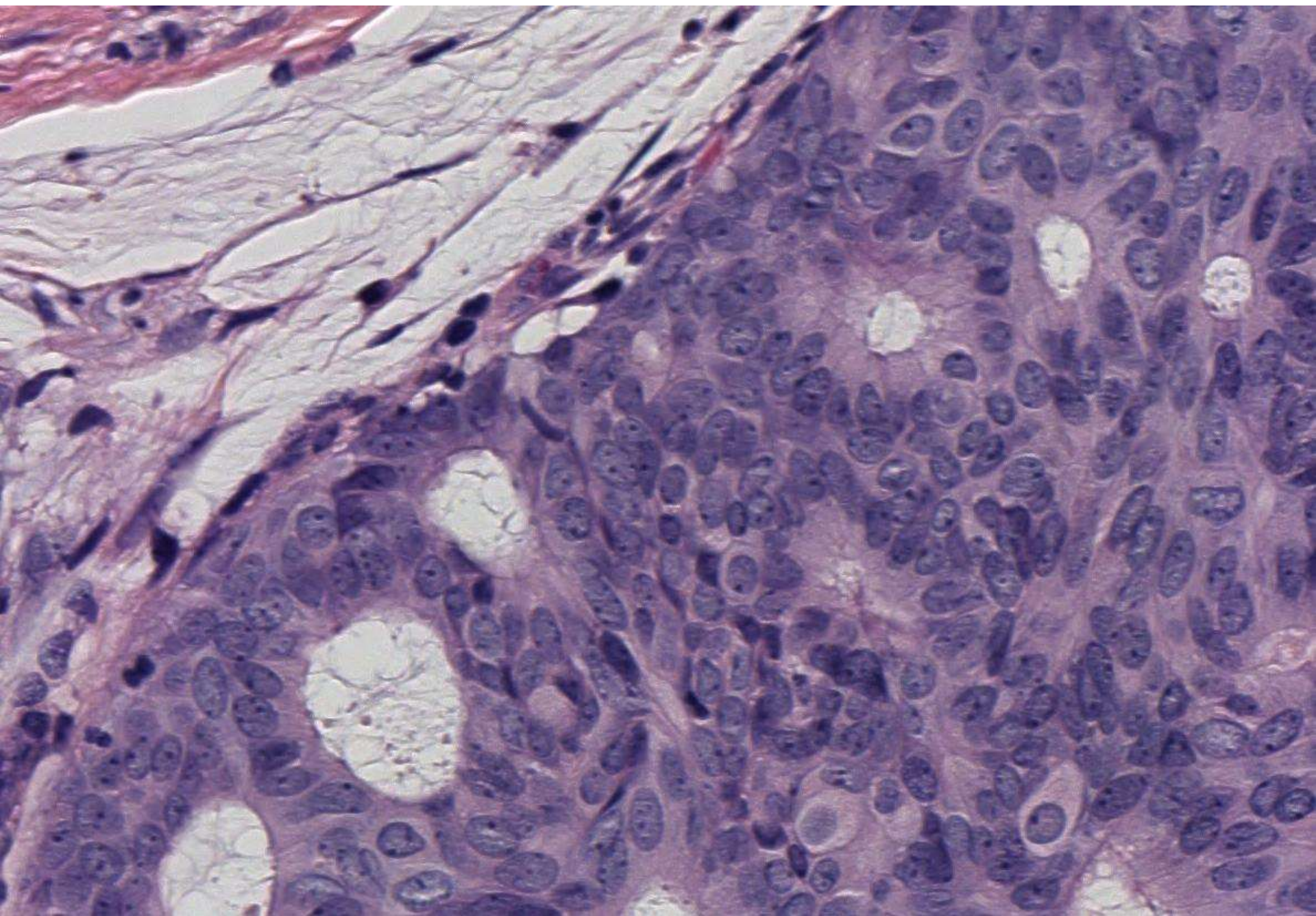




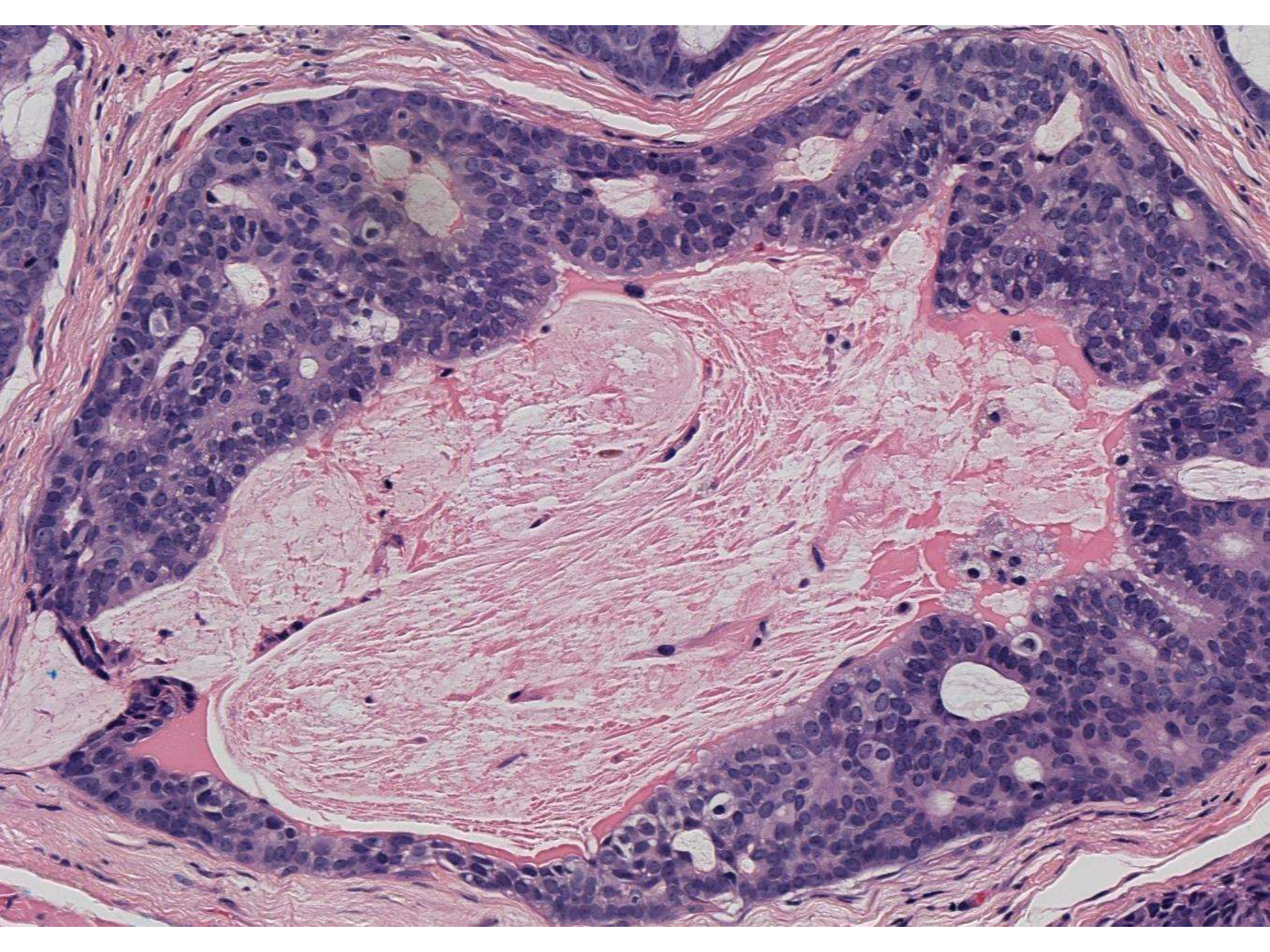














# DIAGNOSIS?







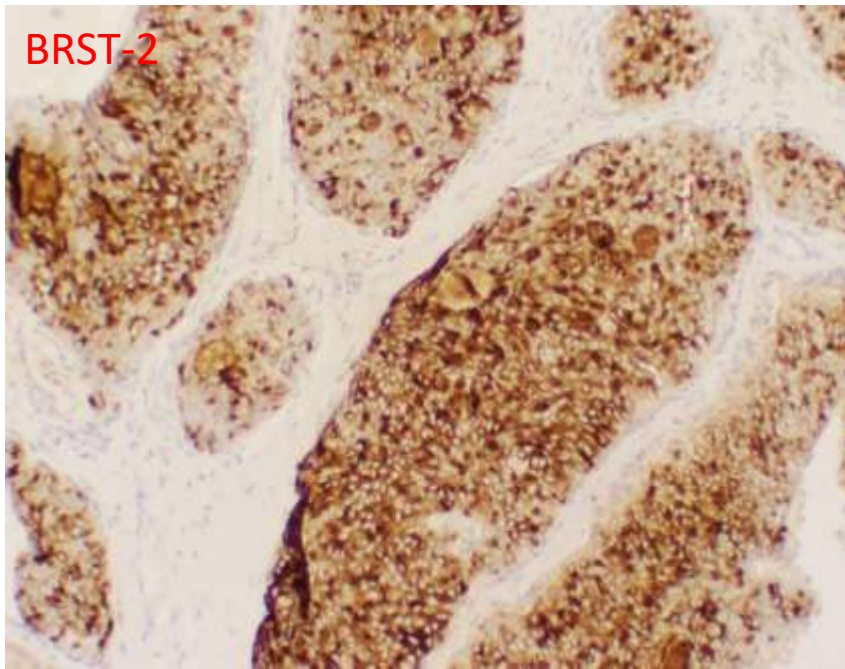
# Endocrine Mucin-Producing Sweat Gland Carcinoma

- First described in 1997 by Flieder et al  
(Am J Surg Pathol. 1997 Dec; 21(12):1501-6)
- Predilection for the eyelid of elderly women
- Analogous to solid papillary ca or DCIS with endocrine differentiation of breast
- Thought to be a precursor lesion for colloid ca in breast and skin

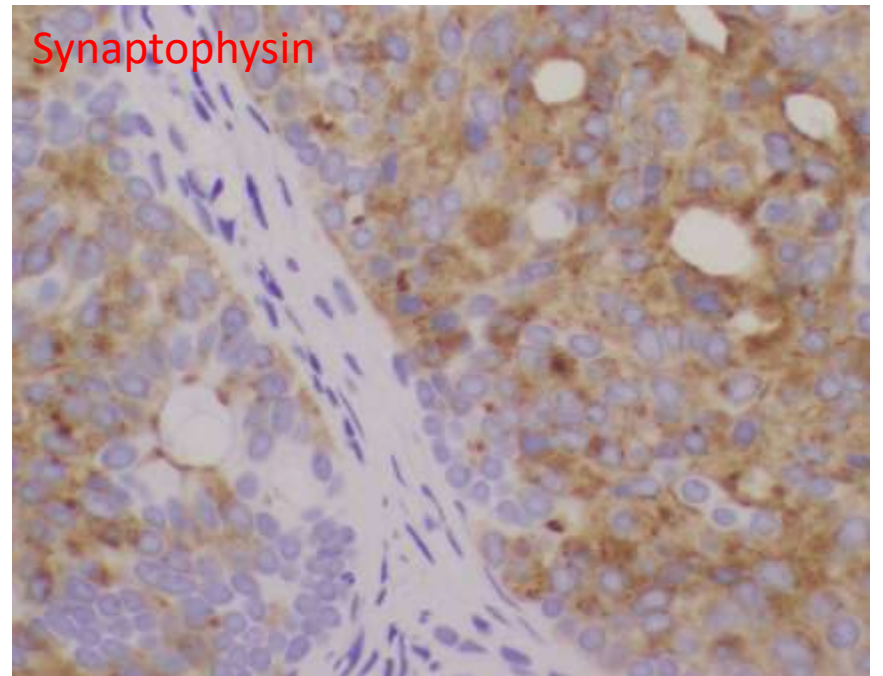


- Tumor typically positive for CK 7,ER, PR, Synaptophysin, Chromogranin, GCDFP-15 and BRST-2

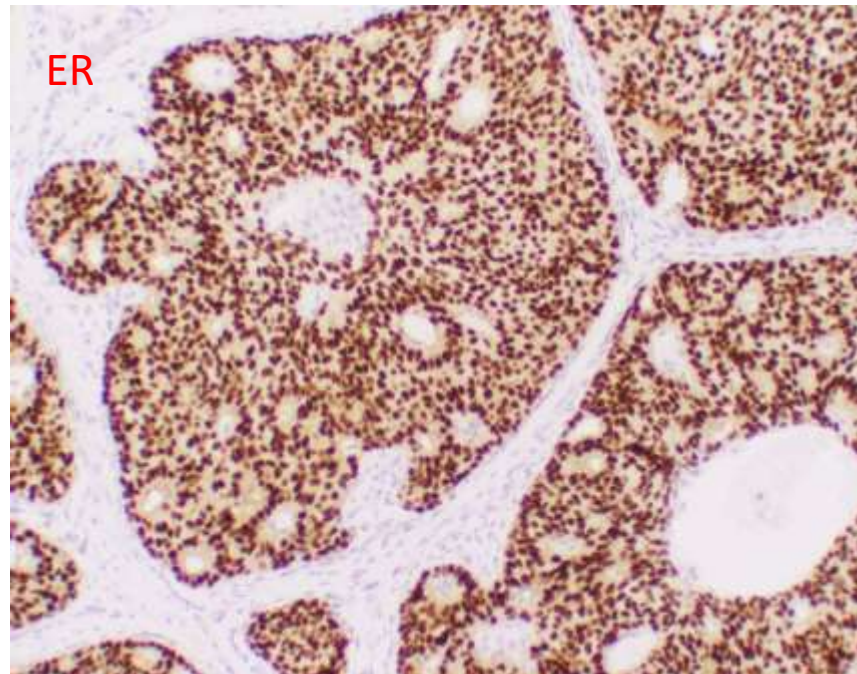
BRST-2



Synaptophysin



ER





- Must R/O metastatic breast ca
- DDX: Hidrocystoma, BCC, Hidradenoma, apocrine adenoma and basal cell adenoma
- Conservative resection recommended
- Excellent prognosis, 2 local recurrences in the literature, no distant metastases reported

# Take Home Message

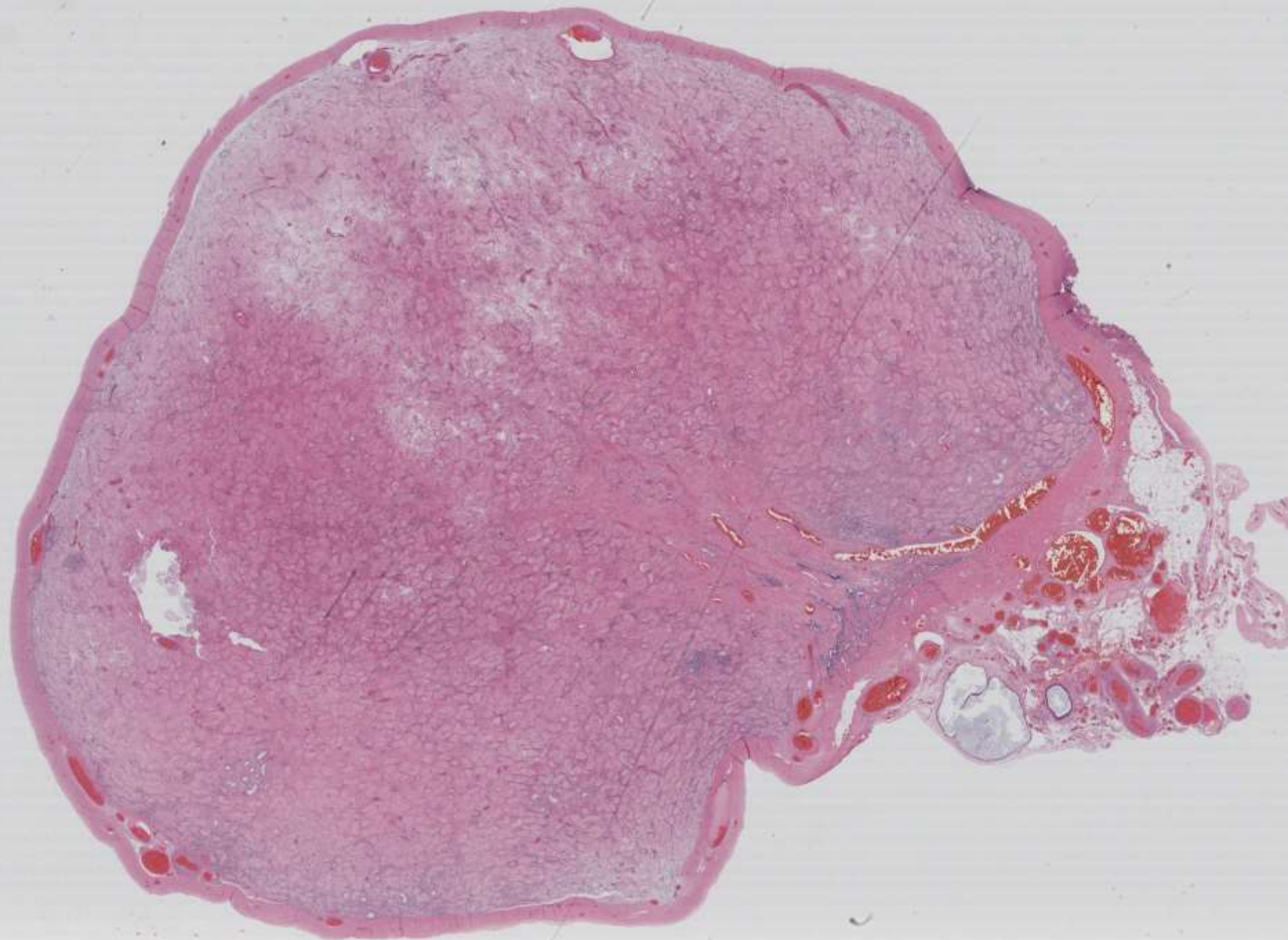
- Look for the classic, breast like morphology
- Confirm with IHC
- Conservative management



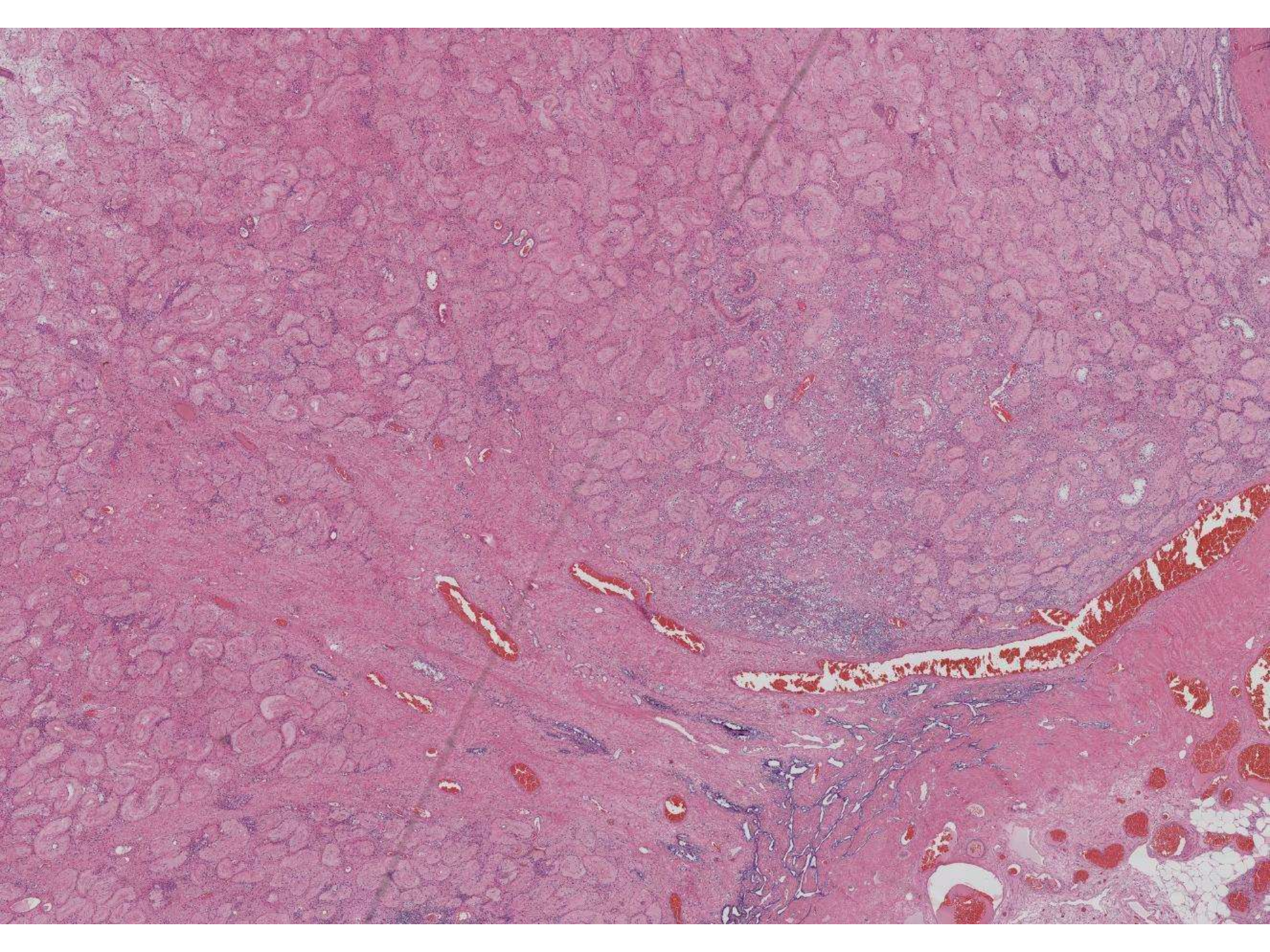
**SB 6156 (scanned slide available)**

**Sunny Kao; Stanford**

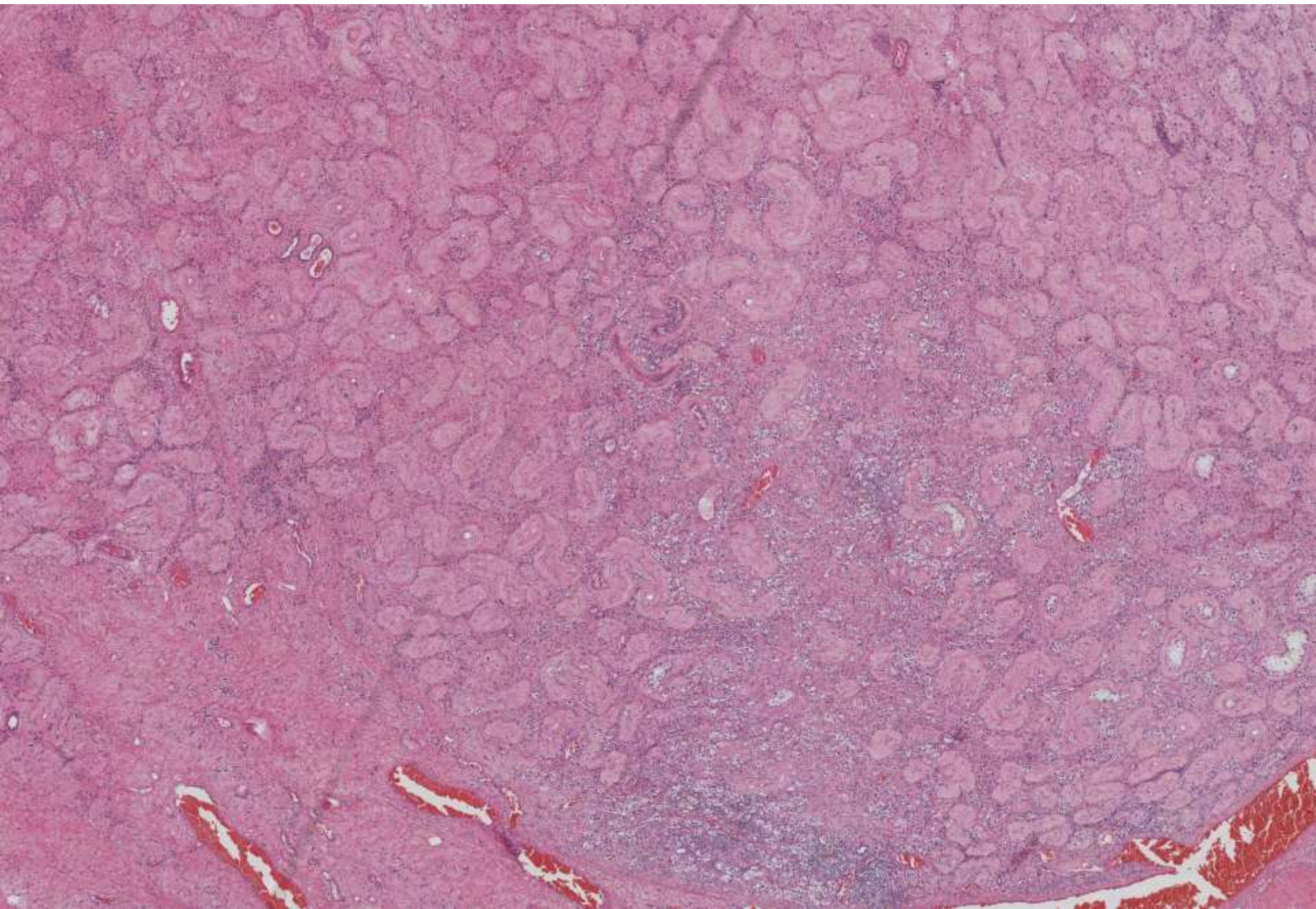
33-year-old man with bilateral  
undescended testes and right inguinal  
hernia.



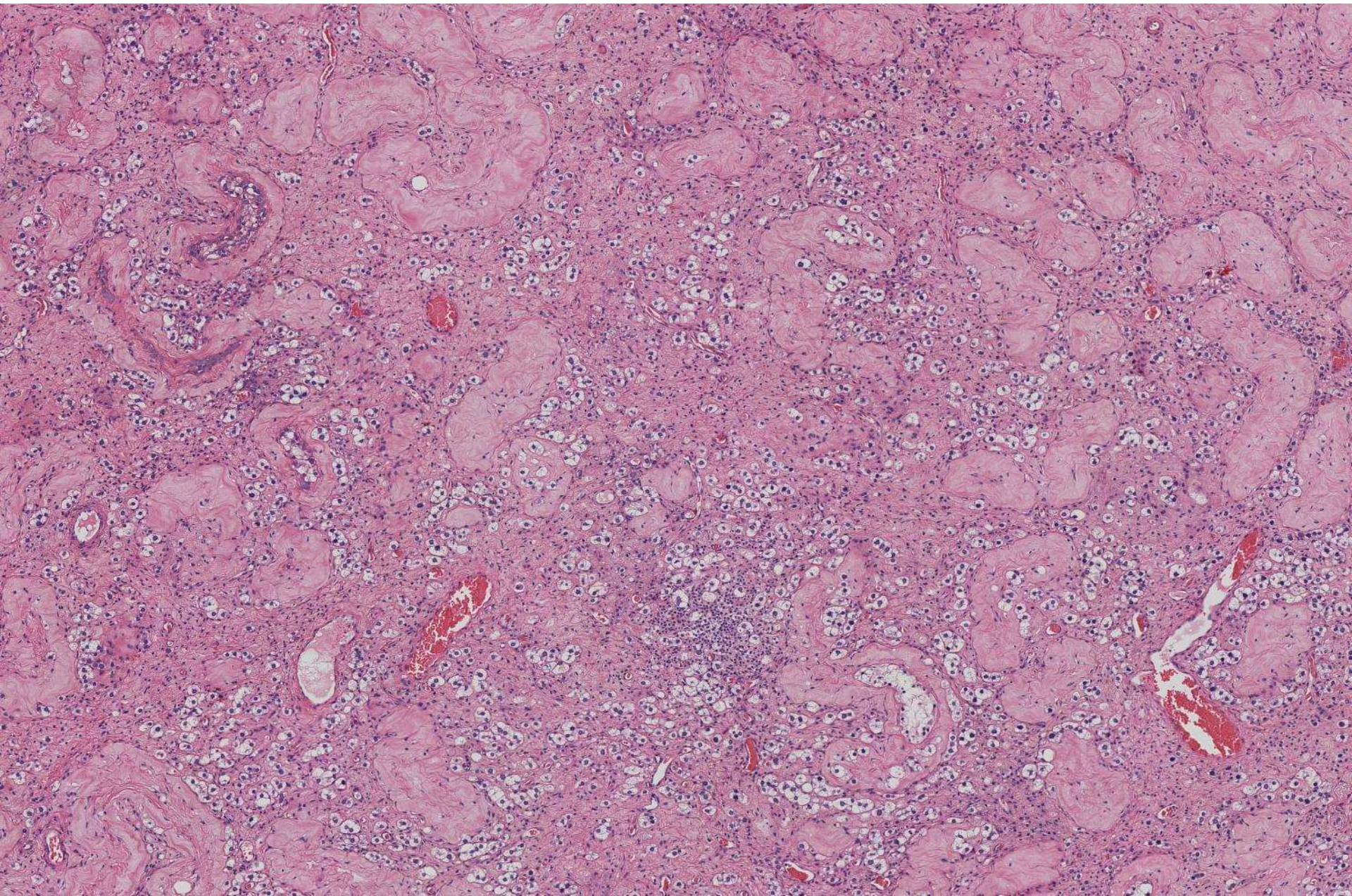




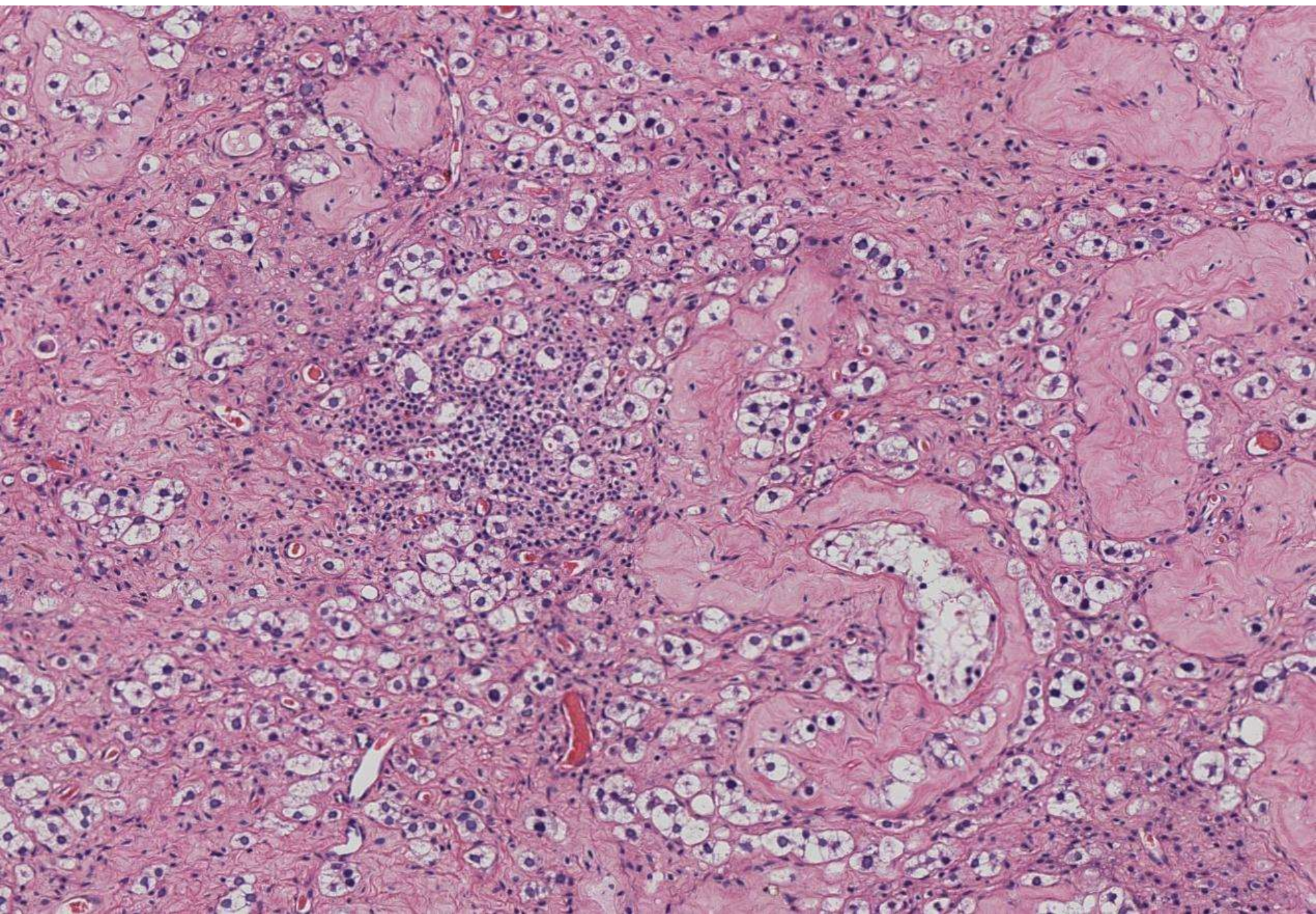




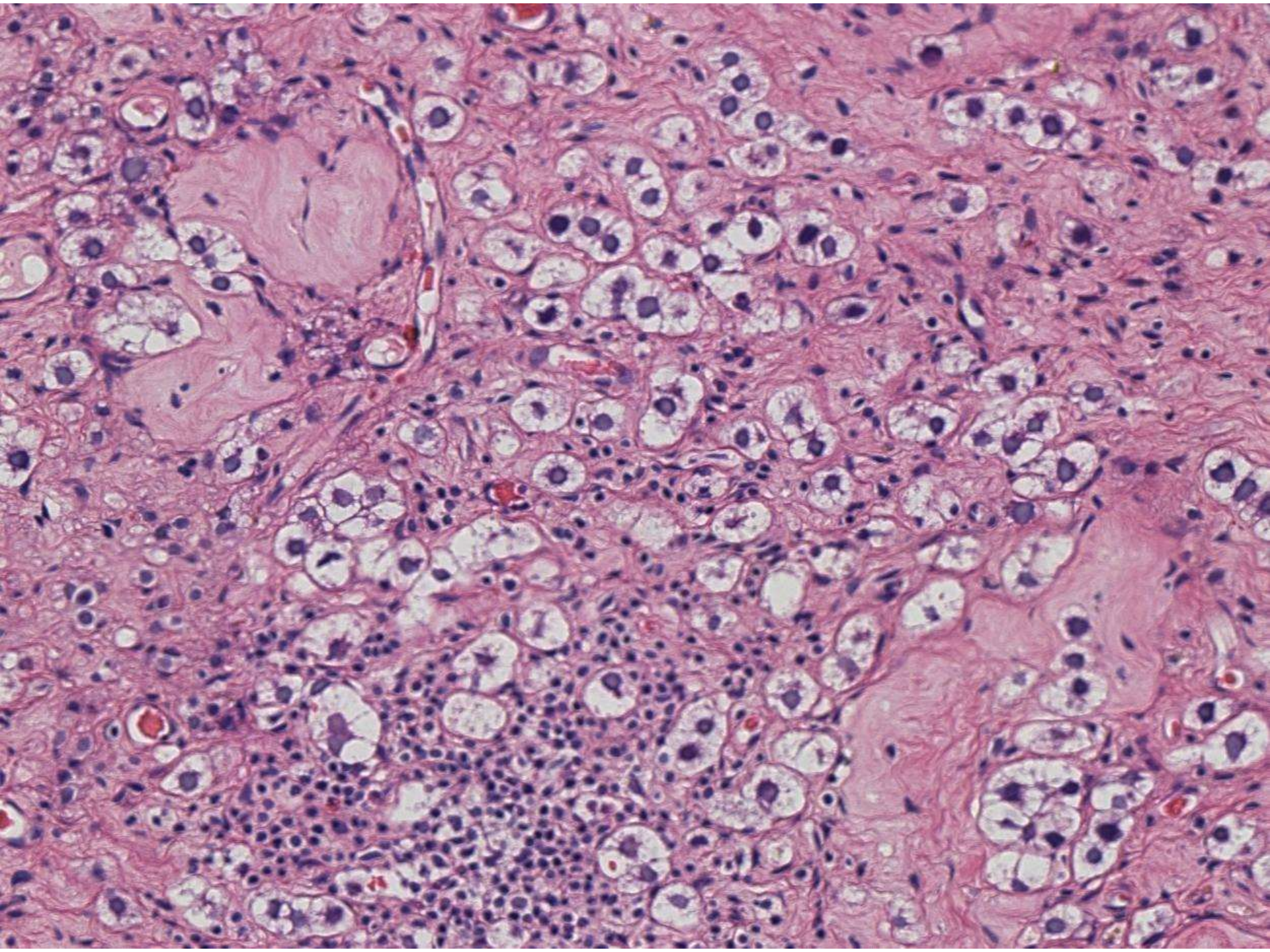














# DIAGNOSIS?





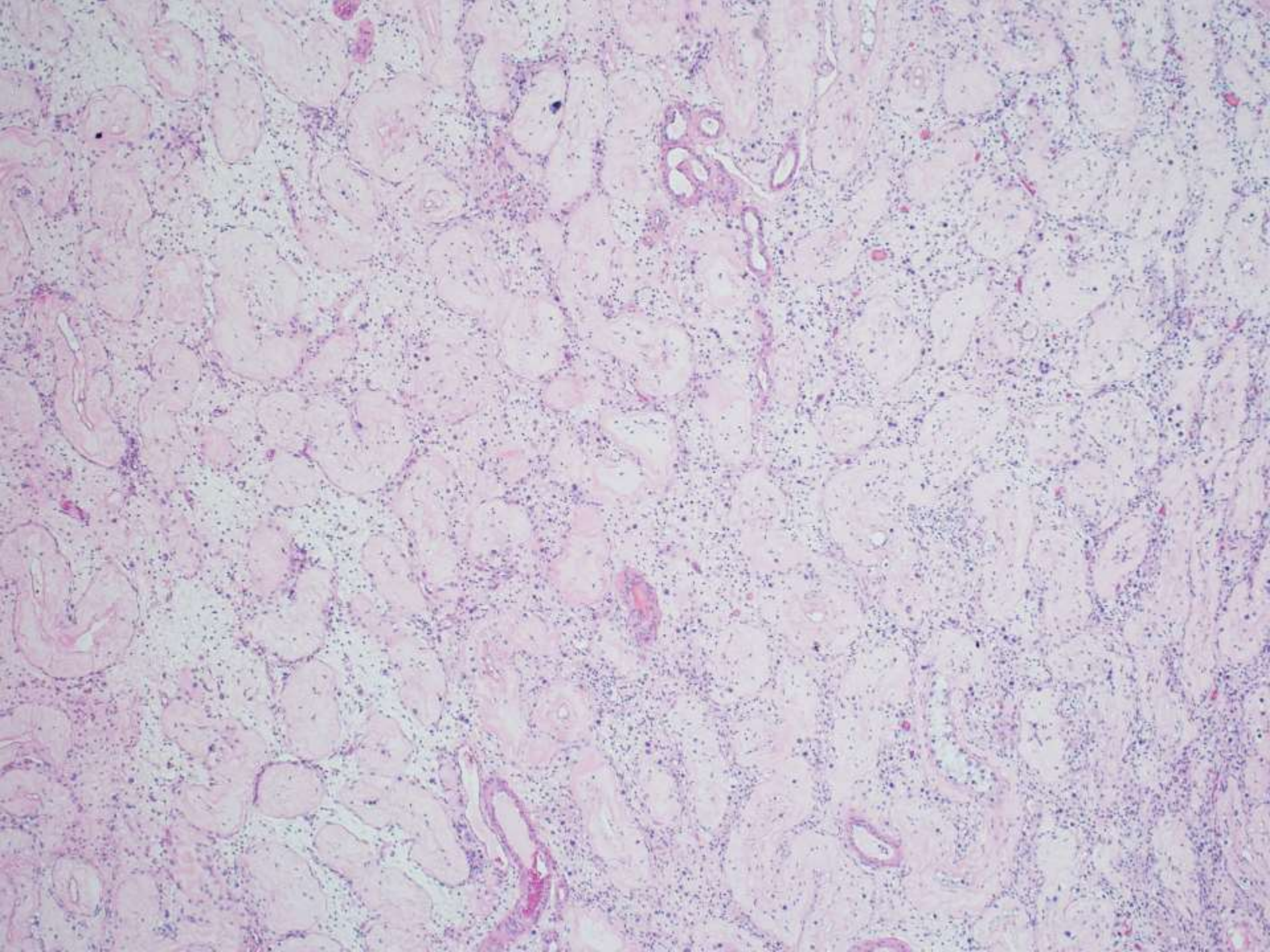
# SB 6156

33 year-old male with bilateral undescended testes  
and right inguinal hernia

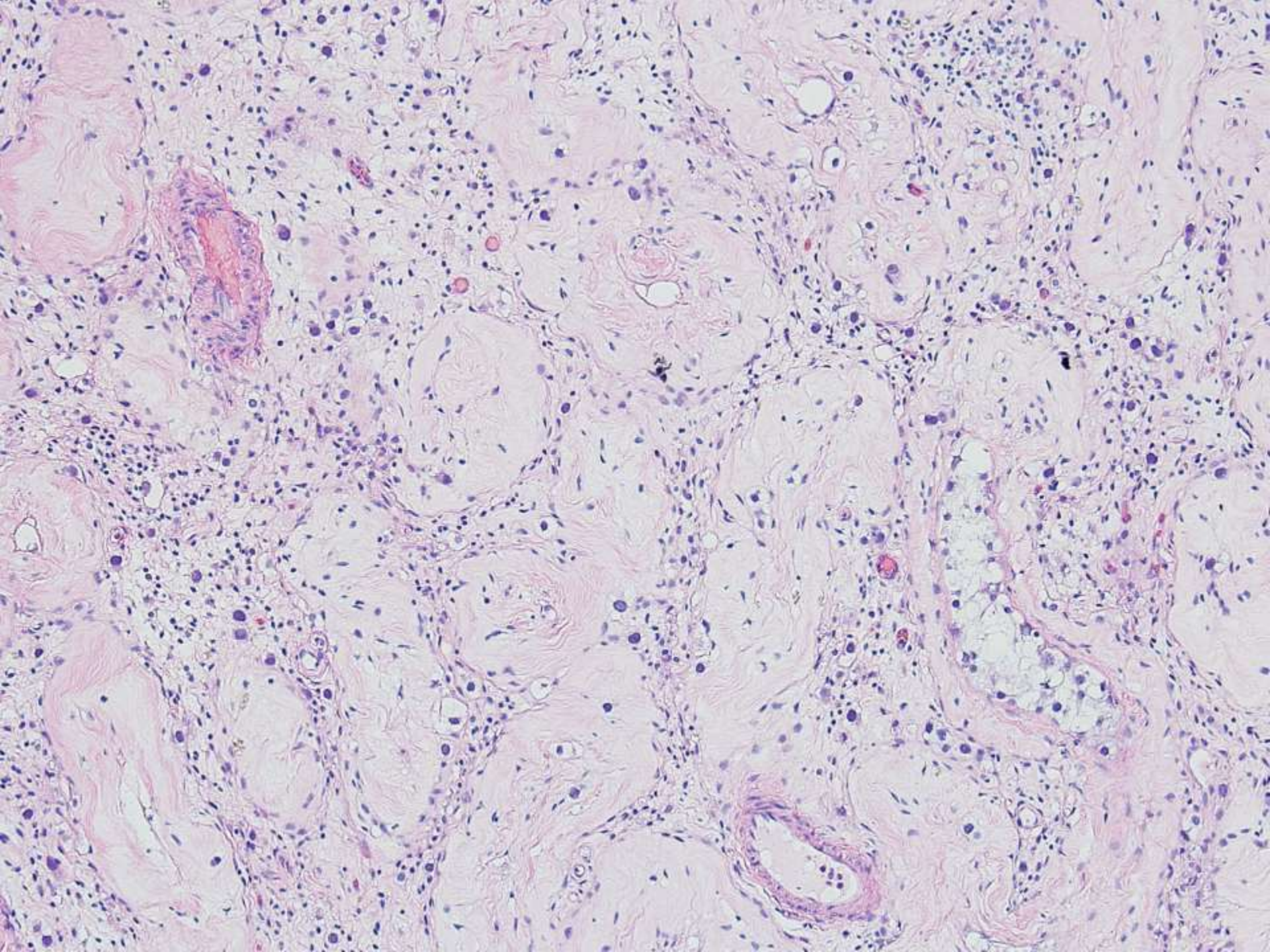
Sunny Kao; Stanford



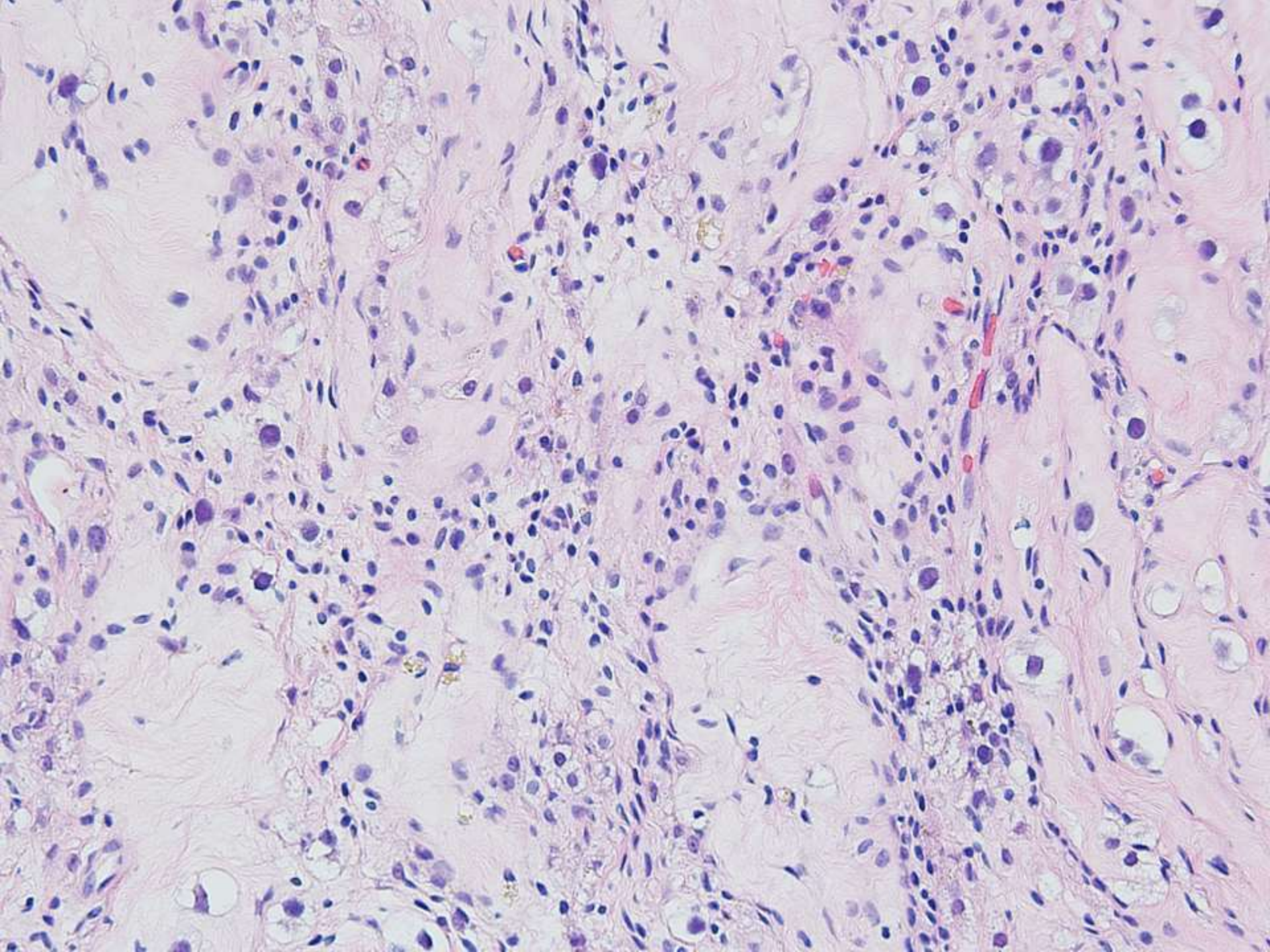












# Cryptorchidism

- **Strongly associated with testicular cancer**
  - **3.5-5x elevated risk**
- **Testicular biopsies are recommended in late adolescence**
- **Orchidopexy does not reduce the subsequent development of germ cell tumors in the original cryptorchid testis, but may reduce the chance of subsequent infertility**



# **Intertubular seminoma**

- **Doesn't cause a mass lesion**
  - **Frequently clinically occult**
  - **Underestimation of size when this pattern predominates**
- **Identify by recognizing the presence of GCNIS cells between the tubules**
  - **Often will be associated with lymphocytes or Leydig cell hyperplasia so make sure to go on higher power for areas of increased cellularity!**

# References

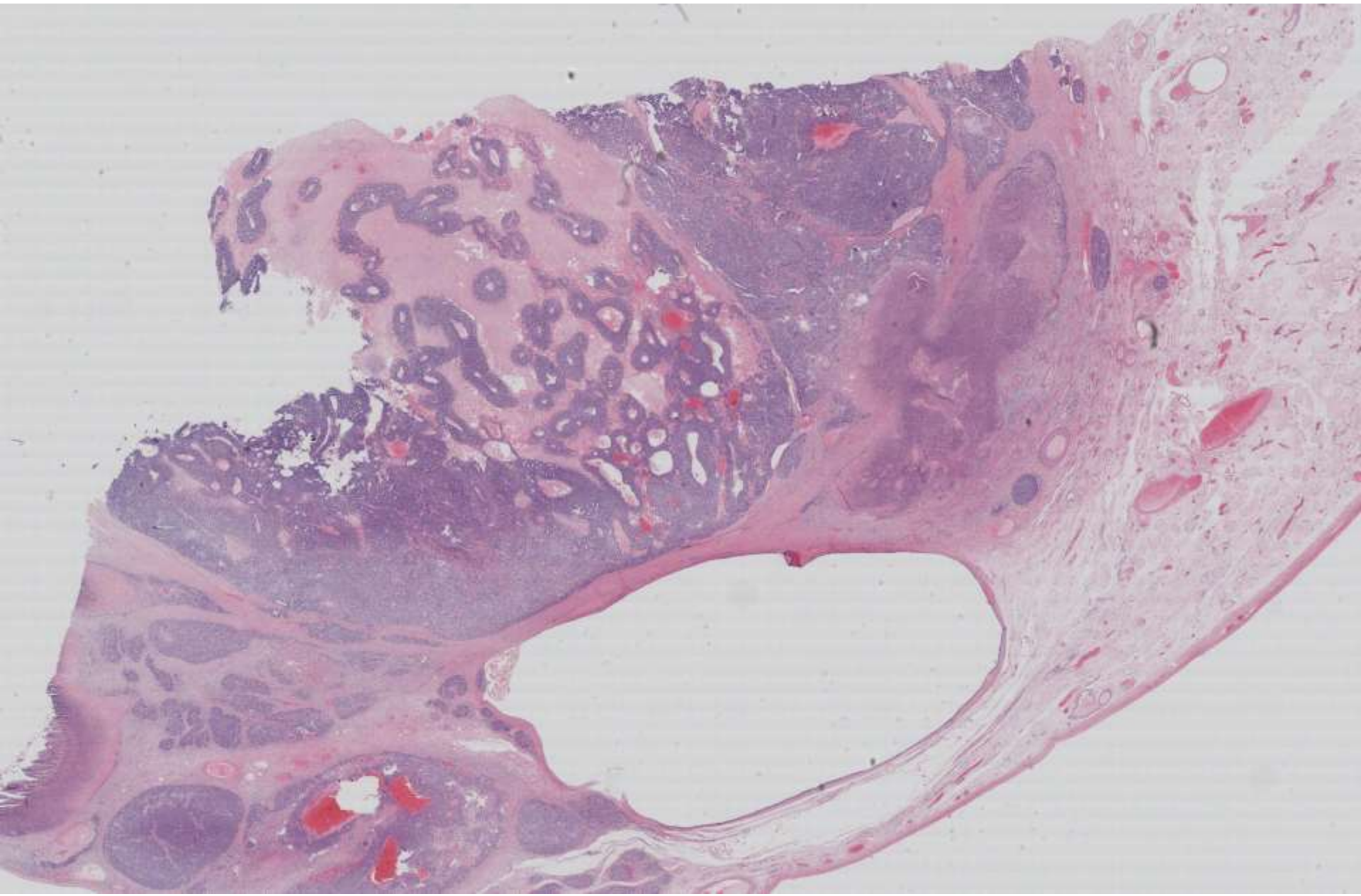
- Giwerzman A, Grindsted J, Hansen B, Jensen OM, Skakkebaek NE. Testicular cancer risk in boys with maldescended testis: a cohort study. J Urol 1987; 138:1214-6**
- Giwerzman A, Muller J, Skakkebaek NE. Carcinoma in situ of the undescended testis. Semin Urol 1986;6:110-9**
- Hezmall HP, Lipshultz LI. Cryptorchidism and infertility. Urol Clin North Am 1982;9:361-9**
- Henley JD, Young RH, Wade CL, Ulbright TM. Seminomas with exclusive intertubular growth: A report of 12 clinically and grossly inconspicuous tumors. Am J Surg Pathol 2004; 28:9:1163-1168.**



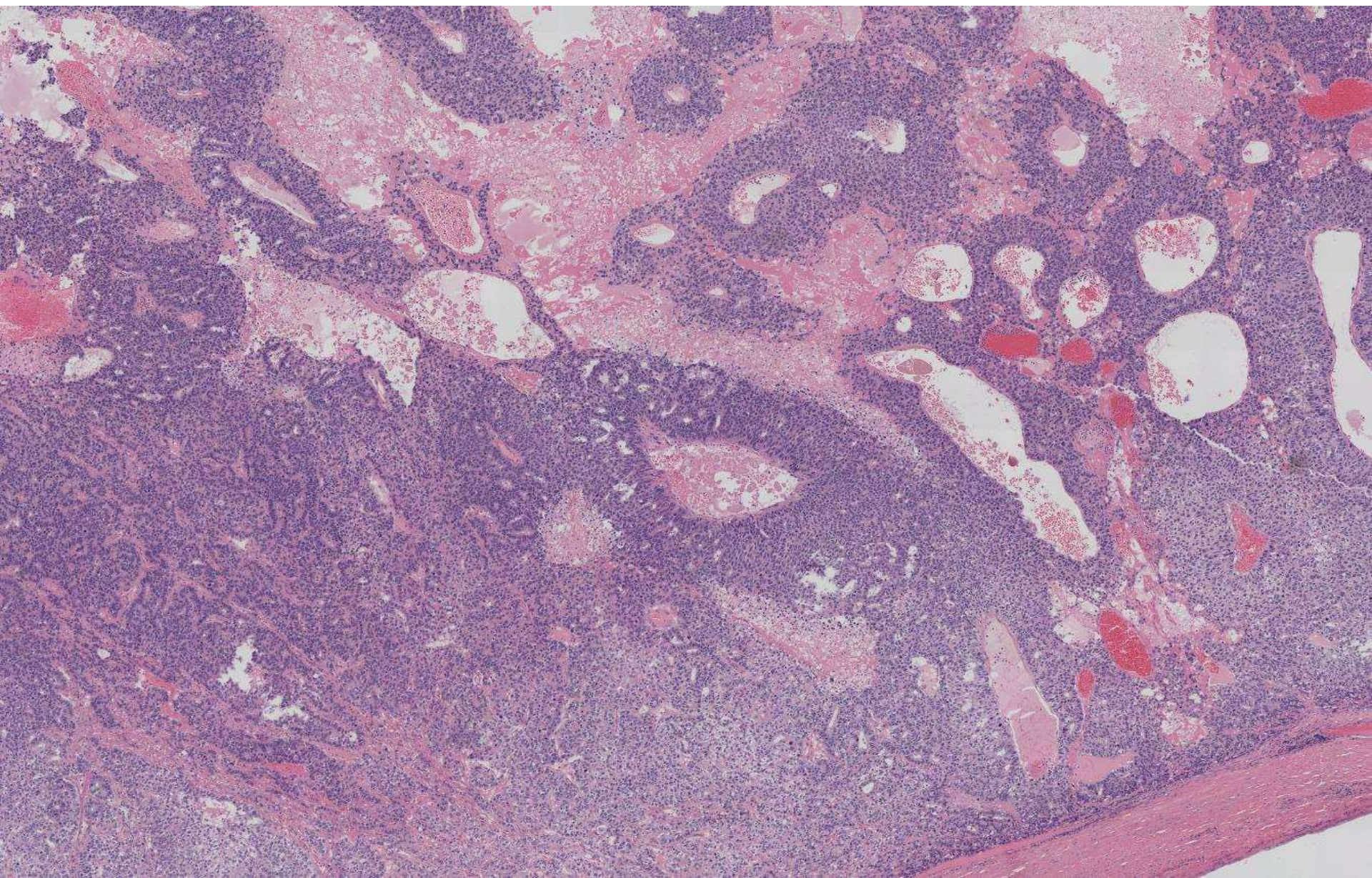
# SB 6157 (scanned slide available)

**Yung Kang/Charles Zaloudek; UCSF**

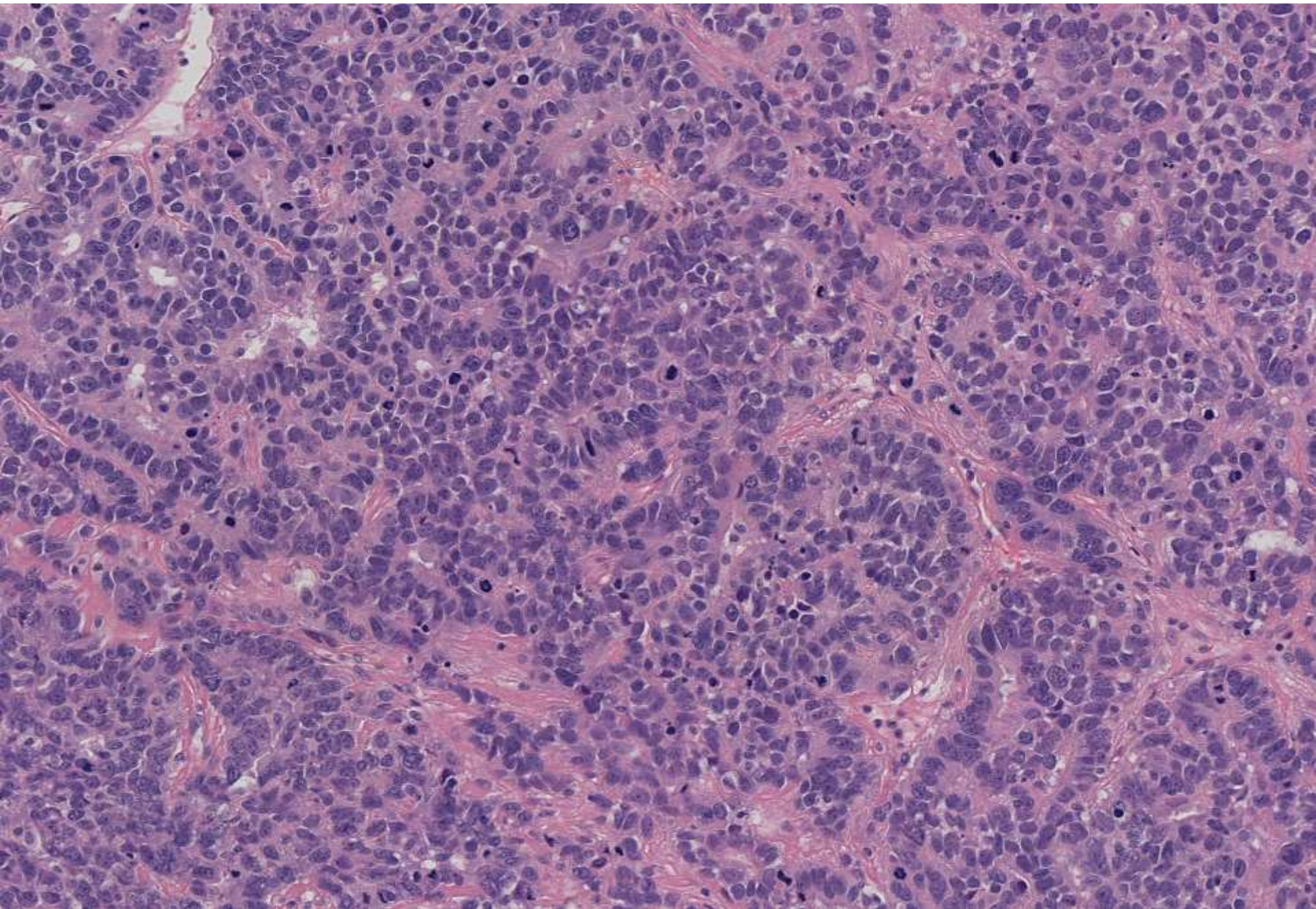
59-year-old man who presented with decreased vision and was found to have masses involving brain and lung. Biopsy of brain and lungs revealed CDX2 positive poorly differentiated carcinoma. He was later found to have a left testicular mass and underwent radical left orchiectomy.



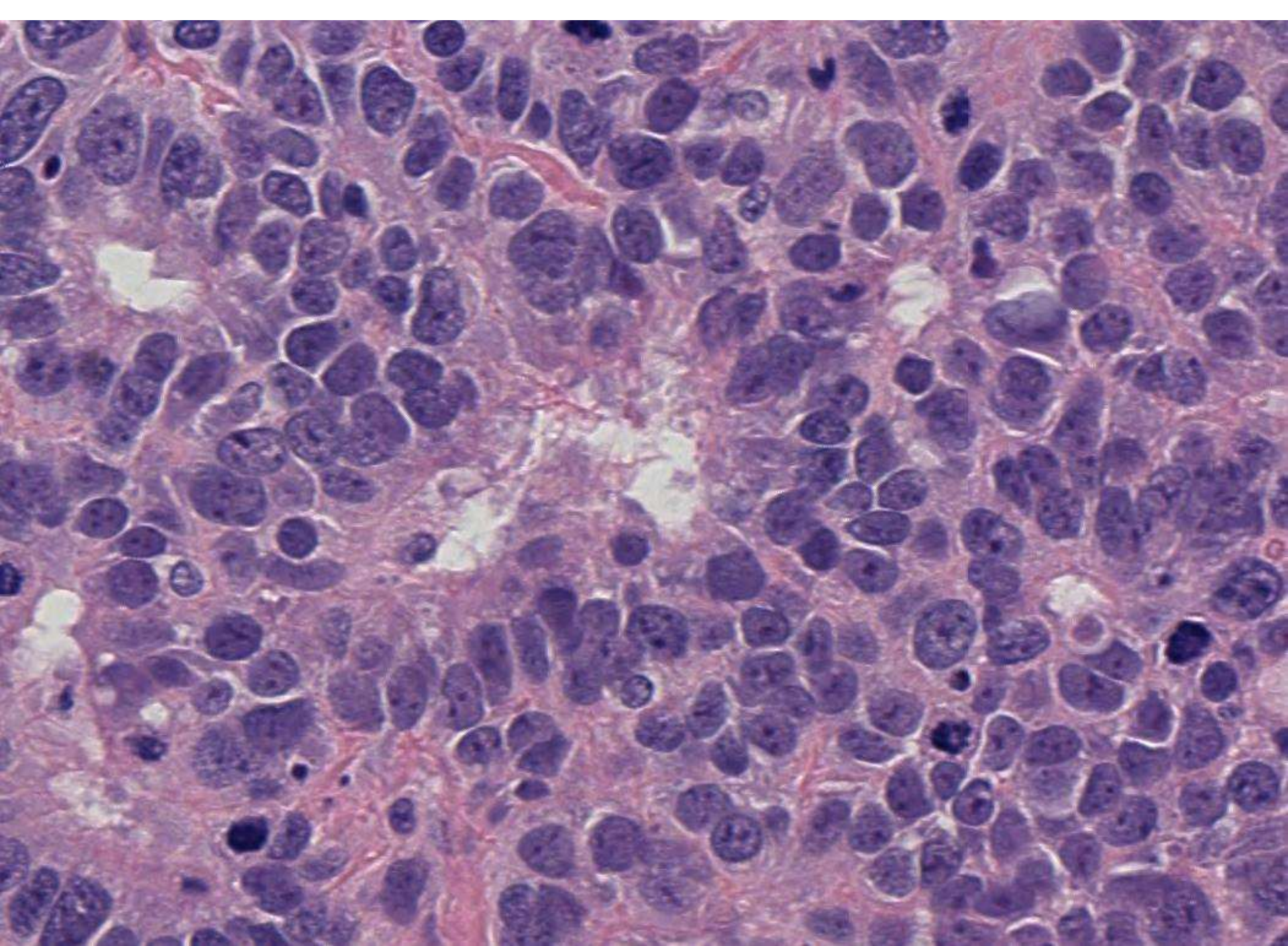




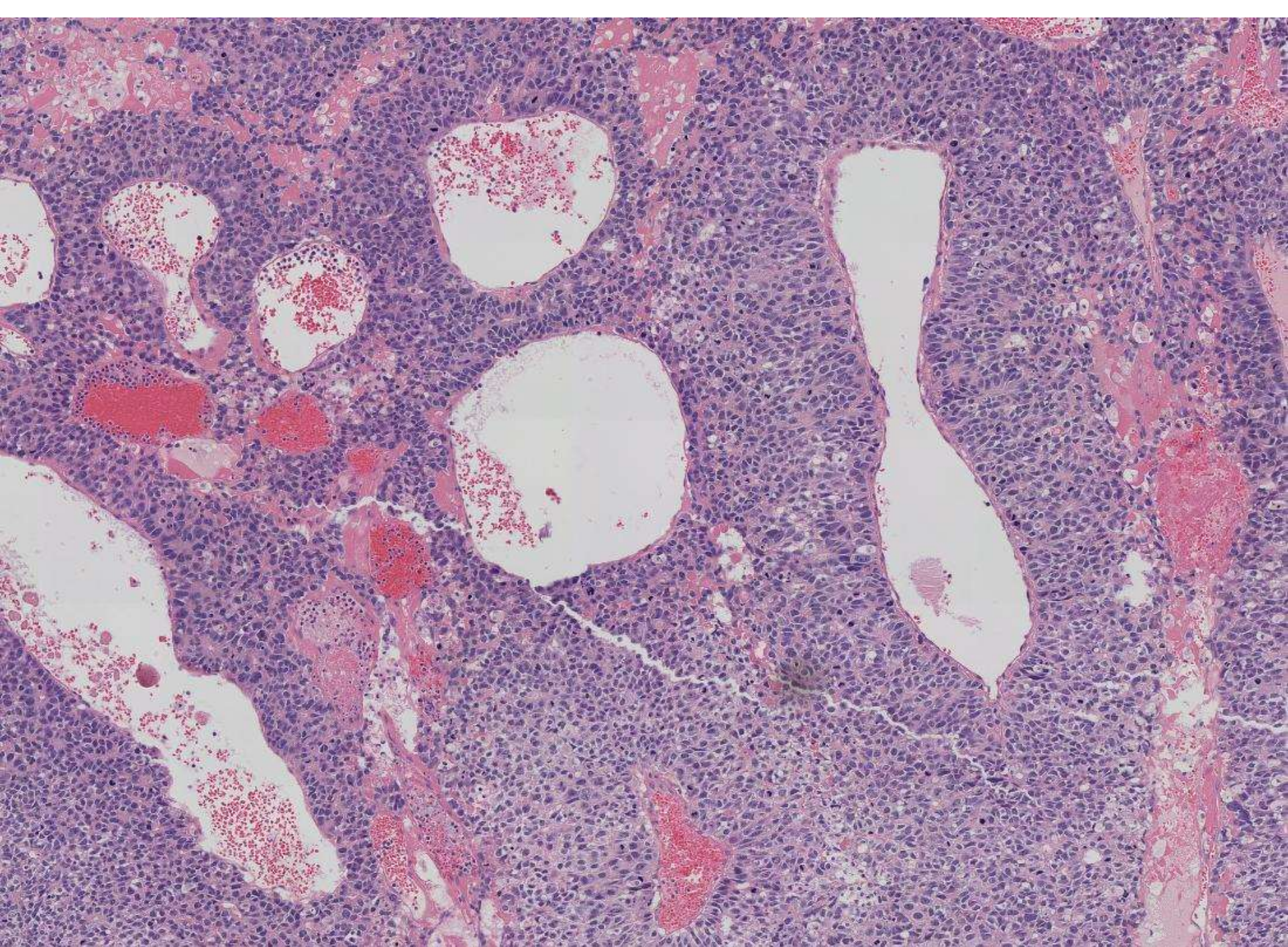




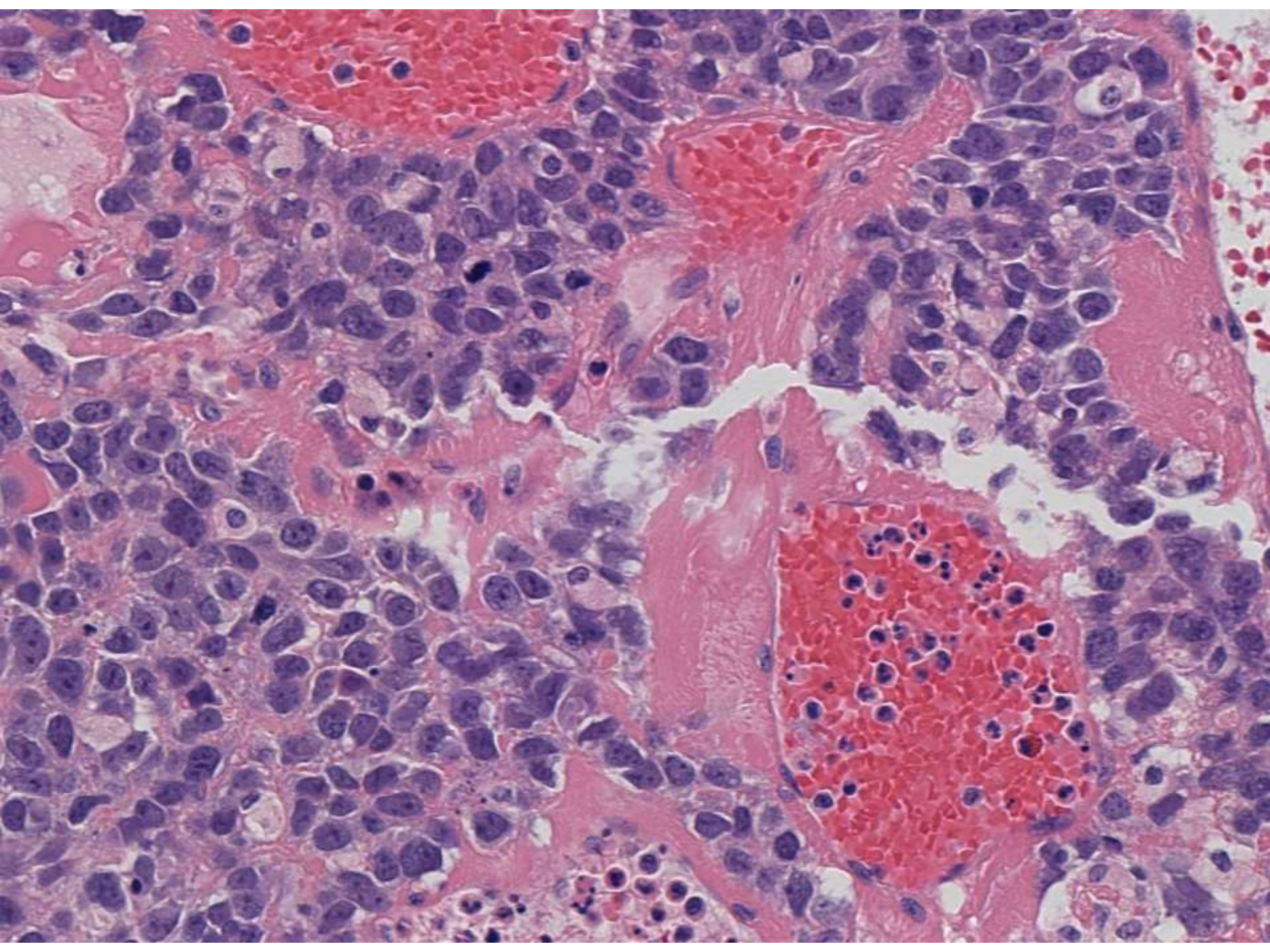




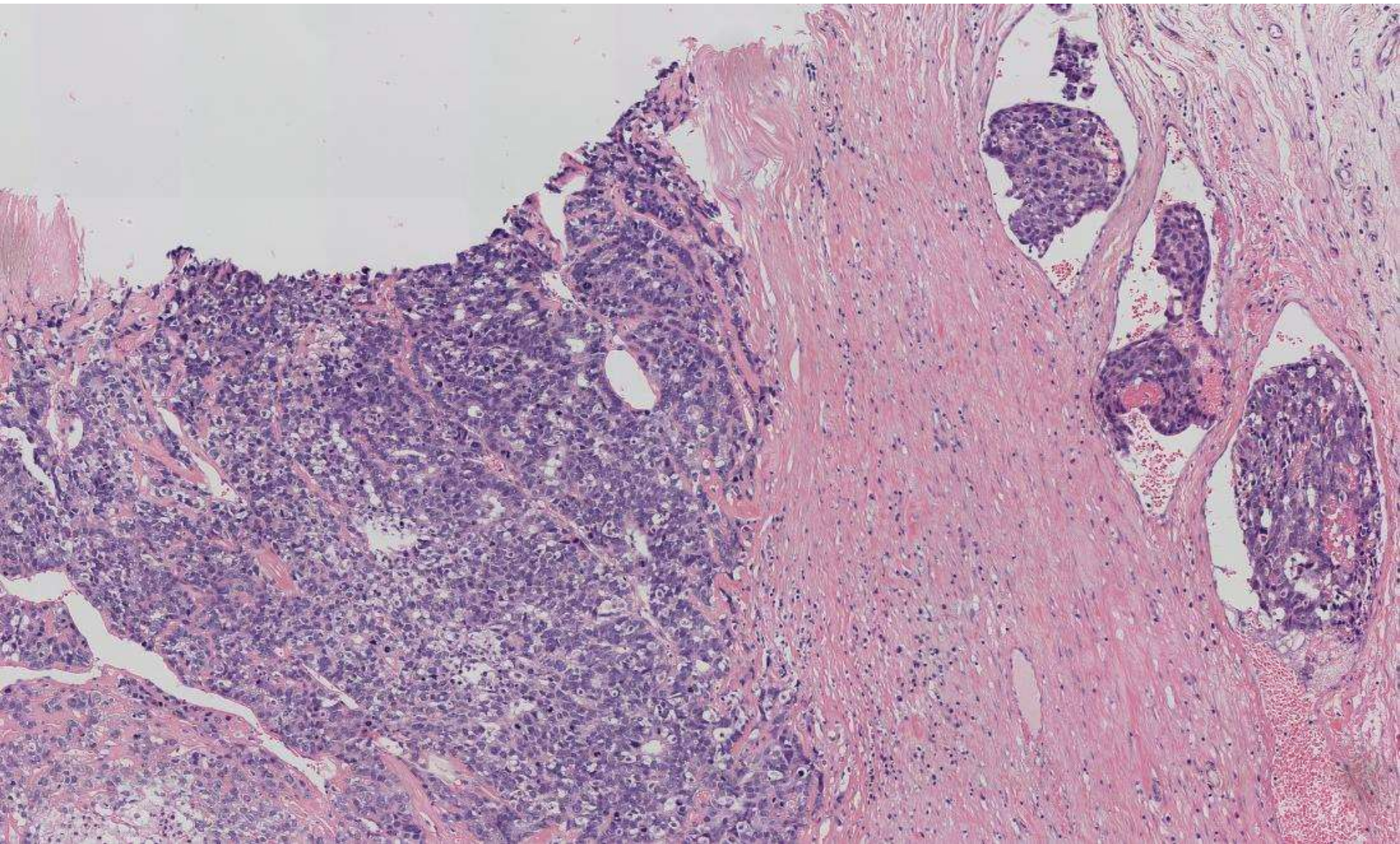














# DIAGNOSIS?



# **South Bay Society case presentation**

## **SB6157**

**University of California San Francisco  
Yuna Kang, MD and Charles Zaloudek, MD**

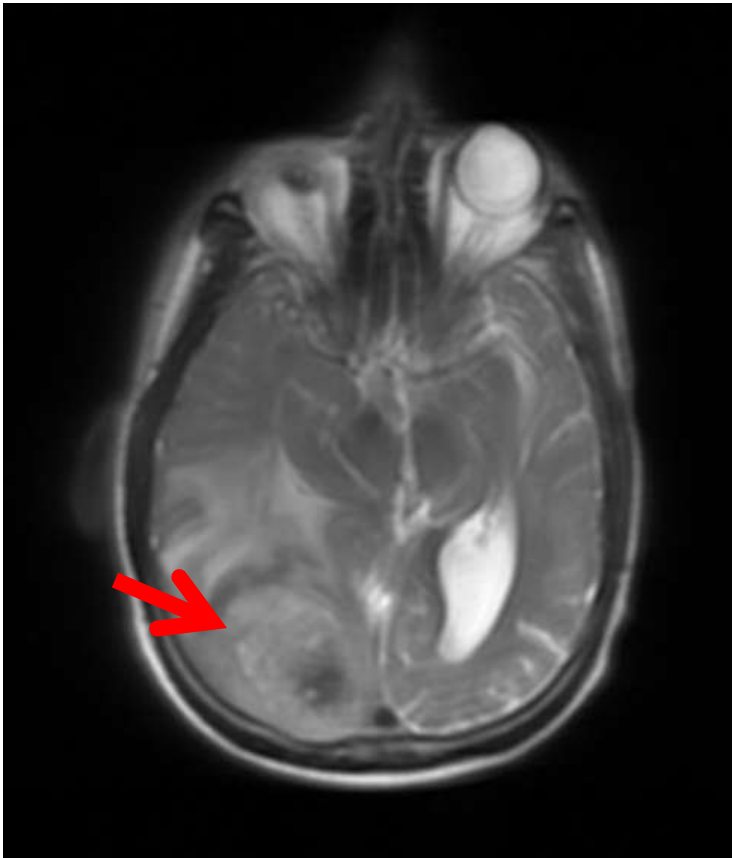




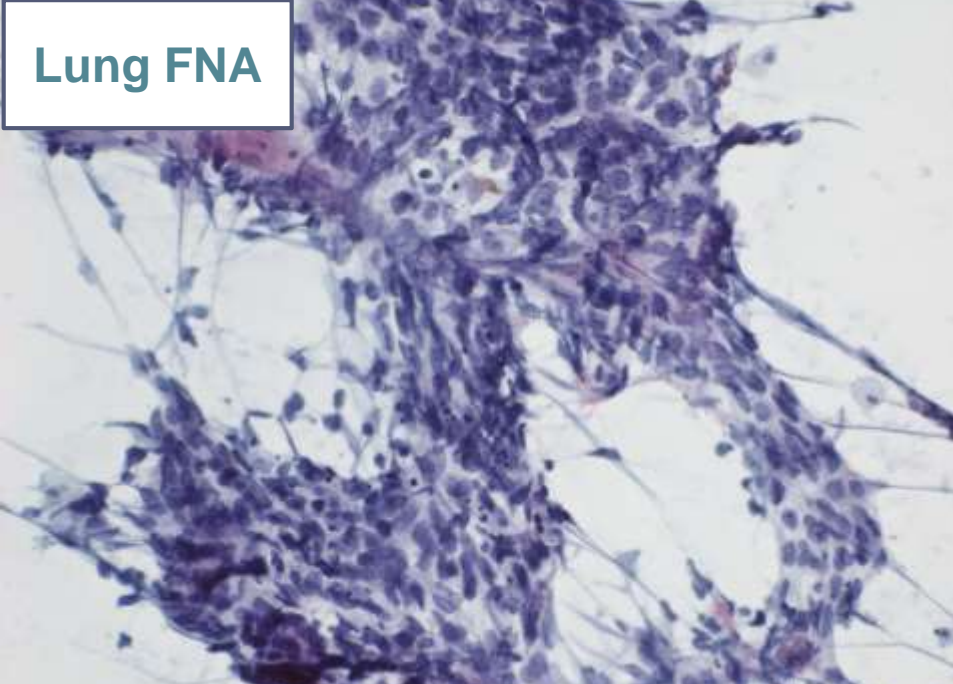
# Clinical history

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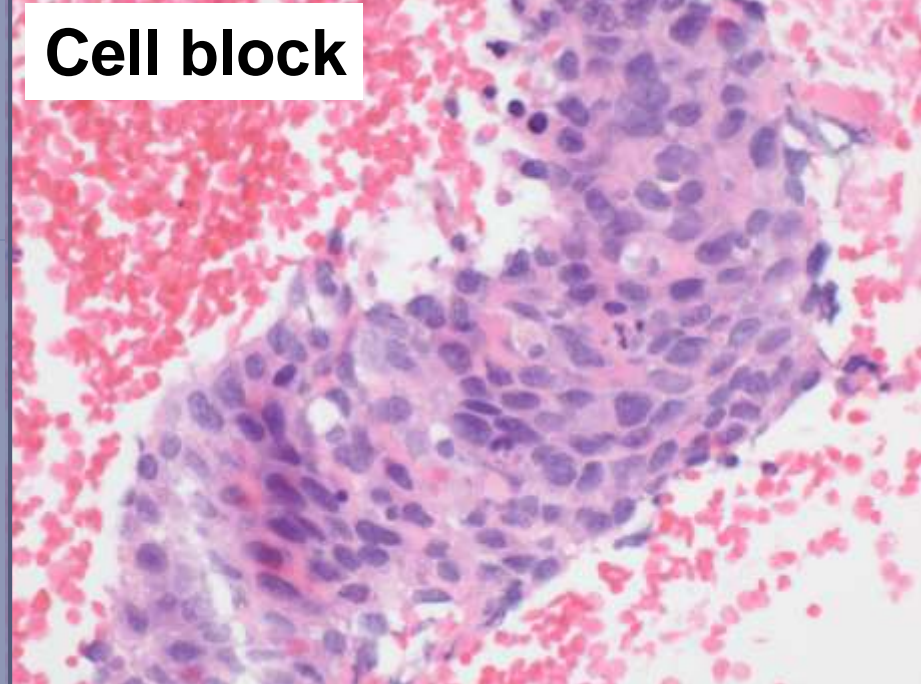
- ▶ 59-year-old man presented with headache and visual loss and was found to have a 5 cm parieto-occipital mass and numerous masses (~10 cm) in bilateral lungs on imaging.



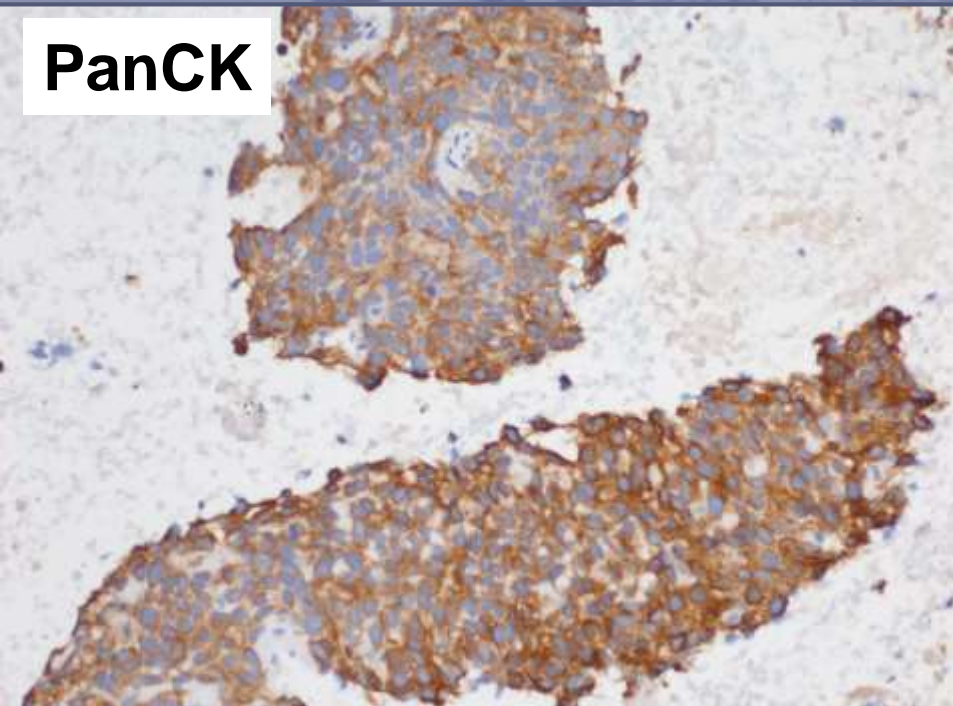
**Lung FNA**



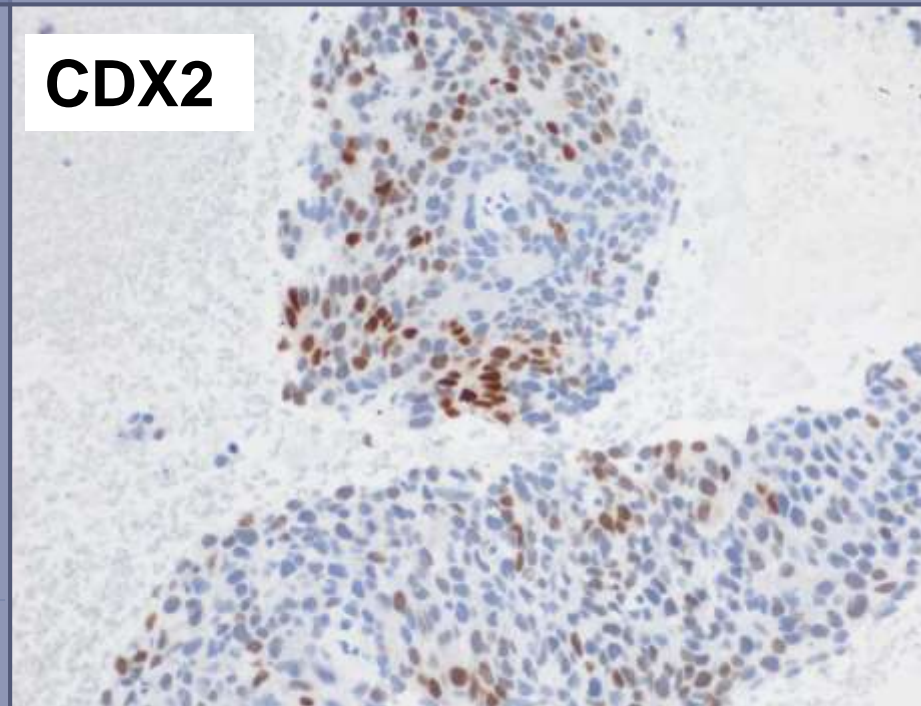
**Cell block**



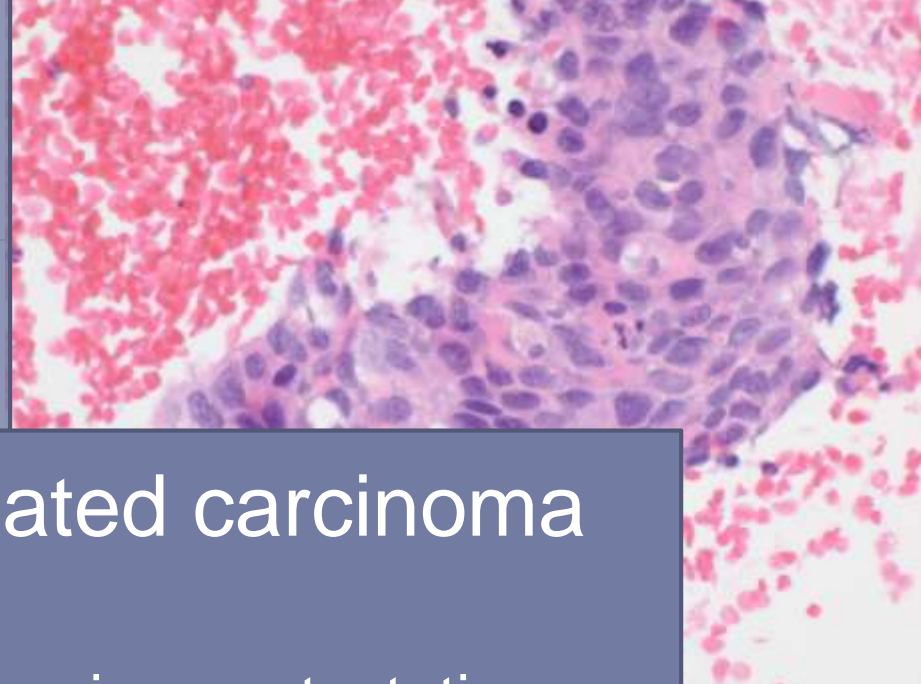
**PanCK**



**CDX2**

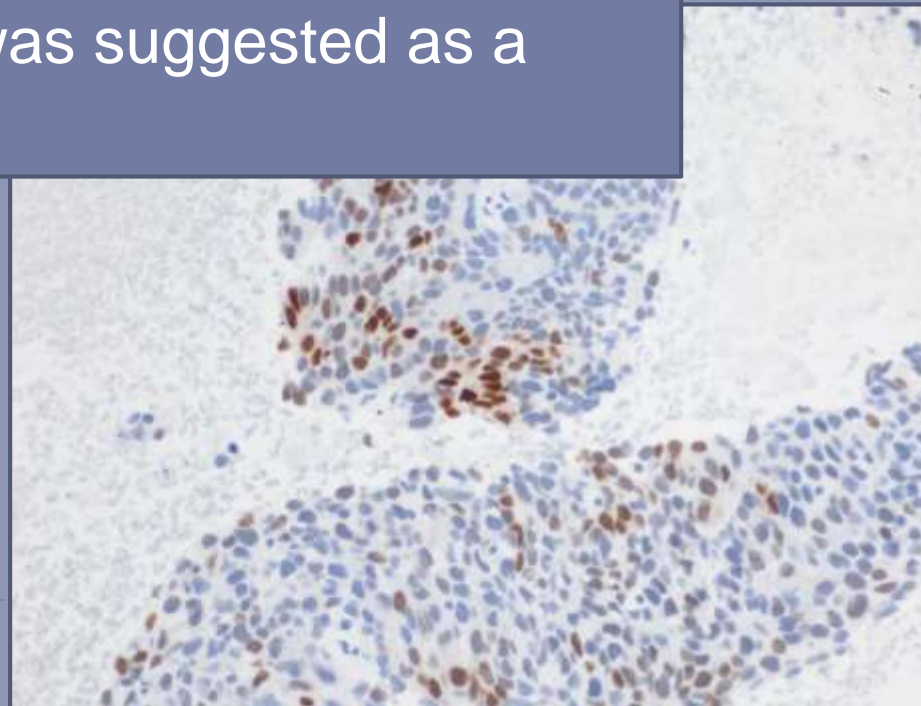
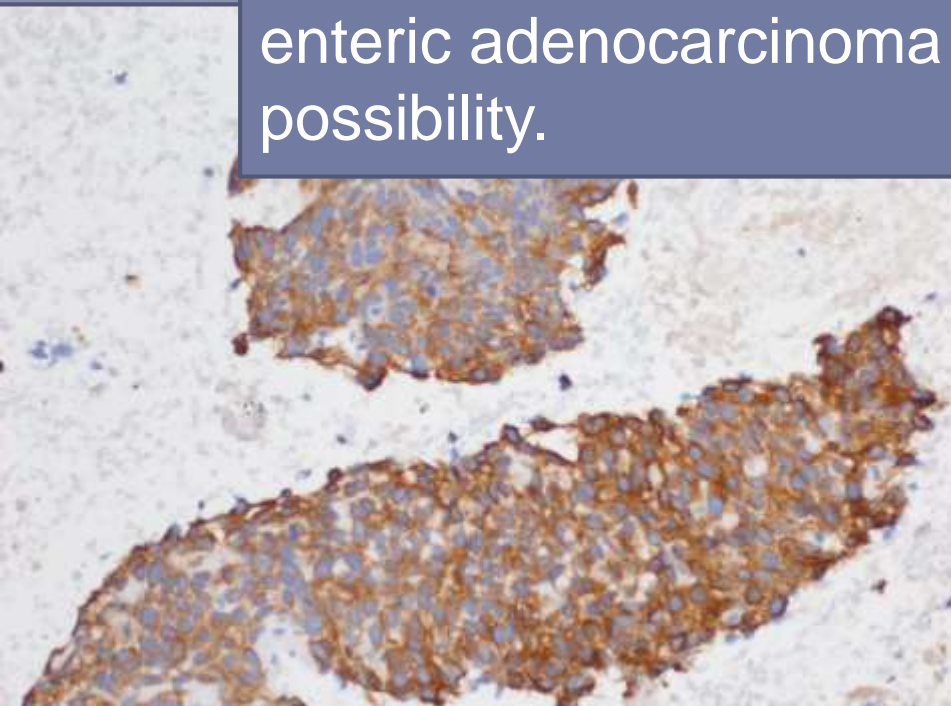






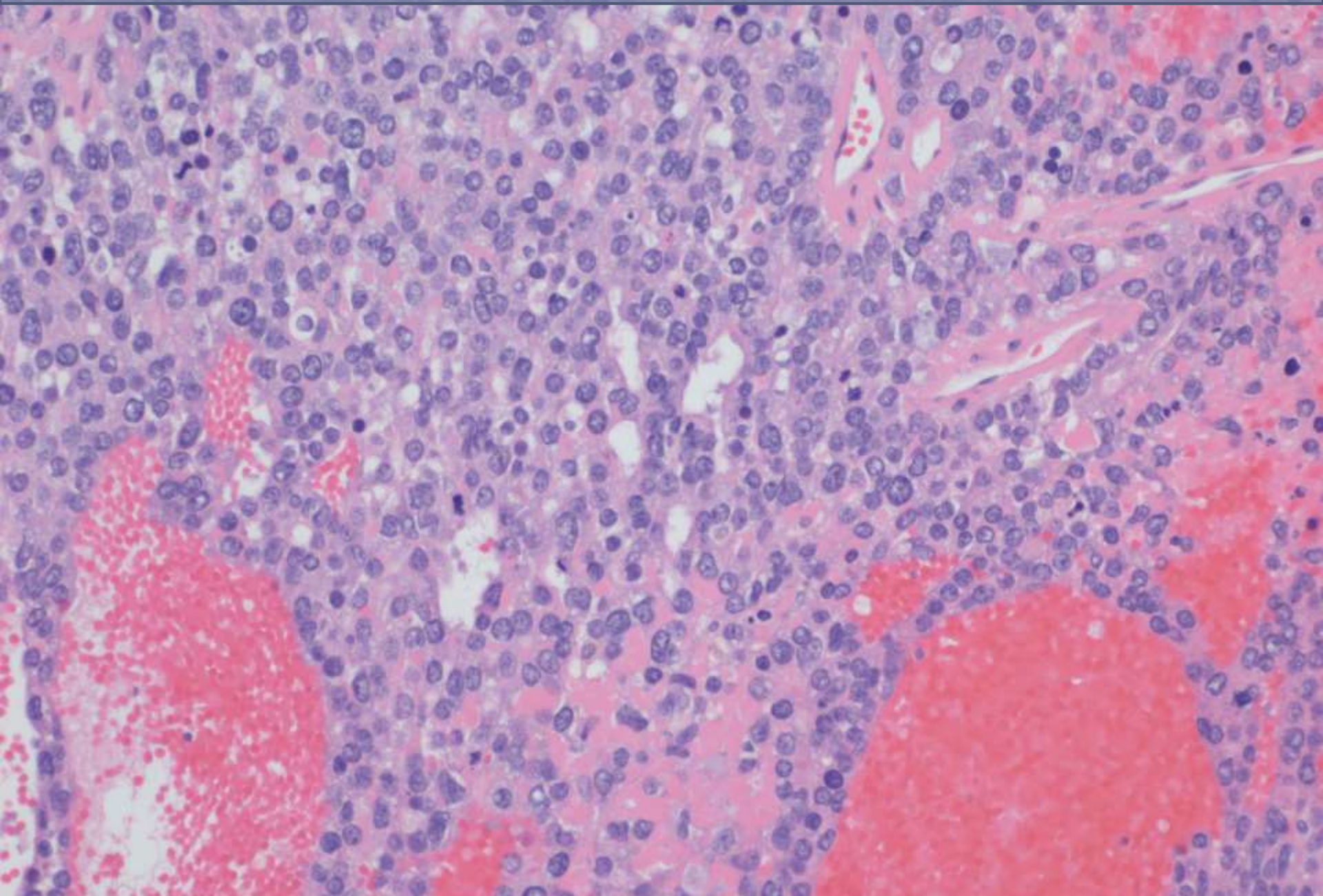
Dx: Poorly differentiated carcinoma

-Based on the CDX2 expression, metastatic enteric adenocarcinoma was suggested as a possibility.





# Brain—tumor resection





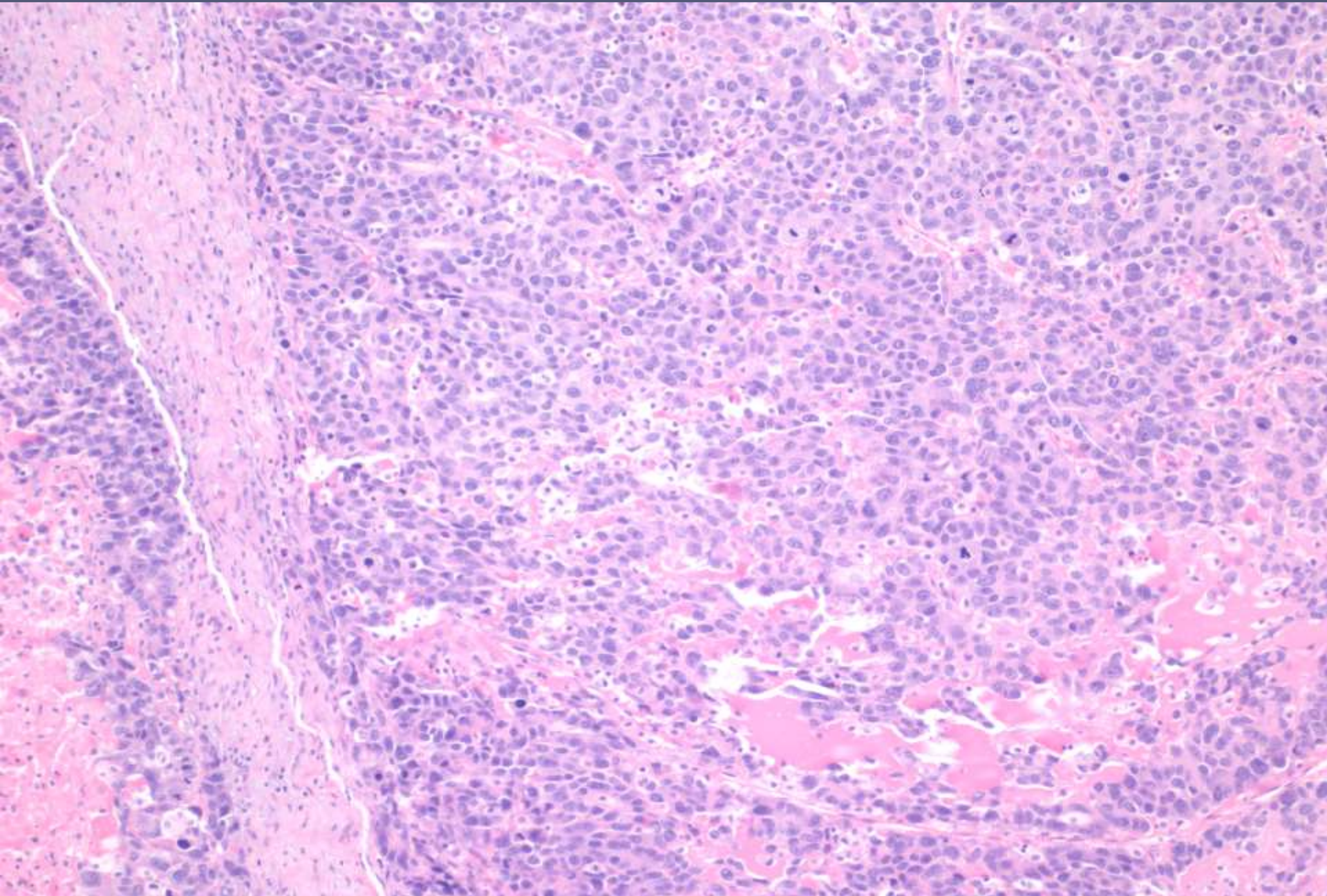
# Interval clinical history

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- ▶ On a detailed examination, the patient was found to have a left testicular mass. He underwent an orchiectomy.

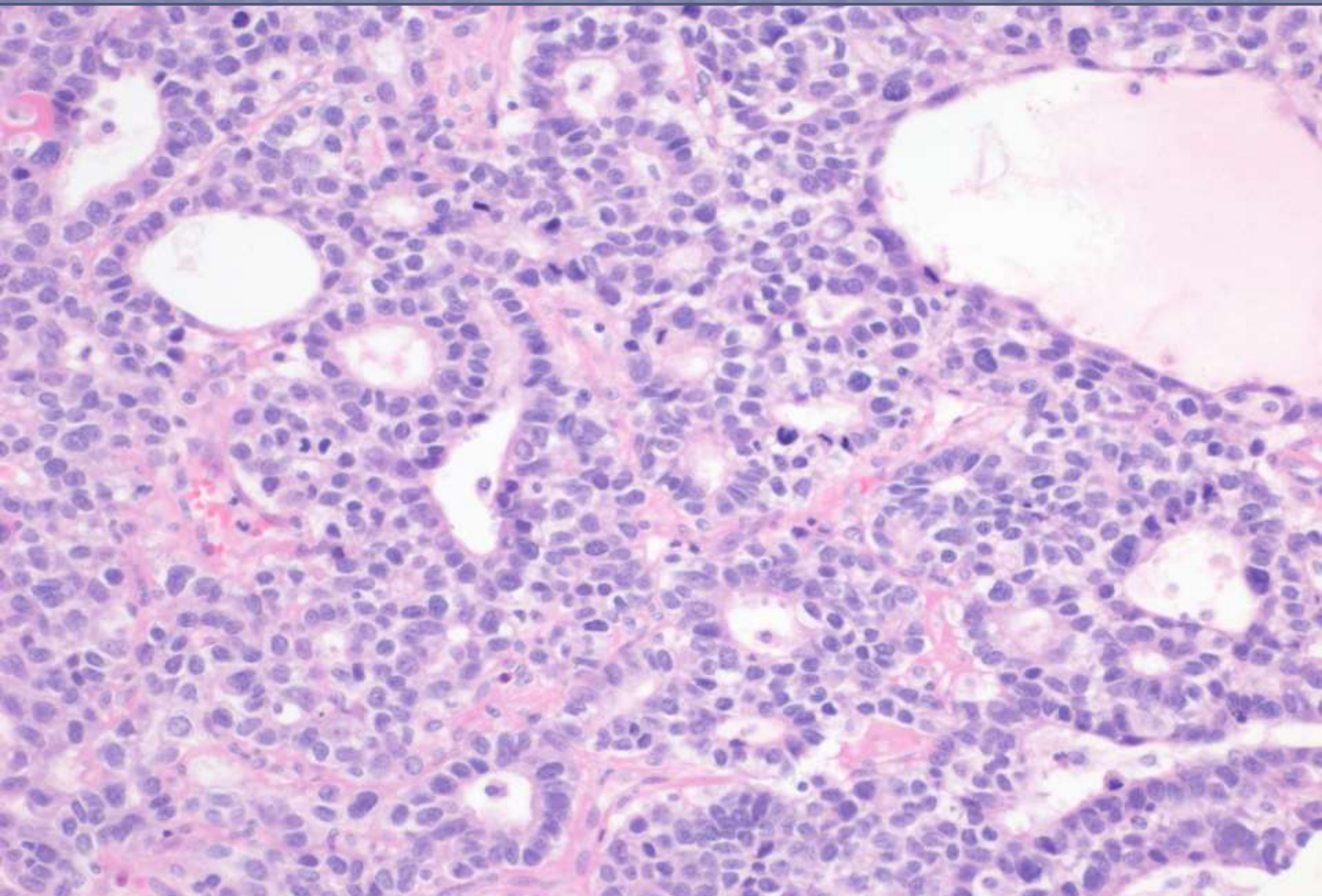


# Testis: Tumor



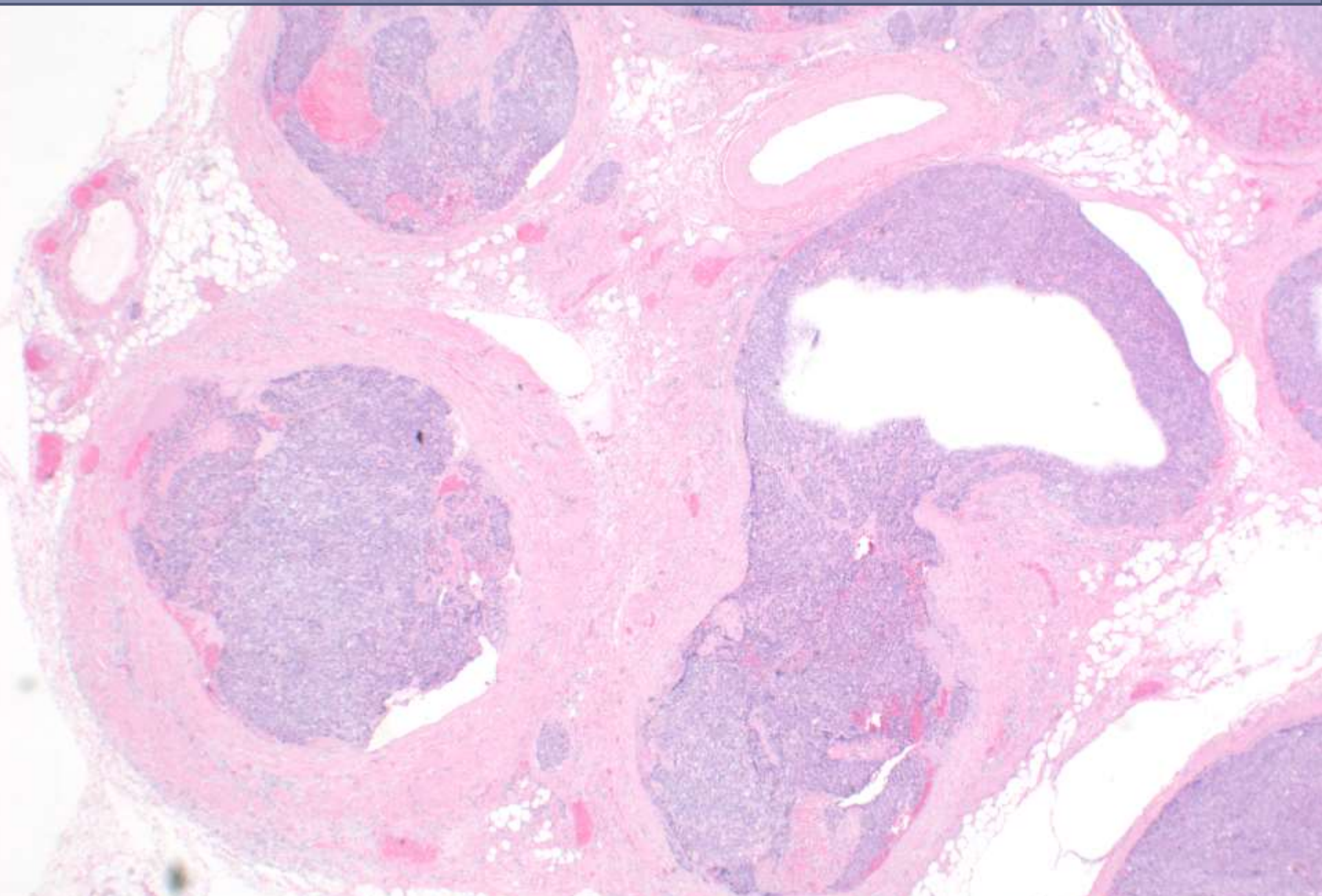


## Testis: Tumor (glandular differentiation)





# Spermatic cord: Intravascular tumor growth





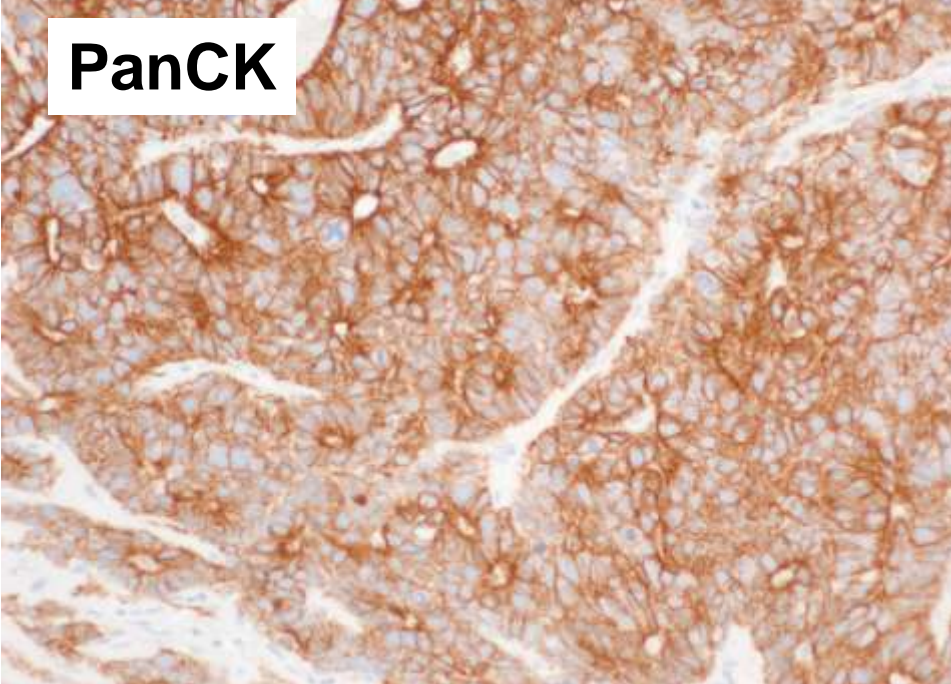
# DDX: Testis mass

---

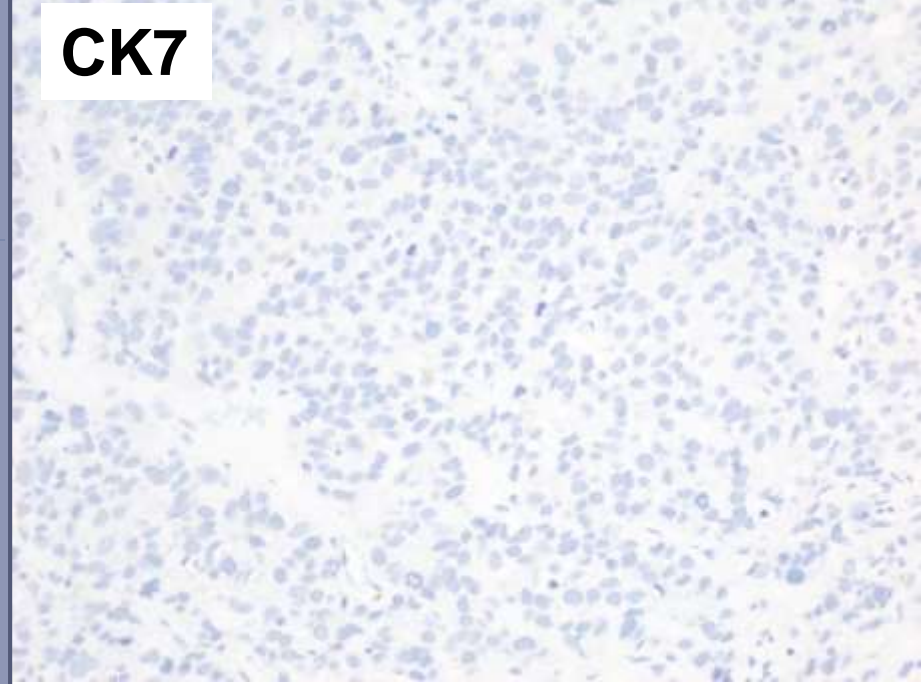
- ▶ Metastatic adenocarcinoma
- ▶ Germ cell tumor
- ▶ Adenocarcinoma arising in the epididymis or rete testis



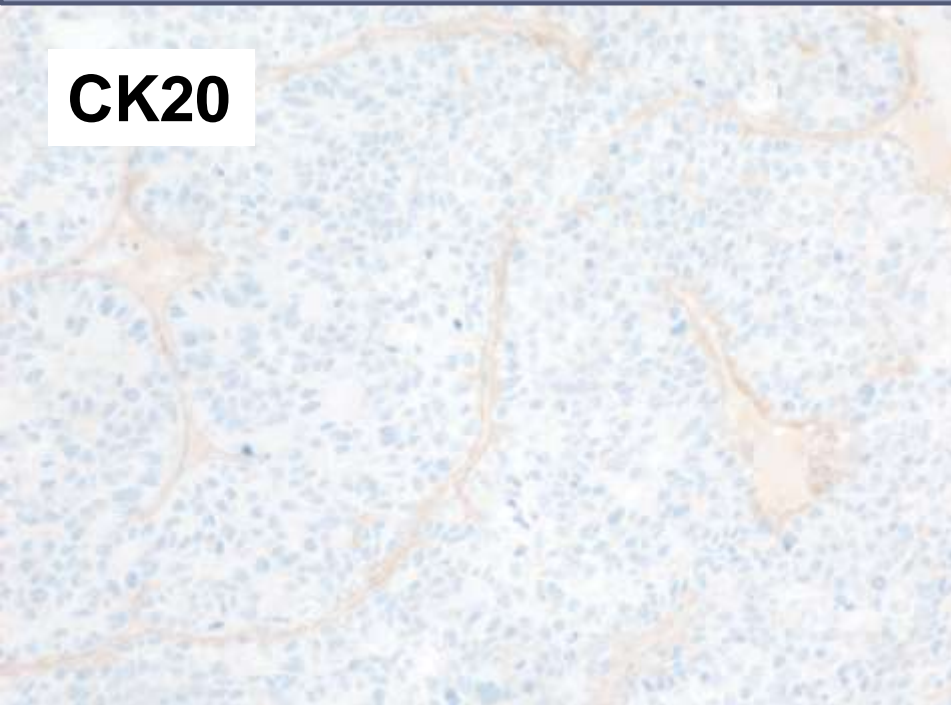
**PanCK**



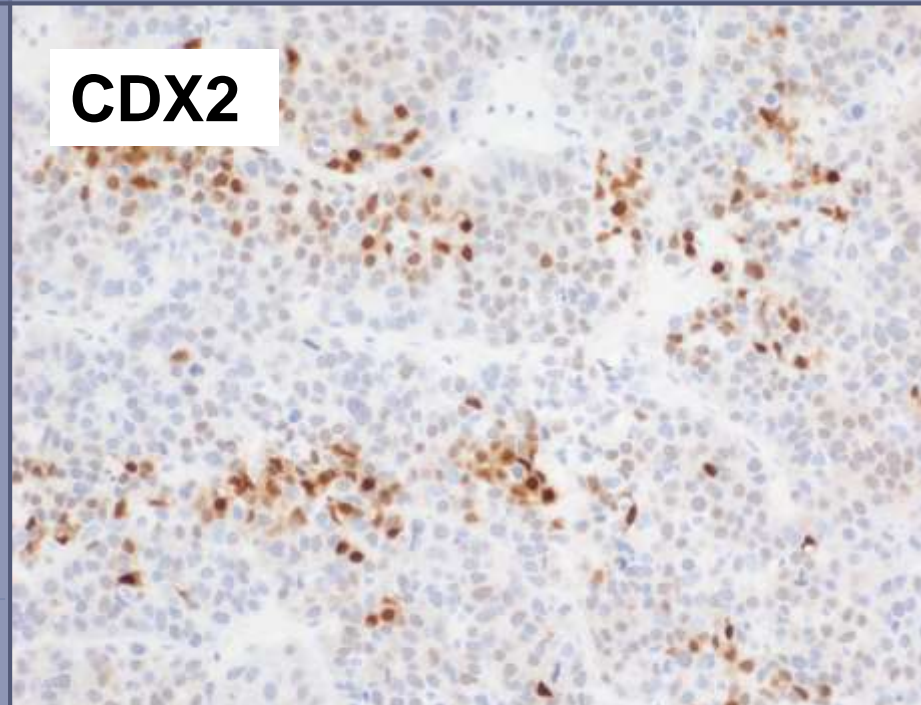
**CK7**



**CK20**



**CDX2**





## **Malignant germ cell tumours in the elderly: a histopathological review of 50 cases in men aged 60 years or over**

Daniel M Berney<sup>1</sup>, Anne Y Warren<sup>2</sup>, Monika Verma<sup>1</sup>, Sak Kudahetti<sup>1</sup>, Jane M Robson<sup>3</sup>,  
Michael W Williams<sup>3</sup>, David E Neal<sup>4</sup>, Thomas Powles<sup>5</sup>, J Shamash<sup>5</sup> and  
R Timothy D Oliver<sup>5</sup>

- ▶ Seminomas were most common, at 82%.
- ▶ Only 18% of the 50 cases were nonseminomatous GCT.
- ▶ Compared to GCT in younger men,
  - ▶ Tumor size was significantly larger
  - ▶ Patients presented at a higher stage
  - ▶ There was frequent vascular and rete testis invasion
  - ▶ Tumors were less associated with ITGN (Germ cell neoplasia in situ)

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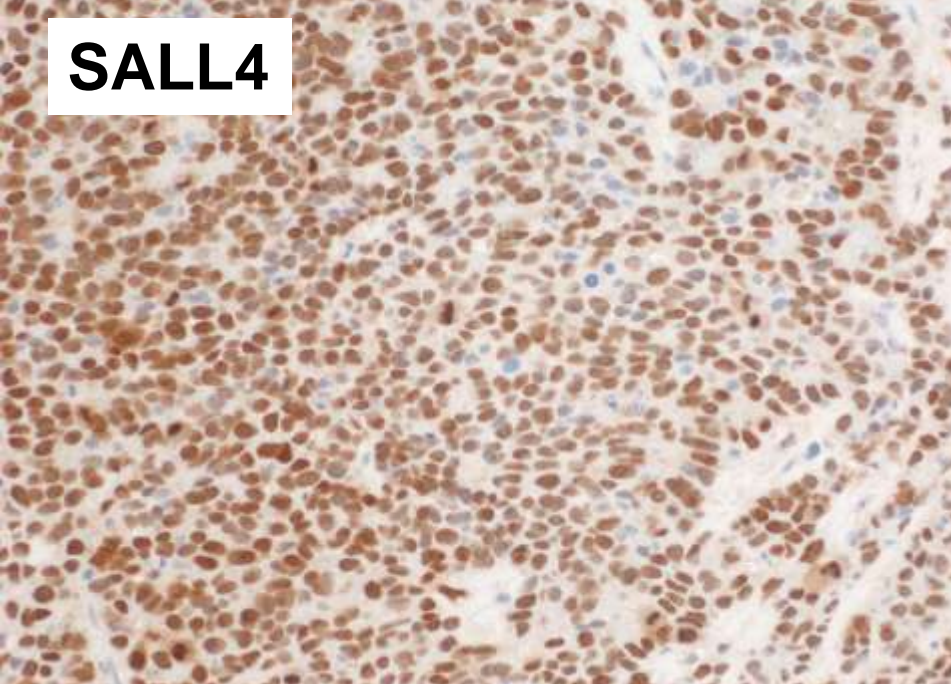
## DDX: Germ cell tumors

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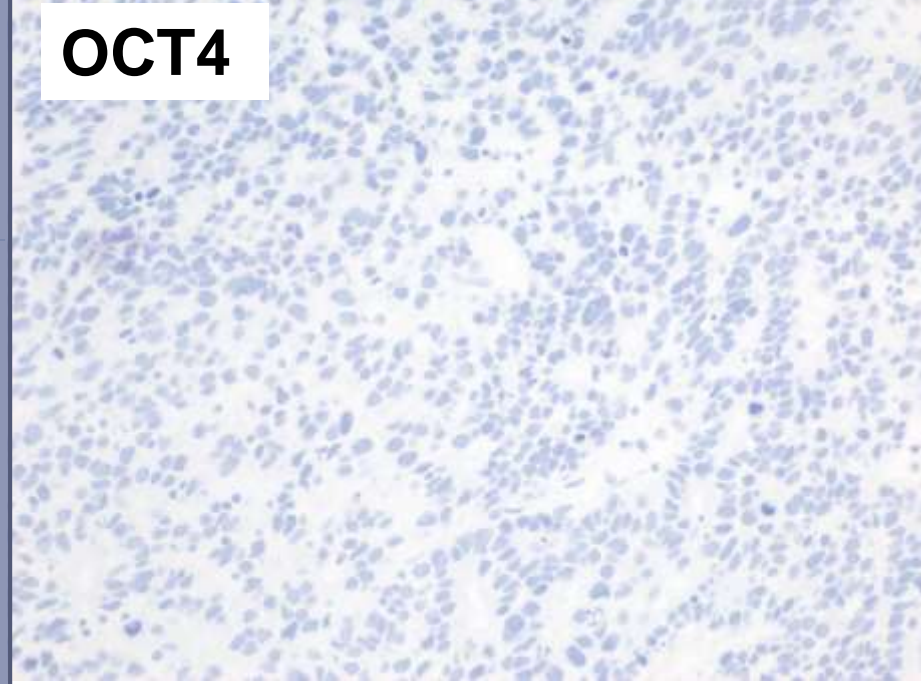
- ▶ Seminoma → unlikely given the keratin+
- ▶ Embryonal carcinoma → unlikely given the CDX2+
- ▶ Yolk sac tumor → possible, as YST are keratin+ and CDX2+



**SALL4**



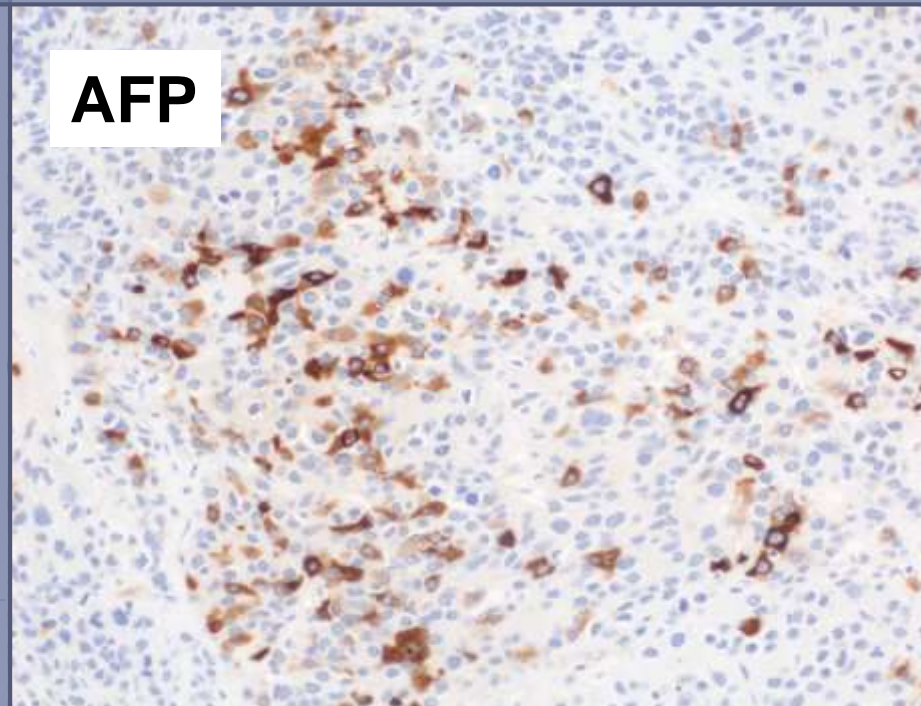
**OCT4**



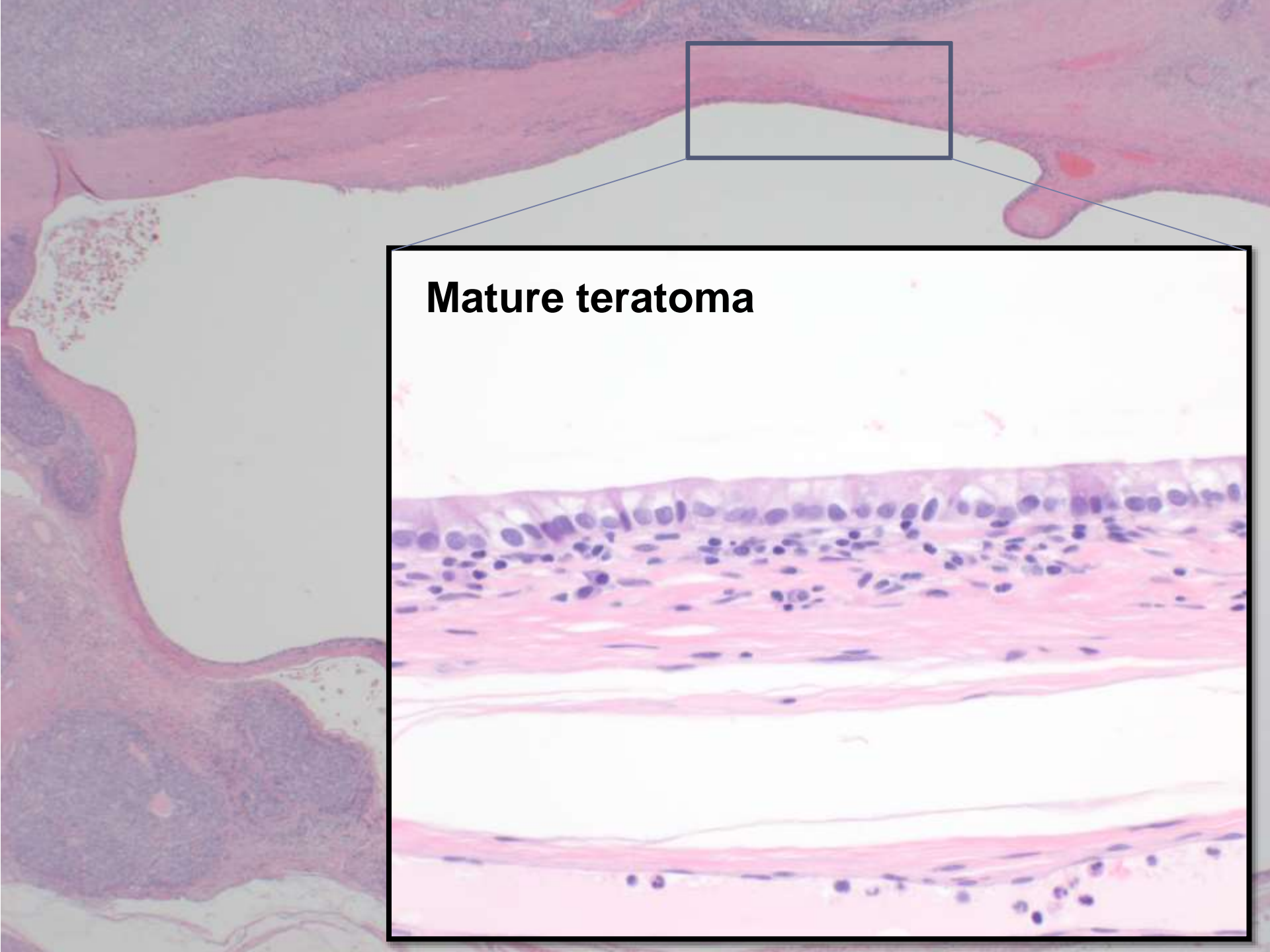
**Glypican-3**



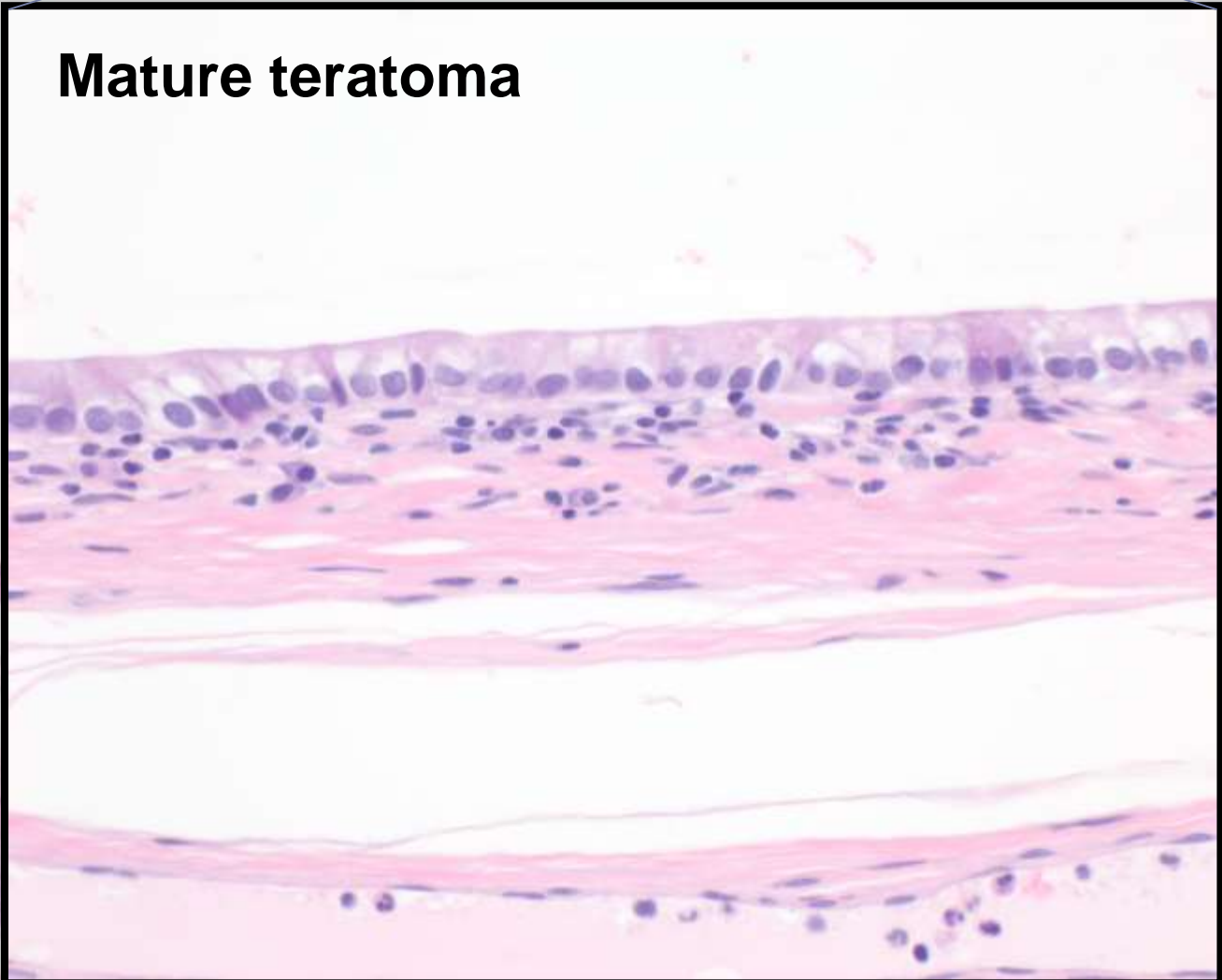
**AFP**







**Mature teratoma**



# Final Diagnosis

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## Malignant mixed germ cell tumor

-99% poorly differentiated glandular variant of yolk sac tumor

-1% teratoma





# Take-home points

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- ▶ GCT occur in older men, and this possibility should be considered in the DDX of tumors with an unusual growth pattern.
- ▶ CDX2+ could be a clue to the diagnosis of a YST, particularly when coupled with negative staining for CK7/CK20 (CK7, CK20 and EMA are negative in YST)
- ▶ Somatic type adenocarcinomas can arise from YST, and this possibility might be considered in some cases (somatic-type are usually EMA+/glypican3-)\*.

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▶ \*Magers, Martin, et al. AJSP 38.10 (2014):1396-1409.

**Thank you**

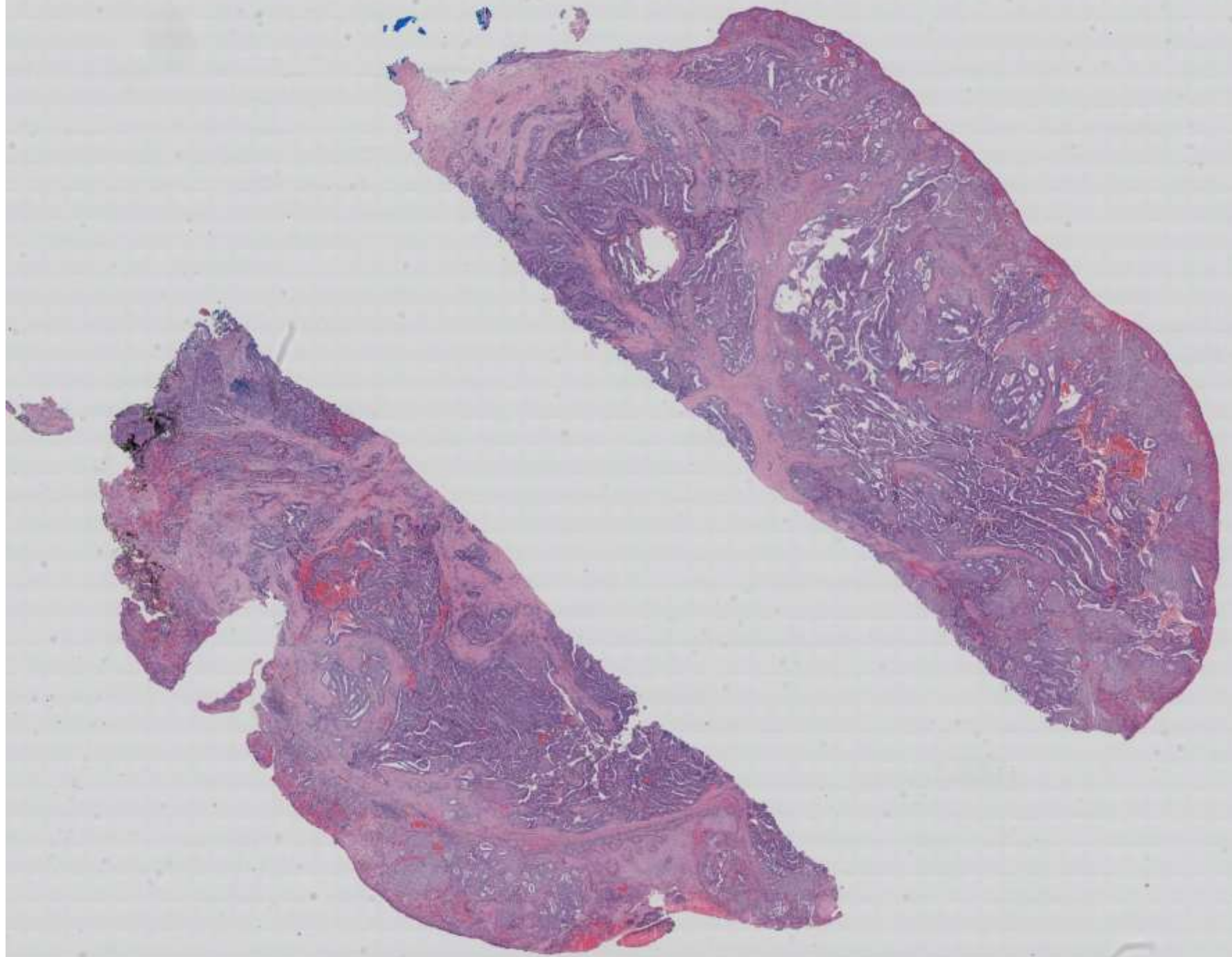




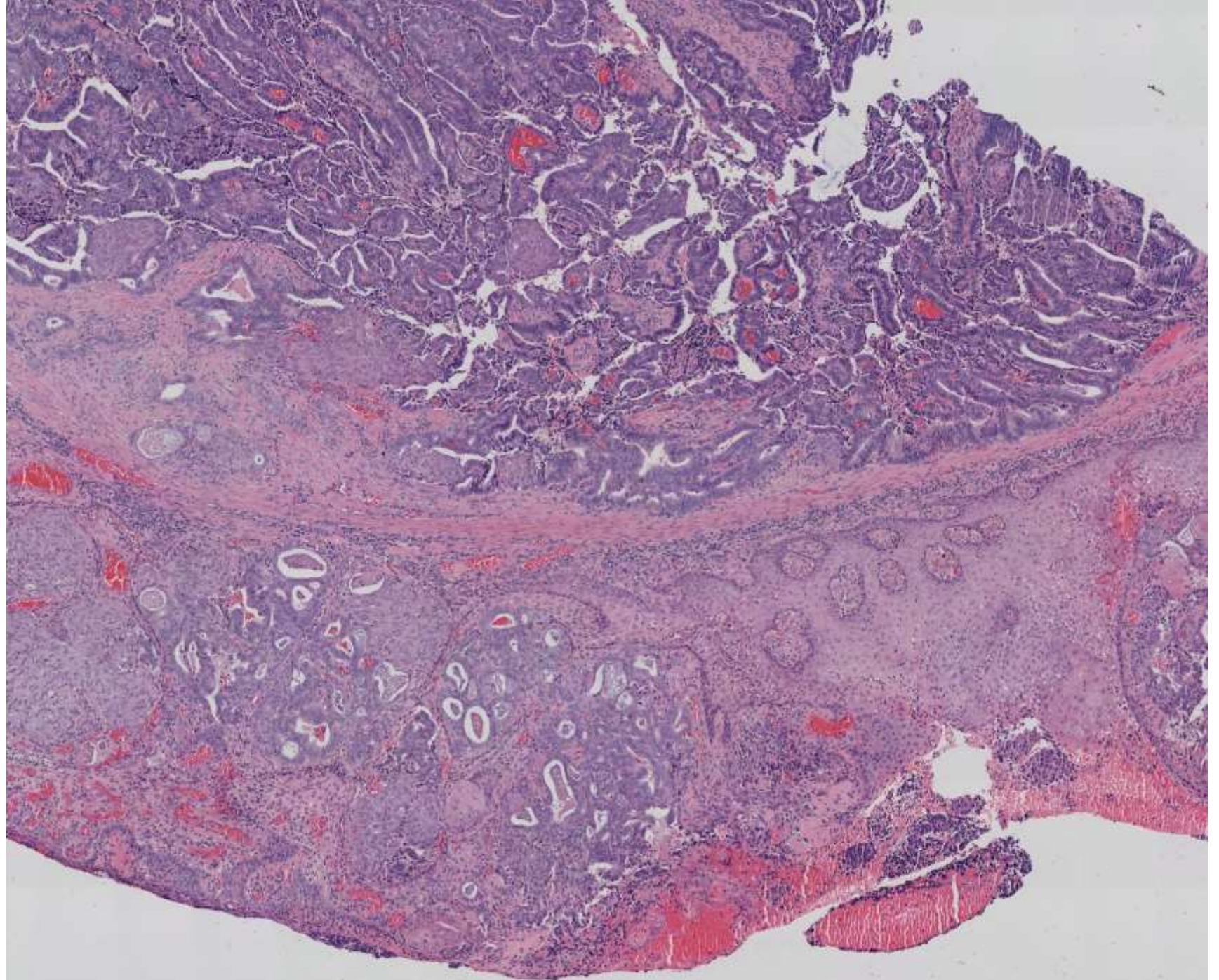
**SB 6158 (scanned slide available)**

**Emily Chan/Charles Zaloudek; UCSF**

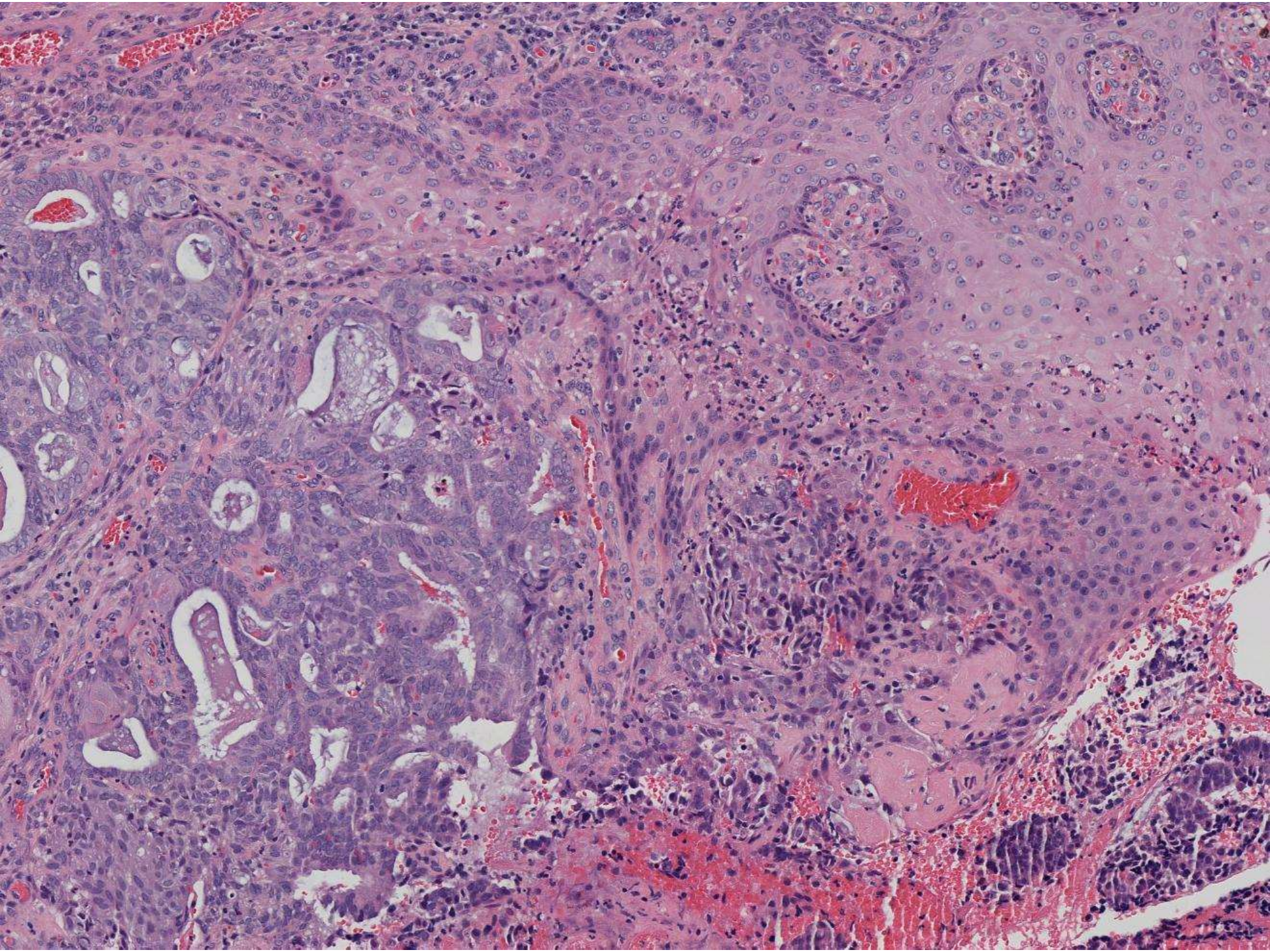
53-year-old woman who presents with  
a painful 1x1cm red glandular mass  
adjacent to clitoris.



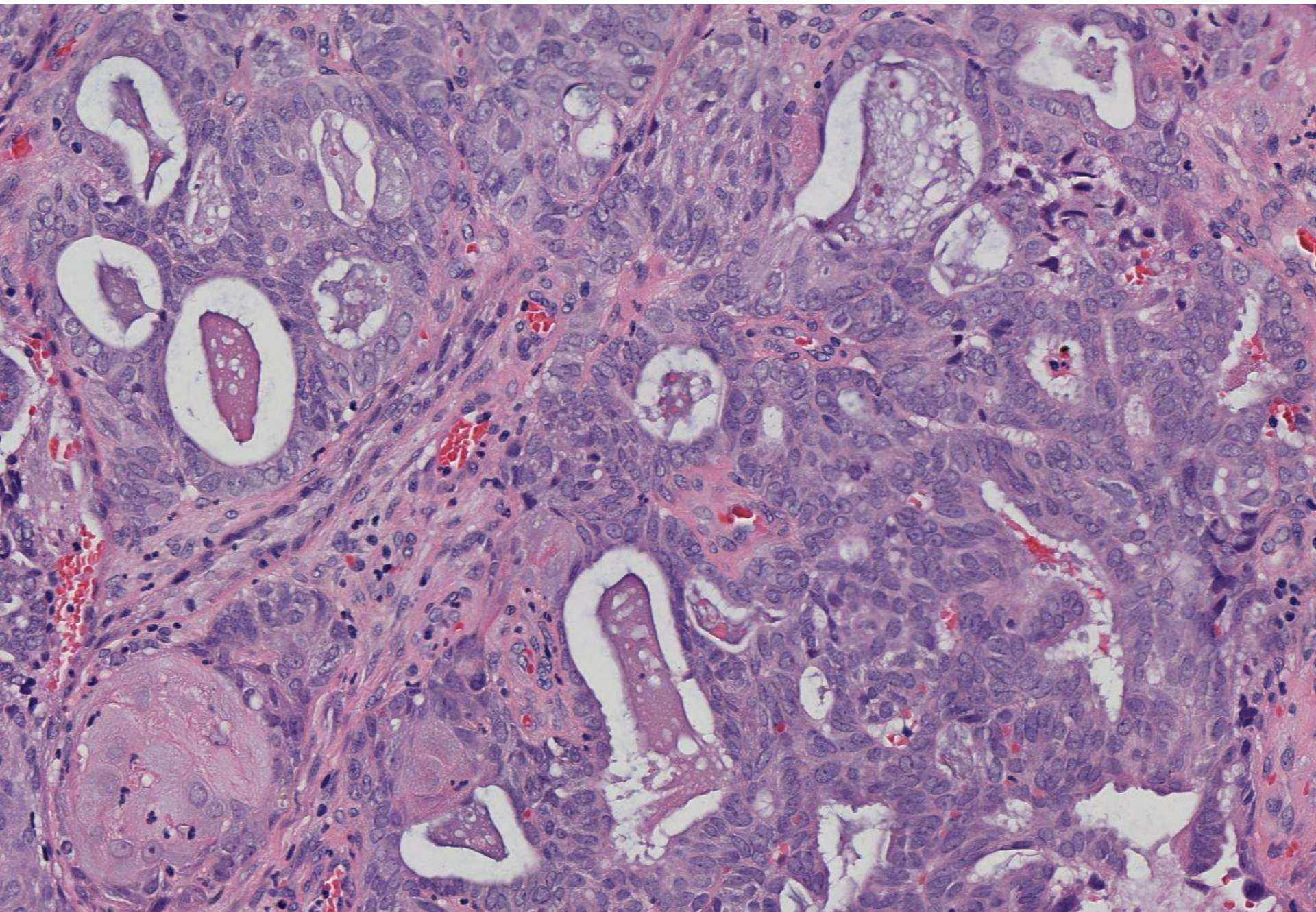




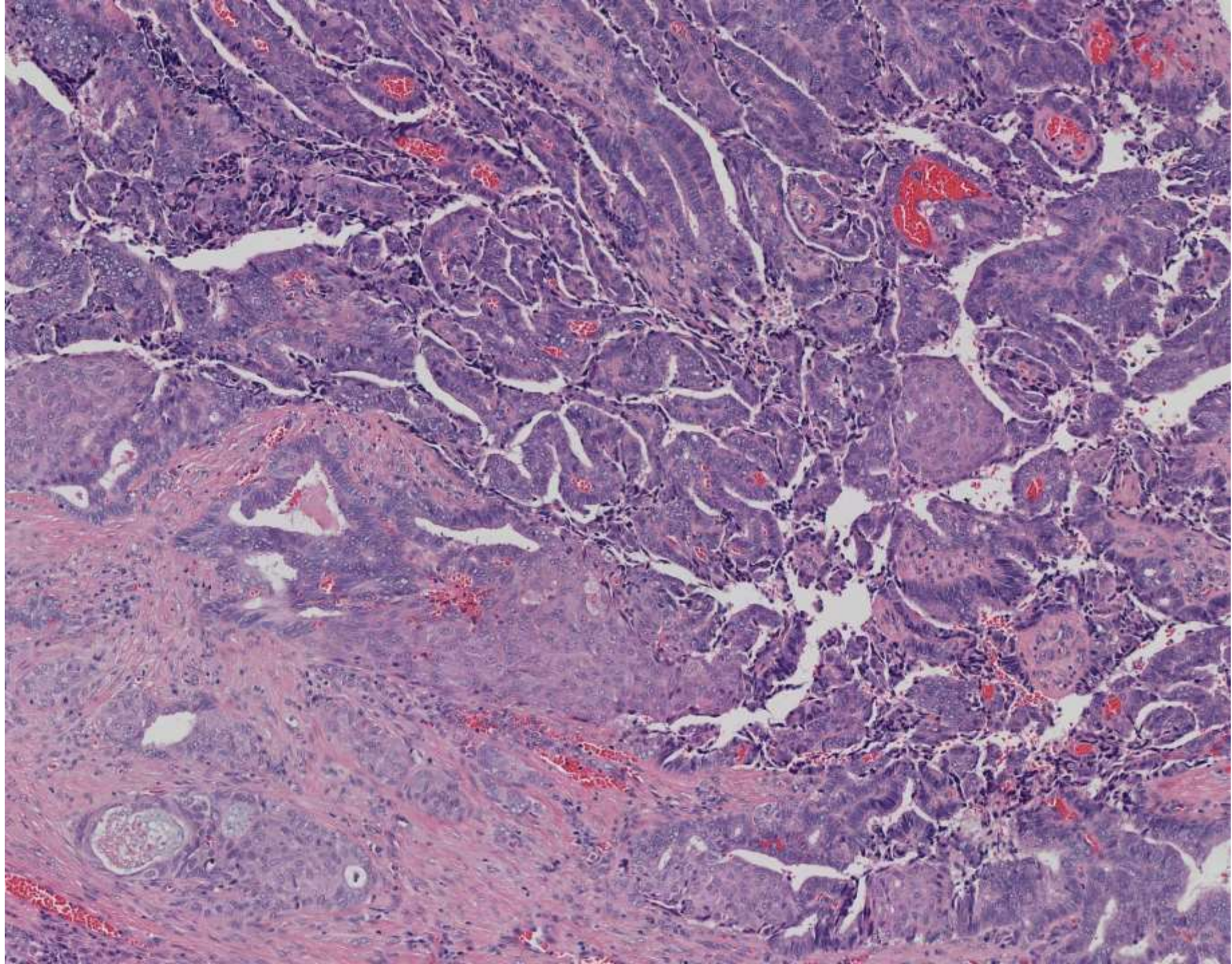




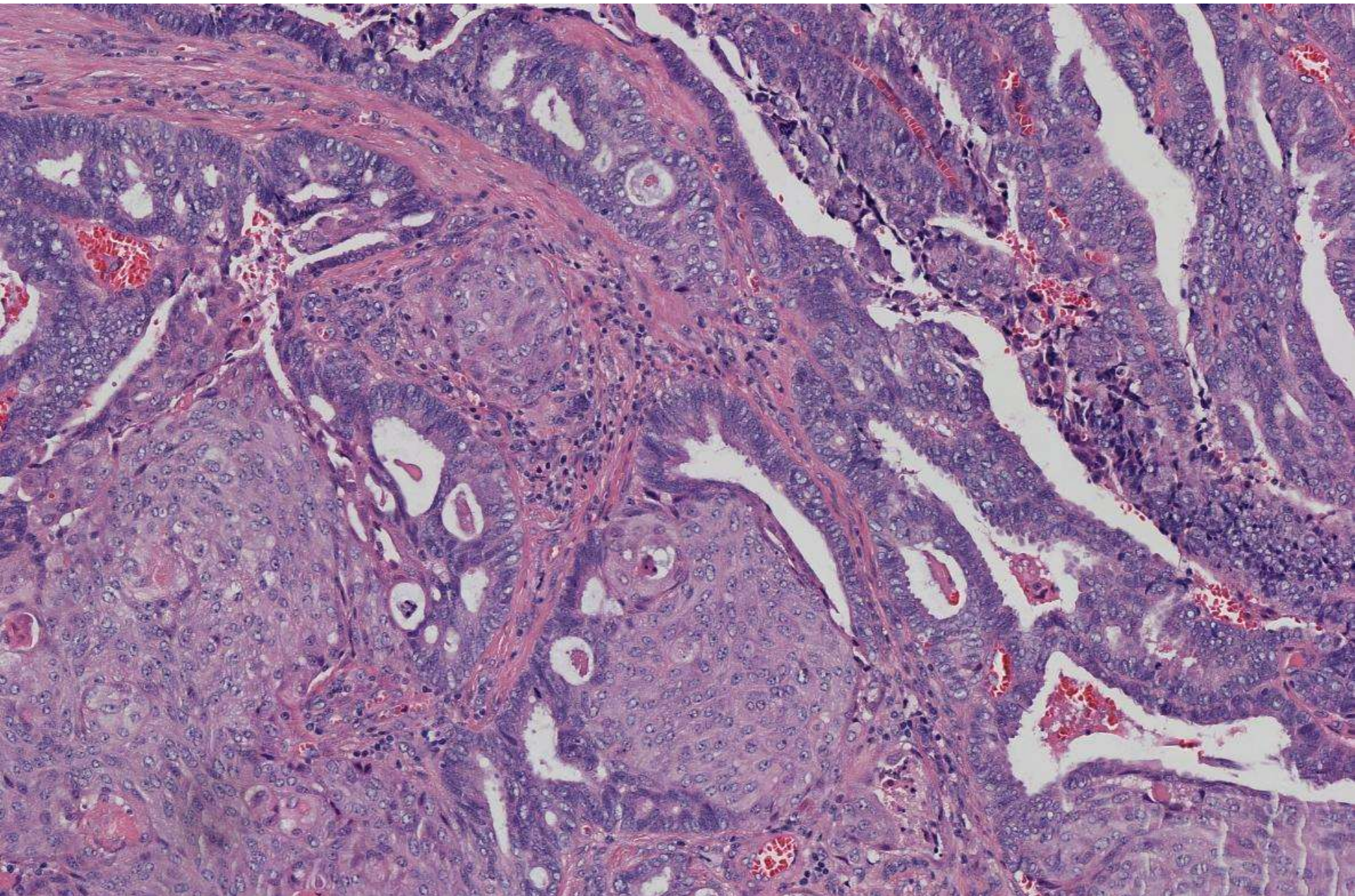




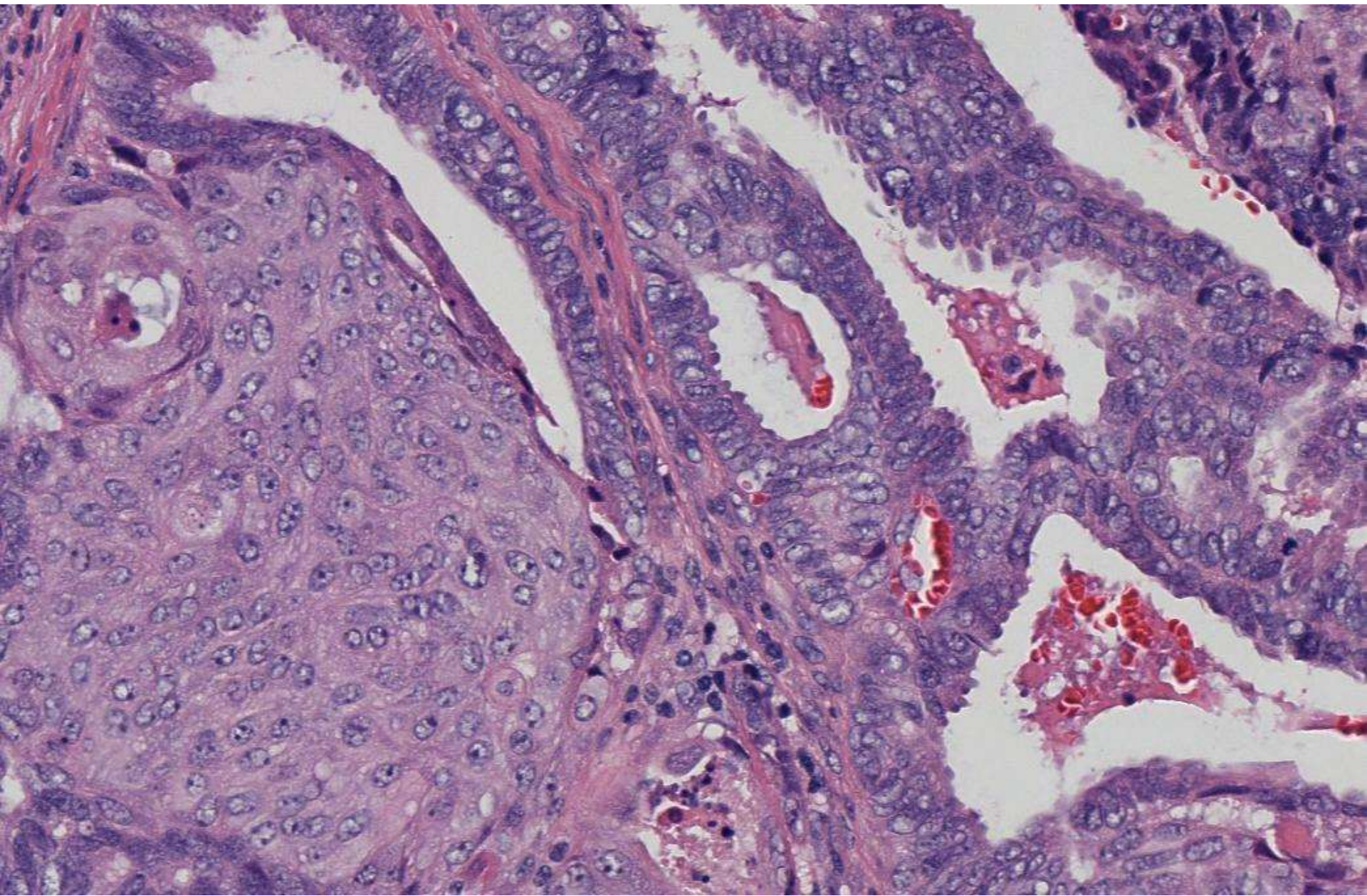




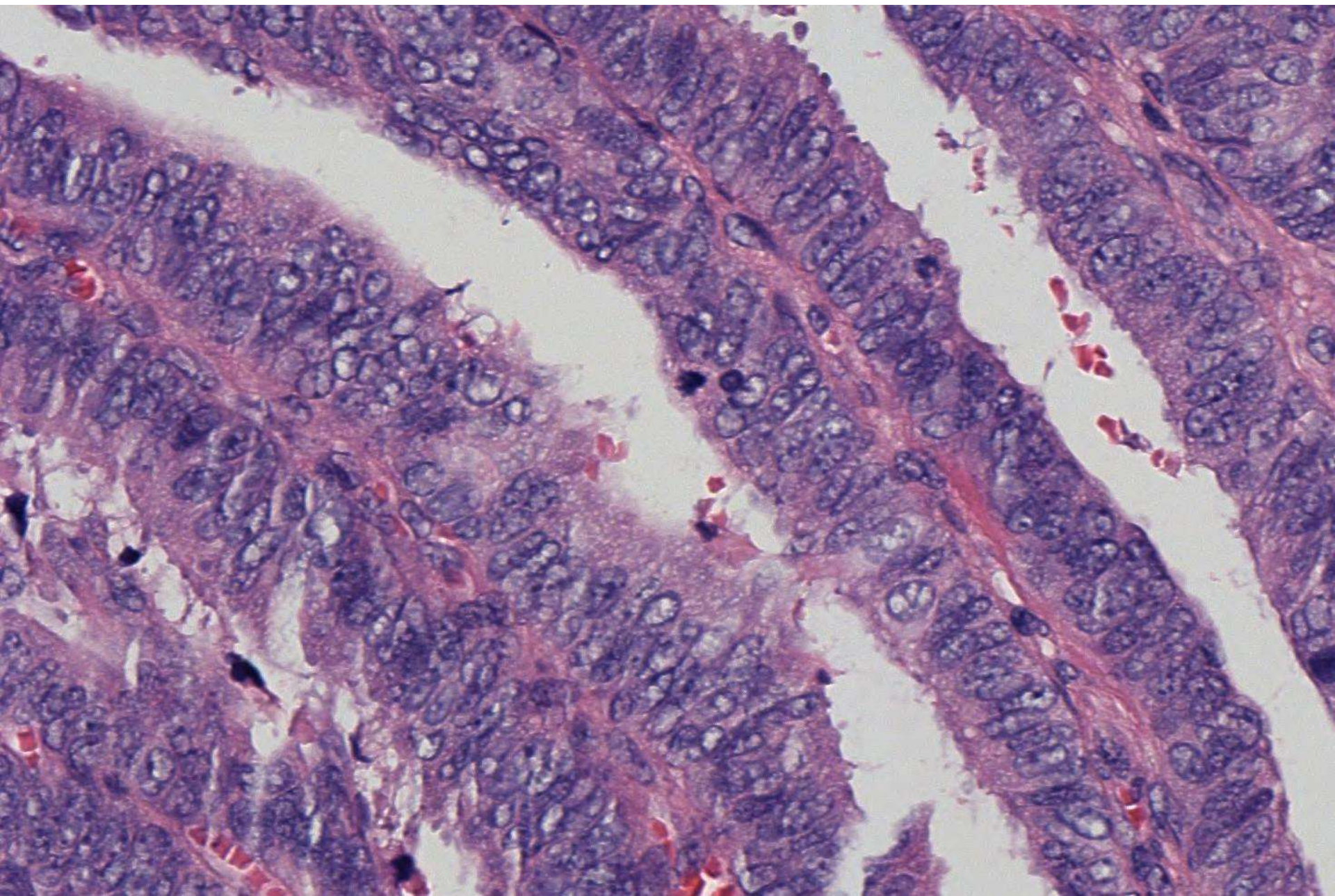












# DIAGNOSIS?





# **A 53 year-old woman who presented with a painful clitoral mass**

Southbay Meeting

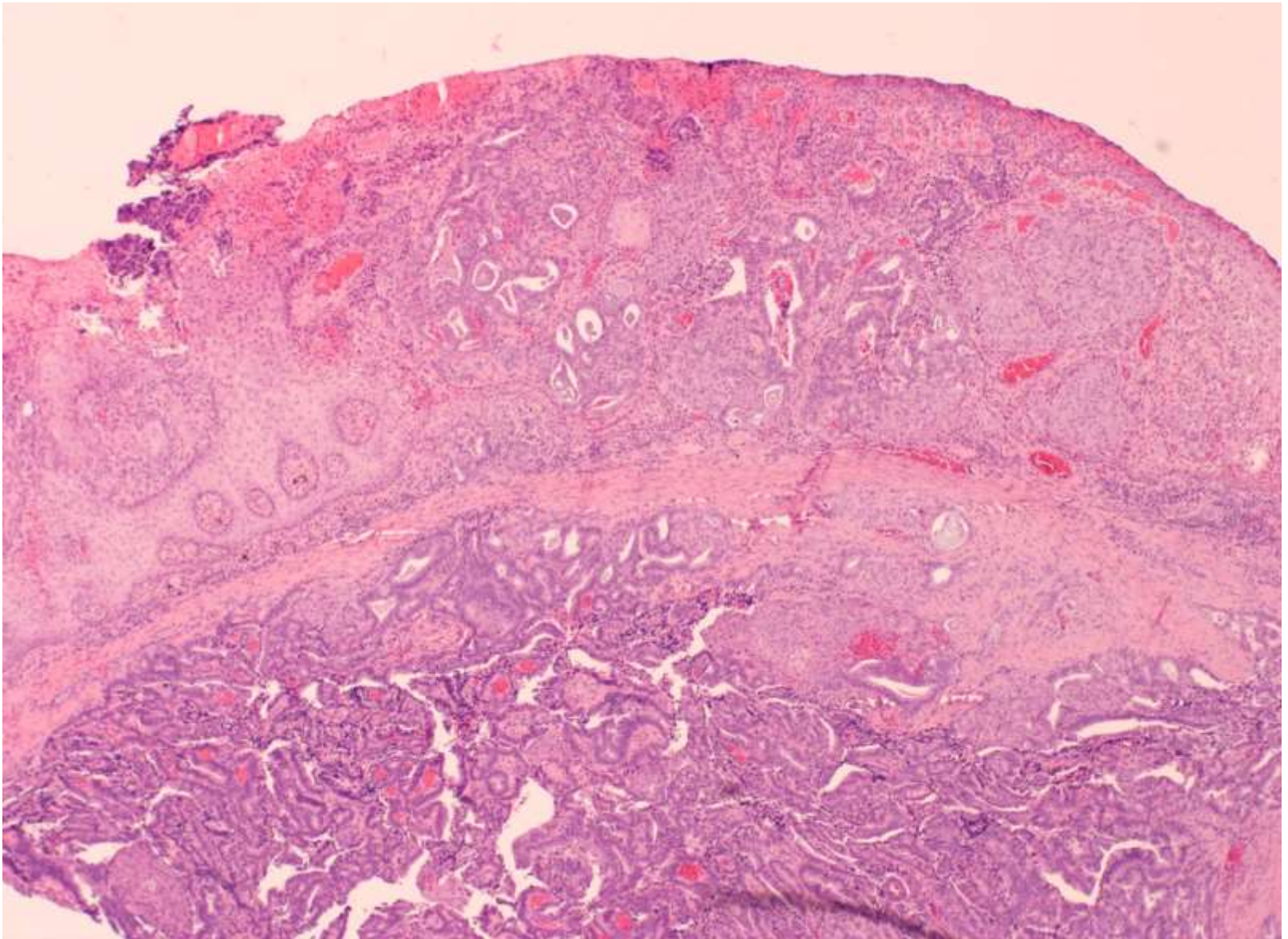
April 3, 2017

Emily Chan, PGY2

Dr. Charles Zaloudek (Faculty Sponsor)

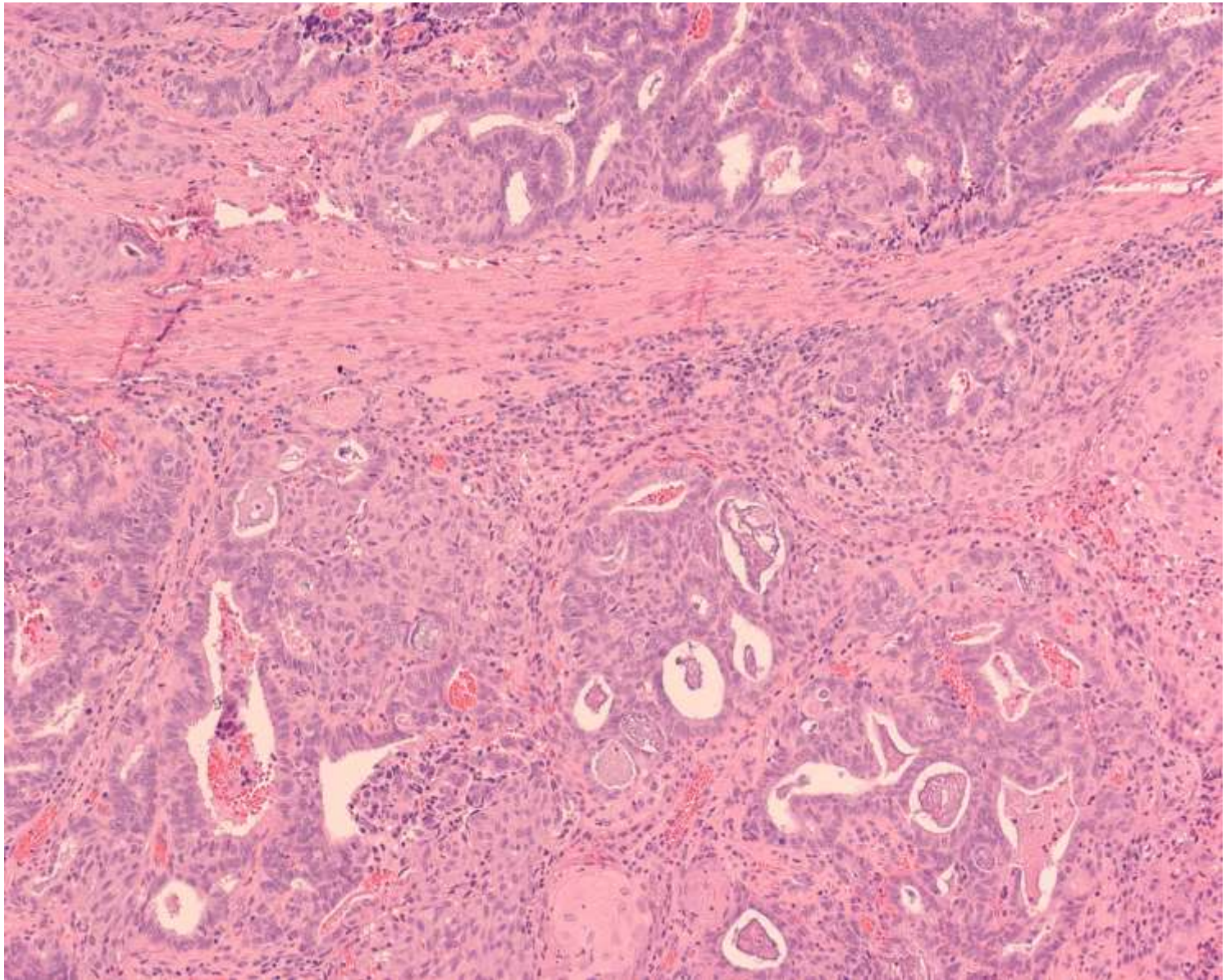
UCSF

# Histology





# Histology



# Differential diagnosis – Primary glandular vulvar lesions

- Benign:
  - Ulcerated hidradenoma papilliferum with squamous metaplasia
- Malignant:
  - Bartholin gland adenocarcinoma
  - Carcinoma of sweat gland/Skene glands
  - Mammary-like gland adenocarcinoma



# Vulvar anatomy

Labia majora

Labia minora

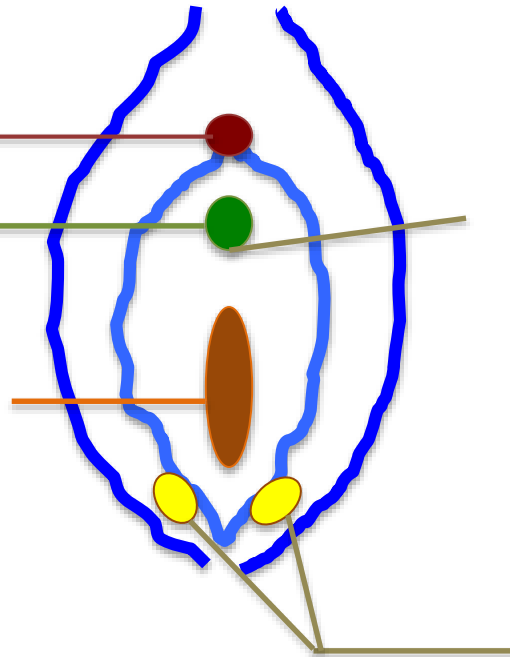
Clitoris

Urethra

Vaginal opening

Skene's glands

Bartholin glands

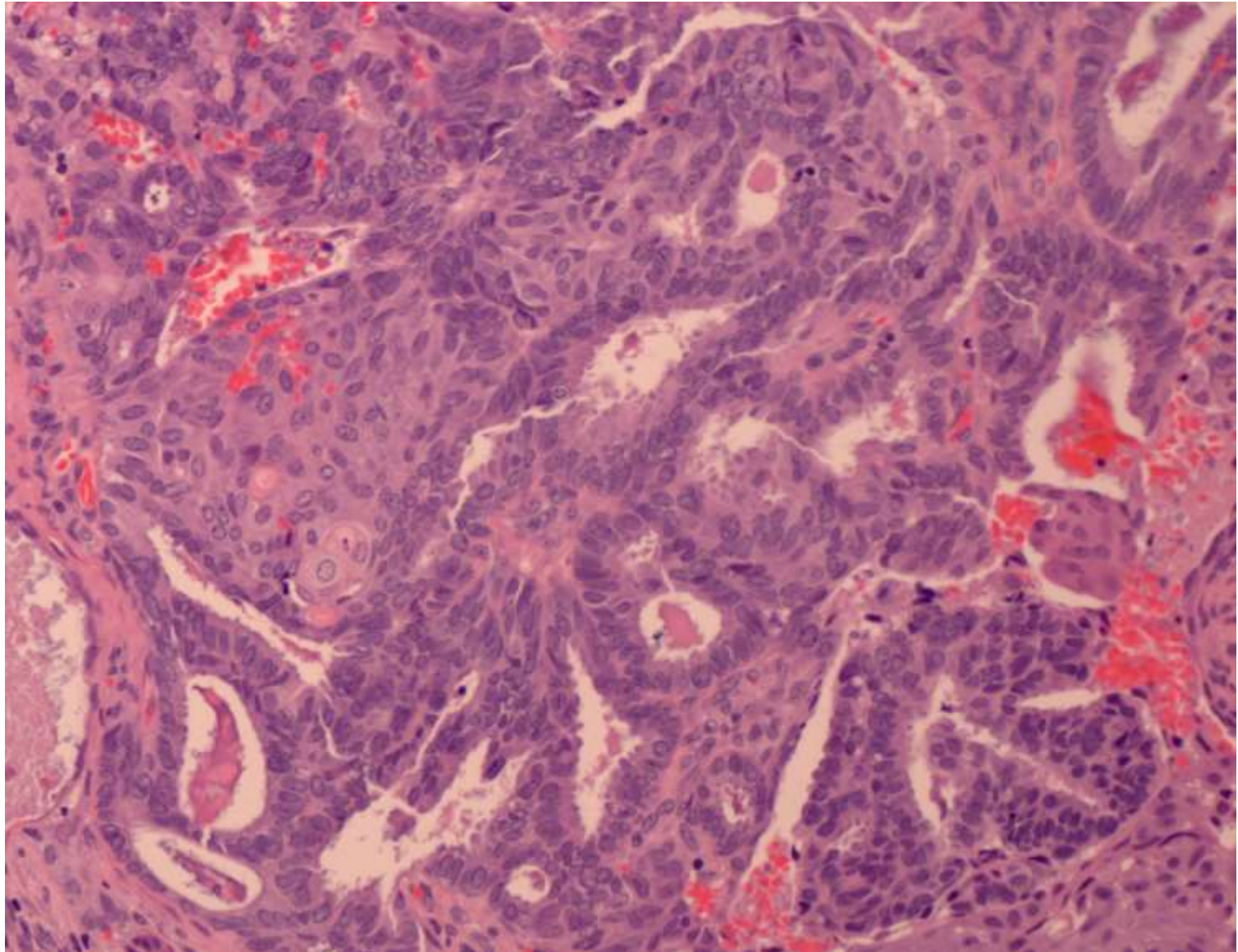


# Metastatic lesions to the vulva

GYN (31)	Total cases (percent)
Cervical (13 squamous + 2 adeno)	15 (22.7%)
Ovarian (4 serous + 1 clear cell + 3 NOS)	8 (12.1%)
Endometrial (1 CC, 1 endometrioid, 4 NOS)	6 (9%)
Vaginal	2 (3%)
NON-GYN (35)	
Gastrointestinal	12 (18.2%)
Breast	4 (6%)
Melanoma	4 (6%)
Lung	3 (4.5%)
Lymphoma	3 (4.5%)
Genitourinary	2 (3%)
Pancreatic	1 (1.5%)
Unknown	6 (9%)



# Vulvar lesion – a closer look



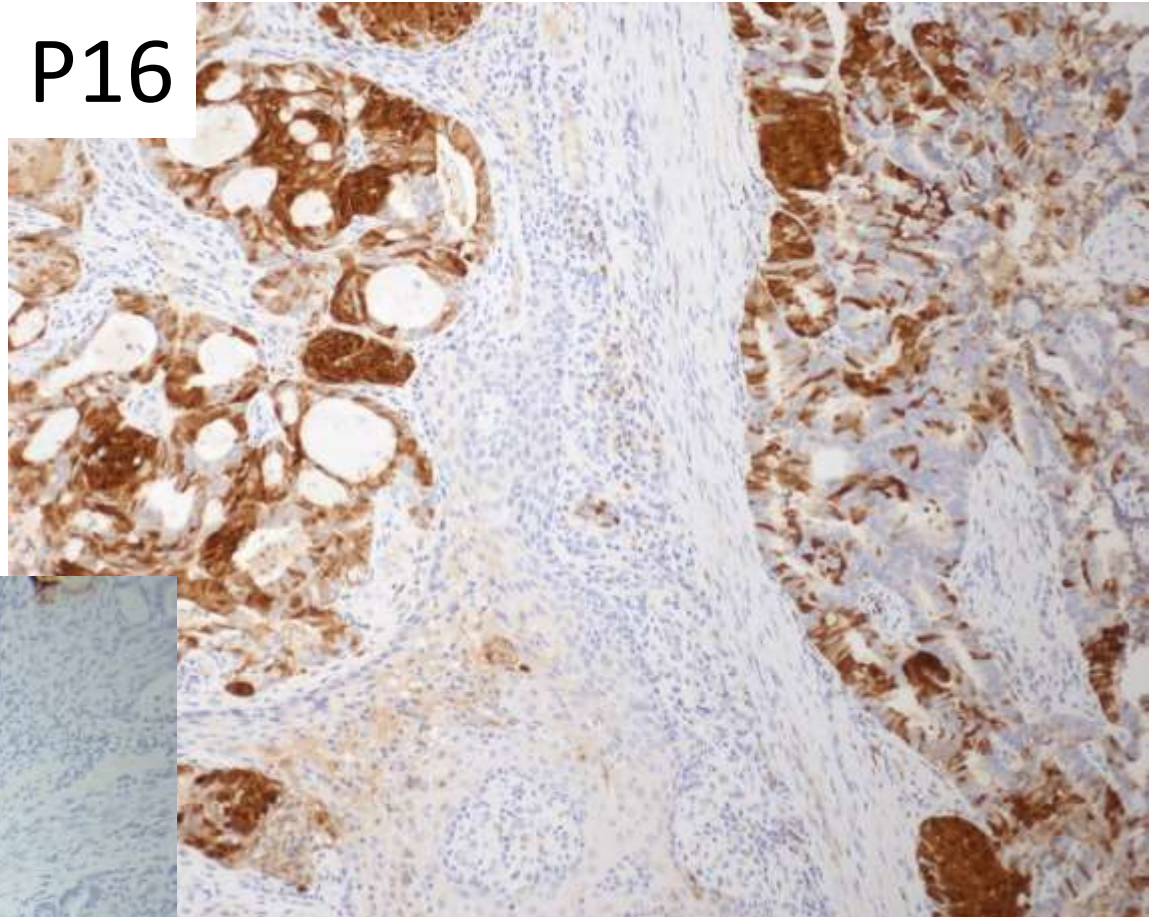
# Our top differential

- Endometrioid adenocarcinoma with squamous differentiation from the endometrium, ovary or endometriosis
- Adenosquamous carcinoma from the cervix

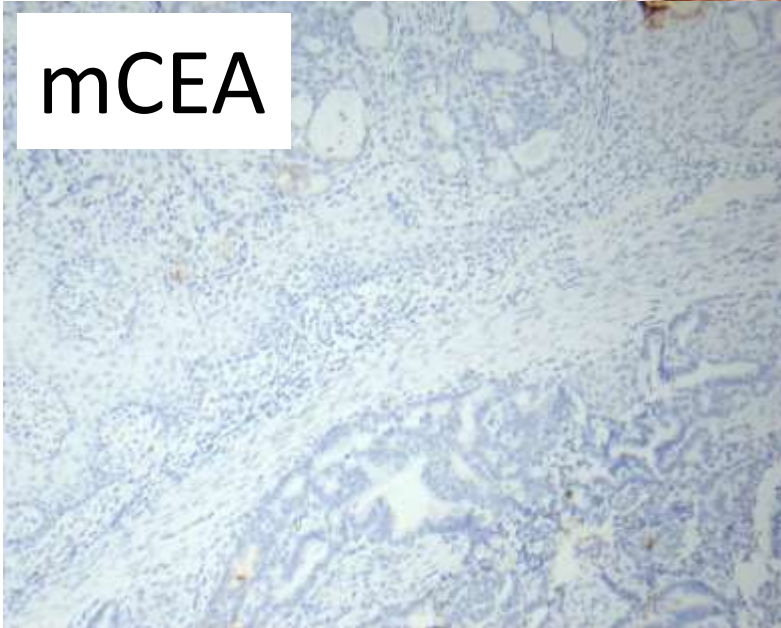


# Our case: IHC against cervical origin

P16



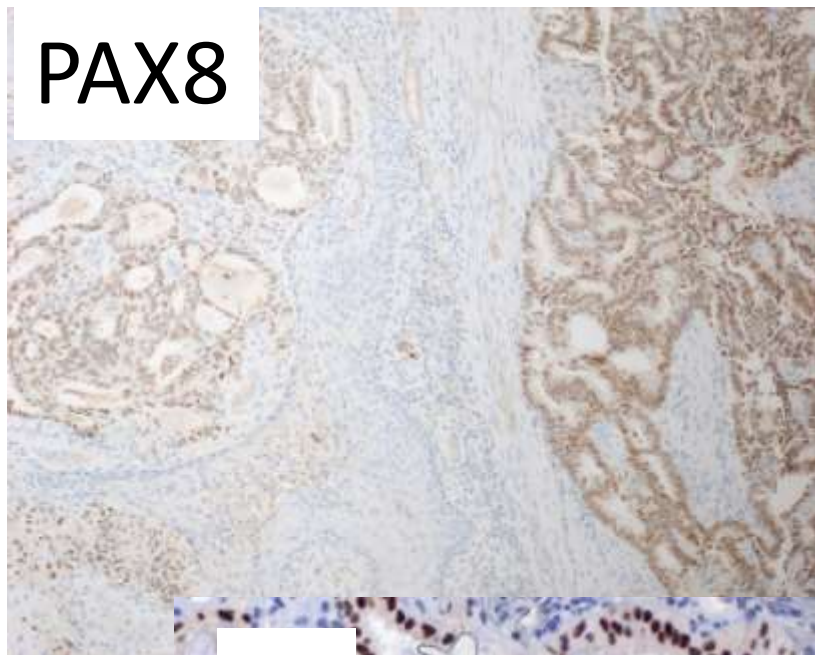
mCEA



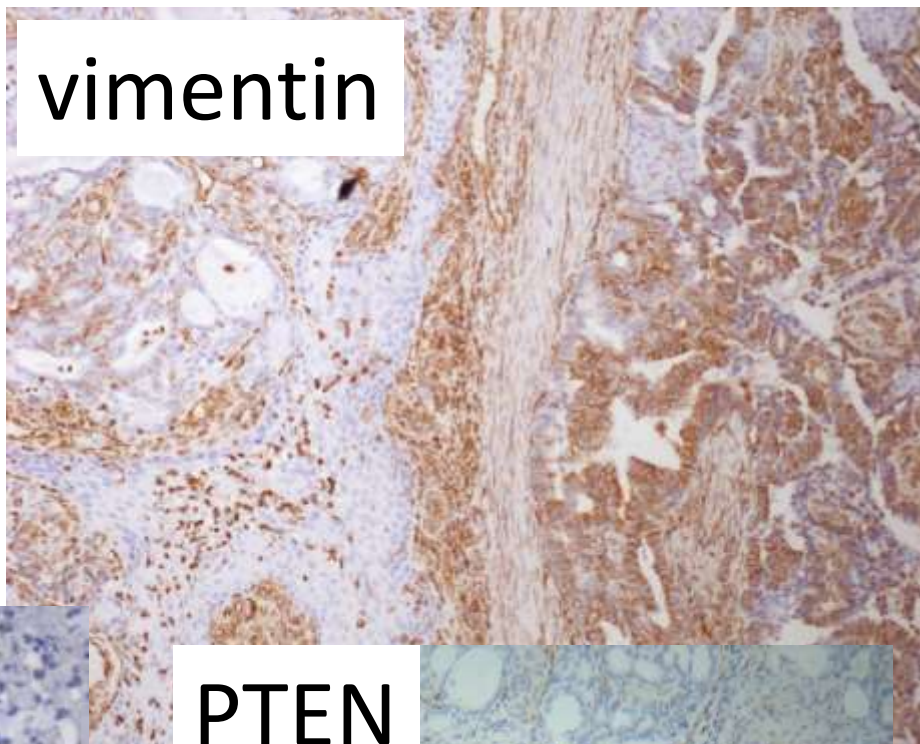


# Our case – IHC supports endometrial carcinoma

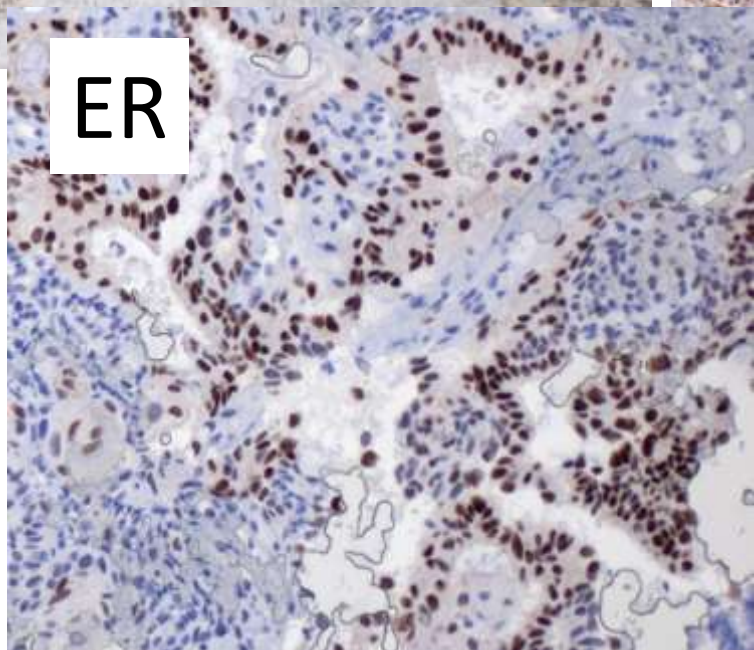
PAX8



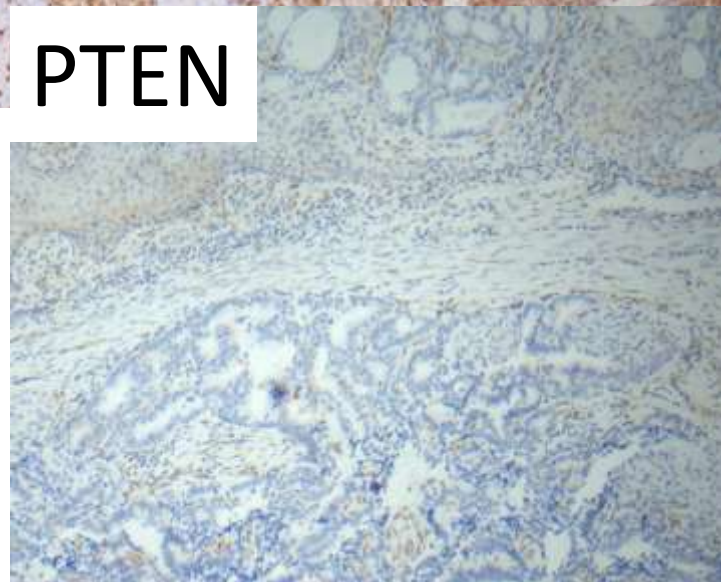
vimentin



ER



PTEN

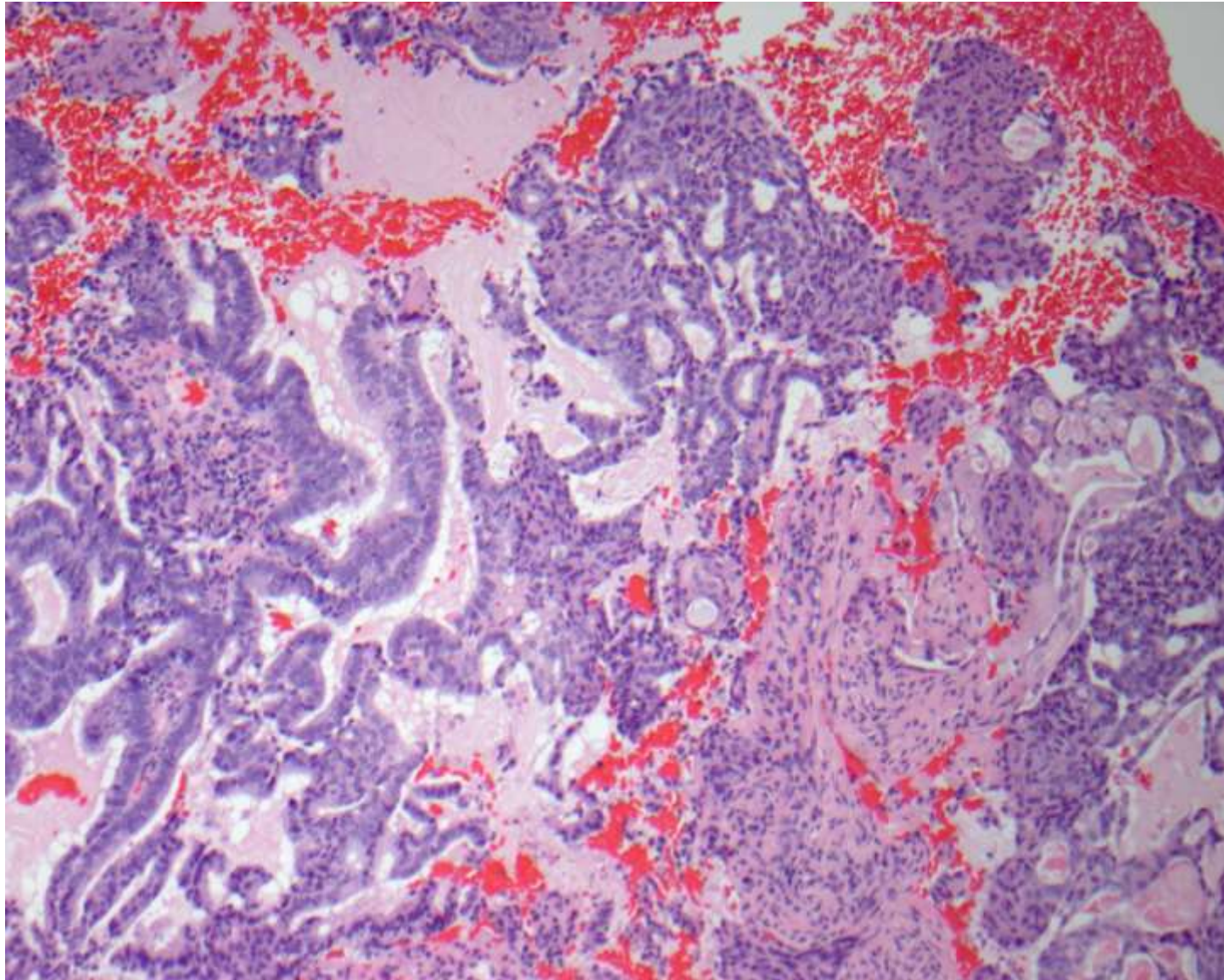




**No endometriosis was identified.**

**FINAL DIAGNOSIS: Endometrioid  
adenocarcinoma, ?endometrial  
origin, recommend endometrial  
biopsy**

# Endometrial biopsy





# Summary

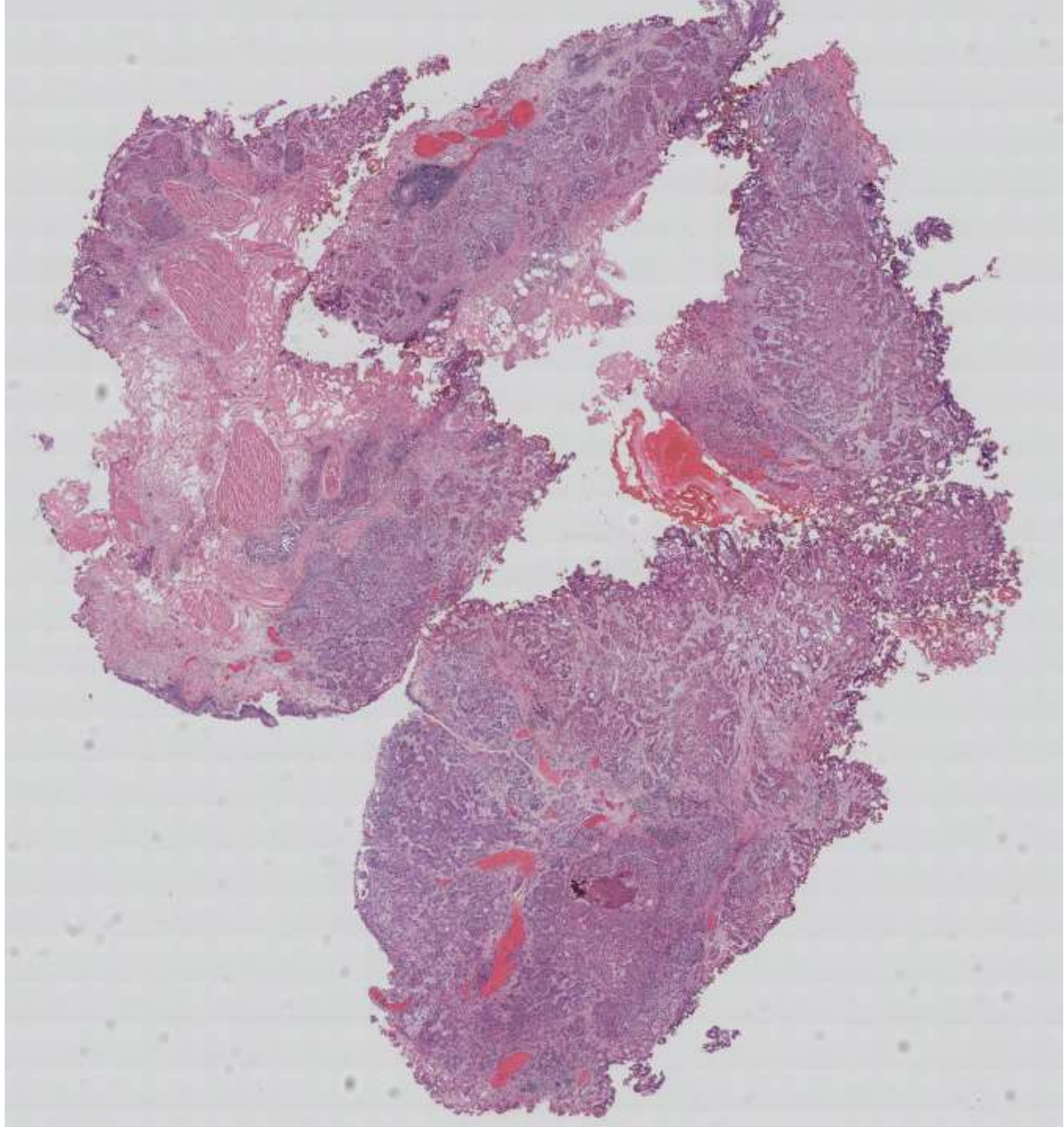
- Remember to consider metastatic lesions when faced with a vulvar lesion with no other history
- This case is first report of vulva as initial presentation of an endometrial endometrioid adenocarcinoma

# SB 6159 (scanned slide available)

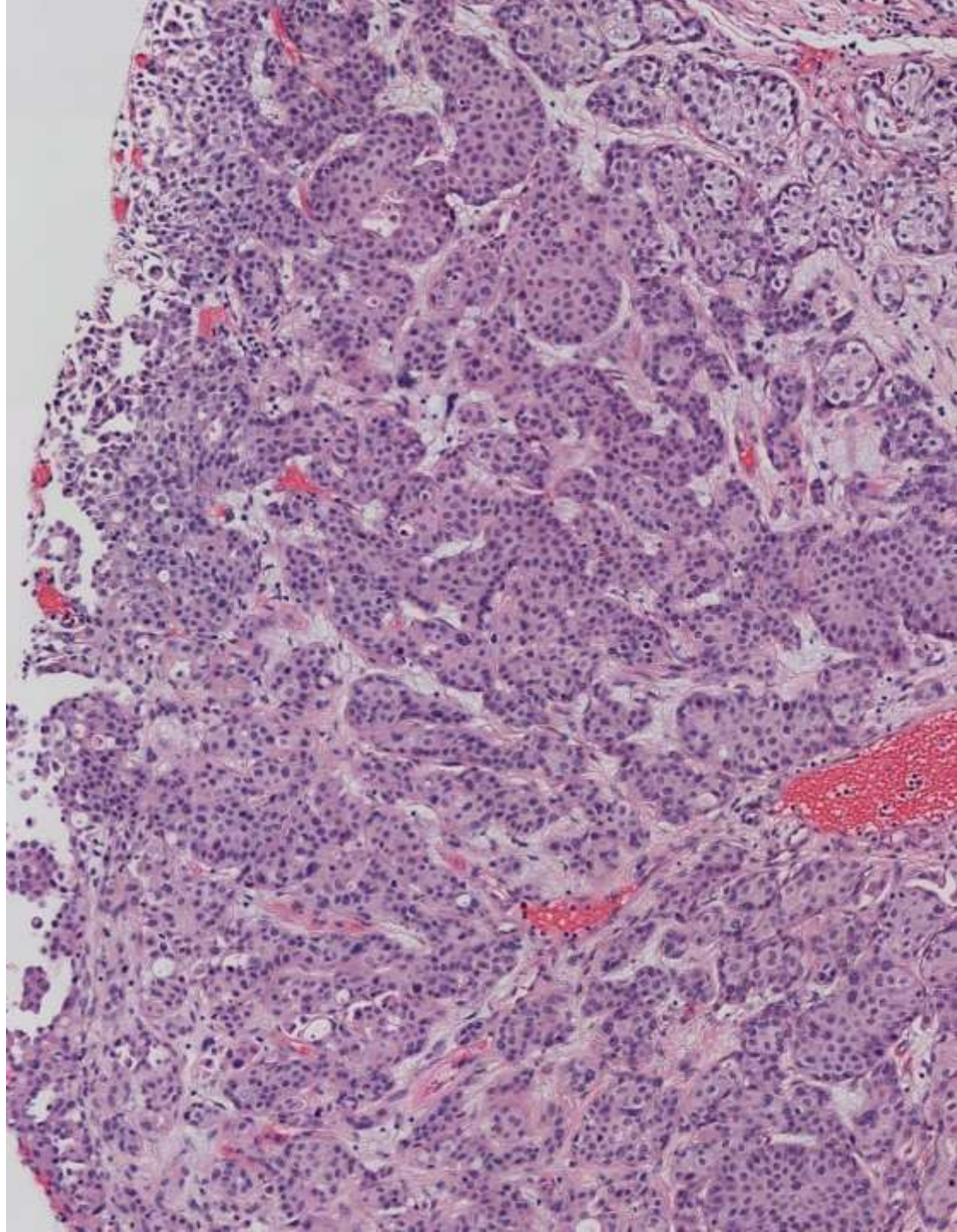
**Makham Tavallaee/Dean Fong; VA Palo Alto**

3cm bladder tumor with both solid and  
papillary components, located on left  
lateral/posterior bladder wall.

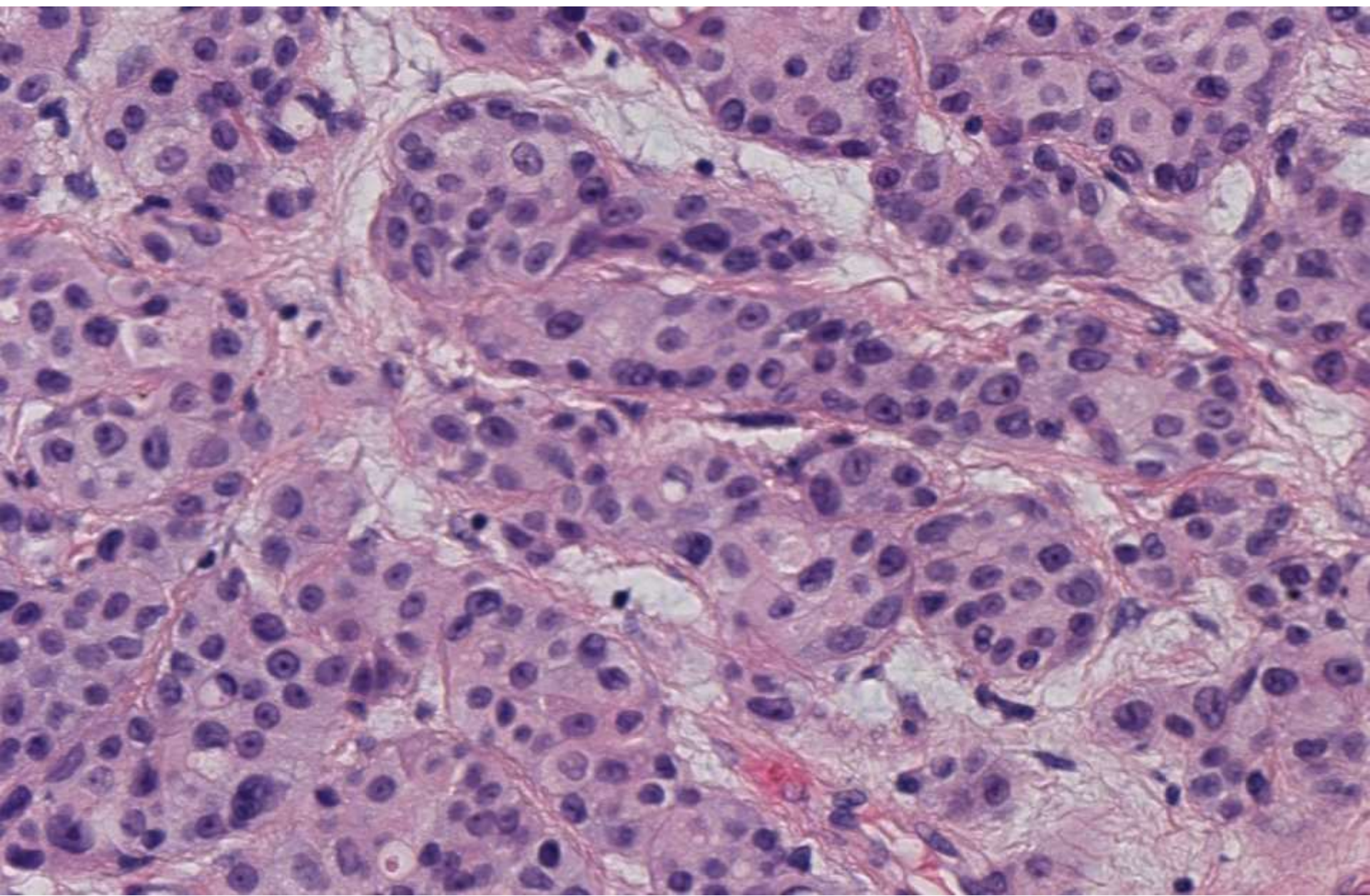




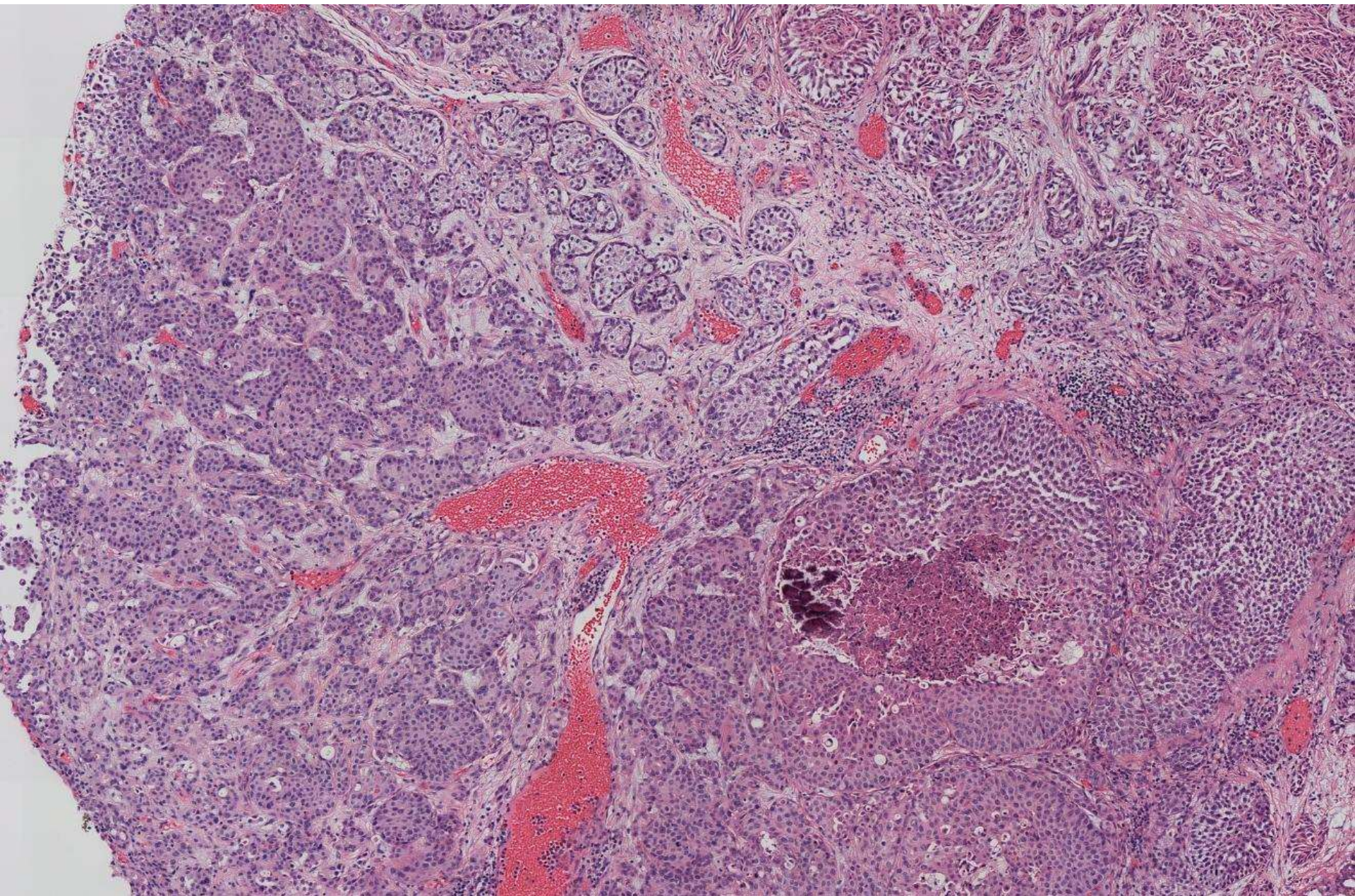




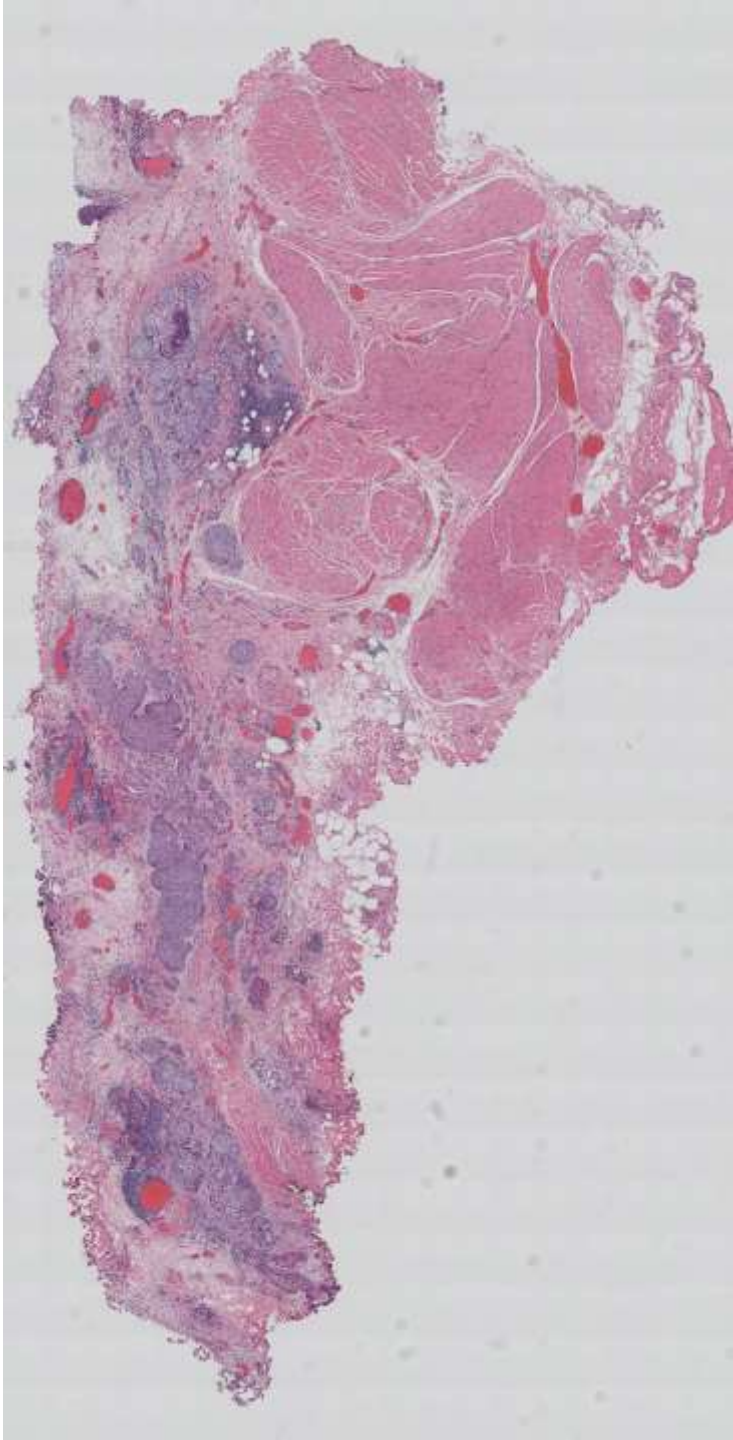


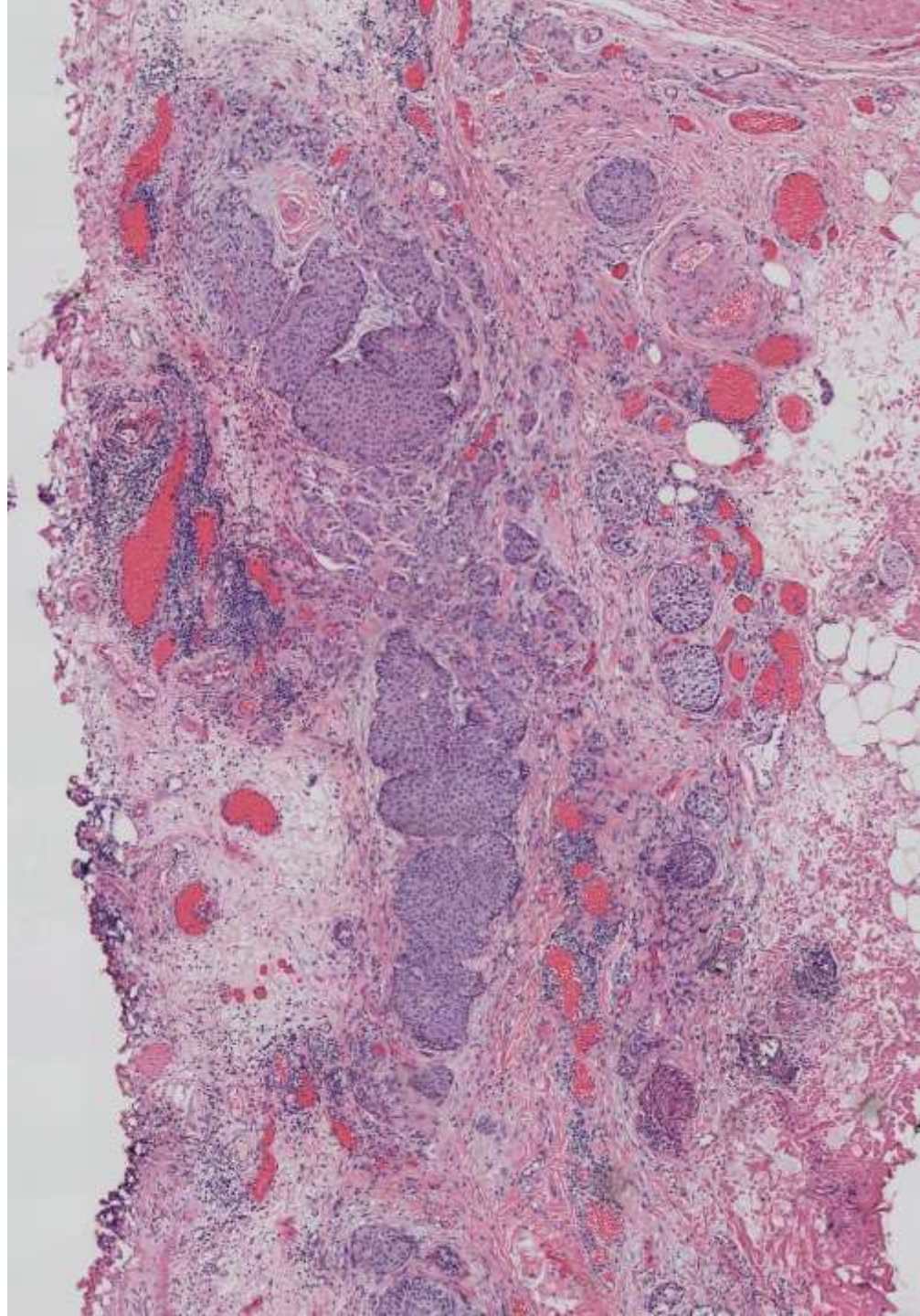




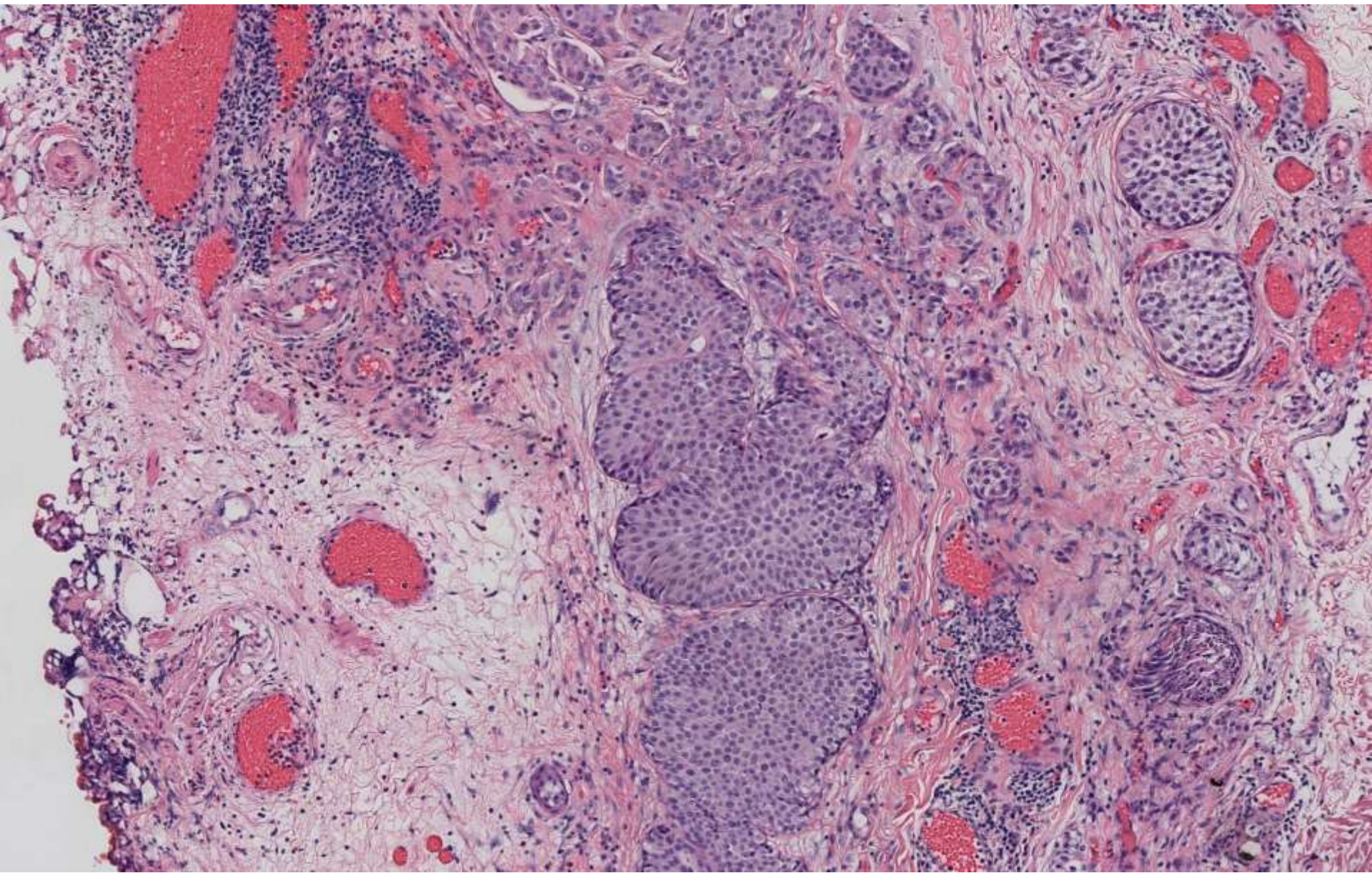




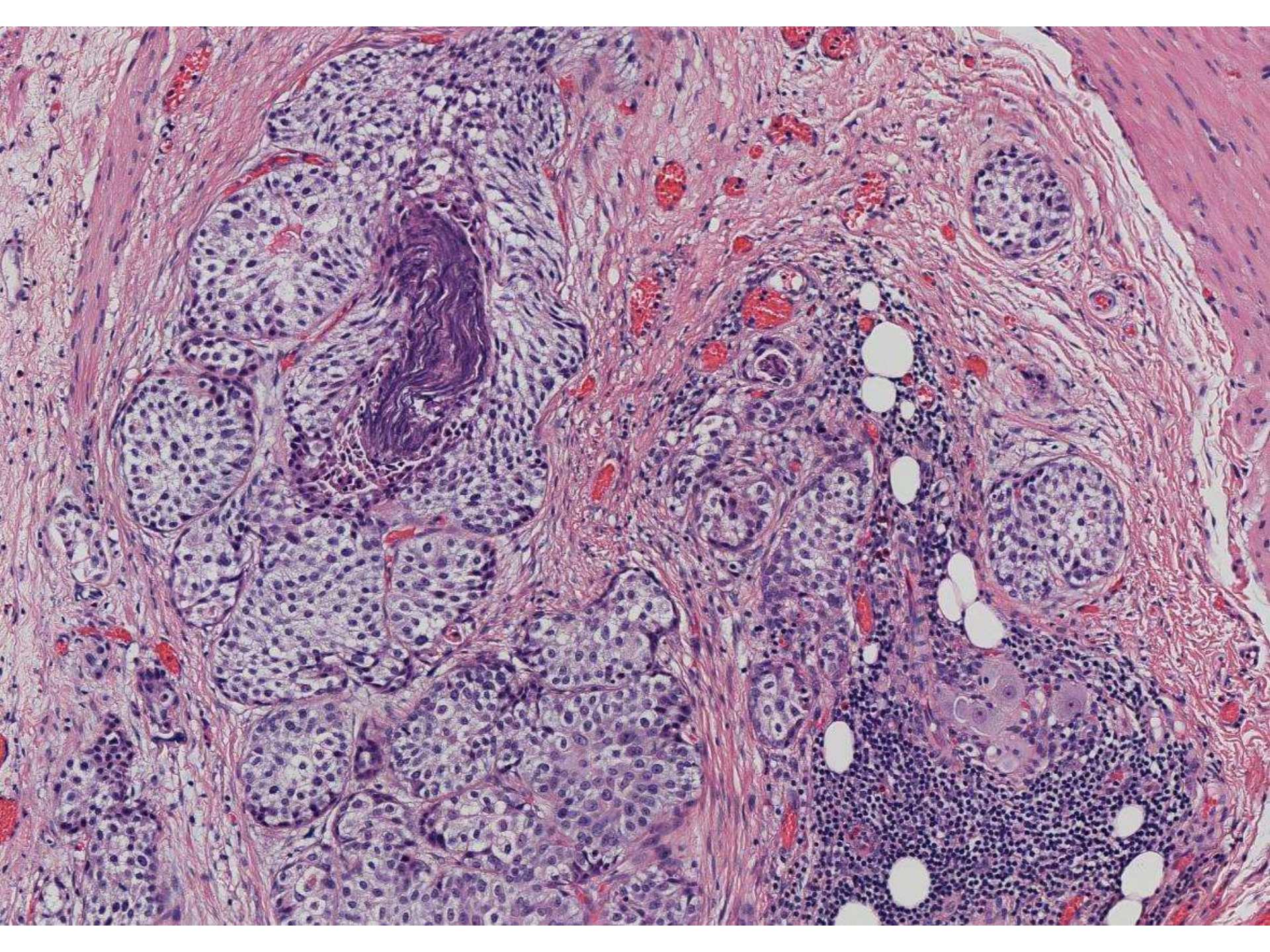














# DIAGNOSIS?



# South Bay Pathology Society

## April 2017

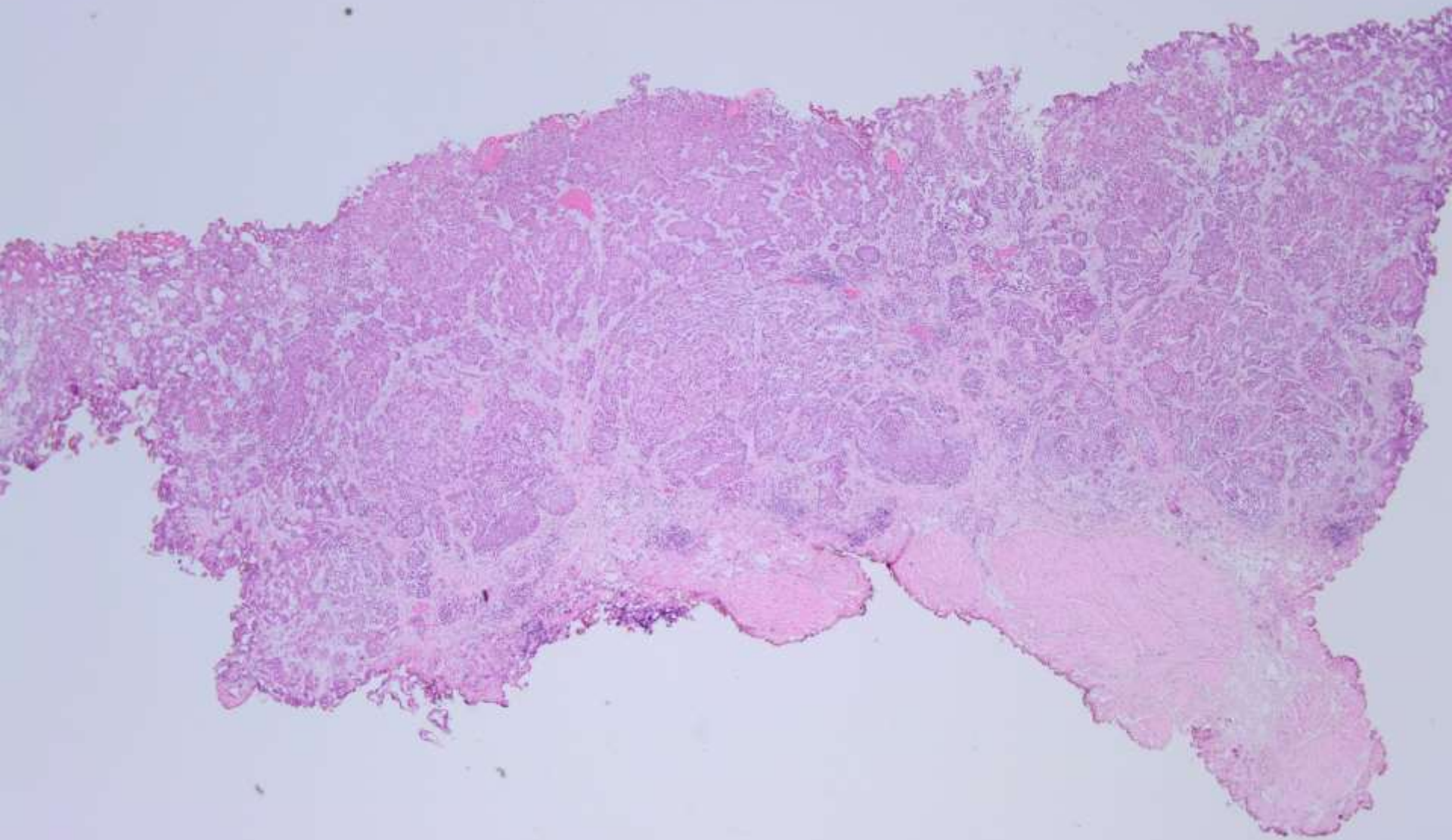
SB 6159

Mahkam Tavallaee

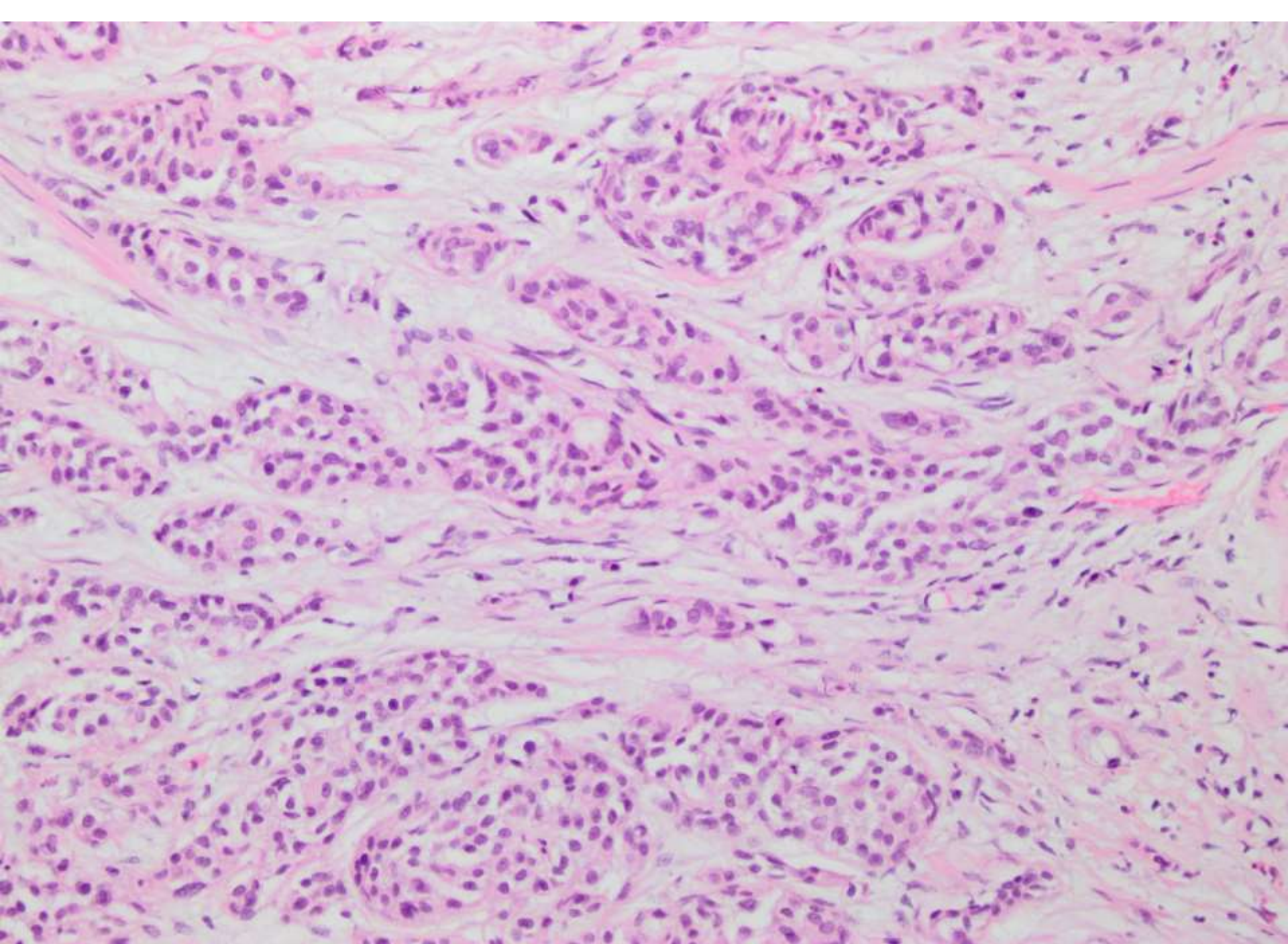
Dean Fong

VA Palo Alto

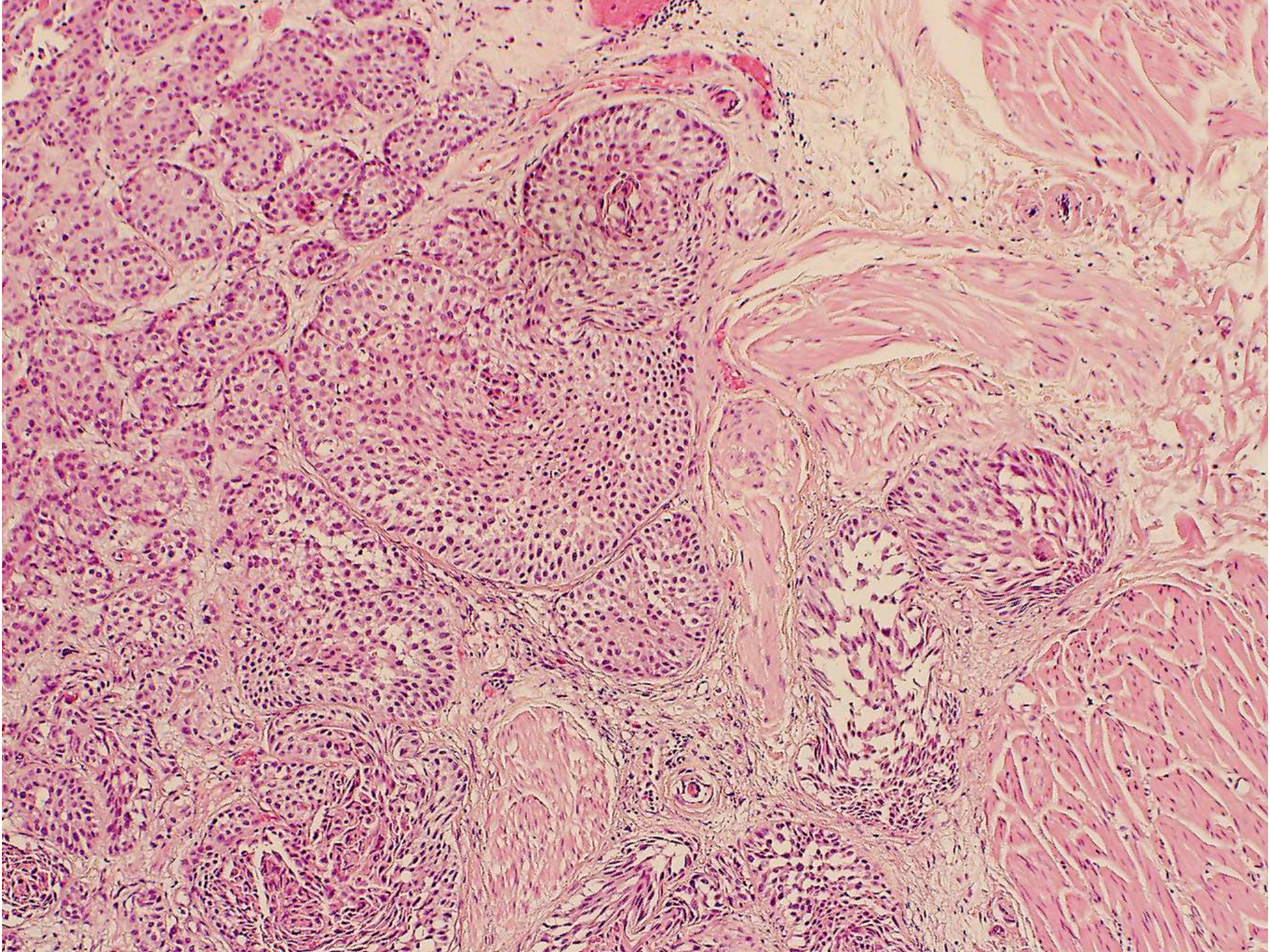














# Diagnosis

- Invasive Nested Urothelial Carcinoma



# Differential Diagnosis

- von Brunn nests
- Cystitis cystica/glandularis
- Nephrogenic adenoma

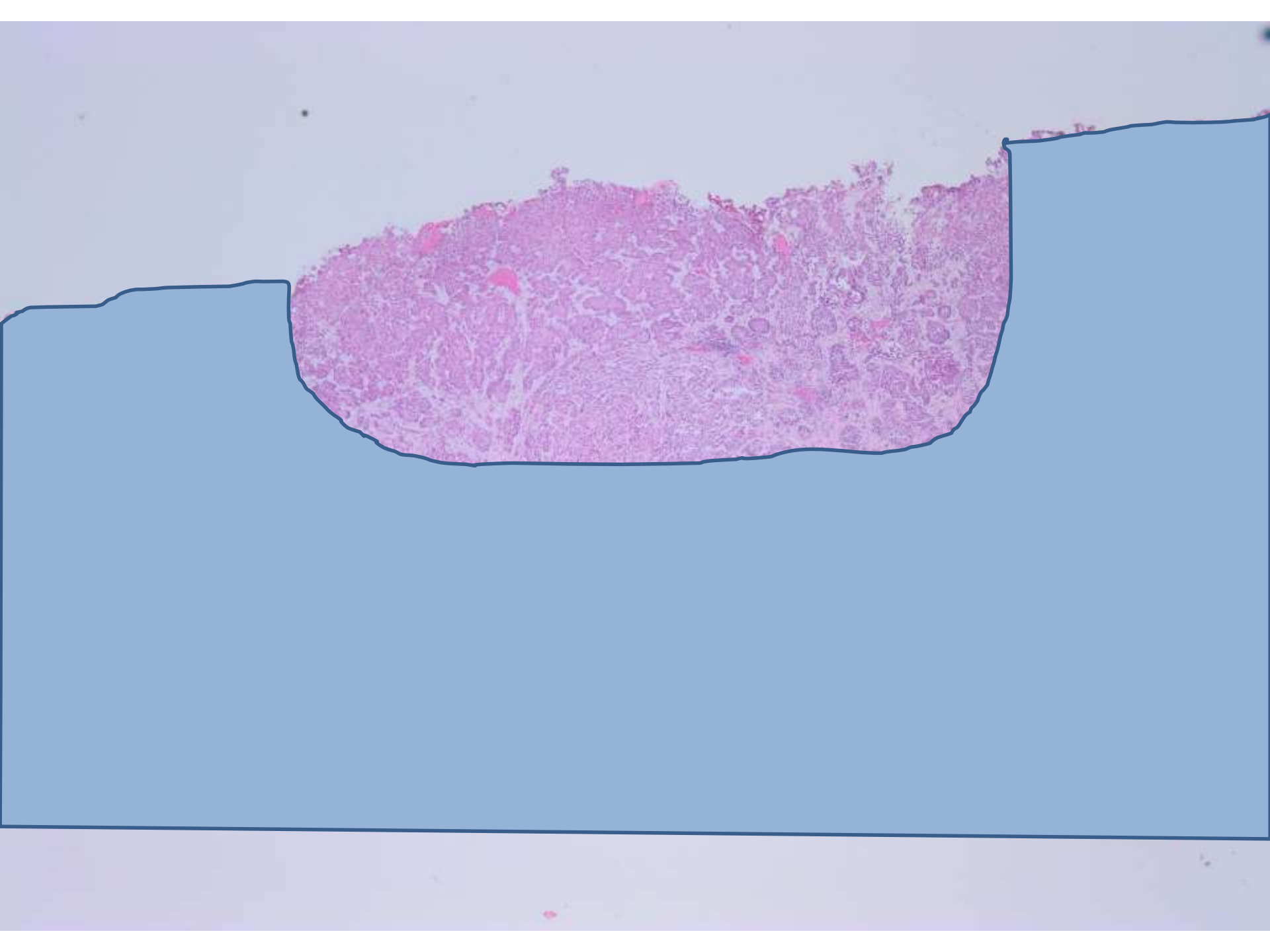
# The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs—Part B: Prostate and Bladder Tumours

*Peter A. Humphrey<sup>a</sup>, Holger Moch<sup>b,\*</sup>, Antonio L. Cubilla<sup>c</sup>, Thomas M. Ulbright<sup>d</sup>, Victor E. Reuter<sup>e</sup>*

EUROPEAN UROLOGY 70 (2016) 106–119

- Locally advanced
- Associated with poor clinical outcome
- Traditional grading scheme does not apply





# Take Home Messages

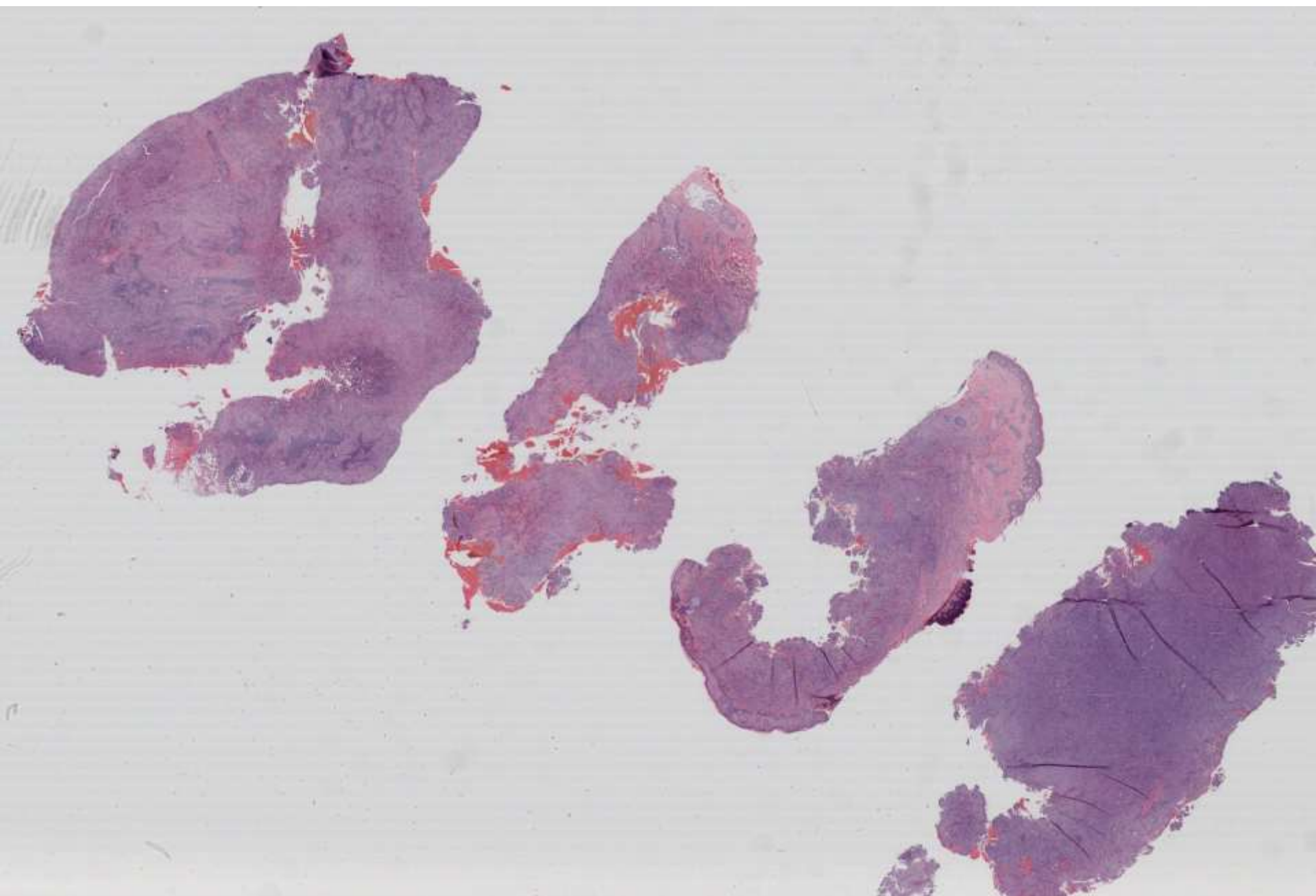
- Recognize nested variants of urothelial carcinoma
- Pitfalls
  - Mimic benign urothelial proliferations
  - Superficial biopsy
- Traditional grading scheme does not apply
- Poor prognosis



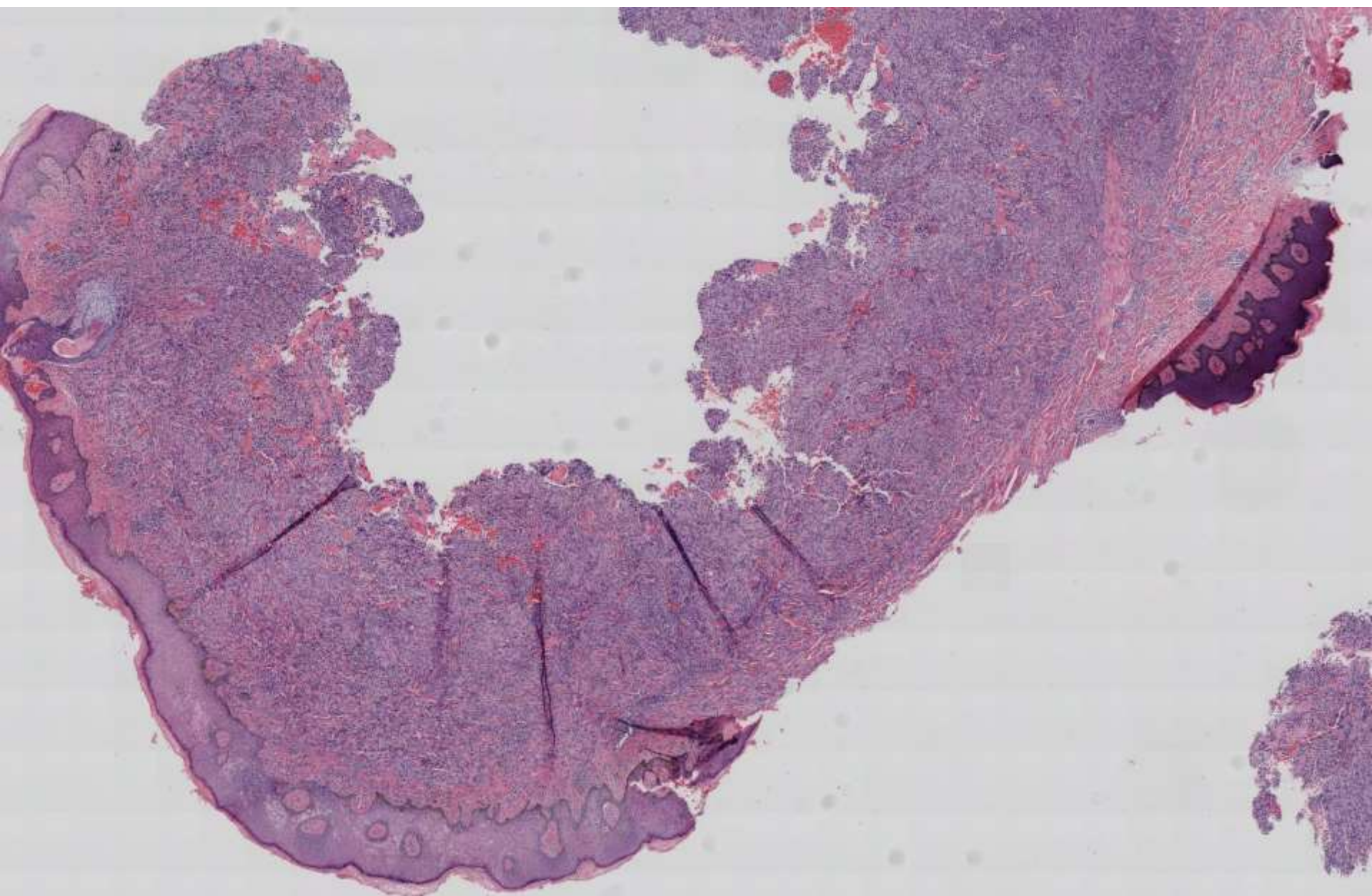
**SB 6160 (scanned slide available)**

**Makham Tavallaee/Dean Fong; VA Palo  
Alto**

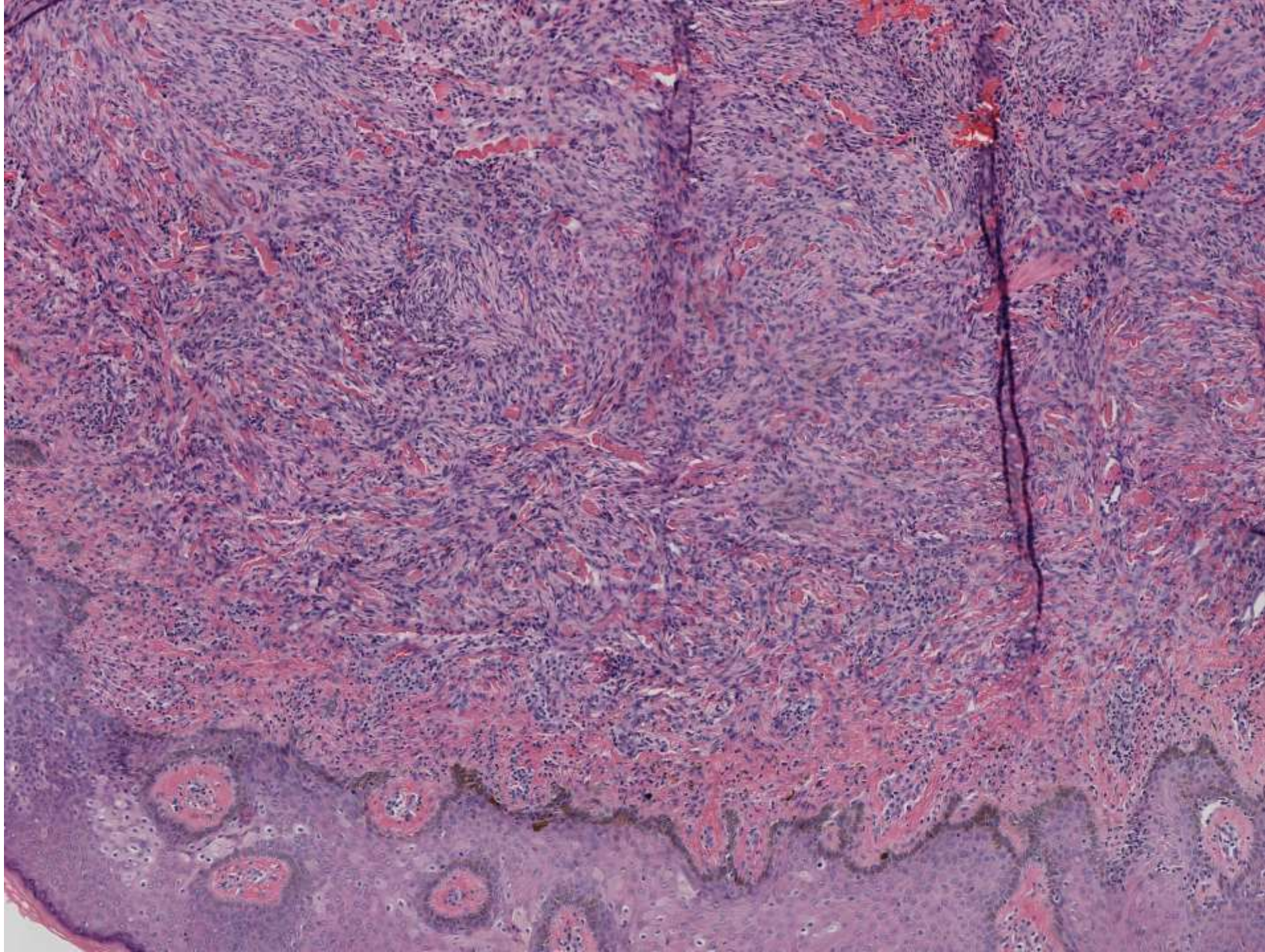
**Skin/soft tissue cyst excision from right  
upper arm.**



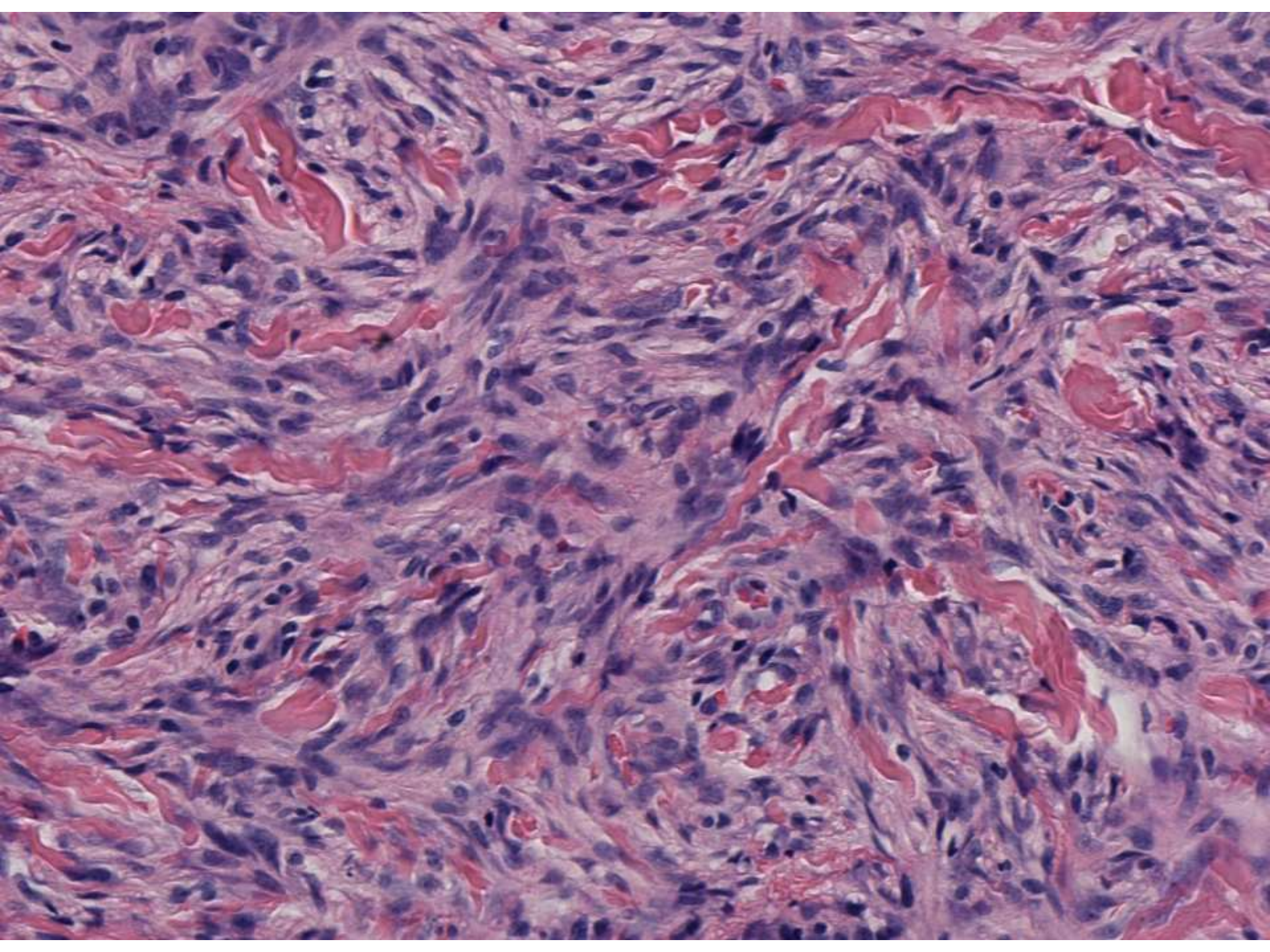




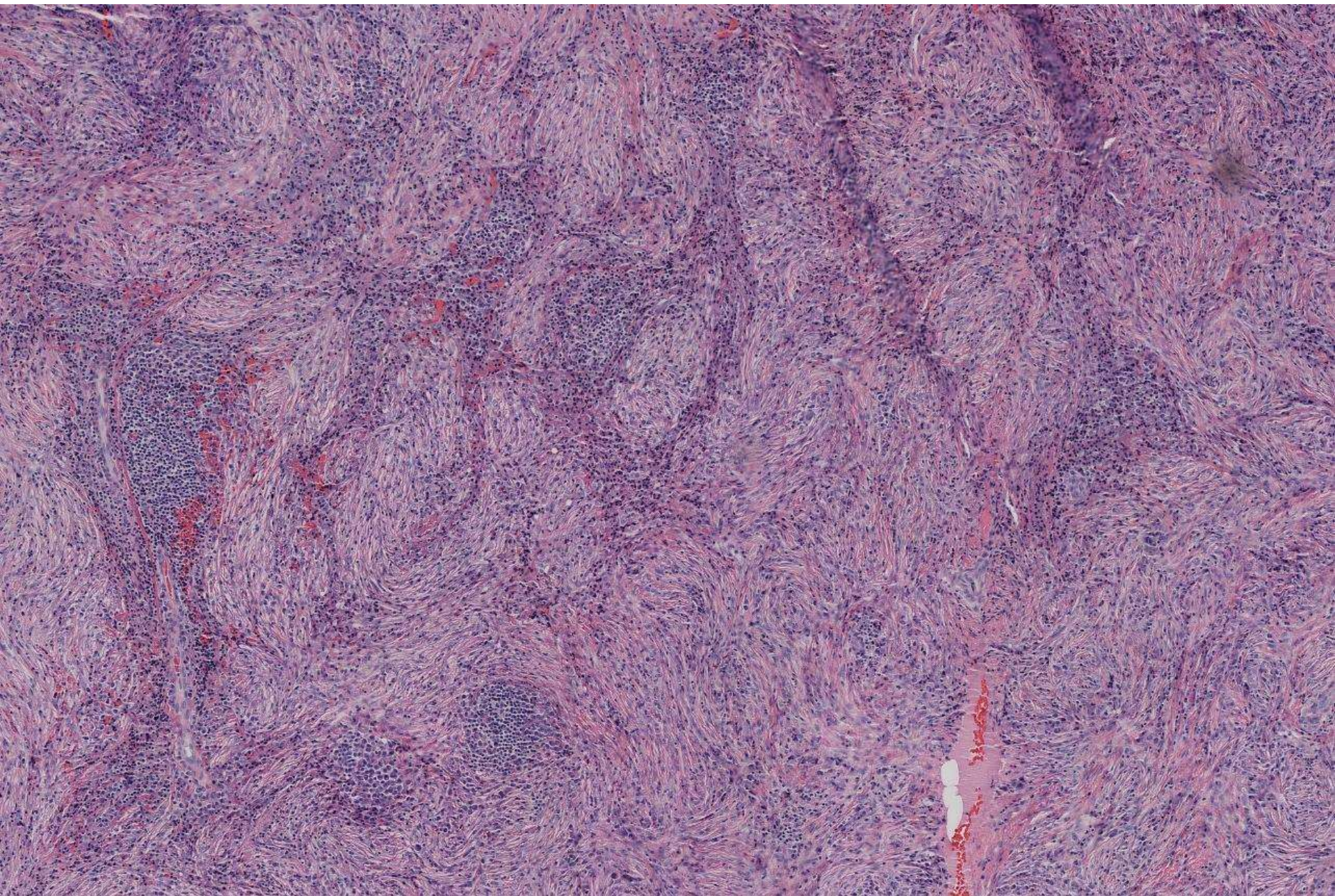




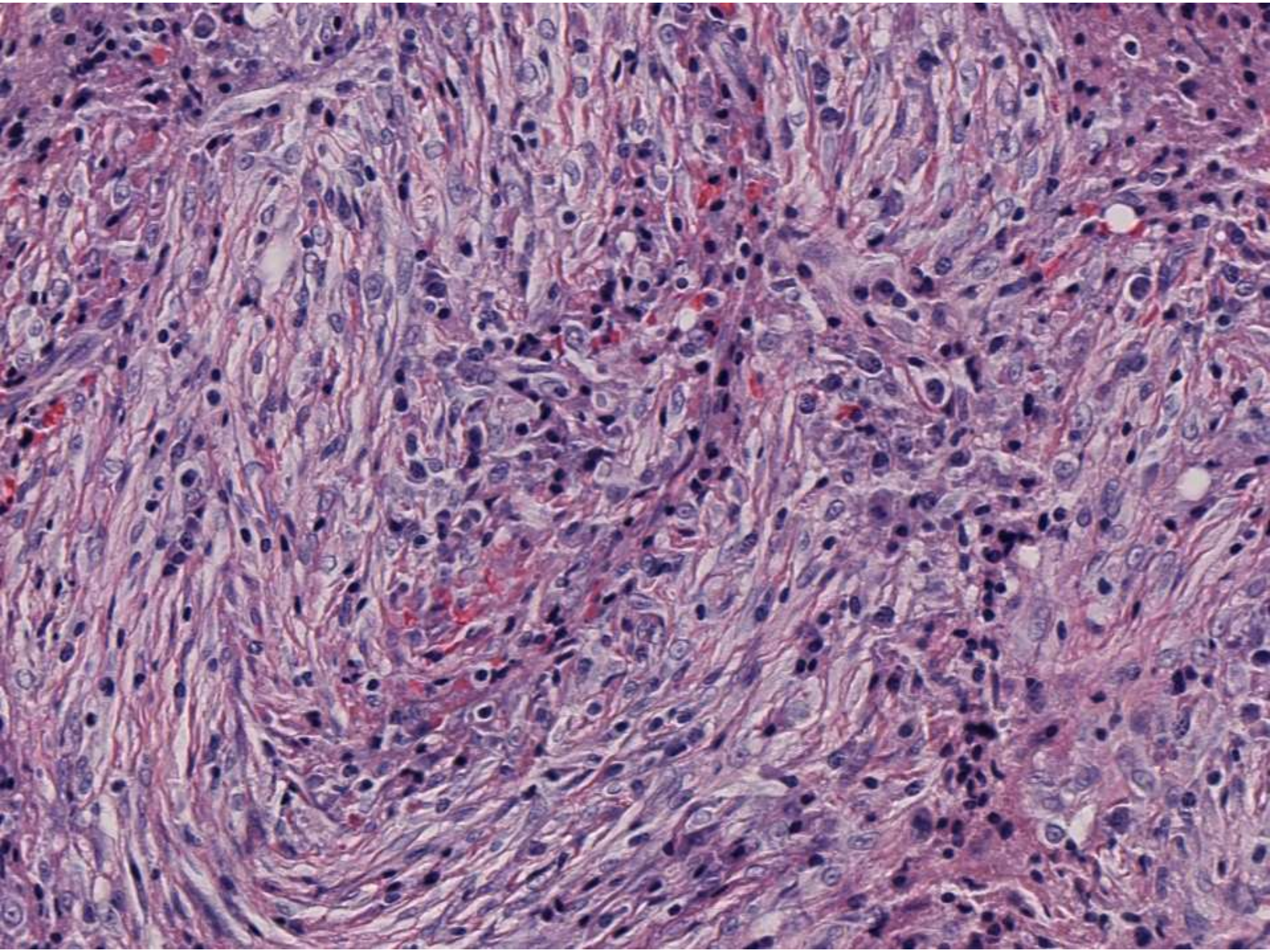




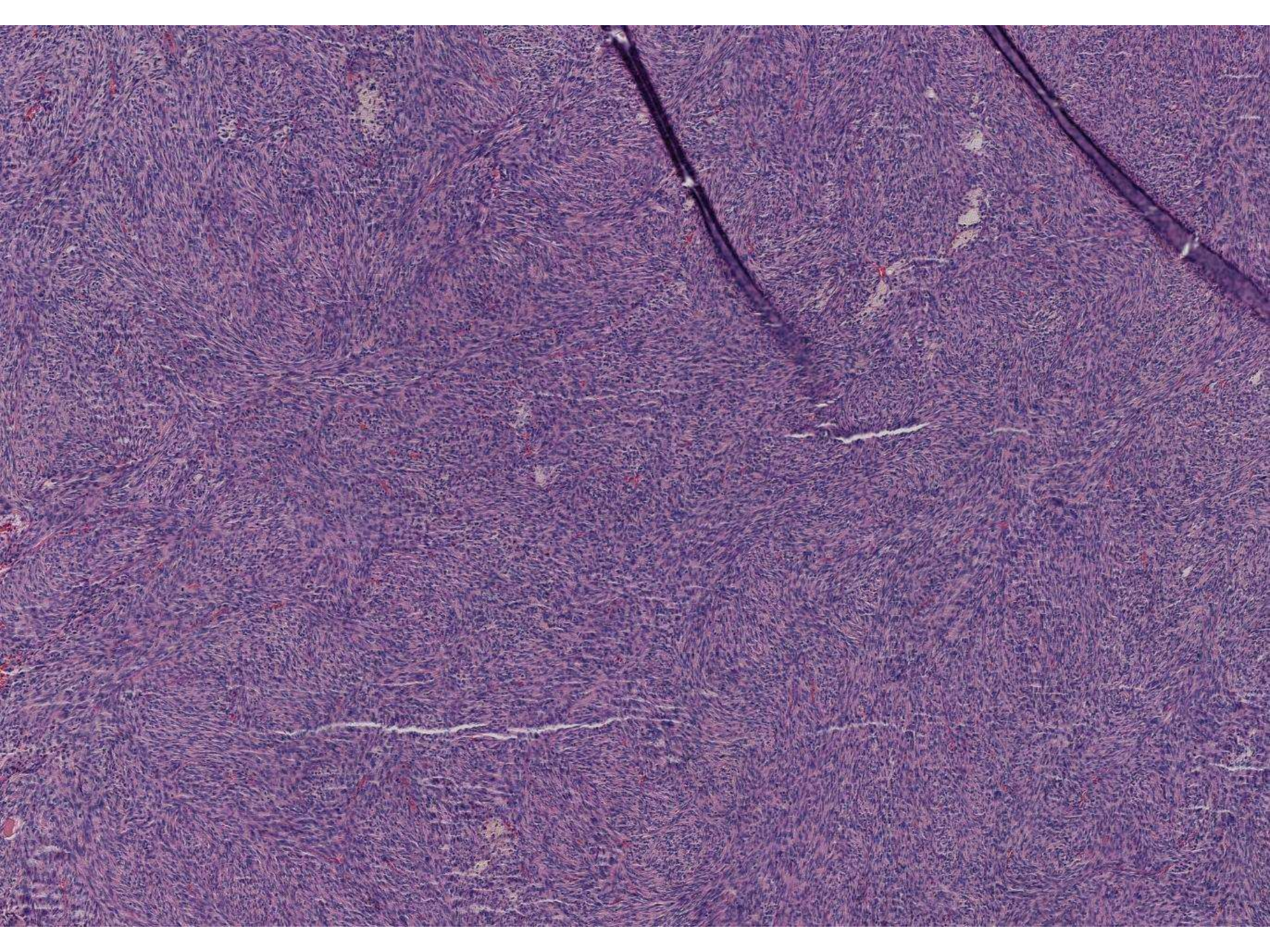




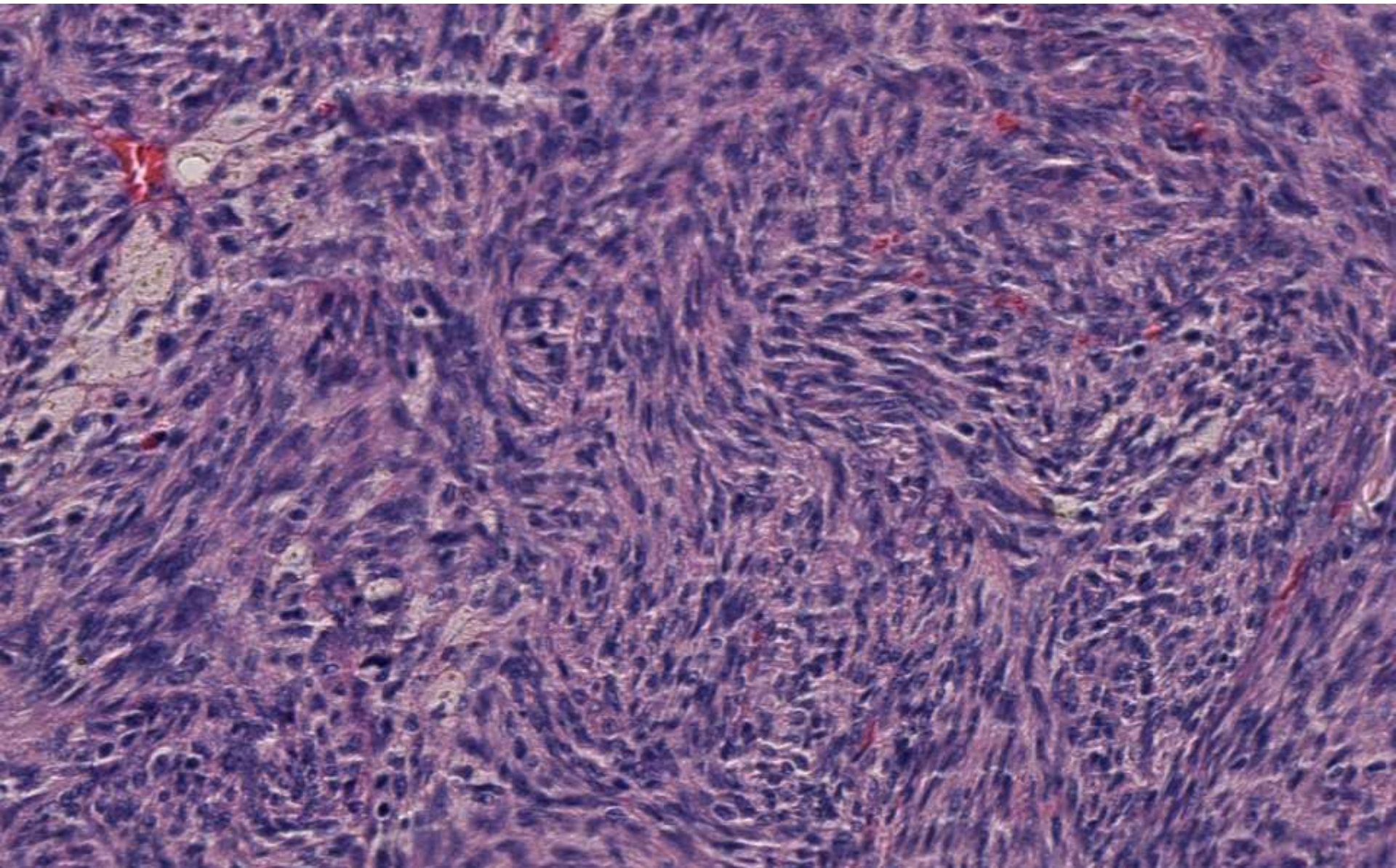












# DIAGNOSIS?





# South Bay April 2017

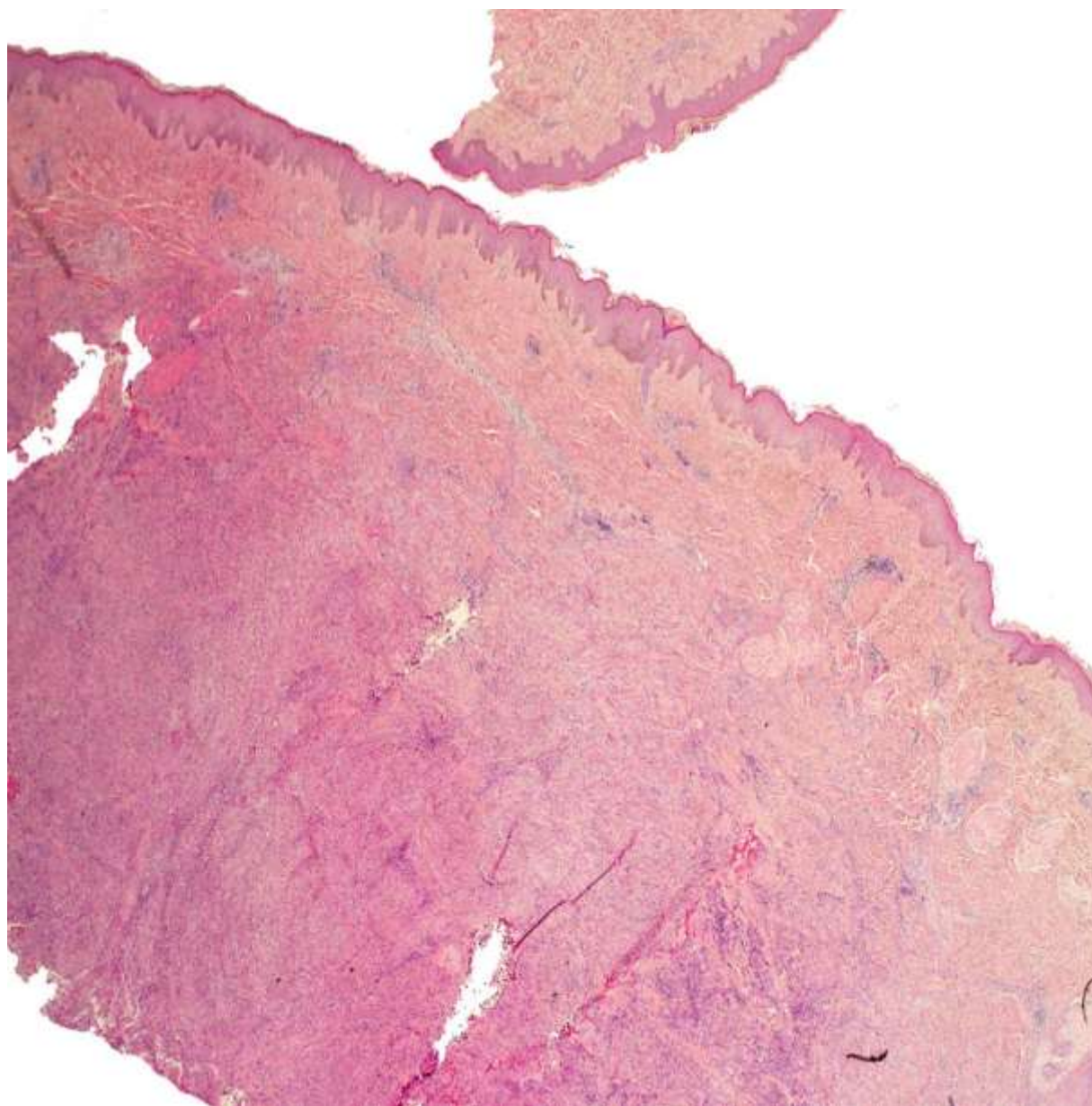
Mahkam Tavallaee, MD, MPH  
Dean Fong, DO

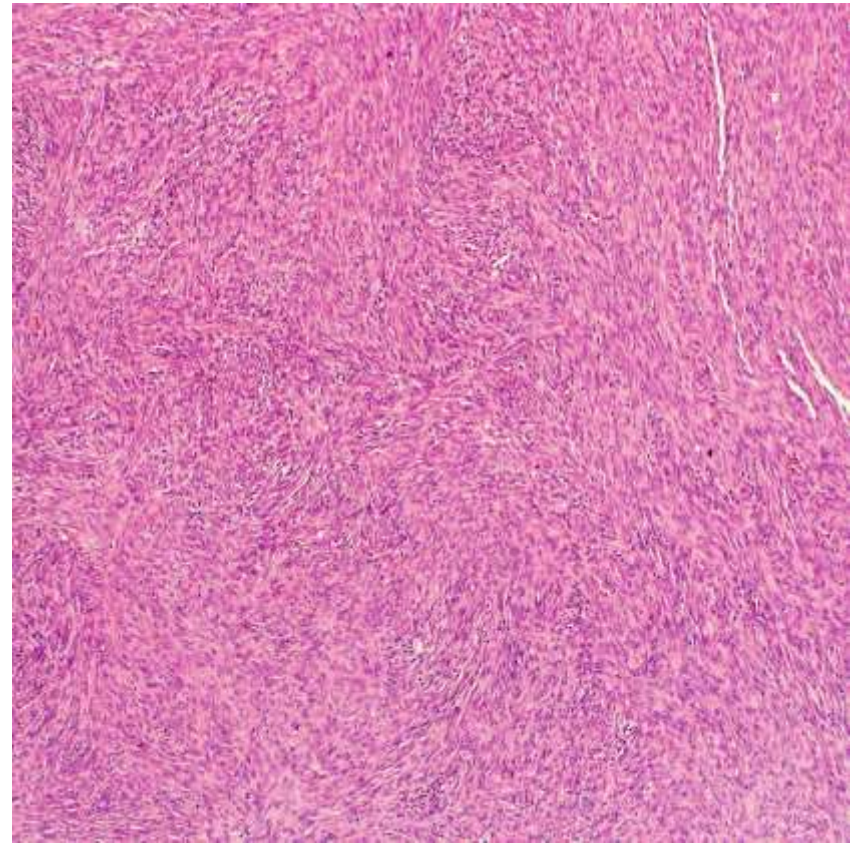
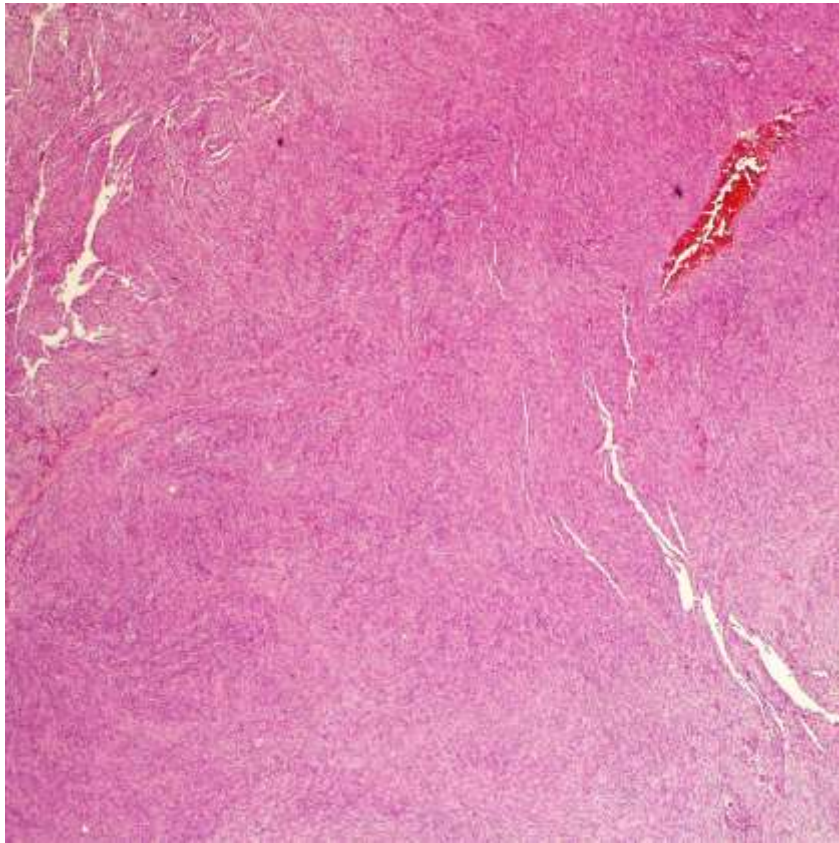
VA Palo Alto

## Brief History

- 40 year old male
- 1.5 cm well circumscribed soft mobile cystic lesion on right upper arm
- Increasing in size
- Getting more tender recently
- No fever, no erythema, no drainage
- 4 cm Excision specimen received





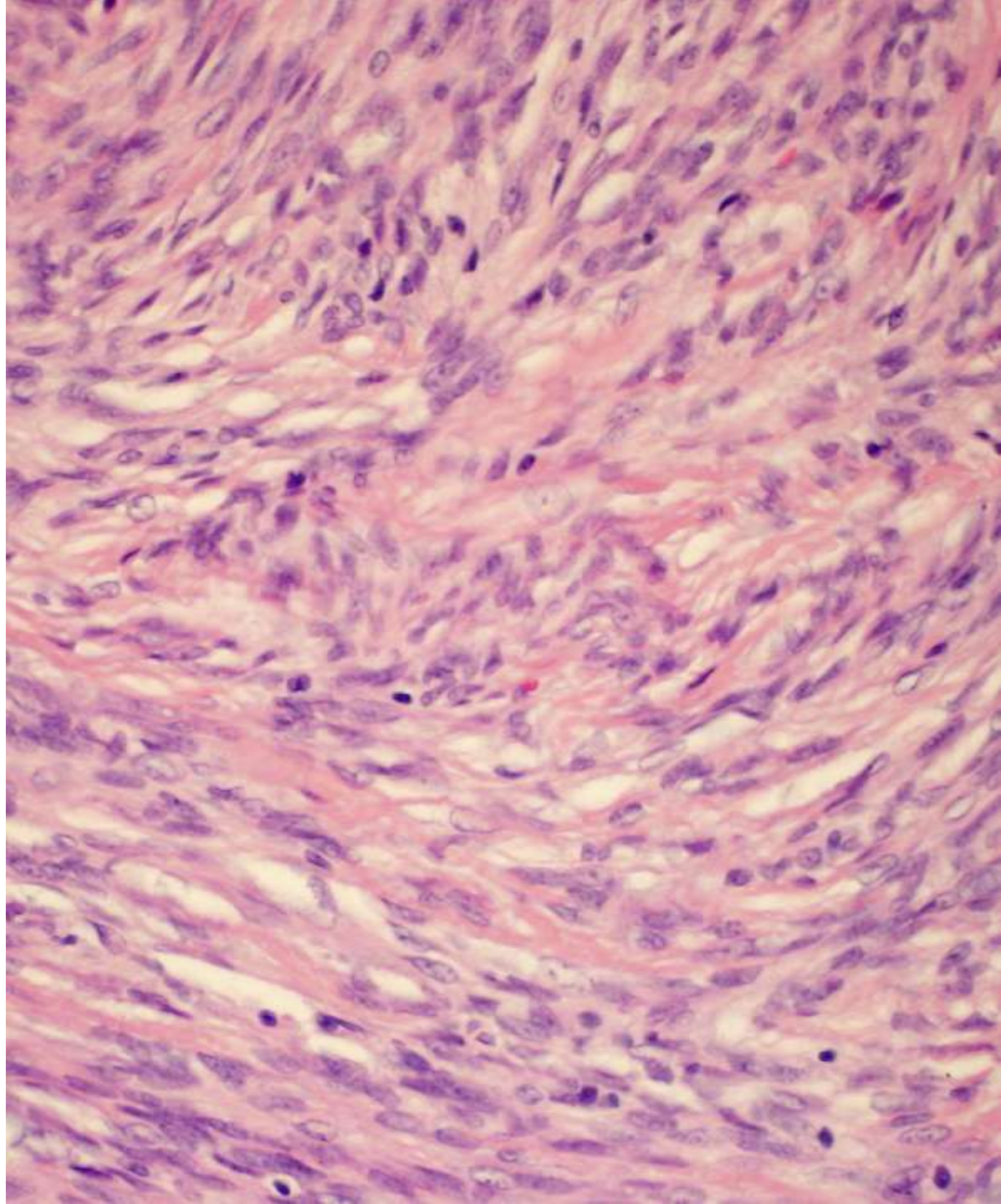


Cellular lesion composed of uniform small elongated cells

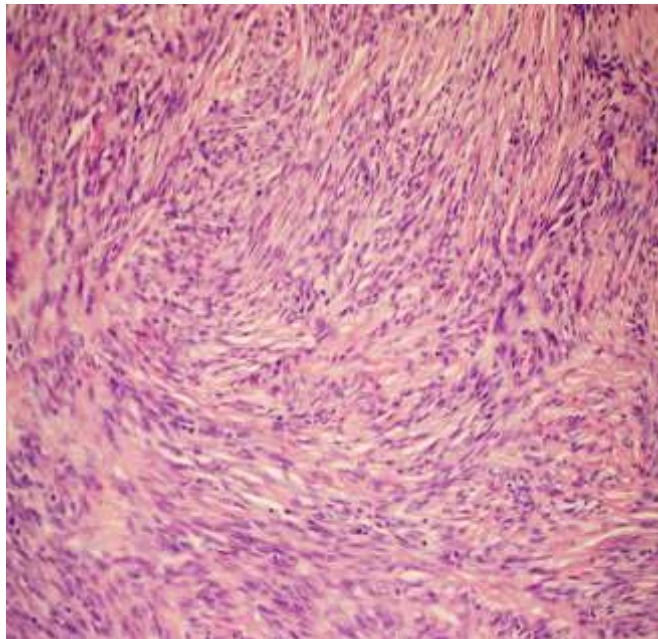
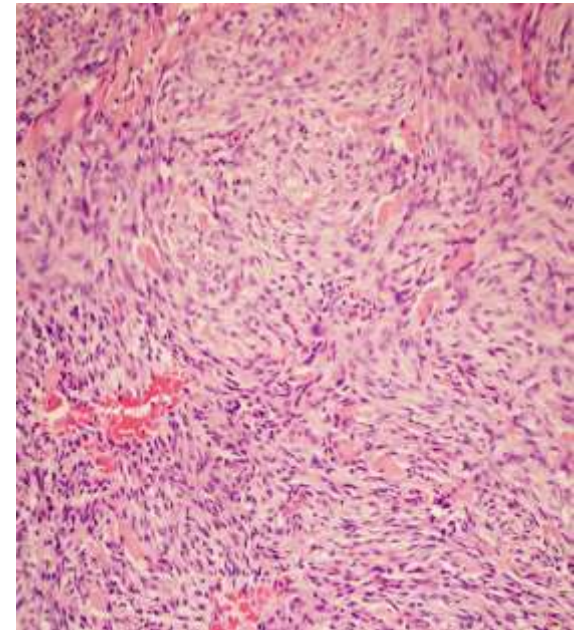
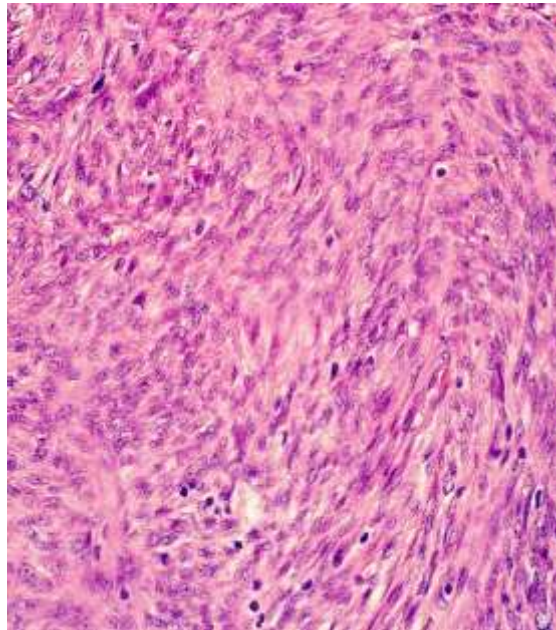
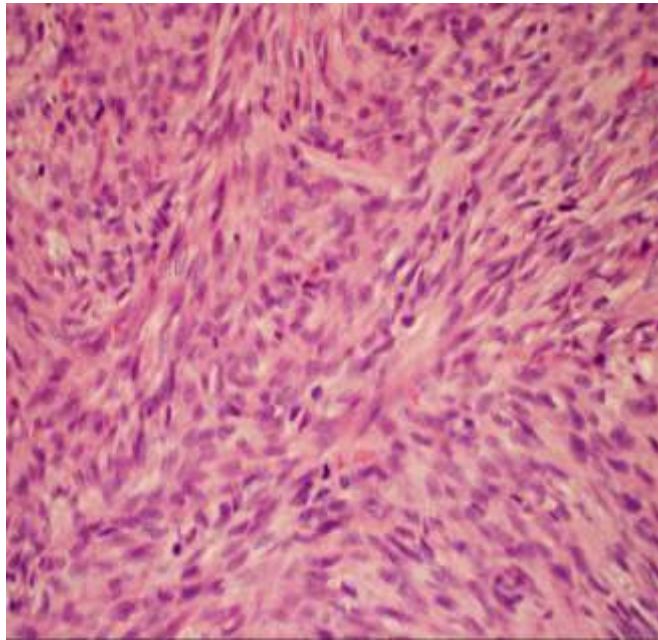
Storiform pattern



- Monomorphic, thin, spindly cells
- Scant eosinophilic cytoplasm
- Hyperchromatic nuclei







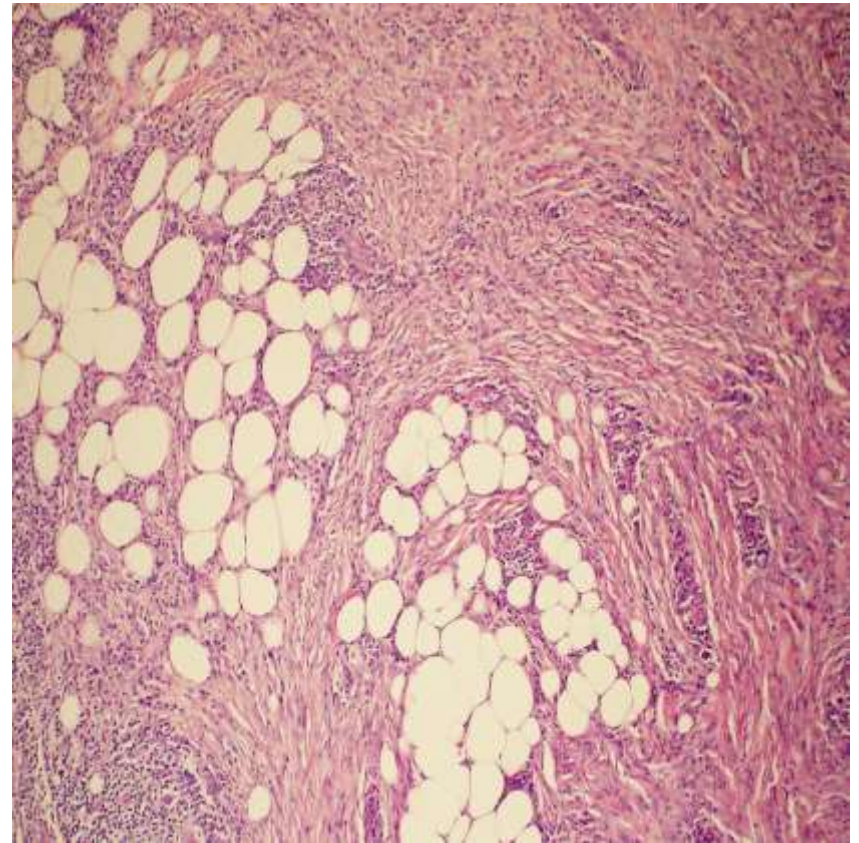
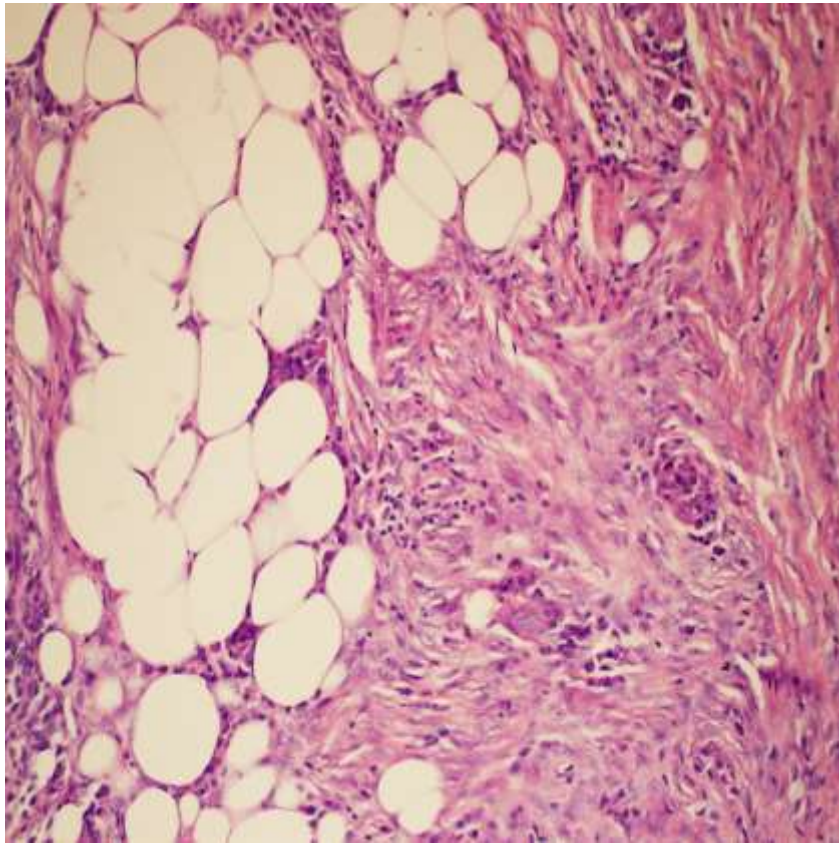
Centered on vessels

Low mitotic activity

No necrosis

No atypical mitoses





Infiltrates between and around fat cells and adnexa

Produces “string of pearls” or “honeycomb” or “lace-like” patterns

# Differential Diagnosis

Dermatofibroma / Dermal fibrous histiocyteoma

Myxoid nerve sheath tumor

Myxoid liposarcoma

Plexiform fibrohistiocytic tumor

Desmoplastic melanoma

Fibrosarcoma

MFH-pleomorphic or atypical fibroxanthoma

Dermatofibrosarcoma Protuberans



Usually <1 cm



```
graph TD; A[Usually <1 cm] --> B[Infrequent infiltration into fat cells]; B --> C[Mixed cell population]; C --> D[Overlying epithelial hyperplasia]; D --> E[CD34 40% + in deep lesions, Negative in dermal lesions];
```

Infrequent infiltration into fat cells

Mixed cell population

Overlying epithelial hyperplasia

CD34 40% + in deep lesions, Negative in dermal lesions

Dermatofibroma / Dermal fibrous histiocytoma

Areas of typical nerve sheath tumor usually present



```
graph TD; A[Areas of typical nerve sheath tumor usually present] --> B[CD34 may stain dendritic cells but not lesional cells]; B --> C[S100 Positive];
```

CD34 may stain dendritic cells but not lesional cells

S100 Positive

Myxoid nerve sheath tumor



Frequently contains lipoblasts



```
graph TD; A[Frequently contains lipoblasts] --> B[CD34 negative in lesional cells]; B --> C[Myxoid liposarcoma];
```

The diagram consists of three main components: an orange rounded rectangle at the top containing the text 'Frequently contains lipoblasts', a grey rounded rectangle in the middle containing the text 'CD34 negative in lesional cells', and a light grey trapezoidal shape at the bottom containing the text 'Myxoid liposarcoma'. A large, semi-transparent orange arrow points downwards from the orange box to the grey box, and another semi-transparent grey arrow points downwards from the grey box to the bottom trapezoidal shape, indicating a logical flow or diagnostic sequence.

CD34 negative in lesional cells

Myxoid liposarcoma

Ray-like extension into surrounding fat

```
graph TD; A[Ray-like extension into surrounding fat] --> B[Nodules of histiocytes and giant cells in most cases]; B --> C[Collagenous stroma]; C --> D[CD34 negative]; D --> E[Plexiform fibrohistiocytic tumor];
```

Nodules of histiocytes and giant cells in most cases

Collagenous stroma

CD34 negative

Plexiform fibrohistiocytic tumor



Lacks storiform pattern

```
graph TD; A[Lacks storiform pattern] --> B[Displaces or destroys fat]; B --> C[Frequently contains lymphoid nodules]; C --> D[S100 positive]; D --> E[CD34 Negative]; E --> F[Desmoplastic melanoma];
```

The diagram is a vertical flowchart with five orange-to-brown gradient rectangular boxes, each containing a diagnostic criterion. The boxes are connected by downward-pointing arrows, starting from the top box and ending at the bottom box. The background is a light gray gradient.

Displaces or destroys fat

Frequently contains lymphoid nodules

S100 positive

CD34 Negative

Desmoplastic melanoma

Virtually always in deep soft tissue



CD34 negative

Fibrosarcoma



<1 cm

usually within skin showing solar damage (e.g. solar elastosis)

Frequent mitotic figures; many atypical mitotic figures

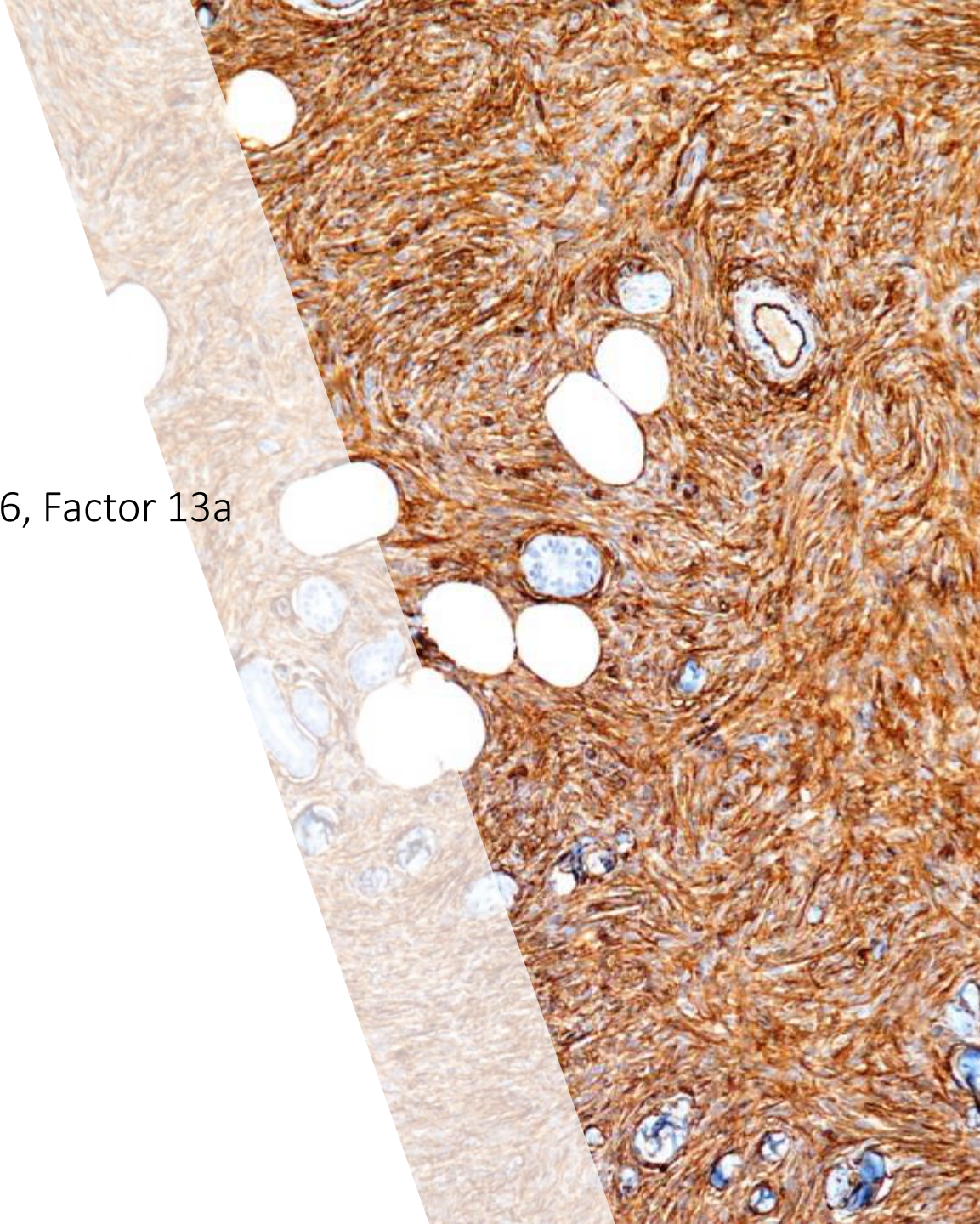
CD34 negative

MFH-pleomorphic or atypical fibroxanthoma

POSITIVE:  
CD34

NEGATIVE:  
S100, CK5/6, P63, Desmin, STAT6, Factor 13a

Narrowed down:  
DF  
DFSP





# DFSP

- Nodular, polypoid or plaque-like, centered in dermis, can occur in deep soft tissue
- Mean 5 cm, gray-white (brown/black if melanocytes present)
- Hemorrhage and necrosis are rare
- Cellular lesion composed of uniform small elongate cells
- Uniform storiform pattern
- Infiltrates between and around fat cells and adnexa
- Located in dermis and subcutaneous tissue
- Scant collagenous stroma
- Giant cells and foam cells almost always absent
- CD34 extensively positive in nearly all cases
- May have myxoid areas
- Very rare/unusual findings; if present, alternative diagnoses should be considered
  - Giant cells
  - Xanthoma cells
  - Hemosiderin
  - Inflammatory cells

# DFSP IHC & Molecular Description

## Positive Stains

- CD34 (strong in 95%)
- Vimentin
- Also actin (focal)
- ApoD
- Bcl2
- NKI-C3
- CD99

## Negative Stains

- Factor XIIIa (usually)
- Keratin
- EMA
- S100
- HMB45
- Desmin
- CD117

t(17,22)(q21;q13)

collagen type 1 alpha 1 gene and platelet derived growth factor beta chain gene found in almost all cases using multiplex RT-PCR



## Also consider....

- **Giant cell fibroblastoma is a closely related lesion**
  - More common in pediatric age group
  - Mixtures may be seen
  - Recurrences may be of the other neoplasm
  - Same t(17;22) translocation
- **Bednar tumor is a pigmented DFSP**
  - Contains elongate, bipolar heavily pigmented melanocytes
  - Melanocytes S100 positive, HMB45 negative
  - More numerous in deep portions of tumor
  - More common in black patients

# Treatment

- Wide local excision of lesion and subcutaneous fat
- Gold Standard in recurrent and inoperable: Imatinib therapy (tyrosine kinase inhibitor)



# References

National Comprehensive Cancer Network (NCCN) guidelines

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Fields R, Hameed M, Qin L. Dermatofibrosarcoma protuberans (DFSP): predictors of recurrence and the use of systemic therapy. *Ann Surg Oncol*, 2011; 18:328–36.

Byrd D, Compton C, Fritz A, et al. editors. American Joint Committee on Cancer Cancer Staging Manual, 7th ed. New York: Springer, 2010

Thway K, Noujaim J, Jones RL, Fisher C. Dermatofibrosarcoma protuberans: pathology, genetics, and potential therapeutic strategies. *Ann Diagn Pathol*. 2016;25:64–71.

Thank you

