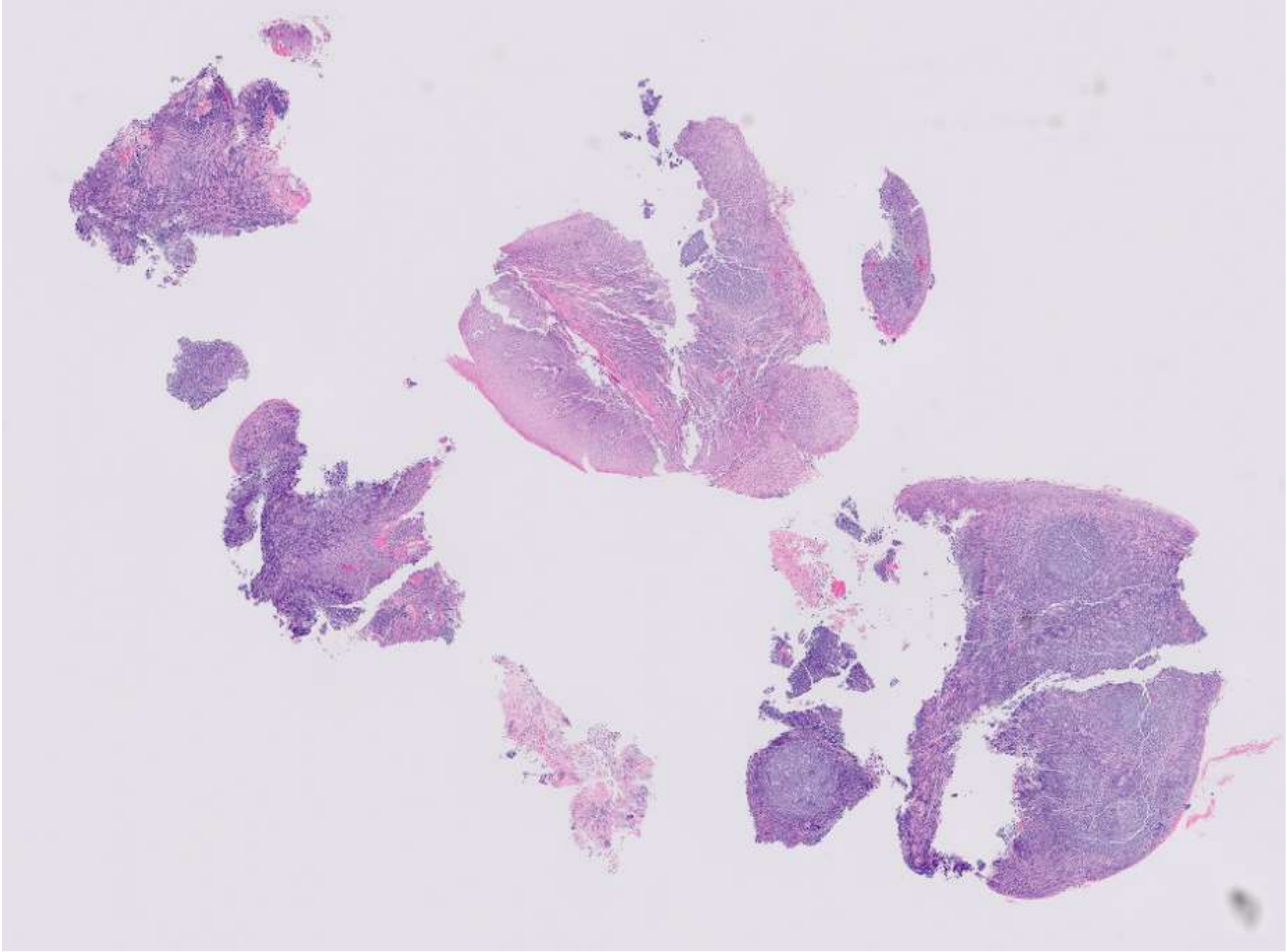
JULY 2022 DIAGNOSIS LIST

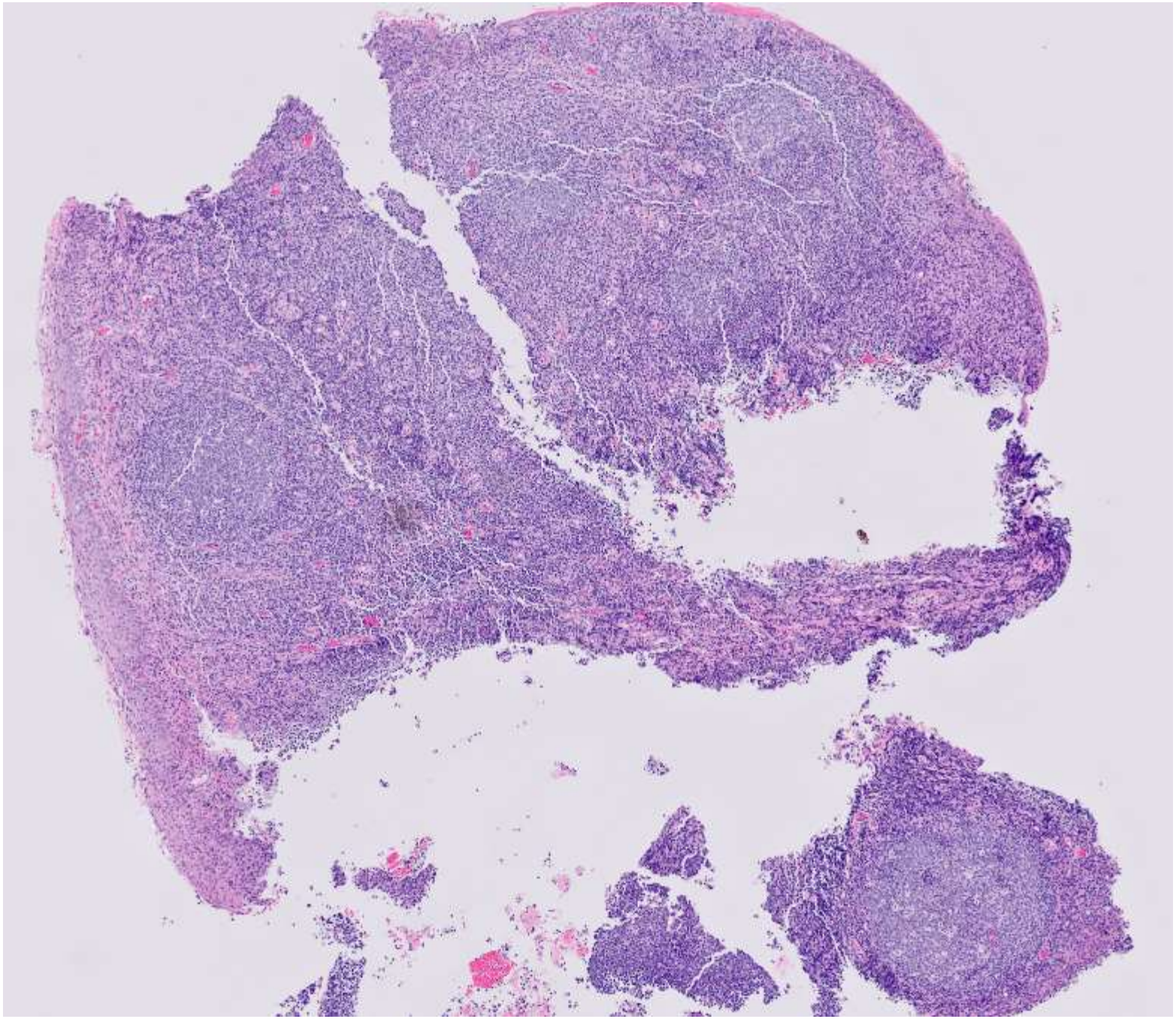
22-0701: syphilis (tonsil; ENTpath & ID path)
22-0702: urothelial carcinoma with glandular differentiation (bladder; GU path)
22-0703: Leishmaniasis (skin; dermpath & ID path)
22-0704: livedoid vasculopathy (skin; dermpath)
22-0705: consistent with lymphocyte-rich hepatocellular carcinoma (liver; liver path)
22-0706: high grade endometrial sarcoma, YWHAE positive (endometrium; GYN path)
22-0707: acute myeloid leukemia with NUP98 rearrangement (bone marrow; heme path)
22-0708: amyloid goiter (soft tissue; HN path)

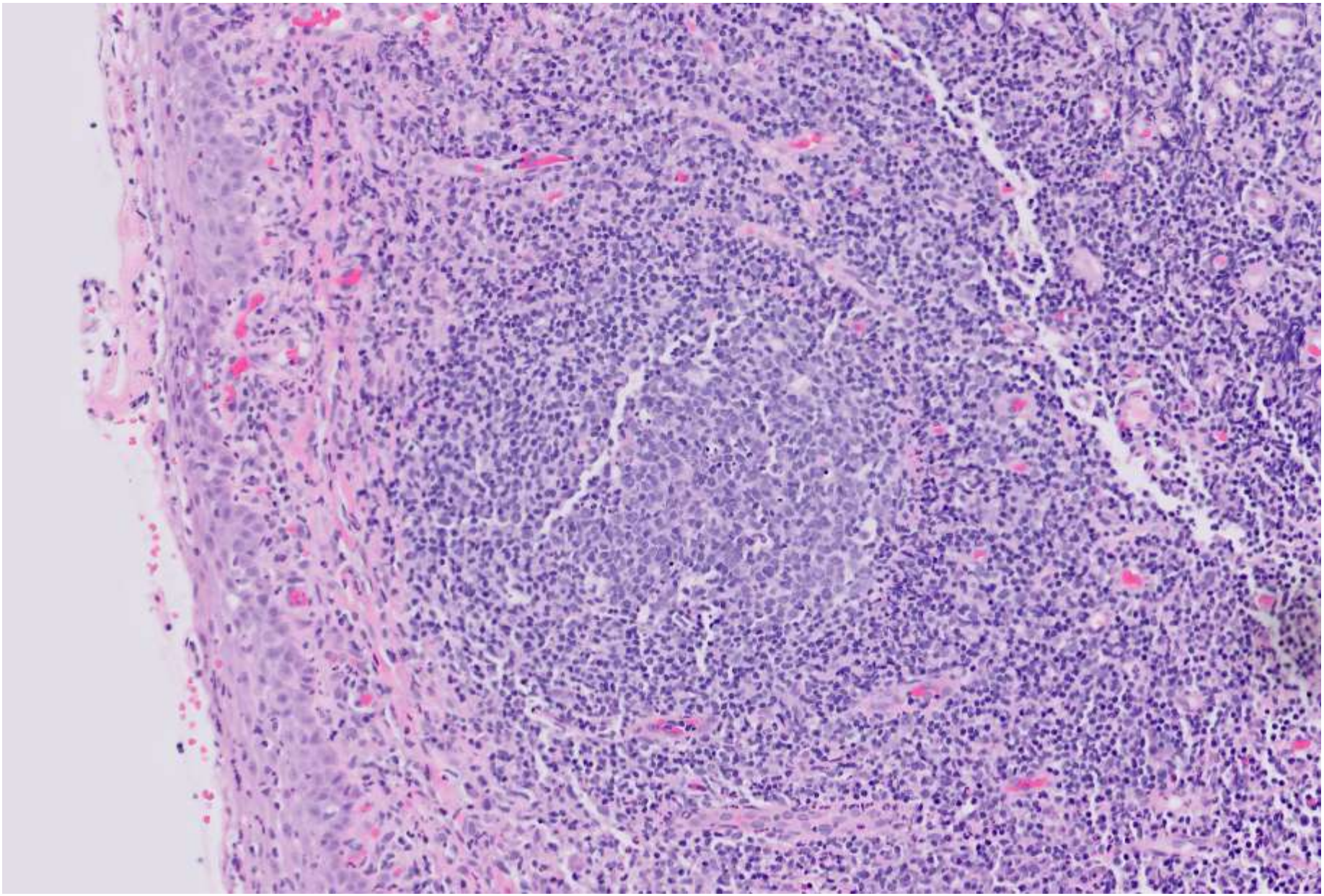
22-0701

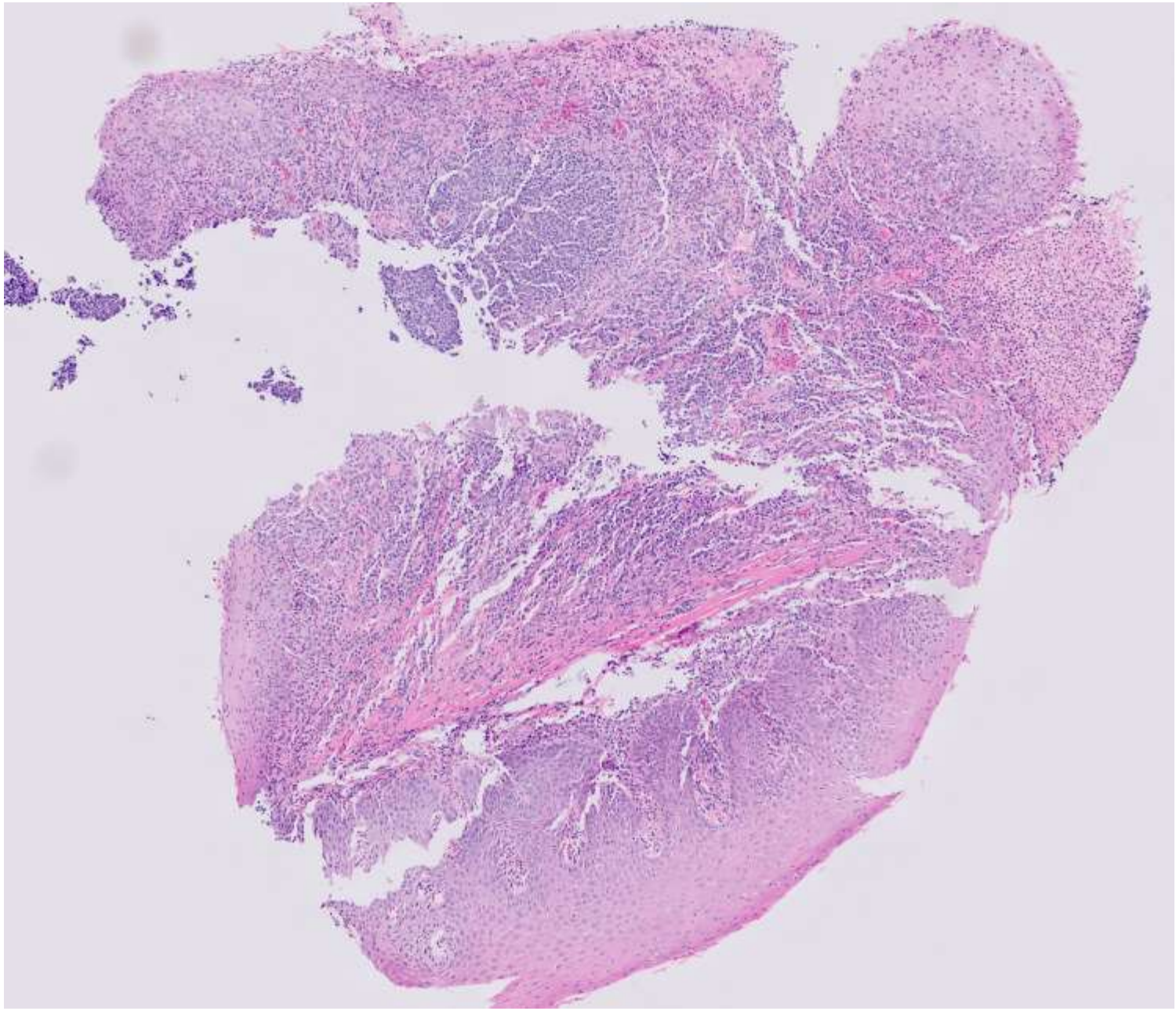
Emily Chan; UCSF

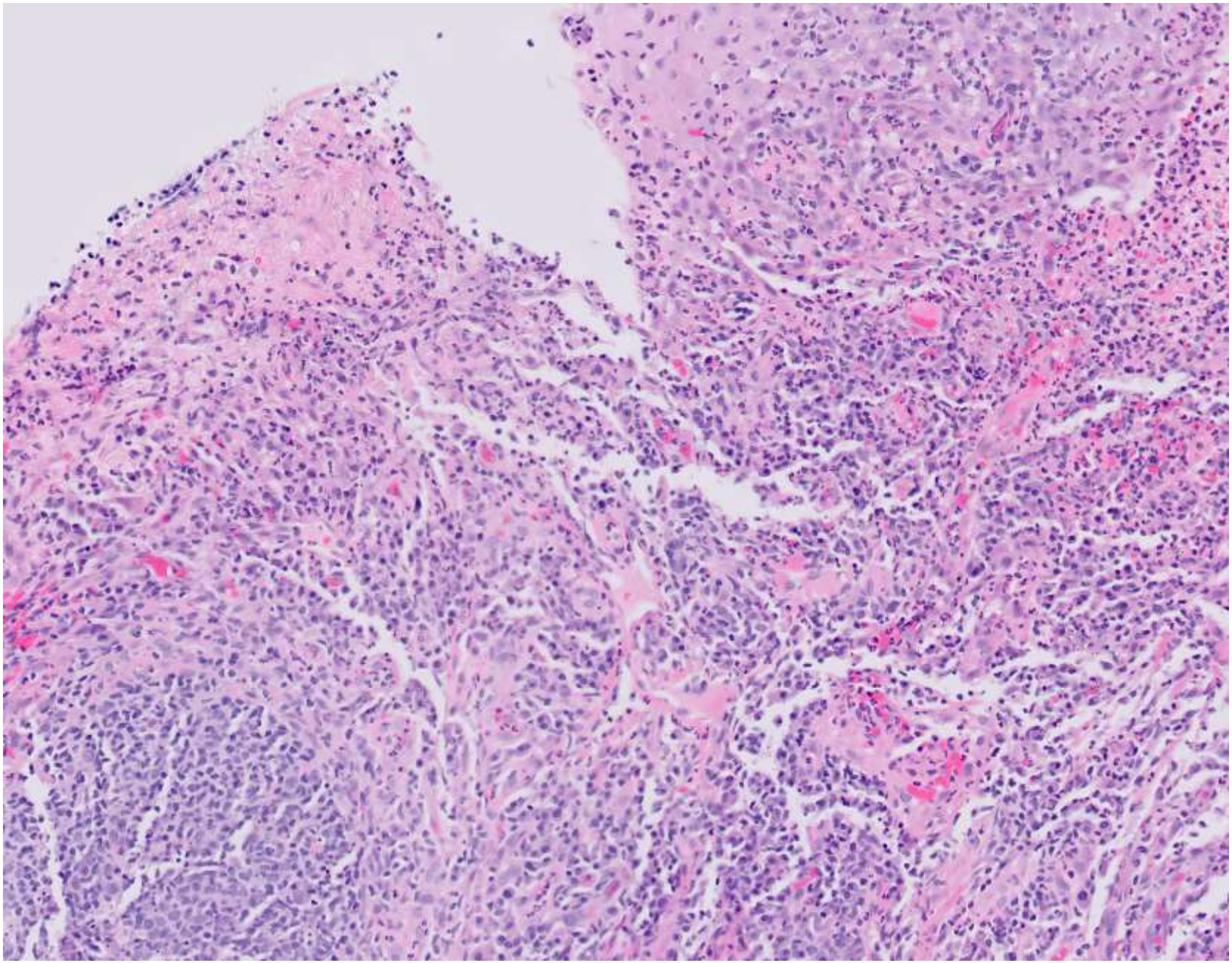
20ish M with recurrent right tonsillary swelling for one year. Biopsy of area with shallow ulceration.

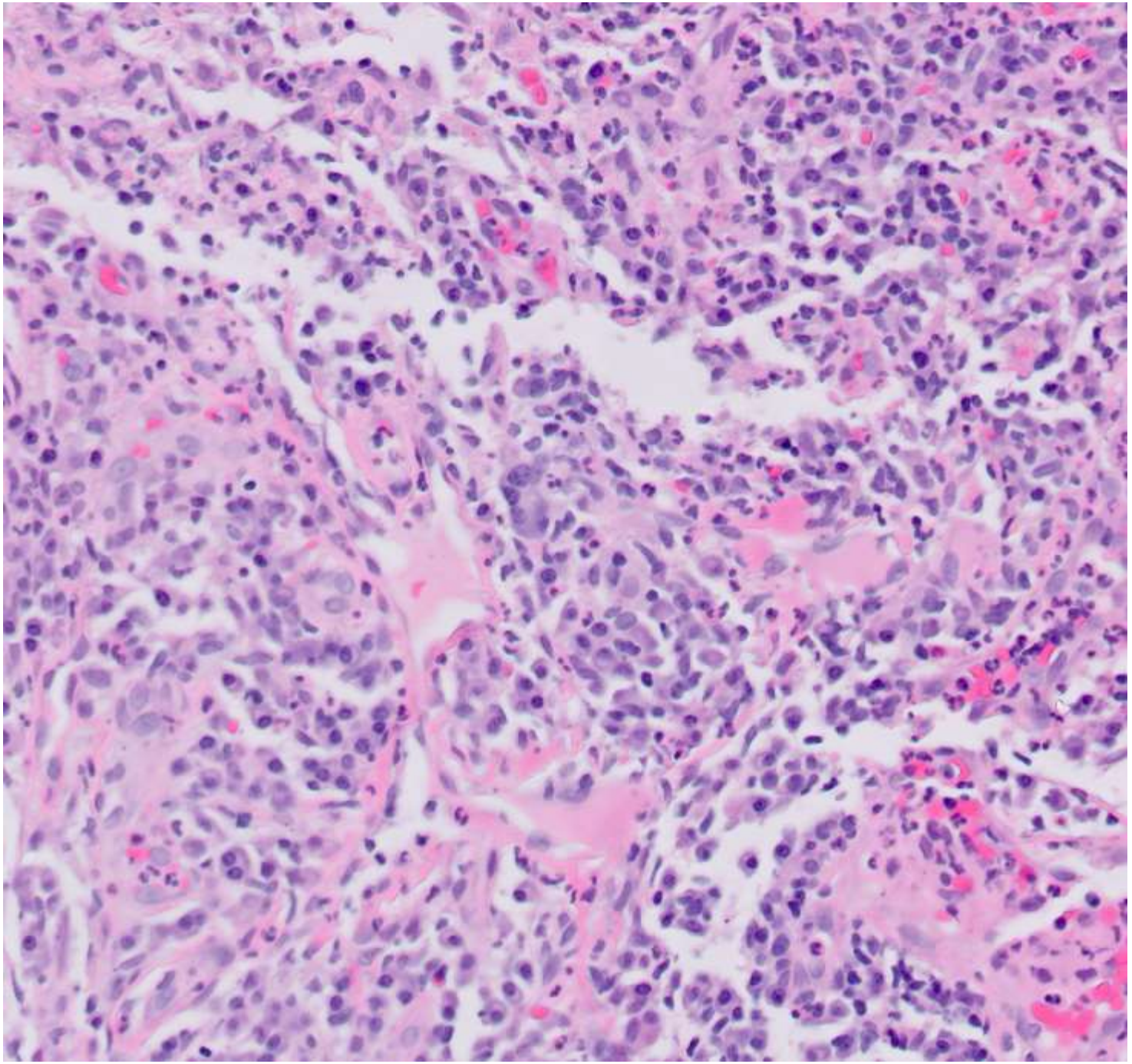










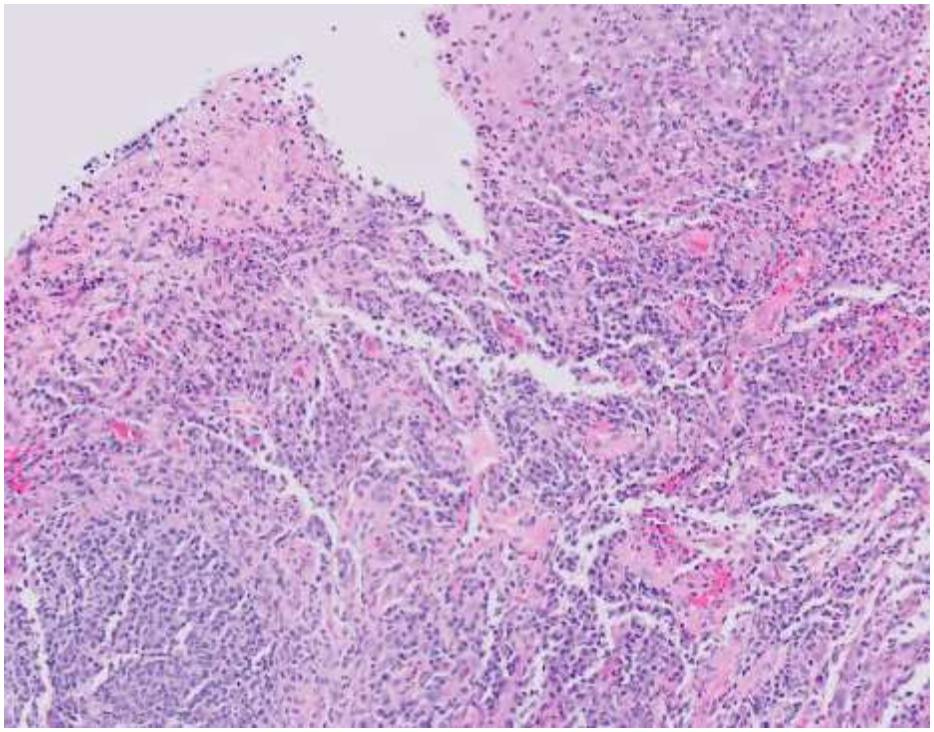


Differential Diagnosis

- ~~Dysplasia/SCC, lymphoma~~
- Traumatic ulcer
- Fungal or viral infection
- Pseudoepitheliomatous hyperplasia
- Lichenoid mucositis

Diagnosis or Differential Diagnosis?

"Acute and chronically inflamed tonsillar mucosa with ulceration, no evidence of malignancy"



…next case!

Diagnosis or Differential Diagnosis?

“Acute and chronically inflamed tonsillar mucosa with ulceration, no evidence of malignancy”

…next case!

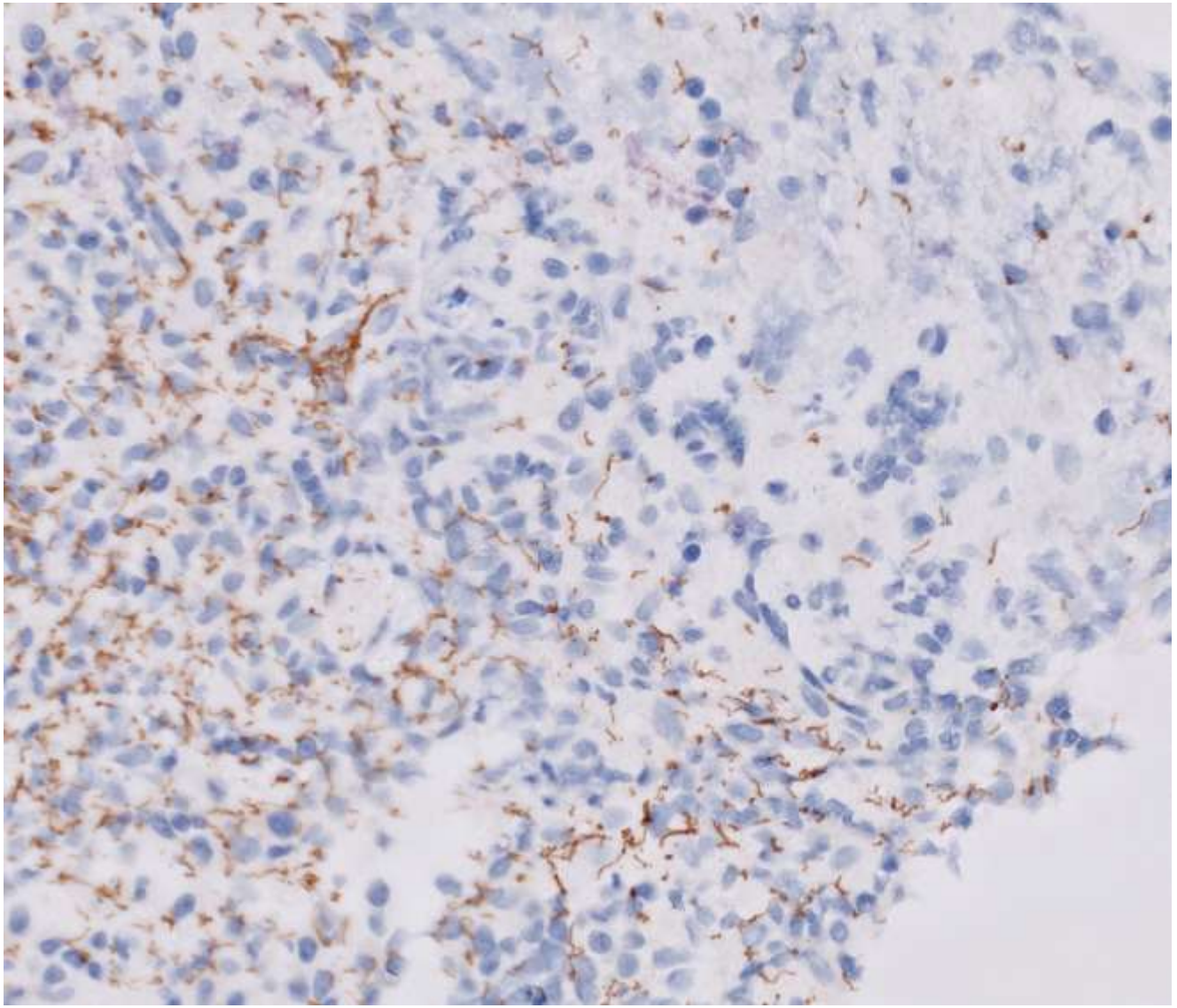
…or not??

Additional workup

- GMS
- HHV8
- HSV
- CMV
- Treponema pallidum

- Review the clinical history
  - Immunocompromised? HIV? MSM?

T. Pallidum IHC



Diagnosis: Tonsillar syphilis

Patient follow up:

- History of MSM
- Subsequent RPR 1:16 which declined to 1:2 following injection of intramuscular Penicillin G
- HIV testing not available
- Required to report to local Department of Public Health for contact tracing

Reportable conditions

Title 17, California Code of Regulations (CCR) §2500, §2593, §2641.5-2643.20, and §2800-2812 Reportable Diseases and Conditions*

§ 2500. REPORTING TO THE LOCAL HEALTH AUTHORITY.

- **§ 2500(b)** It shall be the duty of every health care provider, knowing of or in attendance on a case or suspected case of any of the diseases or condition listed below, to report to the local health officer for the jurisdiction where the patient resides. Where no health care provider is in attendance, any individual having knowledge of a person who is suspected to be suffering from one of the diseases or conditions listed below may make such a report to the local health officer for the jurisdiction where the patient resides.
- **§ 2500(c)** The administrator of each health facility, clinic, or other setting where more than one health care provider may know of a case, a suspected case or an outbreak of disease within the facility shall establish and be responsible for administrative procedures to assure

https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/Reportable-Disease-and-Conditions.aspx

Reportable conditions

https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/Reportable-Disease-and-Conditions.aspx

Coccidioidomycosis	WEEK	Pertussis (Whooping Cough)	FAX ✆✉
Coronavirus Disease 2019 (COVID-19)	✆!	Plague, human or animal	✆!
Creutzfeldt-Jakob Disease (CJD) and other Transmissible Spongiform Encephalopathies (TSE)	WEEK	Poliovirus Infection	FAX ✆✉
Cryptosporidiosis	FAX ✆✉	Psittacosis	FAX ✆✉
Cyclosporiasis	WEEK	Q Fever	FAX ✆✉
Cysticercosis or taeniasis	WEEK	Rabies, human or animal	✆!
Dengue Virus Infection	FAX ✆✉	Relapsing Fever	FAX ✆✉
Diphtheria	✆!	Respiratory Syncytial Virus-associated deaths in laboratory-confirmed cases less than five years of age	WEEK
Domoic Acid Poisoning (Amnesic Shellfish Poisoning)	✆!	Rickettsial Diseases (non-Rocky Mountain Spotted Fever), including Typhus and Typhus-like illnesses	WEEK
Ehrlichiosis	WEEK	Rocky Mountain Spotted Fever	WEEK
Encephalitis, Specify Etiology: Viral, Bacterial, Fungal, Parasitic	FAX ✆✉	Rubella (German Measles)	WEEK
Escherichia coli: shiga toxin producing (STEC) including *E. coli* O157	FAX ✆✉	Rubella Syndrome, Congenital	WEEK
Flavivirus infection of undetermined species	✆!	Salmonellosis (Other than Typhoid Fever)	FAX ✆✉
Foodborne Disease	†FAX ✆✉	Scombroid Fish Poisoning	✆!
Giardiasis	WEEK	Shiga toxin (detected in feces)	✆!
Gonococcal Infections	WEEK	Shigellosis	FAX ✆✉
Haemophilus influenzae, invasive disease, all serotypes (report an incident less than 5 years of age)	FAX ✆✉	Smallpox(Variola)	✆!
Hantavirus Infections	FAX ✆✉	Syphilis (all stages, including congenital)	FAX ✆✉
Hemolytic Uremic Syndrome	✆!	Tetanus	WEEK
Hepatitis A, acute infection	FAX ✆✉	Trichinosis	FAX ✆✉

Oral syphilis

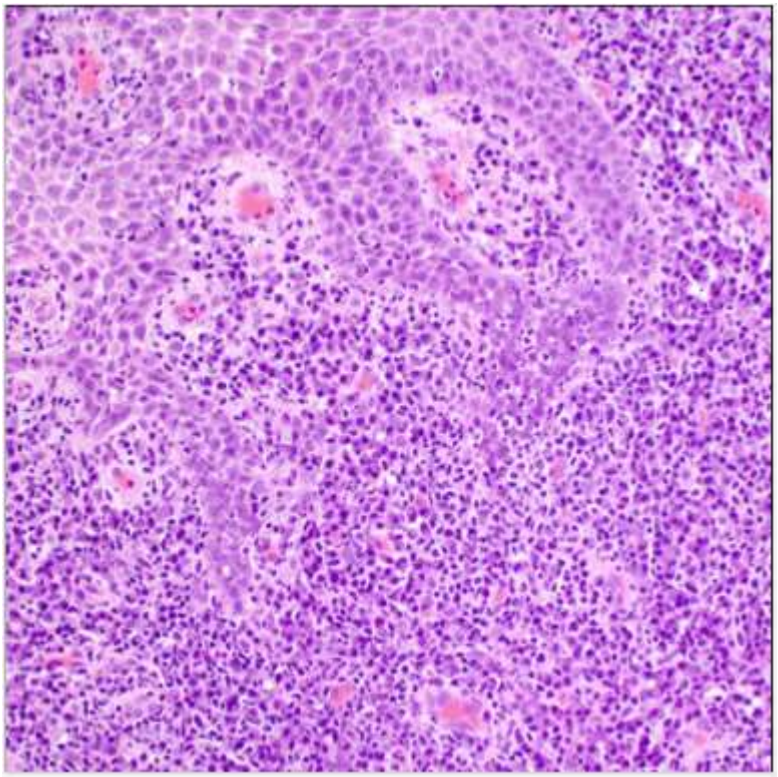
- Sexually transmitted infection
- Can be primary (chancre/painless ulcer) or secondary (more diffuse involvement)
- Most common in 25-29 year olds
- 88% occur in men, especially men who have sex with men (MSM)

https://app.expertpath.com/document/oral-syphilis

Oral Syphilis – Histology nonspecific

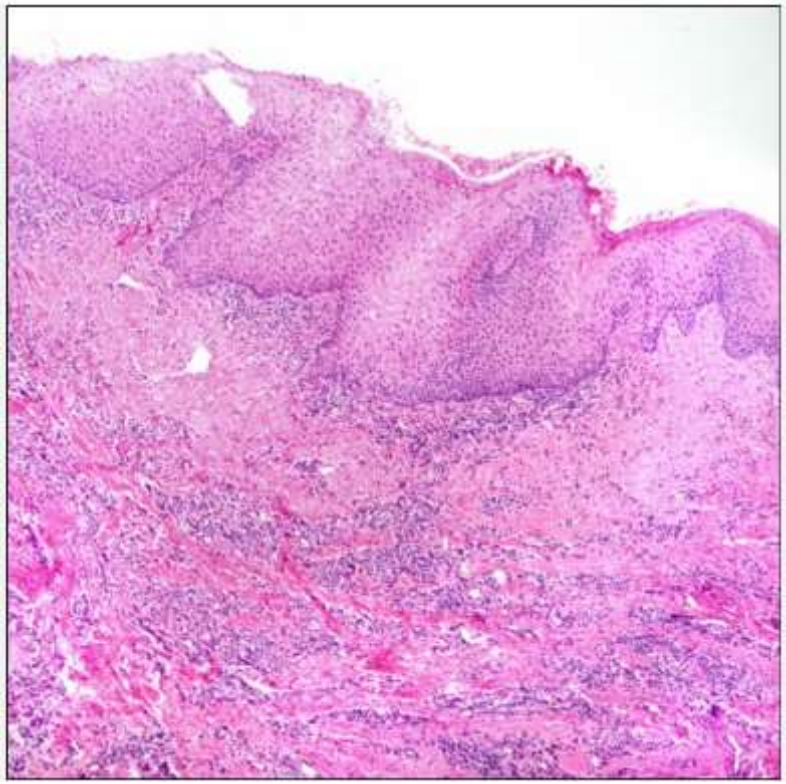
Primary

- Surface ulceration (chancre)
- Dense deep plasma cell-rich inflammatory infiltrate, can be perivascular



Secondary

- Epithelial hyperplasia with spongiosus and “dirty” epithelium
- Perivascular chronic inflammation

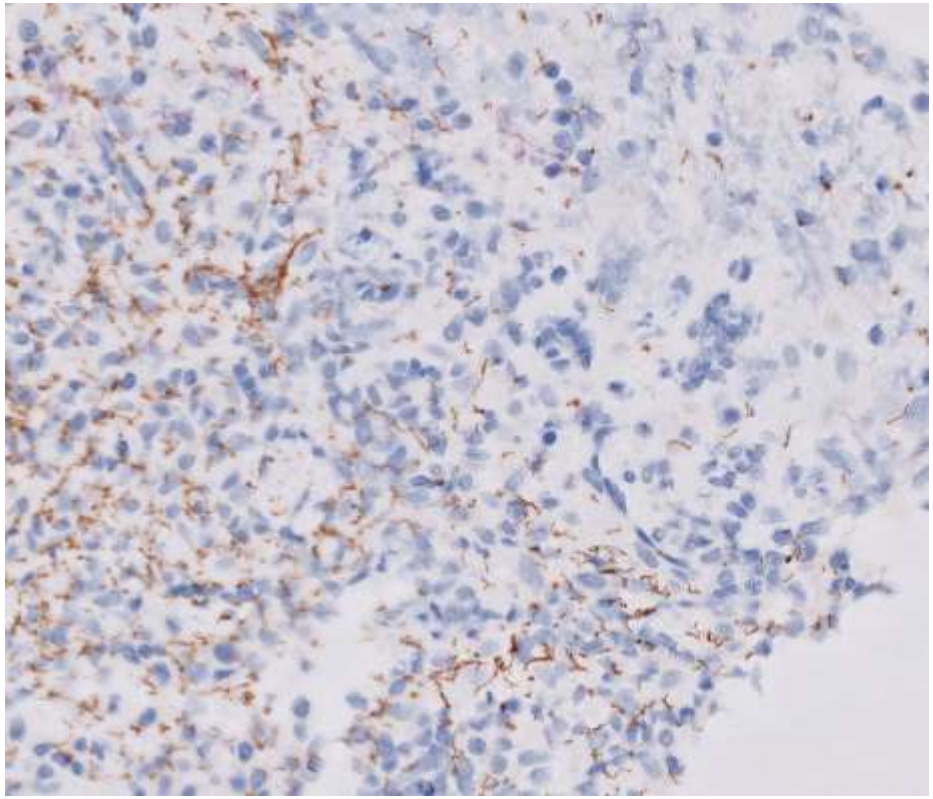


https://app.expertpath.com/document/oral-syphilis

*Plasma cells not always abundant. (Additional reference: Tse JY. Syphilis of the Aerodigestive Tract. Am J Surg Pathol. 2018 Apr;42(4):472-478. PMID: 29135519.)

T. Pallidum IHC

- More sensitive than Warthin-Starry
  - 80% vs 50% (Martin-Ezquerra et al. Hum Pathol 2009 PMID 19157499)
- Can cross react with other spirochetes including *Brachyspira* (Ruiz et al Arch Pathol Lab Med. 2016 PMID 27684969)



Primary tonsillar syphilis

- Only rare case reports in literature
- Increases in oro-genital sex practice have led to increased incidence
- Can present with swelling but may go unnoticed (i.e. painless chancre)

Histopathology 2022 DOI: 10.1111/his.14712

Lesson of the Month

Not your usual tonsillitis: a lesson for recognizing primary tonsillar syphilis

Ruobin Wu, Jennifer Babik, Matthew Russell, Annemieke van Zante, Emily Chan

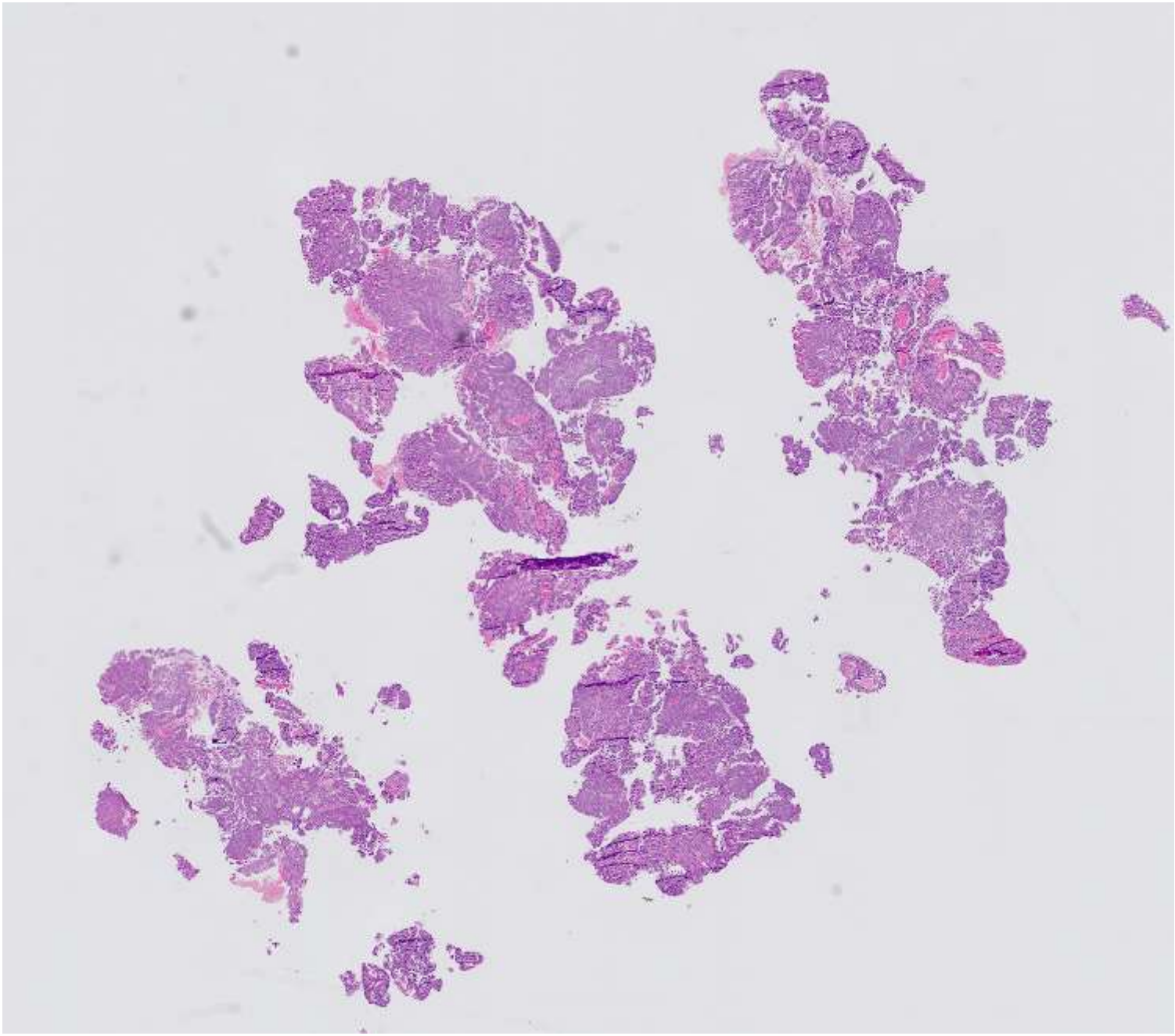
Summary: Inflamed and ulcerated tonsillar biopsy and syphilis

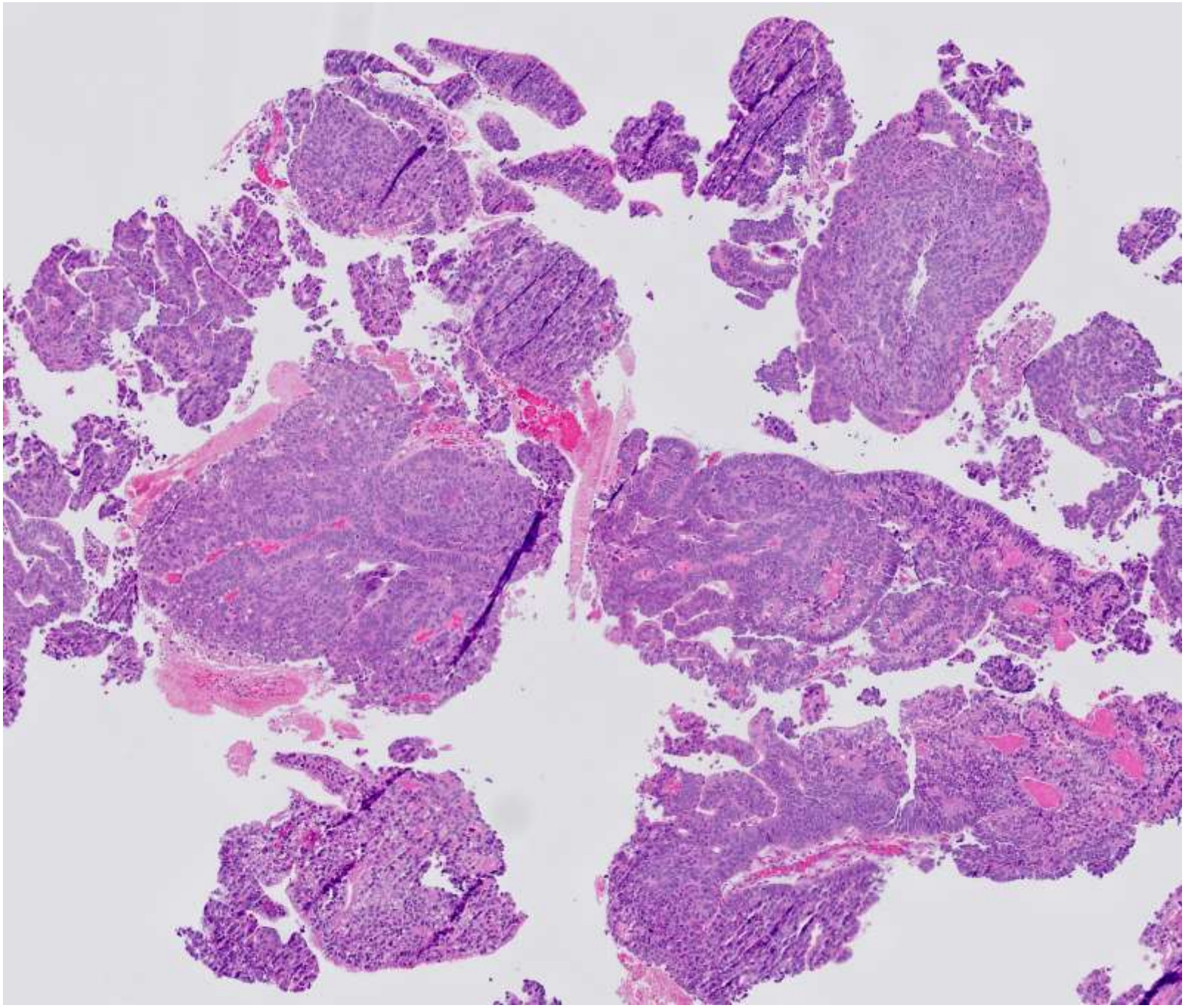
- Exclude dysplasia/SCC/lymphoma
- Review history for risk factors and consider (or suggest) additional evaluation for infectious etiologies
- Early identification of syphilis can facilitate adequate treatment
- Required reporting to local public health department

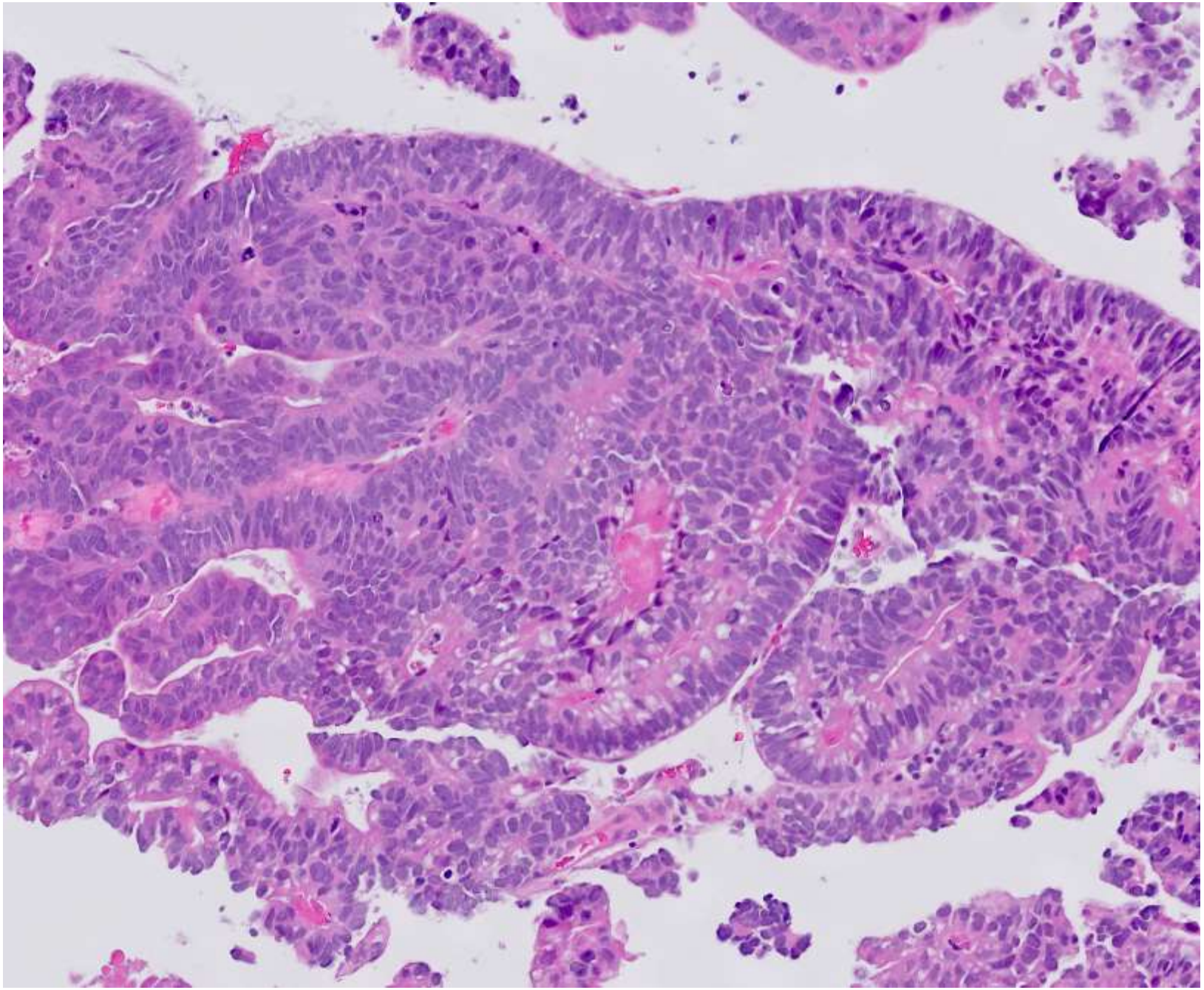
22-0702

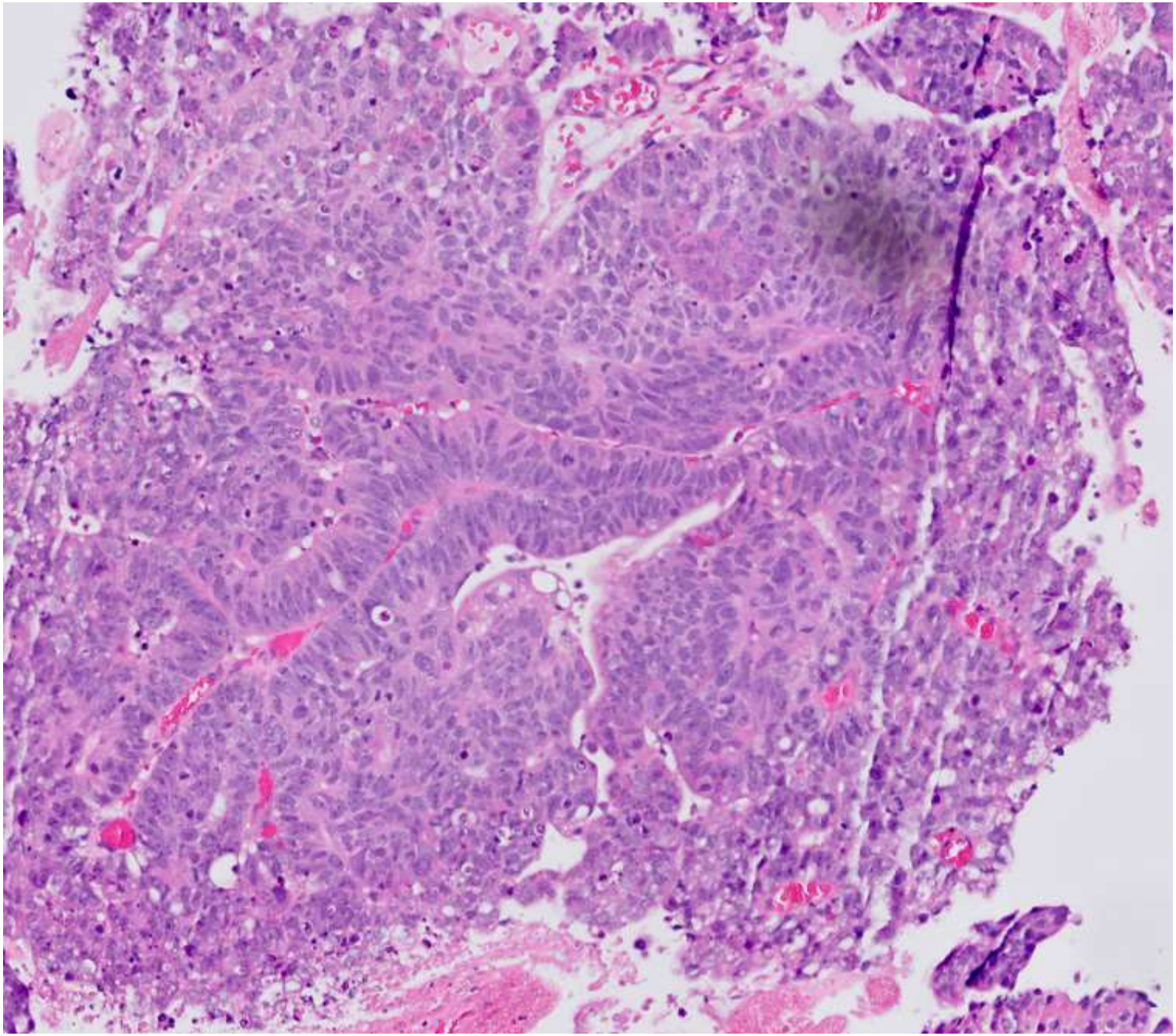
Emily Chan; UCSF

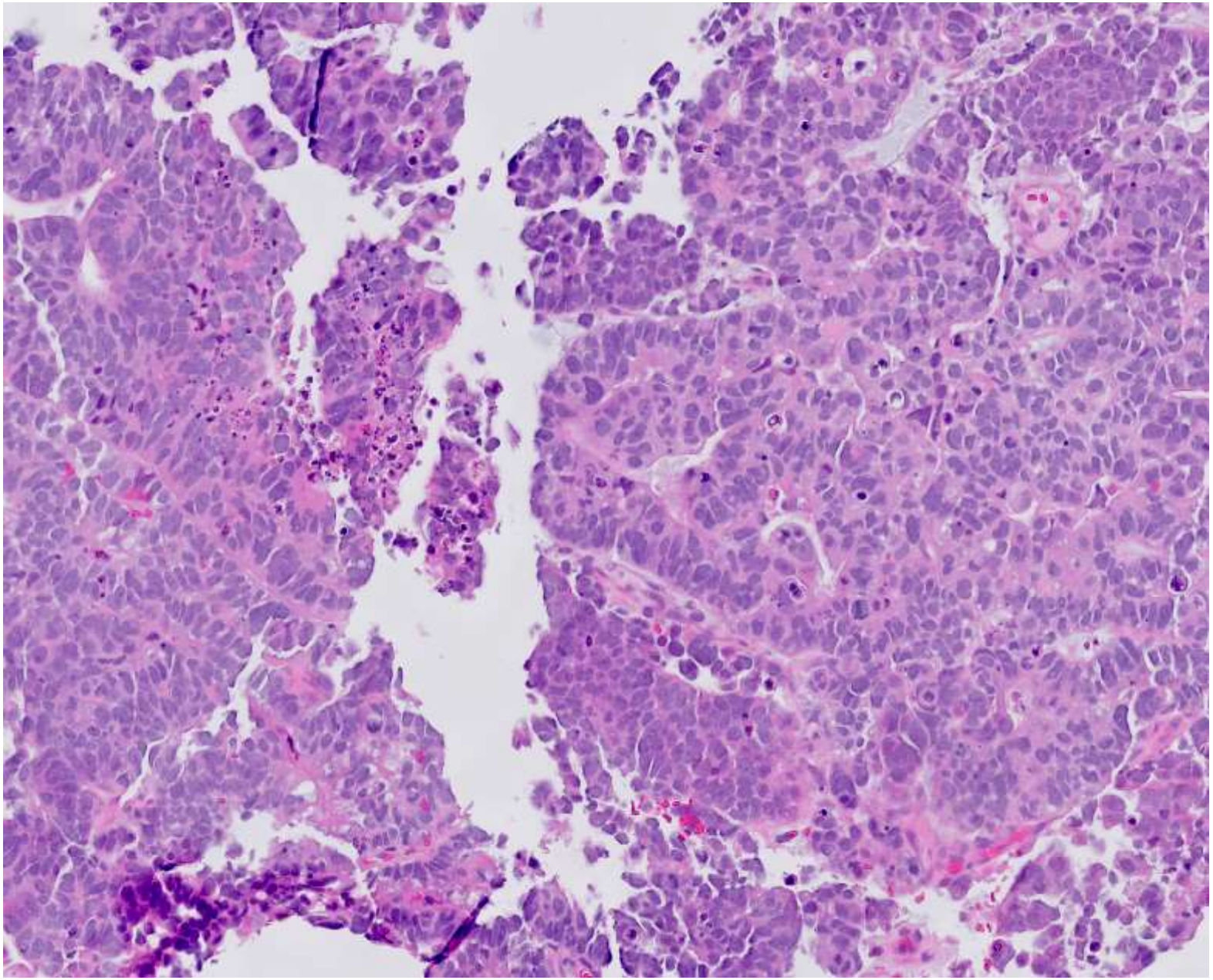
80ish M with dysuria. Cystoscopy showed 3mm right posterior wall mass with surrounding erythema.

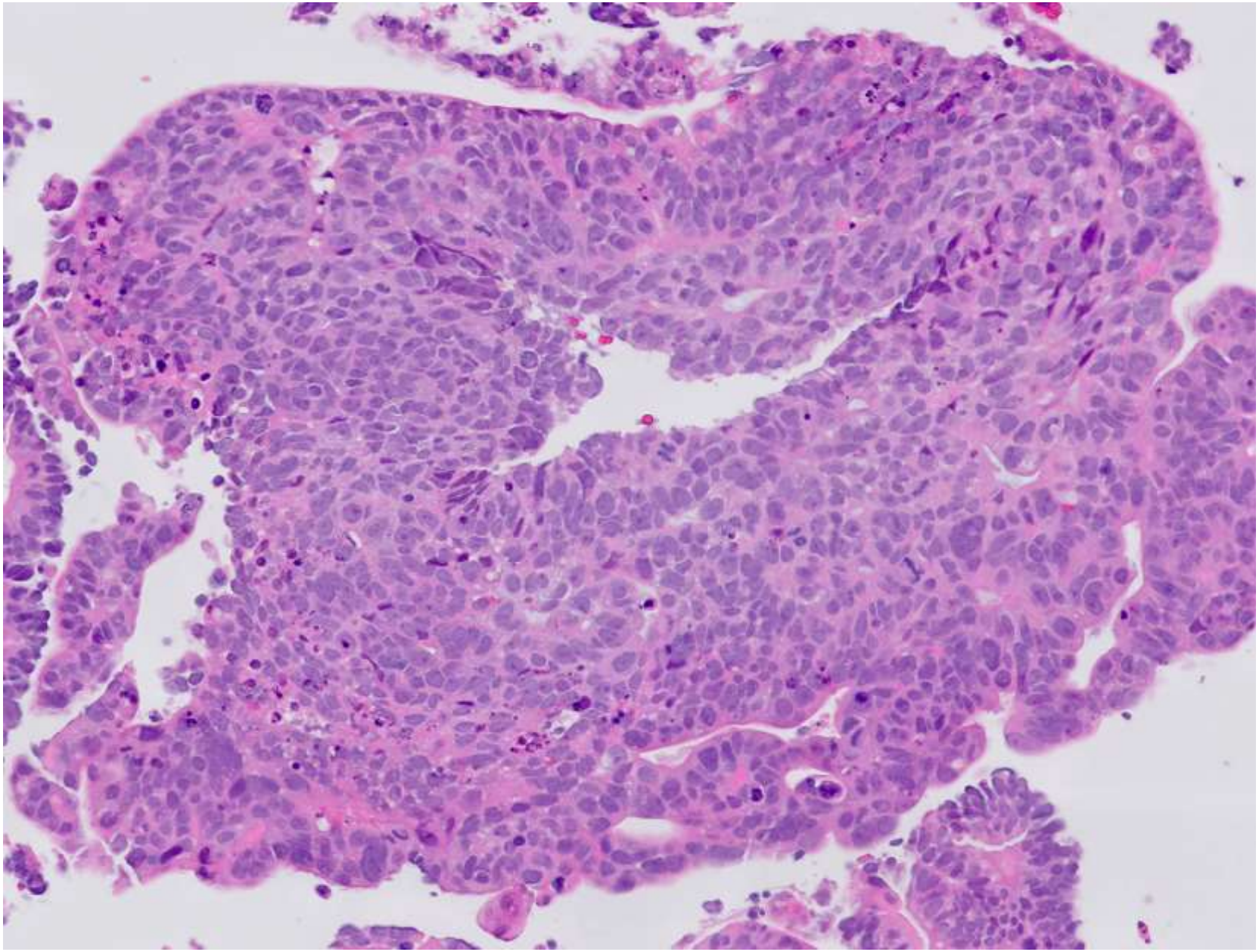


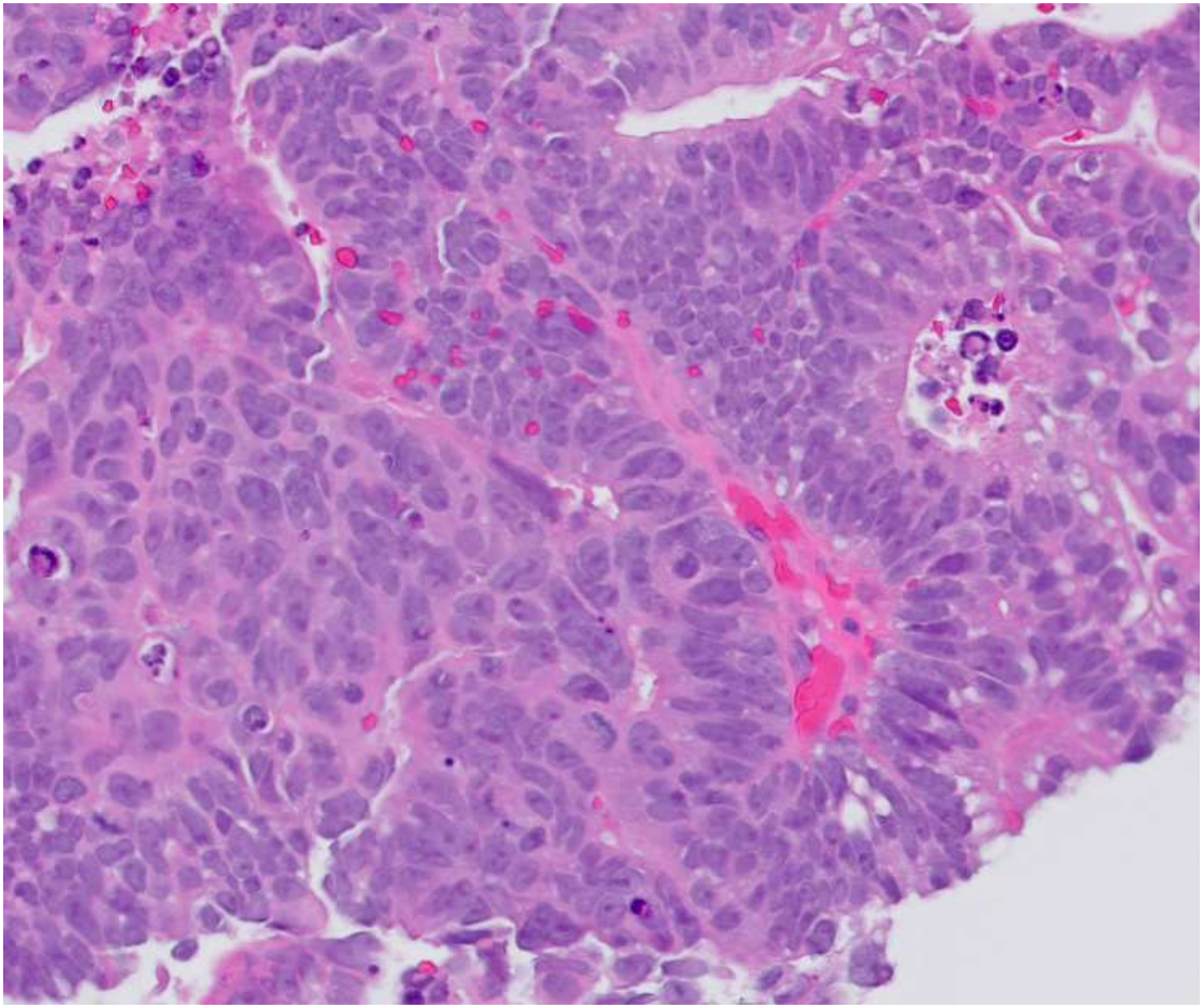


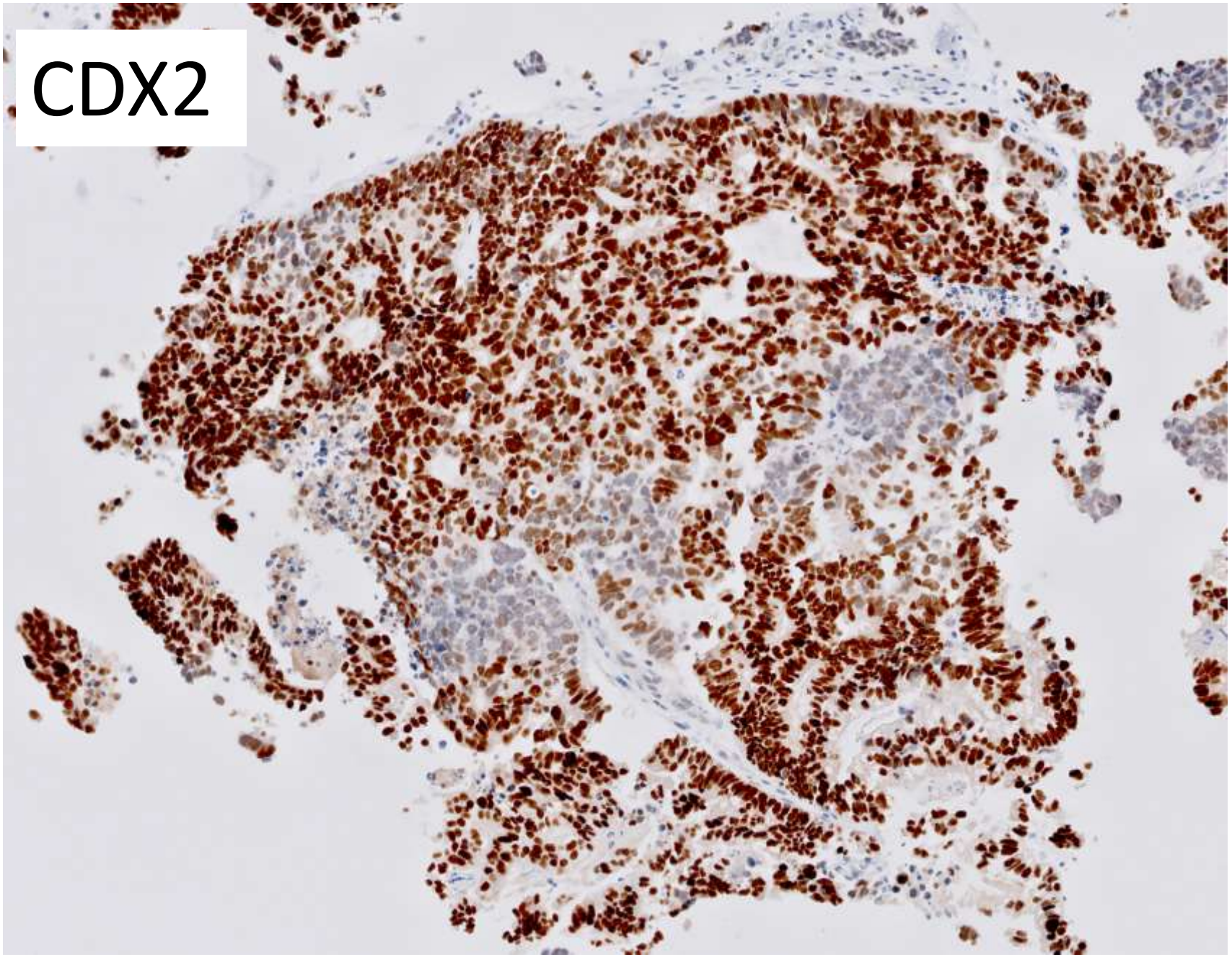








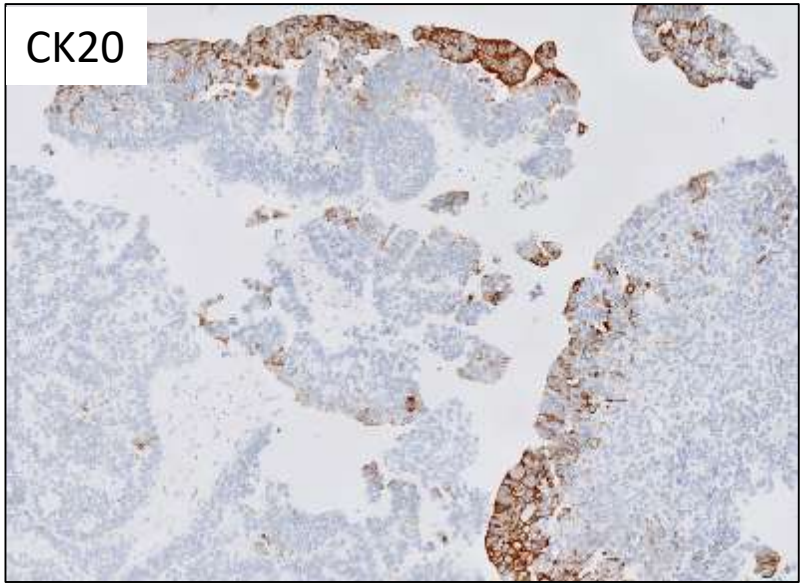


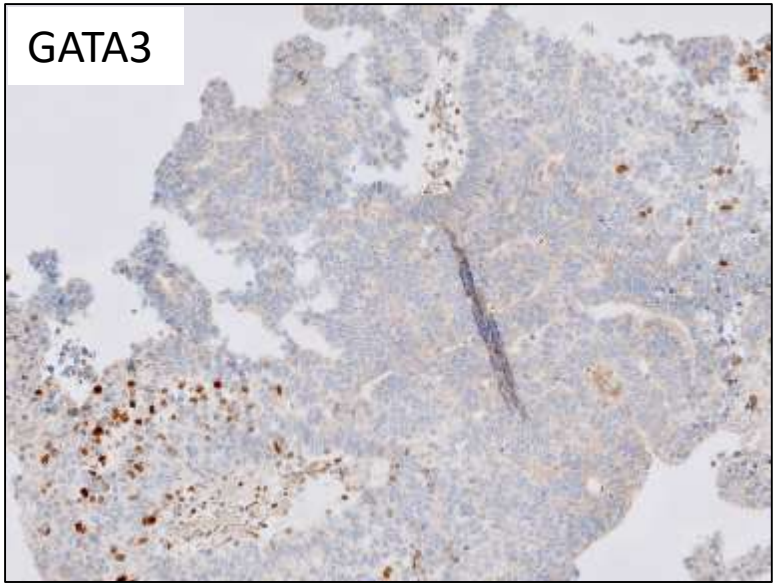

CDX2

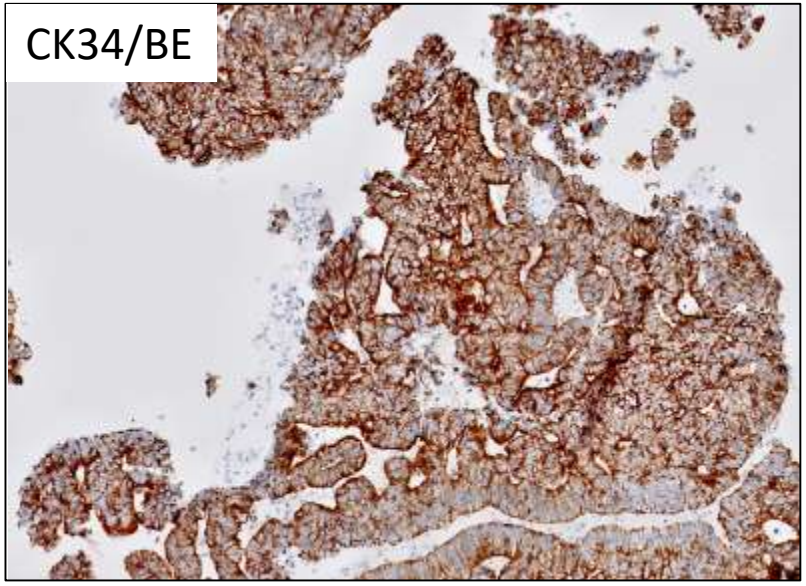
H&E differential diagnosis

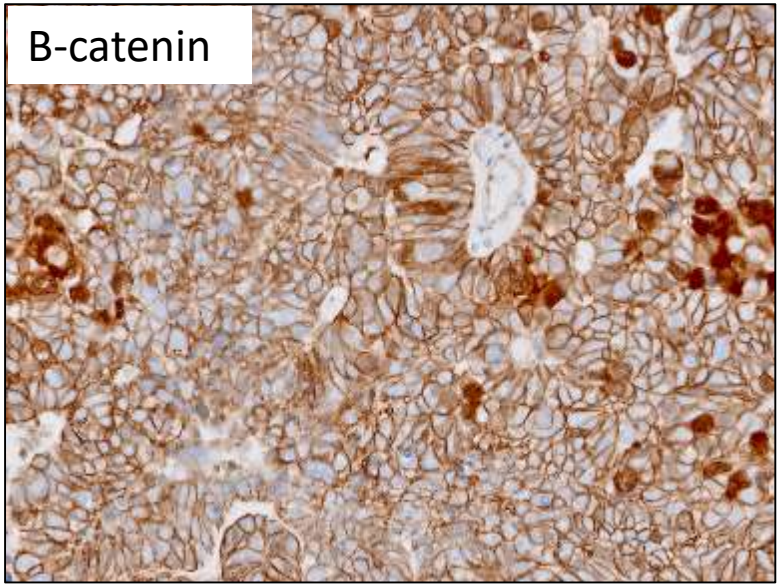
- Urothelial carcinoma with glandular differentiation
- Adenocarcinoma, enteric type, primary to urinary bladder (“primary bladder adenocarcinoma”)
- Adenocarcinoma of colorectal origin (metastatic or via direct extension)
- Neuroendocrine carcinoma
- Prostatic adenocarcinoma

Additional available IHC









CK7: Negative

Problematic differential diagnosis with significant implications for management:

Urothelial Carcinoma with Glandular Differentiation	Primary Bladder Adenocarcinoma
- Glandular component has significant morphologic and immunohistochemical overlap with colorectal adenocarcinoma (CK7-/CK20+/CDX2+) - Identification of bona fide conventional urothelial carcinoma component can help	- Can be enteric, mucinous, or mixed - Immunohistochemically identical to colorectal adenocarcinoma, including can see nuclear b-catenin (though less frequently) - Typically requires clinical and imaging/colonoscopy correlation to exclude colorectal met/direct extension

https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf

Problematic differential diagnosis with significant implications for management:

Urothelial Carcinoma with Glandular Differentiation	Primary Bladder Adenocarcinoma
- Treated like pure urothelial carcinoma of bladder - BCG for non-muscle invasive - Radical cystectomy with neoadjuvant cisplatin-based chemotherapy, bilateral pelvic lymphadenectomy for muscle invasive)	- Local control with surgery or RT - No role for neoadjuvant/adjuvant chemotherapy - Chemotherapy with colorectal regimen for node-positive disease

https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf

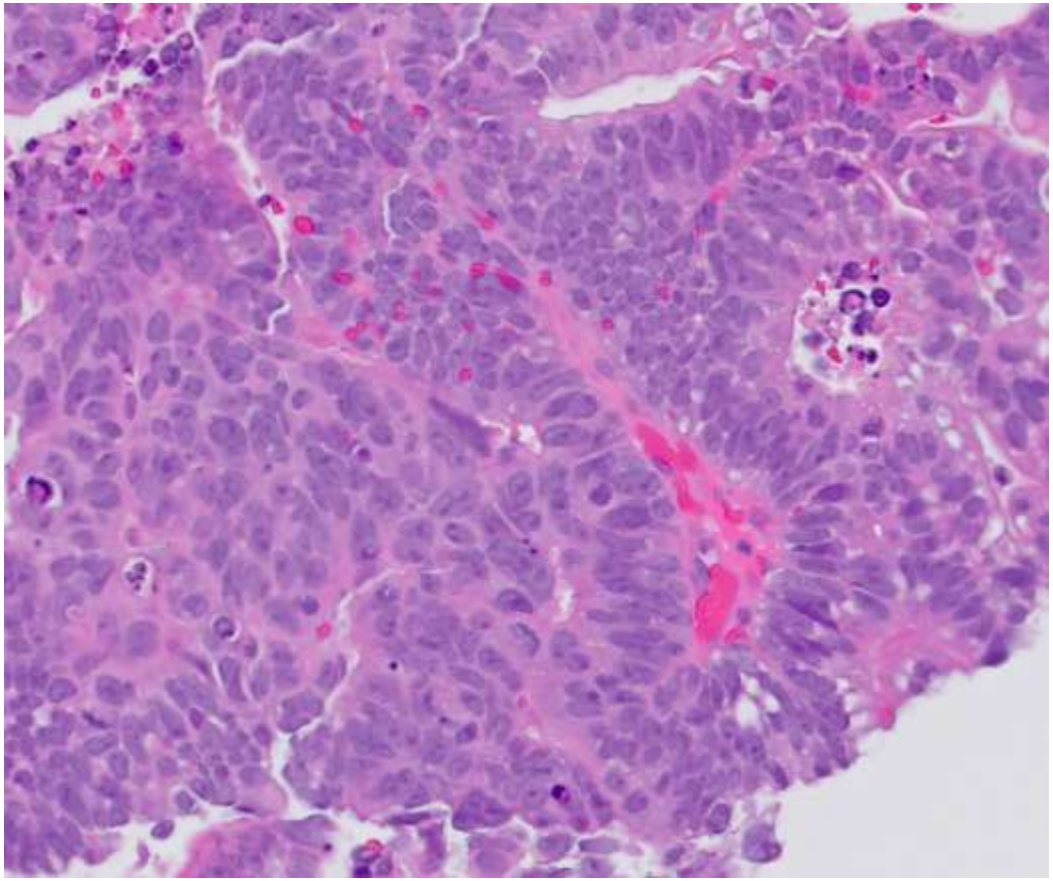
Initial diagnosis:

- High-grade carcinoma with glandular features; see comment.

Comment:

- Favored urothelial
- Suggested UCSF500

given the small biopsy which was entire gross extent of lesion per cystoscopy



Next-generation sequencing-based molecular characterization of primary urinary bladder adenocarcinoma

Somak Roy, Dinesh Pradhan, Wayne L Ernst, Stephanie Mercurio, Yana Najjar, Rahul Parikh, Anil V Parwani, Reetesh K Pai, Rajiv Dhir & Marina N Nikiforova

Modern Pathology **30**, 1133–1143 (2017) | Cite this article

Molecular Genetic Features of Primary Nonurachal Enteric-type Adenocarcinoma, Urachal Adenocarcinoma, Mucinous Adenocarcinoma, and Intestinal Metaplasia/Adenoma: Review of the Literature and Next-generation Sequencing Study

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› Virchows Arch. 2020 Sep;477(3):445-454. doi: 10.1007/s00428-020-02787-8. Epub 2020 Mar 20.

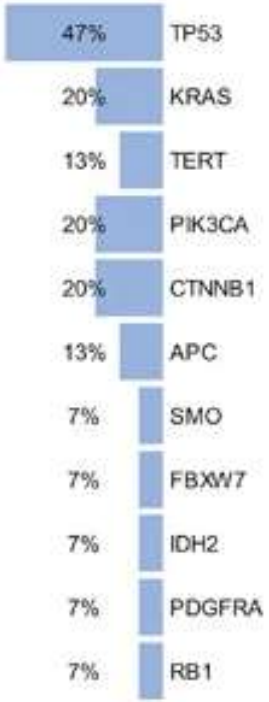
Comparative genomic profiling of glandular bladder tumours

Angela Maurer [1], Nadina Ortiz-Bruechle [1], Karolina Guricova [1], Michael Rose [1], Ronja Morsch [1 2], Stefan Garczyk [1], Robert Stöhr [3], Simone Bertz [3], Reinhard Golz [4], Henning Reis [5], Felix Bremmer [6], Annette Zimpfer [7], Sabine Siegert [8], Glen Kristiansen [9], Kristina Schwamborn [10], Nikolaus Gassler [11], Ruth Knuechel [1], Nadine T Gaisa [12], German study group of bladder cancer

Molecular alterations in:

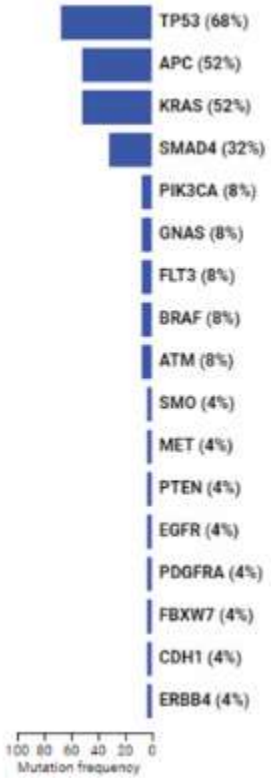
Next-generation sequencing-based molecular characterization of primary urinary bladder adenocarcinoma

Primary bladder Adenocarcinoma (n=15)



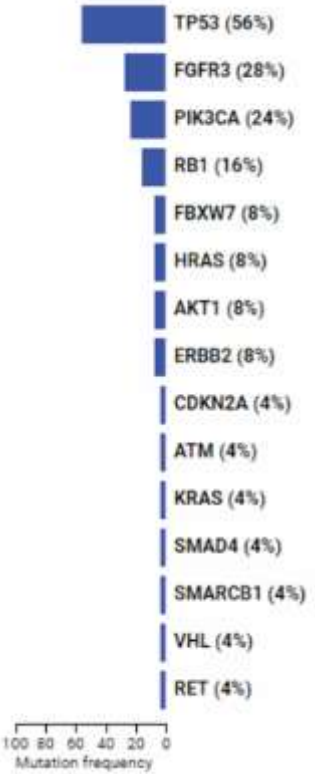
vs

Colorectal adenocarcinoma (n=25)



vs

High-grade urothelial carcinoma (n=25)



Molecular profile of primary bladder adenocarcinoma

- Generally have a more “colorectal” like mutational pattern whereas UC with glandular differentiation exhibits more frequent urothelial-like alterations
- Studies limited by small numbers

UCSF500 NGS testing

PATHOGENIC AND LIKELY PATHOGENIC ALTERATIONS				
VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
KMT2D p.Q800*	NM_003482.3	Pathogenic	2700	70%
TERT c.-124C>T	NM_198253.2	Pathogenic	915	61%
TP53 p.E336*	NM_000546.5	Pathogenic	907	96%
ATR p.R1183*	NM_001184.3	Likely Pathogenic	719	69%
CCND1, FGF19, FGF4, FGF3 amplification	All	Likely Pathogenic	~2x	N/A
CDK4 amplification	All	Likely Pathogenic	~2.5x	N/A

- No FGFR3 mutations have been identified in primary adenocarcinomas.
- Lacks other mutations frequently reported in bladder adenocarcinomas including KRAS, APC, CTNNB1.
- Overall favors urothelial carcinoma with glandular differentiation

Additional follow up:

- Subsequent cystoscopy showed a 3 cm papillary tumor on a stalk which on TURBT reportedly showed additional high-grade papillary urothelial carcinoma with glandular differentiation
- EGD/Colonoscopy negative, no colon mass on CT abdomen

Summary: Glandular lesions in the urinary bladder

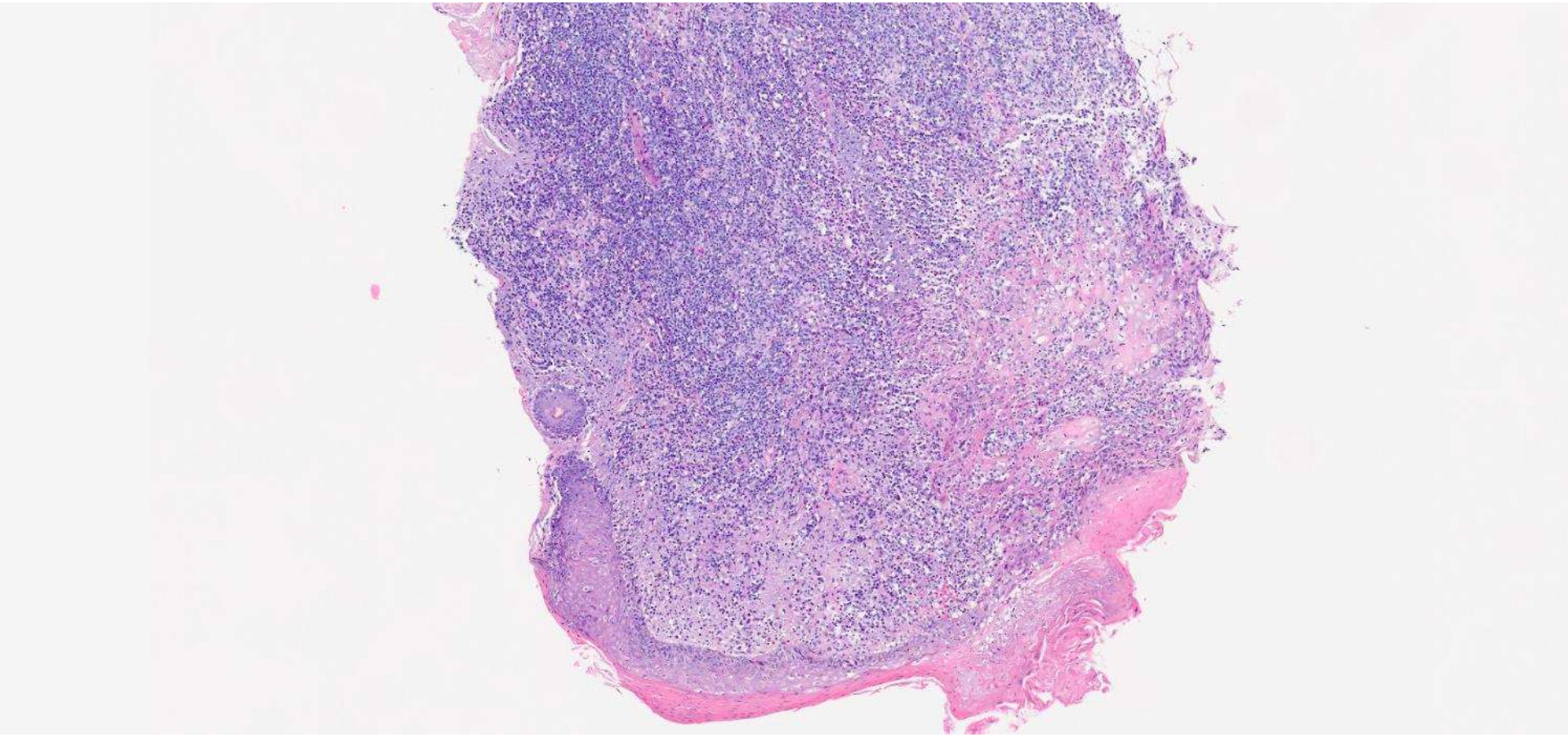
- Primary bladder adenocarcinoma and urothelial carcinoma with glandular differentiation have overlapping morphologic and immunoprofile but significantly different management
- Look for a conventional urothelial component and consider additional sampling if small initial specimen
- Correlate with cystoscopic, imaging and colonoscopy findings
- Consider NGS testing
- Consider more generic carcinoma diagnosis and listing differential to keep treatment options open

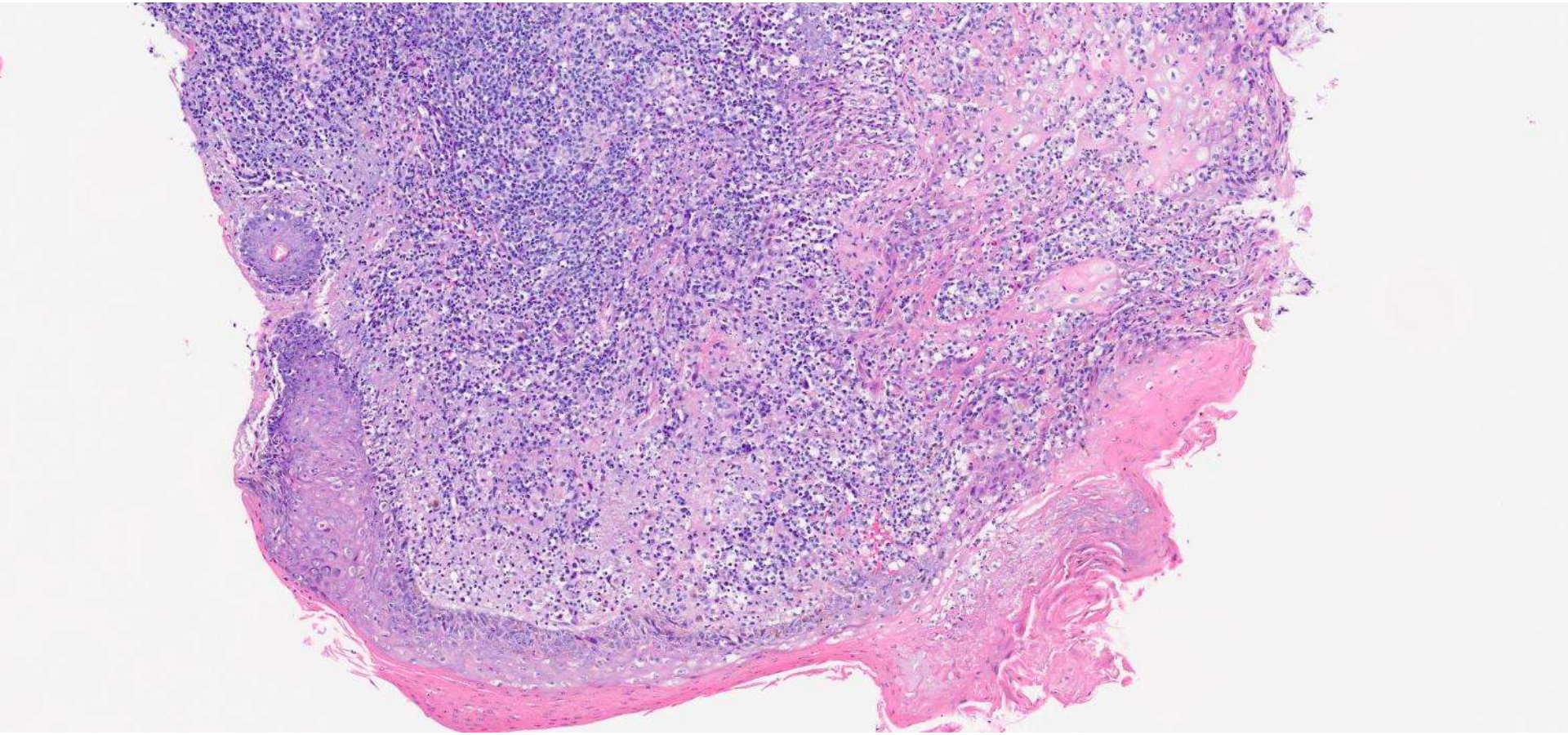
22-0703
Direct link to scanned slide:

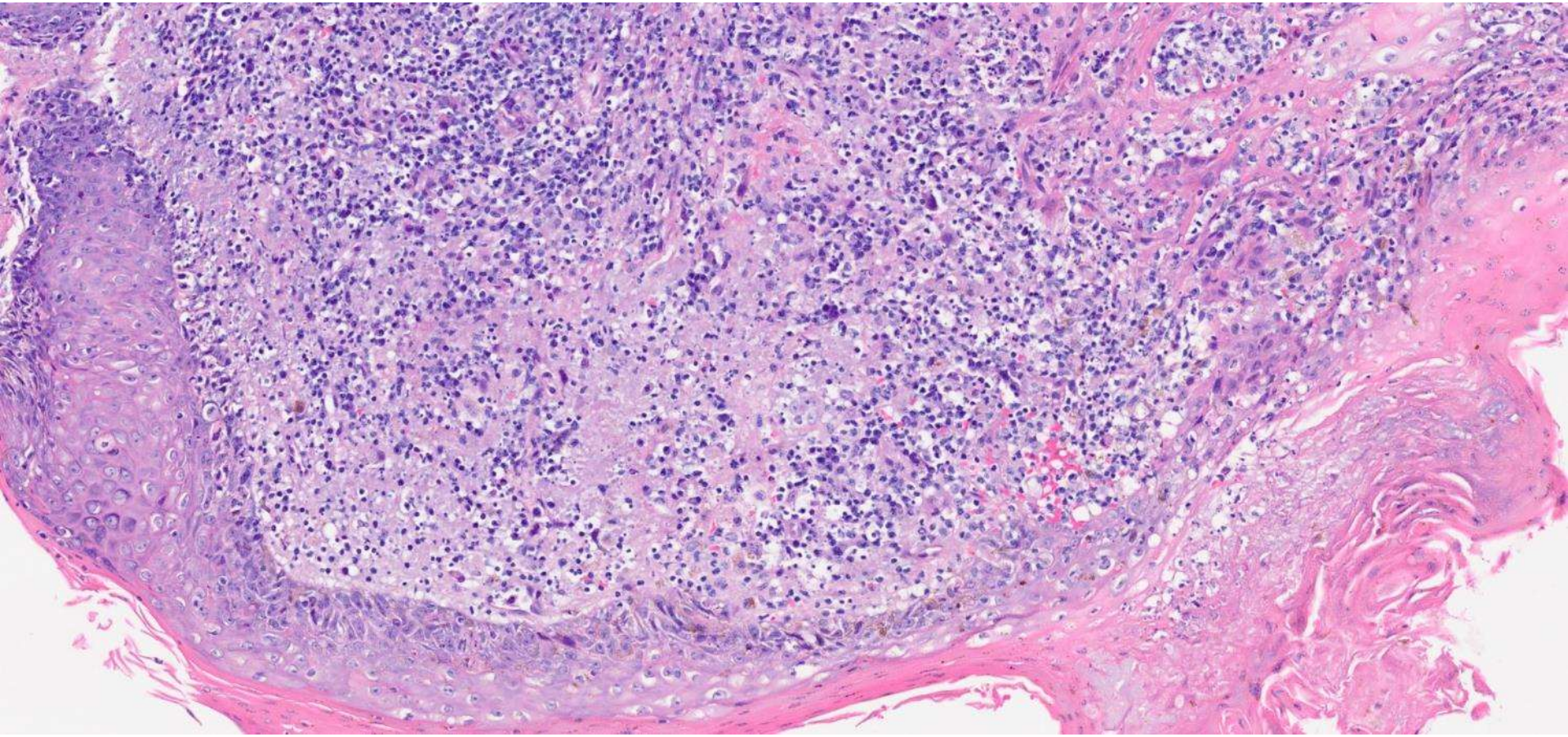
https://pathpresenter.net/public/display?token=fff8b21d

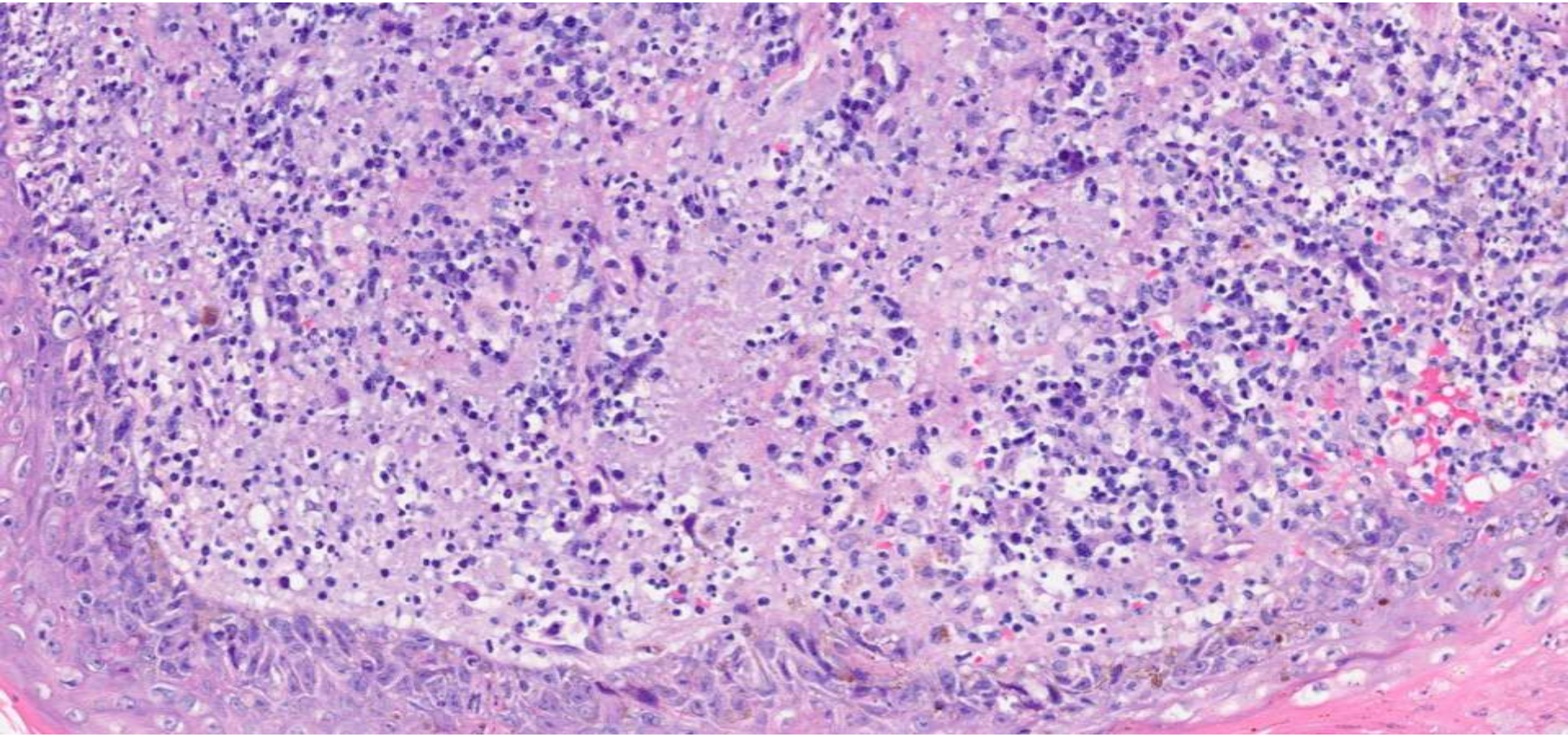
Harris Goodman; Alameda Health System

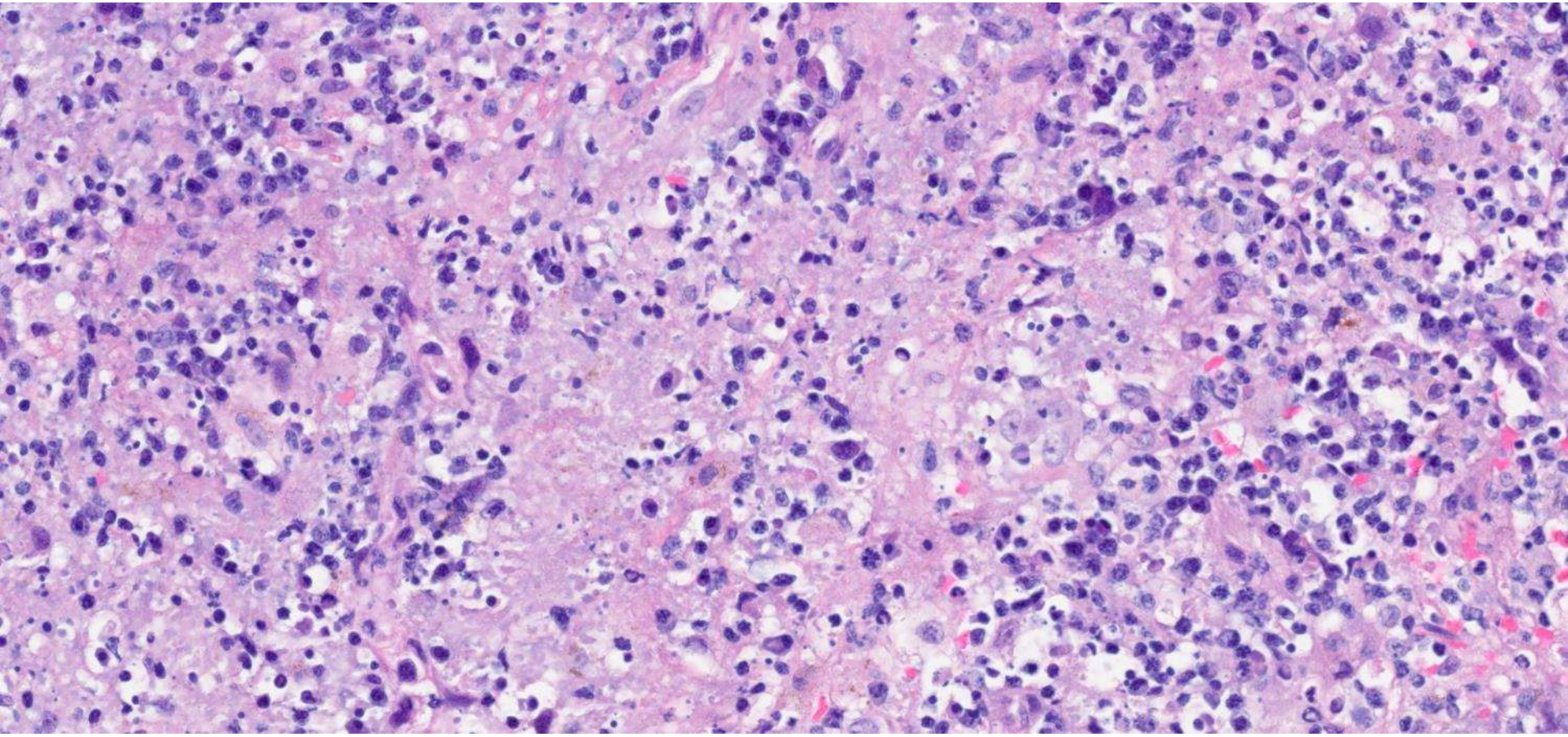
60ish F with plaque over bridge of nose, rosacea rule out infection.

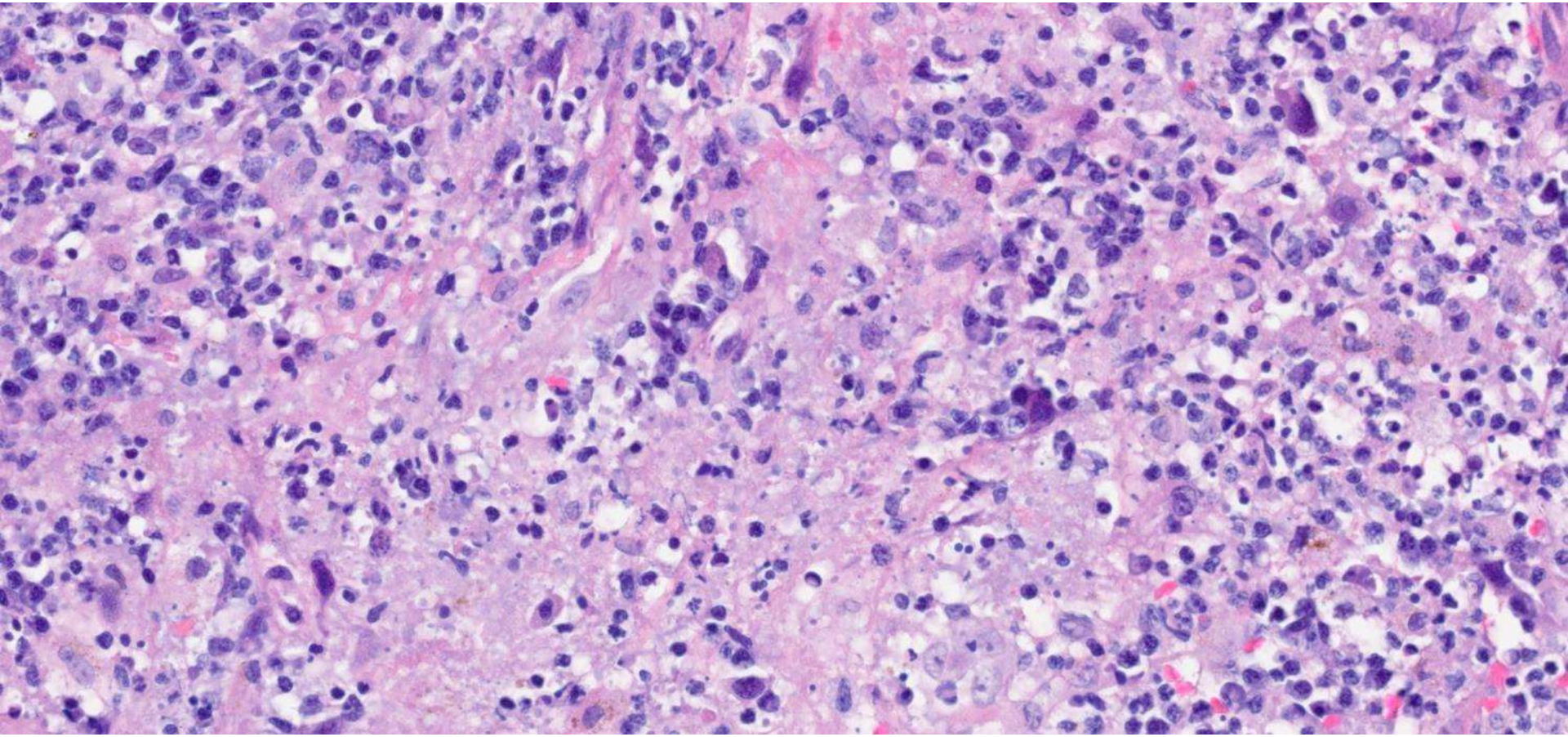


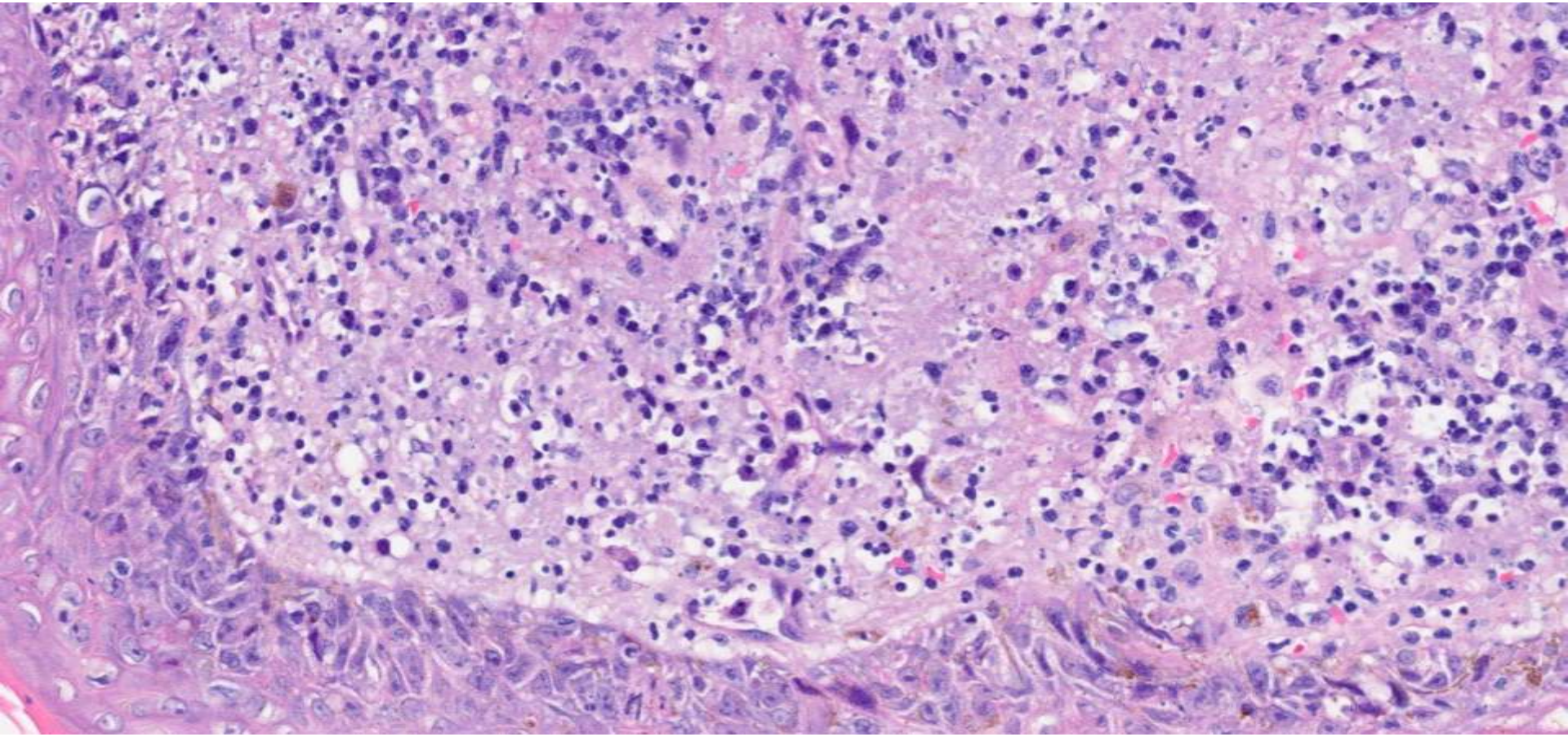


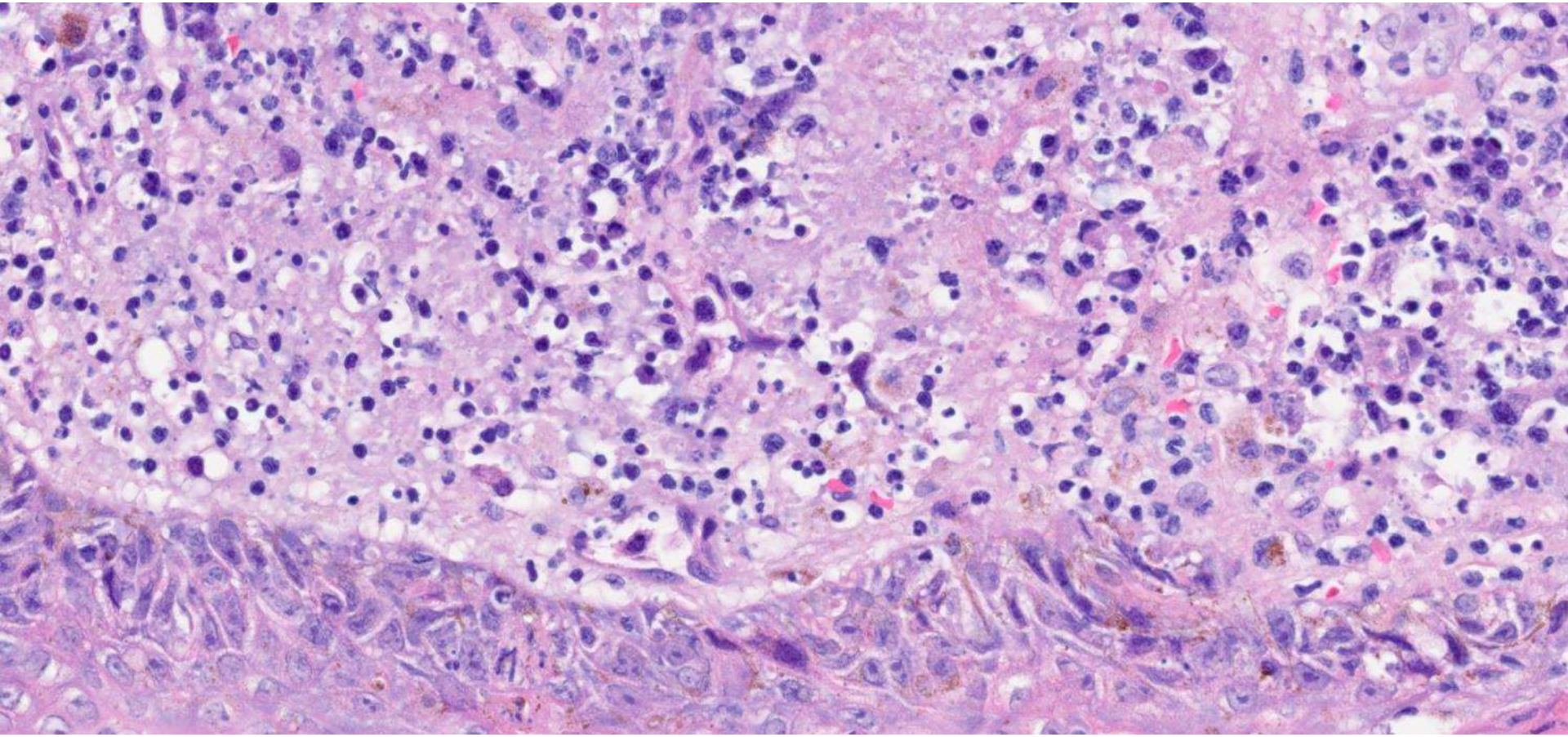






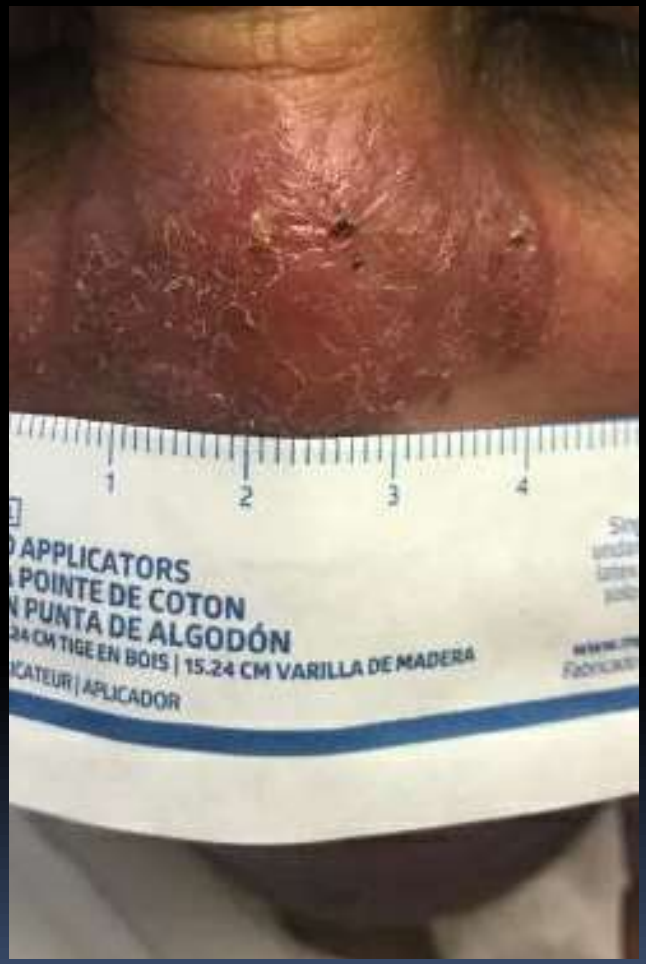




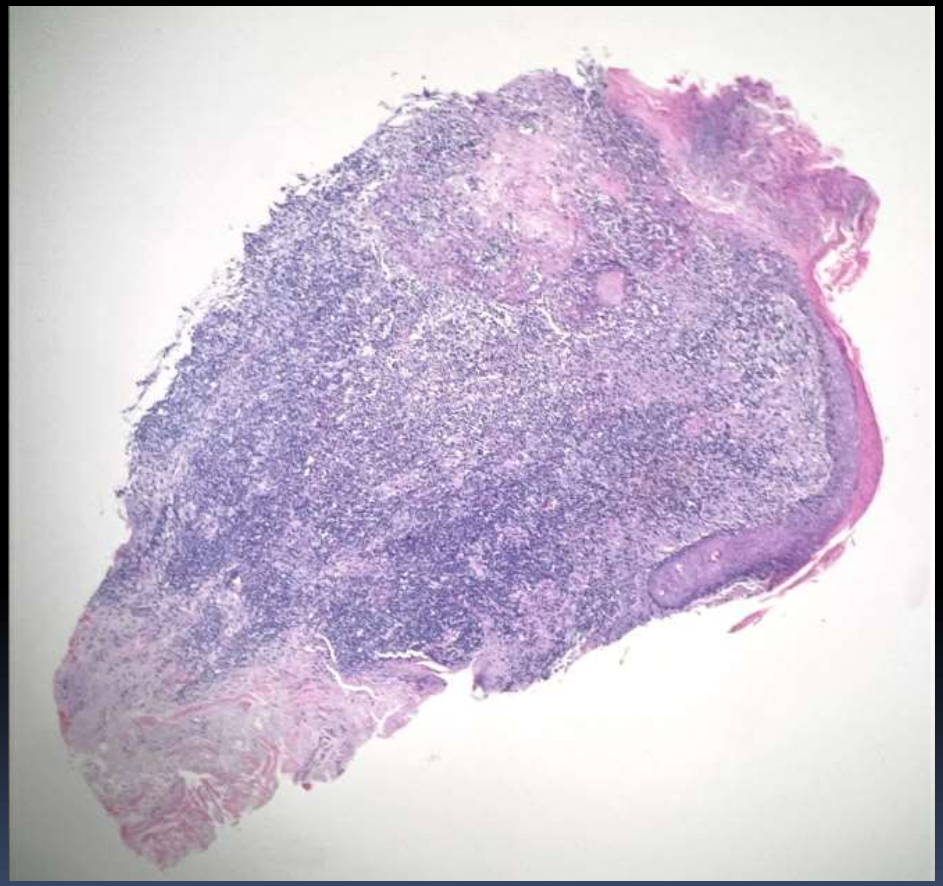


SBPS 22-0703

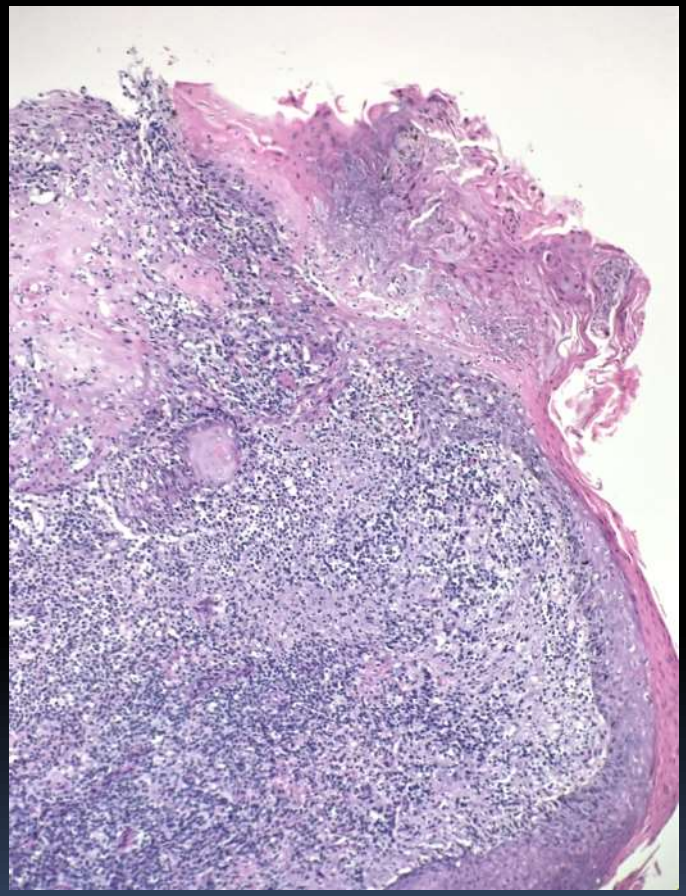
- 60ish year old Tigrinya-only speaking woman who presented for a Dermatology consultation.
- Itchy red bumpy rash over the bridge of her nose for 3 months, unresponsive to doxycycline and metronidazole.
- No significant medical or surgical history.


1
2
3
4
APPLICATORS
POINTE DE COTON
PUNTA DE ALGODÓN
CM TIGE EN BOIS | 15.24 CM VARILLA DE MADERA
APLICADOR

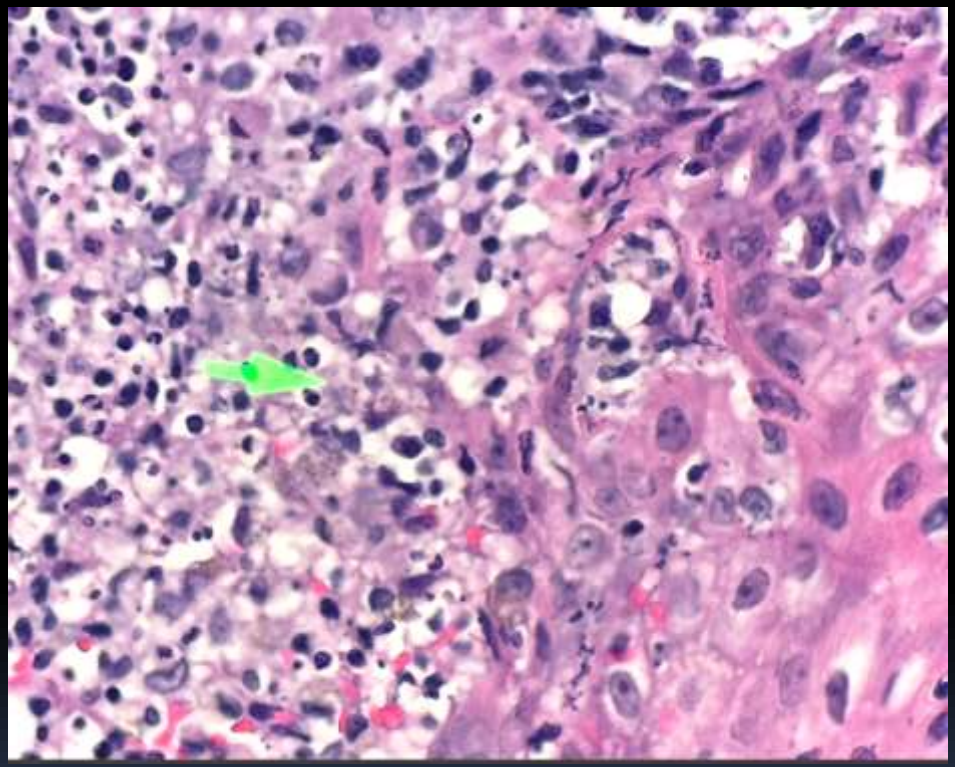
SBPS 22-0703



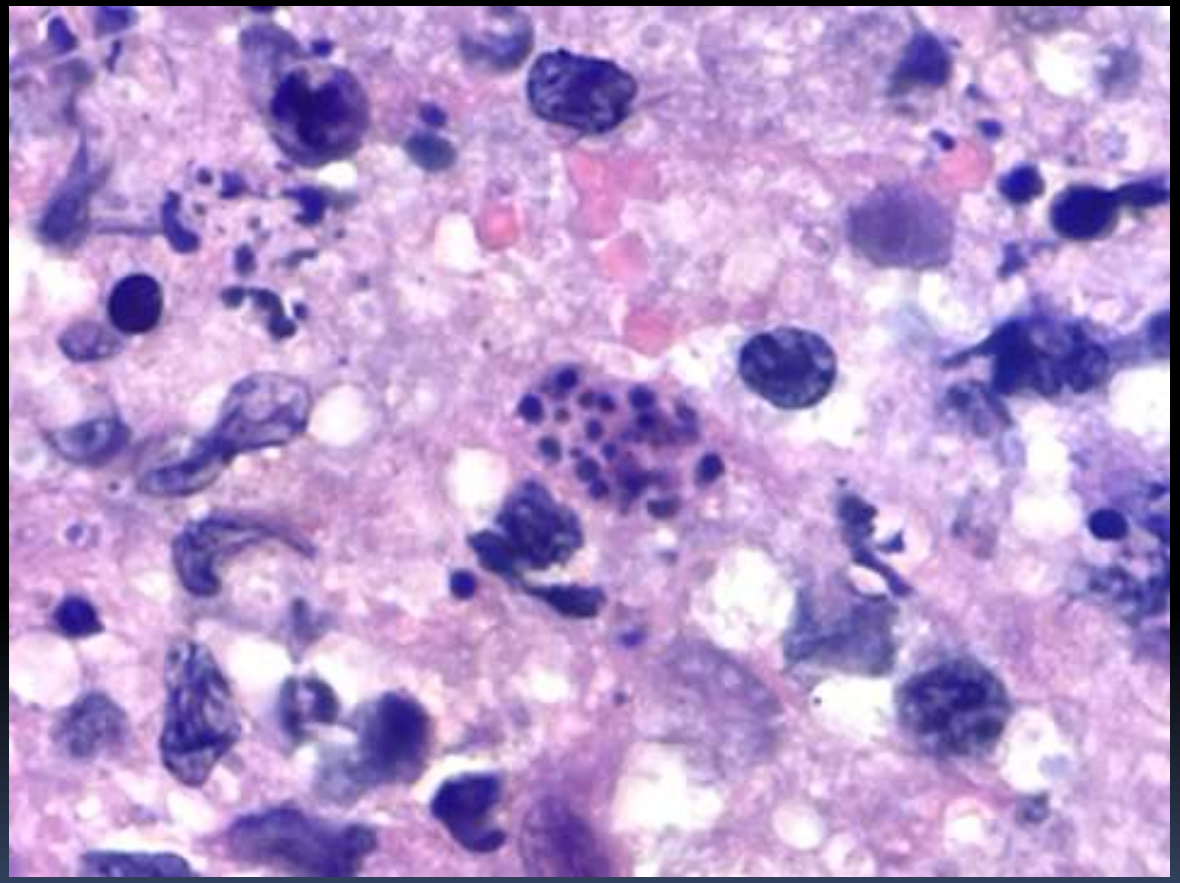
SBPS 22-0703



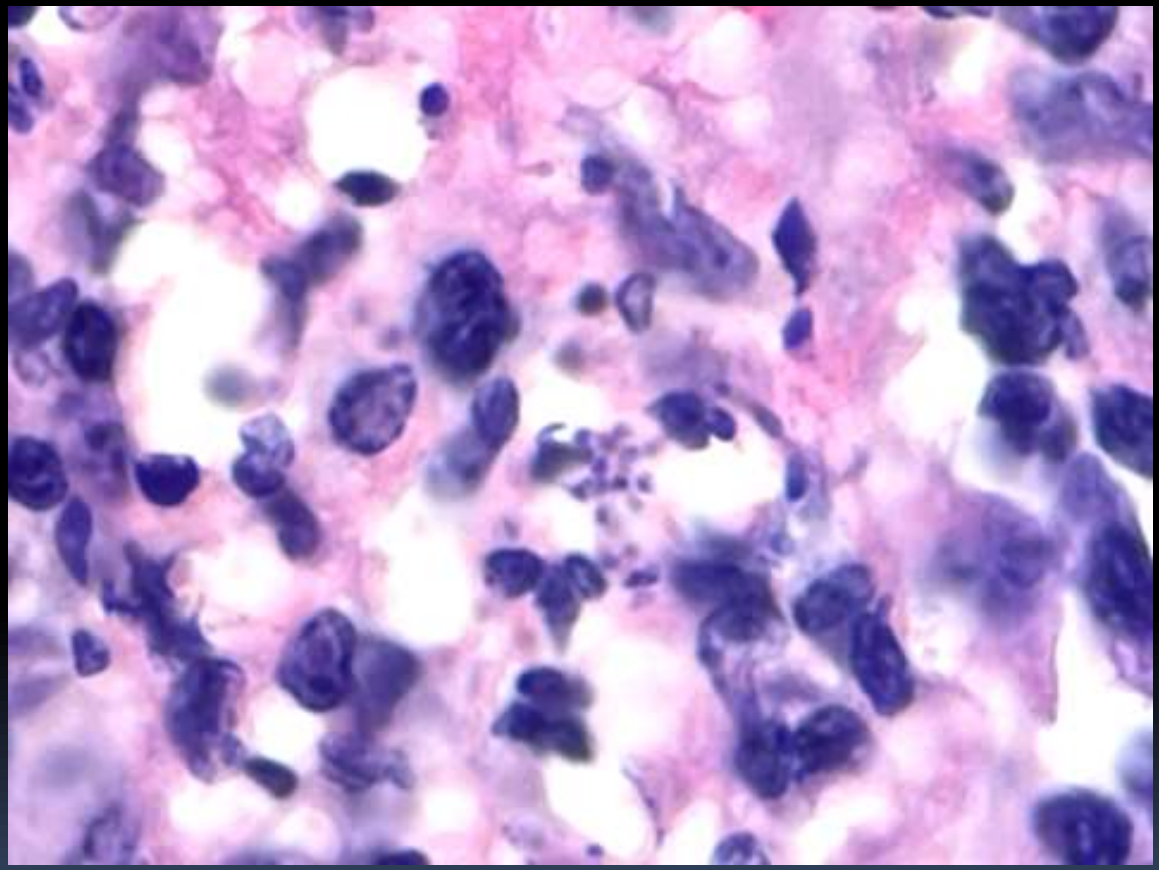
SBPS 22-0703



SBPS 22-0703



SBPS 22-0703



SBPS 22-0703

- Differential diagnosis:
  - Histoplasmosis
  - Toxoplasma gondii
  - Talaromyces marneffei (Penicillium marneffei)
  - Leishmaniasis

SBPS 22-0703

- Tigrinya is a Semitic language commonly spoken in Eritrea and in northern Ethiopia's Tigray Region.

SBPS 22-0703

The specimen was sent to the Centers for Disease Control & Prevention, Division of Parasitic Diseases and Malaria, for additional testing.

Test:

Ova & Parasite Identification

Result:

Amastigotes

Test:

Leishmania Species Identification

Result:

Leishmania real time PCR: Positive.
Leishmania PCR and DNA Sequencing: L. aethiopica.

SBPS 22-0703

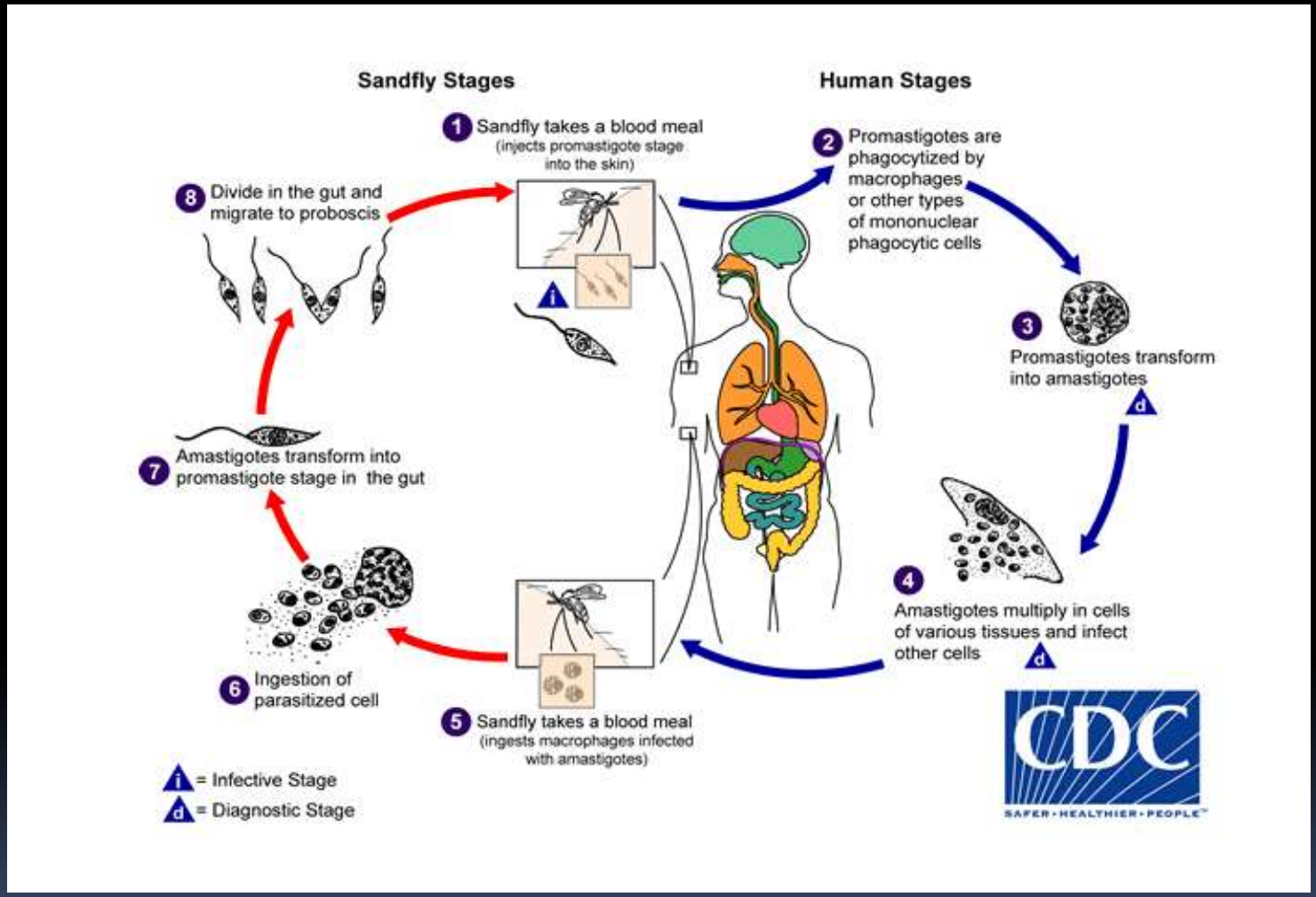
- Cutaneous leismaniasis: mixed inflammatory infiltrate / granulomatous with histiocytes / macrophages containing tiny round hematoxylin-staining intracytoplasmic organisms (amastigotes).

SBPS 22-0703

- Differential diagnosis:
  - Histoplasmosis
    - (similar in size; grows in fungal culture; urine antigen positive)
  - Toxoplasma gondii
    - (cysts may be present; serology; PCR for T. gondii DNA)
  - Talaromyces marneffei (Penicillium marneffei)
    - (dimorphic fungus that also proliferates in macrophages)
  - Leishmaniasis

SBPS 22-0703

- She was treated with IV liposomal amphotericin B (AmBisome ®) daily for 10 days.
- Note that liposomal amphotericin B is FDA-approved for treatment of visceral leishmaniasis (the approved indications do not include cutaneous or mucosal leishmaniasis).


Sandfly Stages
Human Stages
1 Sandfly takes a blood meal
(injects promastigote stage into the skin)
2 Promastigotes are phagocytized by macrophages or other types of mononuclear phagocytic cells
3 Promastigotes transform into amastigotes
4 Amastigotes multiply in cells of various tissues and infect other cells
5 Sandfly takes a blood meal
(ingests macrophages infected with amastigotes)
6 Ingestion of parasitized cell
7 Amastigotes transform into promastigote stage in the gut
8 Divide in the gut and migrate to proboscis
i = Infective Stage
d = Diagnostic Stage
CDC
SAFER·HEALTHIER·PEOPLE™

SBPS 22-0703

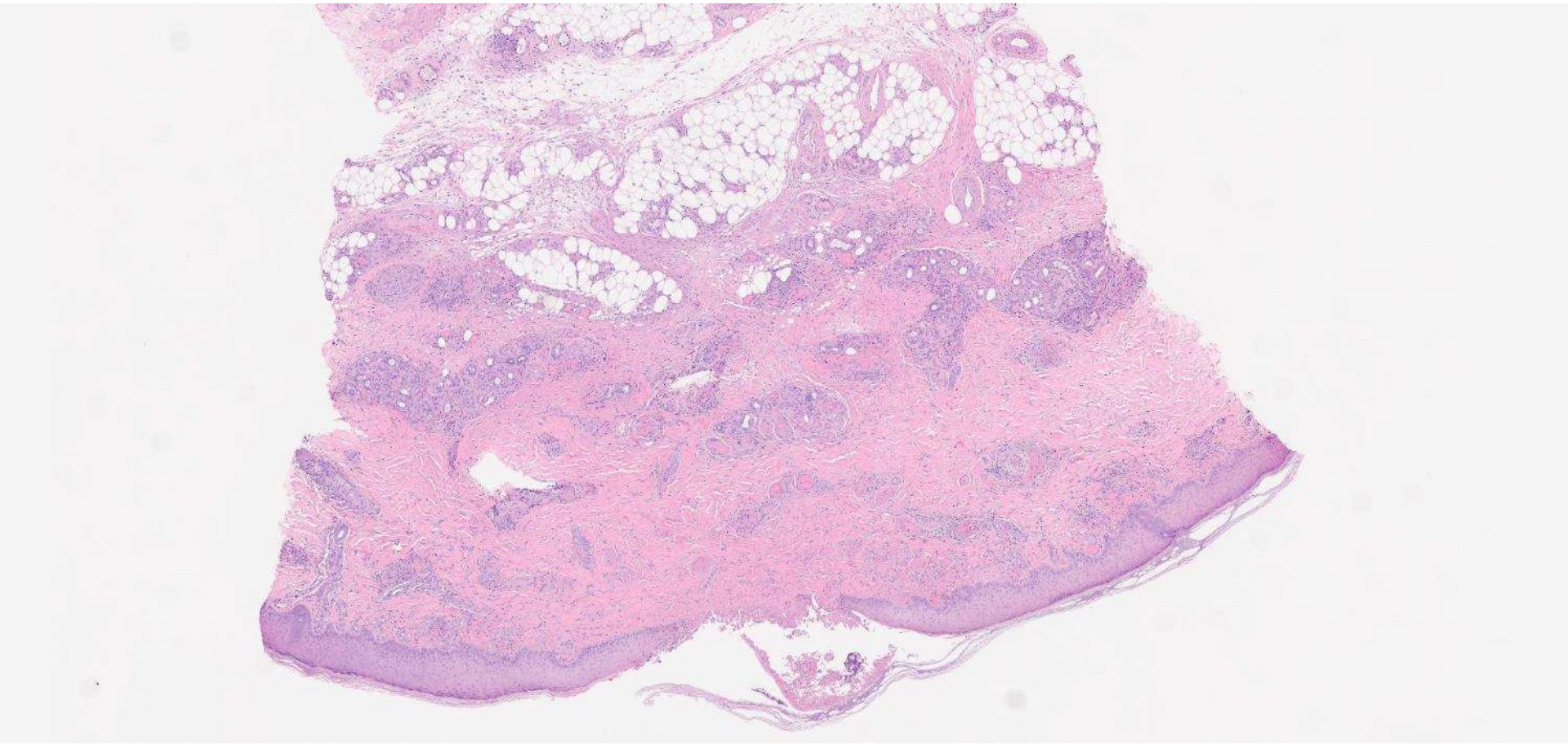
- Z. Handler MD, Parimal A. Patel MD, Rajendra Kapila MD, Yasin Al-Qubati MD, Robert A. Schwartz MD, MPH, FRCP
- Cutaneous and mucocutaneous leishmaniasis: Differential diagnosis, diagnosis, histopathology, and management
- Journal of the American Academy of Dermatology
- Volume 73, Issue 6, December 2015, Pages 911-926

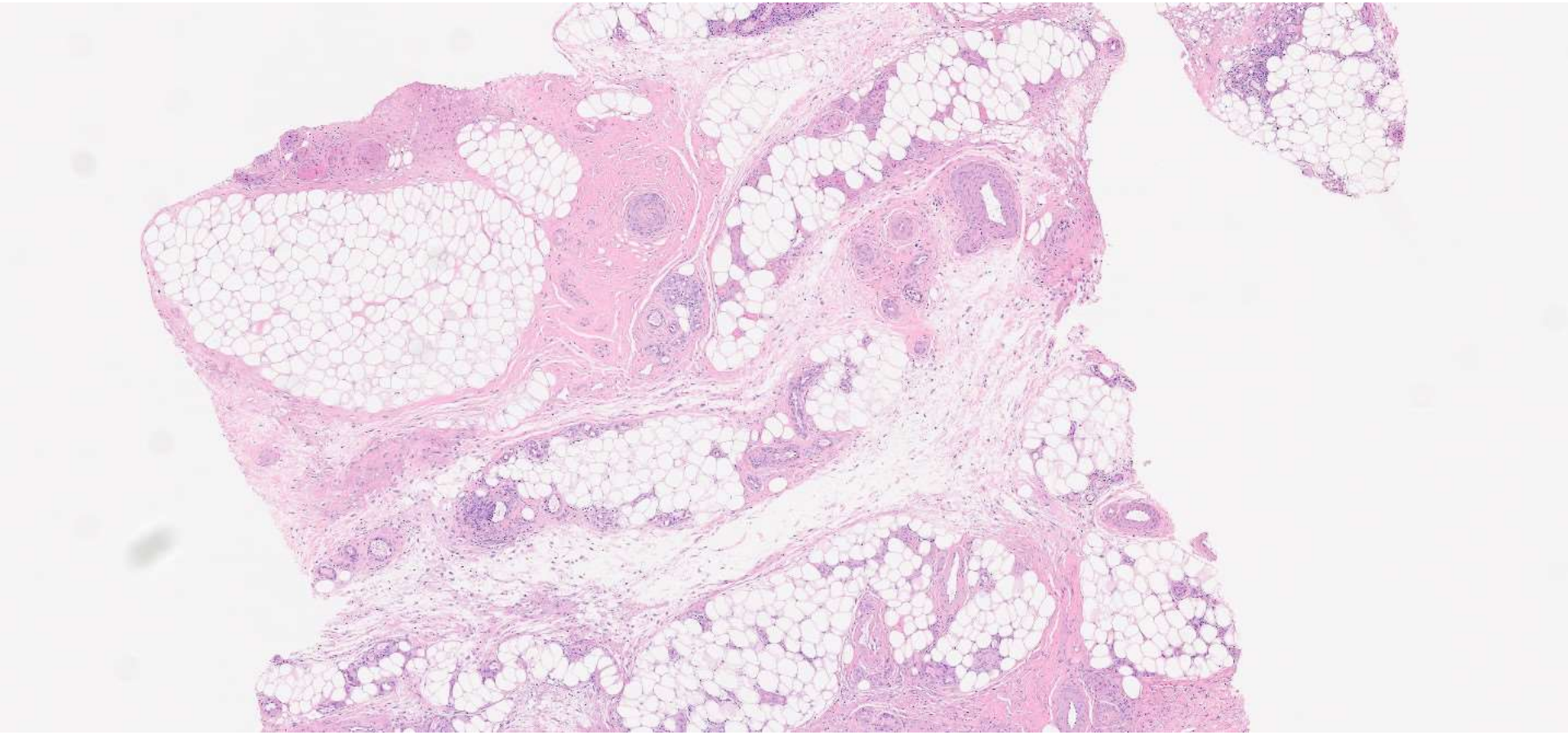
22-0704
Direct link to scanned slide:

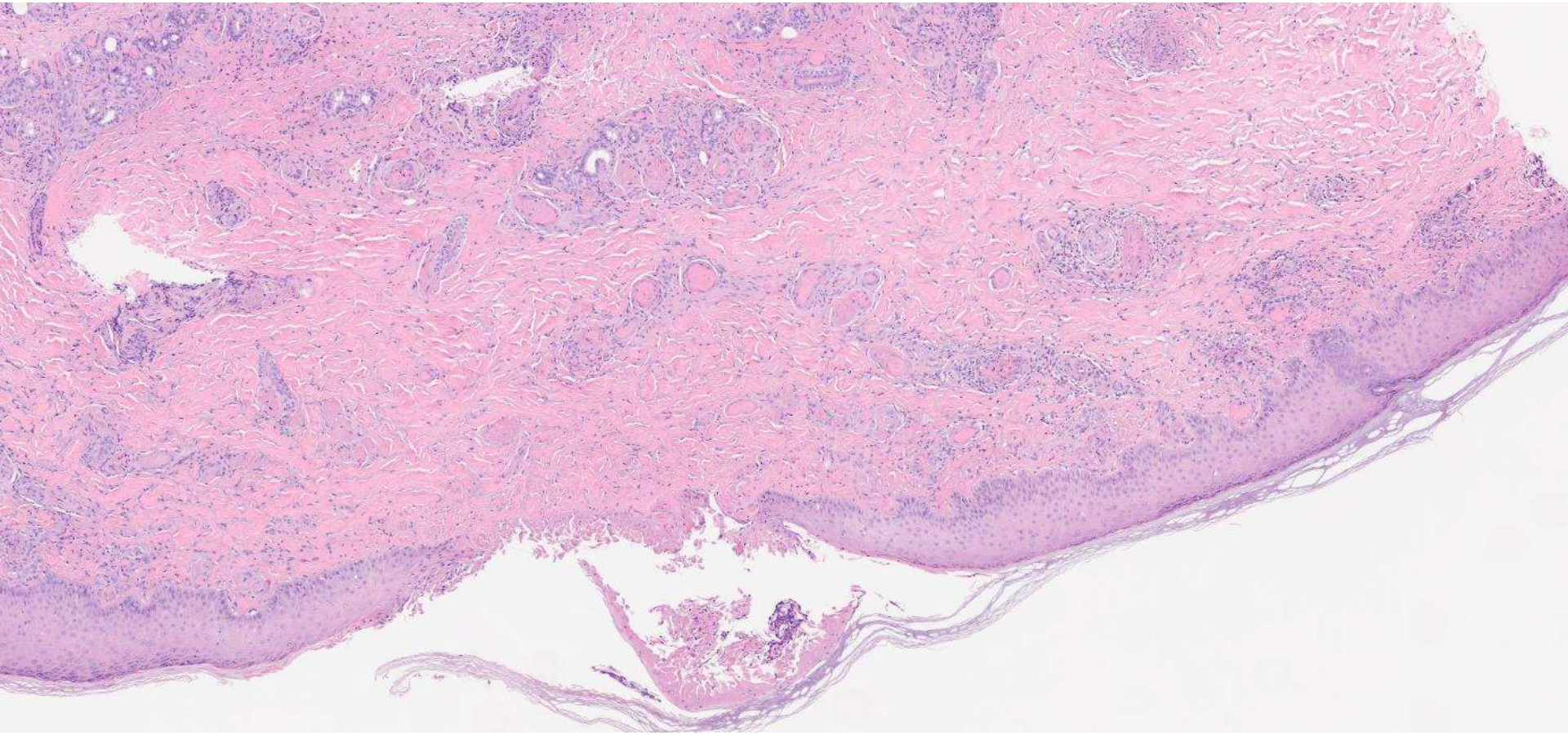
https://pathpresenter.net/public/display?token=70b44996

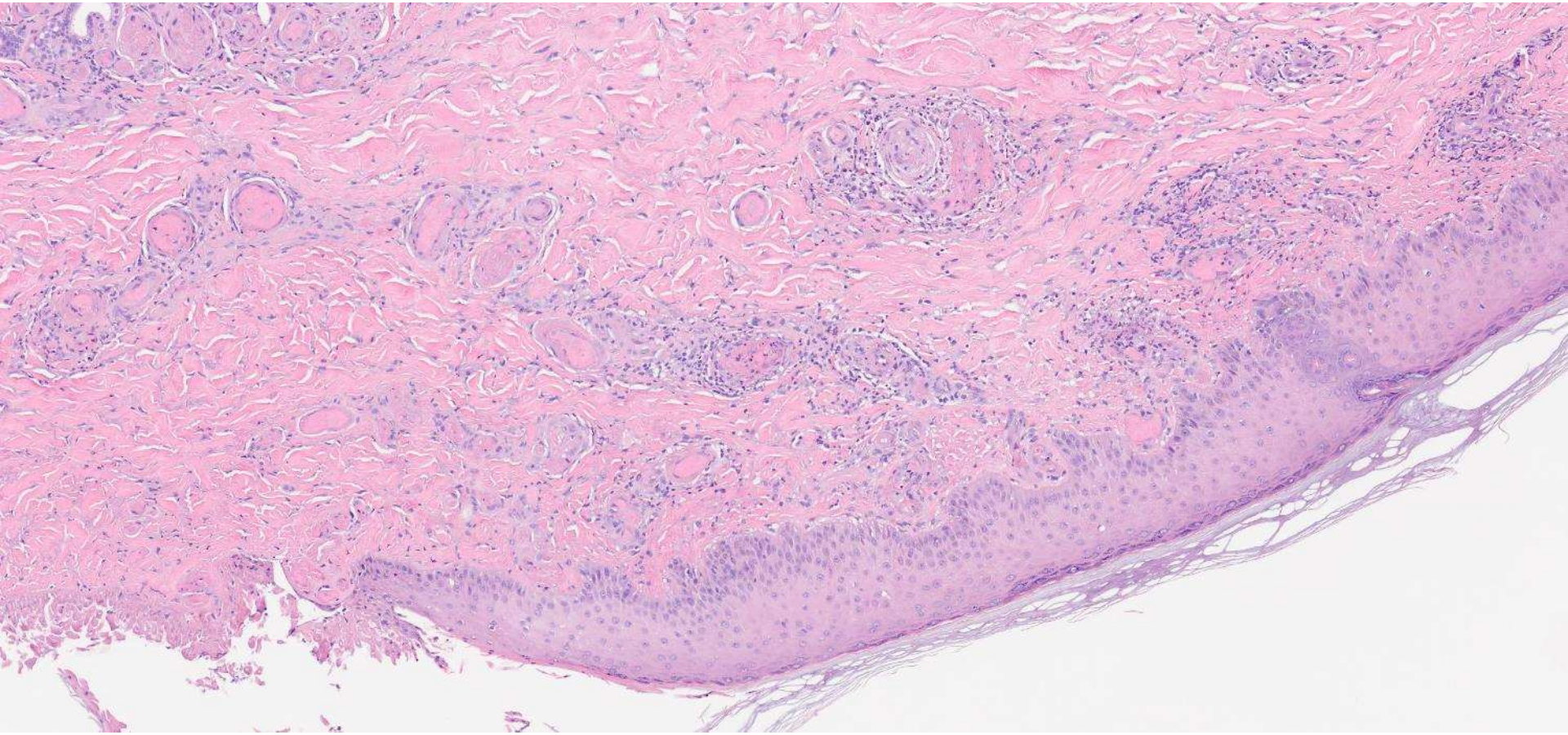
Harris Goodman; Alameda Health System

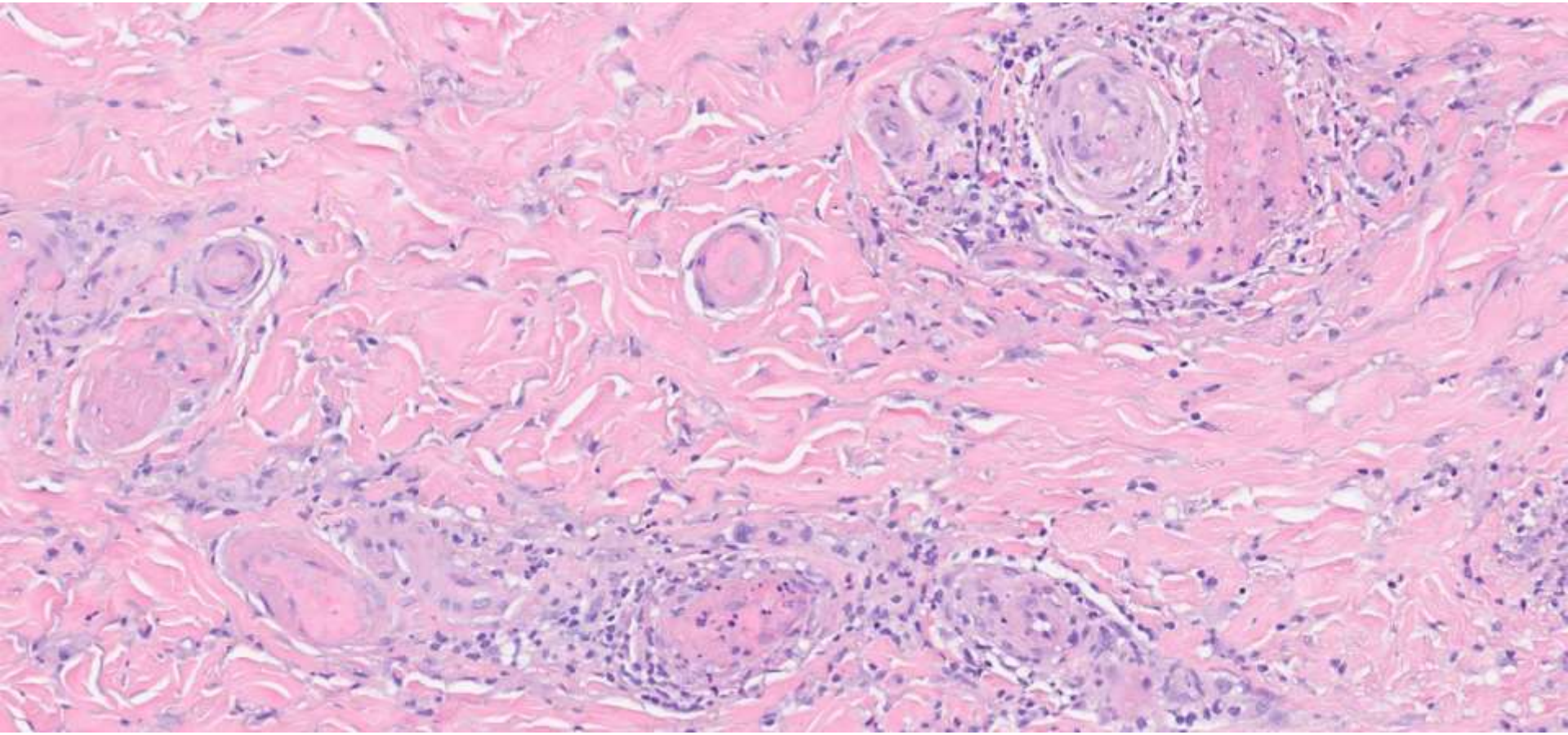
60ish M surgeon with bilateral non-healing lower leg wounds for over a year.

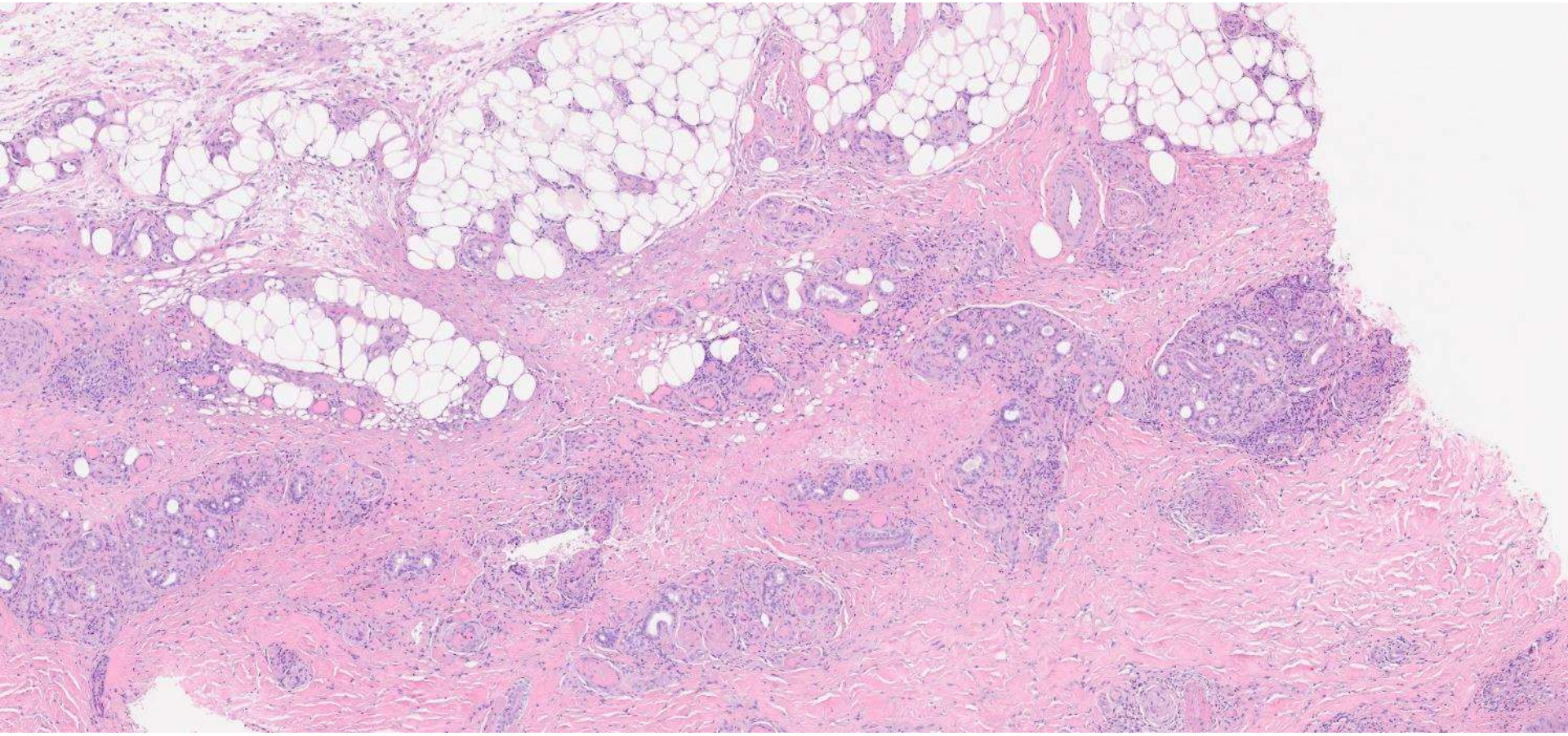


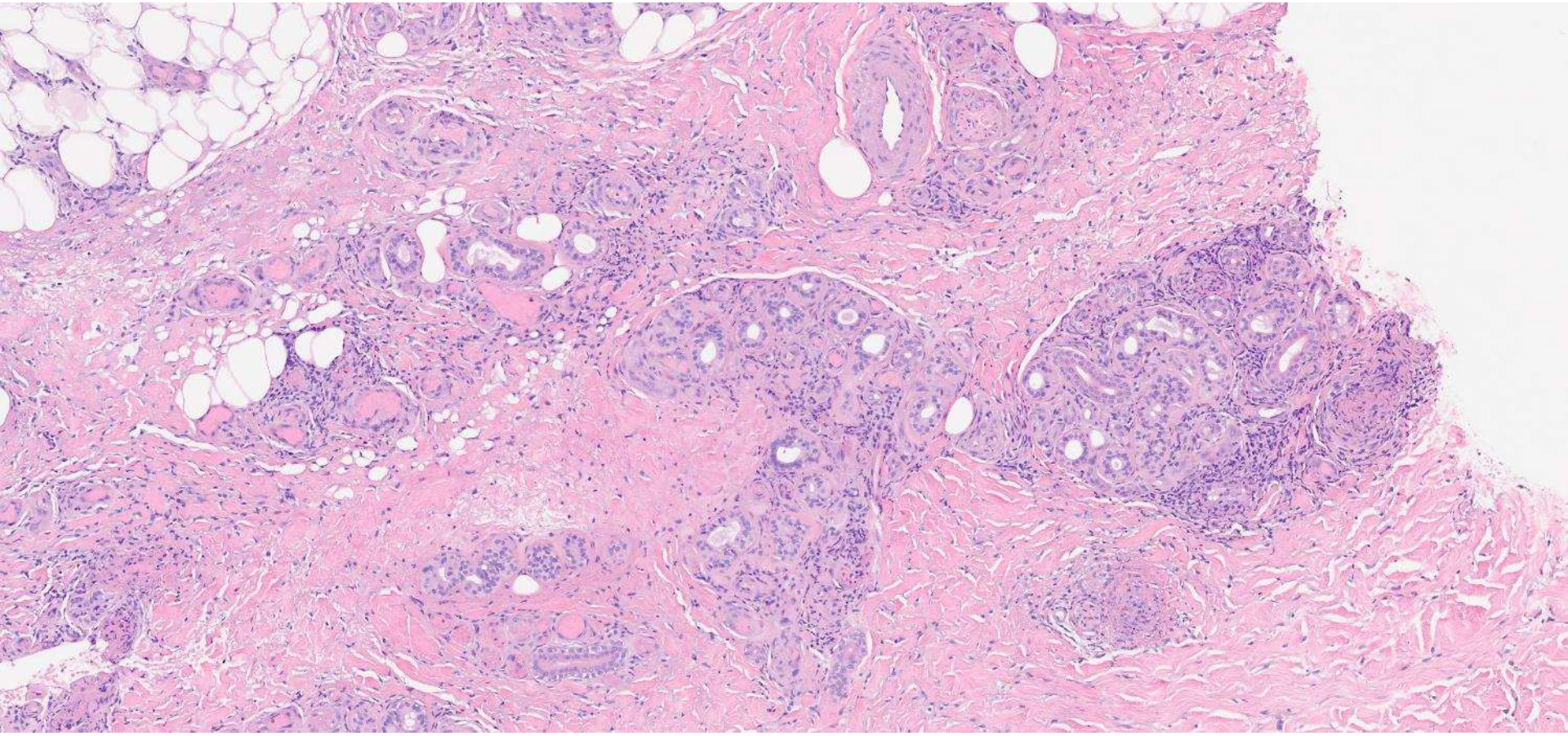


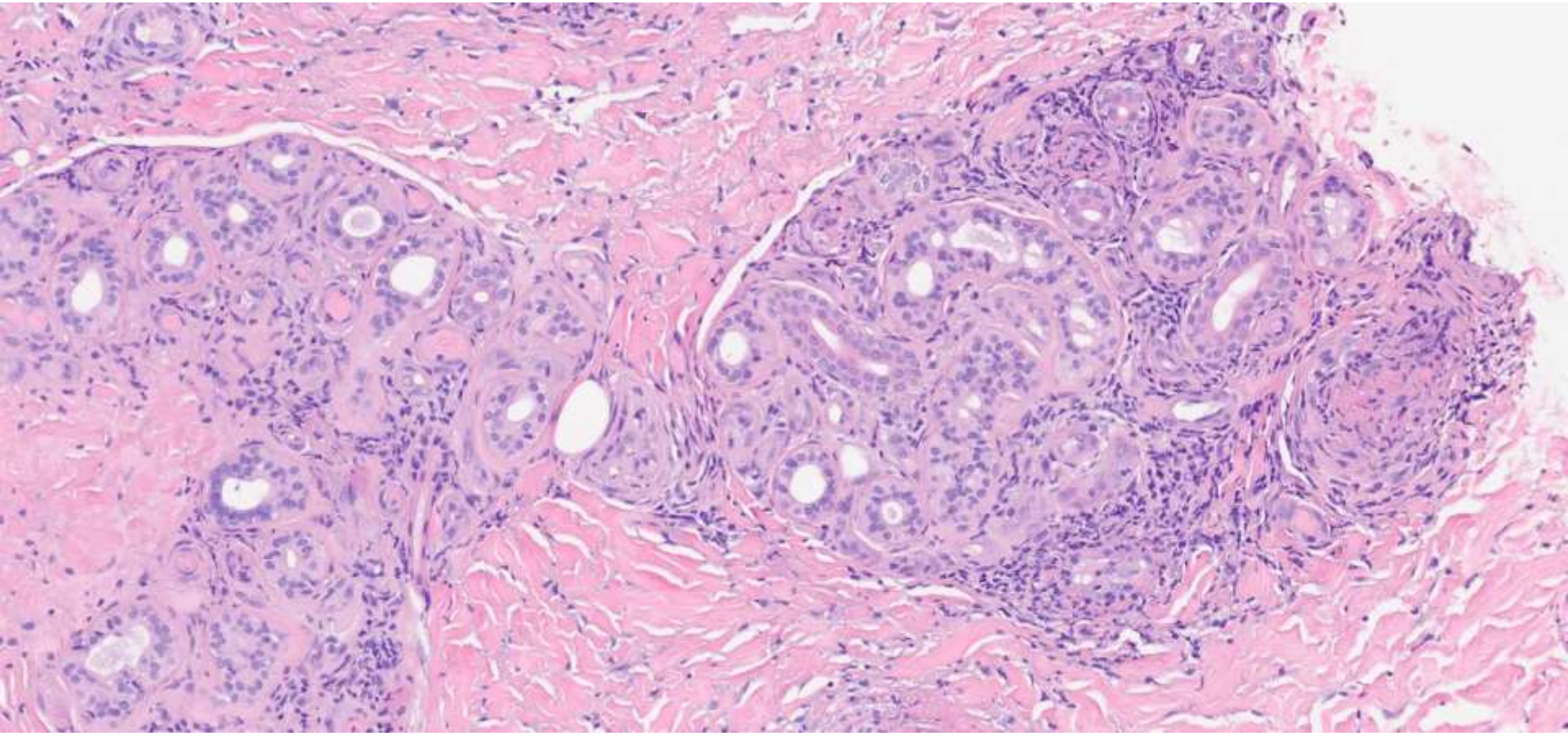


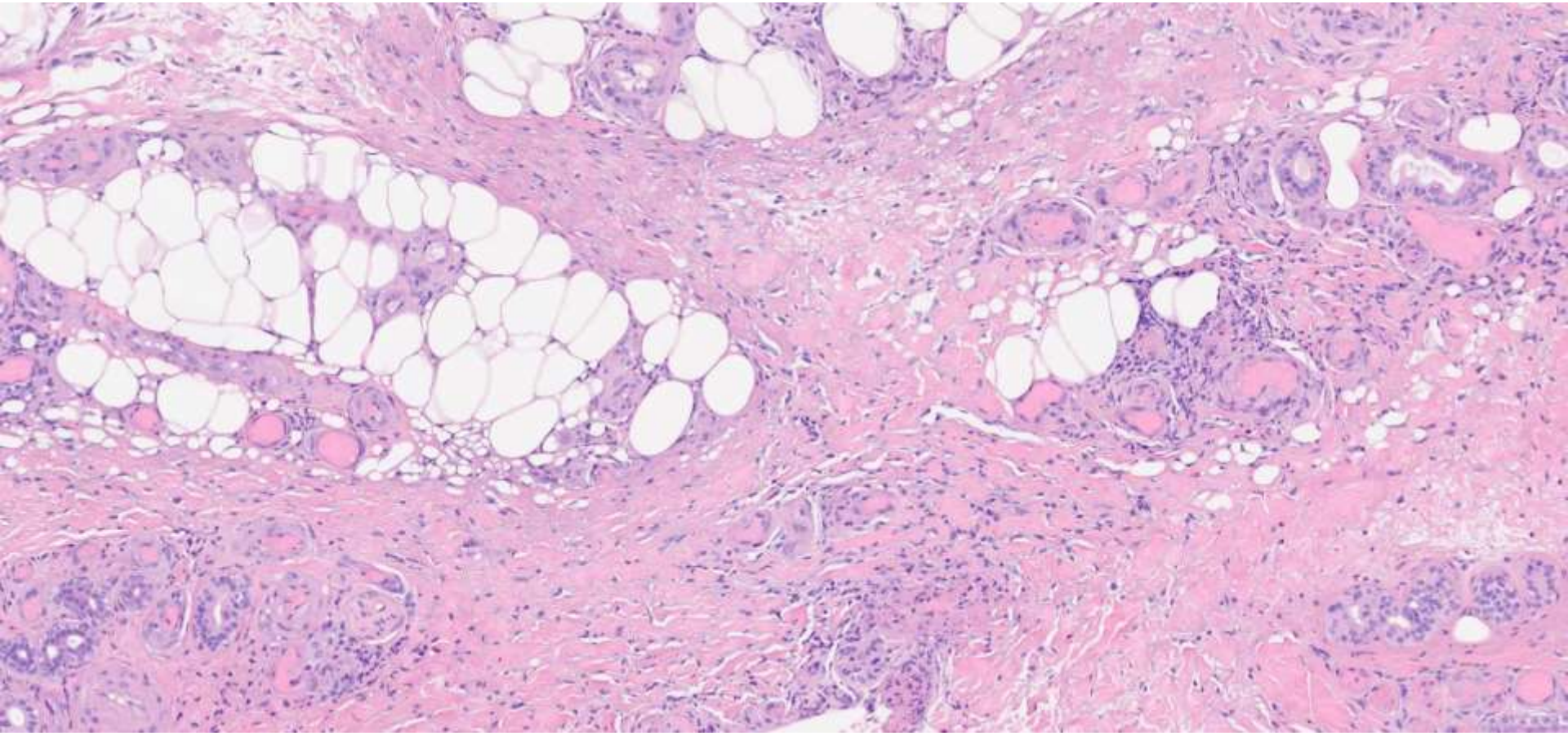






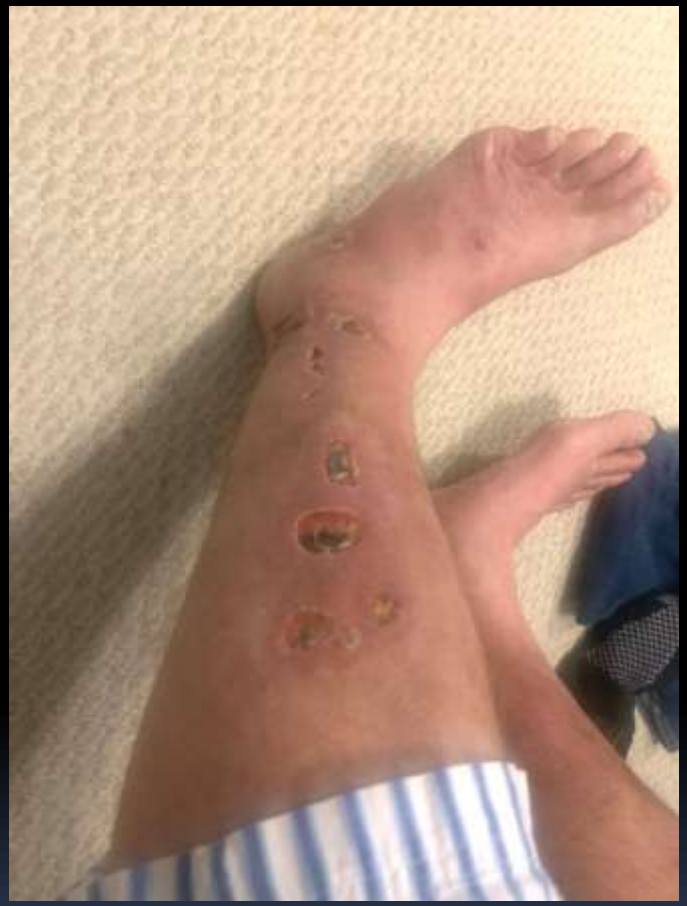


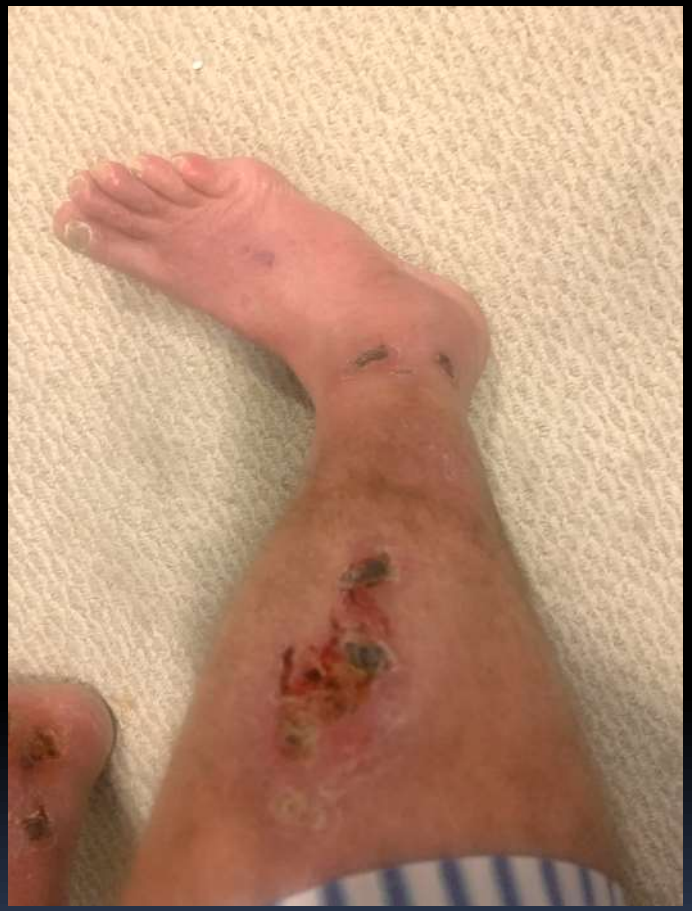




SBPS 22-0704

- 60ish orthopedic surgeon with bilateral non-healing lower leg wounds for over a year.
- No history of diabetes, atherosclerotic cardiovascular disease, or congestive heart failure.

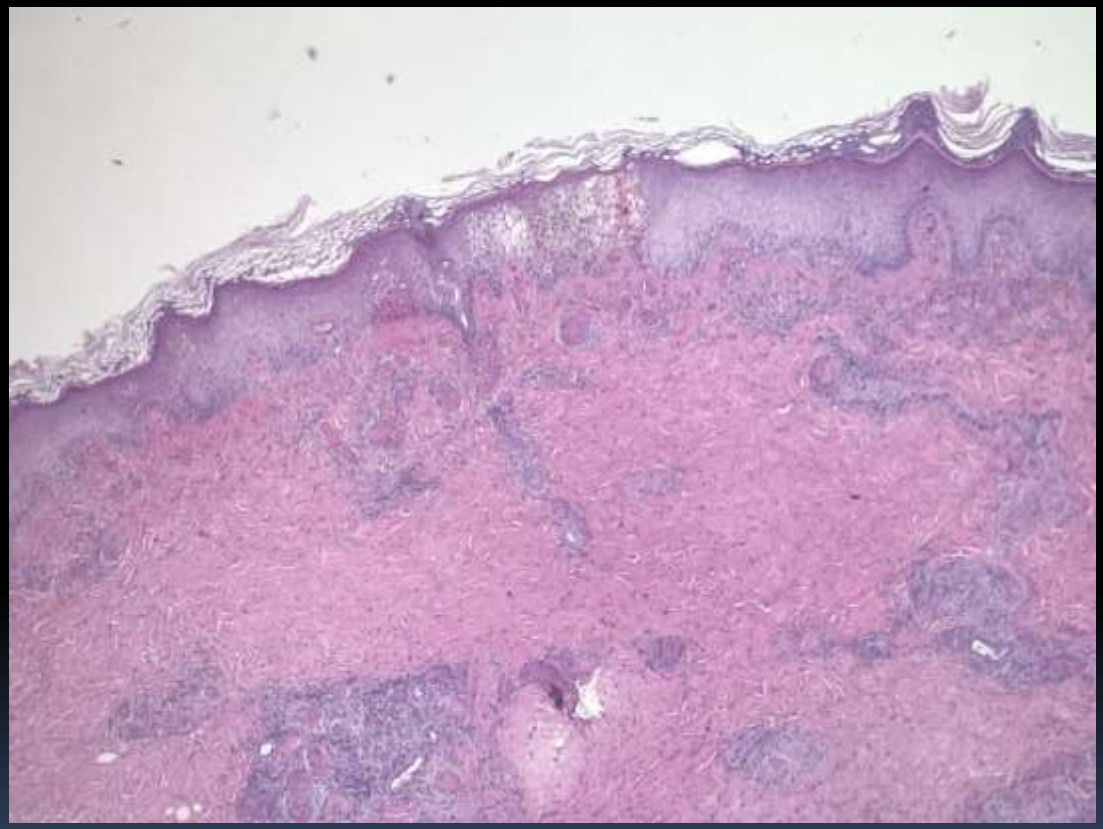




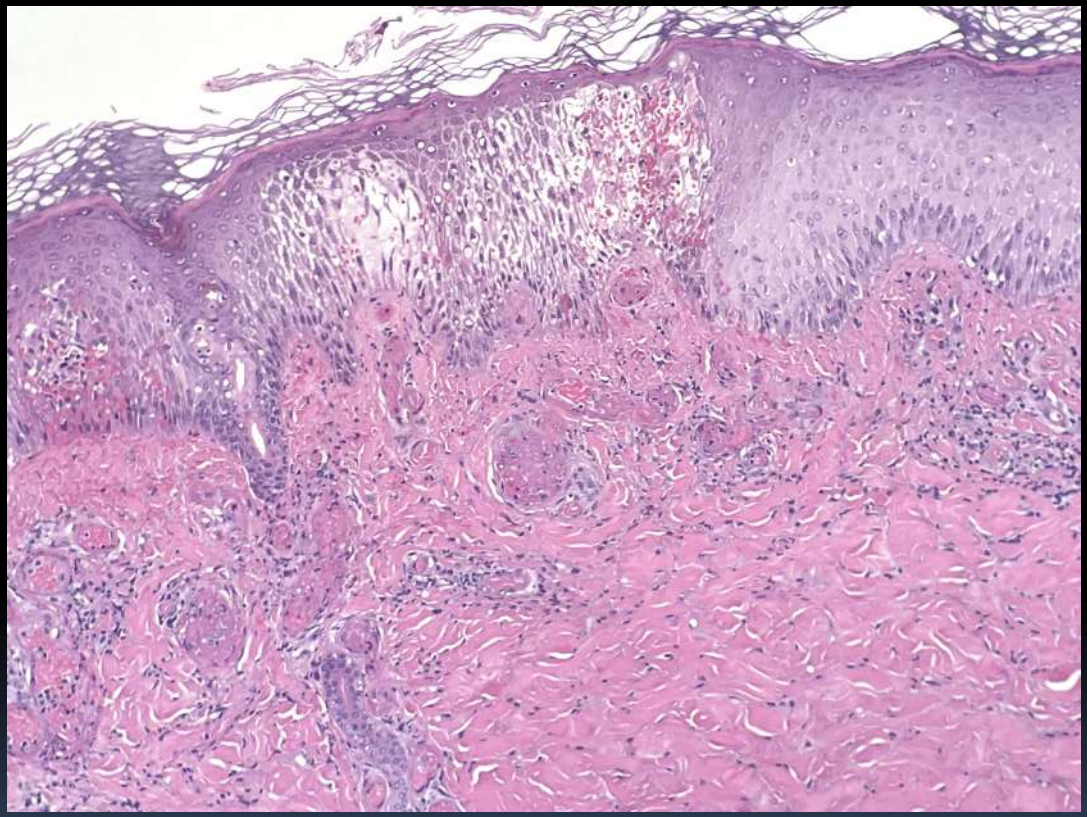
SBPS 22-0703

- Original biopsy (not shown) showed changes consistent with stasis dermatitis, attributed to long hours standing in the OR.
- After multiple interventions (e.g. support stockings, feet up at night, etc.), with significant worsening of the ulcers, this additional biopsy was performed.

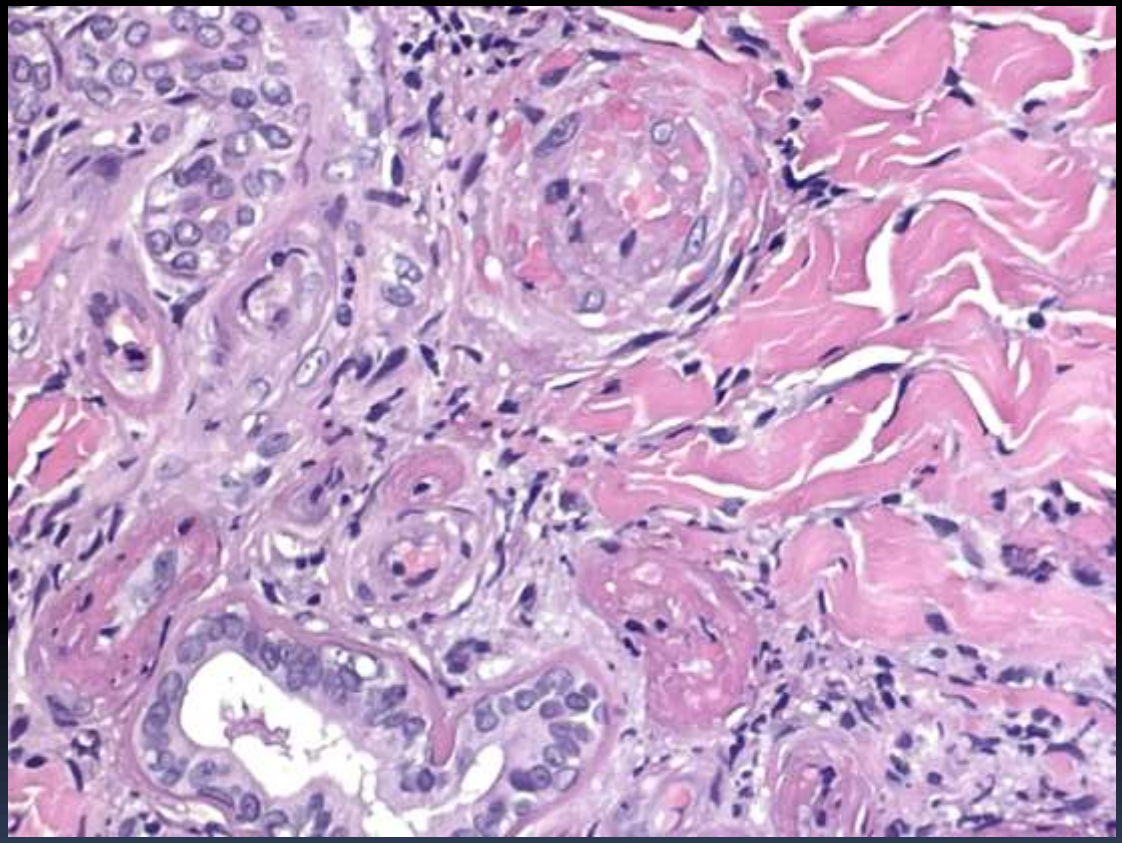
SBPS 22-0703



SBPS 22-0703



SBPS 22-0704



SBPS 22-0704

- Livedoid vasculopathy
  - Affects distal lower extremities and feet;
  - Nodules, plaques and ulceration;
  - Painful thromboocclusive vasculopathy
  - Occurs independently or in association with an acquired or inherited thrombophilia or systemic disease.

SBPS 22-0704

- Blood vessels show thickening, thrombosis, endothelial proliferation and hyaline degeneration of the subintimal layer
- The elastic lamina is preserved, and the vessel is rarely destroyed.
- There is not usually much surrounding inflammation.

SBPS 22-0704

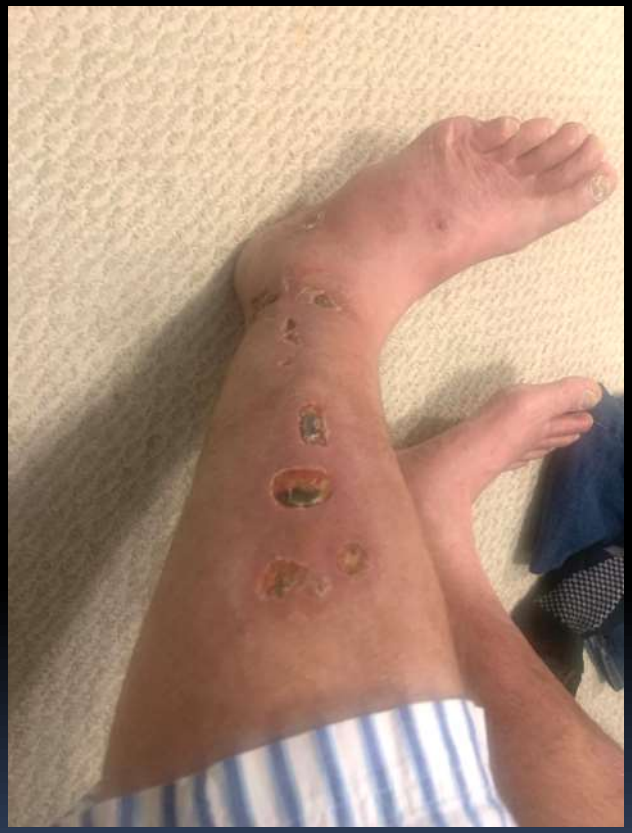
- Differential diagnosis:
  - Chronic venous disease
  - Peripheral vascular disease
  - Vasculitis

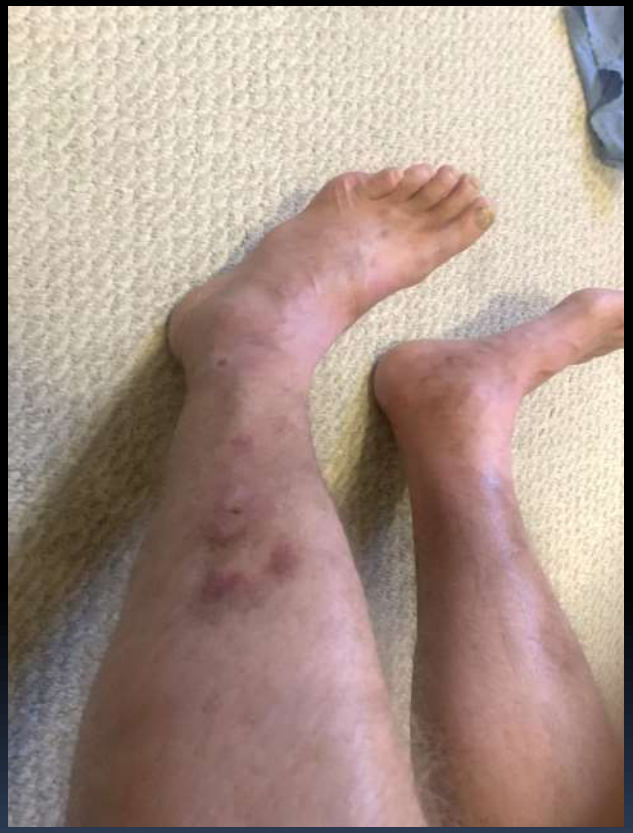
SBPS 22-0704

- Treatment:
  - Aspirin
  - Dipyridamole
  - Pentoxifylline
  - Warfarin
  - Rivaroxaban

  Livedoid vasculopathy often recurs upon discontinuation of treatment. Long-term treatment with an effective regimen is usually necessary.

SBPS 22-0704





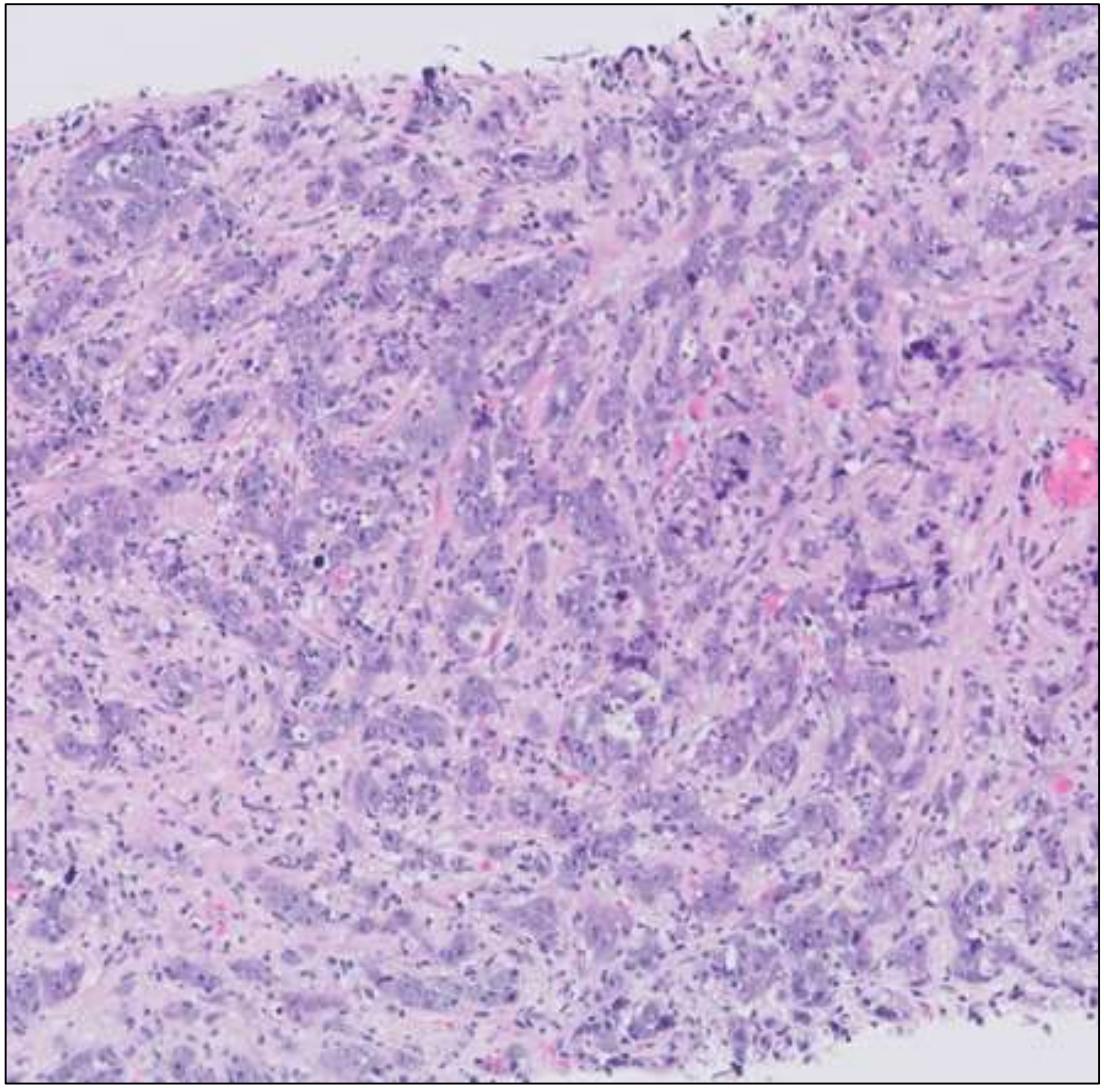
SBPS 22-0704

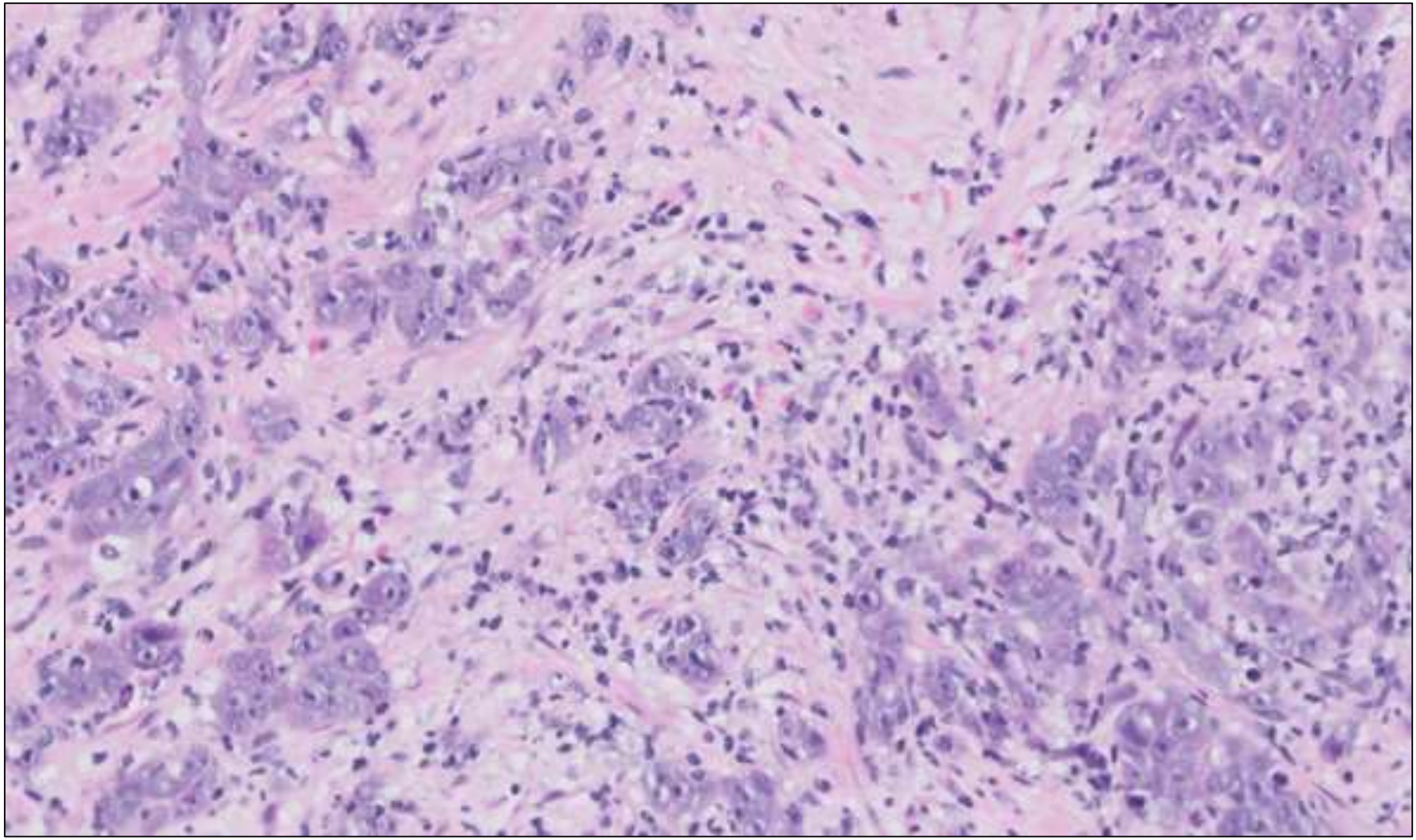
- Robert Micieli, BS; Afsaneh Alavi, MD, MS, FRCPC
- **Treatment for Livedoid Vasculopathy** A Systematic Review
- *JAMA Dermatol.* 2018;154(2):193-202. doi:10.1001/jamadermatol.2017.4374

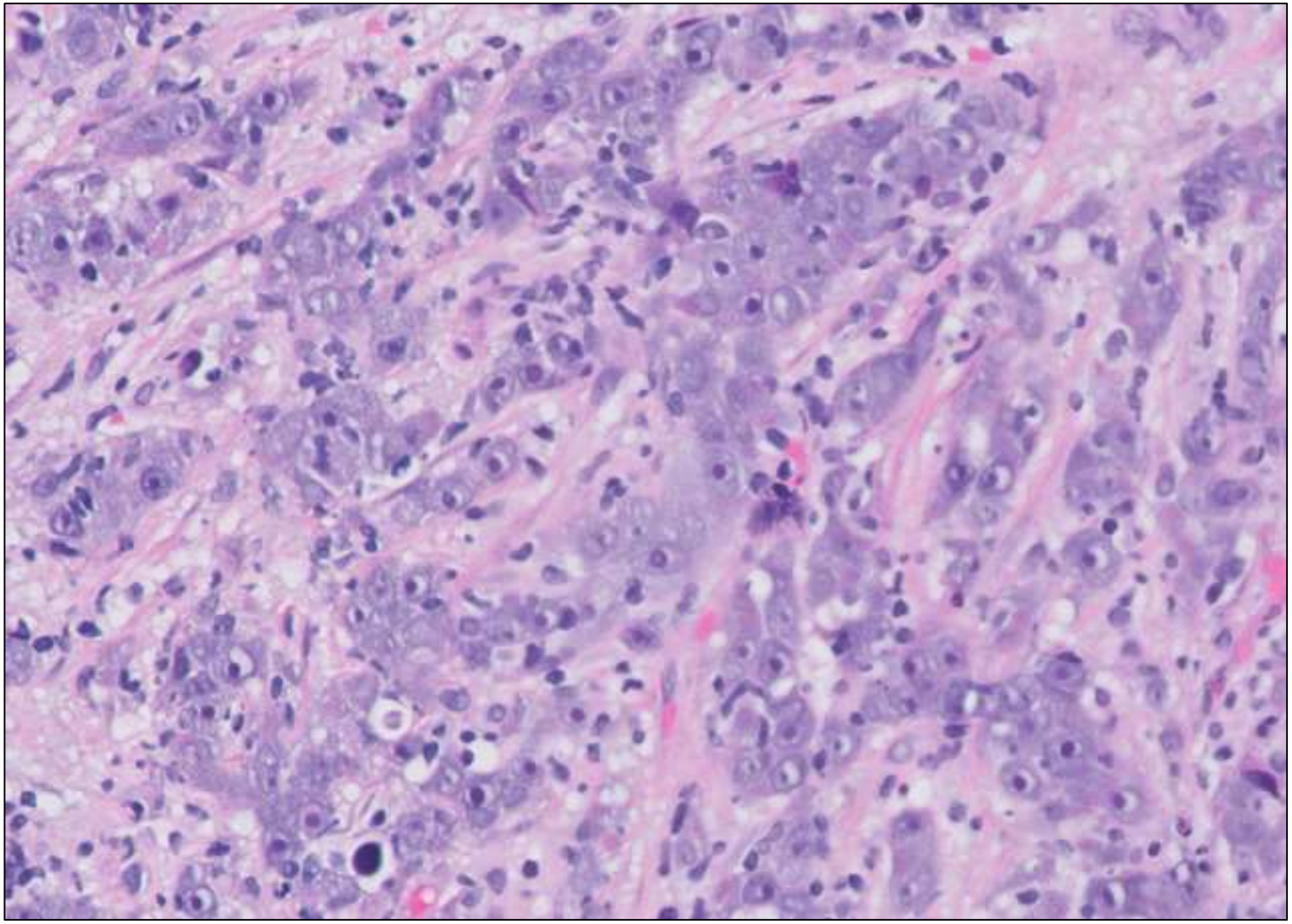
22-0705

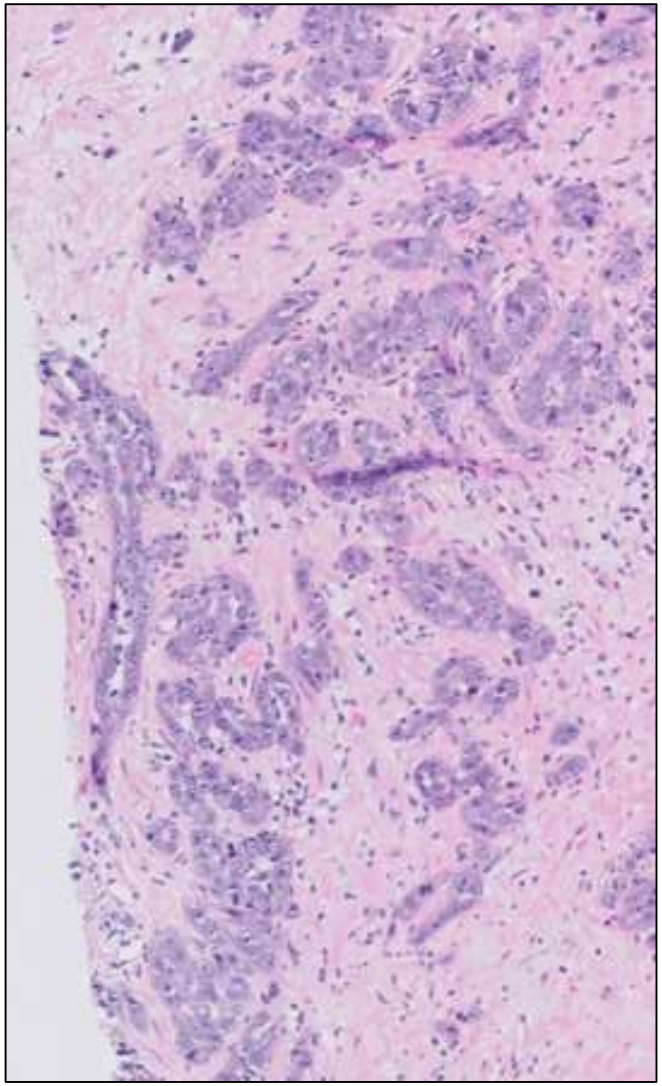
Alexander Kikuchi/Sanjay Kakar; UCSF

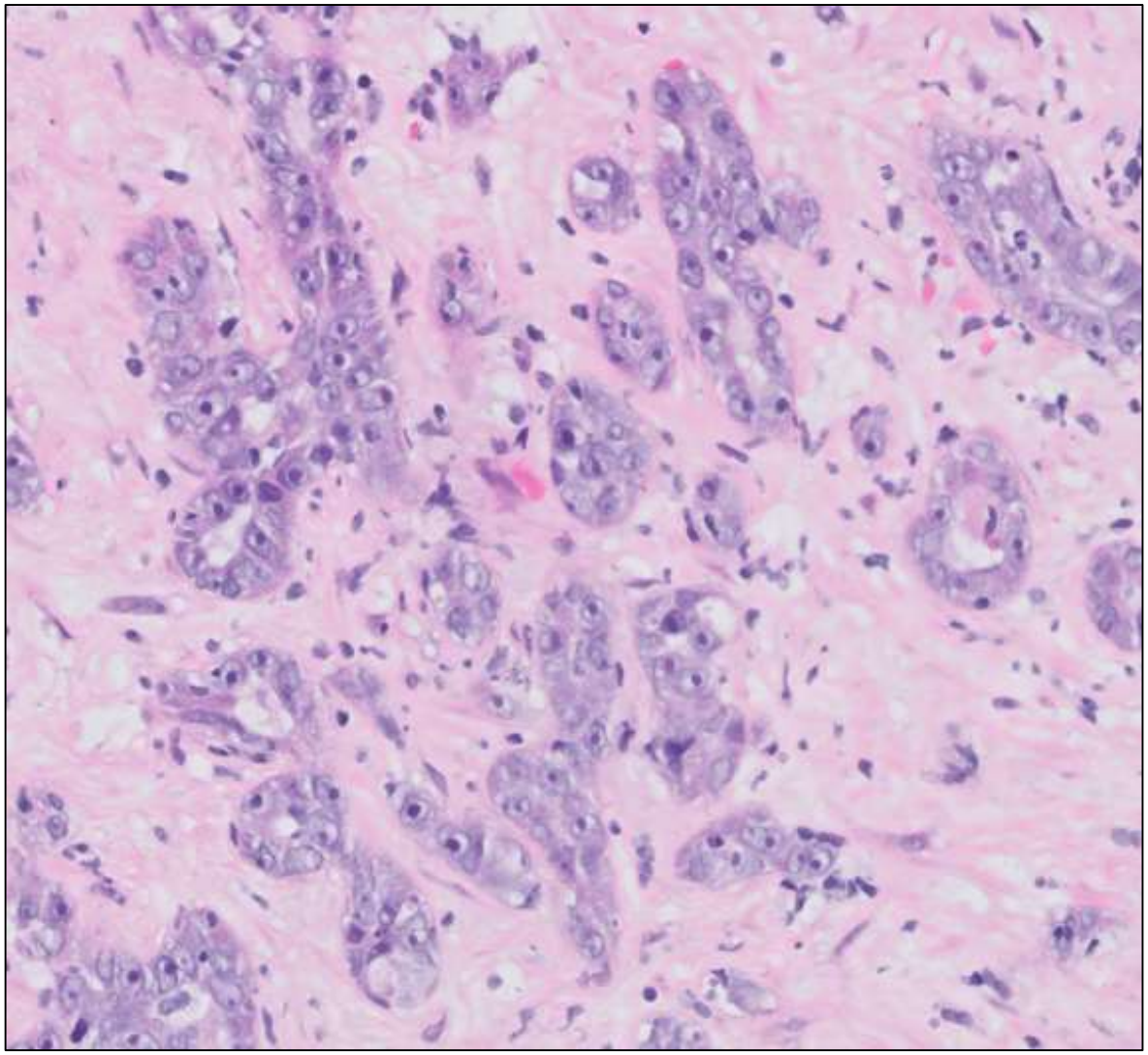
50ish M with h/o HCV cirrhosis status post treatment and SVR, now with two malignant appearing masses (up to 4.1 cm) on MRI, as well as CT angiography showing an occluded superior mesenteric vein, splenic vein and portal circulation by thrombus, as well as an irregularly shaped 3.5 cm hypoattenuated lesion in hepatic segment 4A suspicious for an abscess. AFP, CA19-9, and CEA were in normal range.

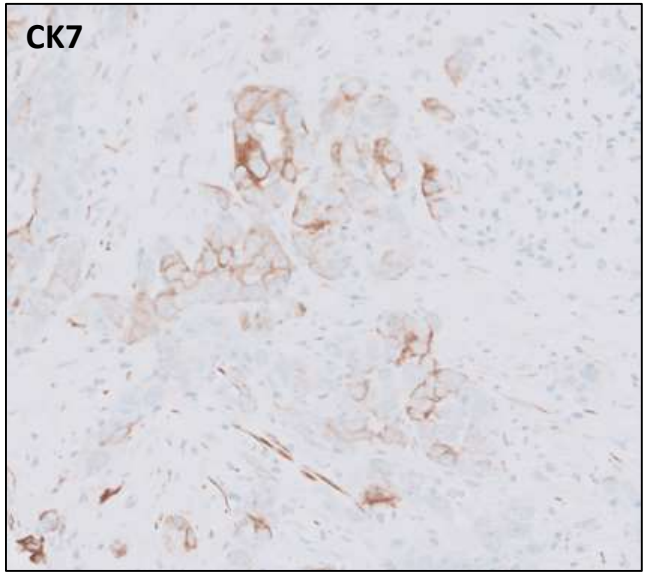


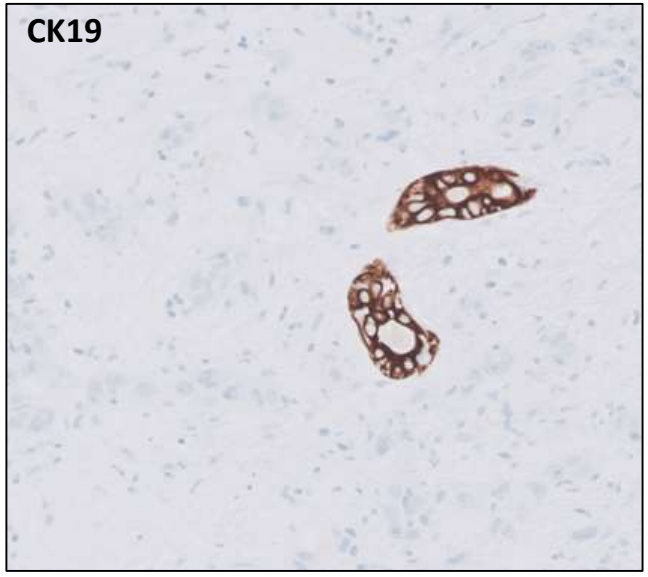


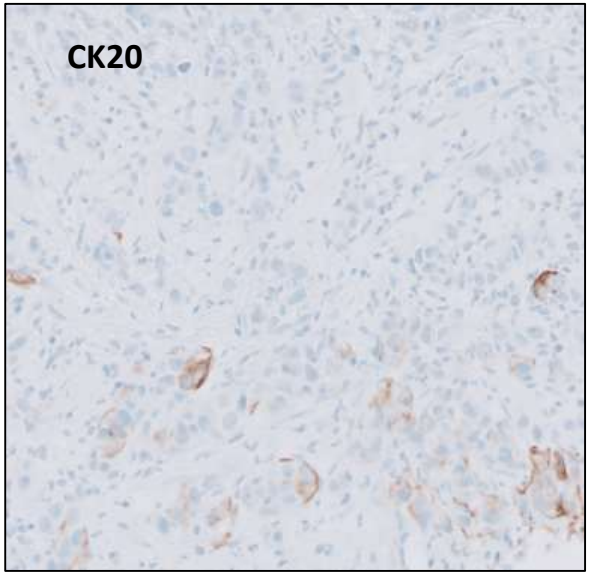


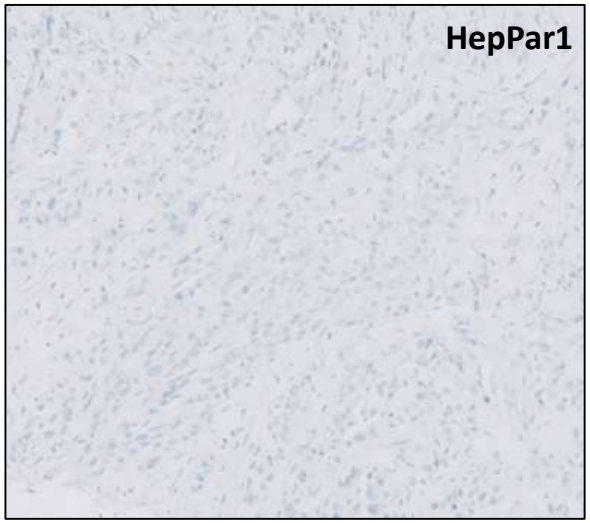


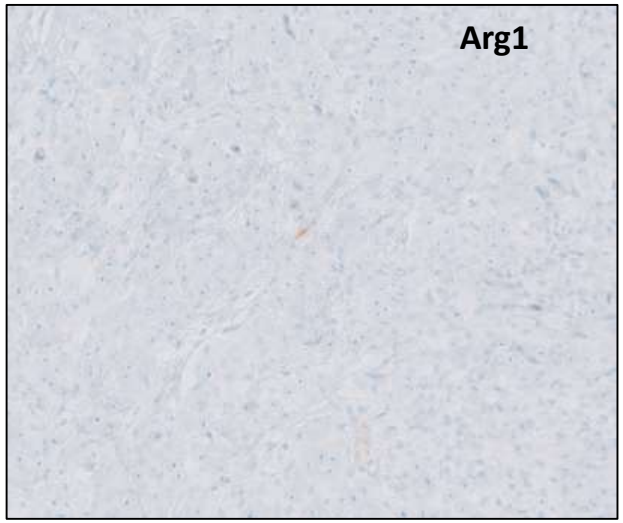


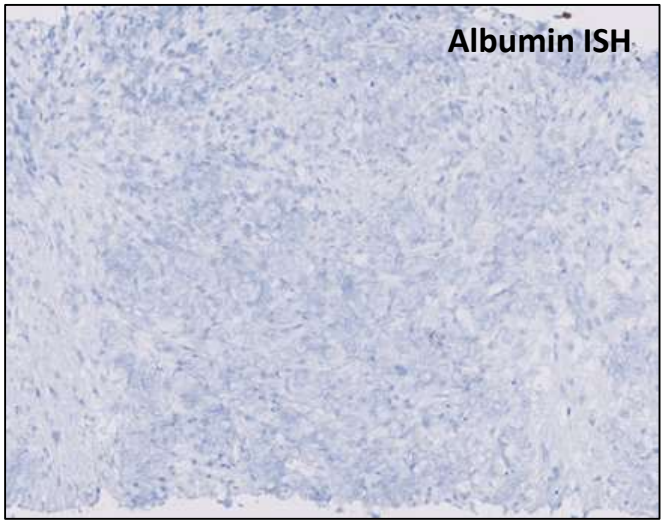

CK7


CK19


CK20


HepPar1


Arg1


Albumin ISH

Additional negative stains

- CK19, CK 5/6, MOC31
- NKX3.1, PAX8, TTF1, synaptophysin, CDX2
- Calretinin, WT1

Differential Diagnosis

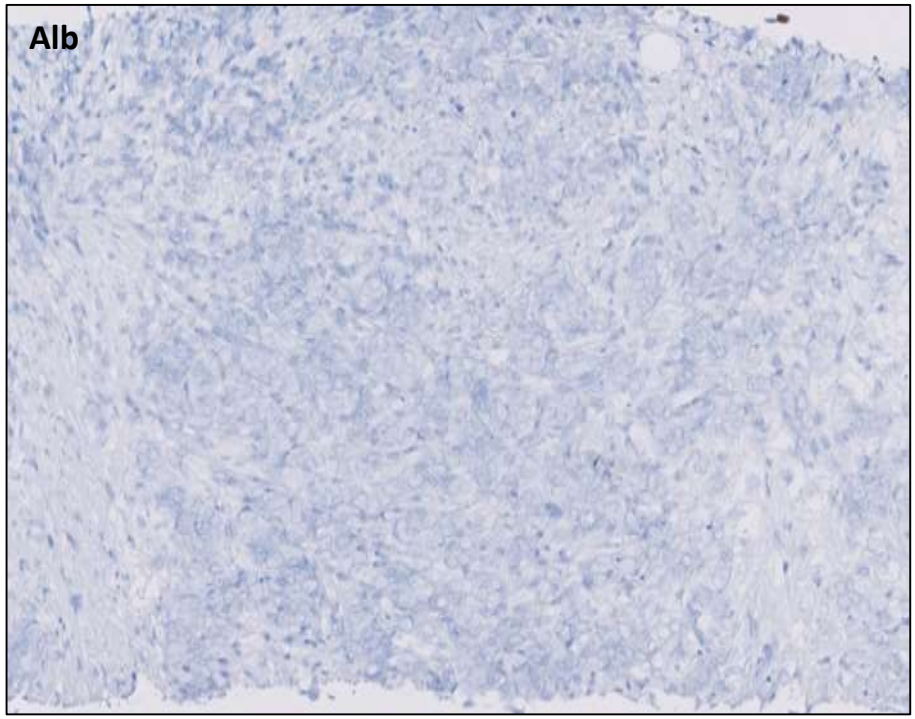
Patchy positive for keratin (AE1/AE3) and CK7 supports carcinoma

- Primary liver carcinoma
  - Hepatocellular carcinoma (HCC)
  - Intrahepatic cholangiocarcinoma (iCCA)
- Metastasis
  - Metastatic adenocarcinoma: pancreas, GI tract, lung
  - Renal cell carcinoma
  - Neuroendocrine carcinoma
  - Mesothelioma

Features arguing against metastatic origin:

- **CDX2**: Negative, does not support intestinal primary
- **NKX3.1**: Negative, does not support prostatic primary
- **TTF1**: Negative, does not support lung primary
- **PAX8**: Negative, does not support renal primary
- **Synaptophysin**: Negative, does not support neuroendocrine neoplasm
- **Calretinin/WT1**: Negative, does not support mesothelioma
- **History/Imaging**: No extrahepatic mass and setting of cirrhosis does not support metastatic adenocarcinoma

Albumin ISH

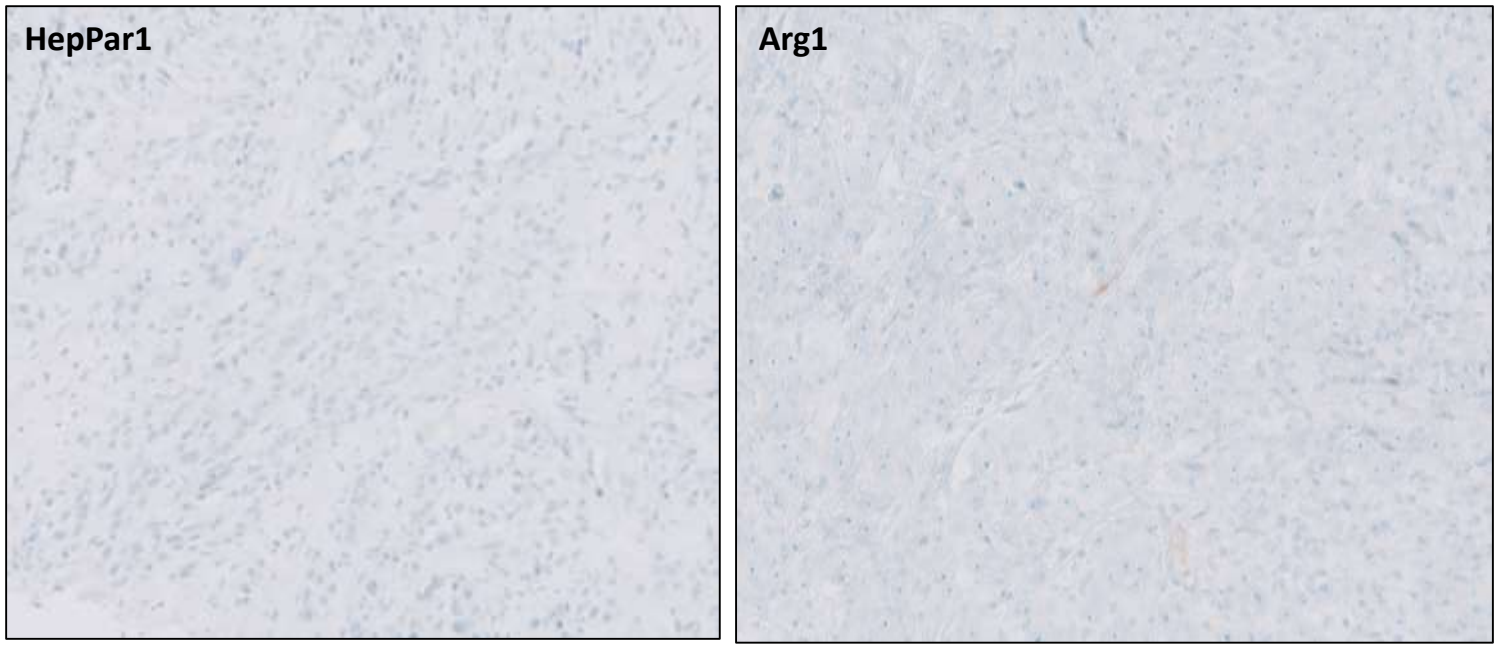


Tumor	Results
HCC	85-90%
Intrahepatic cholangiocarcinoma	60-70%
Acinar cell carcinoma	20-25%
Adenocarcinomas (rare)	Gallbladder, lung

- Does not support hepatic primary, but does not exclude it

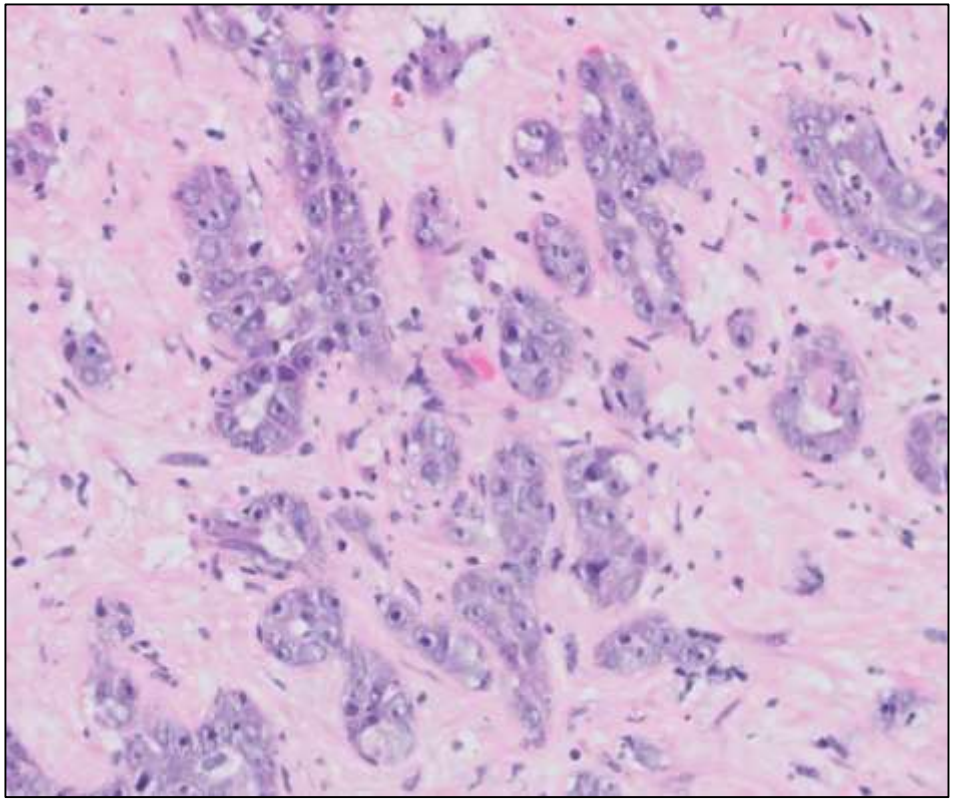
Shahid, AJSP 2015
Lin, AJCP 2018
Askan AJCP 2016
Nasir, AJCP 2019

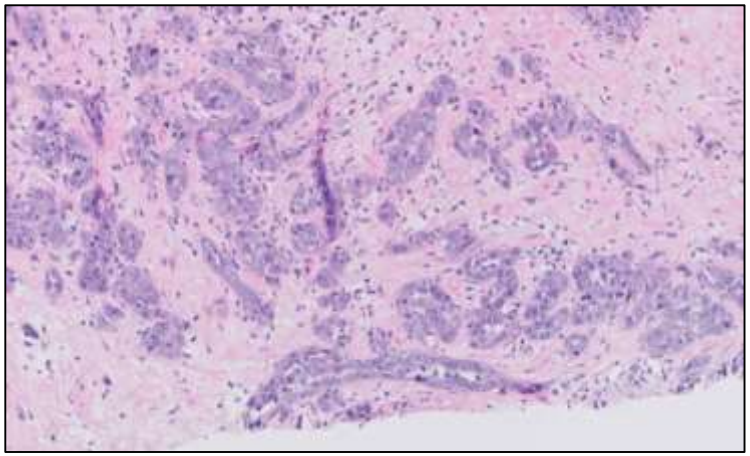
IHC: Negative hepatocellular markers

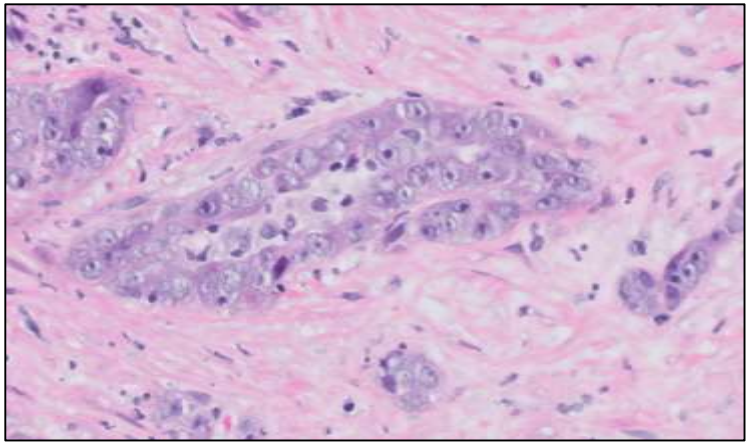


Provided AFP stain was negative

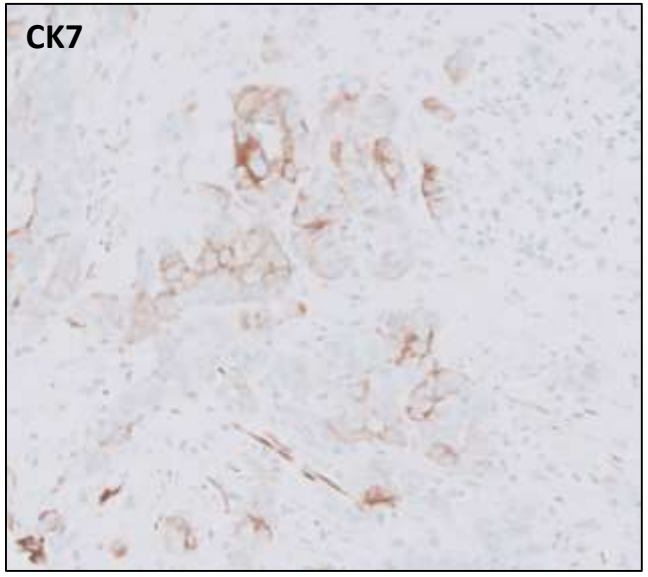
Focal gland formation

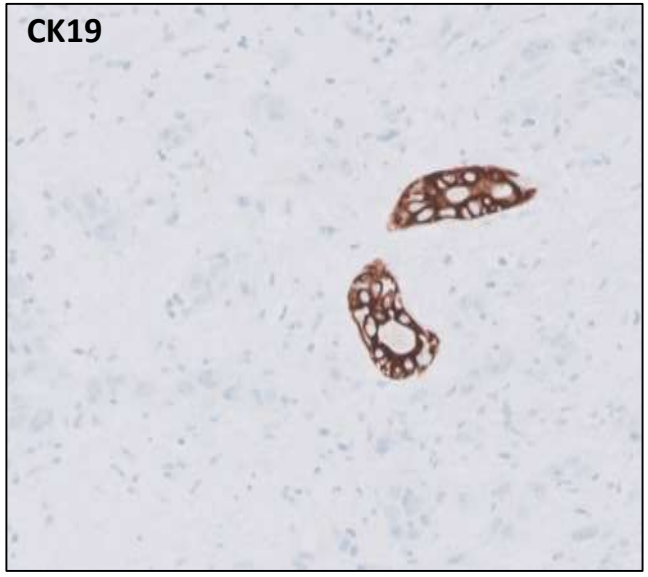


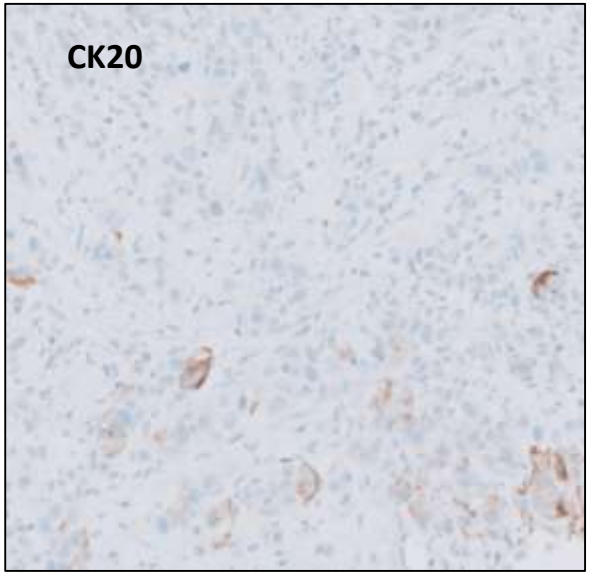




Patchy cytokeratin staining (most cholangiocarcinomas show strong CK7 and/or CK20)



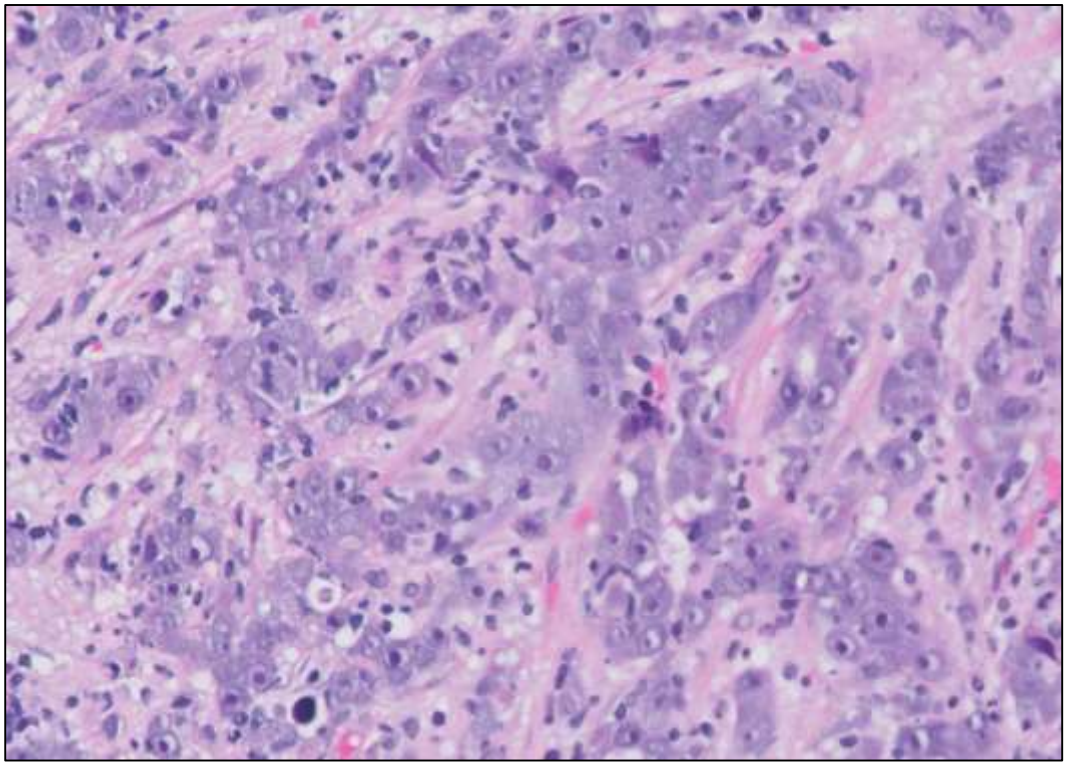




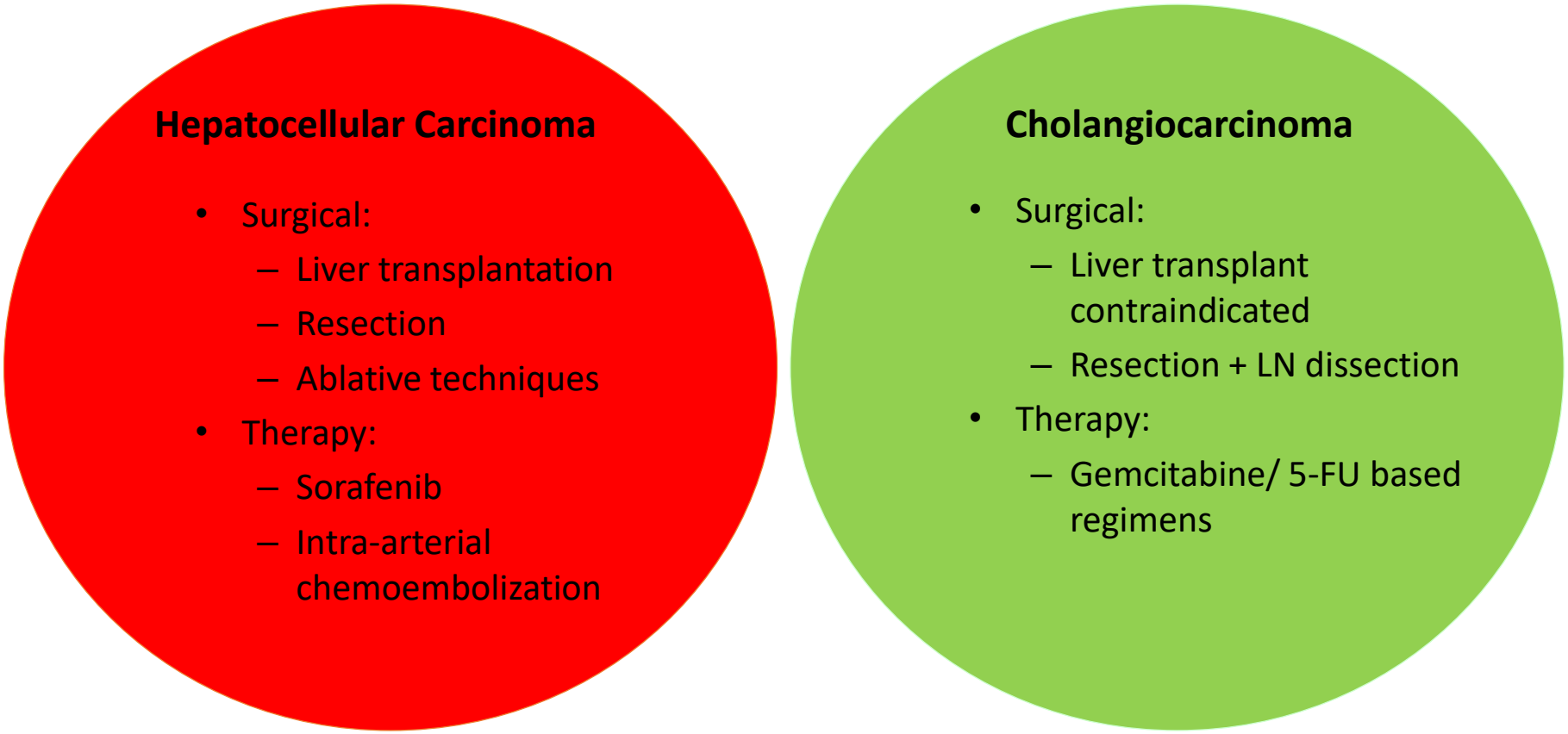
Lymphocyte-rich morphology

- EBV+ Lymphoepithelioma-like carcinoma
- Lymphocyte-rich variant of HCC or intrahepatic cholangiocarcinoma

EBV ISH was negative



Management of HCC vs. iCCA



Poorly differentiated carcinoma: HCC vs. iCCA

Genetic changes	HCC	iCCA
IDH mutations	Rare	19-36%
PBRM1 mutation	Rare	11-17%
FGFR2 fusion	Rare	6-50%
BAP1 mutation	5%	7-29%
CTNNB1 (β-catenin) mutation	20-30%	Uncommon
TERT promoter mutation	44-60%	Rare
MYC amplification	Up to 77%*	17%

* ETOH-related HCCs

Schulze, Nat Genetics, 2015
Zou, Nat Commun, 2014
Moeini, Clin Cancer Res 2016
Ally, Cell, 2017
Schlaeger et al, Hepatol, 2008
Jusakul et al, Cancer discov, 2017

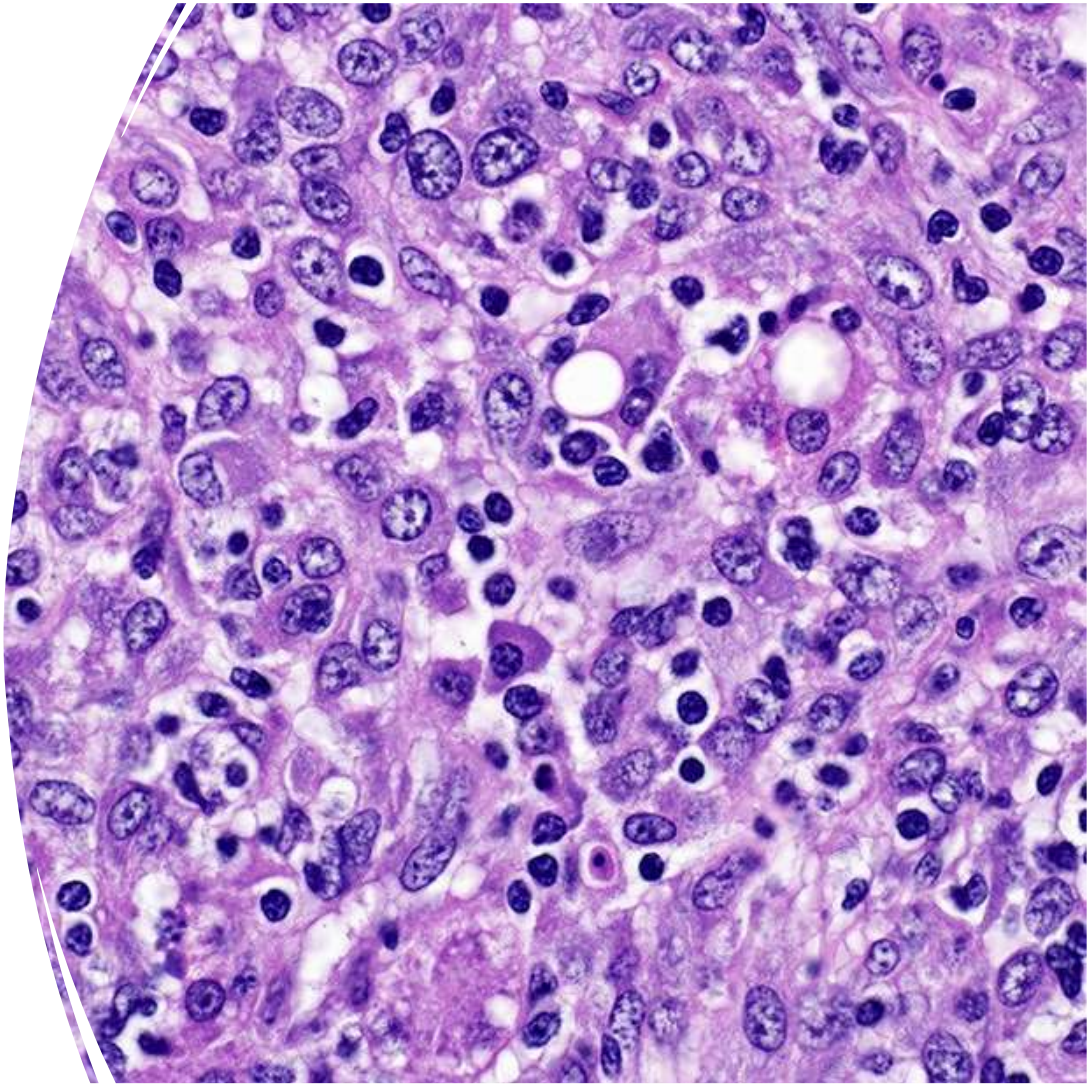
PATHOGENIC AND LIKELY PATHOGENIC ALTERATIONS				
VARIANT	**TRANSCRIPT ID**	**CLASSIFICATION**	**READS**	**MUTANT ALLELE FREQUENCY**
CRKL amplification	All	Pathogenic	~15x	N/A
MYC amplification	All	Pathogenic	~20x	N/A
TERT promoter rearrangement	N/A	Pathogenic	129	N/A
TP53 c.560-2A>T	NM_000546.5	Pathogenic	879	26%
CD274 (PD-L1) amplification	All	Likely Pathogenic	~10x	N/A

NGS findings

- Findings not specific, but highly characteristic of HCC:
  - *TERT* promoter rearrangement
  - *MYC* amplification

Diagnosis

Poorly differentiated carcinoma, consistent with lymphocyte-rich variant of HCC

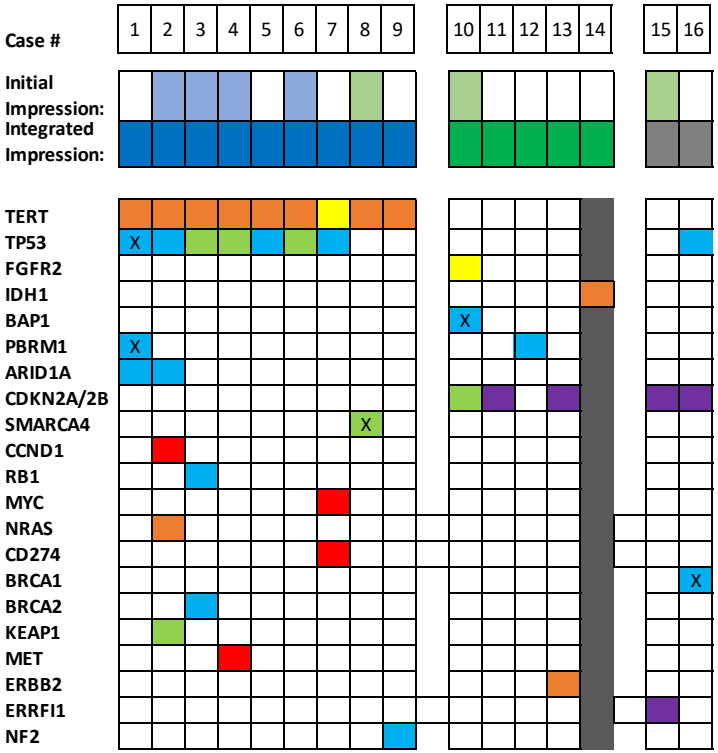


Torbenson, Gastroenterol Clin N Am, 2017

Learning points

- Distinction of HCC and intrahepatic cholangiocarcinoma cannot be reliably achieved based on H&E and additional stains in a subset of cases
- This distinction is crucial for appropriate management
- Negative albumin ISH does not exclude primary hepatic origin
- NGS can reveal unique genomic profiles that can help in the diagnosis of HCC and intrahepatic cholangiocarcinoma
- If multiple tissue cores are received from a mass lesion, these should be submitted in separate blocks to enable complete work-up with IHC and NGS as necessary

Potential Utility of NGS in Poorly-differentiated Primary Liver Carcinomas



- Genomic alterations were helpful in classifying poorly-differentiated PLCs in 14/16 cases (88%)
- *TERT* promoter mutations were consistently identified in PD-PLC found to be HCC

Impression
- HCC
- ICC
- Indeterminate
- Favor HCC
- Favor ICC
- Neither HCC or ICC favored

Genomic Alterations
- Known hotspot mutation
- Truncating mutation (frameshift, nonsense, splice site)
- Rearrangment
- Amplification
- Missense mutation
- Deep deletion
- No genomic alterations by NGS
- Not evaluated by NGS

Kikuchi et al, manuscript in preparation

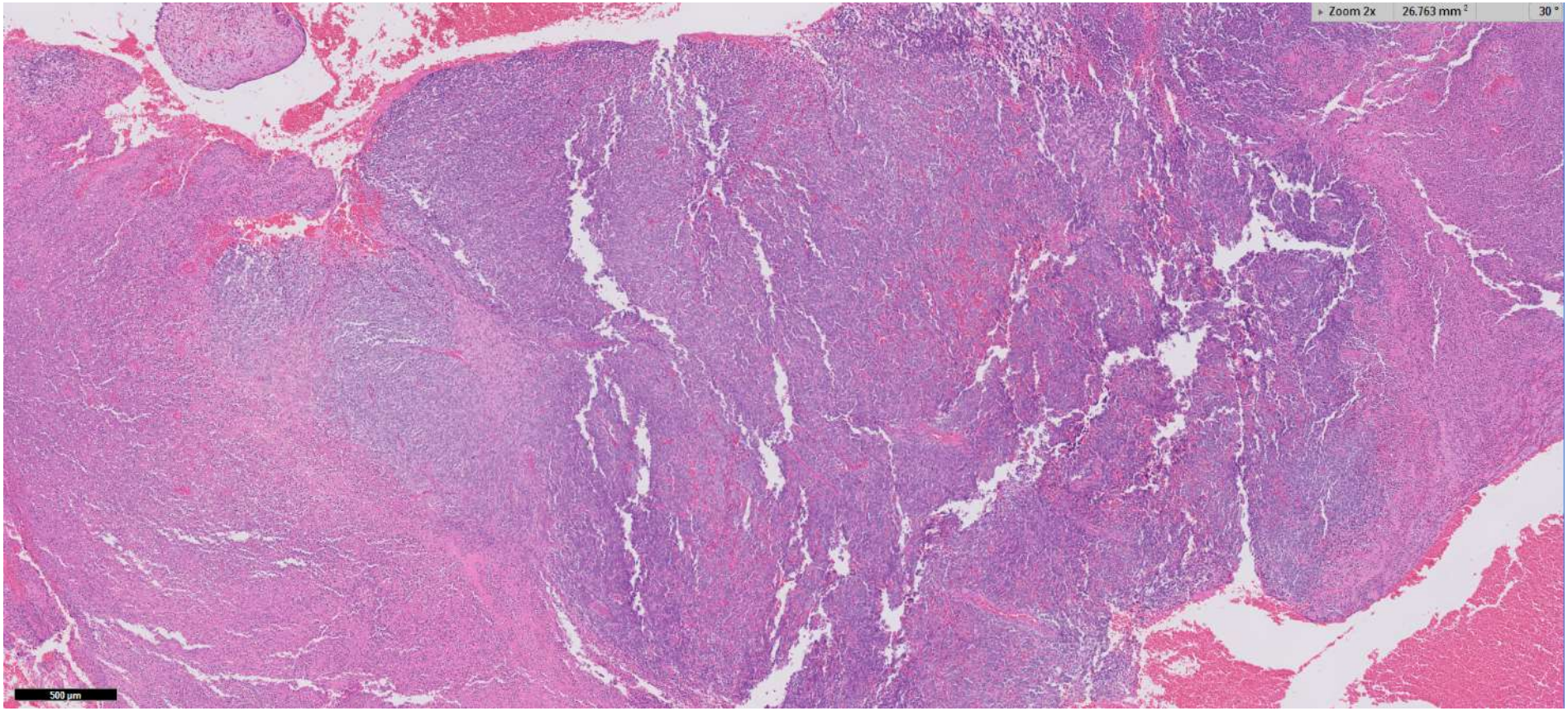
References

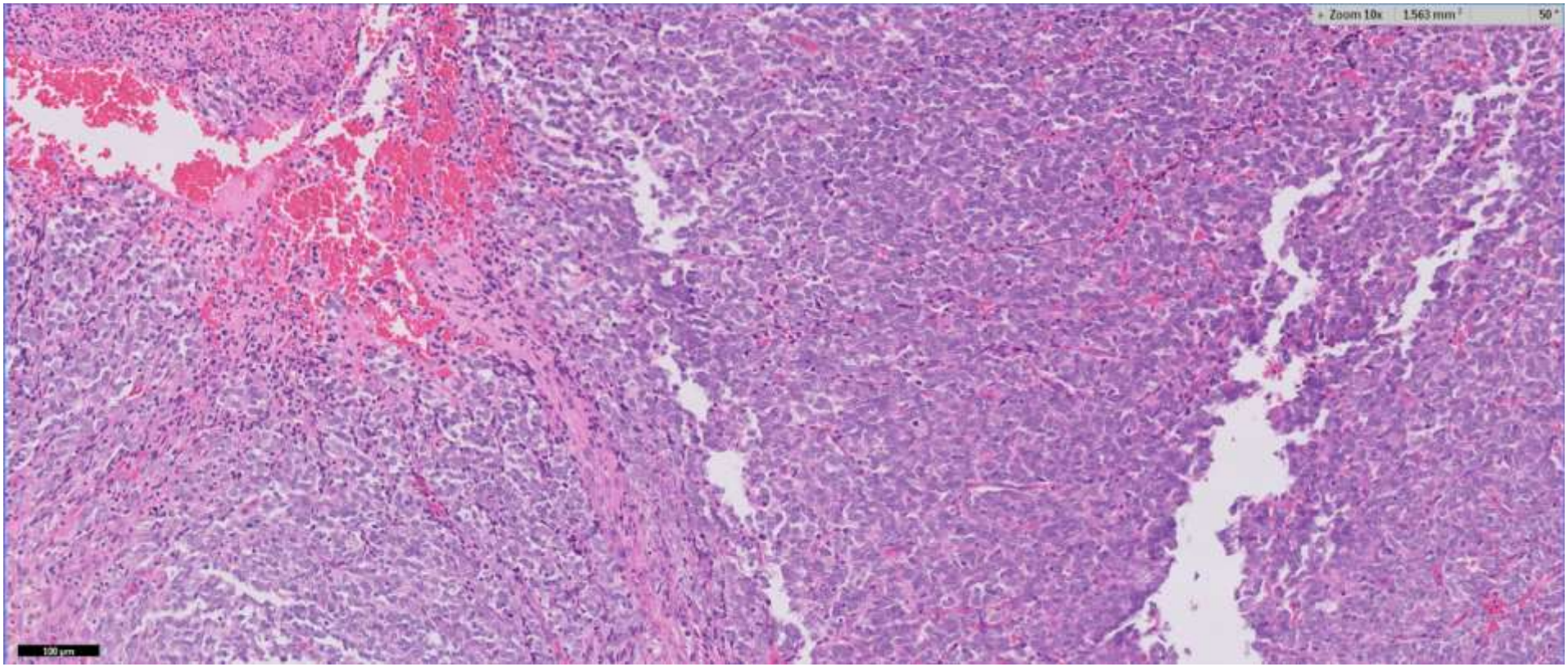
- Ally A, Balasundaram M, Carlsen R, et al. Comprehensive and Integrative Genomic Characterization of Hepatocellular Carcinoma. Cell 2017;169:1327-1341.e23. doi:10.1016/j.cell.2017.05.046.
- Lin F, Shi J, Wang HL, et al. Detection of Albumin Expression by RNA In Situ Hybridization Is a Sensitive and Specific Method for Identification of Hepatocellular Carcinomas and Intrahepatic Cholangiocarcinomas. Am J Clin Pathol 2018;150:58–64. doi:10.1093/ajcp/aqy030.
- Moeini A, Sia D, Bardeesy N, et al. Molecular Pathogenesis and Targeted Therapies for Intrahepatic Cholangiocarcinoma. Clin Cancer Res 2016;22:291–300. doi:10.1158/1078-0432.ccr-14-3296.
- Nasir A, Lehrke HD, Mounajjed T, et al. Albumin In Situ Hybridization Can Be Positive in Adenocarcinomas and Other Tumors From Diverse Sites. Am J Clin Pathol 2019;152:190–199. doi:10.1093/ajcp/aqz032.
- Schulze K, Imbeaud S, Letouzé E, et al. Exome sequencing of hepatocellular carcinomas identifies new mutational signatures and potential therapeutic targets. Nat Genet 2015;47:505–511. doi:10.1038/ng.3252.
- Shahid M, Mubeen A, Tse J, et al. Branched Chain In Situ Hybridization for Albumin as a Marker of Hepatocellular Differentiation. Am J Surg Pathology 2015;39:25–34. doi:10.1097/pas.0000000000000343.
- Zou S, Li J, Zhou H, et al. Mutational landscape of intrahepatic cholangiocarcinoma. Nat Commun 2014;5:5696. doi:10.1038/ncomms6696.

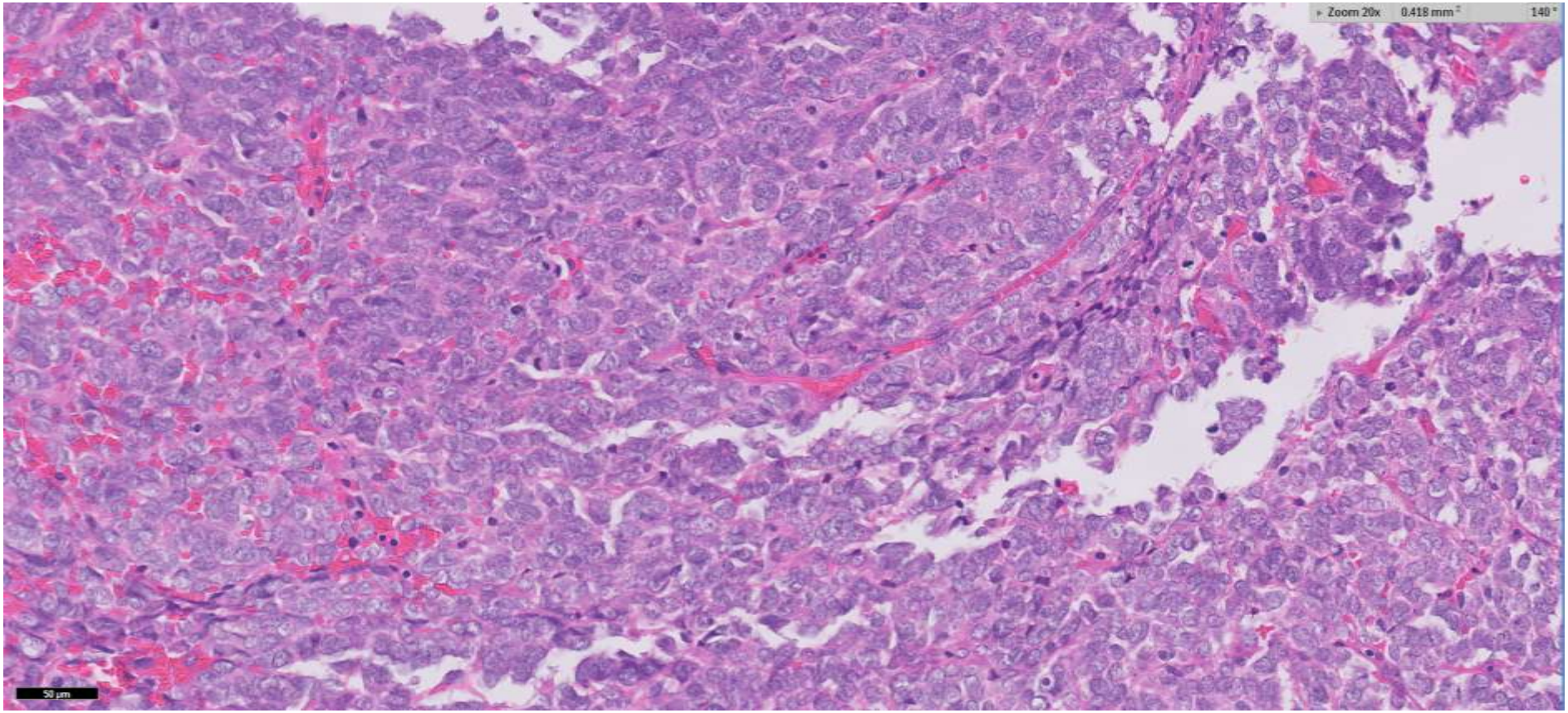
22-0706

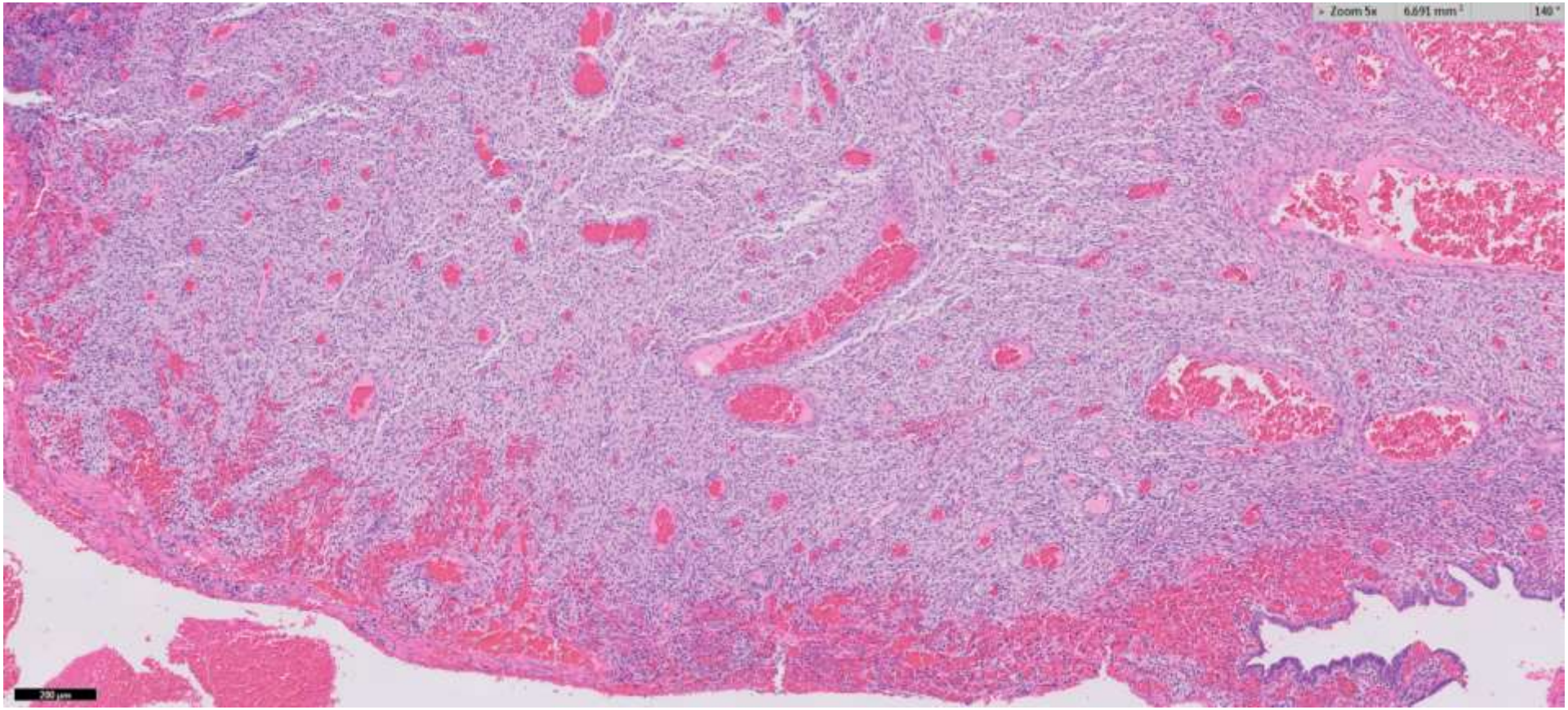
Diane Libert/Brooke Howitt; Stanford

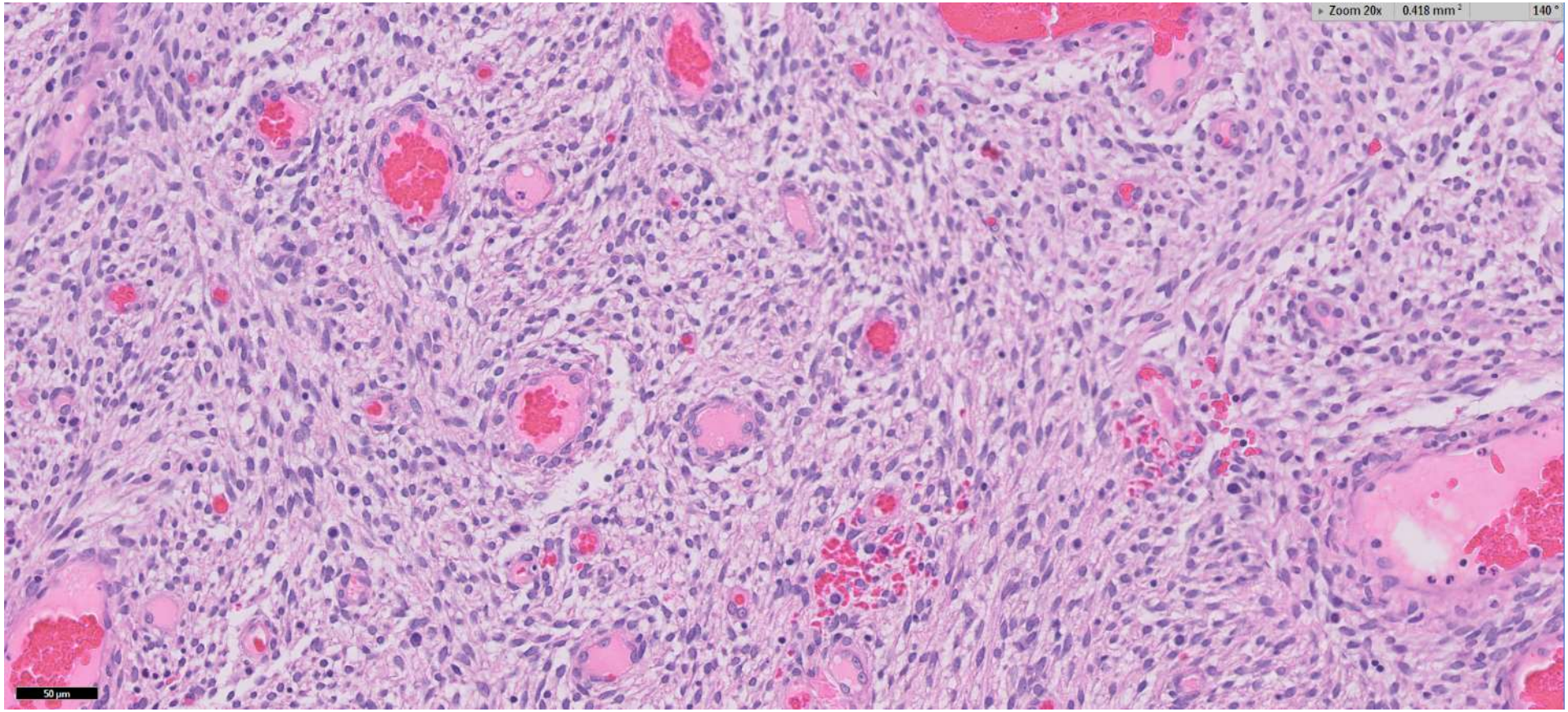
60ish F with necrotic endometrial mass.


Zoom 2x
26.763 mm²
30 °
500 µm


Zoom 10x
1.563 mm²
50 °
100 µm


Zoom 20x
0.418 mm²
140 °
50 µm


Zoom 5x
6.691 mm²
140 °
200 µm

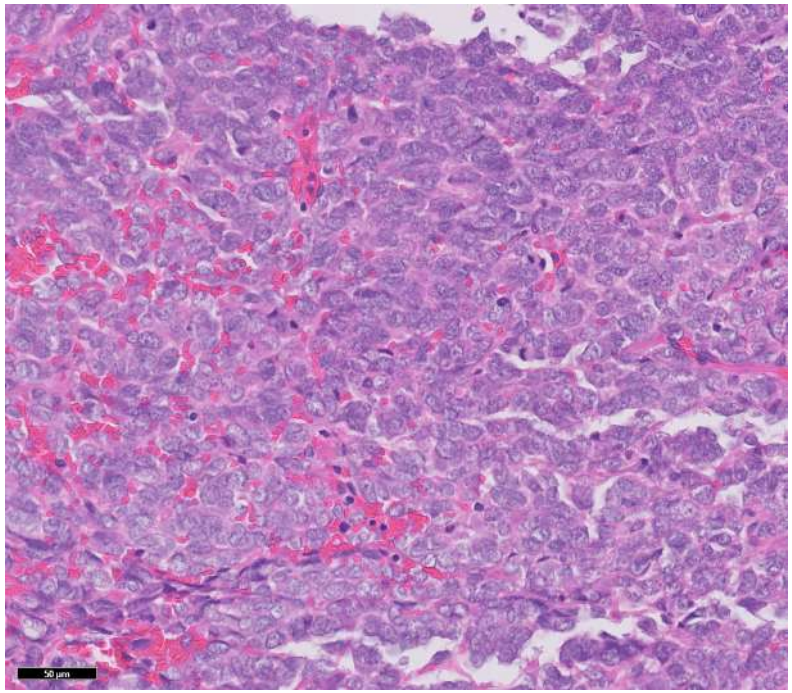

Zoom 20x
0.418 mm²
140 °
50 µm

“60 ish F with necrotic endometrial mass”

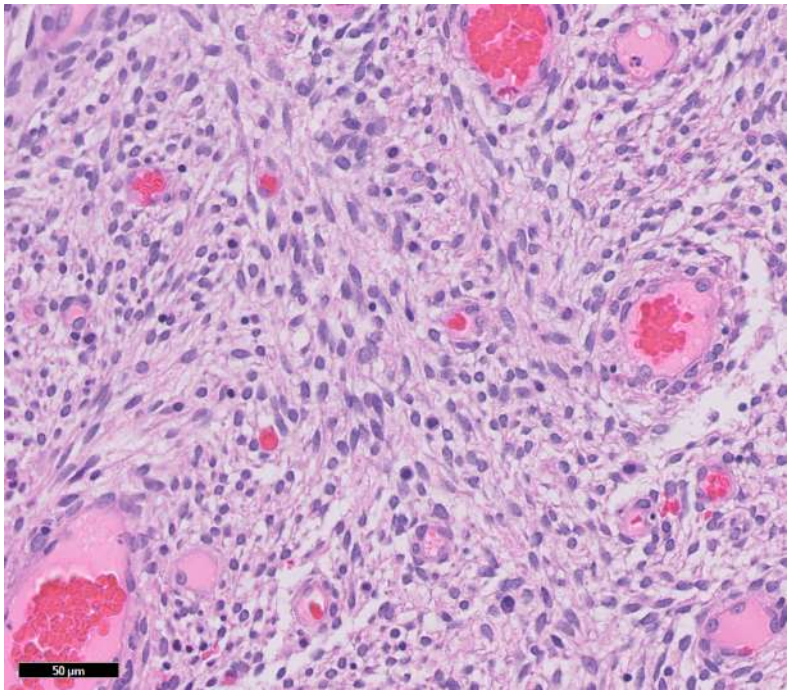
Presented by Diane Libert, MD (PGY3) and Brooke Howitt, MD

Morphology summary

High-grade component

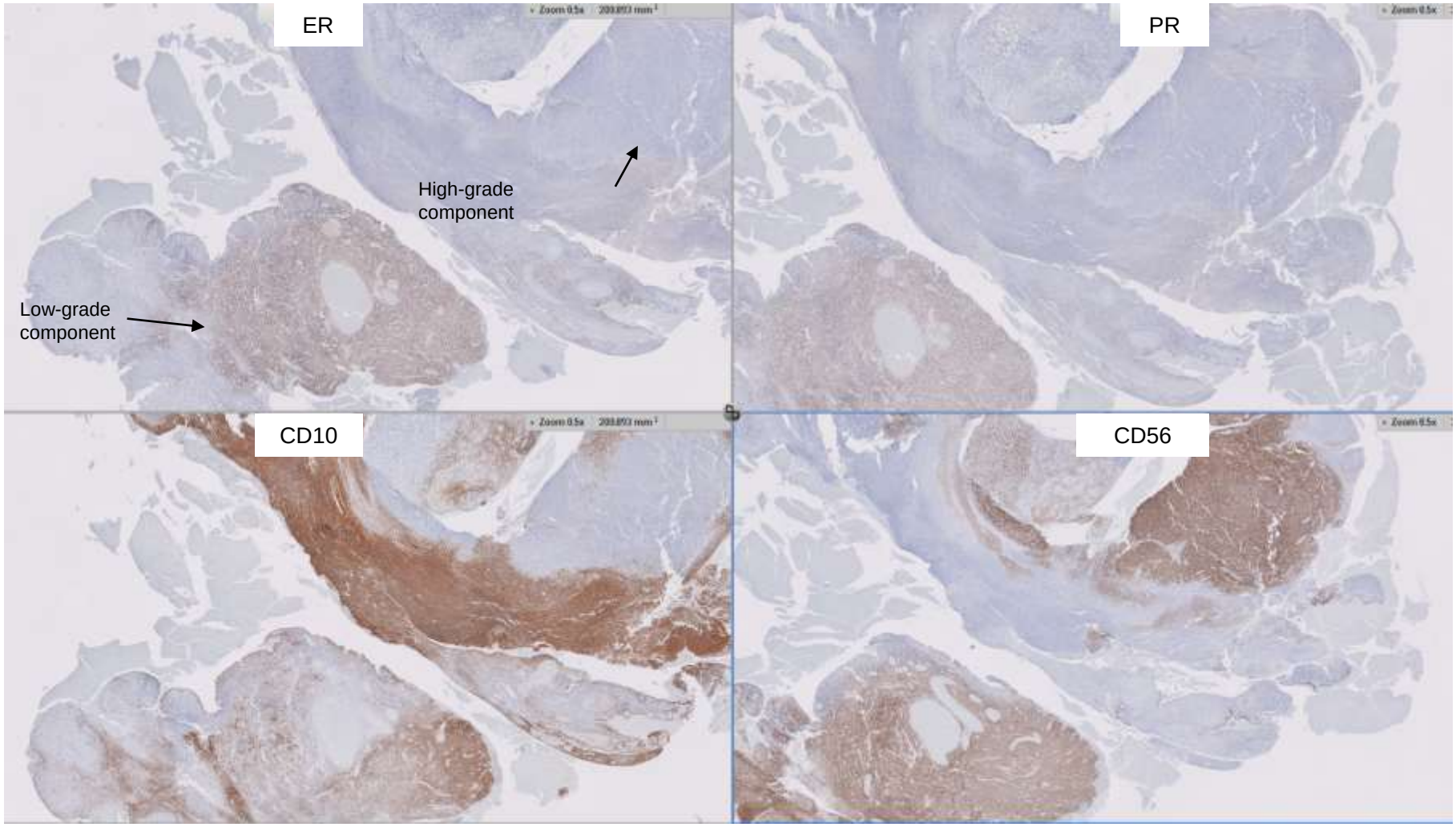


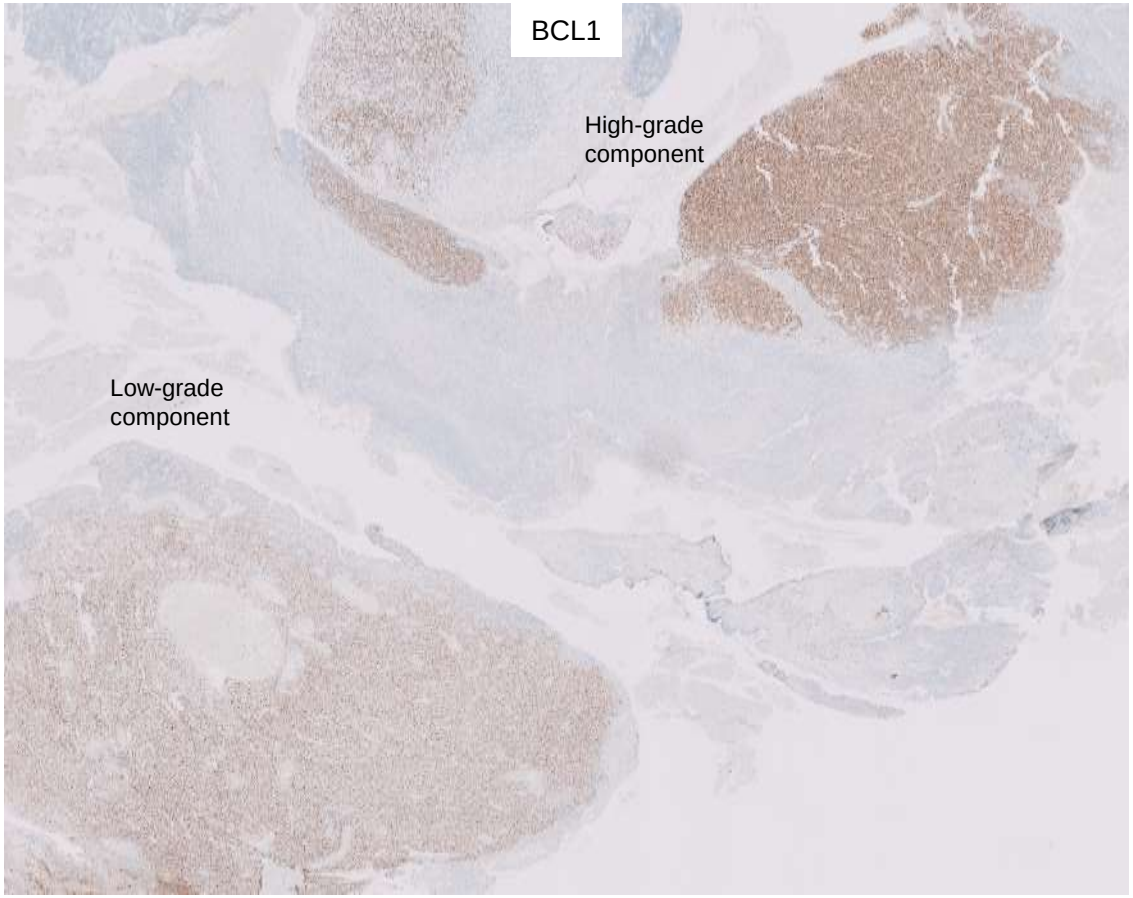
Low-grade component



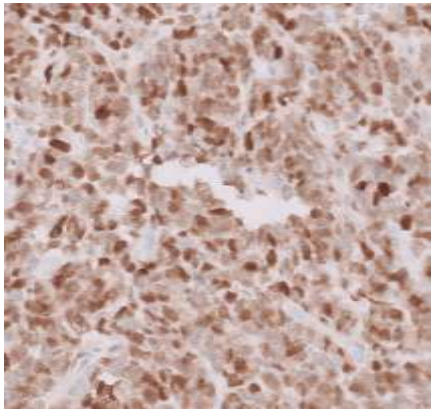
Differential diagnosis

- Epithelioid leiomyosarcoma
- Undifferentiated/dedifferentiated carcinoma
- High-grade endometrial stromal sarcoma (*YWHAE* rearranged, *BCOR* altered)
- Ewing sarcoma
- Gastrointestinal stromal tumor (GIST)

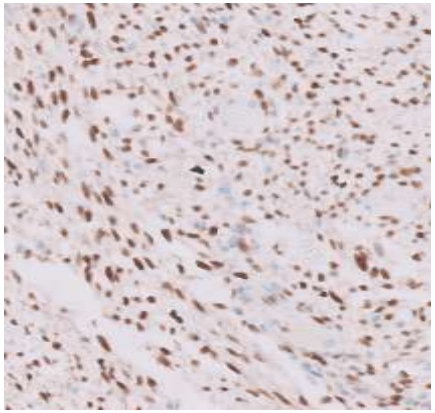

ER
PR
High-grade component
Low-grade component
CD10
CD56



High-grade component:



Low-grade component:

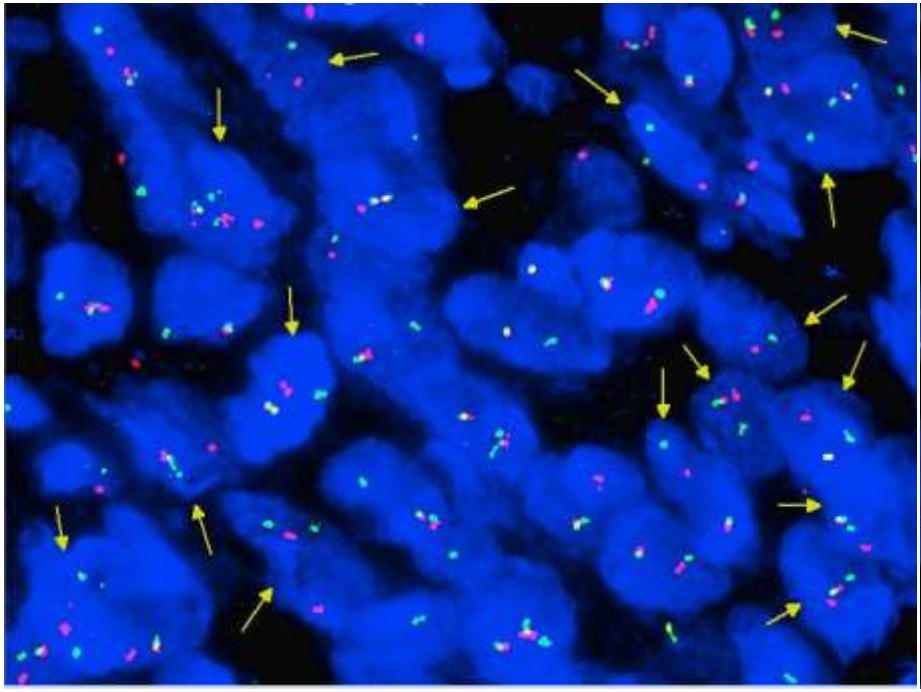


Immunohistochemistry summary

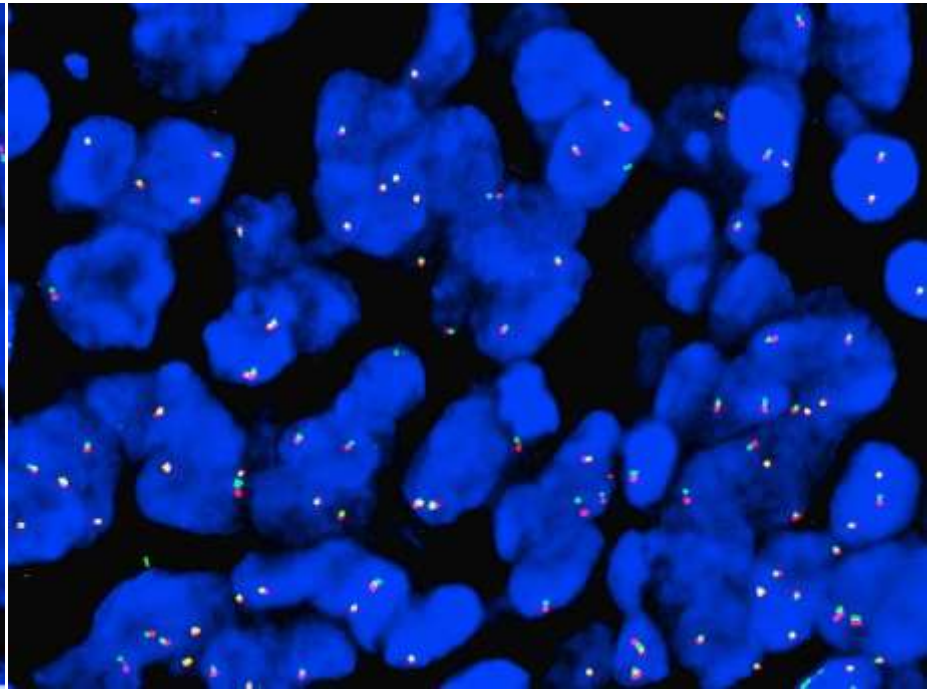
Marker	High-grade component	Low-grade component
CD56	+	+
CD10	-	+
ER	-	+
PR	-	+
BCL1 (cyclin D1)	Increased (nuclear)	Not as increased
Desmin, myogenin	-	-
PAX8	-	-
P53	Wild-type	Wild-type
P16	Non-diffuse	Non-diffuse
PAX7	-	-
PMS2, MSH6	-	-
BRG, INI	-	-
CD45	-	-
Pancytokeratin, cytokeratin AE1/AE3	-	-
Napsin A	-	-
Calponin, inhibin	-	-
Chromogranin, Synaptophysin	-	-
calretinin	-	-
EMA, S100, HMB-45	-	-

YWHAE and BCOR fluorescence in situ hybridization (FISH) with break-apart probes

YWHAE FISH (positive, 72% of nuclei)



BCOR FISH (negative)



Diagnosis: High-grade endometrial stromal sarcoma (see comment), FISH positive for *YWHAE* rearrangment

- Origin:
  - First described in 2012[1], added to WHO in 2014
  - Endometrial stromal sarcomas (ESSs) are heterogeneous, some have features intermediate between classic low-grade endometrial stromal sarcoma (ESS) and undifferentiated endometrial sarcoma (UES)
- Epidemiology:
  - Rare, <2% of all uterine tumors[2]
  - Perimenopausal women
- Clinical implications:
  - *YWHAE*-rearranged HG ESSs are more aggressive and present with more advanced disease
  - Hormonal therapy less likely to be effective! May benefit from anthracycline-based therapy[3]

1. Lee CH, et alAm J Surg Pathol. 2012 May;36(5):641-53.
2. Kurman, R. J., et al. World Health Organization (2014): 1-309.
3. Hemming ML, et. al. Gynecol Oncol. 2017 Jun;145(3):531-535.

Differential Diagnosis

Tumor	Morphology Highlights	Immunohistochemistry Highlights (HG component in ESS)
HG ESS, *YWHAE-NUTM2A/B*	Delicate capillary network, may have area of ESS with different morphology	CD56+, CD99+, CD117+, BCL1+ ;CD10, ER, PR - in HG, DOG-1 -
HG ESS, *ZC3H7B-BCOR*	Frequent myxoid stroma, no areas of conventional endometrial stromal neoplasia	CD10+, BCL1+; ER and PR variable (usually -)
HG ESS, *BCOR* internal tandem duplication (ITD)	Can have myxoid background, numerous small vessels	CD10+, BCL1+; ER-, PR-
Epithelioid leiomyosarcoma	No delicate vessels	Desmin +, ER+, PR+; BCL1- or focal+
Undifferentiated/dedifferentiated carcinoma	Areas of LG carcinoma	Keratins, Pax8, or EMA+
Ewing sarcoma	Nests of cells without delicate vasculature	BCL1 -, *EWSR1* rearranged
Gastrointestinal stromal tumor (GIST)	Spindled and epithelioid areas, eosinophilic cytoplasm	DOG-1+

References:
- Kurman, R. J., et al. World Health Organization (2014): 1-309.
- Expertpath. https://app.expertpath.com/

Conclusion

- YWHAE-rearranged high-grade endometrial stromal sarcoma is rare and important to identify, as there are prognostic and therapeutic implications
  - Intermediate prognosis between LG ESS and UES
  - May benefit from anthracycline-based chemotherapy, hormonal therapy less likely to be effective

- **Thank you! Questions?**

22-0707

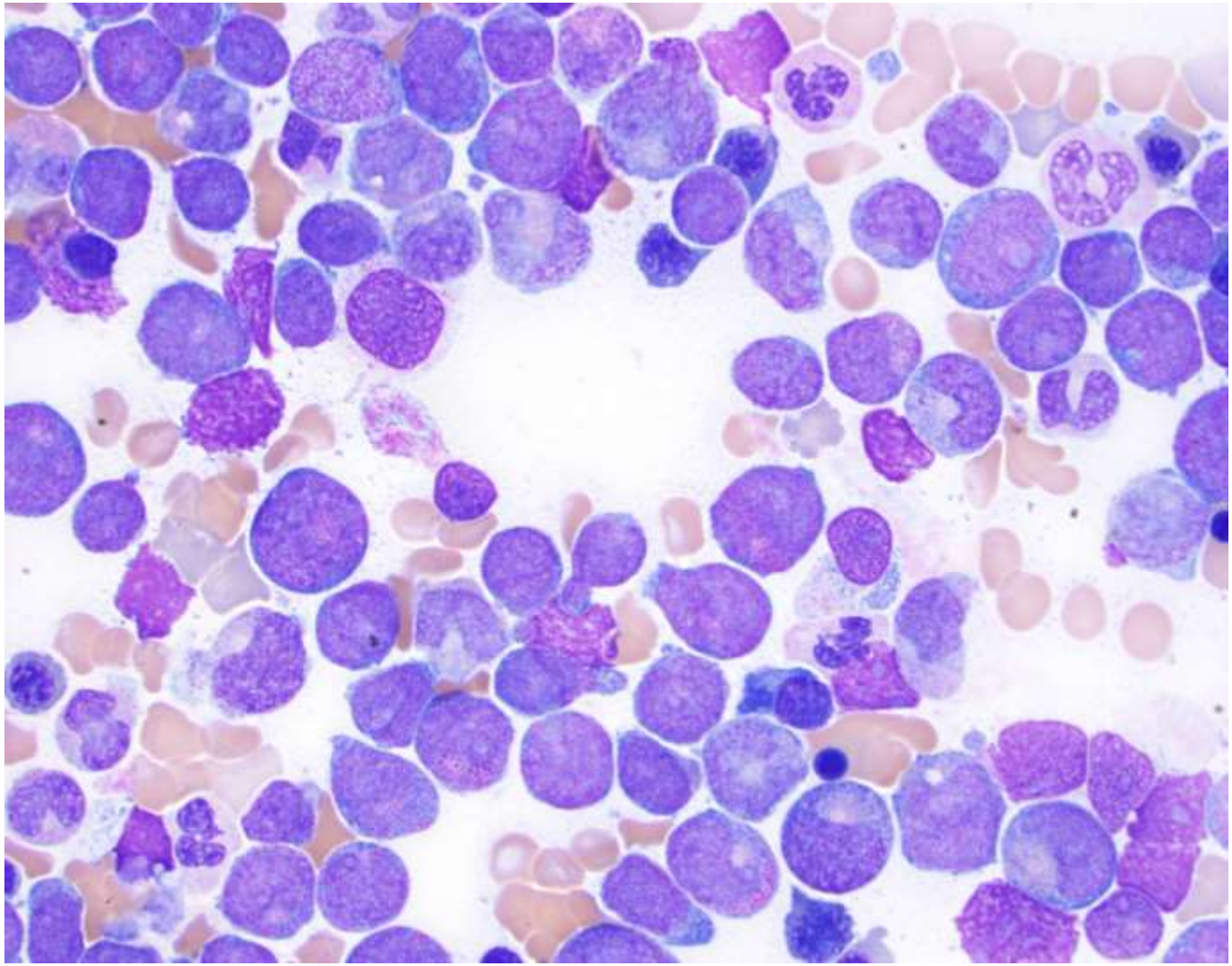
Linlin Wang; UCSF

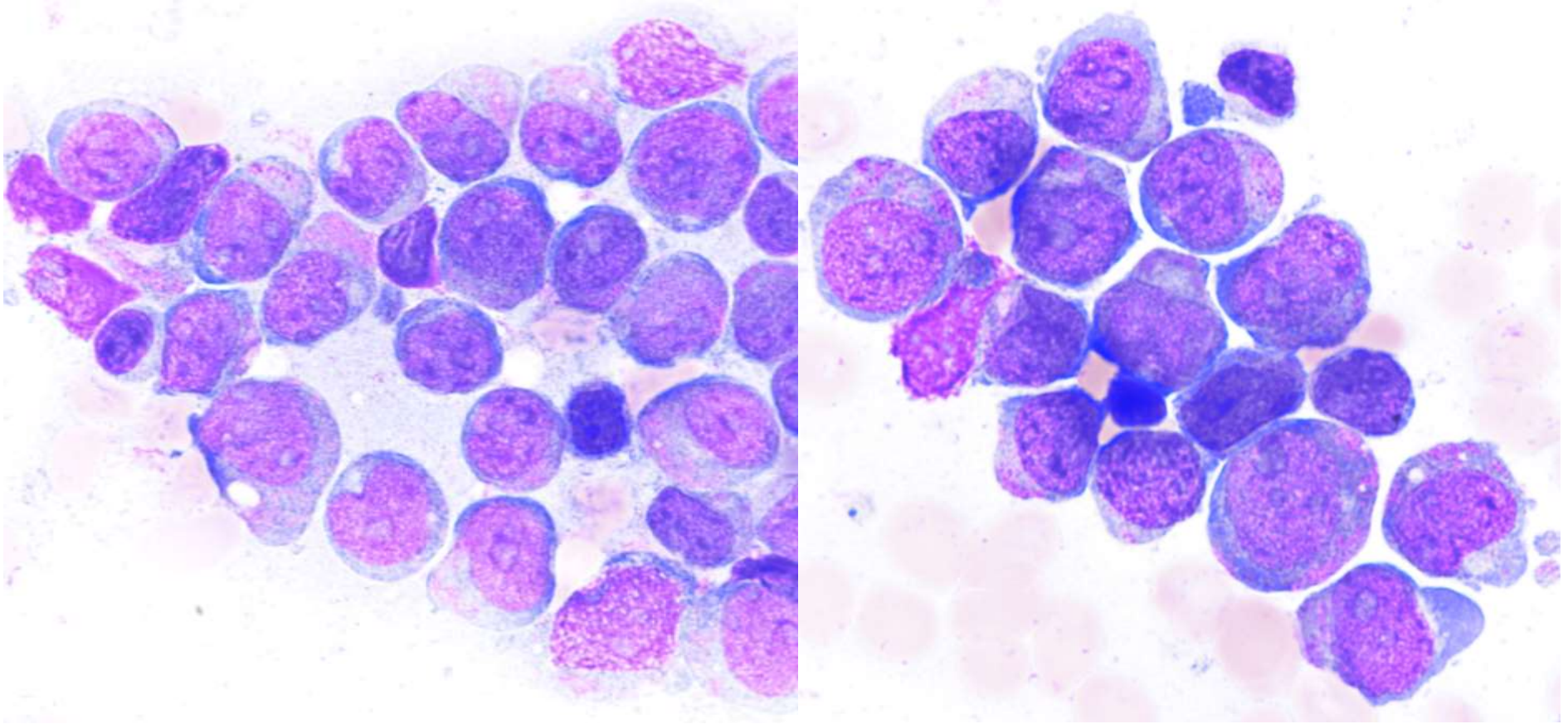
40ish F presents with fatigue, easy bruising, gum bleeding, and increased blasts on peripheral blood smear. She underwent bone marrow biopsy for new leukemic workup.

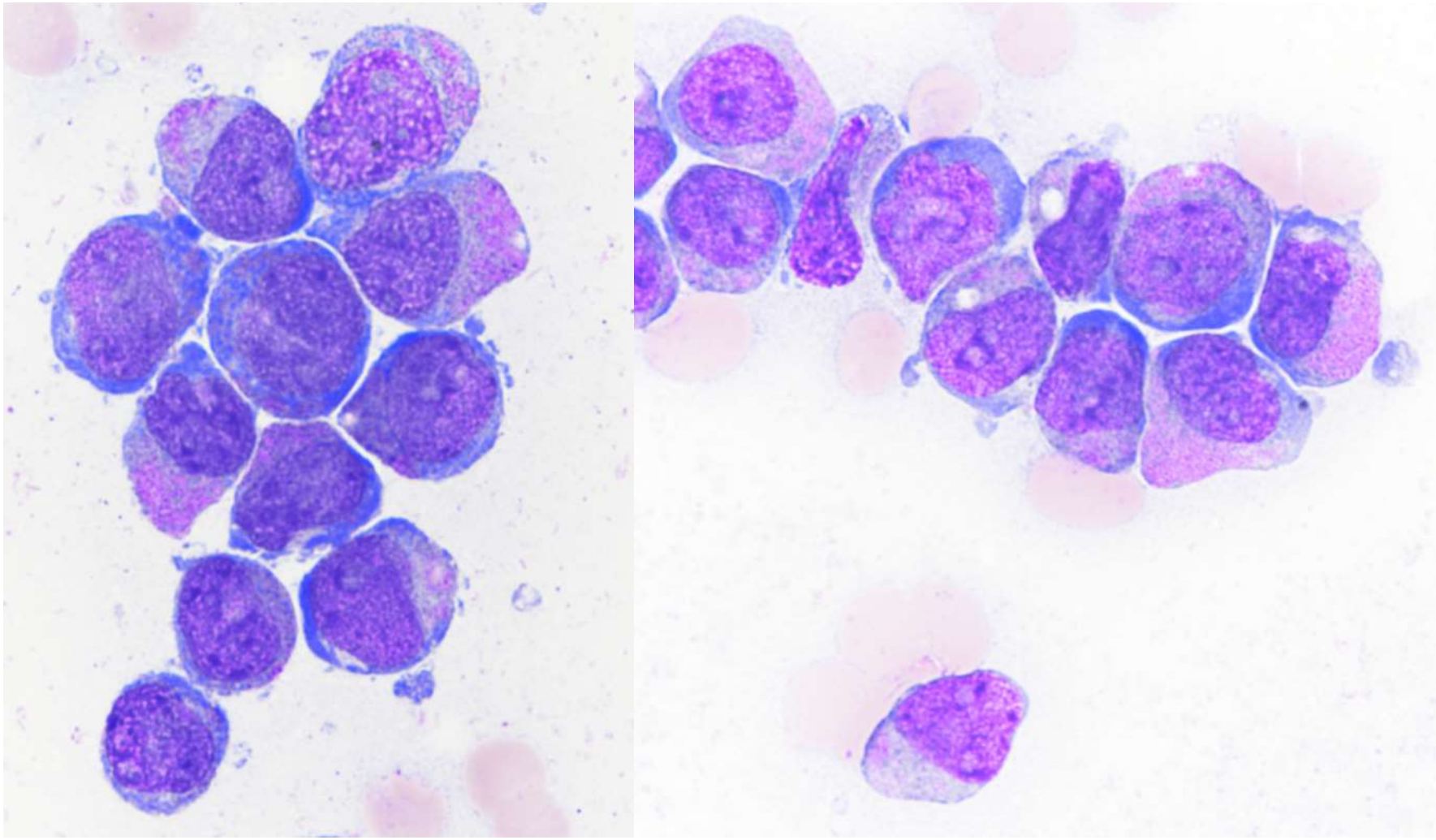
40ish woman presented with fatigue, easy bruising, gum bleeding and increased blasts on peripheral blood smear. She underwent bone marrow biopsy for new leukemic workup.

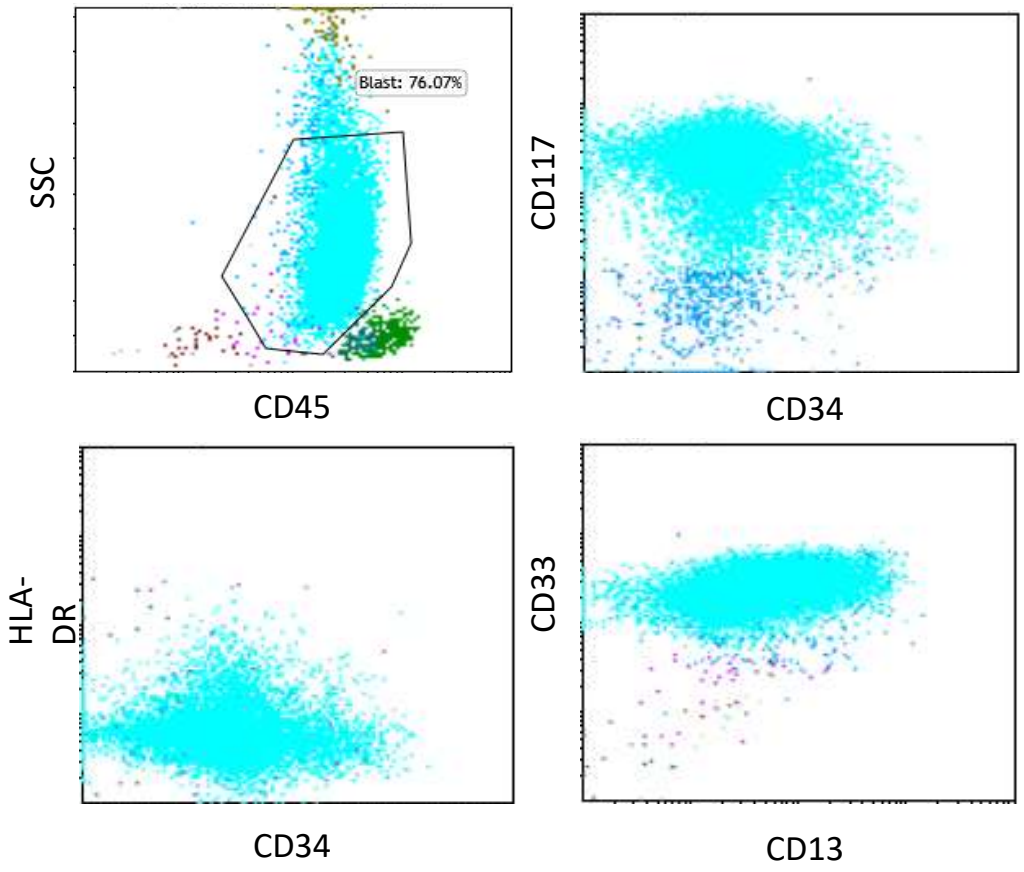
CBC: WBC 8.6 x10E9/L, Hb 8.5 g/dL, Platelets 32x10E9/L

Linlin Wang, UCSF








Blast: 76.07%
SSC
CD45
CD117
CD34
HLA-DR
CD34
CD33
CD13

Morphology: Blasts >20%. Blasts show abundant cytoplasmic granular, rare Auer rod, perinuclear hof

Flow cytometry: Acute myeloid leukemia (blasts are 96% of total events). These abnormal myeloid blasts displayed variable/high side scatter and express weak CD4, variable CD13, weak CD15, CD33, variable/weak CD34, CD38, moderate CD45, weak CD64, CD71, CD117, and weak-to-absent CD123 without co-expression of CD3, CD14, CD16, CD19, or HLA-DR. Given the AML immunophenotype (elevated side scatter, weak/absent CD34, lack of HLA-DR), the differential specifically includes acute promyelocytic leukemia (APL).

Karyotype: 47,XX,t(7;11)(p15;p15),+8[20]
FISH: Negative for PML/RARA gene fusion
Positive for NUP98 rearrangement

Diagnosis: AML with *NUP98* rearrangement

Table 1 Demographics, diagnoses, morphology, immunophenotype, cytogenetics, molecular features, therapy, and clinical outcome of patients with myeloid neoplasms with *NUP98* rearrangement.

Case	Age/ Gender	Diagnosis	Prior Malignancy	Blast (%)	Blast morphology	Karyotype	*NUP98* FISH	Flow cytometry immunophenotype	NGS panel/ mutations	Therapy	Follow up time/ OS(M)	Clinical outcome	CR after induction	Relapse (time to relapse if yes)
1	25/F	MDS/ MPN-U	None	12	Abundant cytoplasmic granules, Auer rods, no perinuclear hof, some with bilobed nuclei.	43-46, XX, t(7;11)(p15;p15)[30]	Positive	Blasts expressing weak CD4, CD13, C33, CD34, CD38, weak CD71, CD117, weak/absent HLA-DR, and MPO. Immature myeloid cells with CD117+/CD34- present.	*WT1*, *KRAS*, *NRAS*	Chemotherapy followed by allogeneic HSCT	45	In remission	Yes	No
2	47/F	AML	None	76	Abundant cytoplasmic granules, Auer rods, perinuclear hof.	47, XX, t(7;11)(p15;p15), +8[20]	Positive	Blasts displaying variable/high side scatter and expressing weak CD4, variable CD13, weak CD15, CD33, weak/variable CD34, CD38, weak CD64, CD71, CD117, MPO, without HLA-DR	*GATA2*, *CSF3R*, *TET2*	Chemotherapy followed by allogeneic HSCT	27	In remission	No	No
3	55/M	AML	None	85	Moderate amount of cytoplasmic granules, Auer rods, perinuclear hof.	46, XY, t(7;11)(p15;p15)[20]	Positive	Blasts expressing weak CD11c, CD13, variable CD33, CD34, variable CD117, variable HLA-DR, CD71 (subset), variable MPO.	*FLT3*-ITD, NGS not performed	Chemotherapy	10	Deceased	Yes	Yes (4 months)
4	28/M	t-AML	Osteosarcoma	80	Moderate amount of cytoplasmic granules, perinuclear hof, no Auer rods.	33-45, XY, t(2,11)(q31;p15), -7[20]	Positive	Blasts expressing weak CD4, variable CD13, CD33, variable CD34, CD38, weak CD71, CD117, variable CD123, HLA-DR, MPO and CD19 (small subset)	*CBL*, *RUNX1*, *WT1*, *KRAS*	Chemotherapy, targeted therapy, study drug	13	Persistent disease	No	Never in CR
5	47/M	CML, myeloid blast phase	None	70	Scant cytoplasmic granules, no perinuclear hof, no Auer rods.	45~46, XY, der(9) t(9;11)(p22;p15) t(9;22)(q34;q11.2), der(11)t(9;11), der(22)t(9;22)[12]/46 ,XY[8]	Positive	1.9% Blasts expressing weak CD4, CD13, CD33, CD34, CD38, CD56, weak CD71, weak-absent CD117, HLA-DR without MPO or TdT. 30% immature myeloid expressing weak CD4, weak CD11b, CD13, CD33, CD38, CD56, weak CD71, variable HLA-DR, and MPO with a subset CD117+ /CD34-.	None identified	Tyrosine kinase inhibitors, allogeneic HSCT	17	Deceased	No	Yes (2 months)
6	72/F	t-AML	DLBCL	21	Scant cytoplasmic granules, perinuclear hof, rare Auer rods, some with monocytic features. Follow-up showed moderate amount of granules.	44-46, XX, t(9;11)(p22;p15)[9]	Positive	Blasts expressing CD4, variable CD13, weak-variable CD15, CD33, CD34, CD38, weak CD64, weak CD71, CD117, weak CD123, HLA-DR and MPO. Additional blasts had similar immunophenotype but without CD34. A relative increase in monocytic events that expressed CD64 without CD14.	*TET2*	Chemotherapy, tyrosine kinase inhibitor	31	Deceased	No	Never in CR
7	65/M	AML	None	96	Scant cytoplasmic granules, perinuclear hof, no Auer rods.	45~46,XY,t(5;11)(q32;p15)[13]/46,XY[7]	Positive	Blasts expressing CD4, weak CD7 (subset), CD13, CD33, variable CD34, variable CD38, CD71, CD117, CD123, MPO and weak-absent HLA-DR.	*FLT3*-ITD, *NPM1*, *WT1*, *DNMT3A*, *TET2*	Chemotherapy	12	Deceased	No	Never in CR
8	79/M	AML	None	70	Scant to moderate amount of cytoplasmic granules, perinuclear hof, no Auer rods.	46, XY [20]	Positive	Blasts expressing weak CD2 (minor subset), weak CD4, weak CD7 (minor subset), variable CD11b, variable CD13, weak CD15, CD33, CD34, CD38, weak CD64, weak CD71, CD117, CD123, and variable HLA-DR and weak MPO.	*FLT-ITD*, *DNMT3A*, *WT1*, *NUP98-NSD1* fusion	Chemotherapy	6	Persistent disease	No	Never in CR

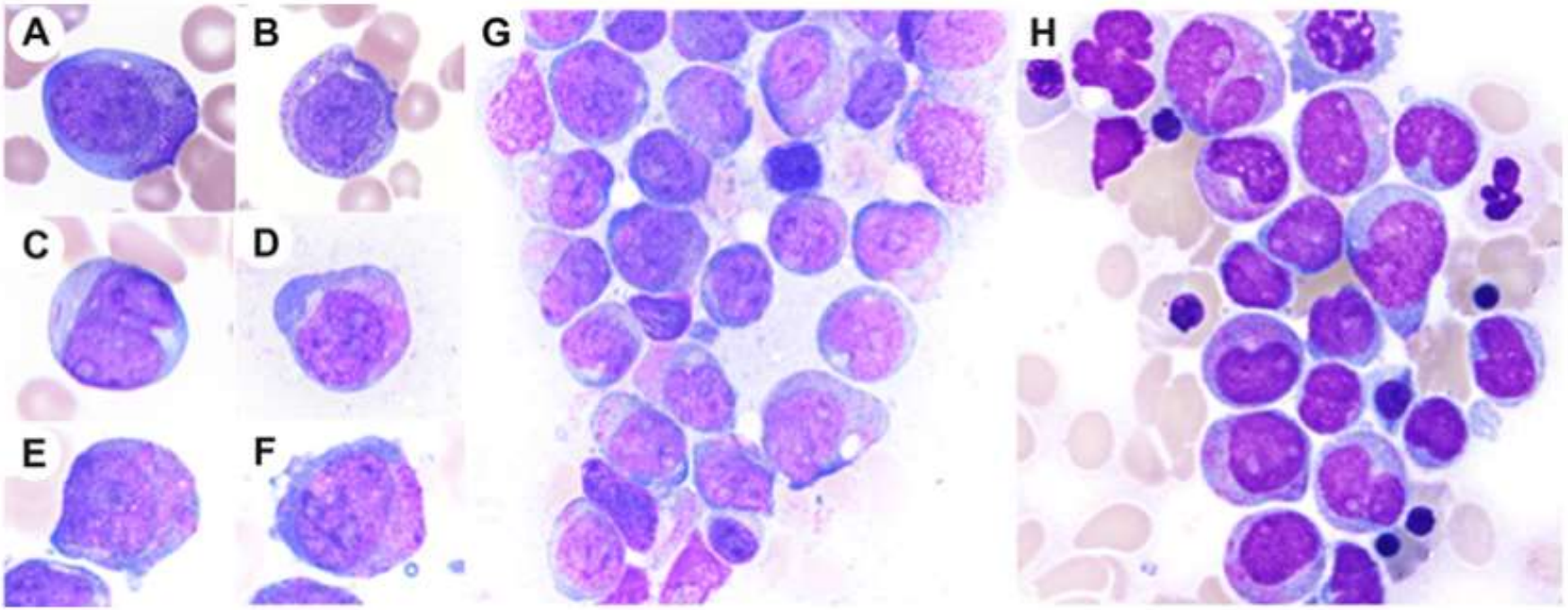


Fig. 2 Morphologic features of blasts in myeloid neoplasms with *NUP98* rearrangement. A–C: blasts in case 1; D–G: blasts in case 2. H: blasts in case 10. These blasts show variable to abundant cytoplasmic pink/red granules, Auer rods, perinuclear hof and occasional bilobed nuclei. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article).

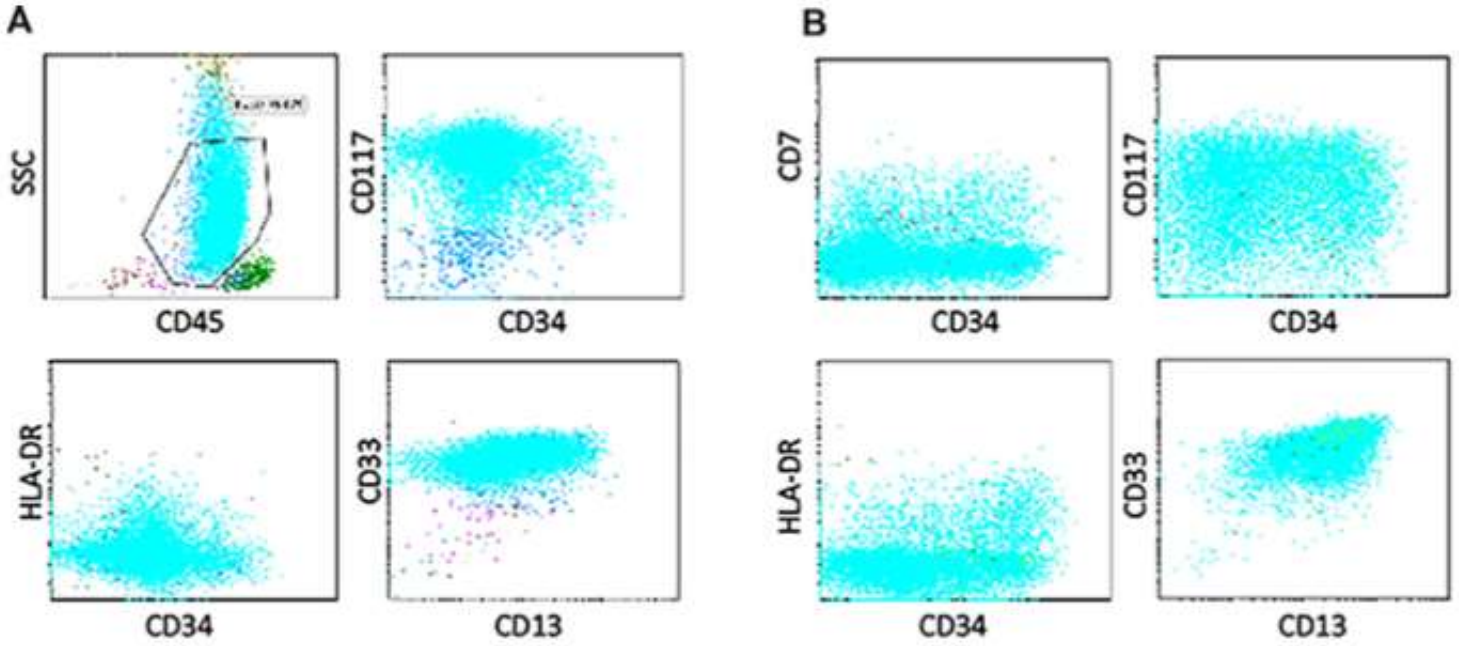


Fig. 3 Representative flow cytometry plots of AML with *NUP98* rearrangement. A. Case 2: the blasts showed high side scatter, absence of HLA-DR, weak/variable CD34, CD117, CD33 and CD13 expression. B. Case 7: the blasts showed weak to absent HLA-DR, variable CD34, CD117, CD33, CD13 and weak CD7 (minor subset) expression.

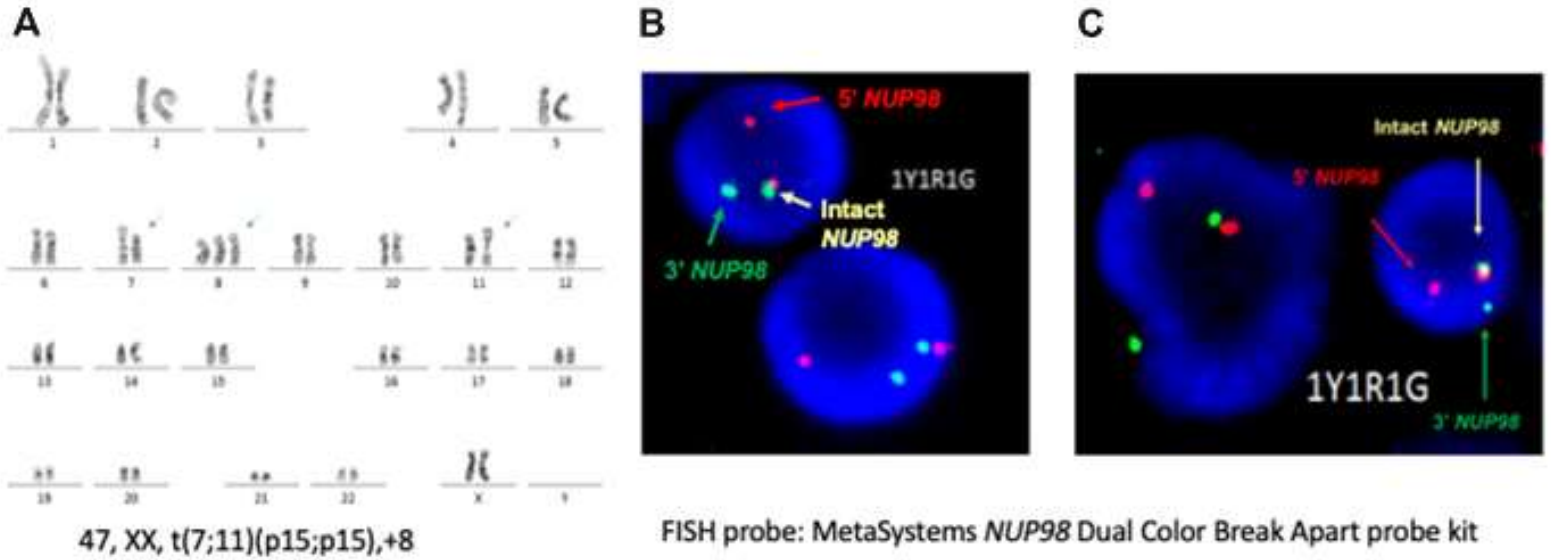


Fig. 4 Karyotype analysis (A), and *NUP98* FISH of case 2 (B) and case 4 (C).

AML with *NUP98* rearrangement

- The blasts shared some common features including pink/red cytoplasmic granules, presence of a perinuclear hof, Auer rods, and occasional bilobed nuclei, mimicking acute promyelocytic leukemia (APML).
- Flow cytometric studies showed blasts positive for MPO, CD117, CD13 and CD33, with a subset of cases negative for CD34 and/or HLA-DR and a subset of cases expressing monocytic markers.
- The translocations of 11p15 included t(7; 11) (p15; p15), t(2; 11) (q31; p15), t(9; 11) (p22; p15), t(5; 11) (q32; p15), and t(11; 12) (p15; q13). Three cases showed cryptic *NUP98* rearrangement.
- AML with *NUP98* can be exempt from from 20% blast rule.

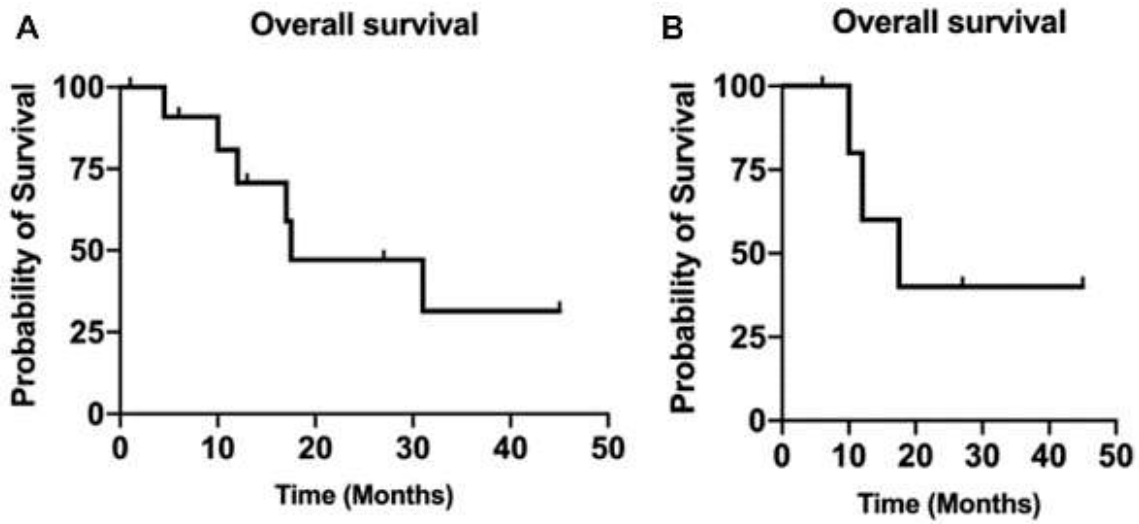


Fig. 1 A: Overall survival curve (OS) for twelve patients with *NUP98* rearrangement by Kaplan–Meier survival analysis. B: Overall survival curve (OS) for six patients of *de novo* AML with *NUP98* rearrangement by Kaplan–Meier survival analysis.

- Incomplete response to therapy with median overall survival of 17.5 months
- A complete remission rate of 25% following chemo- therapy induction
- Primary refractory disease of 58%

- NUP98-rearranged myeloid neoplasms are clinically, morphologically, and cytogenetically distinct and could be considered as a separate entity in the WHO classification defined by cytogenetic abnormality.

Original contribution Human Pathology (2022) 123, 11–19

Distinct pathologic feature of myeloid neoplasm with t(v;11p15); *NUP98* rearrangement☆,☆☆,☆☆☆

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Acute myeloid leukaemia with defining genetic abnormalities
Acute promyelocytic leukaemia with *PML::RARA* fusion
Acute myeloid leukaemia with *RUNX1::RUNX1T1* fusion
Acute myeloid leukaemia with *CBFB::MYH11* fusion
Acute myeloid leukaemia with *DEK::NUP214* fusion
Acute myeloid leukaemia with *RBM15::MRTFA* fusion
Acute myeloid leukaemia with *BCR::ABL1* fusion
Acute myeloid leukaemia with *KMT2A* rearrangement
Acute myeloid leukaemia with *MECOM* rearrangement
Acute myeloid leukaemia with *NUP98* rearrangement
Acute myeloid leukaemia with *NPM1* mutation
Acute myeloid leukaemia with *CEBPA* mutation
Acute myeloid leukaemia, myelodysplasia-related
Acute myeloid leukaemia with other defined genetic alterations
Acute myeloid leukaemia, defined by differentiation
Acute myeloid leukaemia with minimal differentiation
Acute myeloid leukaemia without maturation
Acute myeloid leukaemia with maturation
Acute basophilic leukaemia
Acute myelomonocytic leukaemia
Acute monocytic leukaemia
Acute erythroid leukaemia
Acute megakaryoblastic leukaemia

Take home messages

- AML with *NUP98* rearrangement associated with poor clinical outcome.
- Blasts in AML with *NUP98* rearrangement can be misclassified as promyelocytes.
- *NUP98* rearrangement may be cryptic requiring fluorescence in situ hybridization (FISH) study.
- A blast count of <20% is acceptable for AML with *NUP98* rearrangement.

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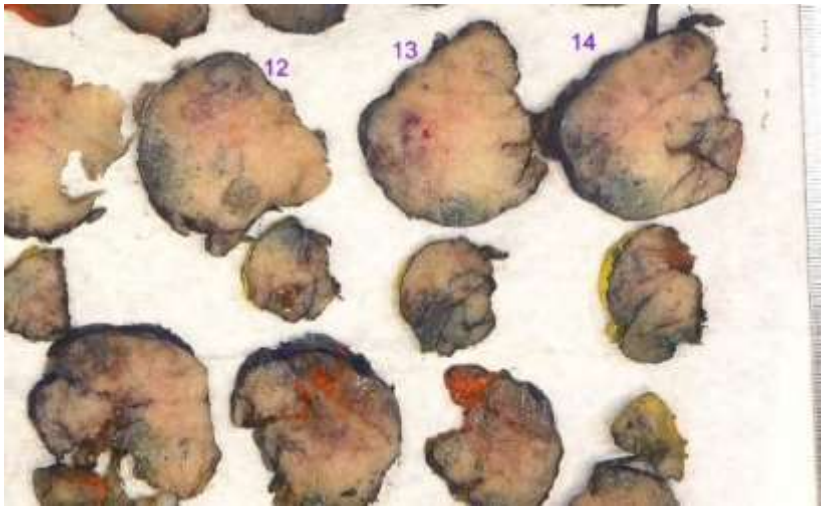
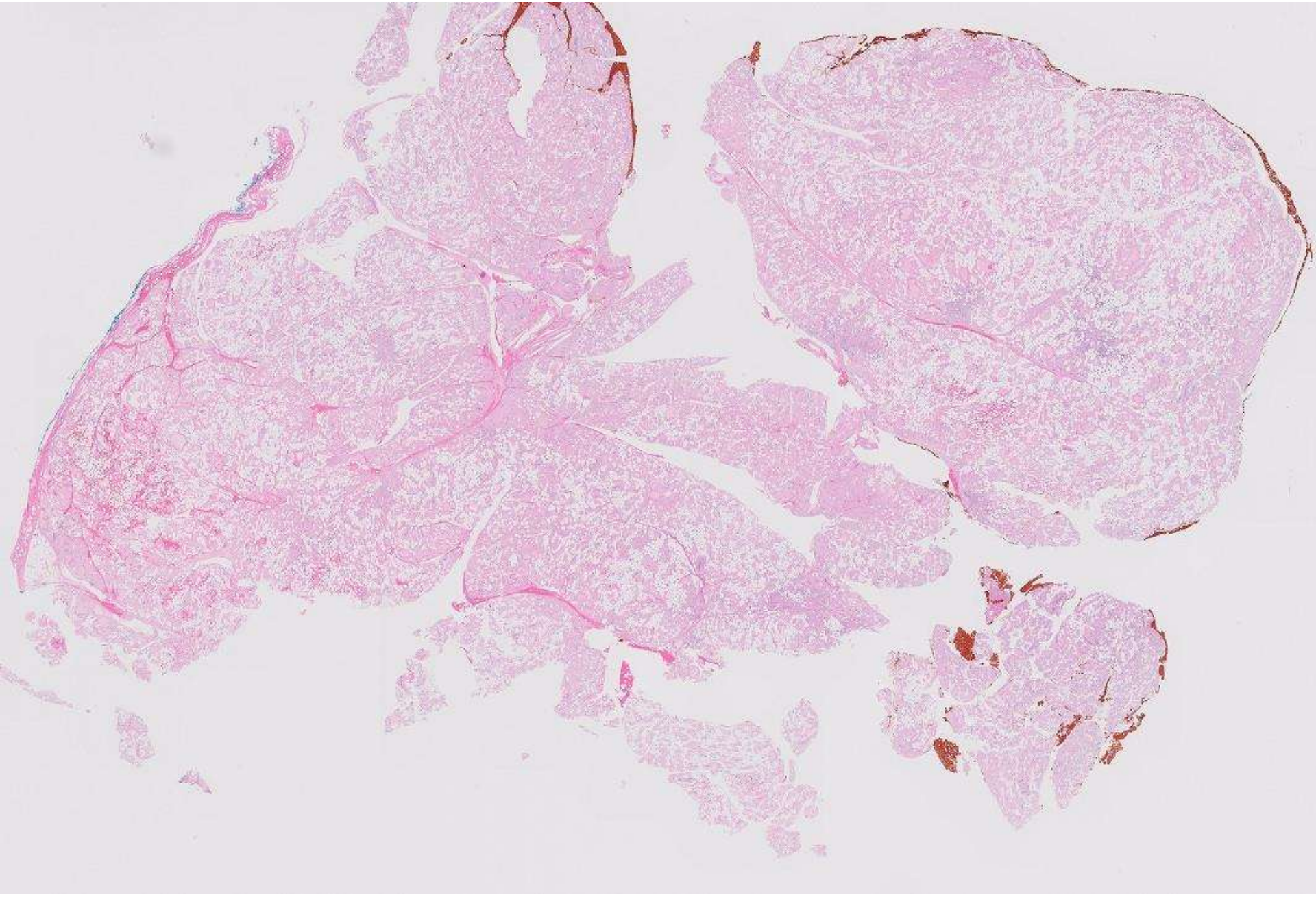
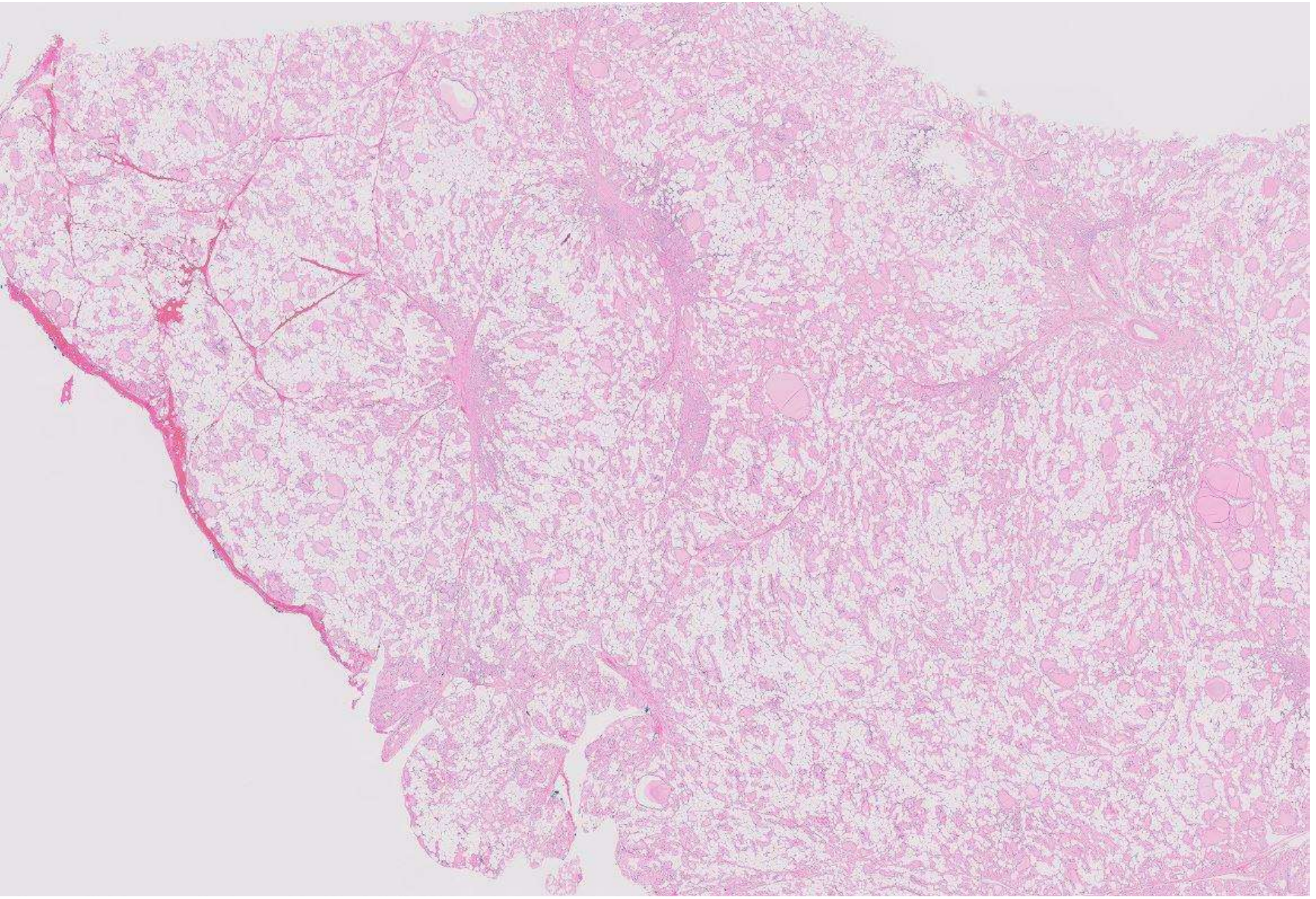
Xiaoming Zhang/Olumide Odeyemi/Megan Troxell; Stanford

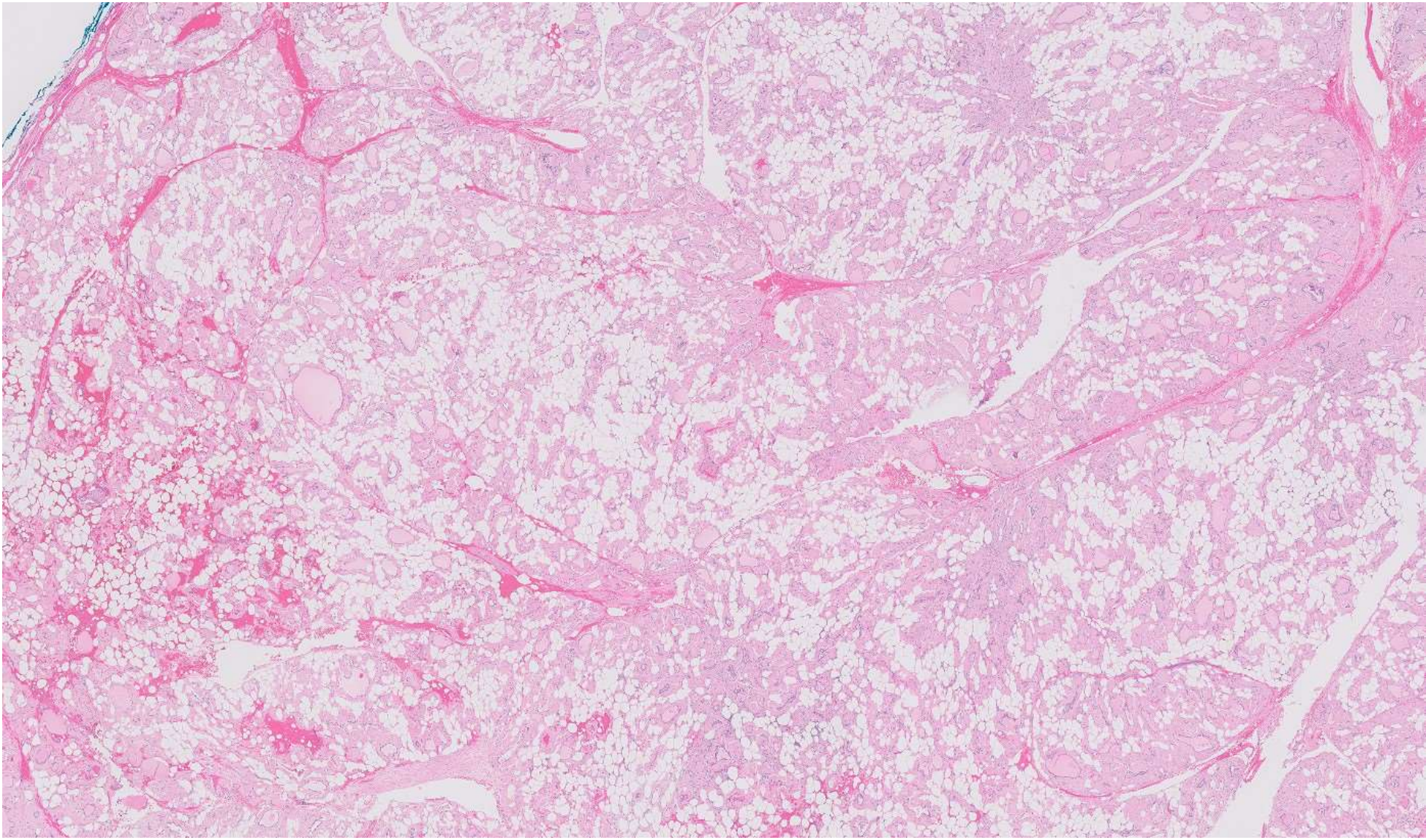
50ish F with 15cm anterior neck mass. History of end-stage renal disease.

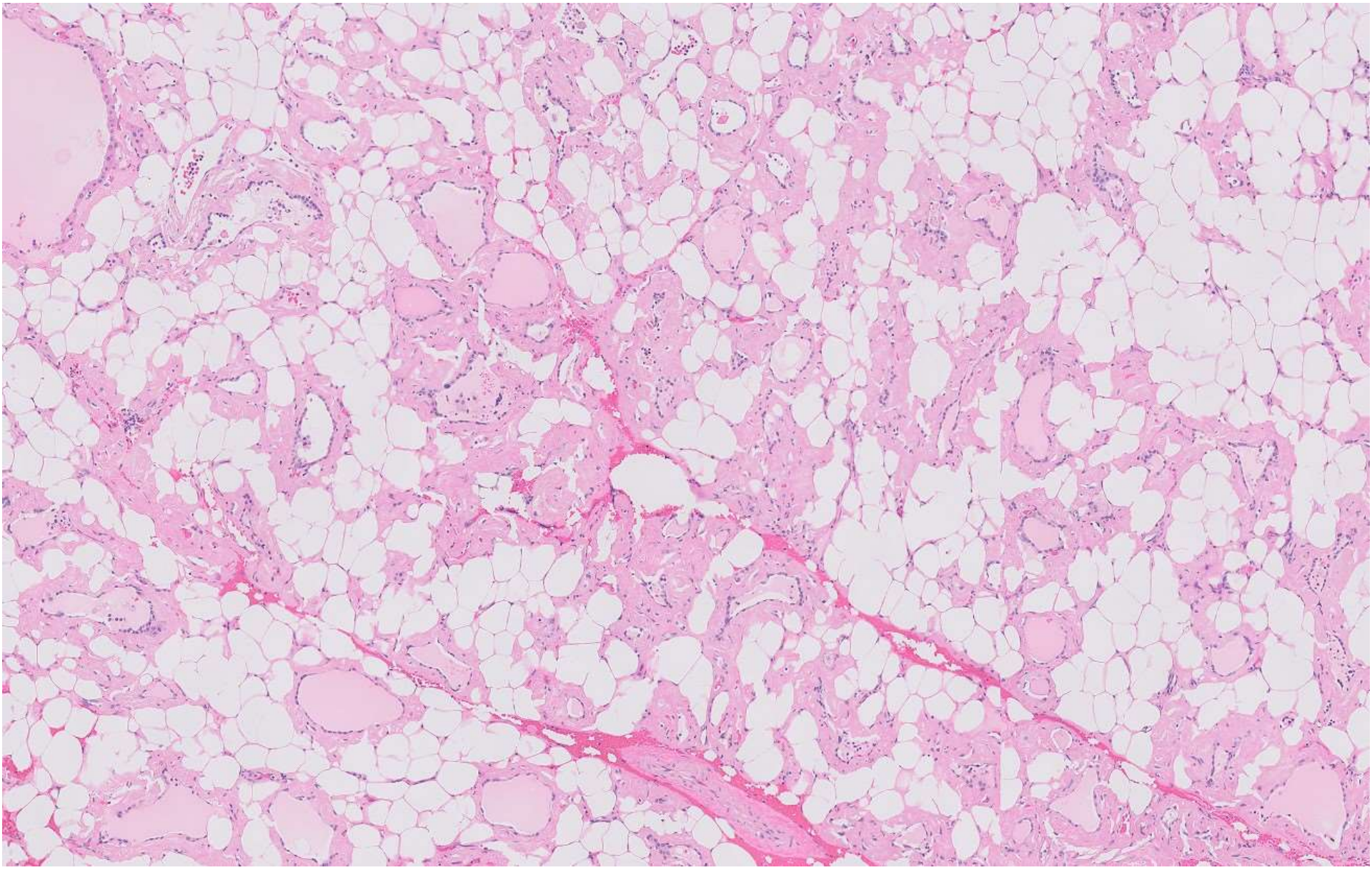
Gross Pathology

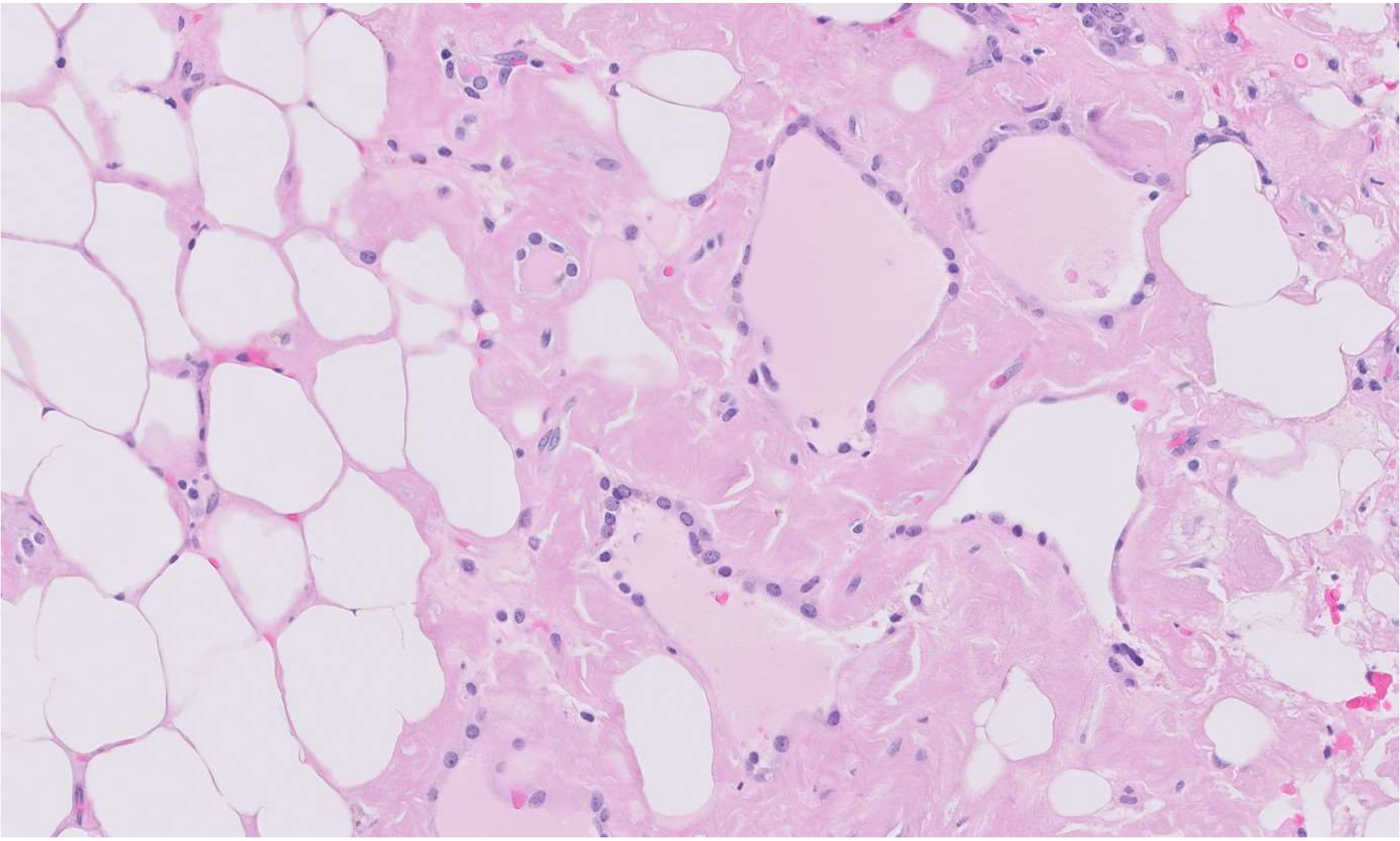


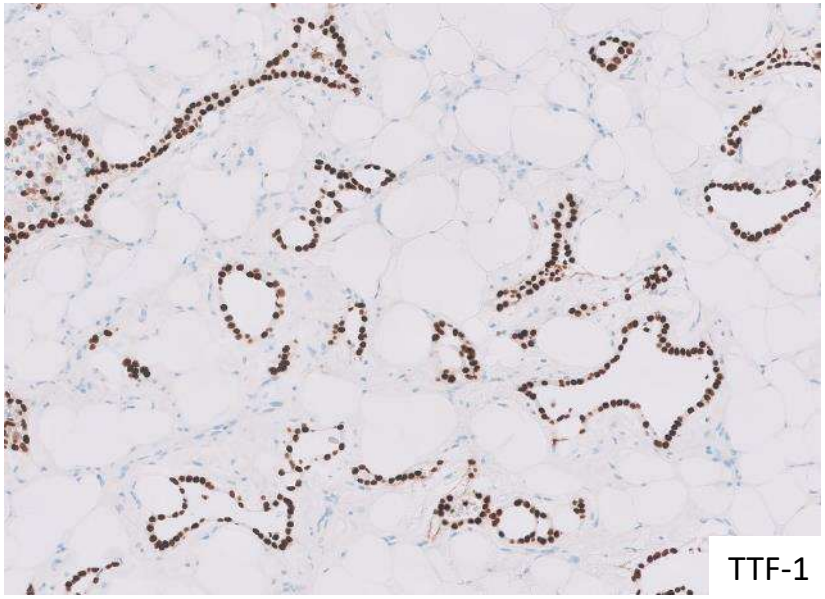




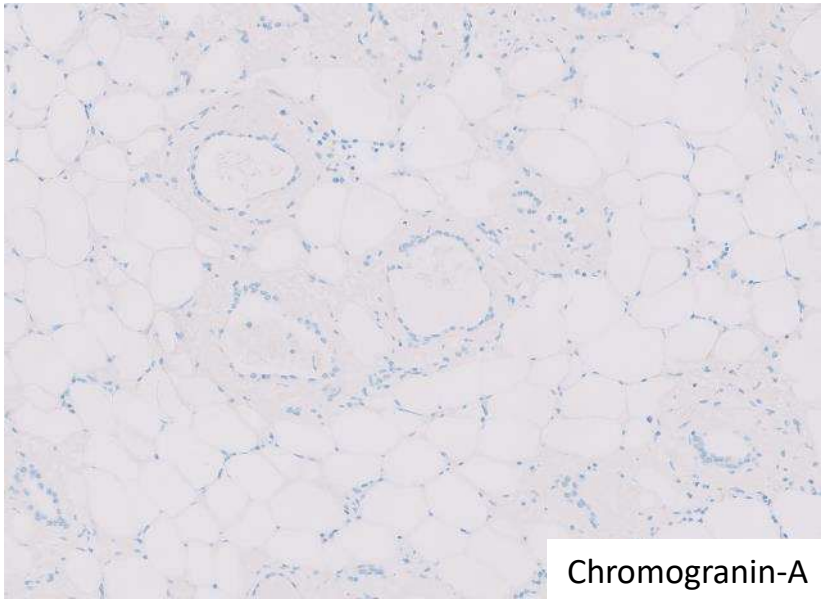








TTF-1



Chromogranin-A

South Bay Pathology Society Case Submission

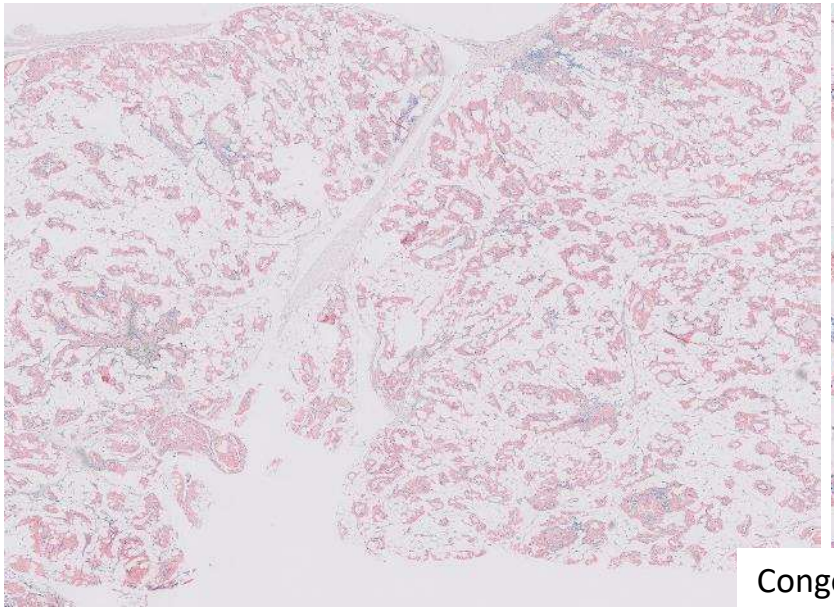
Olumide Odeyemi

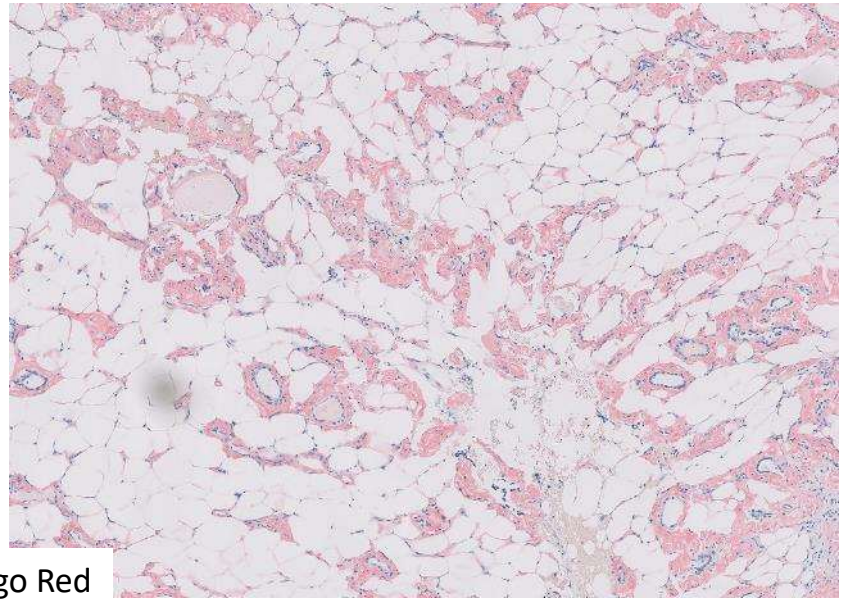
Xiaoming Zhang

Megan Troxell

Stanford University Pathology

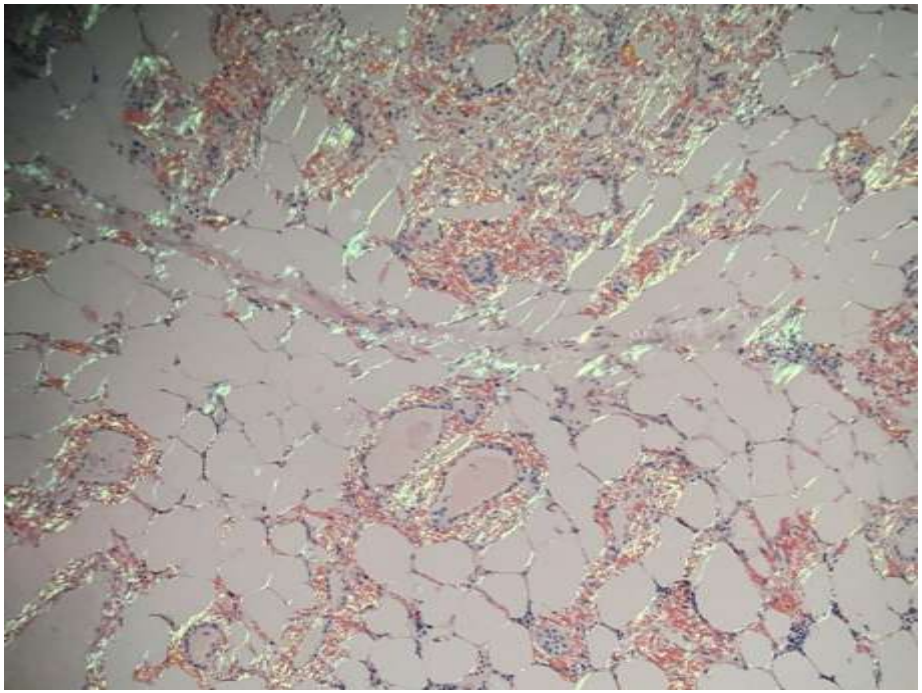
One More Stain





Congo Red

Congo Red Polarized



More Patient History

- Heart failure with preserved ejection fraction (HFpEF)
- End-stage renal disease on HD
  - History of longstanding amyloidosis
  - Reportedly, AL-type
    - No clear documentation of subtyping testing
  - No known history of plasma cell or other hematolymphoid disorder
- Thyroid function test – one month pre-op
  - Free T4 WNL
  - TSH 0.15uIU/mL (nl 0.27-4.20 uIU/mL)

Amyloid Goiter

- Amyloid deposition in thyroid – not uncommon
  - 15% of primary amyloidosis
  - 20% in secondary amyloidosis
- Amyloid in thyroid gland in such quantities to produce clinically apparent goiter →**Amyloid goiter**
  - Non-tender enlargement
  - Very rare
    - First described in 1858 by Beckman
    - Termed “amyloid goiter” in 1904 by Eiselberg
  - Wide age range – middle age or older more common
  - Usually euthyroid

Amyloid Goiter

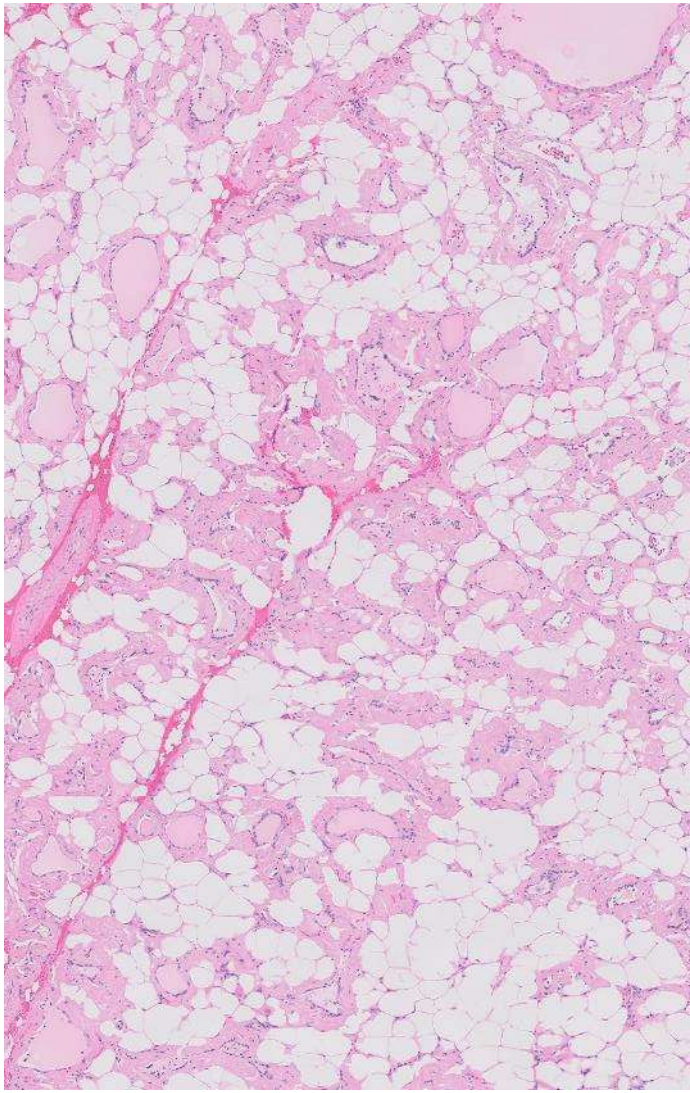
- Etiology:
  - Primary amyloidosis (AL)
    - Plasma cell dyscrasias – systemic amyloidosis with deposition in thyroid
    - Primary thyroid lymphoma – amyloid confined to the thyroid
    - No identifiable cause
  - Secondary amyloidosis (AA)
    - Chronic inflammatory/infectious disease – increased serum amyloid A
      - Rheumatoid arthritis
      - Pulmonary tuberculosis
      - Chronic osteomyelitis
      - Familial Mediterranean fever

Macroscopic Findings

- Diffuse, bilateral enlargement
- Can be variably nodular
- Tan-white with rubbery and/or firm texture
- May appear yellow with fatty infiltration

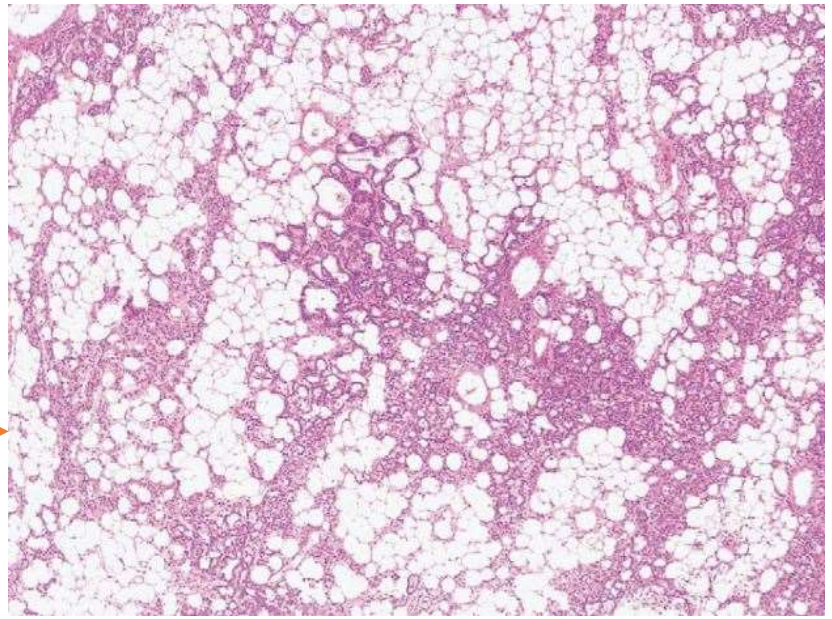
Histologic Findings

- Lobulated parenchyma separated by thin fibrovascular septa
- Diffuse amyloid deposition
  - Perifollicular and interfollicular distribution
  - Scattered amyloid nodules
  - May be angiocentric (less pronounced)
- Follicular compression and atrophy
- Focal lymphocytic thyroiditis and/or fibrosis
- **May contain variable amounts of adipose tissue**
  - Focal to diffuse
  - Amyloid deposition →destruction of capillaries → ischemia →metaplasia of stromal fibroblasts



Differential Diagnoses

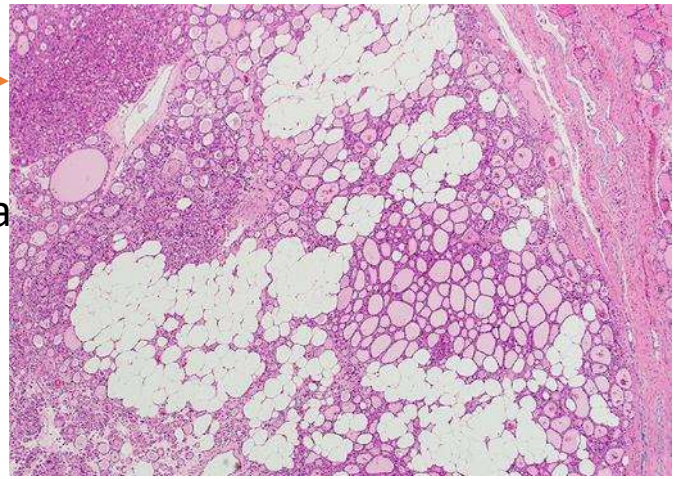
- **Lipoadenoma of Parathyroid Gland**
  - Parathyroid adenoma with >50% adipose content
  - Enlarged
  - Clinical manifestations of hyperparathyroidism
  - Can have prominent follicular architecture
  - TTF-1 negative, chromogranin-A positive
- **Medullary Thyroid Carcinoma**
  - Destructive infiltration by neoplastic C-cells
  - Localized (typically peri-tumoral) amyloid deposition: ~ 80% of MTCs
  - Neuroendocrine markers, calcitonin positive



Seethala et al. Am J Surg Pathol. 2008. 32(12):1854-1867.

Differential Diagnoses

- **Adenomatoid Hyperplasia with Degenerative Changes**
  - Enlarged and multinodular thyroid
  - Hyperplastic follicles
  - Hyalinized stroma
    - Lacks Congo Red apple-green birefringence
- **Adenolipoma of Thyroid, aka thyrolipoma**
  - Rare, benign fat-containing thyroid follicular adenoma
  - Nodular, rather than diffuse
  - Can resemble intrathyroidal parathyroid



https://www.pathologyoutlines.com/topic/Bychkovthyroid.html?mobile=off

Takeaways

- Presence of mature fat in the thyroid gland is rare; differentials include:
  - Normal thyroid: occasionally fat present in perivascular and subcapsular area anteriorly
  - **Amyloid goiter**
  - Adenolipoma of thyroid gland
  - Thyrolipomatosis – extremely rare
  - Heterotopic nest of adipose tissue – restrictive subcapsular location
  - Lymphocytic thyroiditis
  - Intrathyroidal parathyroid or parathyroid lesions
  - Intrathyroidal thymic tissue
  - Other causes of atrophy (i.e. – irradiation)

- Diffuse thyroidal amyloid deposition rare
  - Rule out MTC if macroscopically or histologically suspicious
  - Suggest investigation of amyloid subtyping and hematologic studies

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