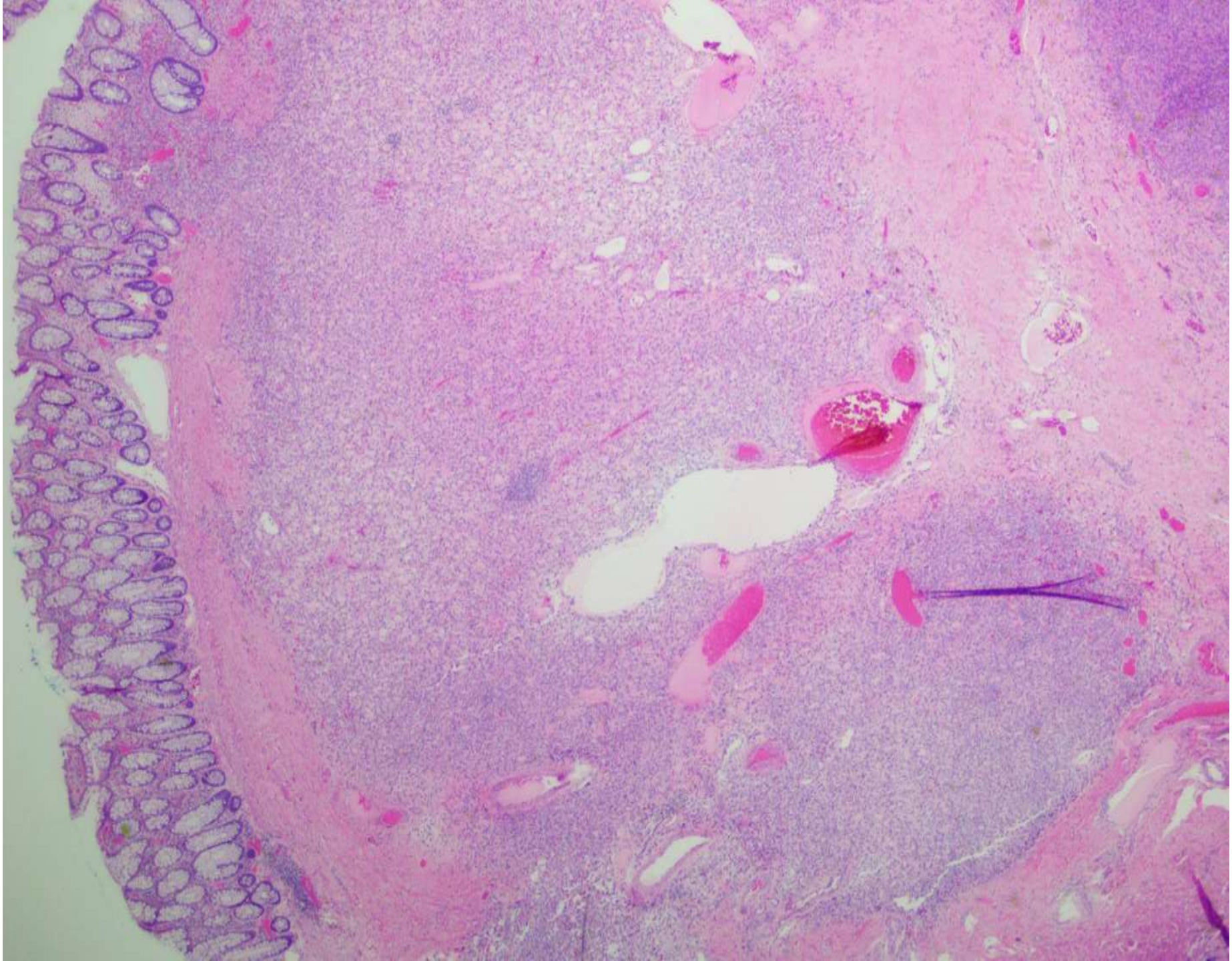
SEPT 2022 DIAGNOSIS LIST

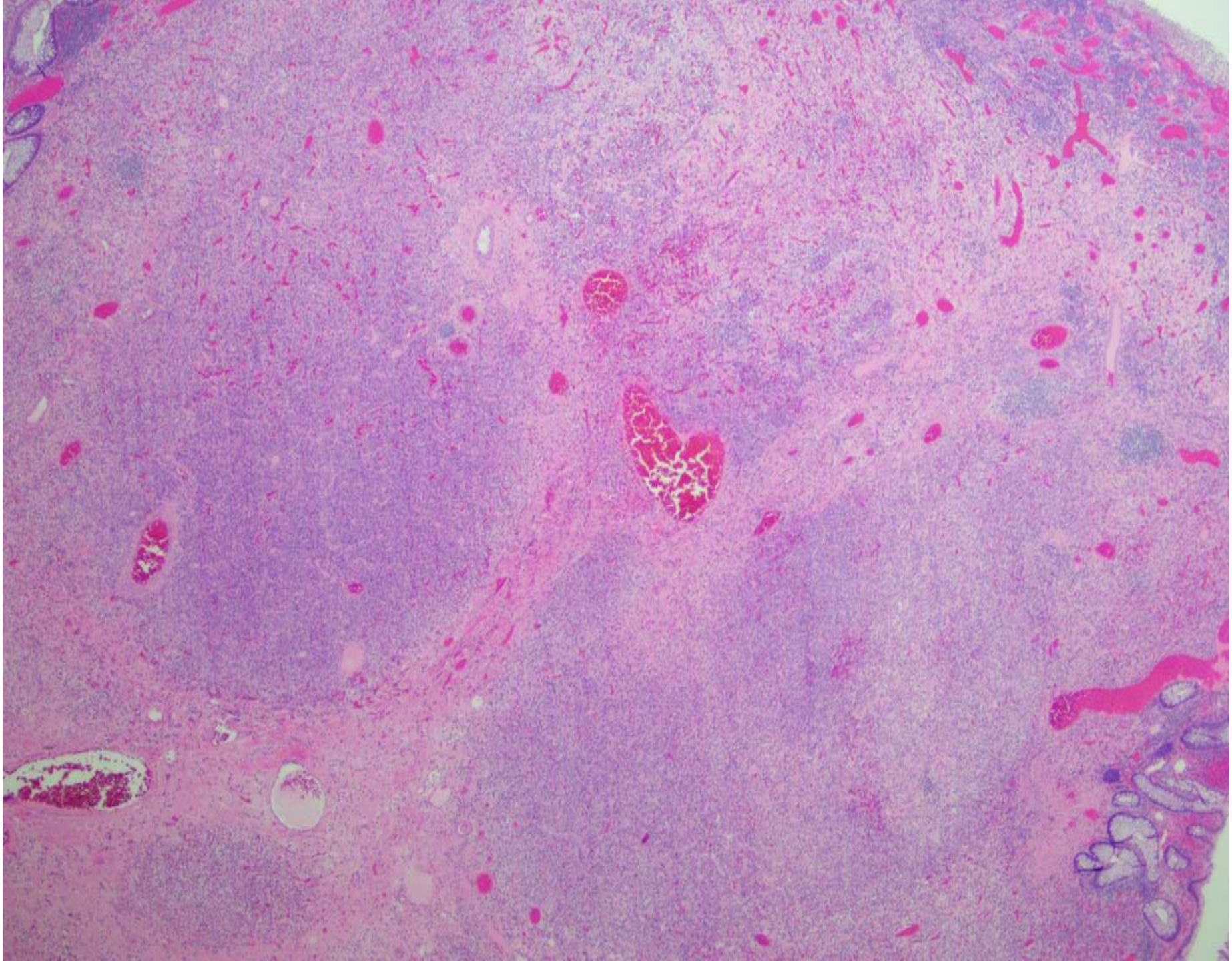
22-0901: low grade stromal sarcoma (colon; GYN path)
22-0902: metastatic hepatocellular carcinoma (scalp; dermpath)
22-0903: dysgerminoma (ovary; GYN path)
22-0904: Merkel cell carcinoma in situ (skin; derm path)
22-0905: renal cell carcinoma with leiomyomatous stroma (kidney; GU path)
22-0906: malignant Brenner tumor (ovary; GYN path)
22-0907: clear cell renal cell carcinoma with granulomas (kidney; GUpath)
22-0908: clear cell renal cell carcinoma with megakaryocytes; clear cell renal cell carcinoma with multinucleate tumor cells (kidney; GU path)

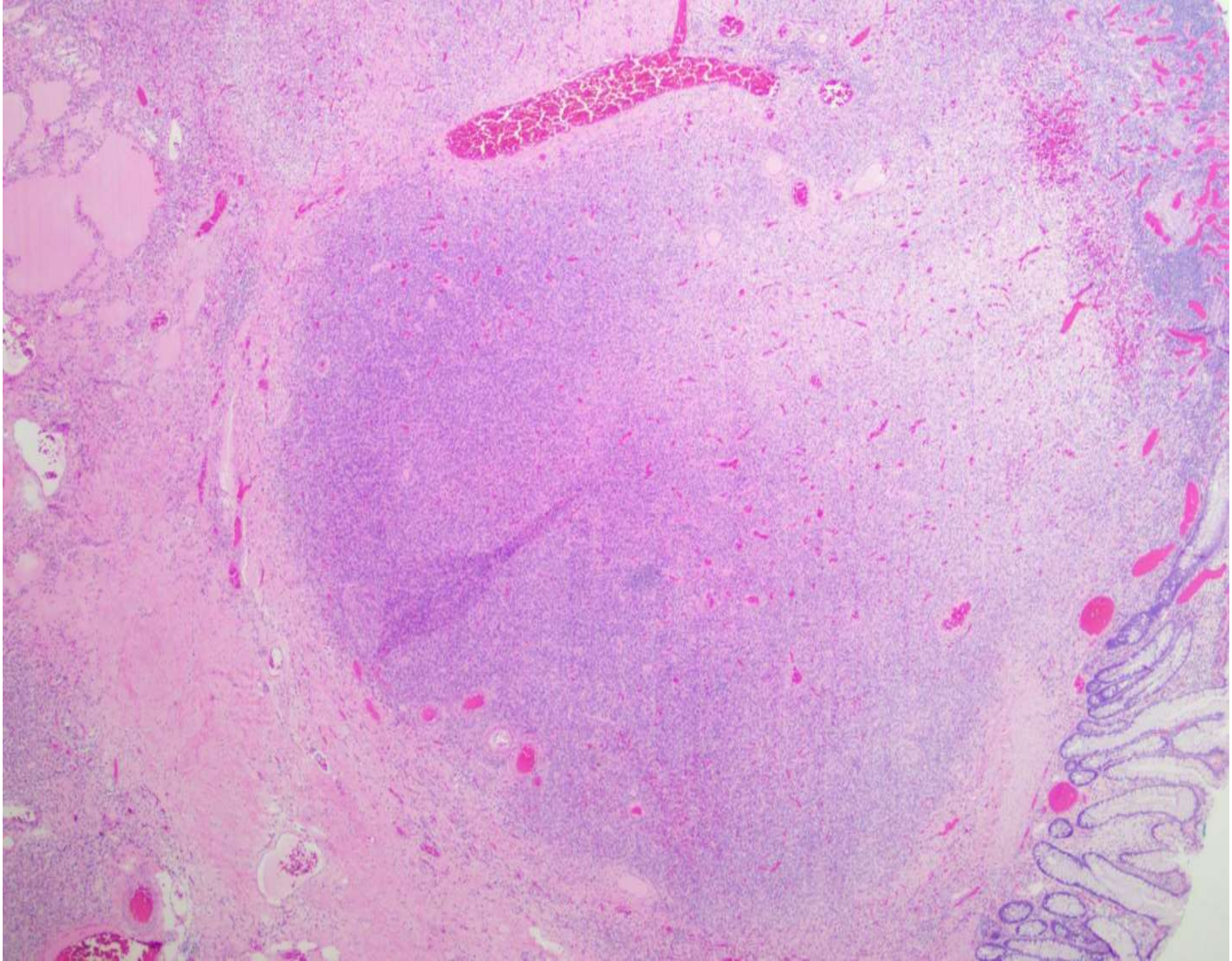
22-0901

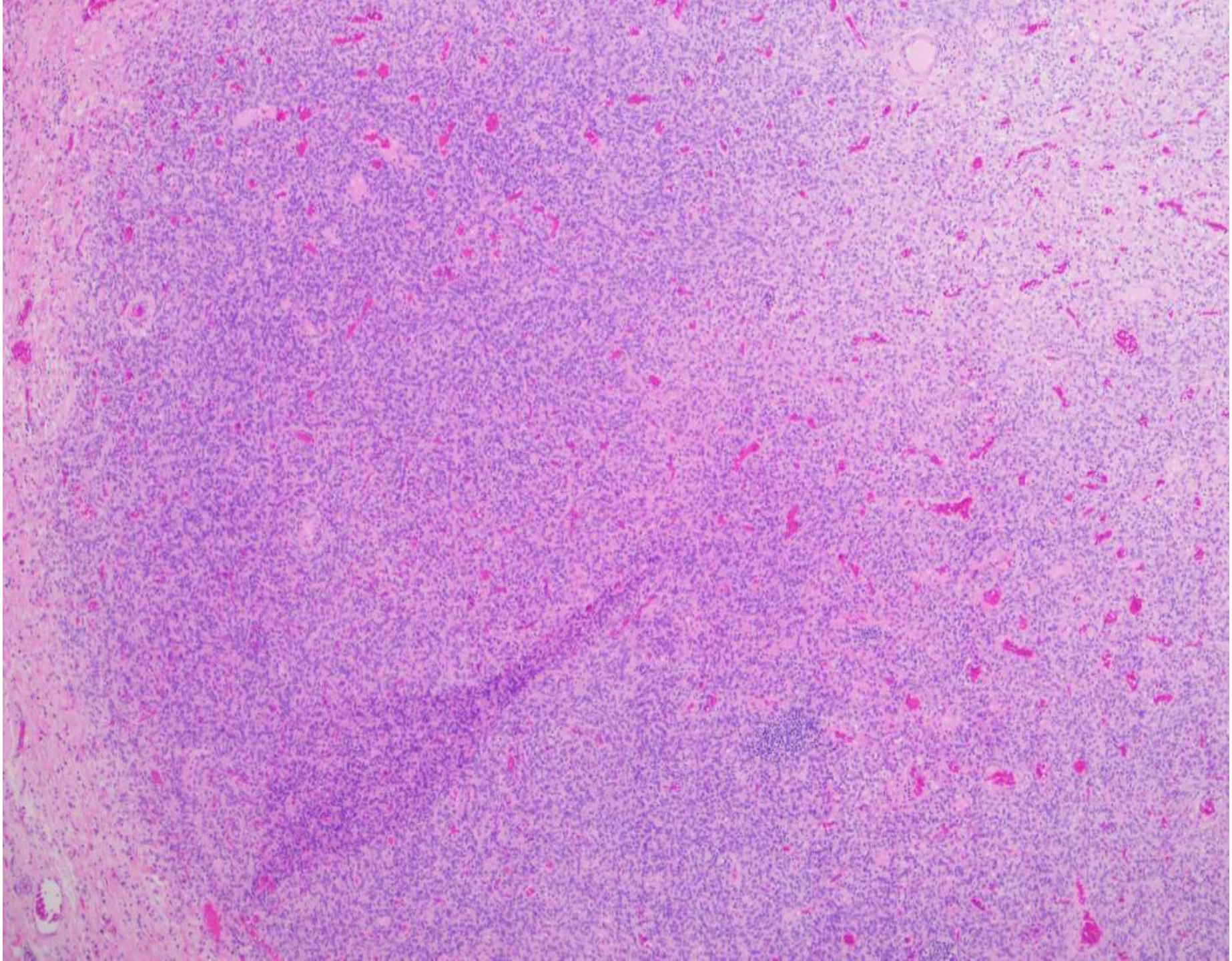
Armen Khararjian; Walnut Creek

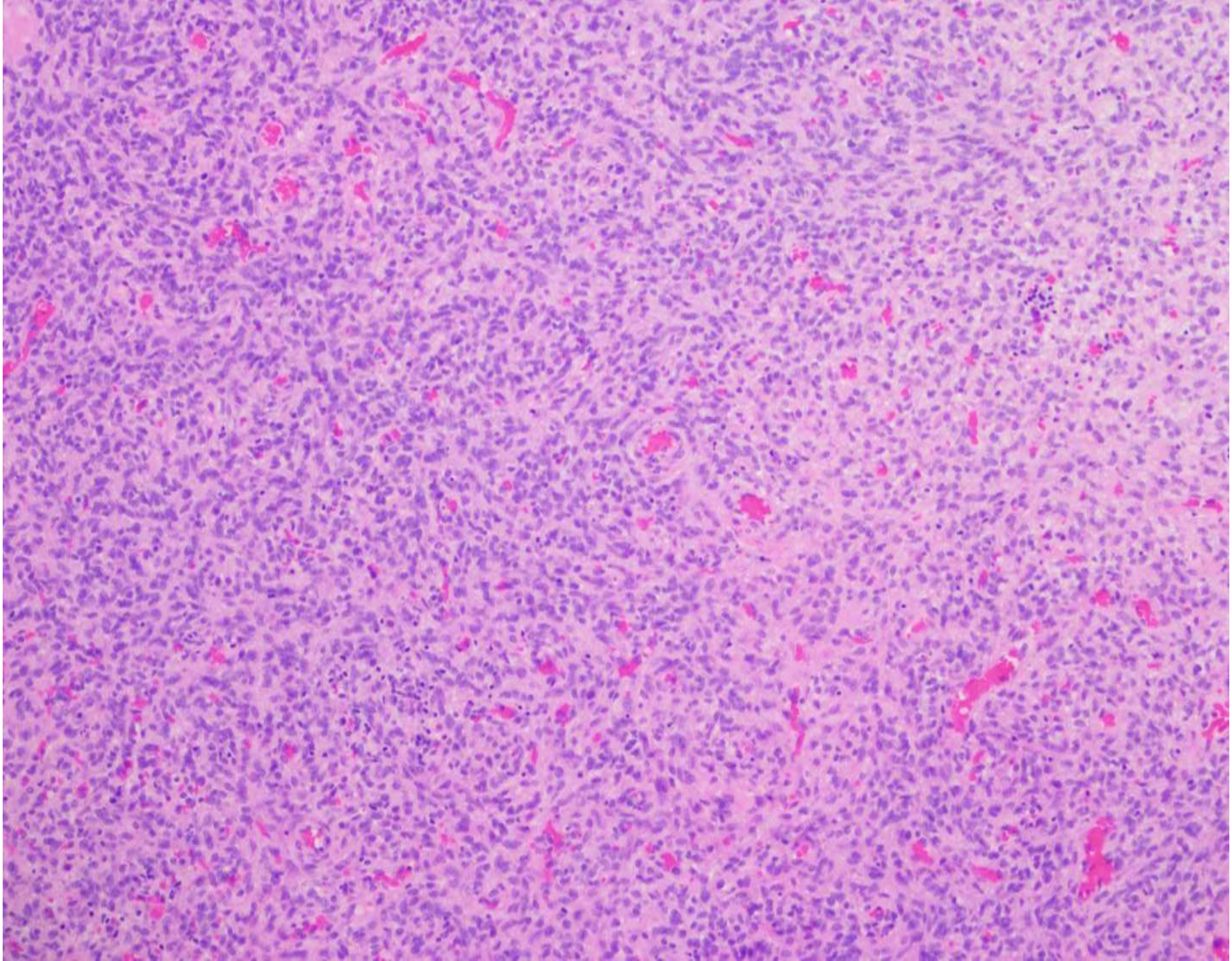
Middle-aged F with sigmoid polyp.

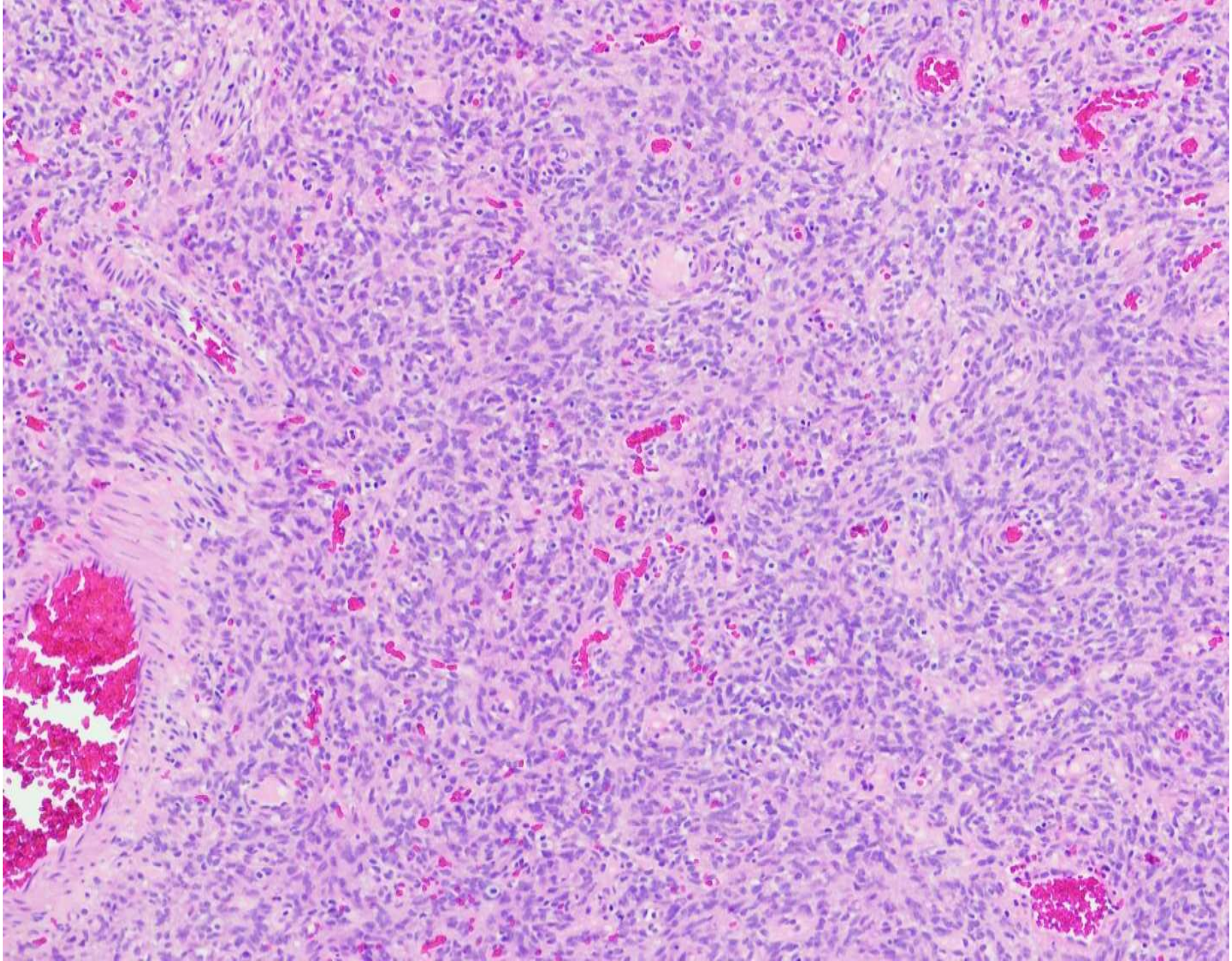


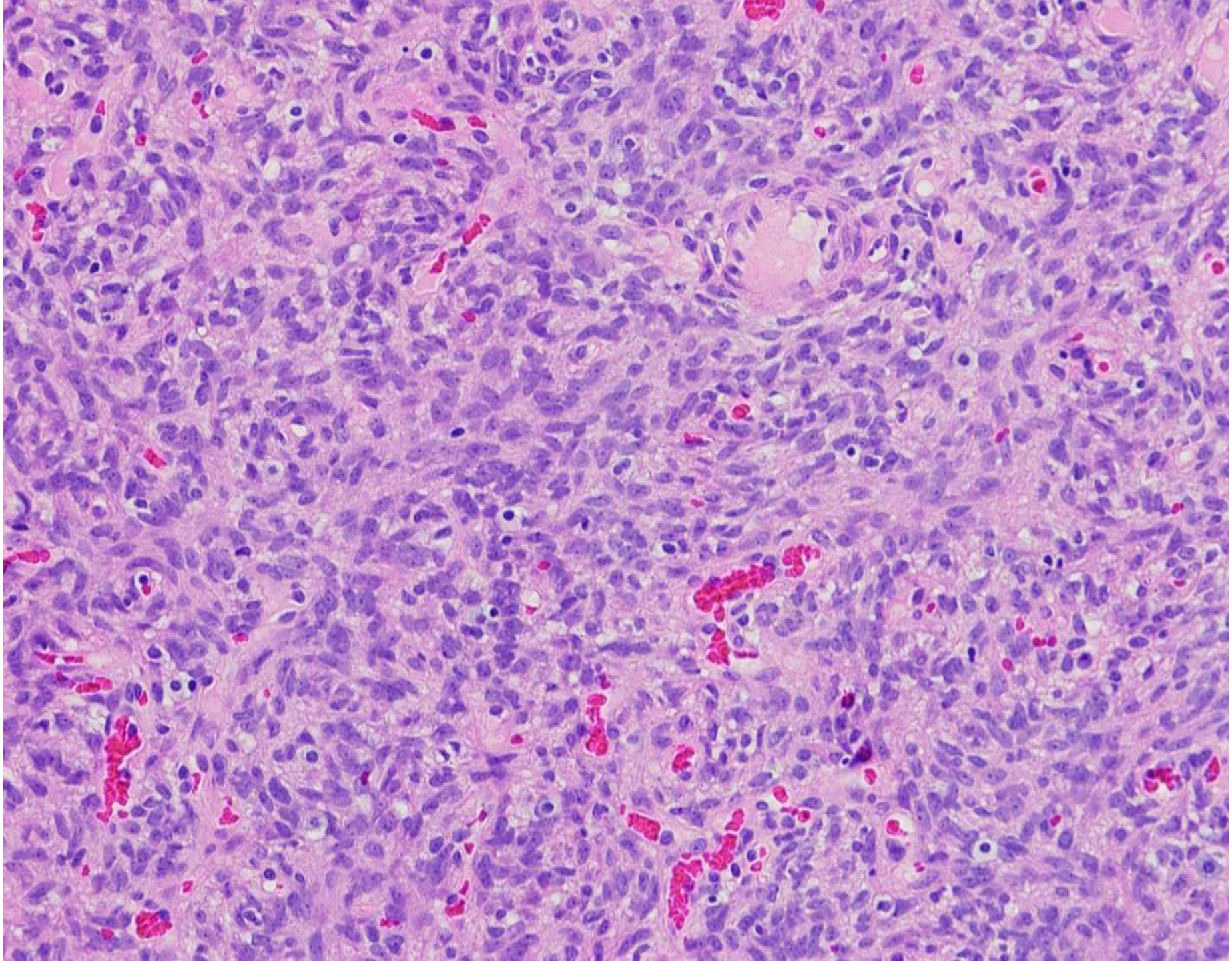


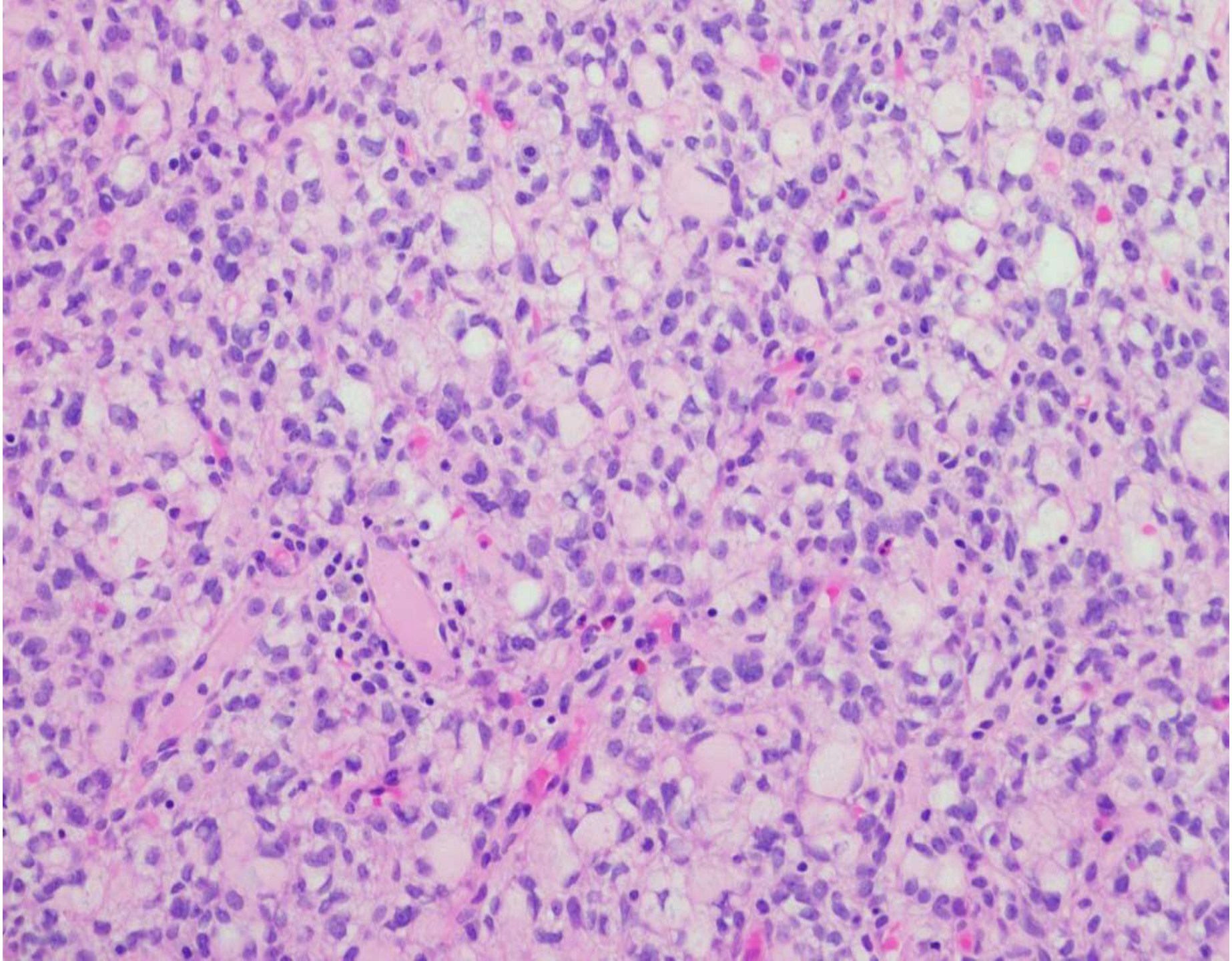


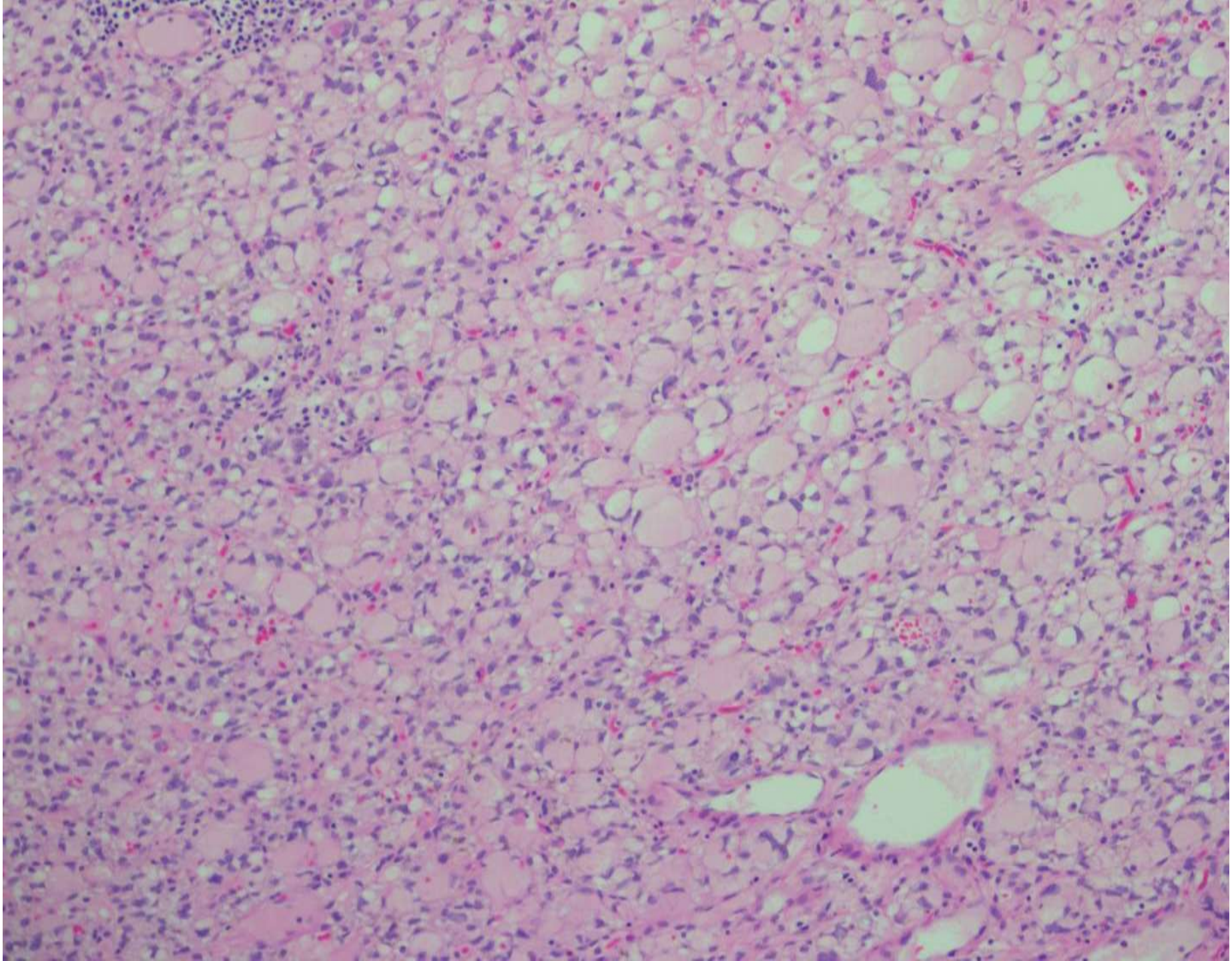


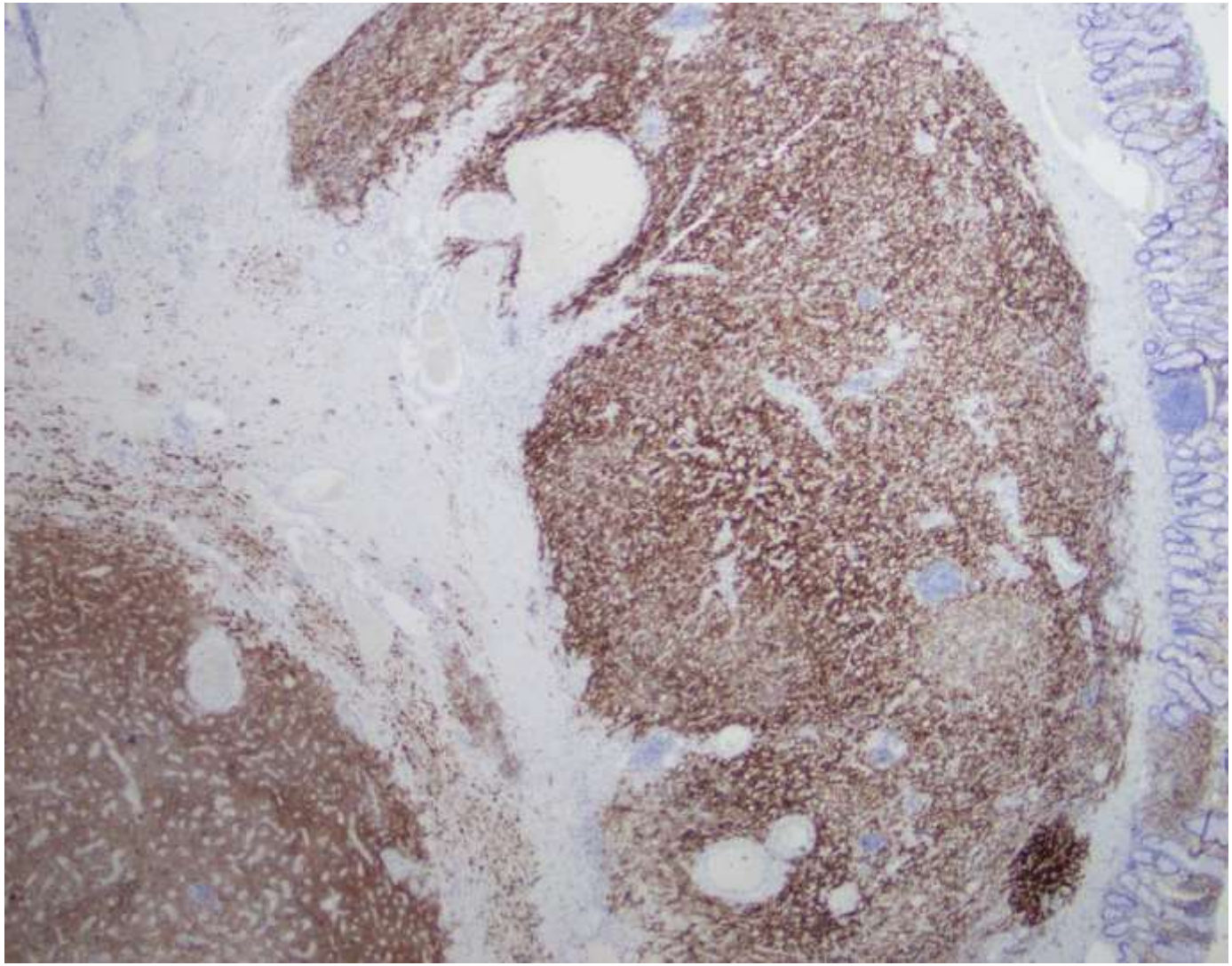




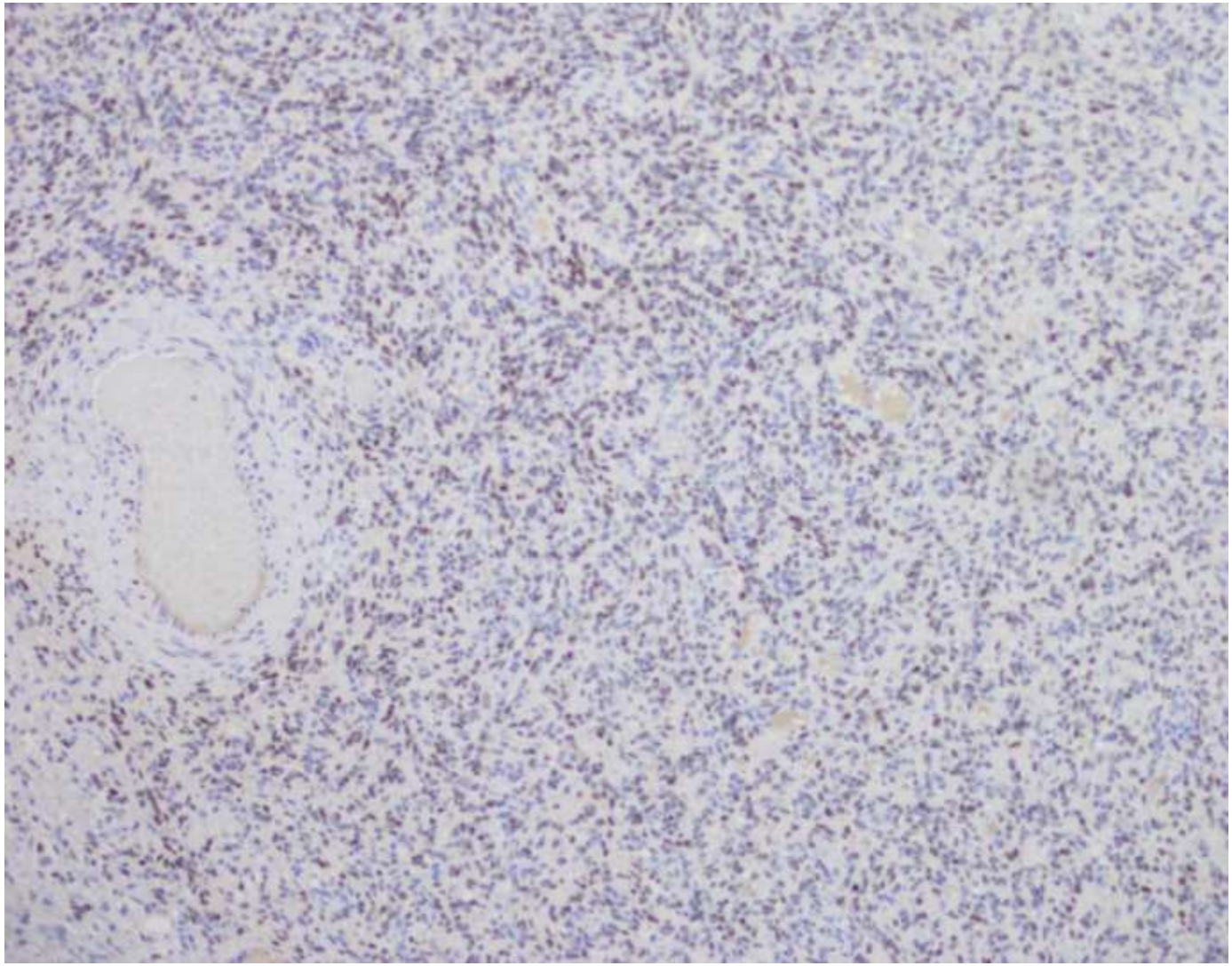








CD10



ER

Stromal Lesion Differential

- GIST: CKIT and DOG1 positive
- Leiomyoma: SMA and Desmin positive
- Schwannoma: S-100 positive
- Inflammatory Fibroid Polyp: CD34 positive
- Other

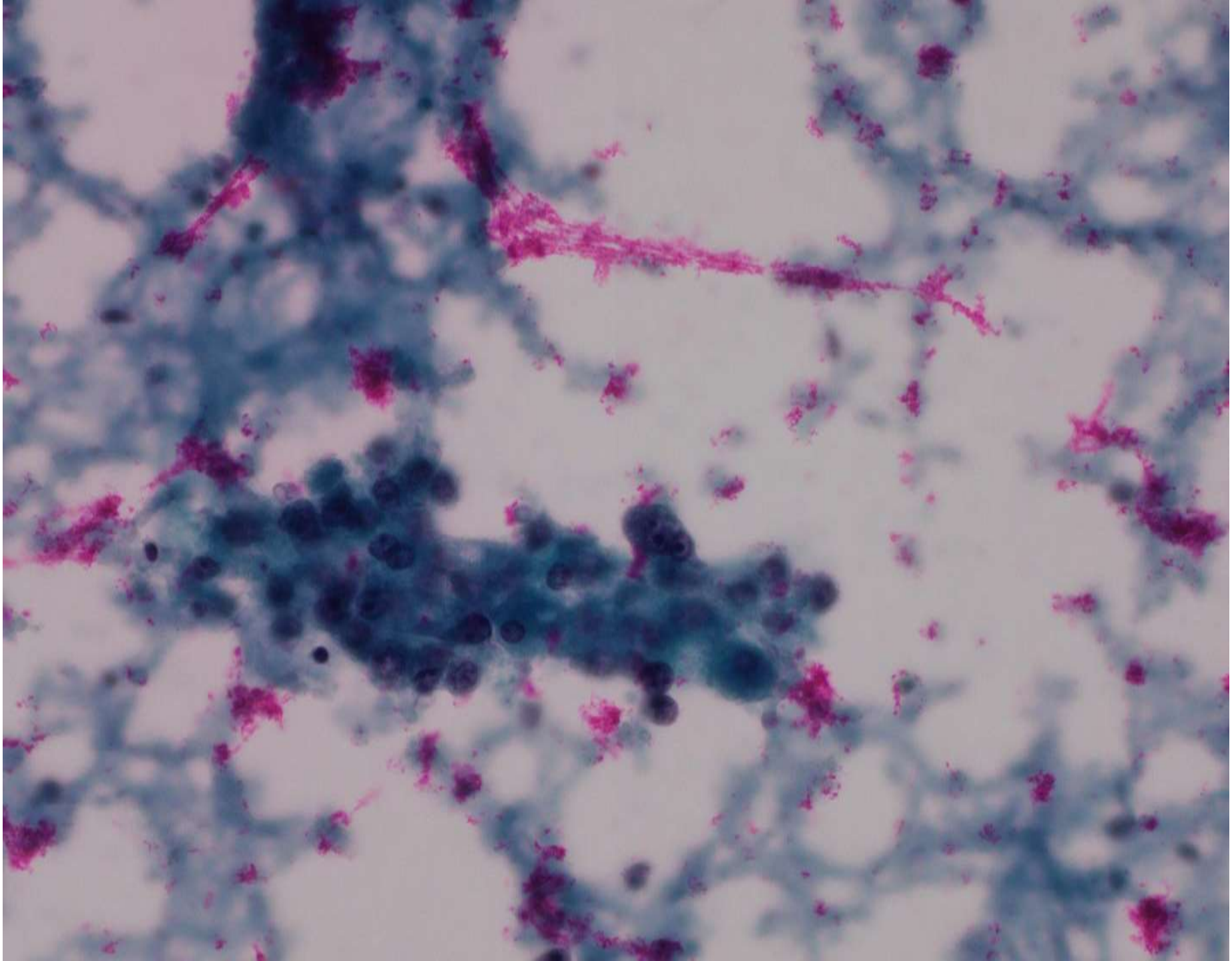
More History…

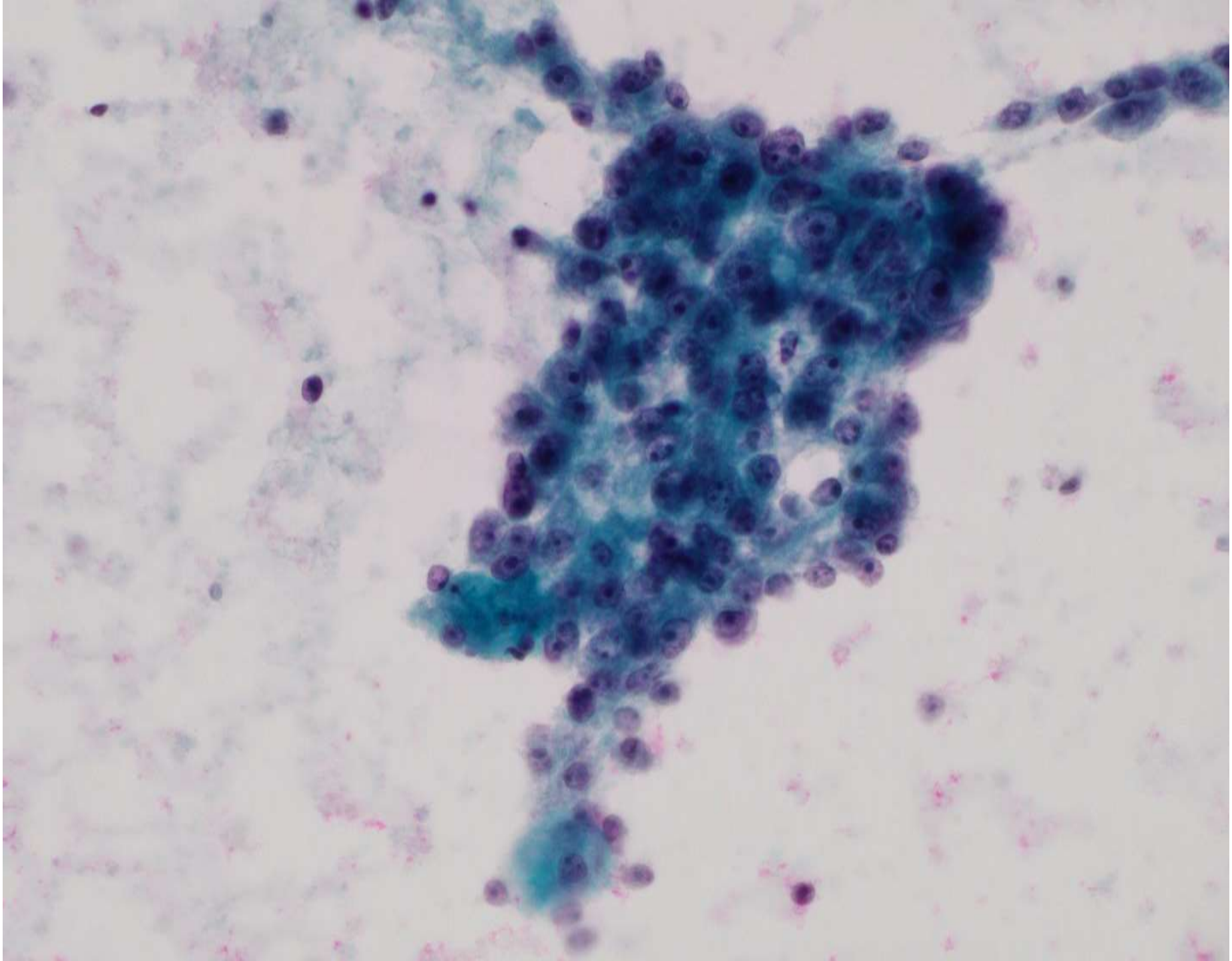
- Patient had history of hysterectomy five years prior for leiomyoma
- Slides re-reviewed with no evidence of ESS
- ? Unsampled primary in uterus

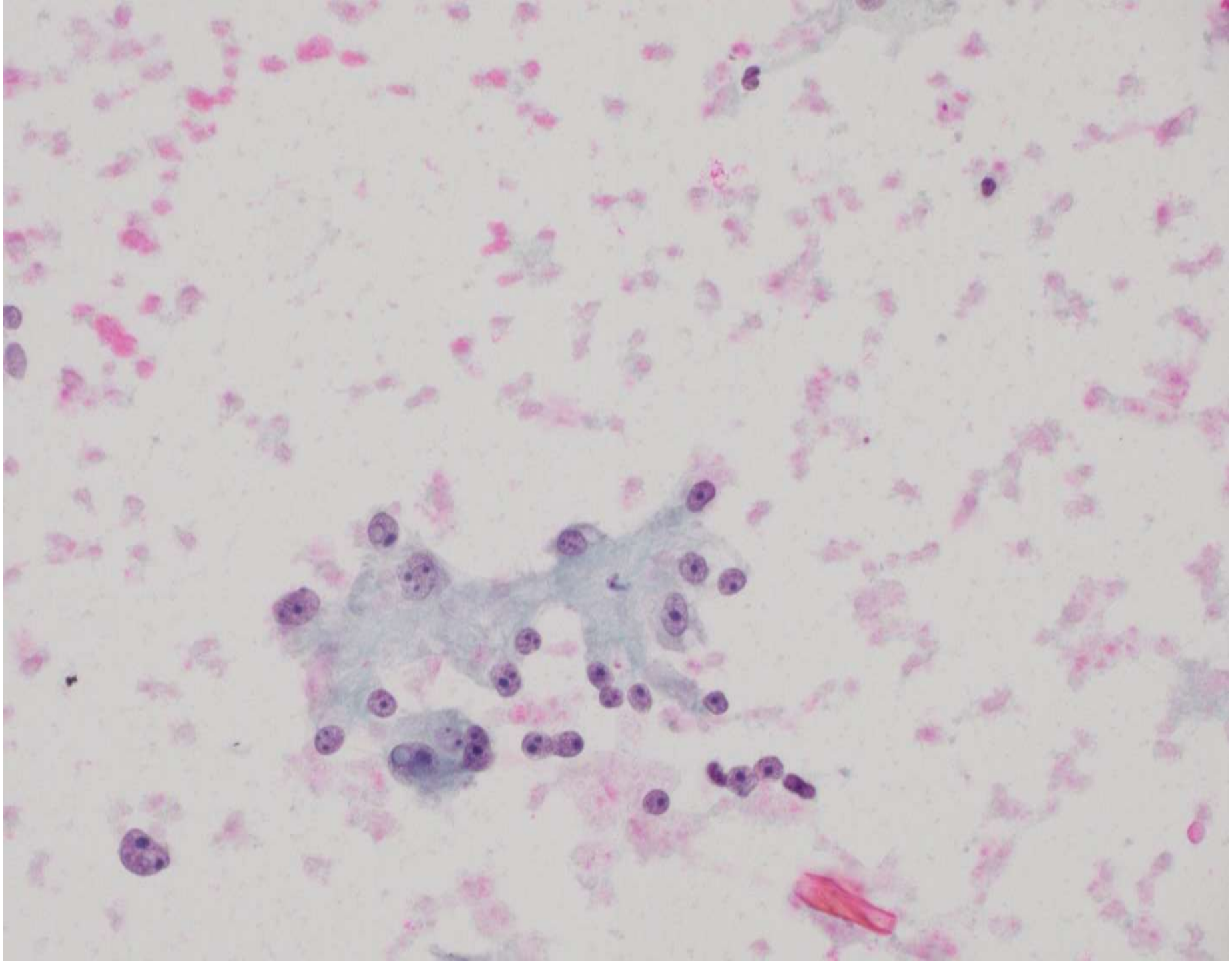
22-0902

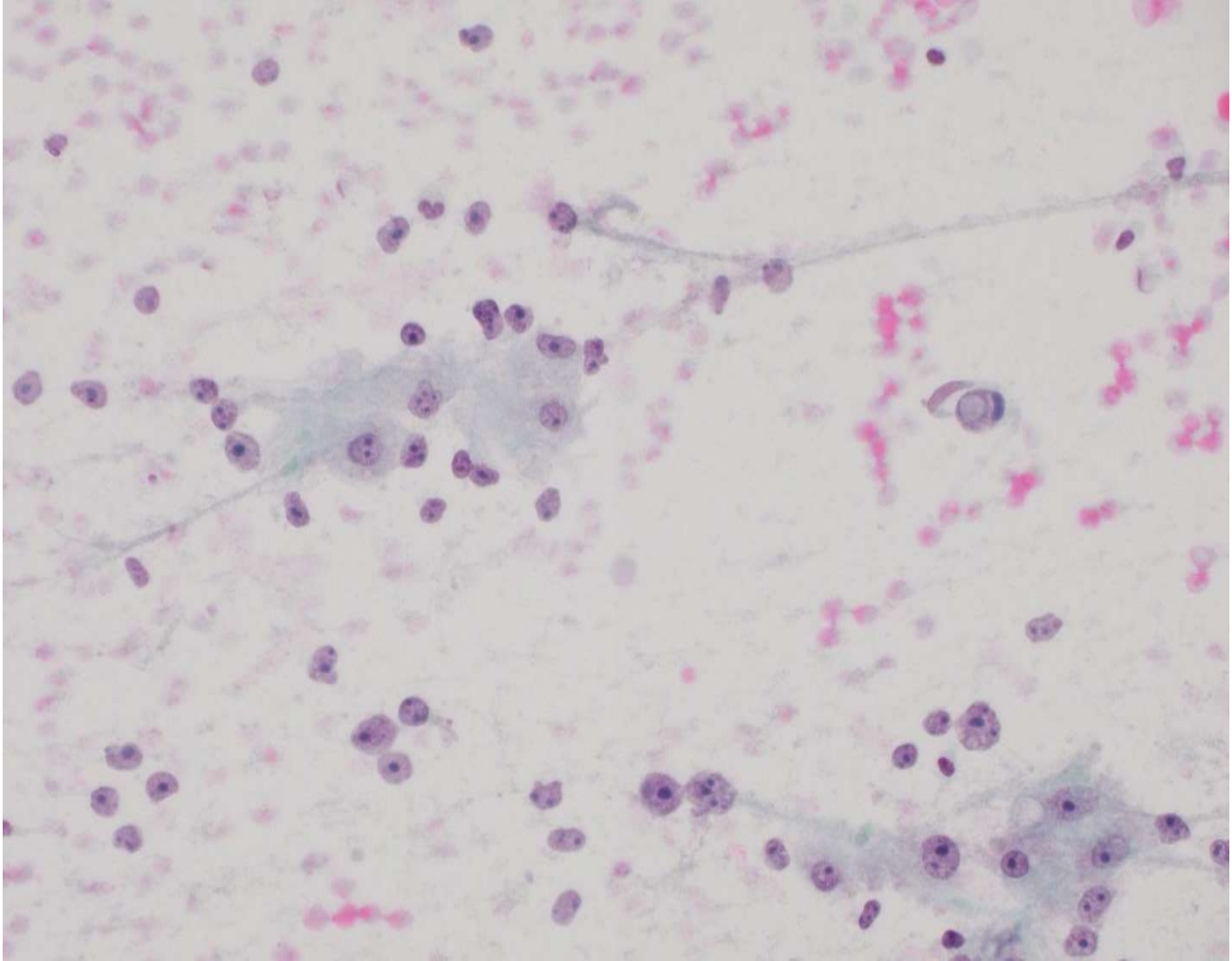
Kristen Jensen; Palo Alto VA

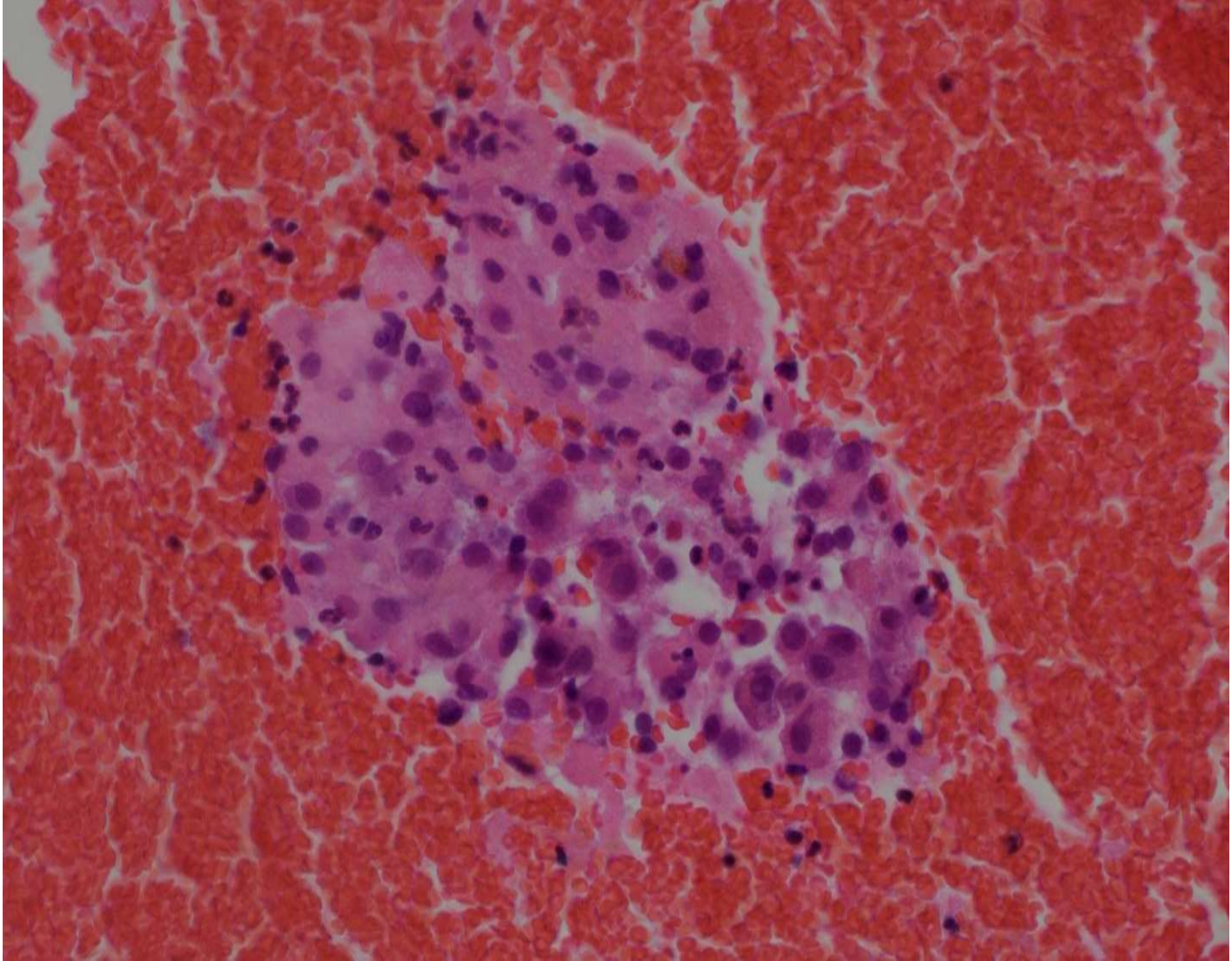
70ish M transplant patient with enlarging scalp lesion (3.5cm), enlarged to size of “half a baseball” in less than 3 months. FNA performed.

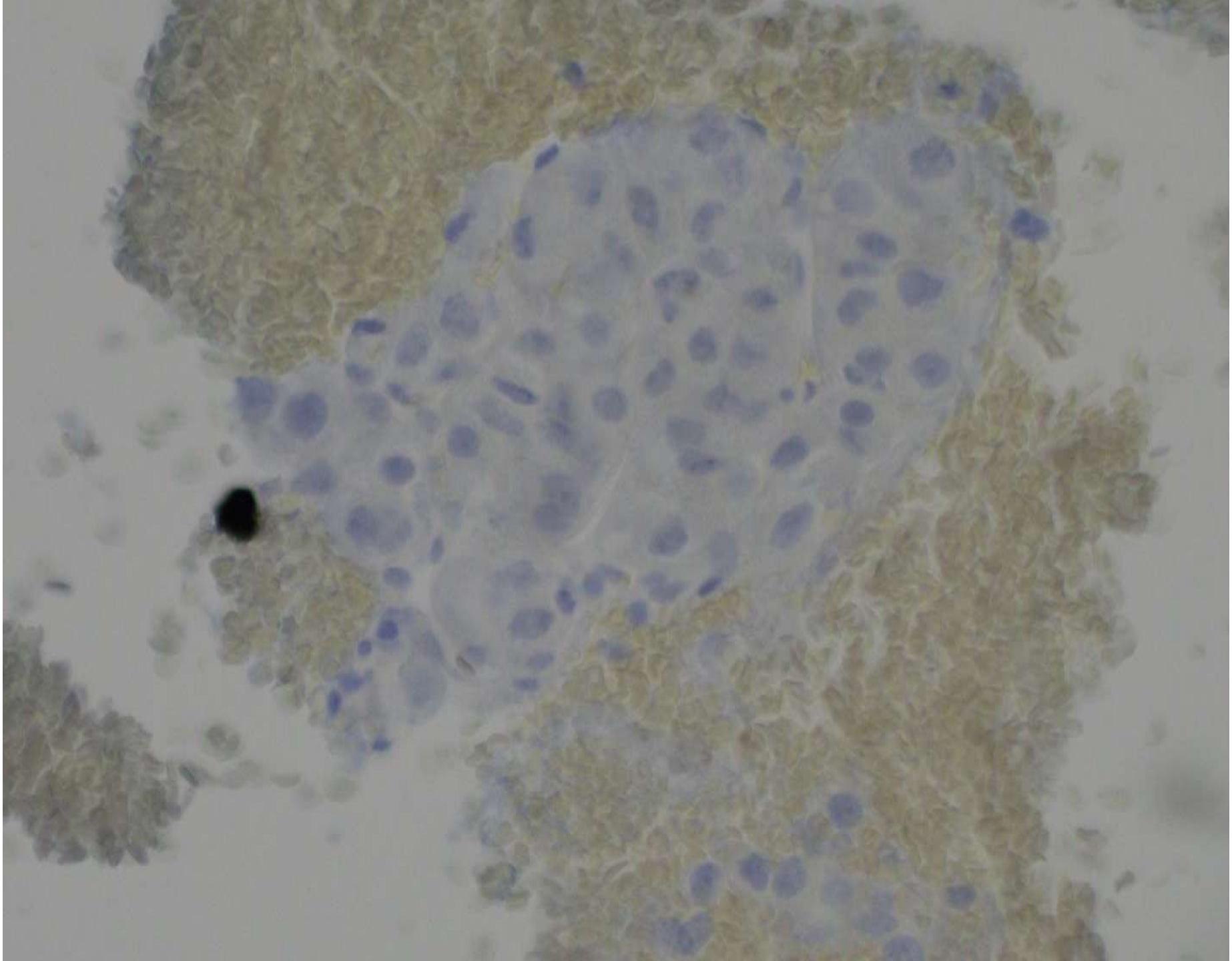


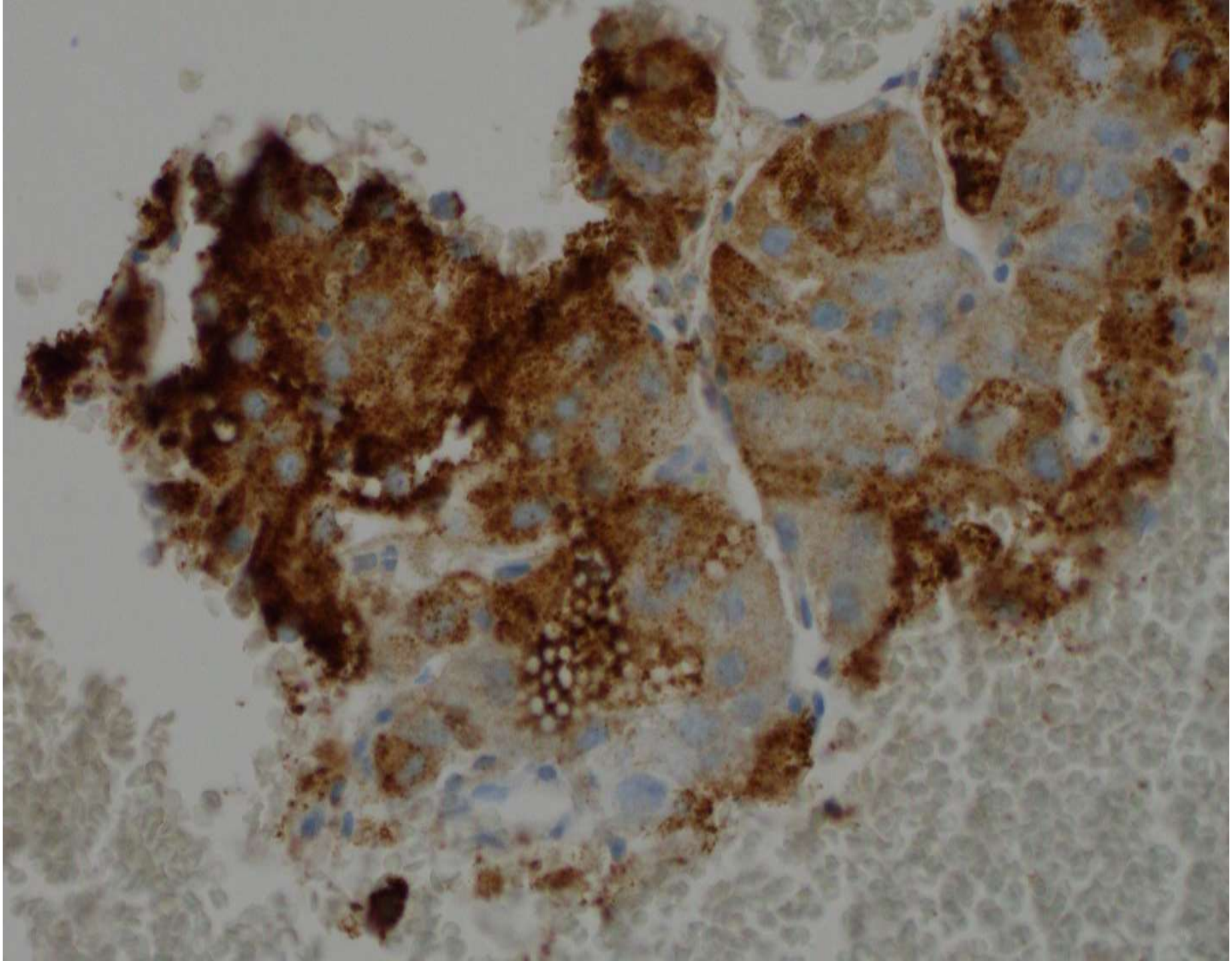


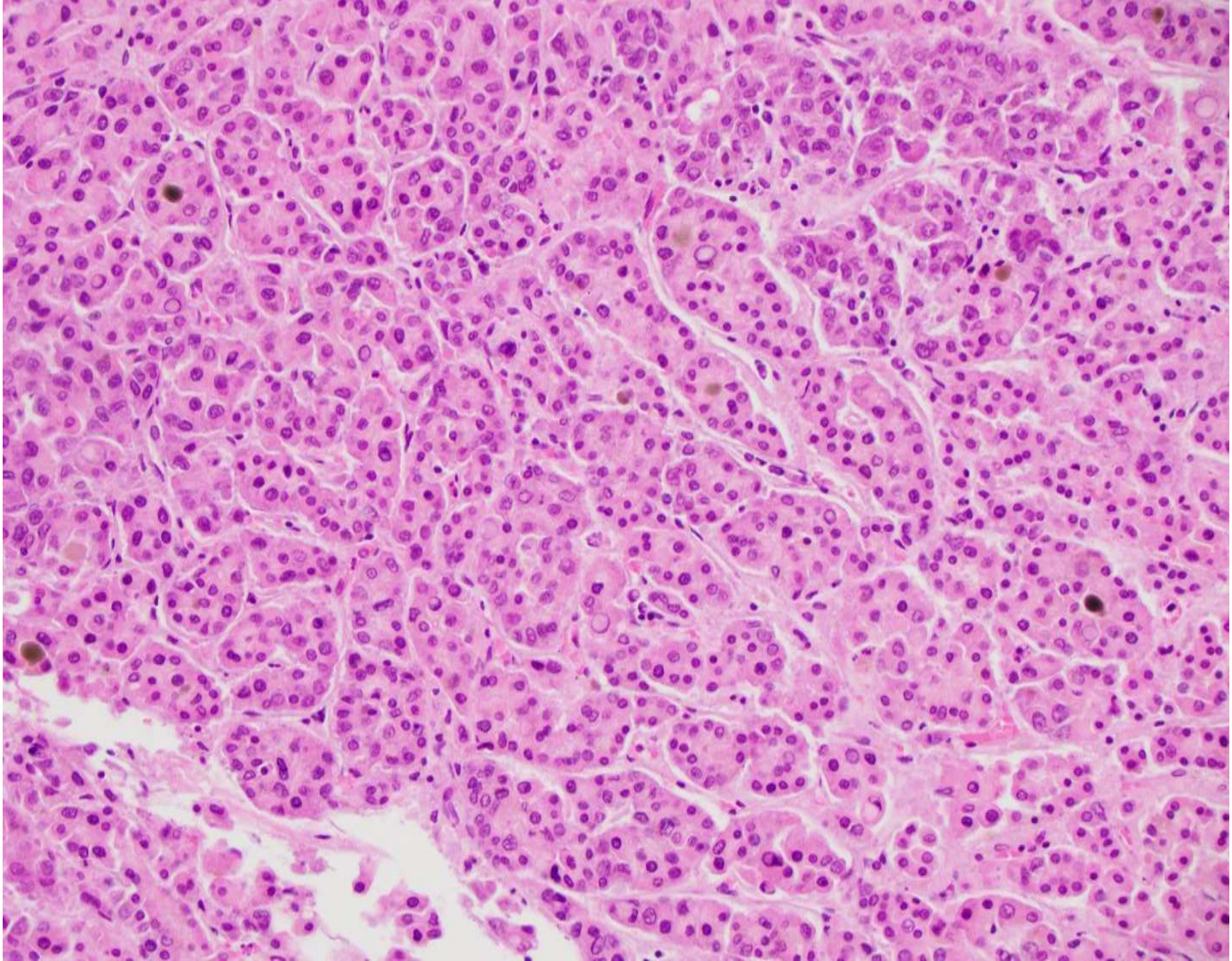


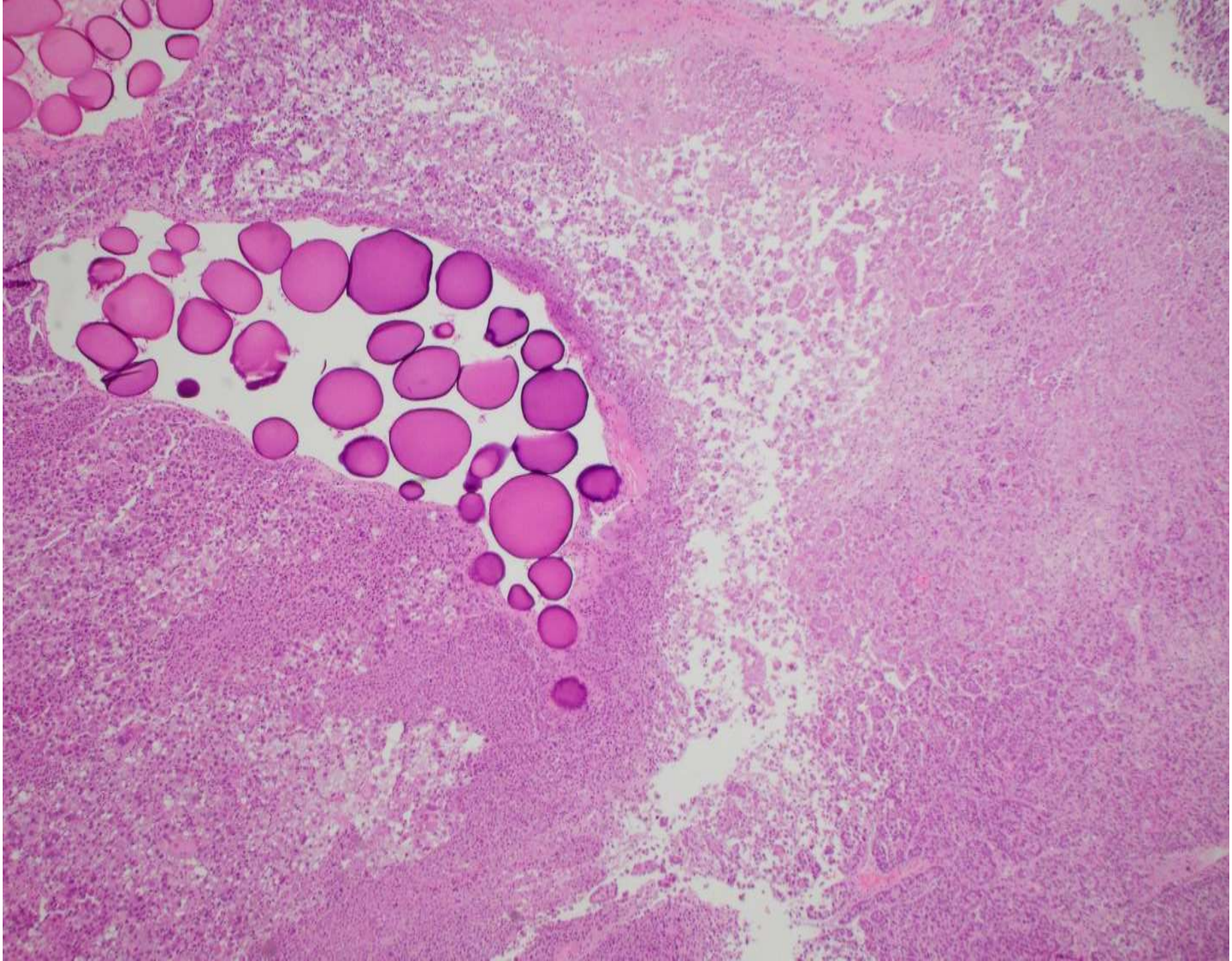












Cutaneous metastatic HCC

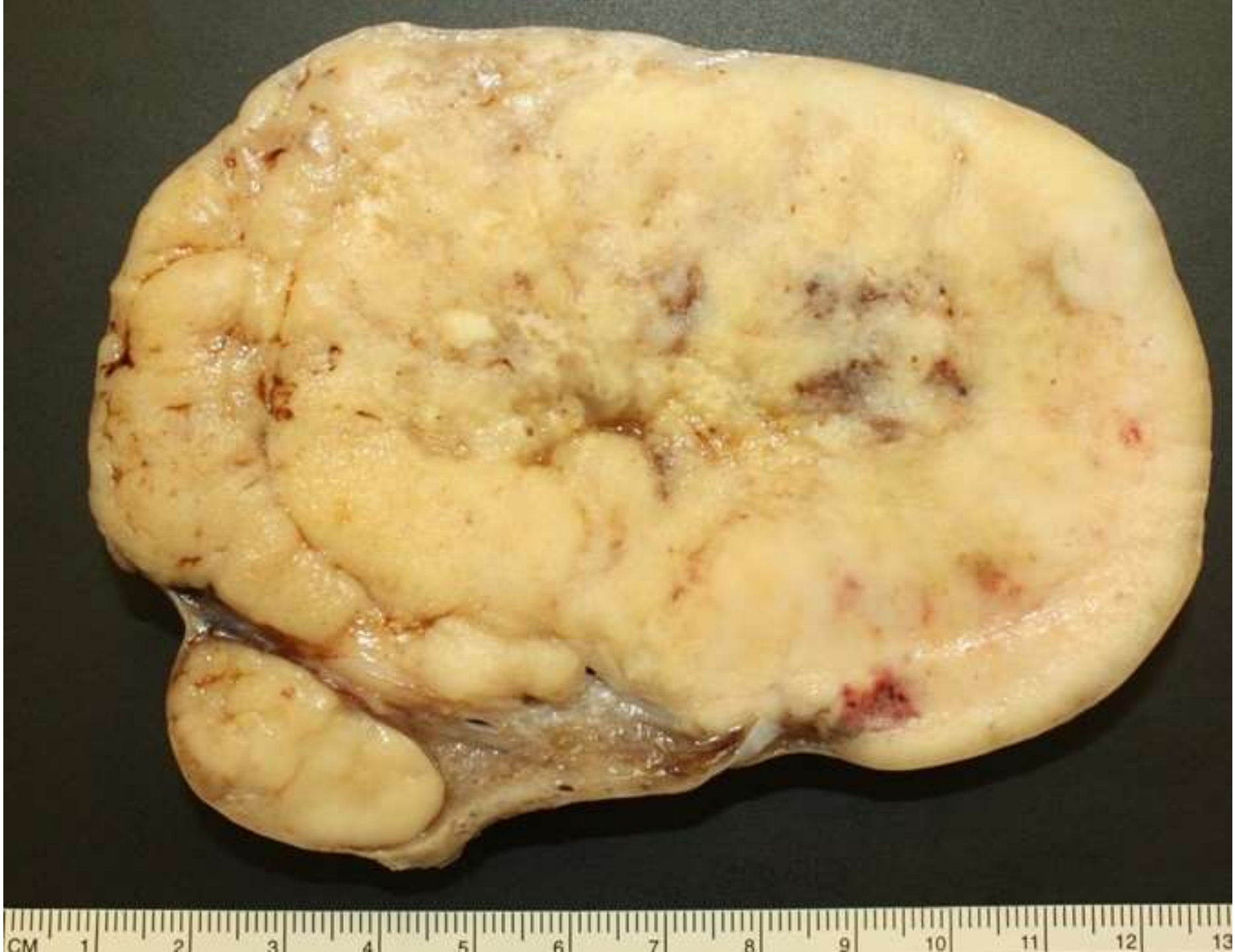
- Rare, sites include scalp, head and neck, shoulders
- May show rapid growth
- Usually firm, non-ulcerated, reddish, painless
- Cyto-histo take-home point:
  - Melanoma mimic
  - Inclusions, pigment not specific to melanoma
  - History and IHC helpful

Morishita A et al. JGH Open. 2022 Apr 23;6(5):361-2.

22-0903

Ankur Sangoi; El Camino Hospital

20ish F with enlarged ovarian mass. Colleague asked to do frozen section on tumor consults you viable telepathology for assistance. Diagnosis?


CM
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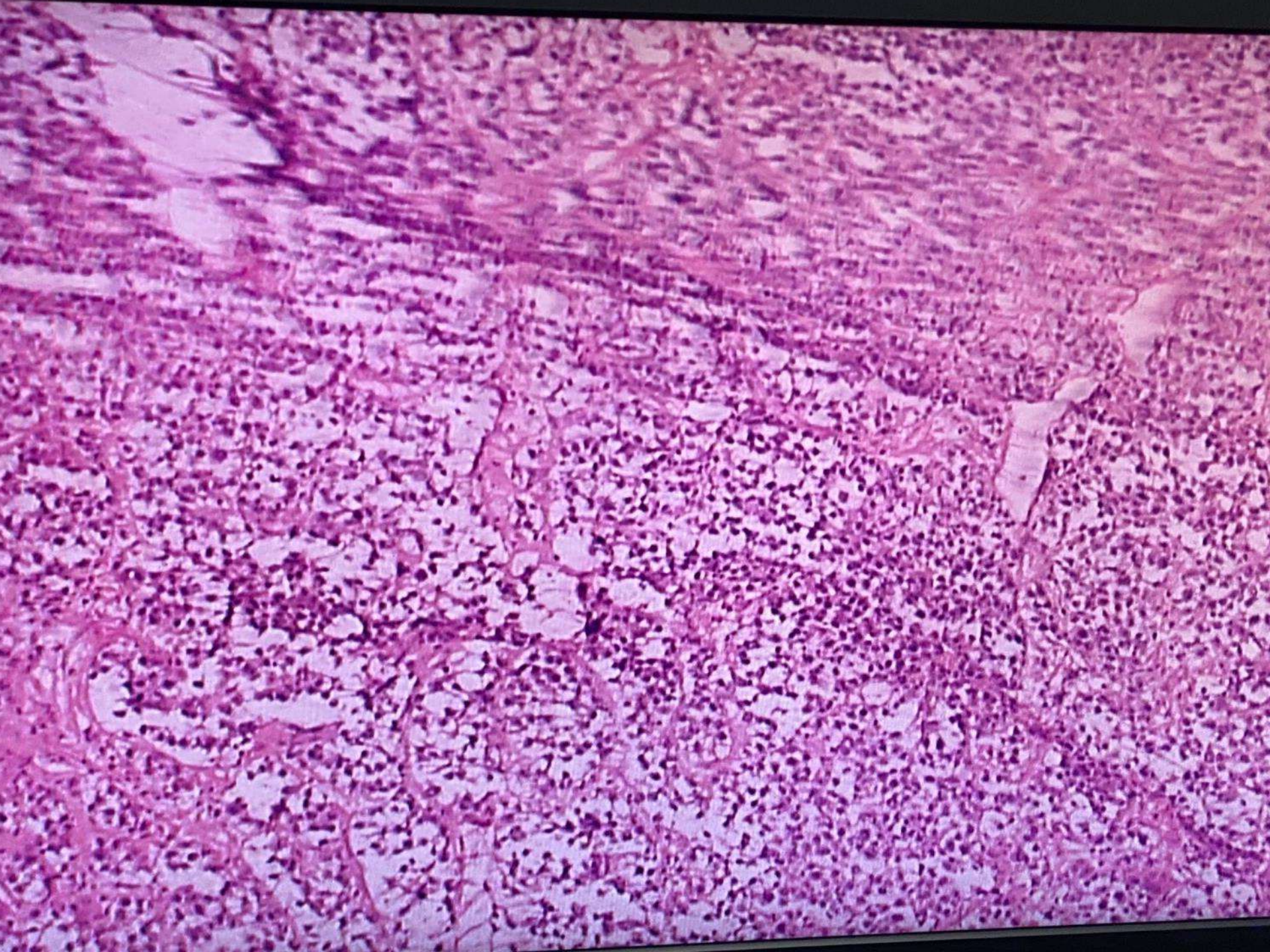
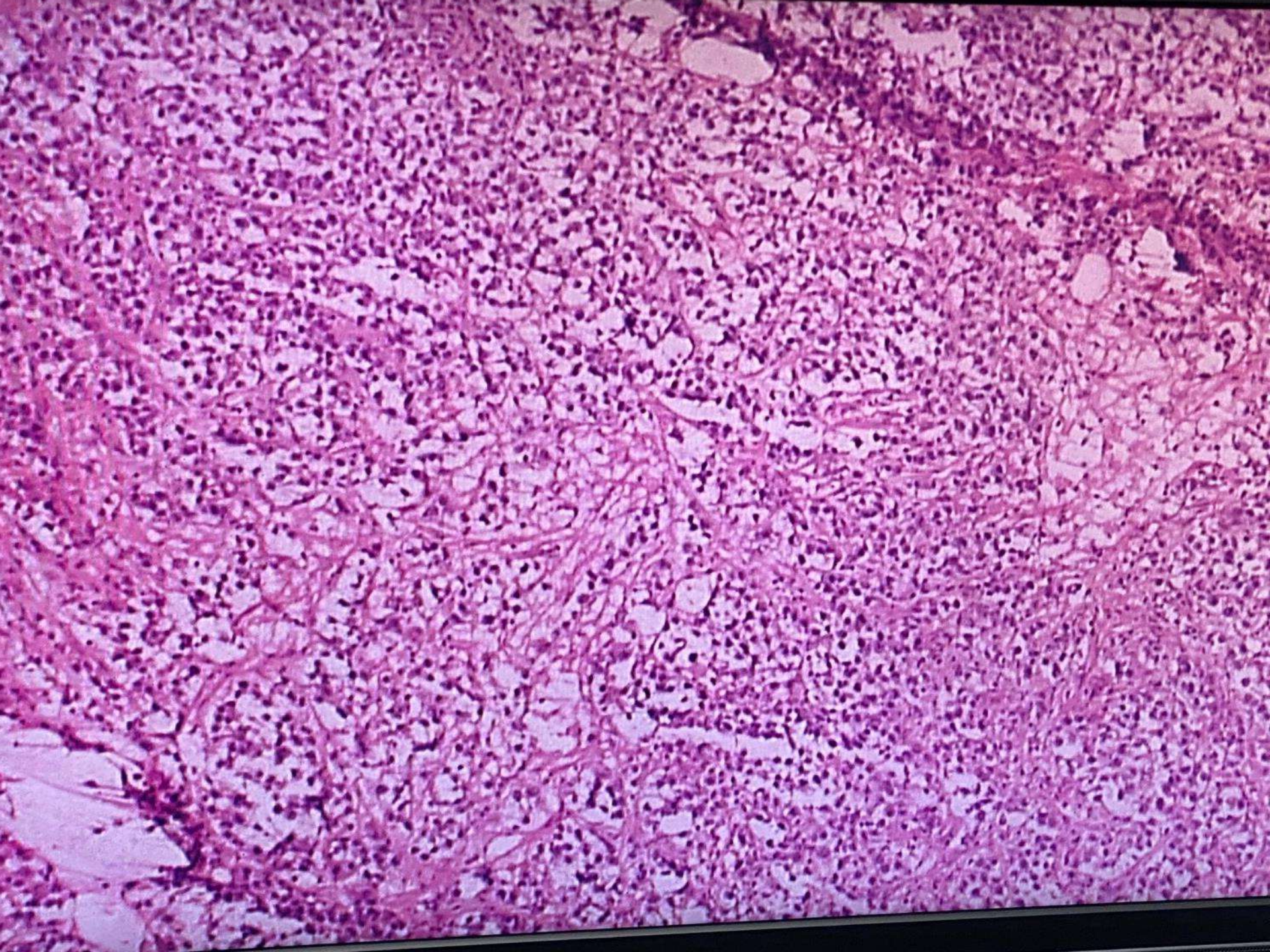
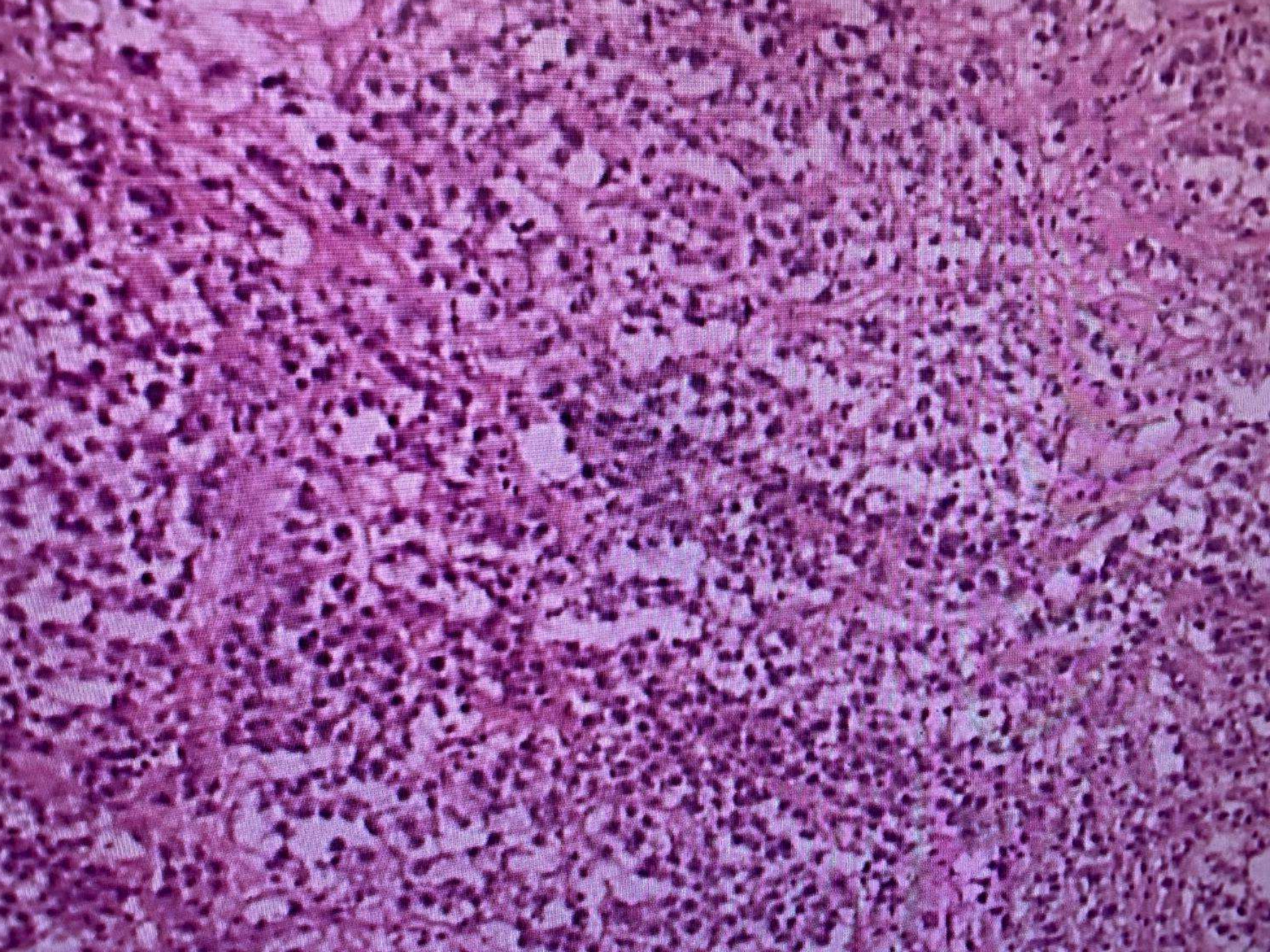
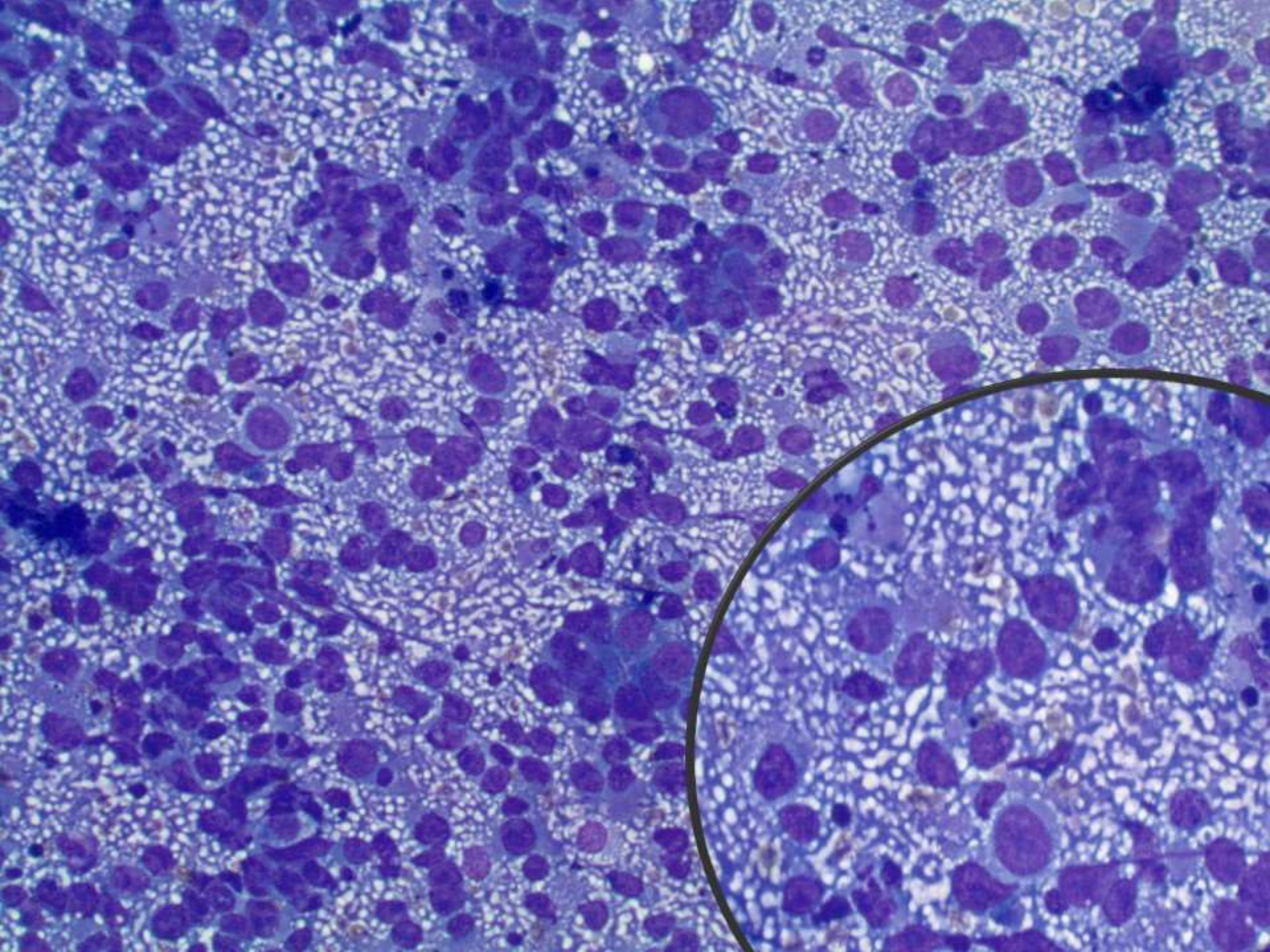
BRAVIA
SONY
OLYMPUS

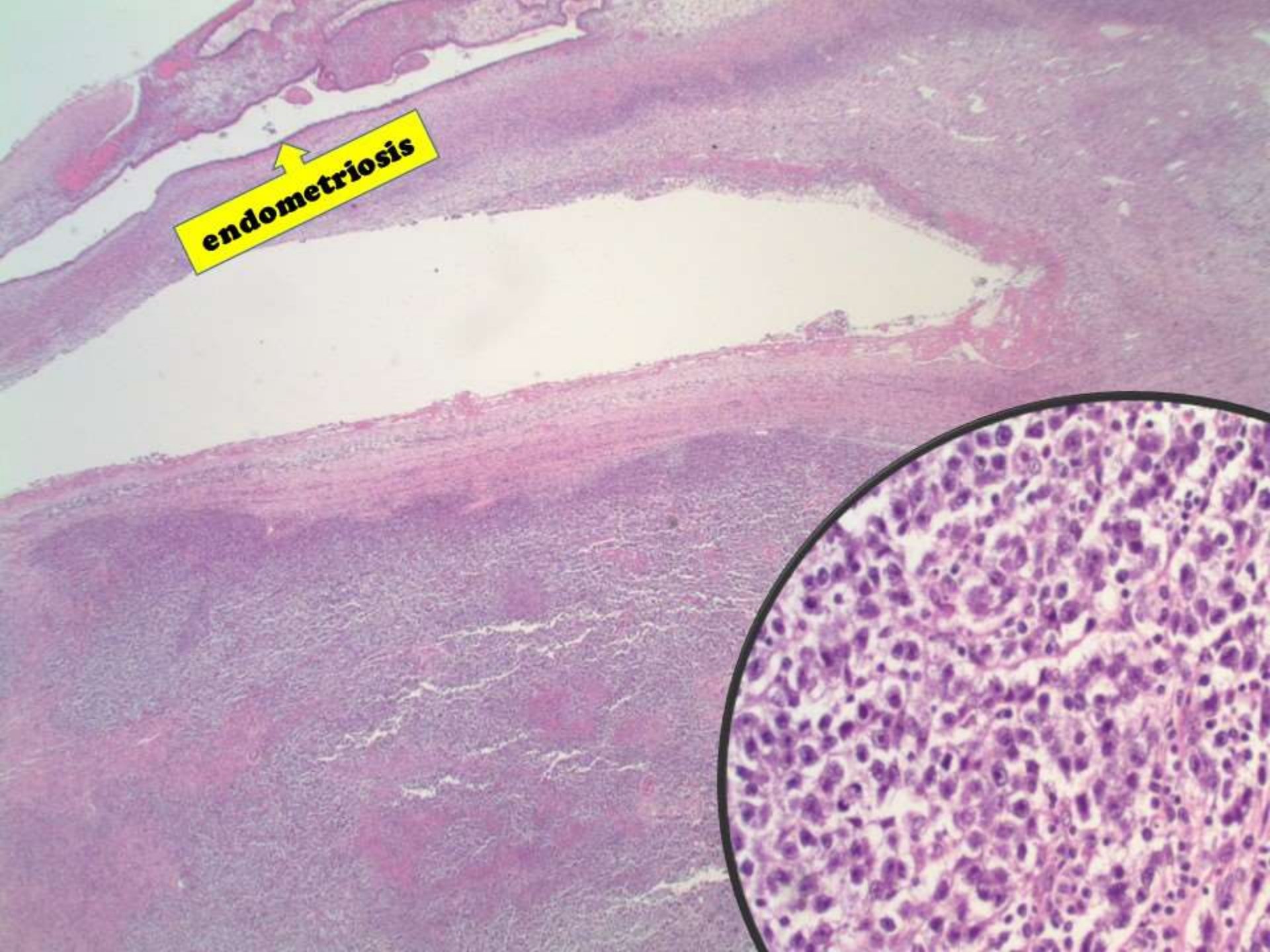






DIAGNOSIS?




endometriosis

DDx of dysgerminoma

LYMPHOMA

- Smear prep: blue blobs not “tigroid”
- Lack admixed fibrovascular septae
- IHC: CD20+ OCT3/4-

CLEAR CELL CARCINOMA

- tubulocystic/papillary architecture
- IHC: PAX8+ NapsinA+ EMA+ OCT3/4-

SMALL CELL CARCINOMA HYPERCALCEMIC TYPE

- pseudofollicular spaces
- BRG1 aberrant loss EMA+ OCT3/4-

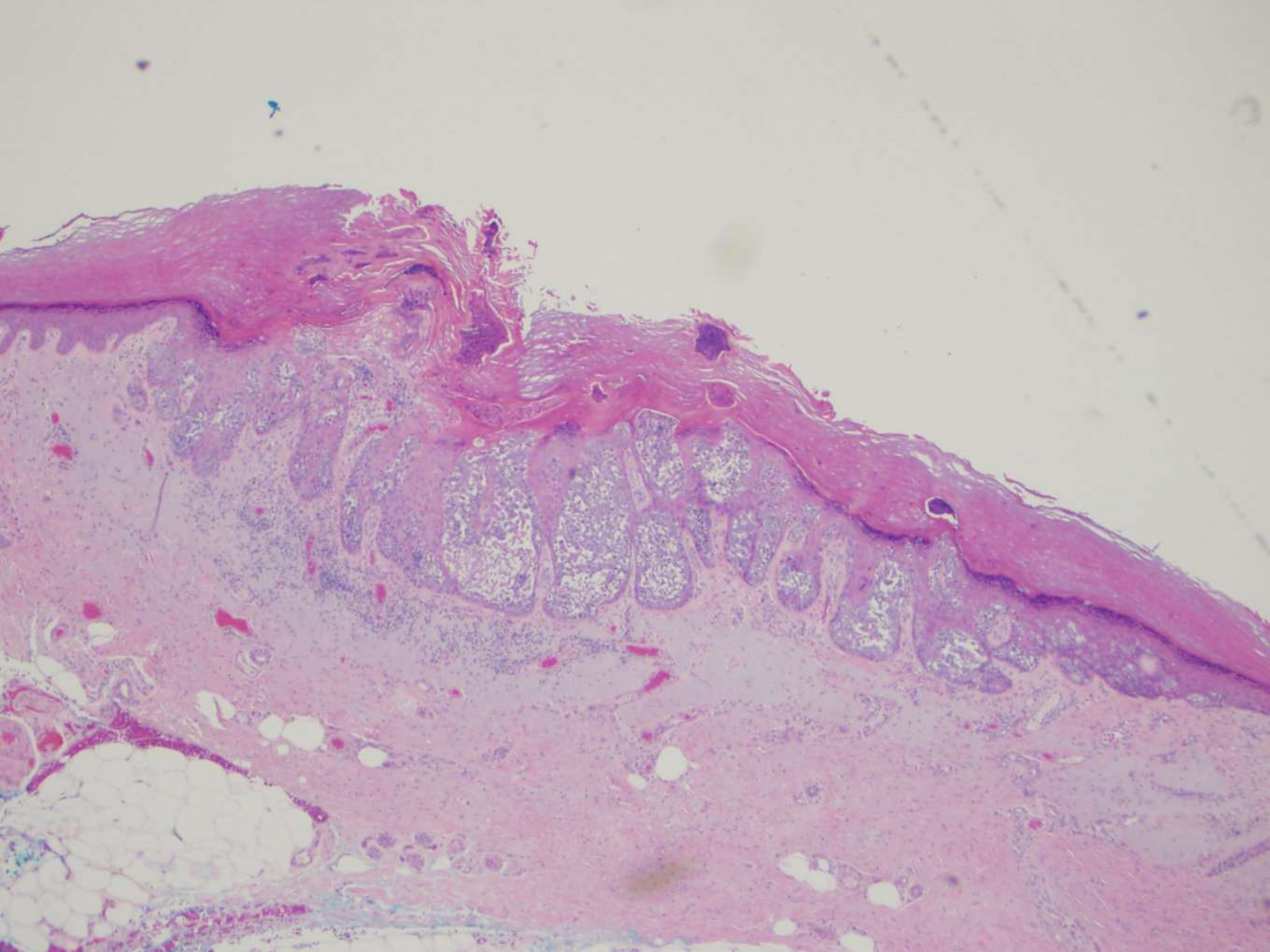
OTHER GERM CELL TUMORS

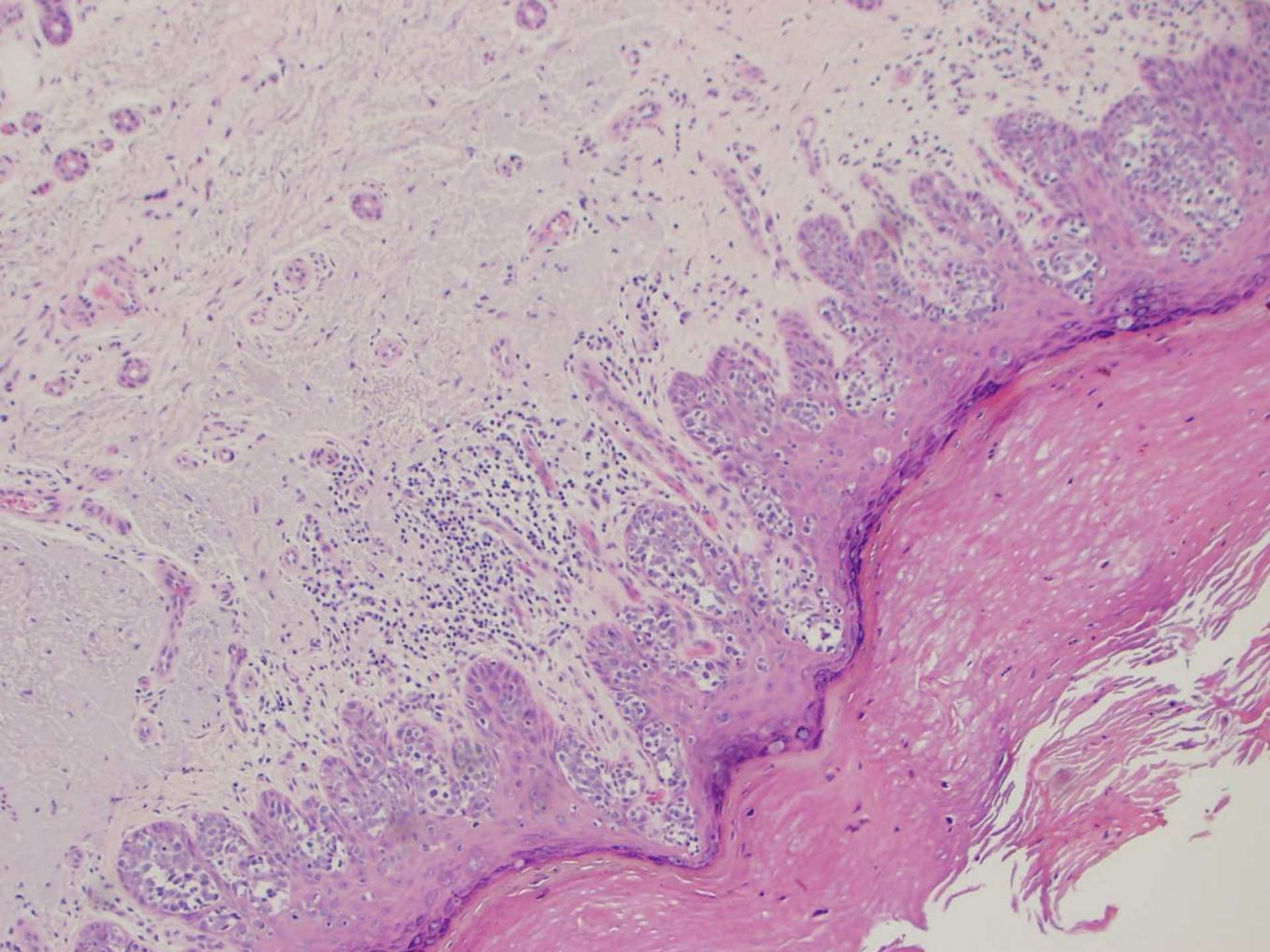
- other typical morphologies of embryonal carcinoma or yolk sac tumor
- IHC (embryonal carcinoma): CD30+ CD117-
- IHC (yolk sac tumor): glypican3+ OCT3/4- CD117-

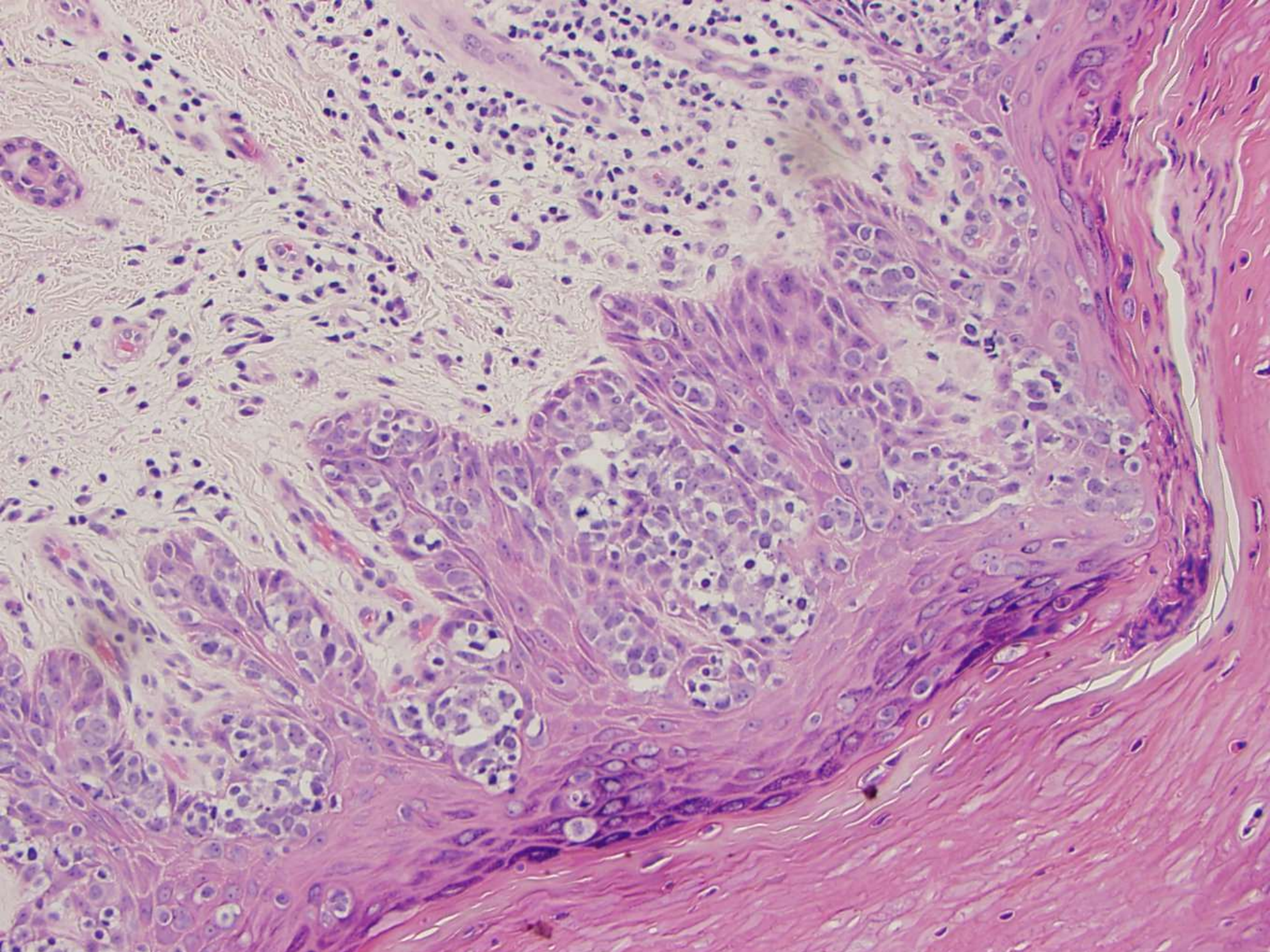
22-0904

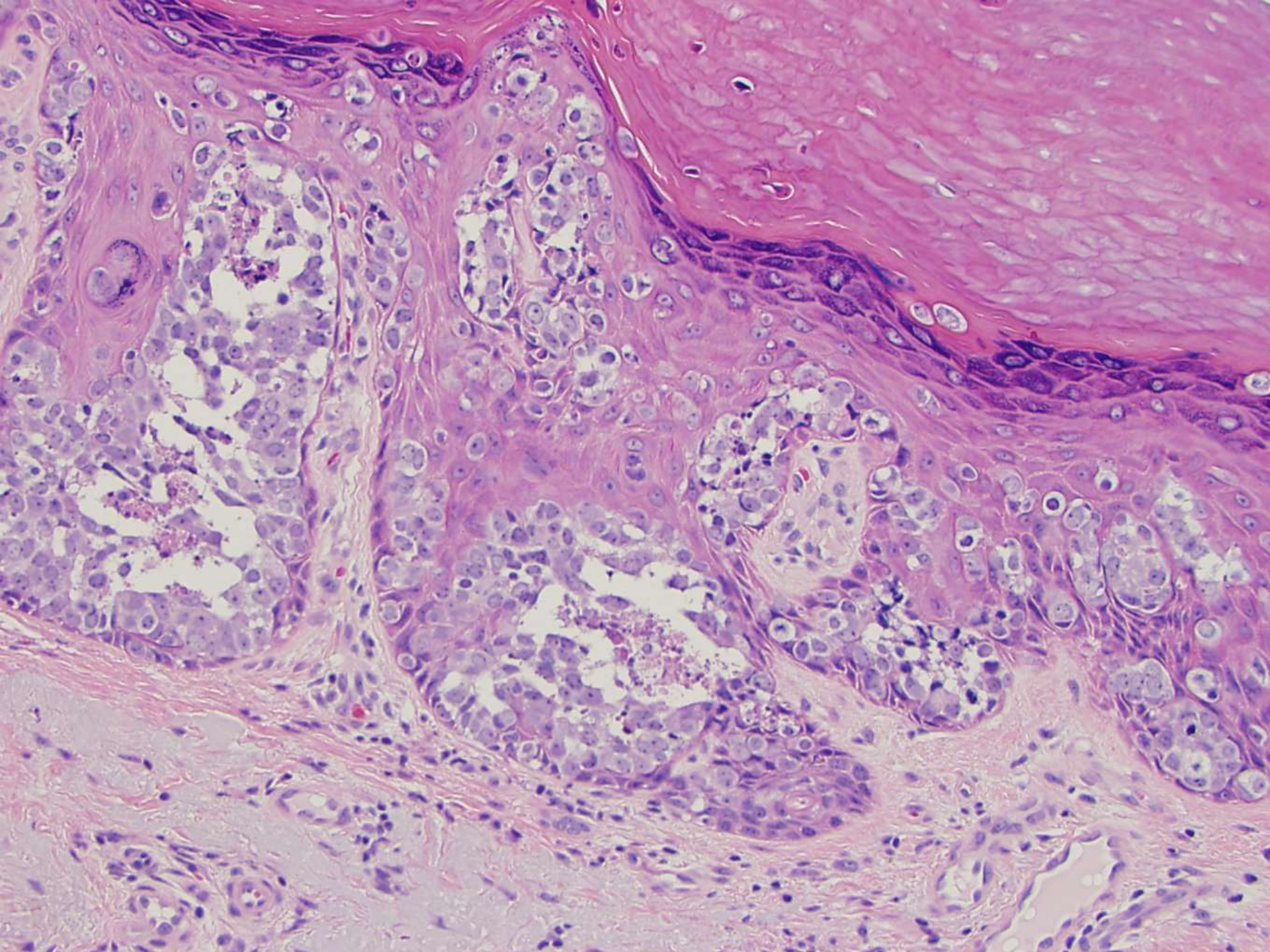
Greg Rumore; Kaiser Diablo

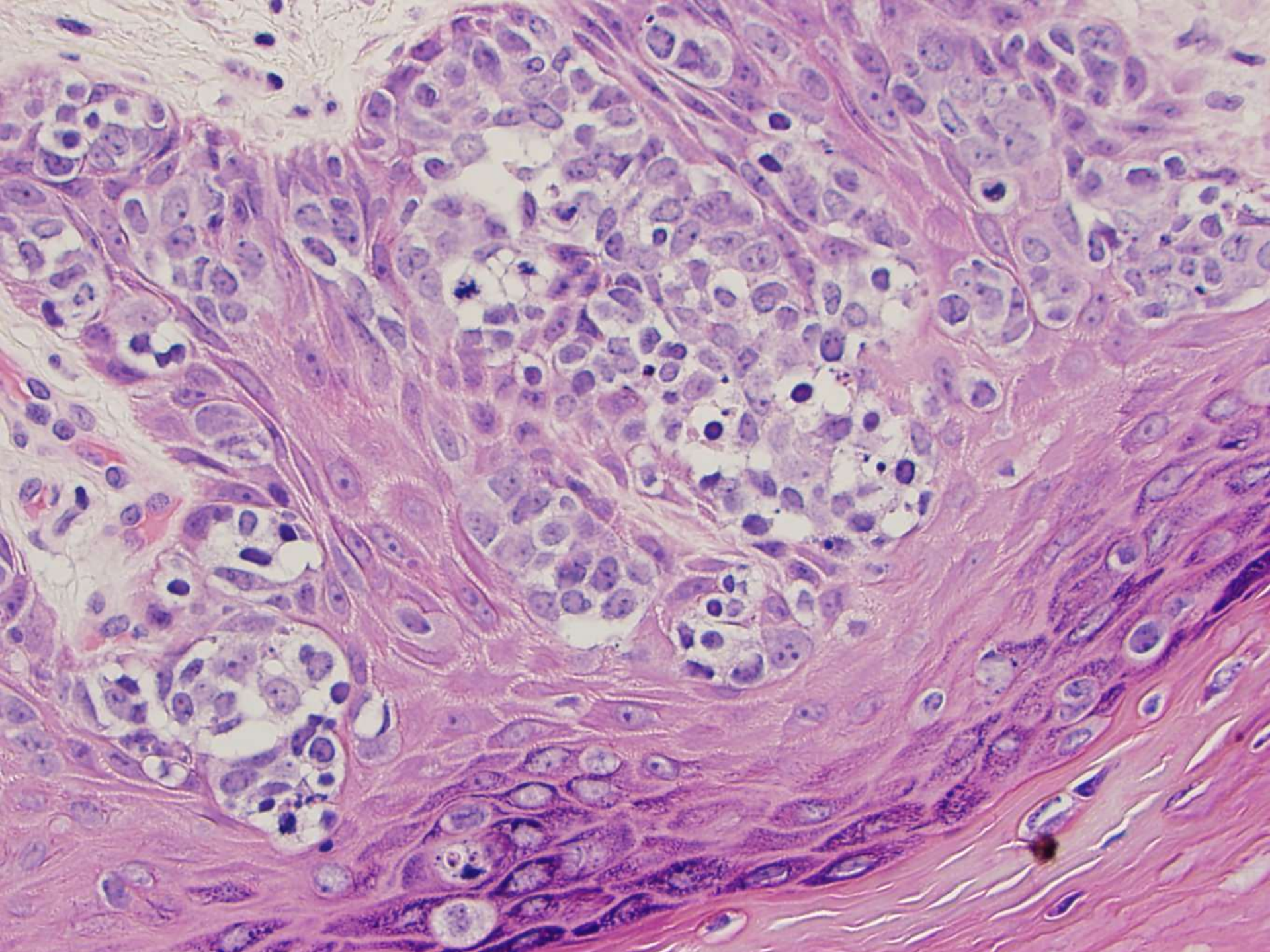
70ish F with pink scaly lesion right hand.

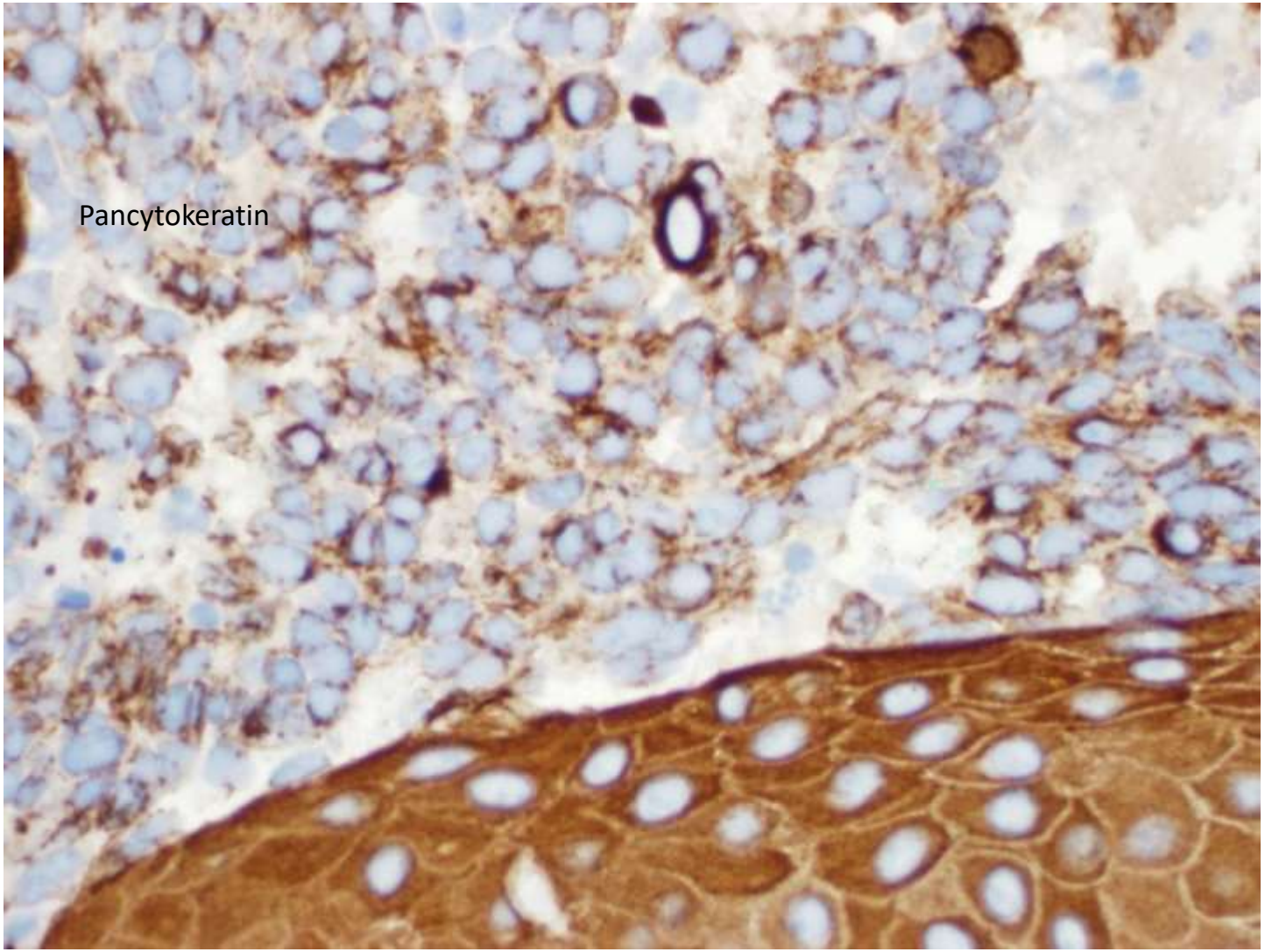


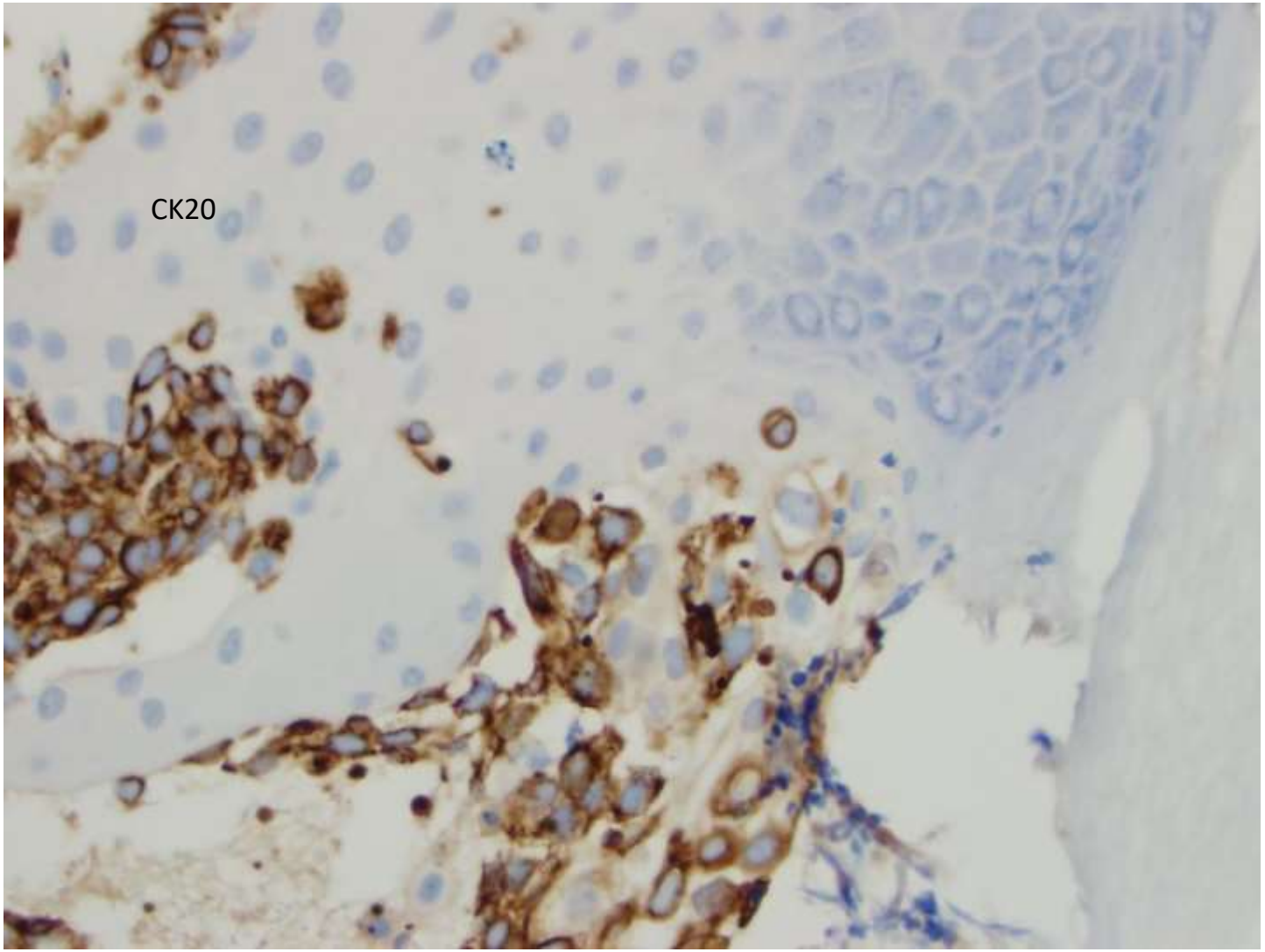


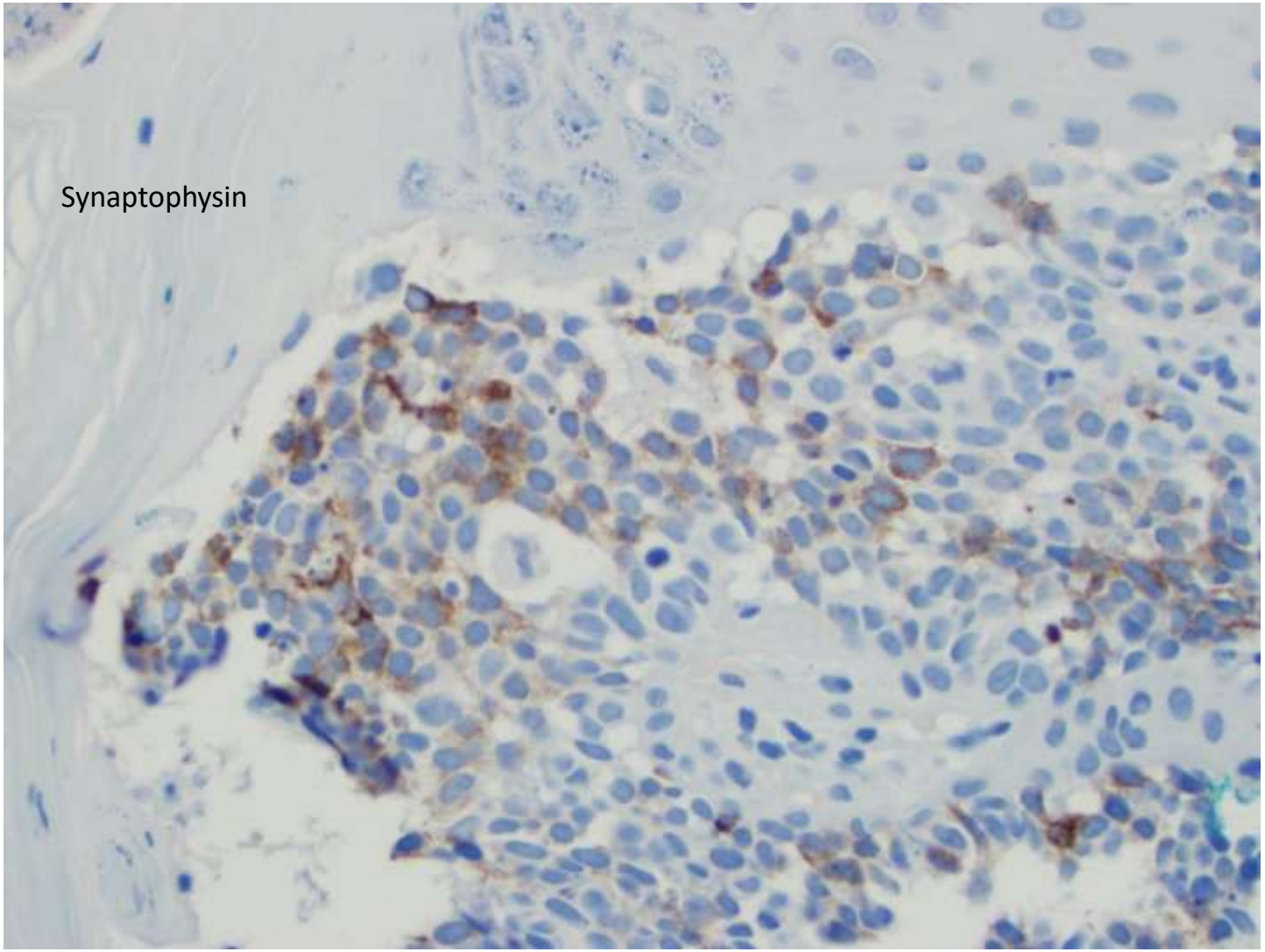







Pancytokeratin


CK20


Synaptophysin

Merkel Cell Carcinoma

- Primary Neuroendocrine carcinoma of skin
- Sun exposed skin of elderly individuals
- Poor prognosis-50% 5 yr survival for localized cases
- 18% associated intraepidermal component

MCCIS

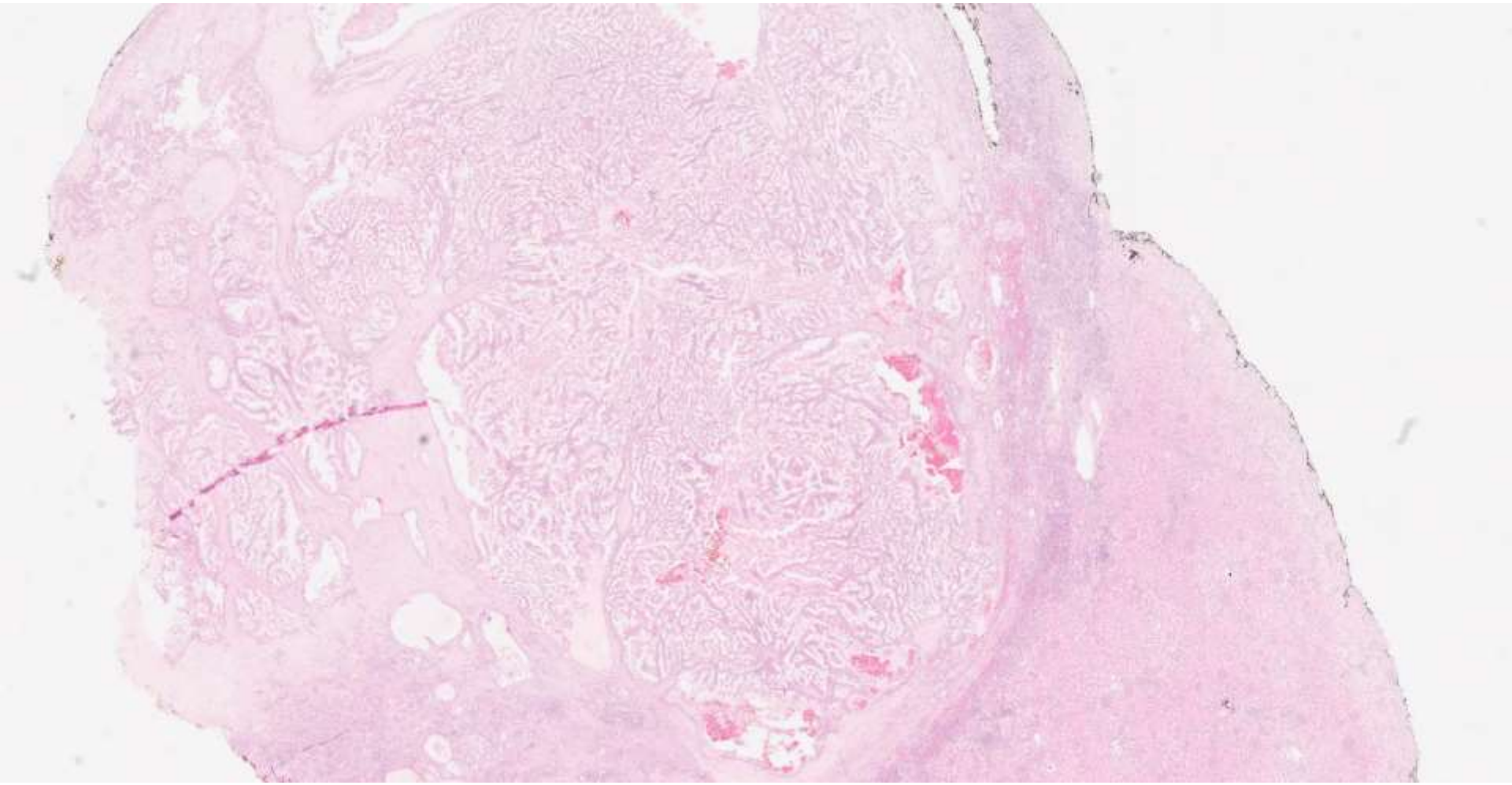
- Very rare (in pure form)
- In DDX of Pagetoid lesions-melanoma, extramammary Paget's, Bowen's, adnexal carcinomas
- Without invasive component appears to have good prognosis

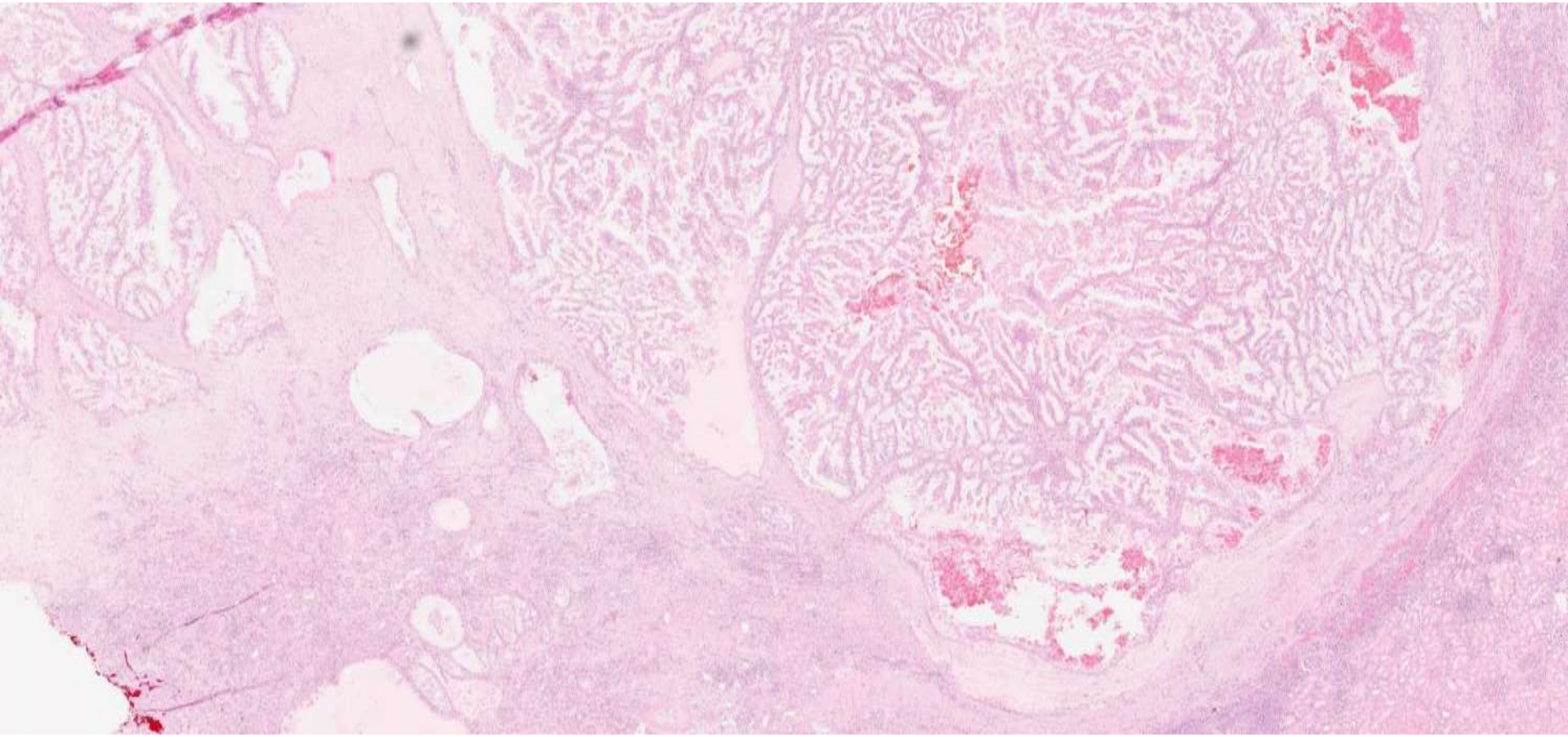
22-0905

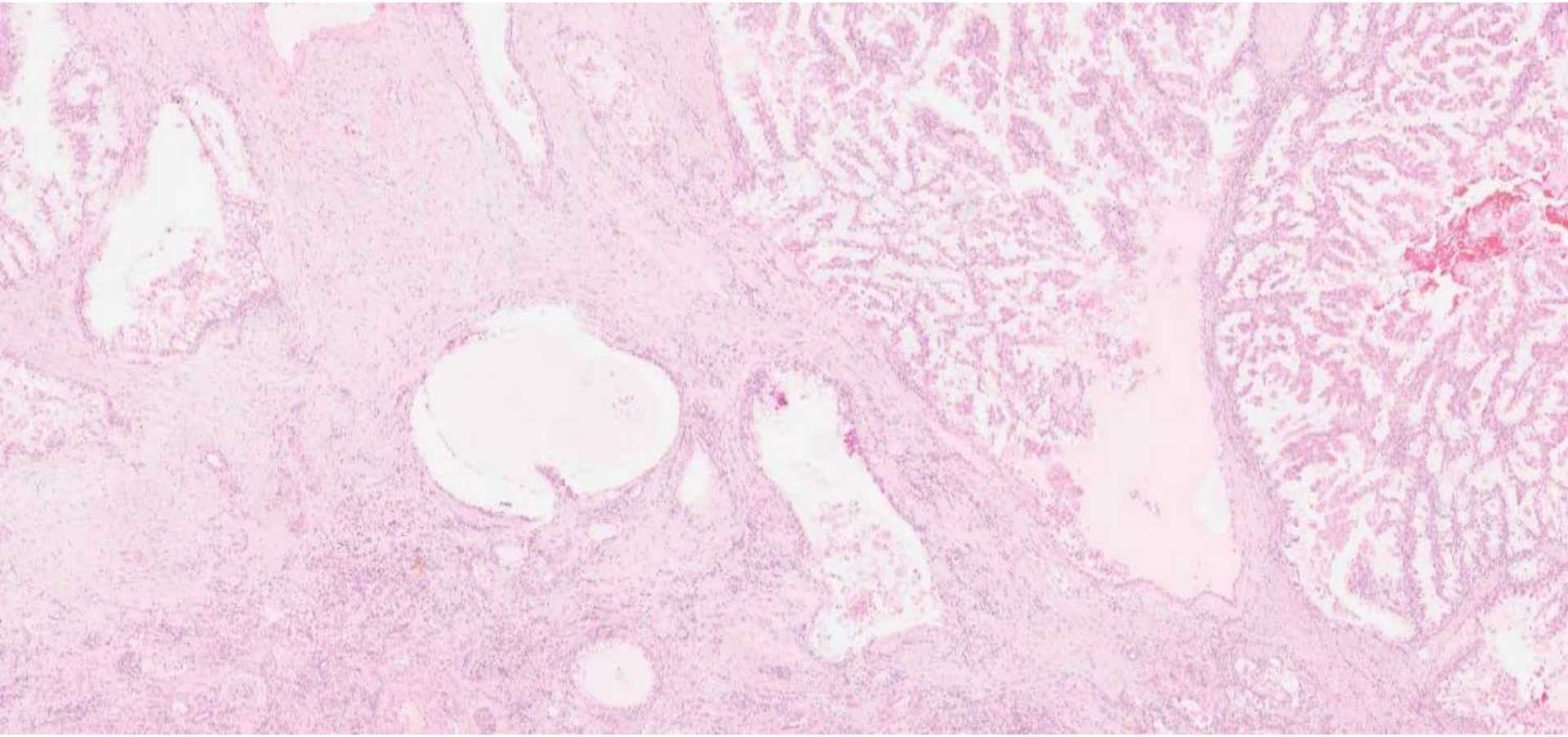
Direct link to scanned slide:
https://pathpresenter.net/public/display?token=21e1a5ef

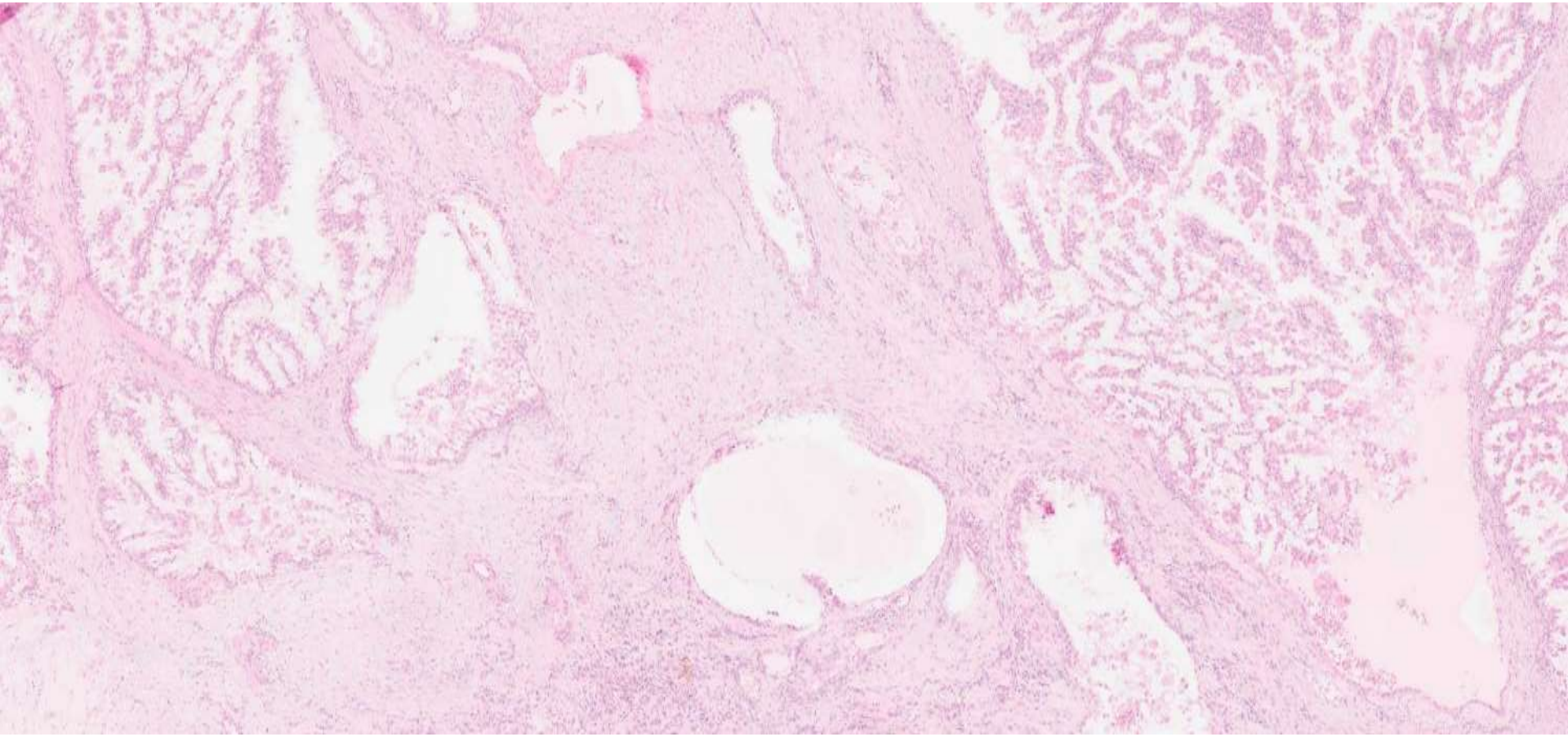
Patrick Mullane/Sunny Kao; Stanford

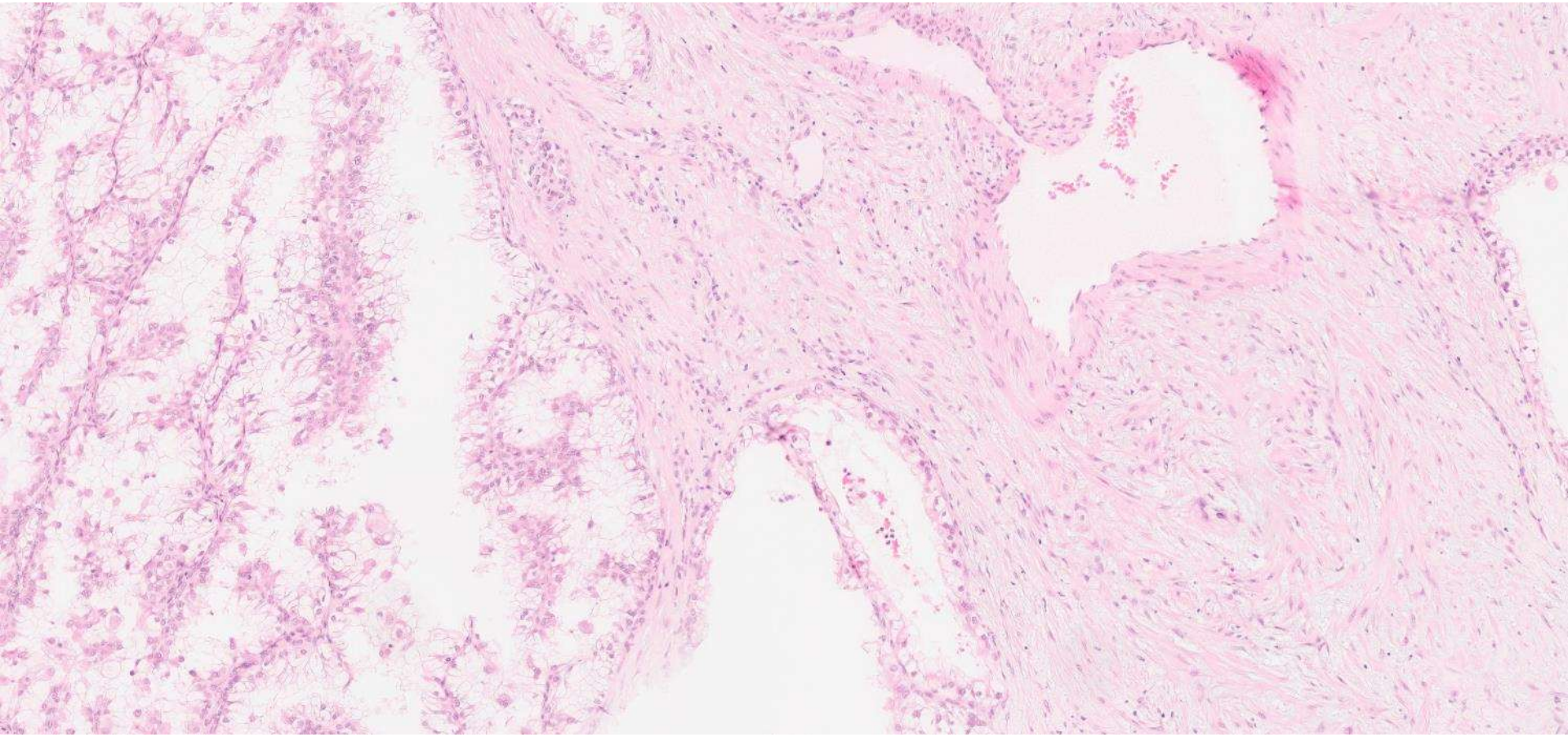
30ish F with incidentally-identified 1.5cm left renal mass discovered during work-up of Crohn's disease.

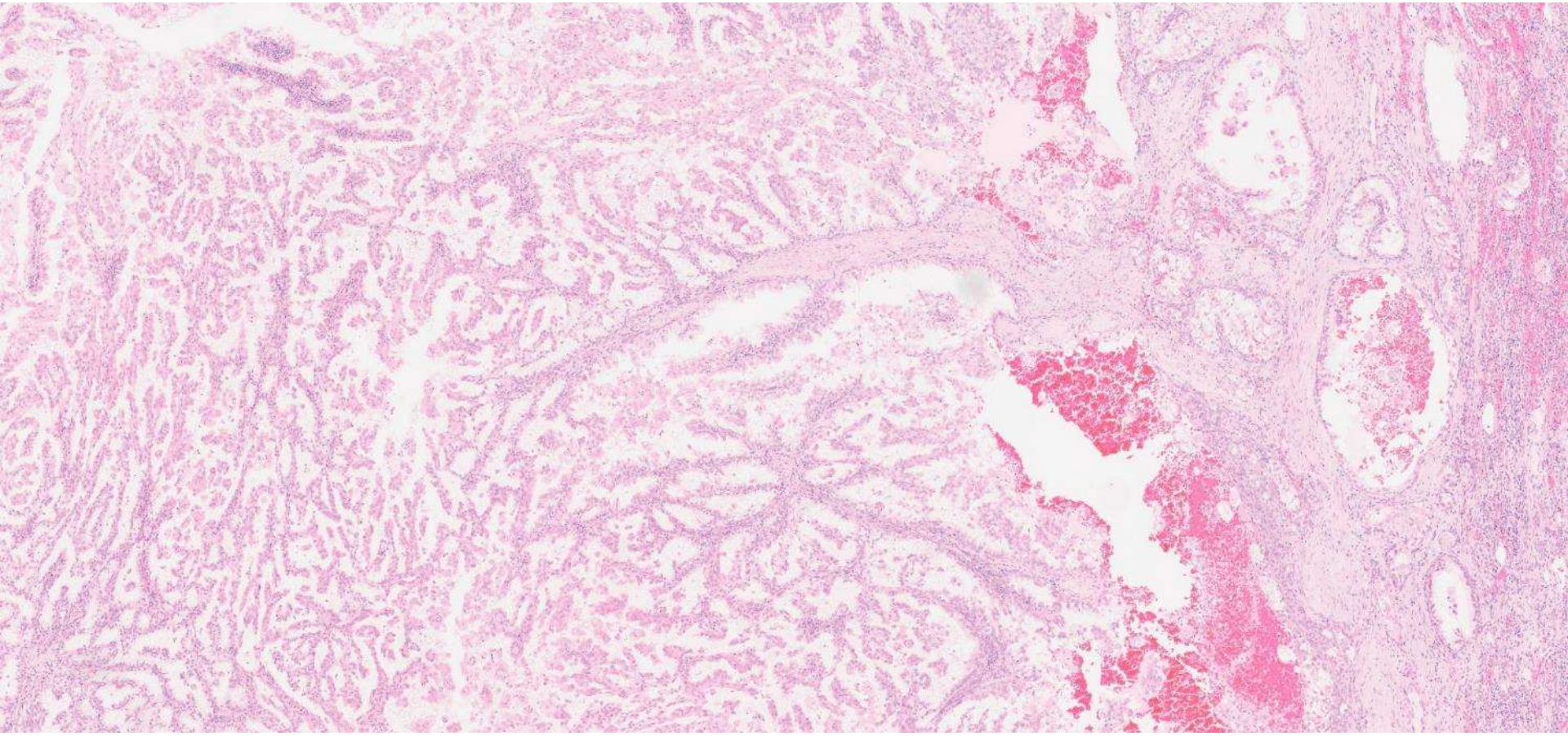


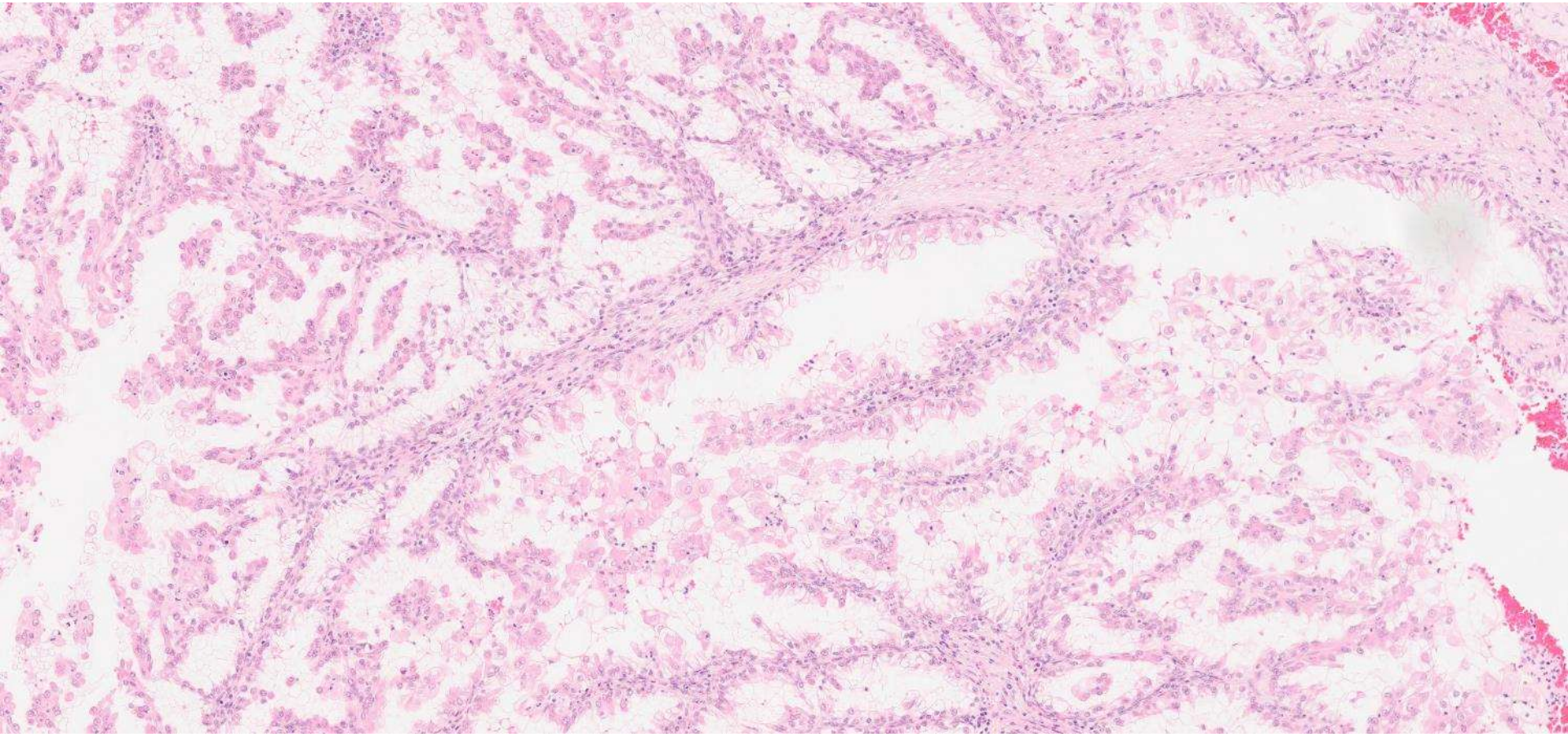


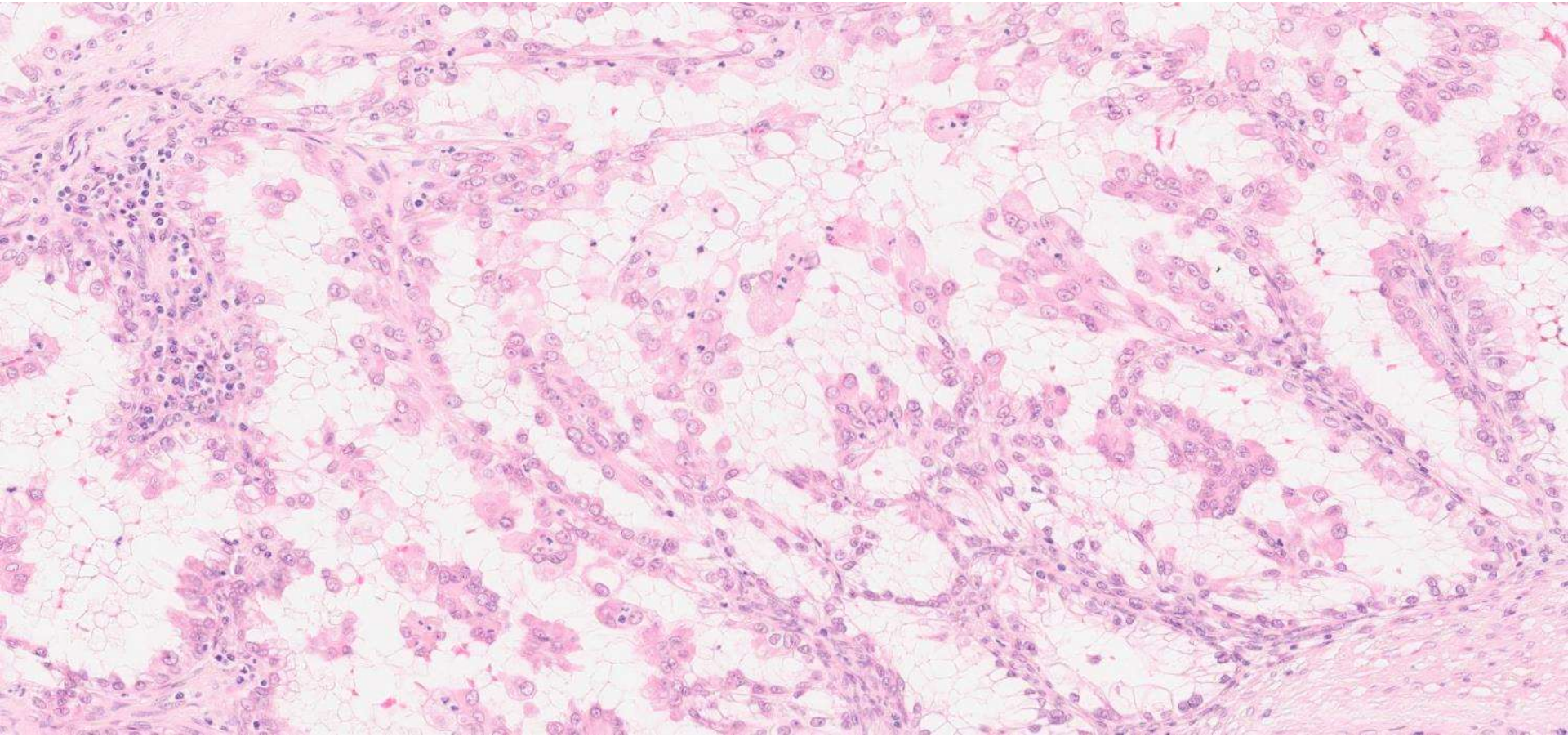


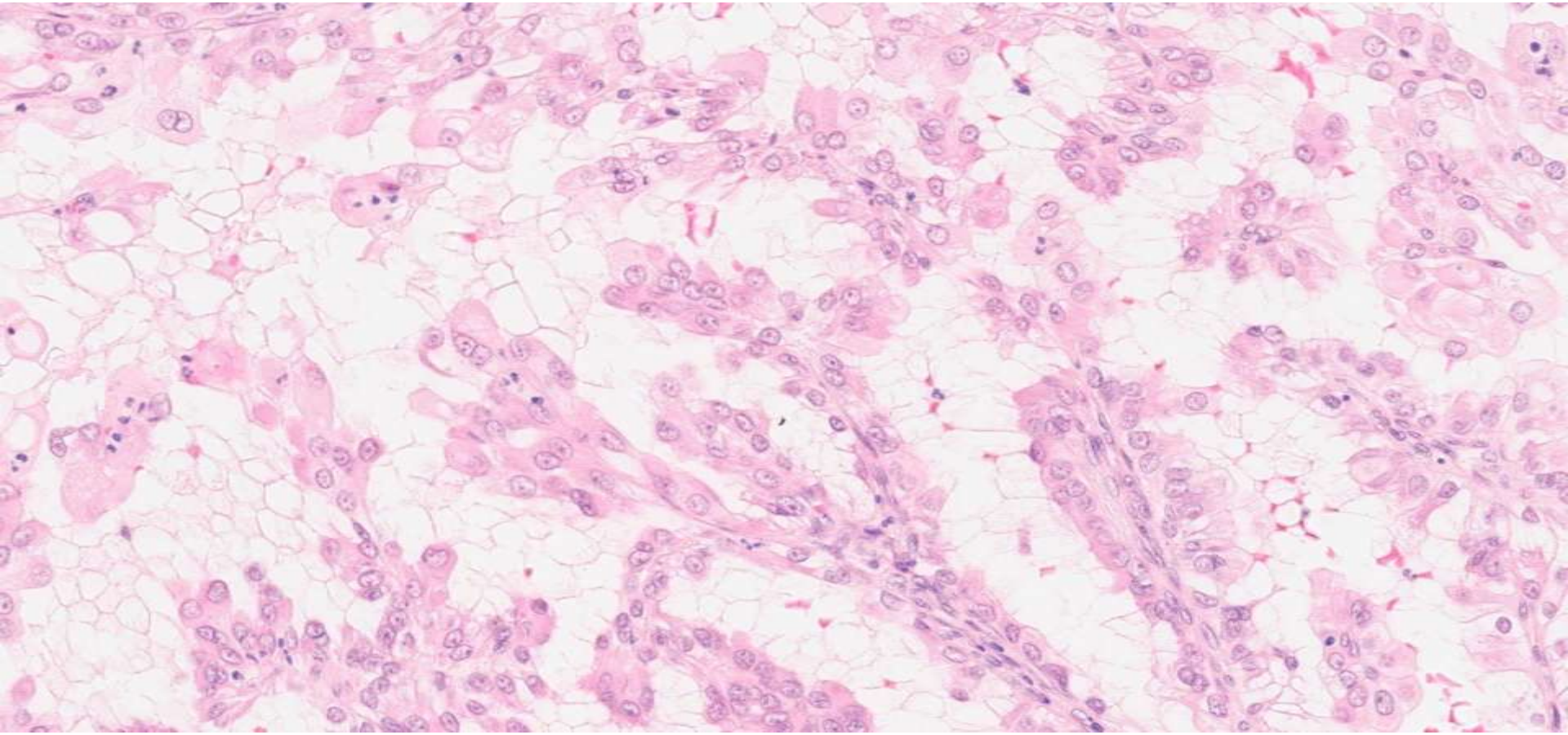






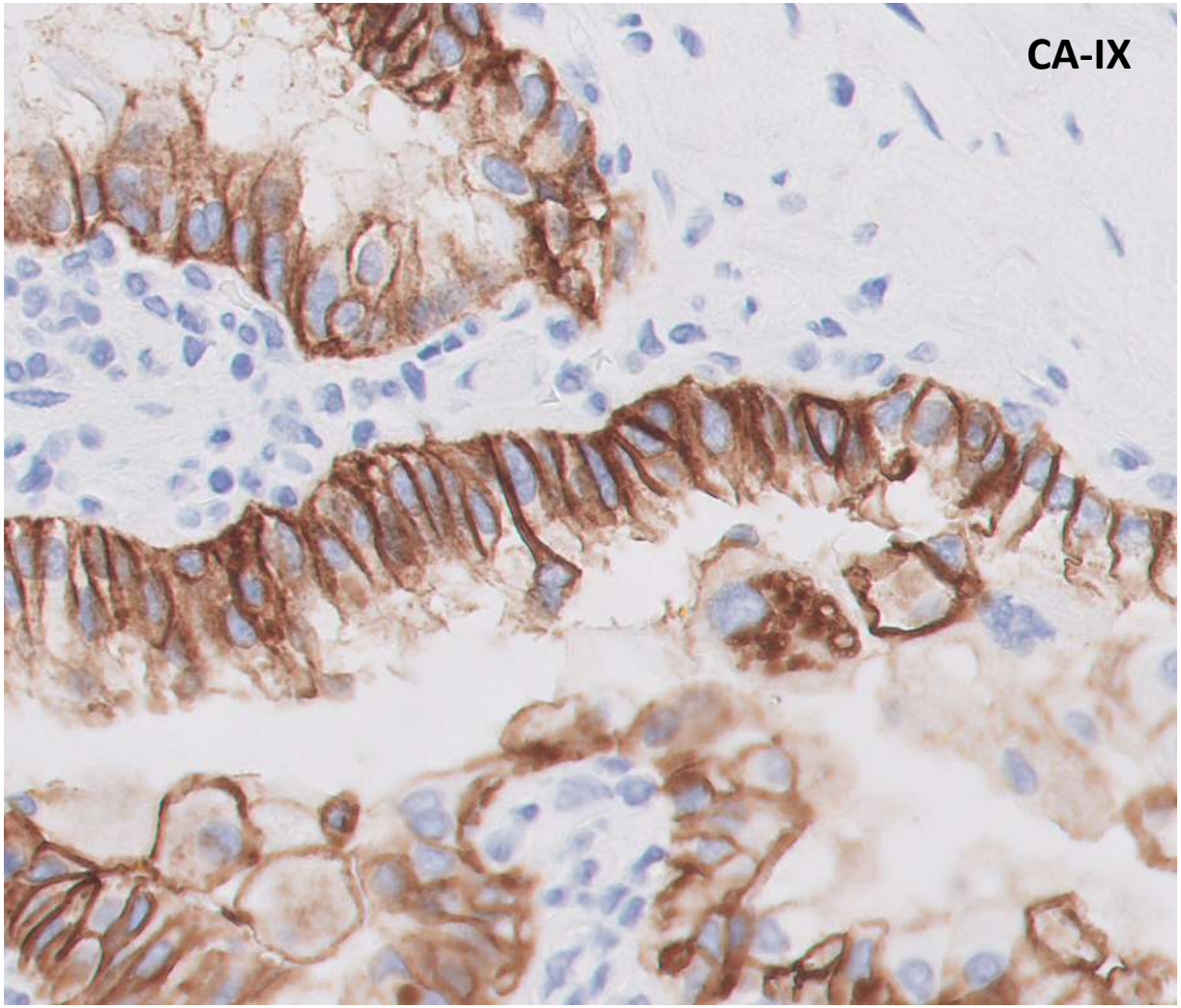






Morphologic Summary

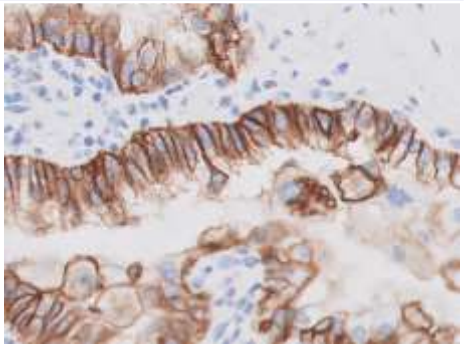
- Architecture
  - Well-circumscribed
  - Solid/nodular
  - Elongated branching tubules
  - Well-formed papillae
  - Fibromuscular bands, predominantly in the periphery
- Cytology
  - Clear to eosinophilic cells
  - Voluminous cytoplasm
  - Round, basally placed nuclei
  - Variably prominent nucleoli
  - Bland spindle cell in fibromuscular areas
- IHC
  - + CK7
  - + CA-IX
  - - cathepsin K

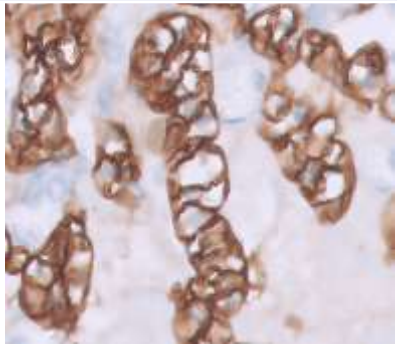

CA-IX

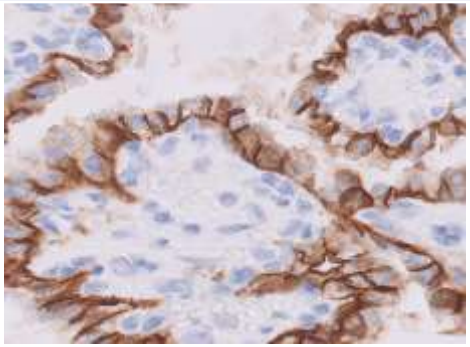
RCC with fibromyomatous stroma (RCC FMS)

- Novel entity
  - Distinct morphologic, immunohistochemical, and molecular features
- Stromal component is polyclonal and variable in extent
- Diffuse CK7 is typical, and required for the diagnosis
- Overlap morphology with ELOC (TCEB1) mutated tumors
- Recurrent TSC/MTOR mutations, both sporadic and hereditary
- Indolent behavior
  - Lymph node metastasis reported in rare cases associated with TSC

	RCC FMS	Clear cell RCC	Clear cell papillary renal cell tumor
Defining architectural features	• Nodules of elongated and branching tubules • Variable fibromyomatous stroma	• Compact acini/nests • Delicate, intricately branching vasculature	• Compact, abortive tubulo-papillary growth • Thick capsule
Defining cytologic features	• Clear to lightly eosinophilic cells • Voluminous apical cytoplasm	• Clear cells	• Scant clear cytoplasm • Abluminal nuclei
CK7	• Diffuse in all cases	• Negative to focal	• Diffuse in all cases
CA-IX	• Diffuse membranous, focally prominent “cup-shape” in about 50%	• Diffuse membranous	• Diffuse “cup-shaped”
CD10	• Positive	• Positive	• Negative
Molecular	• TSC/MTOR mutation	• VHL and/or loss of 3p	• None



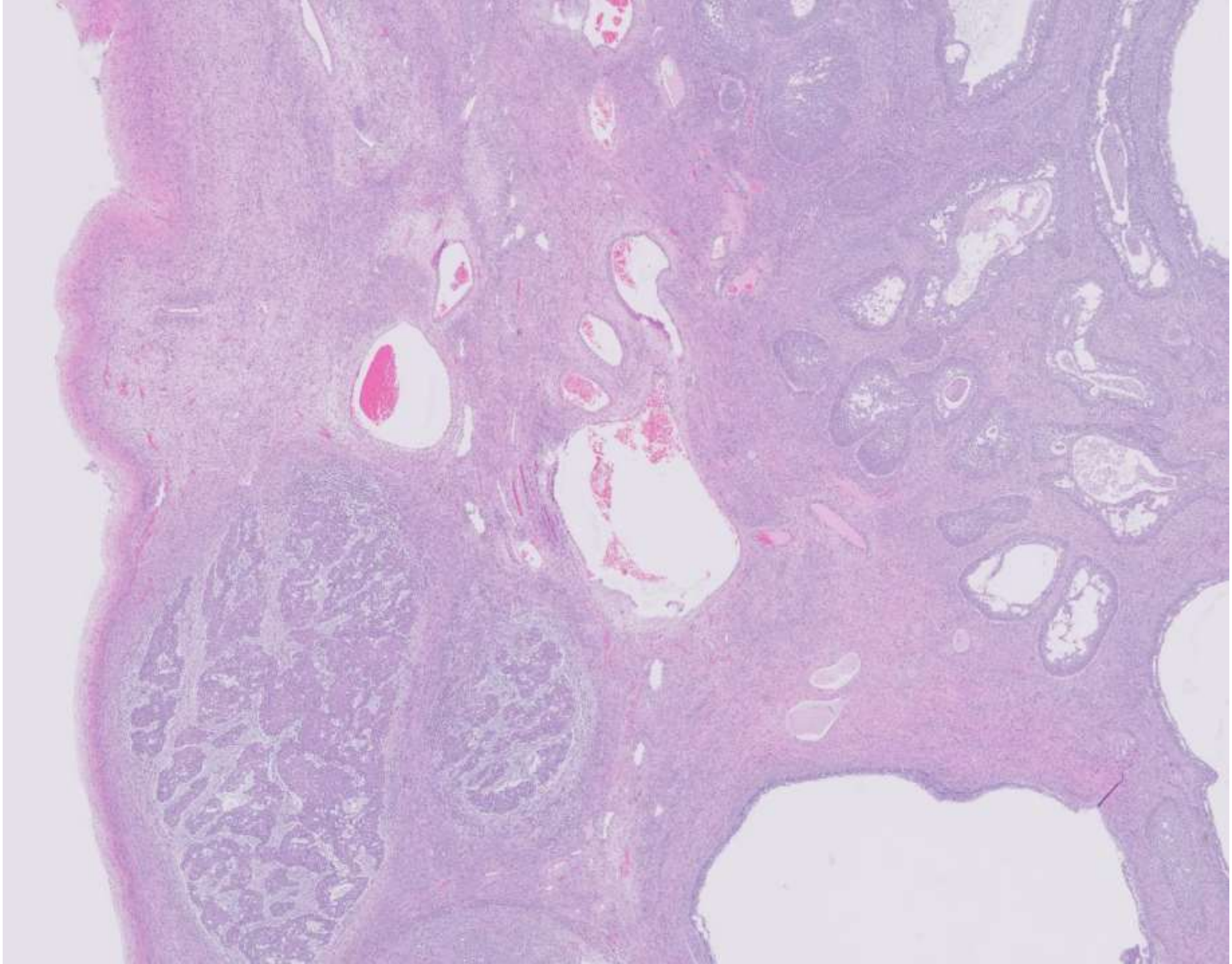


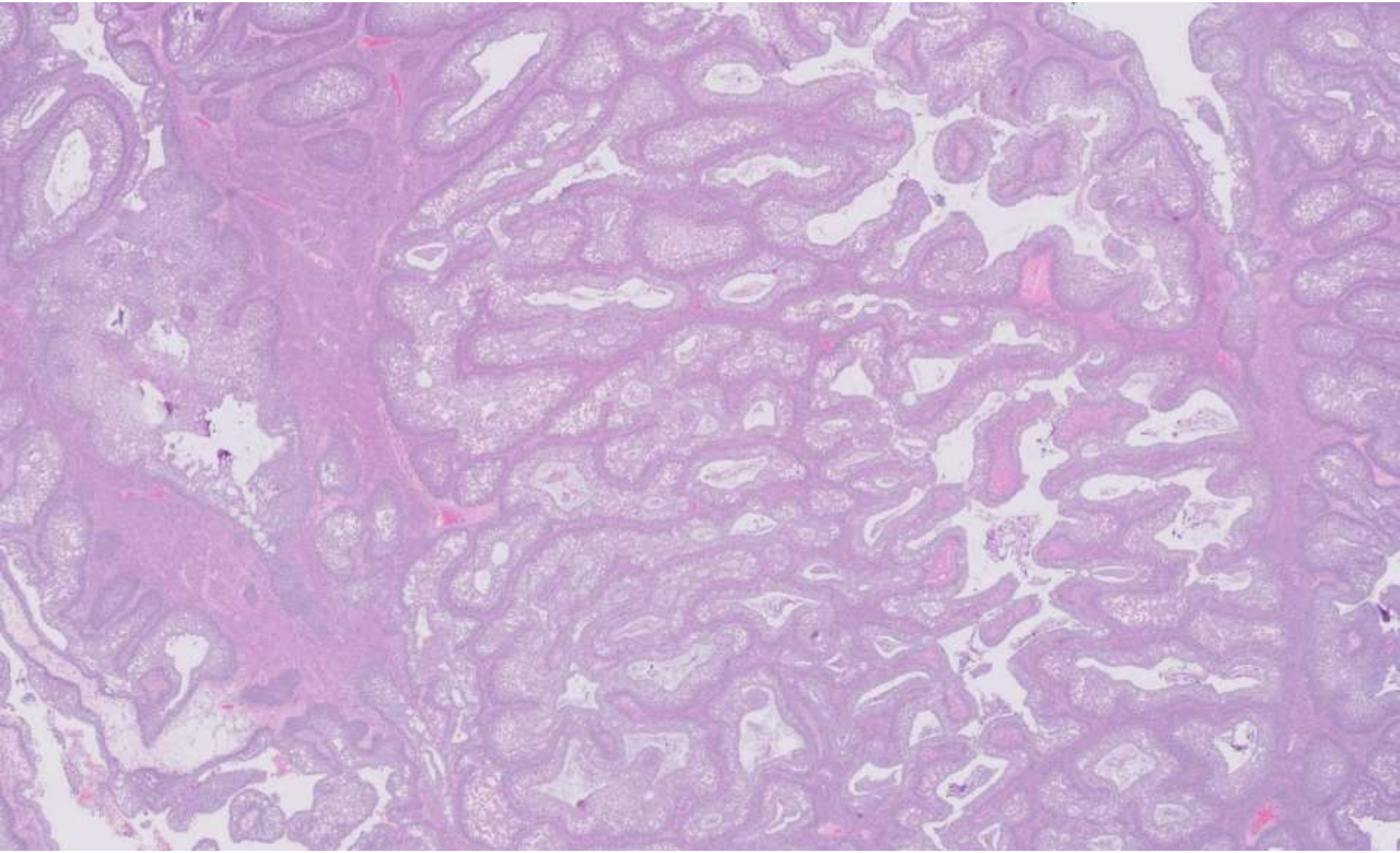


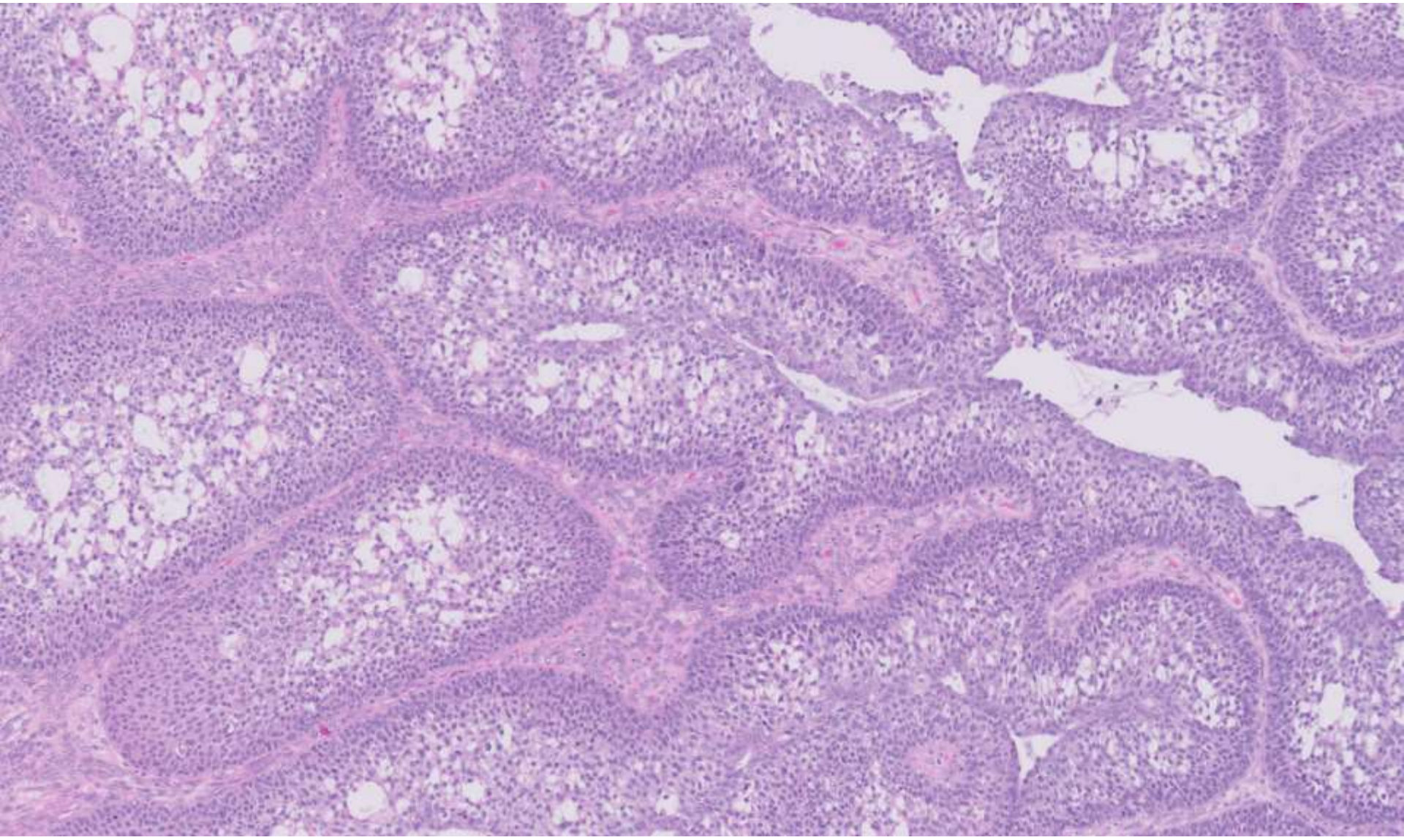
22-0906

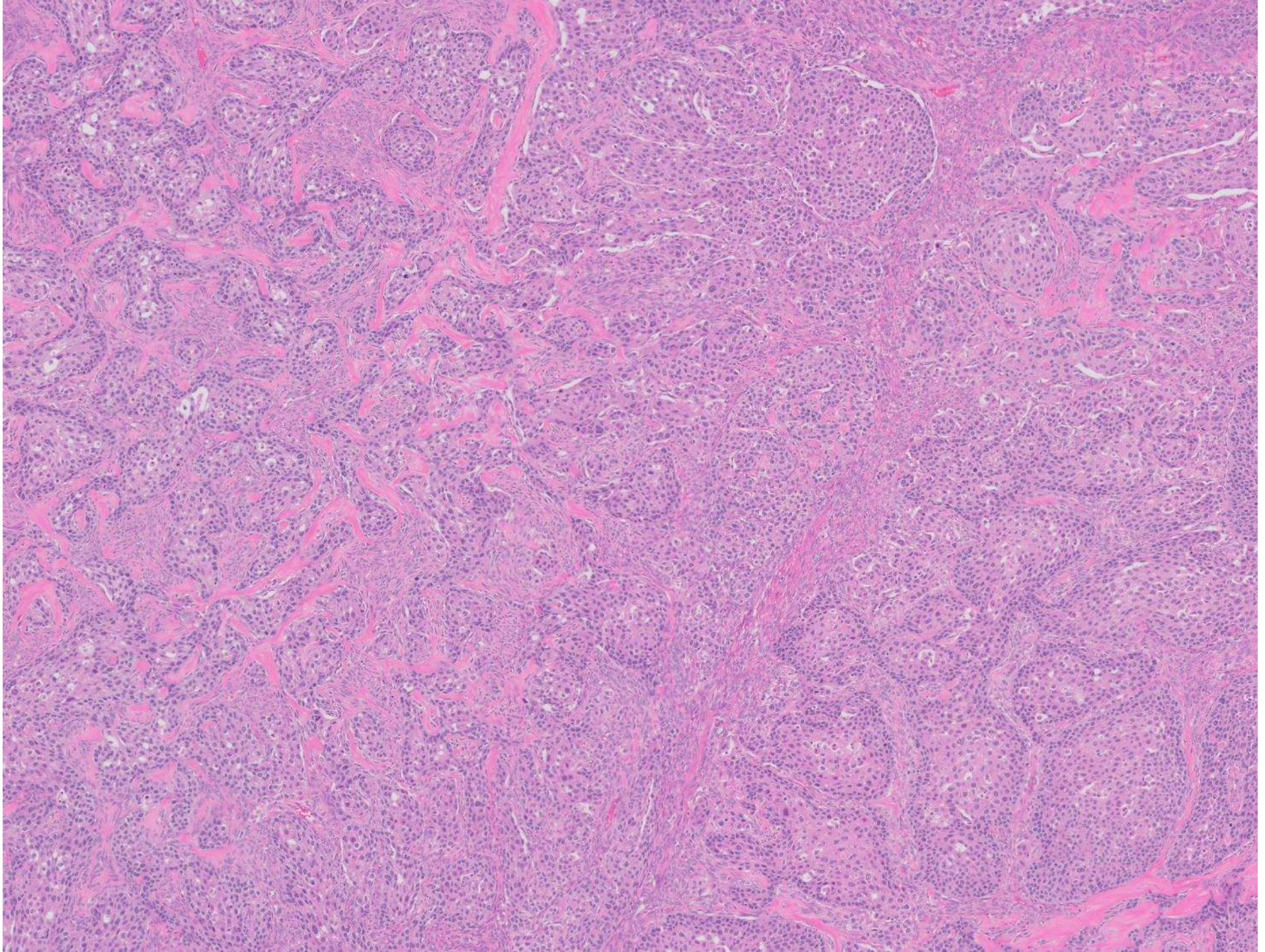
Minami Tokuyama/Brooke Howitt; Stanford

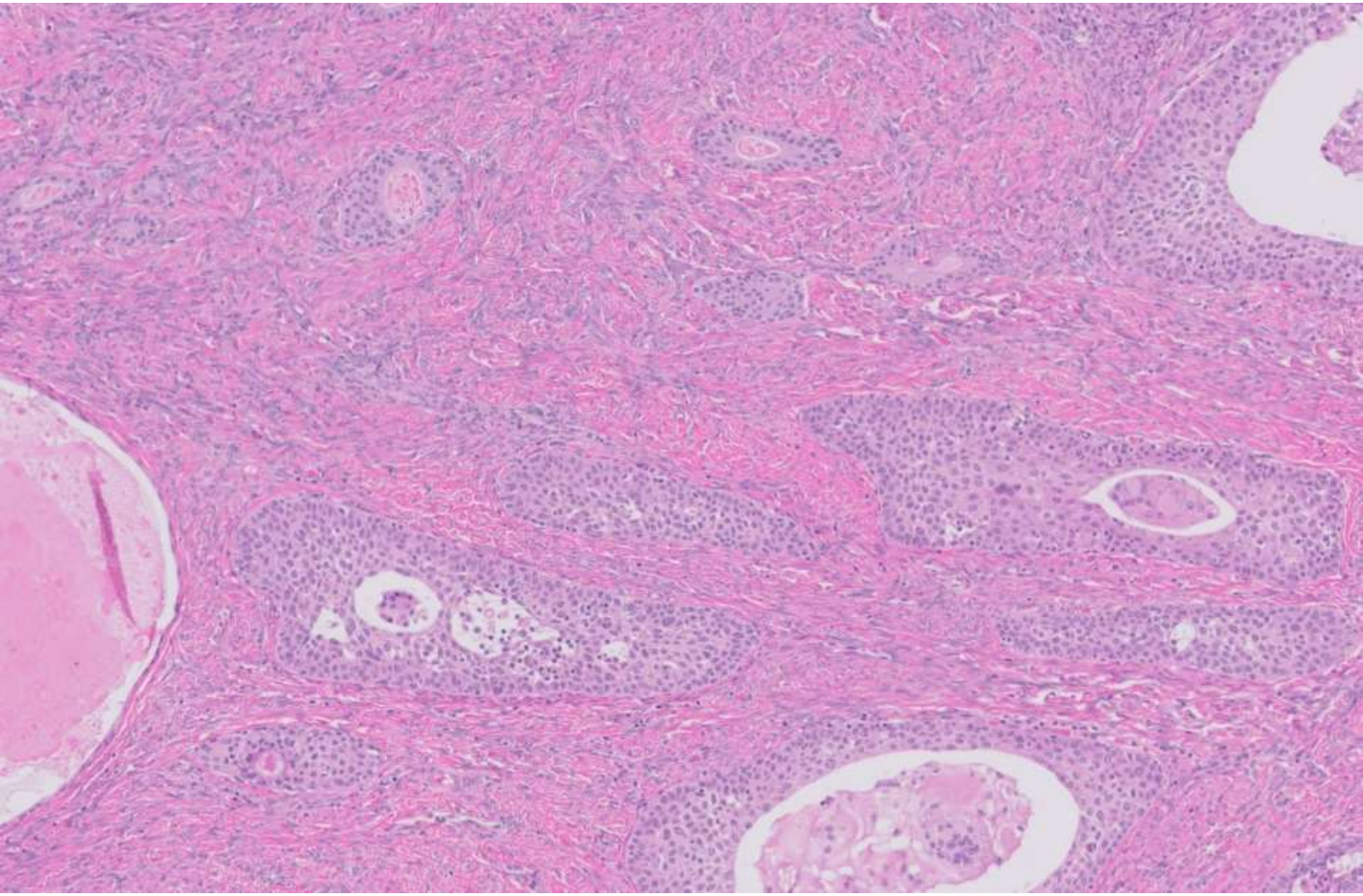
60ish F with 15-20cm complex pelvic mass.

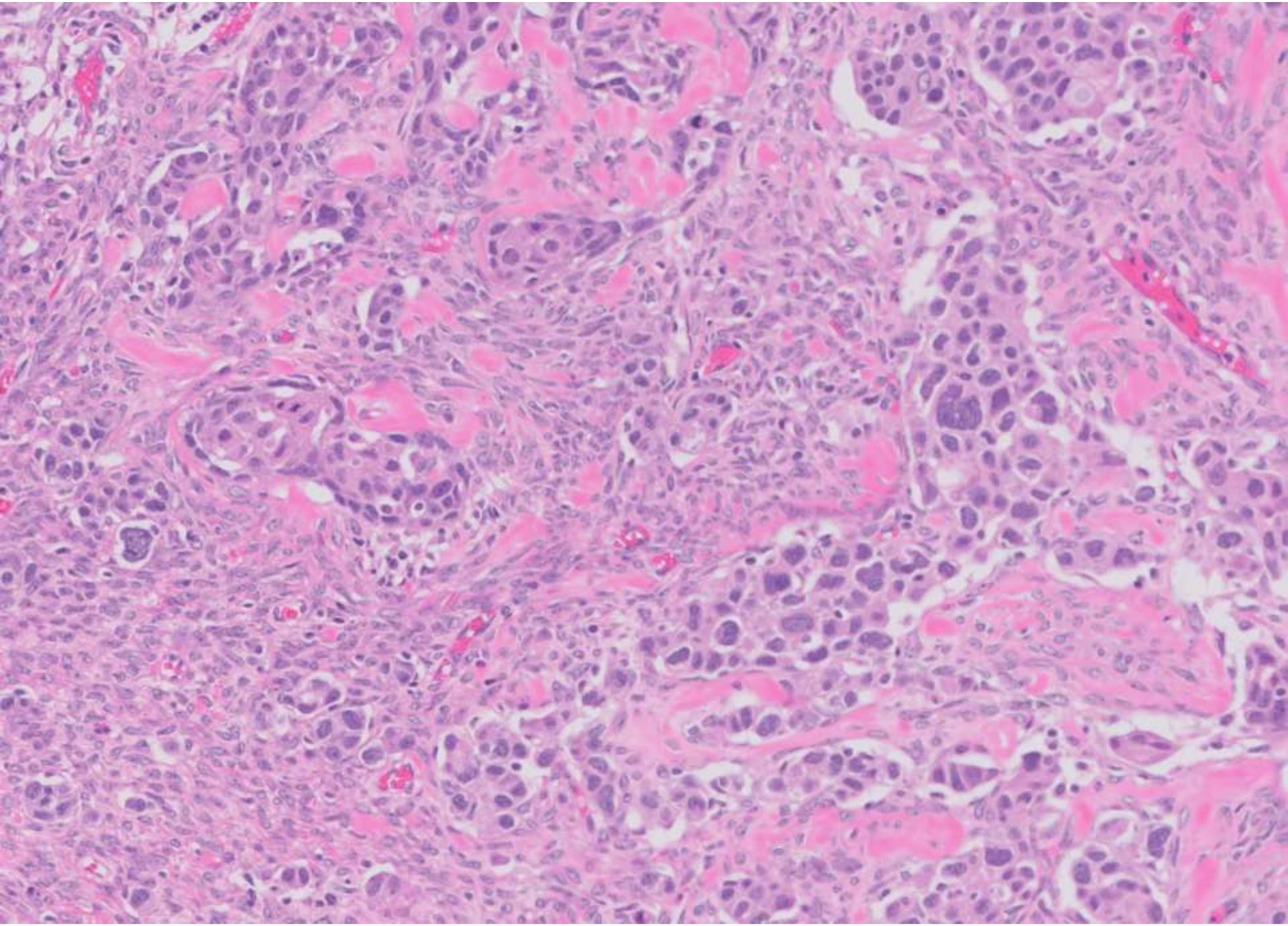






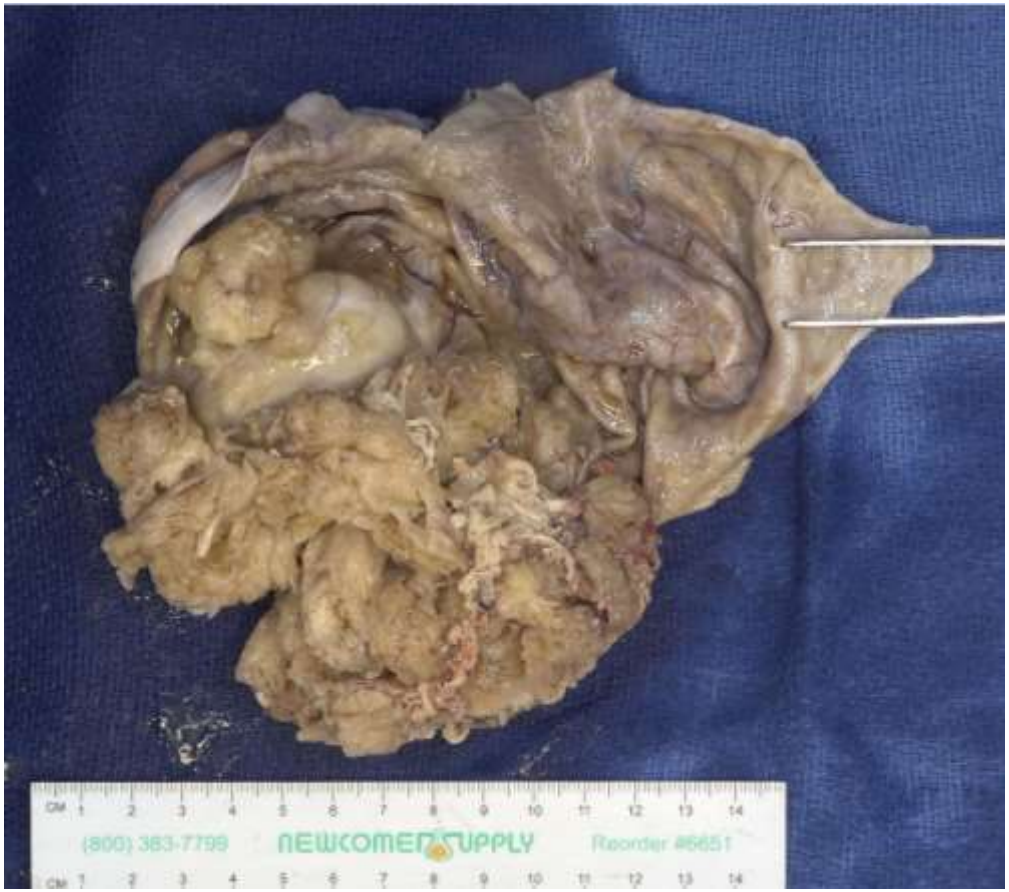






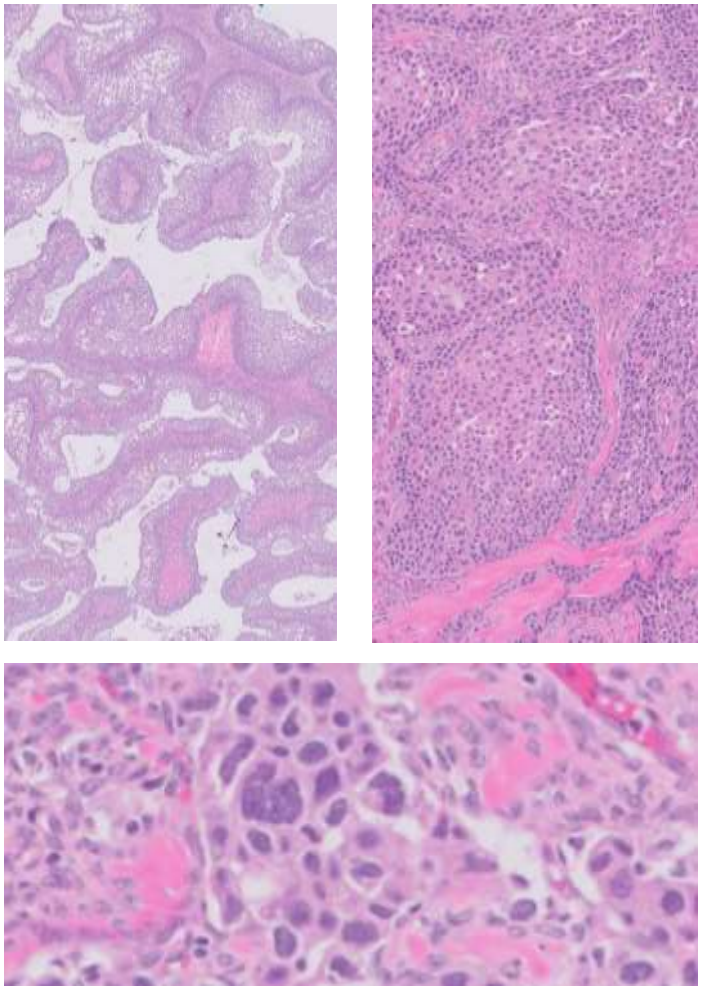
Gross

- Left adnexa weighing 1714g, measuring 19.5 x 16.3 x 10.0cm
- “Firm tan-white tissue with multiple cystic spaces containing green mucoid contents ranging from 0.4-2.0 cm in diameter”



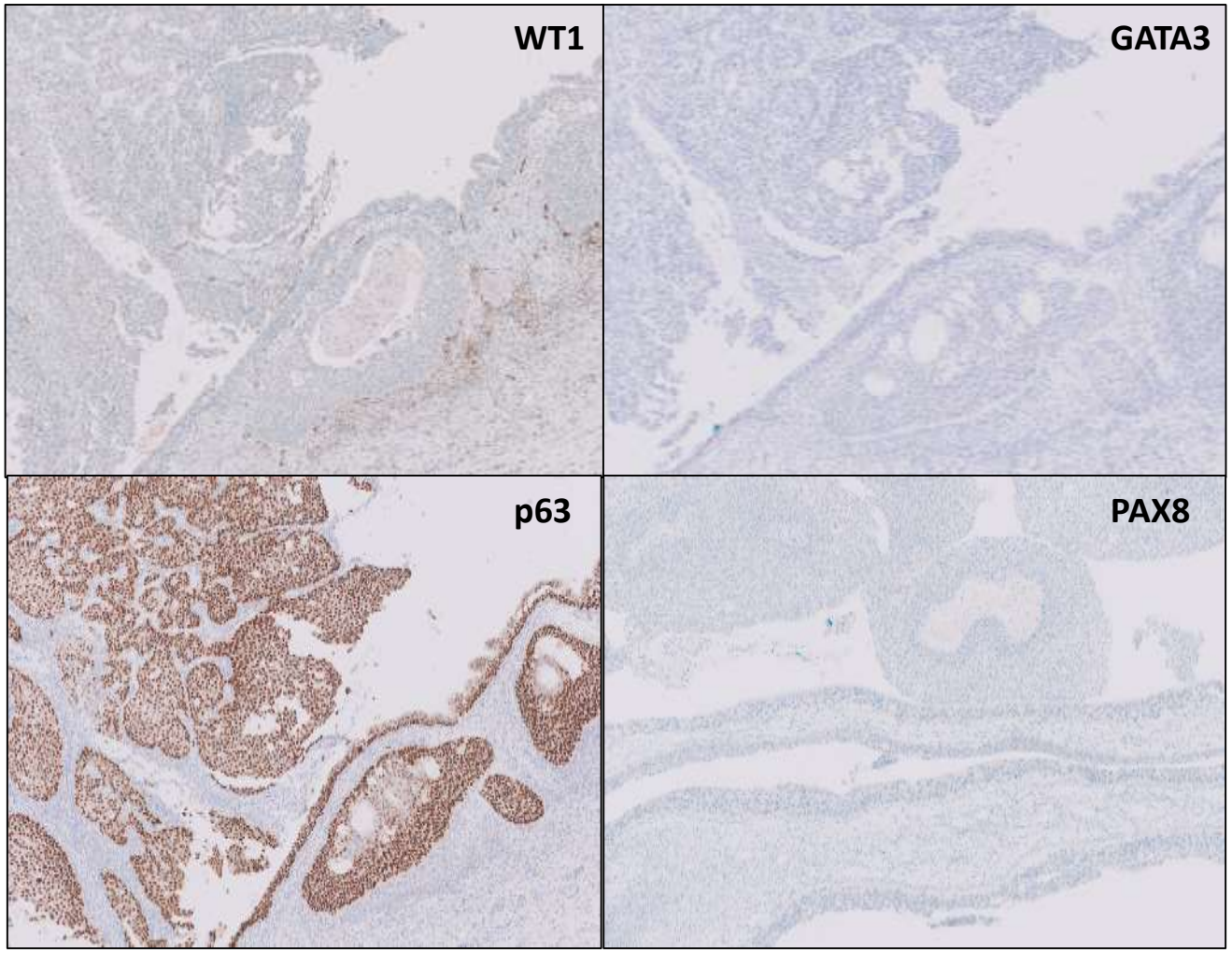
Microscopic

- Transitional- like component and invasive squamoid component
- Malignant Brenner tumors are differentiated from their benign and low-grade counterparts by an invasive growth pattern and high-grade cytology

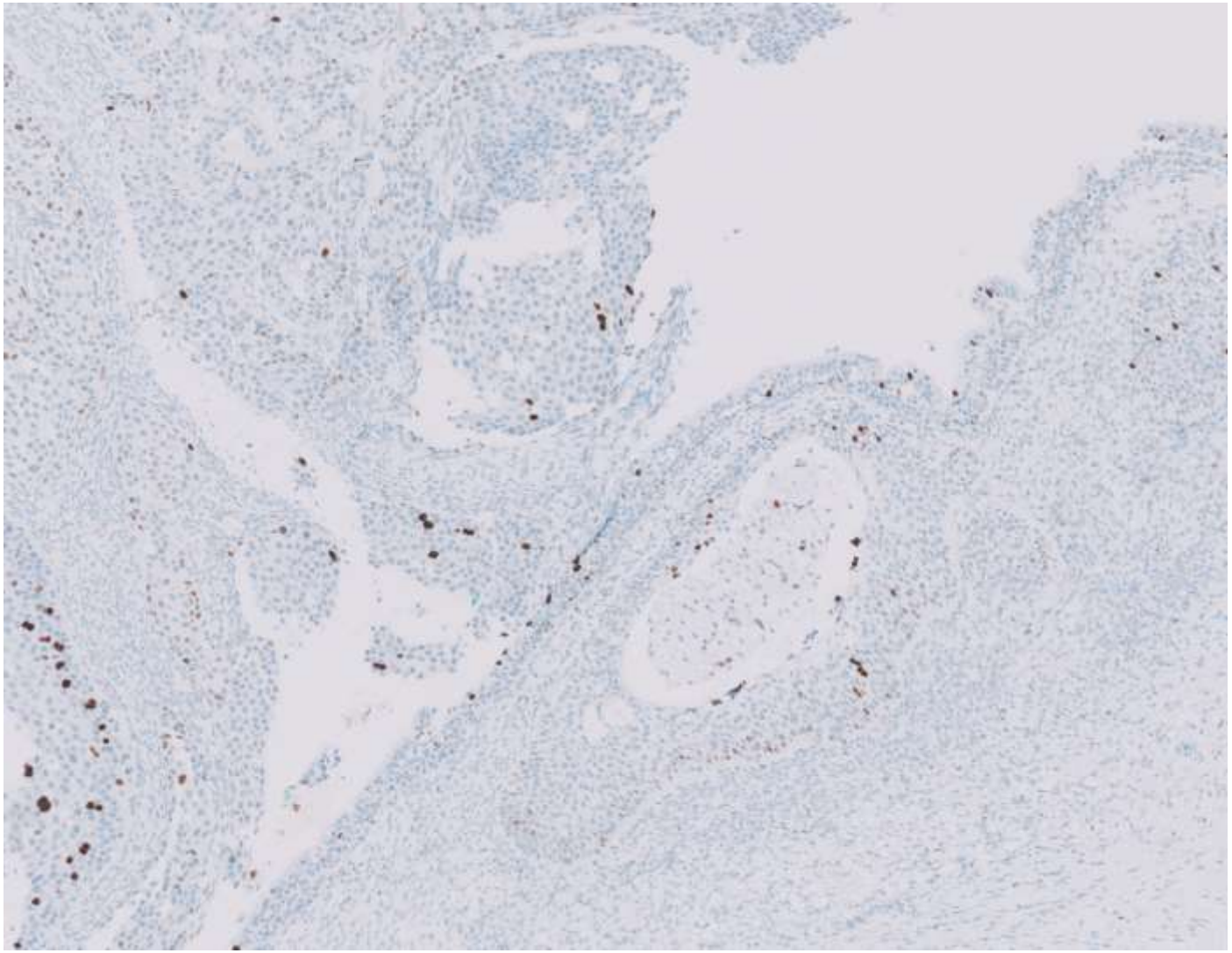


DDX

- “Transitional cell carcinoma”
- Borderline Brenner tumor (BLBT)
- Metastatic papillary urothelial carcinoma
- Endometrioid carcinoma
- Squamous cell carcinoma


WT1
GATA3
p63
PAX8

p53



Immunohistochemistry summary

Antigen	Result
CK7	Positive, negative in areas of squamoid morphology
CK20	Rare positive cells
p63	Positive
PAX8	Negative
p53	Wild type
HPV ISH	Negative
p16	Negative
GATA3	Overall faint with stronger staining in the malignant component
TPRS1	Negative
ER	Negative
PR	Negative
WT1	Negative
MSI	All intact (MSH2, MSH6, PMS2, MLH1)

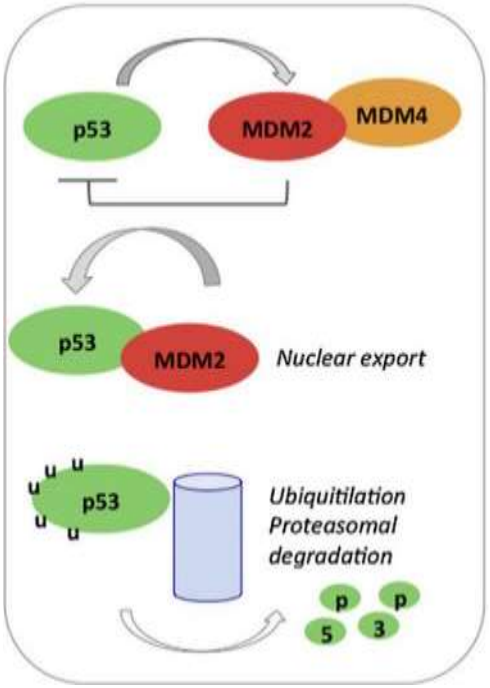
Epidemiology and Clinical Correlates

- Incidence
  - Rare
    - <5% of Brenner tumors
    - <1% of all ovarian tumors
- Clinical
  - Unilateral (90%)
  - Postmenopausal (mean = 65 years)
  - 80% are stage I at diagnosis
    - 5-year survival of 77-94.5% at stage IA

- Cuatrecasas, Miriam, et al. "Transitional cell tumors of the ovary: a comparative clinicopathologic, immunohistochemical, and molecular genetic analysis of Brenner tumors and transitional cell carcinomas." The American journal of surgical pathology 33.4 (2009): 556-567.
- Kurman, R. J., et al. "WHO classification of tumours of the female reproductive organs (IARC WHO Classification of Tumours)." *World Health Organization* (2014): 1-309.
- Nasioudis, Dimitrios, et al. "Malignant Brenner tumors of the ovary; a population-based analysis." *Gynecologic oncology* 142.1 (2016): 44-49.

MDM2 and cell cycle regulation

- MDM2 is a negative regulator of p53
- It binds to p53 resulting in its export from the nucleus and subsequent degradation
- It has been shown to be upregulated in some tumors (sarcomas and breast cancer)
- Has been investigated as potential therapeutic target, particularly in cases with wild type p53



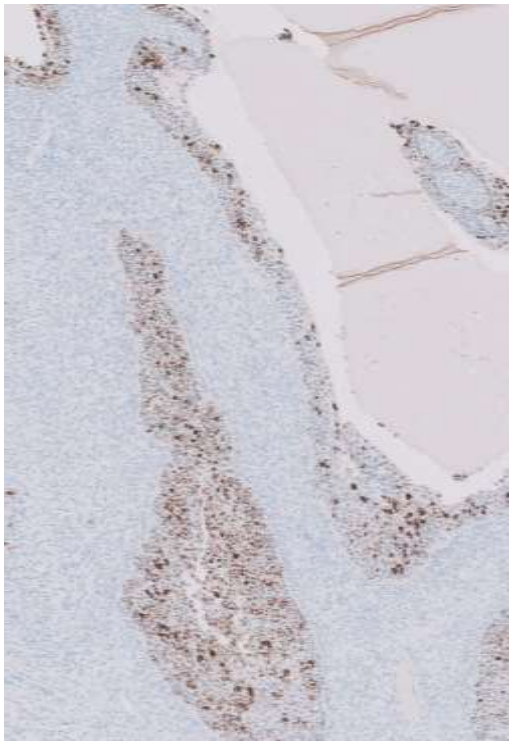
- Burgess, Andrew, et al. "Clinical overview of MDM2/X-targeted therapies." *Frontiers in oncology* 6 (2016): 7.
- Haupt, Ygal, et al. "Mdm2 promotes the rapid degradation of p53." *Nature* 387.6630 (1997): 296-299.
- Urso, Loredana, et al. "Critical review about MDM2 in cancer: Possible role in malignant mesothelioma and implications for treatment." Critical reviews in oncology/hematology 97 (2016): 220-230.

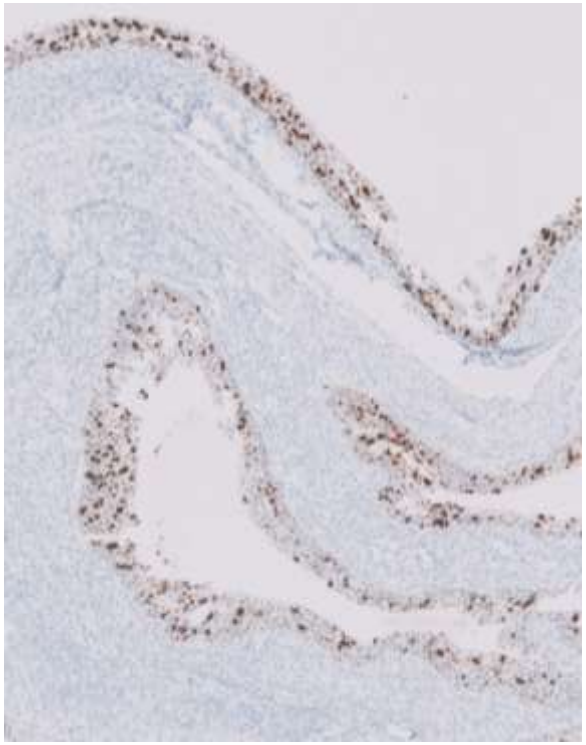
MDM2 and Brenner Tumors

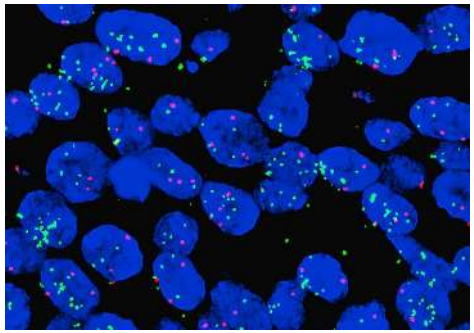
- MDM2 gene amplification was recently detected in malignant Brenner tumors (MBTs), but not ovarian carcinomas with transitional cell histology
- A subsequent study showed this amplification appears specific to MBTs (3/4) while absent in BLBTs (0/3) and benign Brenner tumors (0/26)
  - Positive: diffuse nuclear staining in >25% of cells
  - Equivocal: 10-25% of cells
  - Negative: <10% of cells
  - FISH confirmed amplification in all cases positive by IHC (3/4 MBTs). In cases of equivocal staining (1/4 MBT, 2/3 BLBTs), MDM2 amplification was negative by FISH.
- In the same study, all high-grade serous carcinomas (n=142), ovarian endometroid carcinomas with urothelial-like morphology (n=6) and high-grade urothelial carcinomas (n=49) were negative for MDM2 amplification by IHC using the above thresholds

- Pfarr, Nicole, et al. "Mutational profiles of Brenner tumors show distinctive features uncoupling urothelial carcinomas and ovarian carcinoma with transitional cell histology." *Genes, Chromosomes and Cancer* 56.10 (2017): 758-768.
- Wang, Lucy, Douglas Allison, and Pratibha Sharma Shukla. "Amplification of MDM2 and Loss of p16 expression: do they have a role in malignant transformation of ovarian brenner tumor? A morphologic and immunohistochemical study." *American Journal of Clinical Pathology* 154.1 (2020): 133-141.

MDM2 IHC and FISH







Conclusion

- MDM2 amplification distinguishes malignant Brenner tumors from their low-grade and benign counter parts as well as from non-Brenner malignancies with similar morphology

- MDM2 represents a potential diagnostic tool in cases where the diagnosis is unclear by H&E alone

- MDM2 amplification can be visualized by IHC and can be confirmed by FISH or in cases where the MDM2 IHC is equivocal

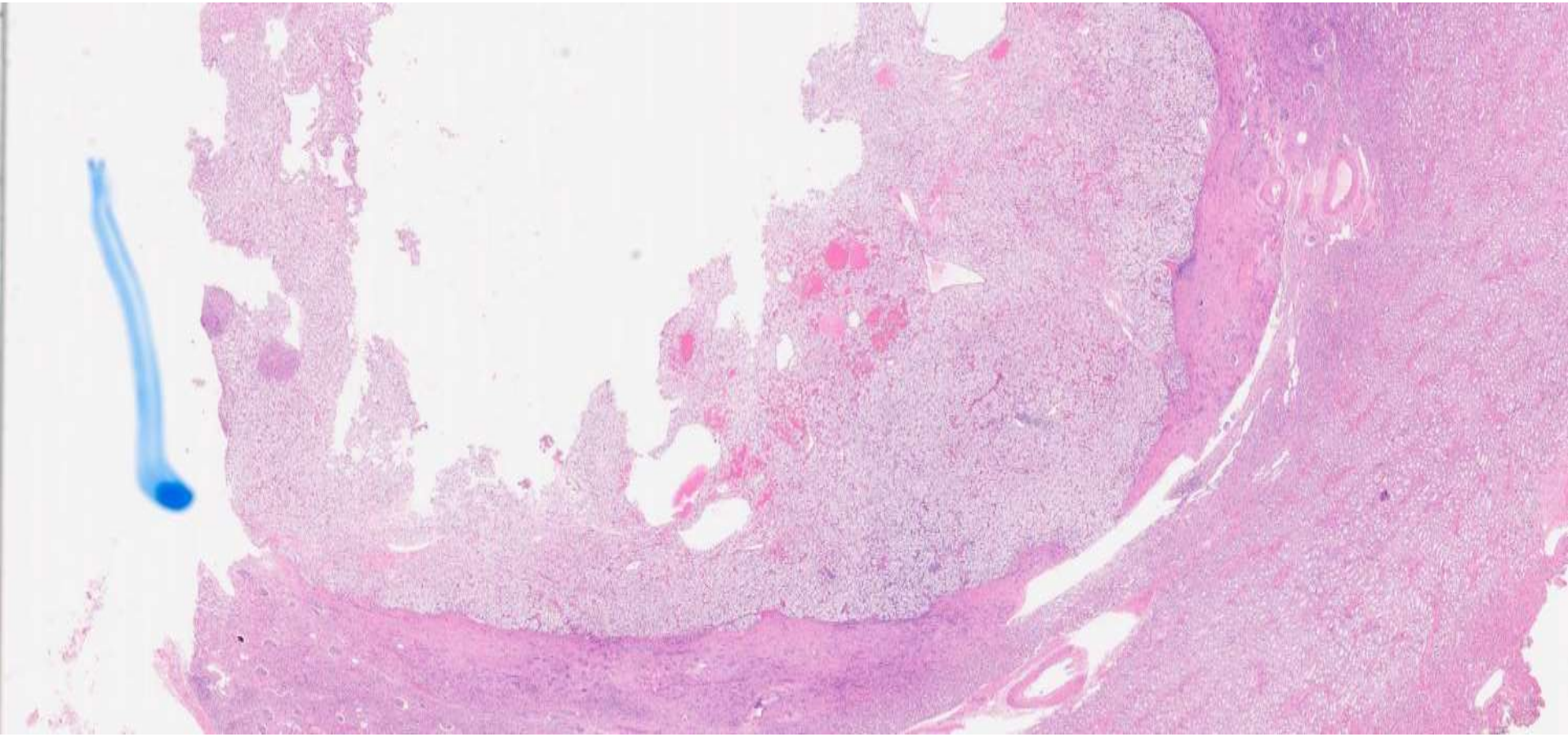
22-0907

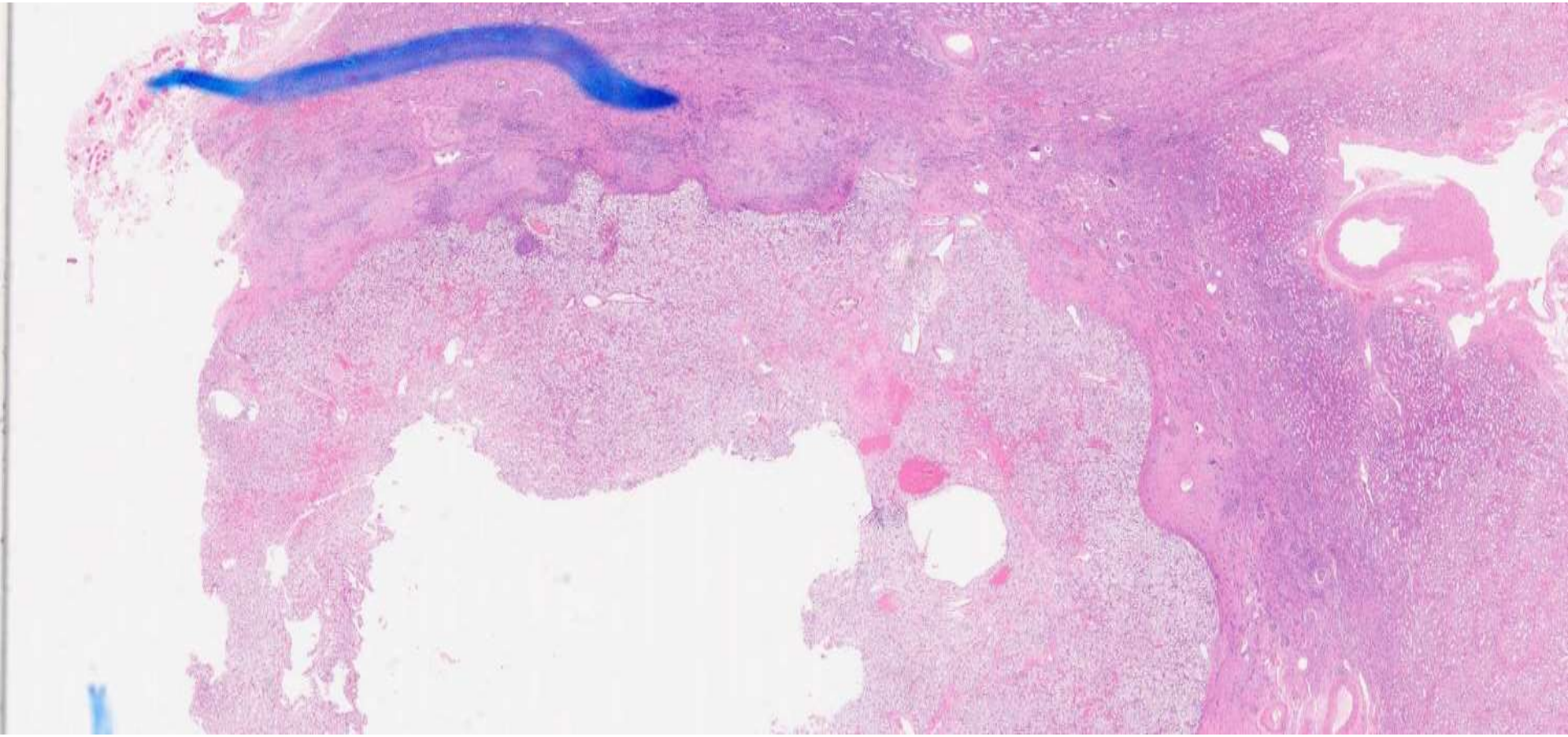
Direct link to scanned slide:

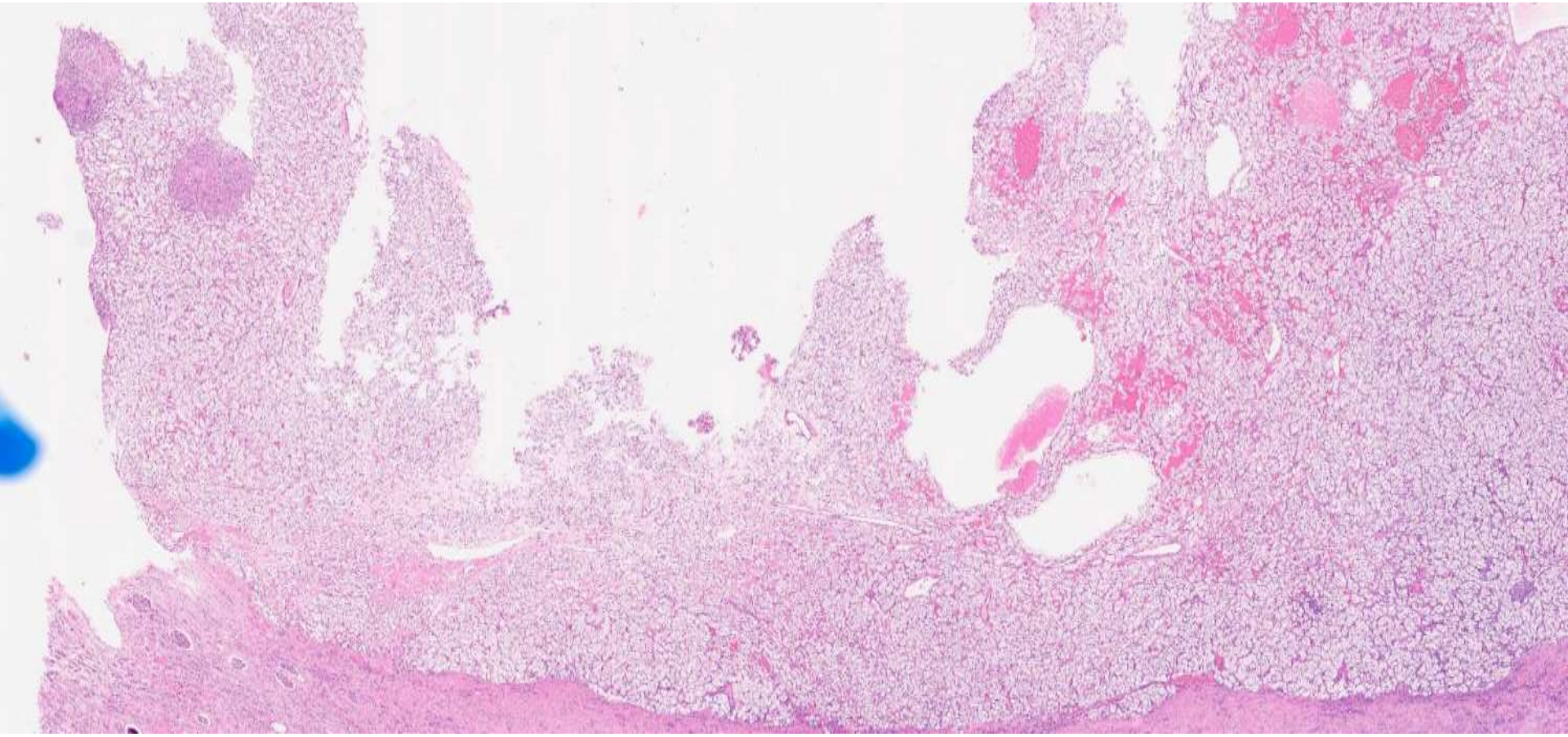
https://pathpresenter.net/public/display?token=d8d12371

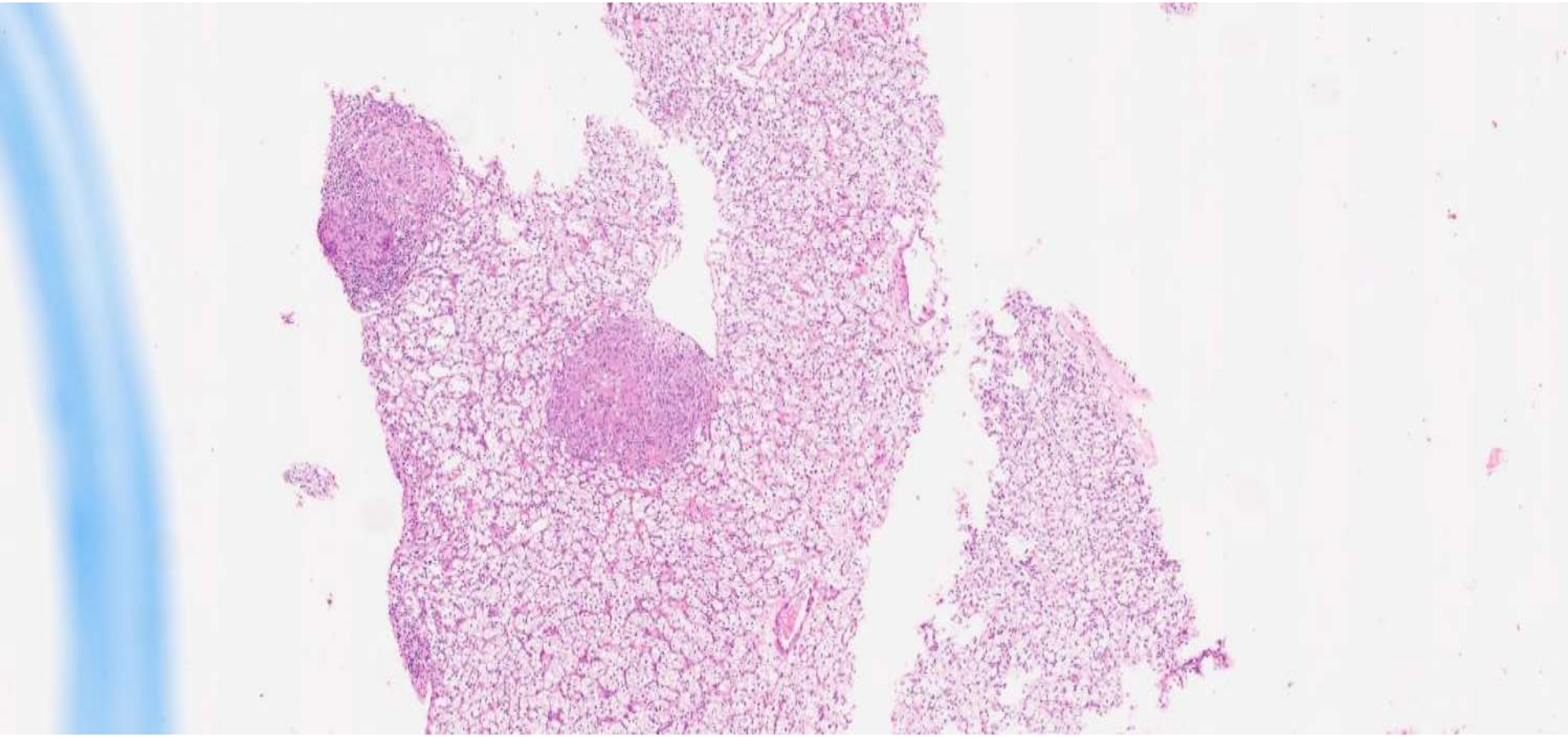
Ankur Sangoi; El Camino Hospital

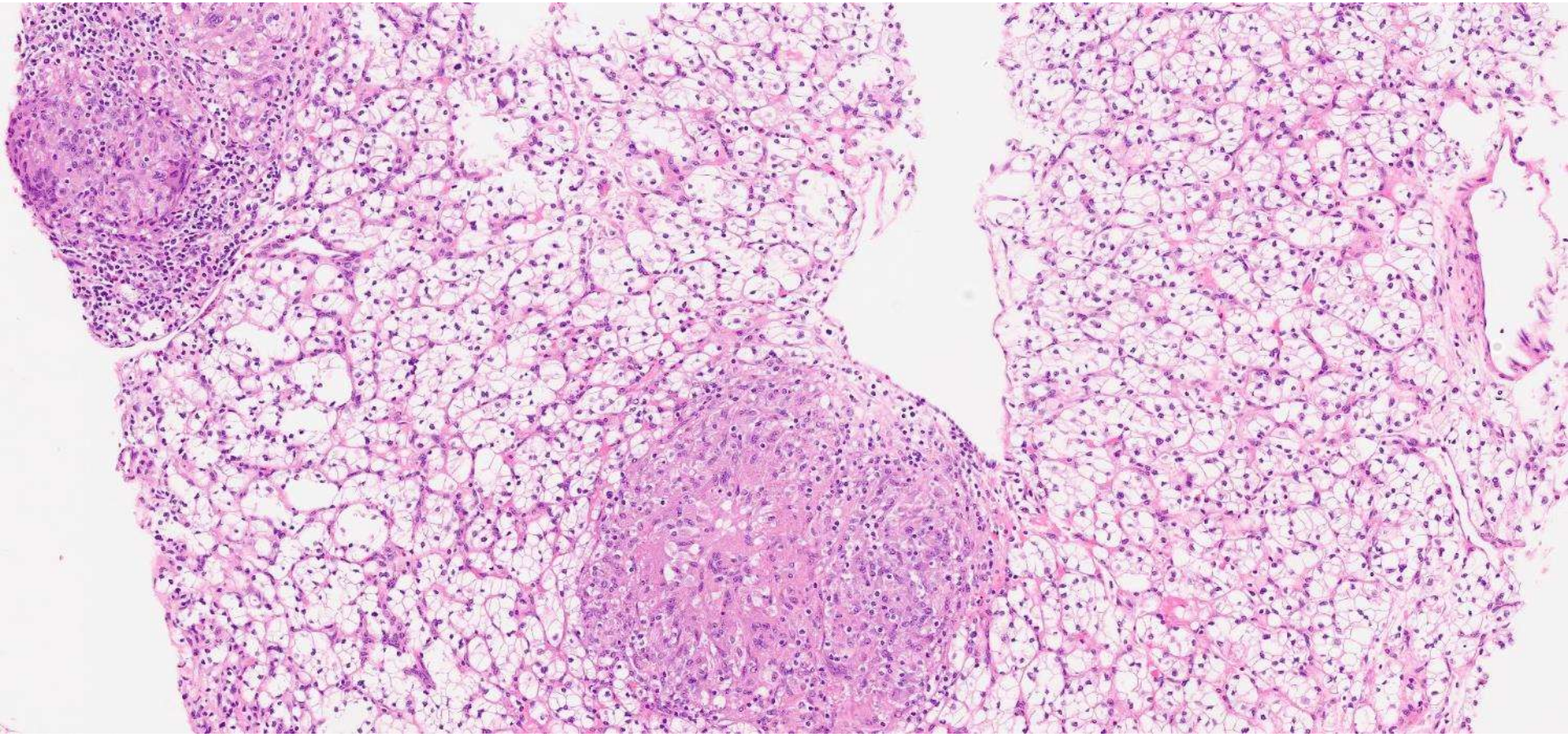
Middle-aged M with 4cm renal mass, nephrectomy.
What is the clinical significance of indicated areas?

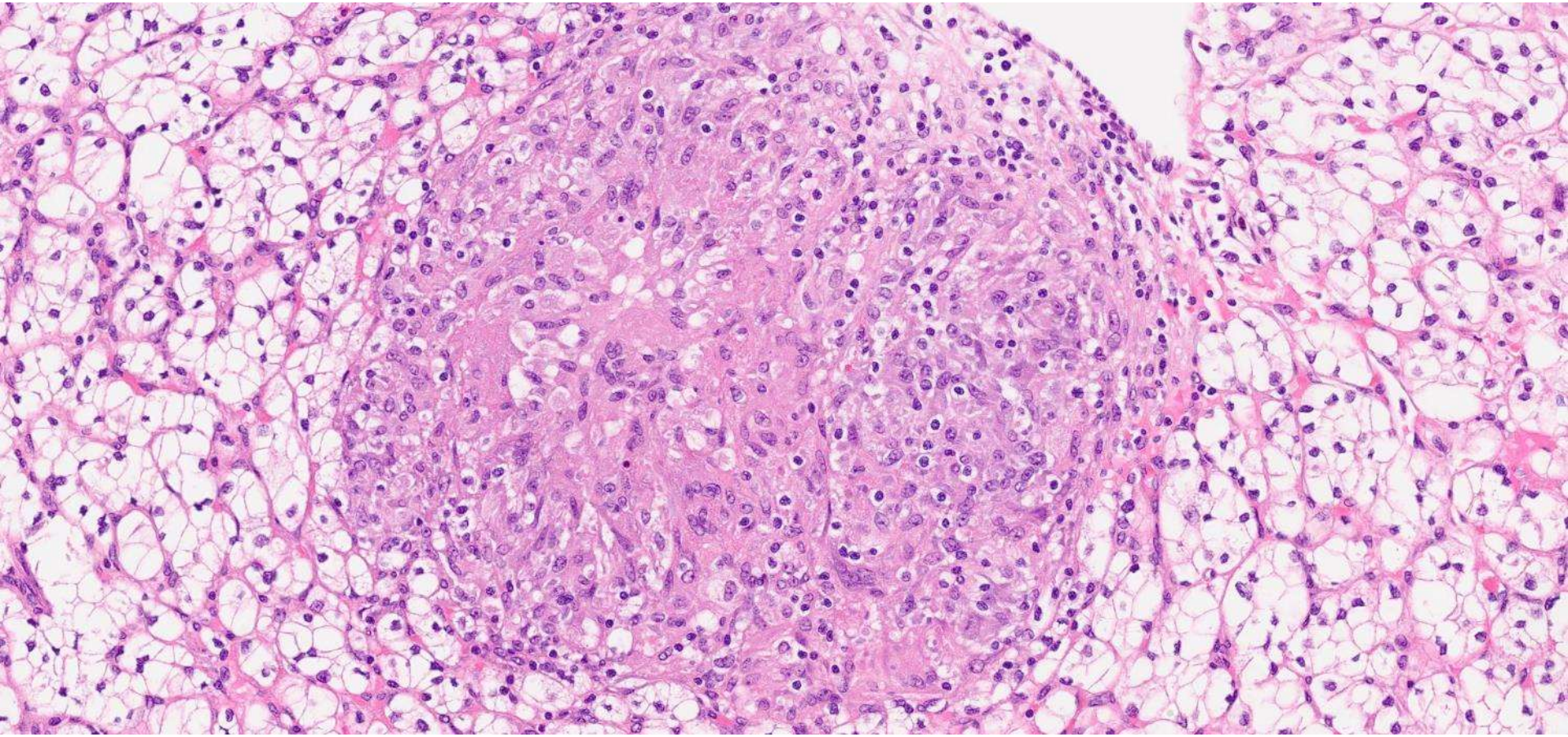


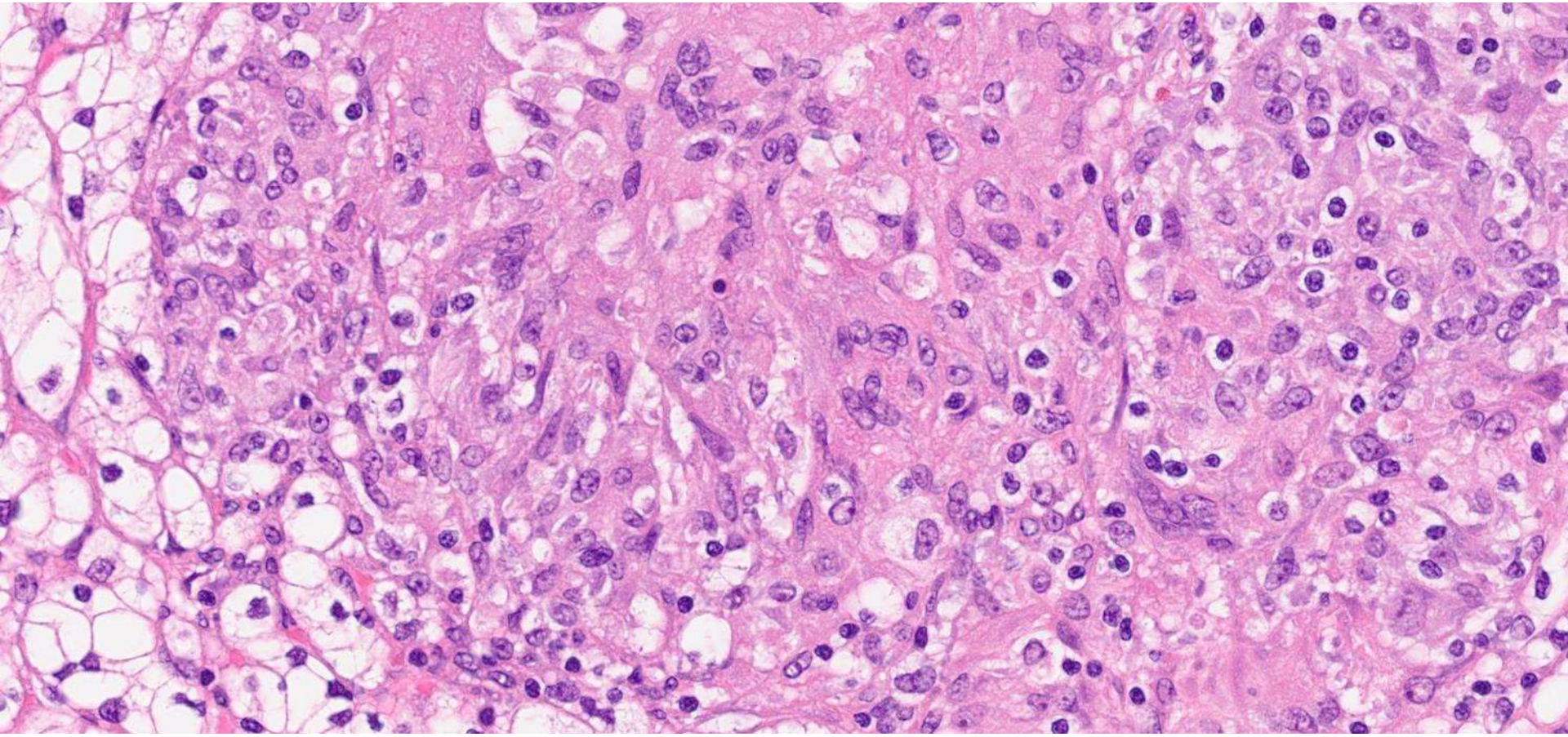


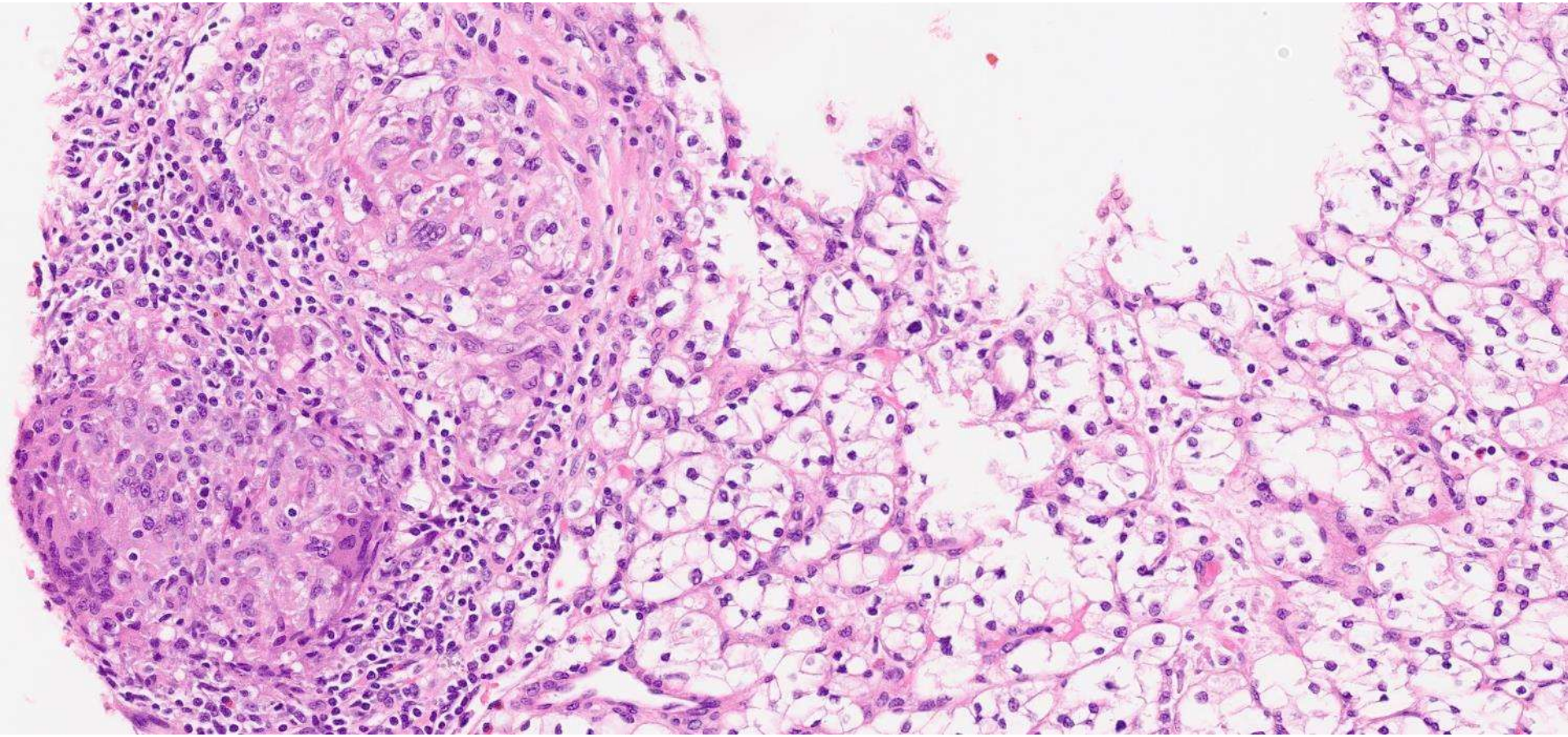


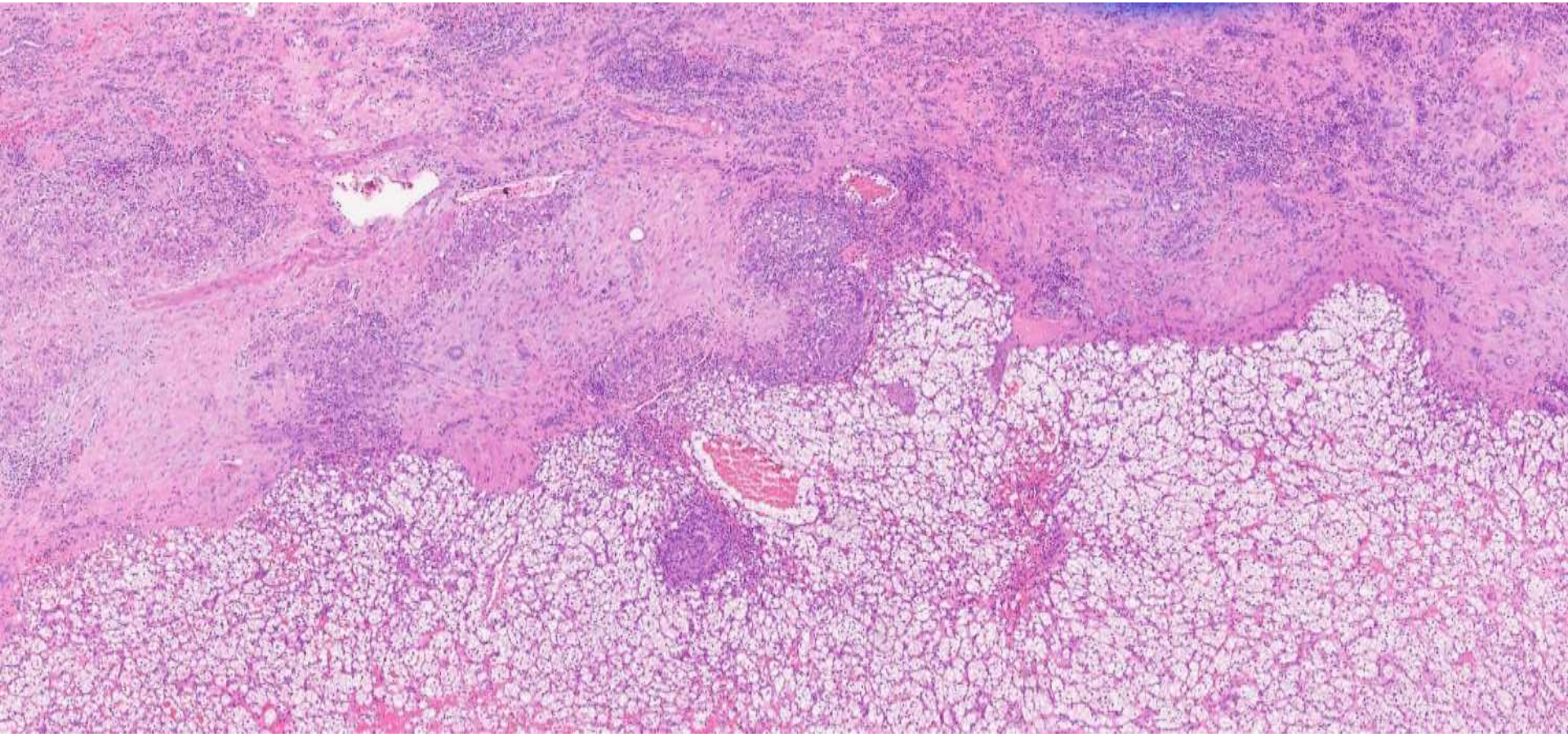


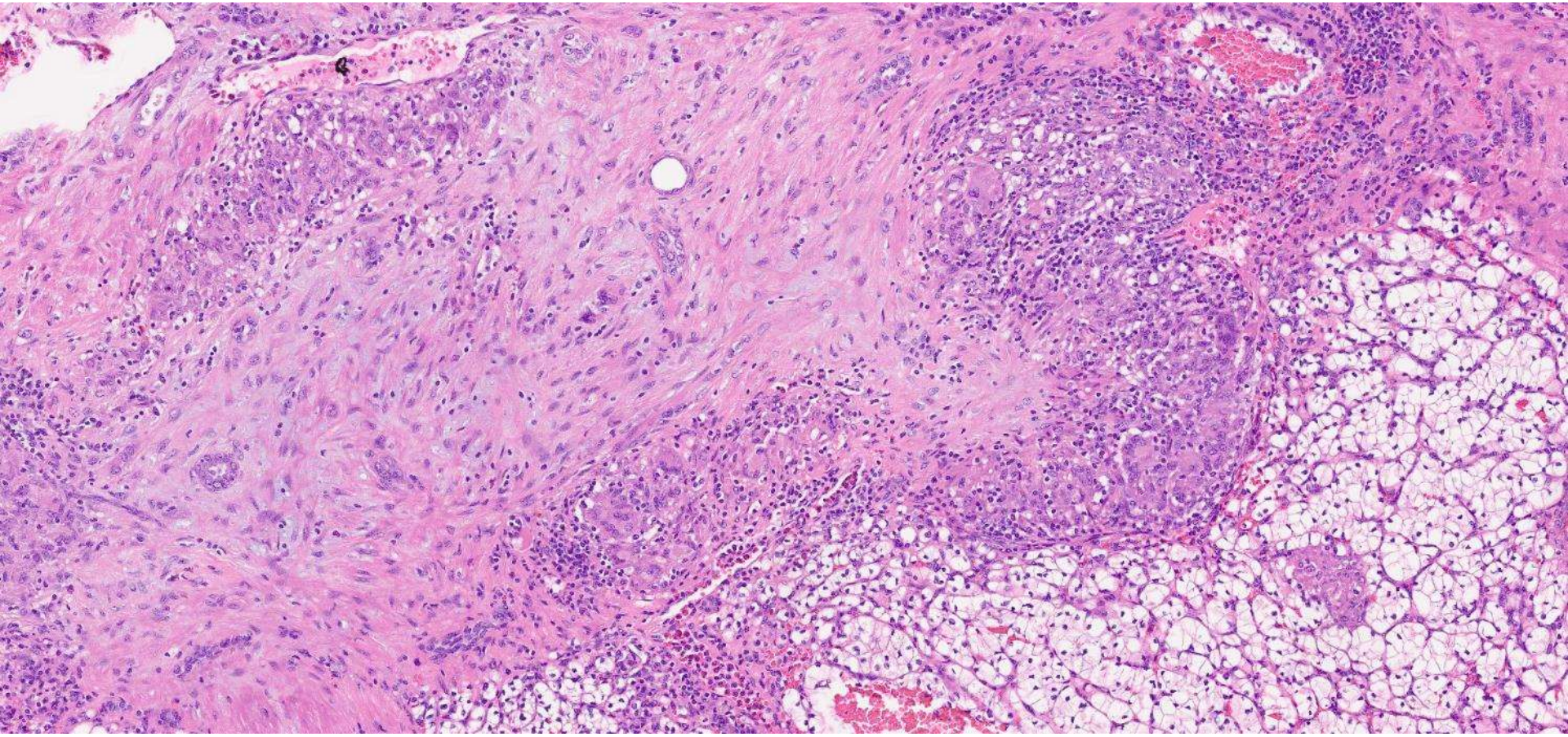


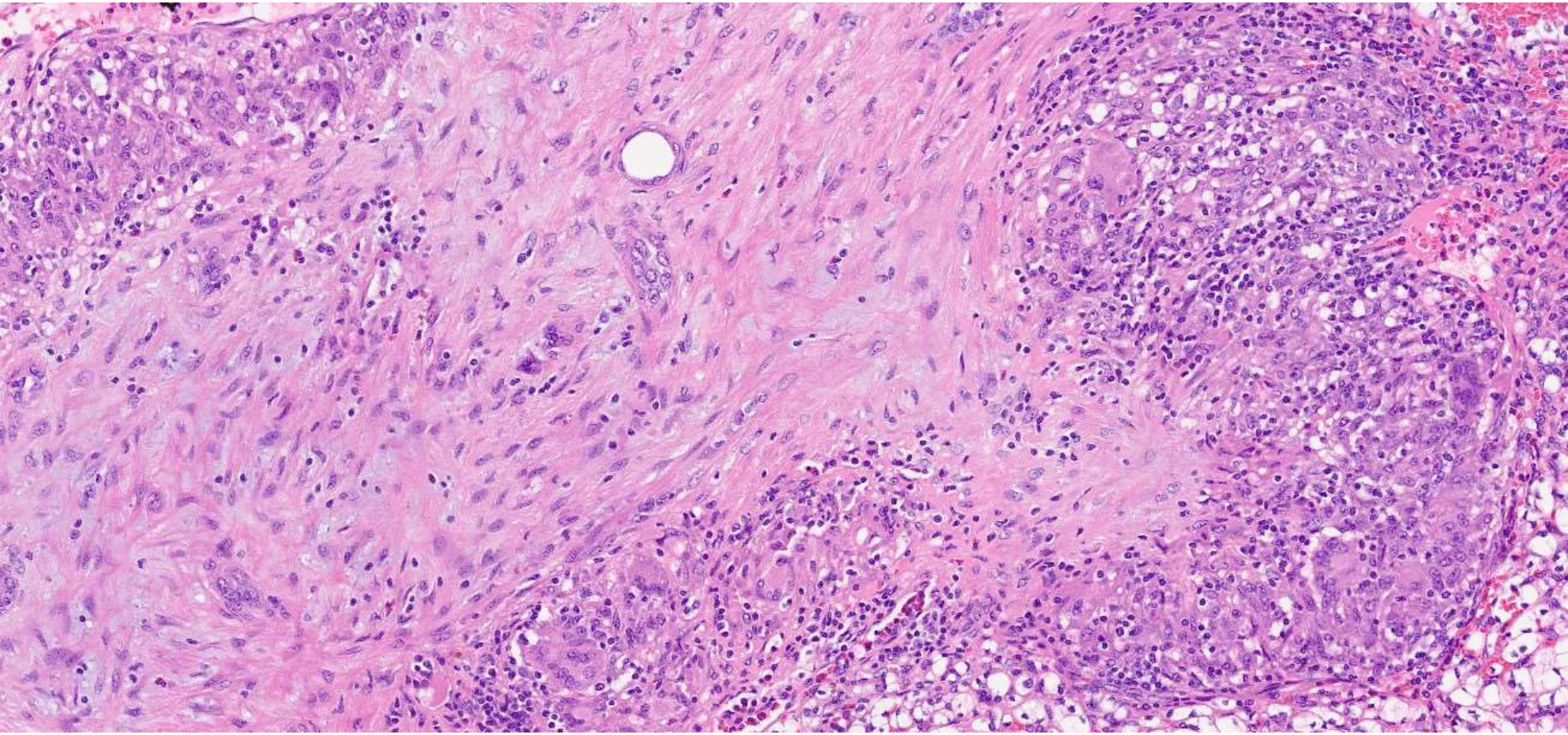






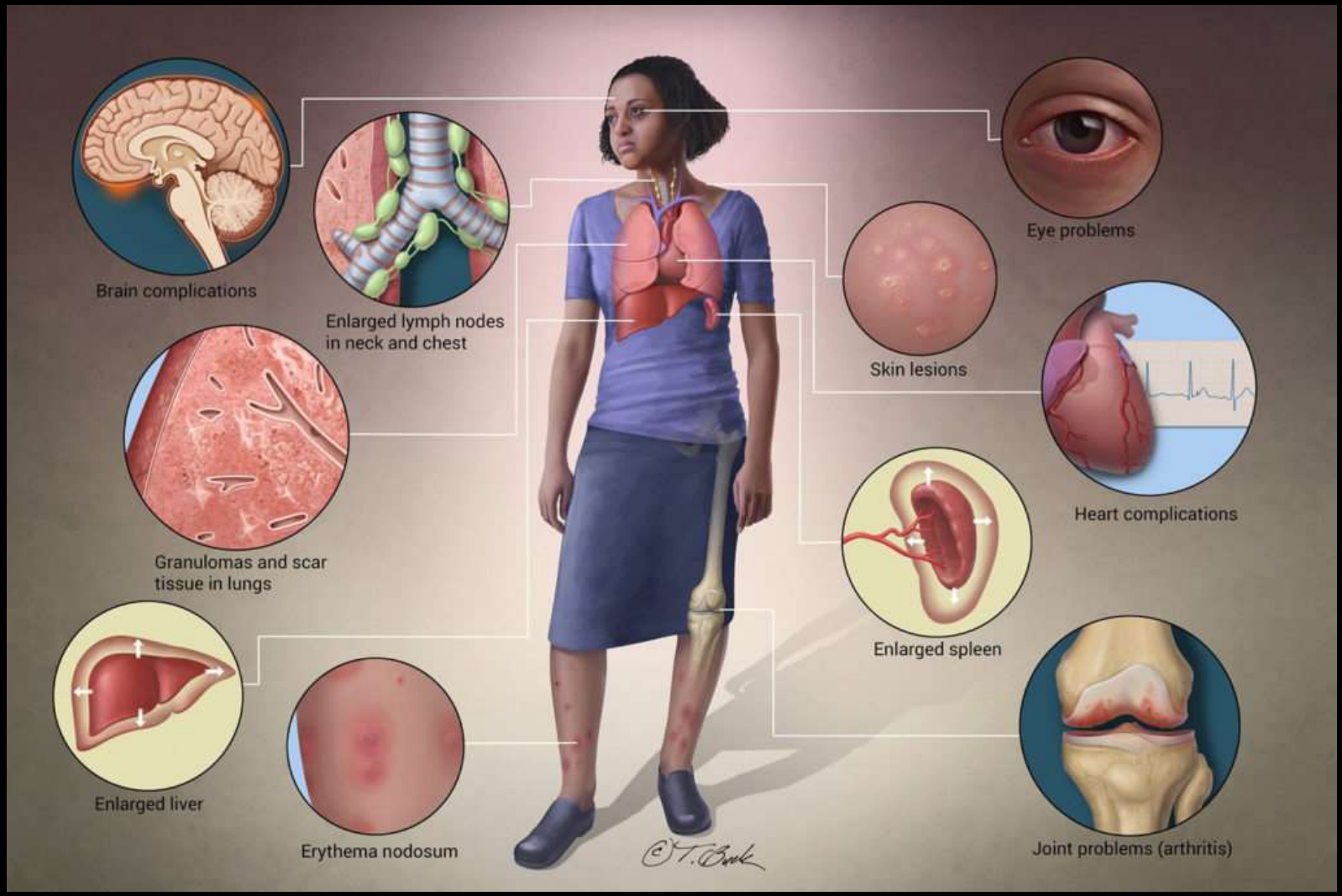






What is the clinical significance of indicated areas?

Is this finding a risk for sarcoidosis or not?



RCC with granulomas: histologic risk factors for sarcoid?

- # of granulomas?
- Size of granulomas?
- Intratumor vs peritumoral granulomas?
- Granulomas +/- with necrosis?

Histopathology

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Granulomas associated with renal neoplasms: A multi-institutional clinicopathological study of 111 cases

Ankur R Sangoi,[1] Fiona Maclean,[2] Sambit Mohanty,[3] Ondrej Hes,[4] Reba Daniel,[5] Priti Lal,[5] Sofia Canete-Portillo,[6] Cristina Magi-Galluzzi,[6] Kristine M Cornejo,[7] Katrina Collins,[8] Michael Hwang,[8] Sara M Falzarano,[9] Mike M Feely,[9] Melad Dababneh,[10] Lara Harik,[10] Maria Tretiakova,[11] Mahmut Akgul,[12] Varsha Manucha,[13] Emily Chan,[14] Chia-Sui Kao,[15] Farshid Siadat,[16] Kanika Arora,[17] Guliz Barkan,[18] Liang Cheng,[8] Michelle Hirsch,[19] Li Lei,[20] Matthew Wasco,[21] Sean R Williamson[22] & Andres M Acosta[19]

[1]*El Camino Hospital, Pathology, Mountain View, CA, USA,* [2]*Department of Anatomic Pathology, Douglass Hanly Moir Pathology, Sonic Healthcare, Macquarie Park, Australia,* [3]*Department of Pathology and Laboratory Medicine, Advanced Medical Research Institute, Bhubaneswar, India,* [4]*Department of Pathology, Charles University Hospital and Medical Facility Plzen, Plzen, Czech Republic,* [5]*Department of Pathology, University of Pennsylvania, Philadelphia, PA, USA,* [6]*Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, USA,* [7]*Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA,* [8]*Indiana University, Pathology, Indianapolis, IN, USA,* [9]*Department of Pathology, Immunology and Laboratory Medicine, University of Florida, Gainesville, FL, USA,* [10]*Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA, USA,* [11]*University of Washington, Department of Laboratory Medicine and Pathology, Seattle, WA, USA,* [12]*Department of Pathology and Laboratory Medicine, Albany Medical Center, Albany, NY, USA,* [13]*Department of Pathology, University of Mississippi Medical Center, Jackson, MS, USA,* [14]*Department of Pathology, University of California San Francisco, San Francisco, CA, USA,* [15]*Stanford Medical Center, Stanford, CA, USA,* [16]*Department of Pathology and Laboratory Medicine, Cumming School of Medicine,University of Calgary, Calgary, AL, Canada,* [17]*Department of Pathology, Henry Ford Hospital, Detroit, MI, USA,* [18]*Loyola University Healthcare Center, Department of Pathology, Maywood, IL, USA,* [19]*Department of Pathology, Brigham and Women's Hospital,Harvard Medical School, Boston, MA, USA,* [20]*Department of Pathology and Laboratory Medicine, University of California Davis Health System, Sacramento, CA, USA,* [21]*St Joseph Mercy Hospital, Ann Arbor, MI, USA, and* [22]*Department of Pathology, Cleveland Clinic, Cleveland, OH, USA*

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Table 1. Previously published studies of granulomas associated with renal neoplasms

Study	No. of cases	Renal tumour(s)	Renal tumour subtype(s)	Distribution of granulomas	Sarcoidosis*
Campbell *et al.*	1	RCC	Clear cell RCC	Intratumoral	None
Bottone *et al.*	1	RCC	Clear cell RCC	Peritumoral	1/1 (100%)
Marinides *et al.*	1	RCC	Papillary RCC	Peritumoral	None
Hes *et al.*	3	RCC	Clear cell RCC	Intratumoral	None
Kovacs *et al.*	1	RCC	Clear cell RCC	Intratumoral/peritumoral	None
Piscioli *et al*	1	RCC	Clear cell RCC	Peritumoral	None
Narasimhaiah *et al.*	3	RCC	Clear cell RCC	Intratumoral	None
Ouellet *et al.*	1	RCC	Clear cell RCC	Peritumoral	None
Burhan *et al.*	1	RCC	Clear cell RCC	Intratumoral	None
Khatua *et al.*	1	RCC	Clear cell RCC	Peritumoral	None
Arora *et al.*	11	RCC	Clear cell RCC (n = 10),	Intratumoral/peritumoral	1/11 (11%)
			Clear cell papillary RCC (n = 1)		
Majeed *et al.*	2	RCC	Clear cell RCC (n = 1),	Intratumoral/peritumoral	2/2 (100%)
		MCNLMP	MCNLMP (n = 1)		
Tarjan *et al.*	1	AML	AML	Unknown†	None
Current study	111	RCC, MEST, oncocytoma	Clear cell RCC (n = 95), papillary RCC (n = 9),	Intratumoral/peritumoral	11/111 (10%)‡
			Chromophobe RCC (n = 3), clear cell papillary RCC (n = 2), MEST (n = 1), oncocytoma (n = 1)		

Granulomas associated with renal tumors

- **111 cases (57 partial, 54 radical)**
  - Wide age range, mixed M/F gender
- **Usually CC-RCC (86%)**
  - Can occur in benign renal tumors as well
- **10% had associated sarcoidosis**
  - 5% diagnosed after nephrectomy finding of granulomas
- **Wide range of # and size of granulomas per case**
  - Can be peri OR intratumoral
- **14% had necrosis**
  - Not specific for sarcoidosis association
- **14% had prior procedure**
- **7% had prior chemo or immunotherapy**

Take home points

- **peri/intratumoral granulomas associated with renal neoplasms may be more common than initially perceived**
- **Extent of granulomatous inflammation can vary widely**
  - +/- have necrosis
  - possible etiologies include prior procedure or immunotherapy/chemotherapy
- **Although a clinical association with sarcoidosis is infrequent it can still occur**
  - warrants mentioning in pathology reports

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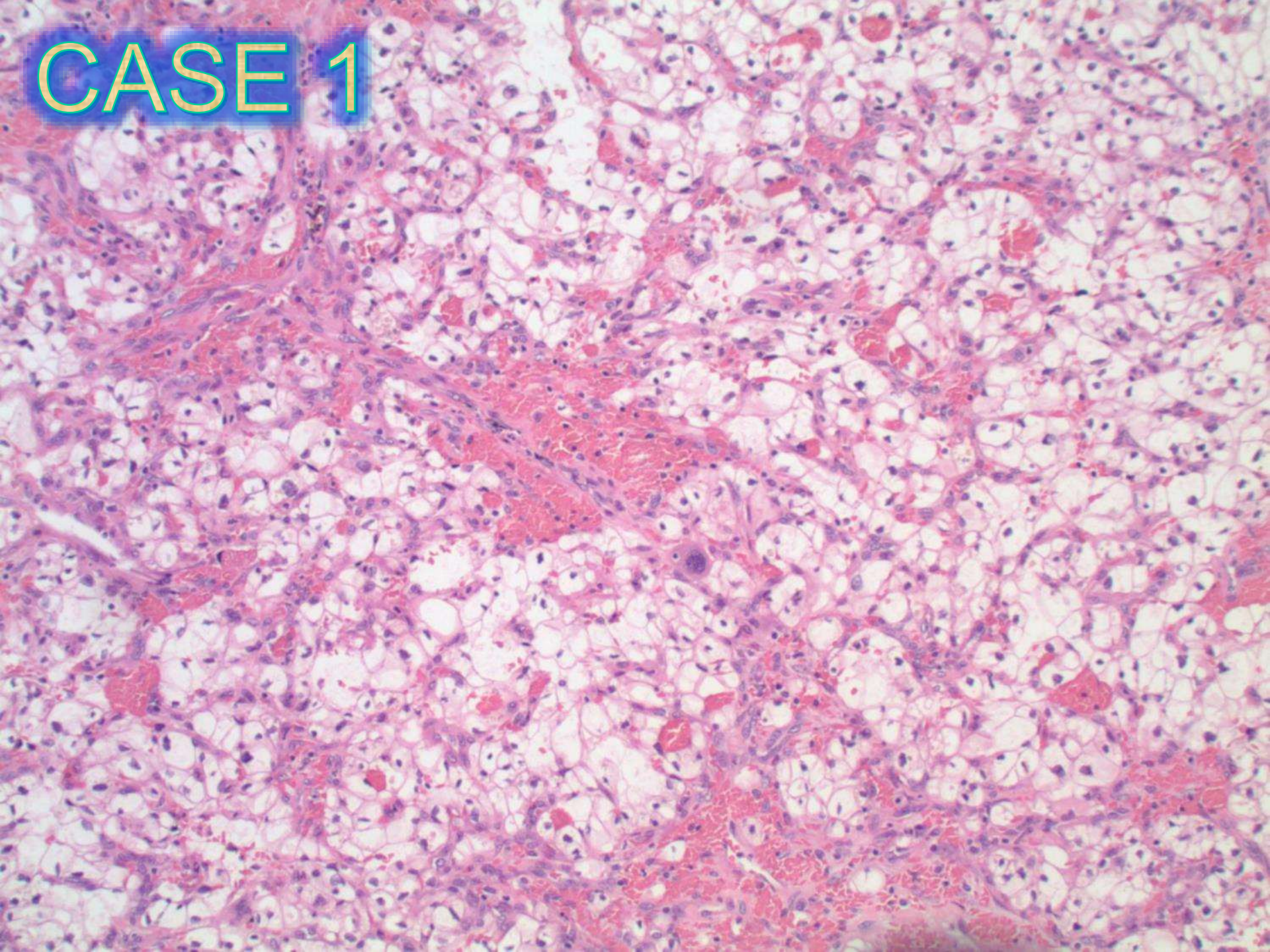
Ankur Sangoi; El Camino Hospital

Sections from 2 different renal masses shown from 2 different nephrectomies. What nuclear grade would you render for each case?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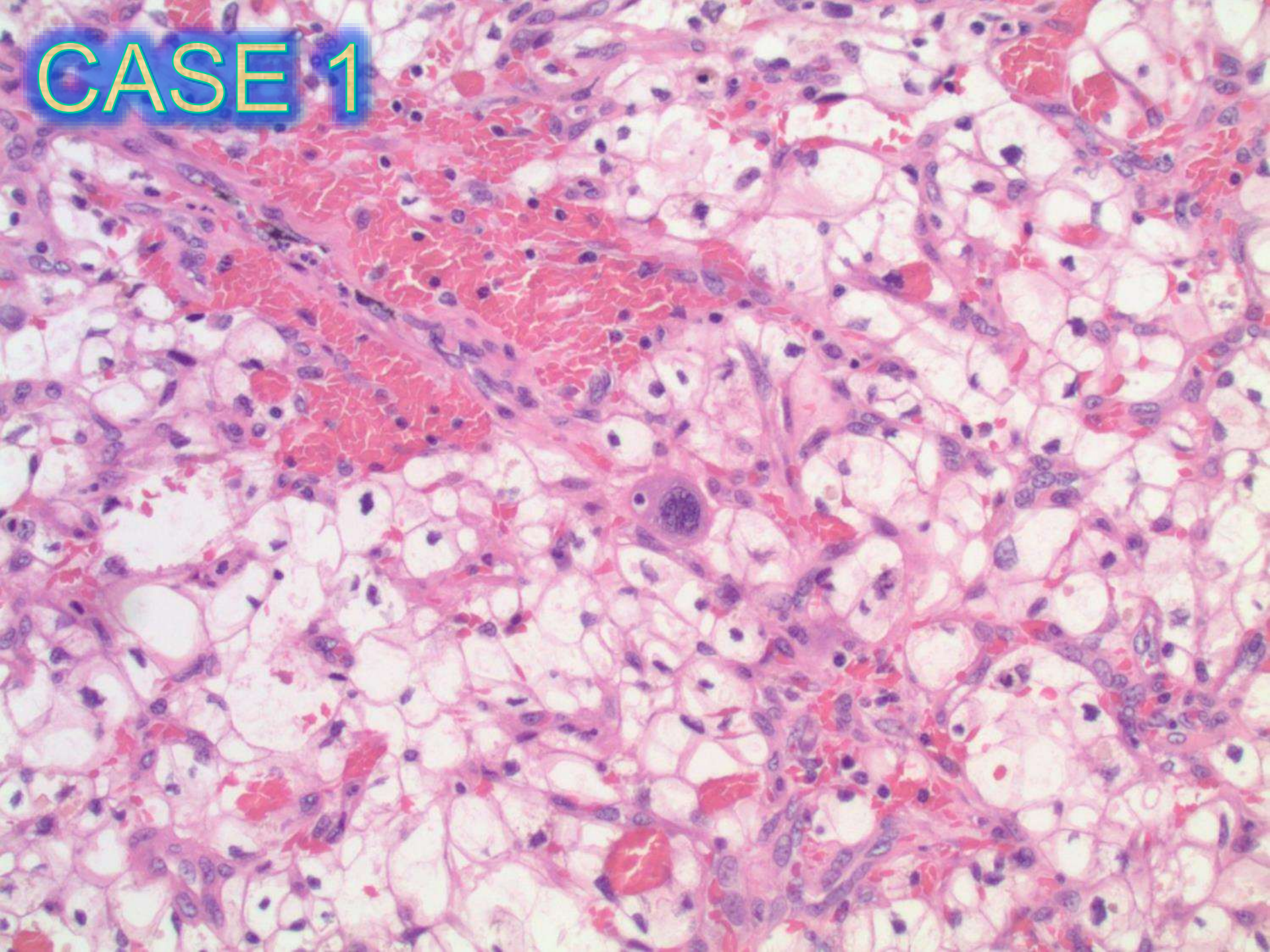
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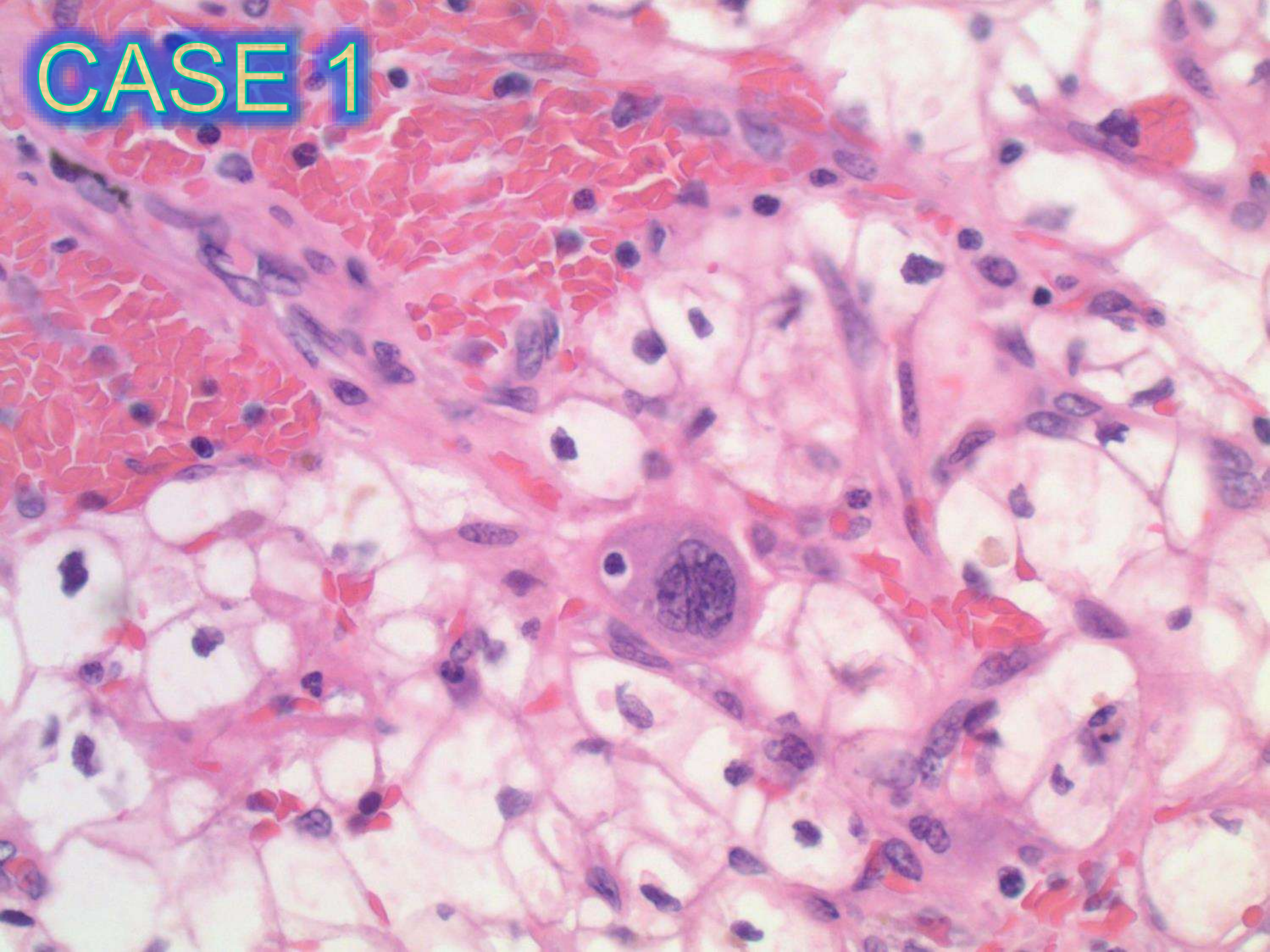
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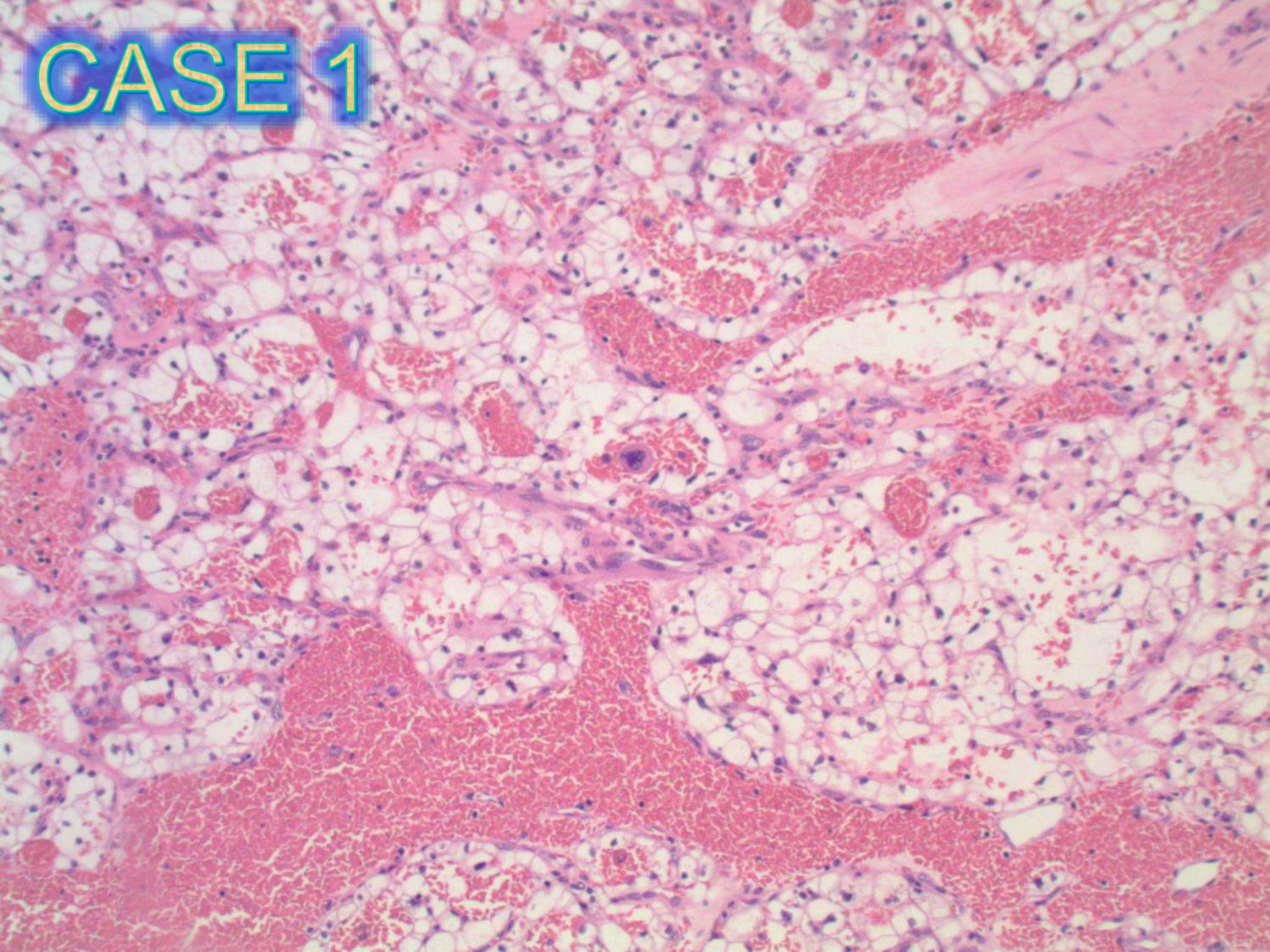
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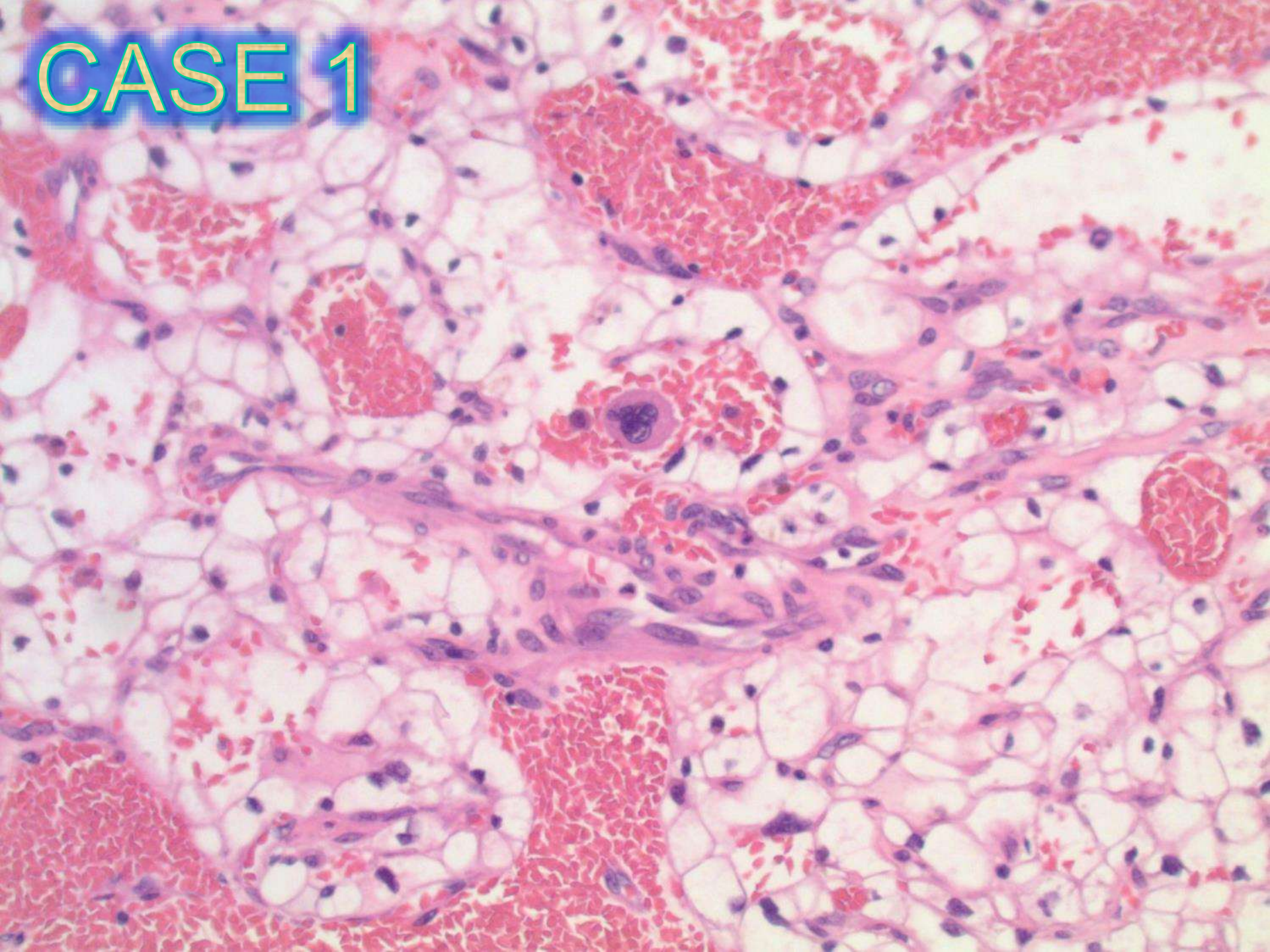
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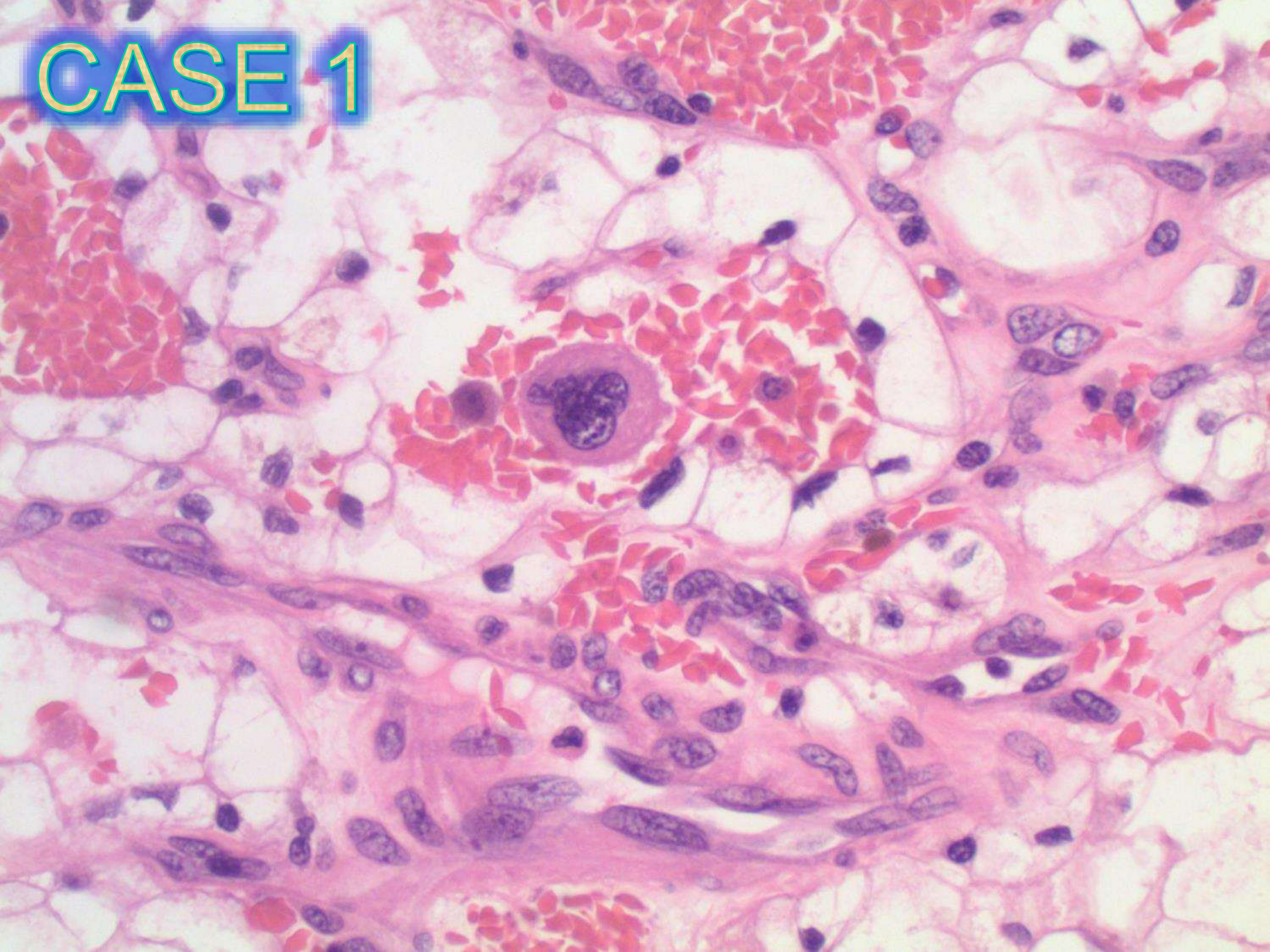
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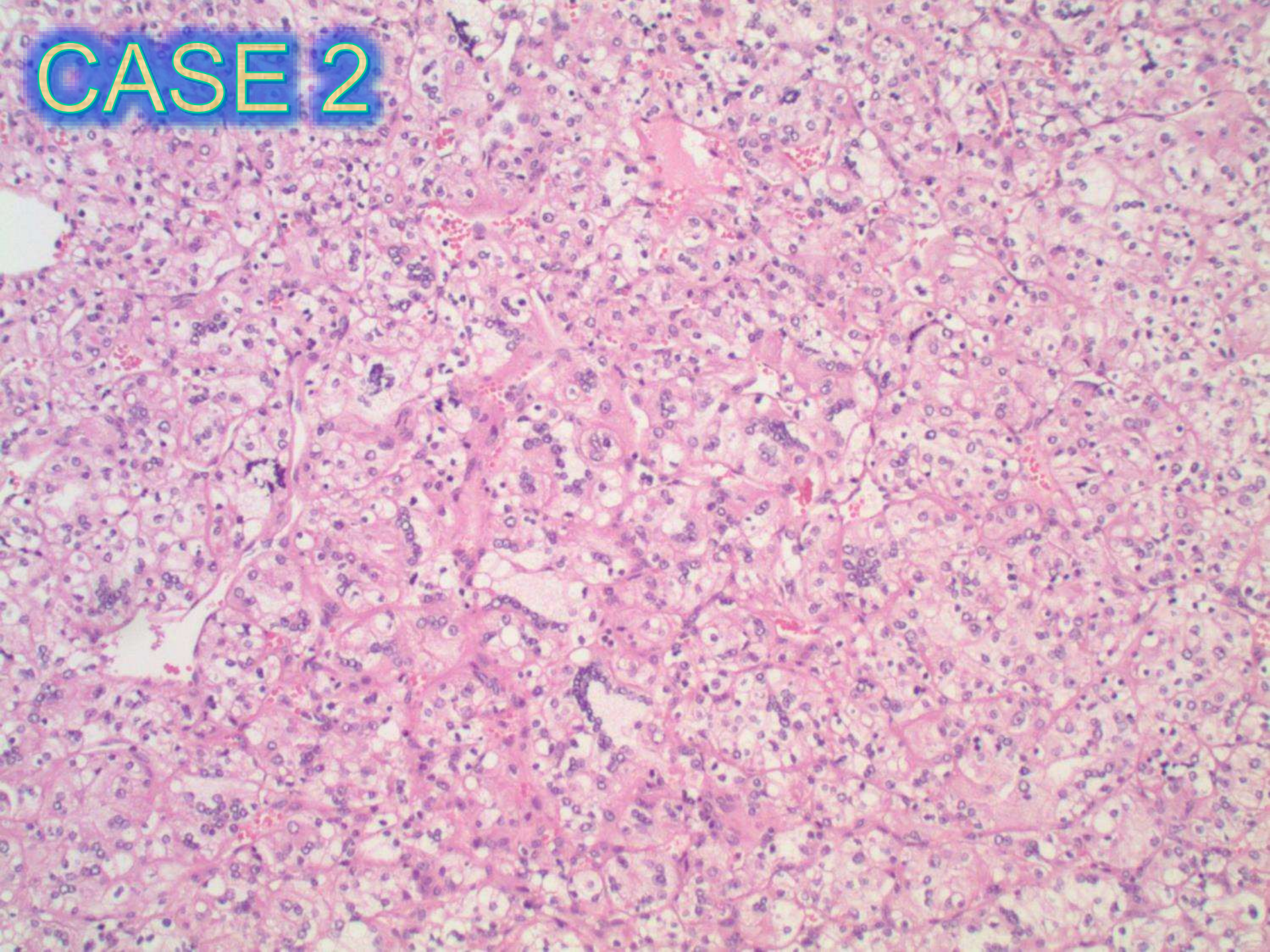
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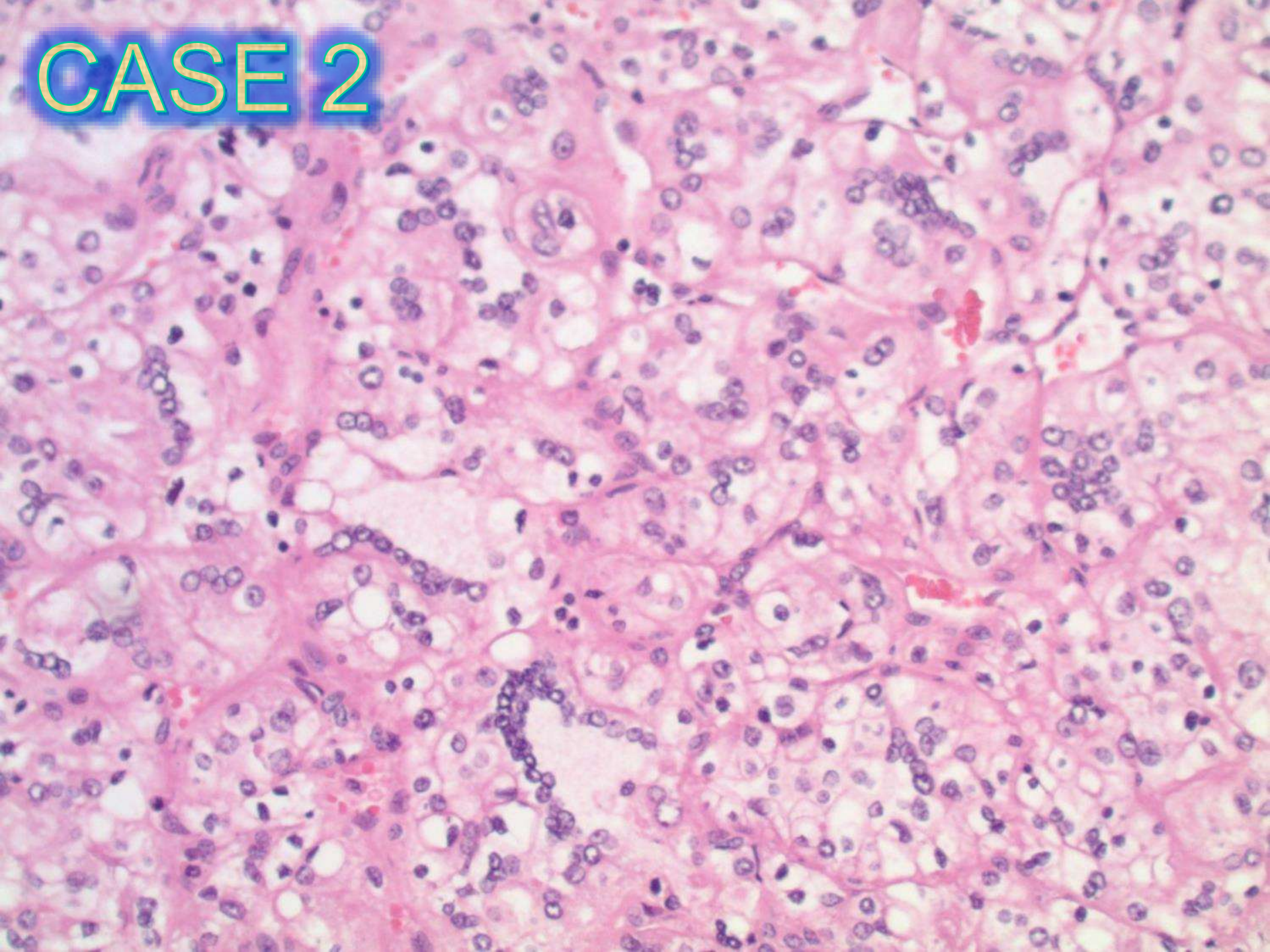
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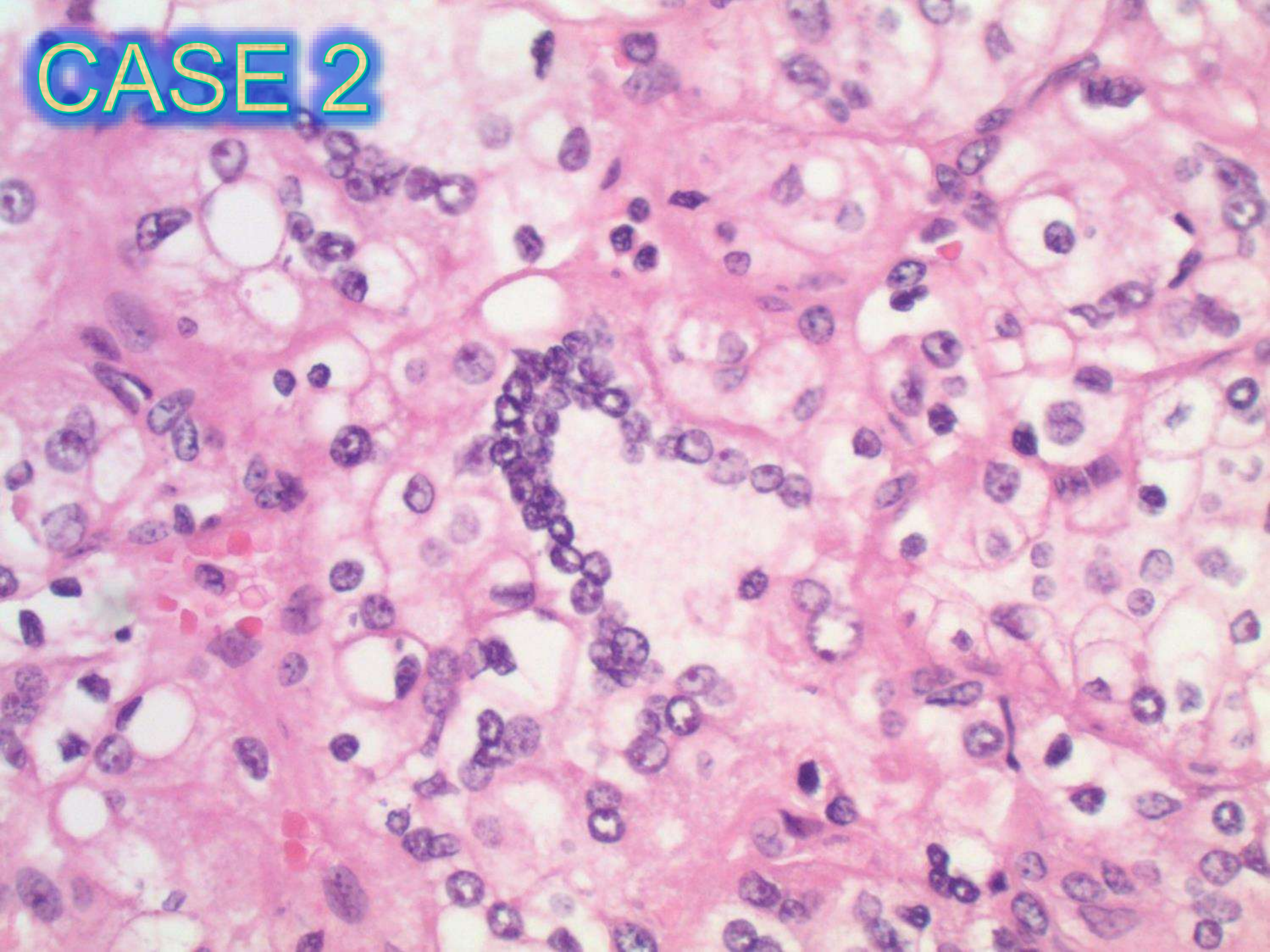
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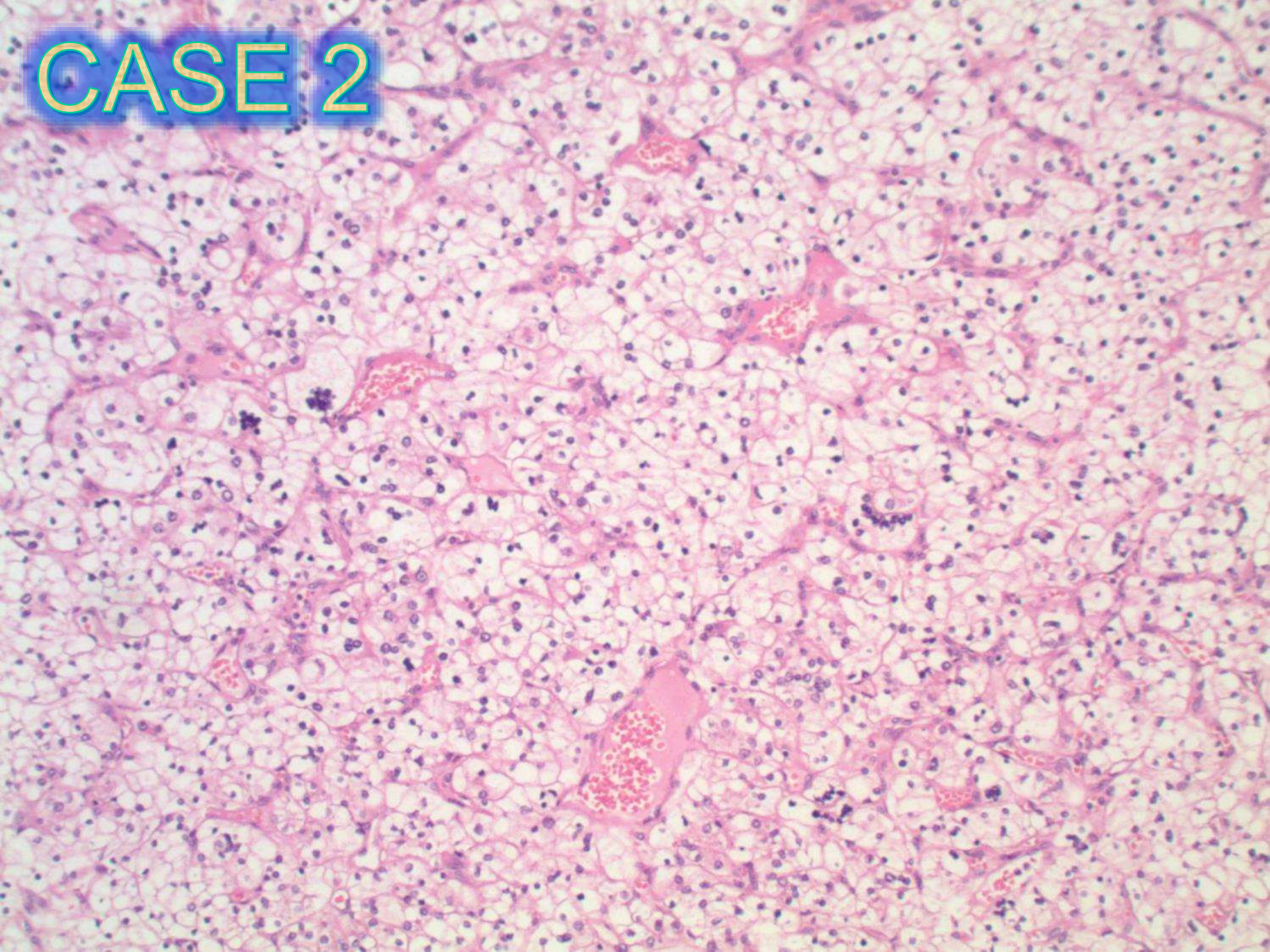
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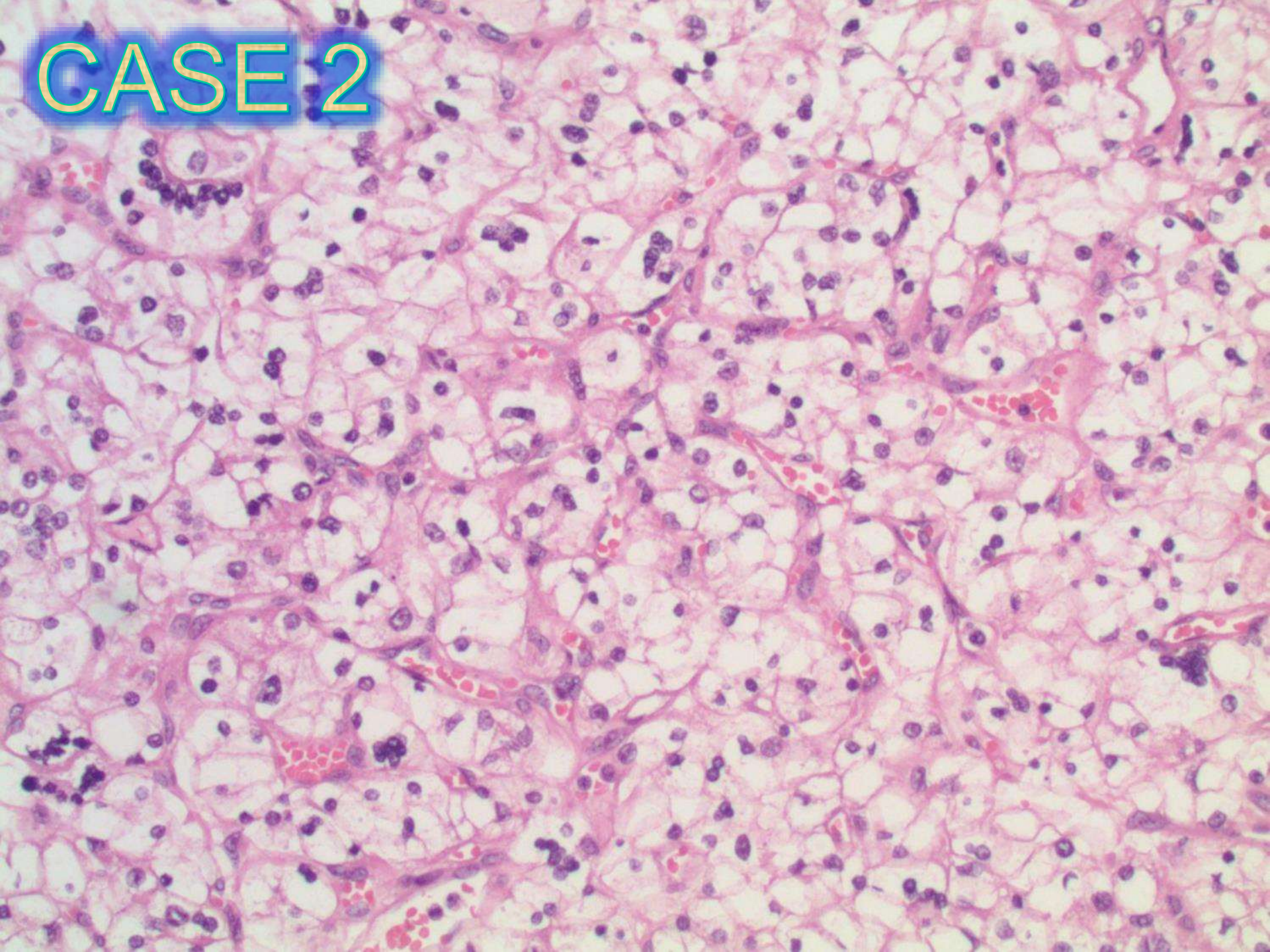
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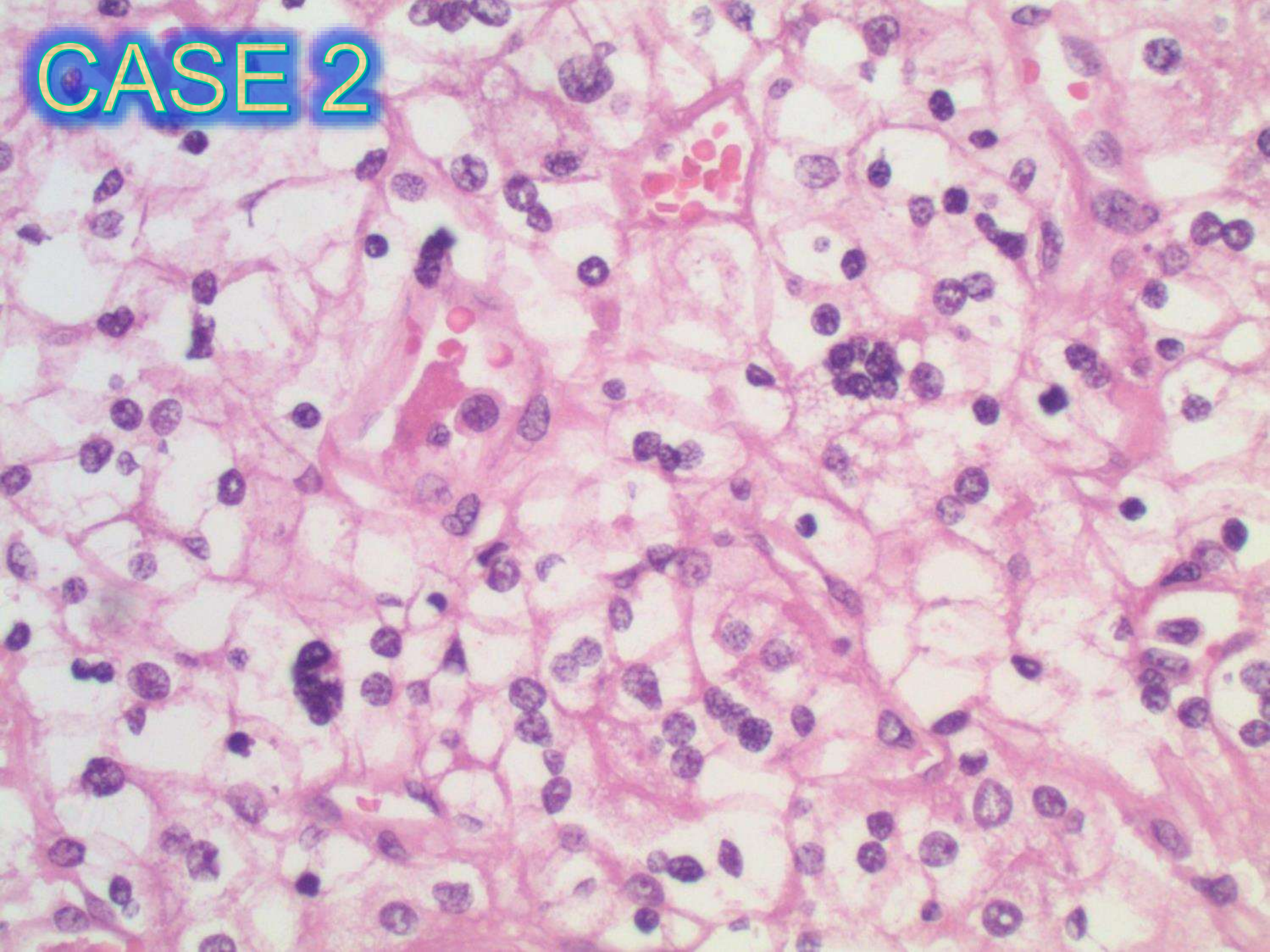
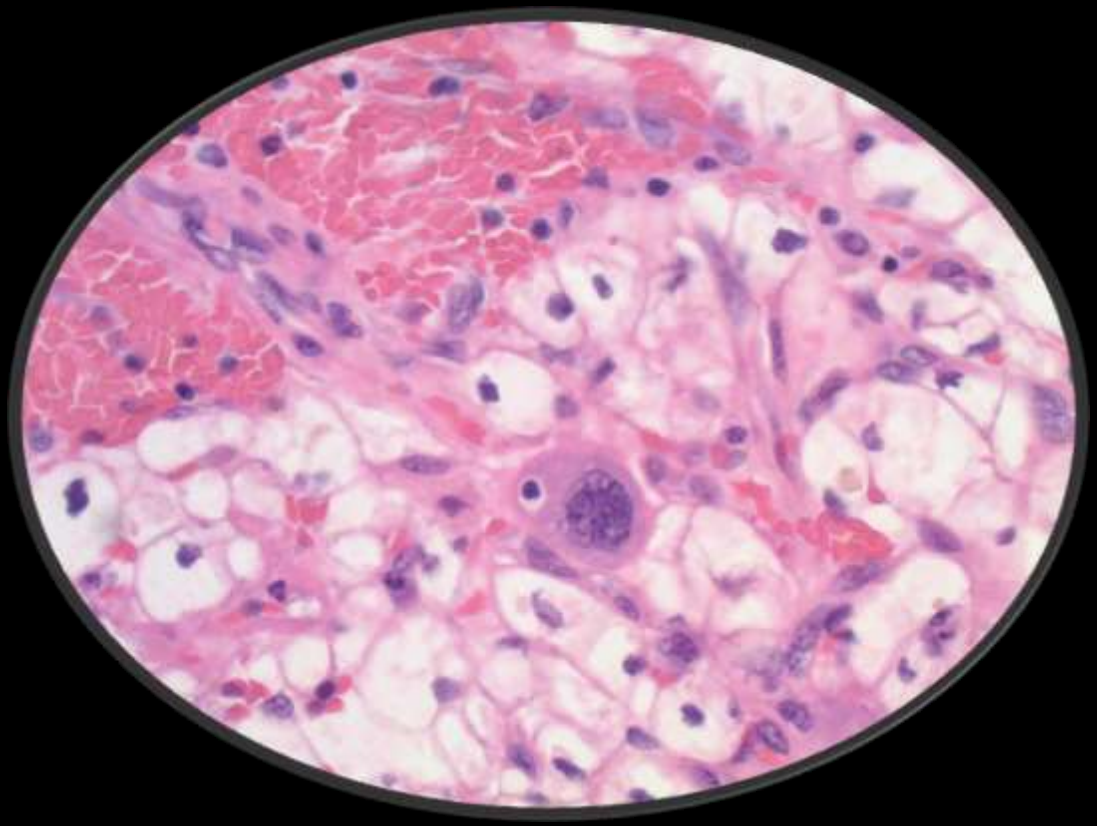

CASE 2

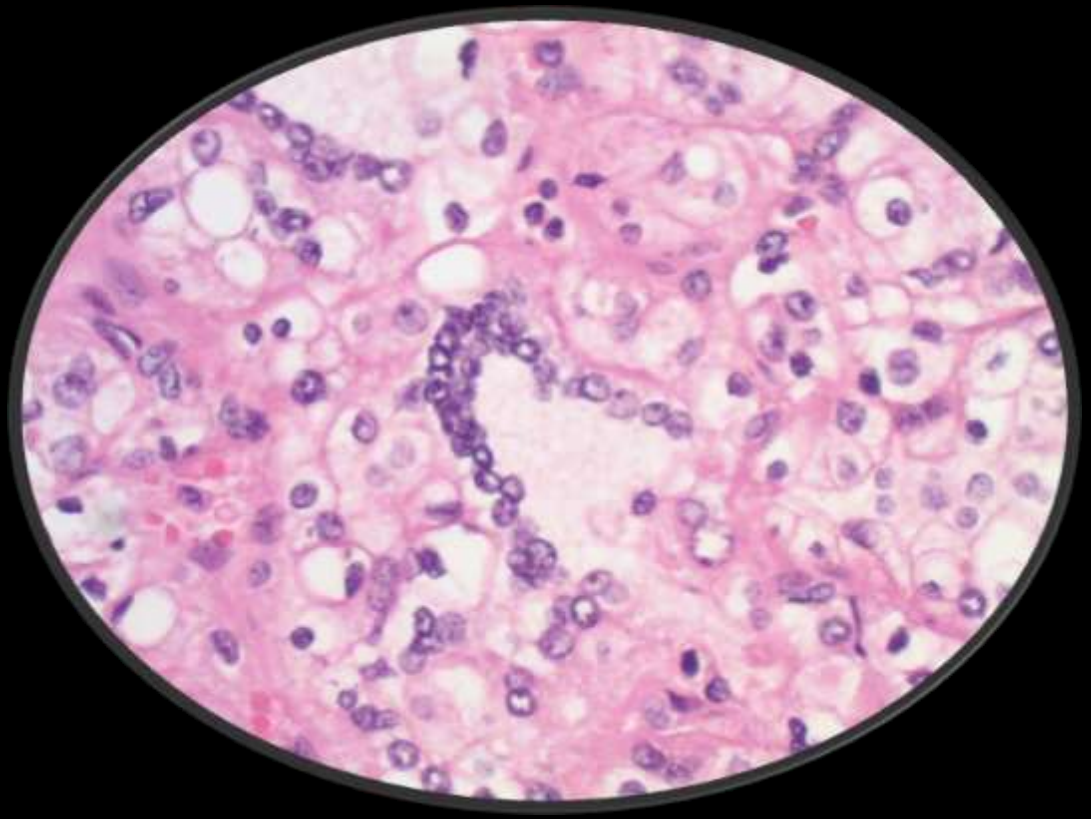
CASE 1

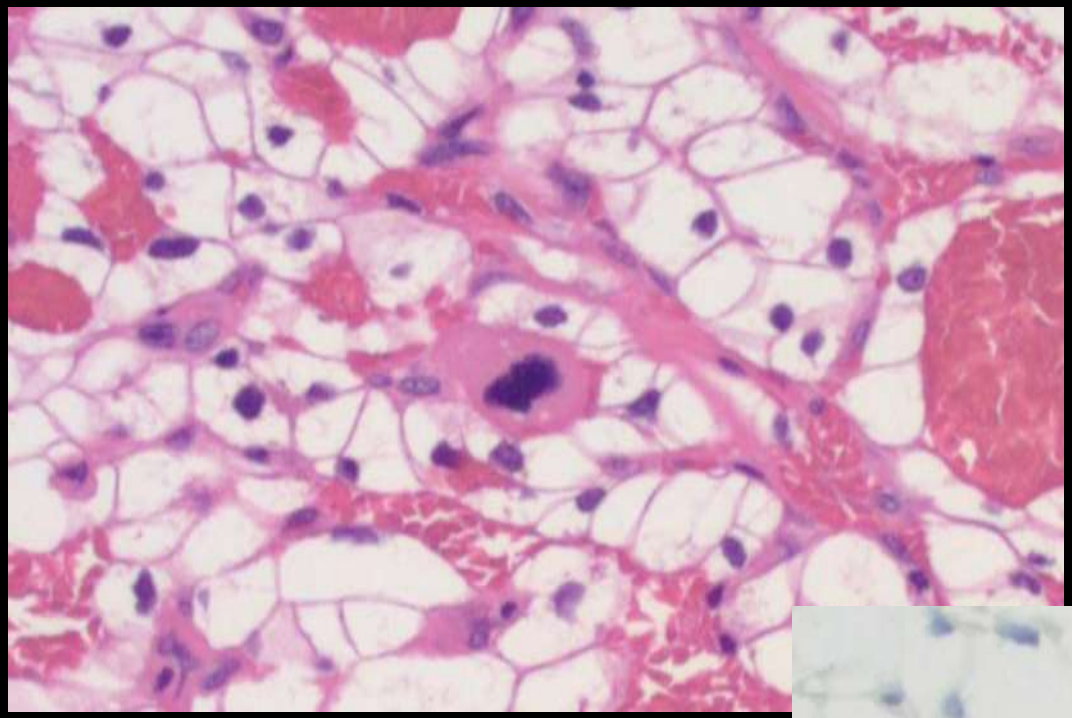
- GRADE 2?
- GRADE 3?
- GRADE 4?



CASE 2

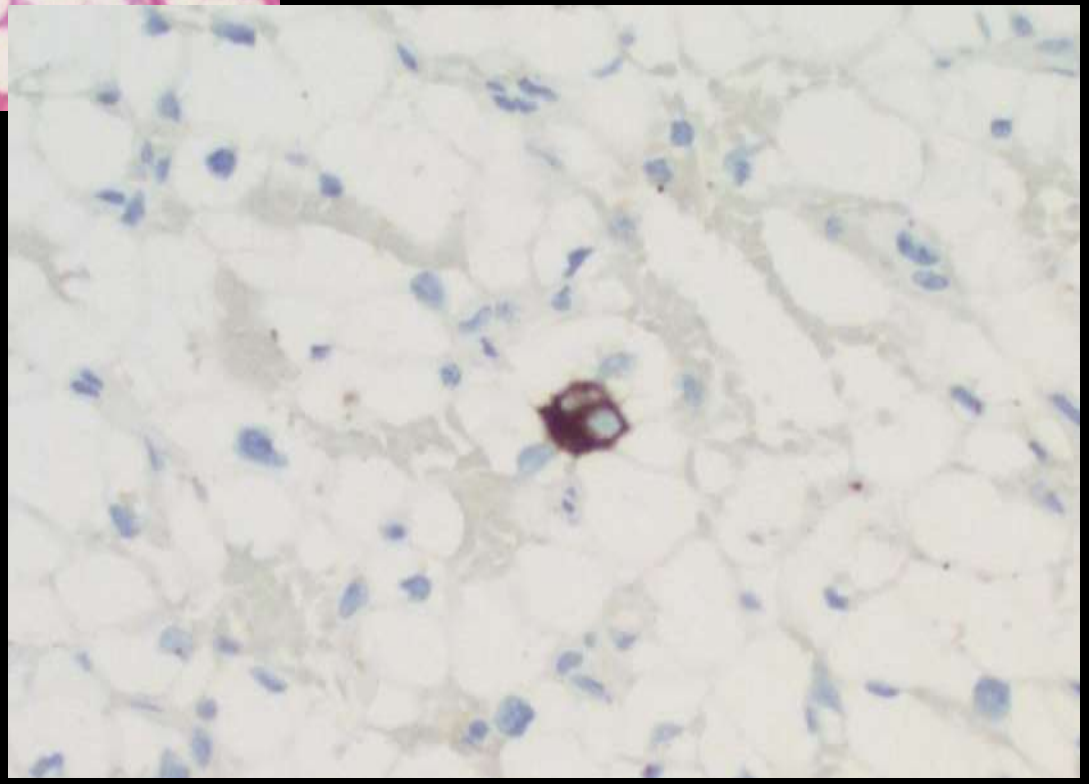
- GRADE 2?
- GRADE 3?
- GRADE 4?

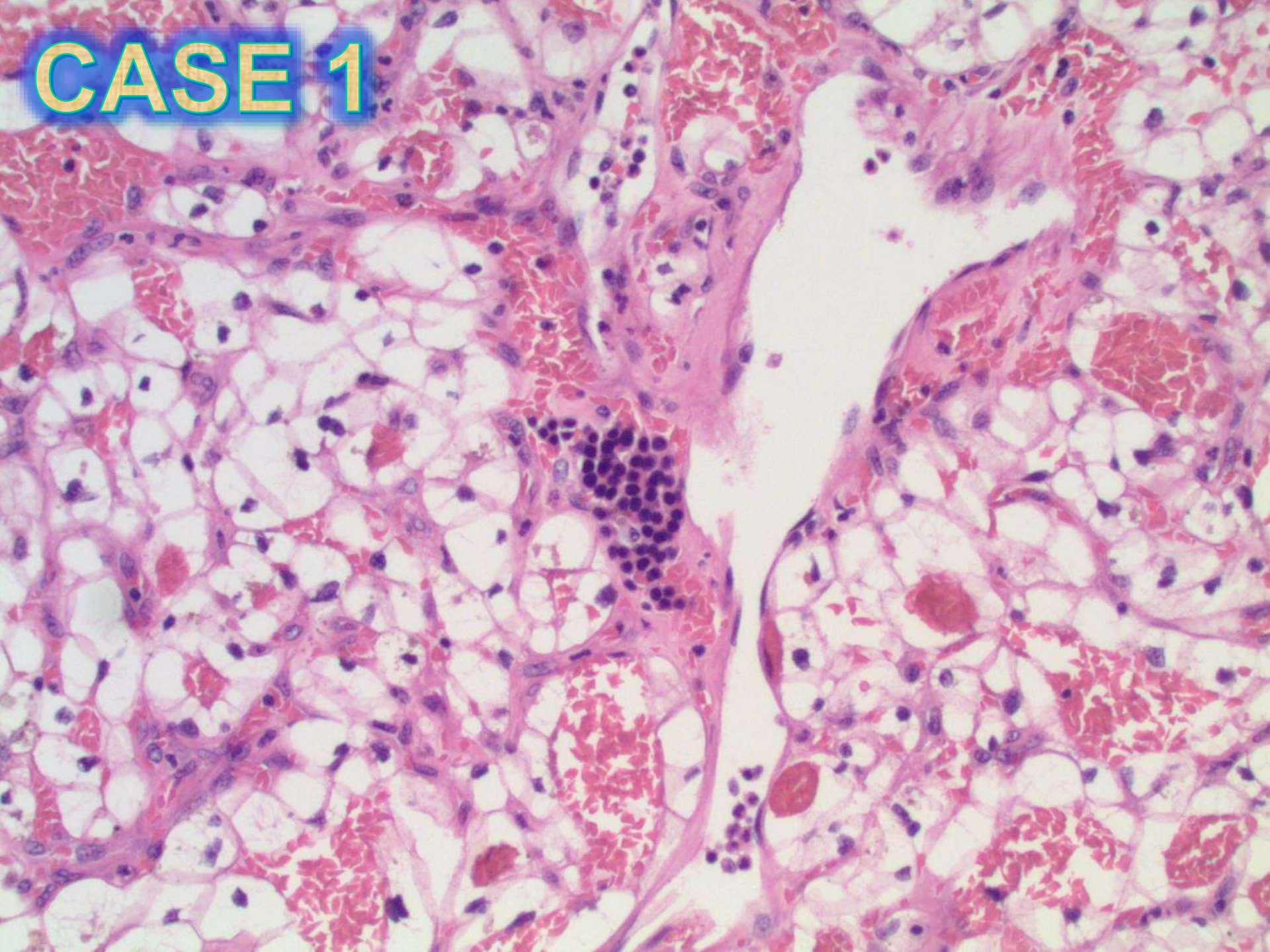


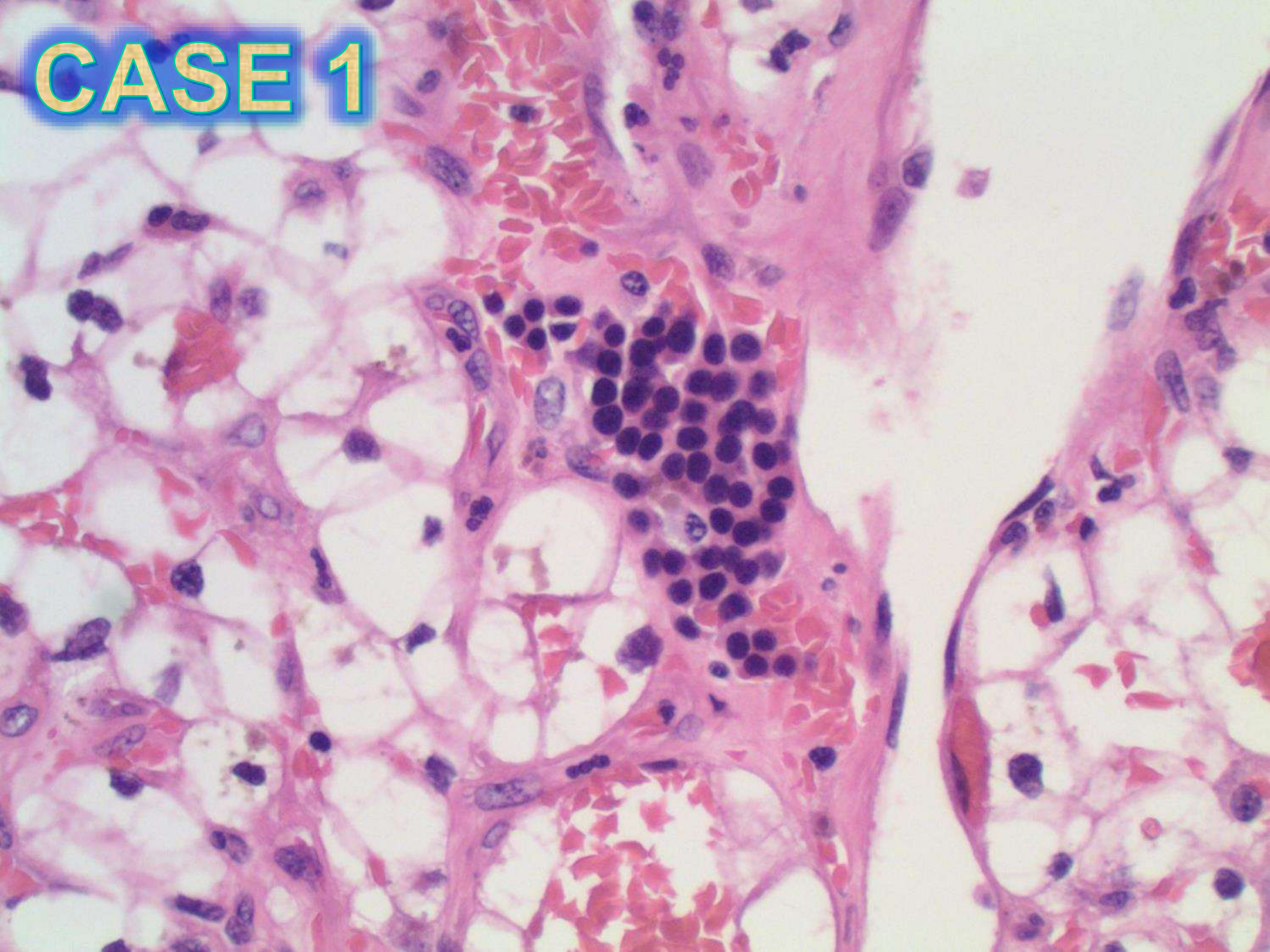


CASE 1:

CD61

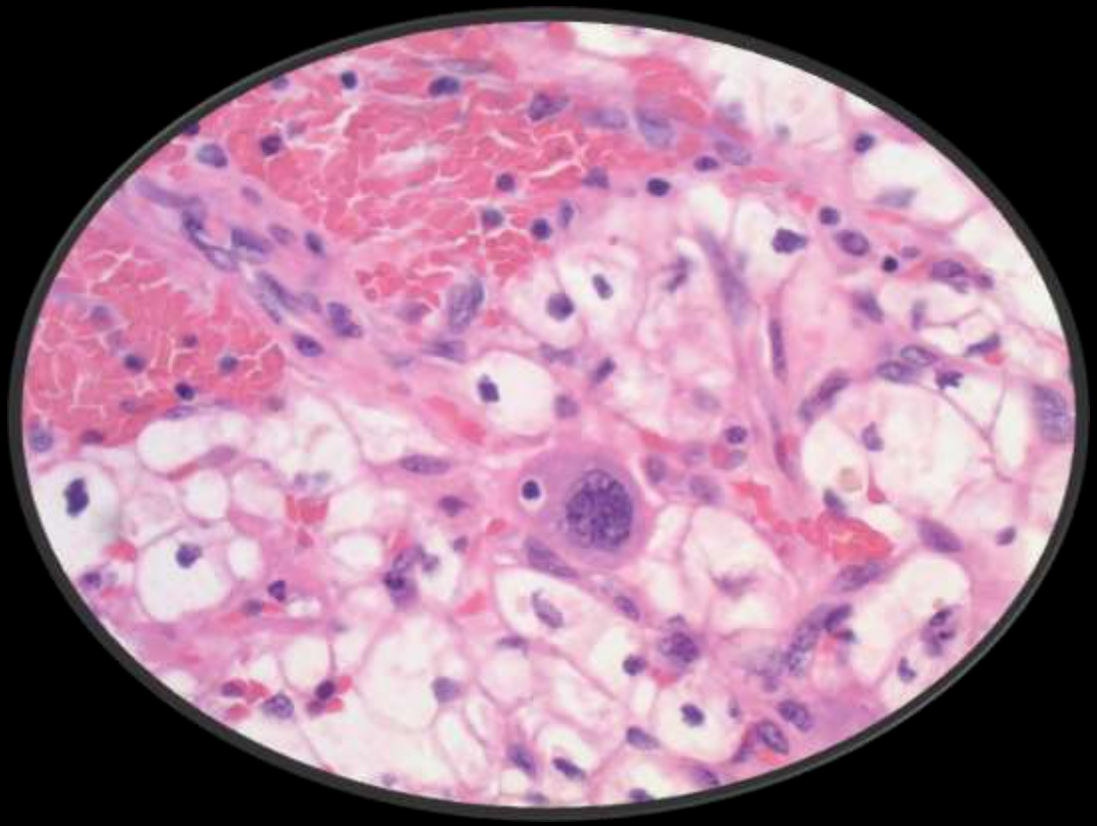



CASE 1


CASE 1

CASE 1

- **GRADE 2**
  - With EMH (megakaryocytes)



Human Pathology (2014) 45, 1306–1309

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Case study

Clear cell renal cell carcinoma with intratumoral and nodal extramedullary megakaryopoiesis: a potential diagnostic pitfall

Sean R. Williamson MD[a,*], Kelley J. Mast MD[b], Liang Cheng MD[c,d], Muhammad T. Idrees MD[c]

[a]*Department of Pathology and Laboratory Medicine, Henry Ford Health System, Detroit, MI 48202*
[b]*Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, TN 37232*
[c]*Departments of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN 46202*
[d]*Department of Urology, Indiana University School of Medicine, Indianapolis, IN 46202*

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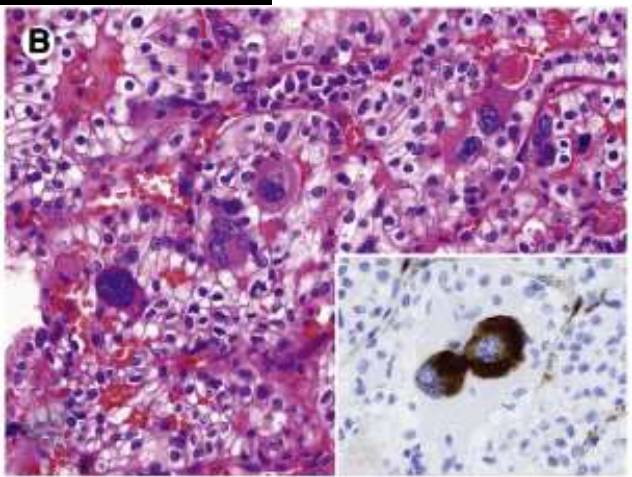
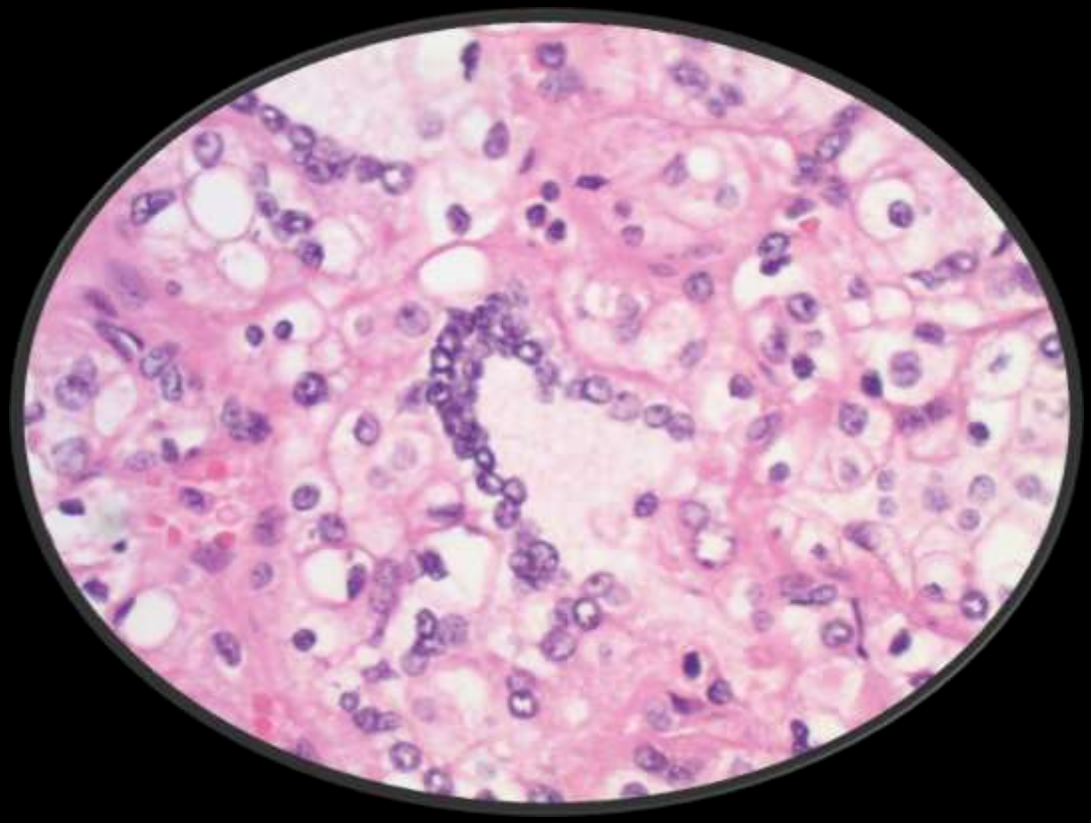


Summary Clear cell renal cell carcinoma is occasionally associated with erythrocytosis, hypothesized to result from tumoral production of erythropoietin. Rarely, intratumoral erythropoiesis has been identified, although intratumoral megakaryopoiesis has not, to our knowledge, been previously described. We report the case of an 81-year-old man with myelofibrosis who underwent resection of a 9.8-cm clear cell renal cell carcinoma. Numerous megakaryocytes were present within the renal cell carcinoma; regional lymph nodes; and, to a lesser extent, the nonneoplastic kidney, glomeruli, and renal hilar soft tissue, in some areas associated with trilineage hematopoiesis. Immunohistochemistry verified the megakaryocytic lineage of the atypical cells (CD61, CD42b, and von Willebrand factor +; cytokeratin −). Intratumoral extramedullary megakaryopoiesis is a novel finding in clear cell renal cell carcinoma with potential to mimic high-grade carcinoma and involvement of lymph nodes. Careful attention to morphology, presence of other hematopoietic elements, and immunoprofile can facilitate recognition of this rare phenomenon.

CASE 2

- **GRADE 3? (syncytial type tumor giant cells)**
- **GRADE 4? (multinucleate tumor giant cells)**



Human Pathology (2014) 45, 735–744

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Original contribution

Clear cell renal cell carcinoma with a syncytial-type multinucleated giant tumor cell component: implications for differential diagnosis ☆

Sean R. Williamson MD[a,b,*], Jennifer B. Kum MD[a], Michael P. Goheen BA, CEMT[a], Liang Cheng MD[a,c], David J. Grignon MD[a], Muhammad T. Idrees MD[a]

[a]*Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN 46202*
[b]*Department of Pathology and Laboratory Medicine, Henry Ford Health System, Detroit, MI 48202*
[c]*Department of Urology, Indiana University School of Medicine, Indianapolis, IN 46202*

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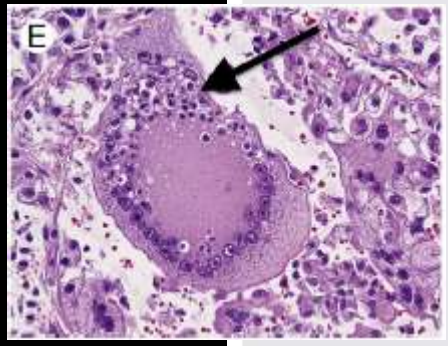
Keywords:
Renal cell carcinoma;
Immunohistochemistry;
Syncytial giant cells;
Emperipolesis;
Hyaline globules



Summary A component of syncytial-type multinucleated tumor giant cells is uncommon in clear cell renal cell carcinoma, and the histogenesis, incidence, and clinical implications of this finding are not well understood. We retrieved 13 such tumors from our pathology archives in patients with a median age of 60 years, comprising 1.5% of clear cell renal cell carcinomas. Stage was typically pT4 or pT3 (each 38%). Microscopically, all tumors included a component of low-grade clear cell renal cell carcinoma with usual features. Syncytial-type giant tumor cells possessed voluminous cytoplasm, usually granular and eosinophilic, and numerous nuclei similar to those of the mononuclear tumor cells. Transition between areas of mononuclear and multinucleated cells was sometimes abrupt. Other findings included necrosis (77%), hyaline globules (46%), emperipolesis (46%), and intranuclear cytoplasmic invaginations (23%). Immunohistochemical staining typically revealed both mononuclear and multinucleated cells to be positive for carbonic anhydrase IX, CD10, epithelial membrane antigen, vimentin, and cytokeratin AE1/AE3 and negative for β human chorionic gonadotropin, TFE3, cathepsin K, cytokeratin 7, cytokeratin 20, HMB45, CD68, smooth muscle actin, and S100. Most patients with available information (7/9) were alive with metastatic disease at the most recent follow-up. Syncytial-type giant cells are an uncommon finding associated with aggressive clear cell renal cell carcinomas. Despite the unusual appearance of this tumor component, its immunoprofile supports an epithelial lineage and argues against trophoblastic, osteoclast-like, or histiocytic differentiation. Reactivity for typical clear cell renal cell carcinoma antigens facilitates discrimination from giant cells of epithelioid angiomyolipoma or other tumors, particularly in a biopsy specimen or a metastatic tumor.

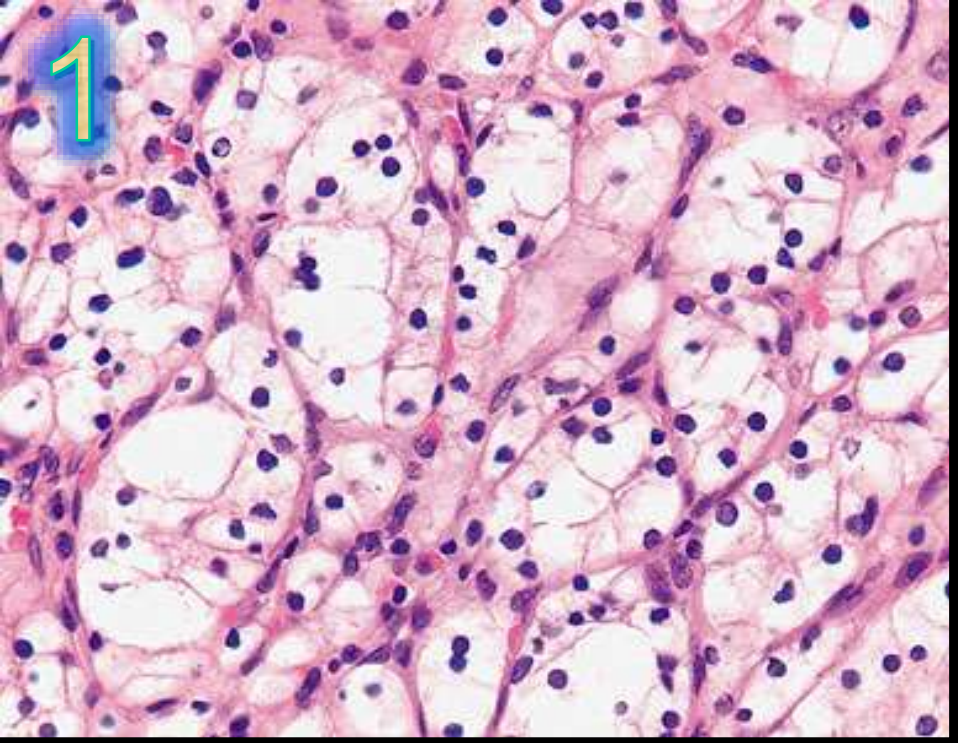
WHO/ISUP grading for clear cell & papillary RCC

Grade 1: nucleoli absent/inconspicuous at x400

Grade 2: nucleoli conspicuous & eosinophilic at x400, visible but not prominent at x100

Grade 3: nucleoli conspicuous & eosinophilic at x100

Grade 4: extreme nuclear pleomorphism, multinucleate giant cells, rhabdoid/sarcomatoid diff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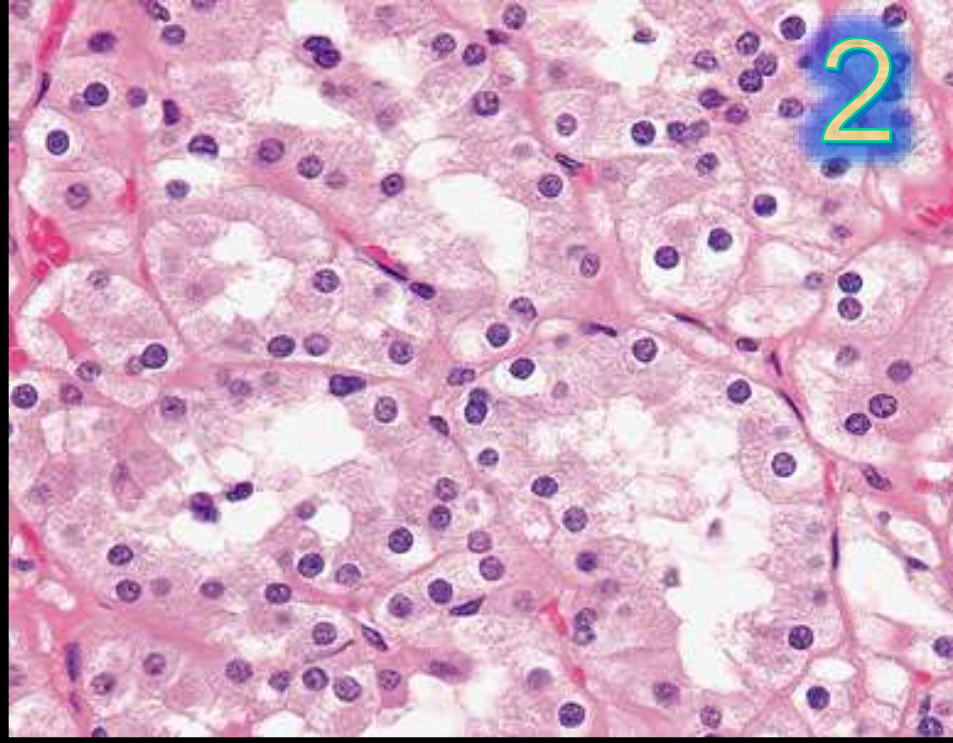
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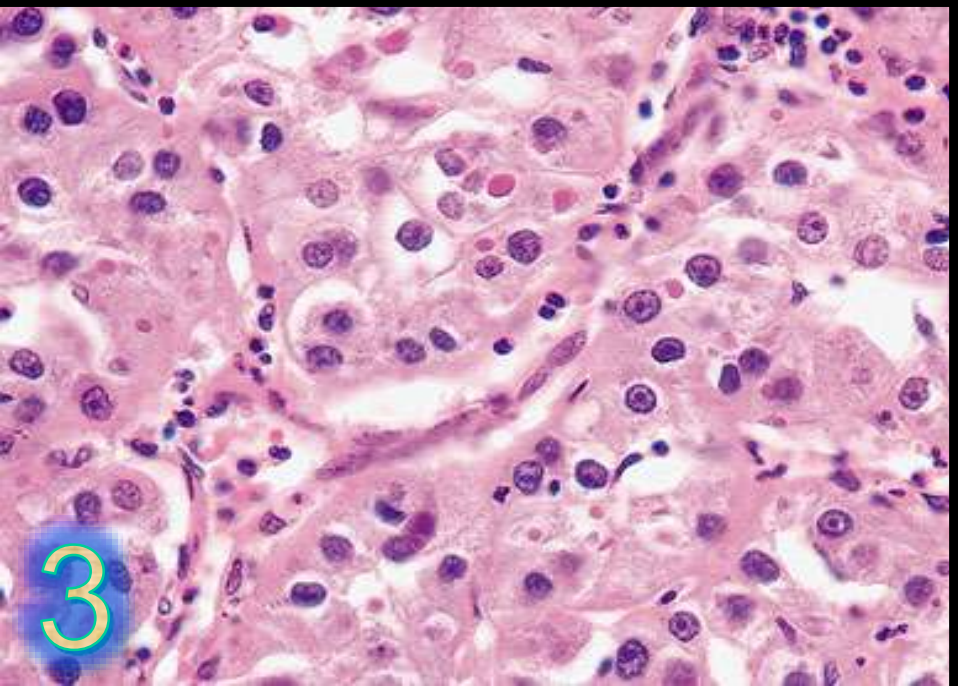
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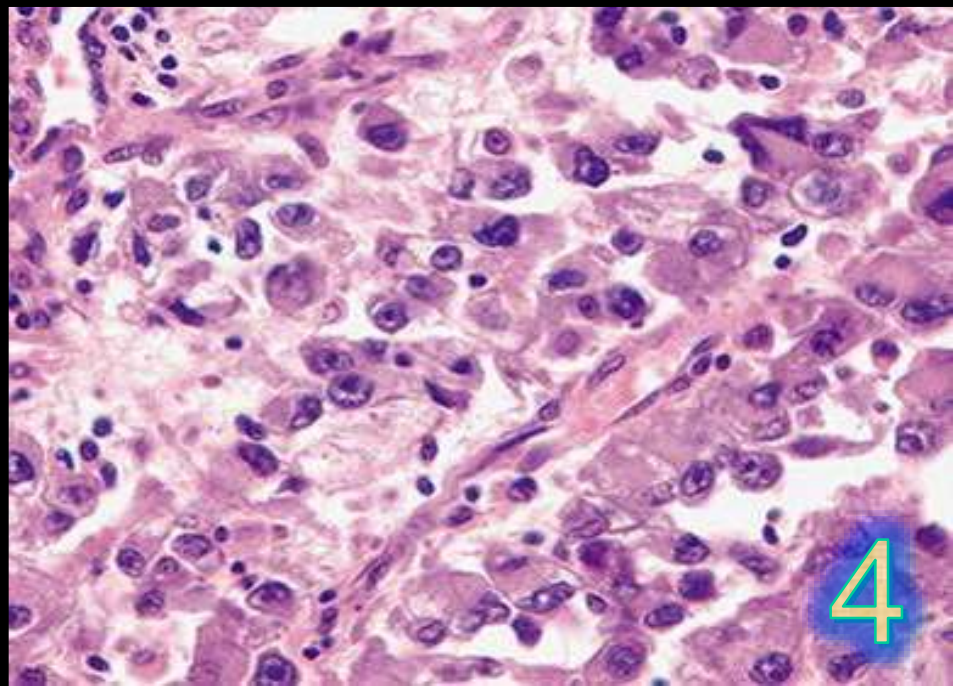

4

To grade or not to WHO/ISUP grade?

- **RCC subtype validated**
  - Clear cell RCC, papillary RCC
- **Not applicable**
  - Chromophobe RCC, TFE3 RCC
- **Grading potentially useful**
  - TFEB RCC, SDH-def RCC, MTSCC, TCEB1-mut RCC, FH-def RCC, RCC unclassified
- **Not useful b/c known to be aggressive**
  - Collecting duct ca, medullary ca

Paner GP et al. Updates in Grading of Renal Cell Carcinomas Beyond Clear Cell Renal Cell Carcinoma and Papillary Renal Cell Carcinoma. Adv Anat Pathol. 2022 May 1;29(3):117-130.

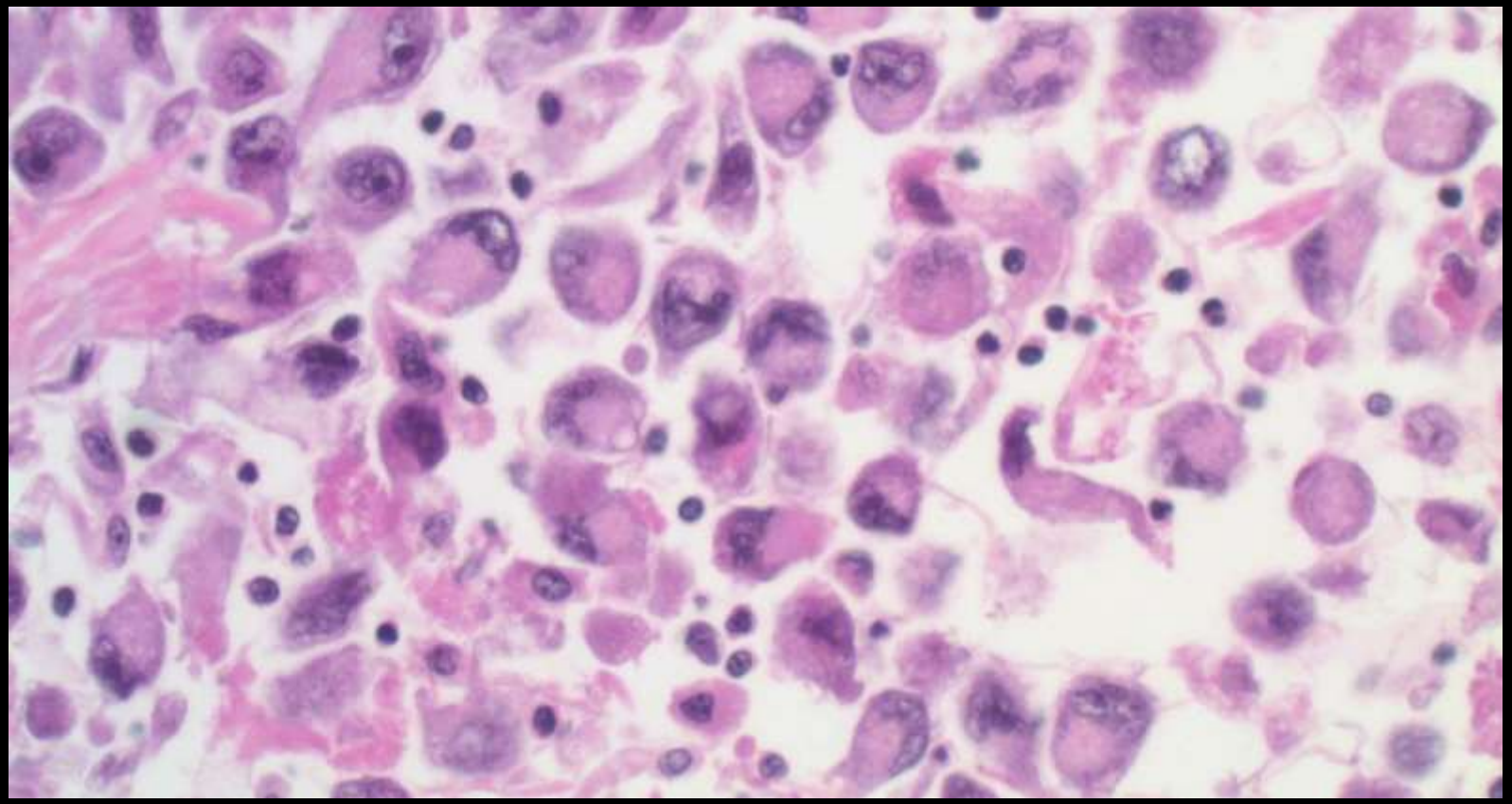
To grade or not to WHO/ISUP grade?

- **Grading potential misleading**
  - Tubulocystic RCC, ACD-RCC, ESC RCC, EVT
- **Grading essential for histologic Dx**
  - Papillary adenoma
  - MCN LMP, clear cell pap RCC
- **Limited or no data on grading**
  - ALK RCC
  - LOT
  - Thyroid like follicular RCC

Paner GP et al. Updates in Grading of Renal Cell Carcinomas Beyond Clear Cell Renal Cell Carcinoma and Papillary Renal Cell Carcinoma. Adv Anat Pathol. 2022 May 1;29(3):117-130.

Rhabdoid differentiation

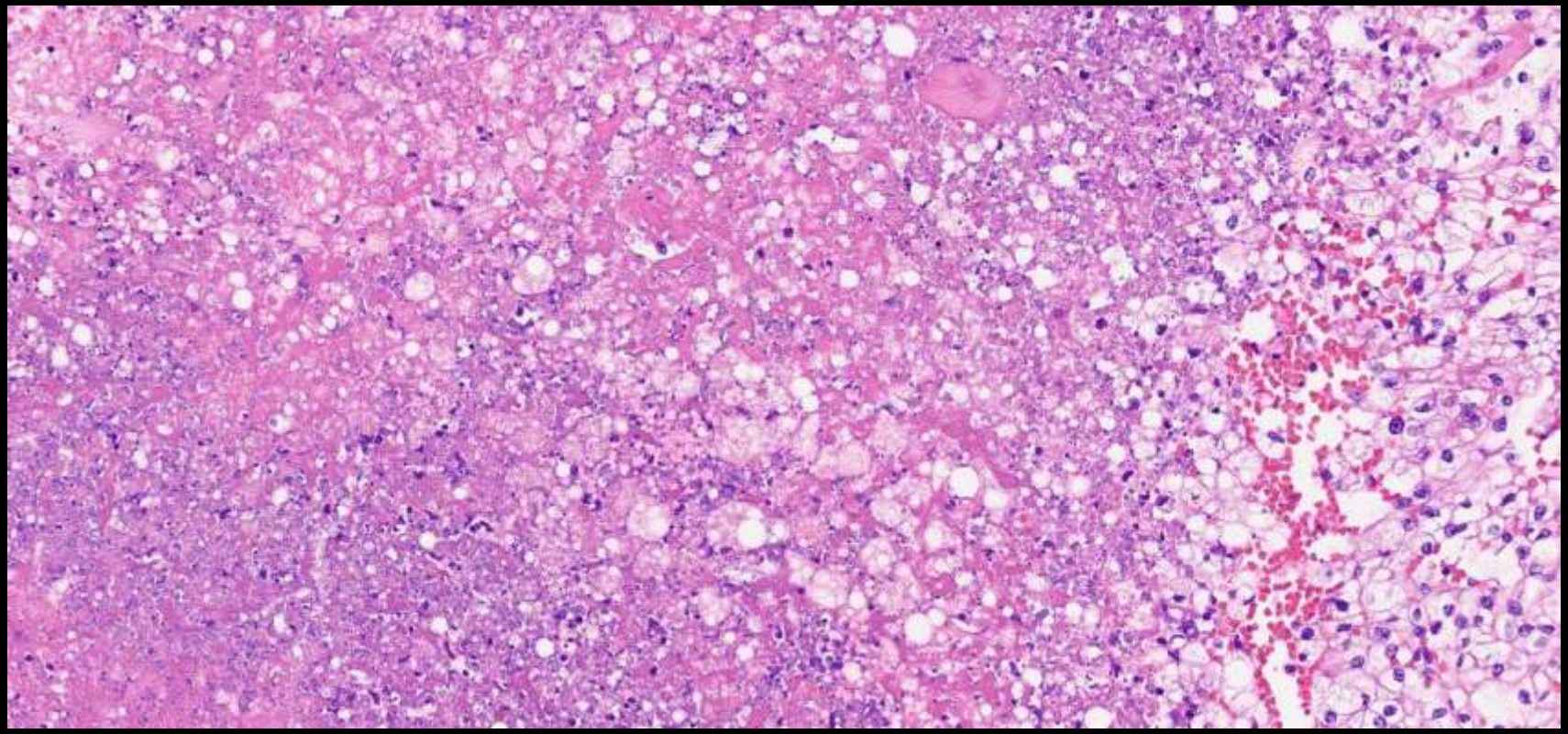
- **Adverse prognostic factor in clear cell RCC (WHO/ISUP grade 4 by definition)**



Przybycin CG, McKenney JK, Reynolds JP, Campbell S, Zhou M, Karafa MT, Magi-Galluzzi C. Rhabdoid differentiation is associated with aggressive behavior in renal cell carcinoma: a clinicopathologic analysis of 76 cases with clinical follow-up. Am J Surg Pathol. 2014 Sep;38(9):1260-5.

Tumor cell necrosis

- **Independent prognostic outcome for clear cell RCC**



Sengupta S, Lohse CM, Leibovich BC, Frank I, Thompson RH, Webster WS, Zincke H, Blute ML, Cheville JC, Kwon ED. Histologic coagulative tumor necrosis as a prognostic indicator of renal cell carcinoma aggressiveness. Cancer. 2005 Aug 1;104(3):511-20.

vs infarct-type necrosis (papillary RCC)