SEPT 2020 DIAGNOSIS LIST

20-0901: metastatic squamous cell carcinoma of prostate (soft tissue/GU pathology)
20-0902: endometrioid adenocarcinoma arising from polypoid endometriosis (pelvis/GYN pathology)
20-0903: oncocytic renal cell carcinoma, MTOR mutated (kidney/GU pathology)
20-0904: pigmented microcystic chromophobe renal cell carcinoma (kidney/GU pathology)
20-0905: perinephric myxoid tumor (kidney/GU pathology)
20-0906: primary renal melanoma (kidney/GU pathology)
20-0907: paraganglioma (spinal cord/soft tissue pathology & neuropathology)

Disclosures
September 1, 2020

The following planners and presenters had disclosures:

Ankur Sangoi: Google-consultant

Keith Duncan: ABBVIE-consultant

South Bay Pathology Society has determined that these relationships are not relevant to the clinical cases being presented. The presentation slides have been reviewed for potential bias and found to contain none.

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

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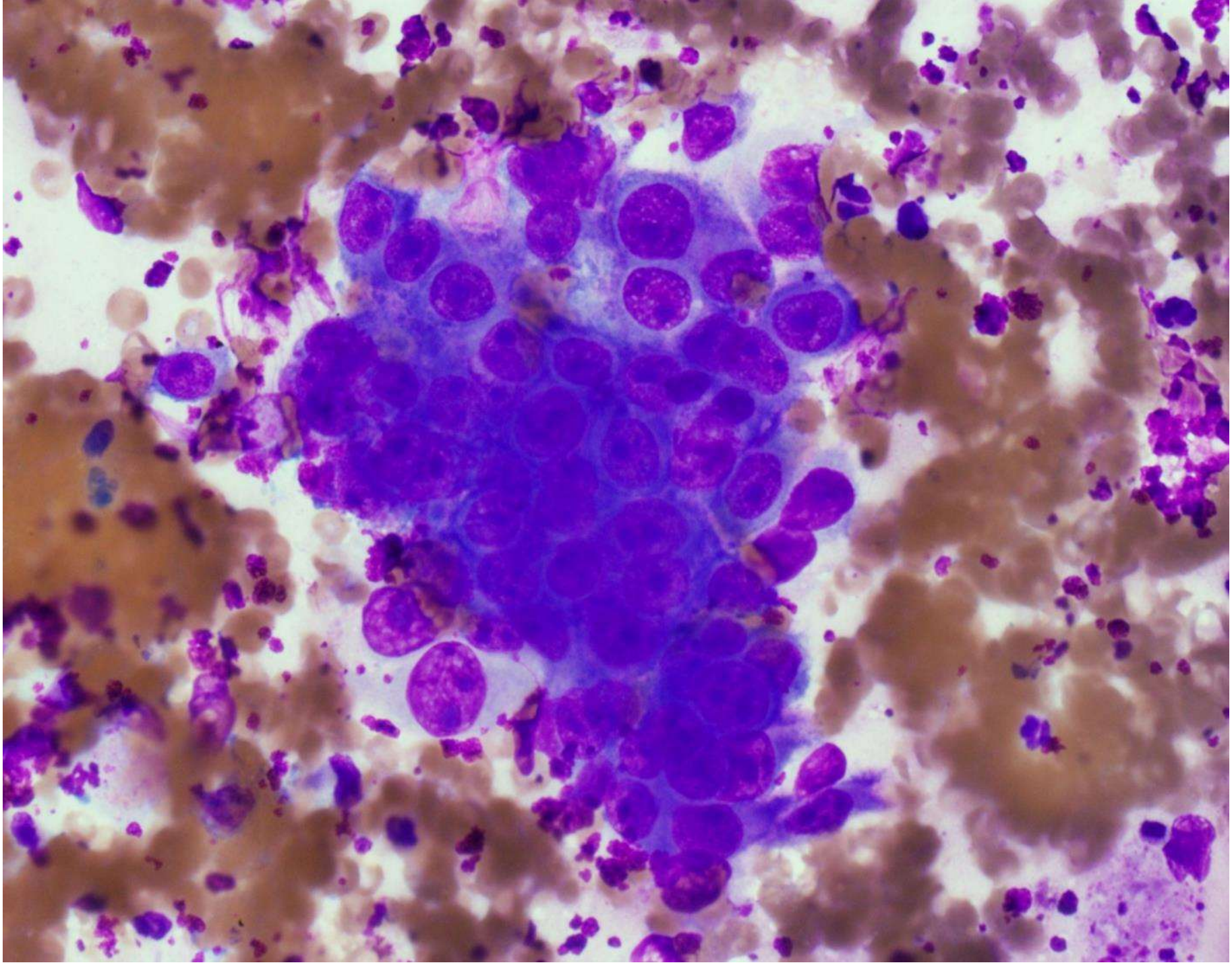
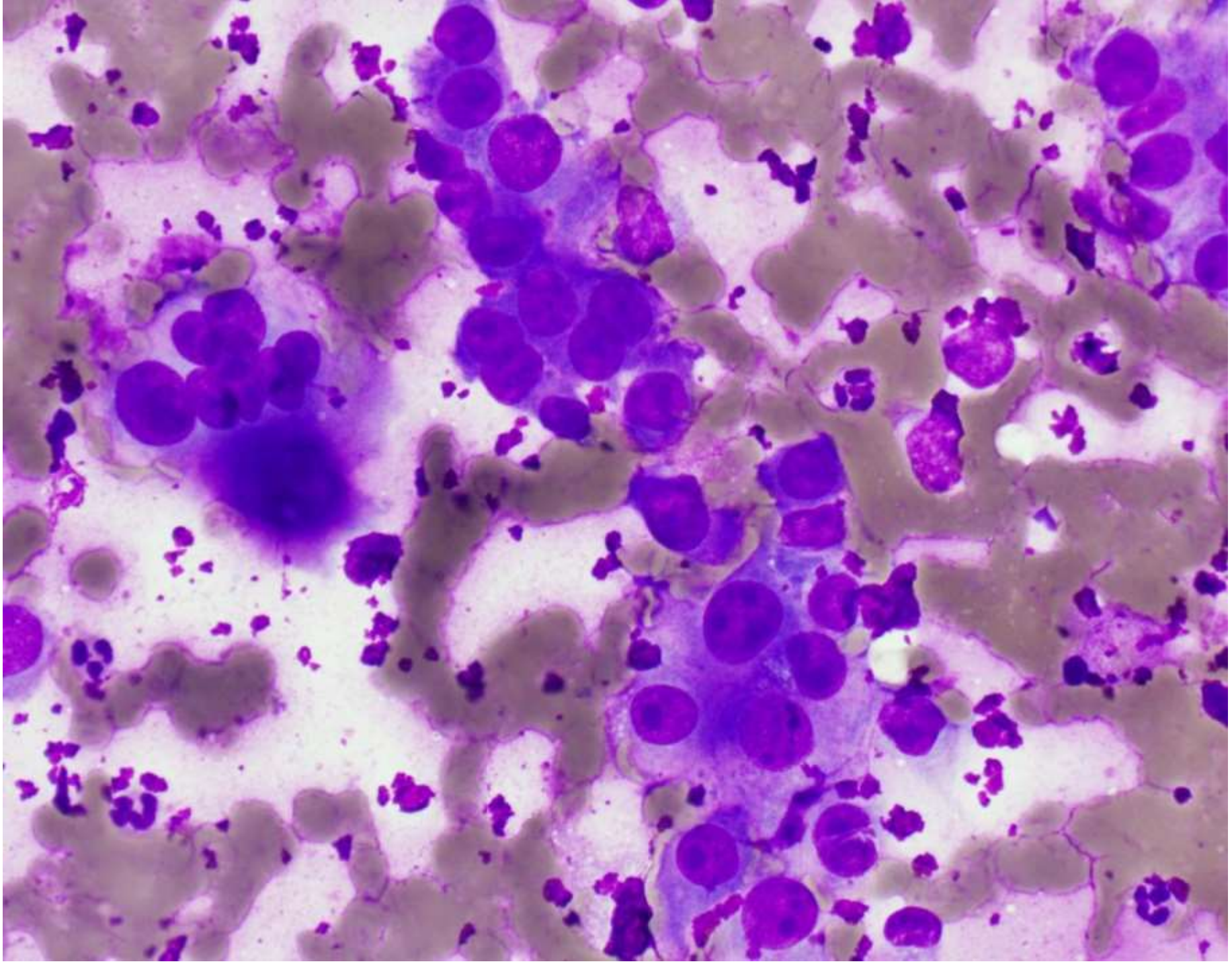
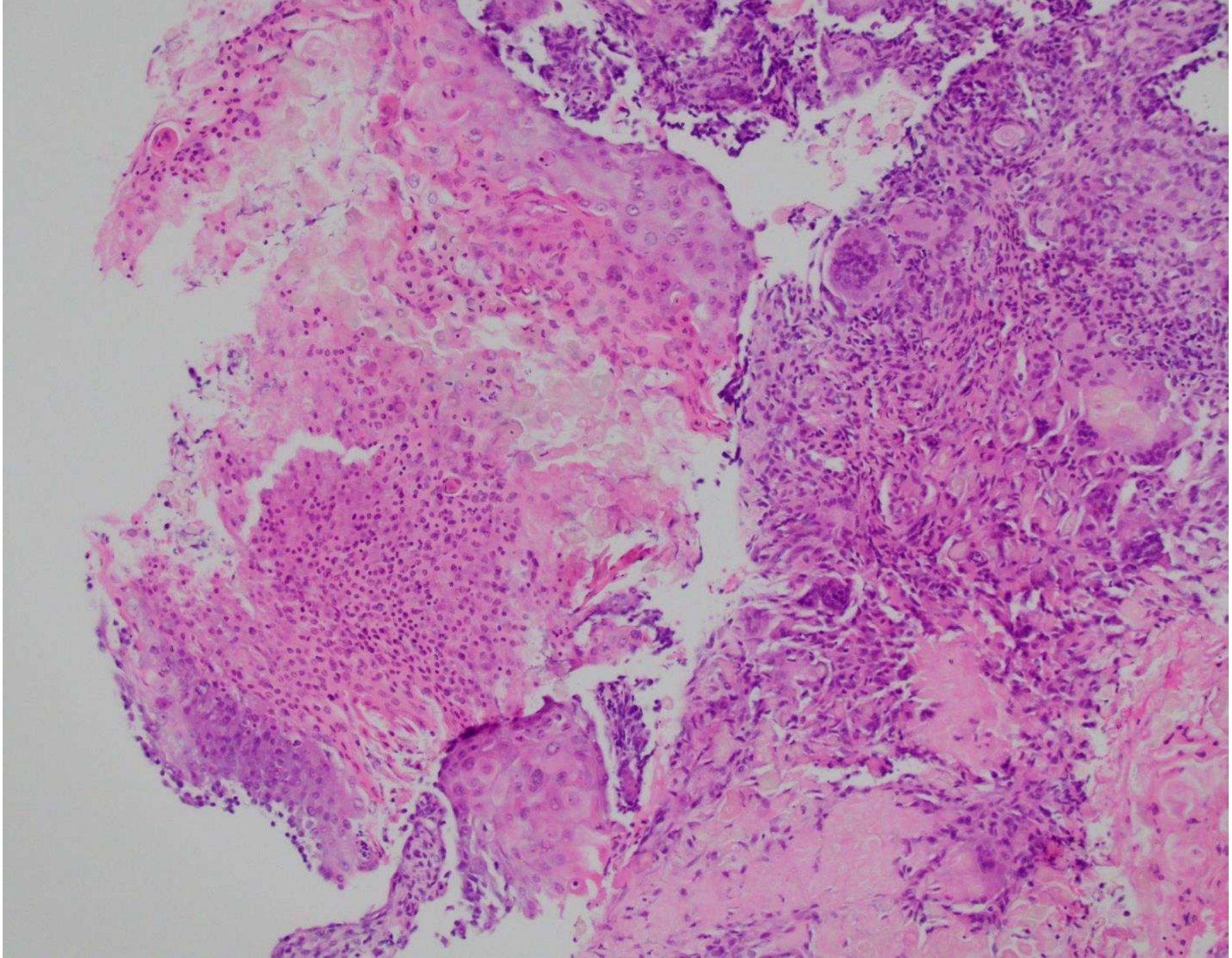
20-0901

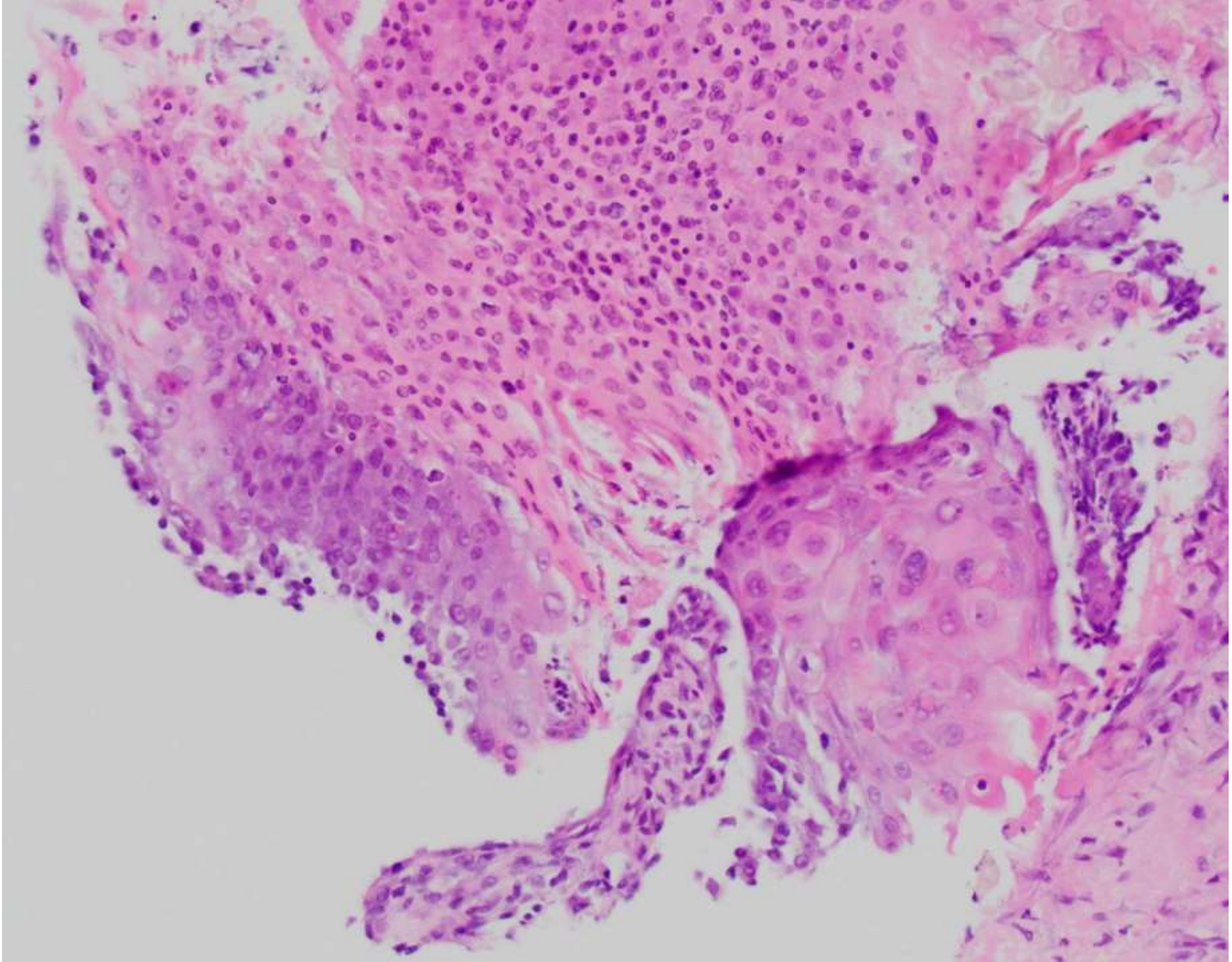
Hubert Lau; VA Palo Alto

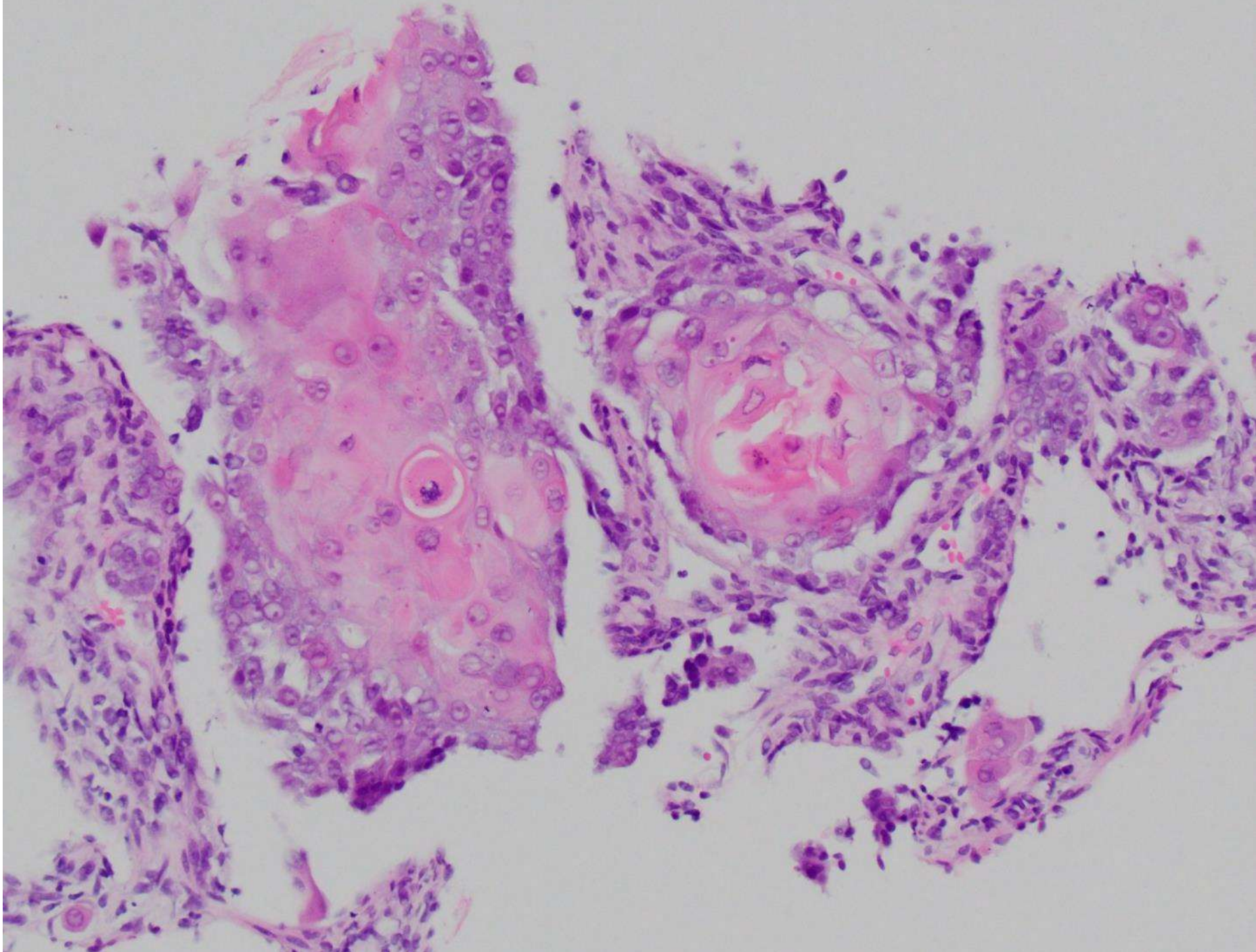
68-year-old M with h/o prostatic adenocarcinoma s/p radical prostatectomy (5 years prior) and subsequent androgen deprivation therapy presents with new chest wall mass and hypermetabolic lesions in lungs, liver, and adrenal glands. Core biopsy of chest wall mass performed.

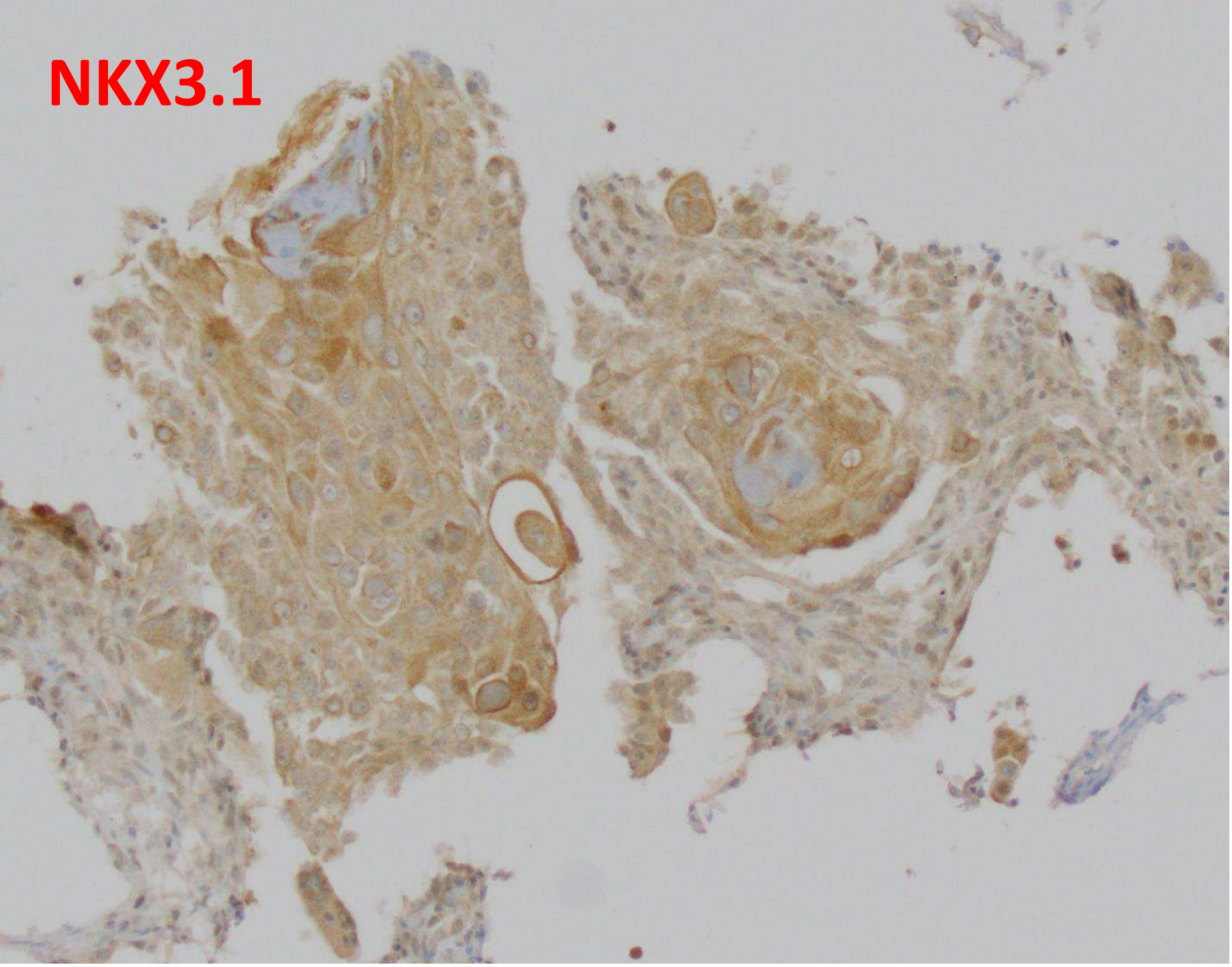











NKX3.1

Diagnosis:

Chest wall mass, core biopsy:

-- Involved by squamous cell carcinoma

Differential diagnosis:

- Squamous transformation of prostatic carcinoma
- Squamous cell carcinoma of pulmonary origin
- Other?

NGS performed on core biopsy specimen

Microsatellite status MS-Stable §

Tumor Mutational Burden 3 Muts/Mb §

CARD11 T128M

CTNNB1 S33C

PTEN loss §

RB1 loss §

TMPRSS2 TMPRSS2(NM_005656)-ERG(NM_004449) fusion (T1; E4) §

NGS performed on core biopsy specimen

Microsatellite status MS-Stable §

Tumor Mutational Burden 3 Muts/Mb §

CARD11 T128M

CTNNB1 S33C

PTEN loss §

RB1 loss §

TMPRSS2 TMPRSS2(NM_005656)-ERG(NM_004449) fusion (T1; E4) §

Squamous transformation of prostatic adenocarcinoma

- Rare phenomenon of uncertain etiology (<100 cases reported)
  - ? Squamous metaplasia
  - ? Prostatic urethral/periurethral duct origin
  - ? Pluripotent stem cells
- May be associated with prior ADT or radiotherapy, de novo cases also reported
- SCC of the prostate carries a poor prognosis
  - Aggressive behavior, tendency to metastasize
  - Does not respond to standard treatments for prostatic adenocarcinoma

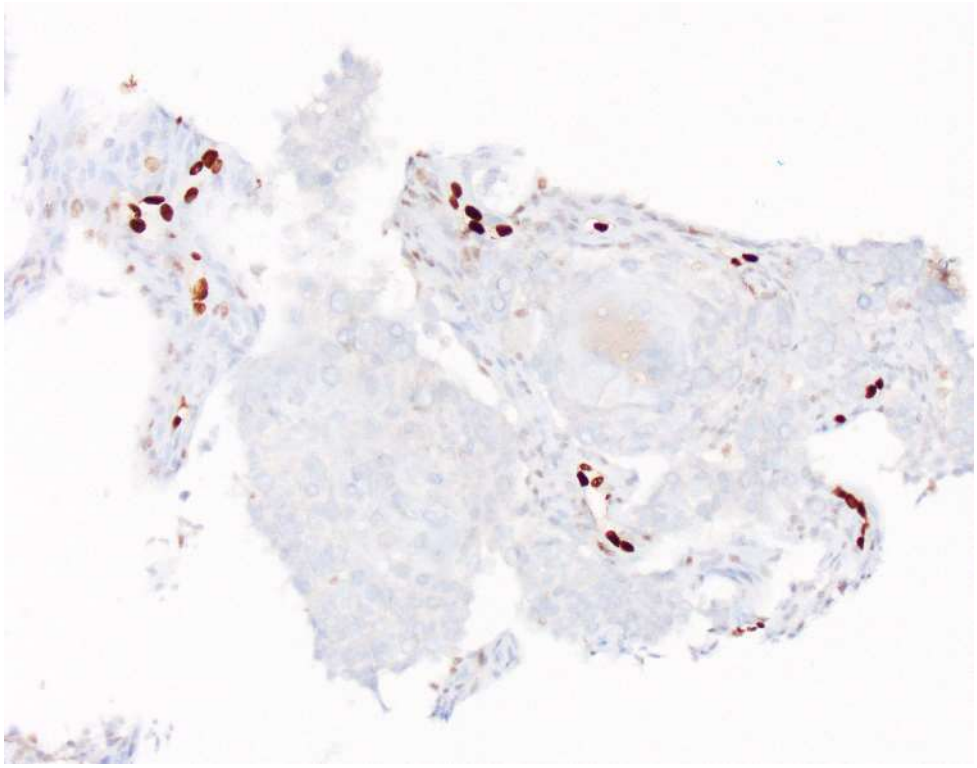
Ancillary studies: SCC of the prostate

- Stains like SCC
- Negative by IHC for PSA, PSAP, P501S/prostein
  - Very focal PSA or PSAP rarely seen (Parwani AV et al. *Am J Surg Pathol.* 2004;**28**:651-657.)
- NKX3.1 IHC not well-characterized, but negative in recent case reports

- NGS/molecular methods may be useful for identifying organ-specific alterations

- Clinical correlation most important

ERG IHC



ERG IHC

- ERG rearrangement detected in ~50% of prostatic adenocarcinomas
- ERG IHC is a useful surrogate for identifying an ERG fusion event
  - Sensitivity 86-98%
    - Chaux A et al. *Am J Surg Pathol*. 2011;**35**:1014-1020.
    - Braun M et al. *Prostate Cancer Prostatic Dis*. 2012;**15**:165-169.

ERG IHC in aggressive variants of prostate cancer

ORIGINAL ARTICLE | Full Access

Gene Fusion Characterization of Rare Aggressive Prostate Cancer Variants - Adenosquamous Carcinoma, Pleomorphic Giant Cell Carcinoma, and Sarcomatoid Carcinoma: An Analysis of 19 Cases

Mohamed Alhamar, Tudor Vladislav, Steven C. Smith, Yuan Gao, Liang Cheng, Laura A. Favazza, Ali M. Alani, Michael M. Ittmann, Nicole D. Riddle, Lisa J Whiteley, Nilesh S. Gupta, Shannon Carskadon, Juan C Gomez-Gelvez, Dhananjay A. Chitale, Nallasivam Palanisamy, Ondrej Hes, Kiril Trpkov, Sean R. Williamson ... See fewer authors

First published: 08 July 2020 | https://doi-org.laneproxy.stanford.edu/10.1111/his.14205

- 19 tumors with 1 or more variant, including sarcomatoid (n=10), adenosquamous (n=7), and pleomorphic giant cell carcinoma (n=7)
- ERG rearrangement detected in 47% (n=9), similar frequency to conventional prostatic adenocarcinoma
- Only 56% of cases showed positive ERG IHC in variant component

Clinical follow-up

- Received systemic therapy for 4 months
  - 3 cycles of carboplatin/nab-paclitaxel/pembrolizumab
  - 1 dose of gemcitabine/docetaxel
- Serum PSA 1.33 ng/mL, but evidence of disease progression by imaging
- Eventually transitioned to comfort care and died ~1 month later

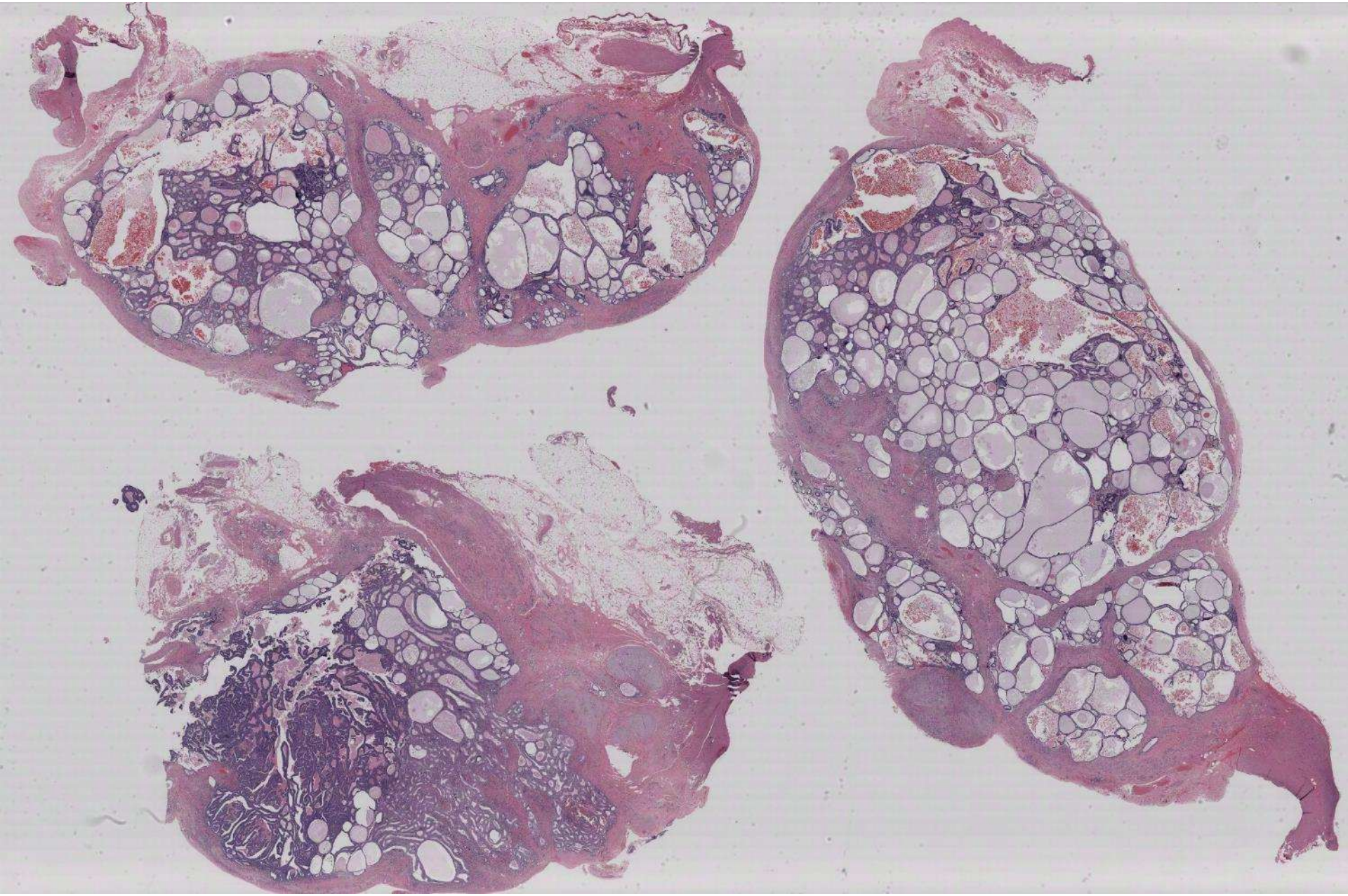
Take home points

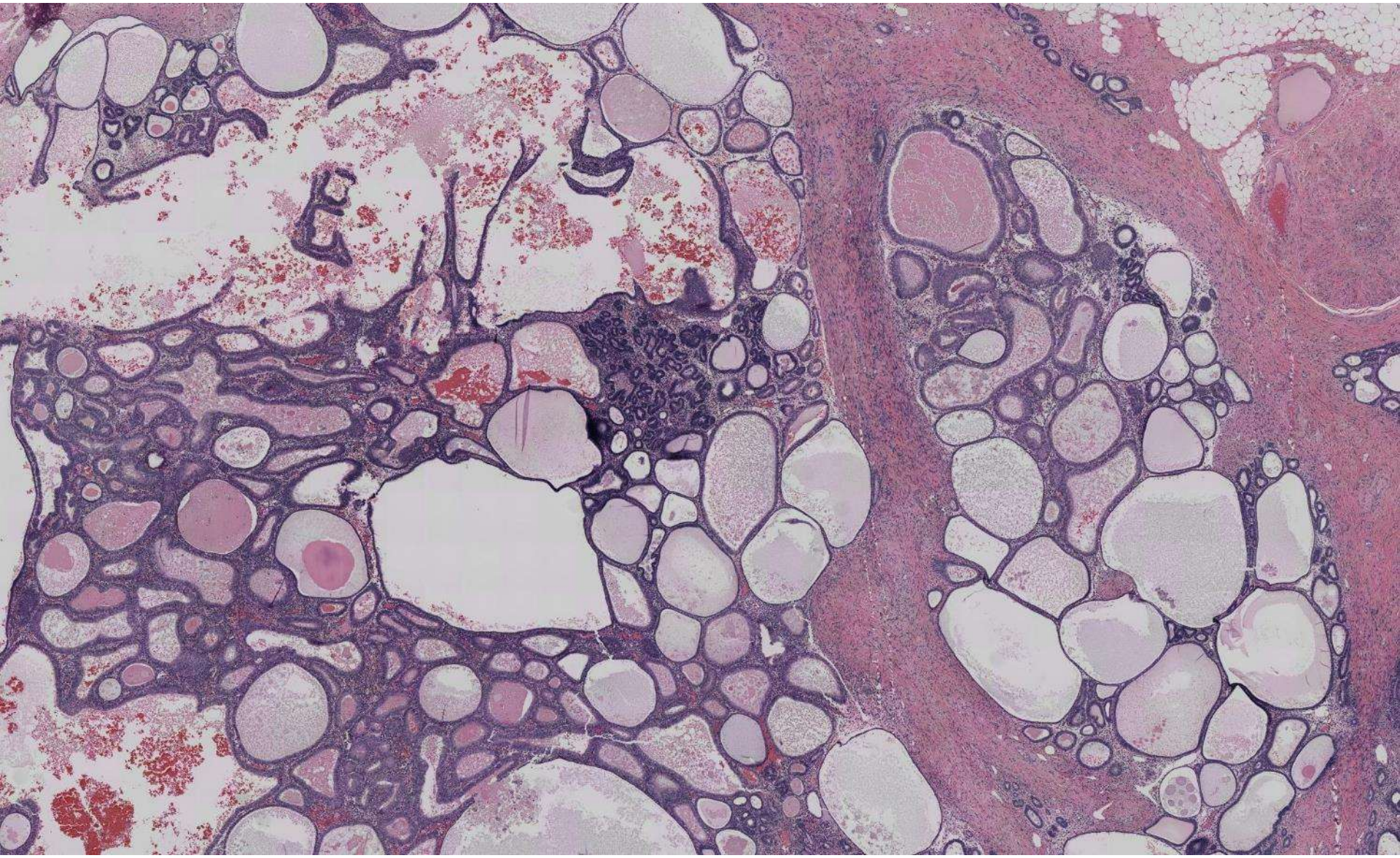
- SCC of the prostate is a rare, aggressive variant that may be associated with prior ADT or radiotherapy
- Morphology and immunohistochemical profile are generally non-specific
- Clinical correlation and molecular methods are most useful for confirming the site of origin
- ERG IHC may be helpful, but appears less sensitive in aggressive variants of prostate cancer

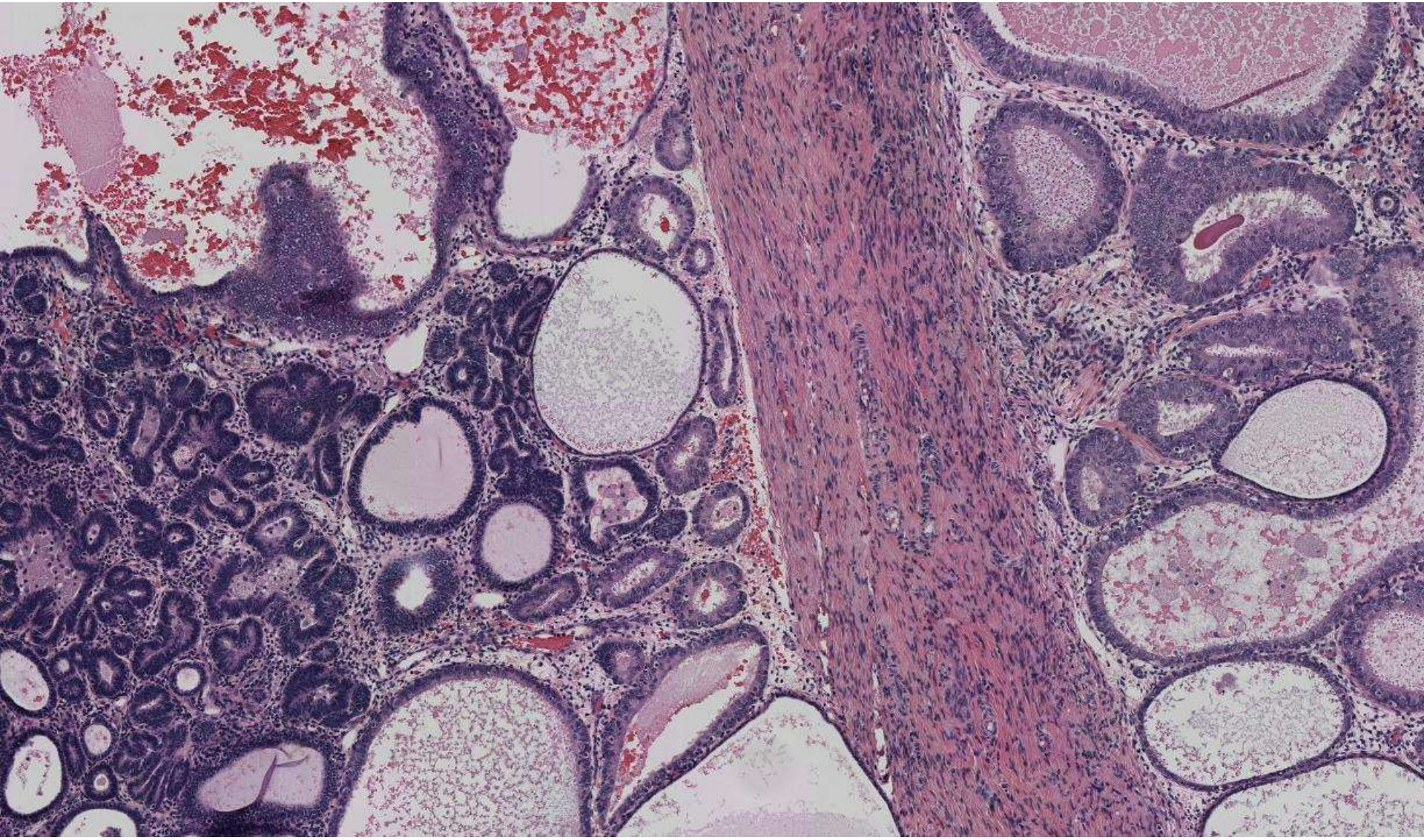
20-0902
scanned slide available!

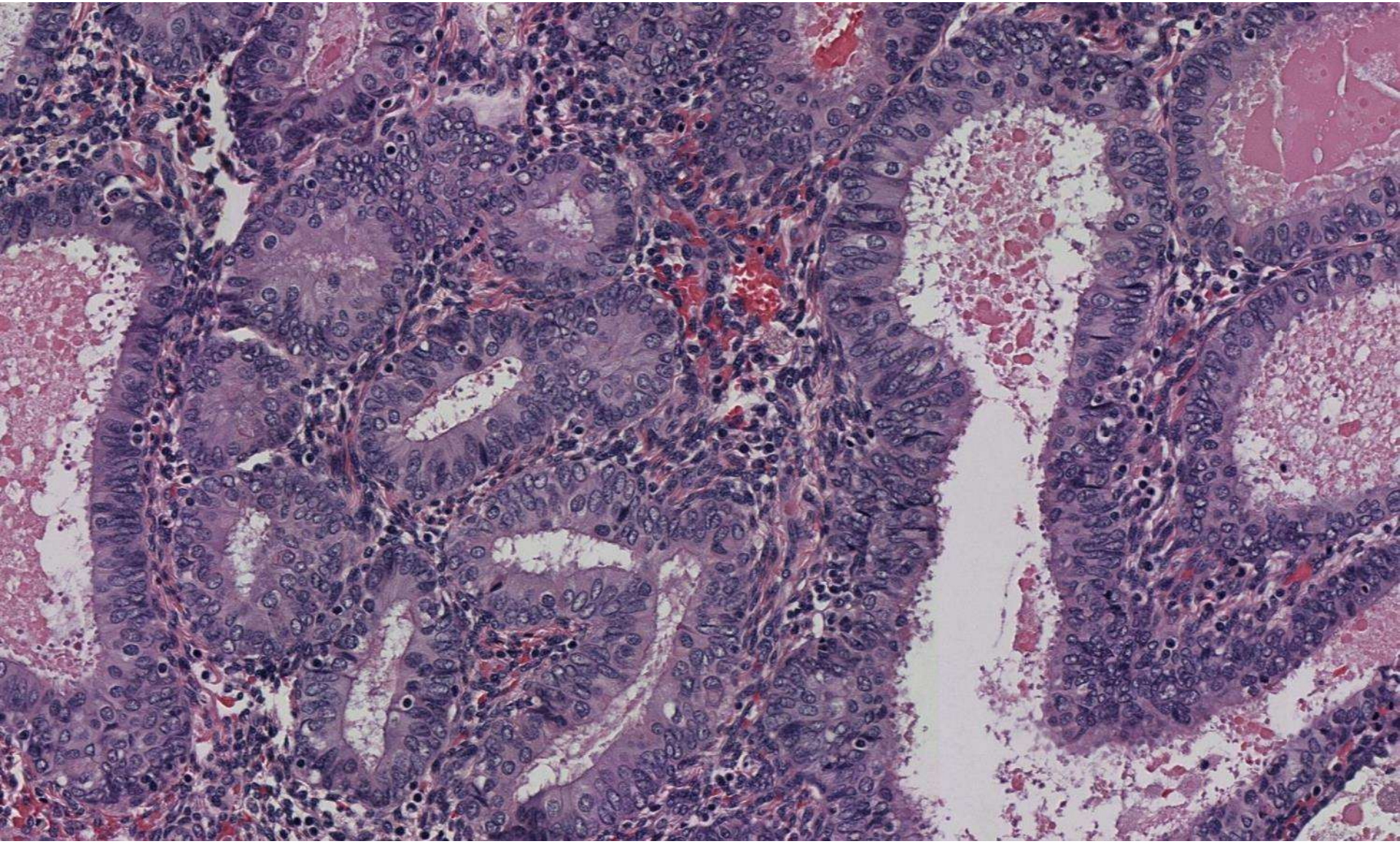
Keith Duncan; Mills-Peninsula

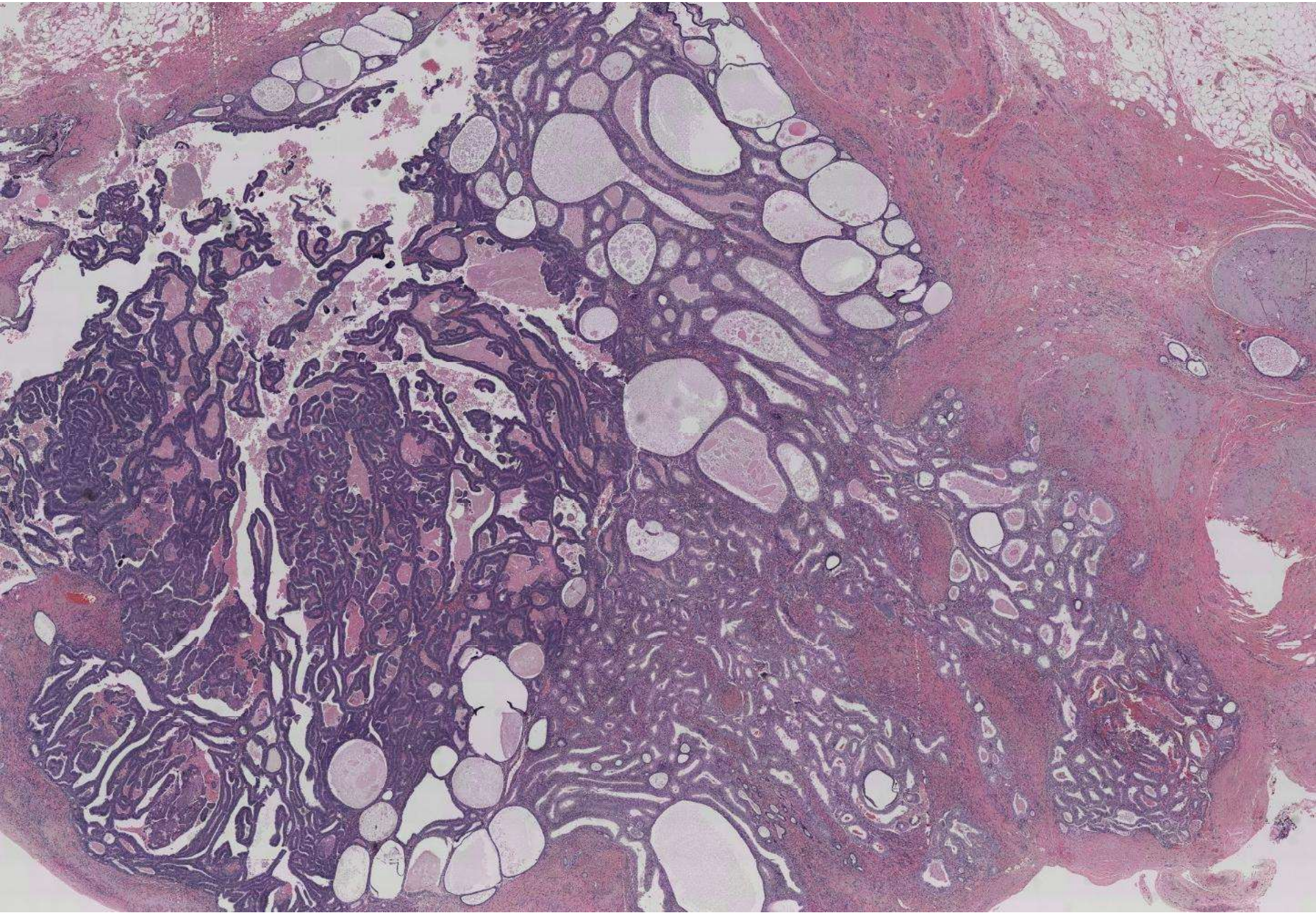
80-year-old F with masses in pelvis, diaphragm, and small intestine.

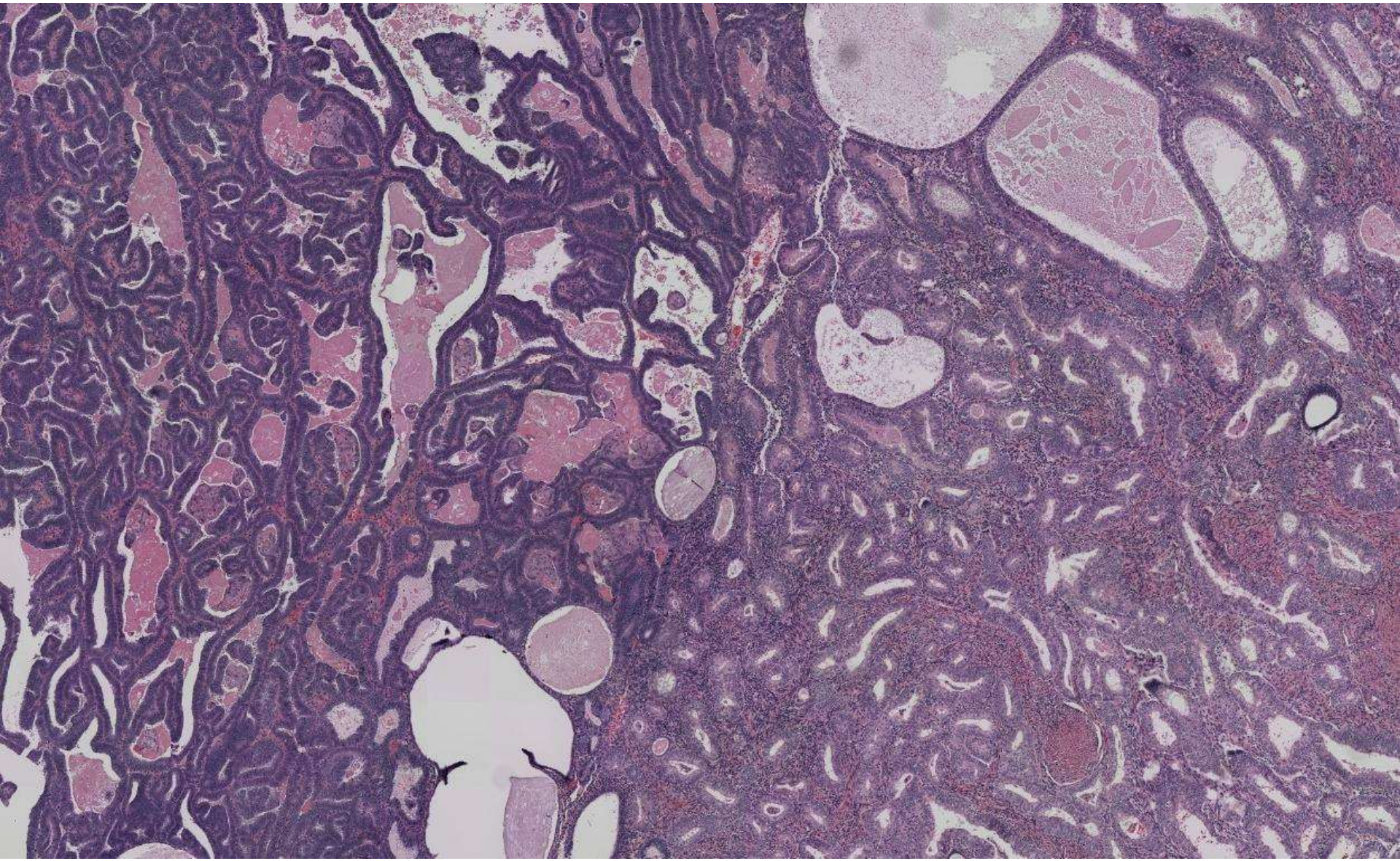


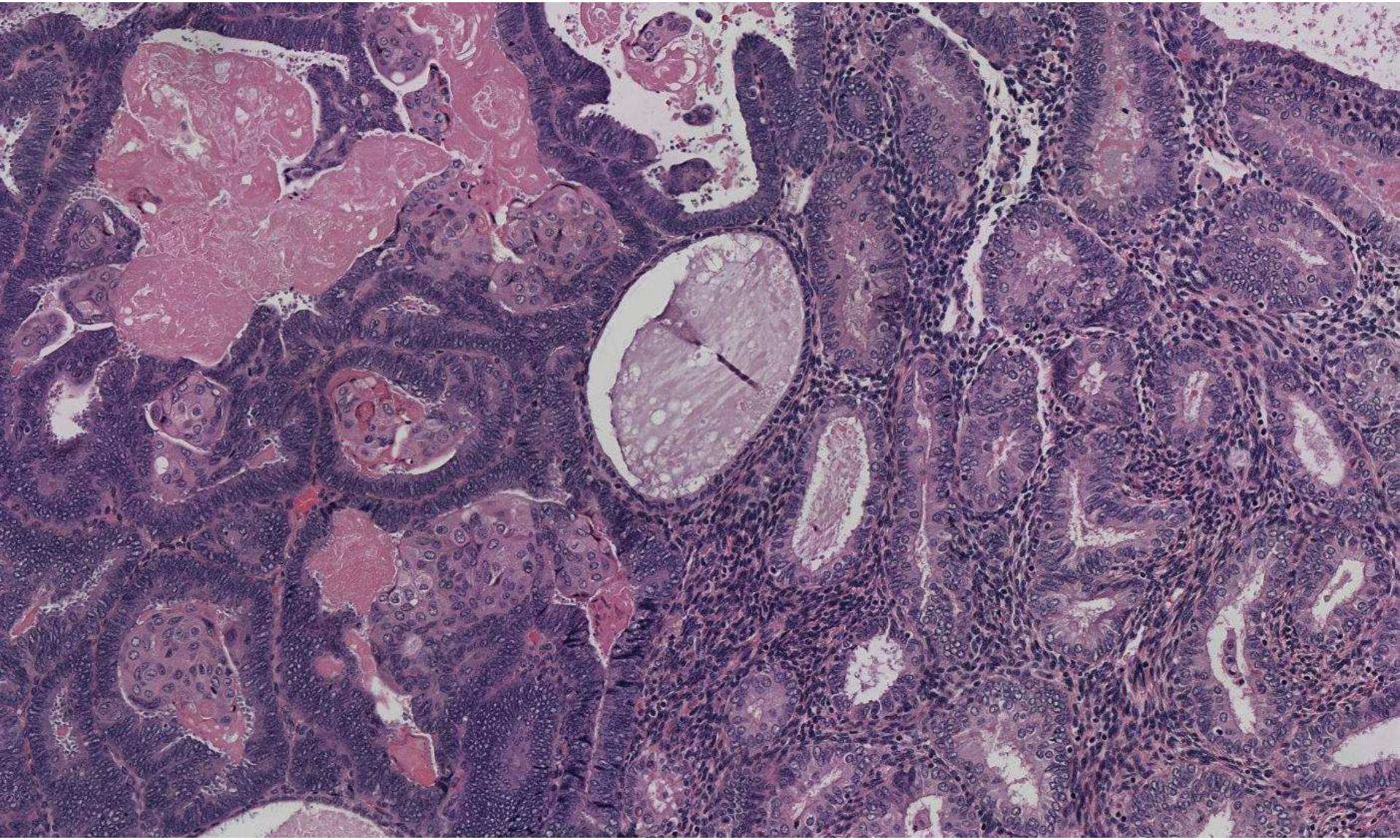


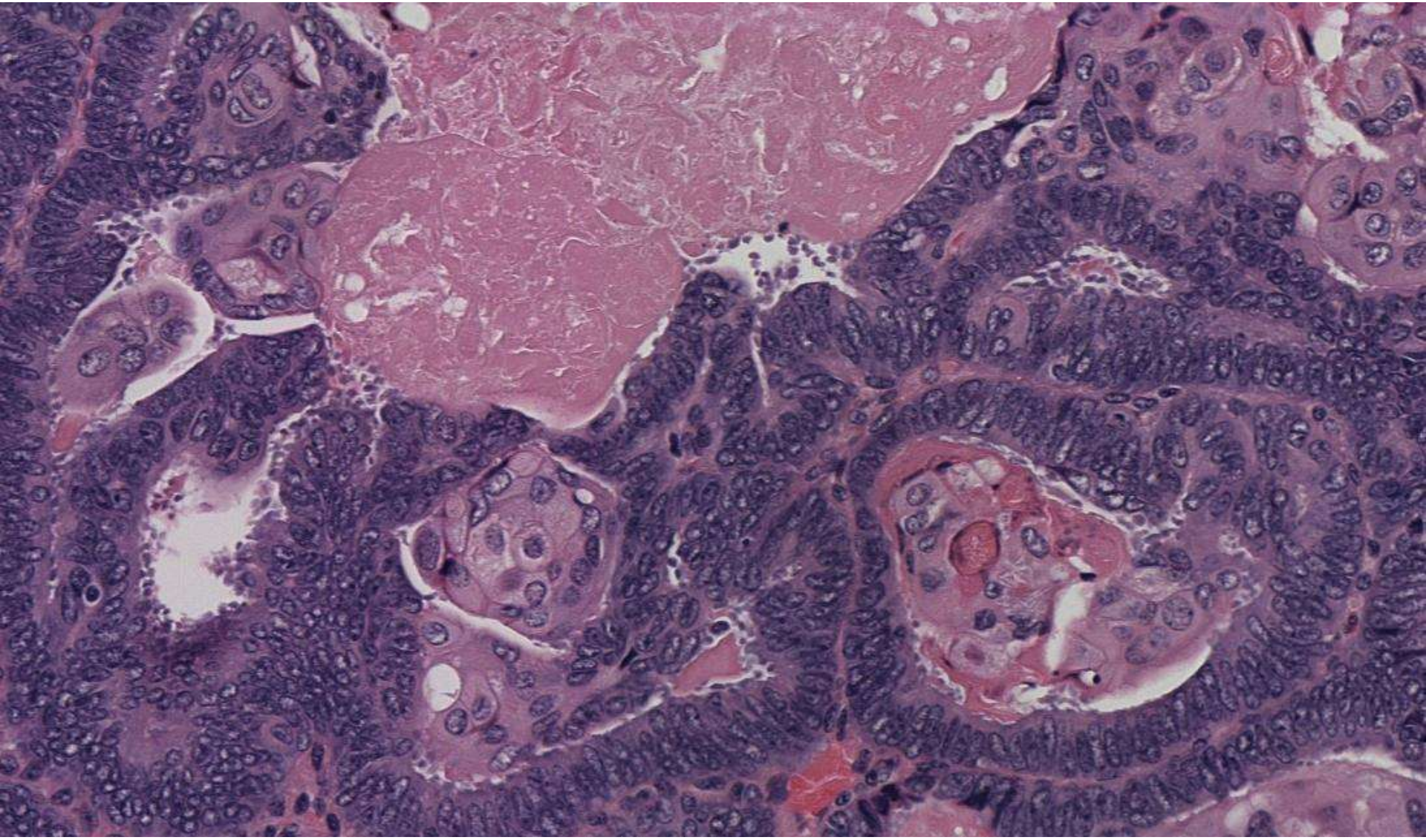


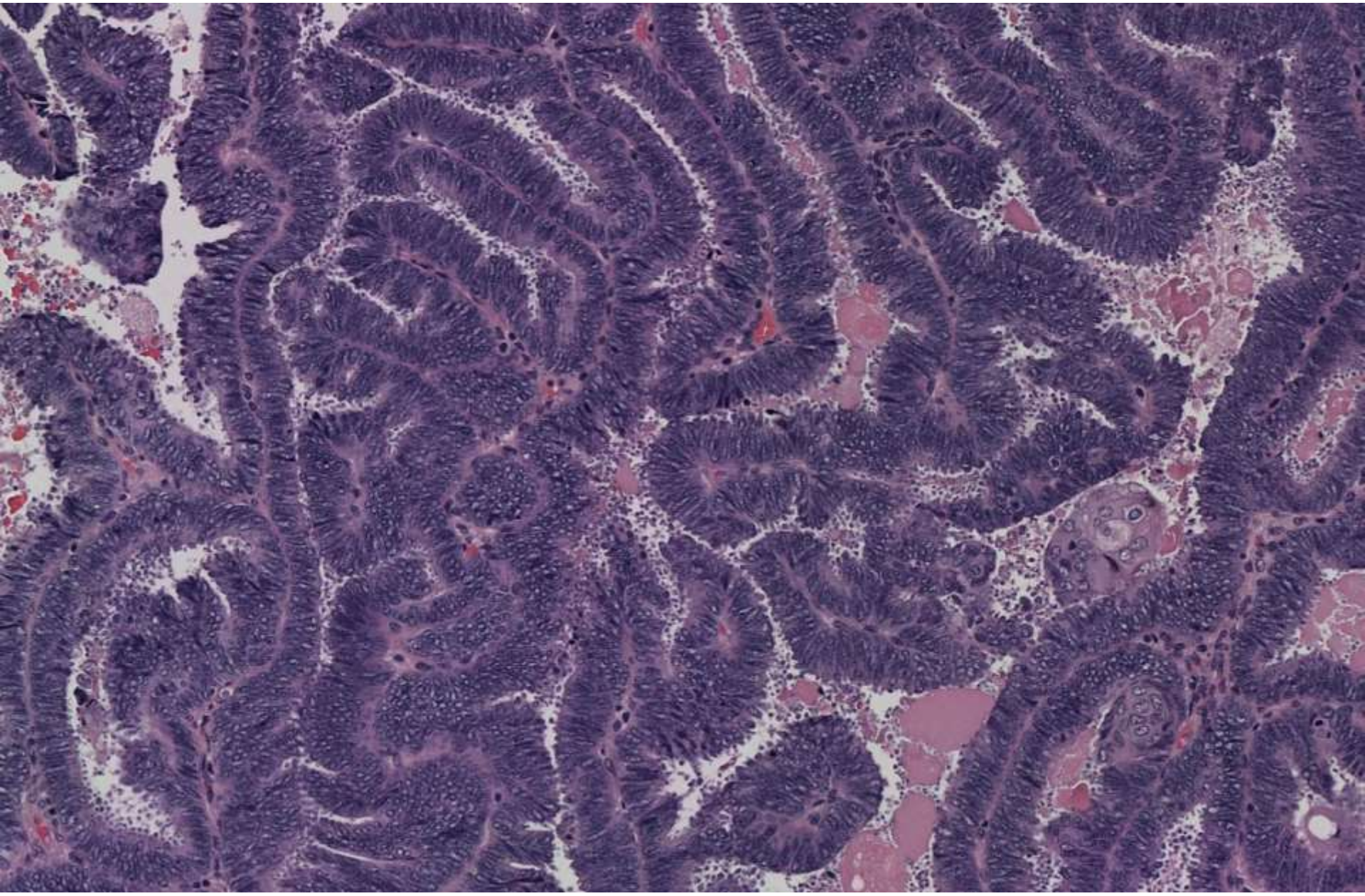


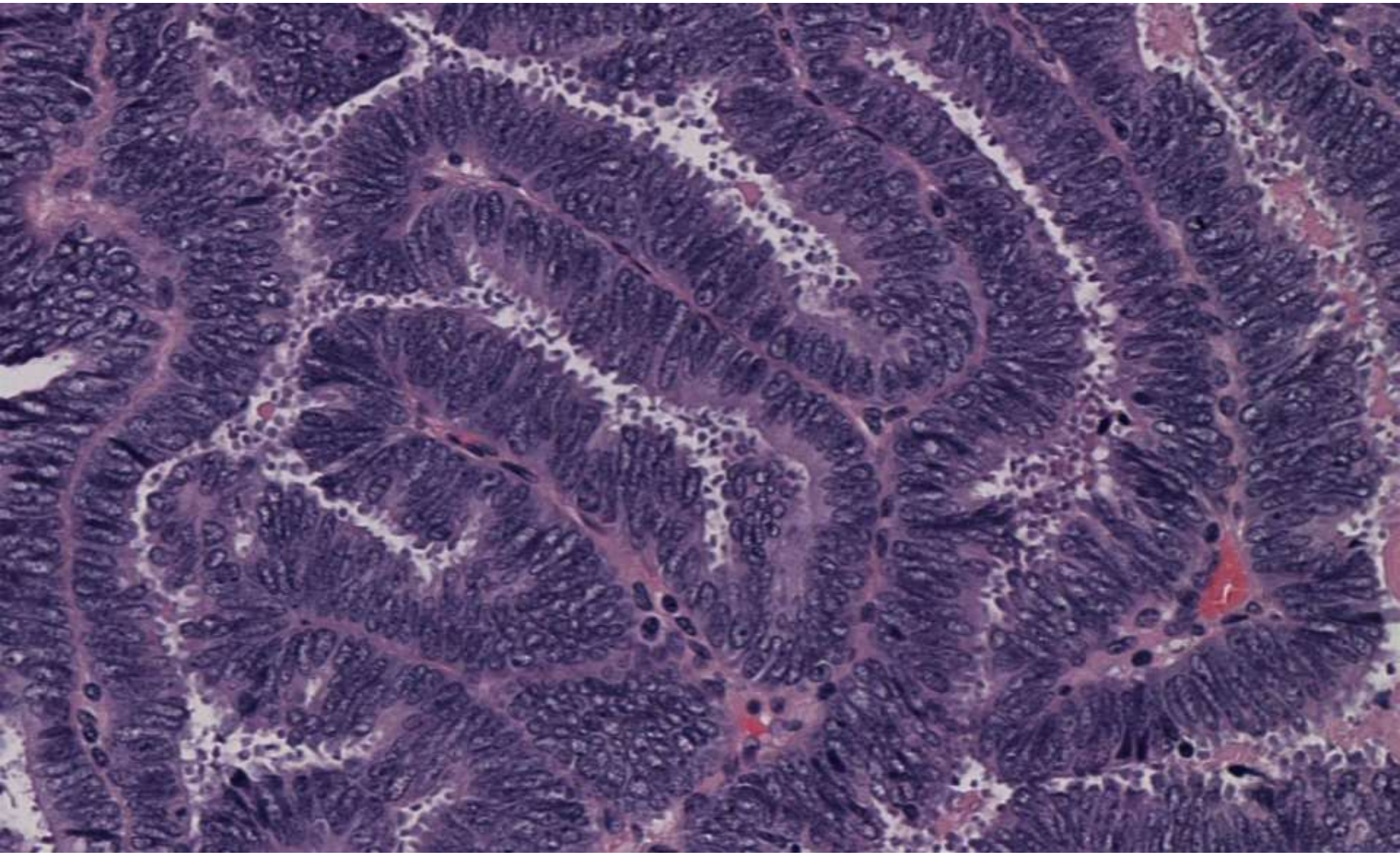












Endometrial adenocarcinoma arising in polypoid endometriosis

Polypoid endometriosis is an uncommon variant of endometriosis that is characterized as a lesion which is similar to an endometrial polyp and can be found most often in the colon, ovarian, uterine serosa, cervical canal, vaginal mucosa, ureter, fallopian tube, omentum, bladder peritoneum and paraurethral and paravaginal regions.

m<ay form large, often multiple, polypoid masses that “not only simulate malignant tumors at operation but may also recur after operative removal”.

Differential diagnosis includes several types of tumors as adenofibroma, endometrial stromal sarcoma and adenosarcoma

First introduced by Mostoufizadeh and Scully in 1980.

Endometrial adenocarcinoma arising in polypoid endometriosis

Multifocal deposits of polypoid endometriosis characterized by cystically dilated endometriotic glands and stroma showing fibrosis and hemosiderin laden macrophages.

Variable glandular architecture ranging from hyperplasia to complex hyperplasia to frank malignancy.

IPOX stains:

Positive: ER, PR, CK7, P53(Wild type expression).
Negative: CK20, CDX-2, WT-1, CEA.

PATHOGENESIS

Pathogenesis of this disease unclear.
Several hypotheses, including conventional retrograde menstruation theory with involvement of mucosal or subserosal sites, or the lining of cyst cavities, permitting polypoid growth.

Other theories include hormonal stimulation, including unopposed estrogen and combined estrogen-progestin therapy, tamoxifen use, or even following withdrawal of gonadotrophin-releasing hormone (GnRH) agonist.

References:

P.B. Clement:
The pathology of endometriosis: a survey of the many faces of a common disease emphasizing diagnostic pitfalls and unusual and newly appreciated aspects
Adv Anat Pathol, 14 (4) (2007), pp. 241-260

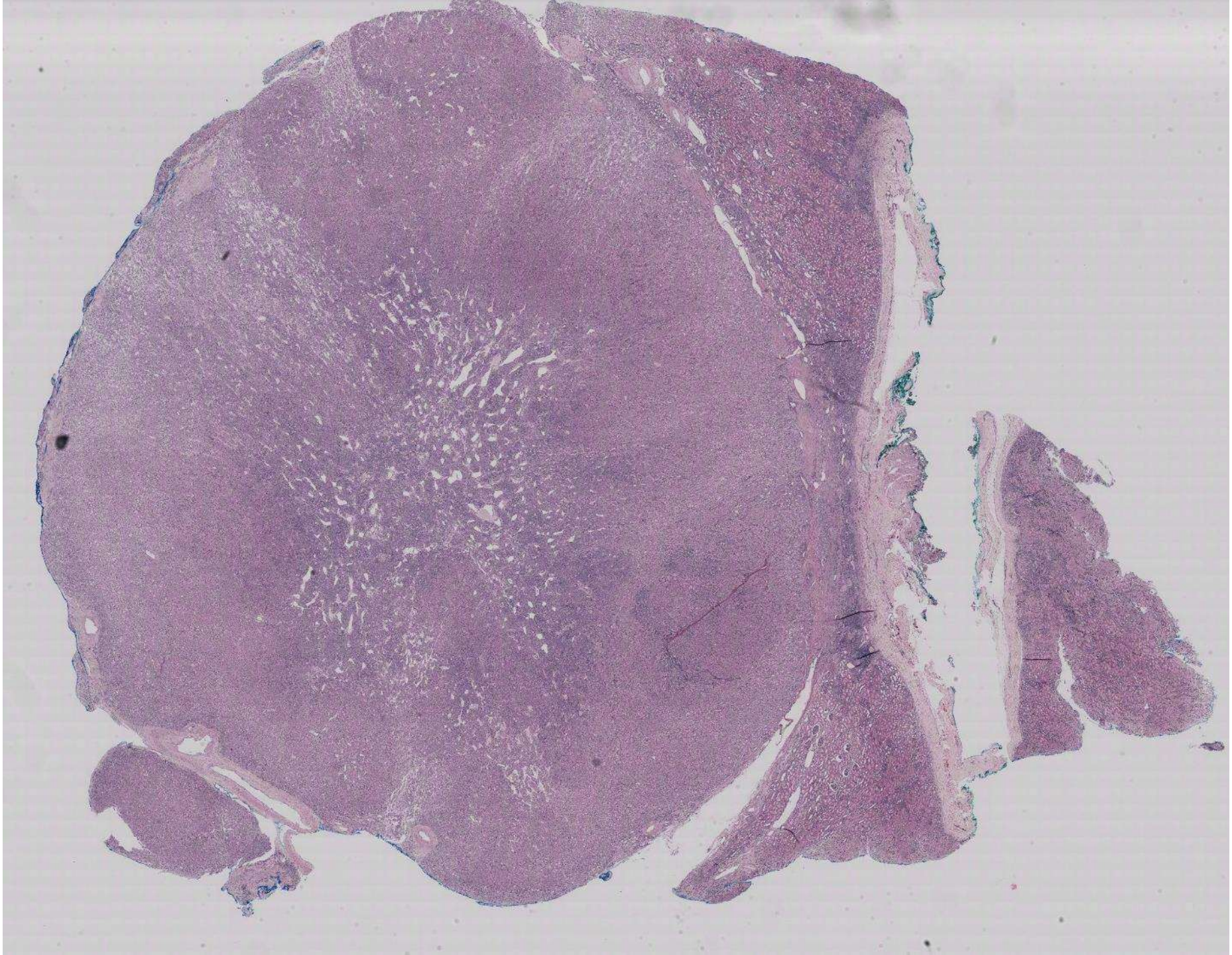
Parker RL, Dadmanesh F, Young RH, Clement PB. **Polypoid endometriosis: a clinicopathologic analysis of 24 cases and a review of the literature**. Am J Surg Pathol. 2004;28(3):285-297

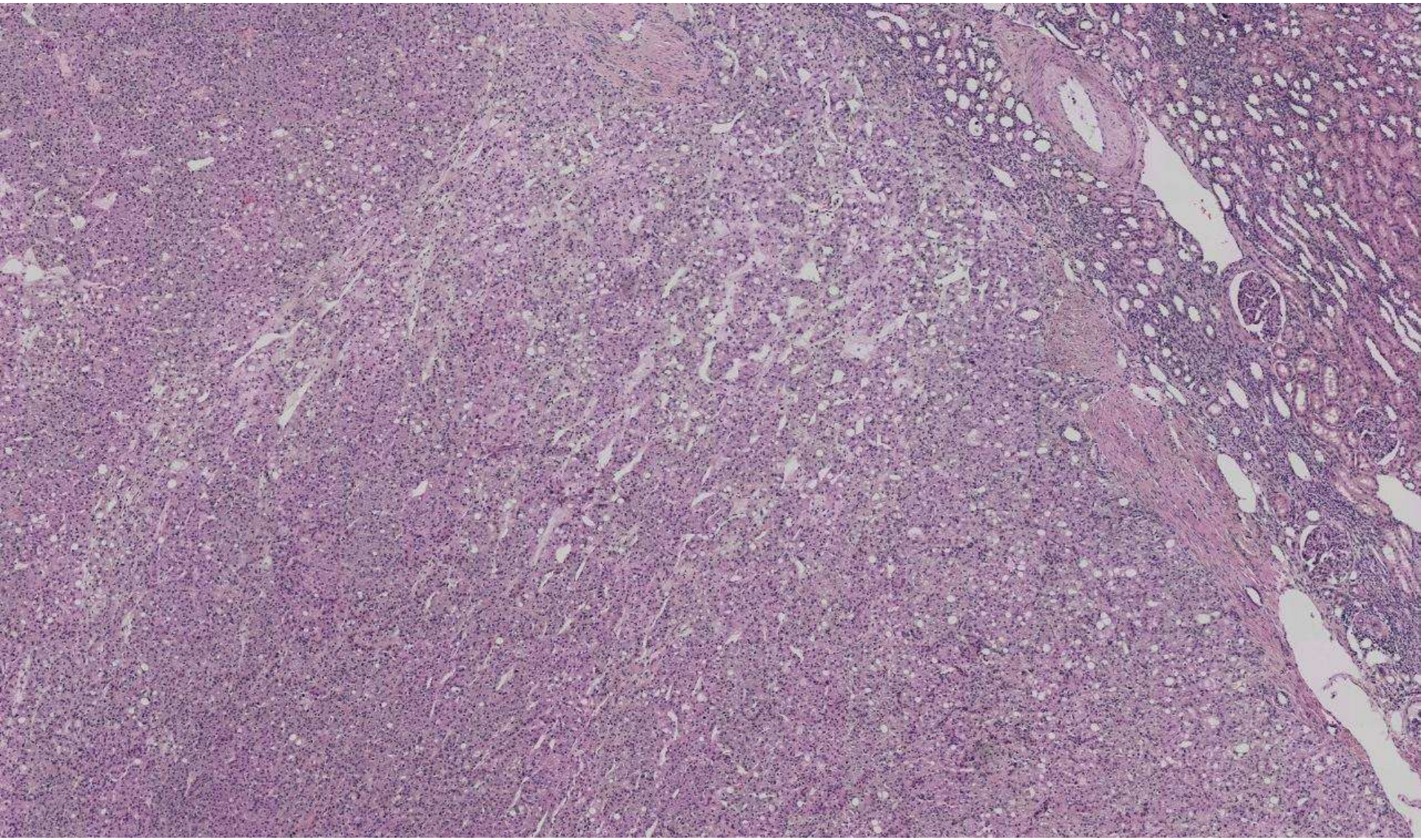
M. Mostoufizadeh, R.E. Scully. **Malignant tumors arising in endometriosis**
Clin Obstet Gynecol, 23 (3) (1980), pp. 951-963

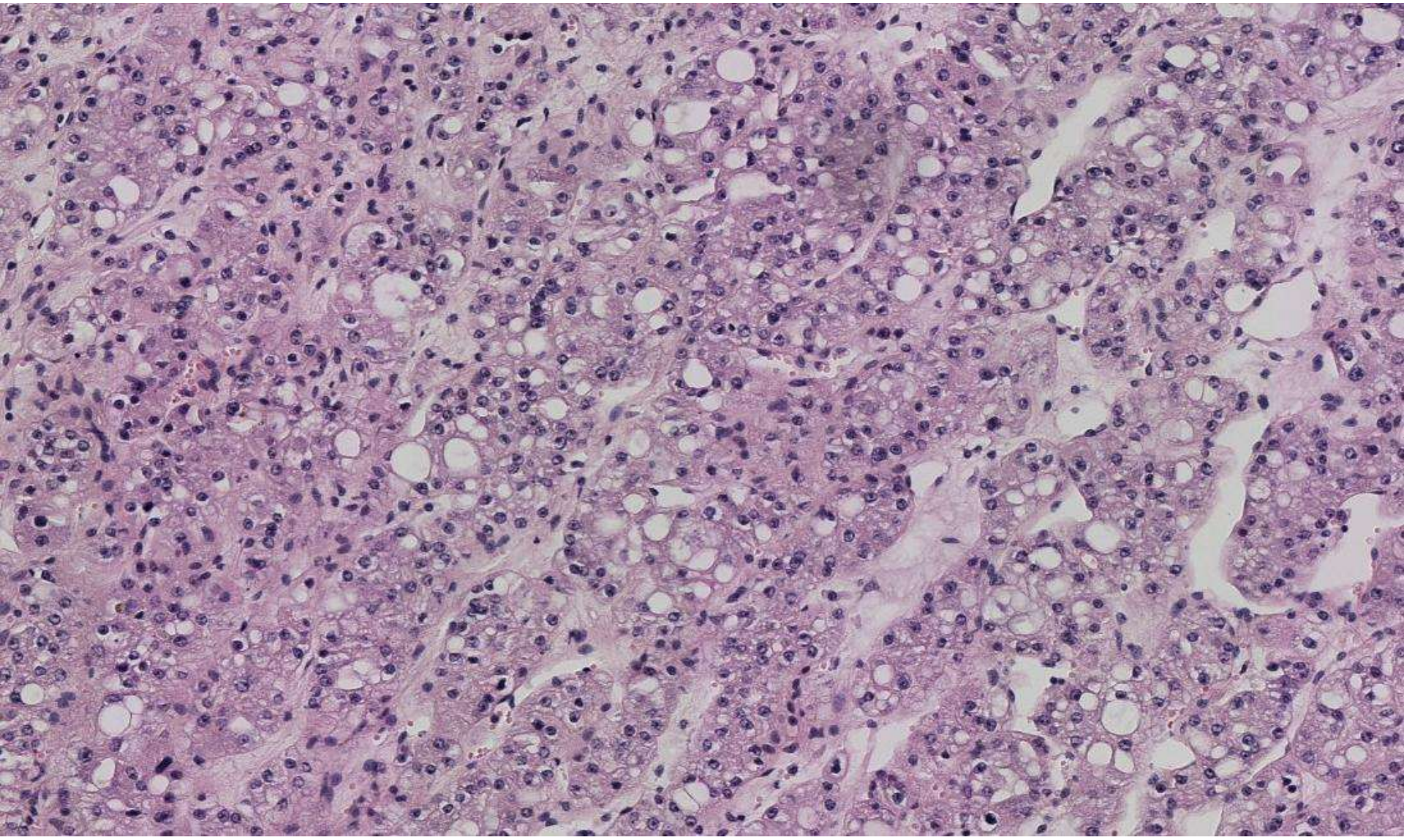
20-0903
scanned slide available!

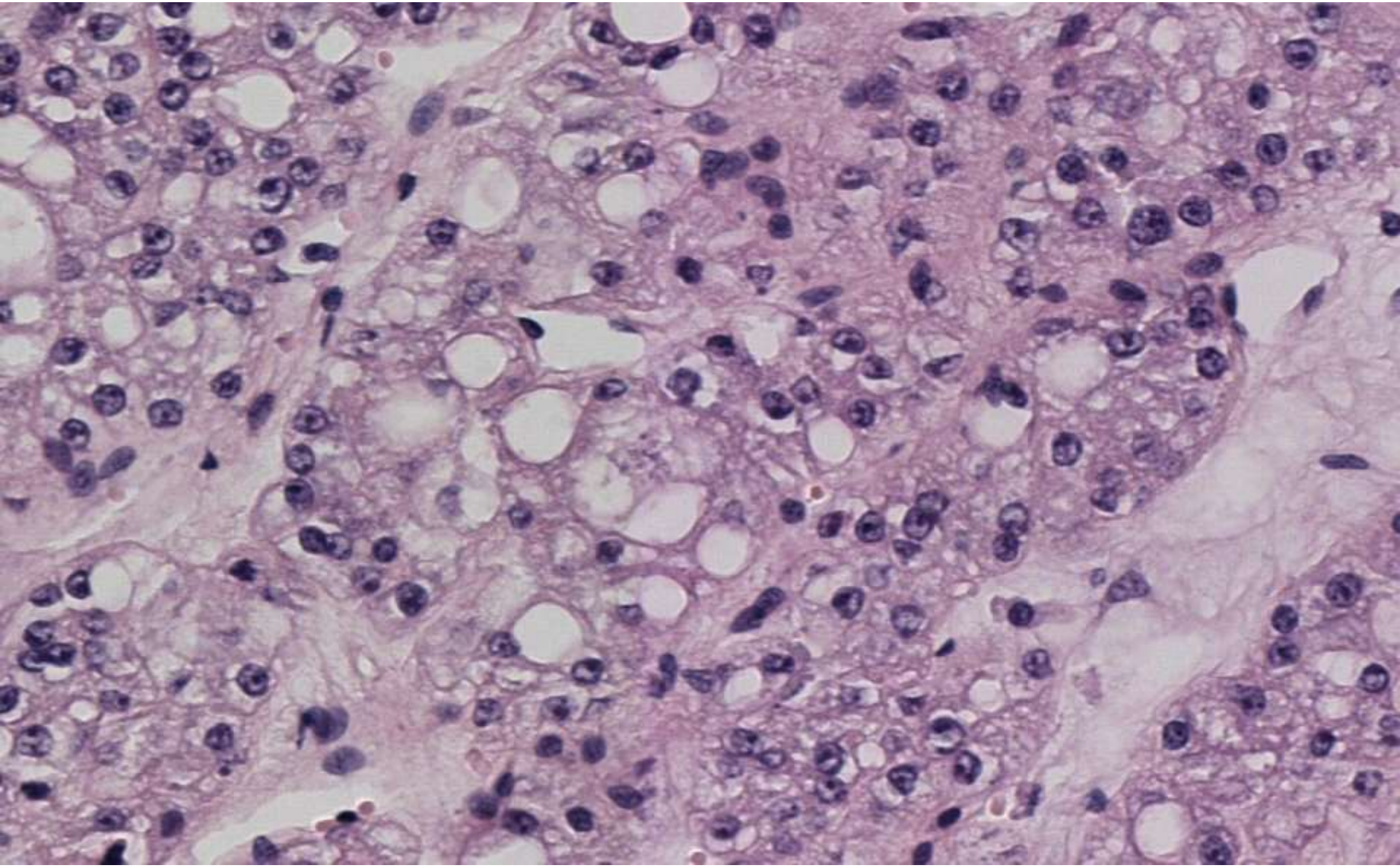
Emily Chan; UCSF

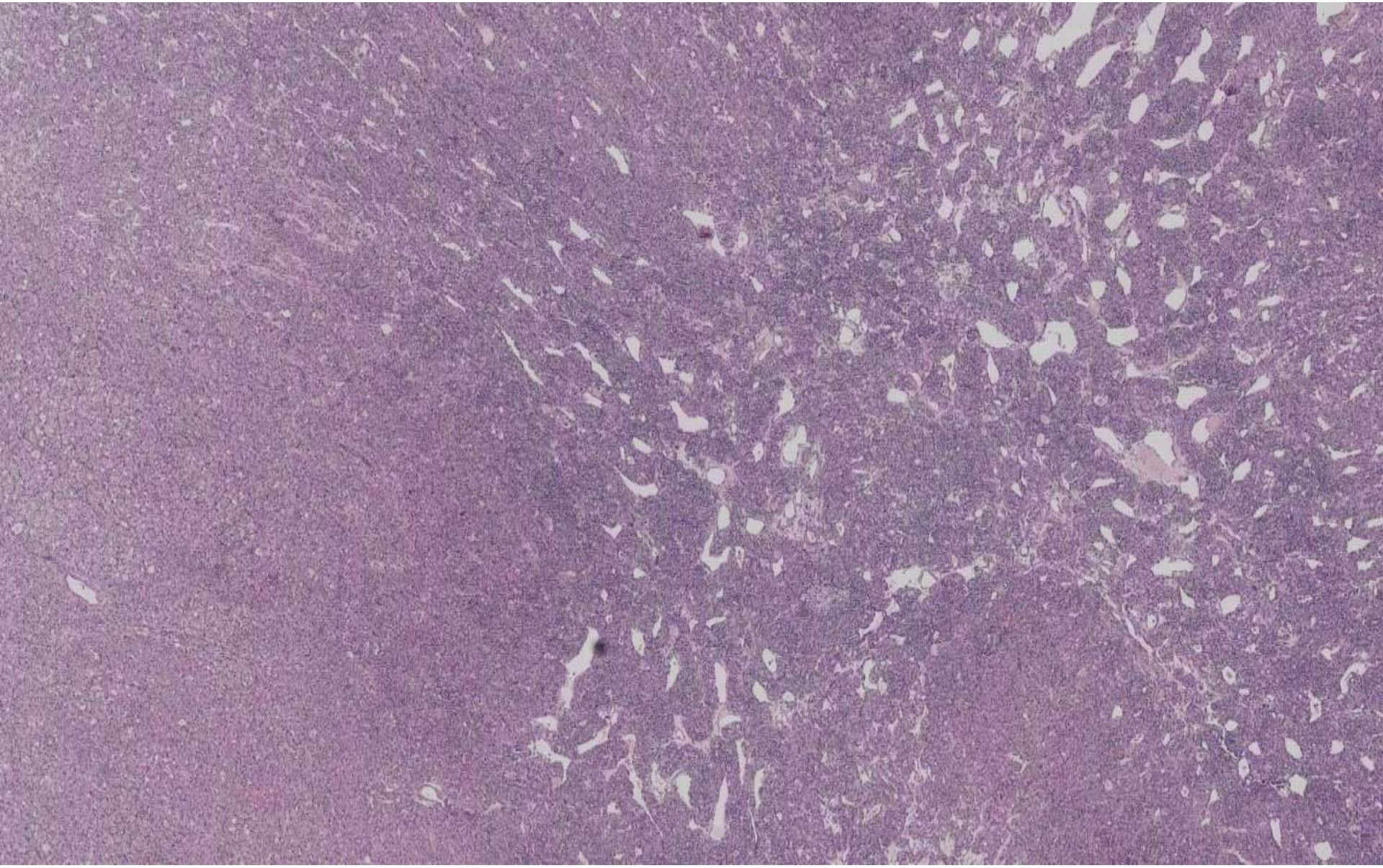
33-year-old F with 2.5cm right kidney mass.

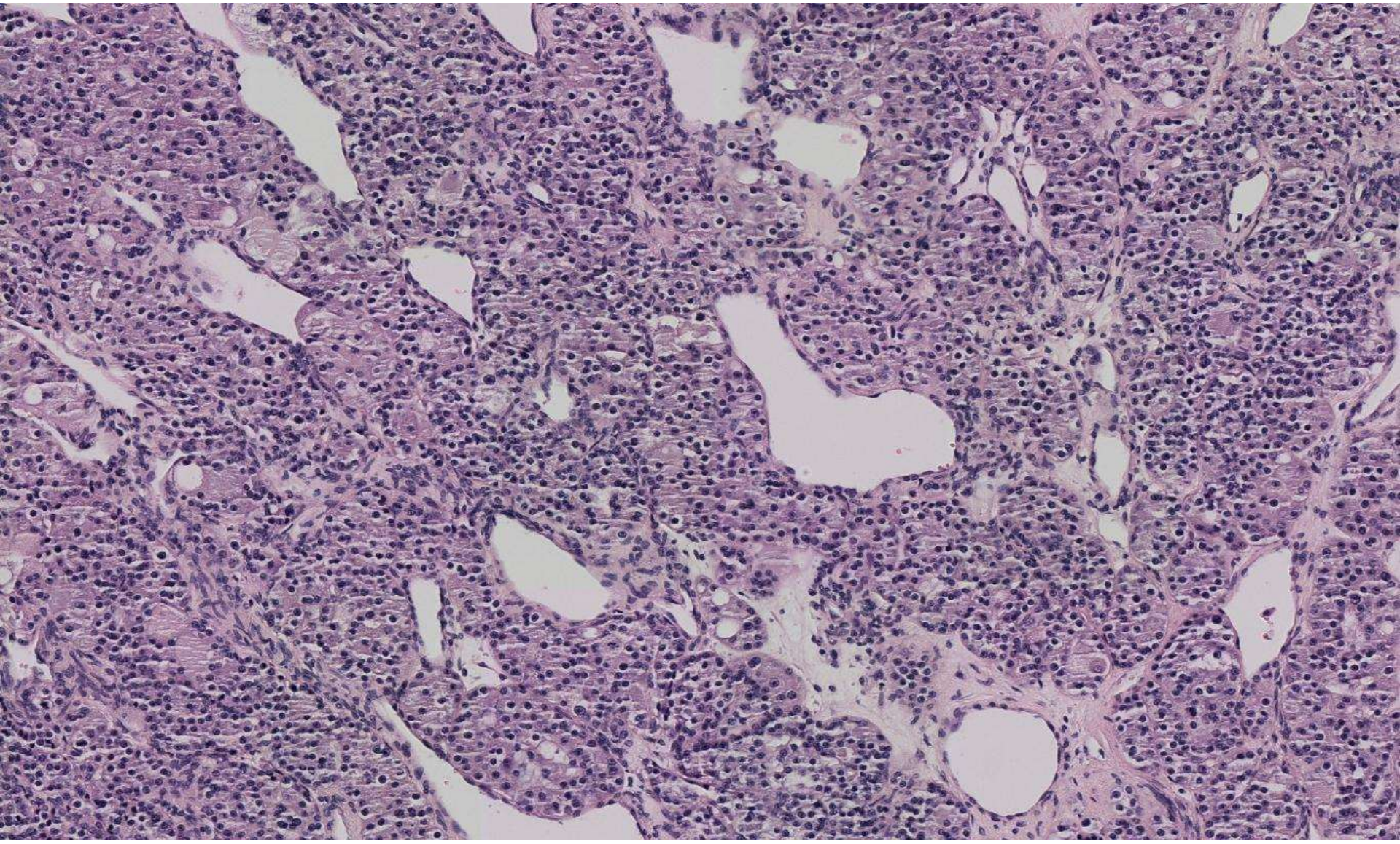


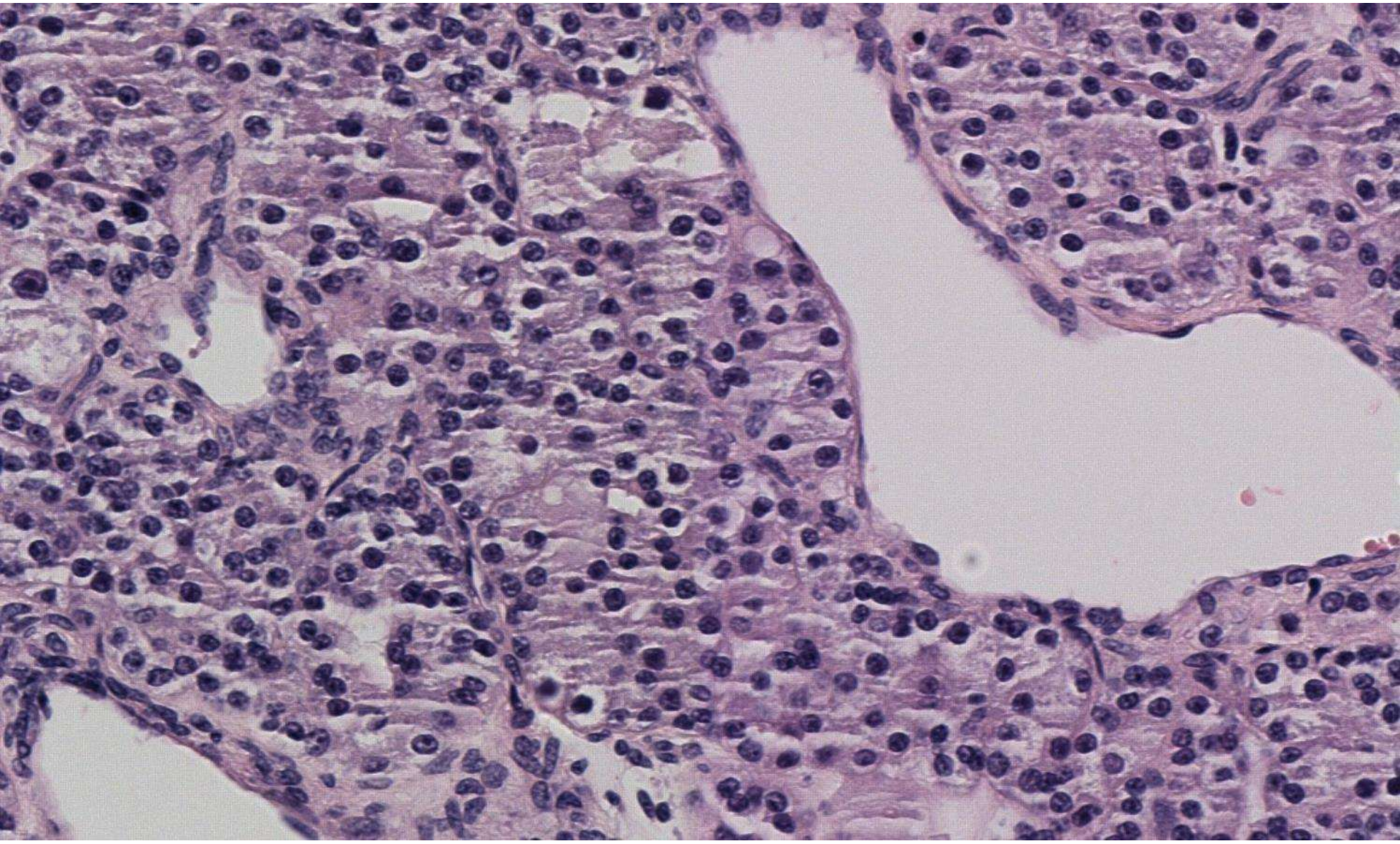


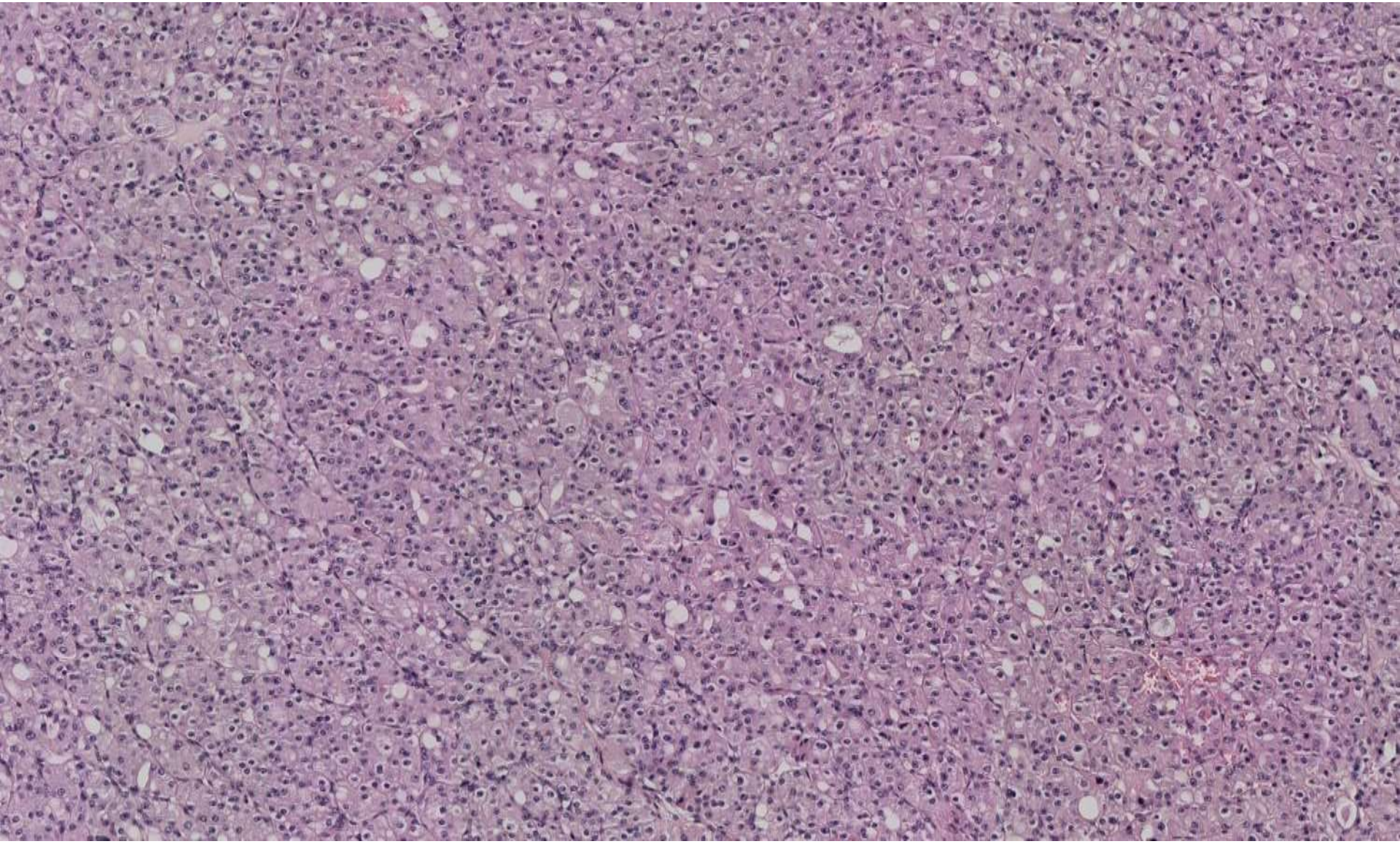


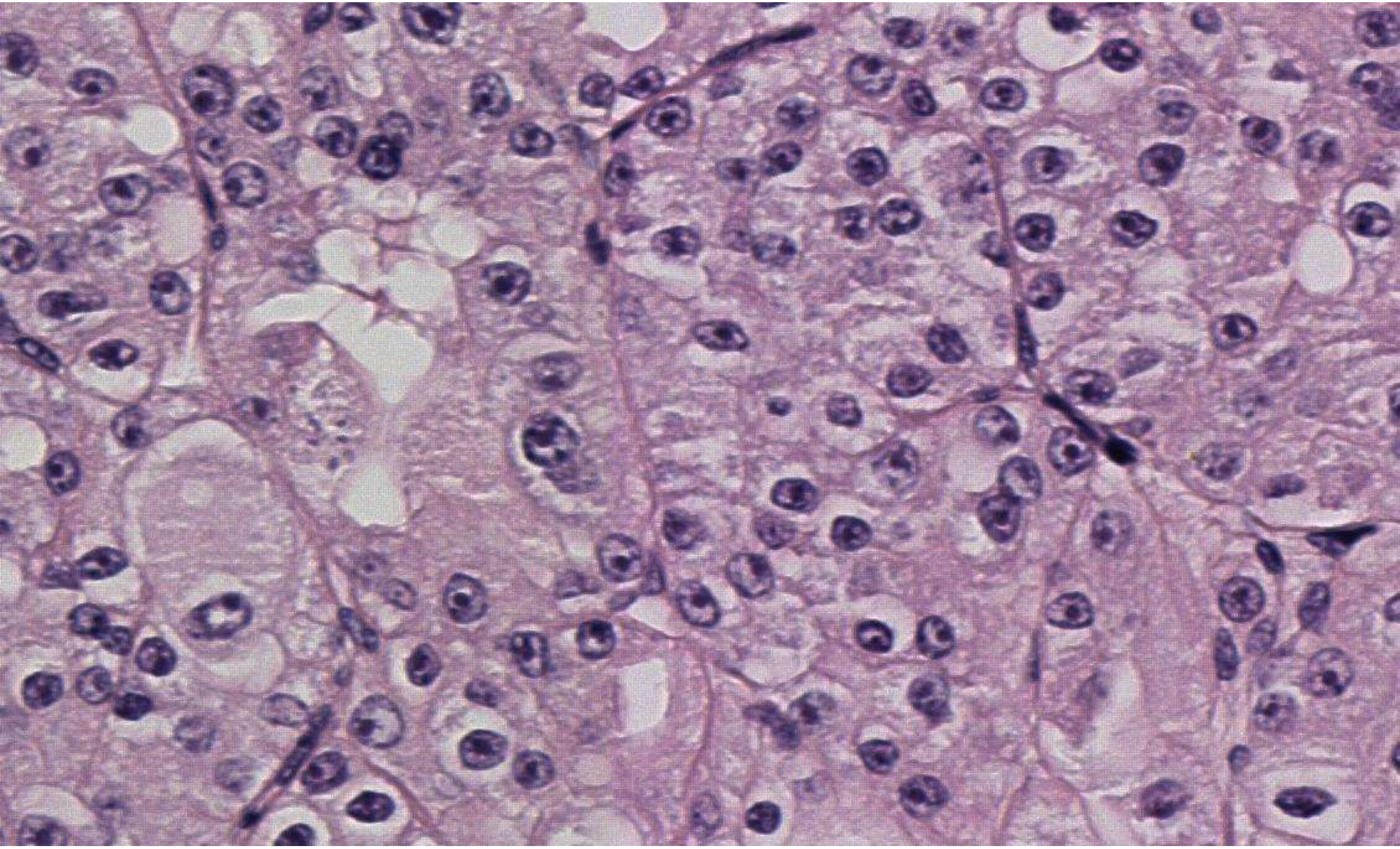




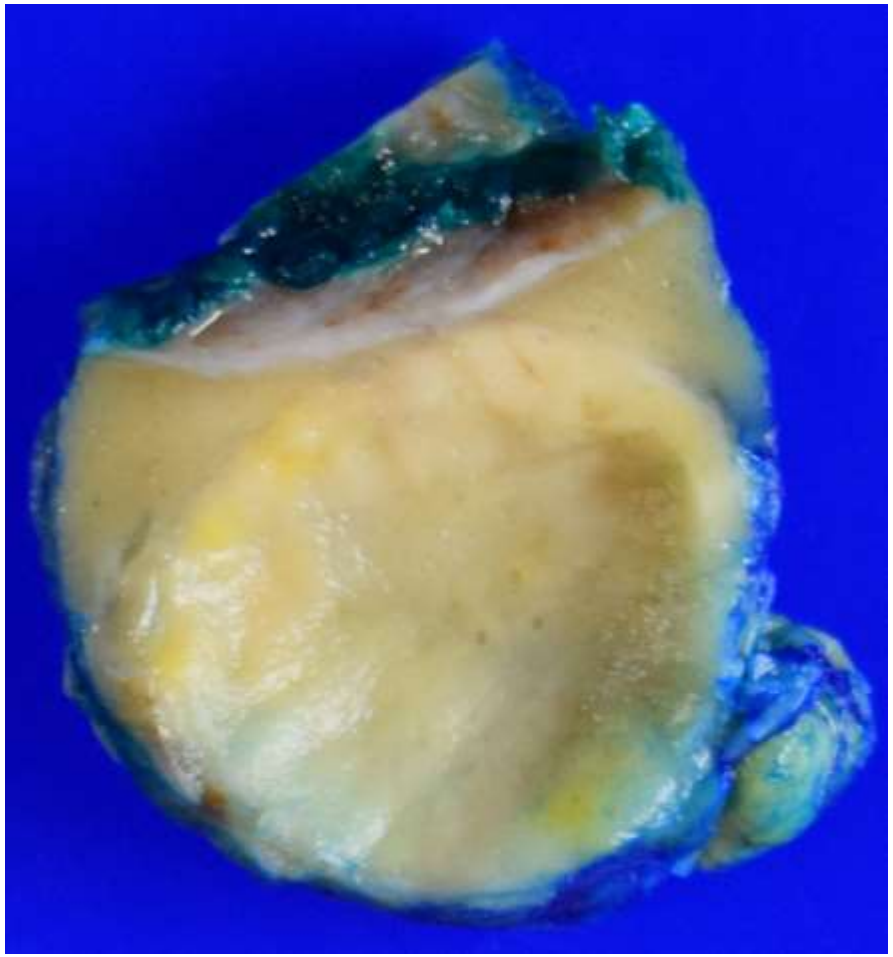


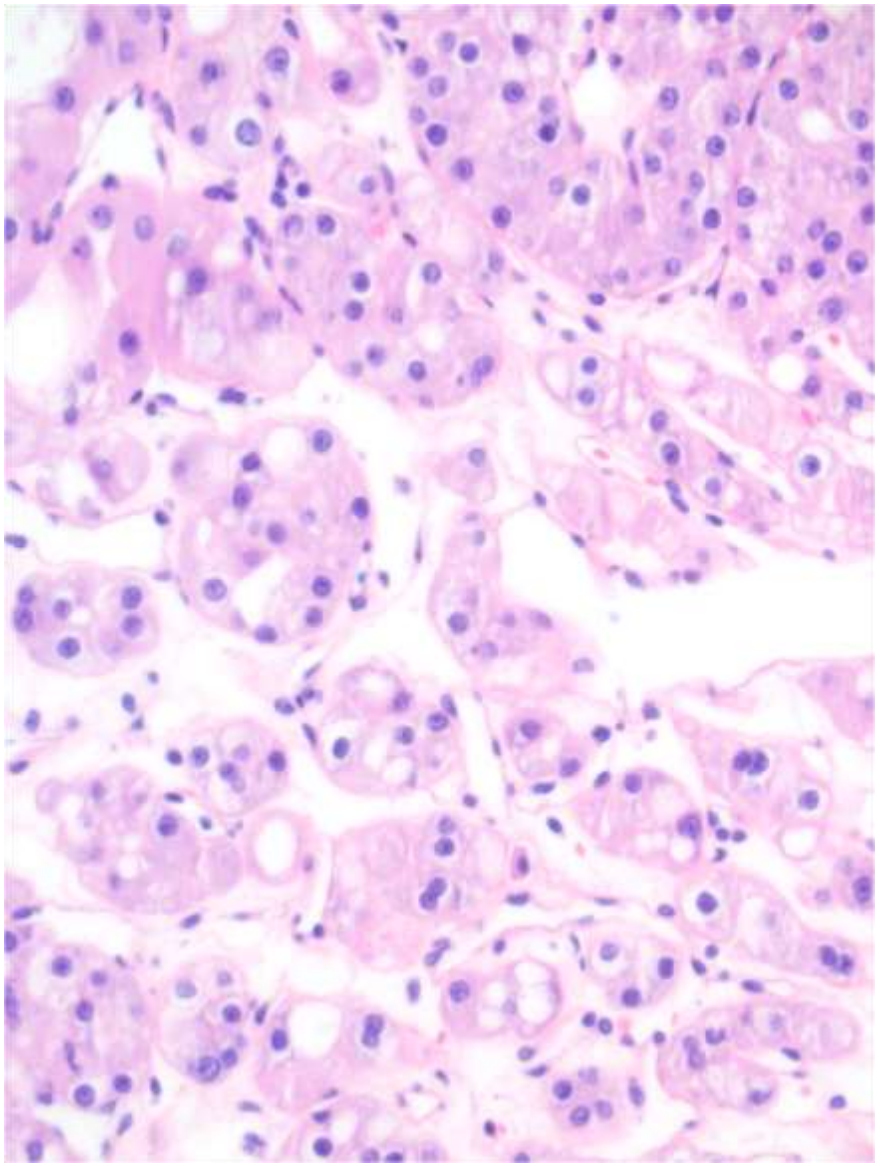




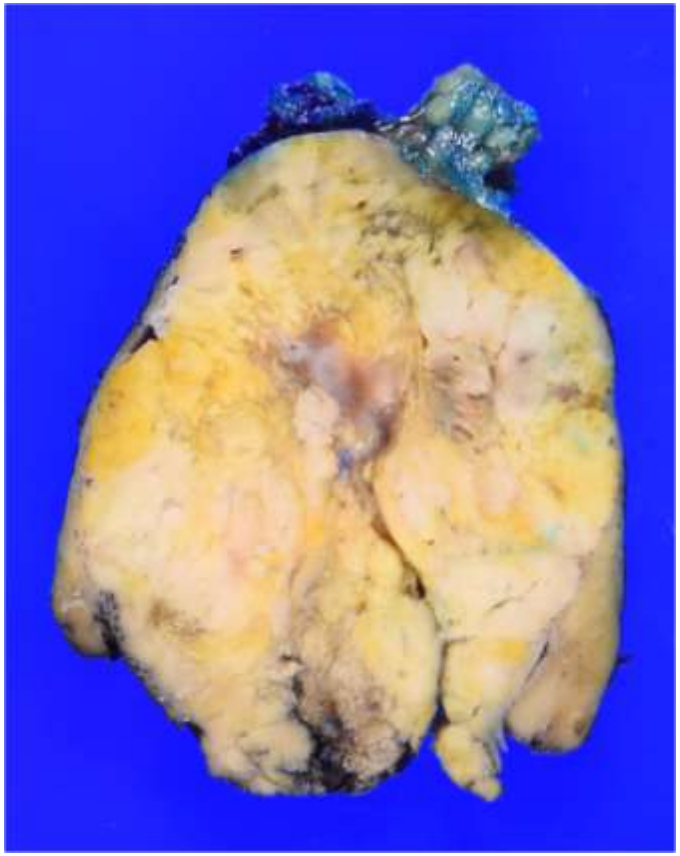


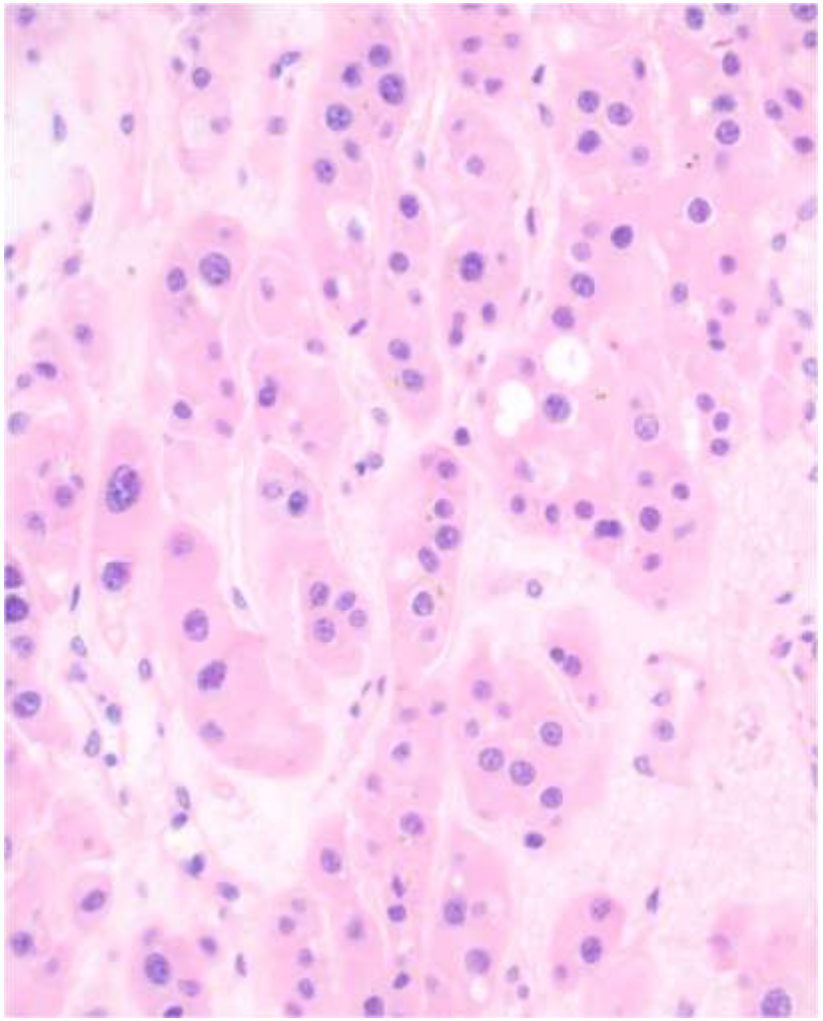
Submitted case





Second case in same week! : 46-year-old woman with 6 cm left renal mass, also underwent partial nephrectomy





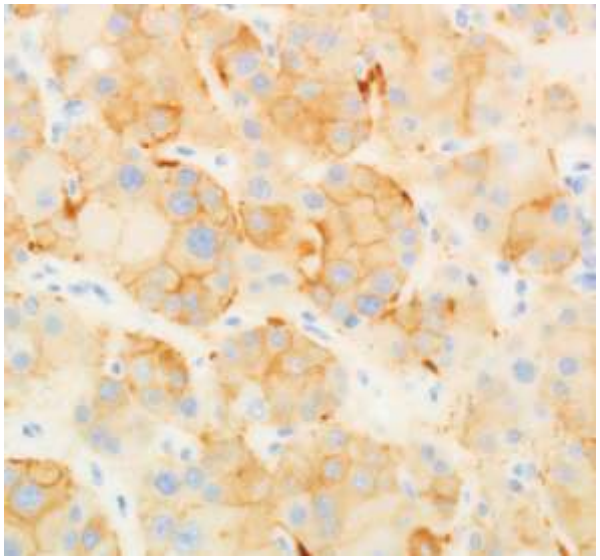
Differential Diagnosis for young woman with oncocytic renal neoplasm

- Oncocytoma (excluded in these cases by morphology)
- Chromophobe RCC
- Hybrid oncocytic/chromophobe tumor (HOCT, associated with Birt-Hogg-Dube, renal oncocytosis, TSC or sporadic hybrids)
- FH-deficient RCC
- SDH-deficient RCC
- Translocation t(6;11)-associated RCC
- Eosinophilic solid and cystic RCC
- Eosinophilic clear cell RCC

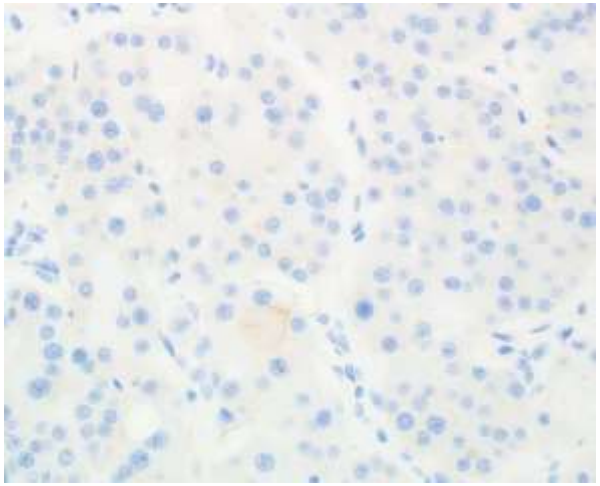
Immunohistochemical profile

Positive stains:
Pax8
CD117 (weak??)
Pancytokeratin

Negative stains:
CK7
CK20
FH (retained)
SDH (retained)
MelanA
HMB45



CD117 1:25 dilution



CD117 1:250 dilution

Diagnosis

- Renal cell carcinoma, with oncocytic features; see comment regarding subtype and grade.
  - Morphology and IHC doesn't fit for any established histologic subtype in most recent WHO
  - Positive CD117 puts it on the oncocytoma-chromophobe-hybrid spectrum.
    - Morphology too atypical for oncocytoma.
    - Some chromophobe features including thick cell borders, binucleates, perinuclear clearing, but not raisinoid, chromophobe usually no nucleoli, and CK7 negative.
    - No IHC support for FH, SDH, translocation.
  - Nucleolar features are those of WHO Grade 2-3, but grading system is based on outcome data for clear cell RCC and to lesser extent papillary RCC. Significance in oncocytic tumors currently not known. Most behave well in literature.
  - Consider molecular testing and/or genetic counseling given young age and possible associations of these oncocytic tumors with germline mutation/syndromes (BHD, TSC)

UCSF500 sequencing

Submitted case

PATHOGENIC AND LIKELY PATHOGENIC ALTERATIONS				
VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
MTOR p.L2427R	NM_004958	Likely Pathogenic	257	49%

- Single copy loss in chromosome 1

Second case

PATHOGENIC AND LIKELY PATHOGENIC ALTERATIONS				
VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
RAD50 p.Q465*	NM_005732	Pathogenic	626	48%
MTOR p.L2427R	NM_004958	Likely Pathogenic	311	50%

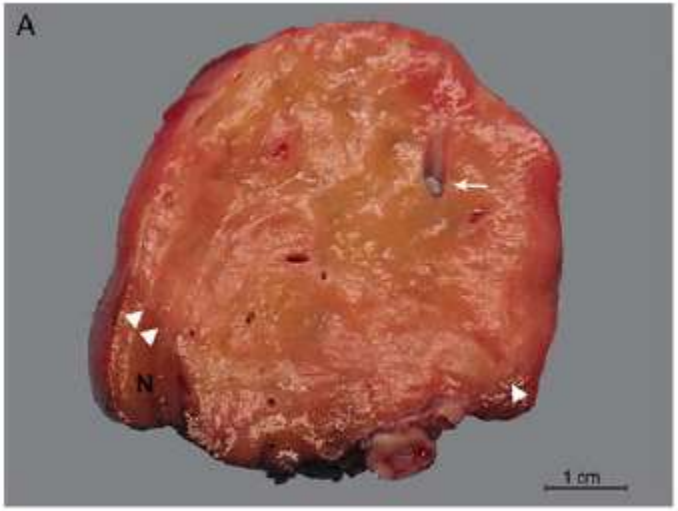
- Single copy loss in chromosome 1

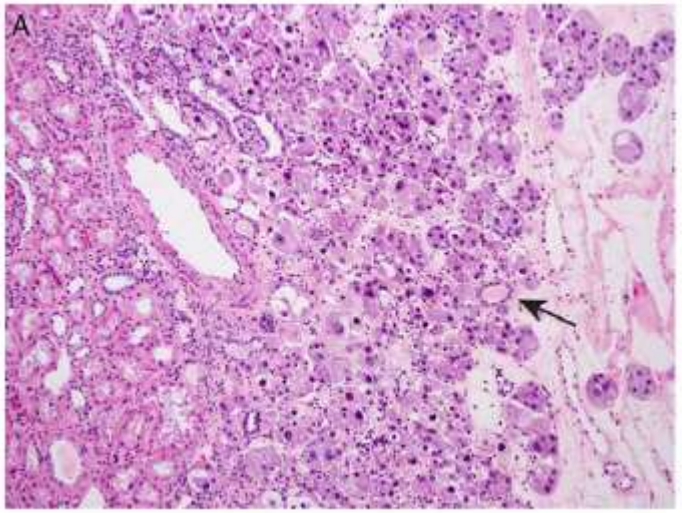
Invitae testing showed no germline mutation in TSC or MTOR in either case. Only RAD50 in second case, likely unrelated

Somatic Mutations of *TSC2* or *MTOR* Characterize a Morphologically Distinct Subset of Sporadic Renal Cell Carcinoma With Eosinophilic and Vacuolated Cytoplasm

Ying-Bei Chen, MD, PhD, Leili Mirsadraei, MD, Gowtham Jayakumaran, MS, Hikmat A. Al-Ahmadie, MD, Samson W. Fine, MD, Anuradha Gopalan, MD, S. Joseph Sirintrapun, MD, Satish K. Tickoo, MD, and Victor E. Reuter, MD

AJSP 2019





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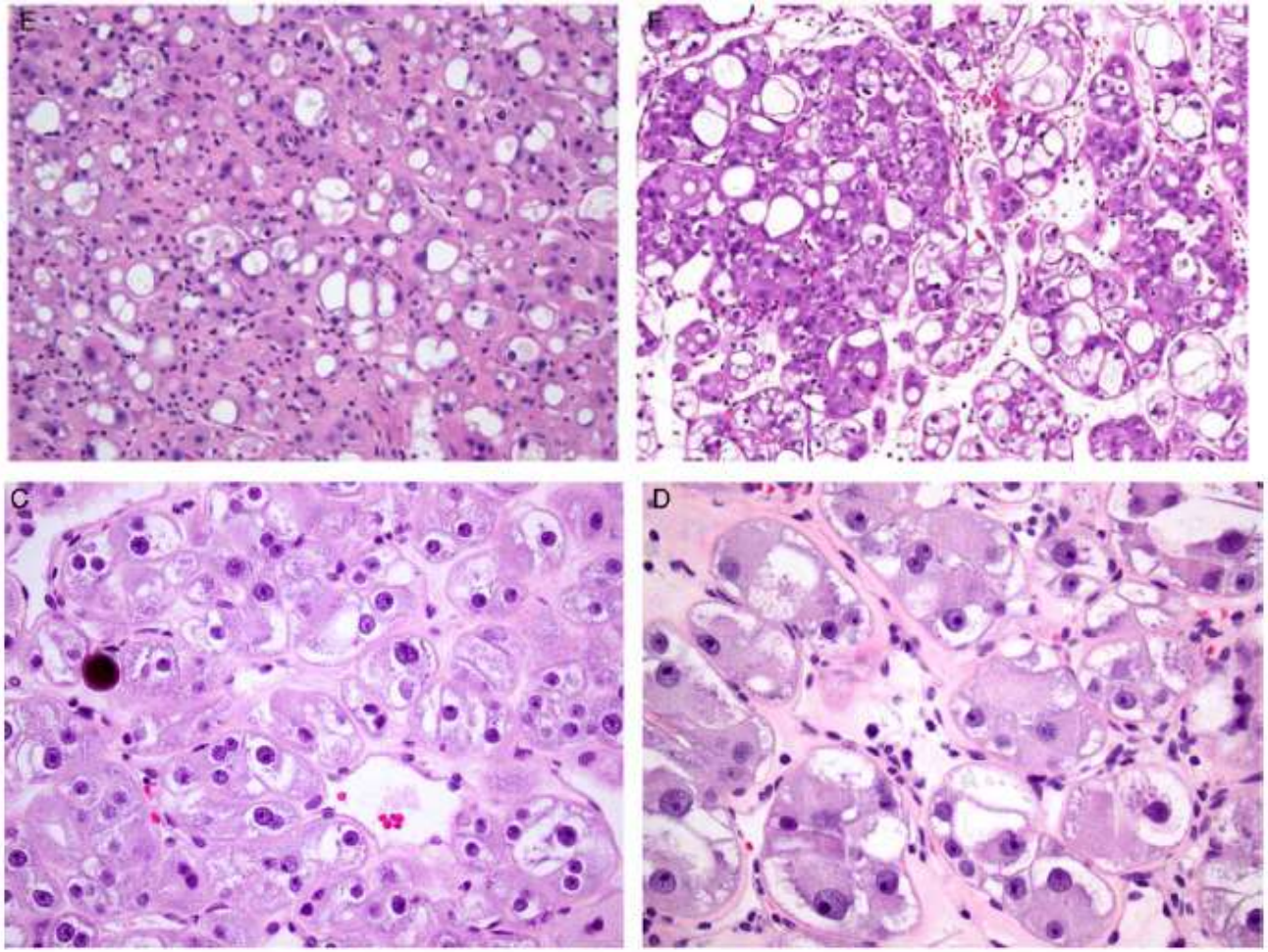

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AJSP 2019

TABLE 2. Immunohistochemical Results and Molecular Alterations Detected

	Immunohistochemistry													
Pt	**PAX8**	**CK7**	**CK20**	**CD117**	**Cathepsin K**	**SDHB**	**FH**	**TFE3**	**HMB45**	**Melan A**	**p-S6***	**p-4EBP1**	**Somatic Mutations†**	**Copy Number Alterations**
1	+	−	−	−	+	R	R	−	−	−	300	300	**TSC2 p.R1138***	ND
2	+	−	−	Weak (+)	+	R	R	−	−	−	300	300	**TSC2 p.X373_splice** **TSC2 p.Q510Sfs***	Focal losses 1p36.3, 1p35 Focal gains 5q35, 6p22, 9q31-34 Minor clone(s) with gains of 4q, 5, 8q, 12§
3	+	−	−	Weak (+)	−	R	R	−	−	−	300	300	ND	ND
4	+	−	−	−	+	R	R	−	├	−	300	300	**MTOR p.L2427R**	Loss of 1
5	+	−	NA	Weak (+)	NA	R	R	−	−	−	NA	NA	**MTOR p.L2427R** NOTCH2 p.D1306N (VUS)‡	Loss of 1 Loss of 6p-q24 LOH and gain of 21 Gain of 6q25-26
6	+	NA	−	−	+	R	R	−	NA	NA	300	230	**TSC2 p.X534_splice** **TSC2 p.K506Sfs*** PTPRD p.T988S (VUS)‡	Loss of 21q Focal gain 10q25-26
7	+	−	−	Weak (+)	Focal (+)	R	R	−	−	−	250	230	ND	ND

*Immunohistochemical stain result is shown in H-scores [H = intensity (0−3)× percentage of positive cells (1−100)].

While all had no evidence of disease, recognition may be of clinical importance as MTOR/TSC pathway is targetable with tyrosine kinase inhibitors in case of mets

Other diagnoses that have been applied to these oncocytic RCC:

- Low-risk oncocytic RCC
- Renal cell carcinoma, unclassified, low grade malignant
- Prefer not to use “high-grade” given no aggressive behavior described…yet

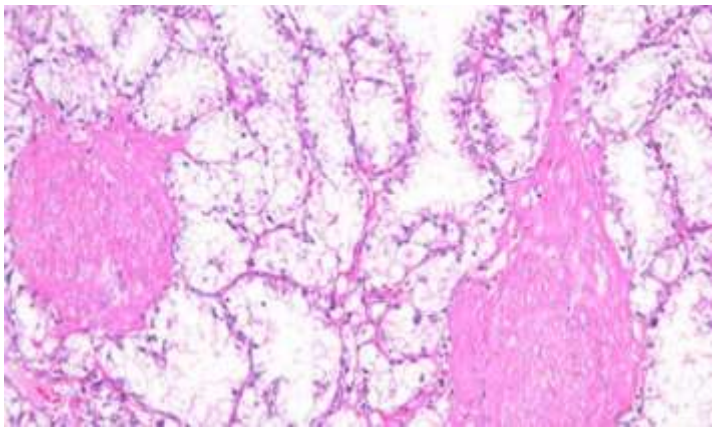
Tuberous Sclerosis–associated Renal Cell Carcinoma

A Clinicopathologic Study of 57 Separate Carcinomas in 18 Patients

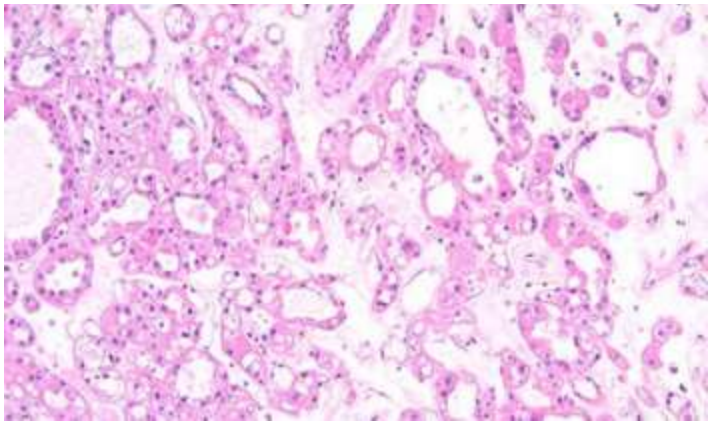
Juan Guo, MD, PhD, Maria S. Tretiakova, MD, PhD,† Megan L. Troxell, MD, PhD,‡*
Adeboye O. Osunkoya, MD,§ Oluwole Fadare, MD,‖ Ankur R. Sangoi, MD,¶
*Steven S. Shen, MD, PhD# Antonio Lopez-Beltran, MD, PhD** Rohit Mehra, MD ††*

AJSP 2014

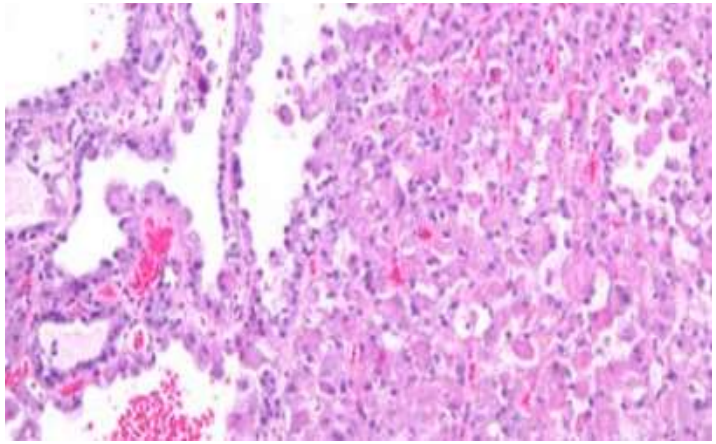
RCC with angioleiomyomatous stroma



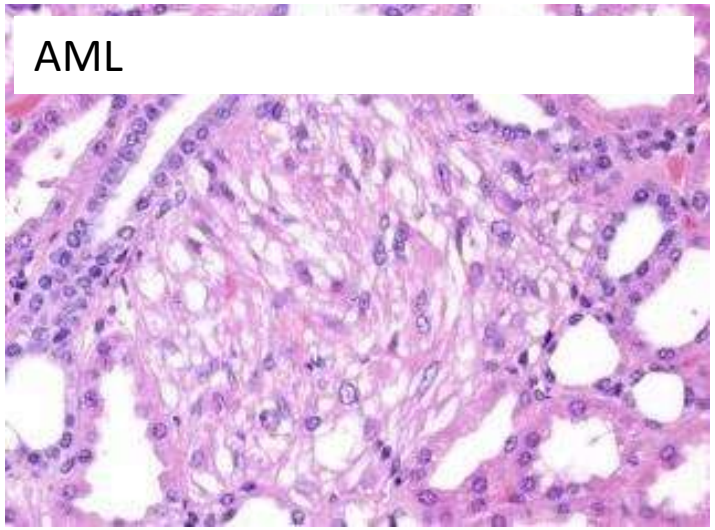
Chromophobe like, hybrid oncocytic



Eosinophilic solid and cystic



AML



Also described in Yang et al AJSP 2014

Solid and nested oncocytic renal neoplasms not yet in the WHO

	Eosinophilic solid and cystic RCC	Low-grade oncocytic tumor (LOT)	RCC with eosinophilic and vacuolated cytoplasm	High-grade oncocytic tumor (HOT)
Other distinctive morphology	Hobnailed cells lining cysts; Purple cytoplasmic granules; leishmaniasis like granules	Areas with tissue culture like appearance	Prominent intracytoplasmic vacuoles	Prominent intracytoplasmic vacuoles
IHC	CD117 negative CK7 negative CK20 positive	CD117 negative CK7 positive	CD117 weak (with 1:1000 dilution) CK7 negative to focal	CD117 positive (with 1:300 dilution) CK7 negative to focal
Genetics	TSC/MTOR	Frequent deletions 1p, 19p, 19q. No mutational analysis	TSC/MTOR	Mutational analysis not performed, but 3/9 cases with chr 1 loss
Behavior	Indolent, though a few mets have been reported	Indolent	No reported aggressive behavior but unclear due to short follow-up	No reported aggressive behavior but unclear due to short follow-up
References	Trpkov K et al. AJSP 2017; 41:1299-1308. McKenney JK et al. Histopathology. 2018; 72:1066-1067.	Trpkov K, et al. Histopathology. 2019, 75: 174-184.	Chen YB et al. AJSP 2019; 43:121-131.	He H et al. Virchows Archiv 2018; 473:725-738.

Solid and nested oncocytic renal neoplasms not yet in the WHO

	Eosinophilic solid and cystic RCC	Low-grade oncocytic tumor (LOT)	RCC with eosinophilic and vacuolated cytoplasm	High-grade oncocytic tumor (HOT)
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IHC	CD117 negative CK7 negative CK20 positive	CD117 negative CK7 positive	CD117 weak (with 1:1000 dilution) CK7 negative to focal	CD117 positive (with 1:300 dilution) CK7 negative to focal
Genetics	TSC/MTOR	Frequent deletions 1p, 19p, 19q	TSC/MTOR	Mutational analysis not performed, but 3/9 with loss of chromosome 1
Behavior	Indolent, though a few mets have been reported	Indolent	No reported aggressive behavior but unclear due to short follow-up	No reported aggressive behavior but unclear due to short follow-up
References	Trpkov K et al. AJSP 2017; 41:1299-1308. McKenney JK et al. Histopathology. 2018; 72:1066-1067.	Trpkov K, et al. Histopathology. 2019, 75: 174-184.	Chen YB et al. AJSP 2019; 43:121-131.	He H et al. Virchows Archiv 2018; 473:725-738.

The same thing???

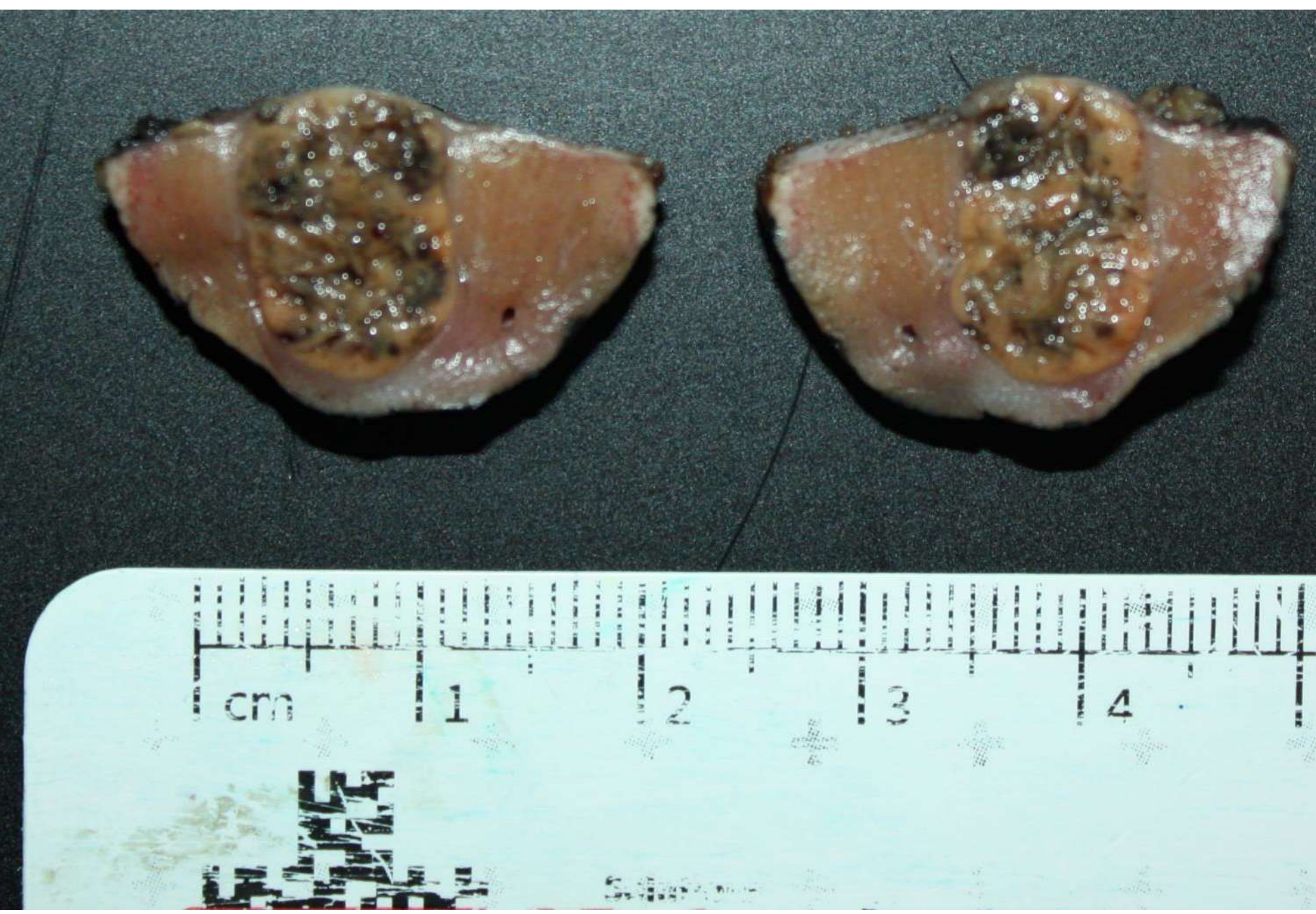
Take-home points

- Recommend using descriptive diagnosis for these oncocytic renal cell carcinomas
- IHC panel: CD117, CK7, CK20. Also consider SDH, FH and translocation associated
- No known aggressive behavior described at this time, therefore avoid using high-grade
- Suggest possible association with TSC/MTOR mutations or folliculin, which can be sporadic or germline
- Consider molecular testing if clinically indicated (or can just do if readily available)
- Also consider genetic counseling, especially if young patient

20-0904
scanned slide available!

Ankur Sangoi; El Camino Hospital

60-year-old M with 1.5cm renal mass. Partial nephrectomy.


cm
1
2
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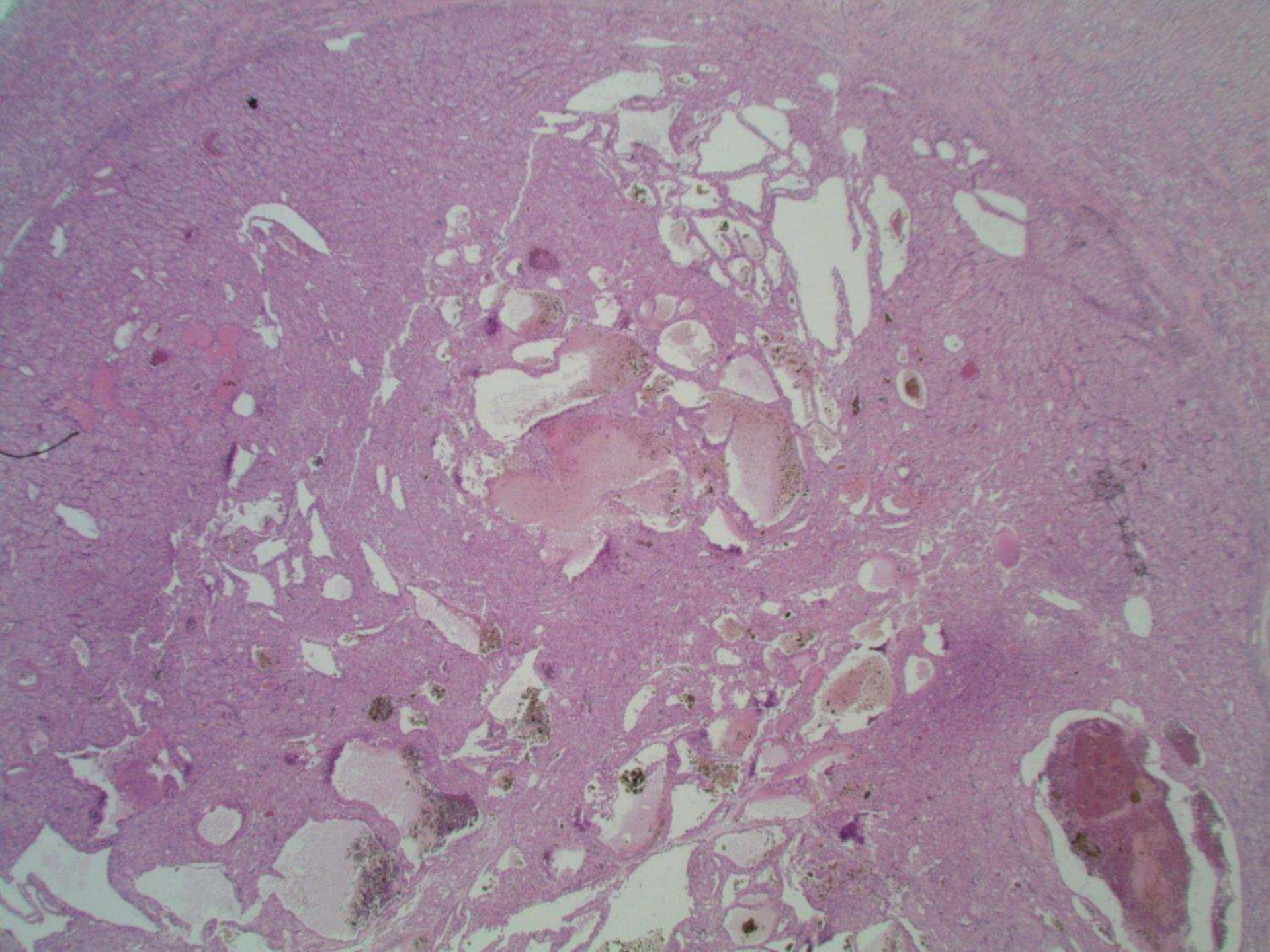
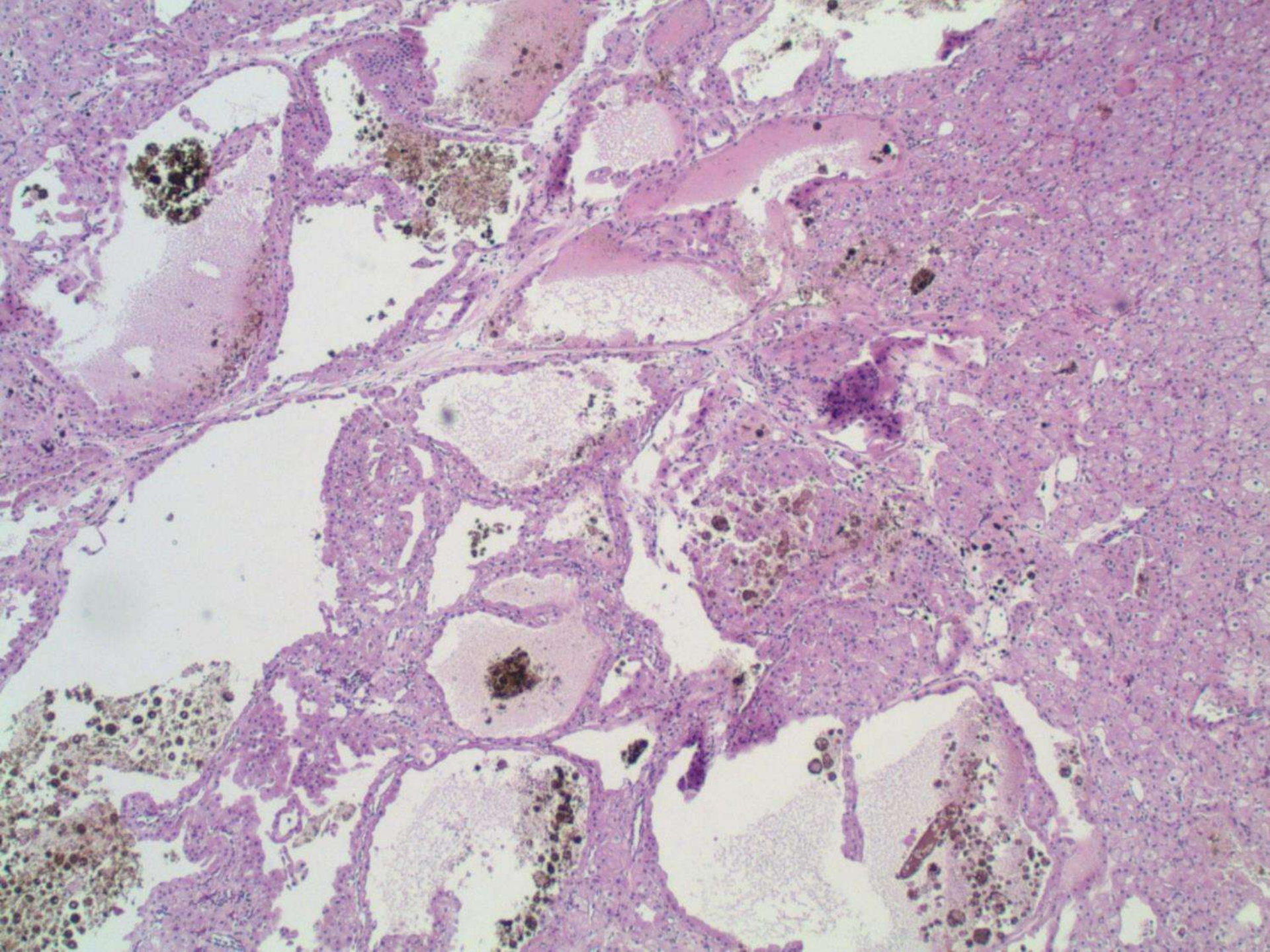
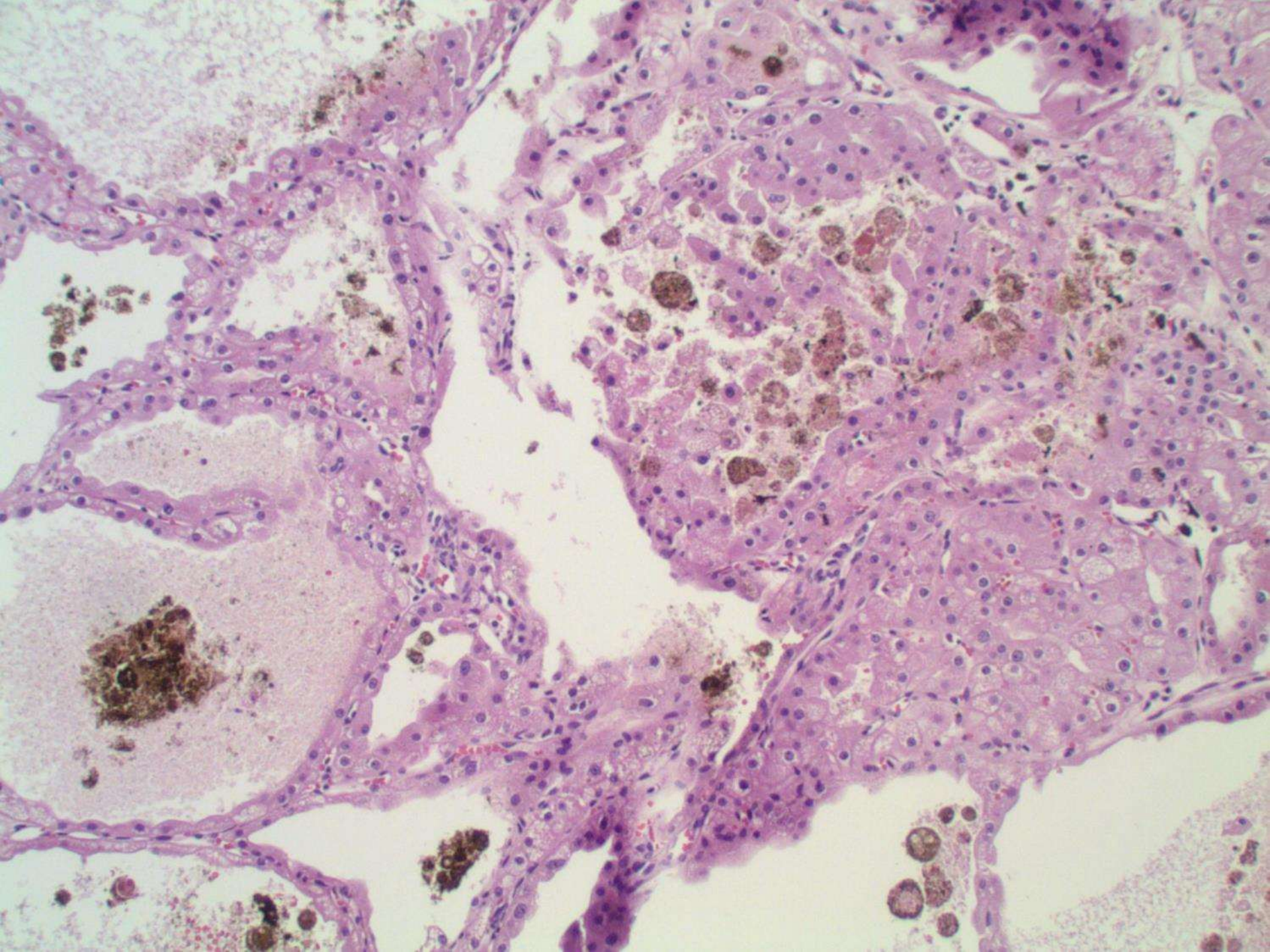
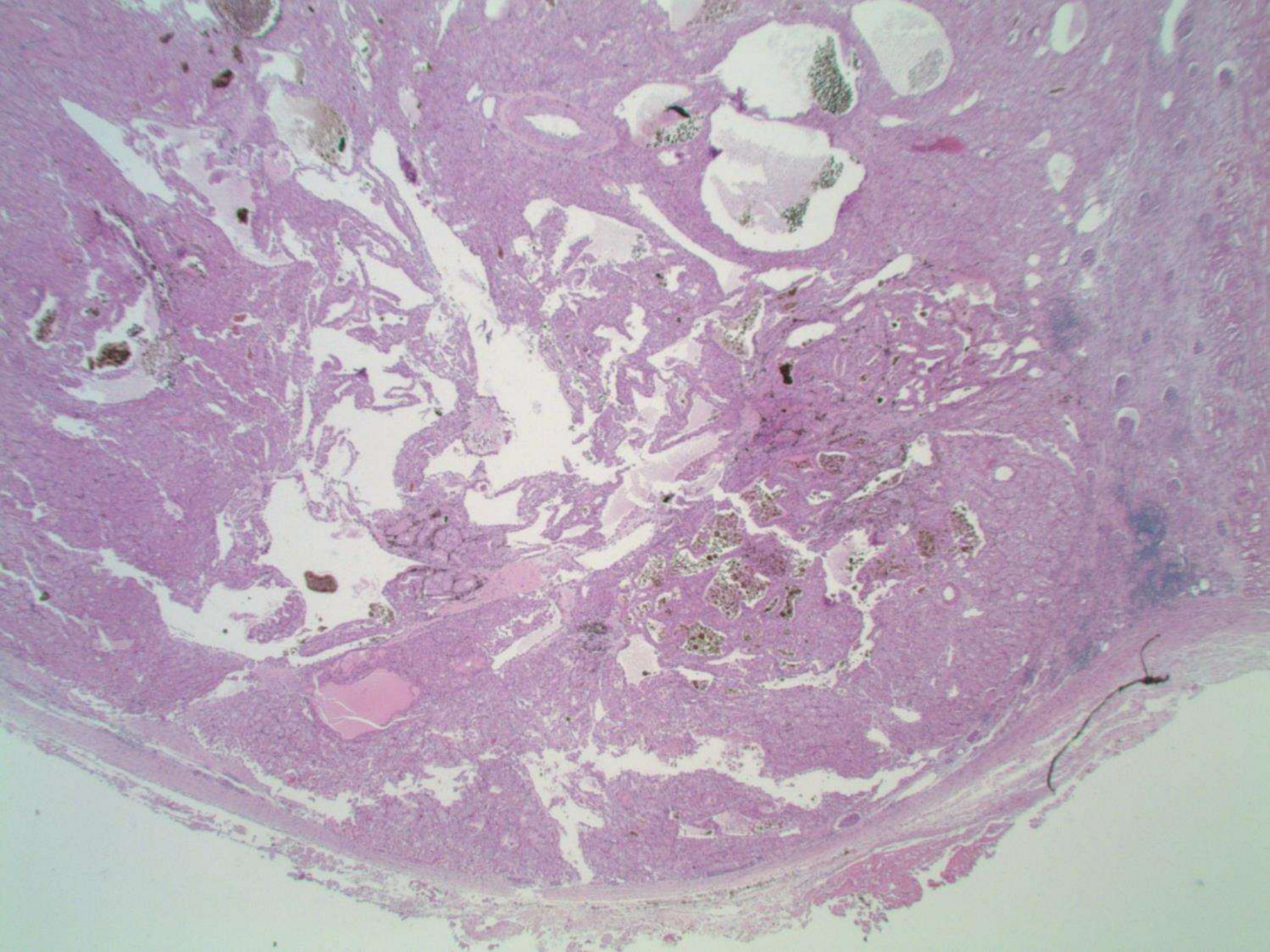
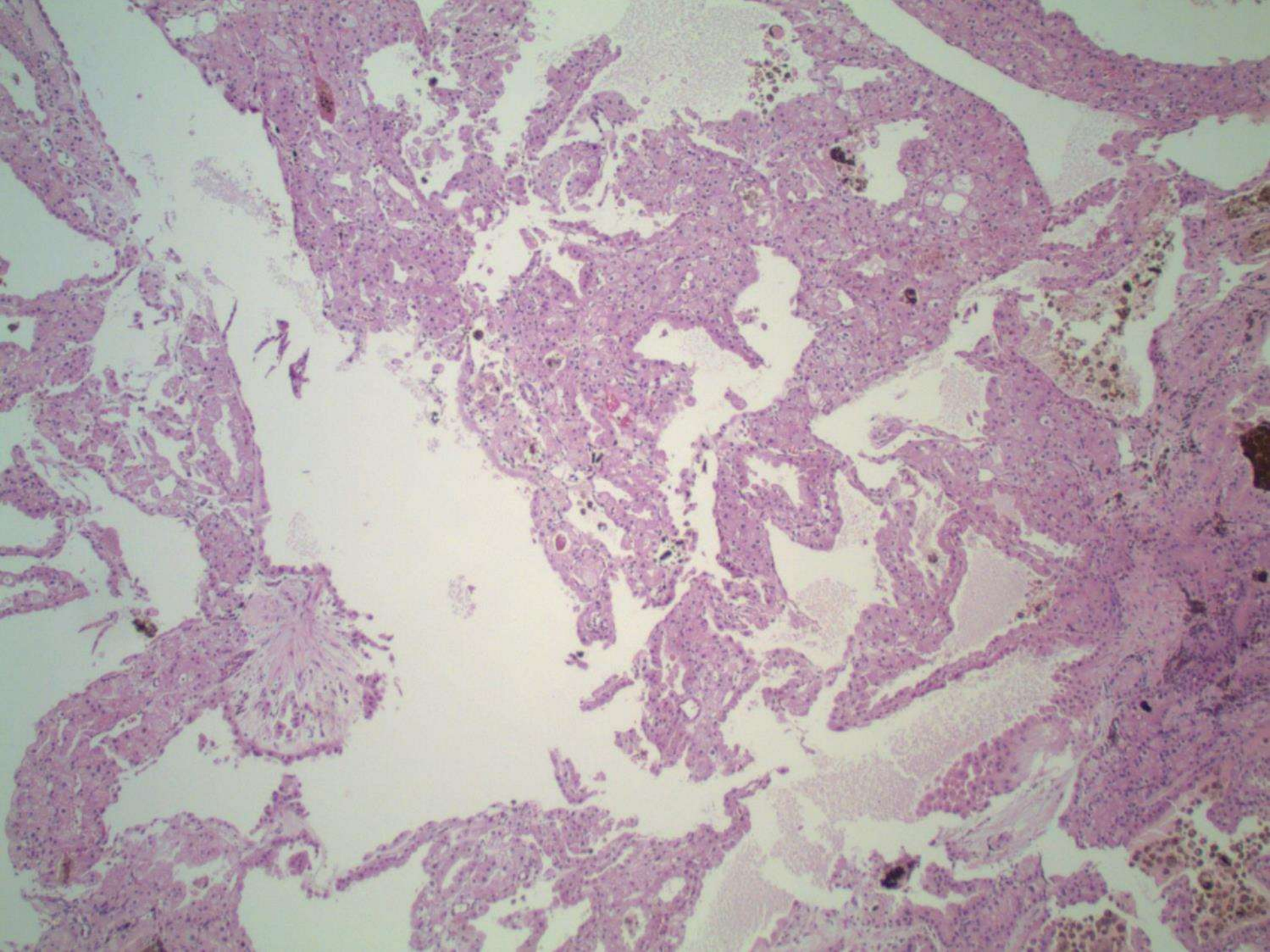
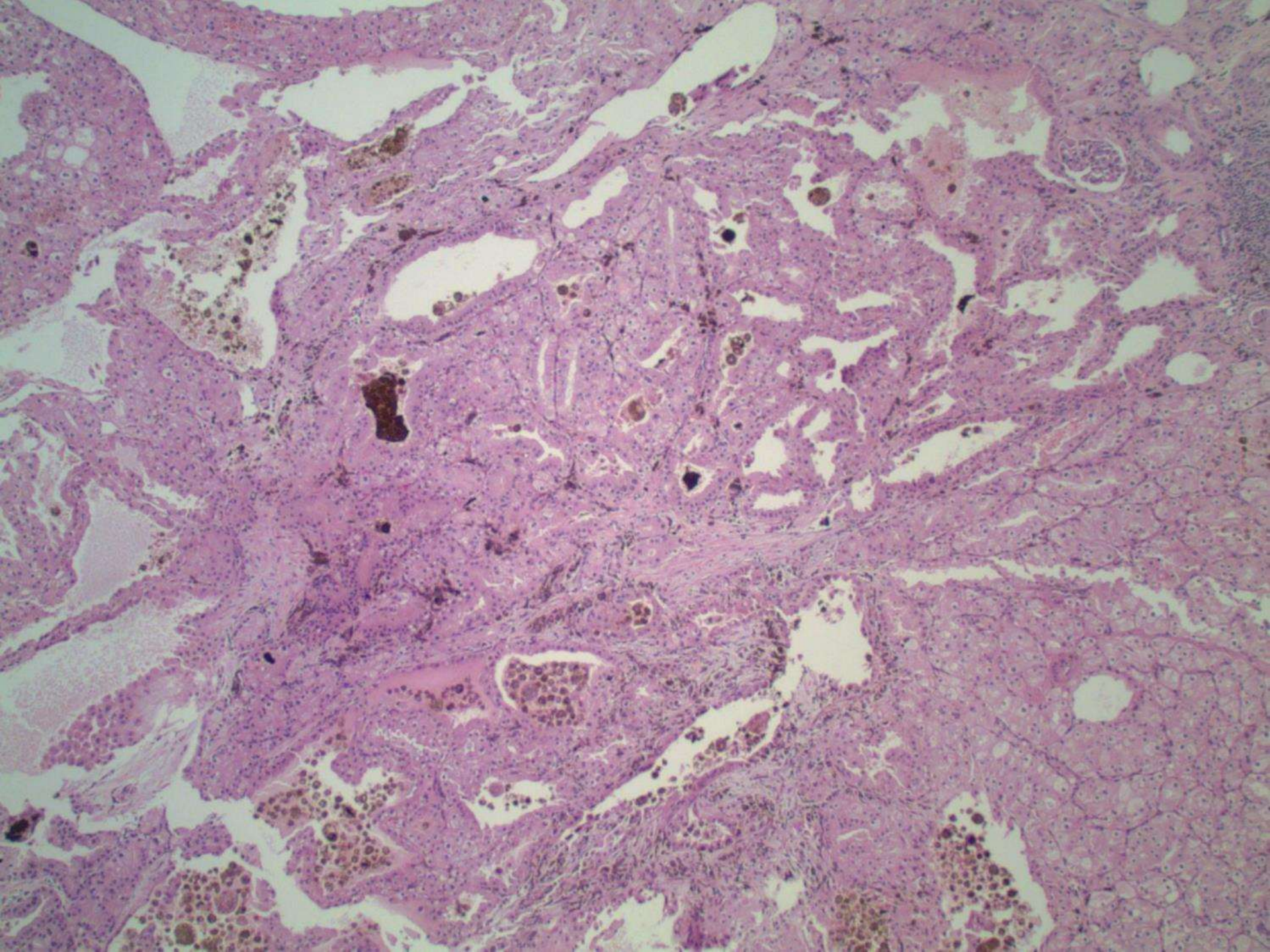


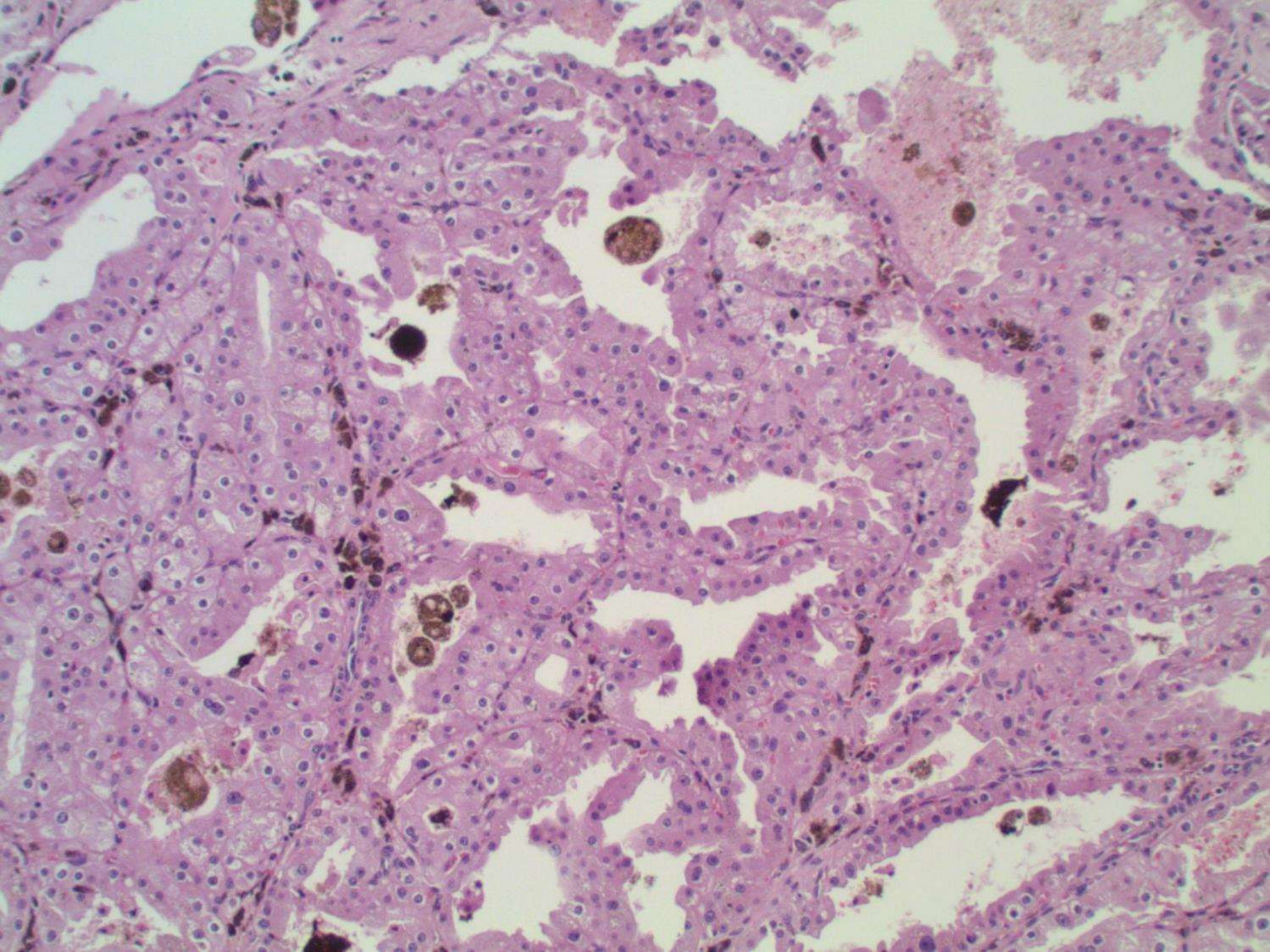


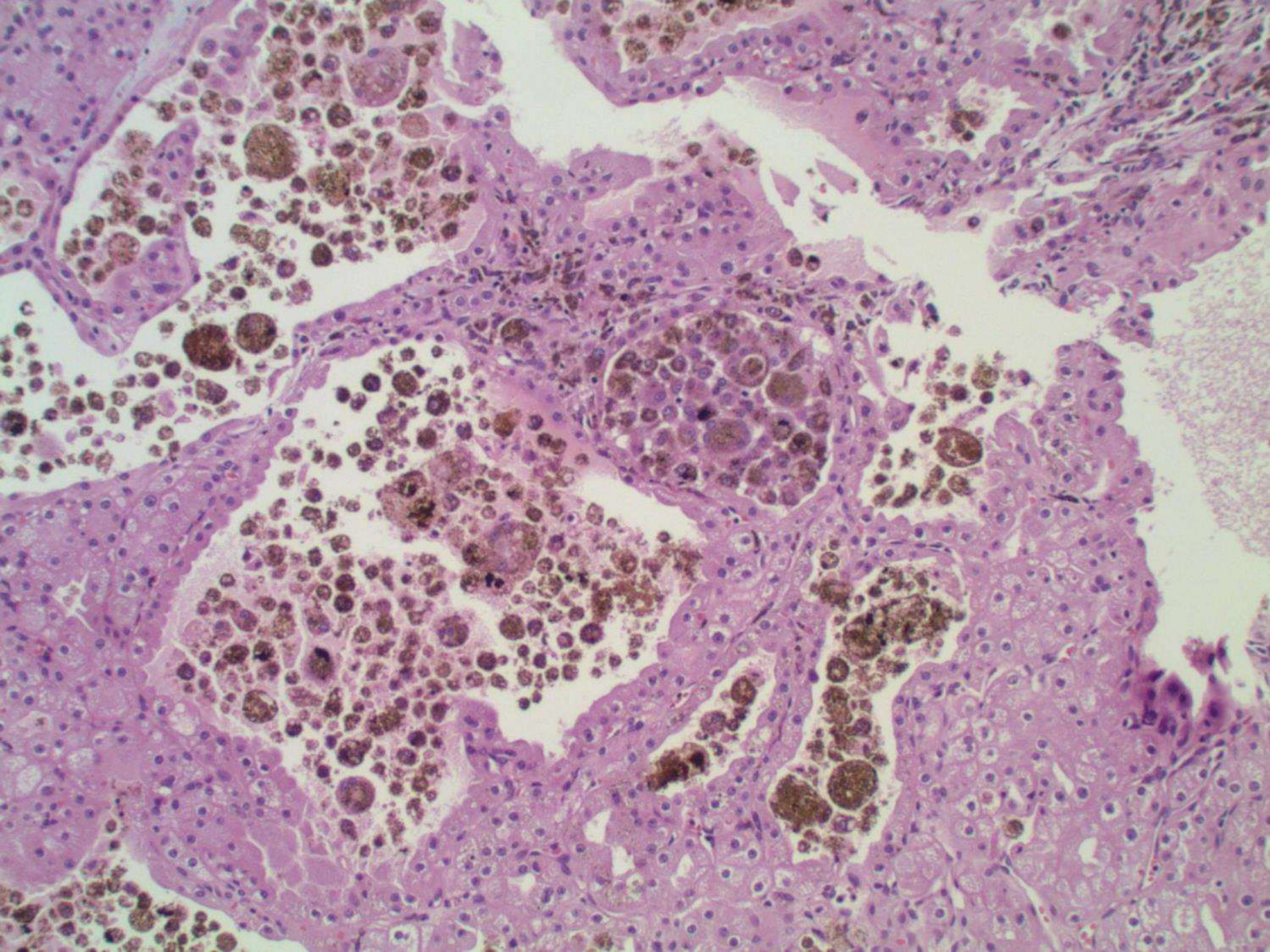


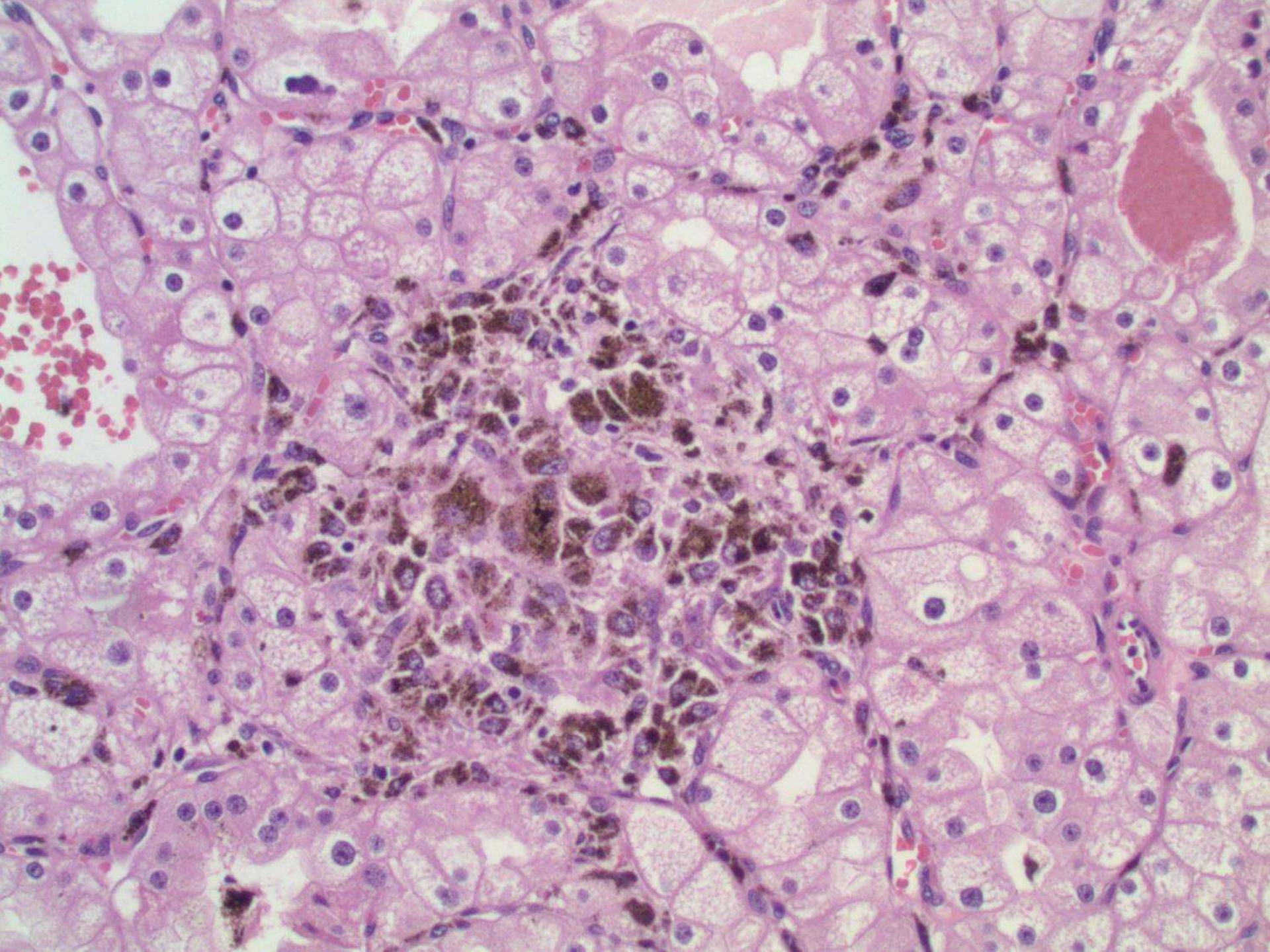


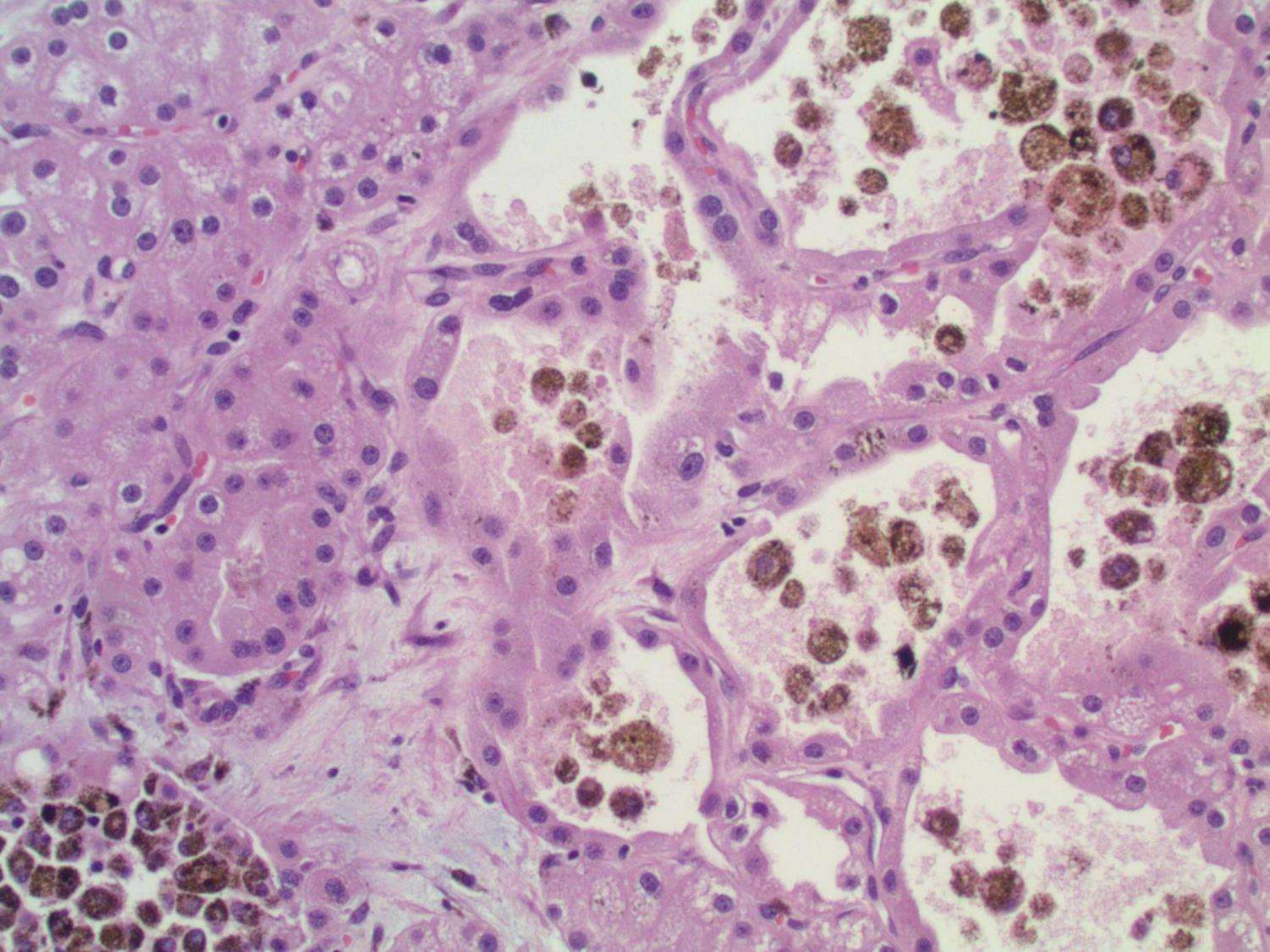












IHC summary

- PAX8+
- CK7+
- CD117+
- Vimentin-
- CAIX-
- CK20-

Annals of
DIAGNOSTIC
PATHOLOGY

VOL 2, NO 3 JUNE 1998

ORIGINAL ARTICLES

Pigmented Microcystic Chromophobe Cell Carcinoma: A Unique Variant of Renal Cell Carcinoma

Michal Michal, MD, Onřej Hes, MD, Alexander Švec, MD, and Marie Ludvíková, MD

Five cases of pigmented chromophobe renal cell carcinoma are presented. The patients included four men and one woman between the ages of 60 and 73 years (median age, 66.5 years), who presented with symptoms due to their renal mass. Surgical resection of the renal mass was performed in all patients. Grossly, the tumors were well encapsulated, yellow to dark gray, with a vague nodular pattern on cut surface. The tumors varied between 2.5 and 9 cm in greatest diameter. Histologically, all tumors shared similar features, namely, a malignant cellular proliferation composed of deeply eosinophilic to clear cytoplasm with round nuclei and inconspicuous nucleoli. The cellular proliferation was arranged in a microcystic and/or microalveolar pattern. In one tumor, conventional areas of clear cell carcinoma in association with the chromophobe component were present. In addition, all tumors contained pigmented areas, which were shown by light microscopy to have features of lipochrome pigment. Ultrastructural studies of these areas demonstrated the presence of intracytoplasmic polygonal to round, electron-dense pigment granules, which in some areas seemed to coalesce to form larger granules. In addition, numerous mitochondria and cytoplasmic vesicles were present. The cases described herein highlight an additional morphologic variant of chromophobe renal cell carcinoma.

Ann Diagn Pathol 2: 149-153, 1998.

Cytogenetic and immunohistochemical study of 42 pigmented microcystic chromophobe renal cell carcinoma (PMChRCC)

Francisco Javier Queipo Gutiérrez[1] · Ángel Panizo[2] · Antonio Tienza[3] · Irene Rodriguez[4] · Jesús Javier Sola[5] · Jordi Temprana-Salvador[6] · Inés de Torres[6] · Javier Pardo-Mindán[7]

Received: 21 September 2017 / Revised: 12 May 2018 / Accepted: 11 June 2018 / Published online: 21 June 2018

Abstract

Pigmented microcystic chromophobe renal cell carcinoma (PMChRCC) is a recently described morphologic variant of ChRCC. We have identified 42 cases in 40 patients in the last 24 years. We have investigated their clinical, morphologic, immunohistochemical, and cytogenetic features. Chromosomal abnormalities of chromosomes 7 and 17 were evaluated by automated dual-color silver-enhanced in situ hybridization on paraffin-embedded tissue. Chromosomal imbalance was defined on the basis of changes in both chromosomal index and signal distribution. The main age was 60.20 years, being 34 males and 6 women. The mean tumor diameter was 4.84 cm, with 39 intrarenal tumors. Grossly, the tumors were solid with a brown dark colored. Microscopically, tumors consisted of pale and eosinophilic cells arranged in microcysts or microalveolar in a cribriform pattern; there were microcalcifications and a dark brown pigment, mostly extracellular. One case showed sarcomatoid transformation. All tumors were positive for epithelial membrane antigen (EMA), Claudin 7, and E-cadherin. Monosomy of 7 and 17 chromosomes was present in 1/36 cases and 2/37 cases, respectively. Polysomy of chromosome 7 and 17 was found in 26/36 cases and in 4/37, respectively. With a median follow-up of 74.05 months, 37 patients were alive without disease and two were alive with disease progression. PMChRCCs expand the morphologic spectrum of the ChRCC with an unusual immunohistochemical profile. Cytogenetically, they showed monosomy to chromosome (CHR) 17 as other ChRCCs and polysomy of CHR 7 infrequent to ChRCCs. We present the probably largest series of PMCRCC, confirming their low aggressive behavior, with exceptional sarcomatoid transformation and distant metastases.

Virchows Archiv (2018) 473:209–217
https://doi.org/10.1007/s00428-018-2389-y

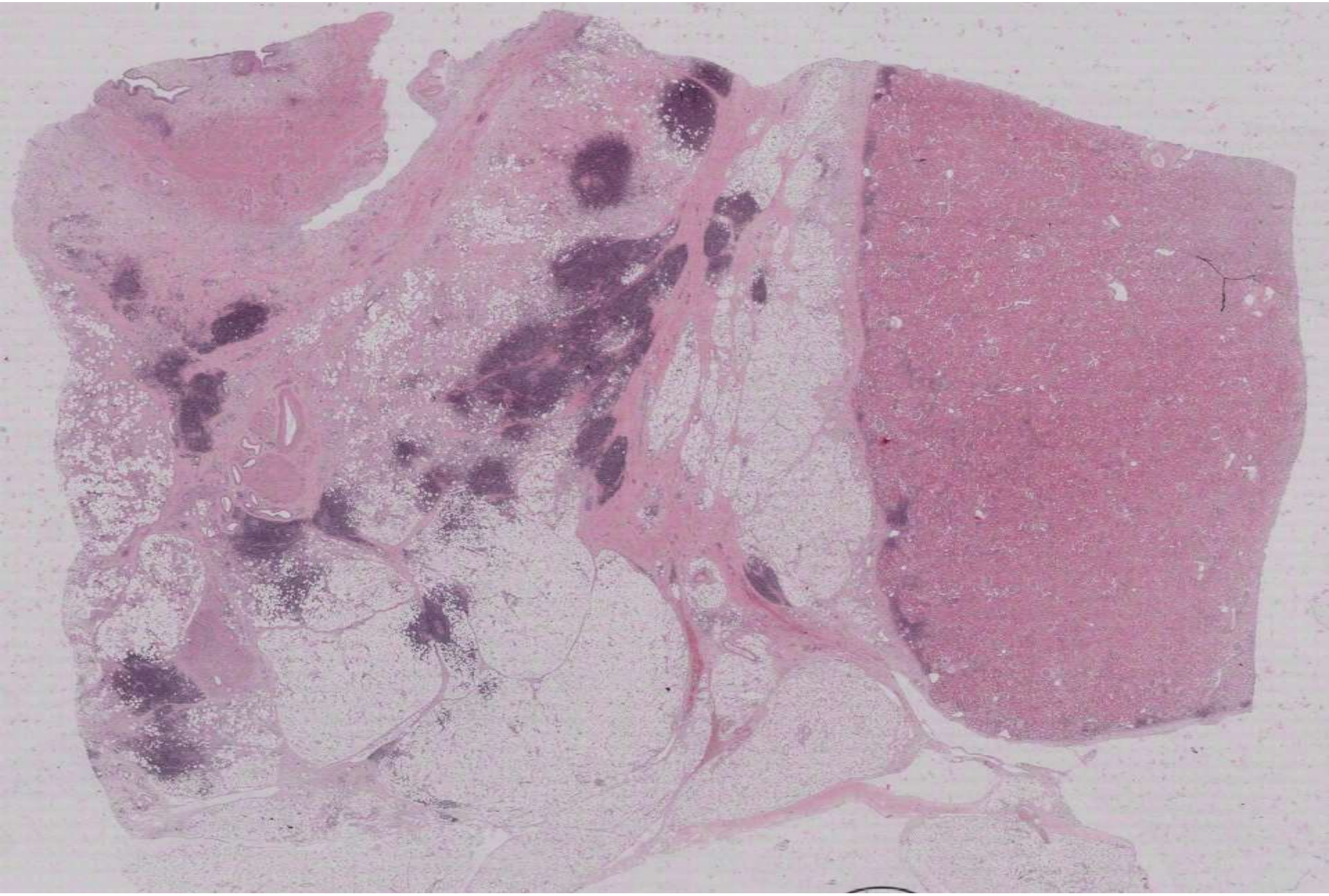
Pigmented microcystic chromophobe RCC

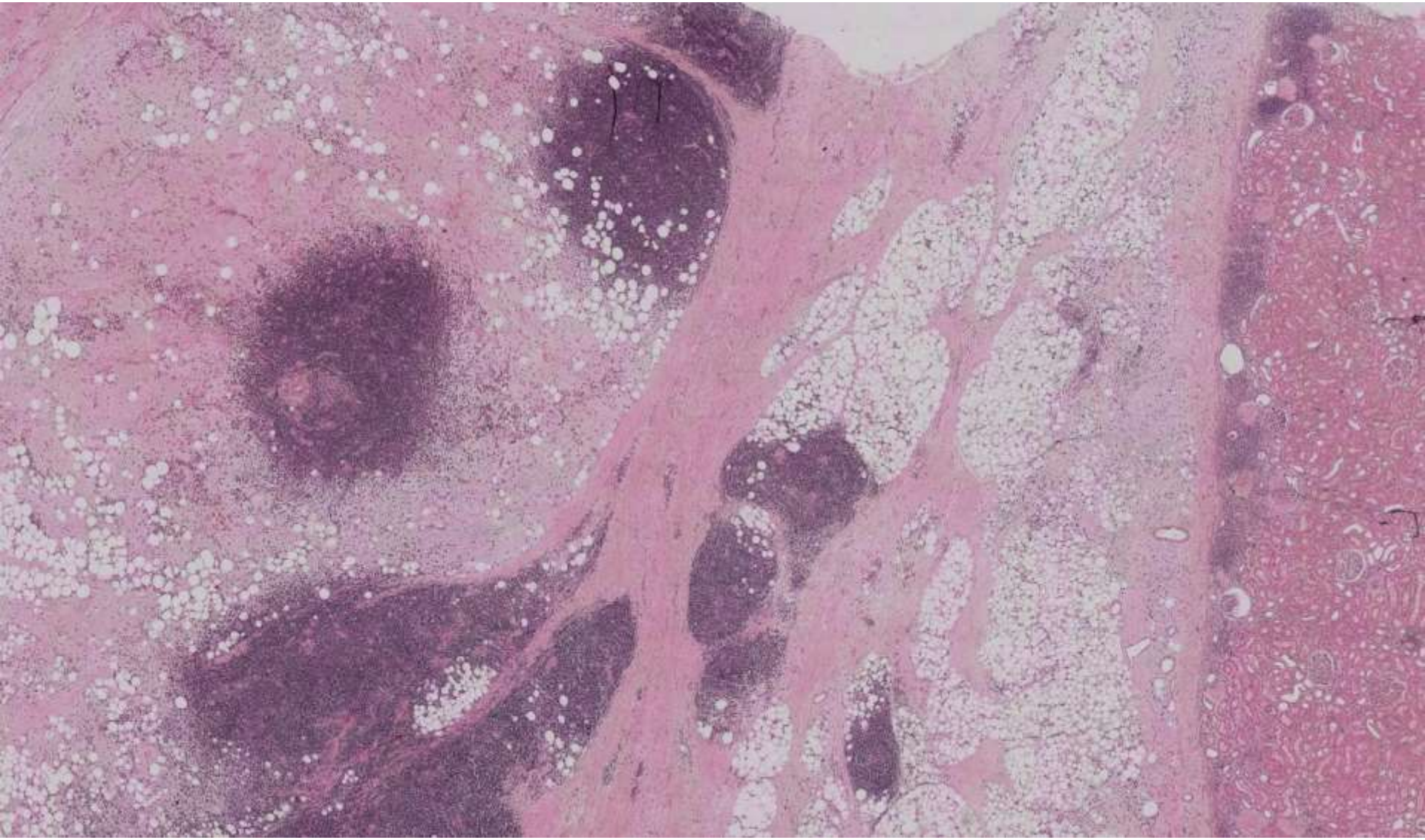
- **Uncommon, unusual variant**
  - Generally similar IHC
    - Higher rate of AMACR+
  - Similar cytogenics to traditional Chr-RCC
  - Generally good behavior
- **Growing list of DDx entities**
  - Oncocytoma, clear cell RCC, SDHB-def RCC, MiTF family/translocation RCC

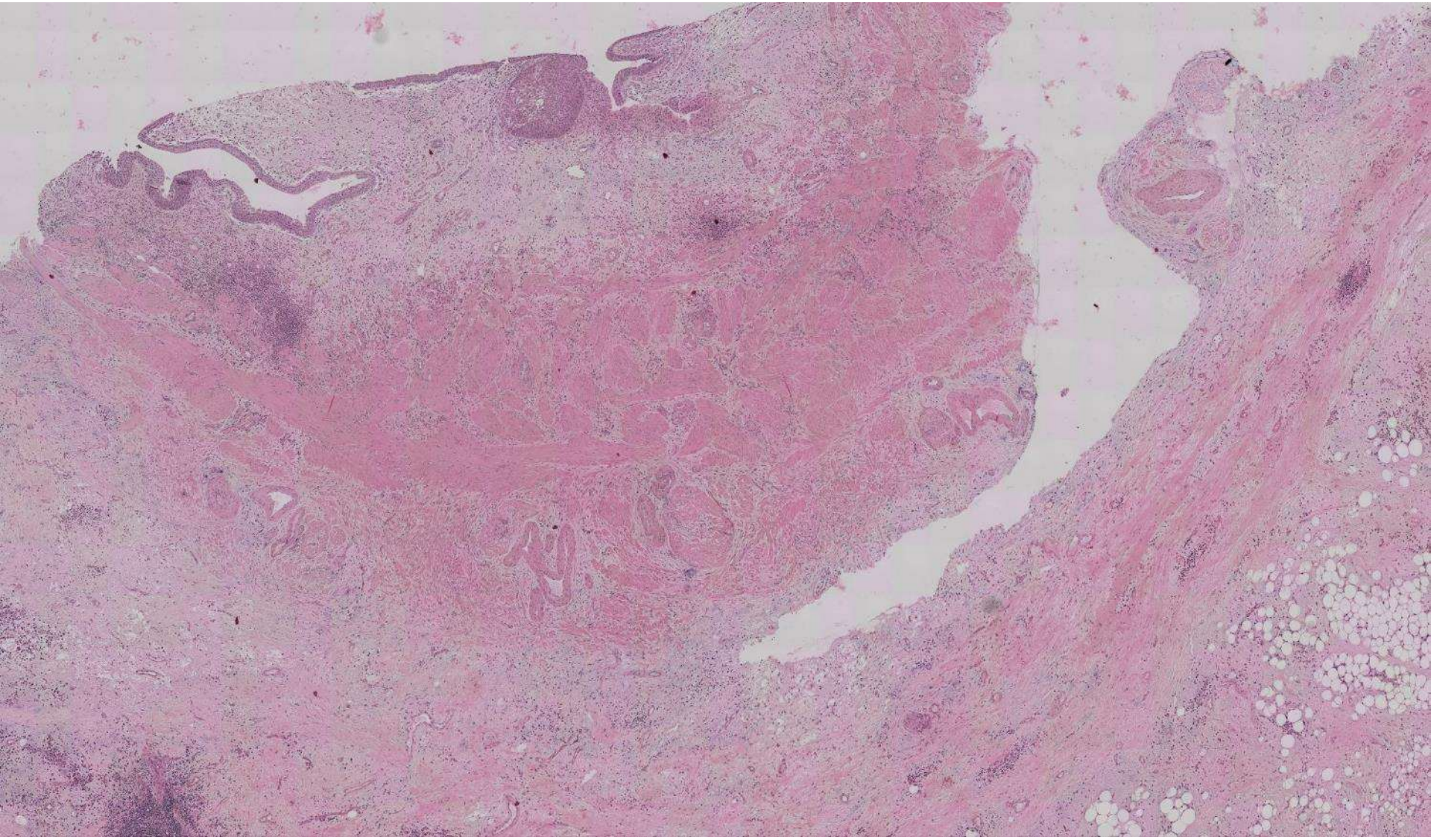
20-0905
scanned slide available!

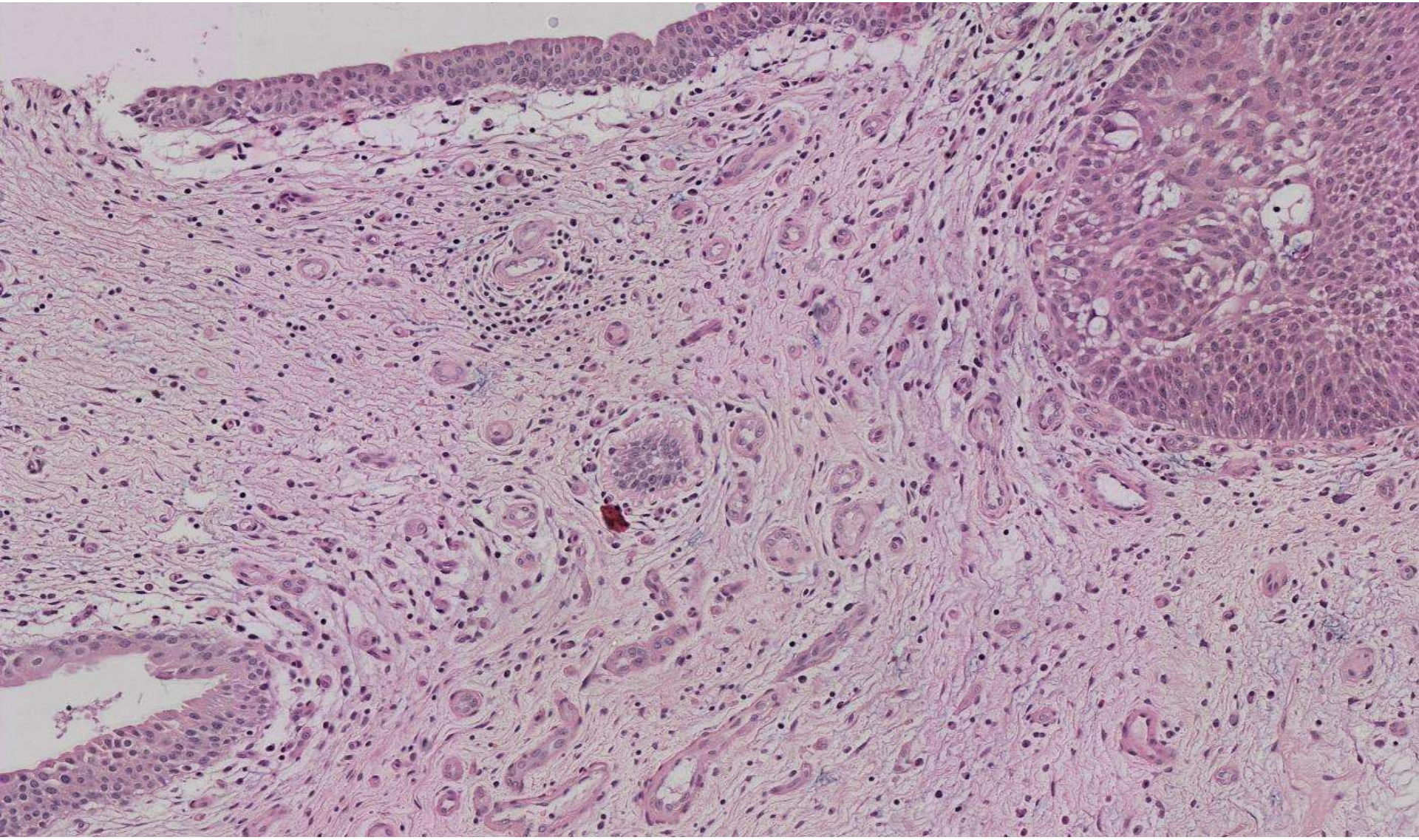
Ankur Sangoi; El Camino Hospital

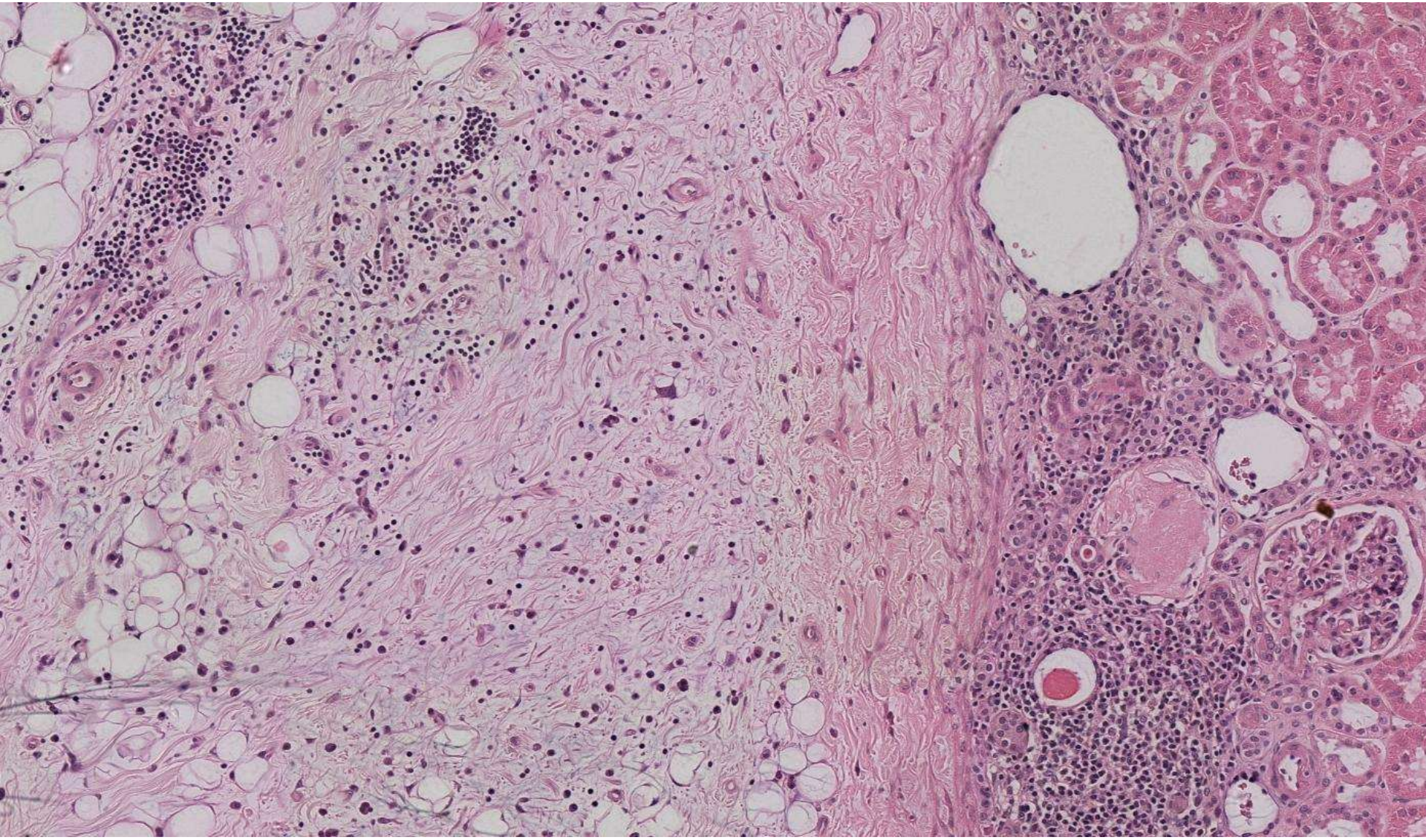
65-year-old F with h/o colon cancer. Radical nephrectomy performed at time of total hysterectomy/ureter resection for recurrent colon cancer debulking, with 7cm ill-defined indurated possibly edematous tumor encasing ureter/renal pelvis.

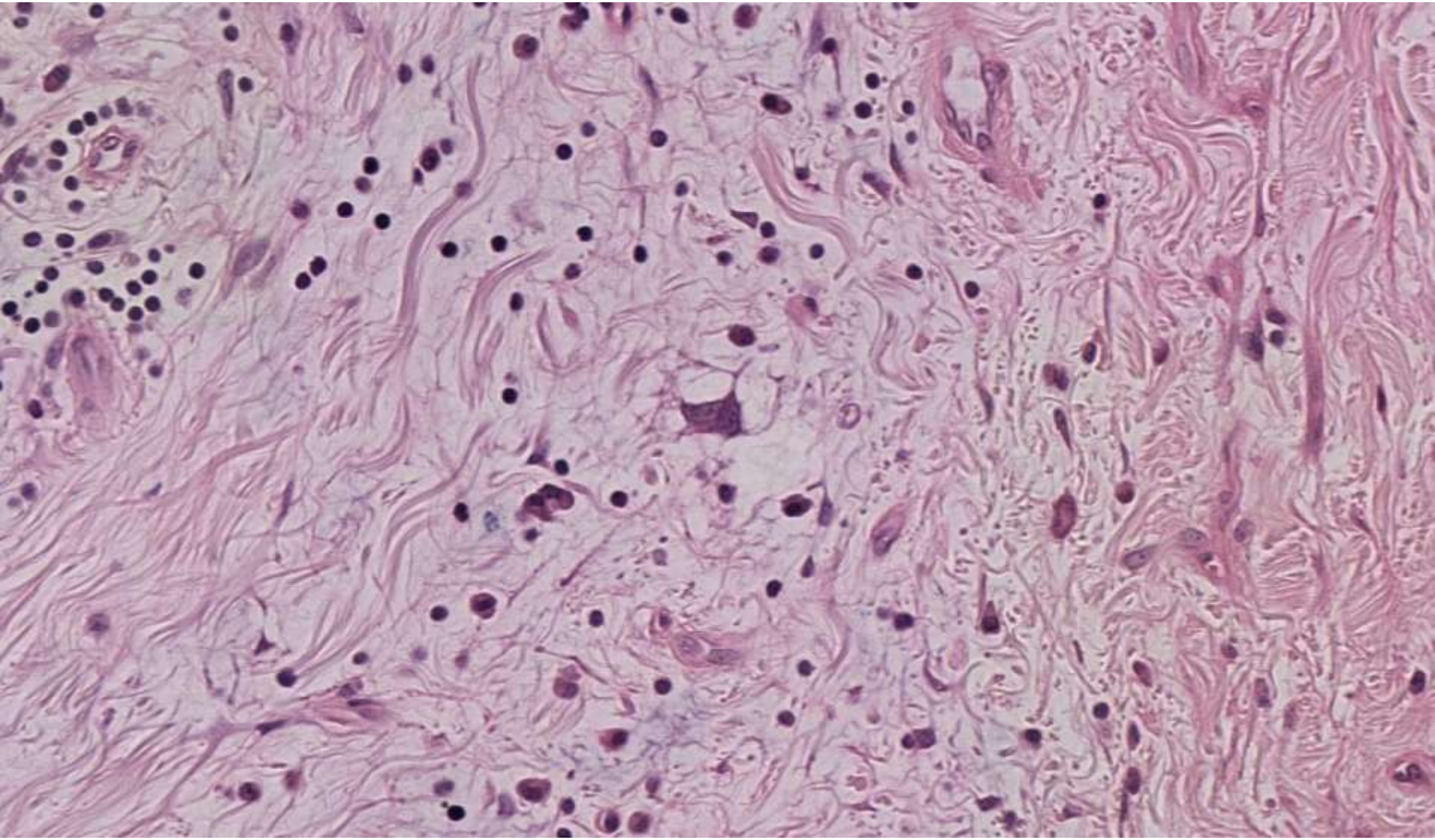


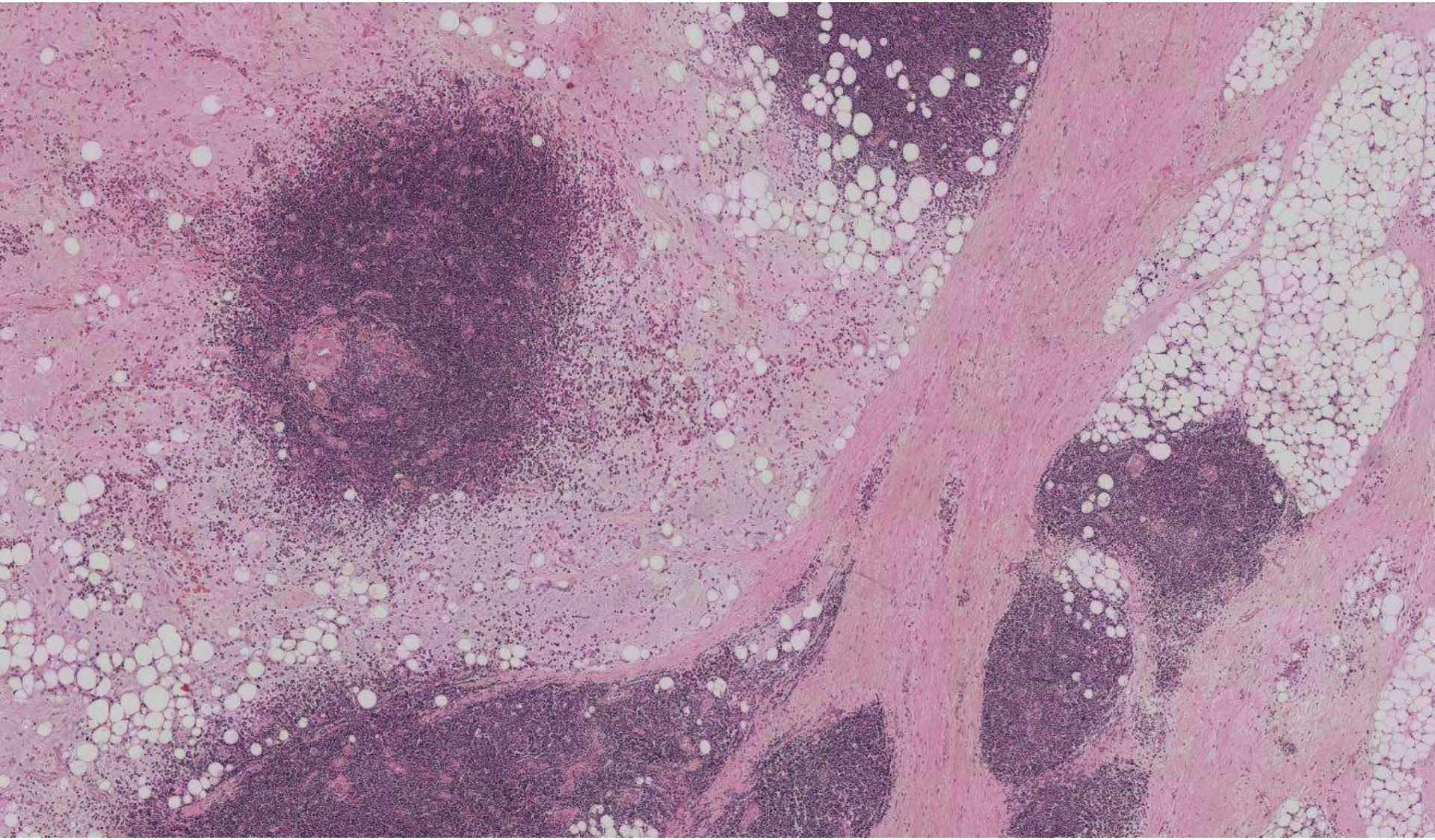


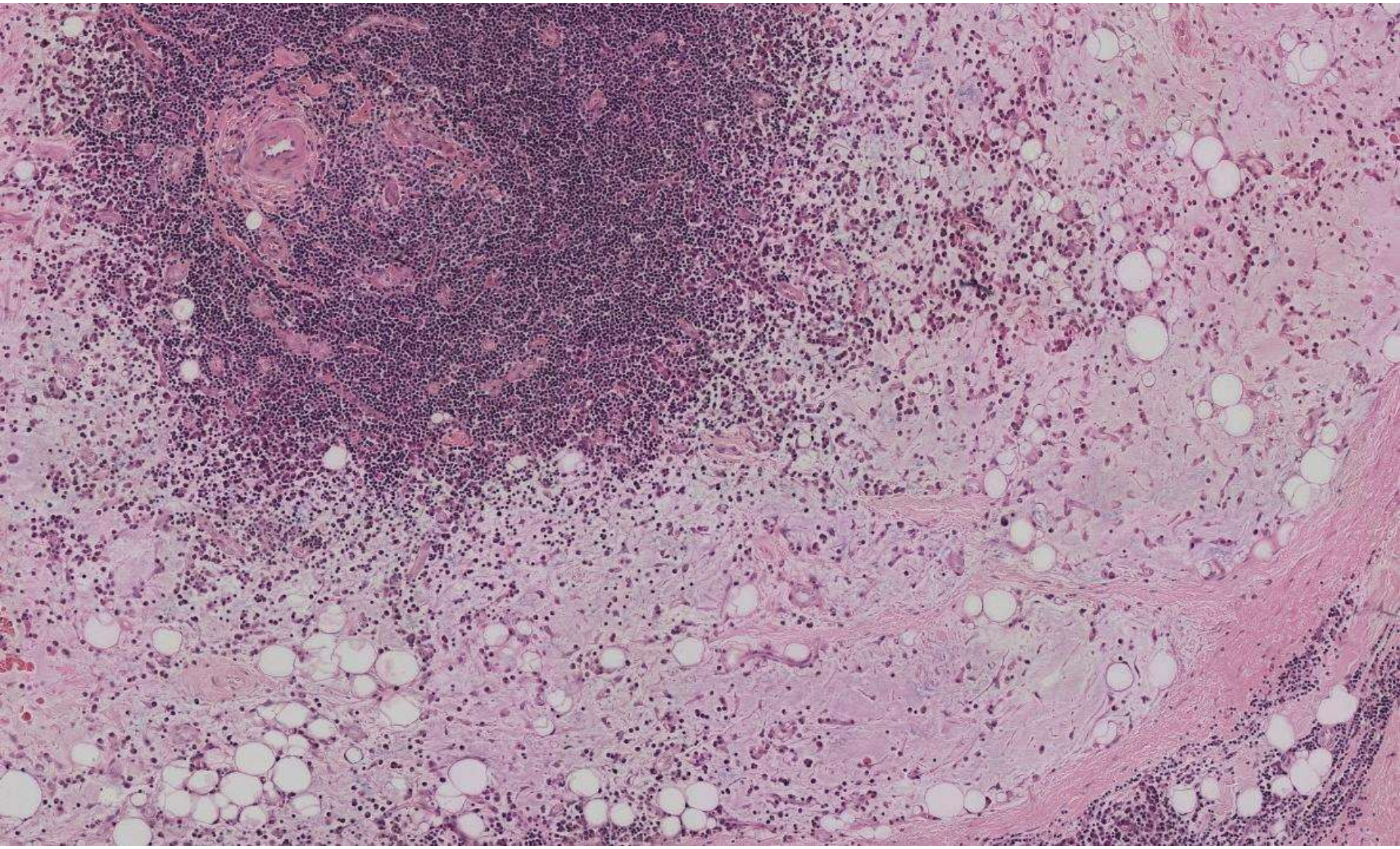


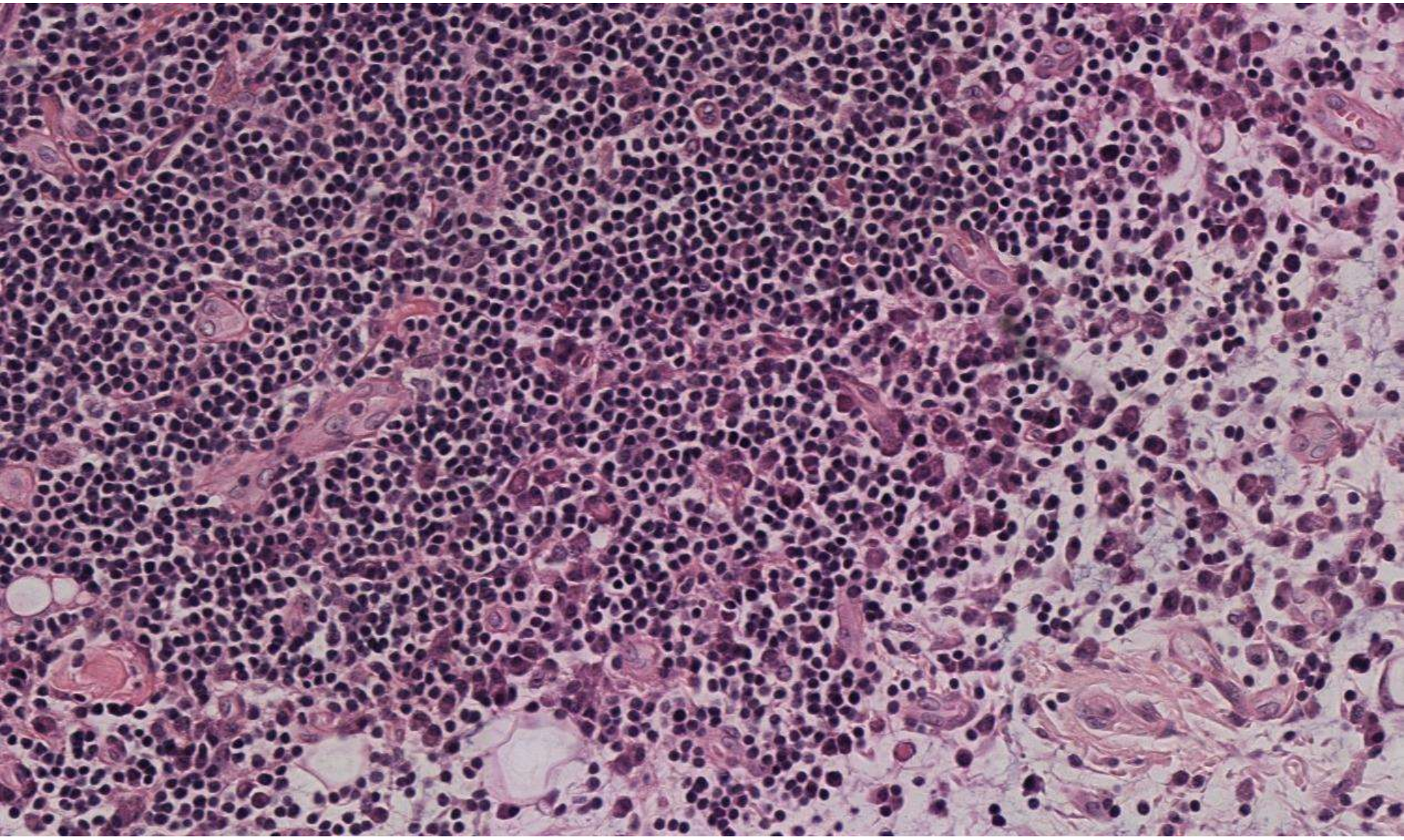


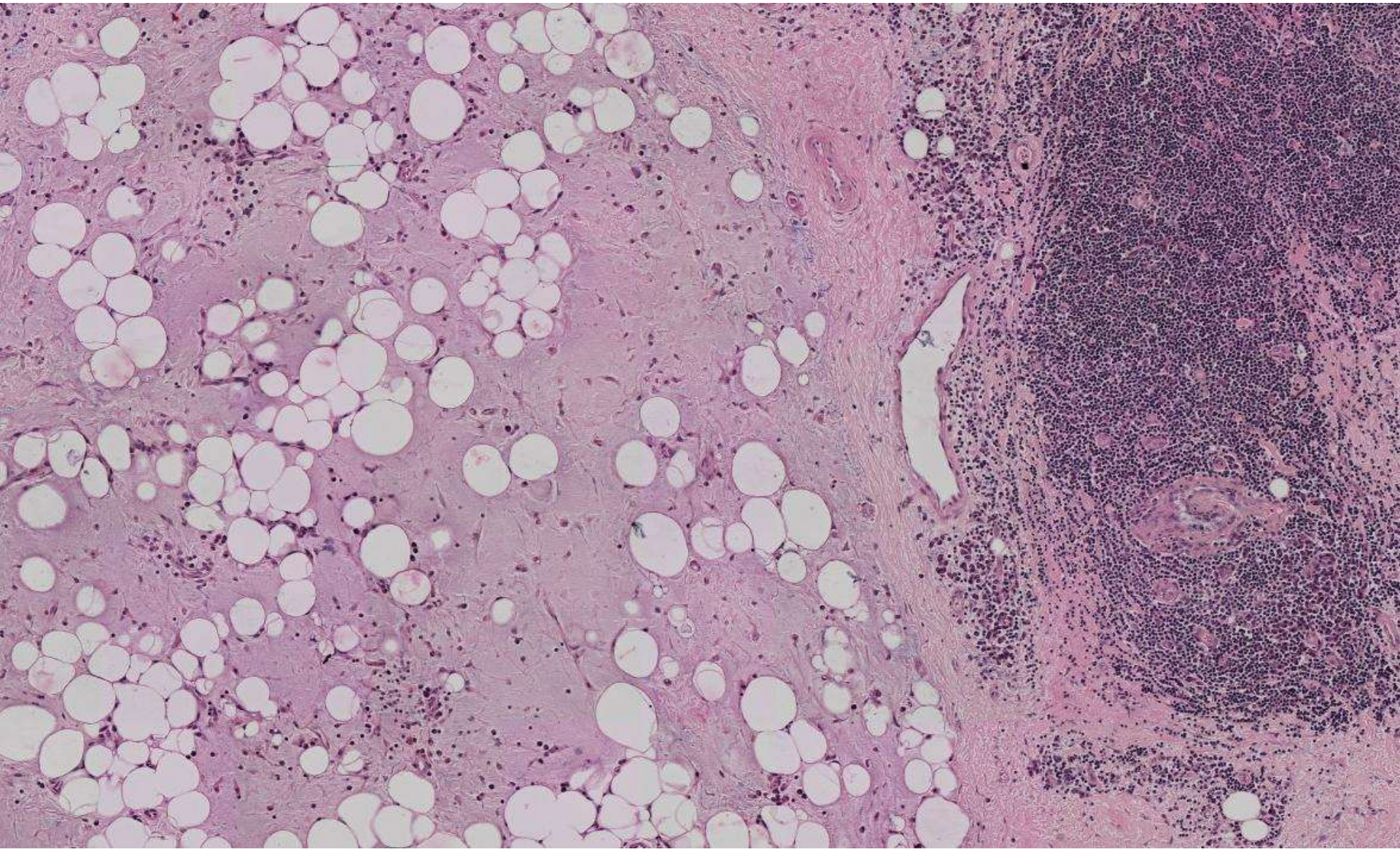


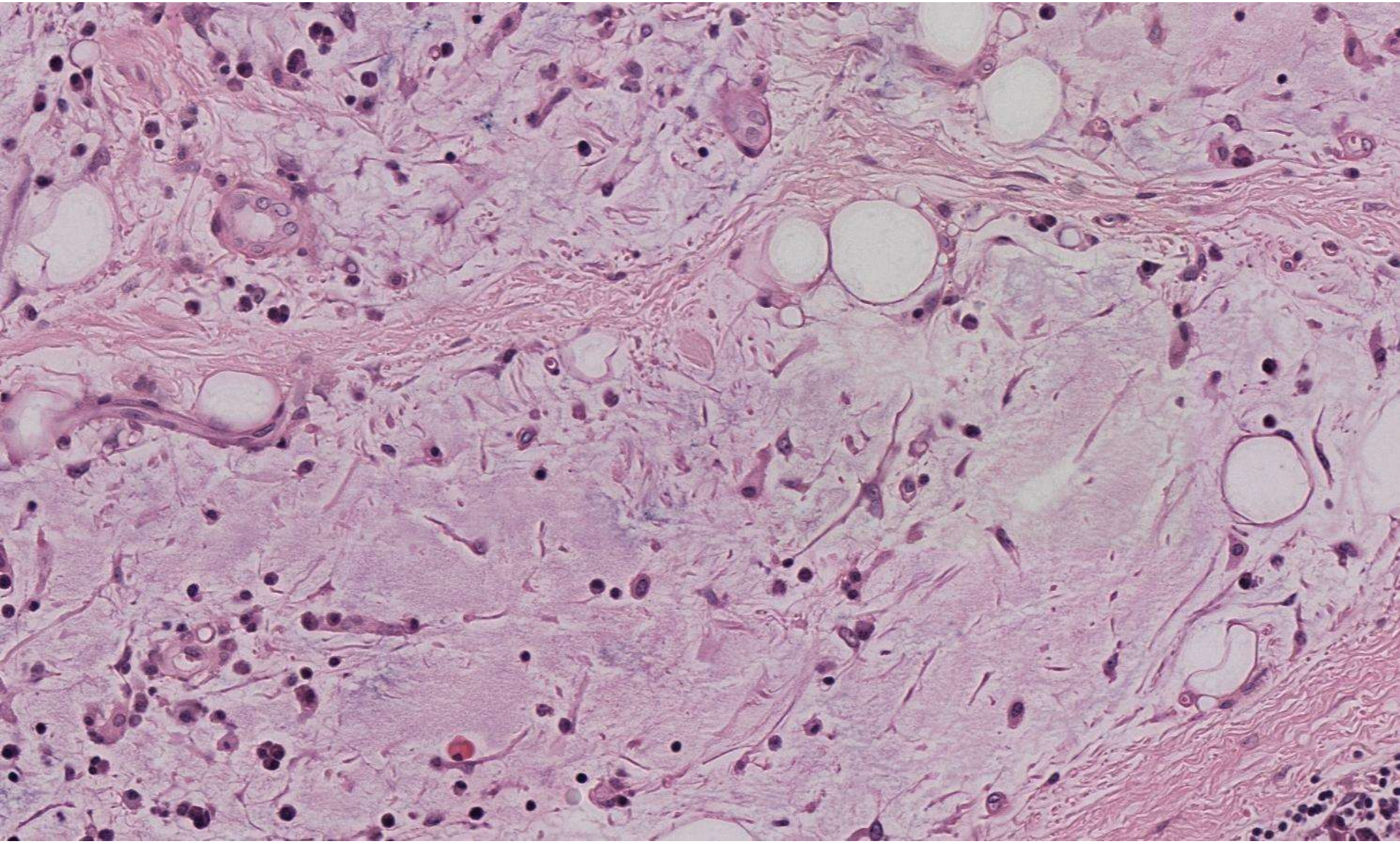


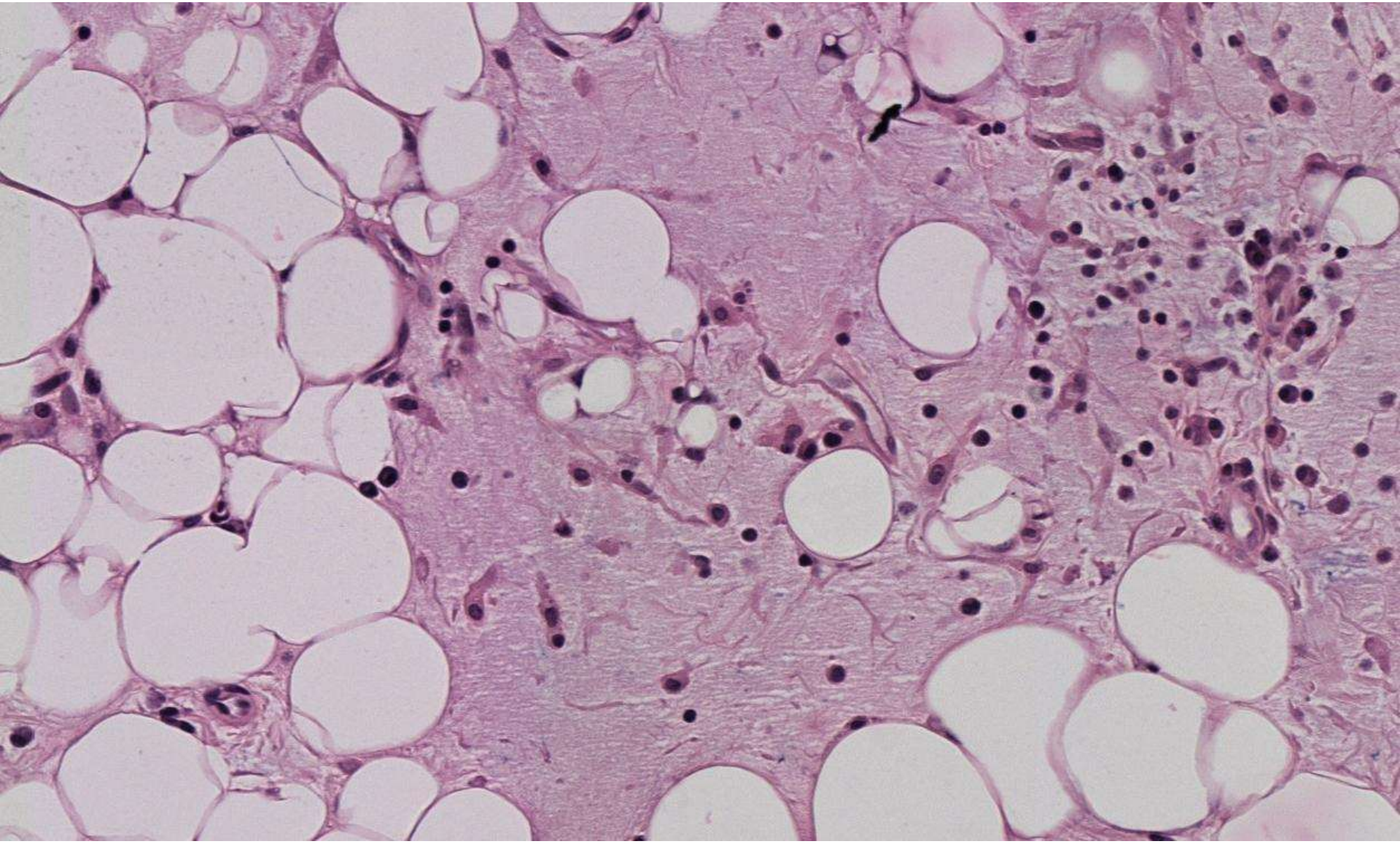


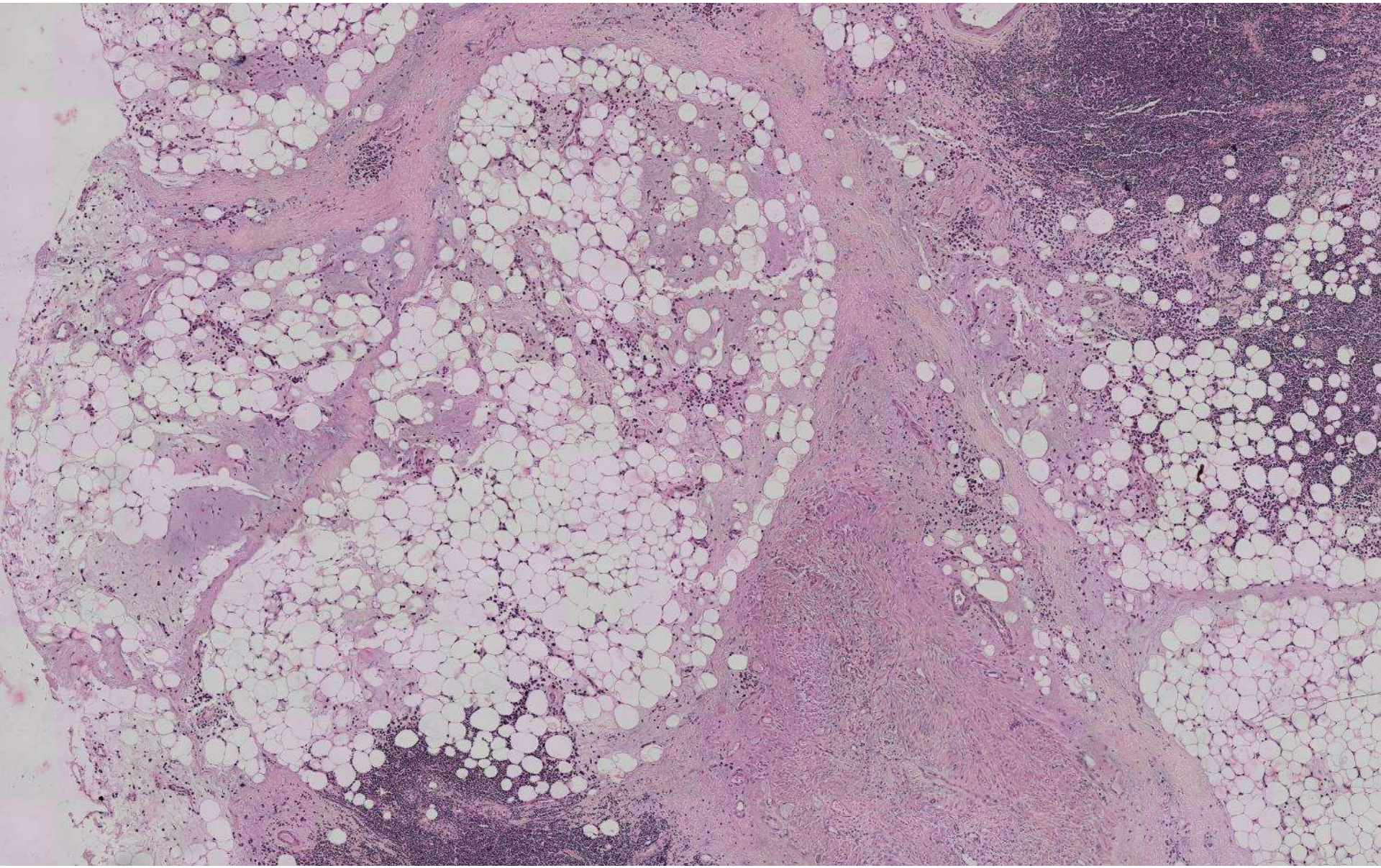


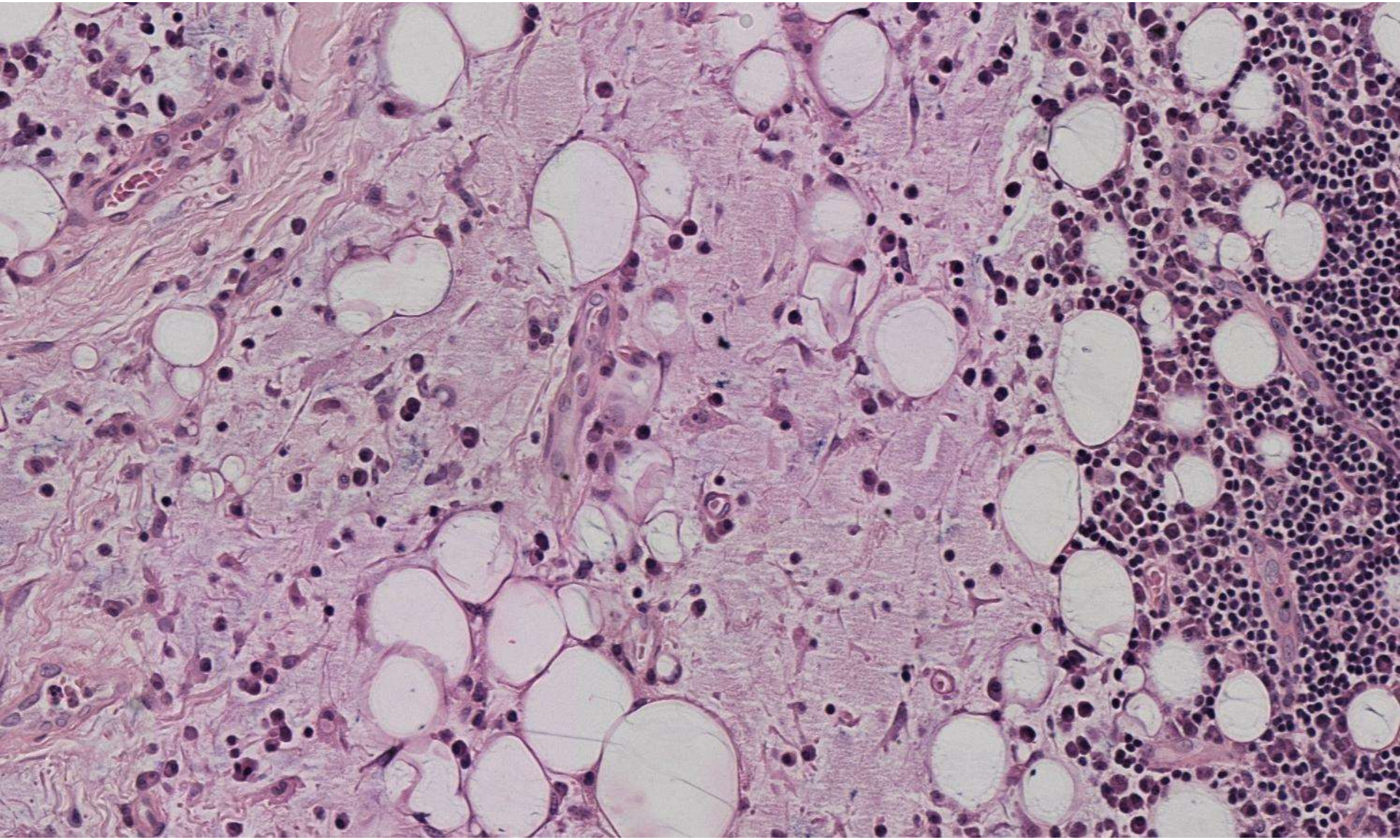


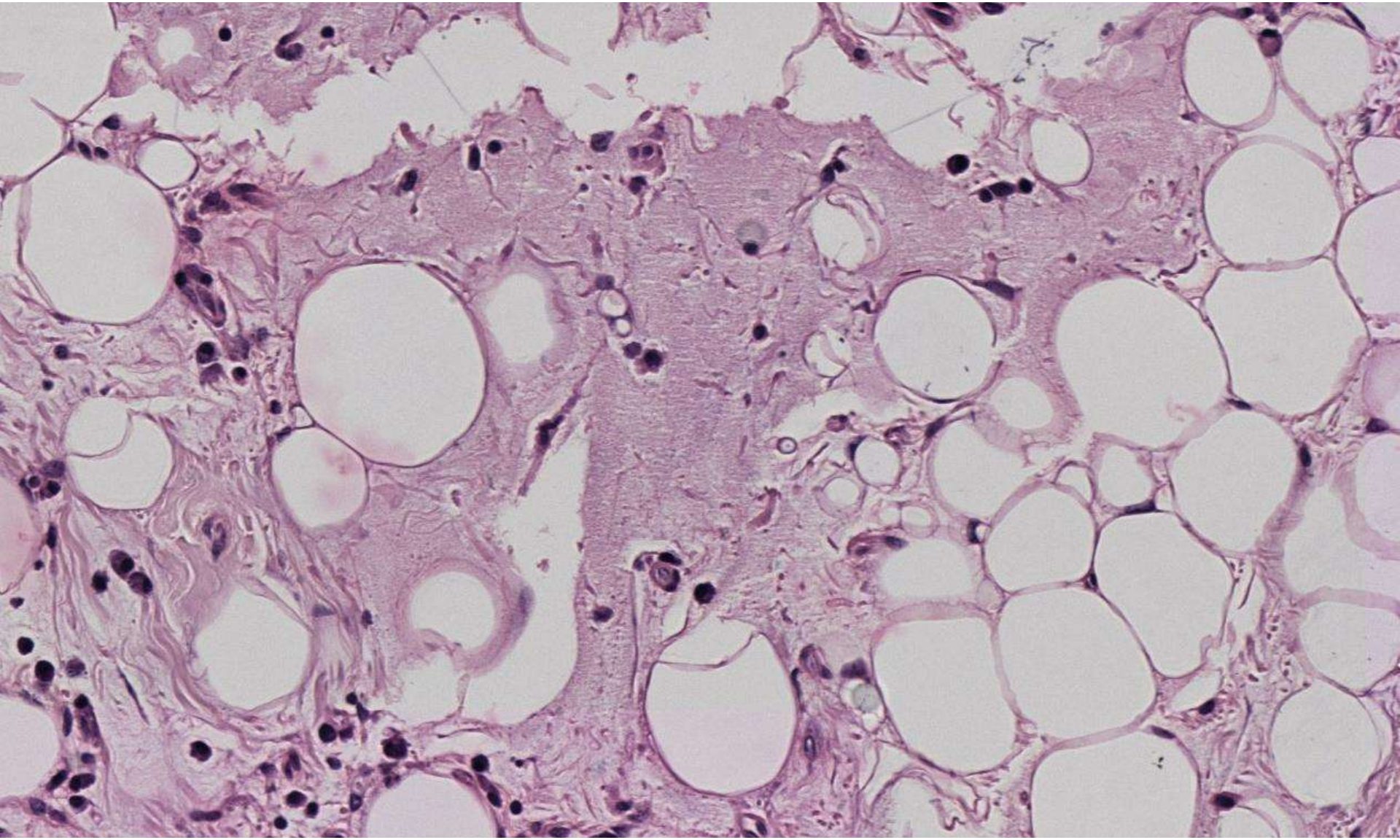


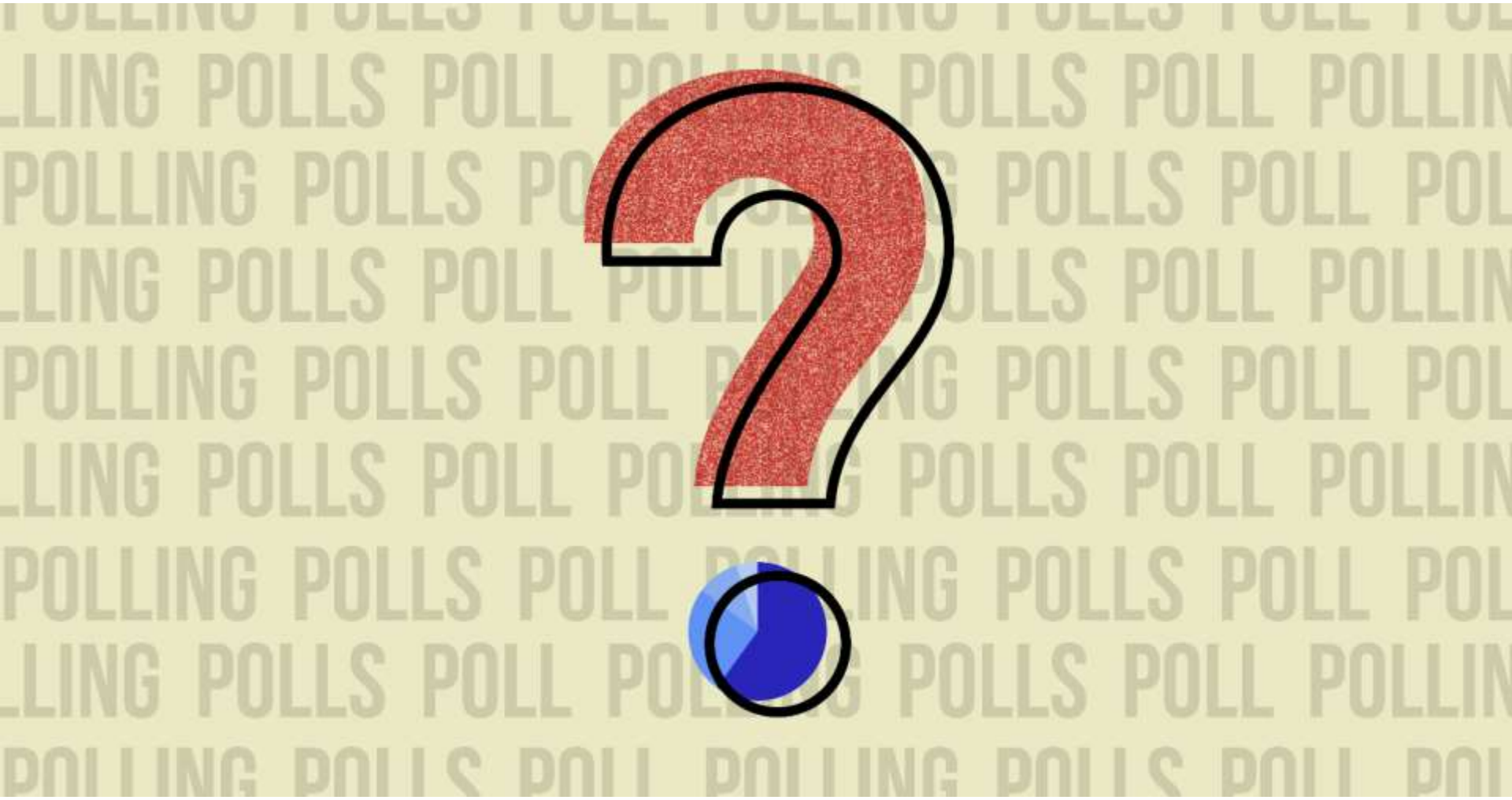











POLLING POLLS POLL

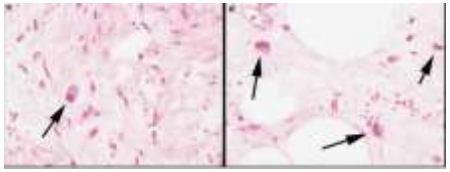
DDx

- Well-differentiated liposarcoma
- Rosai-Dorfman disease
- Carcinoma
- Lymphoma
- (Myxoid) IgG4 disease
- (Myxoid) fibromatosis
- Myxofibrosarcoma
- Angiomyolipoma
- Perinephric myxoid pseudotumor

IHC/molecular summary

- **Keratin-**
- **EMA-**
- **S100-**
- **cathepsinK-**
- **Beta catenin-**
- **Mixed normal pattern CD20/CD3**
- **IgG4 plasma cells-**
- ***MDM2* FISH-**

Pseudosarcomatous fibroblastic/ myofibroblastic proliferation in perinephric adipose tissue adjacent to renal cell carcinoma: a lesion mimicking well-differentiated liposarcoma



Munir R Tanas[1], Chalenpoj Sthapanachai[2], Daisuke Nonaka[3], Jonathan Melamed[3], Andre M Oliveira[4], Michele R Erickson-Johnson[4] and Brian P Rubin[1,5]

[1]*Department of Anatomic Pathology, Pathology and Laboratory Medicine Institute, The Cleveland Clinic and The Cleveland Clinic Lerner College of Medicine, Case Western Reserve University, Cleveland, OH, USA;* [2]*Department of Anatomic Pathology, University of Washington Medical Center, Seattle, WA, USA;* [3]*Department of Pathology, New York University Medical Center, New York, NY, USA;* [4]*Department of Pathology, Mayo Clinic, Rochester, MN, USA and* [5]*Department of Molecular Genetics, Lerner Research Institute and Taussig Cancer Center, Cleveland, OH, USA*

Cytologically atypical stromal cells were found in the perinephric adipose tissue, mimicking well-differentiated liposarcoma in 12 of 59 (20%) consecutive nephrectomy specimens that were resected for renal cell carcinoma. Morphologically, the atypical cells included enlarged, hyperchromatic spindle cells and floret-type multinucleate cells. Of 59, 10 (17%) renal cell carcinomas invaded through the renal capsule into the perinephric adipose tissue. Of these cases, three (30%) contained the aforementioned atypical cells. In contrast, 9 of 49 cases without extrarenal invasion (18%) contained the atypical stromal cells. Of the 12 cases with atypical stromal cells, 3 (25%) were associated with extrarenal involvement. The atypical spindle cells exhibited focal to variable positivity for smooth muscle actin and desmin in 3 of the 14 cases (including two cases from our consultation files) each. Cytokeratin AE1/AE3, cytokeratin Cam 5.2, cytokeratin 7, epithelial membrane antigen, and S-100 were negative in all cases. Amplification of *MDM2* gene region, which is commonly observed in well-differentiated liposarcoma, was absent by fluorescence *in situ* hybridization (FISH) in the atypical stromal cells. Immunohistochemistry and FISH suggest that the atypical cells are most consistent with reactive fibroblasts/myofibroblasts. Recognition of these atypical fibroblasts/myofibroblasts may help in avoiding the potential pitfall of misdiagnosing them as well-differentiated liposarcoma.

Modern Pathology (2009) **22**, 1196–1200; doi:10.1038/modpathol.2009.84; published online 12 June 2009

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Original contribution

Perinephric myxoid pseudotumor of fat: a distinctive pseudoneoplasm most often associated with non-neoplastic renal disease☆

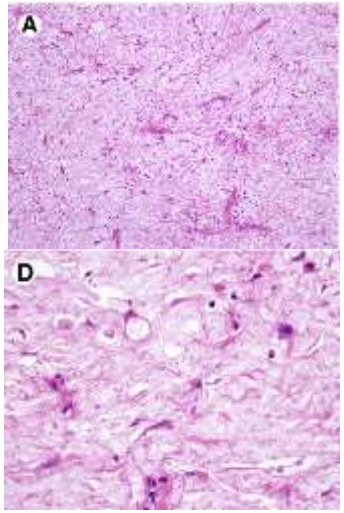
Nooshin K. Dashti MD, Karen J. Fritchie MD, Andrew L. Folpe MD*

Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester 55905, MN

Received 9 January 2019; revised 6 February 2019; accepted 6 February 2019

Keywords:
Pseudotumor;
Renal neoplasms;
Renal disease;
Well-differentiated liposarcoma;
MDM2;
IgG4

Summary In 2009, Tanas et al reported unusual changes in the perinephric fat, mimicking well-differentiated liposarcoma. We report 11 perinephric masses showing similar changes but chiefly arising in patients with non-neoplastic renal disease. Tissue from 11 perinephric masses was retrieved, and immunohistochemistry for IgG/IgG4 and fluorescence in situ hybridization (FISH) for *MDM2* amplification was performed. Clinical information was obtained. Cases occurred in 10 males and 1 female (43-84 years of age; median, 63.5 years). Ten patients presented with perinephric masses (size range, 2-28 cm), and one was an incidental finding. Four patients had bilateral or multiple masses. Underlying renal disease included diabetes mellitus (n = 3), end-stage kidney (n = 2), diabetes and end-stage kidney disease (n = 1), chronic pyelonephritis (n = 1), and non-invasive high-grade papillary urothelial carcinoma of the renal pelvis (n = 1). Three patients were not known to have renal disease. Most tumors were submitted as "well-differentiated liposarcoma." The masses consisted of mature fat, myxoid stroma, moderately variable spindled to stellate cells and a mixed inflammatory cell infiltrate. Enlarged, hyperchromatic stromal cells were absent. IgG4-positive plasma cells and *MDM2* amplification were absent in all tested cases. Clinical follow-up (11 patients; range, 1-120 months; median, 24 months) showed absent or stable disease in 9 patients; 2 died of unrelated causes. This distinctive pseudoneoplasm usually occurs in association with non-neoplastic renal disease, although similar changes may be identified in the perinephric fat of patients with renal carcinoma. Morphologic evaluation and FISH for *MDM2* amplification should allow its distinction from liposarcoma and other mimics.



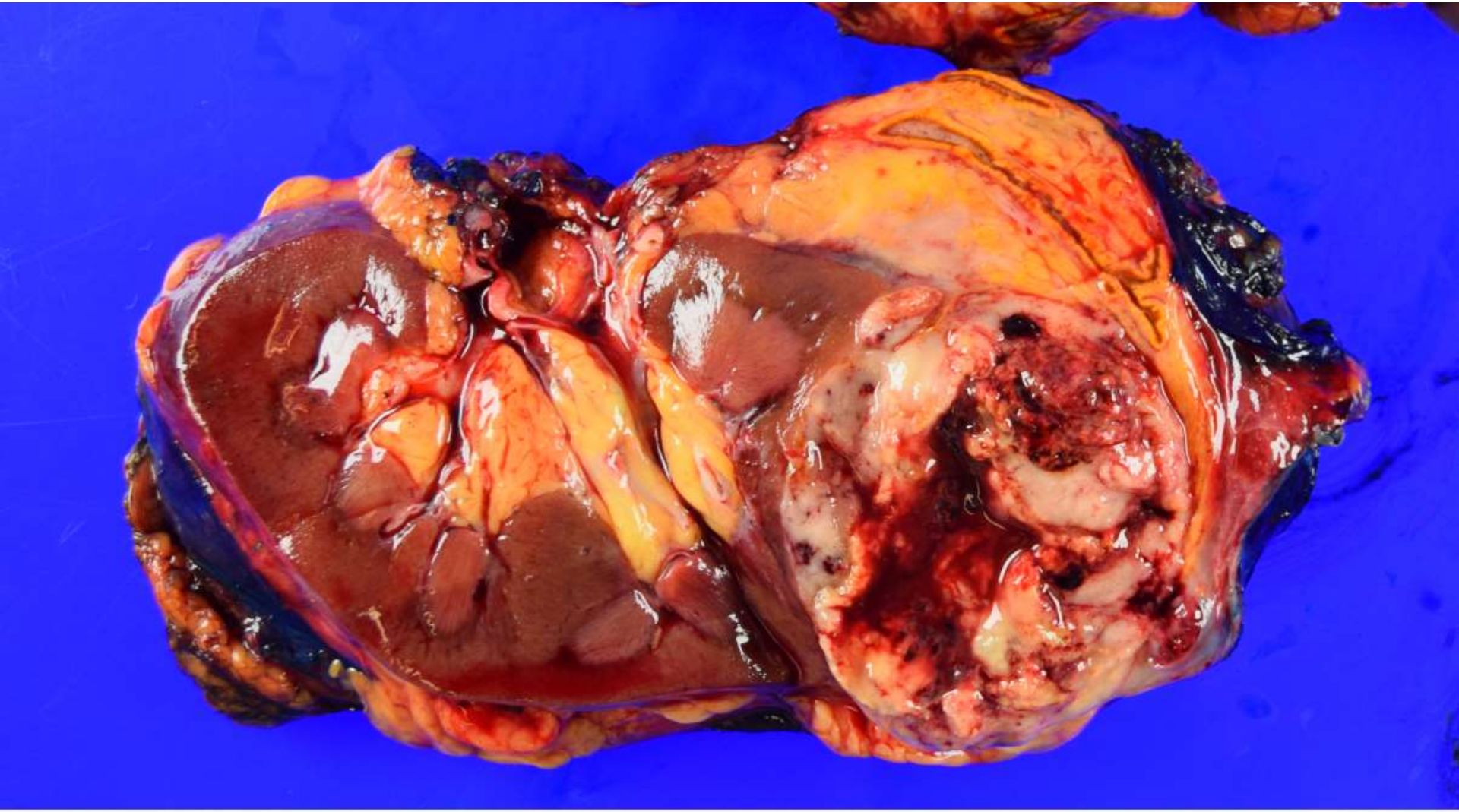
Perinephric myxoid pseudotumor

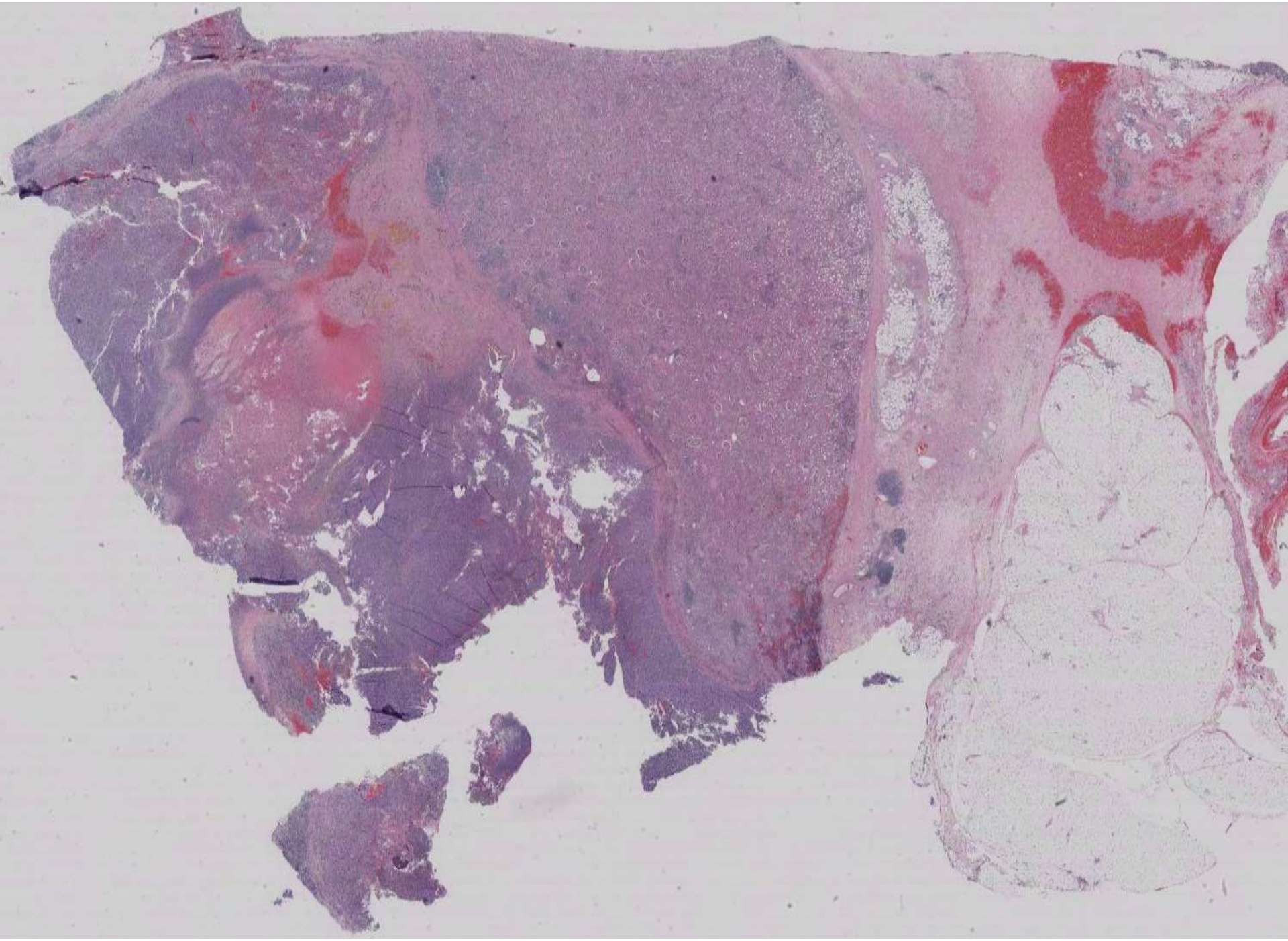
- **Main DDx is well-diff liposarcoma**
  - Stromal cells lack marked nuclear enlargement/hyperchromasia
  - Absent MDM2 amplification
- **Uncommon mass-forming lesion usually associated with non-neoplastic renal disease**

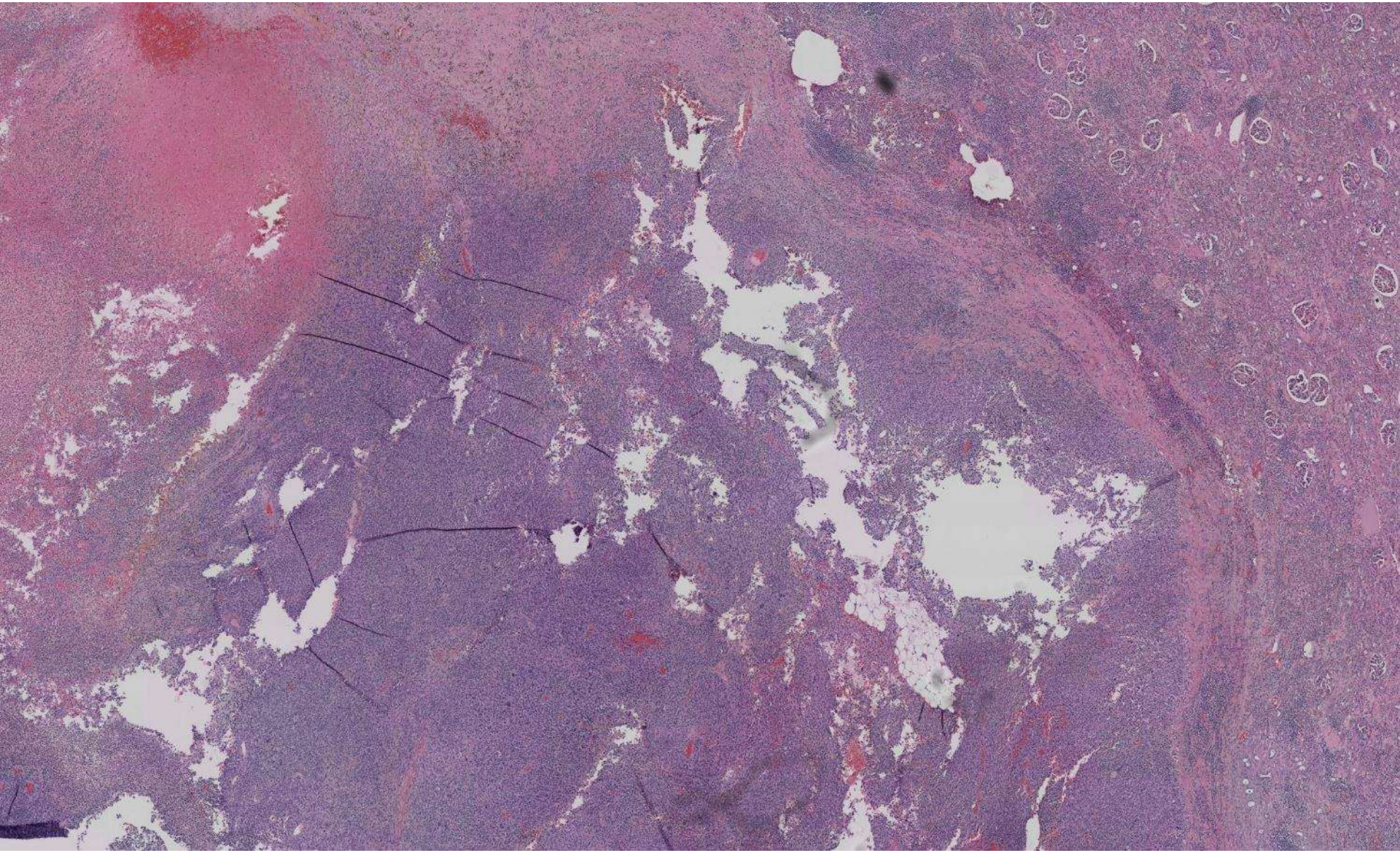
20-0906
scanned slide available!

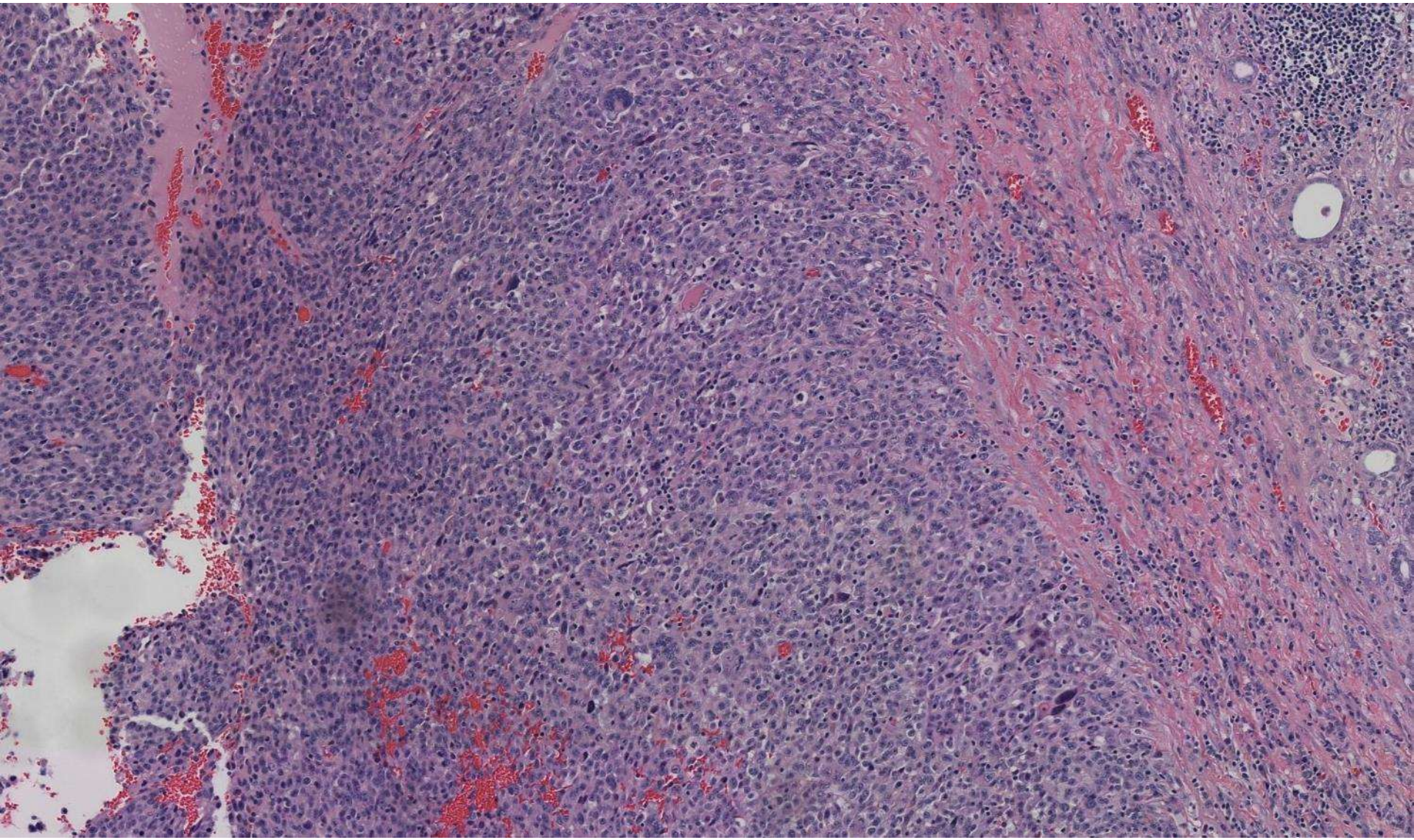
Connie Chen/Emily Chan; UCSF

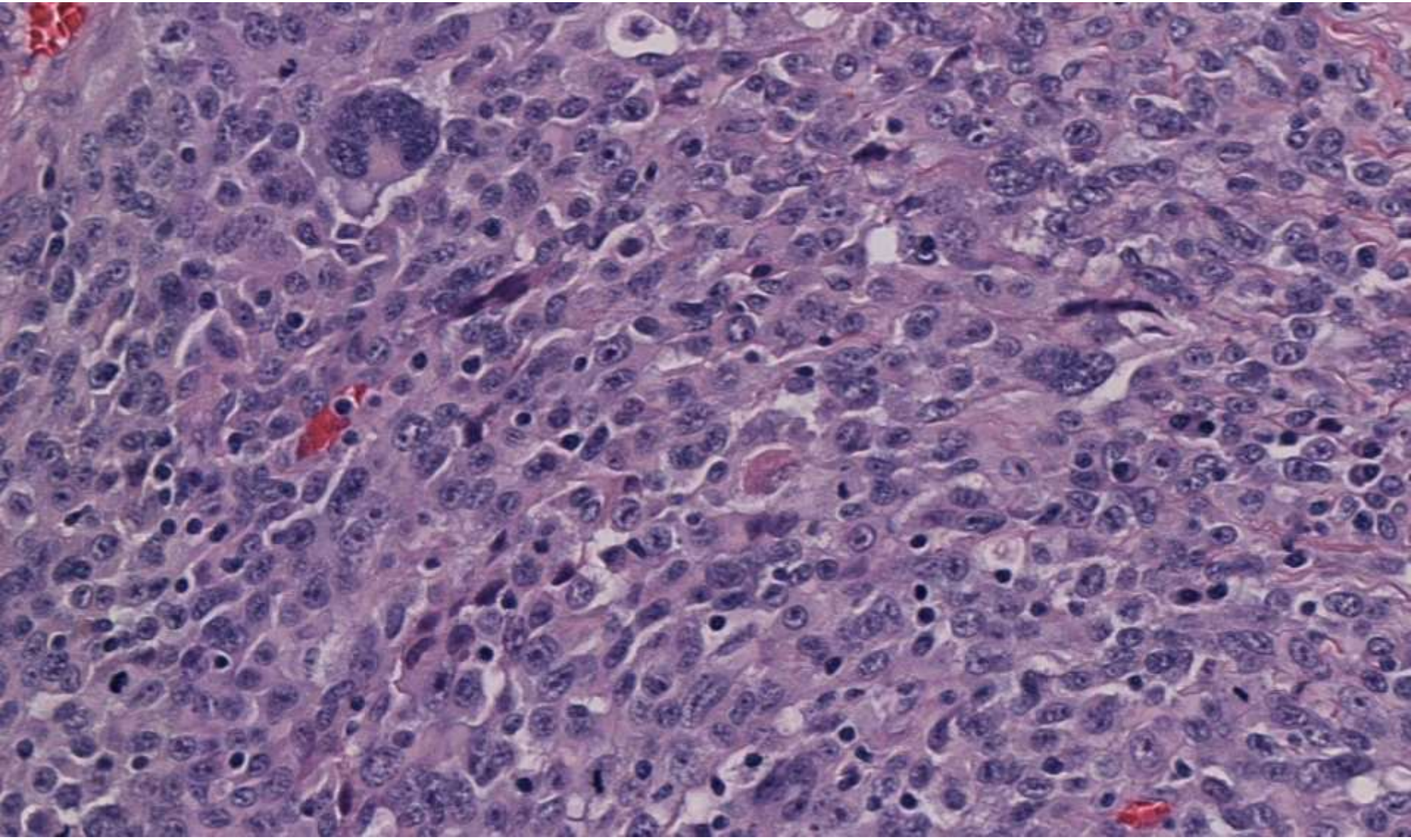
48-year-old F with 5.9cm left superior pole renal mass.

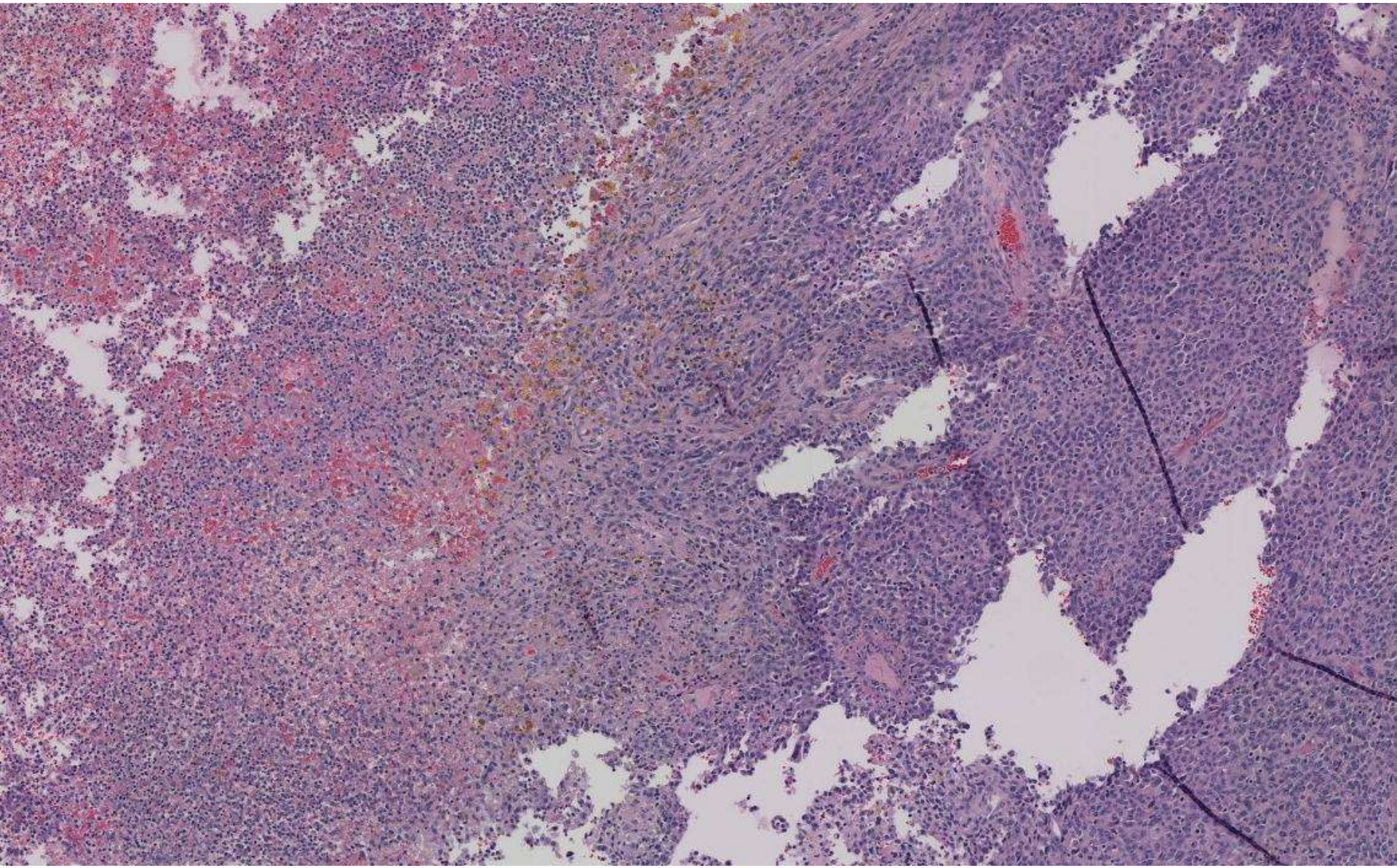


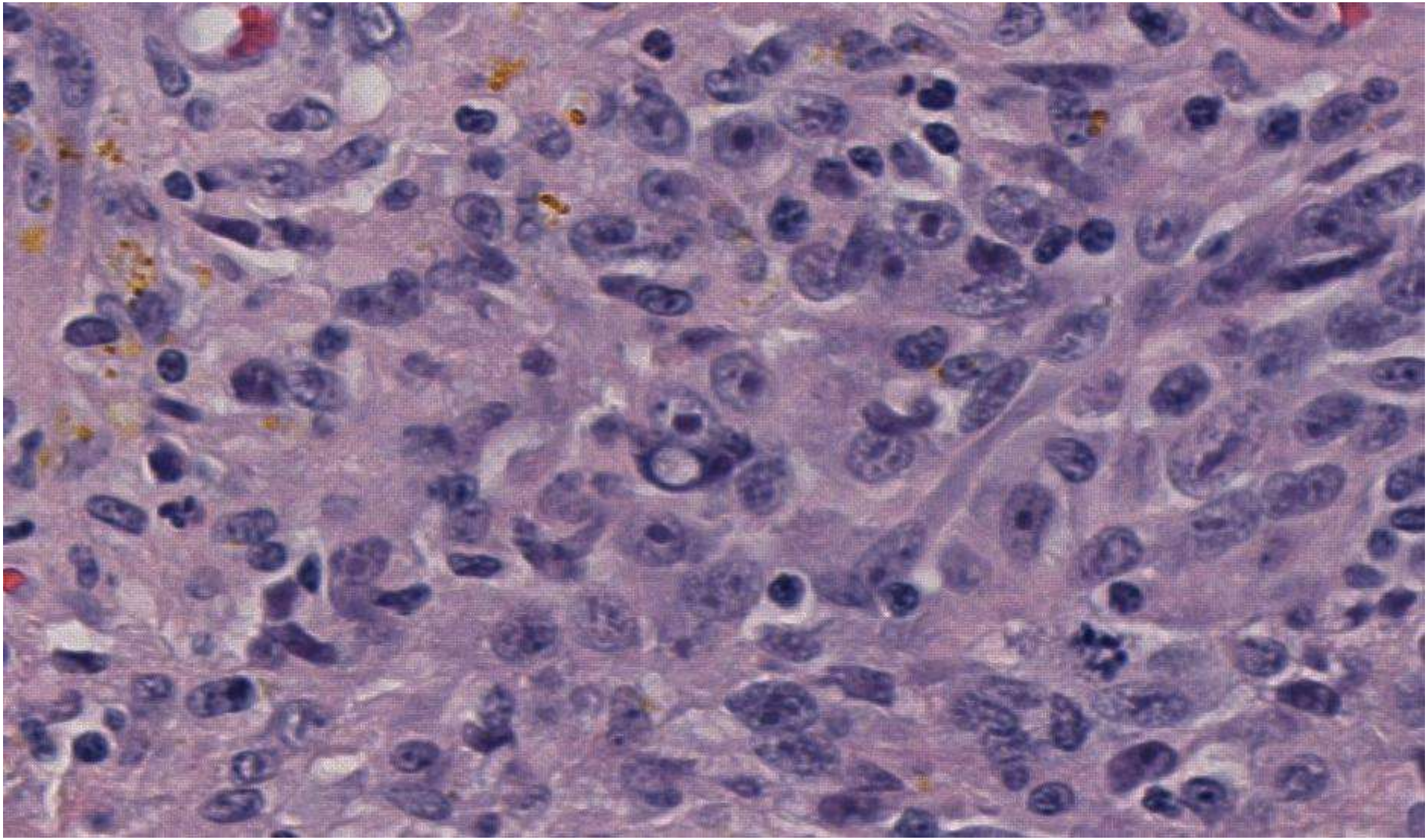


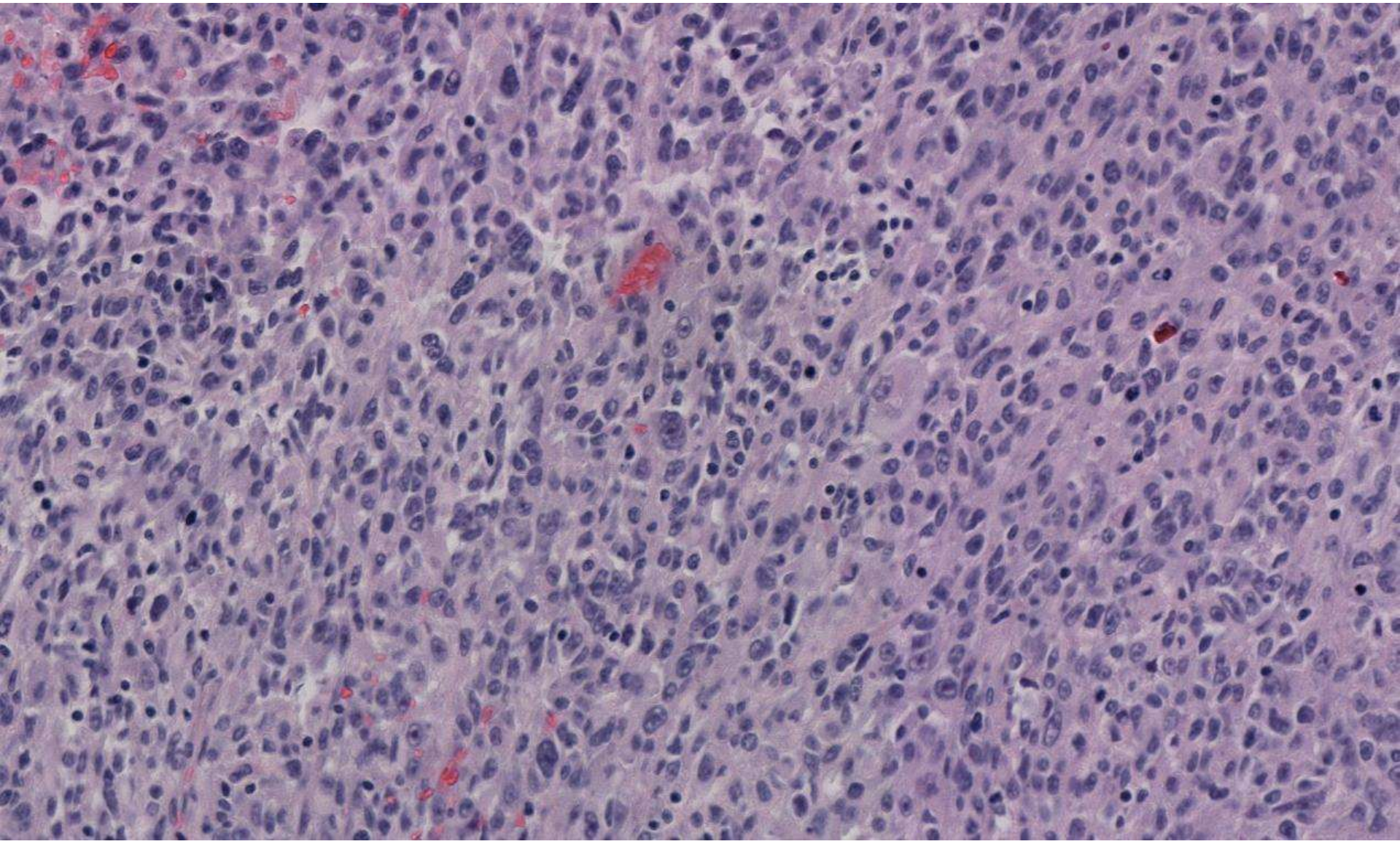


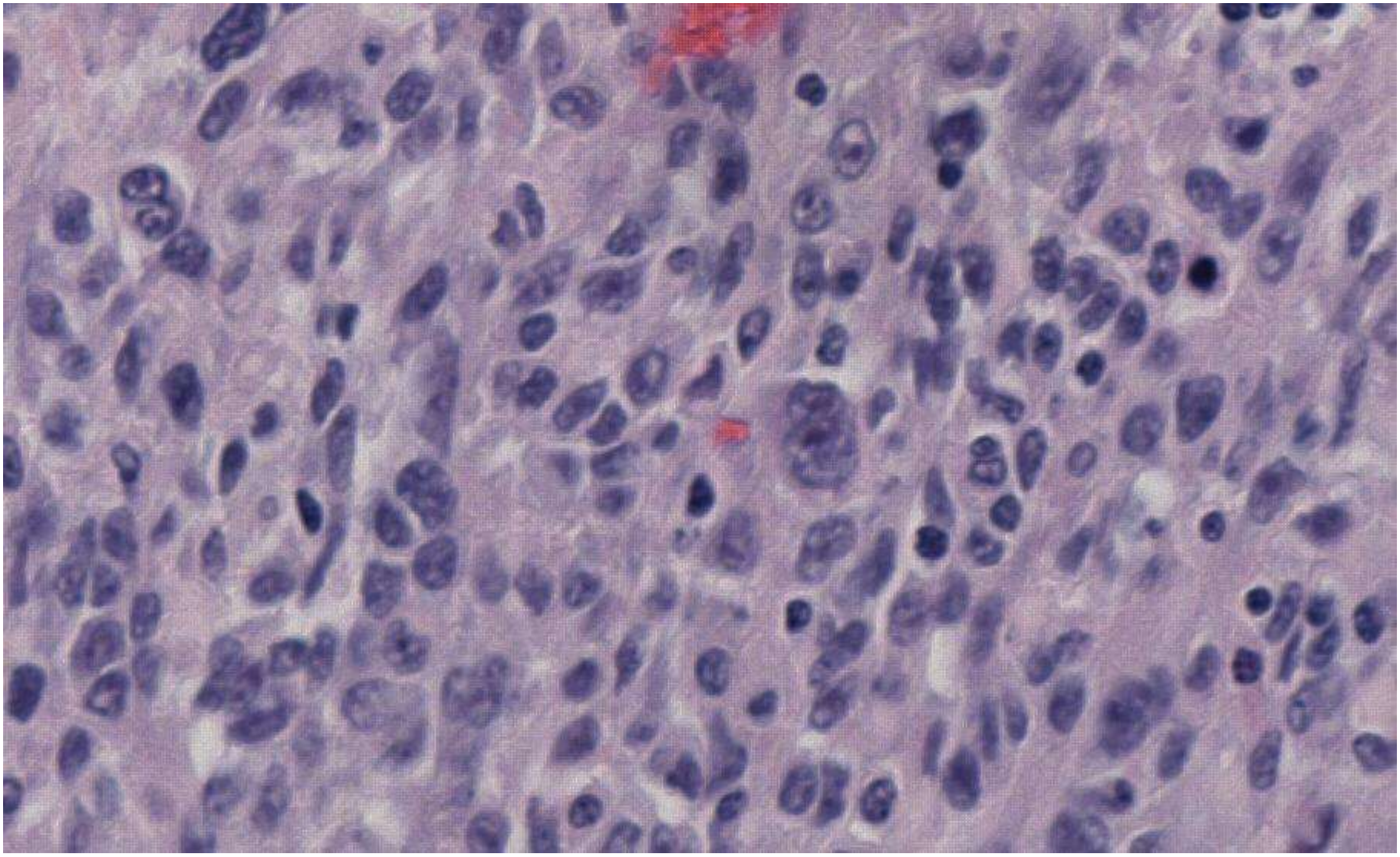






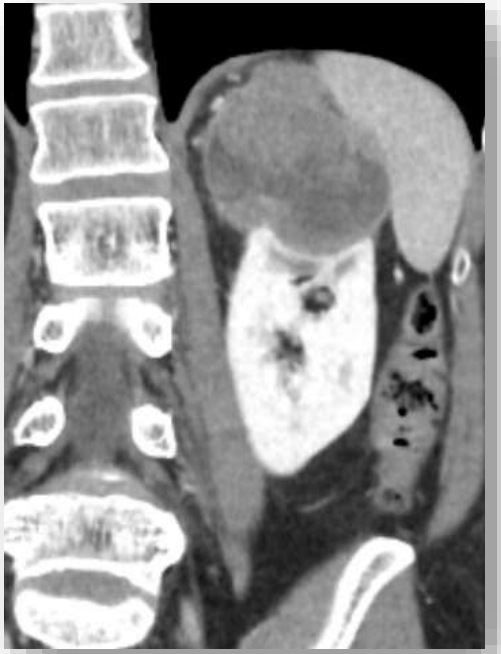


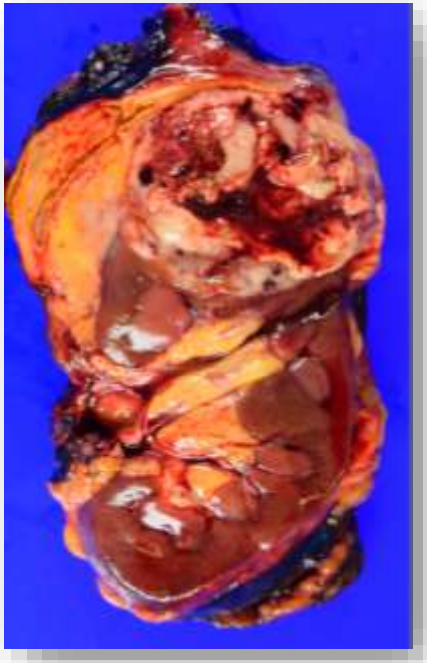




CLINICAL HISTORY

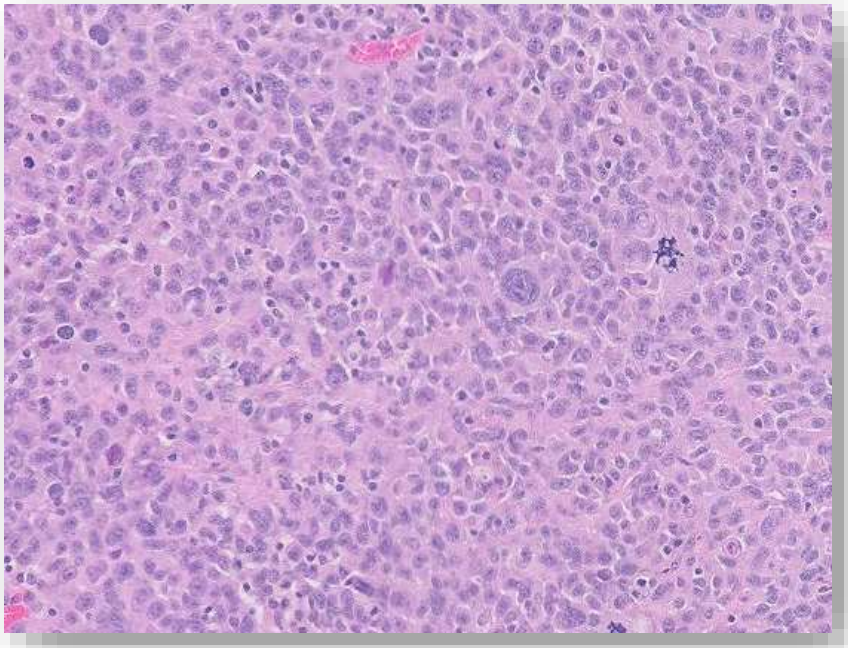
- 48 year-old woman presenting with a 5.9-cm superior pole left renal mass



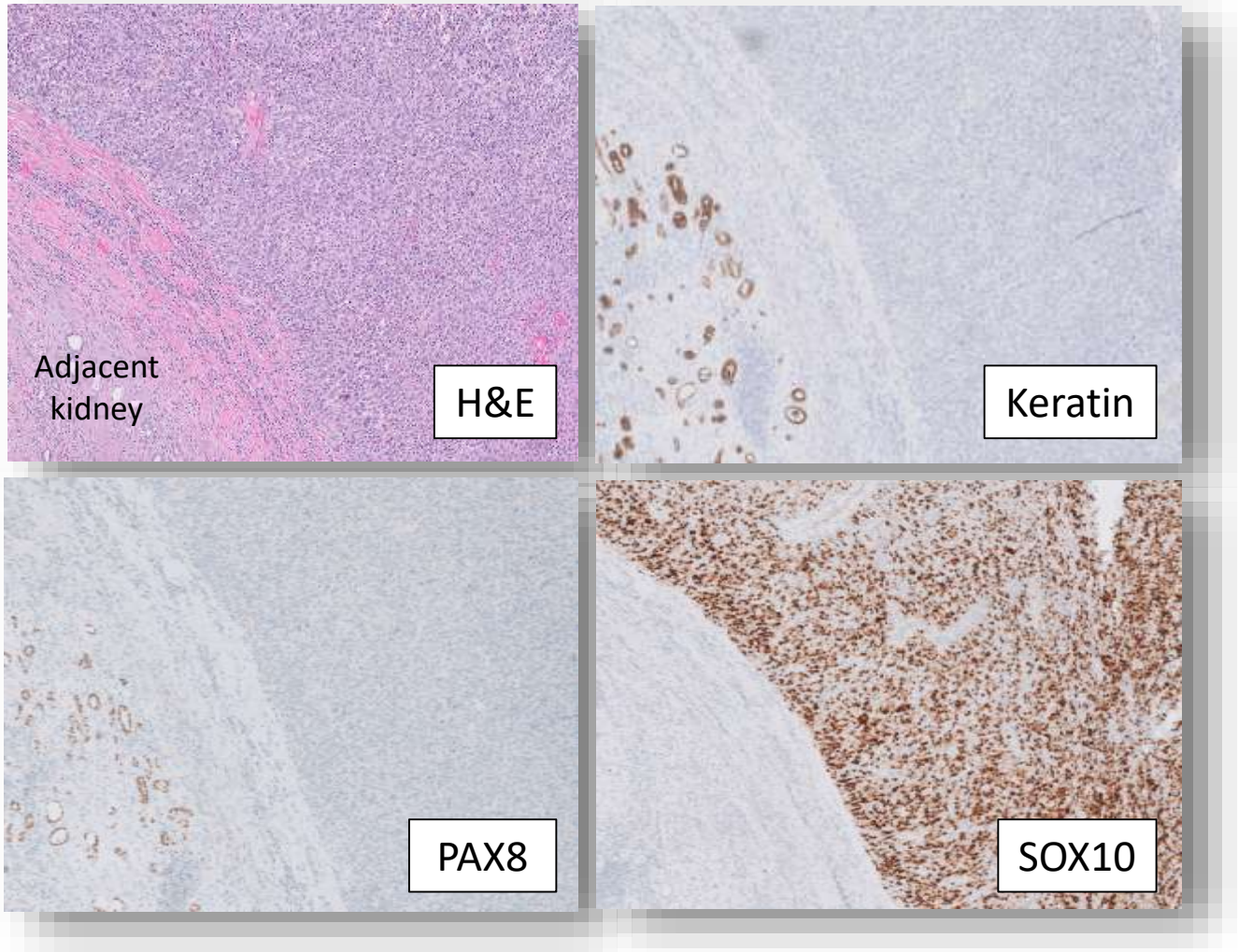


DIFFERENTIAL DIAGNOSES

- Carcinoma
- Sarcoma
- Melanoma
- Perivascular epithelioid cell tumor (PEComa)
- Metastatic carcinoma



IMMUNOHISTOCHEMICAL STAINS



Additional IHC including CK7, CK20, Uroplakin, GATA-3, and muscle-specific actin were performed and were negative

FINAL DIAGNOSIS

LEFT KIDNEY:

MALIGNANT MELANOMA, 6.5 CM, NEGATIVE MARGINS; SEE COMMENT.

MELANOMA IN THE KIDNEY

- 1958 - First reported melanoma presenting as a solitary renal mass without a skin or ocular lesion (Agnew)
  - Did not classify as primary renal origin (presumed metastasis)

- 1970s-90s: Solitary renal melanomas reported, with fewer than 10 characterized as “primary” melanomas of the kidney

- Cutaneous regression is a relatively common event in melanoma, whether spontaneous or in response to treatment
  - Overall regression incidence of melanomas 10-35%, and up to 58% of thin melanomas

PRIMARY v. METASTATIC IN THE KIDNEY?

- Established criteria for defining primary melanoma of the bladder has been applied to renal pelvis melanomas:
  - No cutaneous or ocular lesion
  - Contains adjacent atypical melanocytes in urothelium

“Primary” melanoma	**Metastatic melanoma**
No history of cutaneous or ocular lesion	Known cutaneous or ocular lesion
	Multiple cortical nodules <1 cm, bilateral kidneys (at autopsy)
Single solitary mass	Widespread involvement of other visceral organs or CNS
	UV molecular signature

OUR PATIENT'S SEQUENCING

UCSF Clinical Cancer Genomics Laboratory

SELECTED SOMATIC ALTERATIONS				
VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
ARID1B p.Y1061fs	NM_020732.3	Pathogenic	319	66%
NF1 p.Q11*	NM_001042492.2	Pathogenic	938	26%
NRAS p.Q61R	NM_002524.4	Pathogenic	321	37%
TERT c.-124C>T	NM_198253.2	Pathogenic	977	38%
TP53 p.S241F	NM_000546.5	Pathogenic	400	60%

- Heavy tumor mutation burden - more than 50 somatic mutations were present, along with *NRAS Q61R*

NRAS Q61R Mutation – UV

- *NRAS Q61R* is a preferentially UV sensitive site, leading to tumorigenesis
  - UV photoproducts in UV-irradiated human skin fibroblasts were mapped at a high frequency to codon 61 of *RAS* genes

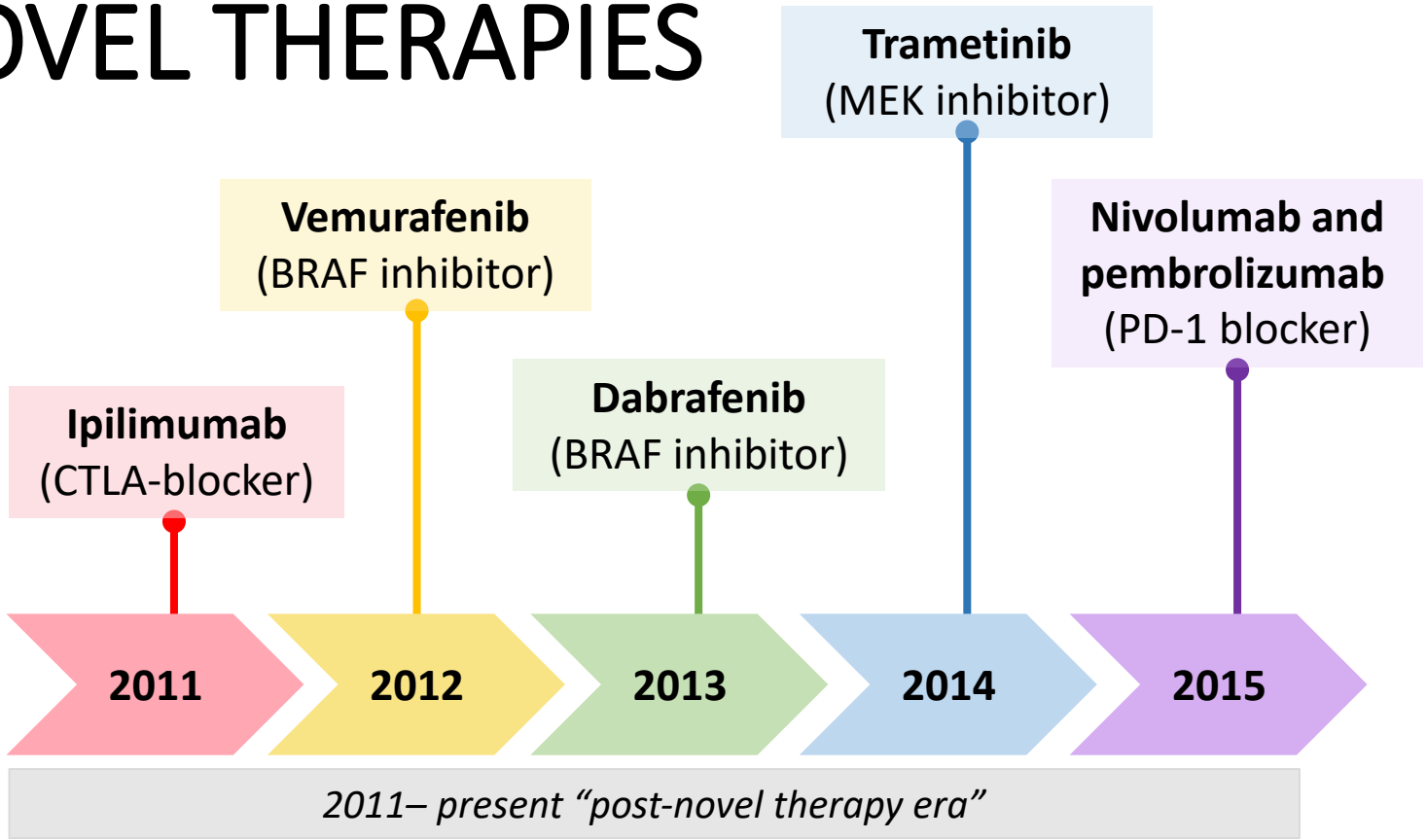
- *NRAS* mutations are associated with chronic sun damage in a meta-analysis of sites of origin
  - vs. *BRAF*, which was seen more in **non**-sun damaged skin

Image from Coppertone.com

NRAS – PROGNOSIS

- 2011 MD Anderson study:
  - 313 patients with non-uveal metastatic melanoma tested for *BRAF* and *NRAS*
    - *NRAS* mutation conferred shorter survival (8.2 months) than *BRAF* (10.3 months)
  - Etiology unclear, although possible that these melanomas have a greater number of pathogenic mutations compared to melanomas from non-sun exposed sites
  - Prior to advent of immunotherapies

NOVEL THERAPIES



2019 Dutch population study:

Median overall survival for patients with stage IV melanoma of unknown primary was superior for those receiving novel therapy compared to those not (4 months vs. 11 months)

TAKE-HOME POINTS

- Few reported cases of melanoma presenting as a large solitary mass in kidney
- Difficult to rule out kidney metastases from regressed cutaneous melanomas
- *NRAS Q61R* mutation and heavy tumor mutation burden suggests a UV-induced cutaneous melanoma
- For solitary lesions, treatment is usually surgery, but adjuvant therapies may be offered as well
- Immunotherapy is promising in improving survival for stage IV melanomas of unknown primary

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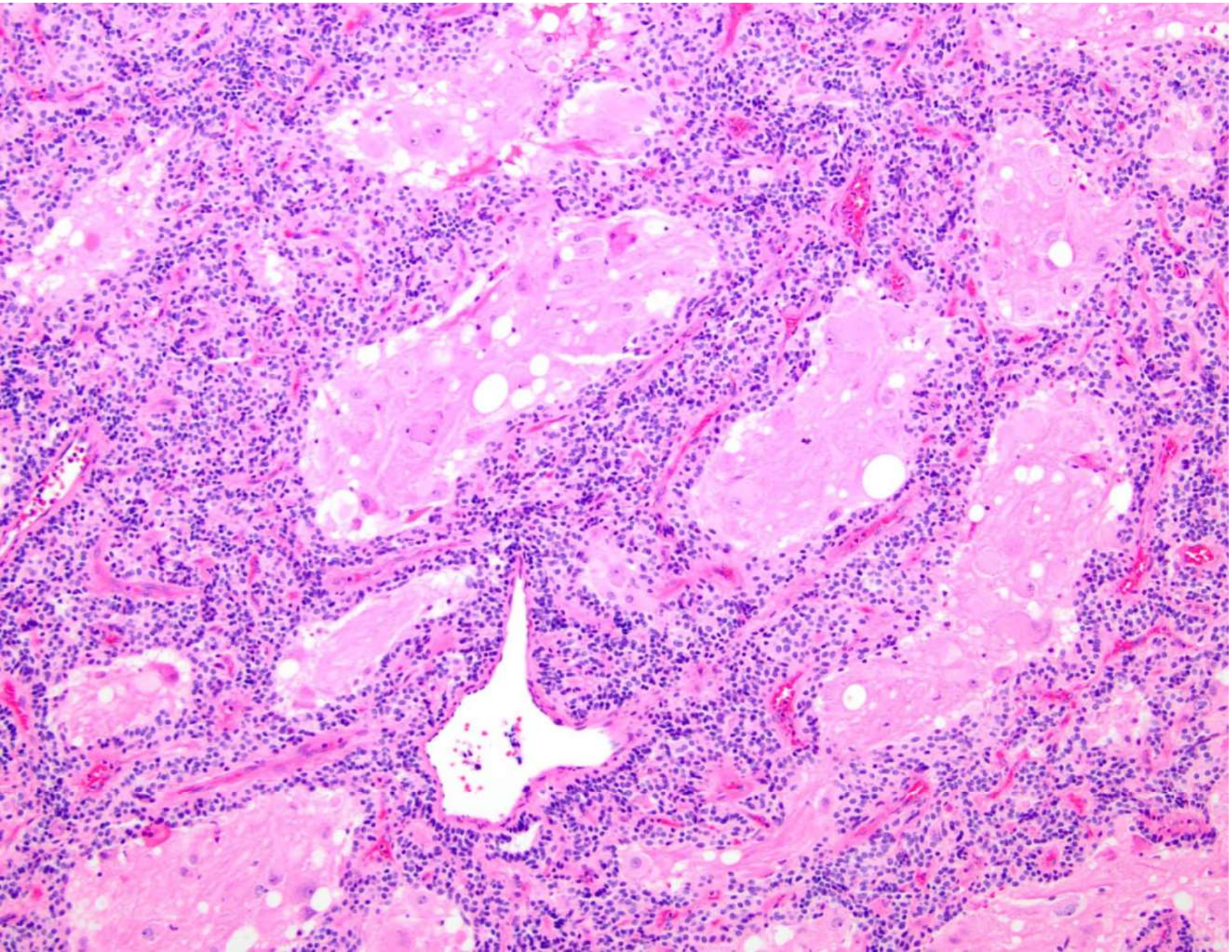
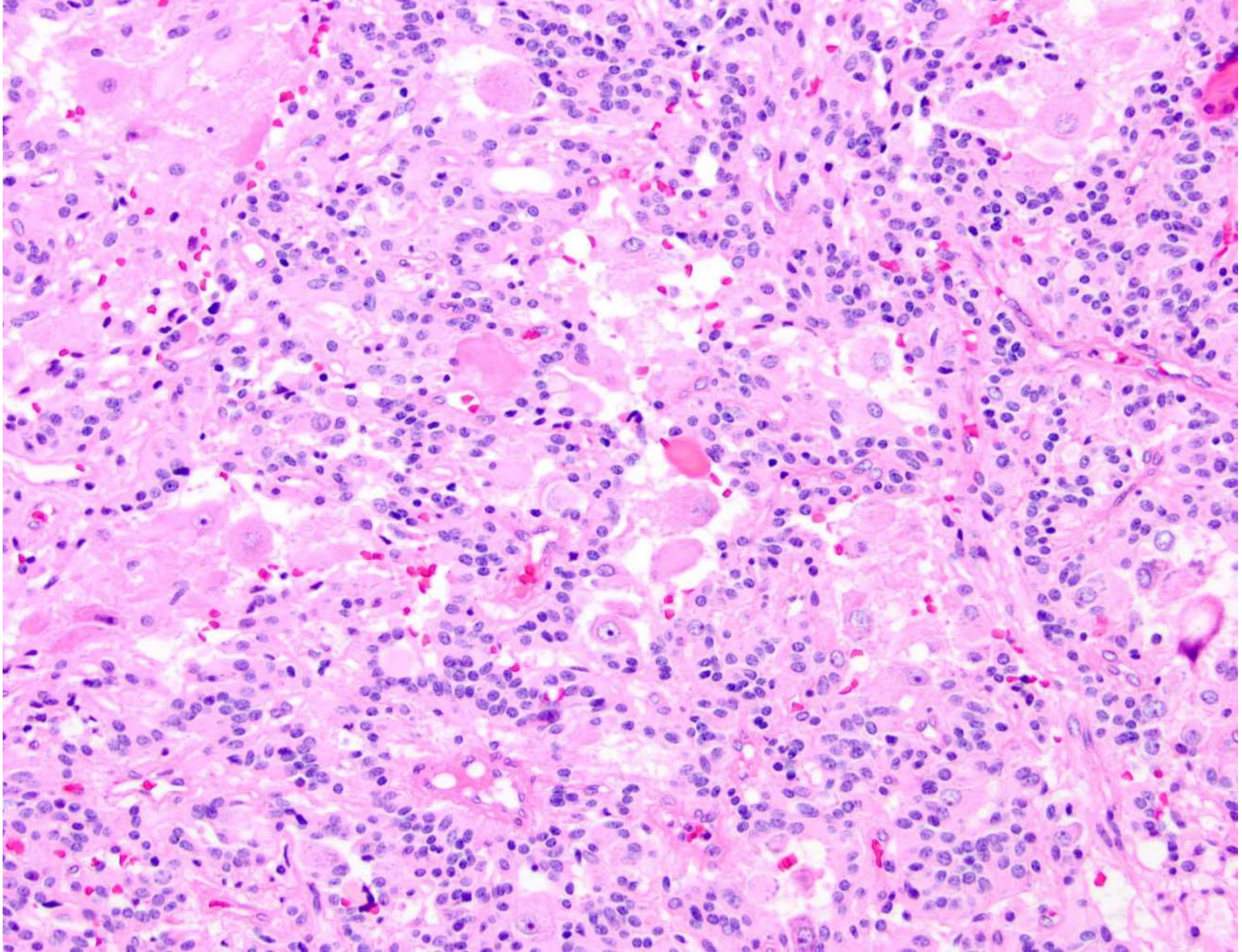
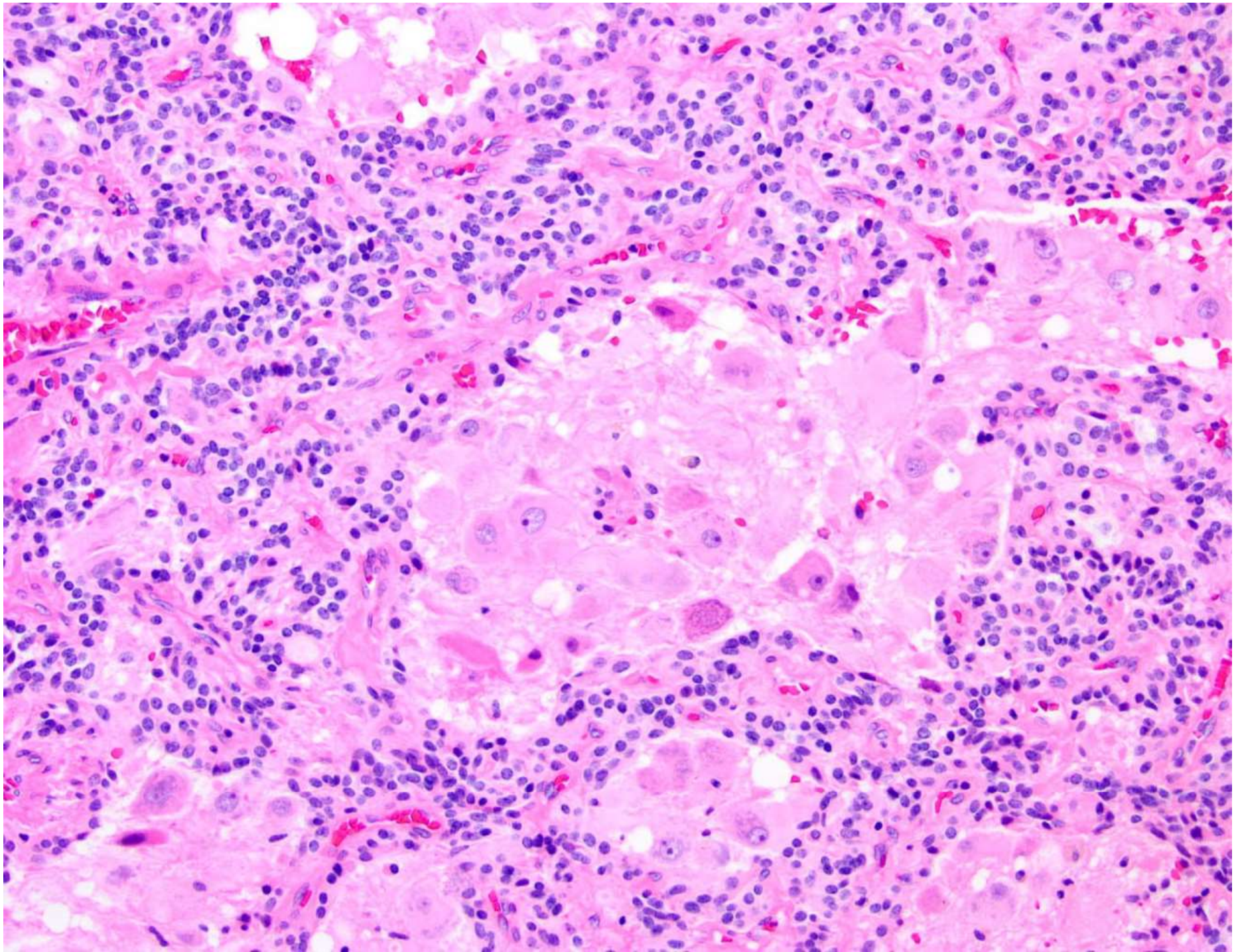
20-0907

Biswa Ramani/Liz Treynor/Arie Perry; UCSF

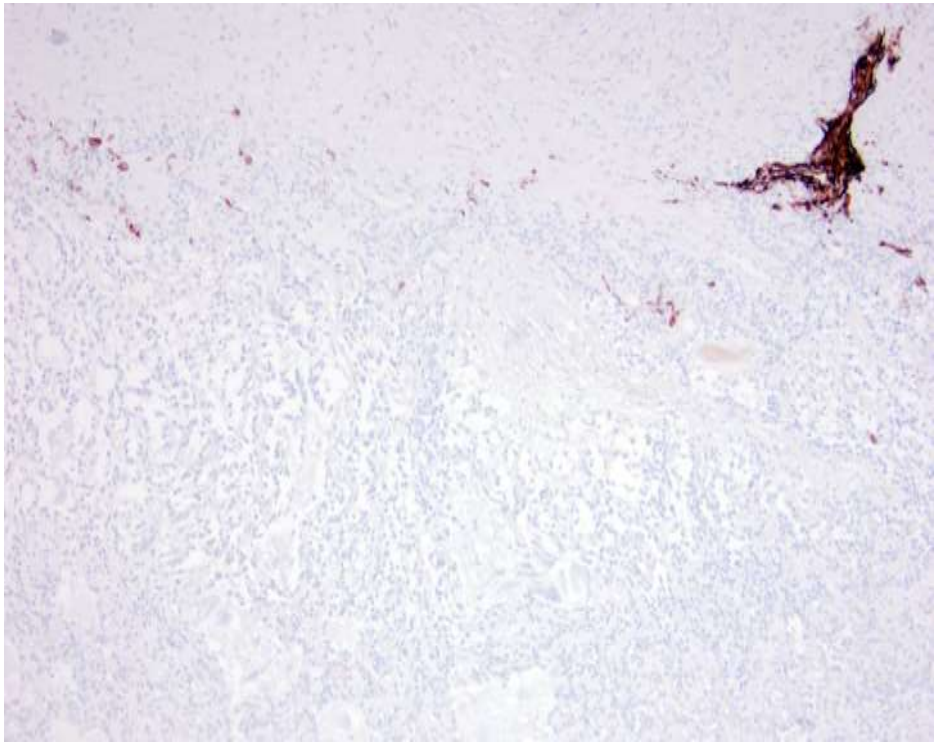
63-year-old M with L4-5 intradural spinal cord mass.



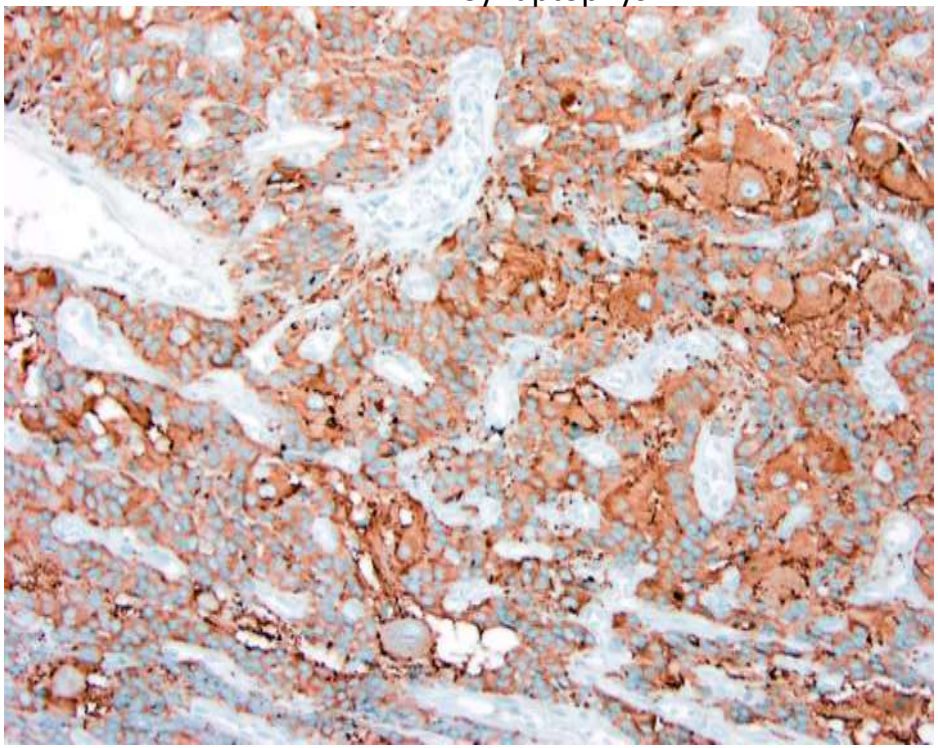




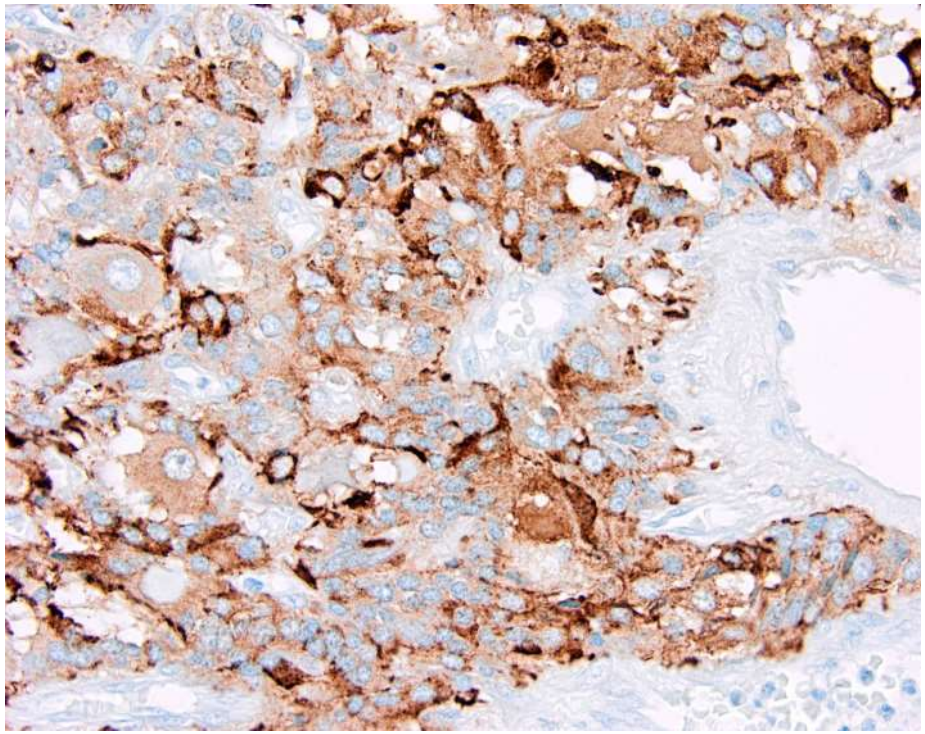
GFAP



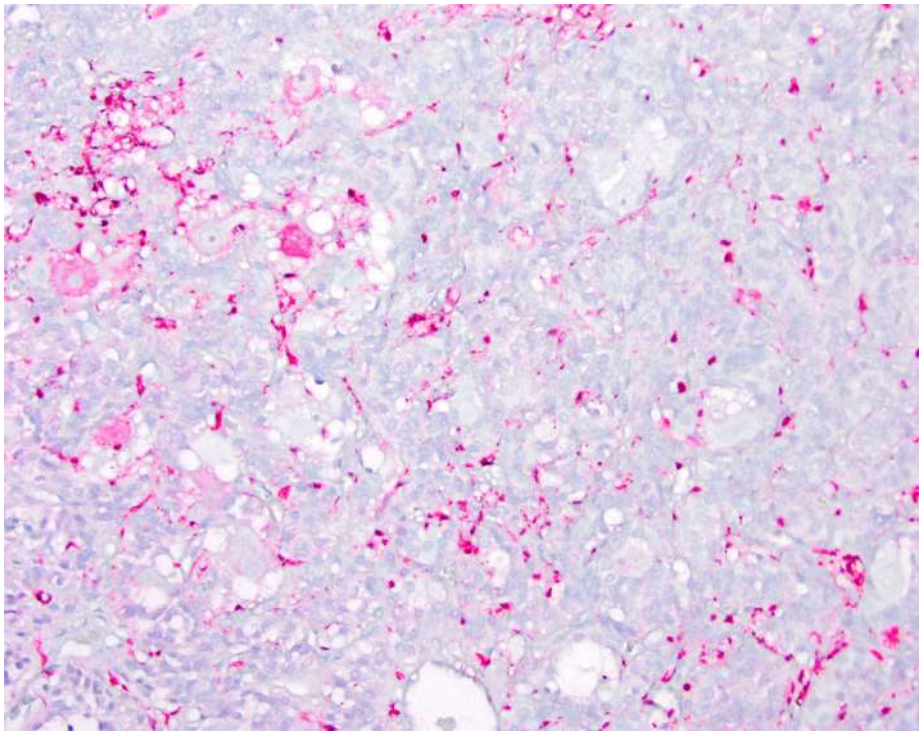
Synaptophysin



Chromogranin



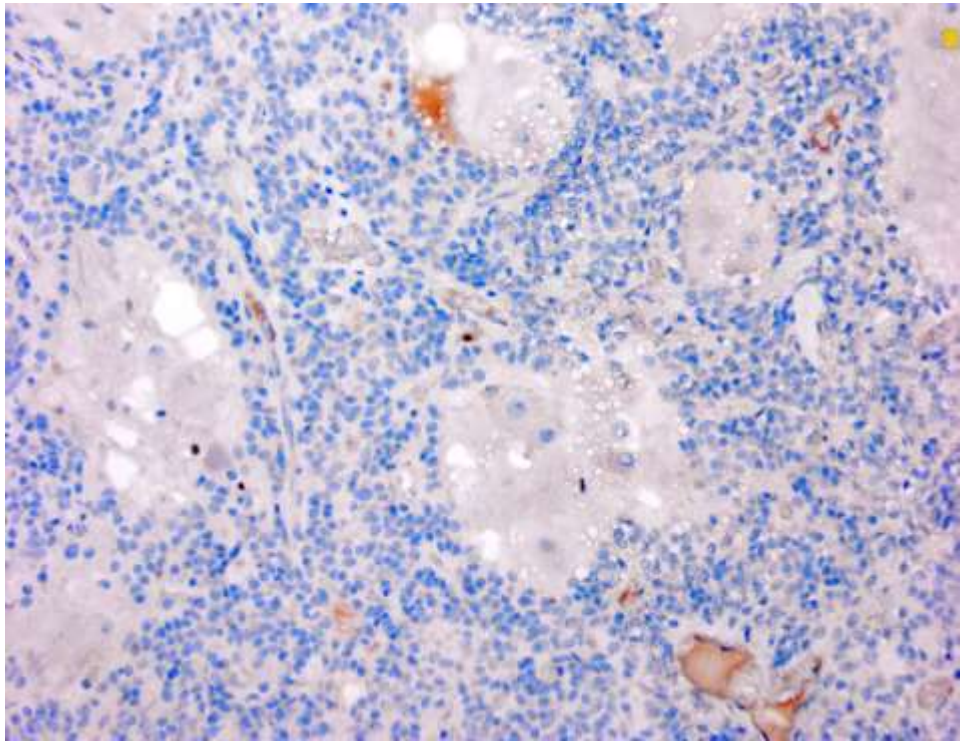
S100



Paraganglioma/pheochromocytoma

- Neuroendocrine tumor of autonomic nervous system
- Most common locations are head and neck (parasympathetic) and abdomen (sympathetic)
- Risk for metastasis
- **Up to 40%** associated with hereditary paraganglioma syndrome
  - SDH subunit mutations most common
- Characteristic Zellballen histologic pattern, almost never gangliocytic
- IHC:
  - Synaptophysin and chromogranin positive chief cells
  - S100 positive sustentacular cells
  - **GATA3 positive**
  - **Keratin negative**
  - **SDHB loss** in hereditary cases

GATA3



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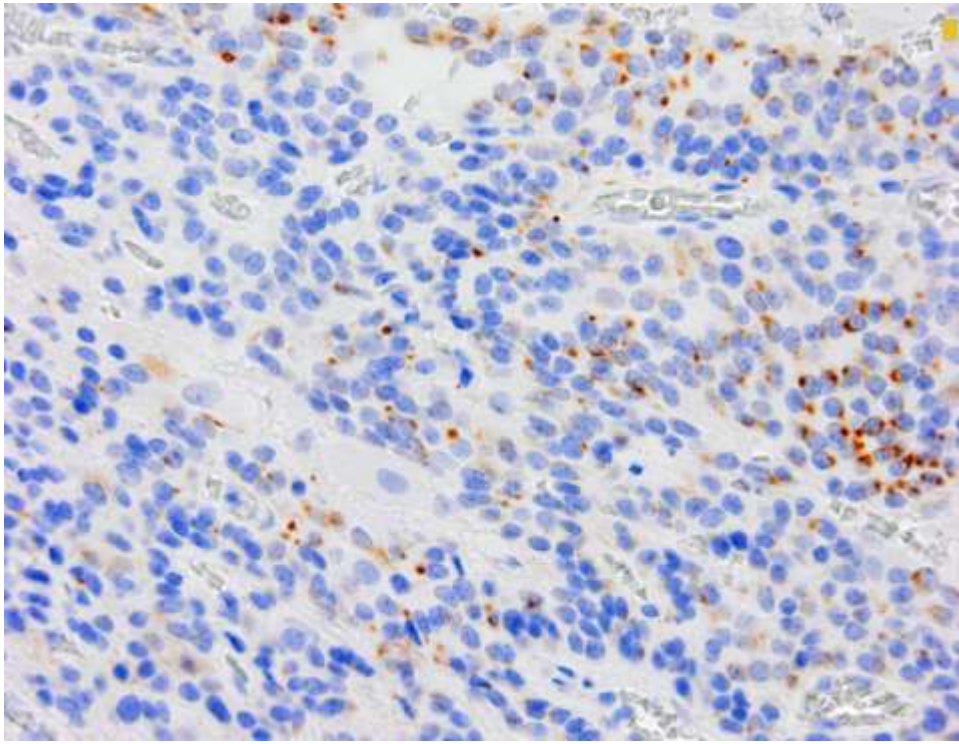
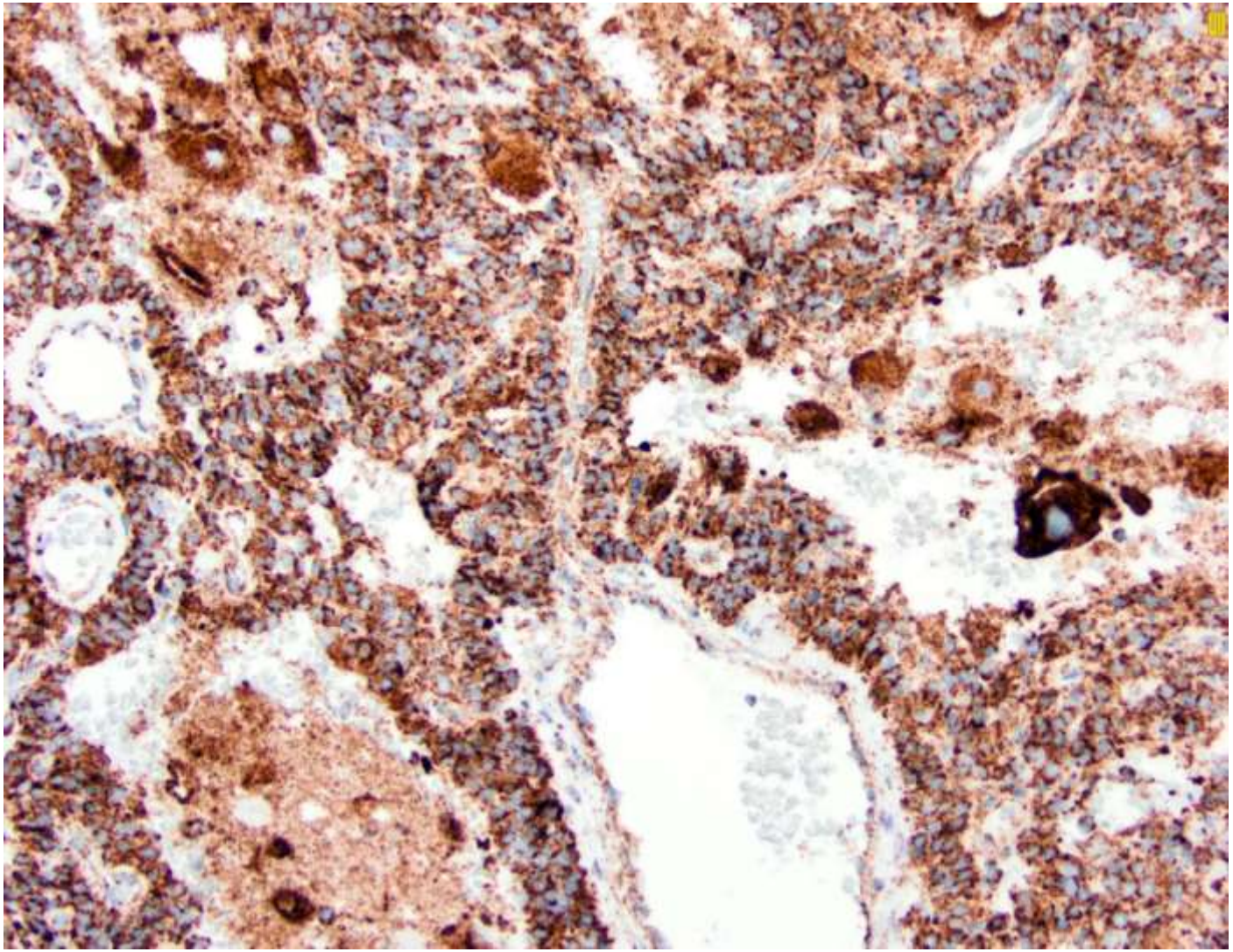
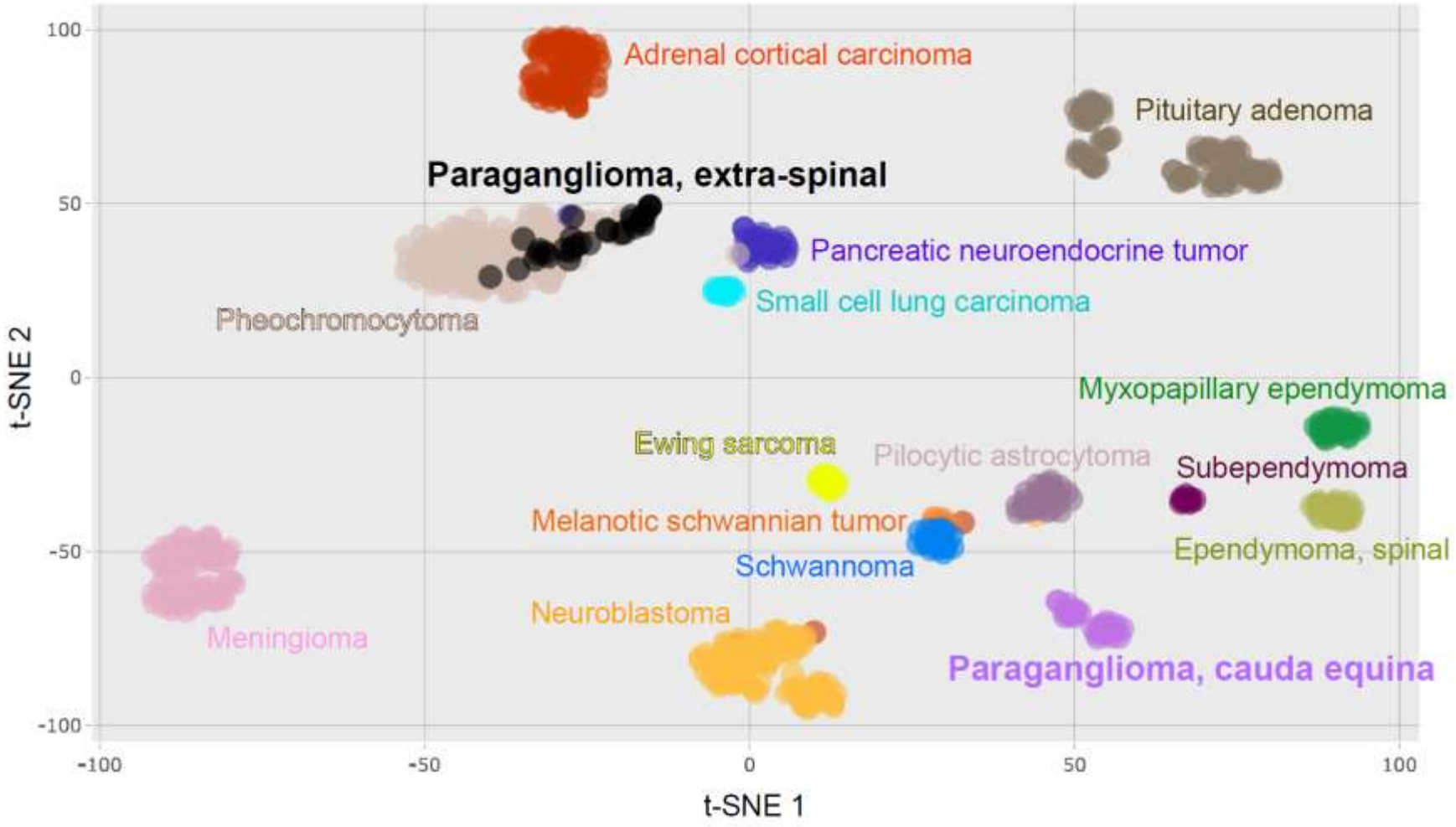


SDHB



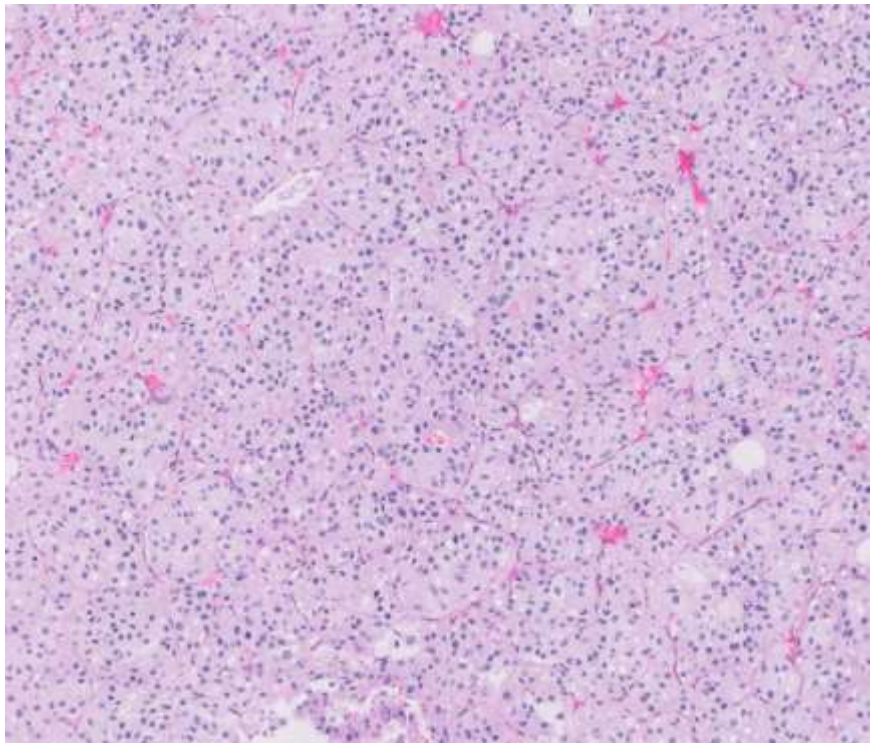
Cauda equina paraganglioma

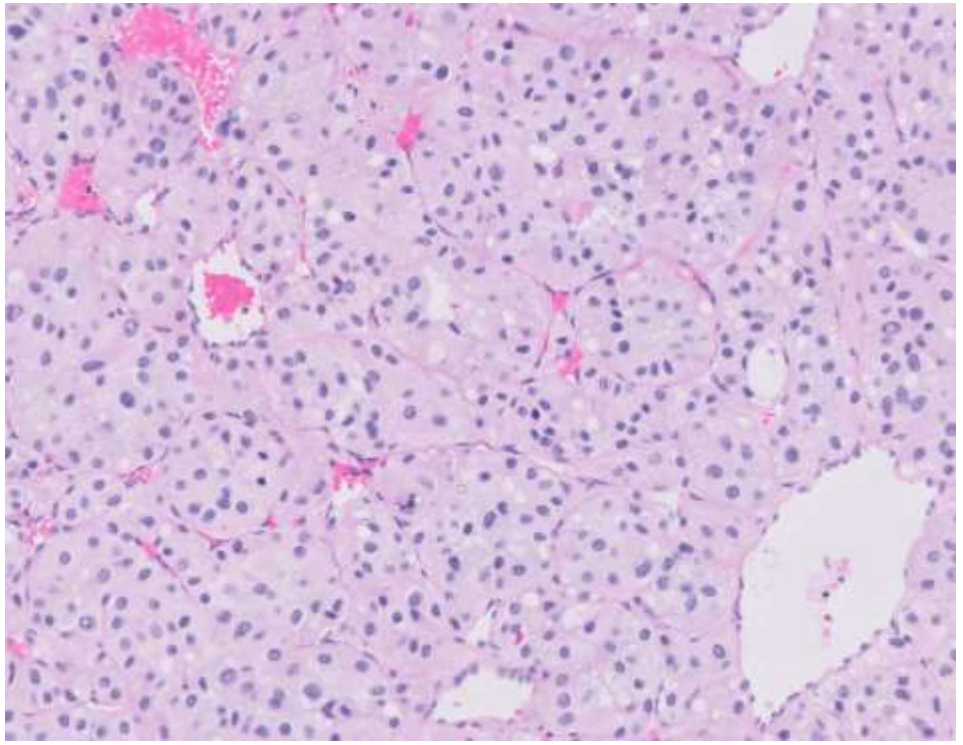
- Histologic and IHC overlap with extraspinal paragangliomas and pheochromocytoma
  - Zellballen pattern, Synaptophysin/chromogranin positive chief cells, S100 positive sustentacular cells
- Major differences from extraspinal paraganglioma/pheo:
  - Often gangliocytic (occasionally ganglioneuromatous with Schwann cells)
  - Cytokeratin-positive
  - GATA3 negative
  - Clinically indolent, hormonally inactive, not known to metastasize
  - No known association with SDH mutations or other hereditary syndromes
- Main differential is with ependymoma



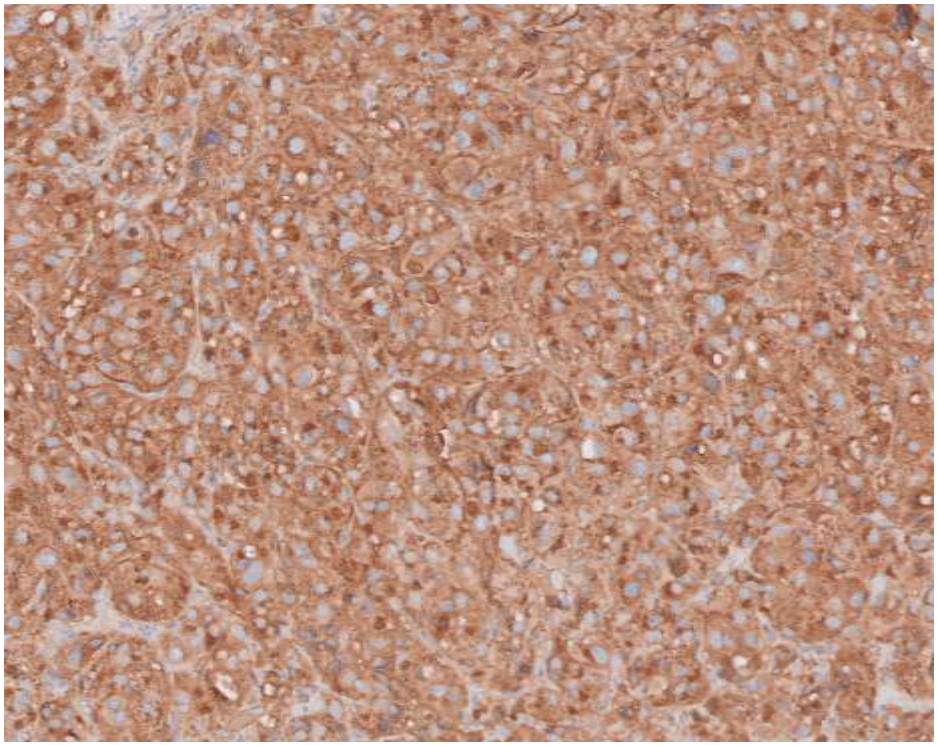
Ramani, Gupta, Solomon, Perry, et al. in review

63-year-old with posterior C7 spine lytic mass

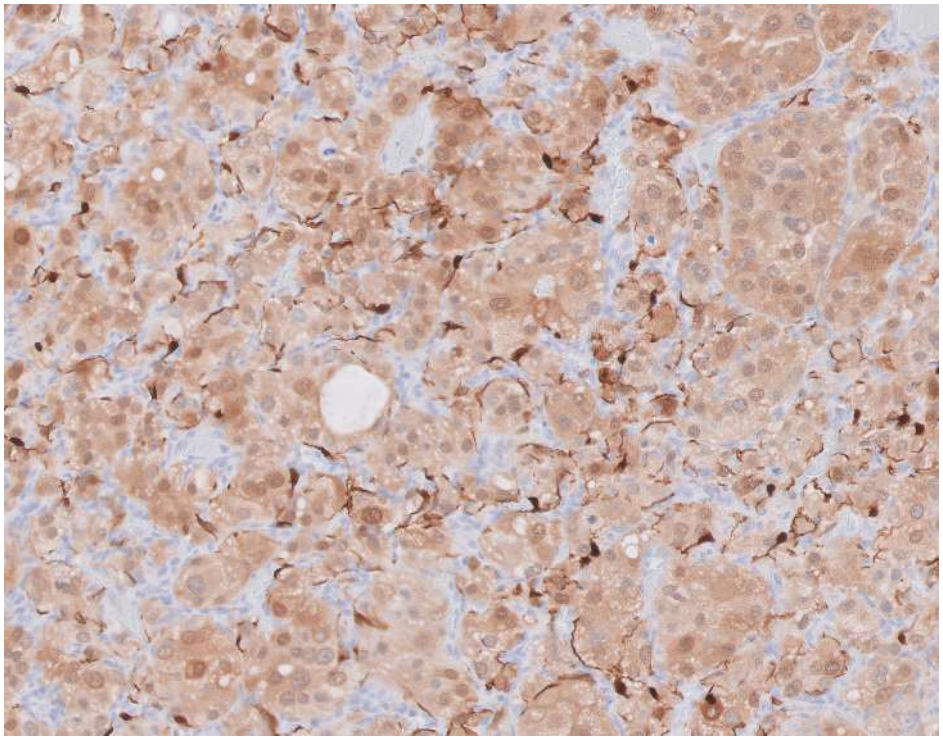




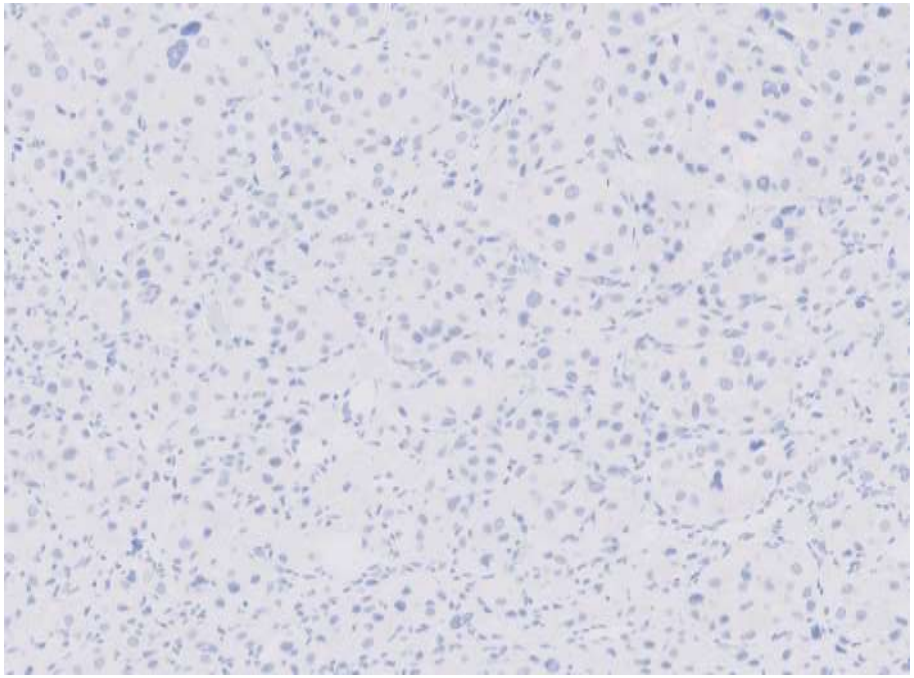
Chromogranin



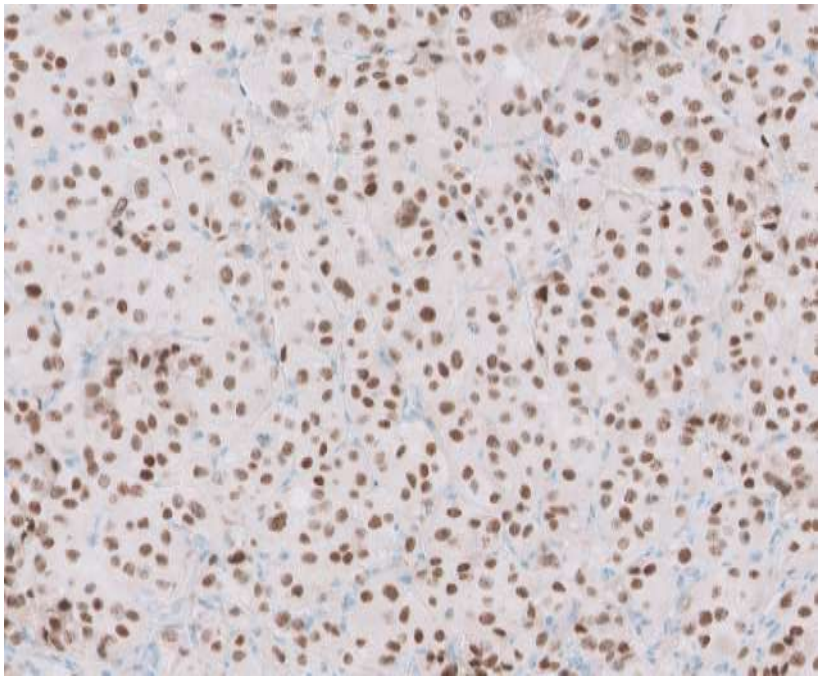
S100



Keratin cocktail



GATA3



SDHB