NOV 2021 DIAGNOSIS LIST

21-1101: epithelioid sarcoma (soft tissue; soft tissue path)
21-1102: urachal adenocarcinoma (bladder; GUpath)
21-1103: ORF viral infection (skin; dermpath+ID path)
21-1104: consistent with malignant struma ovarii (soft tissue; GYN path)
21-1105: adenosquamous prostatic carcinoma (prostate; GU path)
21-1106: metanephric adenoma (kidney; GU path)
21-1107: microcystic elongated fragmented (MELF) pattern endometrial carcinoma (uterus; GYN path)

Disclosures
November 1, 2021

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

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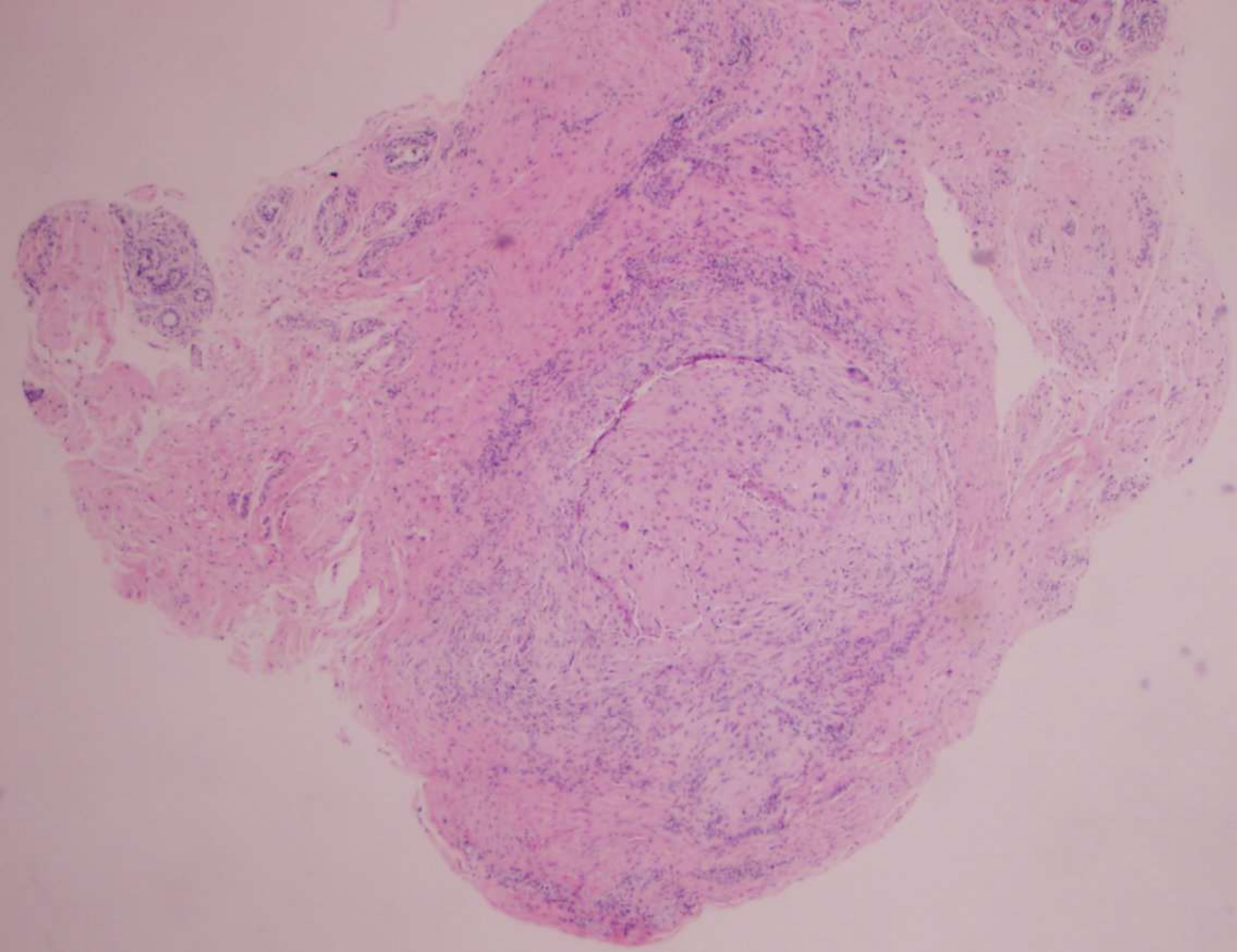
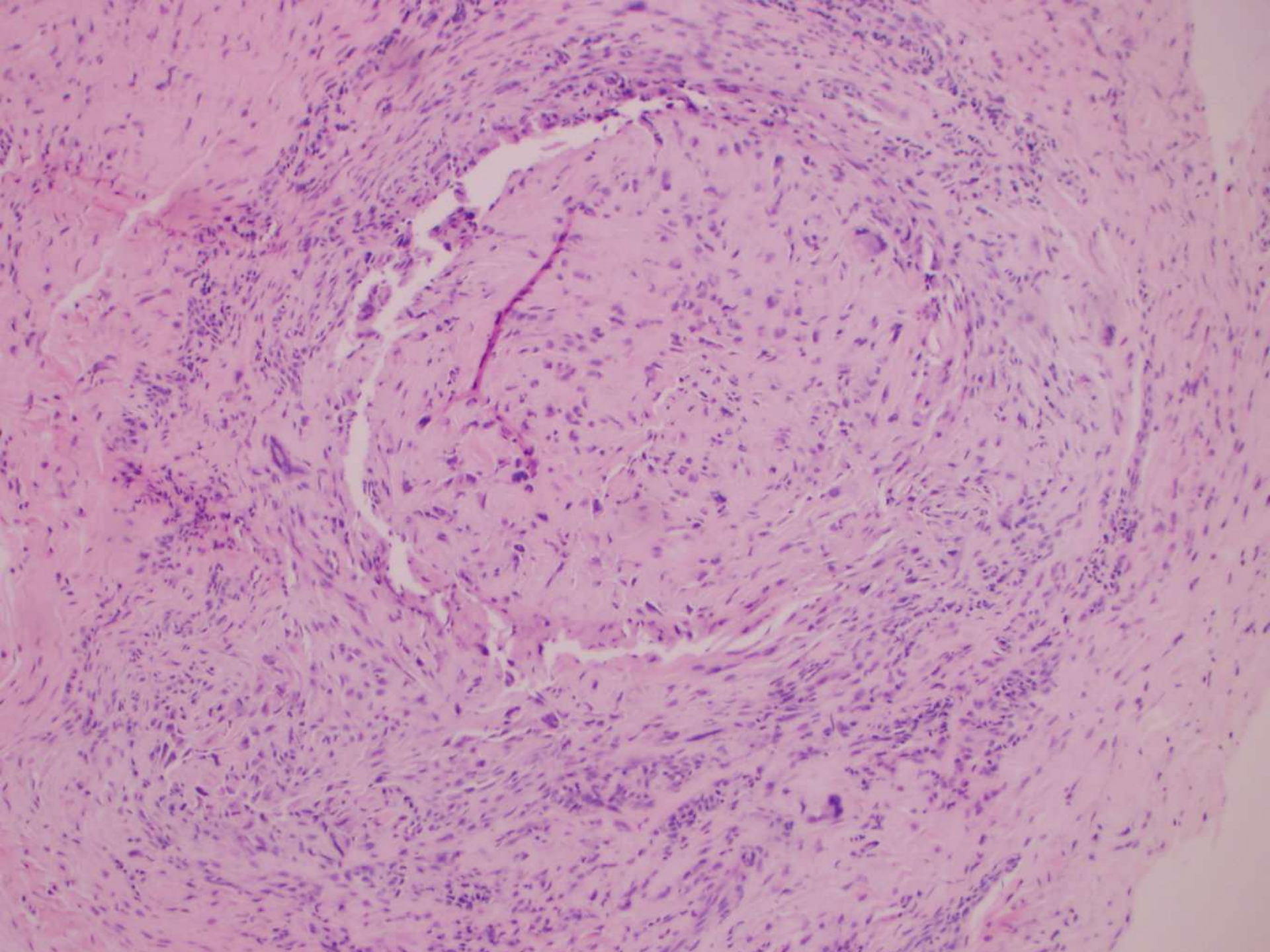
Ankur Sangoi, MD

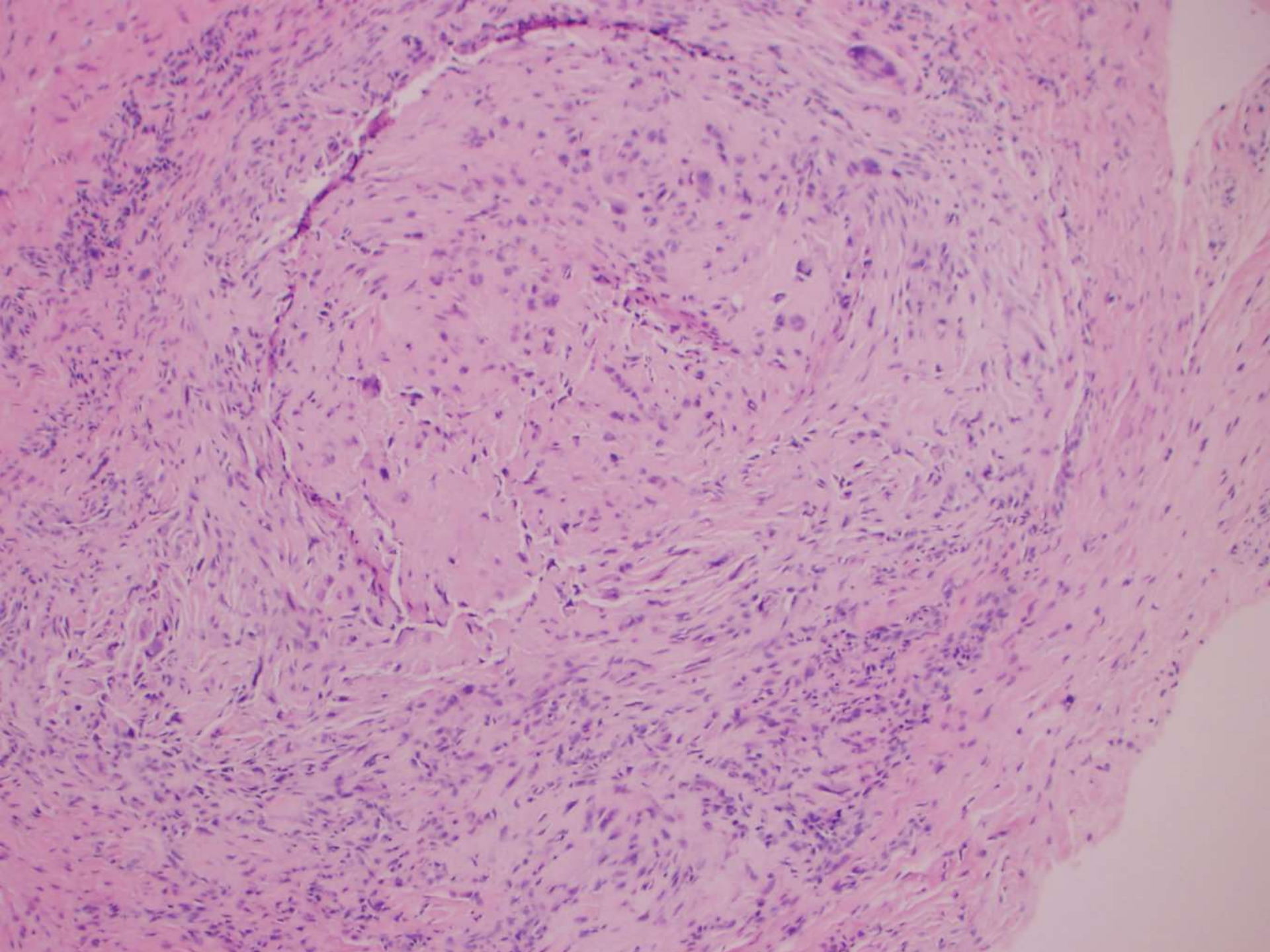
21-1101

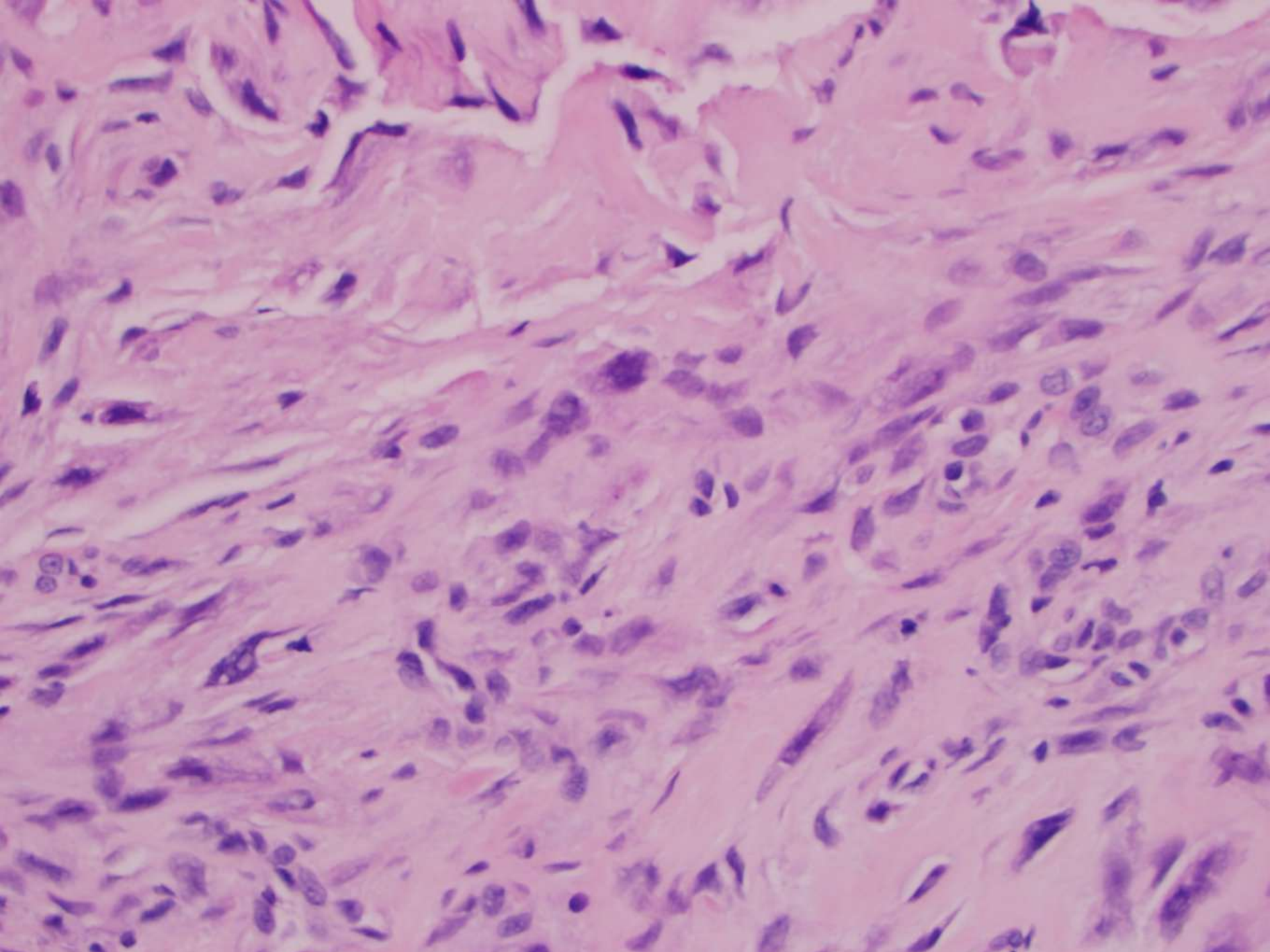
Greg Rumore; Kaiser Diablo

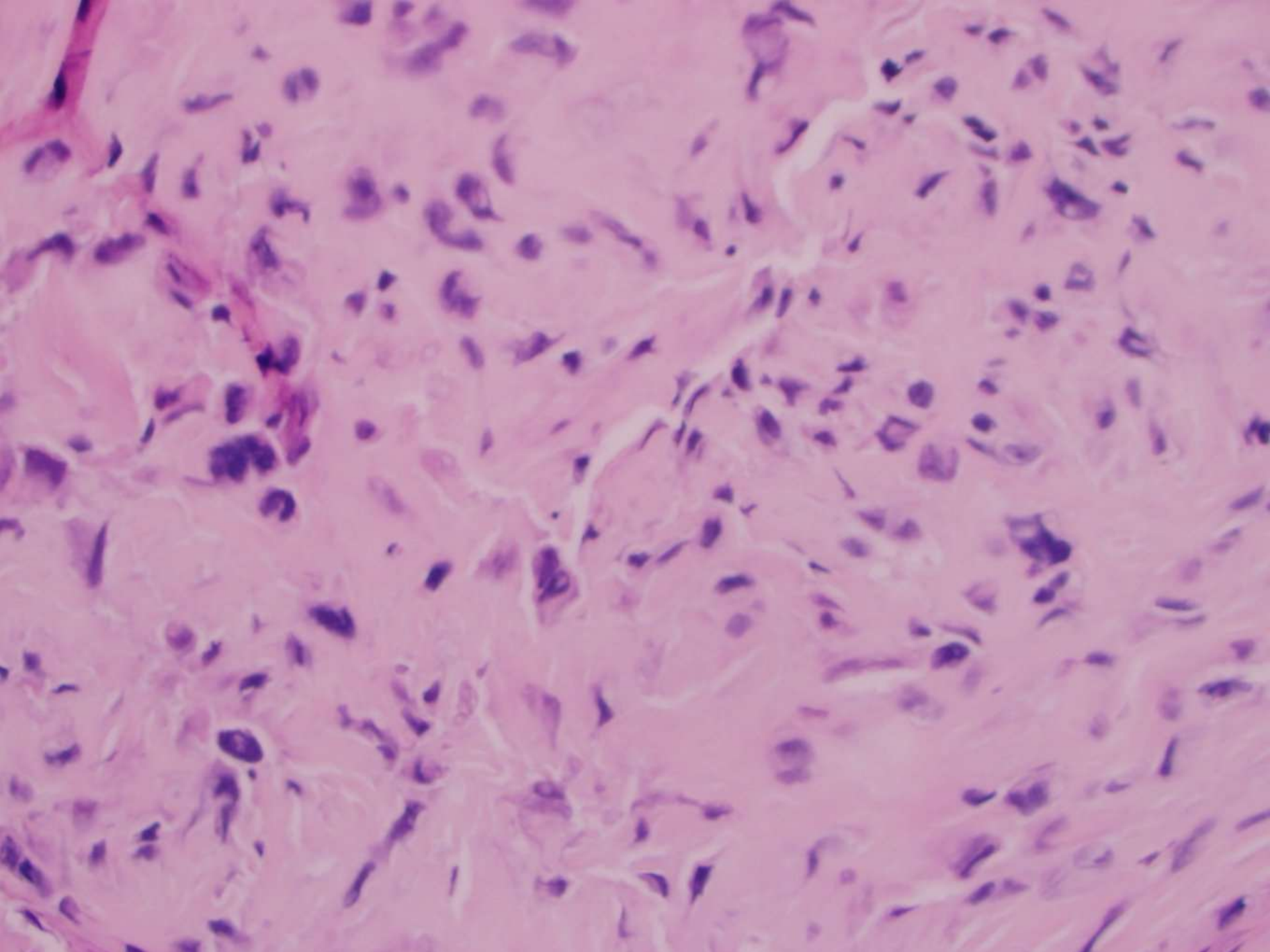
56-year-old F with finger mass for several months.

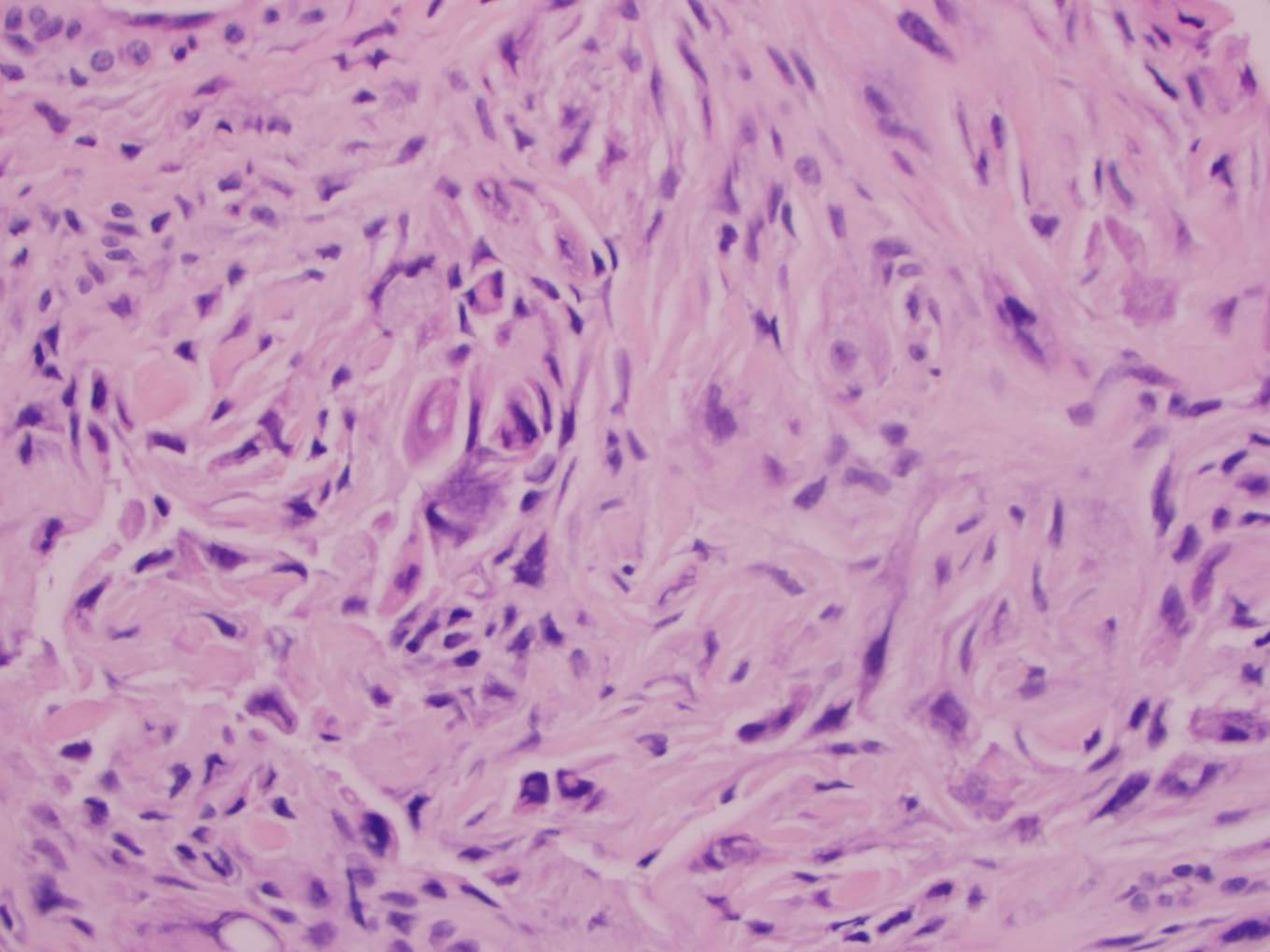


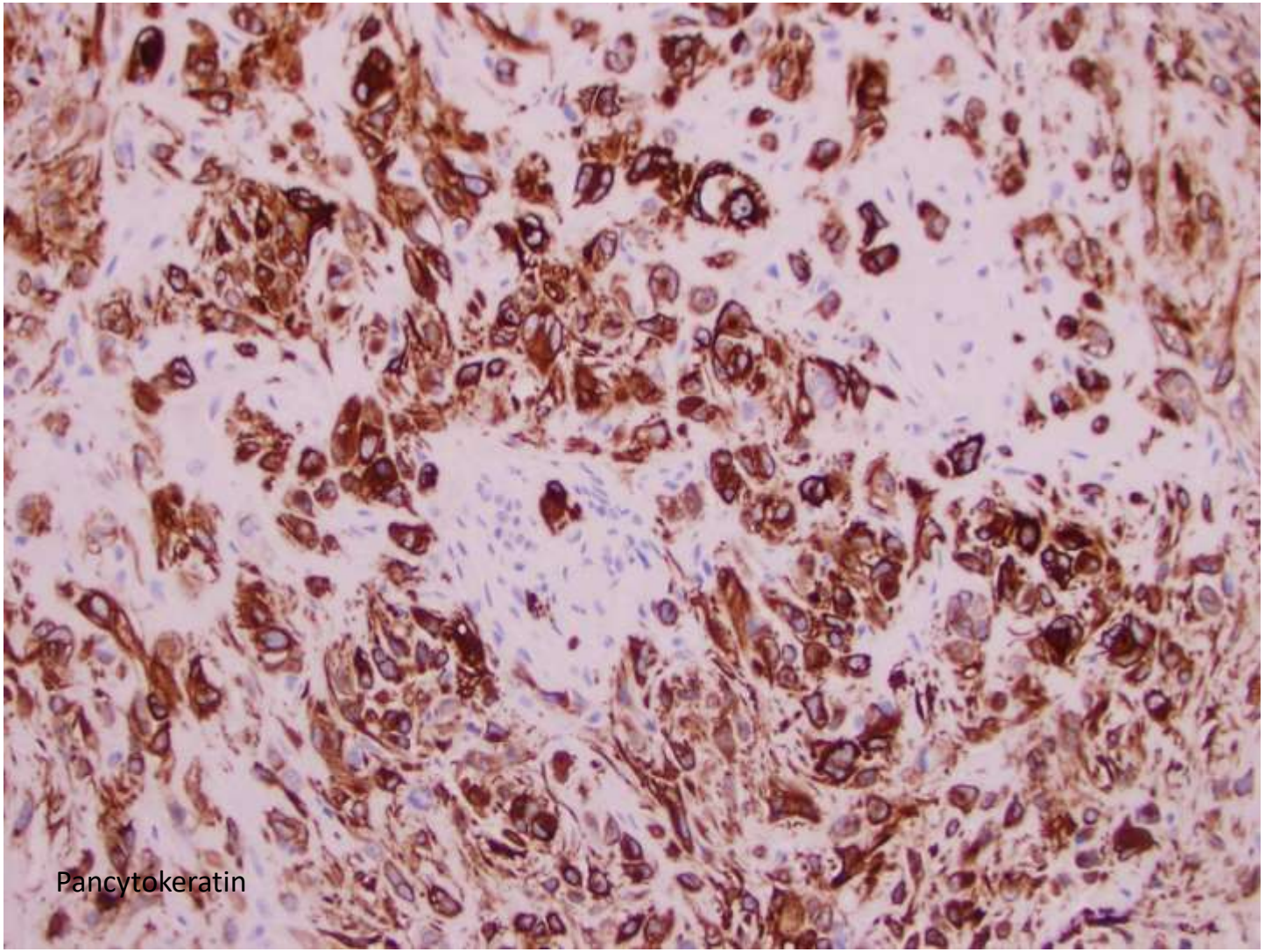


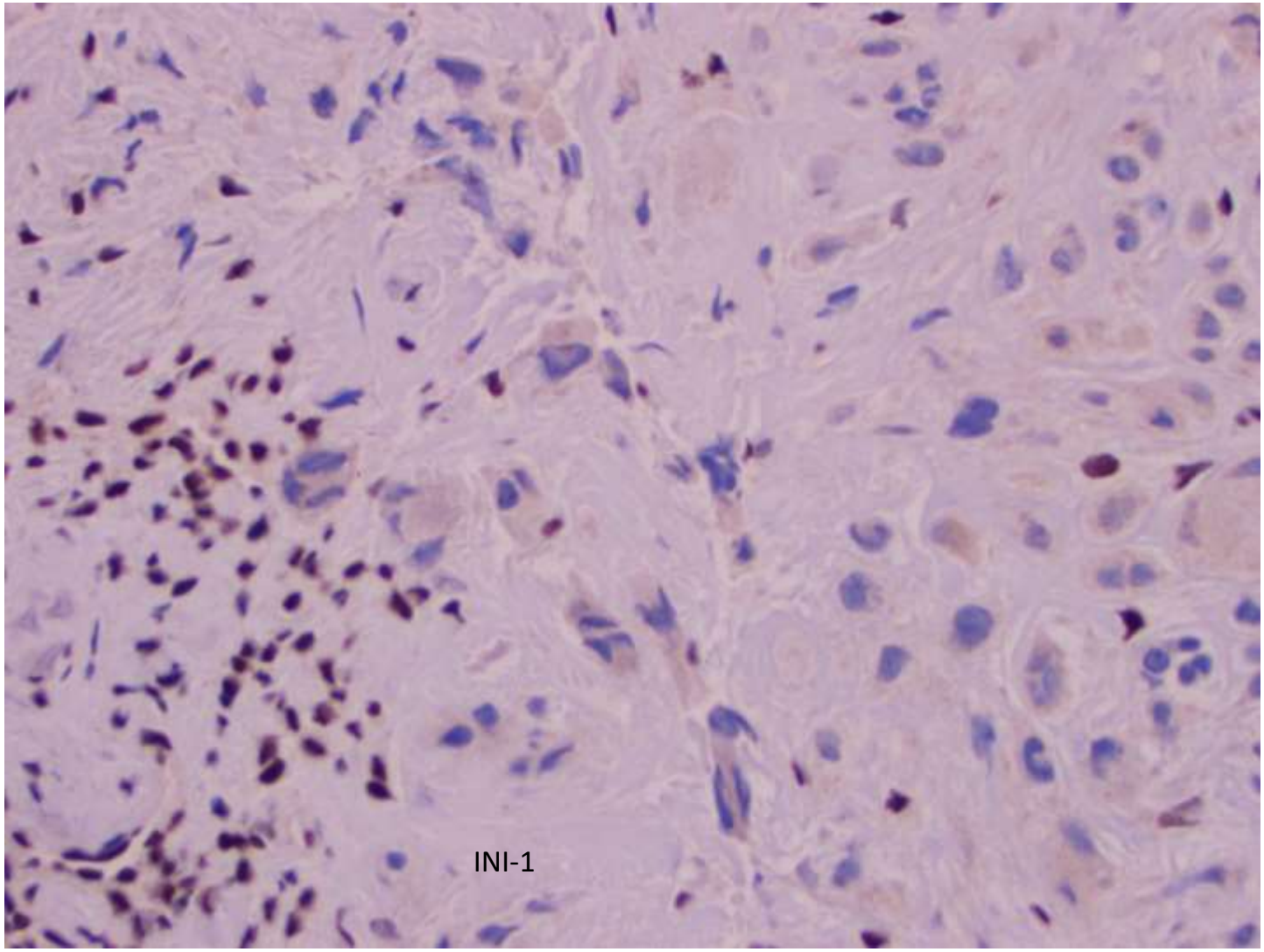









Pancytokeratin


INI-1

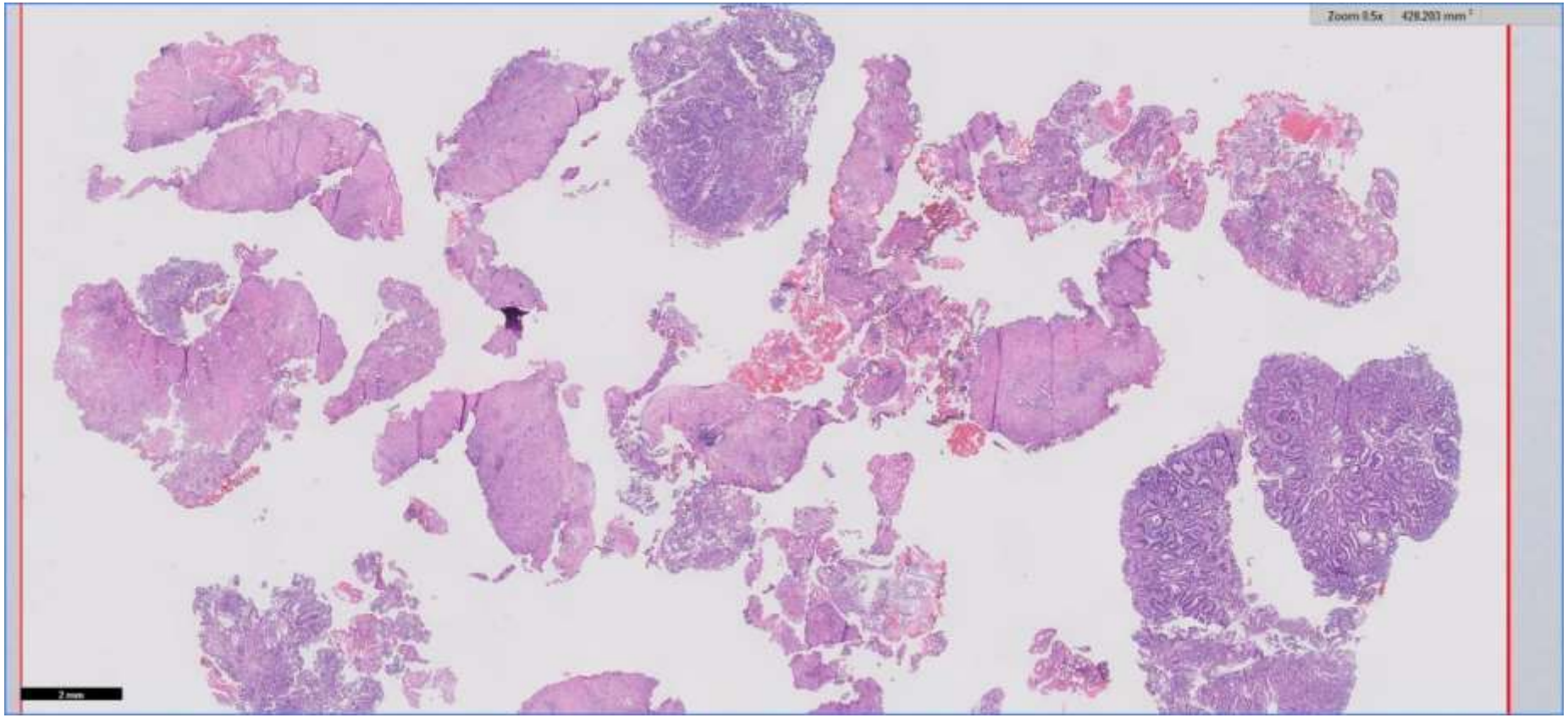
Epithelioid Sarcoma-”distal type”

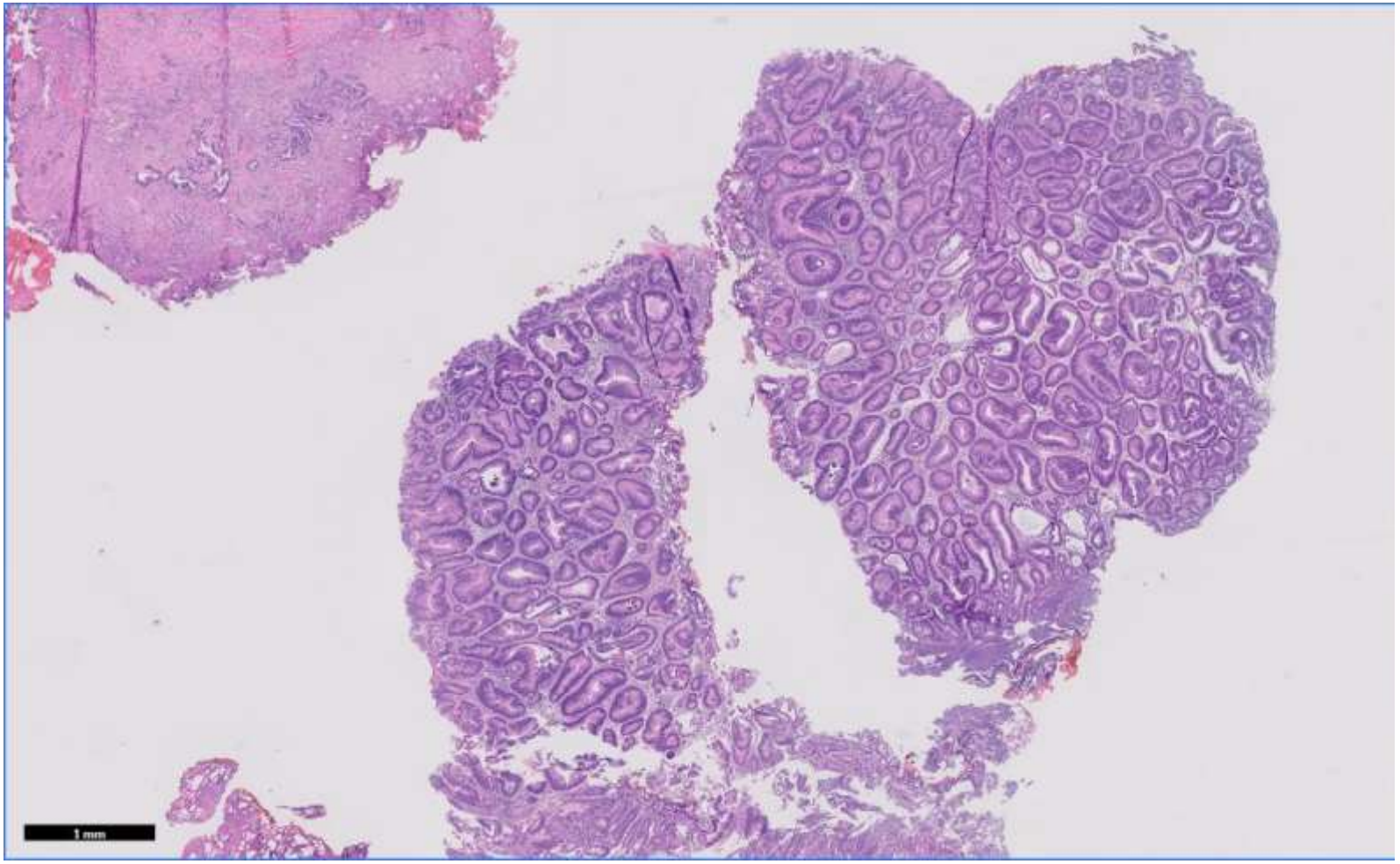
- young males
- Subcutaneous or deep soft tissue of distal extremities
- Relatively bland histiocytoid epithelioid cells
- Frequent central necrosis-”granuloma-like” appearance
- Positive for pancytokeratin and EMA, +/- CD-34
- Negative for INI-1 (SMARCB1)
- Tendency for local recurrence
- May metastasize to LN’s or distant sites

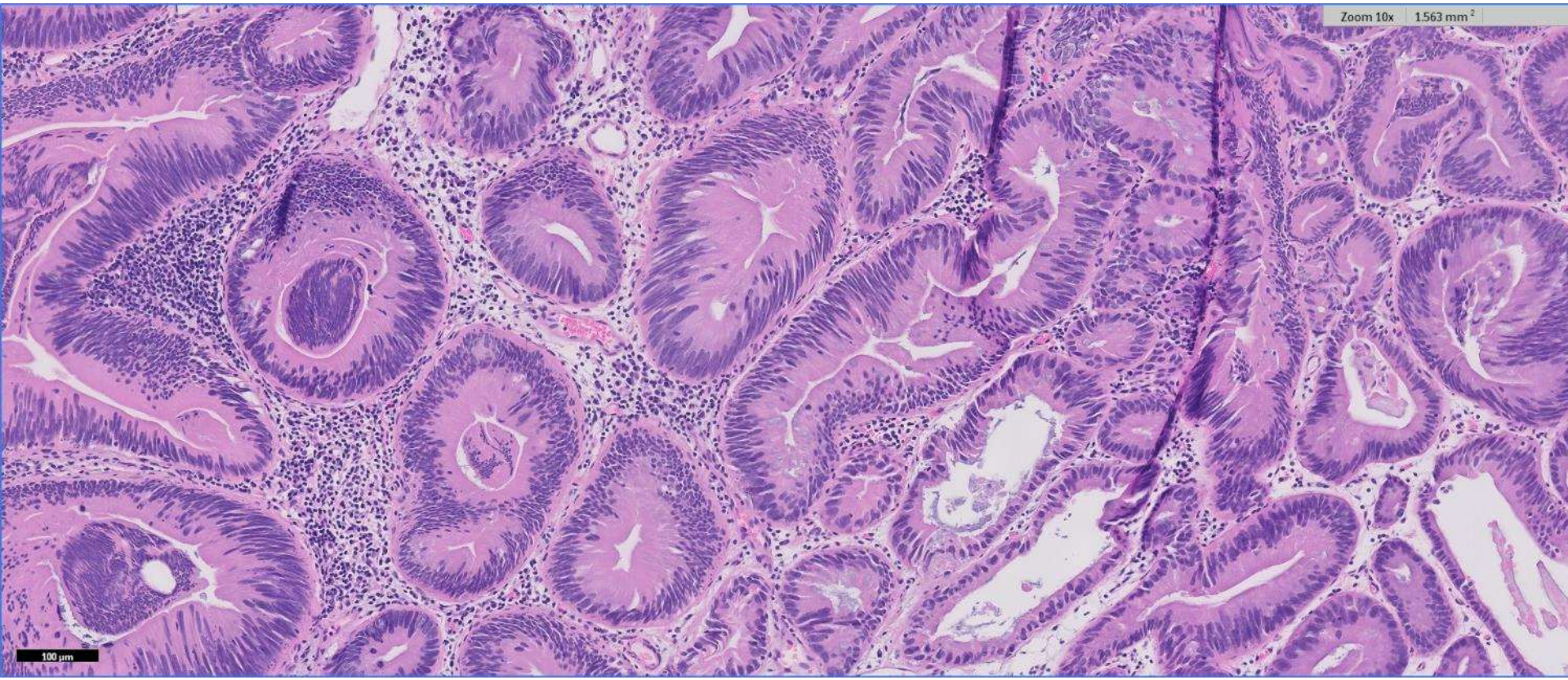
21-1002

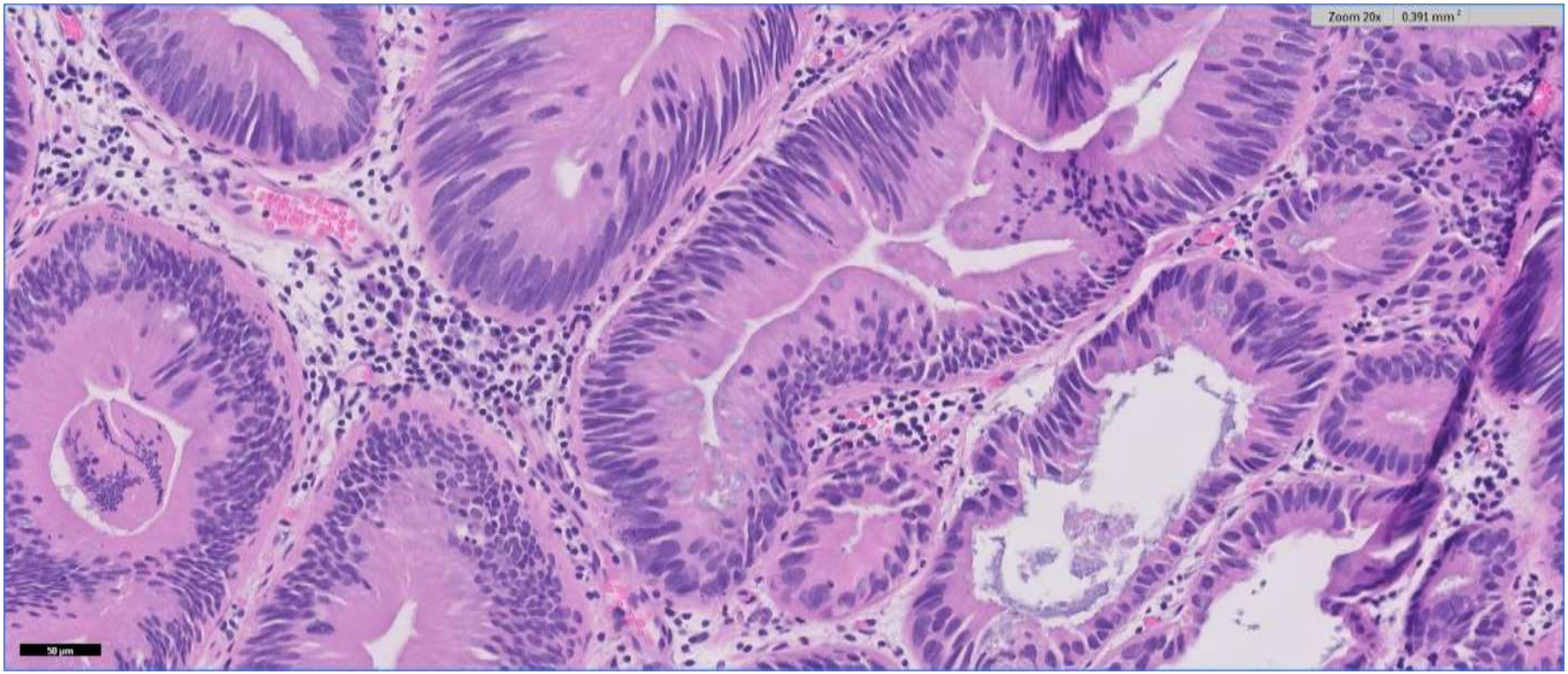
Osama Khan/Ali Lowe; Stanford

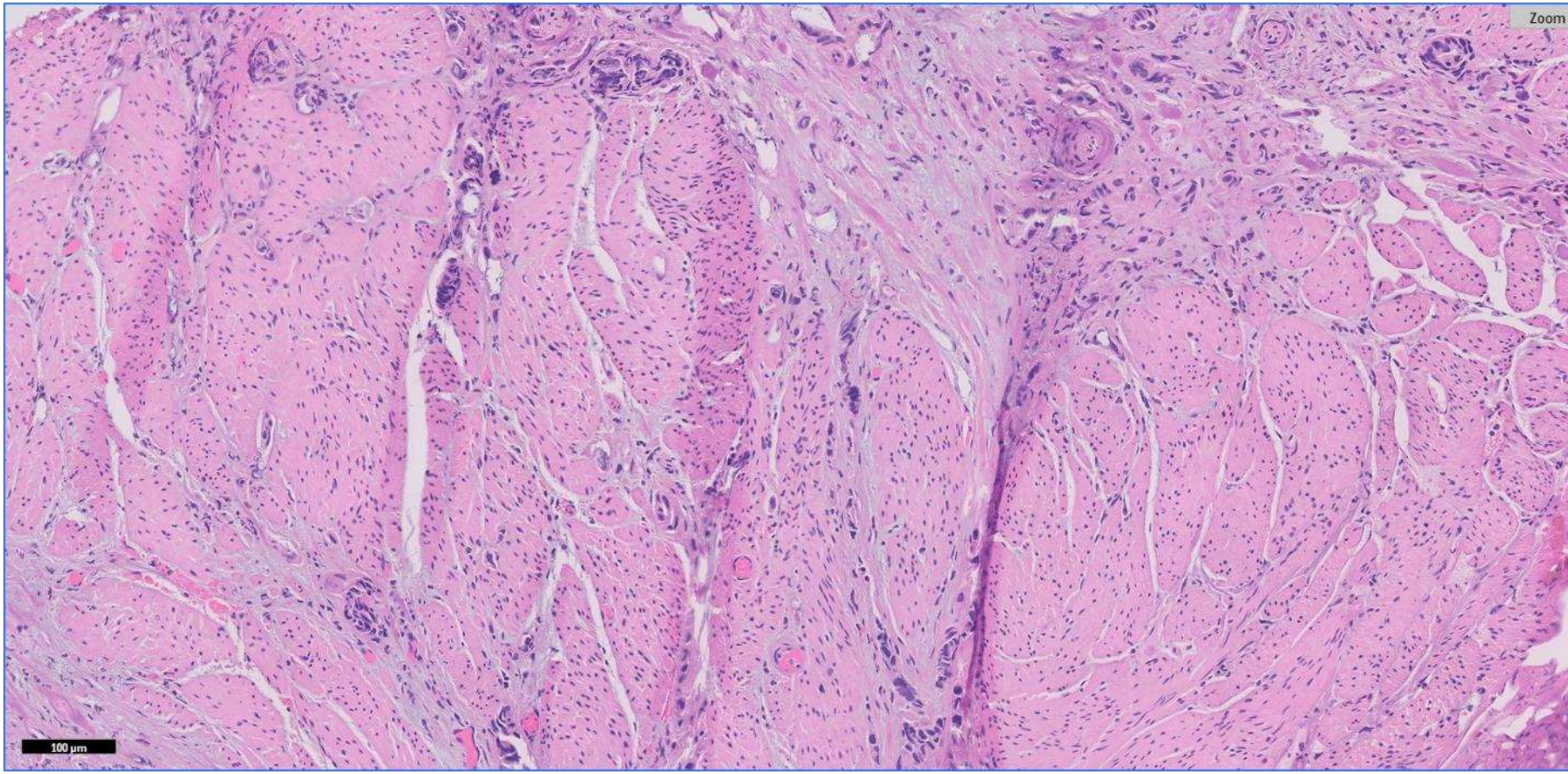
67-year-old F with bladder dome tumor.


Zoom 0.5x
428.203 mm²
2 mm


1 mm


Zoom 10x
1.563 mm²
100 µm


Zoom 20x
0.391 mm²
50 µm


Zoom
100 µm

Differential Diagnosis

- Local extension of a colonic adenocarcinoma or other adenocarcinoma
- Metastatic Adenocarcinoma
- Urachal Adenocarcinoma
- Adenocarcinoma of bladder
- Invasive urothelial carcinoma with glandular differentiation
- Villous Adenoma

Immunohistochemistry results

Positive

- CK7, CK2-0 and CDX2

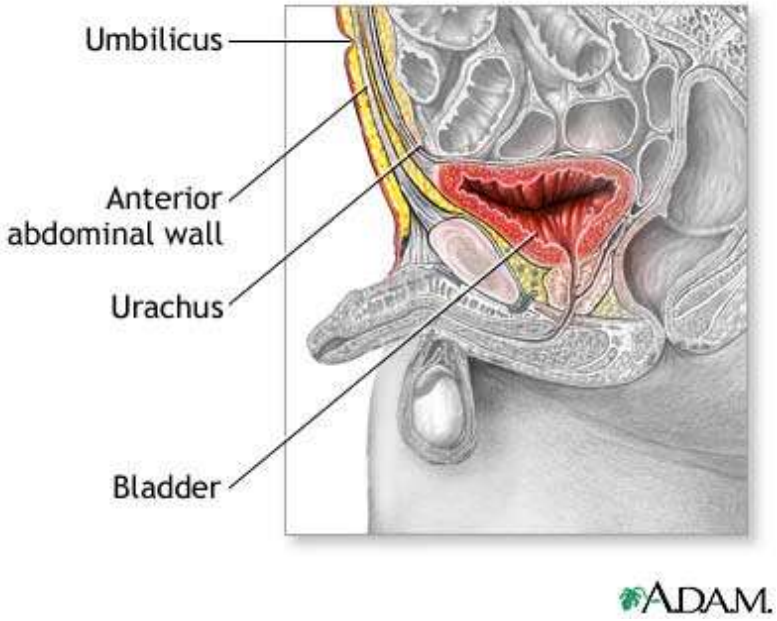
Negative

- GATA-3, p40 and PAX-8

DIAGNOSIS

- Adenocarcinoma, enteric type consistent with a urachal primary
- Muscularis propria is present and involved by tumor

Urachus



Urachal Adenocarcinomas

- Rare malignant epithelial neoplasms arising from urachal remnants
- Less common than non-urachal adenocarcinomas
- Often present in bladder dome, anterior wall and may extend to umbilicus
- Strict criteria for diagnosis

Diagnostic Criteria

- Location of the tumor in the dome/anterior wall
- Epicenter of carcinoma in the bladder wall
- Absence of widespread cystitis cystica/glandularis beyond the dome/anterior wall
- Absence of a known primary elsewhere

Glandular neoplasms
Adenomas
Villous adenoma
Mucinous cystadenoma
Mucinous cystic tumor of low malignant potential
Adenocarcinomas
Noncystic adenocarcinomas
Enteric (intestinal)
Mucinous (colloid)
Signet ring cell
Not otherwise specified
Mixed
Cystic adenocarcinomas
Mucinous cystadenocarcinoma
With microinvasion
Frankly invasive
Nonglandular neoplasms
Urothelial neoplasms
Squamous cell neoplasms
Neuroendocrine neoplasms
Mixed type neoplasms
Mixed carcinomas

*Modified from Amin et al.[5]

Immunohistochemistry/Pitfalls

- CDX2, CK20 are positive (cannot distinguish from colonic AC)
- 50% positive for CK7
- Nuclear Beta-Catenin negative

Sheldon Staging for Urachal Adenocarcinomas

Stage	Definition
Stage I	Urachal cancer confined to urachal mucosa
Stage II	Urachal cancer with invasion confined to urachus itself
Stage IIIA	Local urachal cancer extension to bladder
Stage IIIB	Local urachal cancer extension to abdominal wall
Stage IIIC	Local urachal cancer extension to peritoneum
Stage IIID	Local urachal cancer extension to viscera other than bladder
Stage IVA	Metastatic urachal cancer to lymph nodes
Stage IVB	Metastatic urachal cancer to distant sites

Treatment/Prognosis

- En bloc surgical removal of the umbilicus with the urachal ligament and partial cystectomy.
- Prognostic factors
  - Stage of the disease, surgical margin status, pathological tumor grade, presence of positive lymph nodes, and type of surgery

Genetic Profile

- KRAS Mutations at codon 12 (40%)
- Molecular characterization of Urachal Neoplasms (Stanford Project)

Key Learning Points

- DDx of Urachal Carcinomas
- Strict Diagnostic Criteria
- Immunohistochemistry Staining and Pitfalls
- Staging important for Prognosis

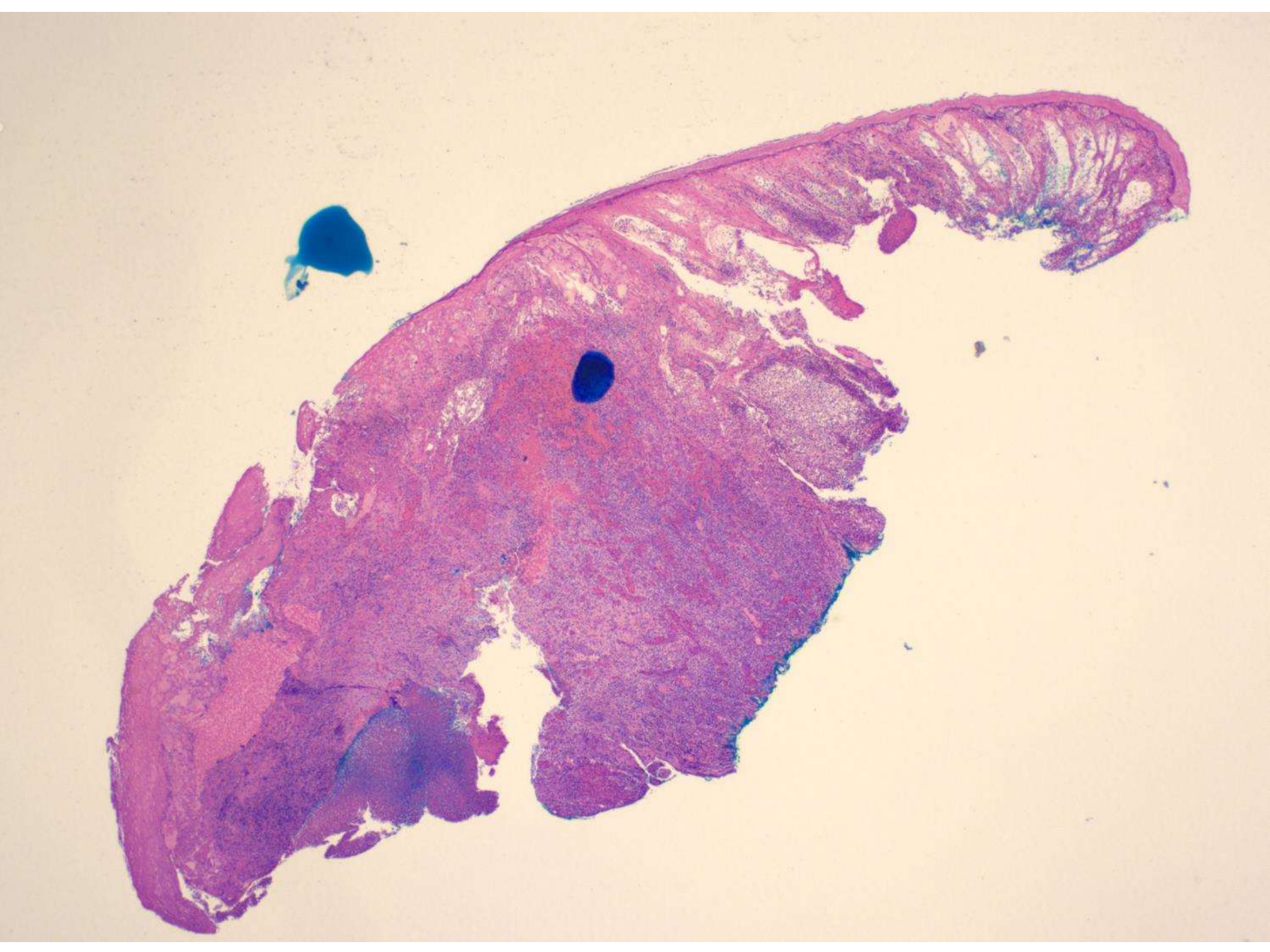
References

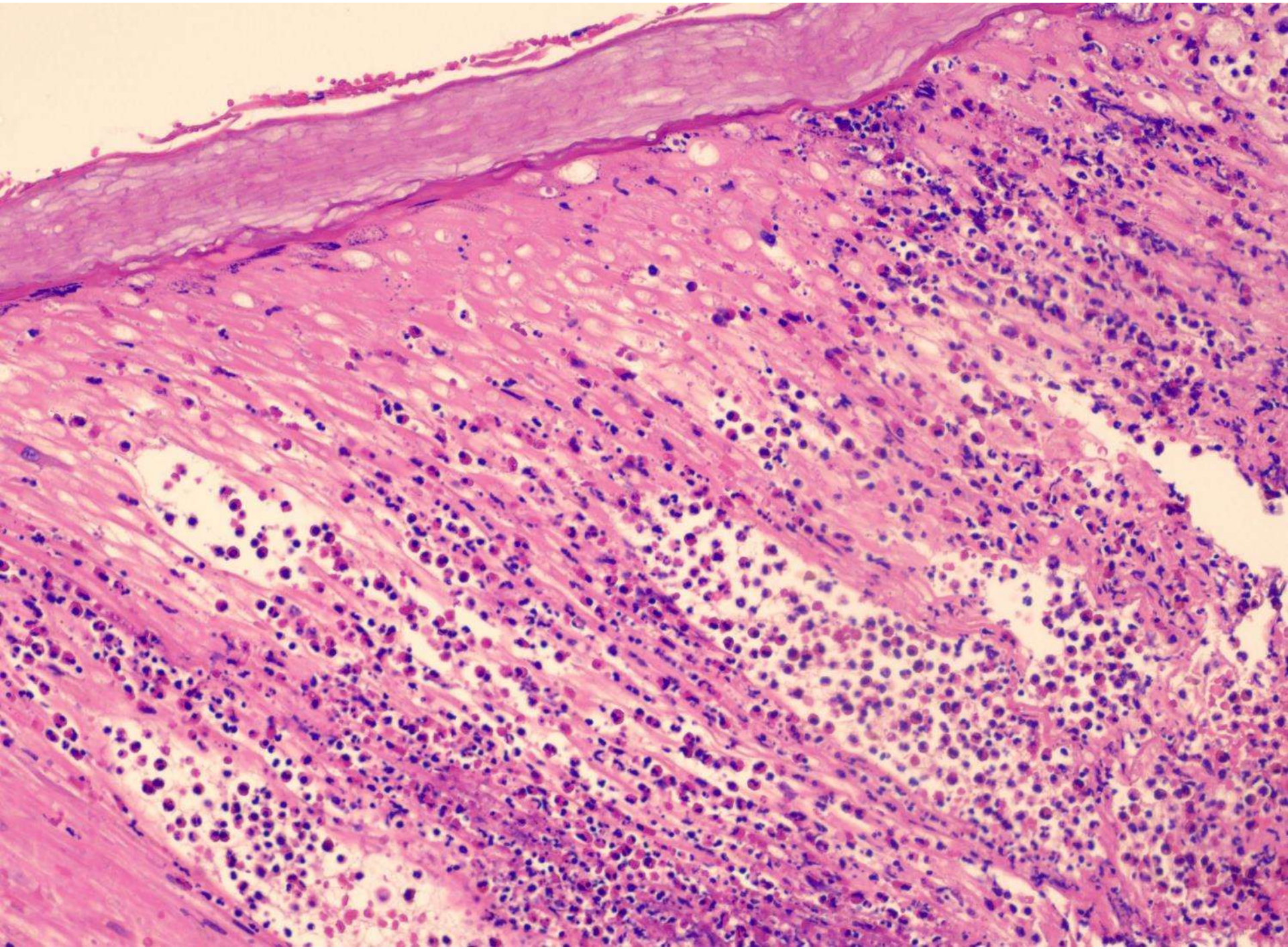
- Gopalan A, Sharp DS, Fine SW, et al. Urachal carcinoma: a clinicopathologic analysis of 24 cases with outcome correlation. *Am J Surg Pathol*. 2009;33(5):659-668. doi:10.1097/PAS.0b013e31819aa4ae
- Paner GP, Lopez-Beltran A, Sirohi D, Amin MB. Updates in the Pathologic Diagnosis and Classification of Epithelial Neoplasms of Urachal Origin. Adv Anat Pathol. 2016 Mar;23(2):71-83.

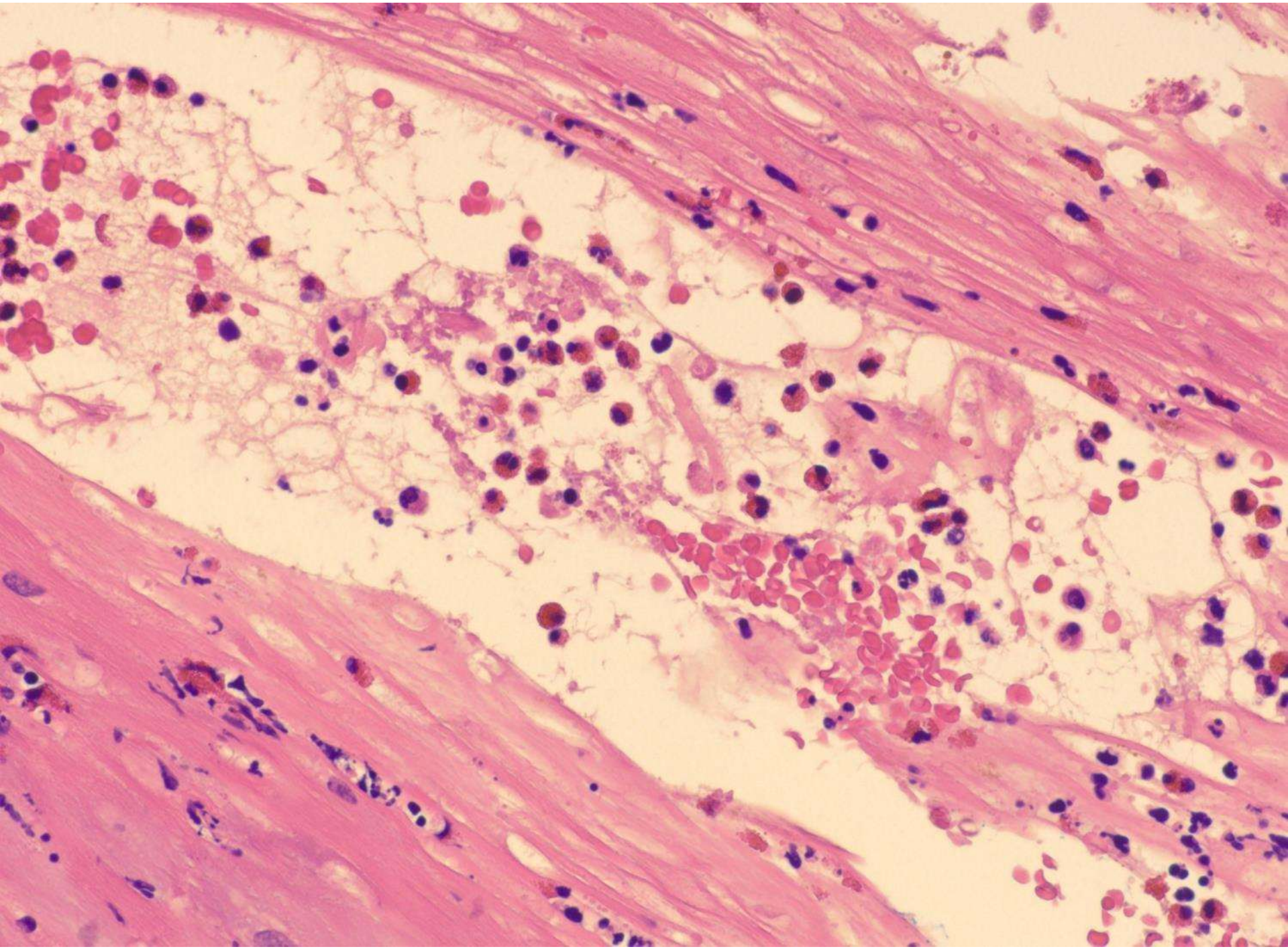
21-1003

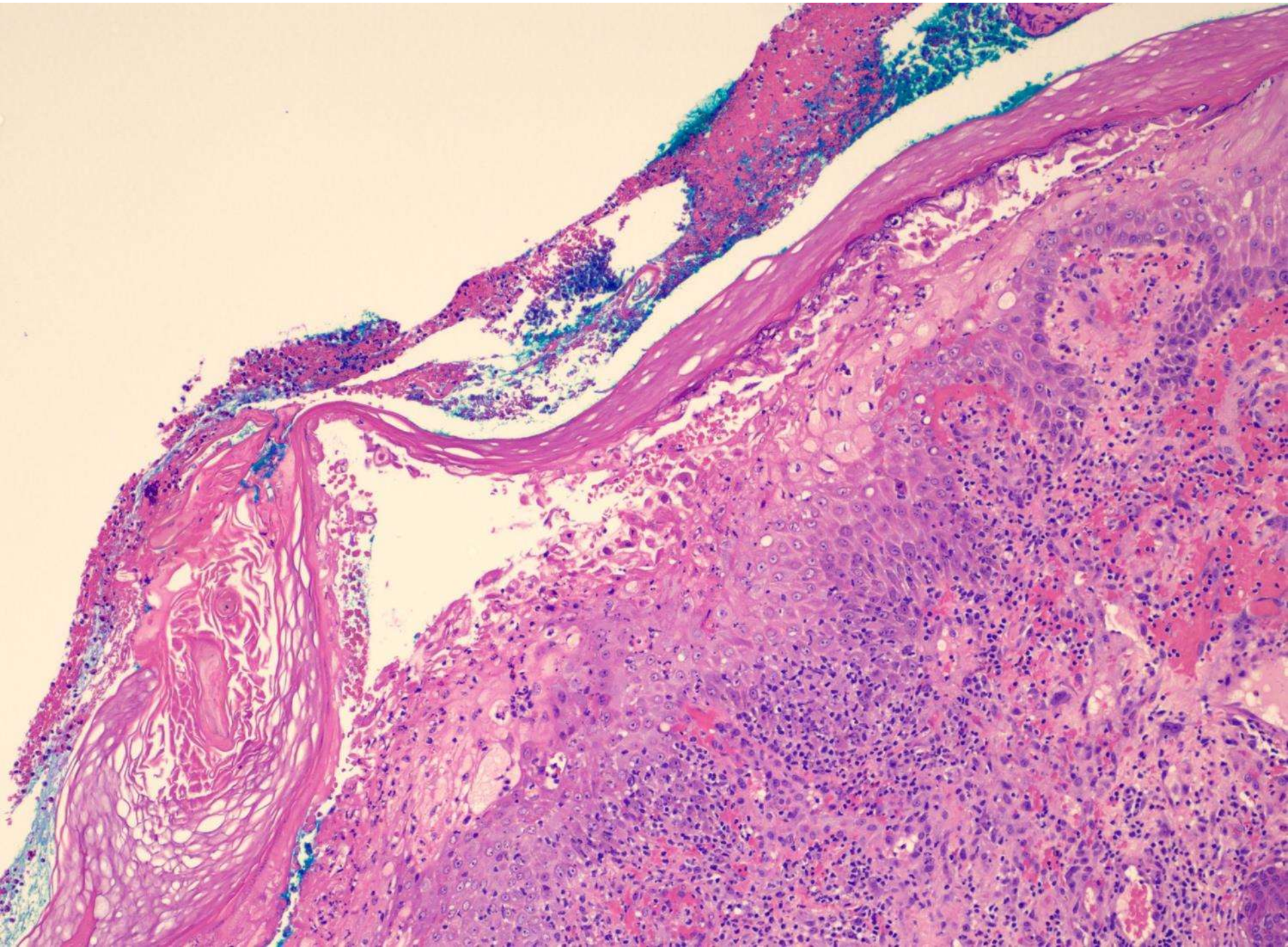
Beth Ruben; PAMF

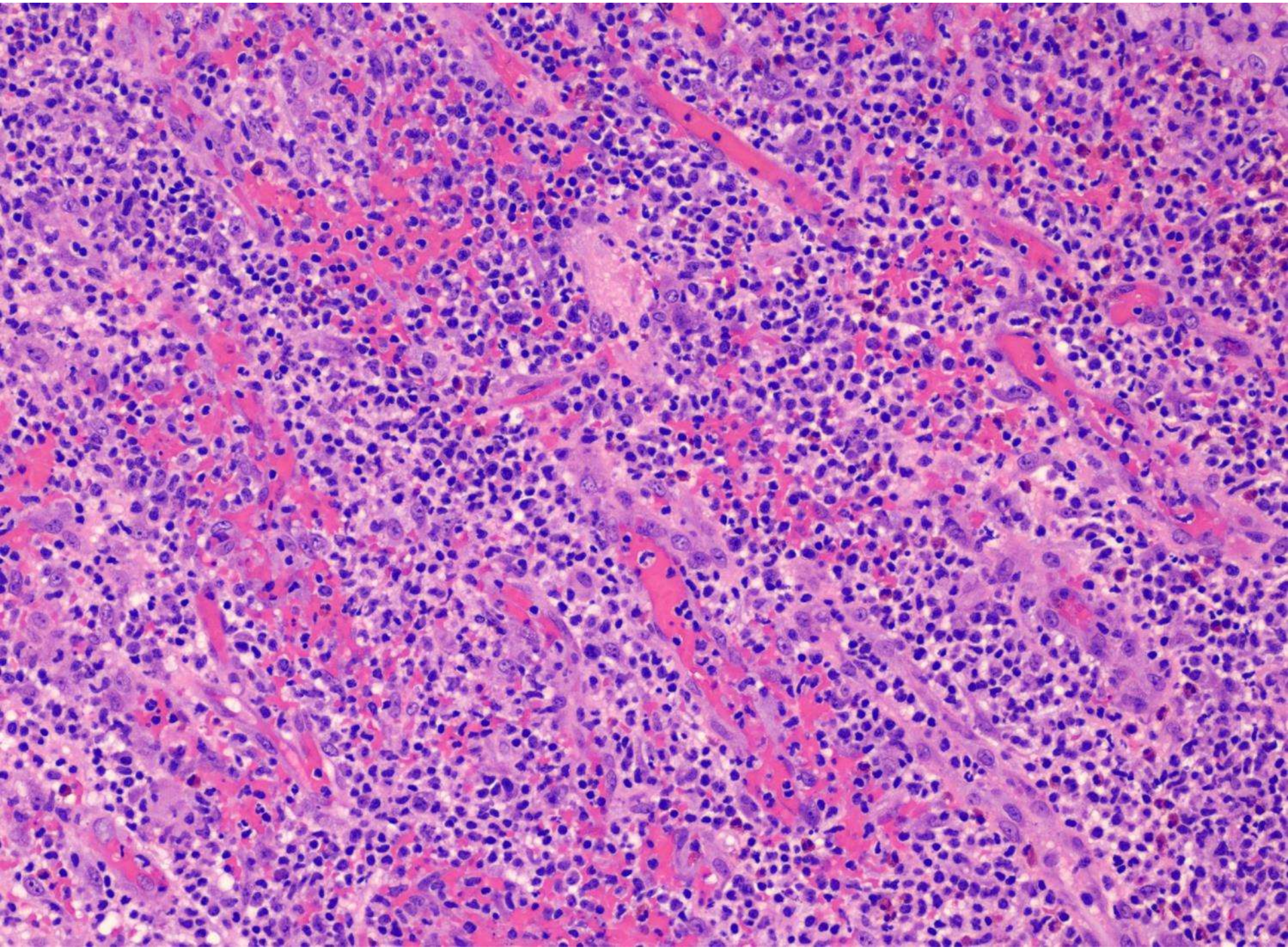
39-year-M with lacerated hand cleaning goat meat in central valley. Sutures placed and removed 3 weeks earlier, but would persists.

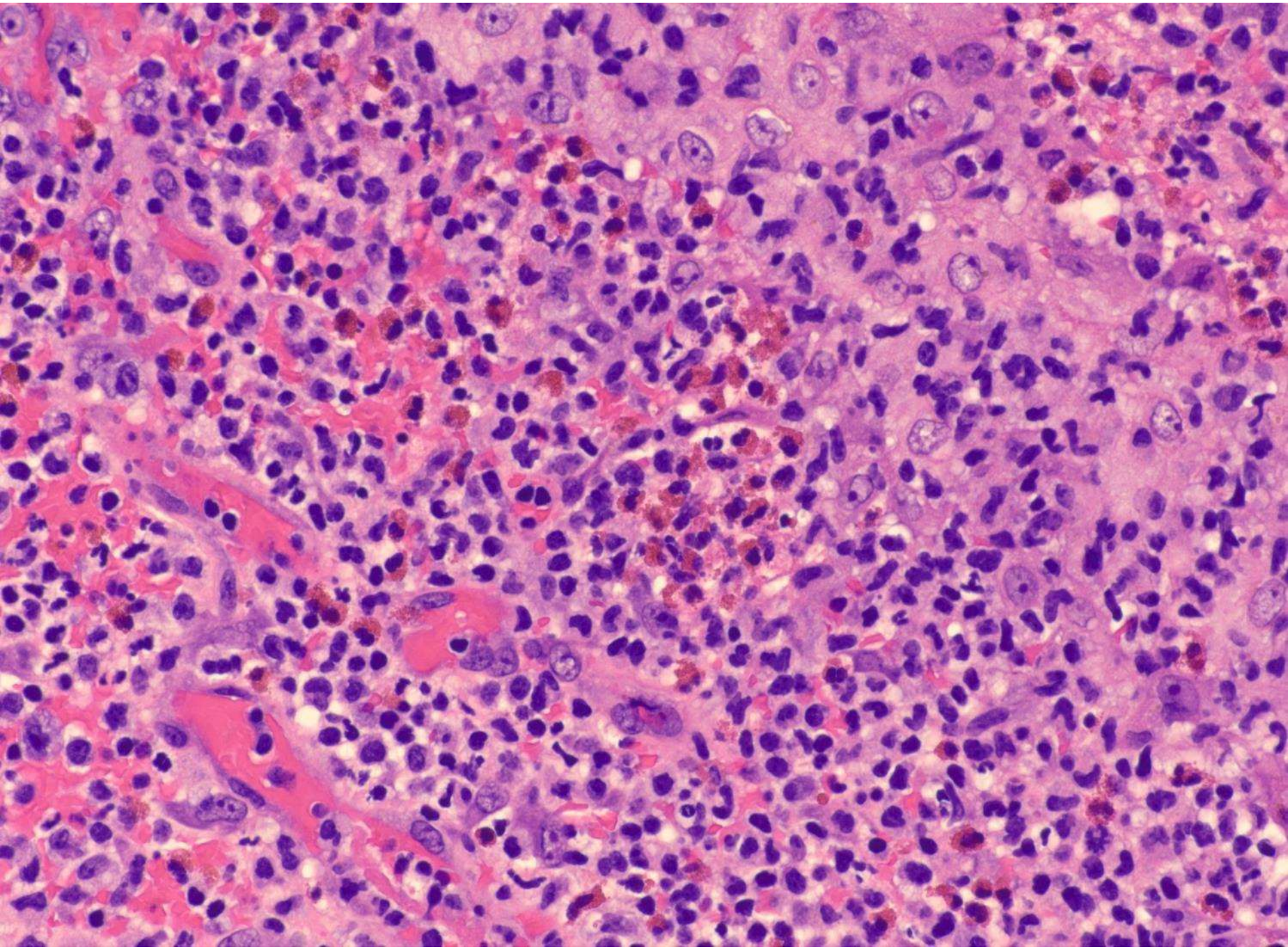


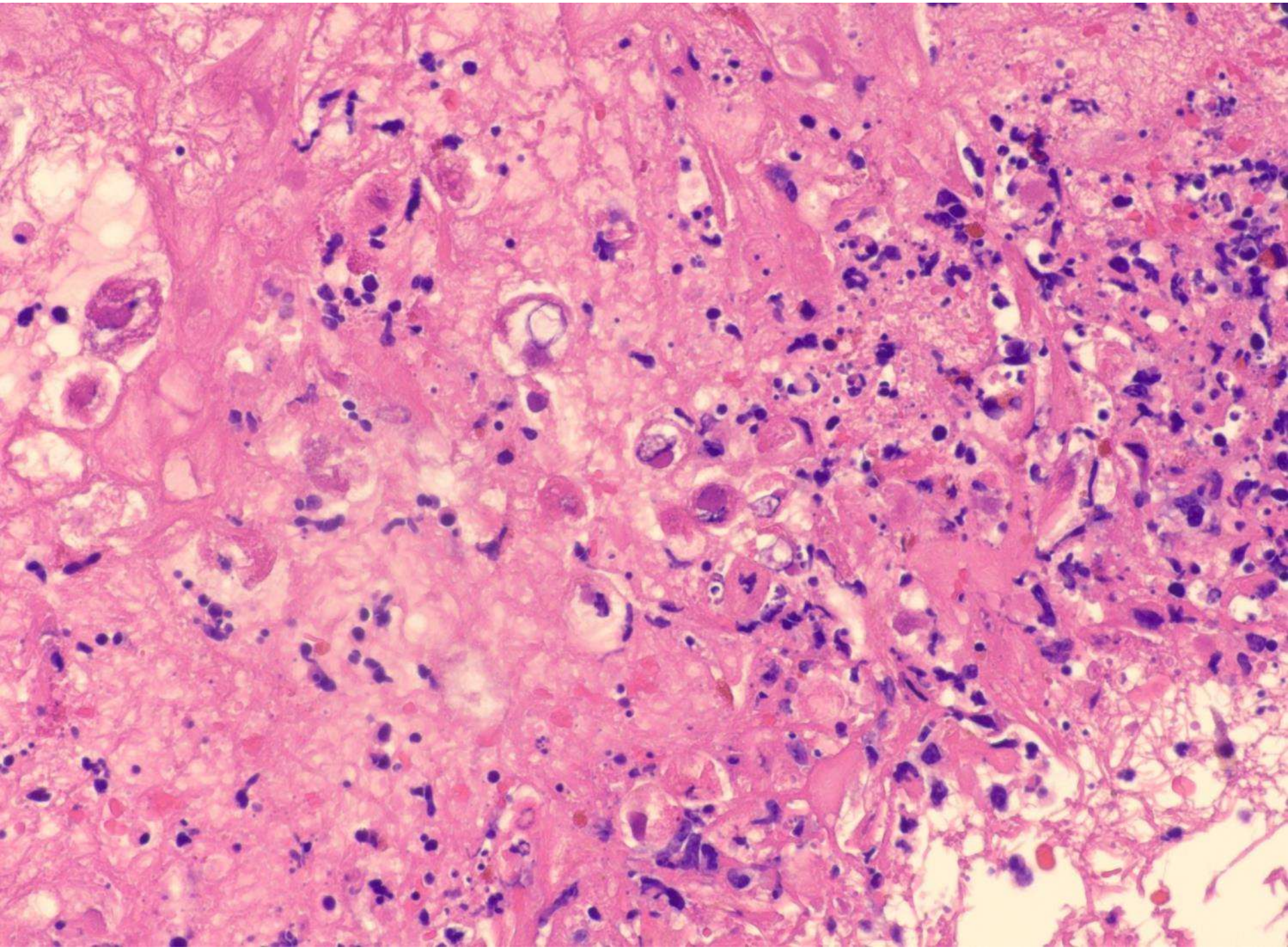


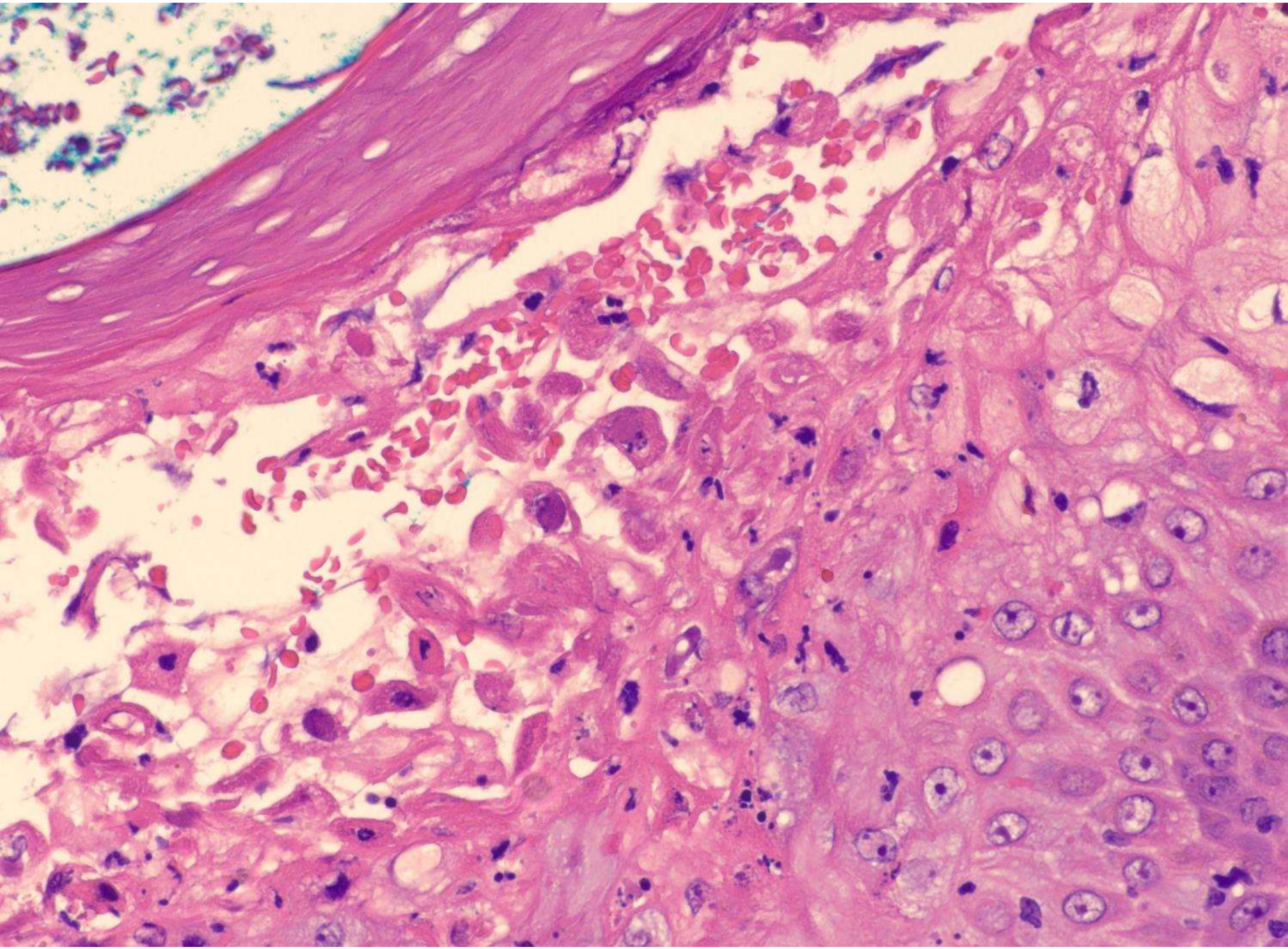


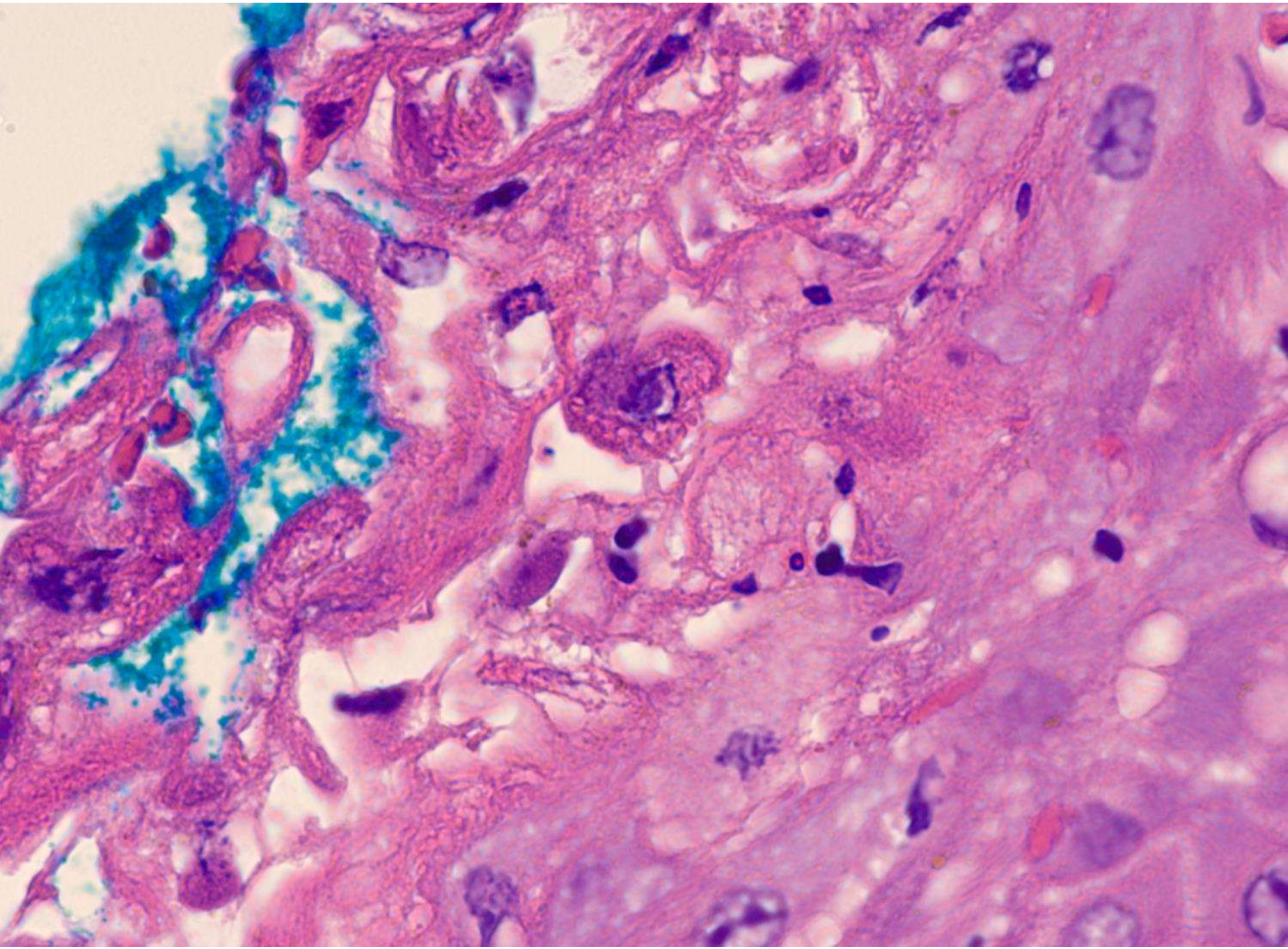


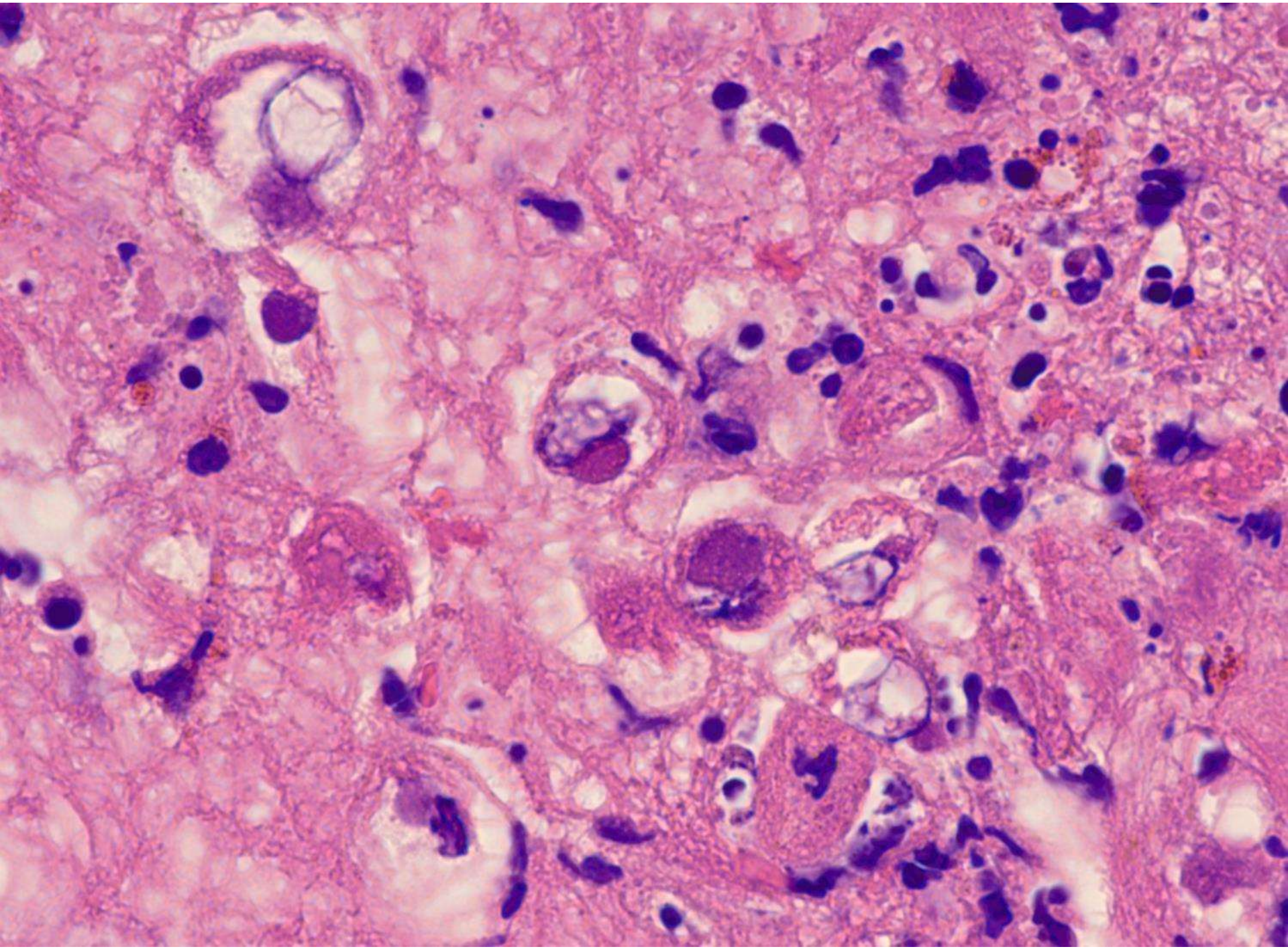


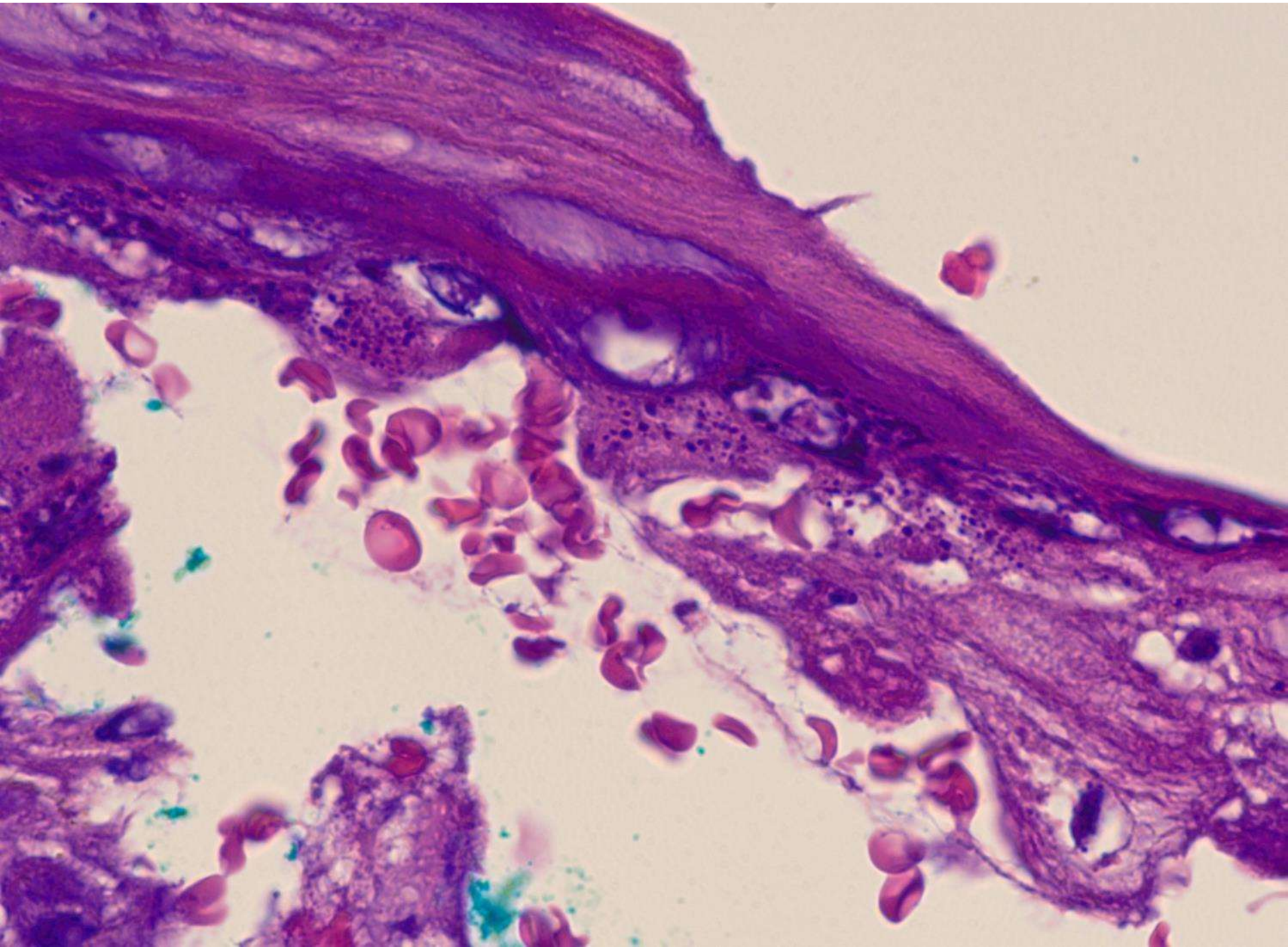


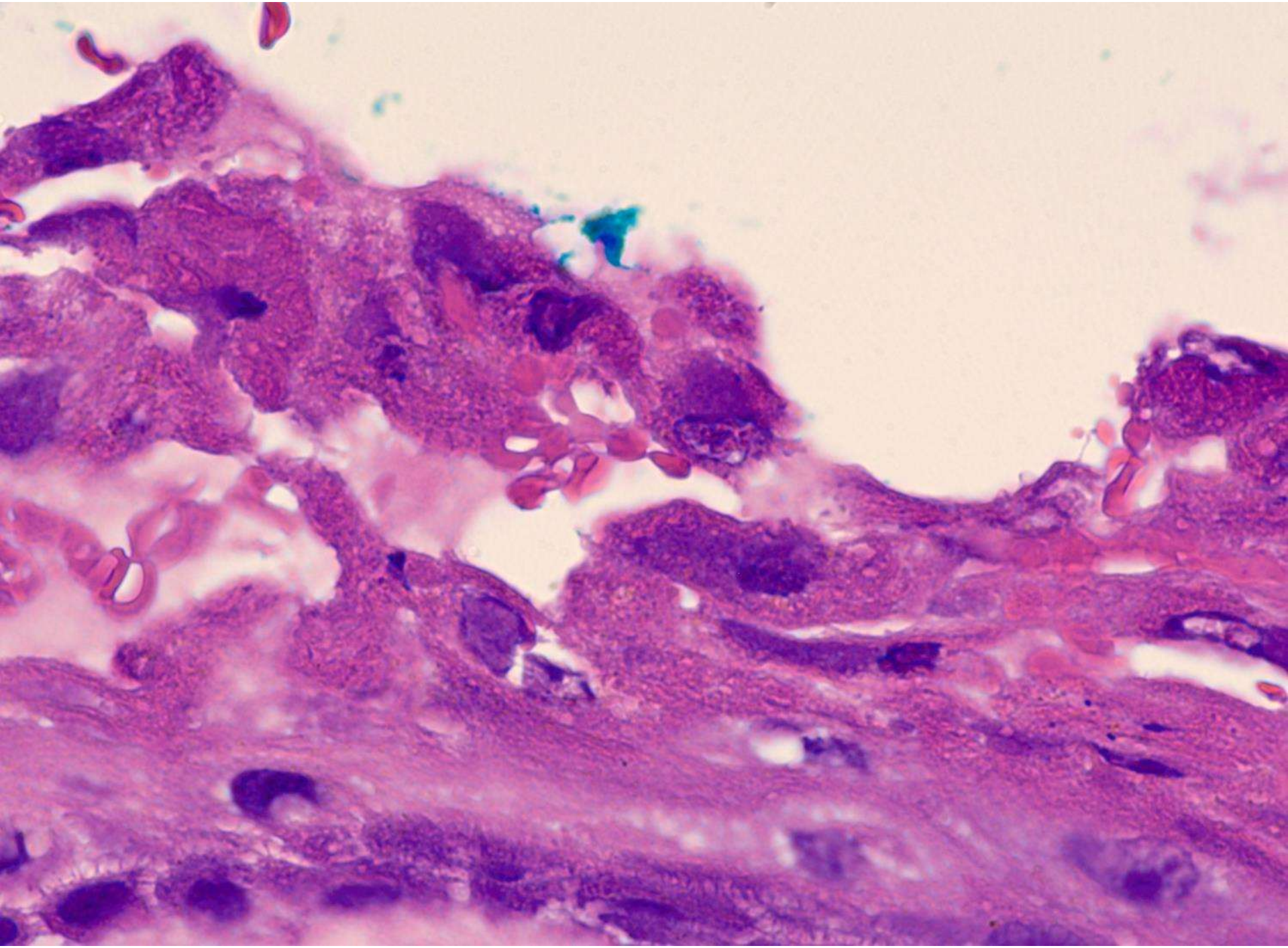


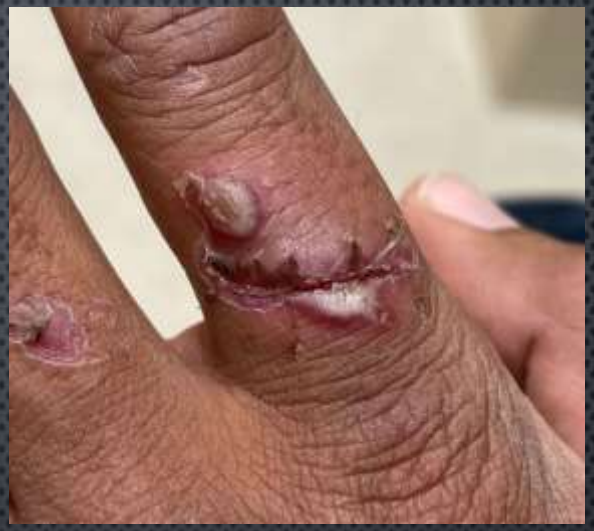


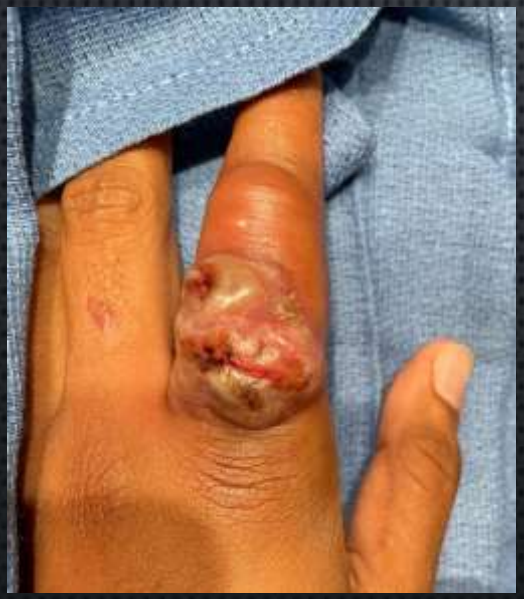


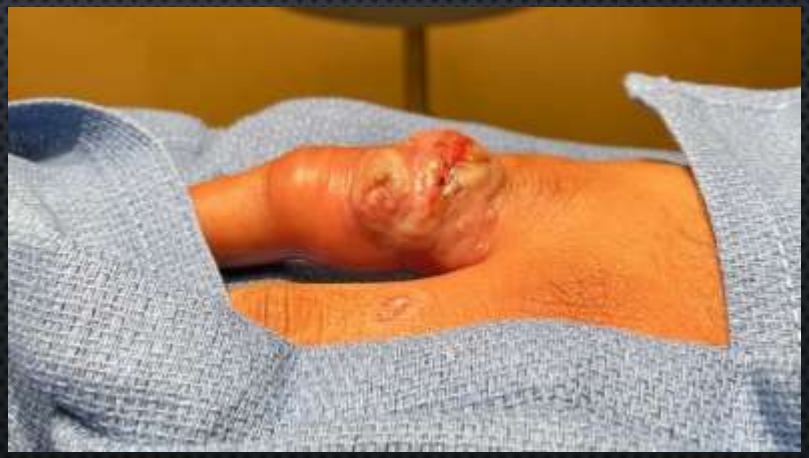


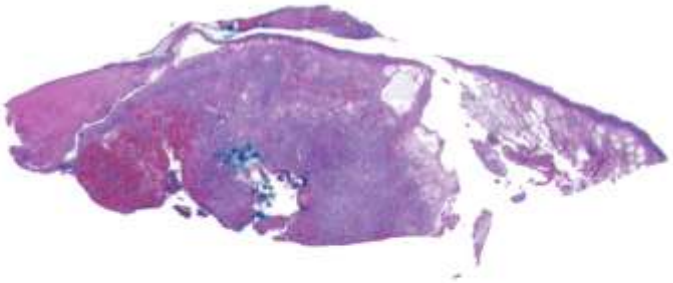


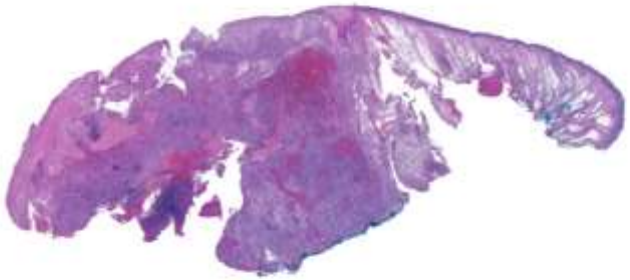


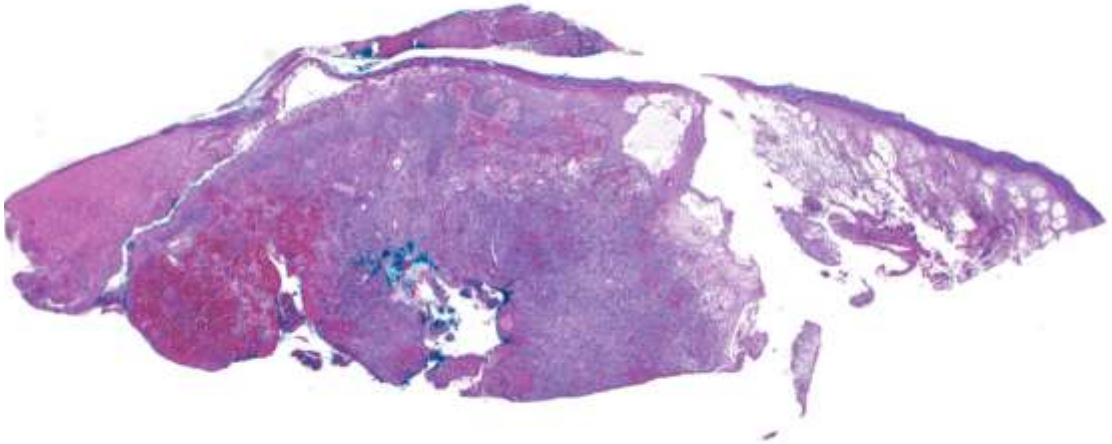


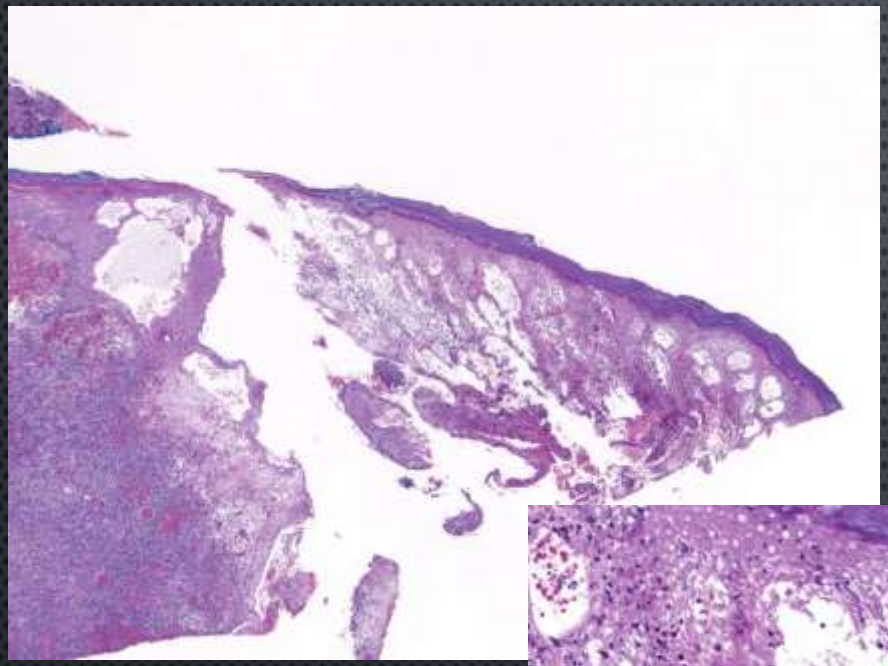
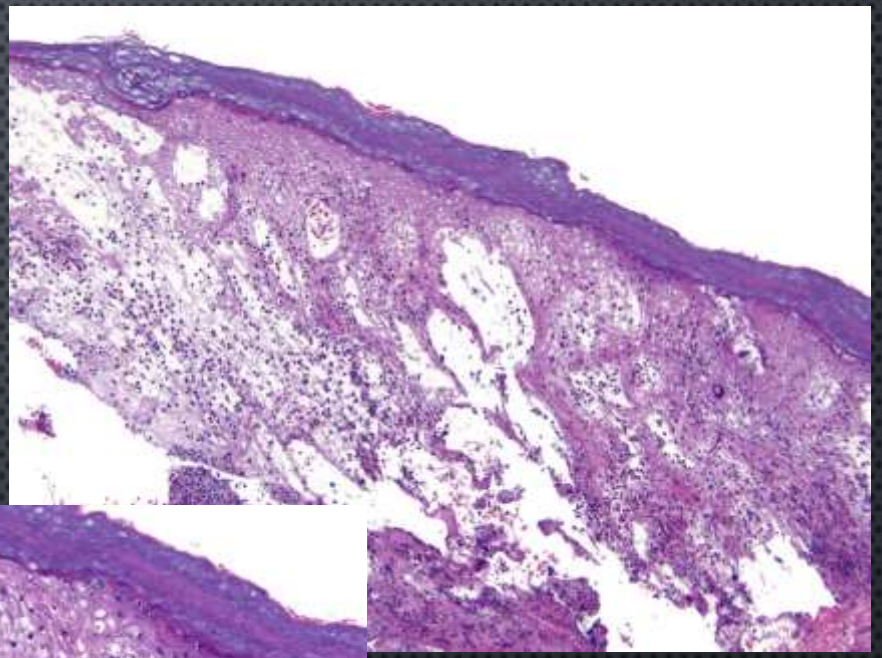
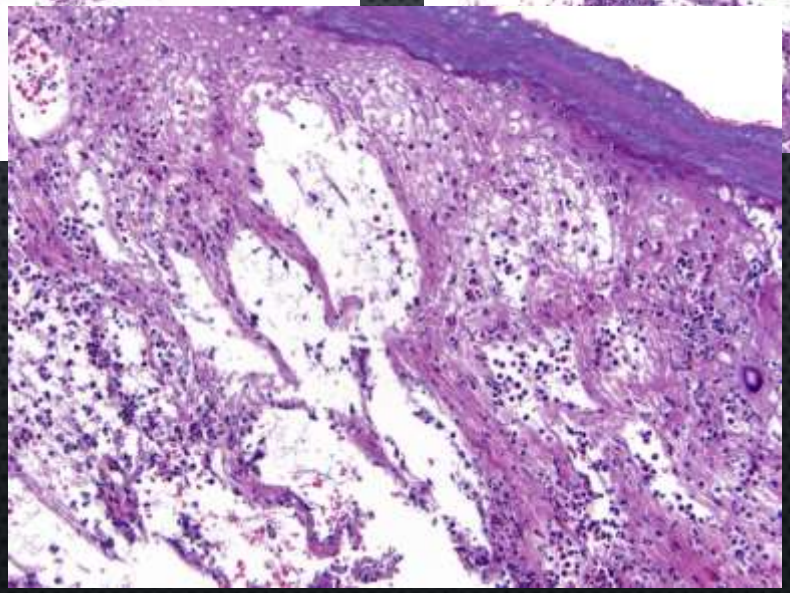


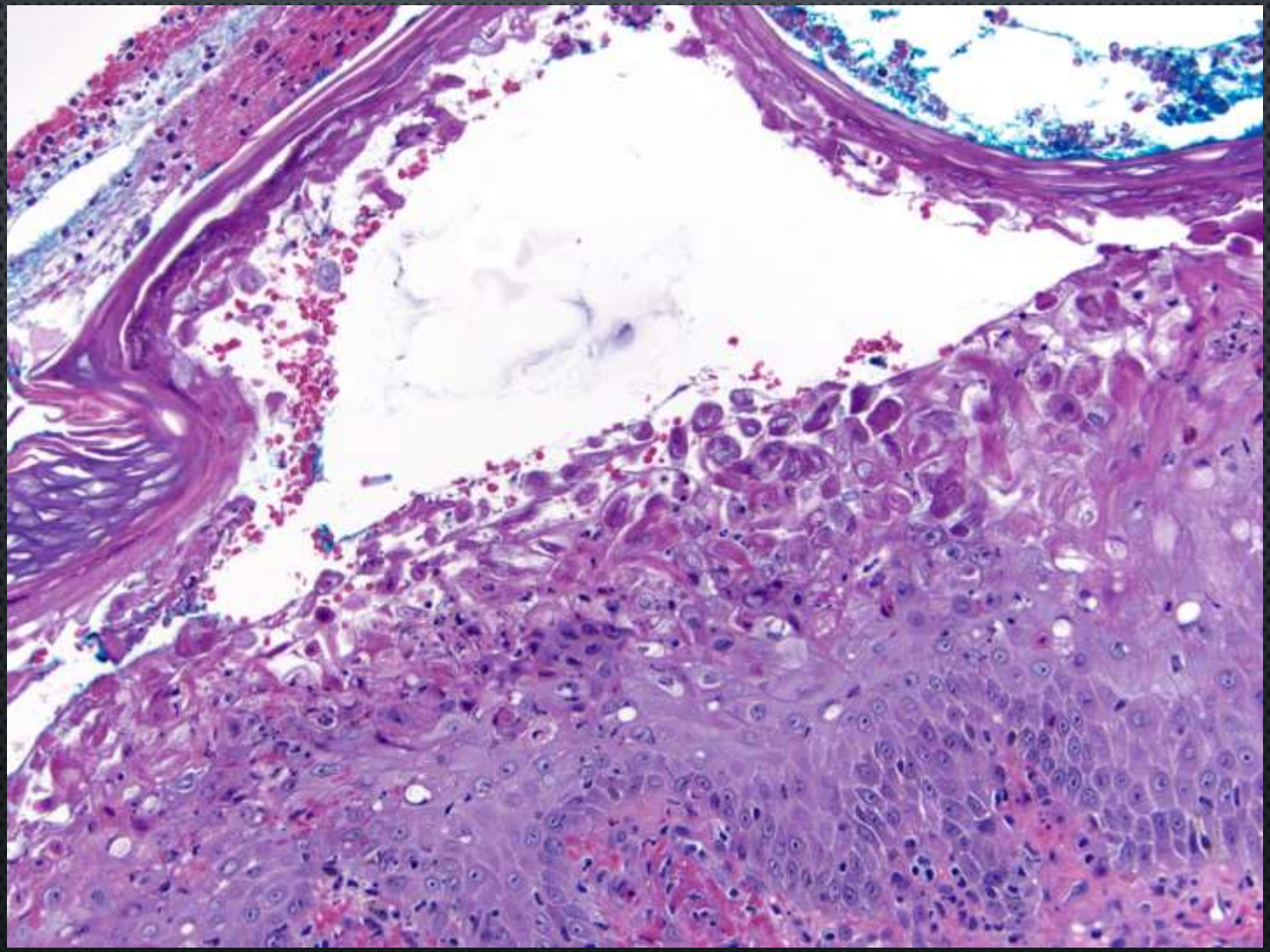


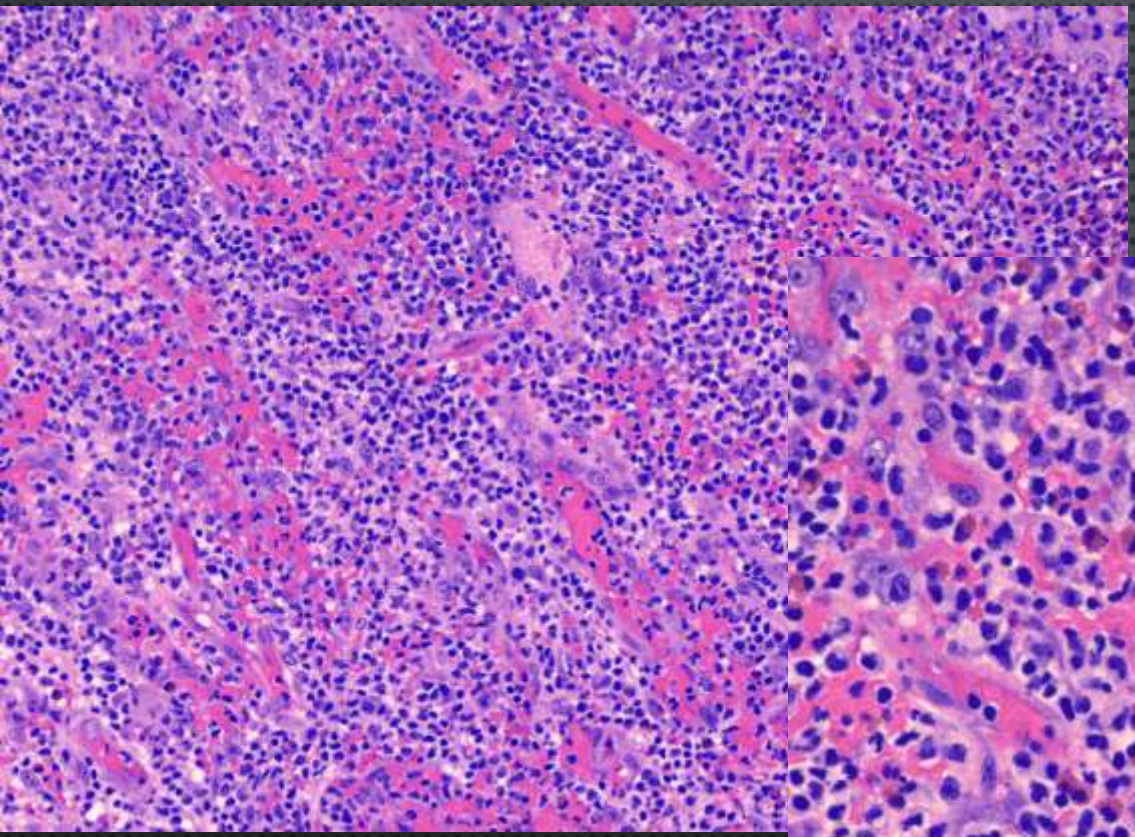


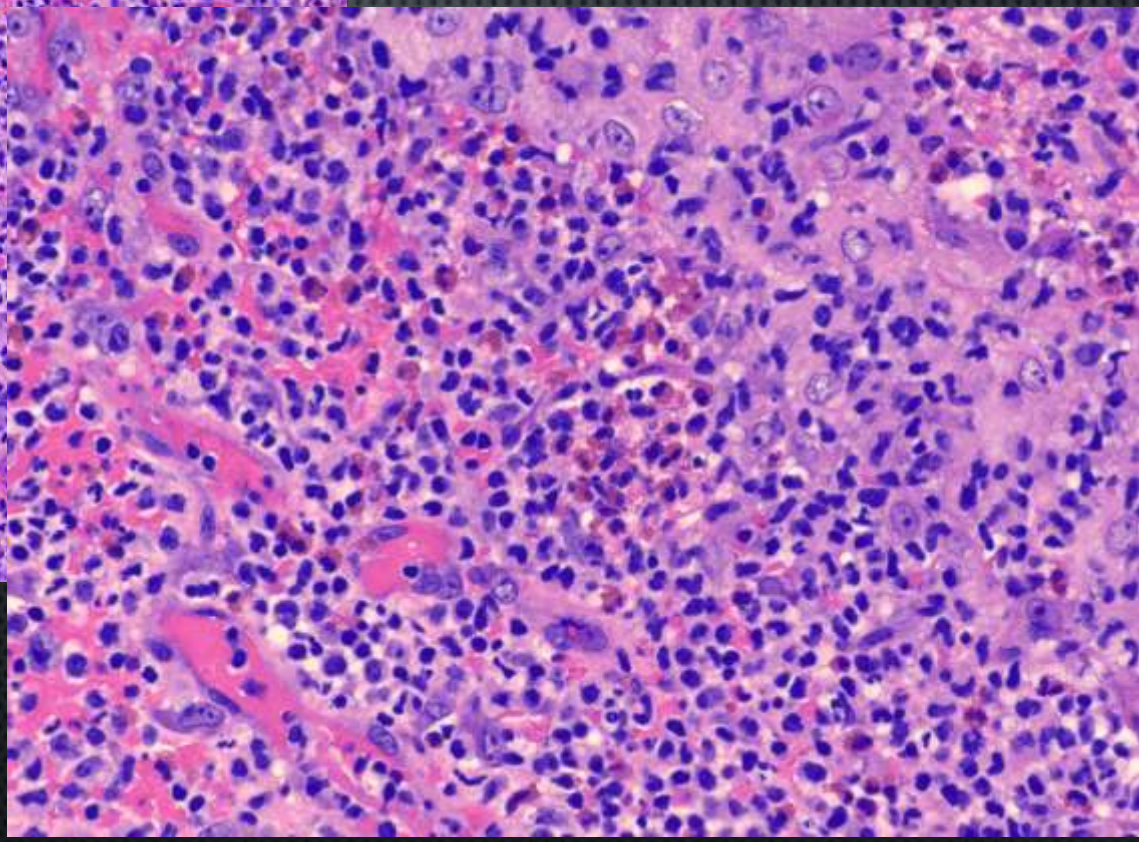


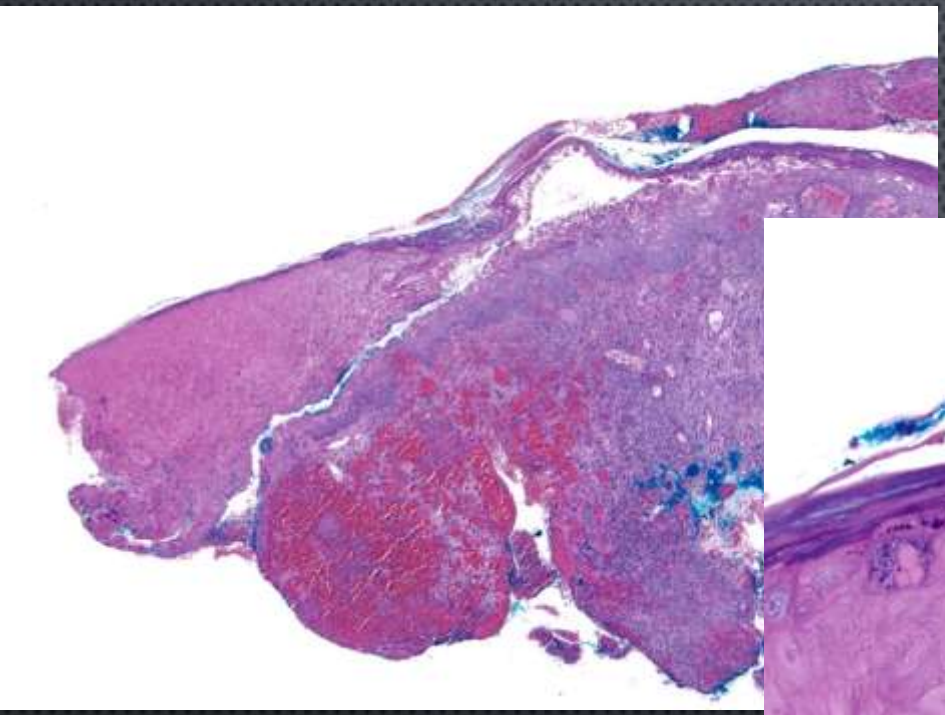


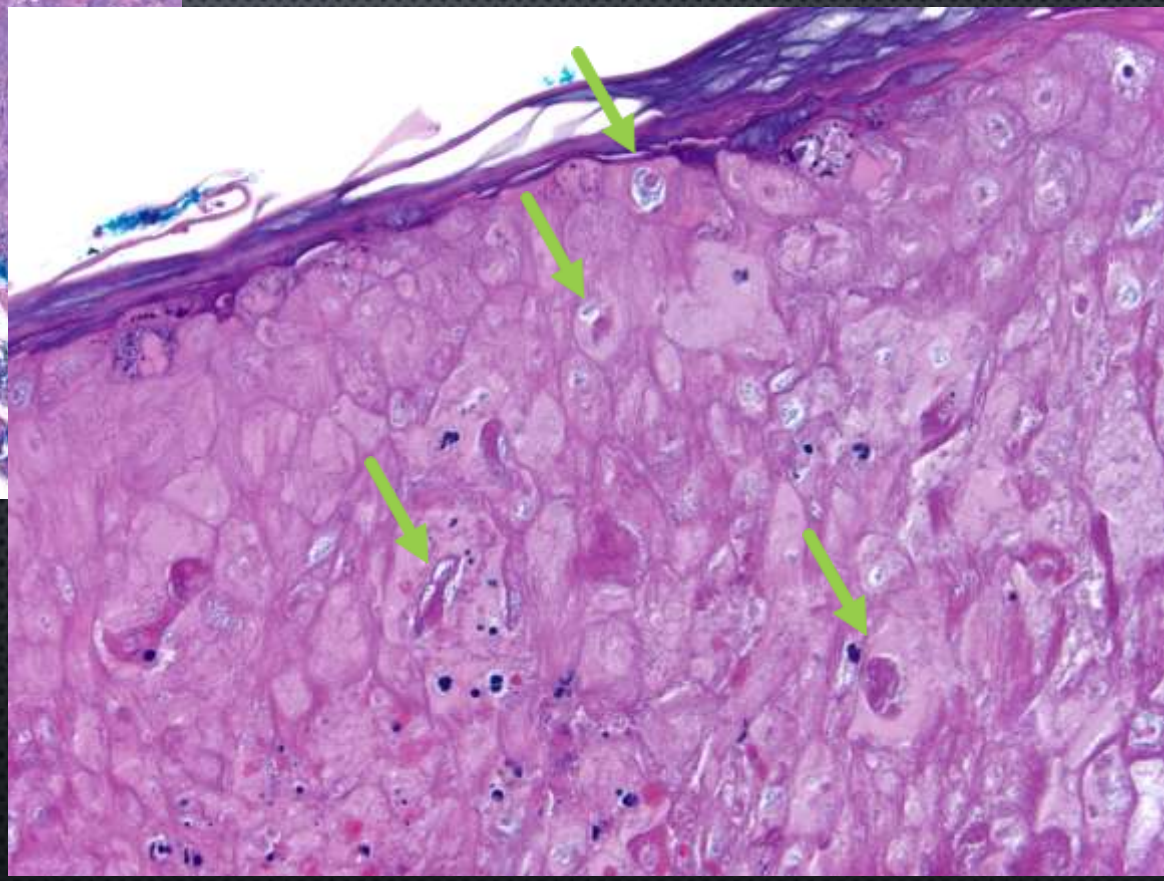




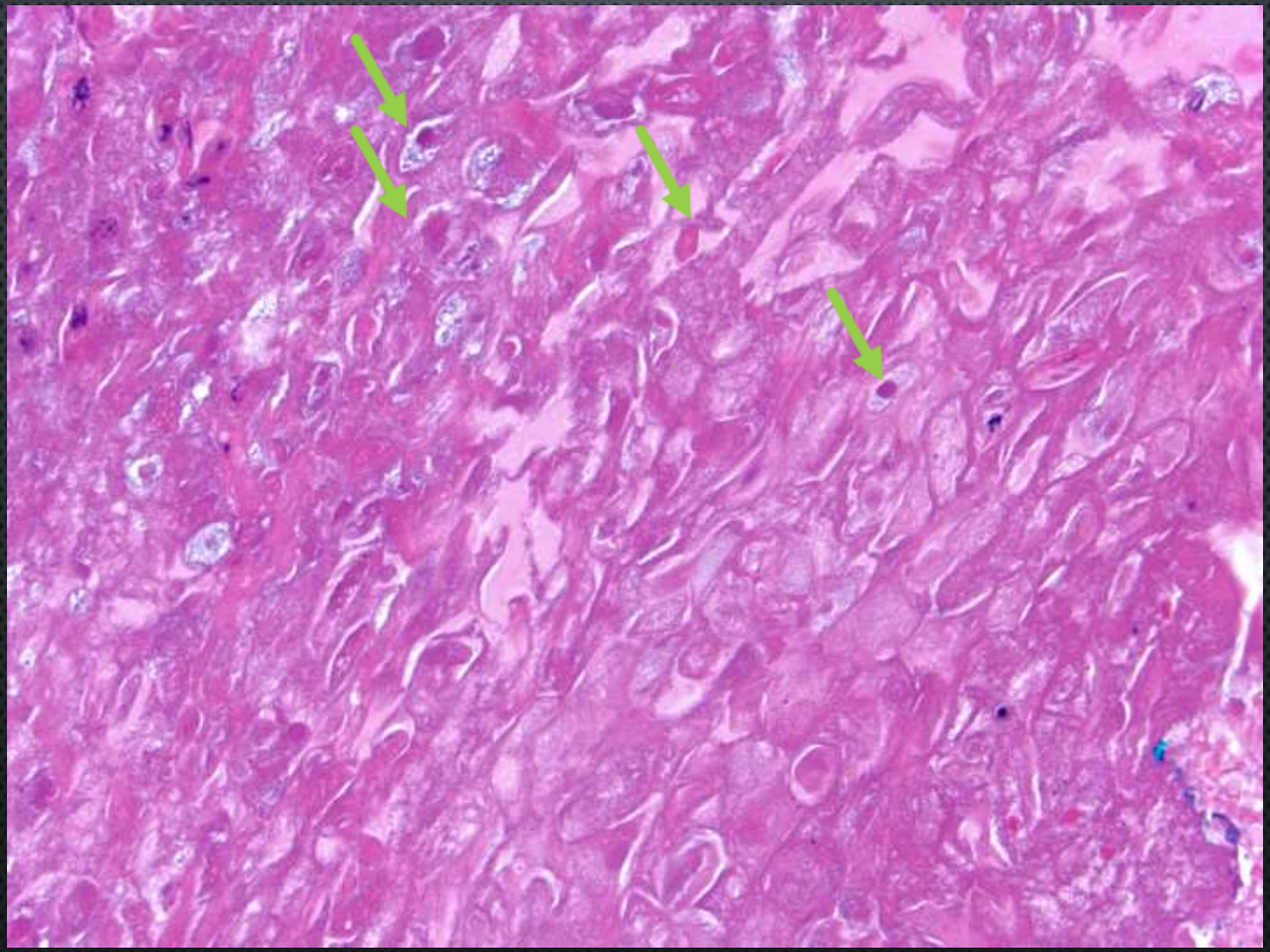


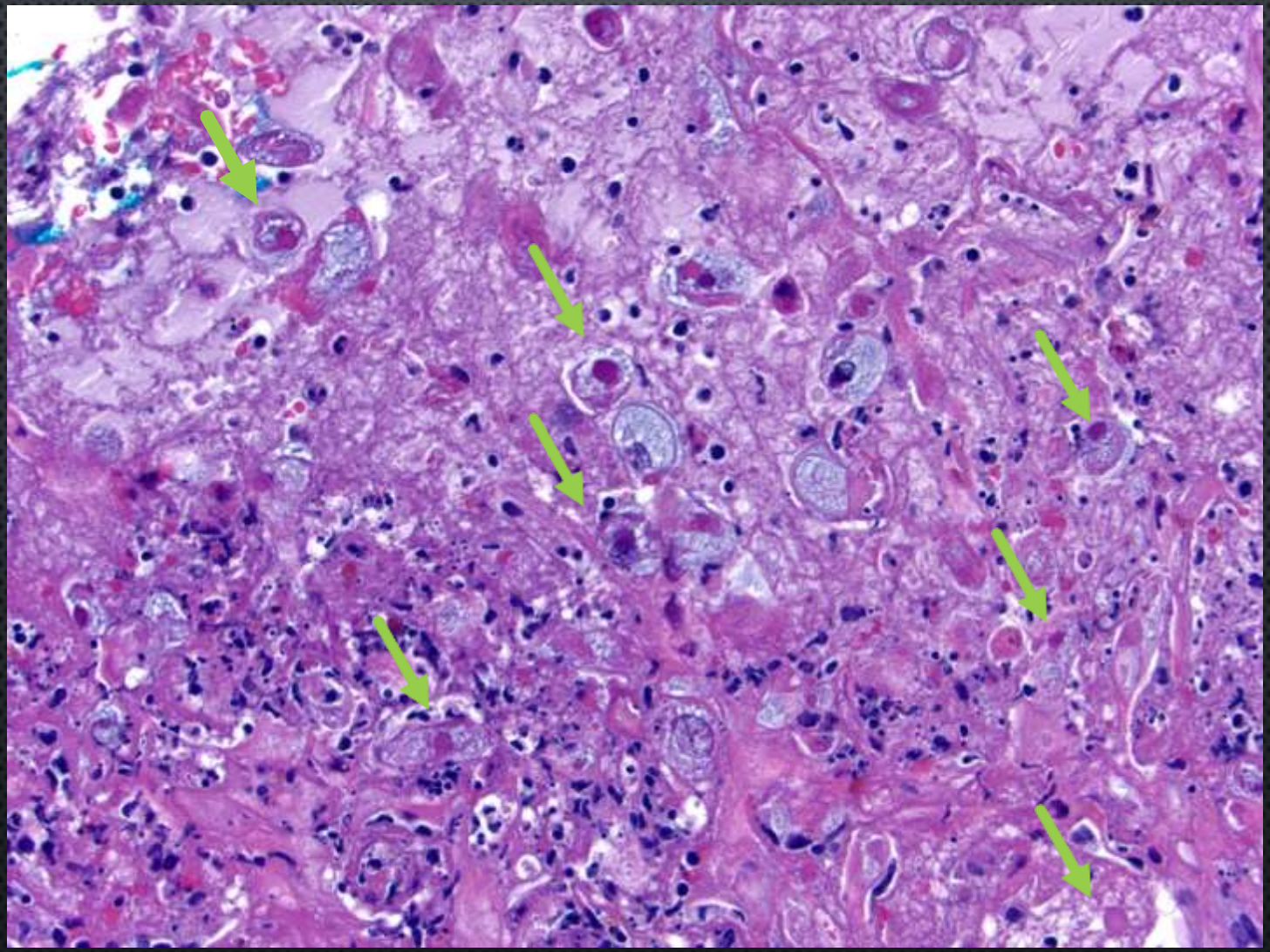


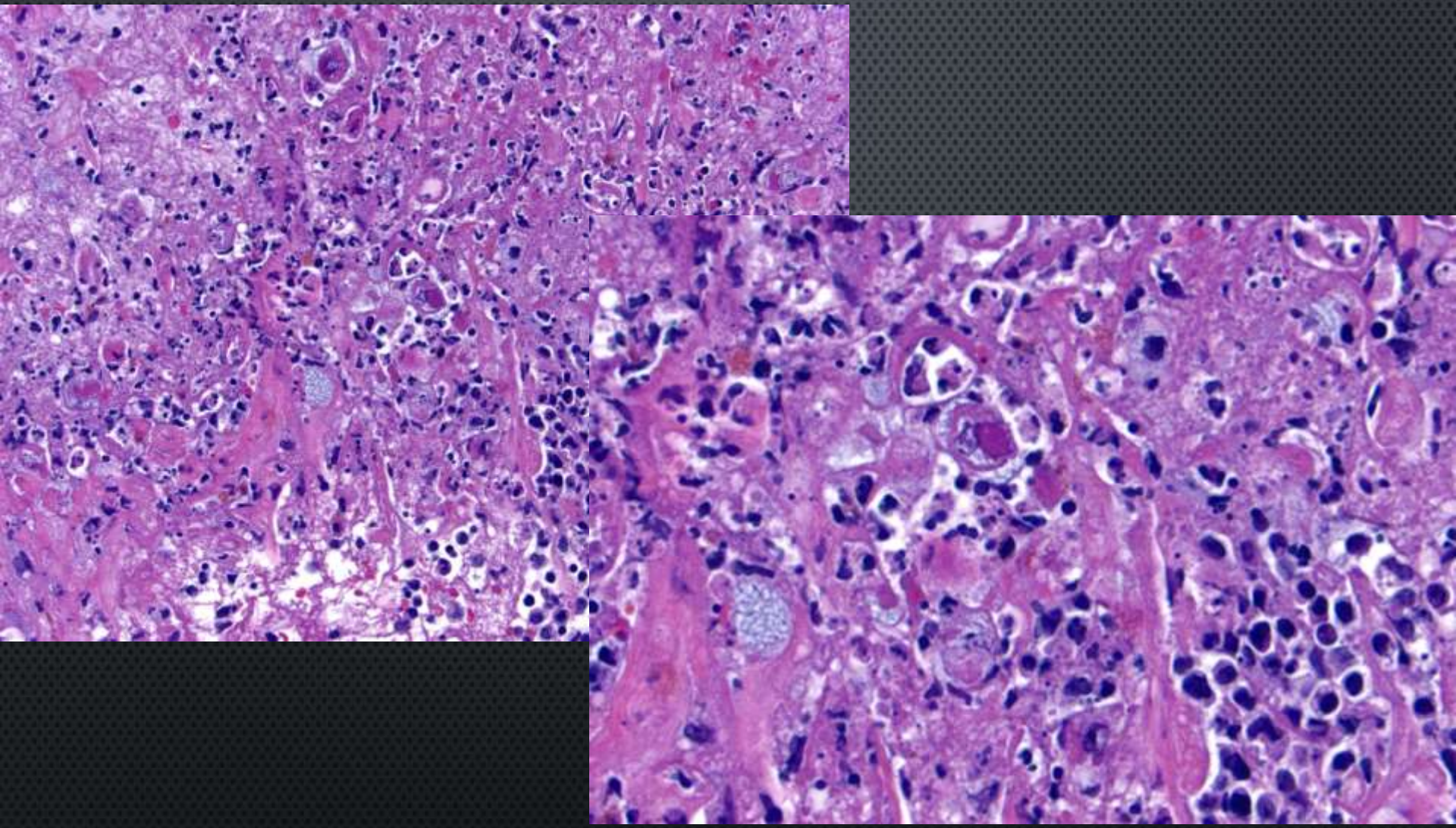


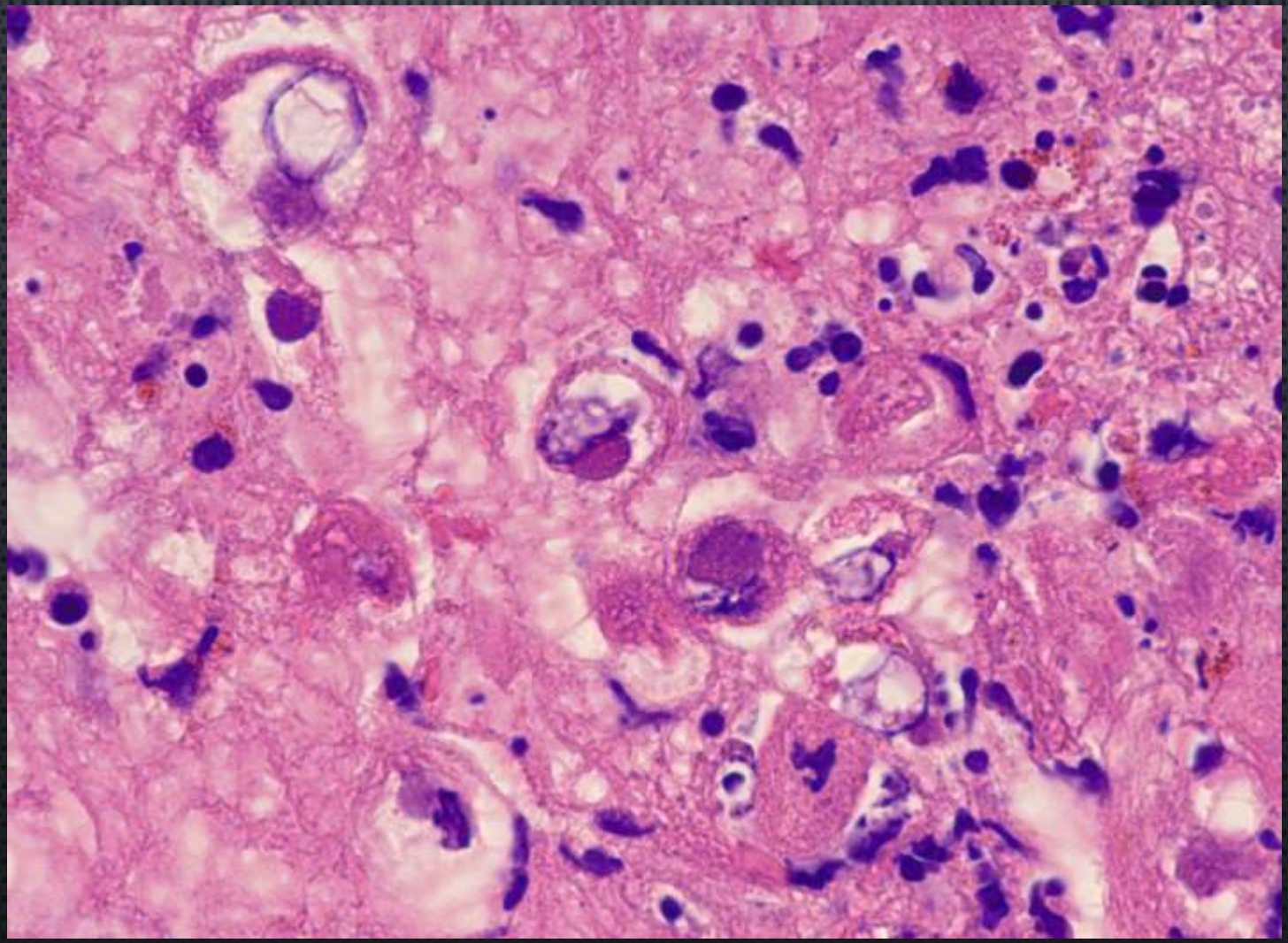












THE BEST DIAGNOSIS IS…

ORF!

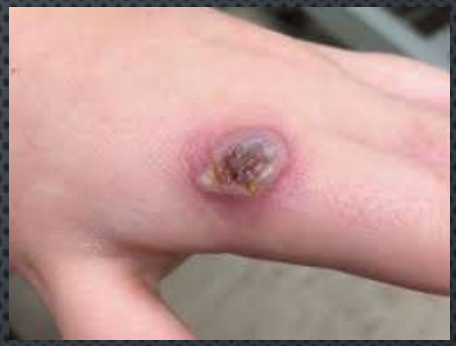
POSITIVE SEROLOGY FOR ORF (SANTA CLARA PUBLIC HEALTH LAB)

ORF (ECTHYMA CONTAGIOSUM)

- AN UNCOMMON INFECTION, OFTEN IN RURAL AREAS
- CONTACT WITH INFECTED GOATS AND SHEEP, EQUIPMENT, RARELY PERSON TO PERSON
- FARMERS, BOTTLE FEEDERS, SHEARERS, SLAUGHTERERS, BUTCHERS, VETS AT RISK
- EVEN THROUGH CASUAL CONTACT SUCH AS PETTING, NON-OCCUPATIONAL
- INFECTED ANIMALS HAVE PUSTULAR/CRUSTED AREAS ON MOUTH, NOSE, TEATS ("SCABBY MOUTH")
- CAN BE PAINFUL AND LEAD TO ANOREXIA/STARVATION

CDC.gov
Bergqvist, C, Kurban, M, Abbas, O. Orf virus infection. Rev Med Virol. 2017; 27:e1932. https://doi.org/10.1002/rmv.1932

Orf (Ecthyma Contagiosum) Clinical Features

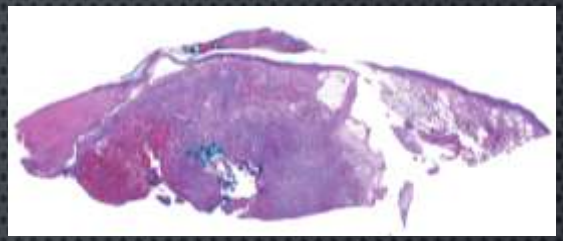


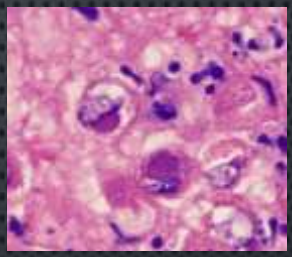
DermNet NZ

- Incubation period of 5-6 days
- 6 phases: Progresses from macular, targetoid, nodular, vesicopustular/weeping plaque, papillomatous, dry crust
- May be associated lymphangiitis, lymphadenopathy and fever
- Immunosuppression may predispose
- Self-limited, usually resolves in roughly 6 weeks
- Secondary bacterial infection, erythema multiforme may occur

Estela Cubells J, R, Braverman I, Kashgarian M, Lazova R: A 65-Year-Old Female from Connecticut with Orf Infection. Dermatopathology 2016;3:55-60.

ORF (ECTHYMA CONTAGIOSUM) HISTOLOGIC FEATURES





- VESICULATION WITH BALLOONING, EPIDERMAL NECROSIS, HYPERPLASIA
- CHARACTERISTIC EOSINOPHILIC NUCLEAR OR CYTOPLASMIC INCLUSIONS
- DENSE MIXED INFILTRATE
- IDENTICAL TO MILKER'S NODULE (PARAPOX FROM COWS, PSEUDOCOWPOX)

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WILEY

REVIEW

Orf virus infection

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Summary

Orf virus (ORFV) is an important pathogen responsible for a highly contagious zoonotic viral infection that threatens those who handle sheep and goats. Orf virus is the prototype of the *Parapoxvirus* genus, and its resilience in the environment and ability to reinfect its host has contributed to the spread and maintenance of the infection in many species. In healthy humans, the disease usually resolves spontaneously within 3 to 6 weeks. There is no specific treatment and many different approaches such as use of imiquimod, cidofovir, curettage, shave excision, cryotherapy, and electrocautery have all been reported to be successful, without supporting evidence from controlled clinical trials. Throughout its interaction with the different hosts, ORFV has evolved a strategy for immune evasion via the development of an array of virulence factors. The interaction of ORFV with the immune system has been the subject of research for decades. Whole inactivated ORFV has been used as a type of immunomodulating drug: a so called paramunity inducer proposed as both a preventative and a therapeutic immunomodulator across various species. Additional research on the remarkable strategies underlying ORFV infection could lead to improved understanding of skin immunity.

KEYWORDS

ecthyma contagiosa, immunity, orf, poxvirus, virology, virulence factor

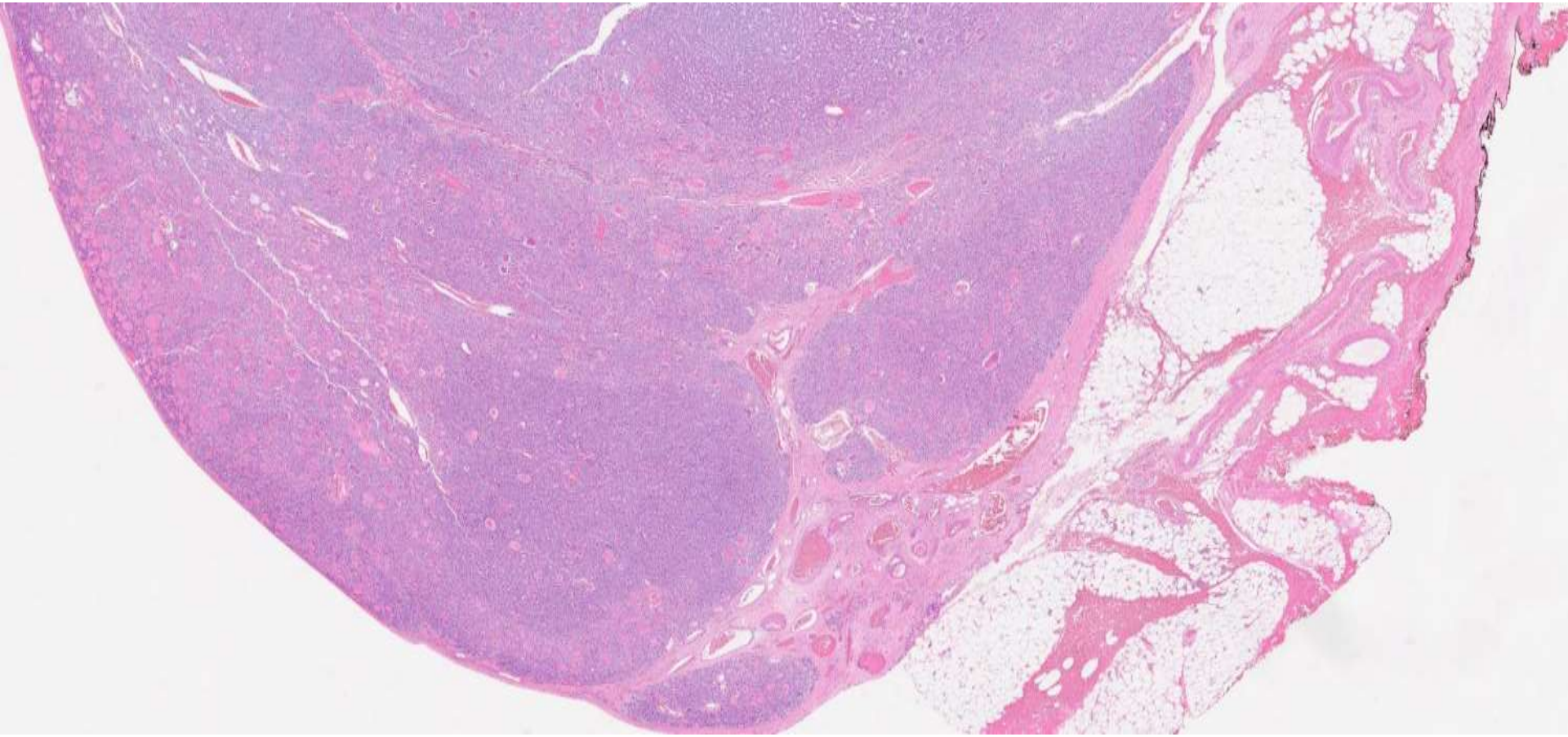
Bergqvist, C, Kurban, M, Abbas, O. Orf virus infection. Rev Med Virol. 2017; 27:e1932. https://doi.org/10.1002/rmv.1932

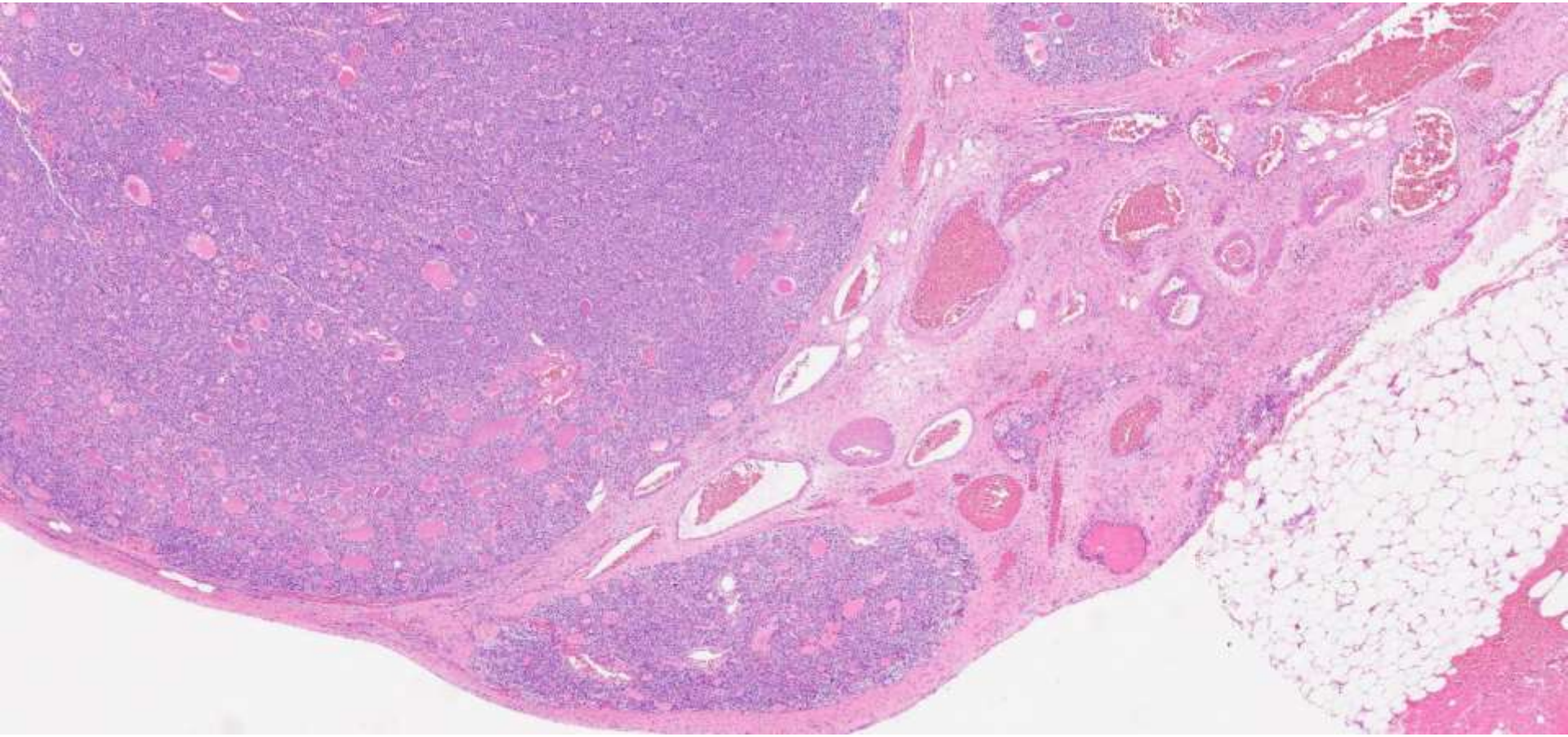
Orf can also occur in a nonoccupational setting. Farmer's children and housewives, zoological garden visitors, and people who practice farming as a hobby as well as people who slaughter lambs and sheep for traditional rituals are also at risk.[10,15,16] Orf virus has also been reported in a 53-year-old woman after being scratched by a stray kitten.[17] A yearly outbreak occurs in countries in which there is a Muslim population such as Turkey, Jordan, Iran, France, Belgium, United States, Kingdom of Saudi Arabia, because of increased animal slaughter for the feast of sacrifice (Eid el Adha).[6,14,18-23] In the nonprofessional setting, safe practices are difficult to implement, so cuts in the skin can ensue from handling animals thereby facilitating orf inoculation.[10] Profes-

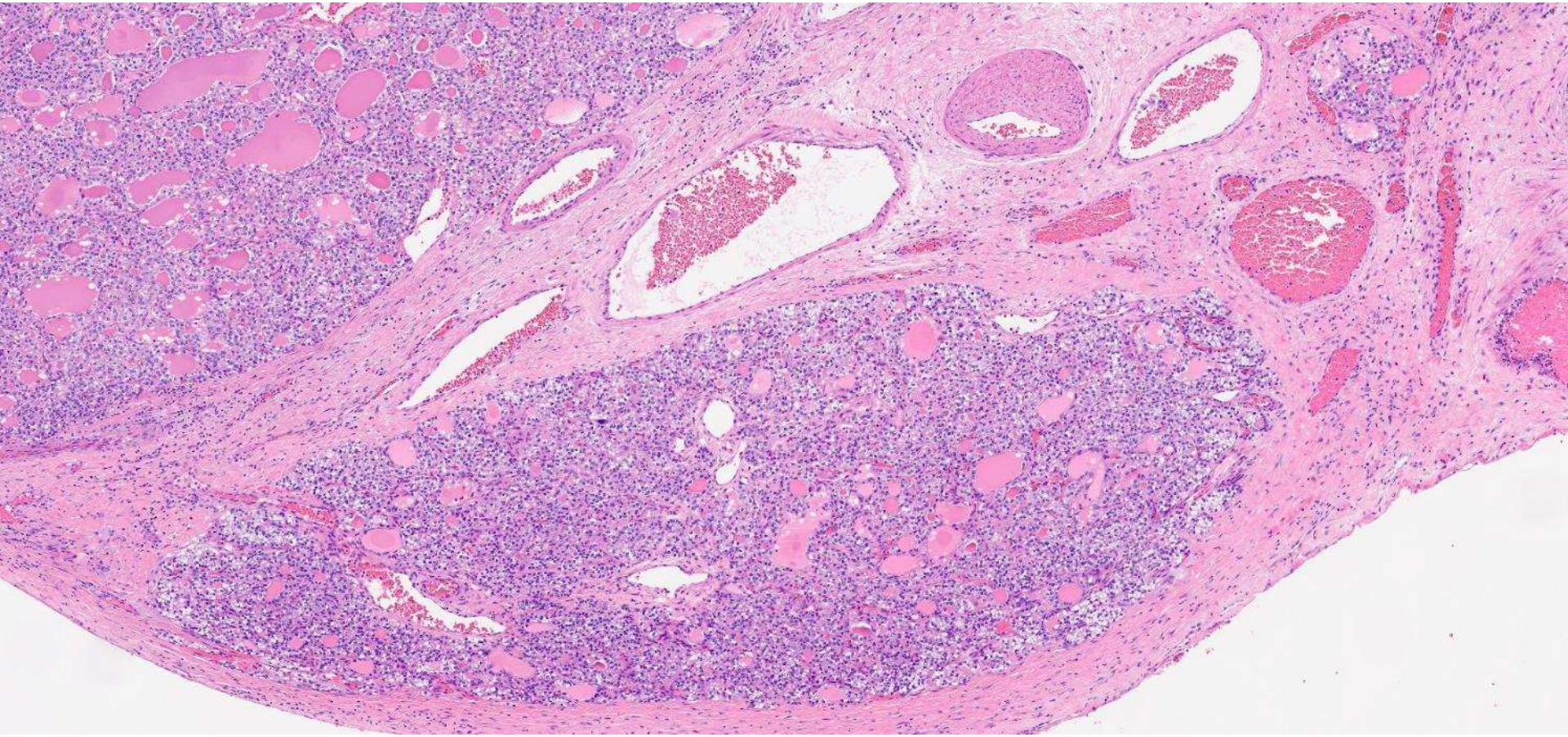
21-1004

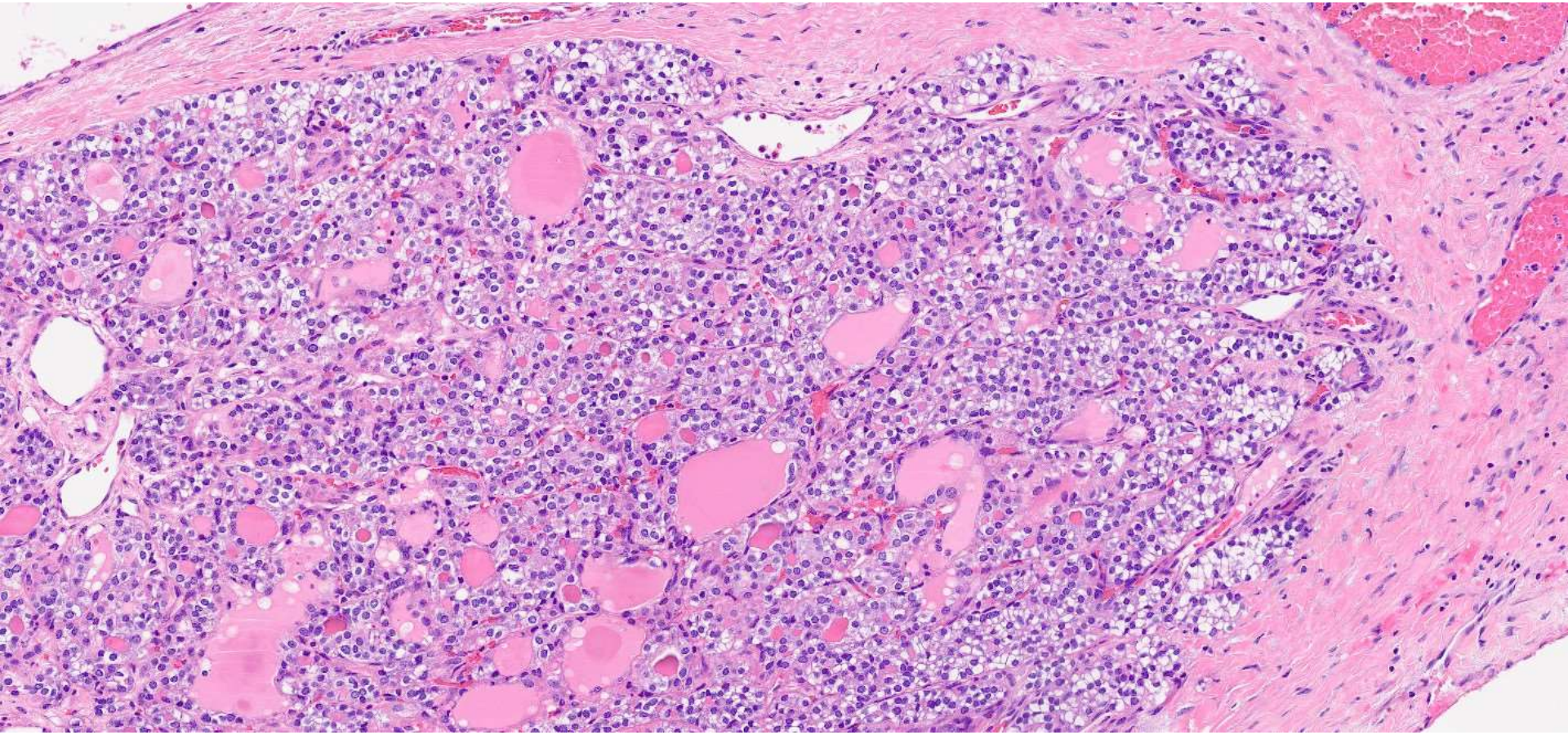
Lucas Massoth; El Camino Hospital

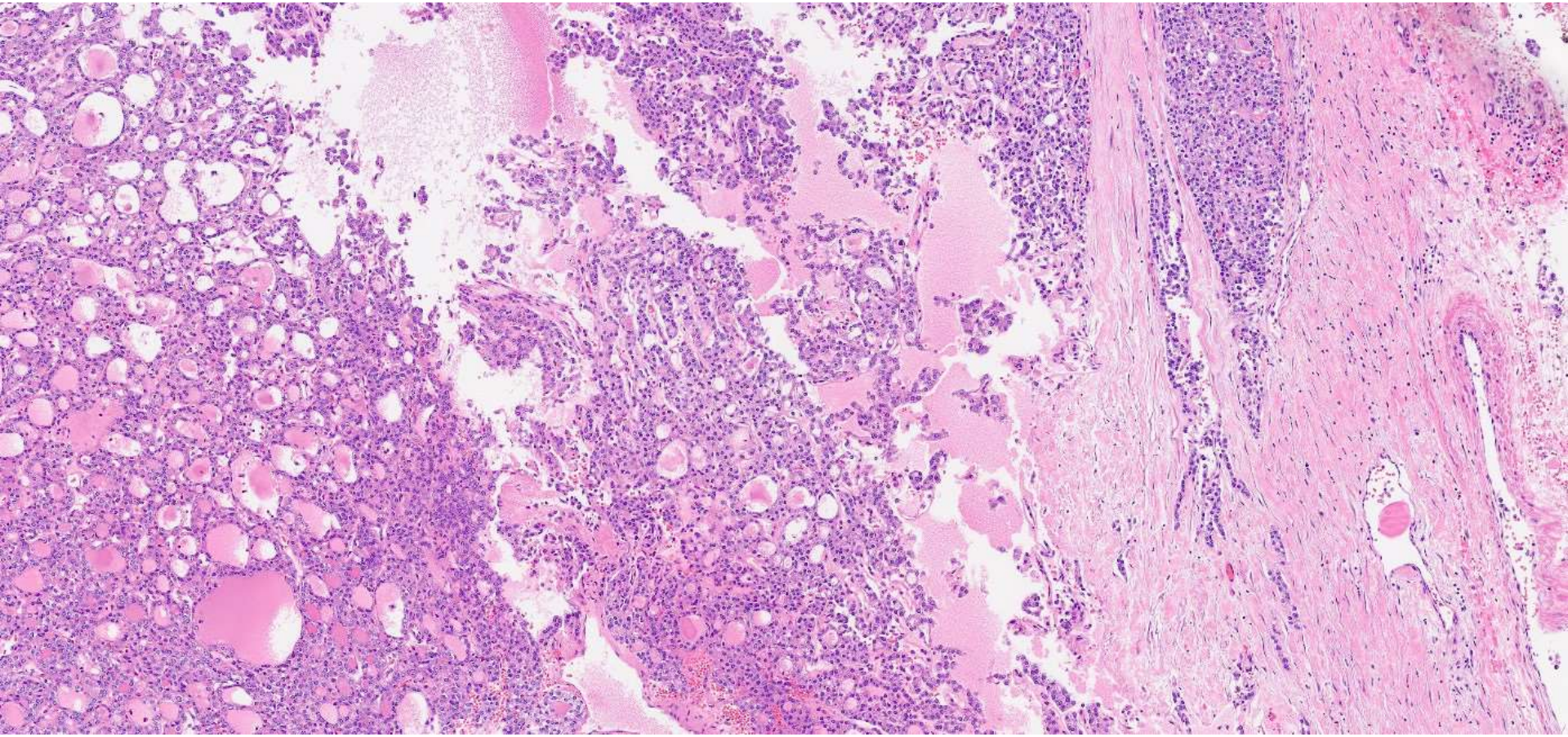
35-year-old F with interior abdominal mass excision.

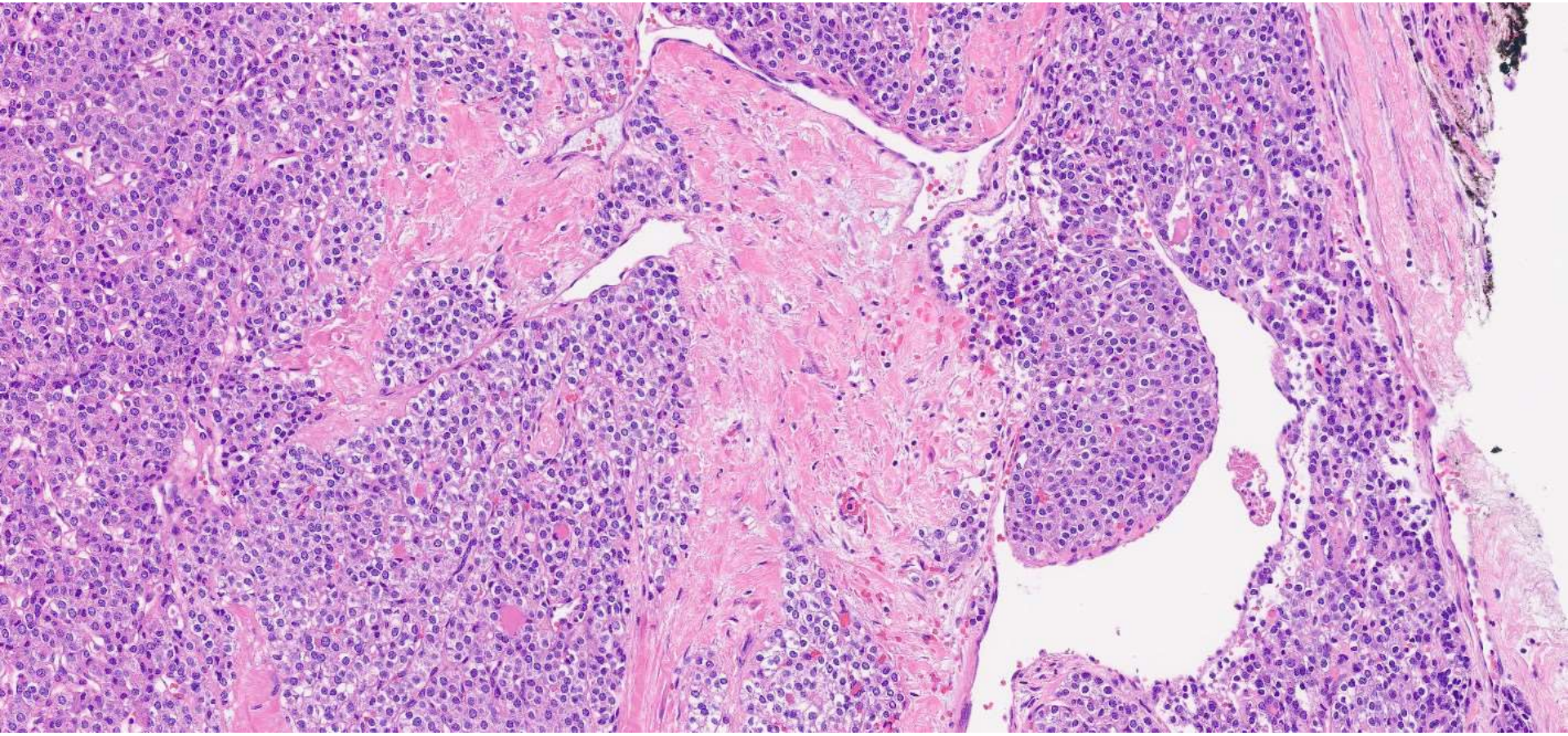


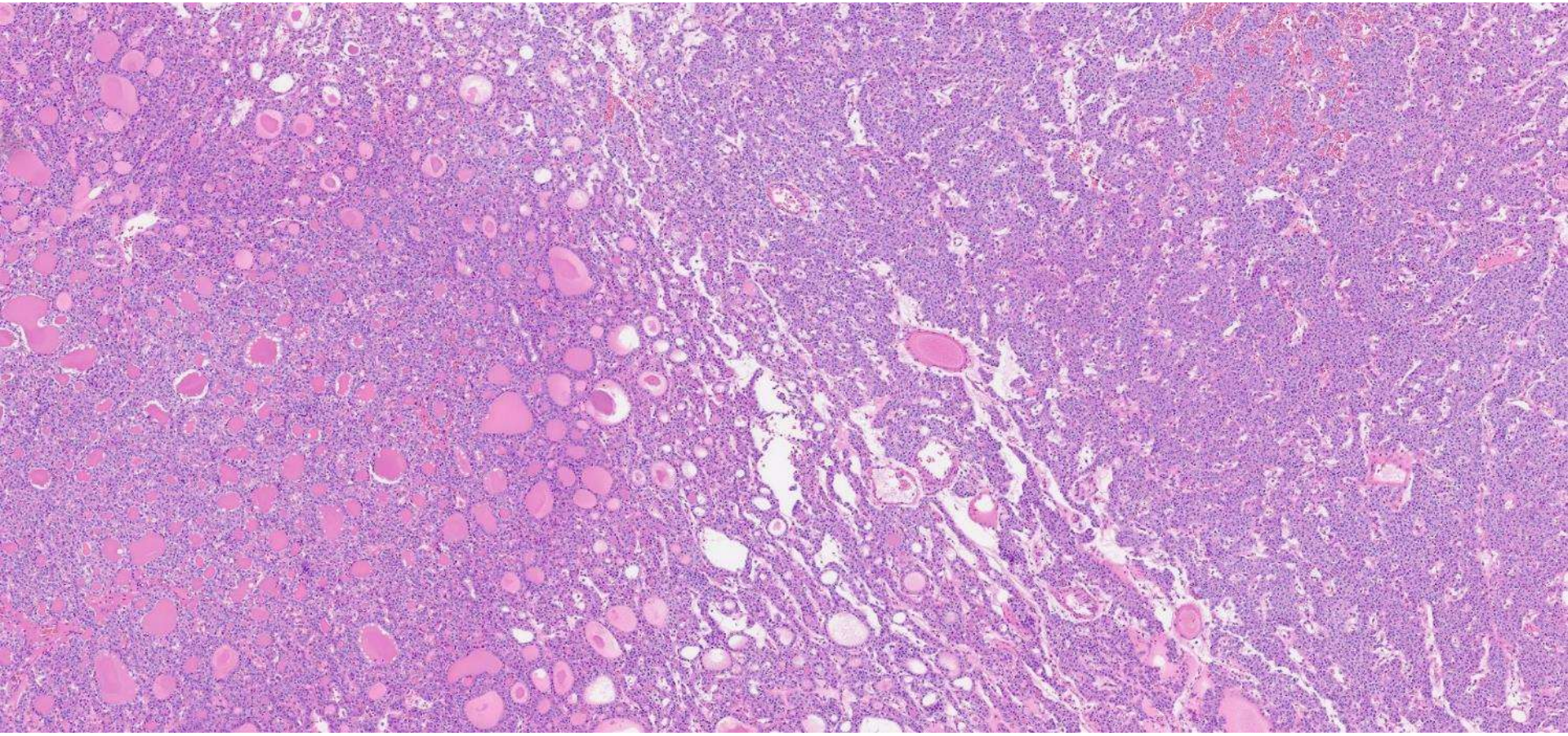


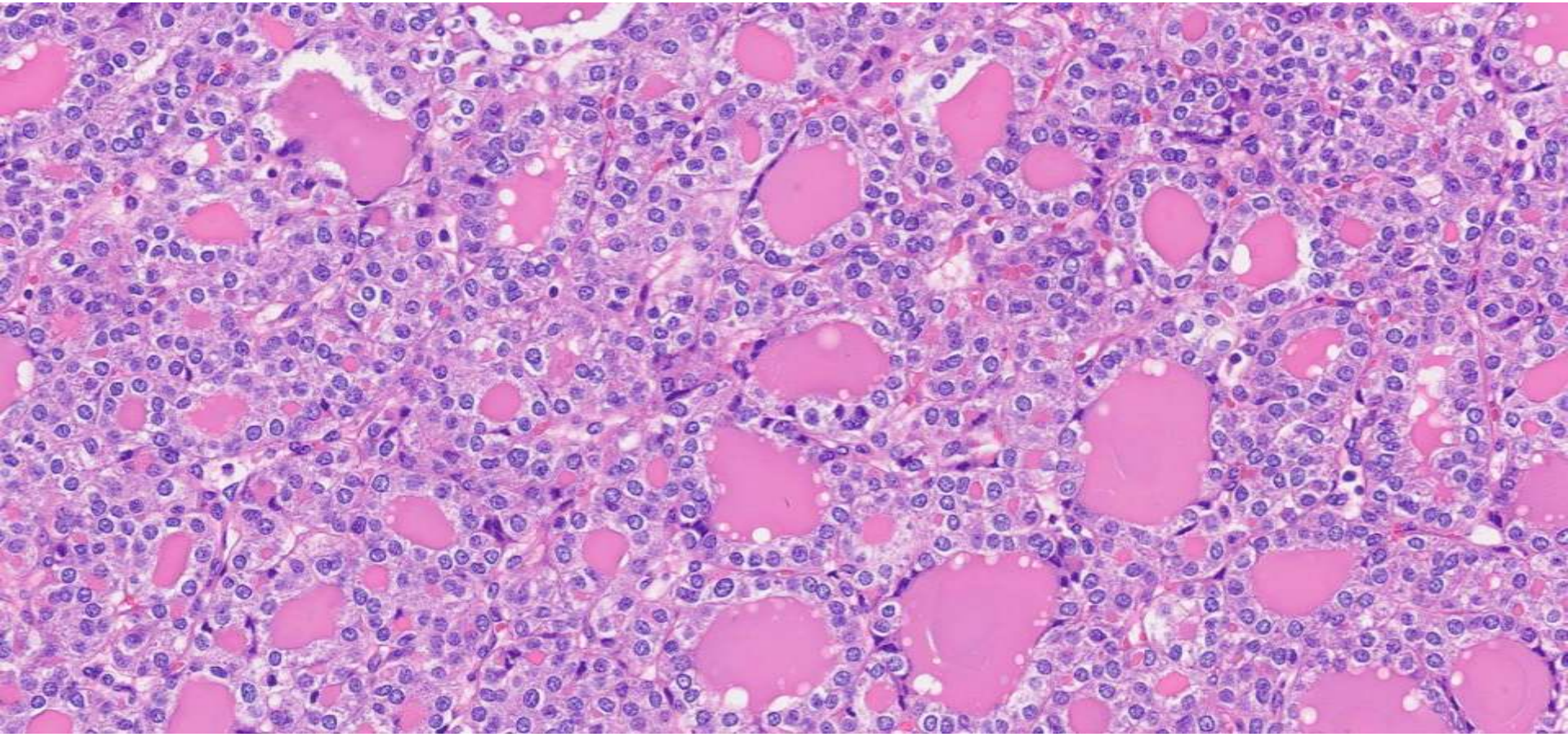


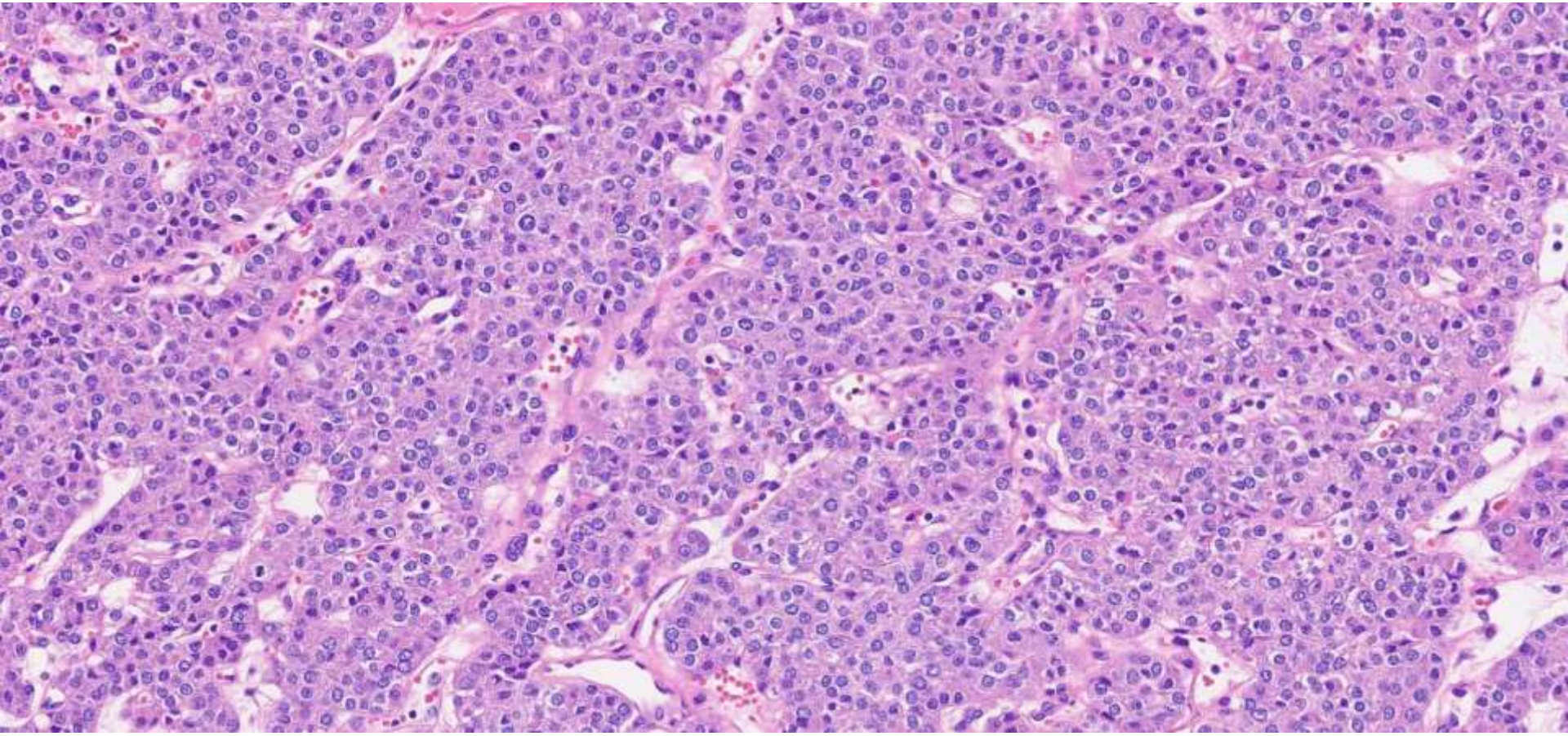


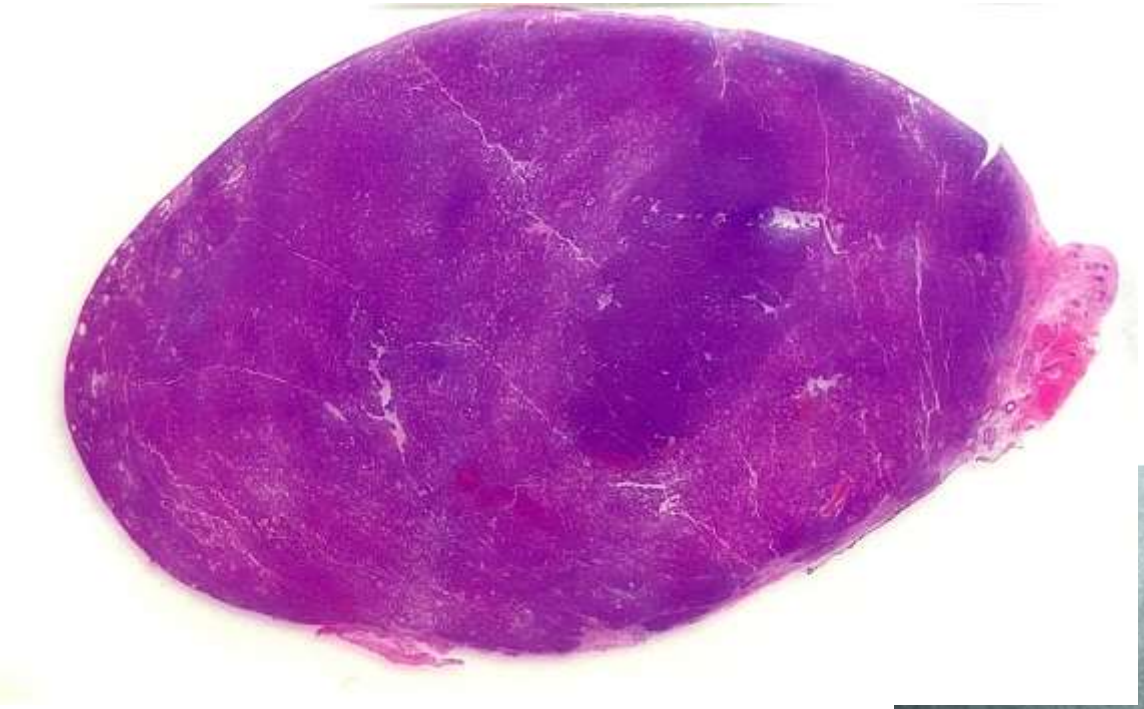


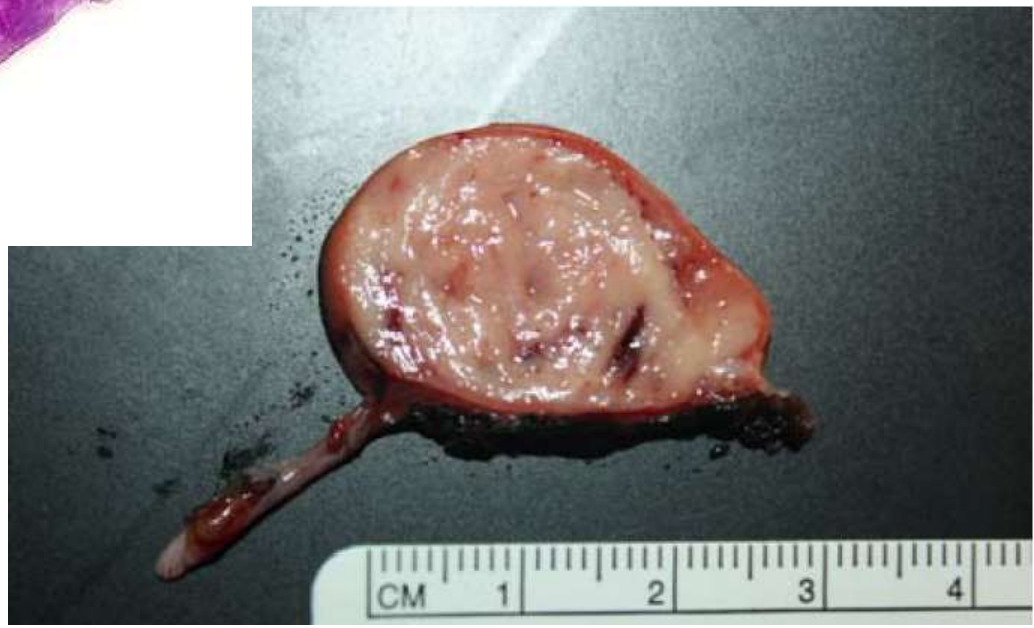








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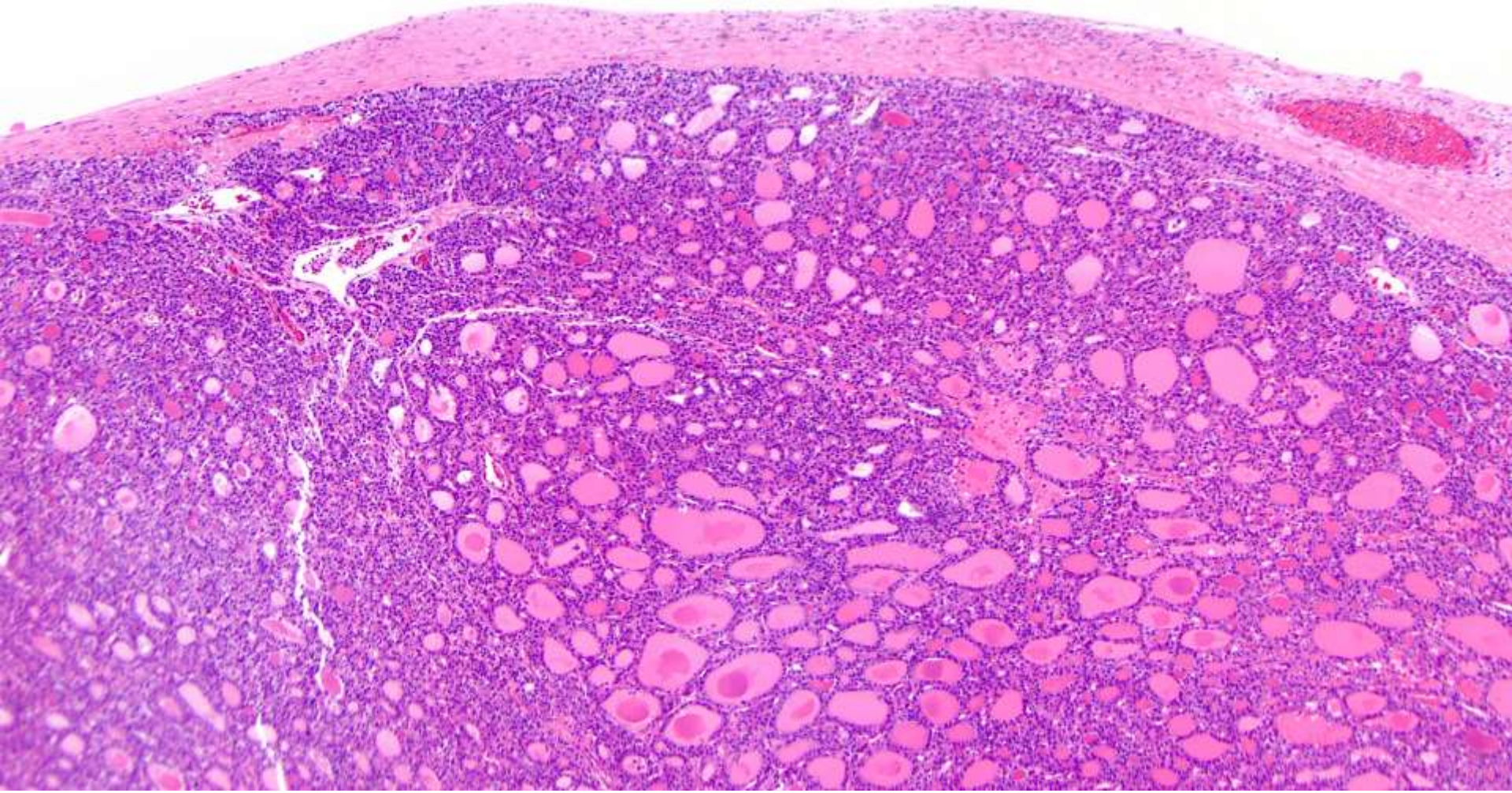

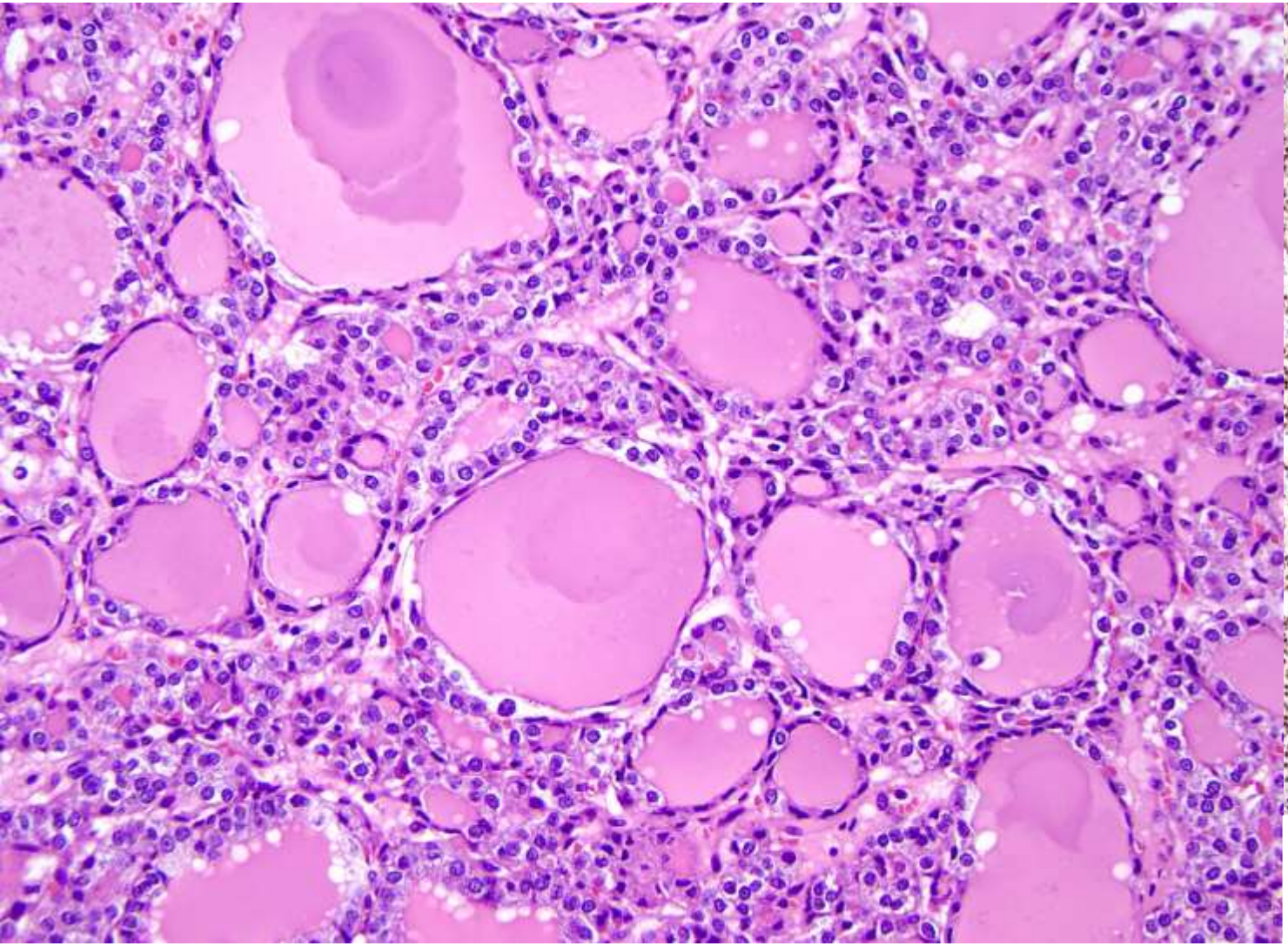

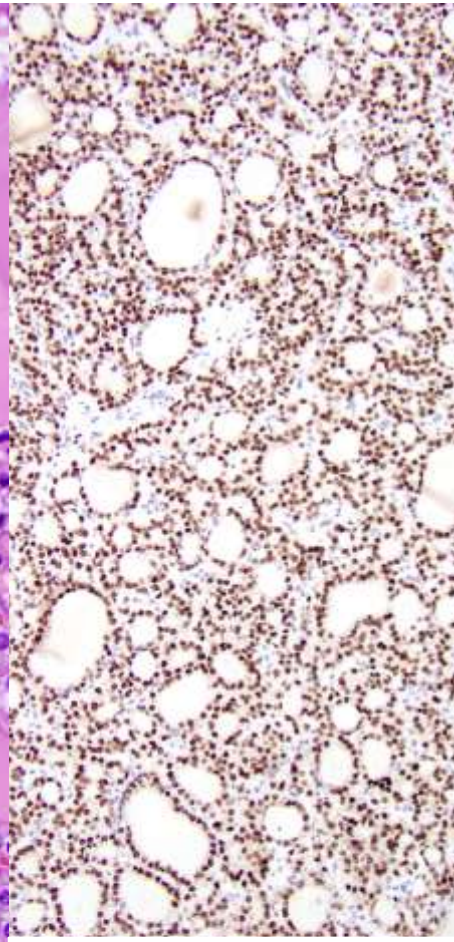

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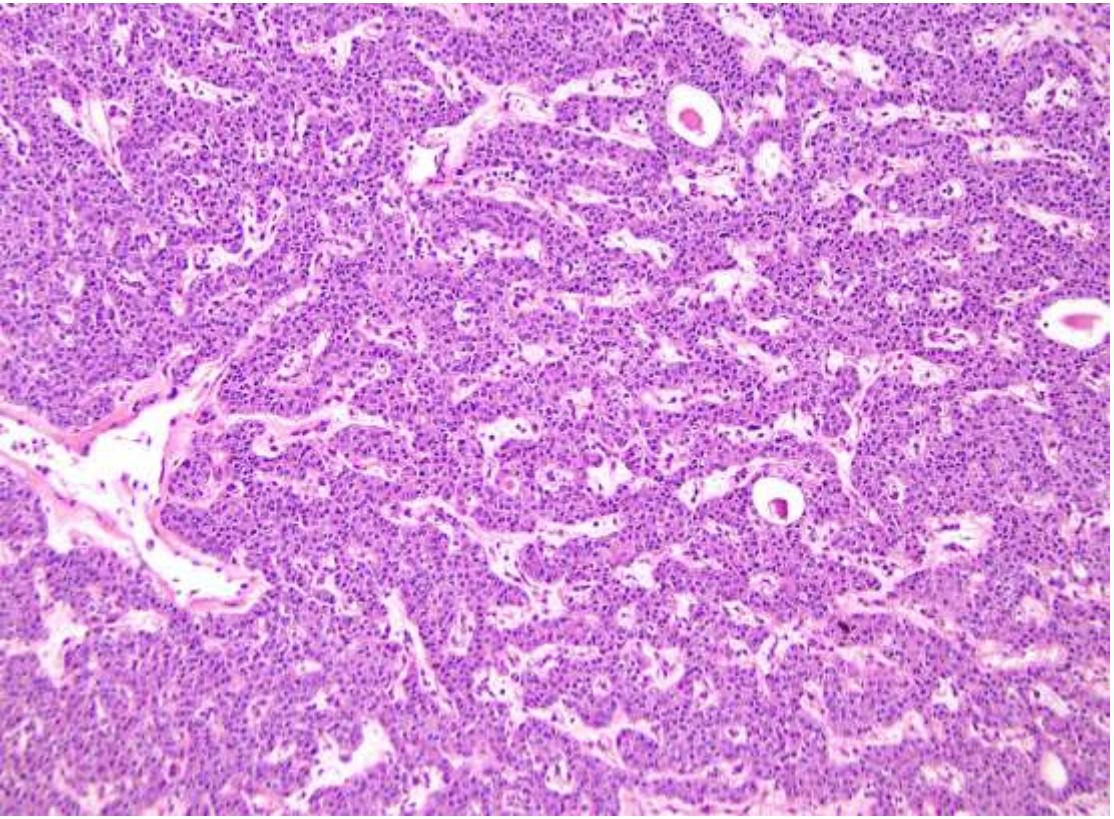

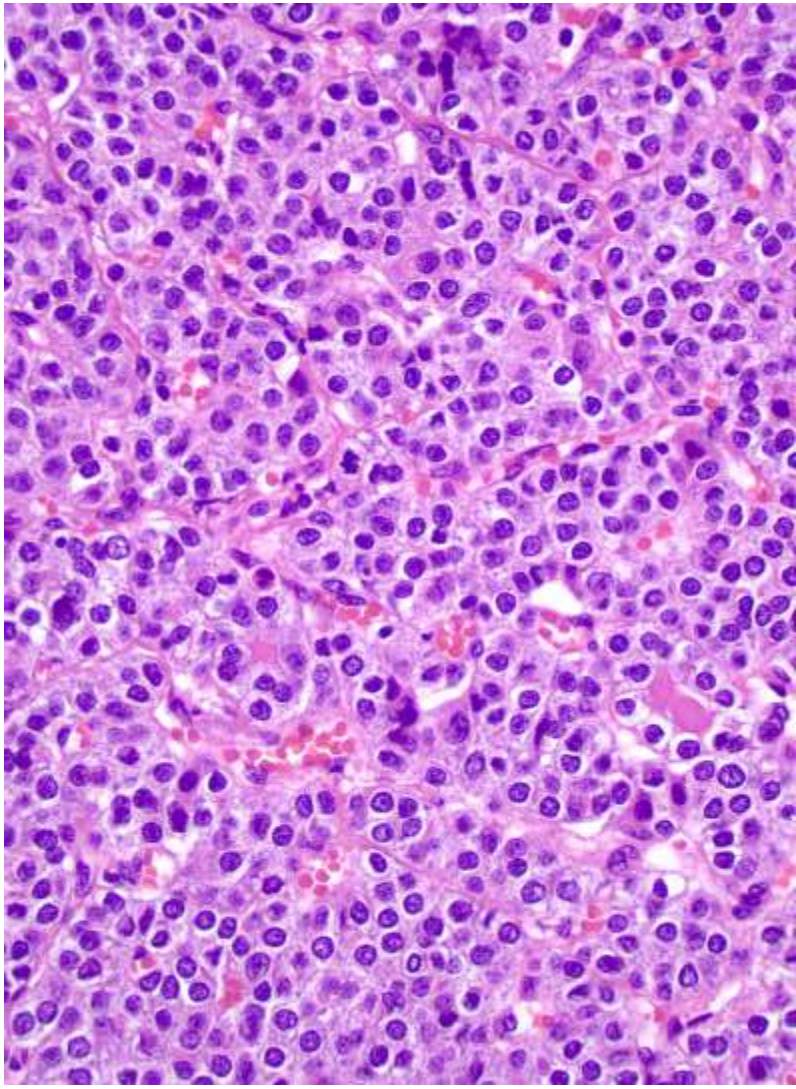

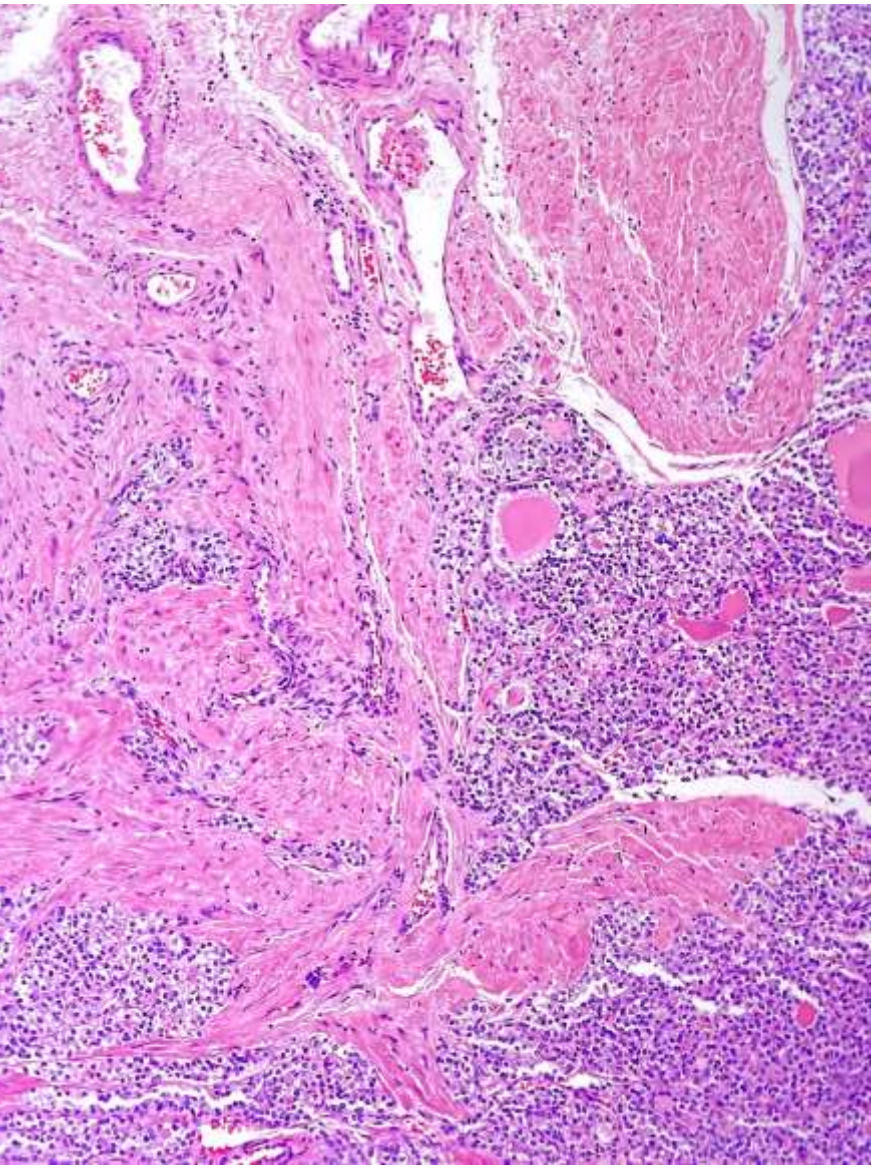

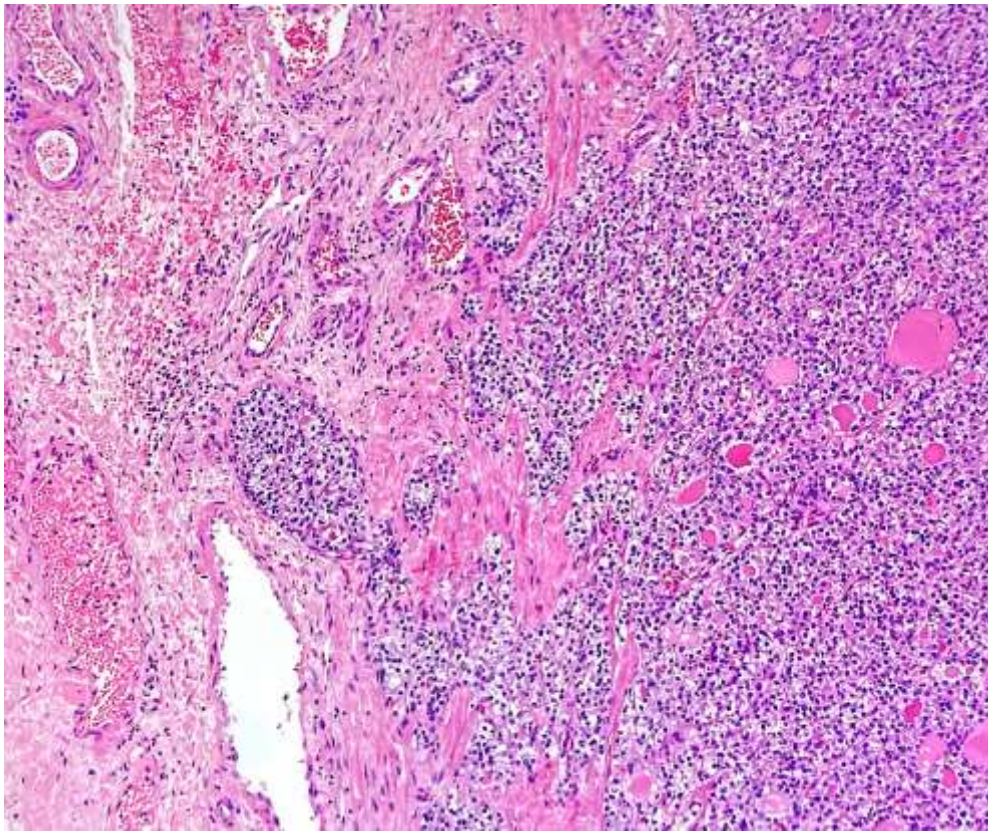

Additional information

- Mass discovered during a cesarean section
  - Bleeding at the edge of surgical incision
  - Anterior abdominal wall between the peritoneum and the rectus muscle
- Patient history of mature cystic teratoma, removed 5 years ago at another institution
  - Specimen reportedly received fragmented and reported to contain struma ovarii
  - No malignant elements were noted

Final Diagnosis

Follicular carcinoma of thyroid type, consistent with malignant struma ovarii

Malignant Struma Ovarii

- Struma ovarii: ~3% of teratoma; <<1% exhibit malignant transformation
- ~1/3 exhibit malignant biologic behavior: recurrence, extra-ovarian spread
- Follicular carcinoma histology is rare (3/87 cases in one study)
  - All were associated with malignant biologic behavior
- Malignant biologic behavior may be observed in the absence of overtly malignant histology
  - microfollicular and macrofollicular adenomas, normal thyroid pattern

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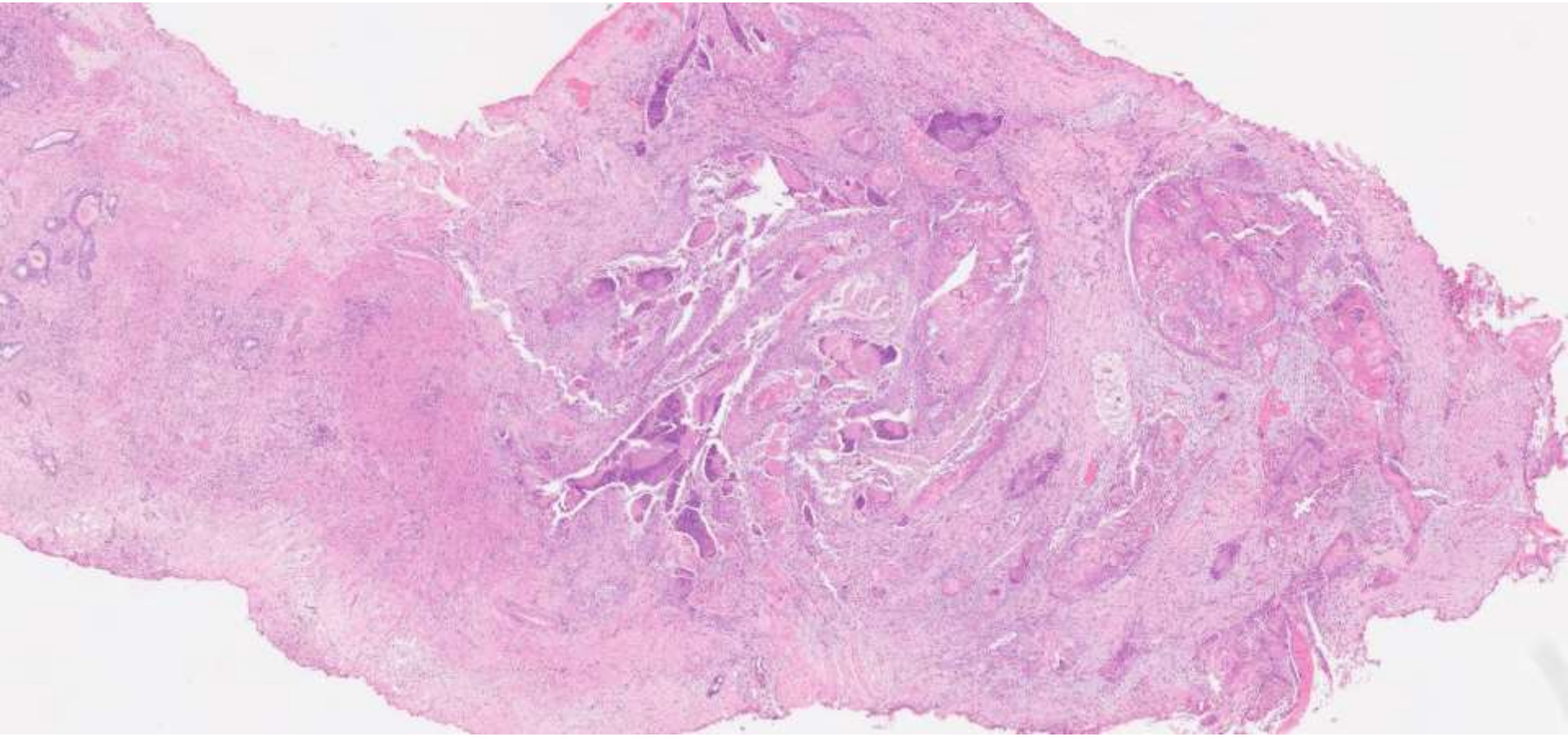
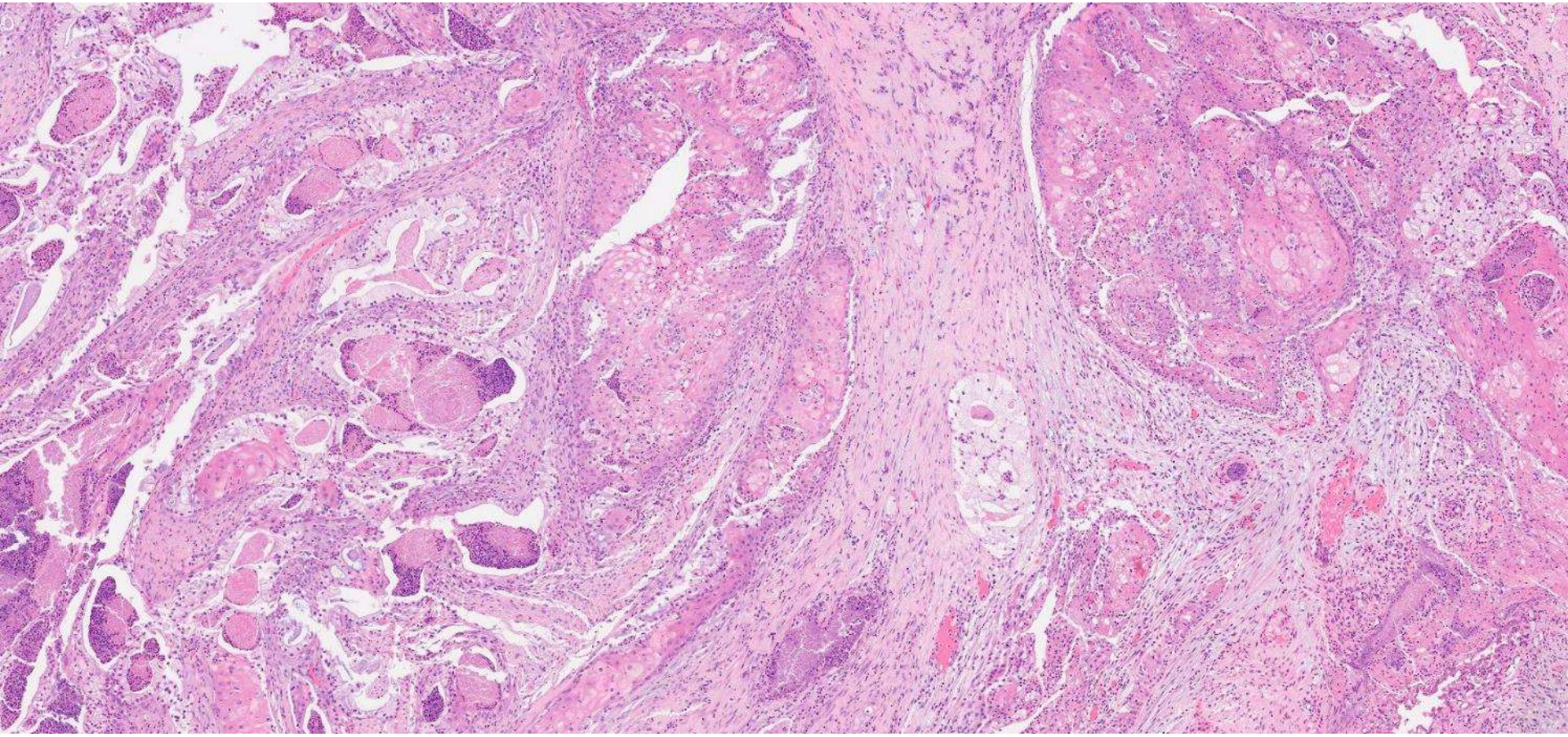
- Reference 2: Goffredo P, Sawka AM, Pura J, Adam MA, Roman SA, Sosa JA. Malignant struma ovarii: a population-level analysis of a large series of 68 patients. Thyroid. 2015 Feb;25(2):211-5. Epub 2014 Dec 5. PMID:25375817.

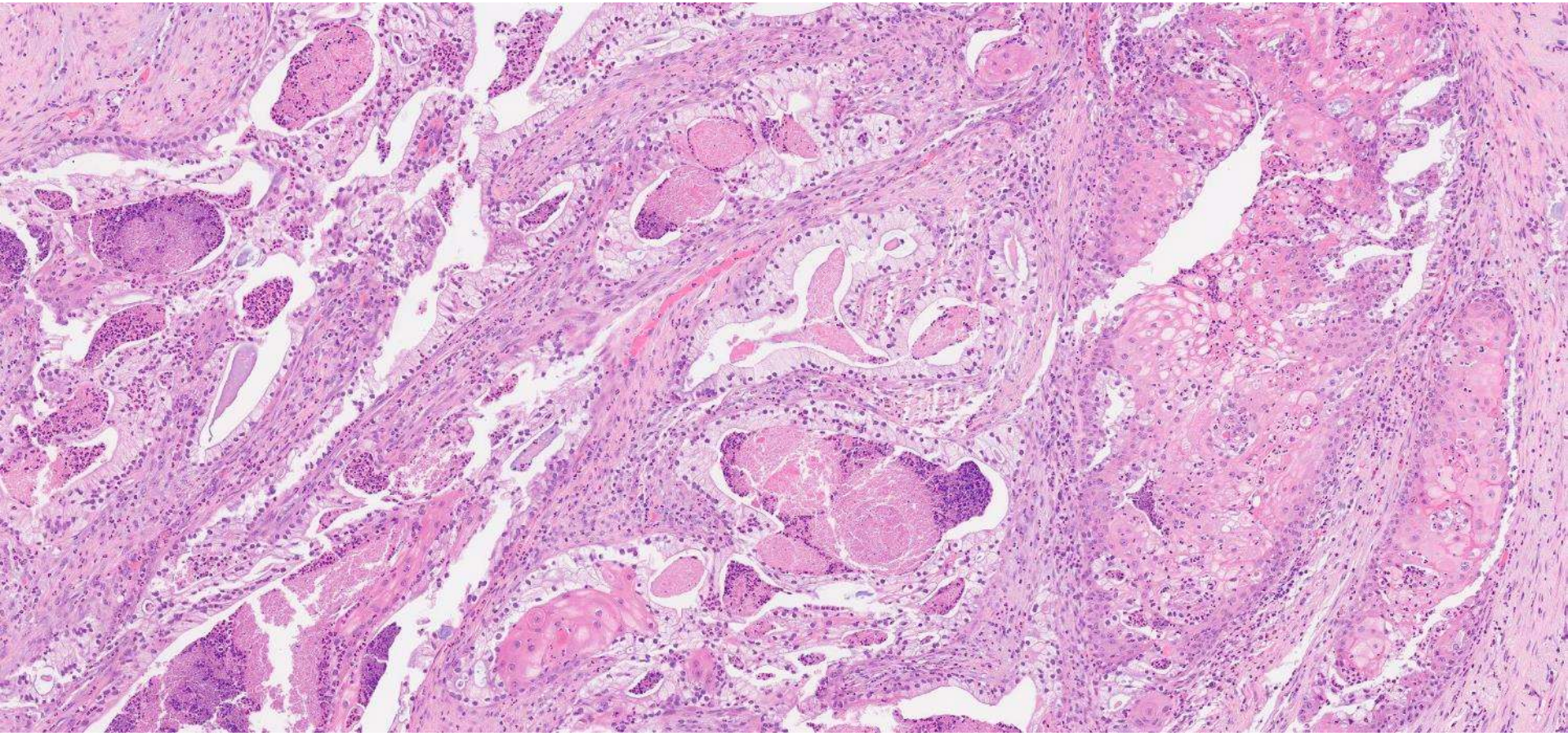
21-1005

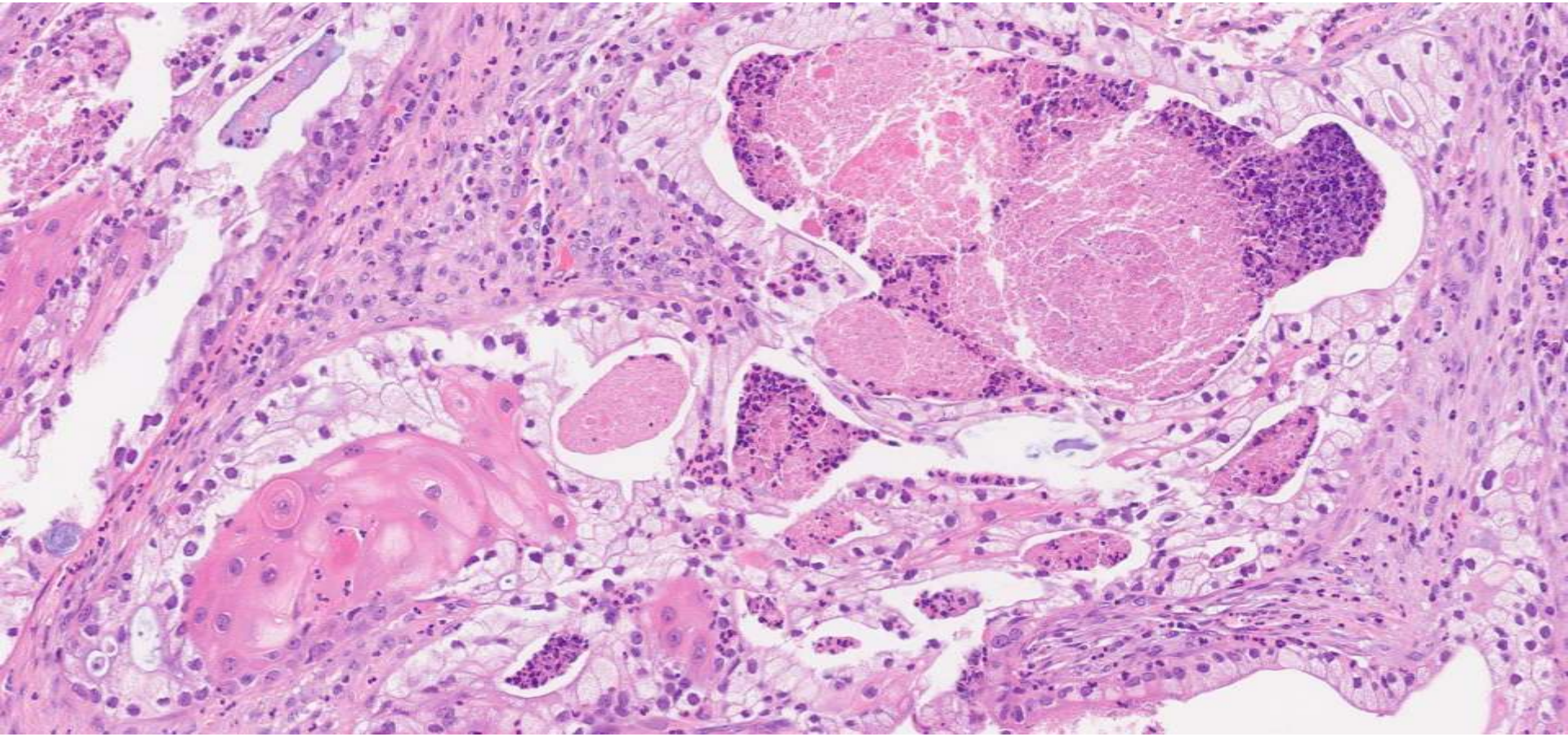
Ankur Sangoi; El Camino Hospital

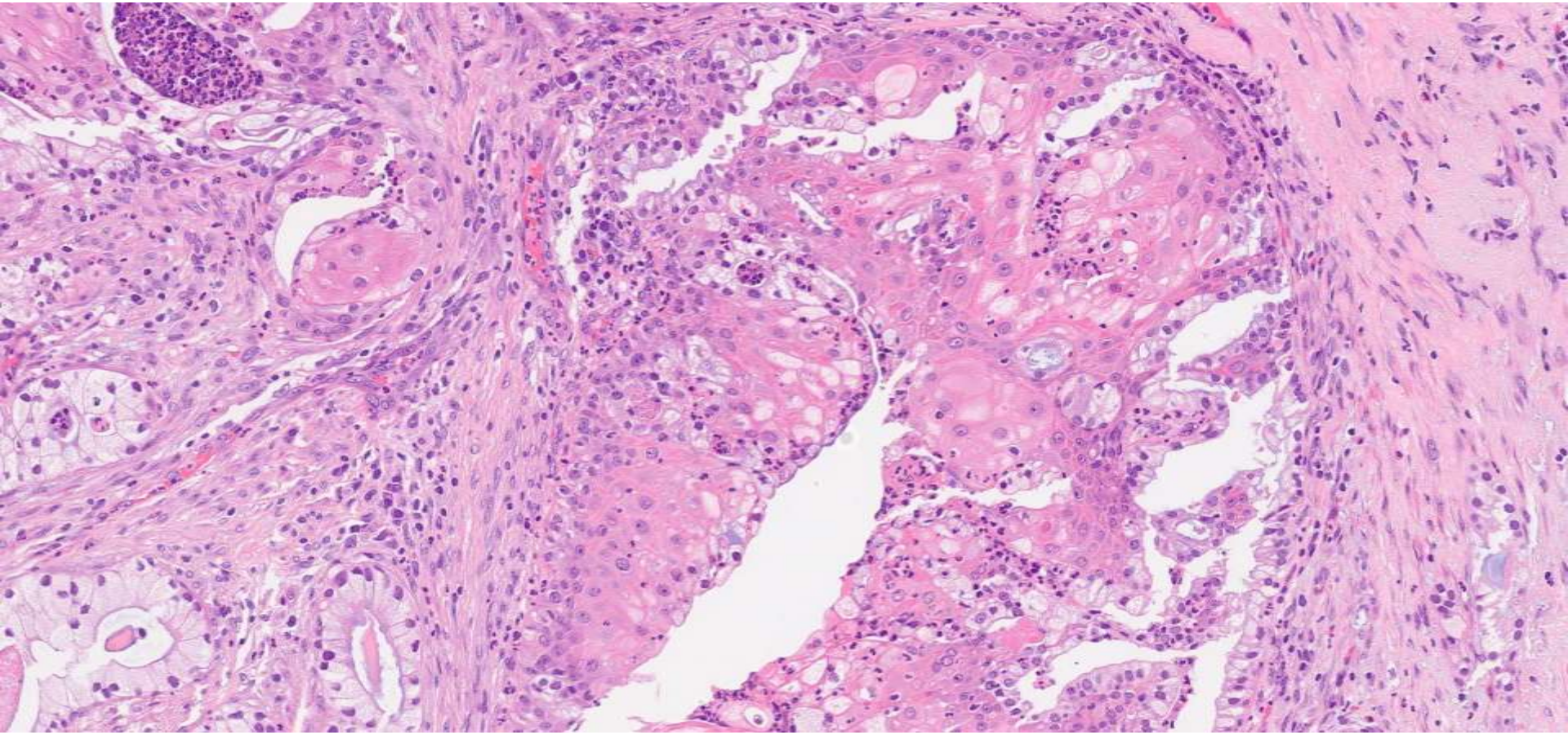
87-year-old F with BPH, undergoes TURP.

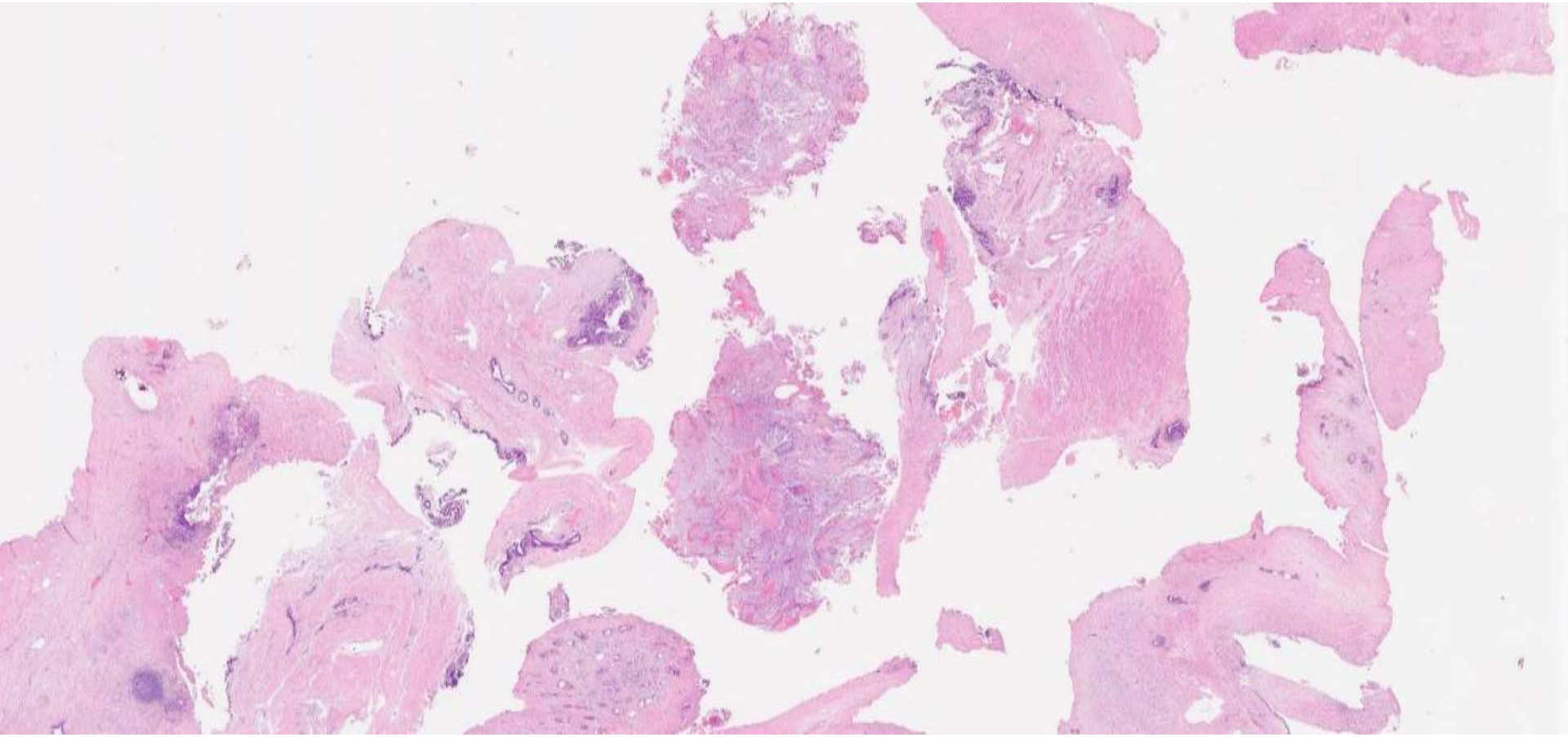


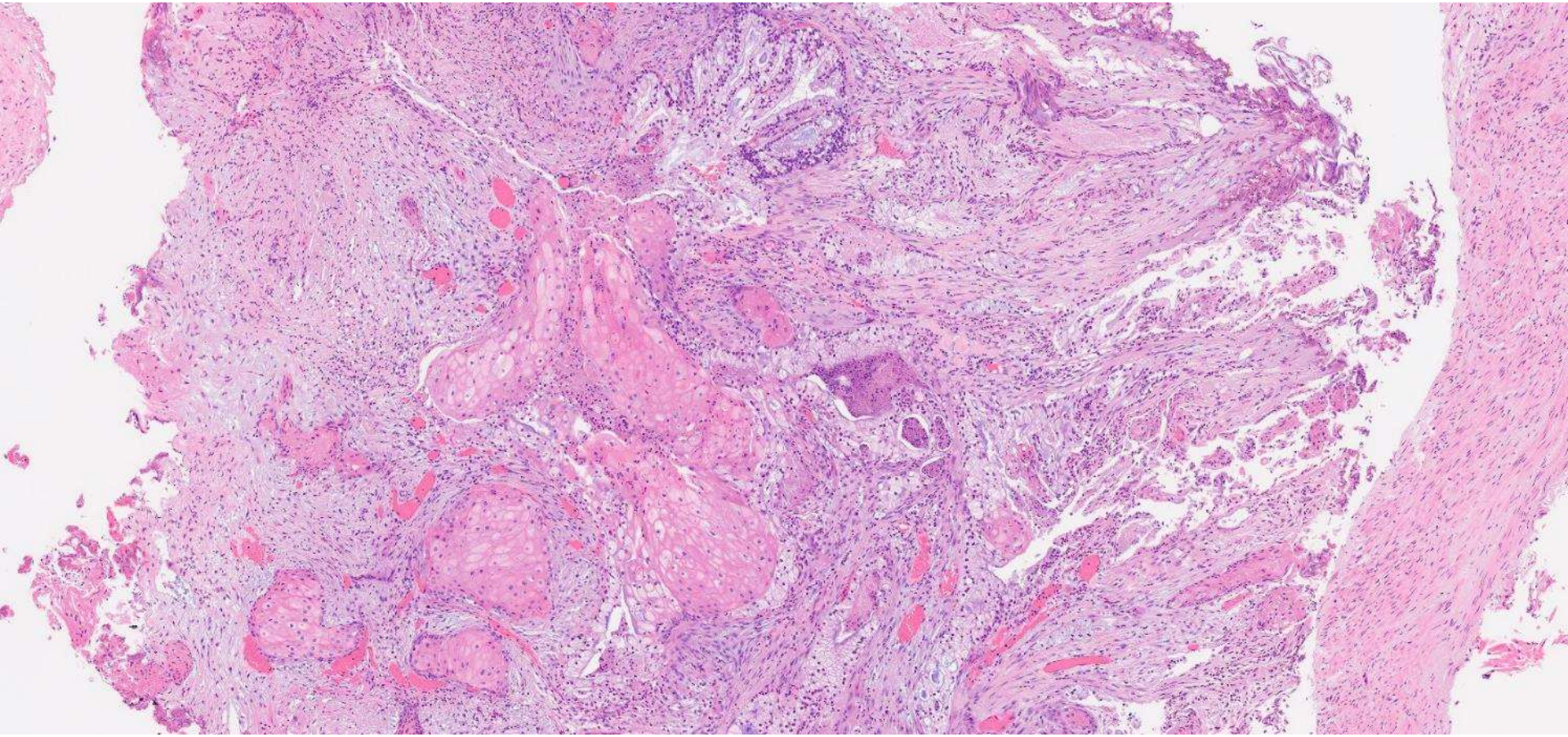


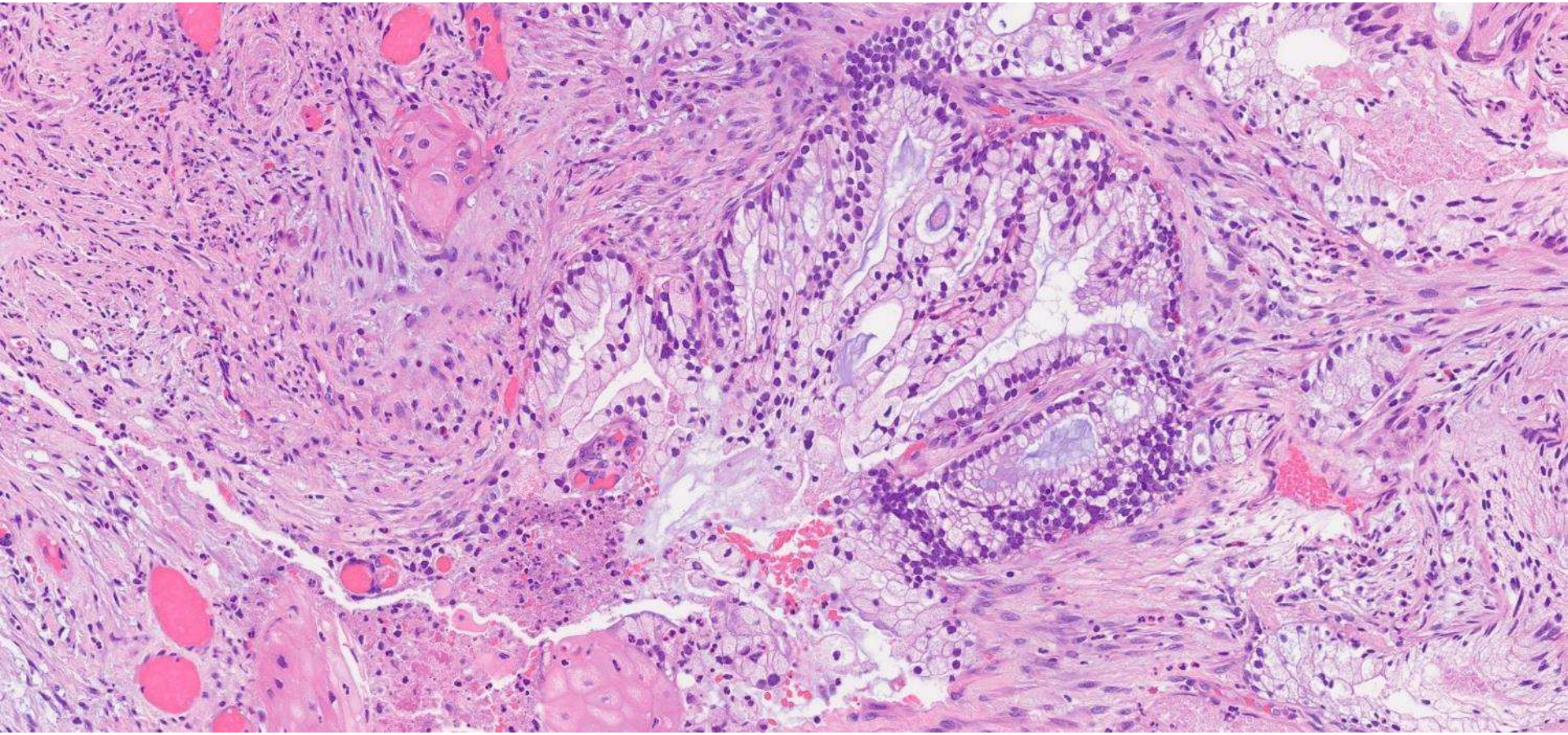


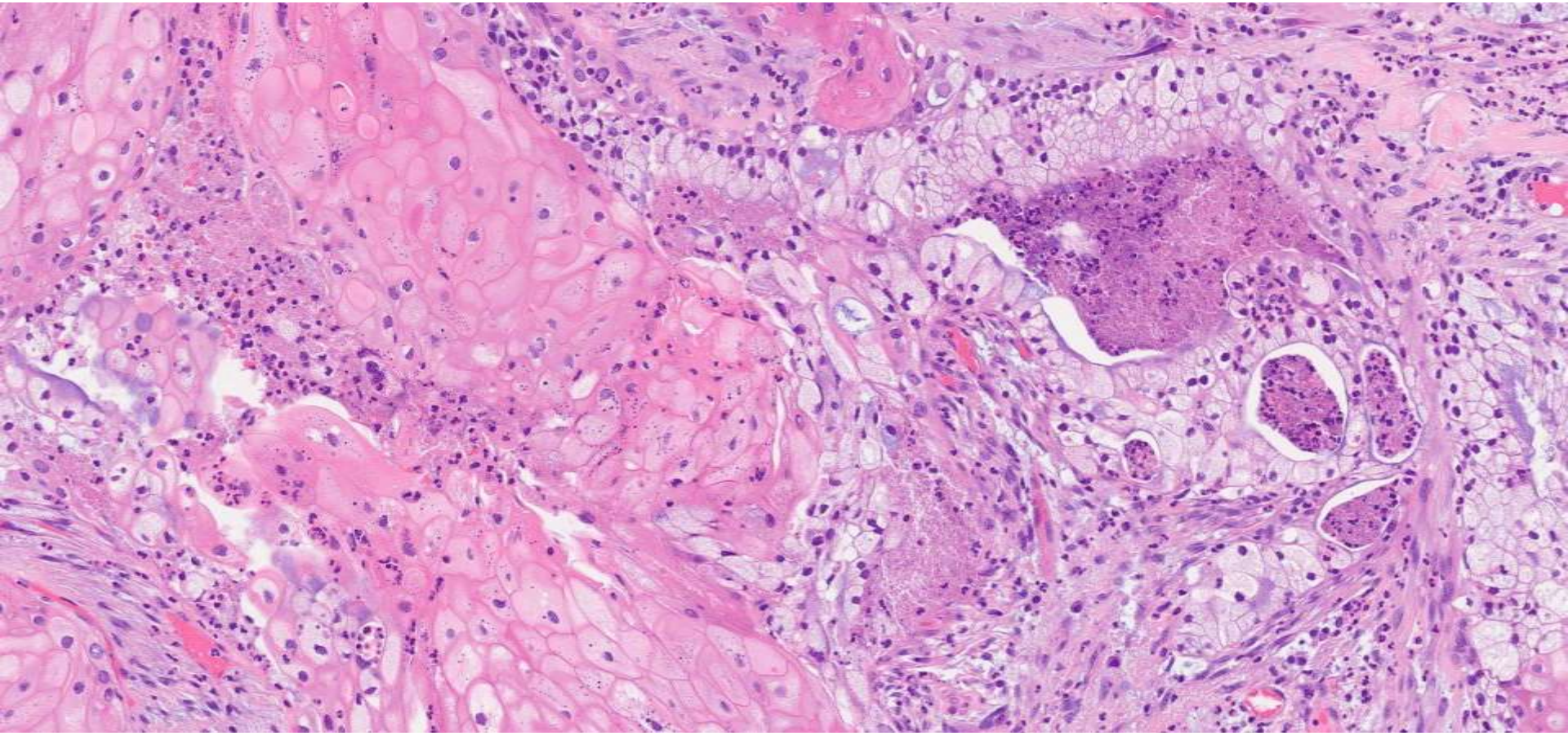








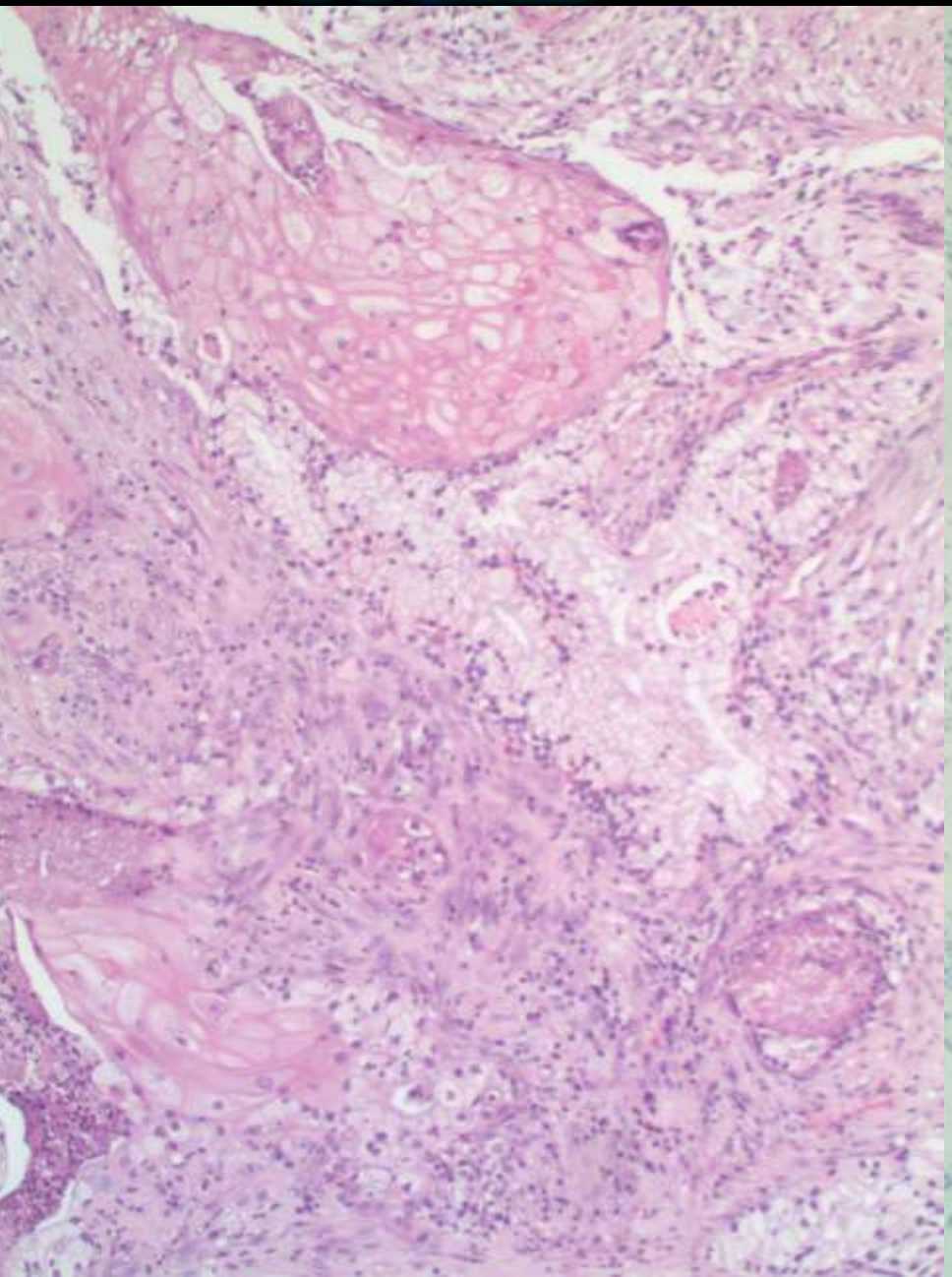




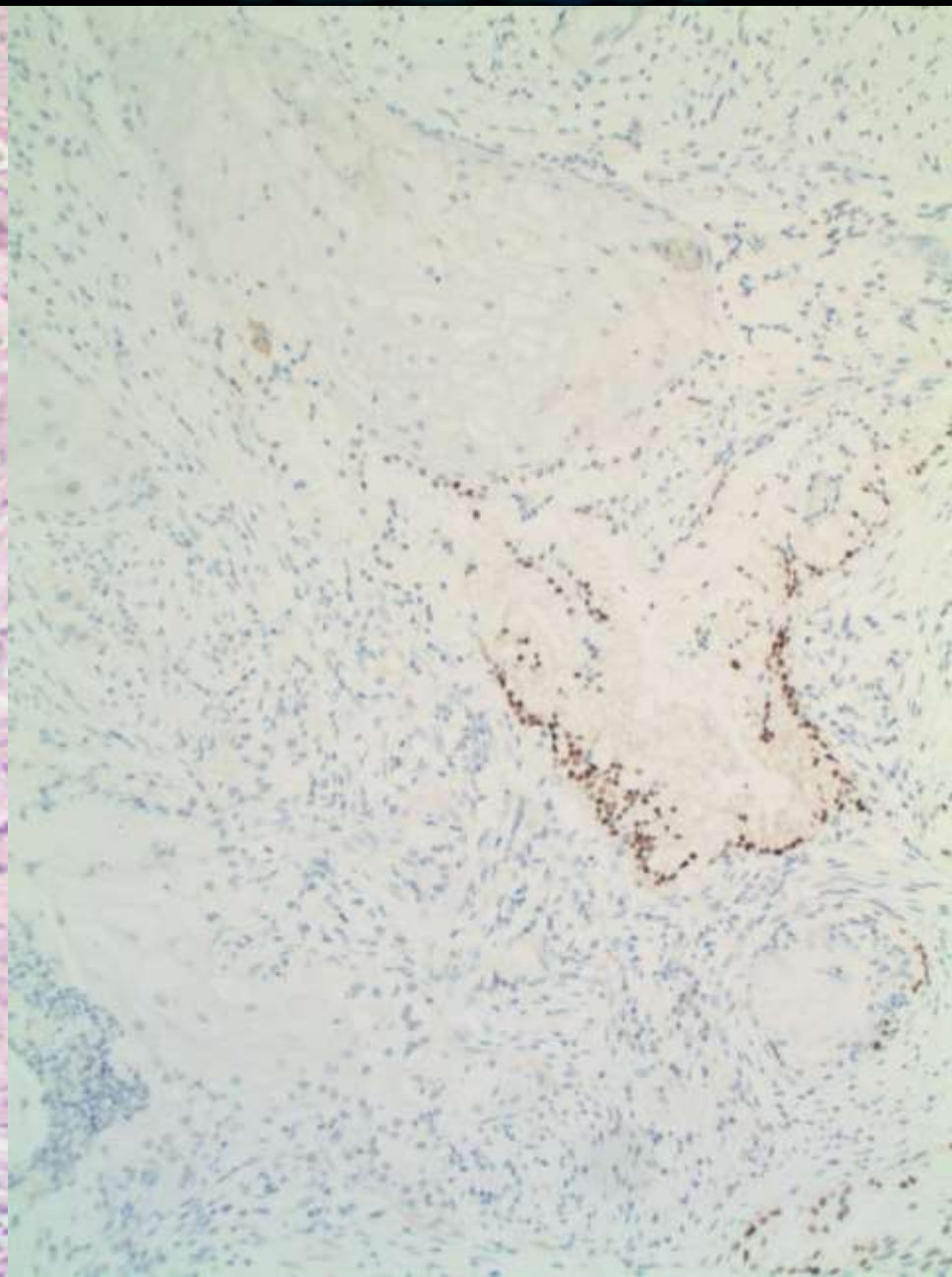
DDx

- Prostatic adenosquamous carcinoma
- Prostatic adenocarcinoma
- Prostatic squamous cell carcinoma
- Secondary prostatic involvement by squamous/urothelial carcinoma

H&E



NKX3.1



IHC summary

- **Glandular tumor elements:**

  POSITIVE: NKX3.1, PSAP, racemase

  NEGATIVE: PSA, p63, CK903

PCA with squamous differentiation

- **Uncommon!**
- **most cases occur in patients with prior PCA s/p XRT or hormone therapy**
  - Rarely can occur de novo
- **Genitourinary schistosomiasis also proposed**
- **CLINICAL:**
  - Serum PSA often normal
  - More aggressive than typical PCA; poor prognosis

IHC

- Squamous foci + for squamous markers
- Glandular elements + for prostatic markers

Prostate Carcinoma With Squamous Differentiation

An Analysis of 33 Cases

Anil V. Parwani, MD, PhD, J. D. Kronz, MD,* E. M. Genega, MD,† P. Gaudin, MD,† S. Chang, MD,† and J. I. Epstein, MD**

Background: Only sporadic cases of prostate carcinomas with squamous differentiation have been reported.

Design: The files of two institutions were reviewed for prostate cancers with squamous differentiation.

Results: A total of 33 cases were studied. The average age at diagnosis was 68 years (range 49–86 years). The most common presenting symptoms included bladder outlet obstruction and dysuria. Thirteen men had a positive digital rectal examination. Diagnosis was made by needle biopsy (n = 23); transurethral resection of the prostate (n = 5); needle and transurethral resection of the prostate (n = 1); transurethral resection of the bladder (n = 1); or biopsy of metastases (n = 3). In 21 of 33 cases, there was a prior diagnosis of adenocarcinoma of the prostate; 8 patients were treated with hormones, 4 were treated with radiation, and 1 received both radiation and hormone therapy. Of the 12 men without a prior diagnosis of adenocarcinoma, 2 patients had received hormonal therapy for benign prostatic hyperplasia. Eight of 33 cases were pure squamous carcinomas. The remaining cases were adenosquamous carcinoma (n = 16), adenosquamous and urothelial carcinoma (n = 3), and adenosquamous carcinoma and sarcoma (n = 6). The squamous carcinoma component of these mixed cases averaged 40% of the tumor volume (range 5%–95%) and had a range of cytologic atypia (mild [n = 6], moderate [n = 17], severe [n = 10]). In the 25 cases with adenocarcinoma, the glandular component tended to be high-grade (Gleason grade >6 in 19 cases). Immunohistochemistry for prostate specific acid phosphatase and prostate specific antigen was positive in a large percentage of the adenocarcinomas (85% and 75%, respectively) and only very focally positive in 12% of the squamous carcinomas. 34βE12 was diffusely positive in >95% of the squamous carcinomas and only focally positive in <10% of the adenocarcinomas. Cytokeratins 7 and 20 did not differentiate the squamous and adenocarcinoma components. Follow-up was available on 25 of 33 cases, with the average survival being 24 months (range 0–63 months).

Conclusion: Squamous differentiation in prostate cancer is uncommon, often but not necessarily arising in the setting of prior hormone or radiation therapy, and is associated with a poor prognosis. In addition to pure squamous cell carcinoma and adenosquamous cancer, other patterns may be seen. Whereas the adenocarcinoma component is typically high grade, the squamous component has a wide range of differentiation.

Key Words: prostate, squamous, radiation, hormonal therapy

(*Am J Surg Pathol* 2004;28:651–657)

While adenocarcinoma is the most common type of carcinoma of the prostate, squamous cell carcinoma of the prostate is extremely rare.[5,9,11–13,16] In the majority of the cases of squamous cell carcinoma of the prostate described in the literature, the patients present initially with prostatic adenocarcinoma and several years later present with pure squamous cell carcinoma or squamous cell carcinoma mixed with other components, usually following therapy. When the patients presented with squamous cell carcinoma, the usual clinical presentation was of urinary obstructive symptoms.[12] The therapeutic response to the usual hormonal manipulation is not good with these tumors and prognosis is worse, making squamous cell carcinoma of the prostate a highly aggressive tumor that responds poorly to any mode of therapy.[8,14] In the present report, we describe the clinical and pathologic features of a large series of prostate carcinoma with squamous differentiation.

METHODS AND MATERIALS

TABLE 1. Morphology Stratified by Prior History of Adenocarcinoma

	Prior Adenocarcinoma (n = 21)	No Prior Adenocarcinoma (n = 12)	Total [no. (%)]
Pure squamous cell	3	5	8 (24)
Adenosquamous	12	4	16 (49)
Adenosquamous and UC	1	2	3 (9)
Adenosquamous and sarcoma	5	1	6 (18)
Total	21	12	33 (100)

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Histopathology

Histopathology 2020, 77, 890–899. DOI: 10.1111/his.14205

Gene fusion characterisation of rare aggressive prostate cancer variants—adenosquamous carcinoma, pleomorphic giant-cell carcinoma, and sarcomatoid carcinoma: an analysis of 19 cases

Conclusions: *ERG* fusions are present in these rare prostate cancer variants with a frequency close to that in conventional prostate cancer (9/19, 47%). ERG immunohistochemistry usually detects rearrangement in the adenocarcinoma, but is less sensitive for the variant histology, with weak to negative staining. Adenosquamous and sarcomatoid variants can, particularly, occur together. Molecular assessment may be an additional tool in selected cases to confirm the prostatic origin of unusual tumours. The presence of two *BRAF* rearrangements suggests that this gene fusion may be enriched in this setting, as RAF kinase fusions have been previously reported in 1–2% of prostate cancers.

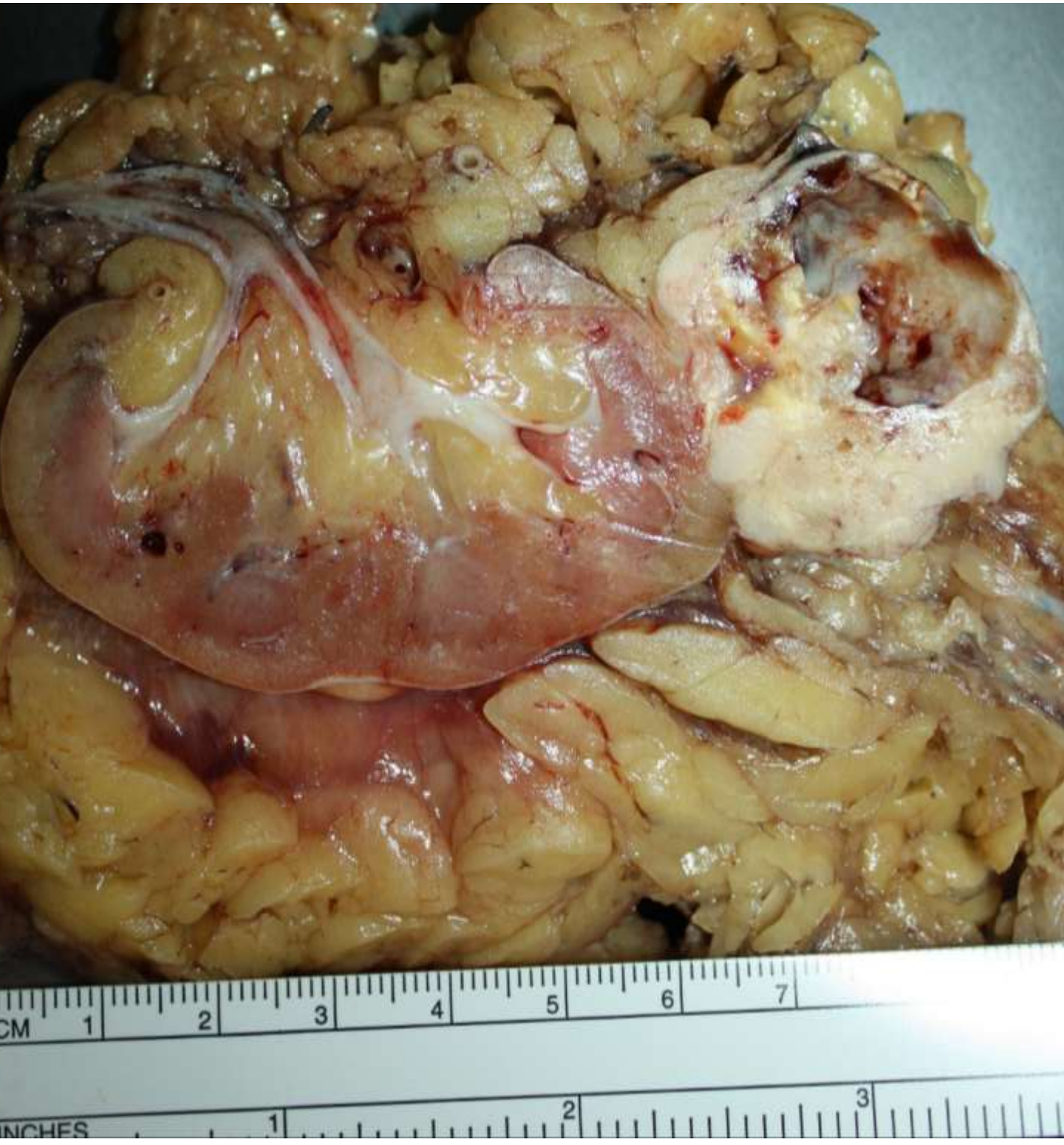
Table 1. Types of divergent differentiation and overall molecular status

Patient	Location of divergent differentiation	Type of divergent differentiation	Overall molecular status	FISH for *BRAF*	FISH for *ERG*	NGS
1	Lymph node metastasis	Adenosquamous	*ERG*	Negative	5′ deletion	Not done
2	Lymph node metastasis and perirectal mass	Adenosquamous and sarcomatoid	*BRAF*	Positive	Negative	*FAM131A–BRAF* fusion
3	Prostate	Sarcomatoid	Negative	Negative	Negative	Quality control failed × 2
4	Retroperitoneal metastasis	Pleomorphic giant cell	*BRAF*	Positive + aneuploid	Negative	*SND1–BRAF* fusion
5	Prostate/bladder	Pleomorphic giant cell	Negative	Negative	Negative	Not done
6	Prostate	Sarcomatoid	*ERG*	Negative	Not done	*TMPRSS2–ERG* fusion
7	Prostate	Adenosquamous	*ERG*	Negative	Not done	*TMPRSS2–ERG* fusion
8	Prostate	Adenosquamous and sarcomatoid	*ERG*	Negative	Not done	*TMPRSS2-ERG* fusion
9	Prostate/bladder neck	Sarcomatoid	Negative	Negative	Negative	Quality control failed
10	Prostate	Adenosquamous and sarcomatoid	Negative	Negative	Negative	Quality control failed
11	Prostate	Pleomorphic giant cell	Negative	Negative	Negative	Negative
12	Prostate	Adenosquamous and sarcomatoid	*ERG*	Not done	Not done	*TMPRSS2–ERG* fusion
13	Prostate	Sarcomatoid	Negative	Negative	Negative	Negative
14	Prostate	Pleomorphic giant cell	Negative	Negative	Negative	Negative
15	Prostate	Pleomorphic giant cell	*ERG*	Not done	Not done	*TMPRSS2–ERG* fusion
16	Prostate	Sarcomatoid	Negative	Negative	Negative	Quality control failed
17	Prostate/bladder neck	Sarcomatoid and pleomorphic giant cell	*ERG*	Negative	5′ deletion	Negative
18	Femoral head metastasis	Adenosquamous	*ERG*	Not done	Failed	*GRHL2–ERG* fusion
19	Prostate	Pleomorphic giant cell	*ERG*	Not done	Not done	*TMPRSS2–ERG* fusion

21-1006

Ankur Sangoi; El Camino Hospital

81-year-old F with 4.7cm renal mass, radical nephrectomy performed.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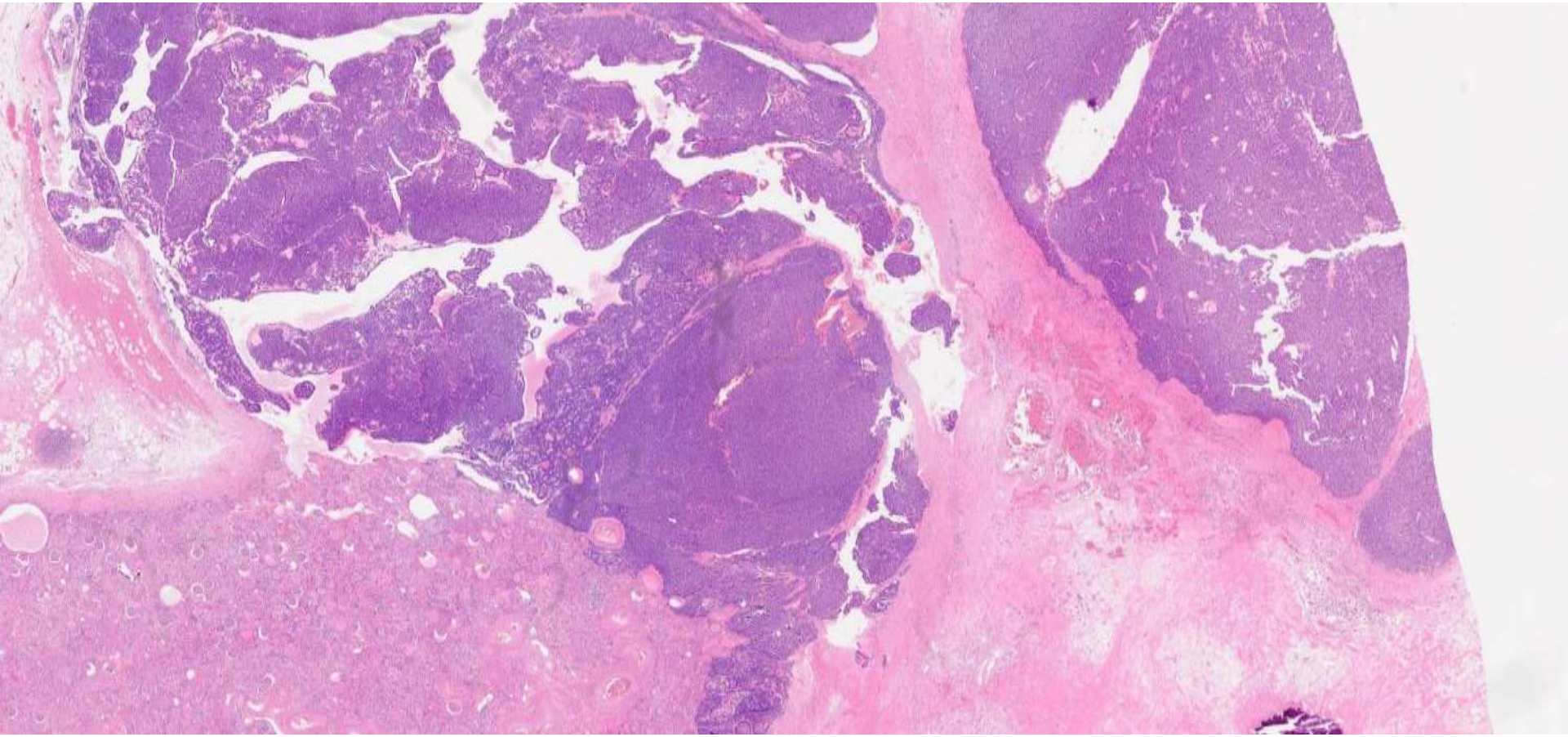
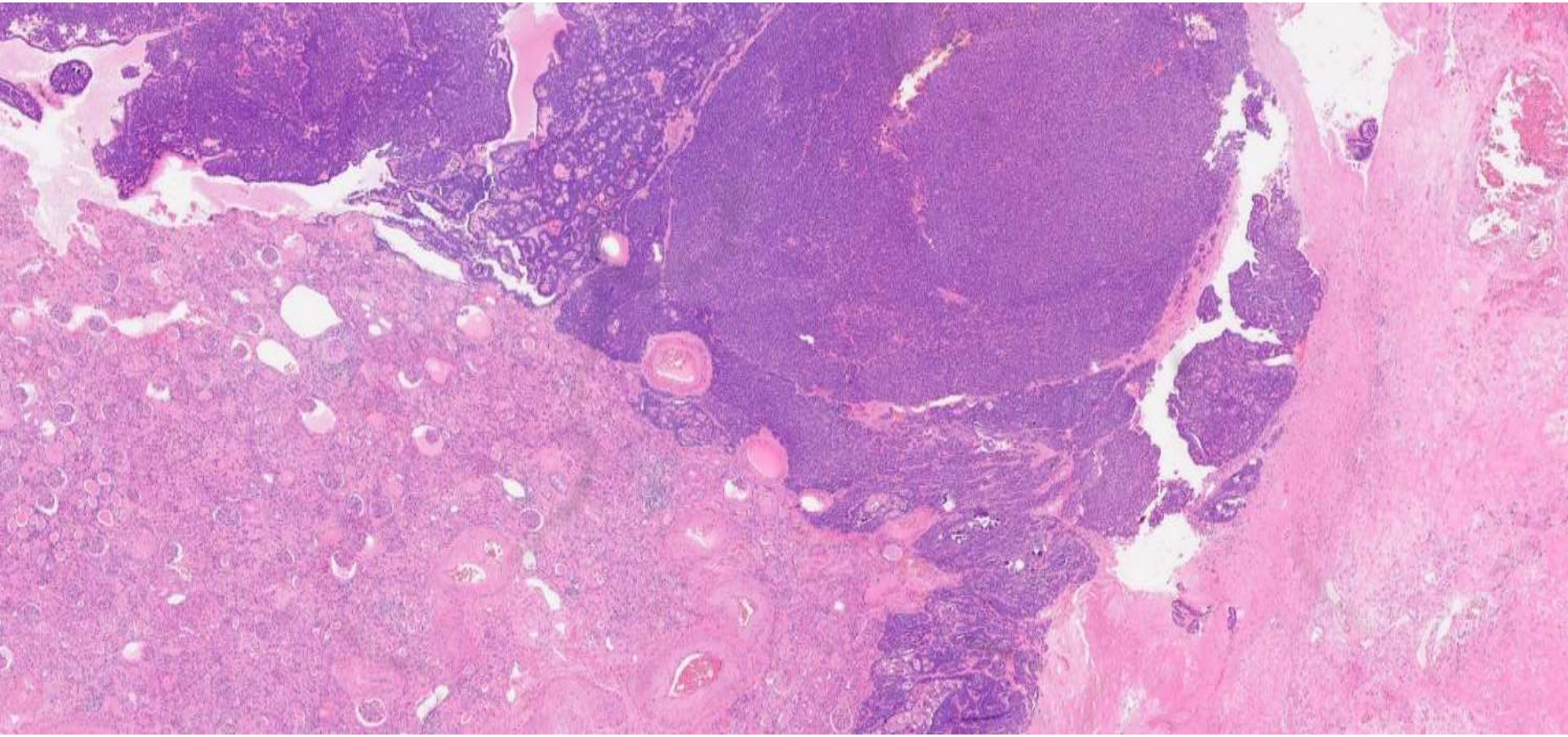
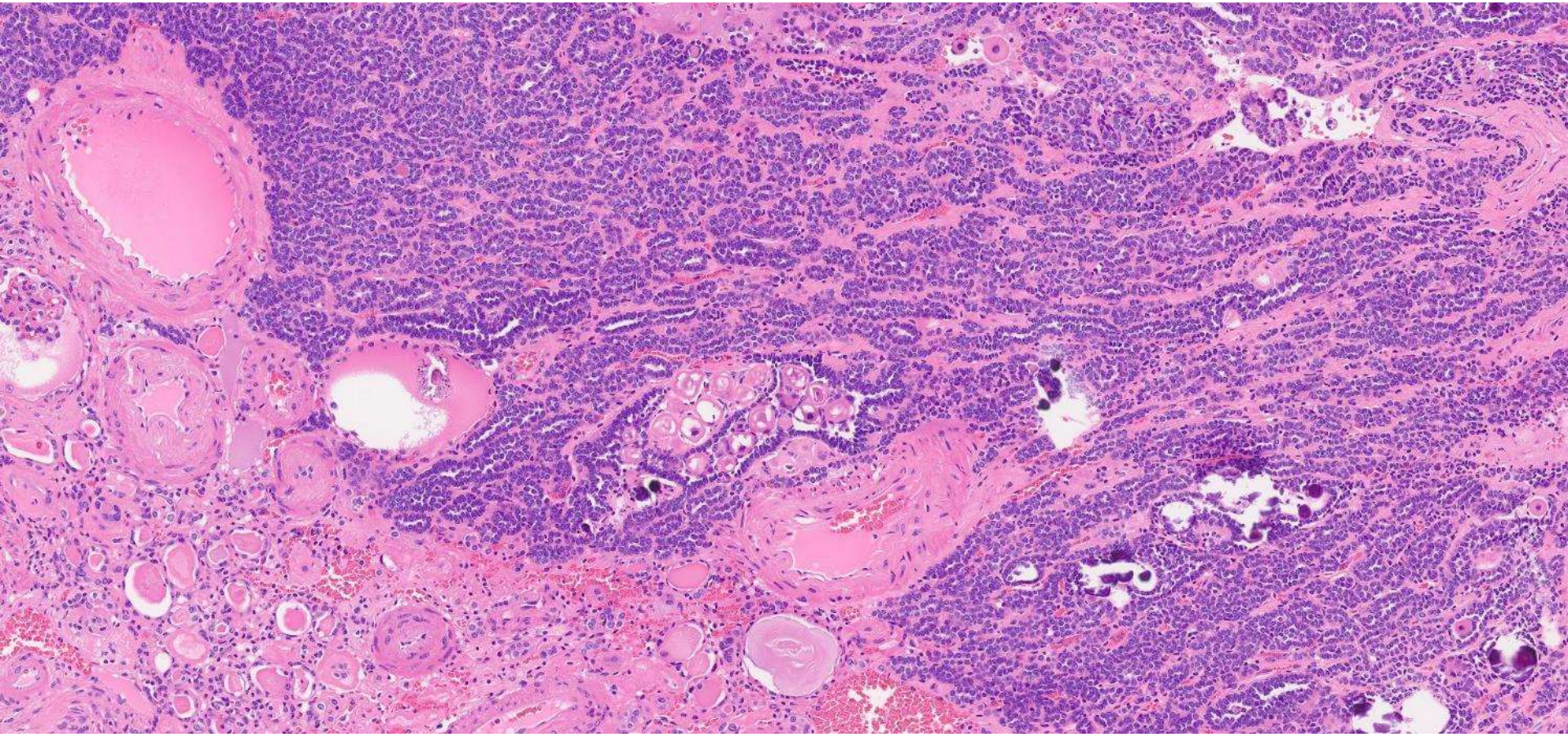
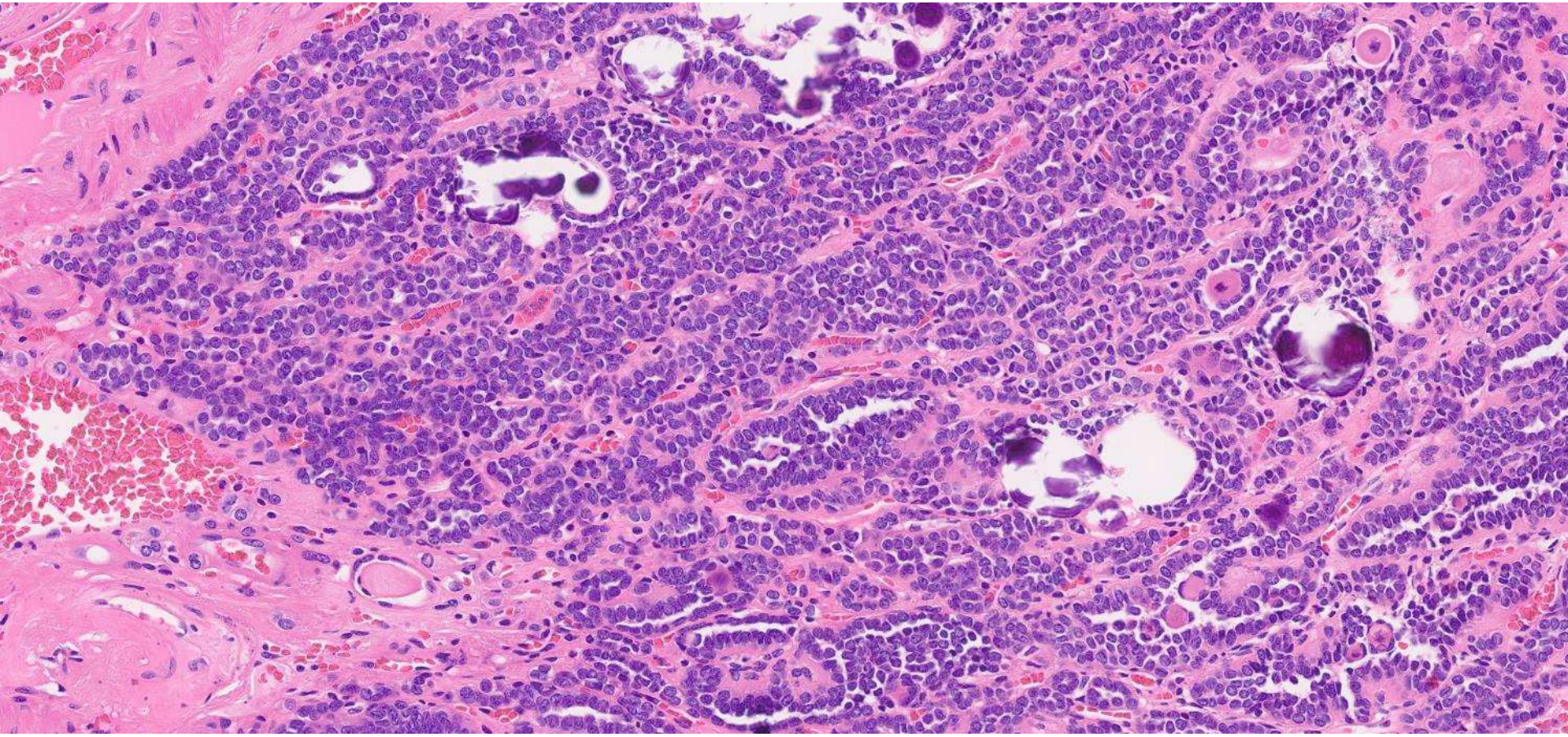
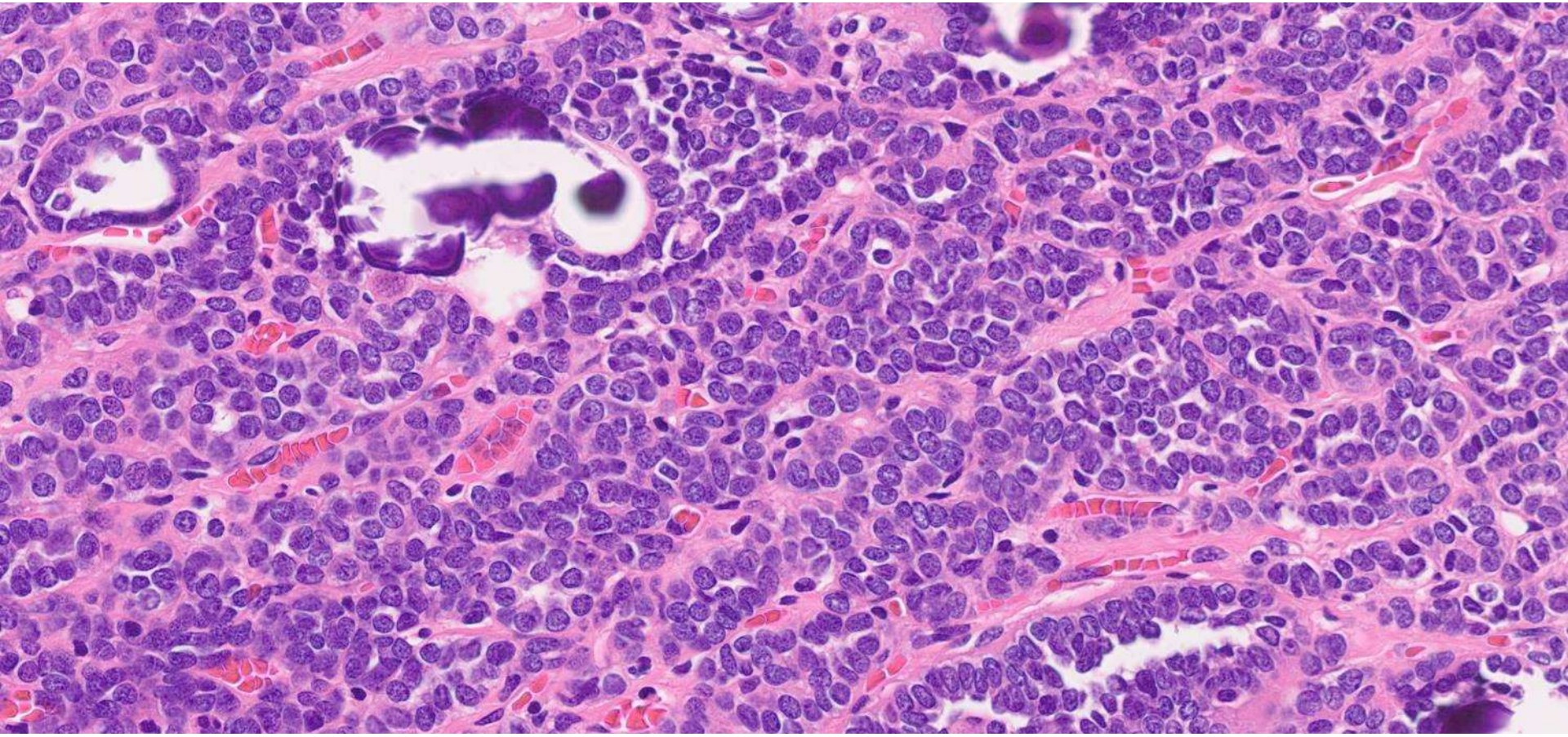
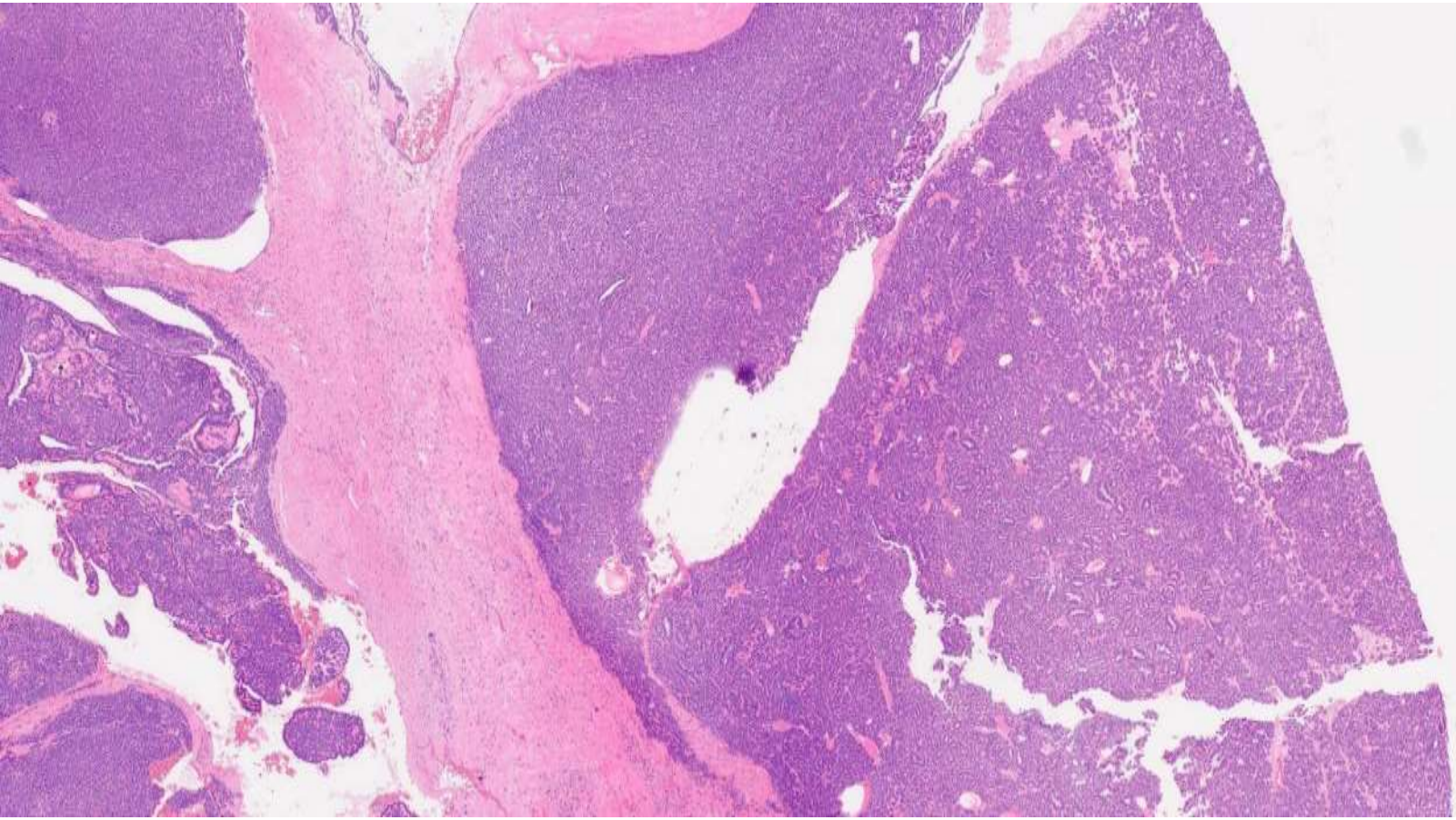


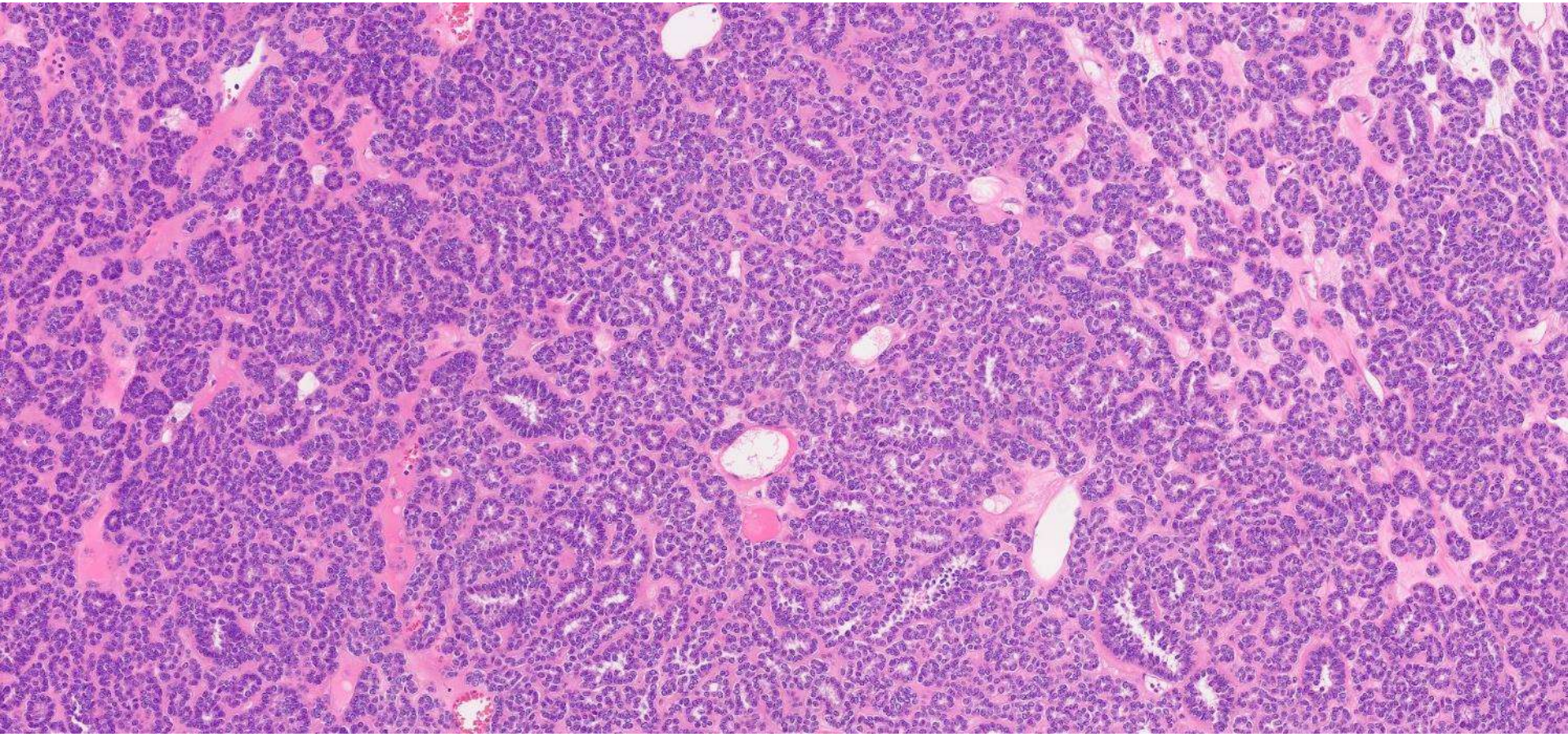


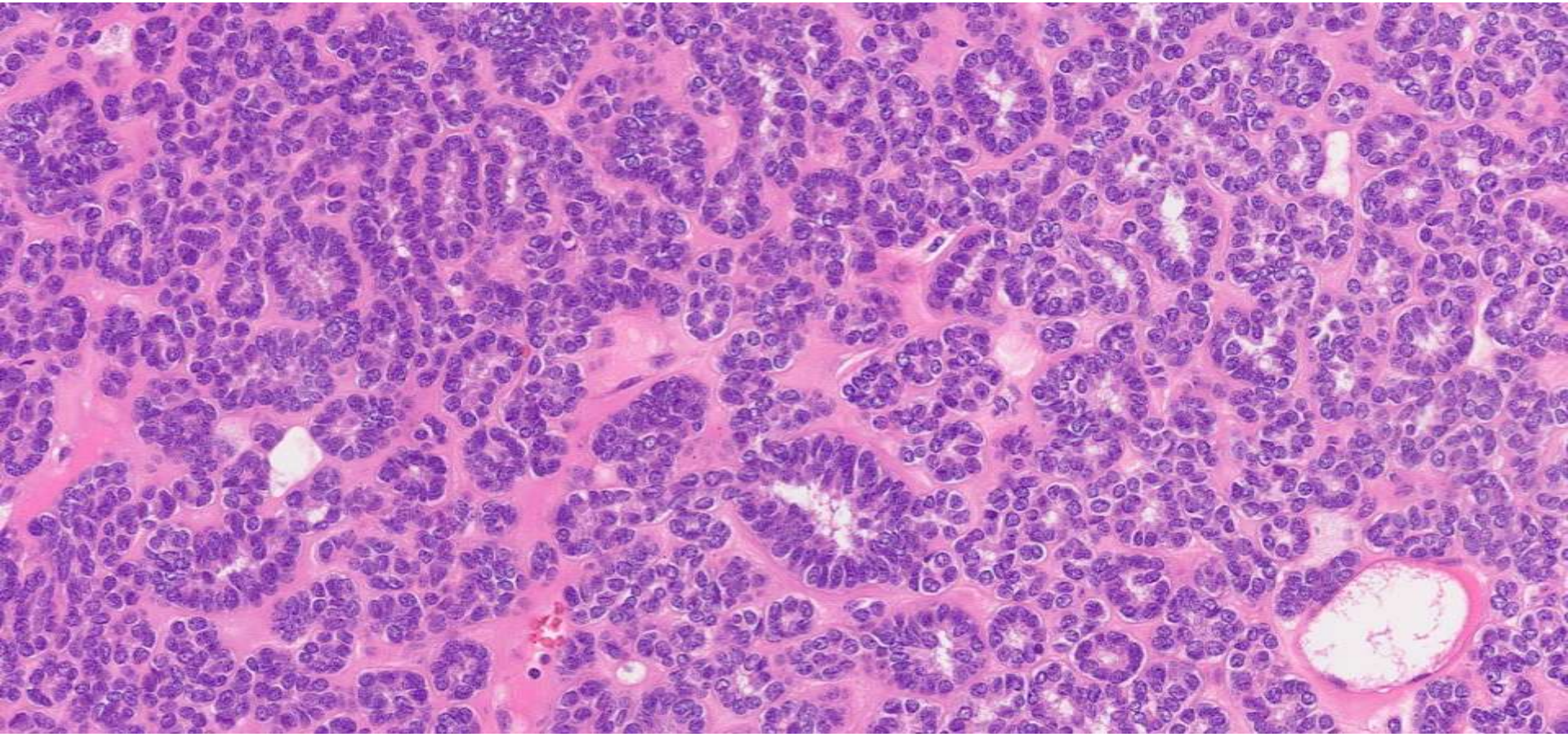


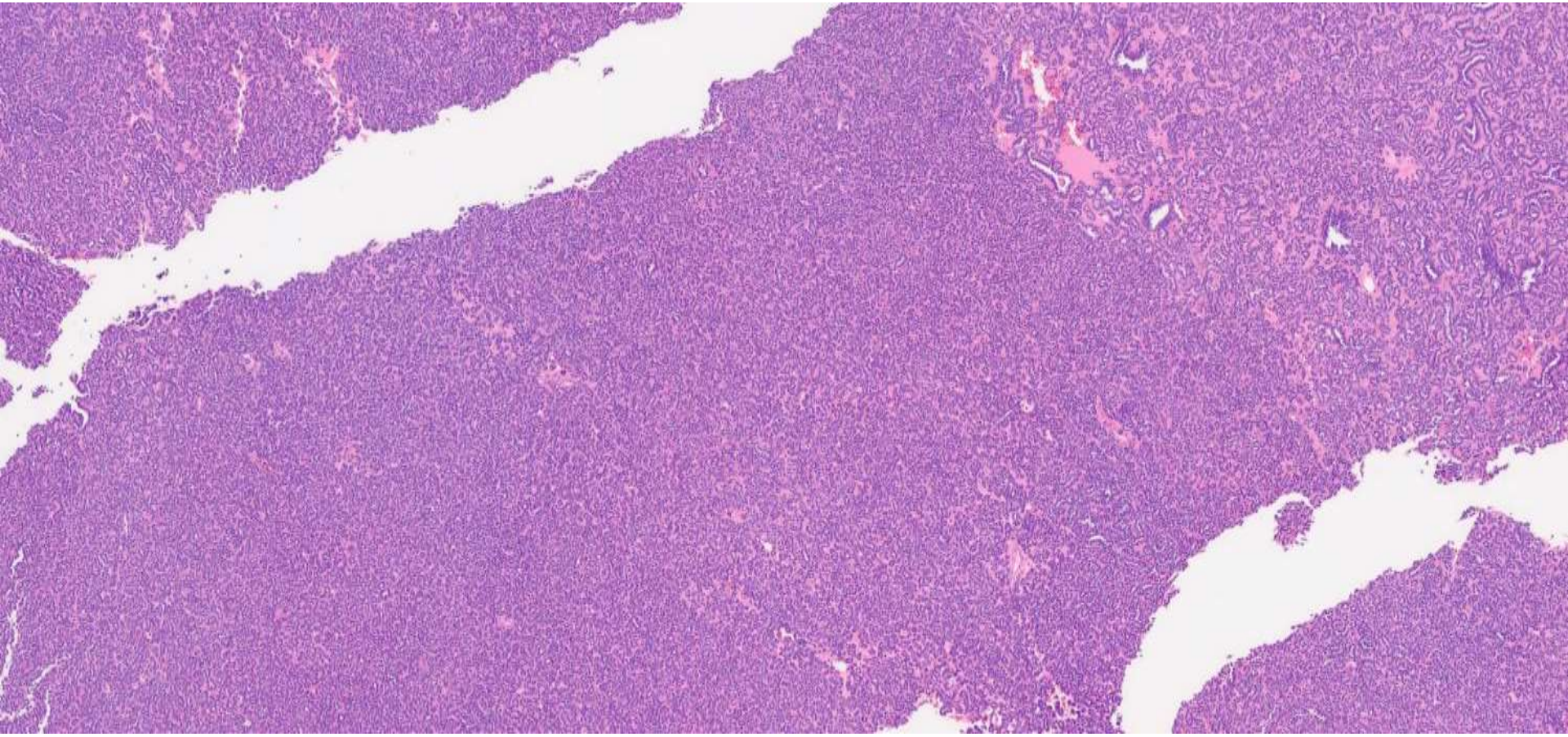


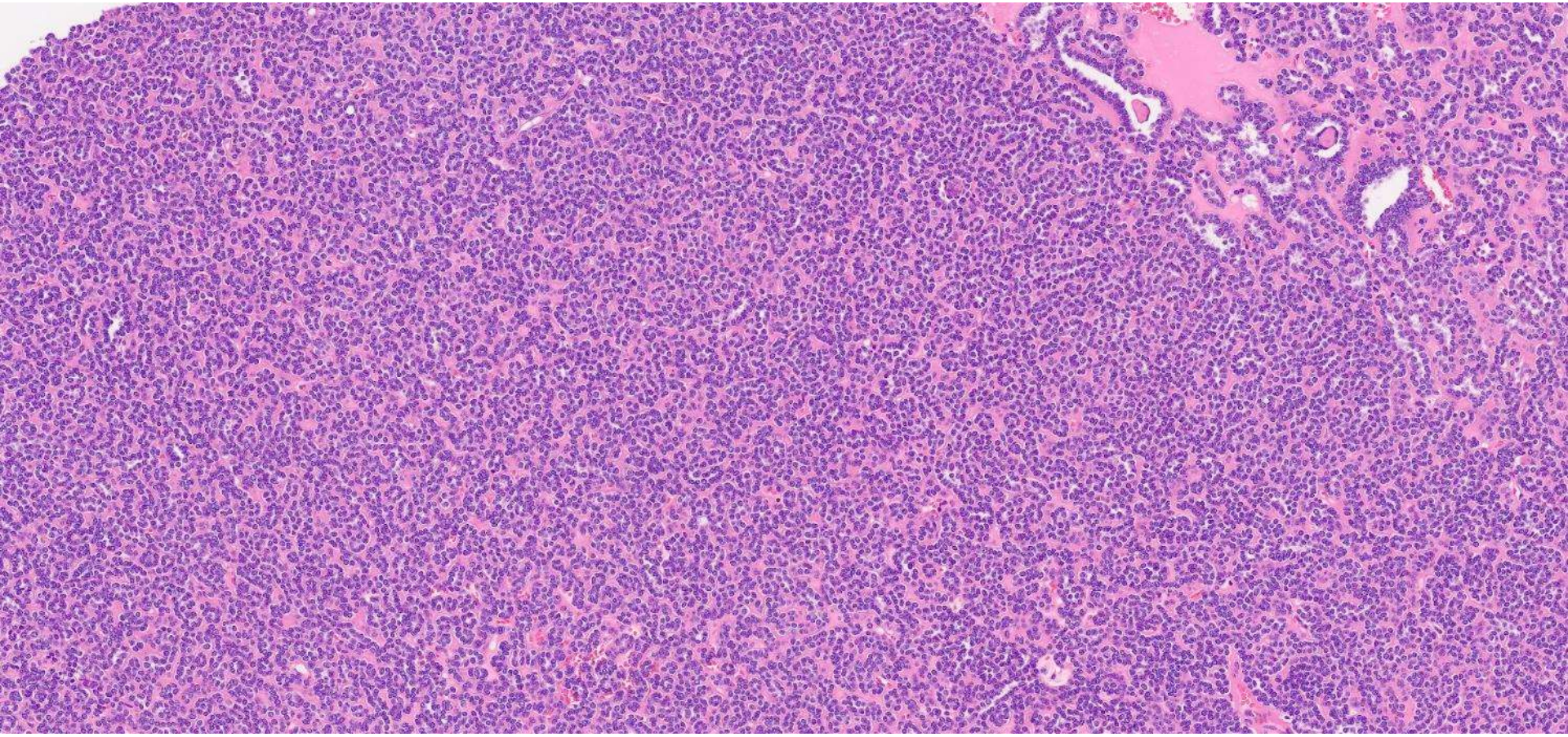


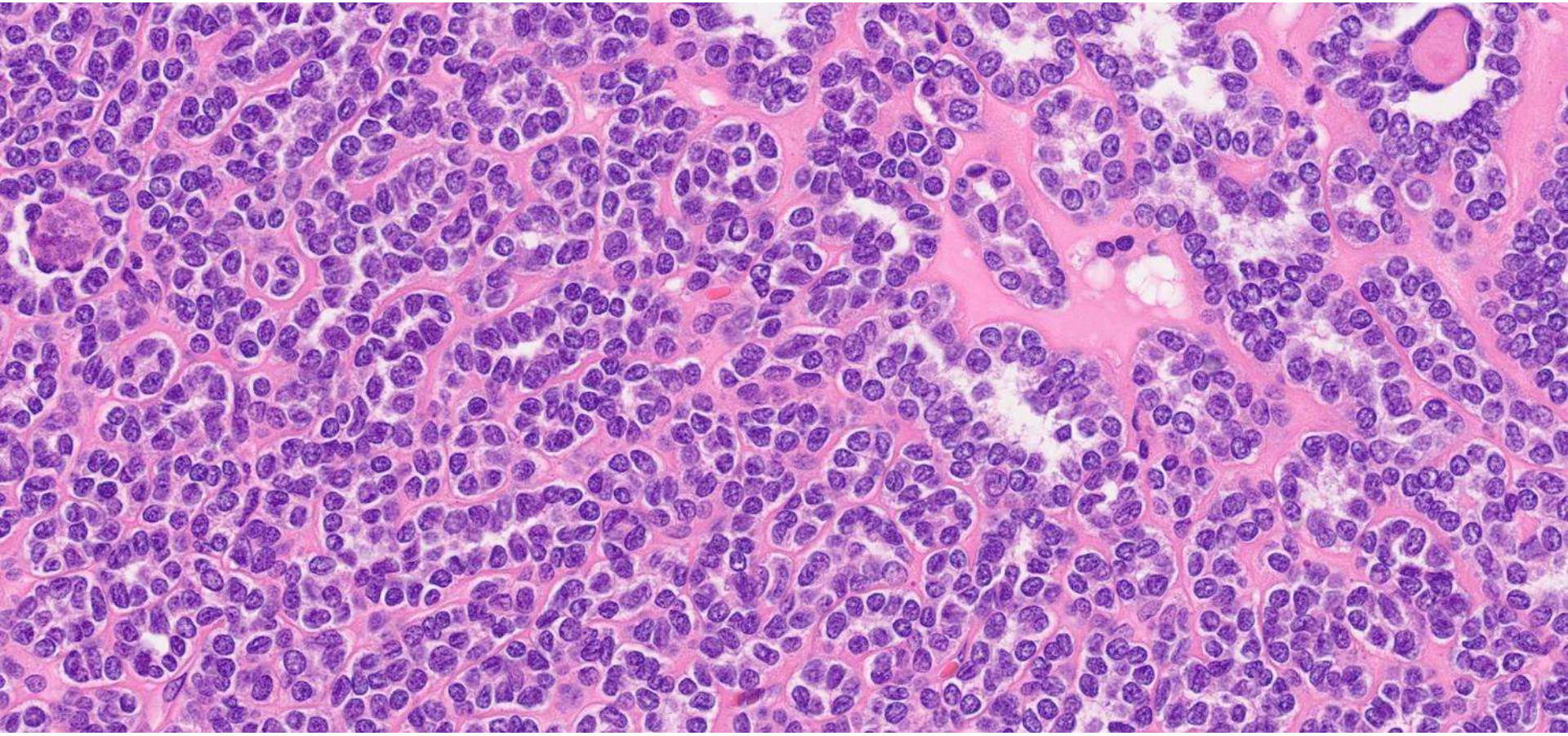






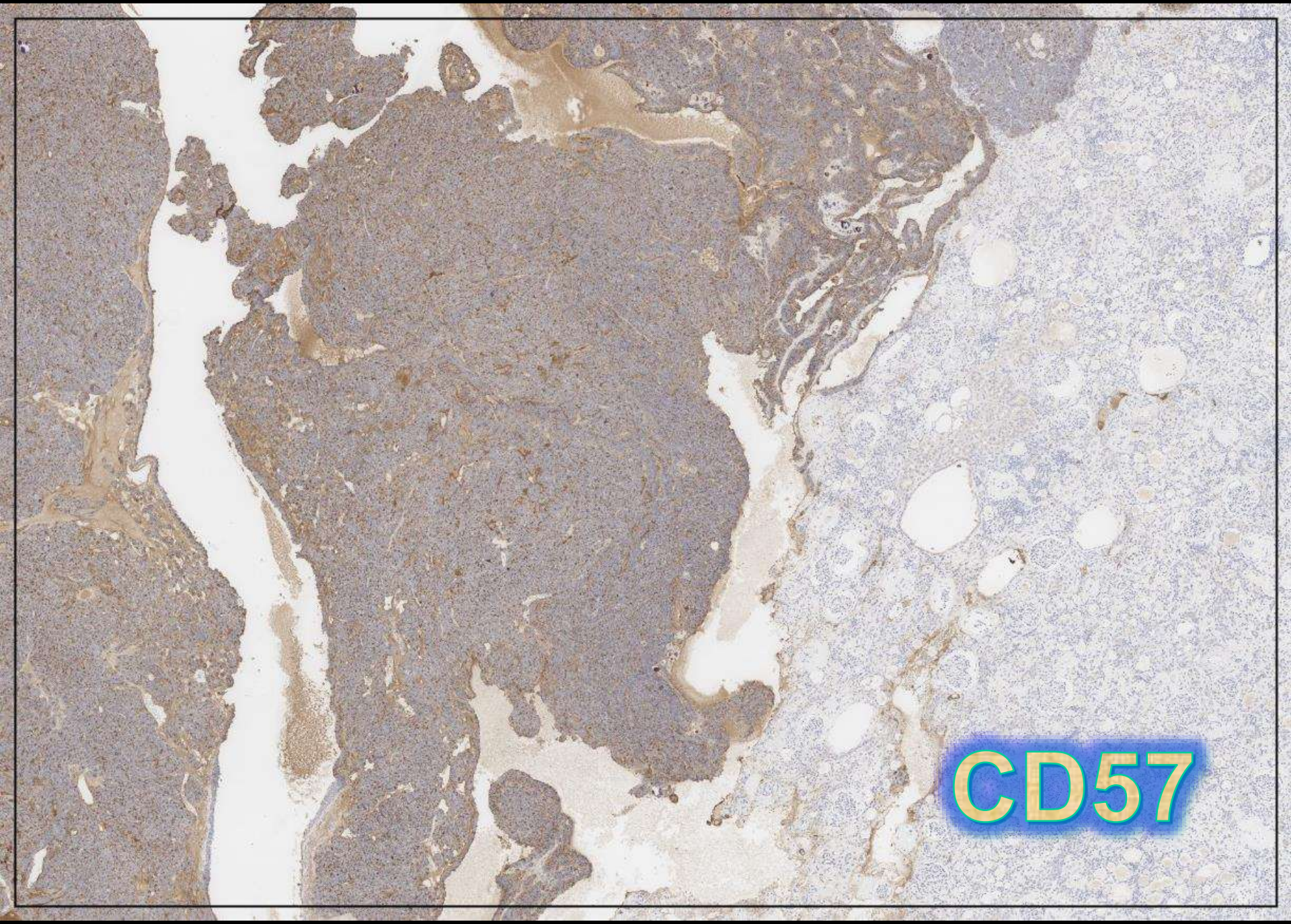


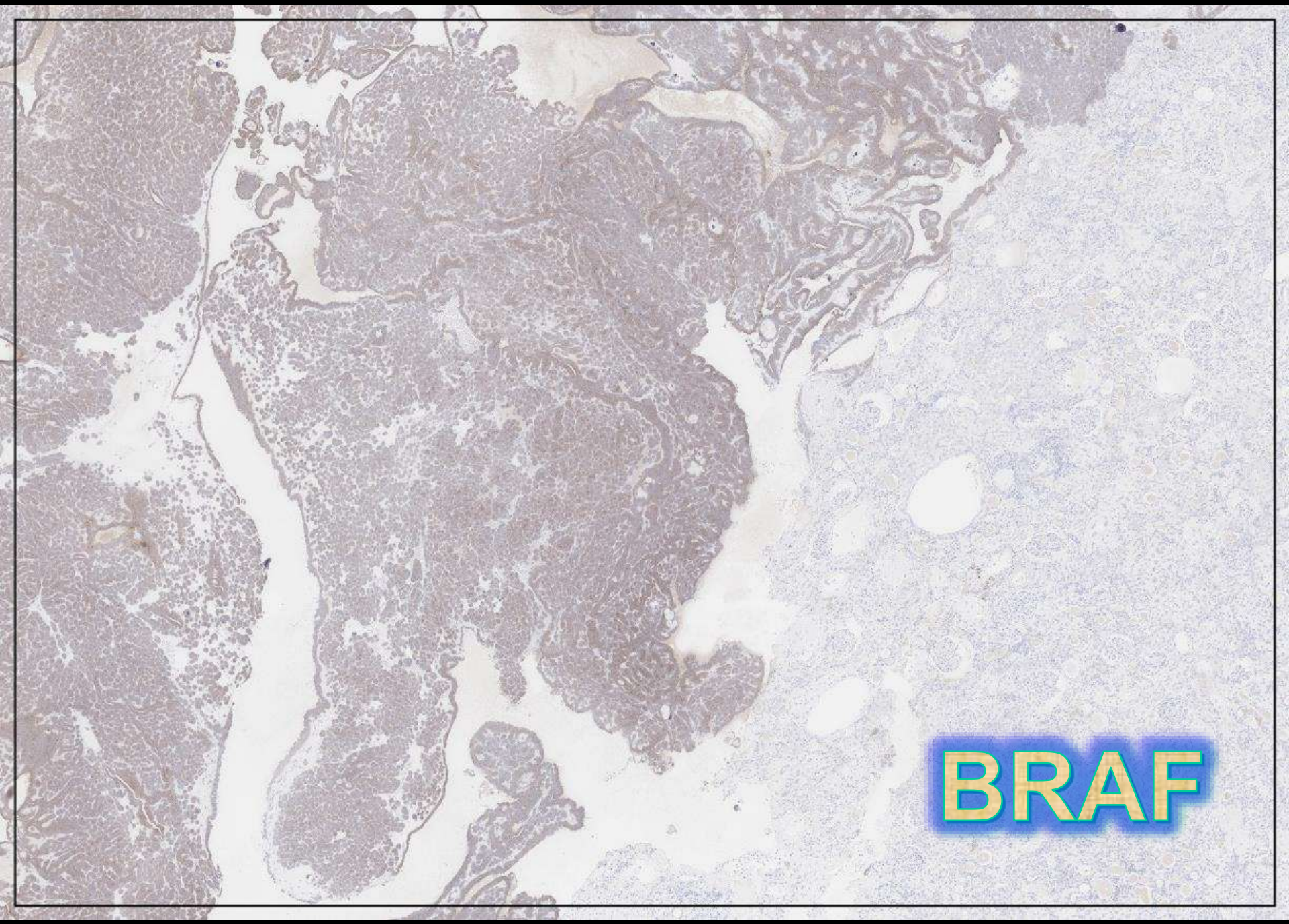




DDx

- Metanephric adenoma
- Epithelial-predominant Wilm's tumor
- Papillary renal cell carcinoma
- Metastatic carcinoma


CD57


BRAF

IHC summary

PAX8: positive (diffuse strong)
WT1: positive (diffuse strong)
CD57: positive (diffuse strong)
BRAF: positive (diffuse strong)
AMACR: positive (patchy weak)
EMA: positive (focal weak)
CK7: negative
TTF1: negative

Table 2 Results of staining with AMACR, CK7, WT1 and CD57 antibodies

	AMACR		*CK7*		*WT1*		*CD57*	
	Positive	*Negative*	*Positive*	*Negative*	*Positive*	*Negative*	*Positive*	*Negative*
MA	1 (F, W)	9	0	10	7 (F, 4W)	3	6	0
PRCC	24 (23D, 3W)	1	20 (11D, 5W)	5	3 (F, W)	22	1 (F, S)	24
WDWT	0	8	1 (F, W)	7	8 (D, S)	0	1 (F, S)	7

Modern Pathology (2006) 19, 218–224

Table 4 Typical immunohistochemical and cytogenetic profiles of metaphoric adenoma, epithelial-predominant nephroblastoma, and solid variant papillary renal cell carcinoma

Markers	*Metanephric adenoma*	*Epithelial-predominant nephroblastoma*	*Solid variant papillary renal cell carcinoma*
AMACR	Negative	Negative	Positive
WT1	Positive	Positive	Negative
CK7	Negative	Negative	Positive
CD57	Positive	Negative or focal	Negative
Loss of Y chromosome	Negative	Negative	Positive
Trisomy 7/17	Negative	Negative	Positive

MODERN PATHOLOGY (2015) 28, 1236–1248

European Association of Urology

Kidney Cancer

BRAF Mutations in Metanephric Adenoma of the Kidney

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Abstract

Background: Metanephric adenoma (MA) of the kidney is a rare, indolent tumor that may be difficult to differentiate from other small renal masses (SRMs). Genetic alterations associated with MA remain largely unknown.
Objective: We aimed at defining genetic events in MA of the kidney and determining their influence in the management of this disease.
Design, setting, and participants: Multiplexed mass spectrometric genotyping was performed on 29 MA cases after tumor DNA extraction. We also conducted a mutational screen in an additional 129 renal neoplasms. Immunohistochemistry was performed on the MA cases to assess molecular markers of signaling pathway activation. Patients' baseline characteristics, as well as follow-up data, were captured.
Outcome measurements and statistical analysis: We used descriptive statistics for baseline clinical characteristics and incidence of mutations. The Wilcoxon rank-sum test was used to correlate patient characteristics with mutational status.
Results and limitations: We identified the v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) V600E mutation in 26 of 29 MA cases. These results were validated in all cases using the commercially available BRAF Pyro Kit (QIAGEN). In contrast, *BRAF* mutations were rare in the other 129 non-MA renal neoplasms that were screened. We detected a *BRAF* mutation (V600E) in only one papillary renal cell carcinoma case. In all MA tumors, we documented expression of phosphorylated mitogen-activated protein kinase and phosphorylated extracellular signal–regulated kinase, accompanied by immunoreactivity for p16 (INK4a). All patients were treated with a partial or radical nephrectomy, and after a median follow-up of 26.5 mo, there were no local or distant recurrences. Limitations include the retrospective nature of this study.
Conclusions: *BRAF* V600E mutations are present in approximately 90% of all MA cases, serving as a potential valuable diagnostic tool in the differential diagnosis of SRMs undergoing a percutaneous biopsy. The presence of *BRAF* V600E and mitogen-activated protein kinase activation in a largely benign tumor supports the necessity for secondary events (eg, p16 loss) in *BRAF*-driven oncogenesis.

Metanephric Adenoma–Epithelial Wilms Tumor Overlap Lesions

An Analysis of BRAF Status

Sara E. Wobker, MD, MPH,† Andres Matoso, MD,‡ Christine A. Pratilas, MD,§ Shamlal Mangray, MB, BS,‖ Gang Zheng, MD, PhD,‡ Ming-Tseh Lin, MD, PhD,‡ Marija Debeljak, PhD,‡ Jonathan I. Epstein, MD,‡§ and Pedram Argani, MD‡§*

Abstract: Metanephric adenoma (MA) has historically been considered to represent a differentiated form of epithelial Wilms tumor (WT), based in part upon cases that morphologically overlap these 2 neoplasms. More recently, *BRAF* V600E mutations have been demonstrated in the majority of MAs but not in unselected or even epithelial-predominant WTs, suggesting 2 genetically distinct entities. However, no prior study has examined *BRAF* status in neoplasms with overlapping histologic features of epithelial WT and MA. We studied a cohort of 11 such overlapping lesions, 2 of which we considered morphologically to be otherwise typical MAs with unusually prominent mitotic activity and 9 of which we classified as epithelial WTs with areas resembling MA. Both mitotically active MAs demonstrated the *BRAF* V600E mutation. While the majority (5/9) of epithelial WTs with areas resembling MA were negative for *BRAF* V600E mutation, 4 such cases were positive. Two BRAF V600E mutation-positive WTs occurred in children. One case in a 6-year-old male was morphologically similar to the BRAF V600E mutation-positive adult cases and subsequently metastasized to the lungs; remarkably, the metastases then completely resolved on Braf targeted therapy. A second occurred in a 3-year-old girl whose posttherapy nephrectomy specimen's tumor was encapsulated and mitotically active like a typical WT, but also had more differentiated areas resembling MA. Immunohistochemistry for Braf V600E paralleled the molecular findings, demonstrating immunoreactivity in both the WT and MA-like areas of all 4 of these neoplasms. In summary, we demonstrate that *BRAF* V600E mutations are not entirely restricted to typical MA, as they may be seen in MAs showing mitotic activity along with a subset of epithelial-predominant WTs in adults and children that have foci which overlap morphologically with MA.

Key Words: renal neoplasm, *BRAF*, metanephric, Wilms

(*Am J Surg Pathol* 2019;43:1157–1169)

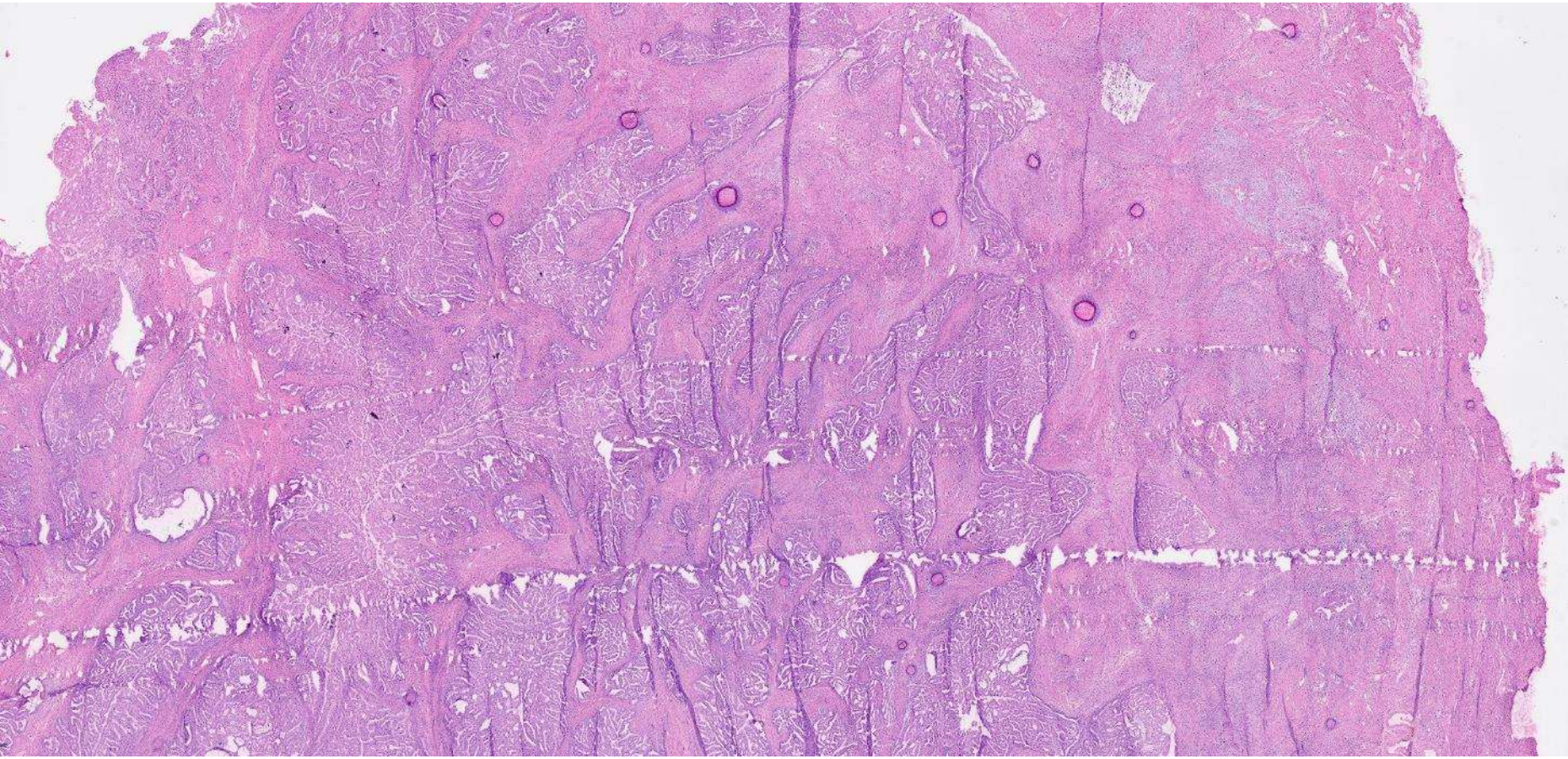
Two primary renal neoplasms closely resemble embryonal renal tubules, metanephric adenoma (MA) and Wilms tumor (WT). MA typically occur in adult females and represent benign renal neoplasms resembling differentiated primitive renal tubules.[1–3] Most MA are well-circumscribed but unencapsulated masses comprised of closely packed, embryonal-appearing epithelial cells which directly abut the renal parenchyma. The cells typically form closely packed tubules, but solid areas, elongated tubules, glomeruloid structures, and true papillae are often present. The cells are bland and uniform; however, they have a high nucleus to cytoplasm ratio, imparting a deeply basophilic appearance to the neoplasm. The stroma is usually edematous or hyalinized, and psammoma bodies are common. Mitotic figures are characteristically extremely scarce or absent.

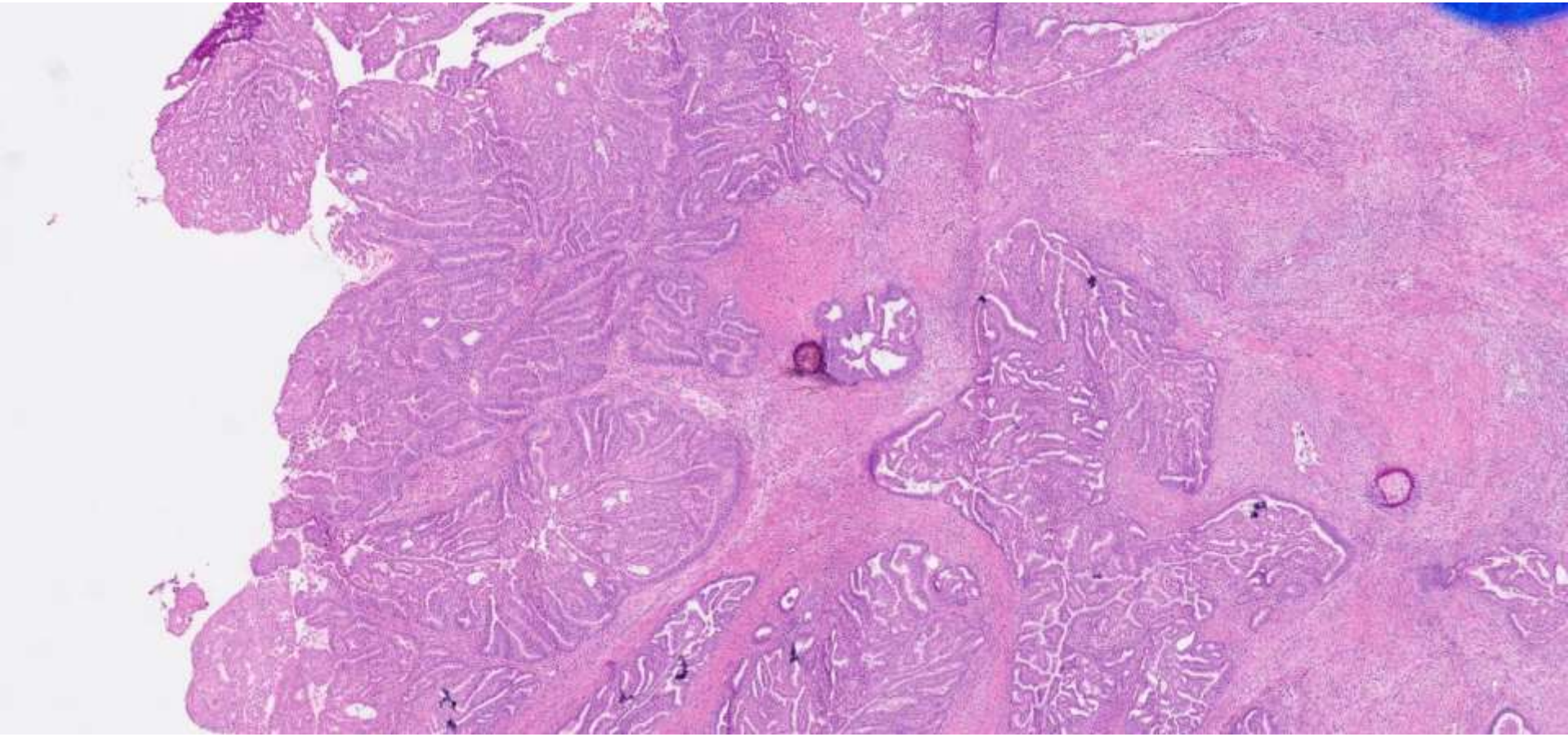
In contrast, WT, the most common pediatric renal neoplasm, is a malignant embryonal neoplasm derived from metanephric blastema which recapitulates the developing kidney. Unlike MA, WT generally has a fibrous pseudocapsule separating it from the surrounding parenchyma, and typically demonstrates a high mitotic rate. Classically, WT is comprised of 3 elements (blastema,

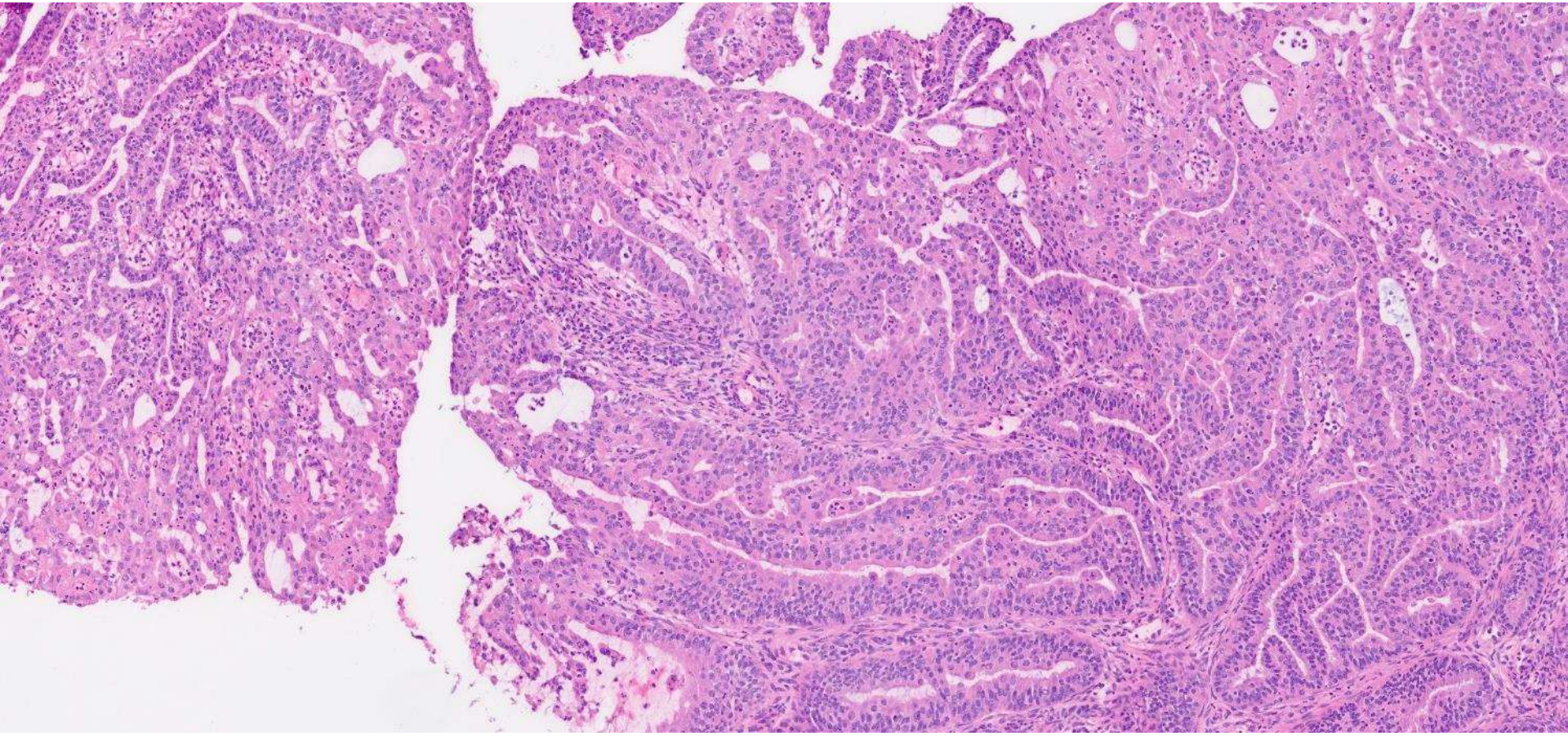
21-1007

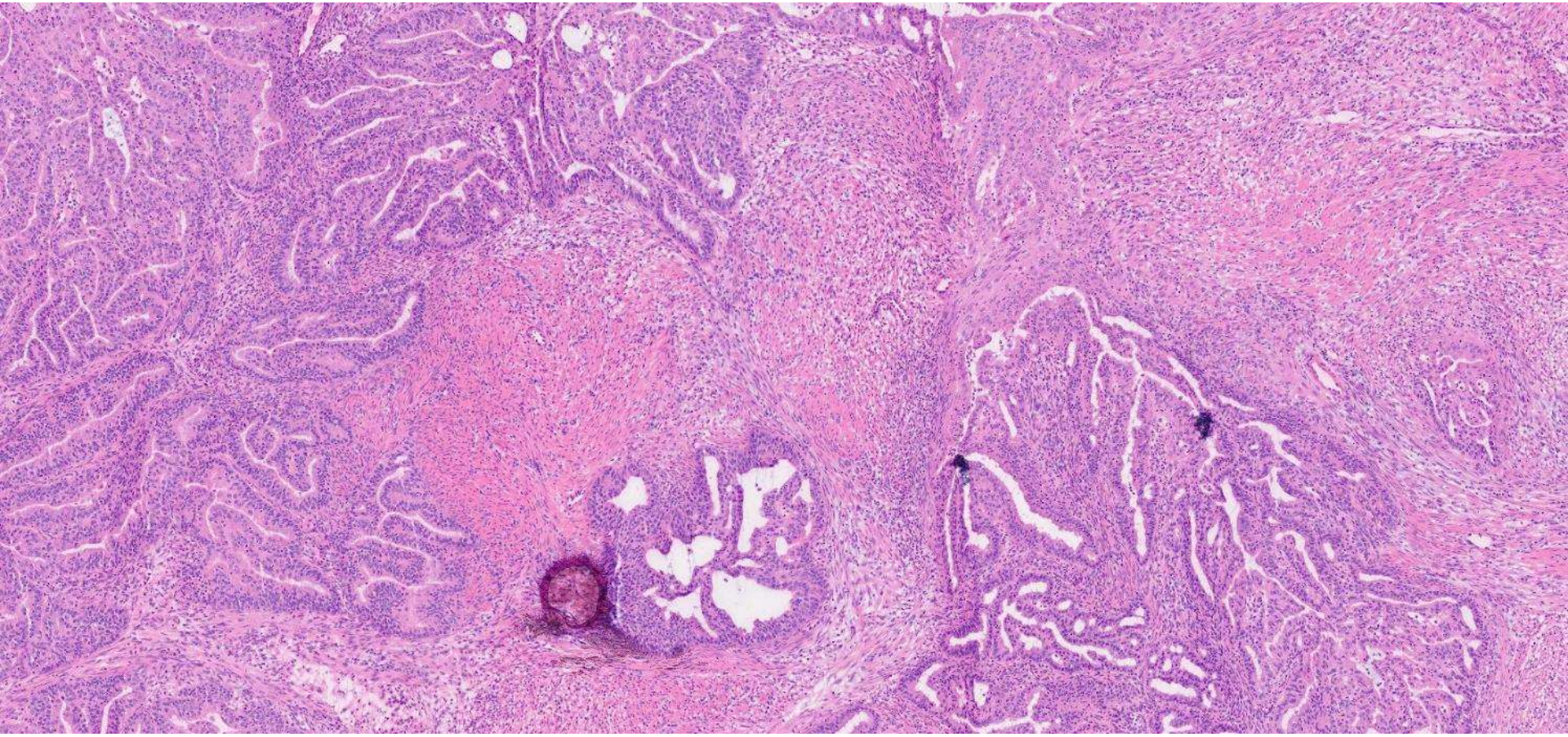
Ankur Sangoi; El Camino Hospital

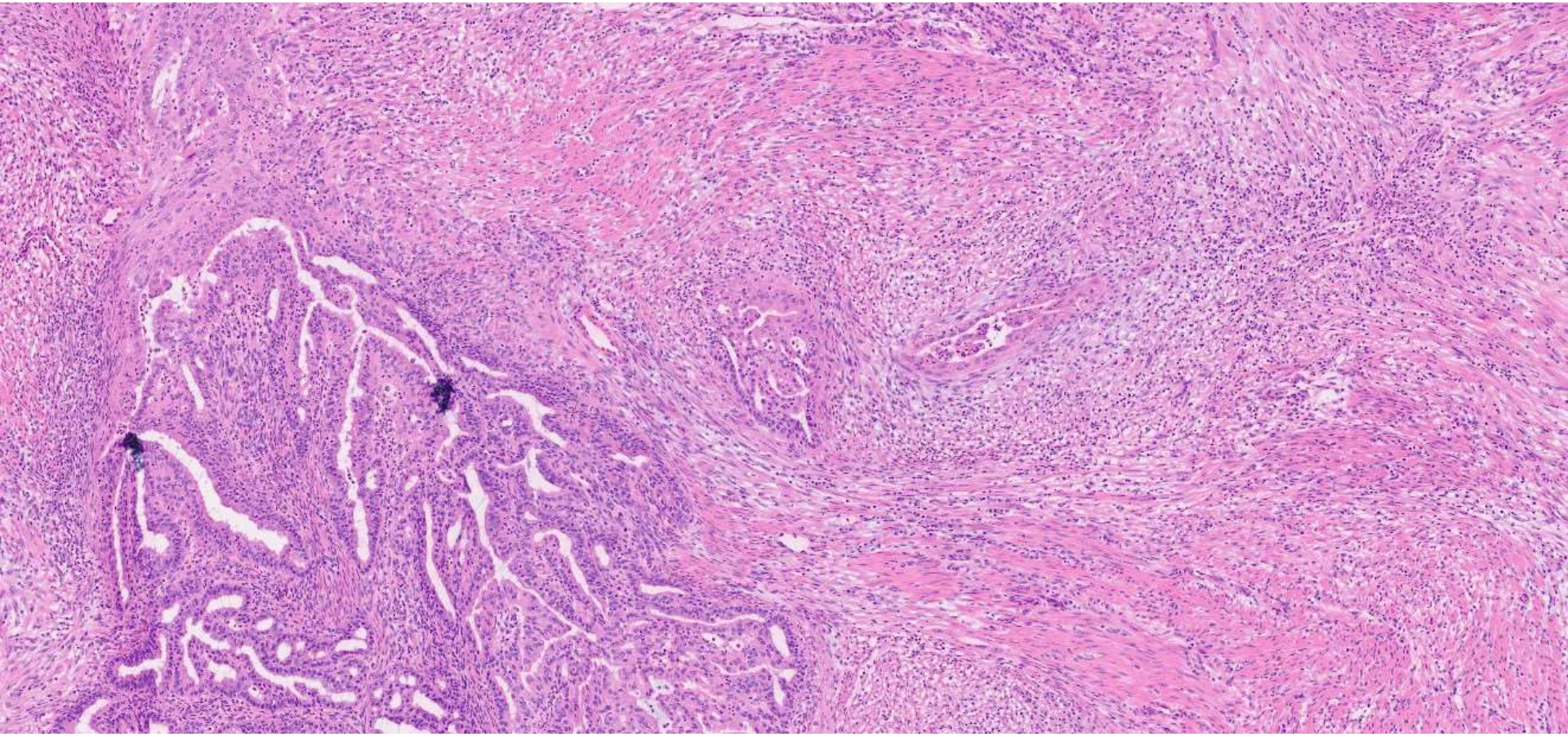
50-year-old F undergoes TAH for endometrial cancer. Frozen section of endomyometrium performed.

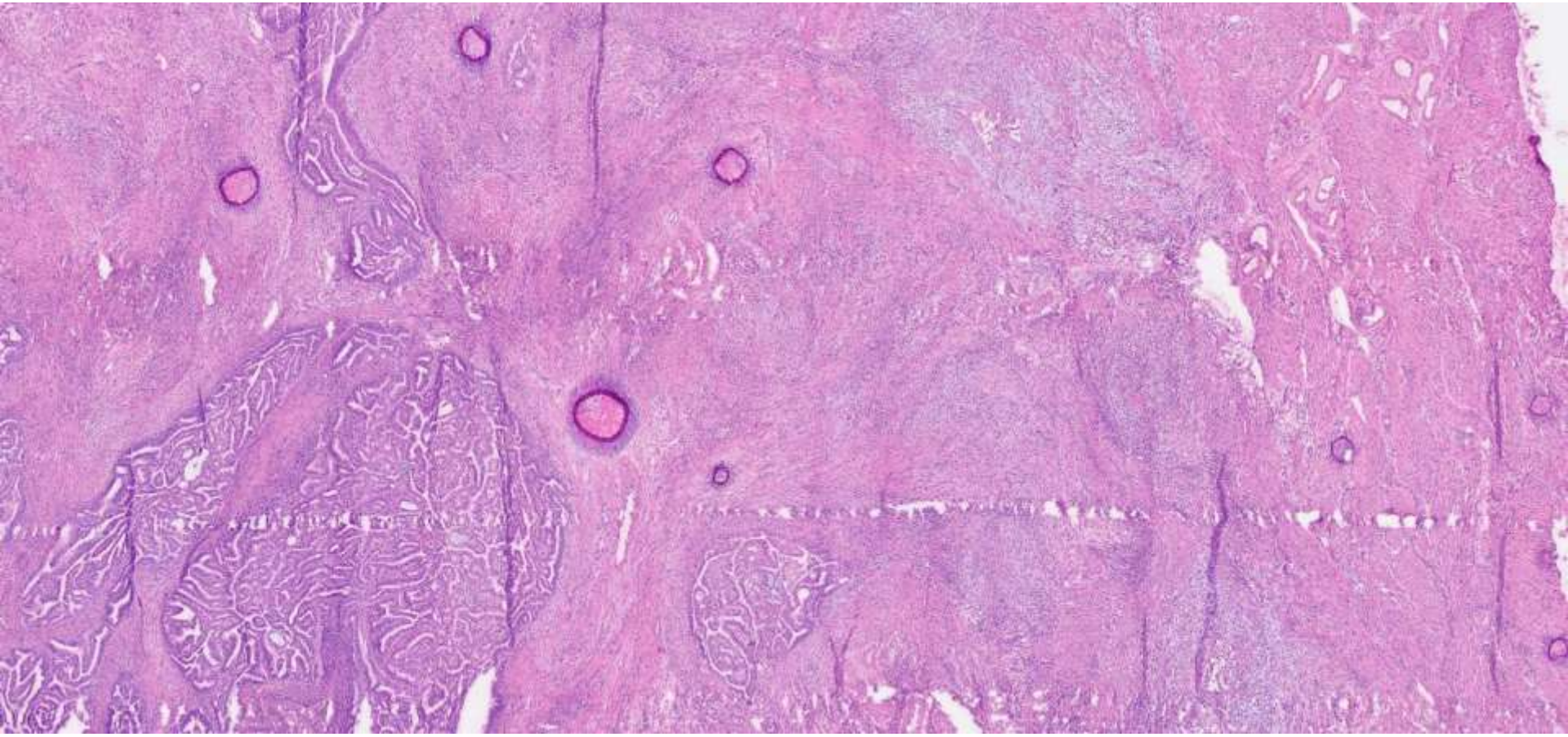


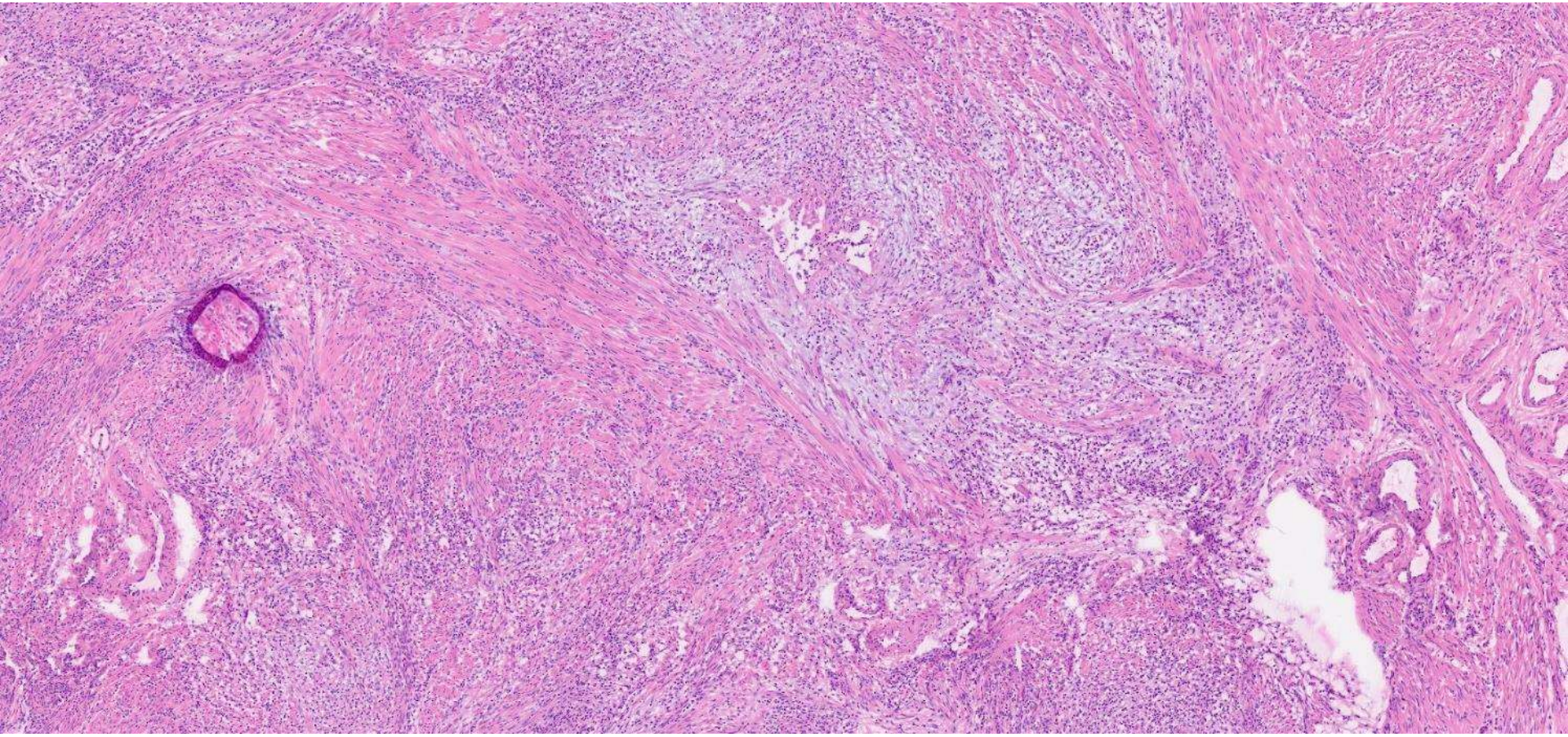


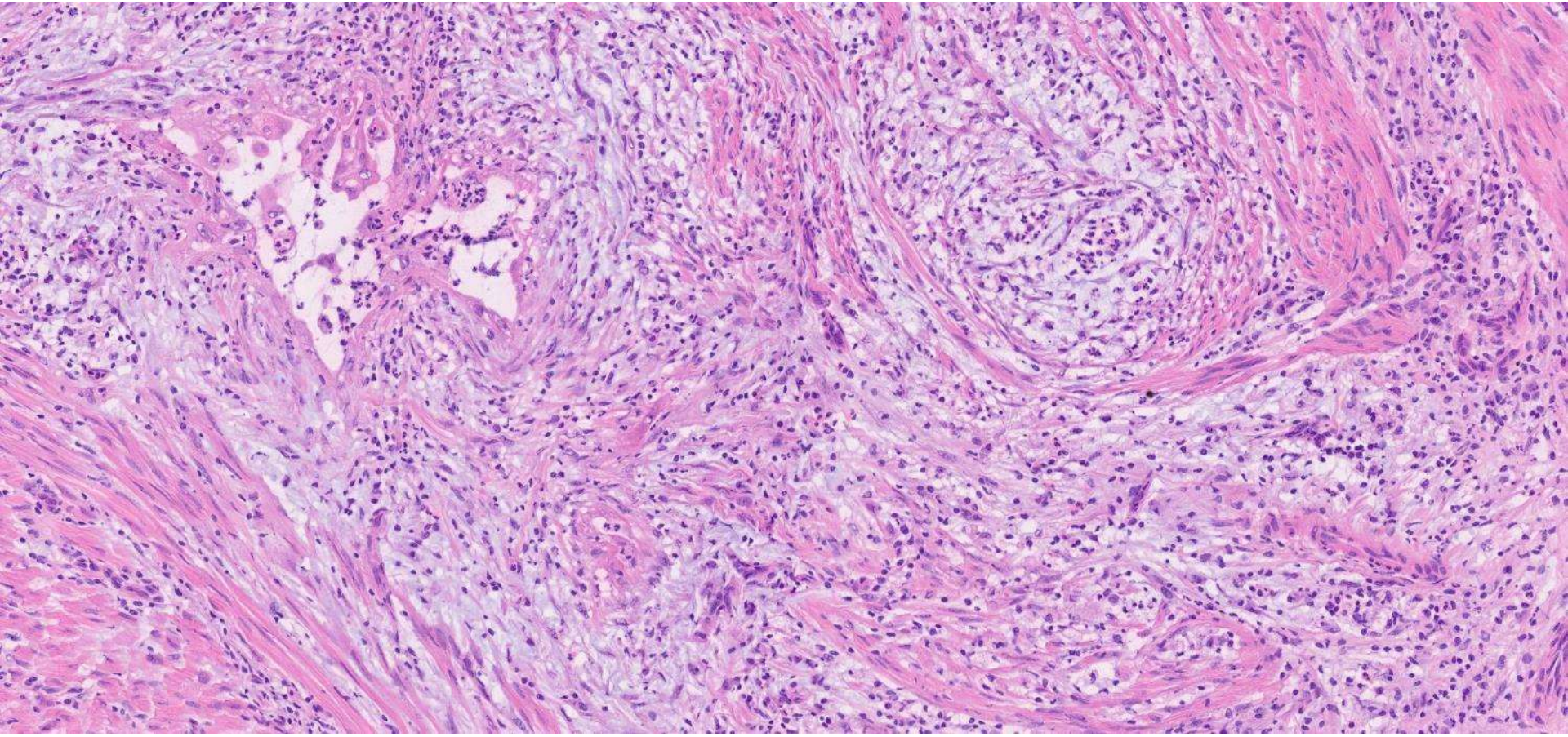


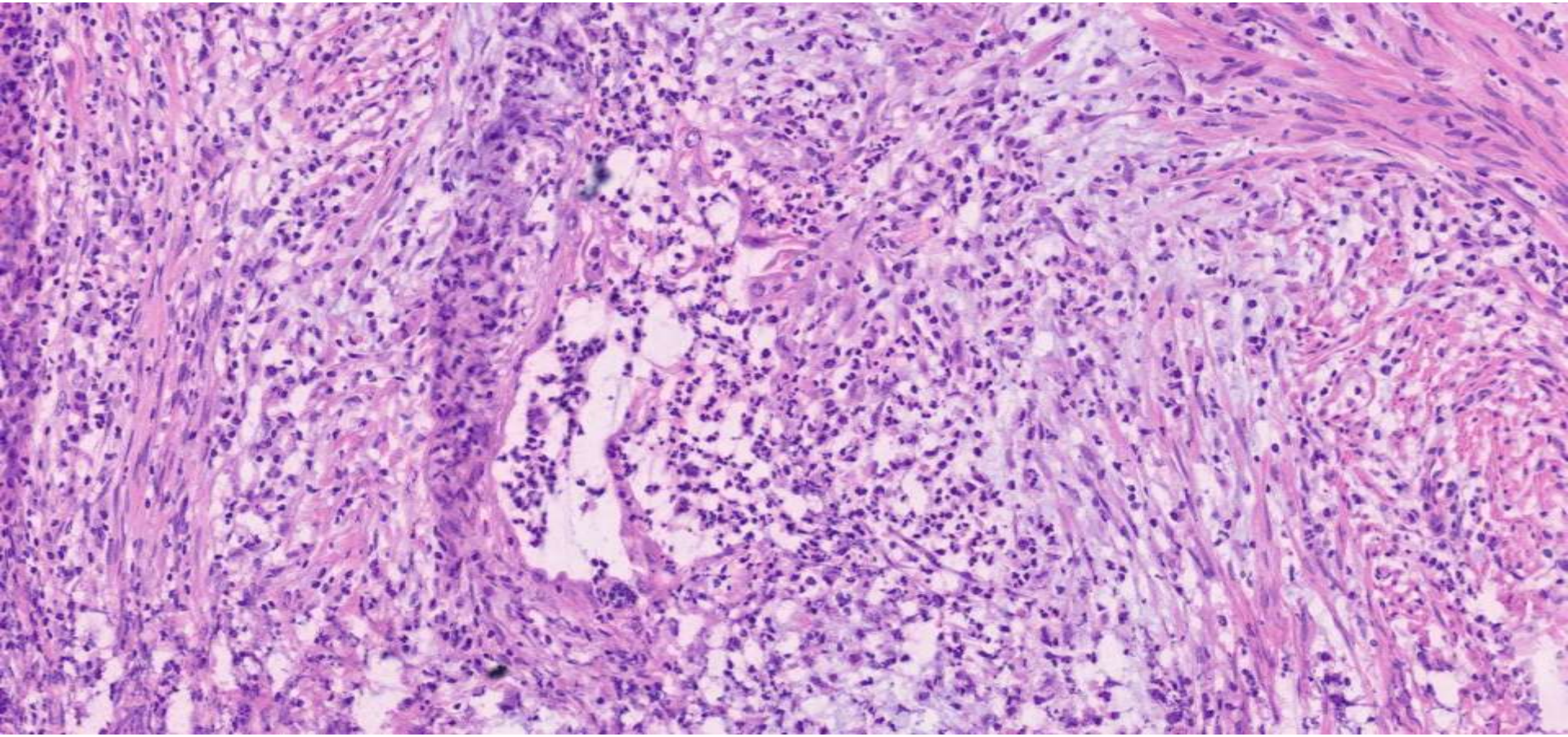


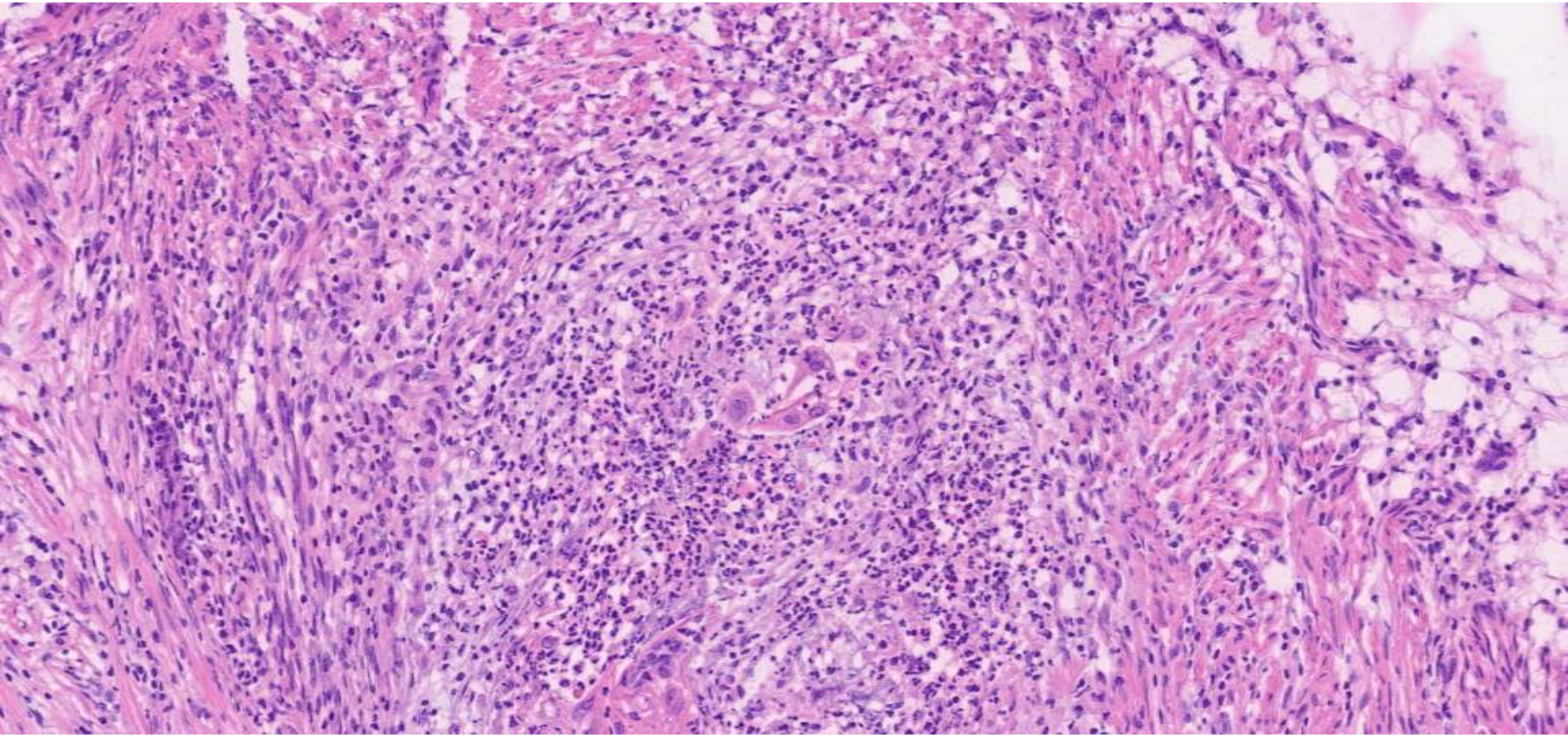


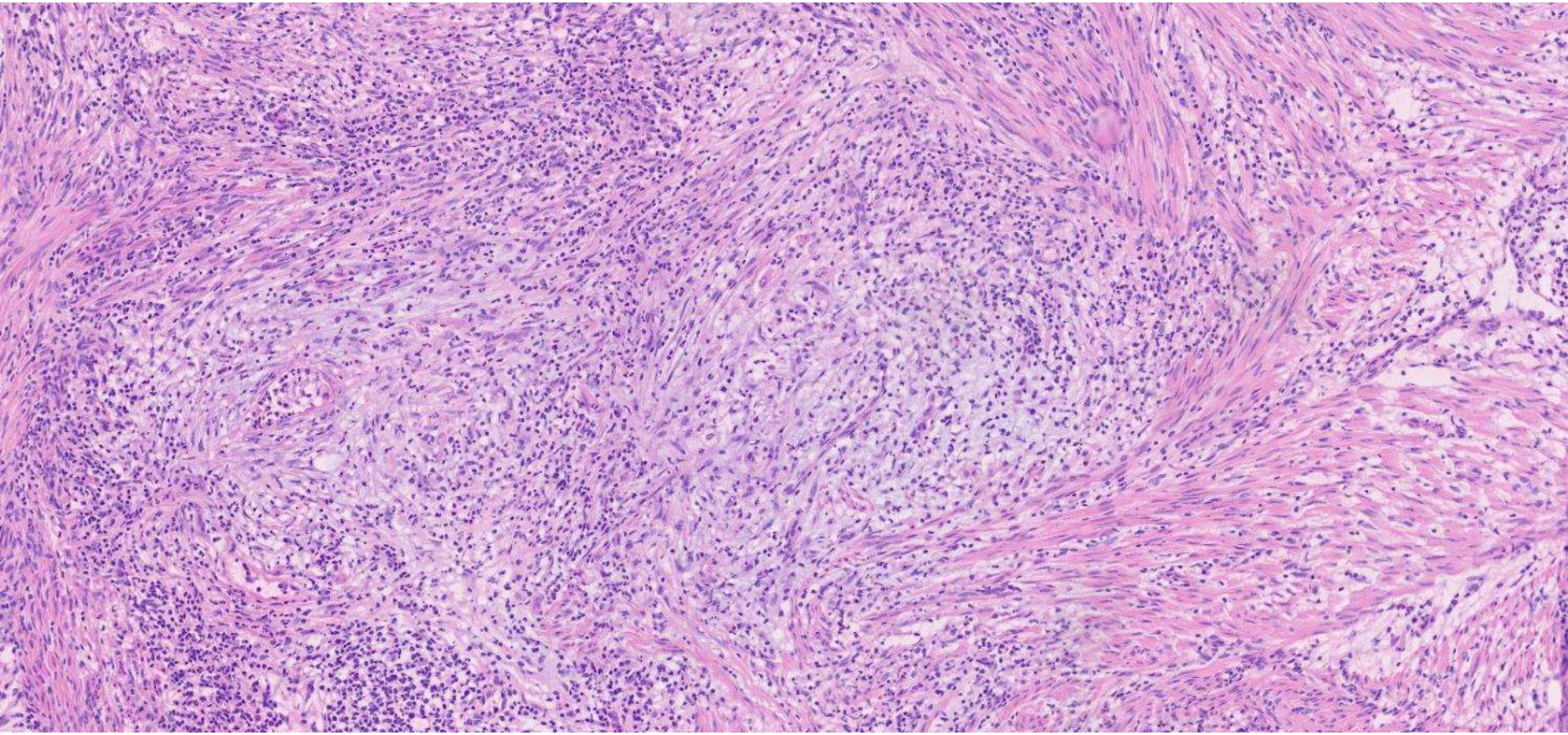


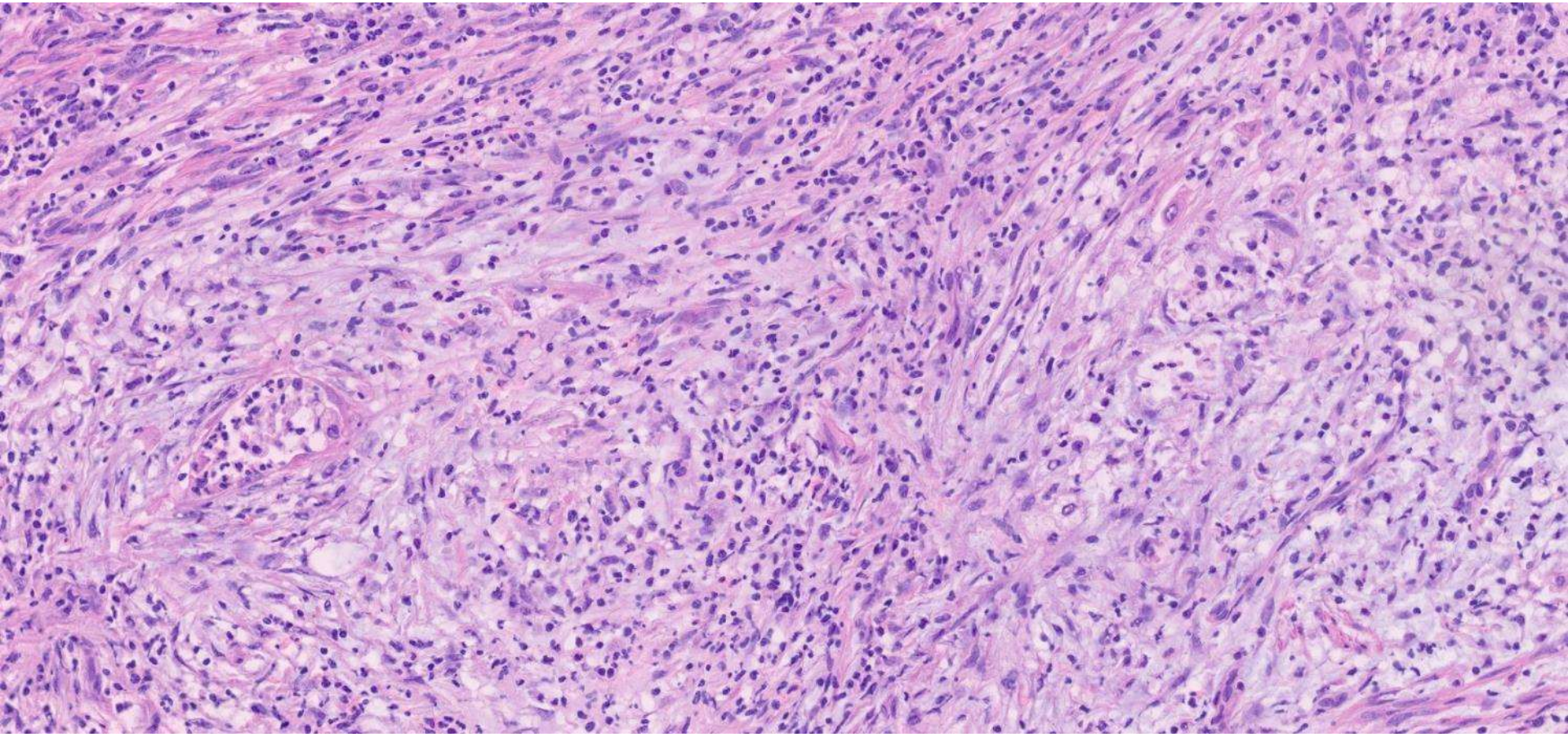












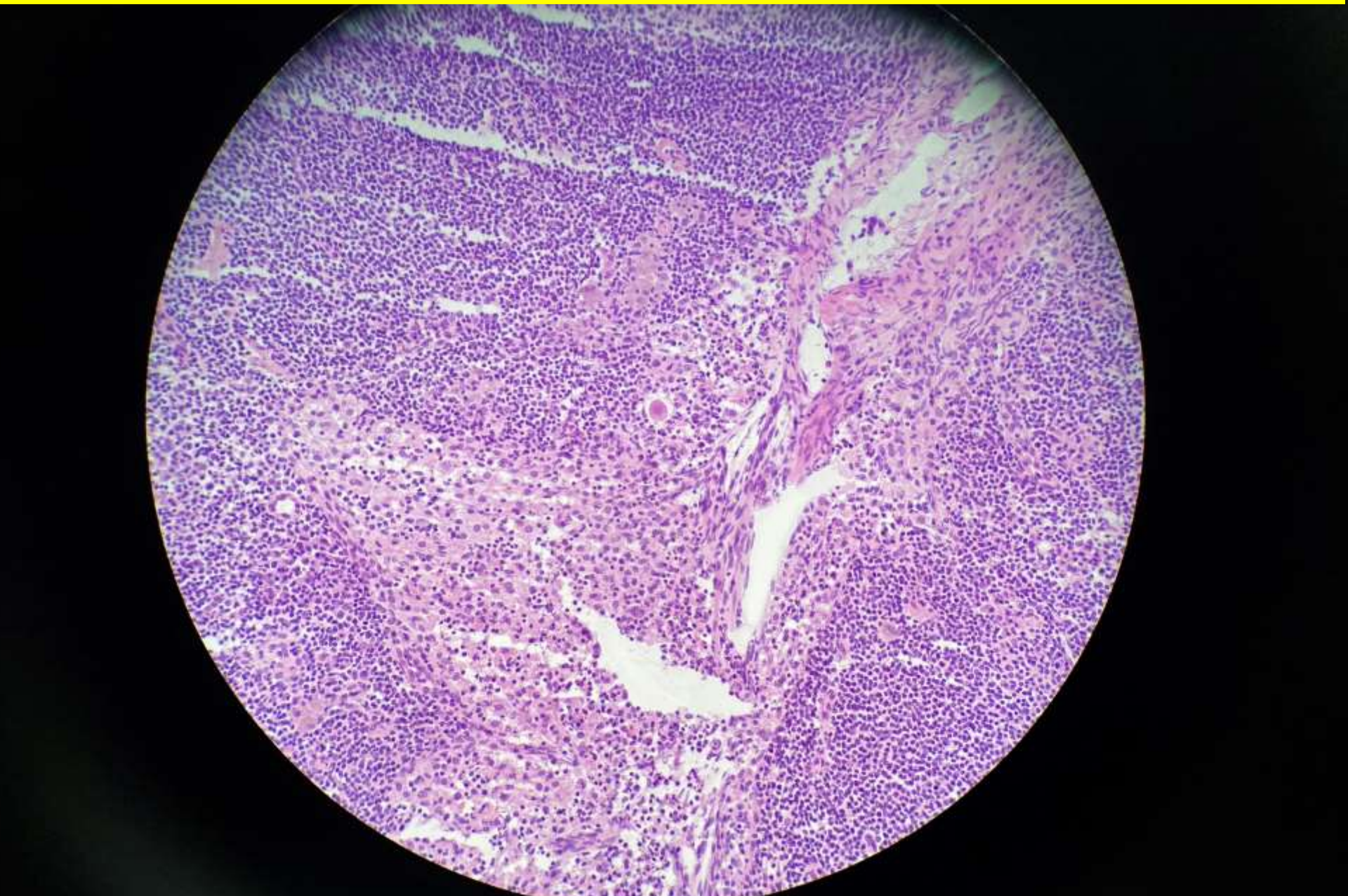
DDx

- microcystic elongated & fragmented (MELF) pattern endometrial carcinoma
- serous carcinoma
- endometrioid adenocarcinoma + isolated vasculitis of GYN tract
- carcinosarcoma

Dx

- **Microcystic elongated & fragmented (MELF) pattern endometrial carcinoma**
- **Serous carcinoma**
- **Endometrioid adenocarcinoma + isolated vasculitis of GYN tract**
- **carcinosarcoma**

SENTINEL LYMPH NODE FROZEN SECTION



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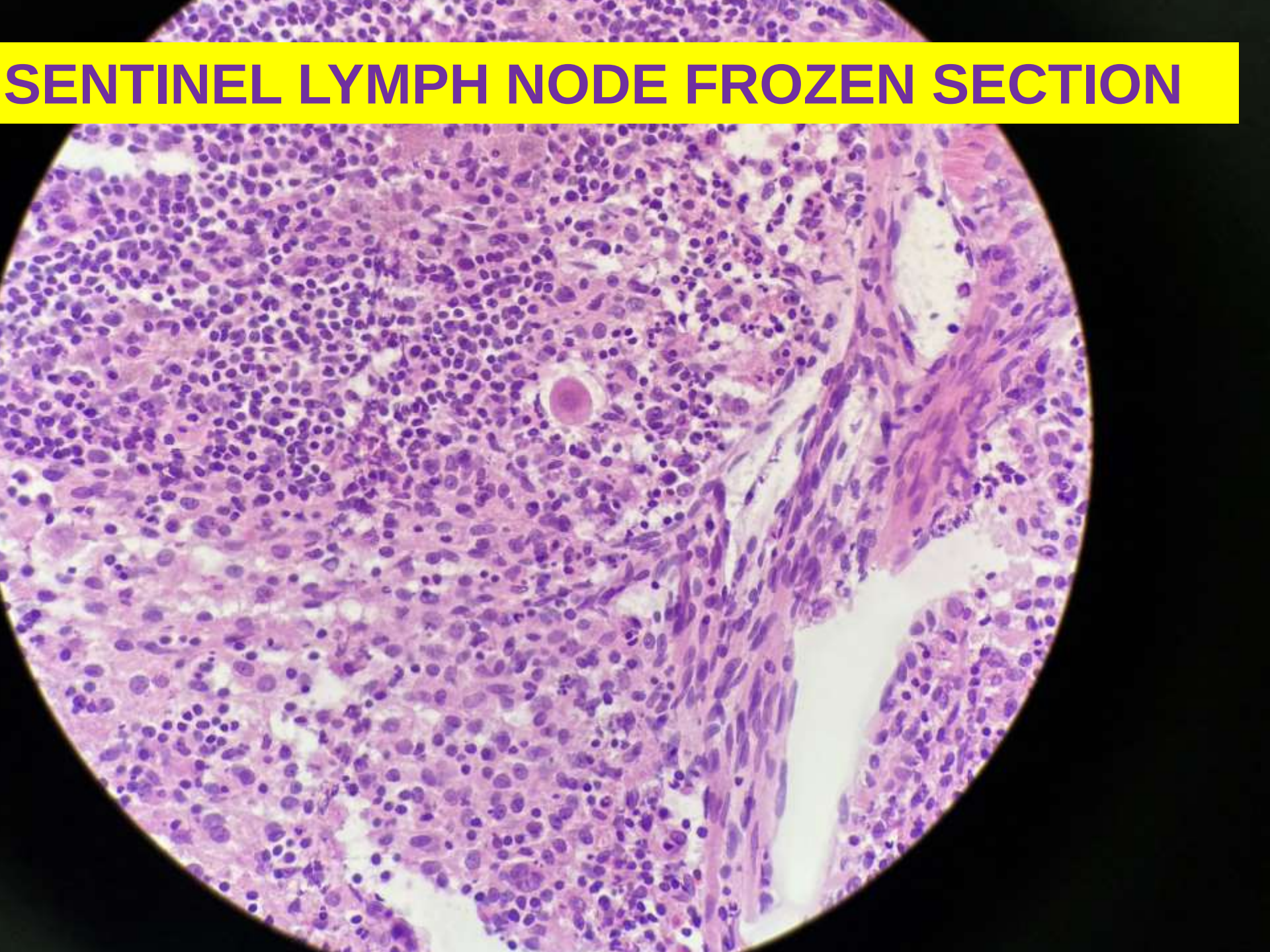

Unusual Epithelial and Stromal Changes in Myoinvasive Endometrioid Adenocarcinoma: A Study of Their Frequency, Associated Diagnostic Problems, and Prognostic Significance

Shawn K. Murray, M.D., Robert H. Young, M.D., and Robert E. Scully, M.D.

Summary: The authors have noted that when the myoinvasive glands of endometrioid carcinomas evoke a prominent fibromyxoid stromal reaction, they sometimes undergo distinctive changes. These are characterized by outpouchings from typical neoplastic glands that become detached and often lined by flattened epithelium, sometimes appearing as microcysts. The glands may less often become elongated or undergo fragmentation into small solid clusters or single cells. For this constellation of changes, which in aggregate are distinctive, the authors have coined the acronym MELF (microcystic, elongated, fragmented). The authors evaluated the prognostic significance of these stromal and glandular features and their association with each other and with other histopathologic and clinical prognostic factors by studying 115 unselected myoinvasive endometrial endometrioid carcinomas. The histologic slides and clinical records were reviewed to collect data on age, recurrences or metastases, survival, stromal reaction pattern (fibromyxoid, lymphocytic, or absent), presence of MELF, FIGO grade, depth of myometrial invasion, vascular invasion, squamous differentiation, and presence or absence of necrosis. Factors associated with an unfavorable outcome (recurrence or death) included a fibromyxoid stromal reaction, age older than 70 years, advanced stage, vascular invasion, FIGO grade, depth of myoinvasion, and the presence of tumor necrosis. The presence of a host lymphocytic reaction was associated with a favorable outcome. A multivariate logistic regression model identified stage and age older than 70 years as independent prognostic factors. The MELF changes were associated with the presence of a host stromal reaction (most strongly with a fibromyxoid reaction) and vascular invasion. Within the group associated with a fibromyxoid reaction, patients exhibiting MELF had a better survival. In conclusion, a fibromyxoid reaction in cases of endometrioid carcinoma is associated with a higher frequency of death or recurrence and it is frequently accompanied by distinctive morphologic changes (MELF) in myoinvasive glands as well as lymphatic or blood vessel invasion. MELF is associated with a fibromyxoid reaction but is not independently associated with an adverse effect on prognosis. A lymphocytic stromal reaction is associated with a favorable effect on prognosis and is less often accompanied by the distinctive morphologic changes (MELF) highlighted herein. **Key Words:** Endometrium—Carcinoma—Endometrioid carcinoma—Fibromyxoid stroma—Lymphocytic reaction—Prognosis.

TABLE 2. *Proportion with unfavorable outcome (recurrence or death) for each histopathologic factor except MELF*

	Alive [no. (%)]	Unfavorable [no. (%)]	p value	Multivariate analysis
Stromal reaction				
Fibromyxoid	29 (55.8)	23 (44.2)	p (F/L) = 0.009	0.29
Lymphocytic	26 (83.9)	5 (16.1)	p (F/N) = 0.038	
No reaction	25 (78.1)	7 (21.9)	p (L/N) = 0.561	
FIGO stage				
I/II	74 (73.3)	27 (26.7)	0.013	0.045
III/IV	6 (54.5)	5 (45.5)		
VI				
Absent	64 (76.2)	20 (23.8)	0.011	0.92
Present	16 (51.6)	15 (48.4)		
FIGO grade				
1	38 (71.7)	15 (28.3)	p (G1/G2) = 0.433	0.36
2	30 (78.9)	8 (21.1)	p (G1/G3) = 0.065	
3	12 (50)	12 (50)	p (G2/G3) = 0.018	
Depth of invasion*				
<½	55 (79.7)	14 (20.3)	0.008	0.411
≥½	19 (59.4)	13 (40.6)		
Necrosis				
Absent	74 (73.3)	27 (26.7)	0.032	0.54
Present	6 (42.9)	8 (57.1)		
Age				
>70	20 (51.3)	19 (48.7)	0.003	0.02
≤70	60 (78.9)	16 (21.1)		

TABLE 3. *Outcome related to type of stromal reaction and degenerative gland changes (MELF)*

Stromal reaction	Degenerative gland changes (MELF)		Survival			Total
			ANED	DOD	AWD	
Lymphocytic	MELF	absent	16	1	2	19
			84.2%	5.3%	10.5%	100.0%
		present	10	2	0	12
			83.3%	16.7%	.0%	100.0%
	Total		26	3	2	31
			83.9%	9.7%	6.5%	100.0%
Absent	MELF	absent	23	3	2	28
			82.1%	10.7%	7.1%	100.0%
		present	2	0	2	4
			50.0%	.0%	50.0%	100.0%
	Total		25	3	4	32
			78.1%	9.4%	12.5%	100.0%
Fibromyxoid	MELF	absent	8	8	1	17
			47.1%	47.1%	5.9%	100.0%
		present	21	7	7	35
			60.0%	20.0%	20.0%	100.0%
	Total		29	15	8	52
			55.8%	28.8%	15.4%	100.0%

Histopathology

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Histological features associated with occult lymph node metastasis in FIGO clinical stage I, grade I endometrioid carcinoma

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Histological features associated with occult lymph node metastasis in FIGO clinical stage I, grade I endometrioid carcinoma

Aims: Lymph node involvement affects prognosis/treatment in endometrial carcinoma patients. We assessed various histological features associated with nodal metastasis in patients with grade I, stage I endometrial endometrioid carcinoma (EEC).

Methods and results: Eighteen stage I EECs with occult positive lymph nodes and 36 controls were assessed for depth of myoinvasion; microcystic, elongated and fragmented (MELF) pattern of myometrial invasion; lymphovascular invasion (LVI); and epithelial metaplasia. Nodal metastases were subclassified as isolated tumour cells (ITCs; ≤0.2 mm), micrometastasis (>0.2 mm and <2 mm), or macrometastasis (≥2 mm). Node-positive cases had significantly higher rates of LVI ($P < 0.001$) and MELF invasion ($P = 0.003$) on univariate analysis. Only LVI was associated significantly with nodal metastasis on multivariate analysis ($P = 0.002$). Tumours with MELF invasion demonstrated reduced E-cadherin expression. Macrometastases were identified in seven cases (39%) with or without micrometastasis/ITCs. Eight (44%) contained only ITCs. Eleven (61%) had histiocyte-like nodal metastases. Biopsy material from four of six (67%) and five of 17 (29%) cases with and without nodal metastasis showed detached eosinophilic tumour cell buds. Of the former, three were associated with histiocyte-like nodal metastases – a feature absent in biopsies without tumour budding.

Conclusions: Lymph nodes from grade I EEC exhibiting cellular budding or LVI should be examined for occult metastases, especially in the form of histiocyte-like cells.

Endometrioid endometrial carcinomas with microcystic, elongated, and fragmented (MELF) type of myoinvasion: role of immunohistochemistry in the detection of occult lymph node metastases and their clinical significance☆,☆☆

Iñigo Espinosa MD, PhD[a], Neus Serrat MD, PhD[a], Gian Franco Zannoni MD, PhD[b], Ramón Rovira MD[c], Emanuela D'Angelo MD, PhD[a], Jaime Prat MD, PhD, FRCPath[a,*]

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Keywords:
Endometrial carcinoma;
Myometrial invasion;
MELF;
Occult lymph node metastasis;
Immunohistochemistry

Summary In endometrioid endometrial carcinomas (EECs), microcystic, elongated, and fragmented (MELF) myoinvasion is associated with easily overlooked lymph node metastases; however, the role of immunohistochemistry in their detection and their clinical significance have not been addressed. We identified MELF in 43 of 101 (43%) myoinvasive EECs. Nodes were removed in 49 (49%), 25 with MELF and 24 without MELF. Metastases were initially reported in 3 of the former (12%) and 2 of the latter (8%). All negative nodes were reviewed, and cytokeratin immunohistochemistry was performed. Three metastases were identified in the MELF group but none in the EECs without MELF. By immunohistochemistry, metastatic nodal isolated tumor cells (ITCs) were found in 6 of the remaining 19 MELF-positive cases. In contrast, lymph node metastases were detected in only 2 of the 22 EECs without MELF. MELF-positive cases had more lymph node metastases ($P = .03$) than myoinvasive EECs without MELF. At follow-up, all 6 patients with grade 1-2 EECs and nodal ITCs/micrometastases were alive (5 no evidence of disease and 1 with perineal disease). In contrast, 3 of 4 patients with grade 3 EECs and nodal ITCs/micrometastases died of disease, and the other patient was alive with tumor. In MELF, the frequency of ITCs/micrometastases in apparently negative lymph nodes is high. In patients with grade 1-2 EEC who had not received chemotherapy, the presence of nodal ITCs/micrometastases did not affect survival. In contrast, in high-grade tumors, ITCs/micrometastases were associated with unfavorable prognosis. Immunohistochemistry should be done in MELF-positive cases to detect occult lymph node metastases, especially in high-grade tumors.

Clinicopathologic Association and Prognostic Value of Microcystic, Elongated, and Fragmented (MELF) Pattern in Endometrial Endometrioid Carcinoma

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Abstract: Microcystic, elongated, and fragmented (MELF) pattern is seen in the invasive front of some endometrial endometrioid carcinomas. Although MELF pattern can be expected as an indicator of patient outcomes, its prognostic significance remains unclear. This study was conducted to elucidate clinicopathologic features and the prognostic impact of MELF pattern in patients with endometrial endometrioid carcinoma. We retrospectively analyzed data of 479 consecutive patients with endometrial endometrioid carcinoma that had been surgically resected. In 45 of 427 patients (11%) with low-grade endometrioid carcinoma, MELF pattern was found, but it was found in none of the 52 patients with high-grade endometrioid carcinoma. Among the patients with low-grade endometrioid carcinoma, MELF pattern was associated significantly with larger tumor size, myometrial invasion of more than 50%, advanced International Federation of Gynecology and Obstetrics stages, lymphovascular space invasion, lymph node metastasis, papillary architecture, and mucinous differentiation. However, survival analysis revealed that the patients with MELF pattern showed no significantly worse prognosis than those without MELF pattern either in disease-specific survival or in recurrence-free survival. MELF was not a significant prognosticator after adjustment for International Federation of Gynecology and Obstetrics stage (disease-specific survival [hazard ratio, 1.47; 95% confidence interval, 0.28-7.67; $P = 0.64$], recurrence-free survival [hazard ratio, 0.98, 95% confidence interval, 0.32-2.99, $P = 0.98$]). Immunohistochemical analysis revealed that MELF pattern was positive for p16 and p21 and almost negative for Ki-67 labeling, which suggested that tumor cells in MELF pattern were involved in growth arrest or cellular senescence. We conclude that MELF pattern could have little impact on outcomes of patients with low-grade endometrial endometrioid carcinoma.

Key Words: endometrial endometrioid carcinoma, "microcystic, elongated, and fragmented (MELF)" pattern, growth arrest, cellular senescence, prognosis

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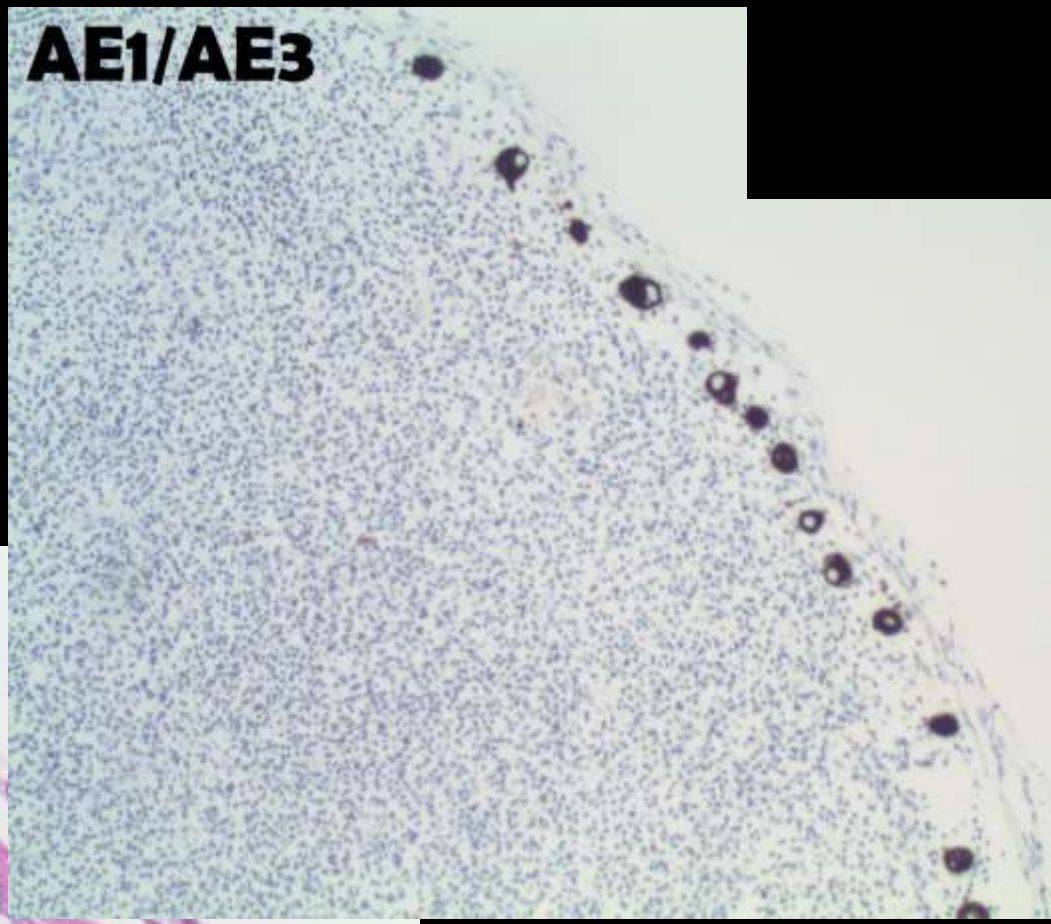
The incidence of endometrial carcinoma is increasing. Its most common histologic subtype is endometrioid carcinoma.[1] Although patients with low-grade (grades 1 and 2) endometrioid carcinoma have better outcomes than those with high-grade (grade 3) endometrioid carcinoma,[2,3] a subset of patients with low-grade endometrioid carcinoma have a recurrence and adverse prognosis. A histologic indicator of adverse outcome is still necessary for careful follow-up, early detection of a recurrence, and improvement of prognosis in patients with low-grade endometrioid carcinoma.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