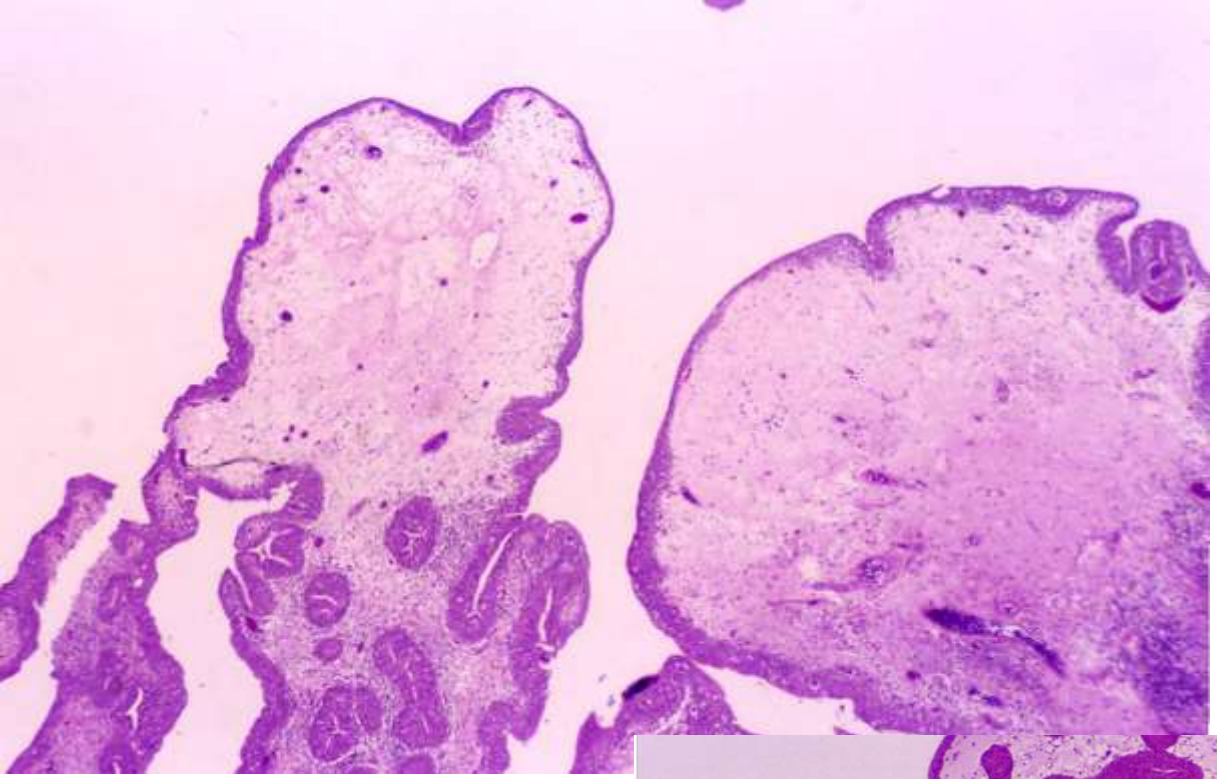
Mimics of bladder cancer NW EQA May 2022

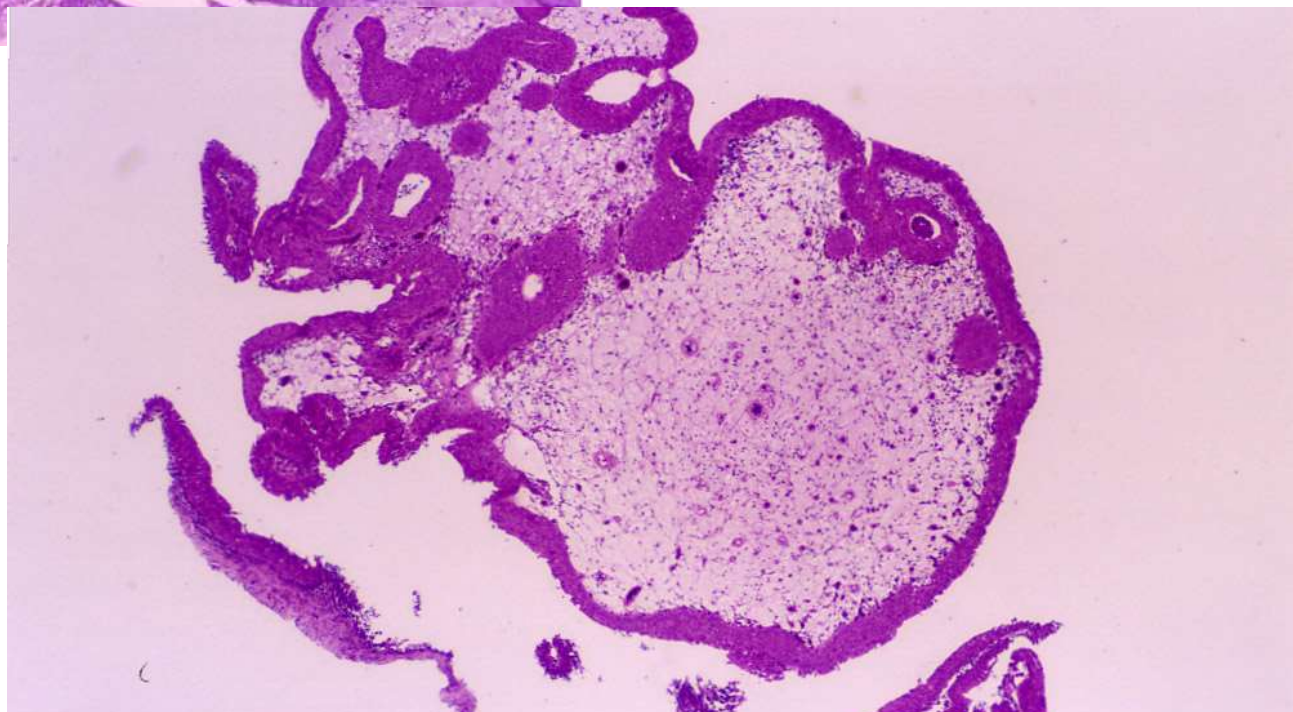
Dr Jonathan H Shanks

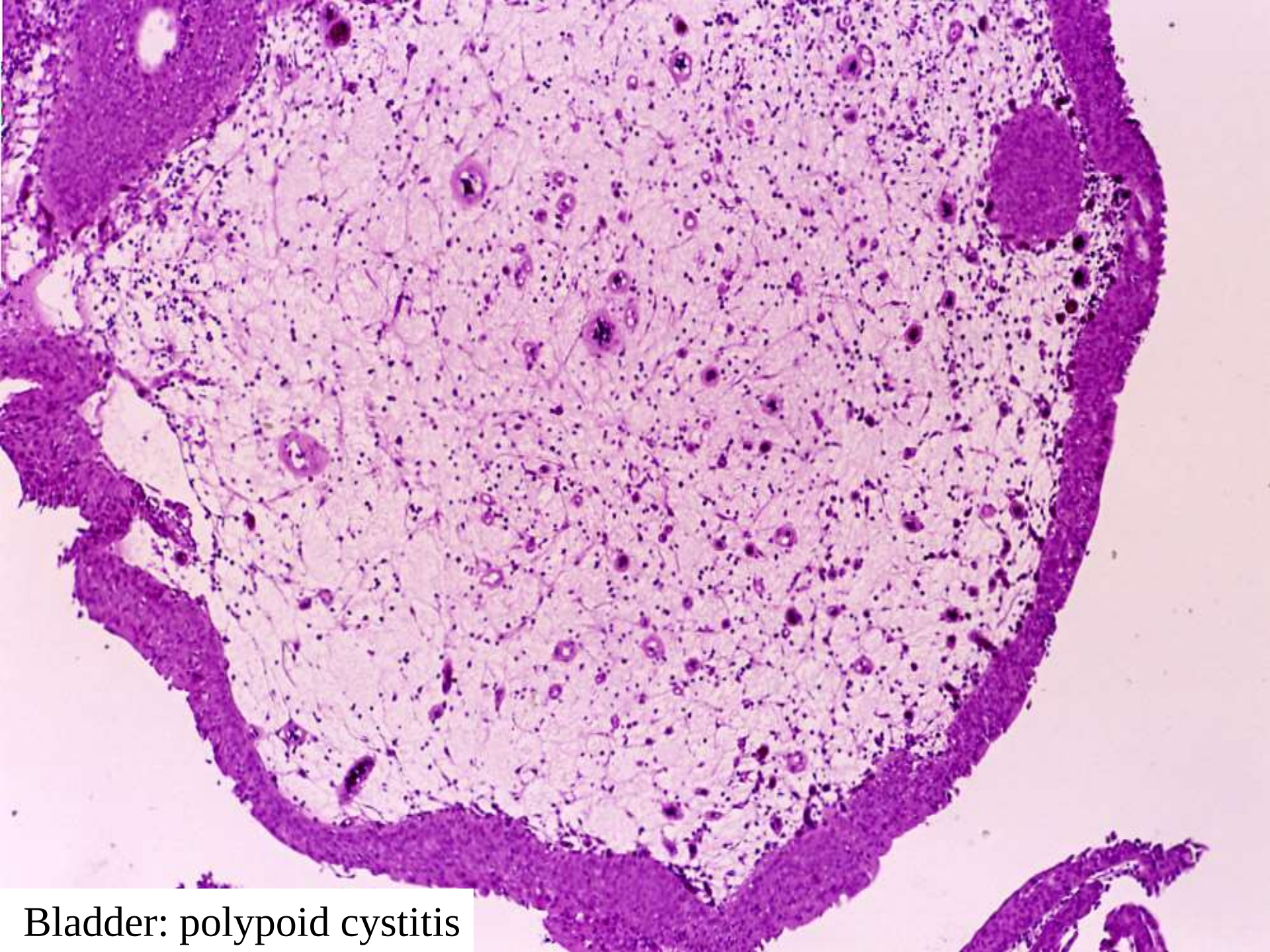
The Christie NHS Foundation Trust, Manchester, UK

Polypoid/papillary cystitis

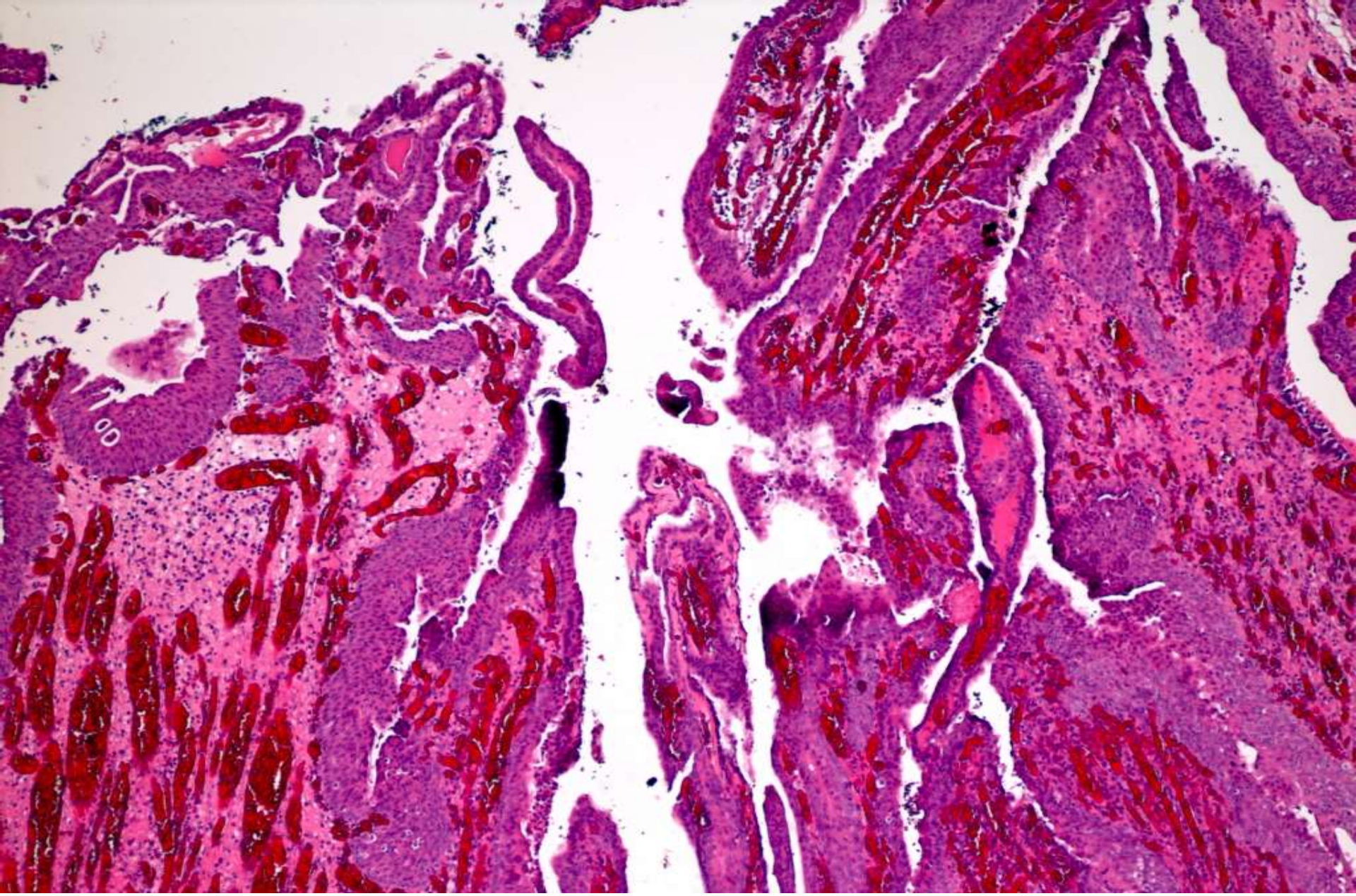
- Most common on dome/ posterior wall
- Associated with indwelling catheter or vesical fistula (diverticular disease, Crohn's, colorectal cancer), calculi, outflow obstruction
- Broad base, oedematous core; no fibrovascular core in most projections
- Normal surface urothelium
- May have some minor branching; no complex branching
- Lesion resolves on removal of catheter



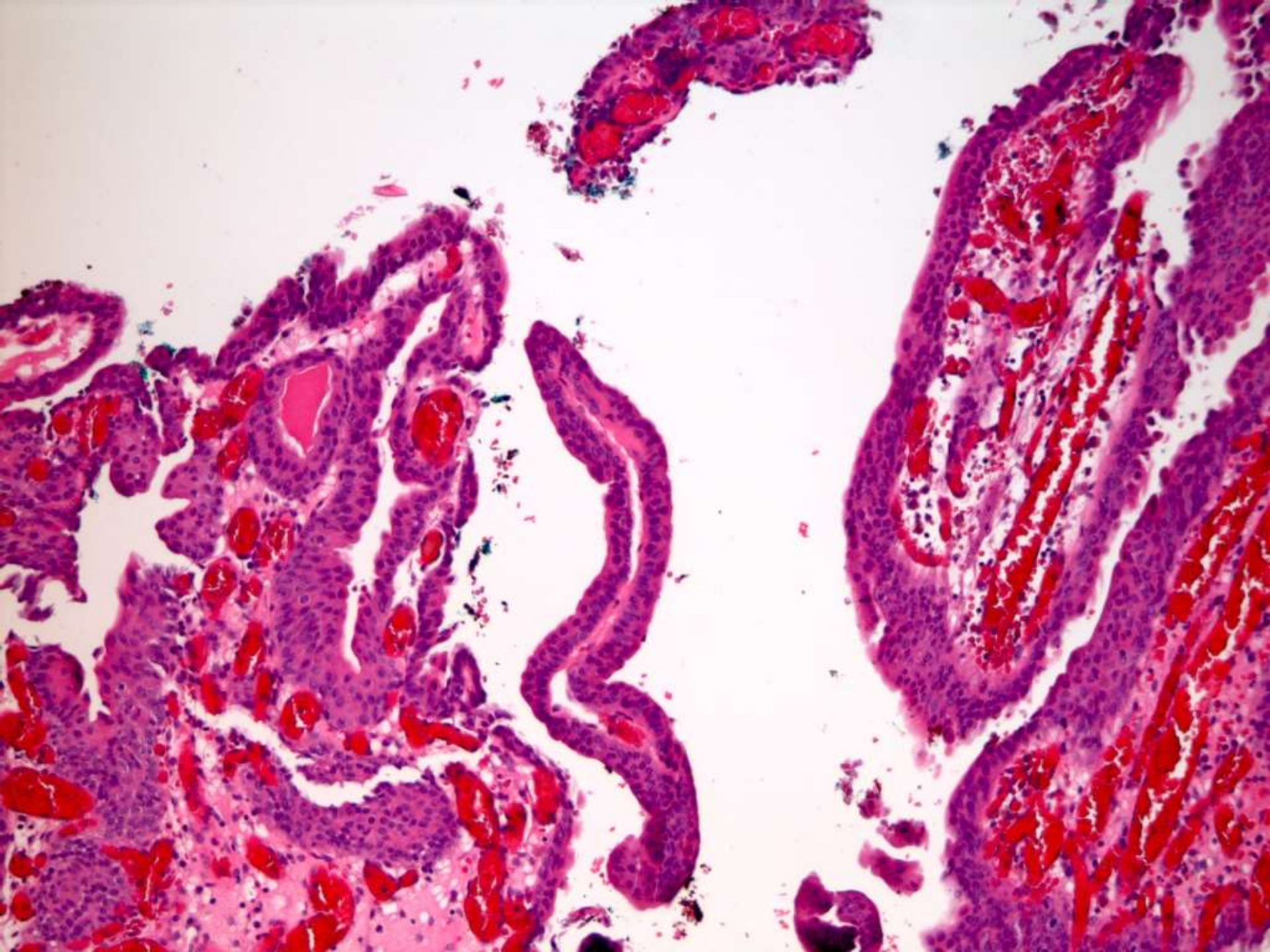




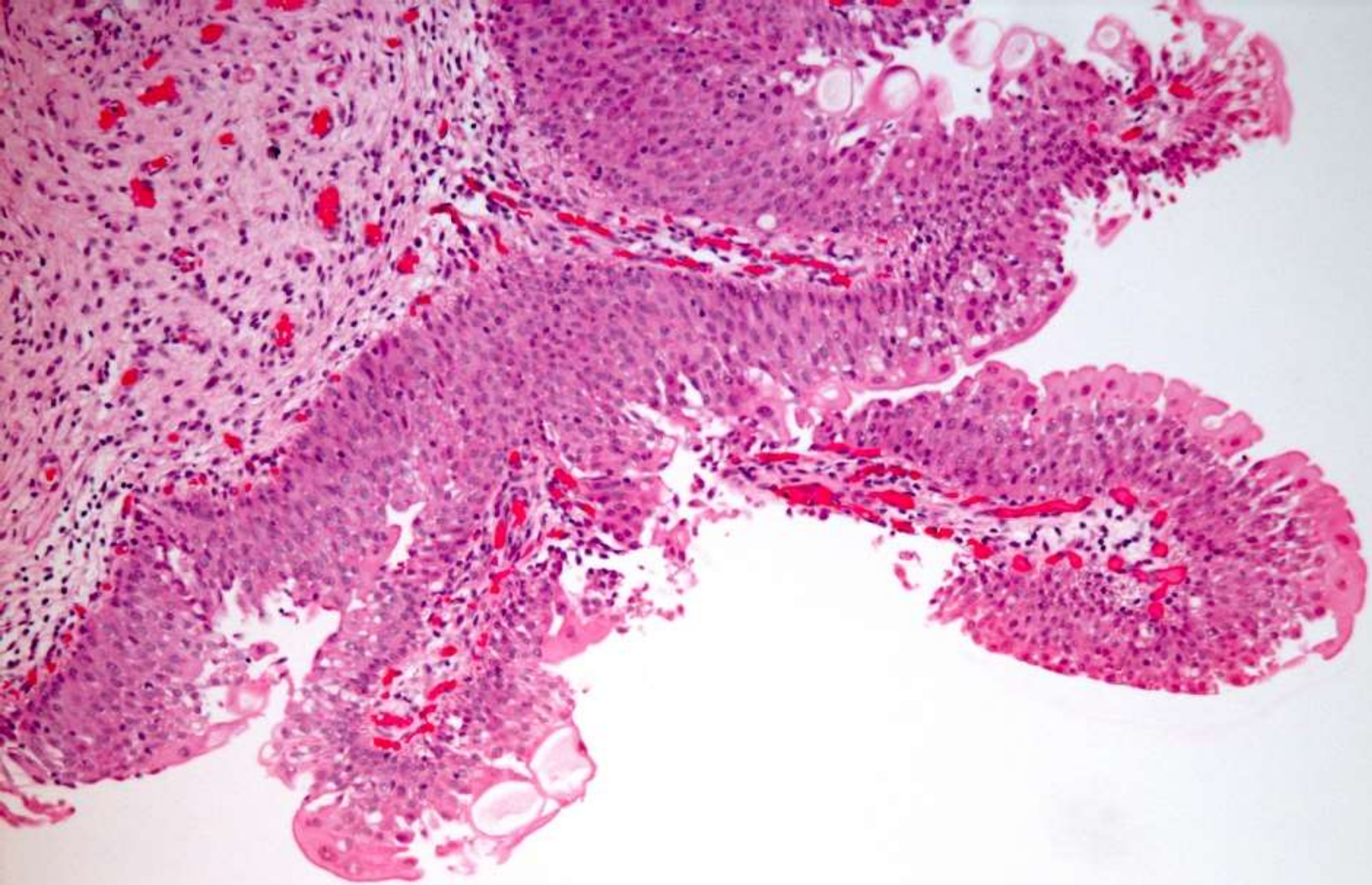
Bladder: polypoid cystitis

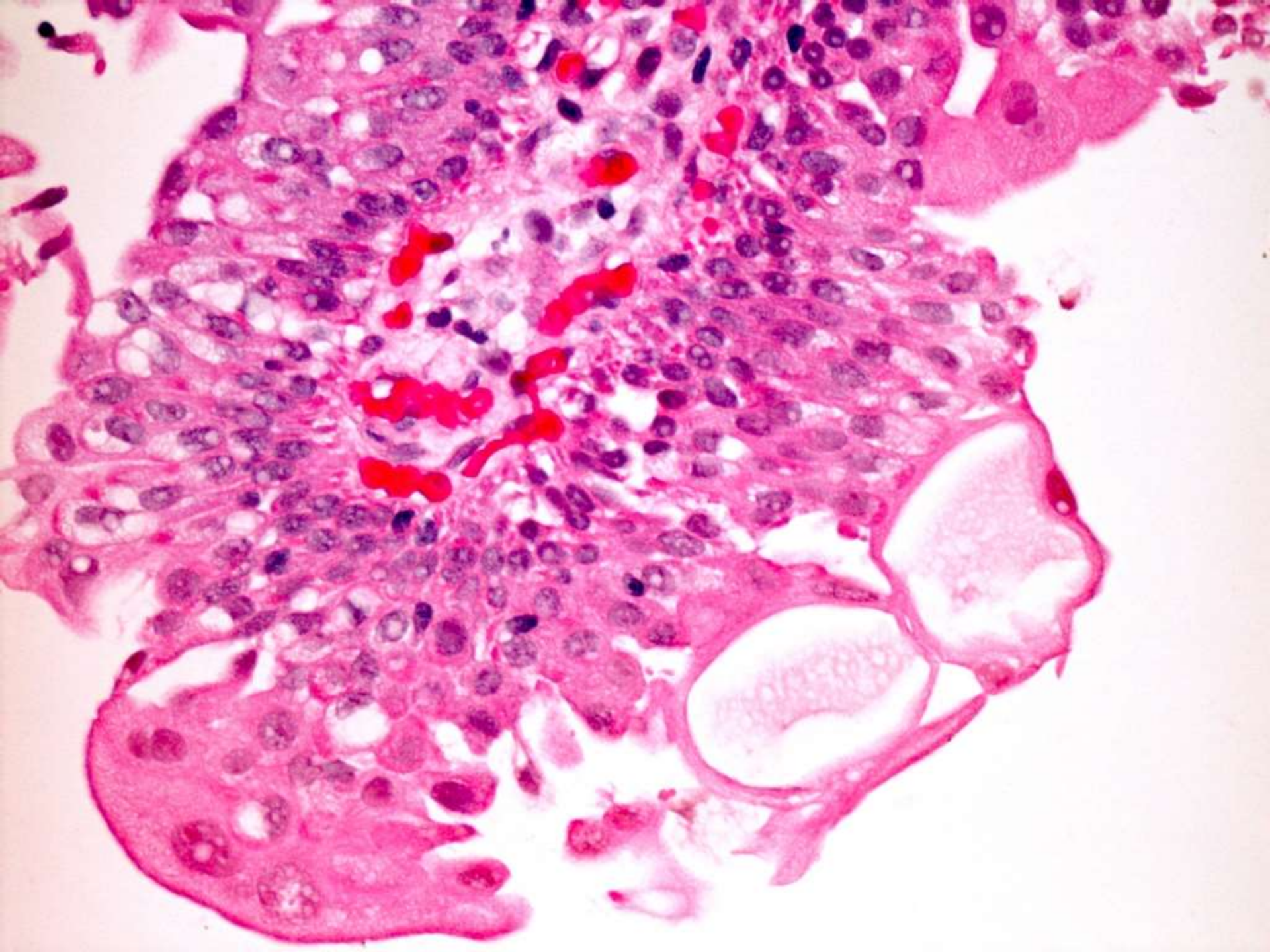


Section from cystectomy – patient had colovesical fistula related to diverticular disease



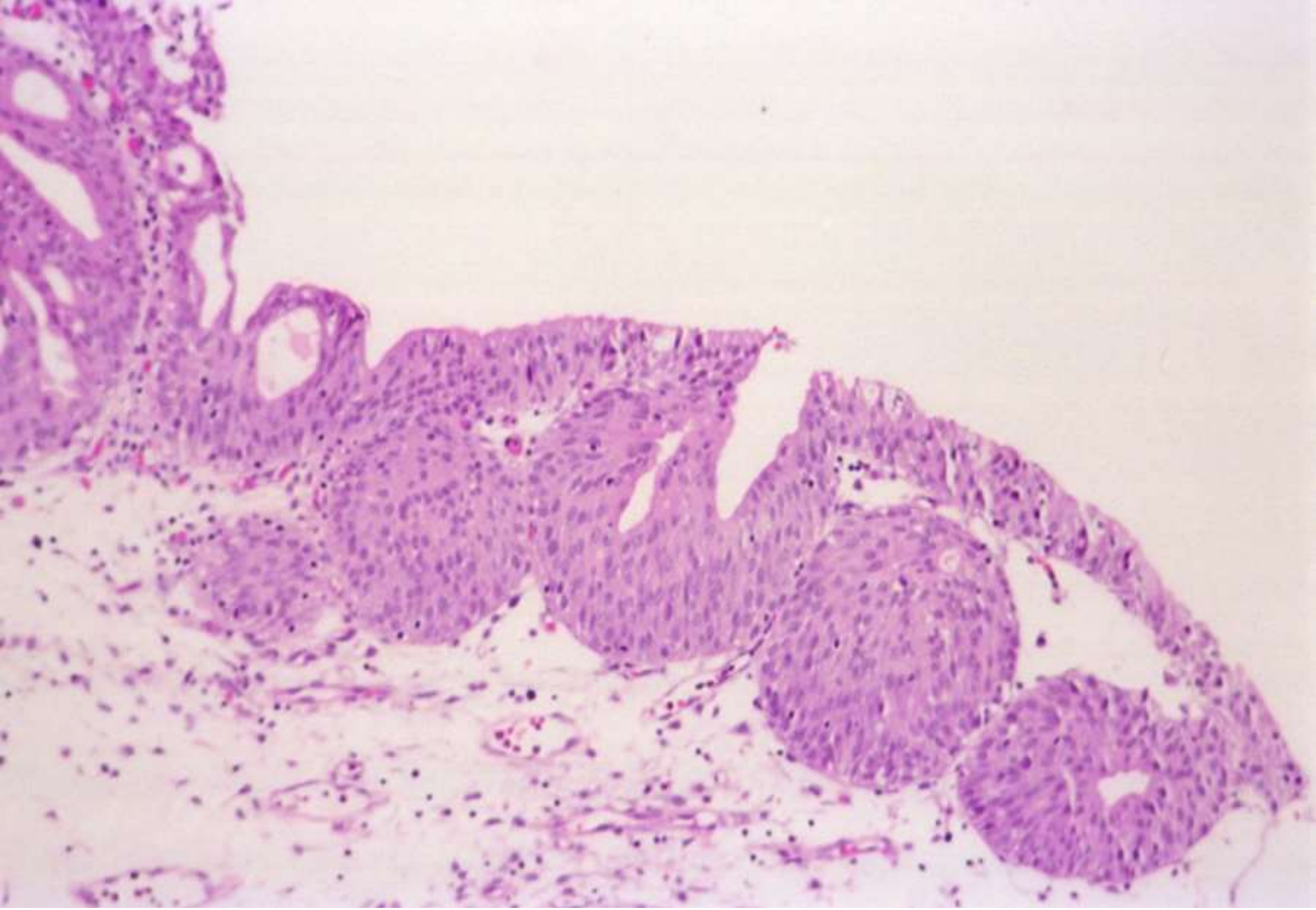
Polypoid/papillary cystitis: a series of 41 cases misdiagnosed as papillary urothelial neoplasia. Lane Z and Epstein JI.



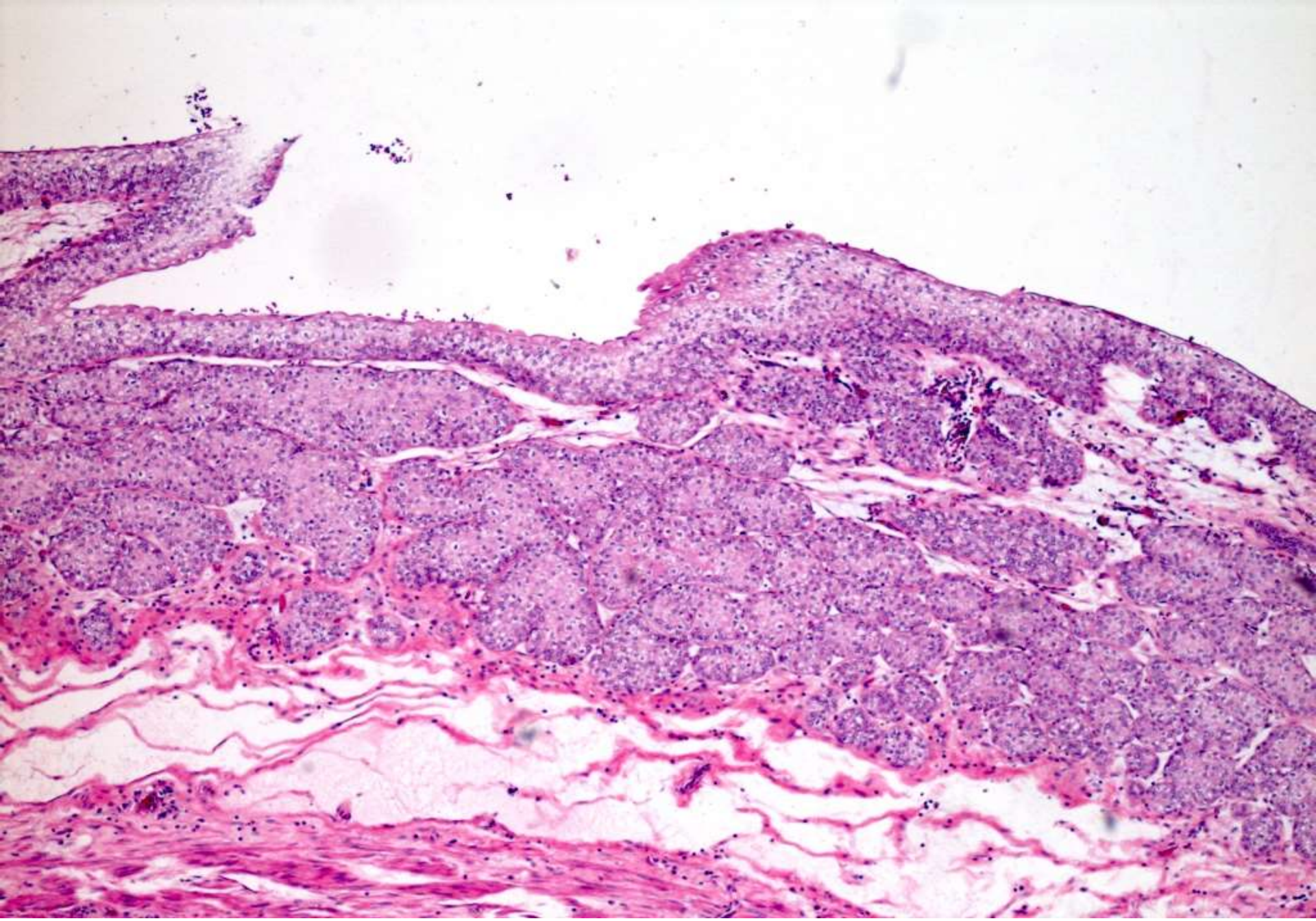


Urothelial papilloma

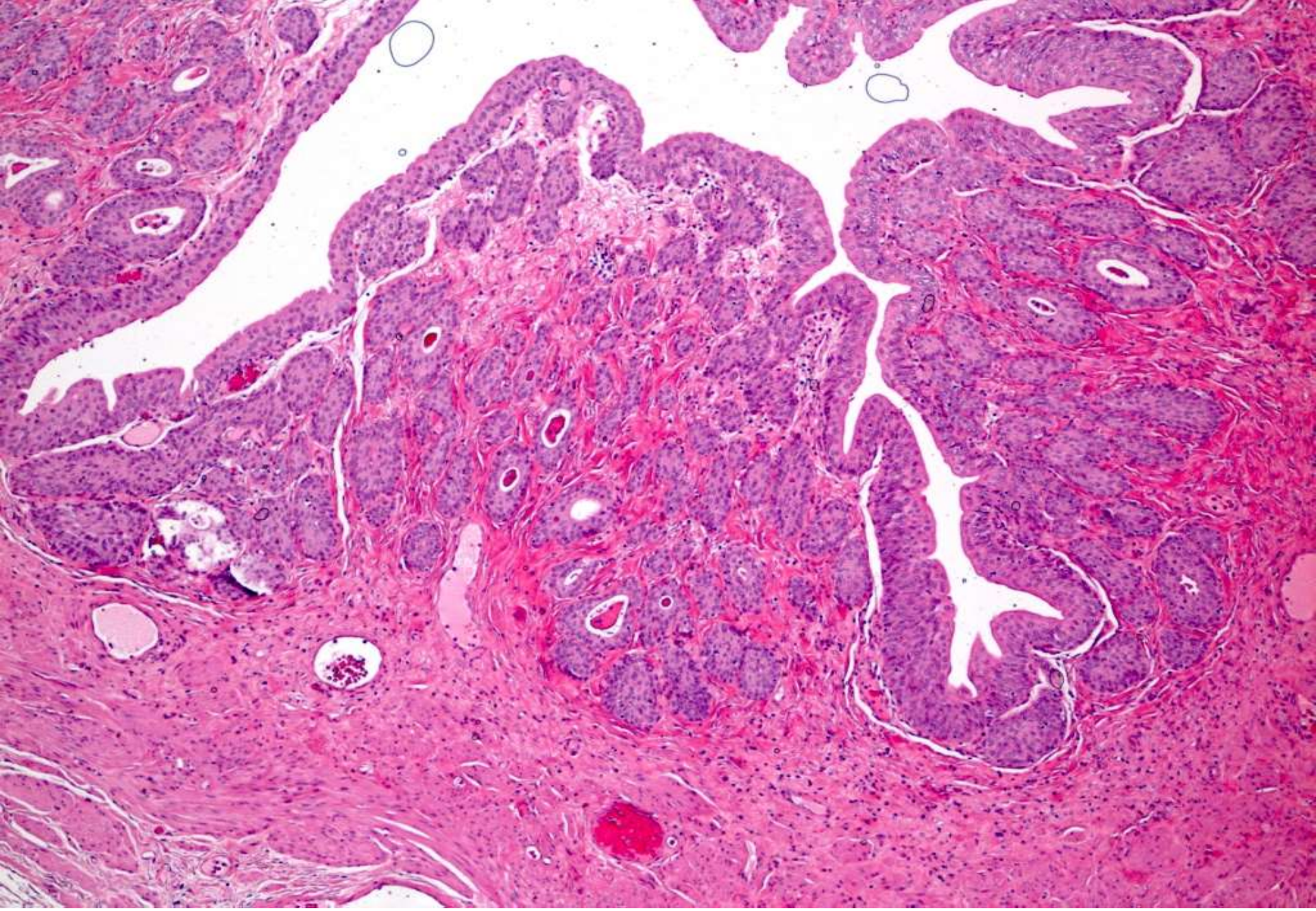
- Solitary lesion
- Usually young individuals
- Delicate fibrovascular stalks covered by normal urothelium (normal cytology and thickness)
- Minimal/absent branching is typical
- CK20 expression like normal bladder (umbrella cells only)
- Umbrella cells may be prominent and may show enlarged nuclei with degenerate atypia that should be disregarded (+/- cytoplasmic vacuolation)



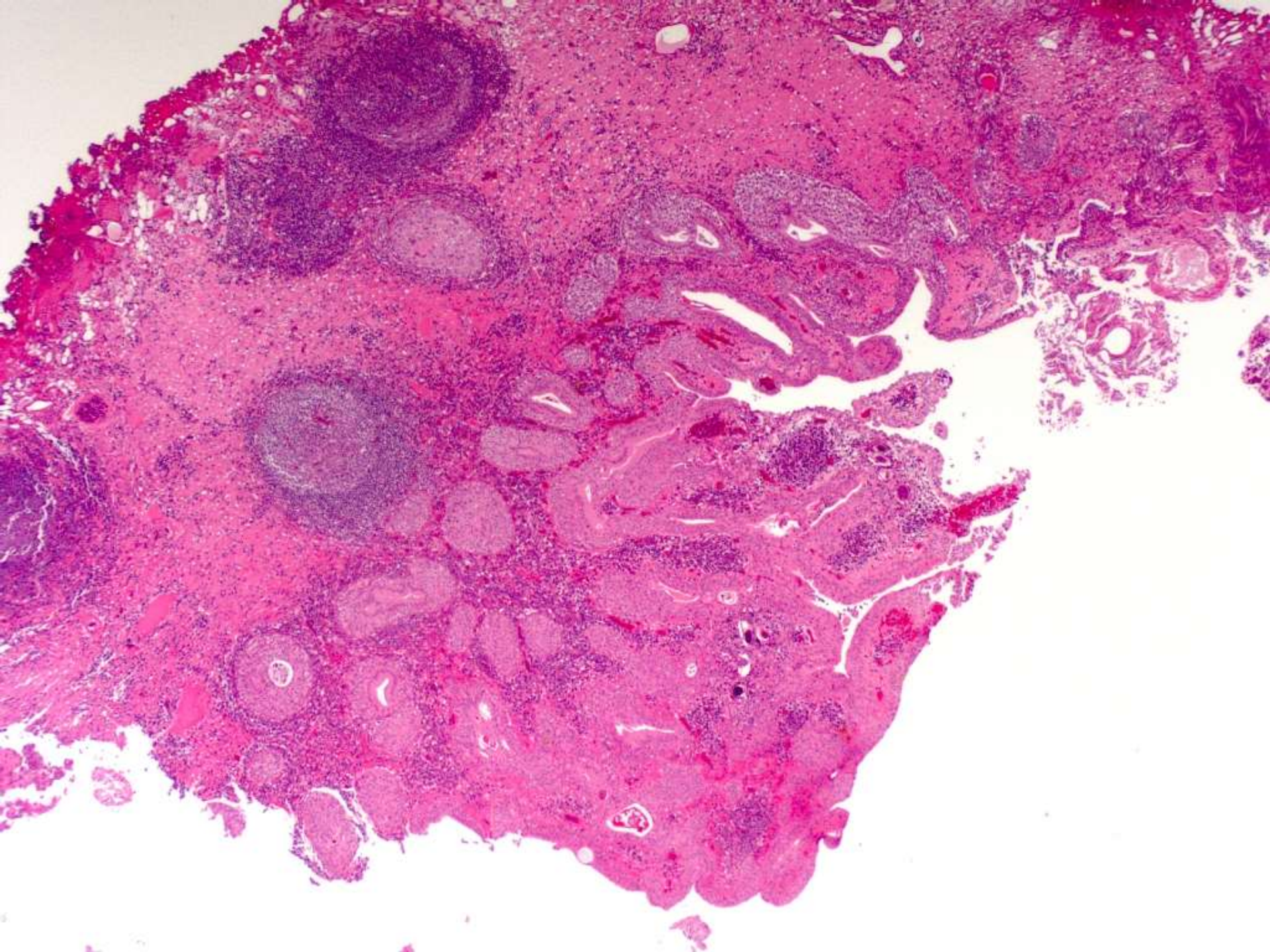
Normal bladder with von Brunn’s nests

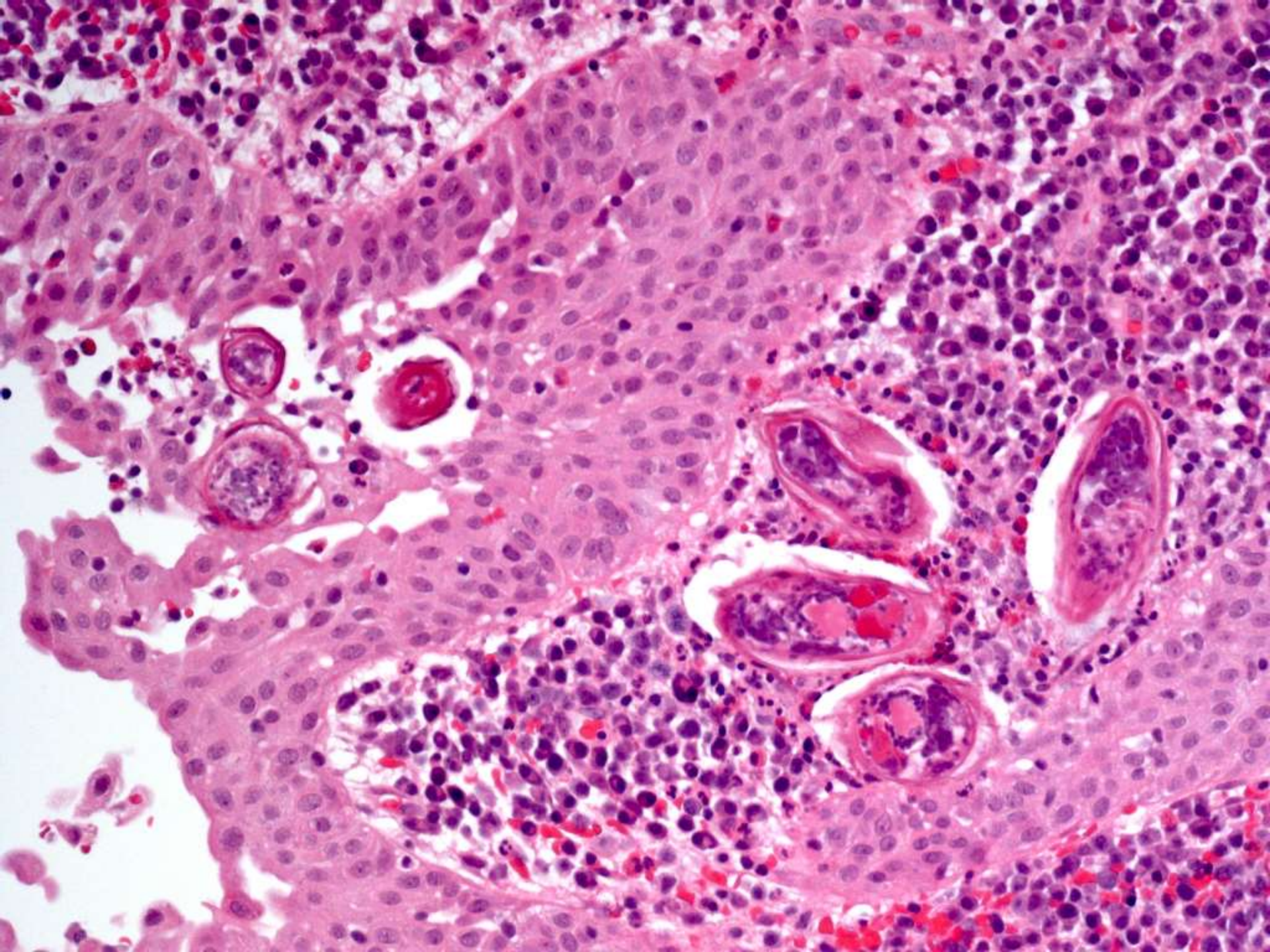


Reactive proliferation of von Brunn’s nests (relatively frequent in ureter/renal pelvis)



Reactive proliferation of von Brunn’s nests





Reactive proliferations (Amin MB)

Normal mucosa → von Brunn's nests (normal variant) → Florid proliferation of von Brunn's nests

↓

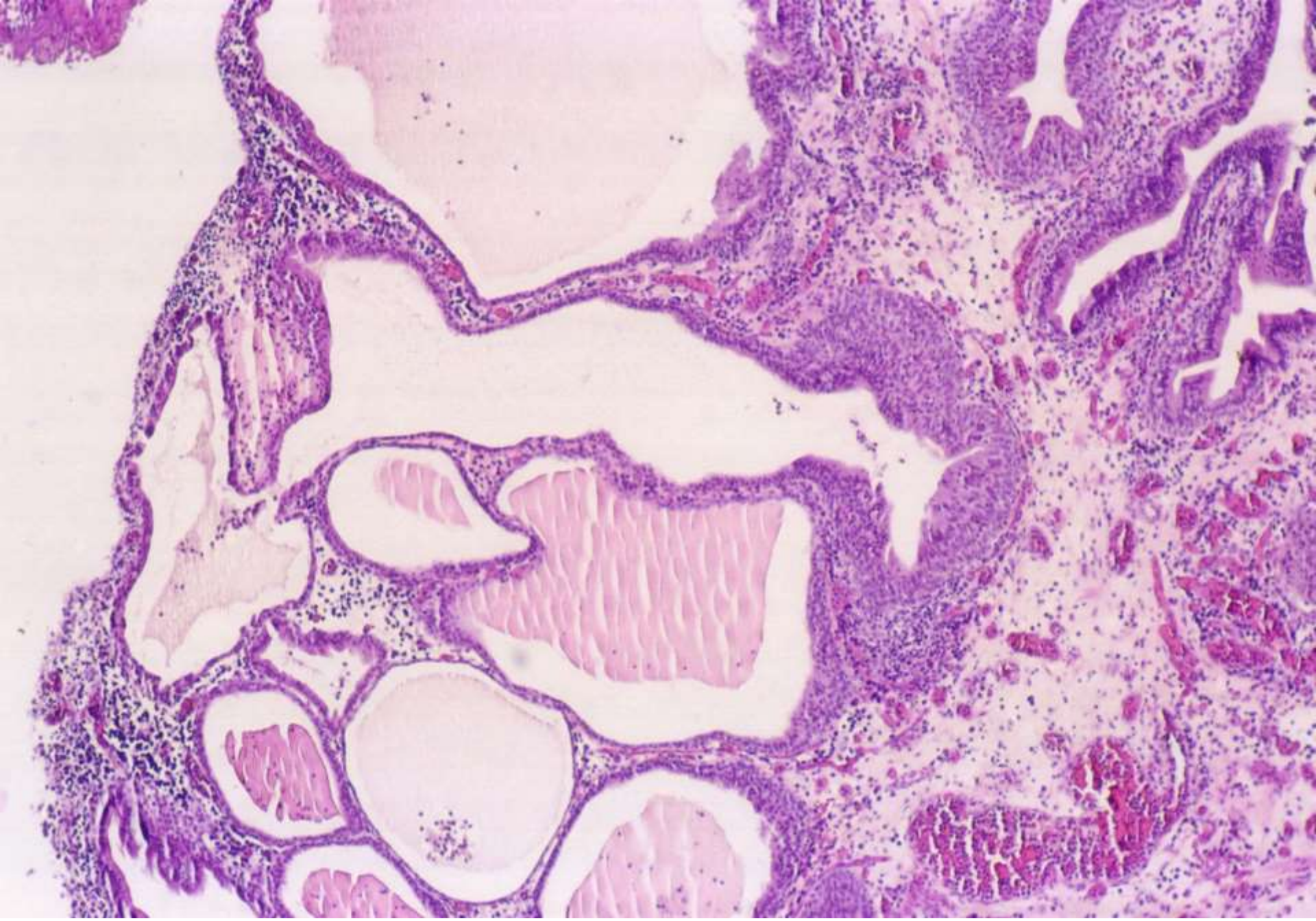
Cystic change (cystitis cystica)

↓

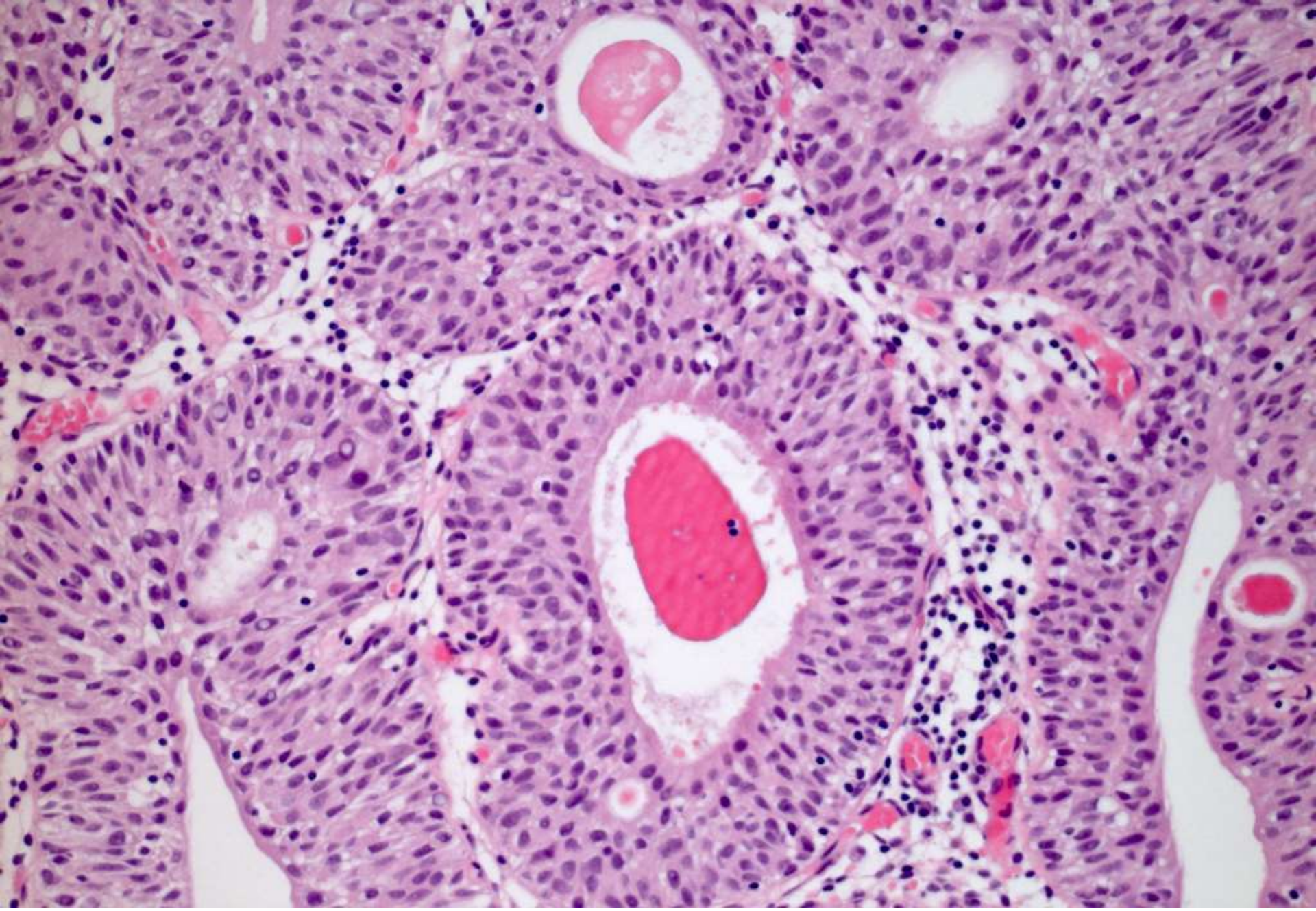
Columnar/cuboidal Cells ('usual' cystitis glandularis)

↓

Goblet cells/Paneth cells (intestinal metaplasia)



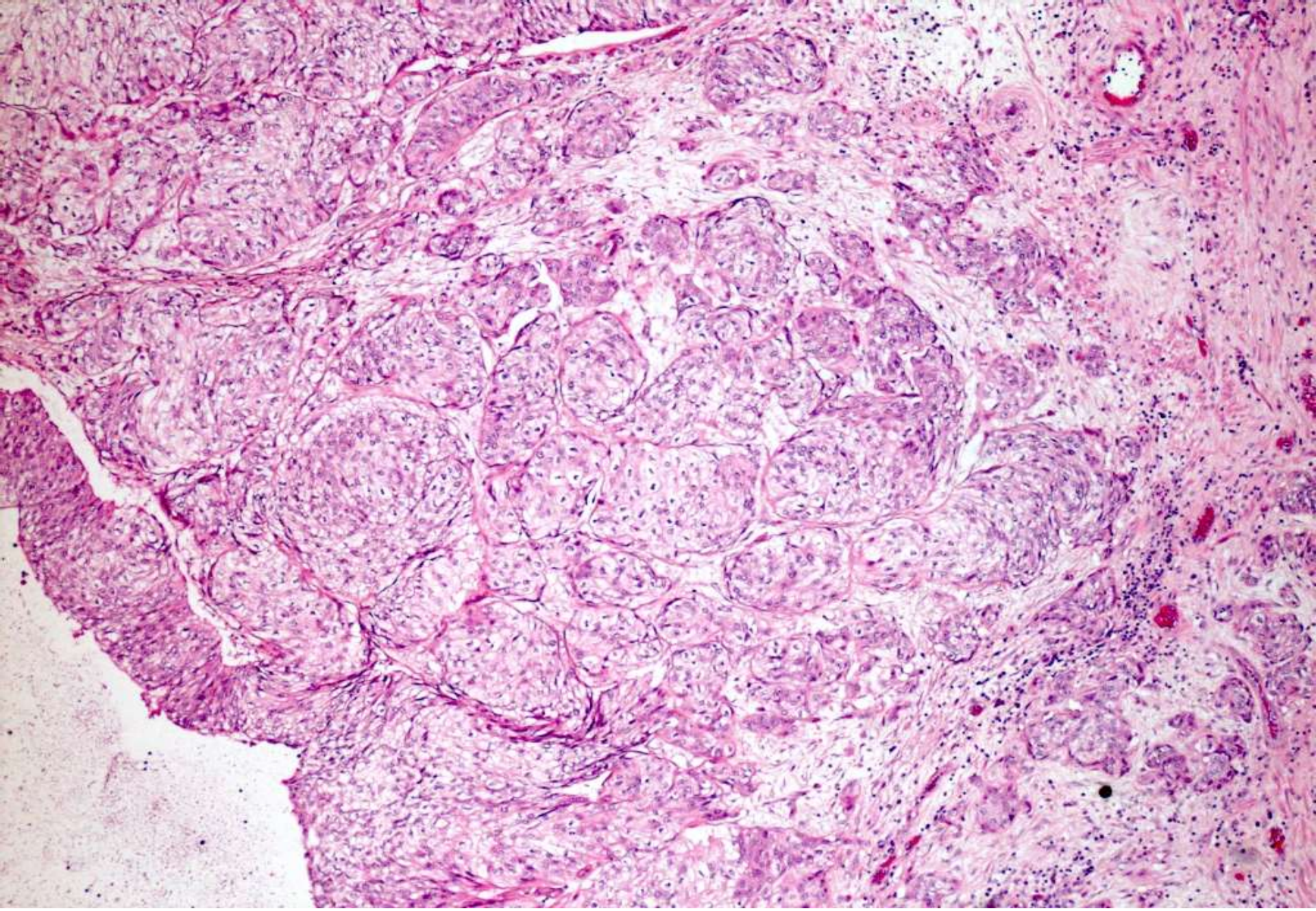
Cystitis cystica



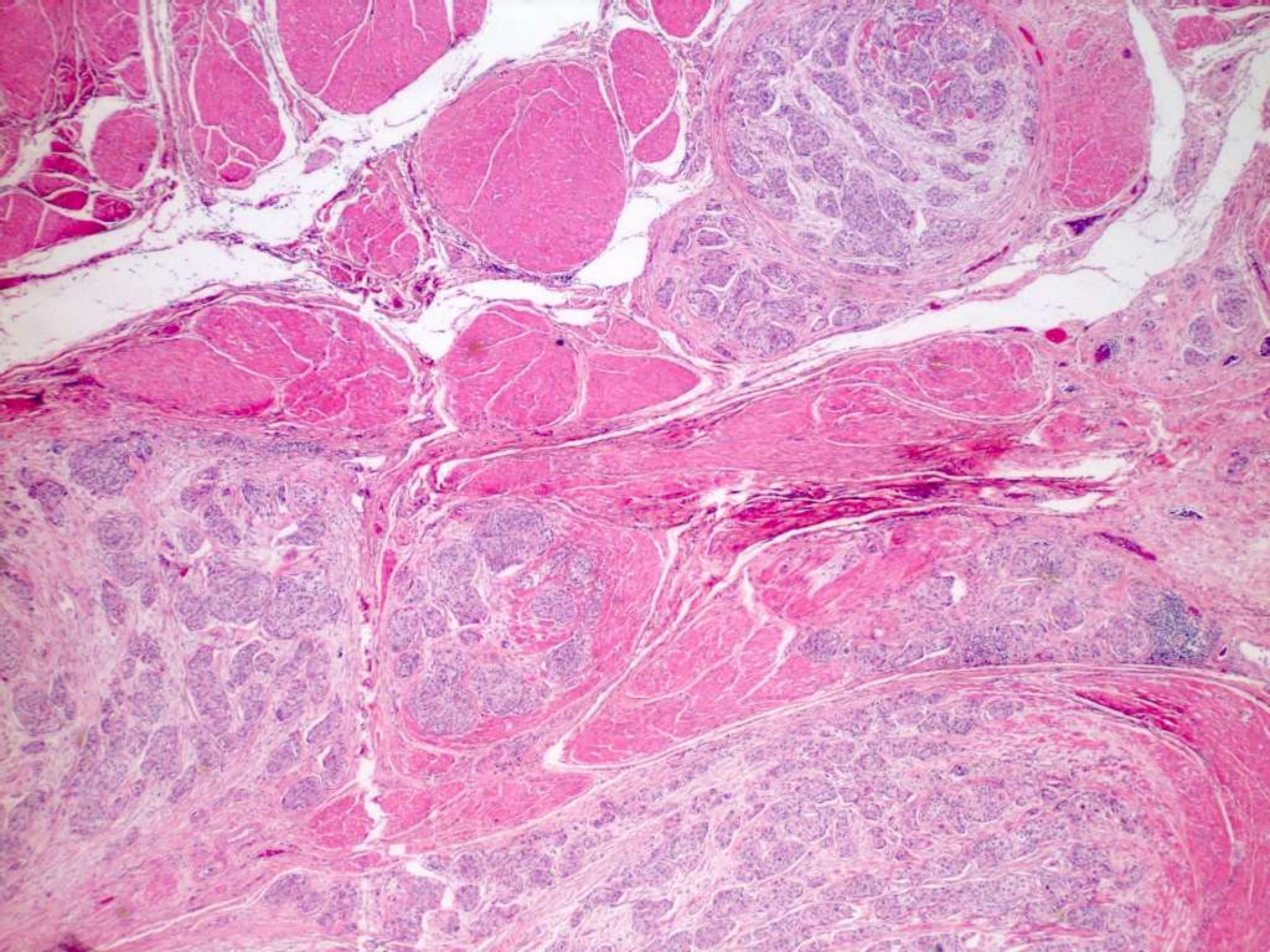
Cystitis glandularis (usual type)

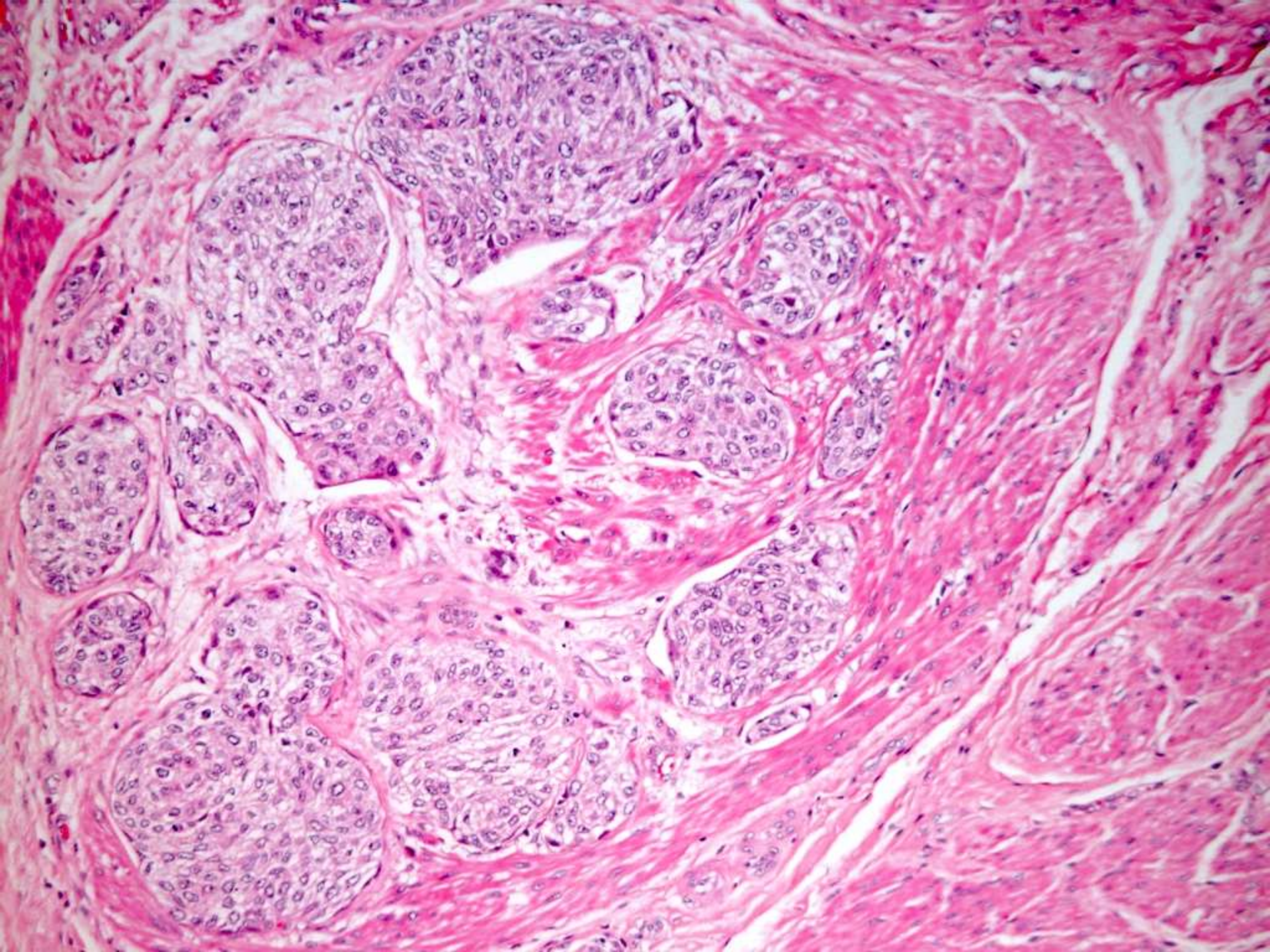
Cystitis glandularis (usual type)

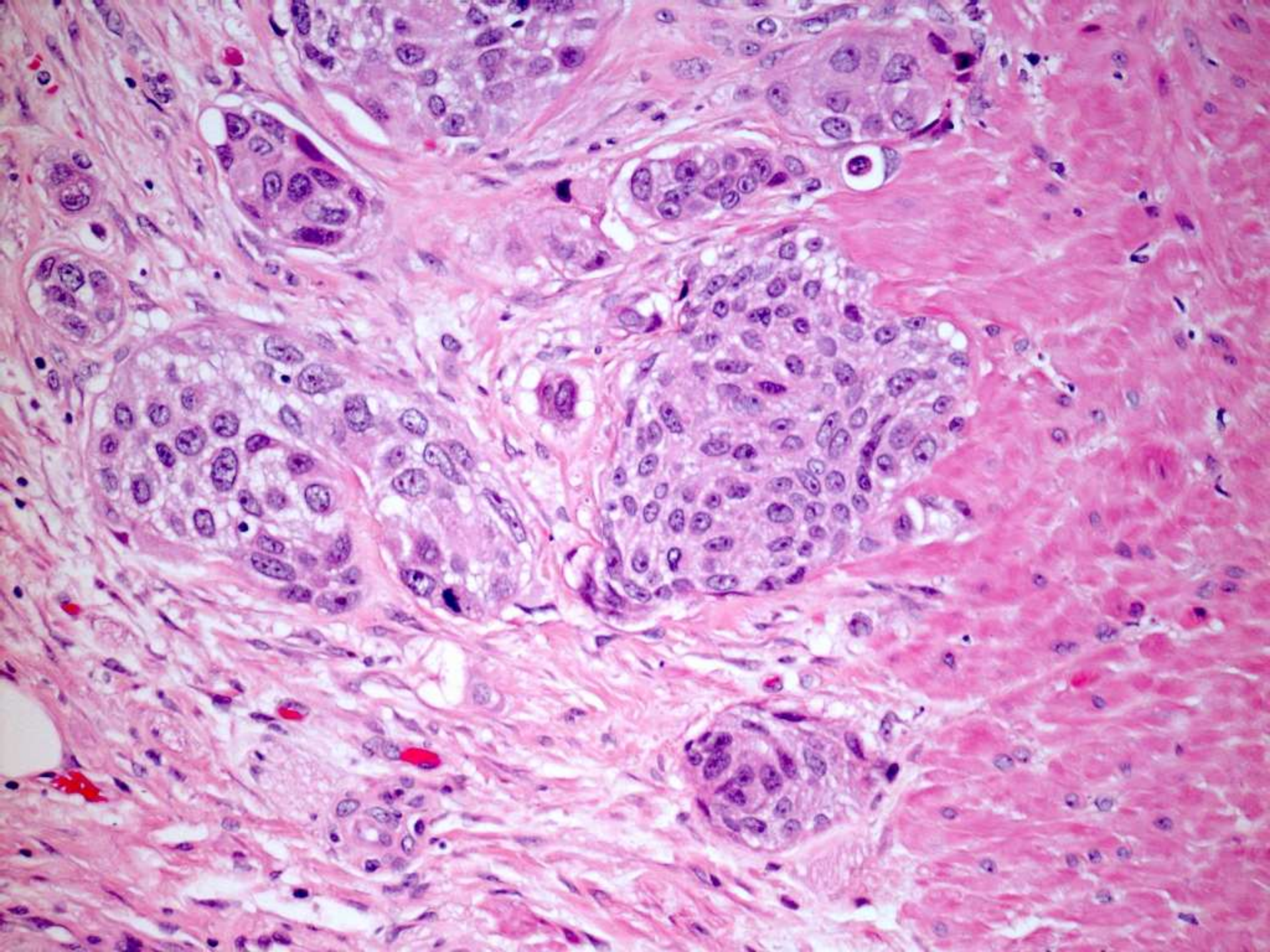
- Very common (up to 70%, mostly in trigone)
- Generally microscopic (but may form nodular/polypoid lesion)
- No risk of adenocarcinoma for typical variant (risk with intestinal metaplasia, but not if only focally present)

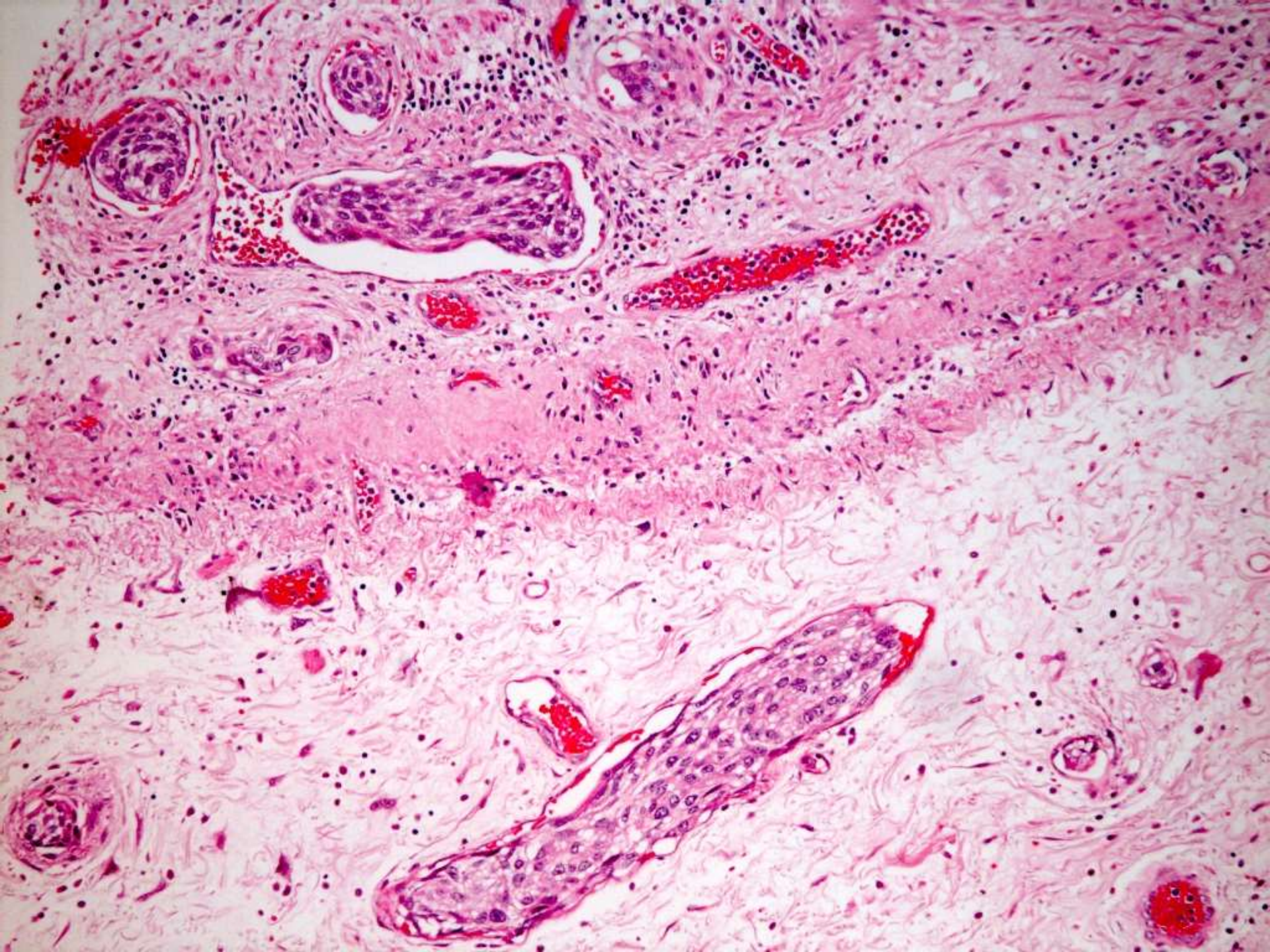


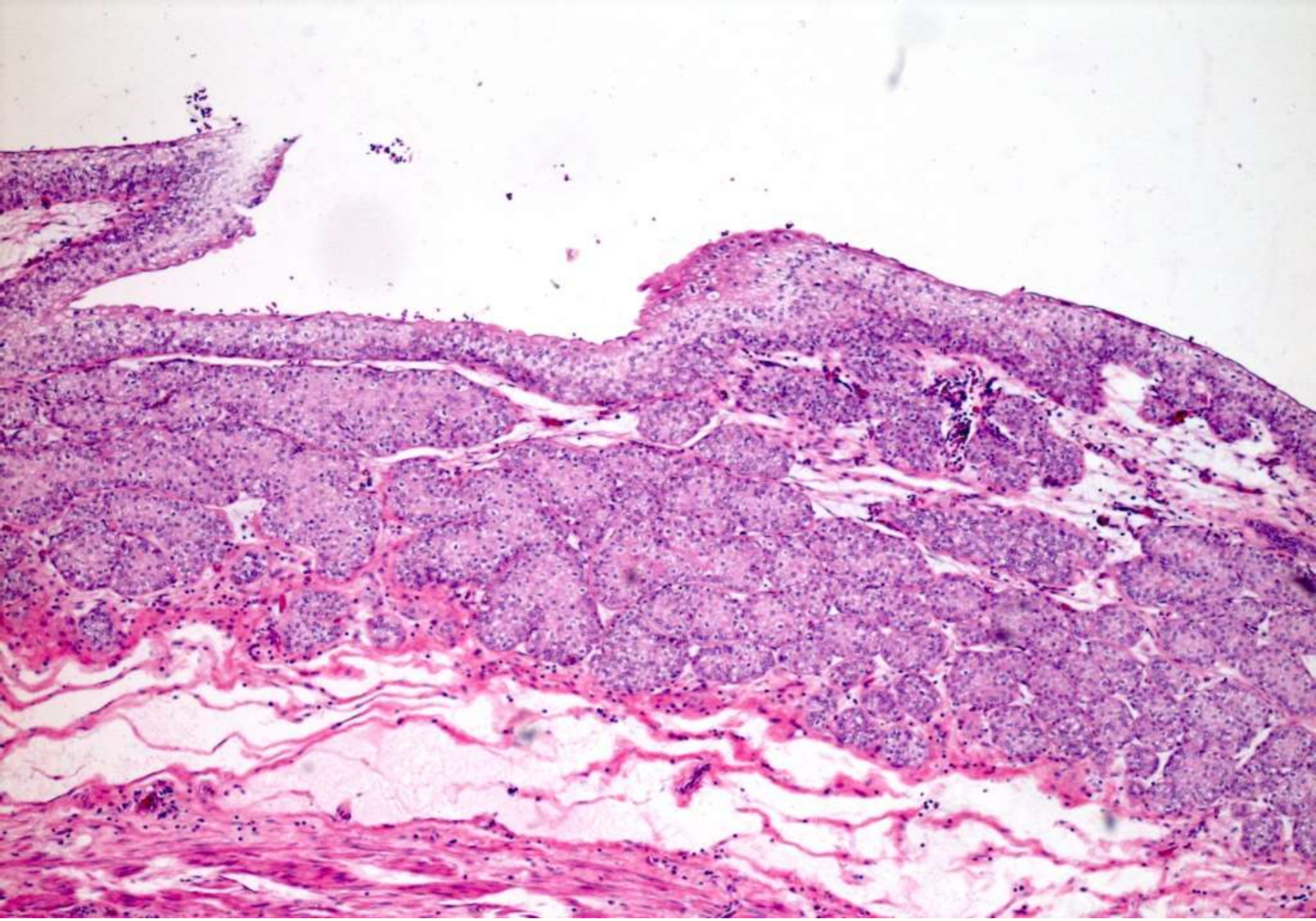
Nested variant urothelial carcinoma











Reactive proliferation of von Brunn’s nests

von Brunn's nest proliferation: features against nested urothelial carcinoma

- Regular shape and spacing
- Lobular or linear arrangement (with flat non-infiltrative base)
- No muscularis propria involvement
- No significant nuclear atypia (exception: CIS extending into von-Brunn's nests)

Distinguishing nested variants of urothelial carcinoma from benign mimickers by *TERT* promoter mutation Zhong *et al.*

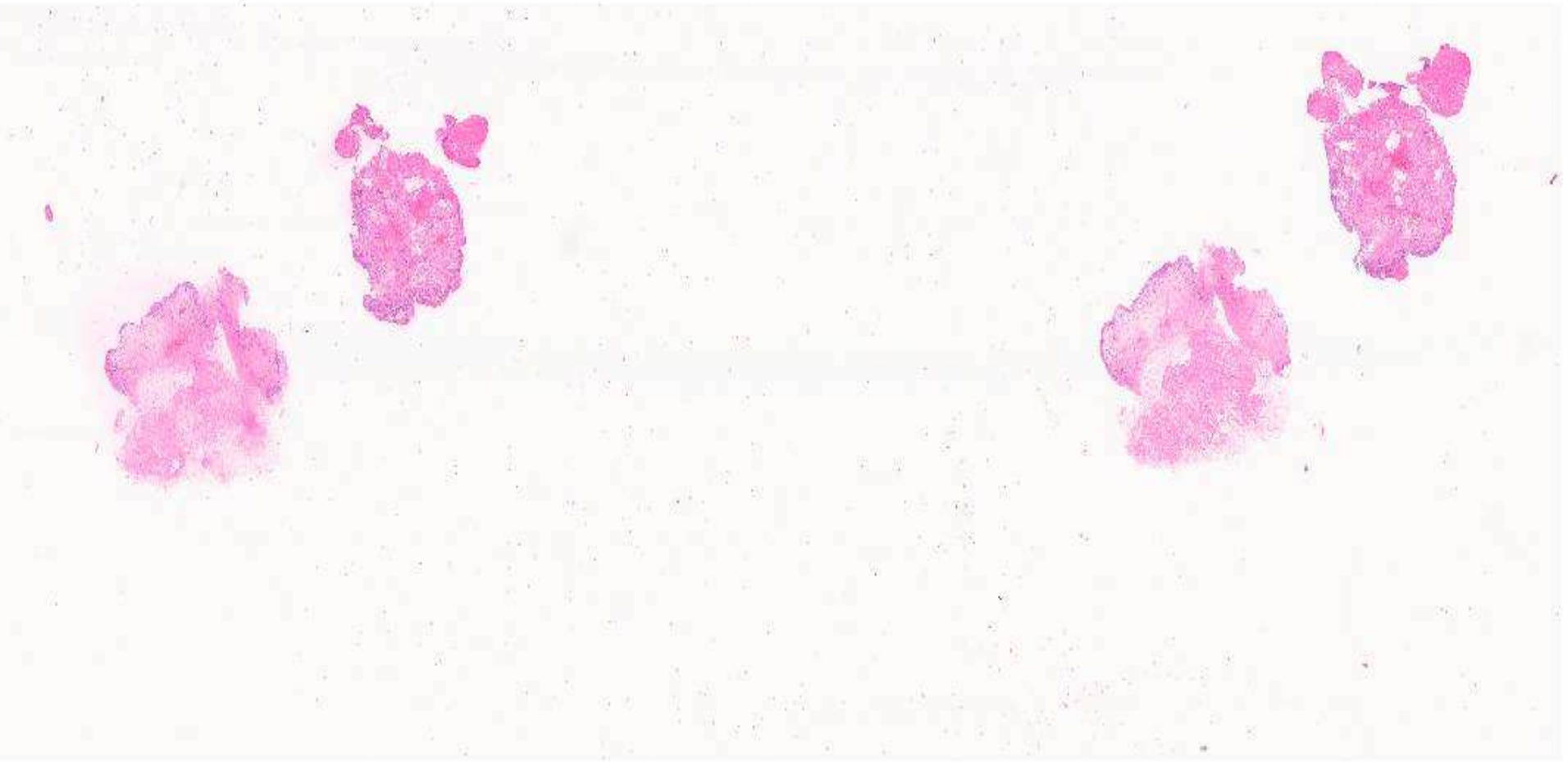
PAX8 expression and TERT promoter mutations in the nested variant of urothelial carcinoma: a clinicopathologic study with immunohistochemical and molecular correlates Taylor AS *et al.*

- PAX 8 positive in approx 50% nested variant urothelial carcinoma
- *TERT* promoter mutation found in most cases of nested variant urothelial carcinoma but very rare in mimics (in small series)

Case: history

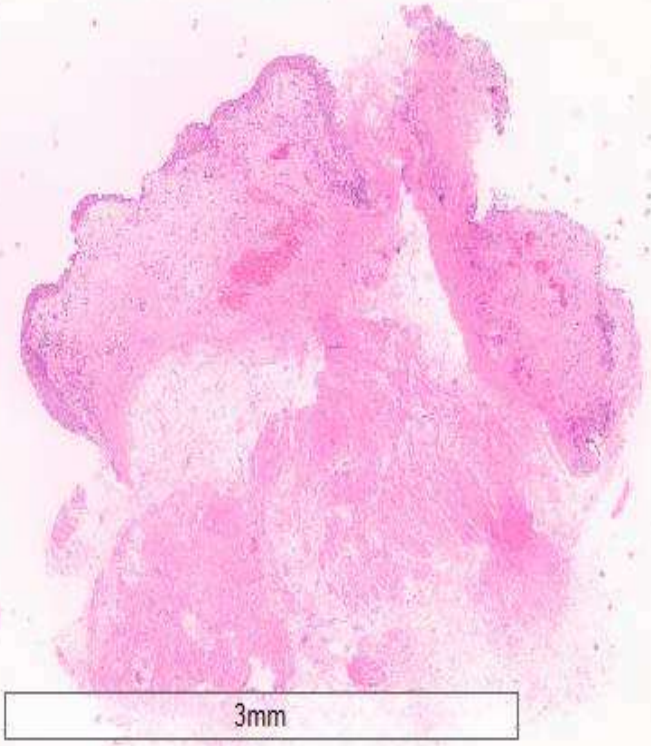
- Female 67 years old
- “Previous G3 pT3 TCC Rx with radiotherapy. Now ? Recurrence in bladder plus around left ureteric orifice”
- Specimens: A = “Right bladder wall”

  B = “Left ureteric orifice”

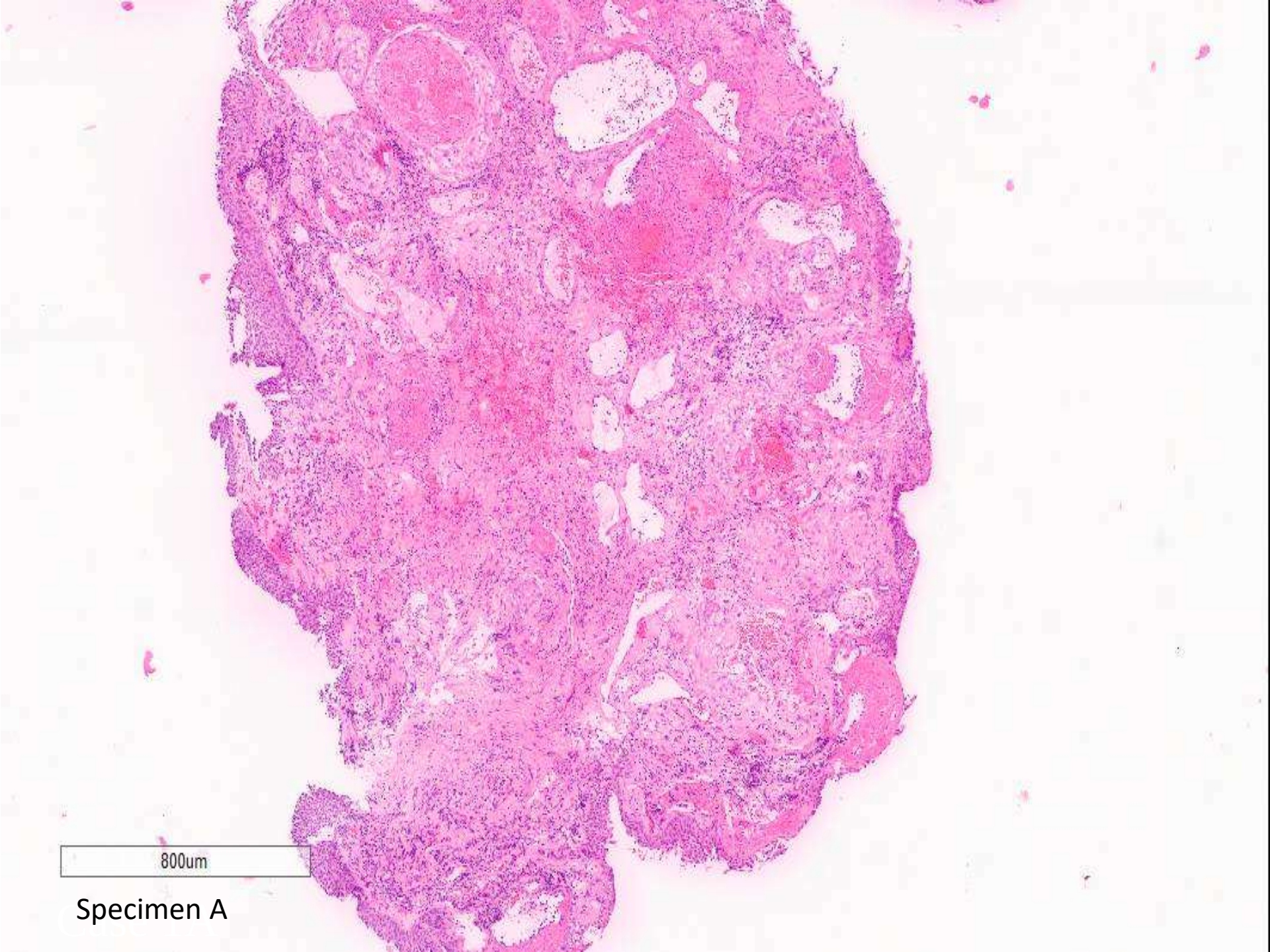


Specimen A

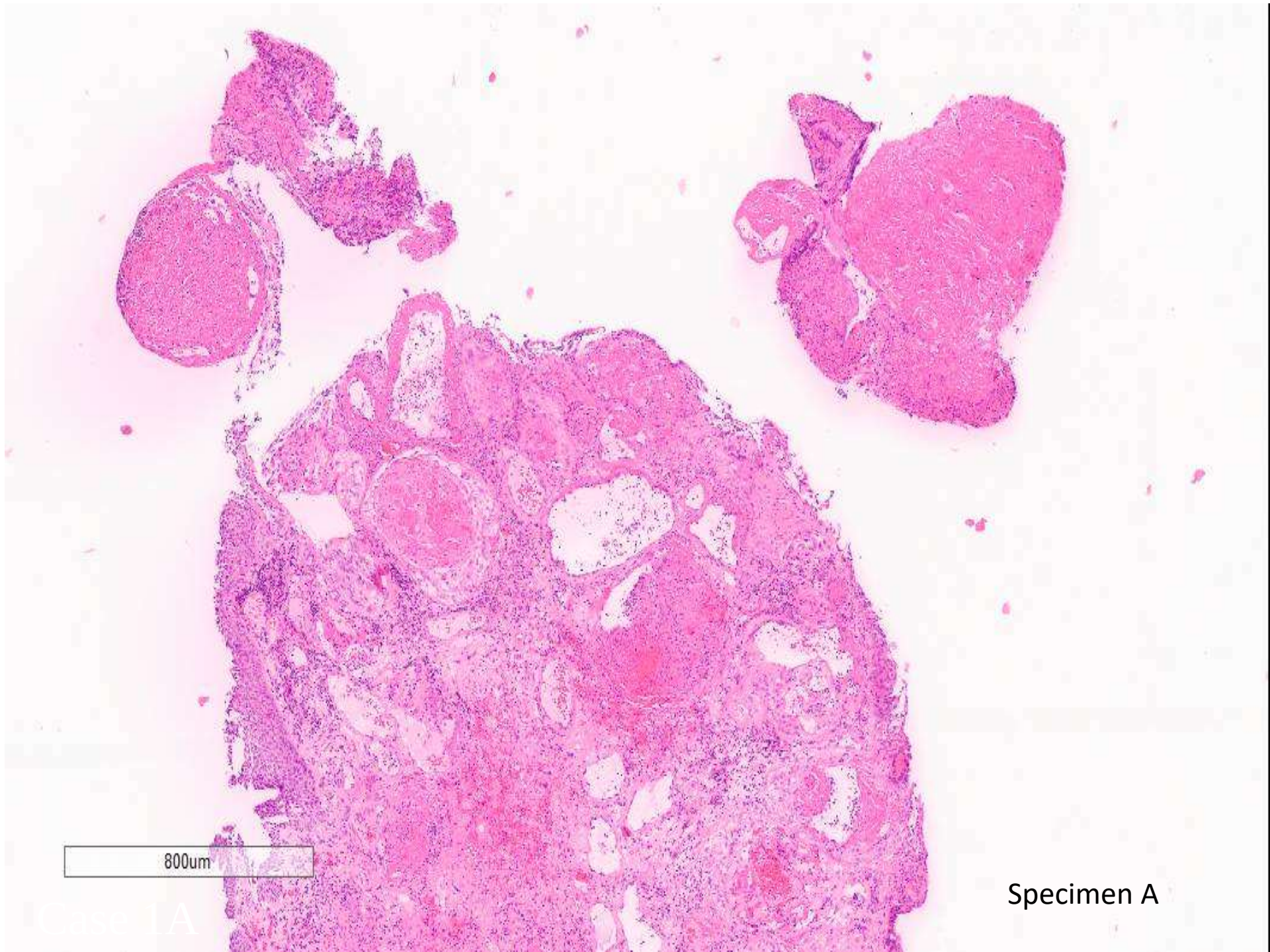
Case 1A



Specimen A



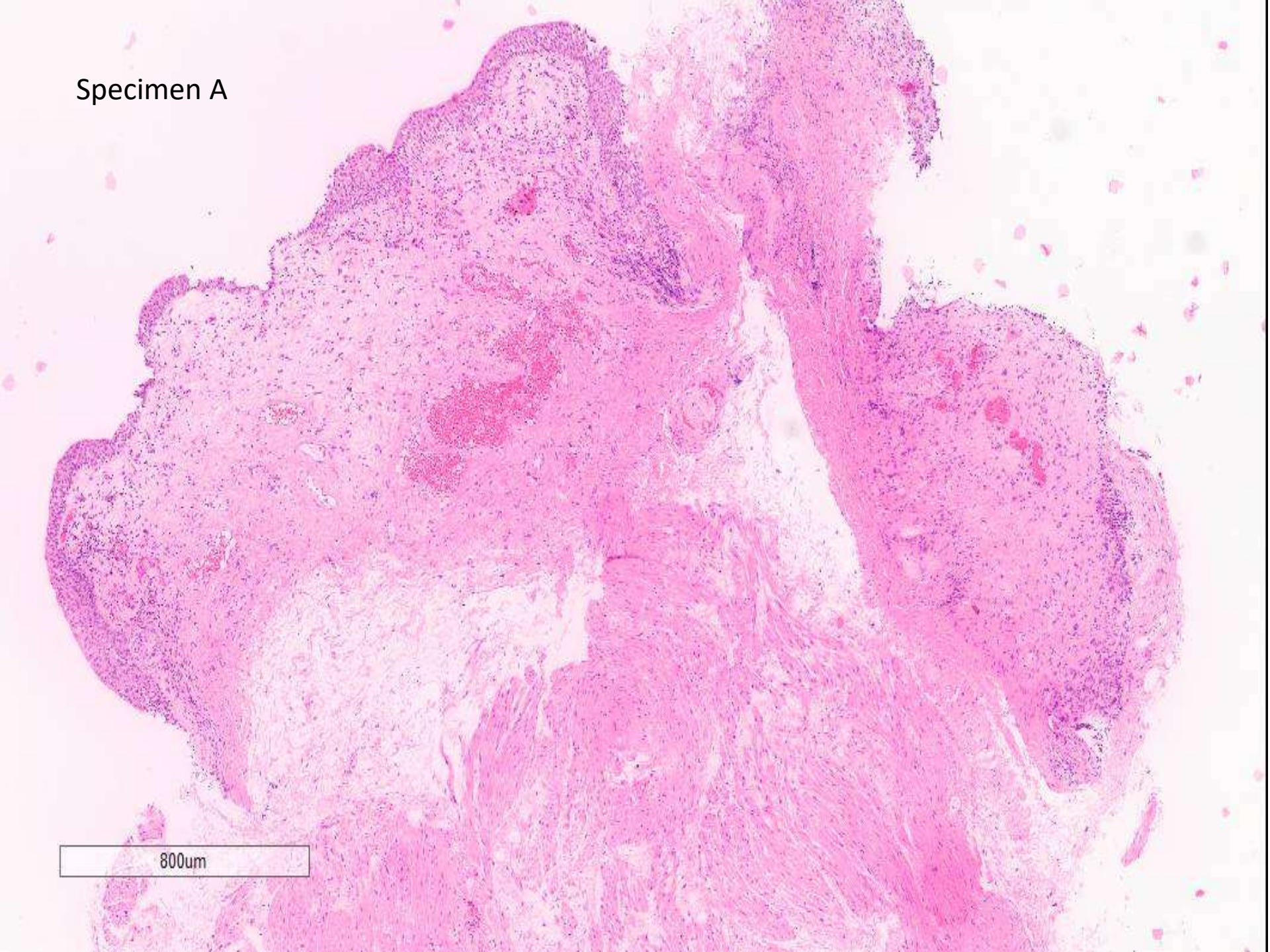
Specimen A

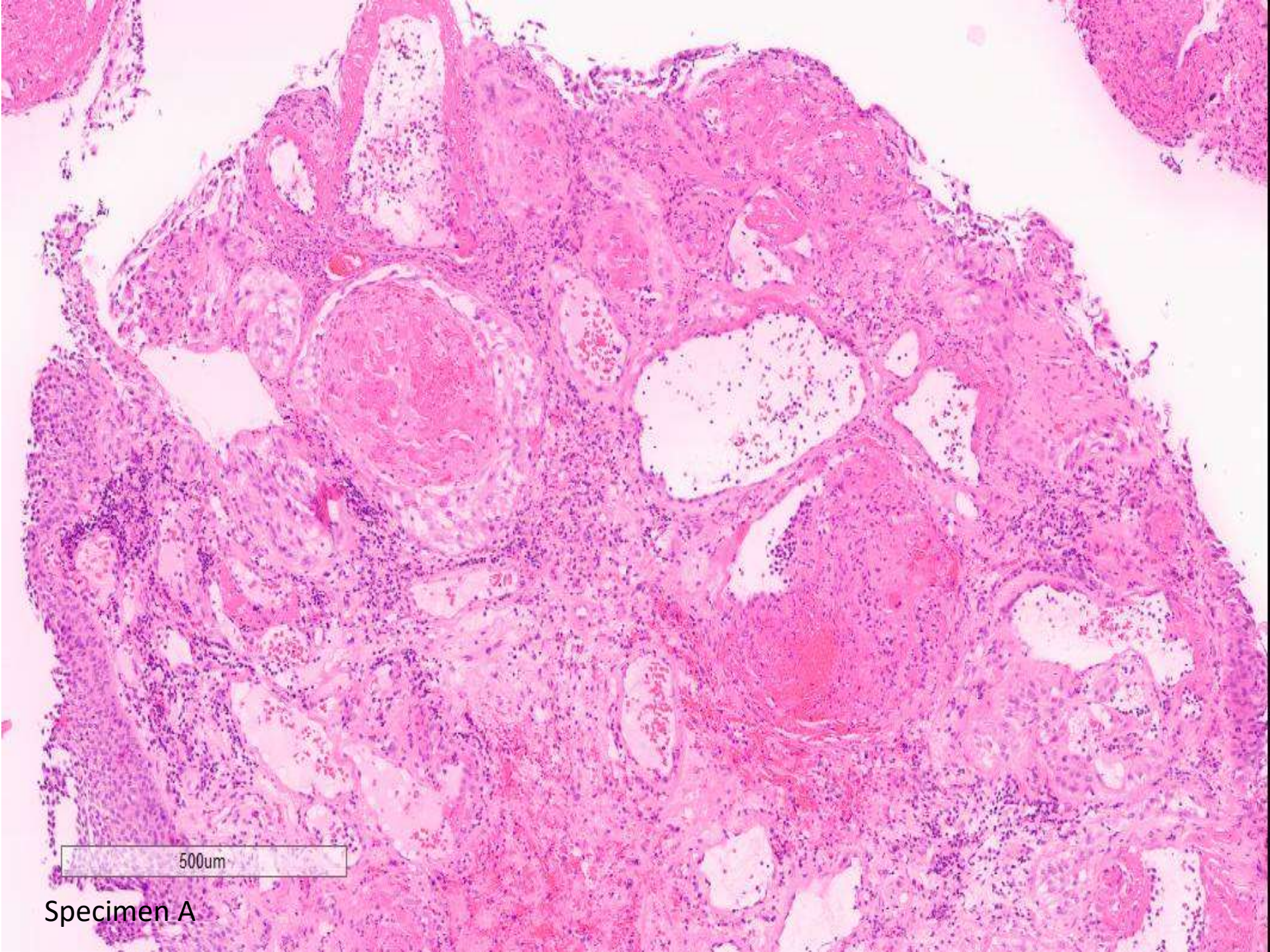


Specimen A

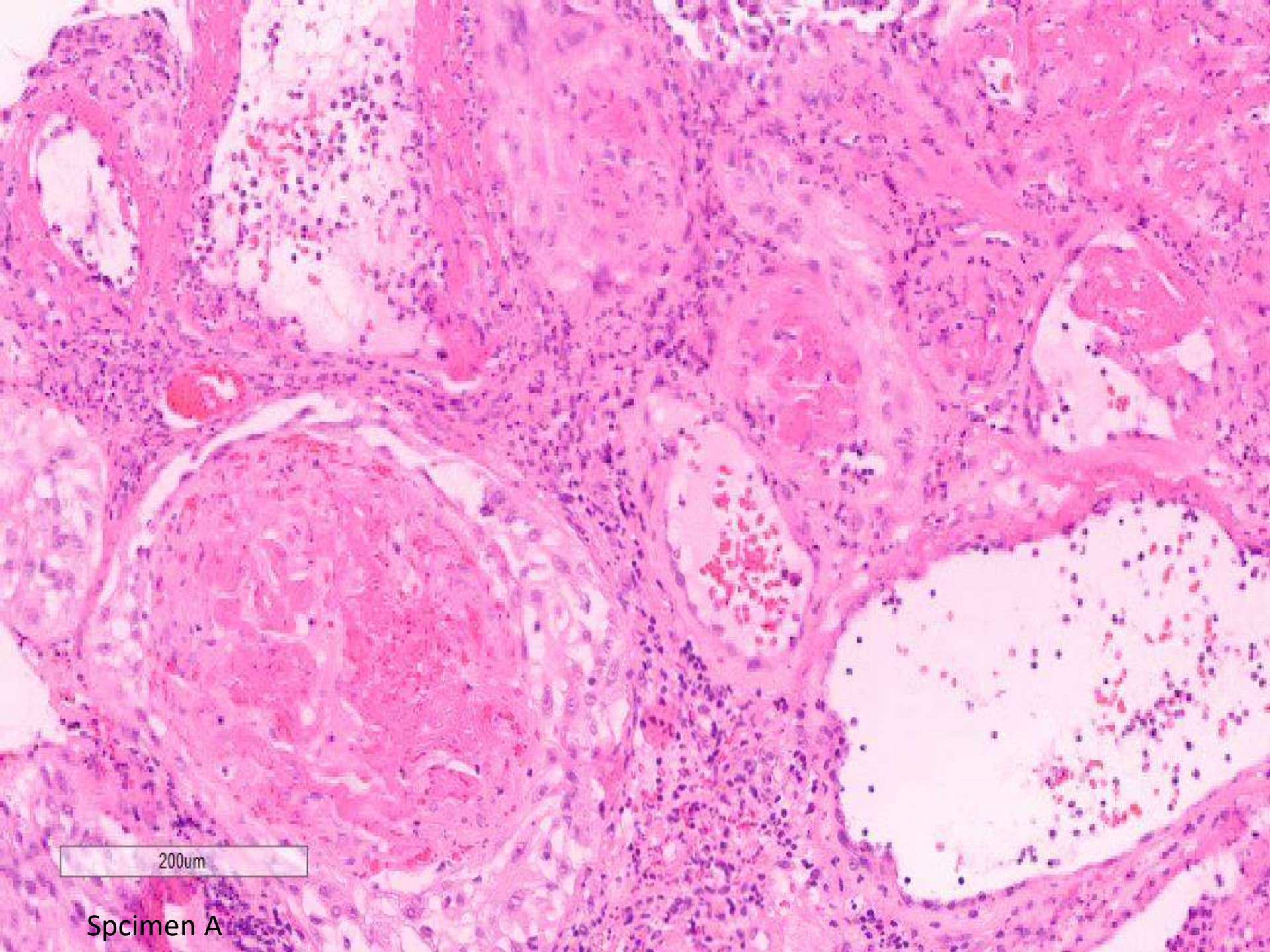
Case 1A

Specimen A

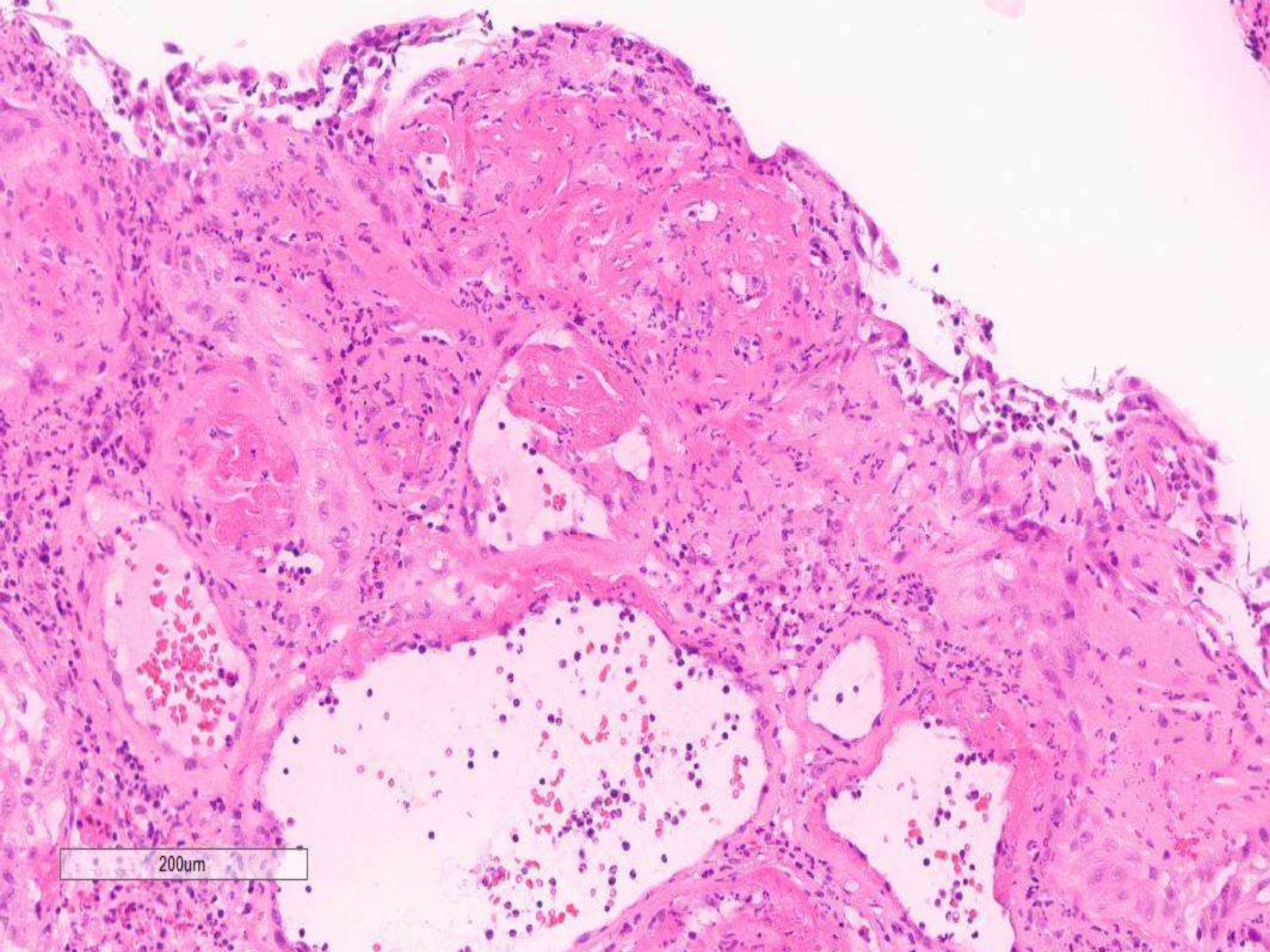


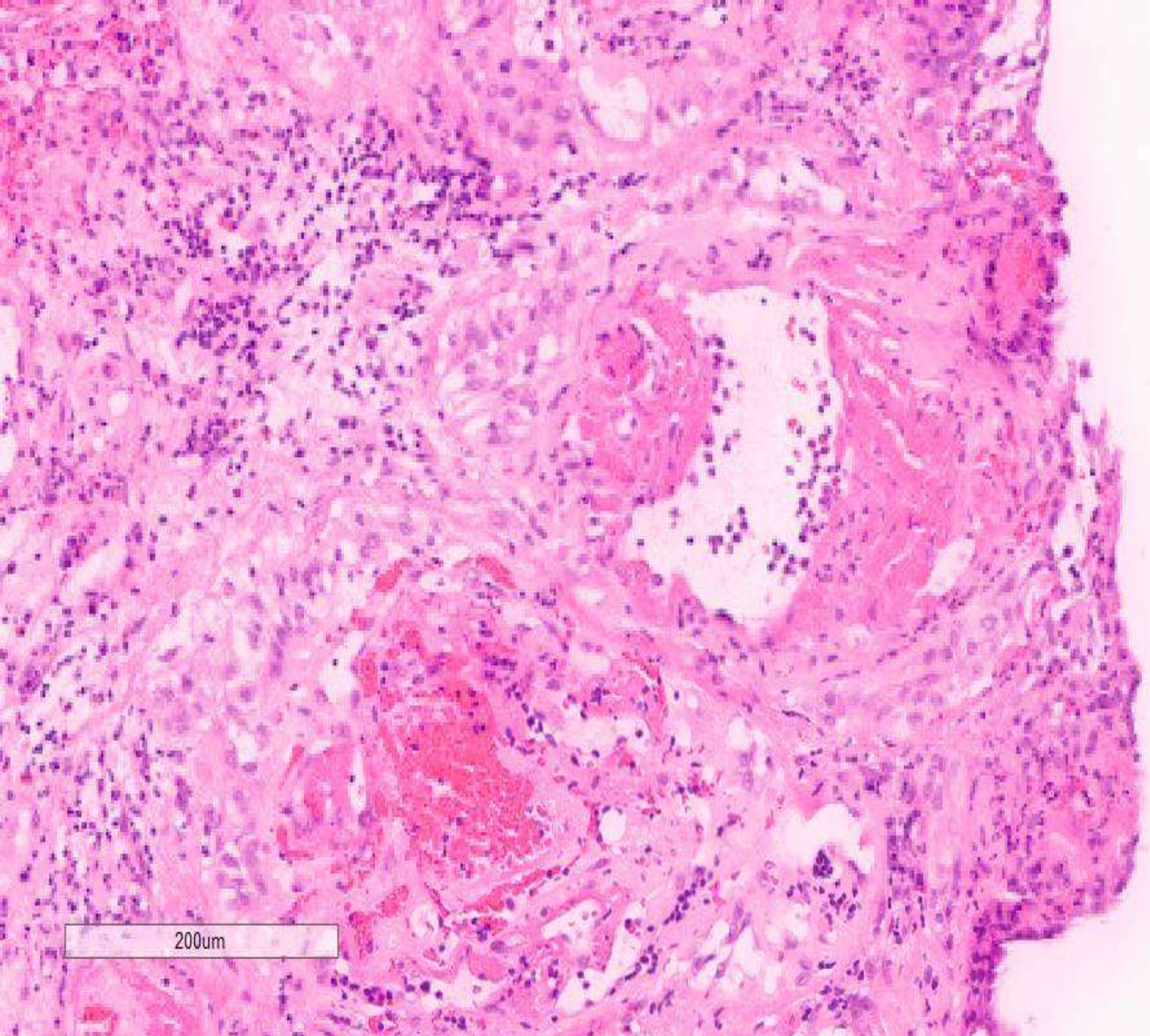


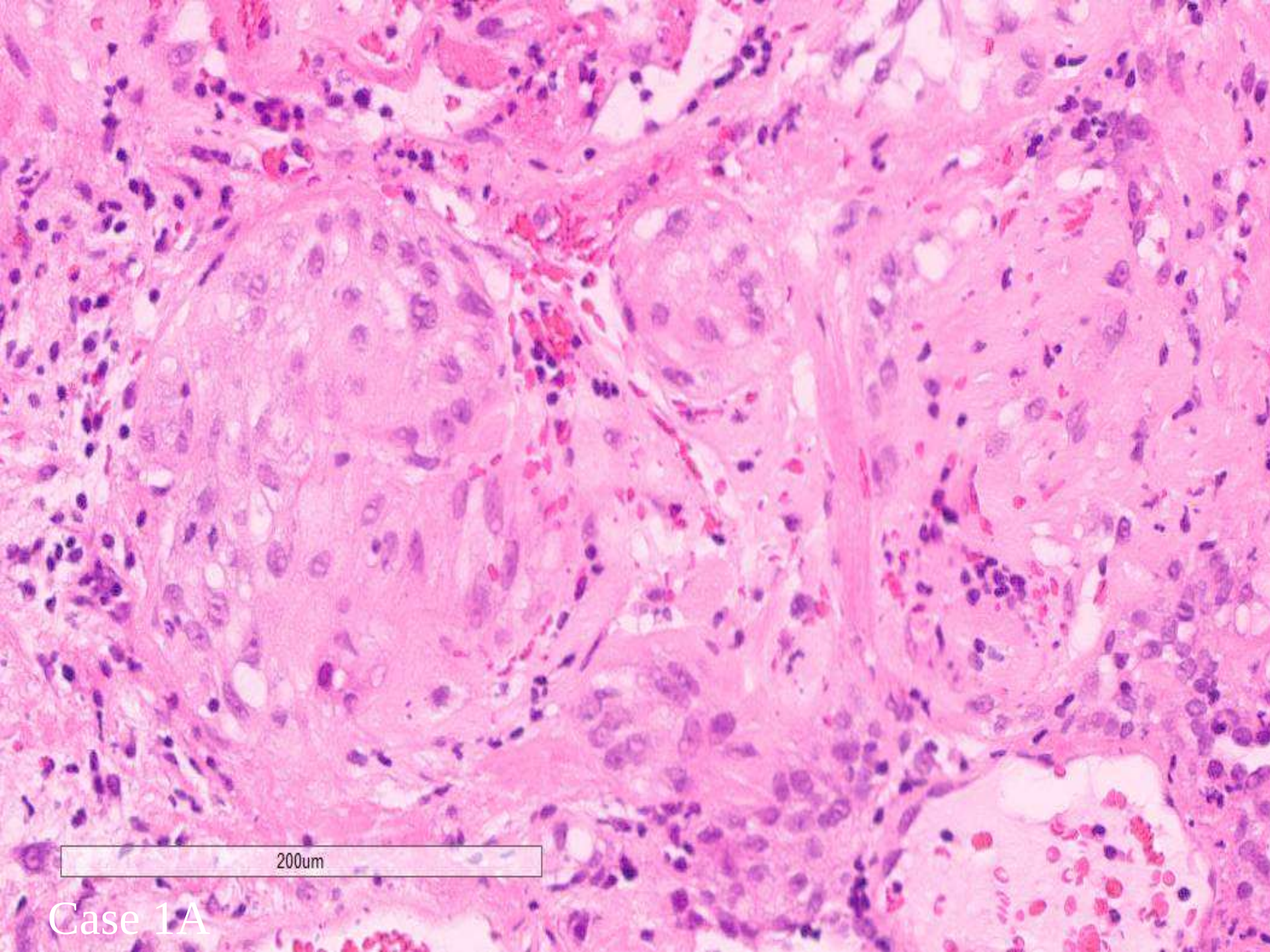
Specimen A



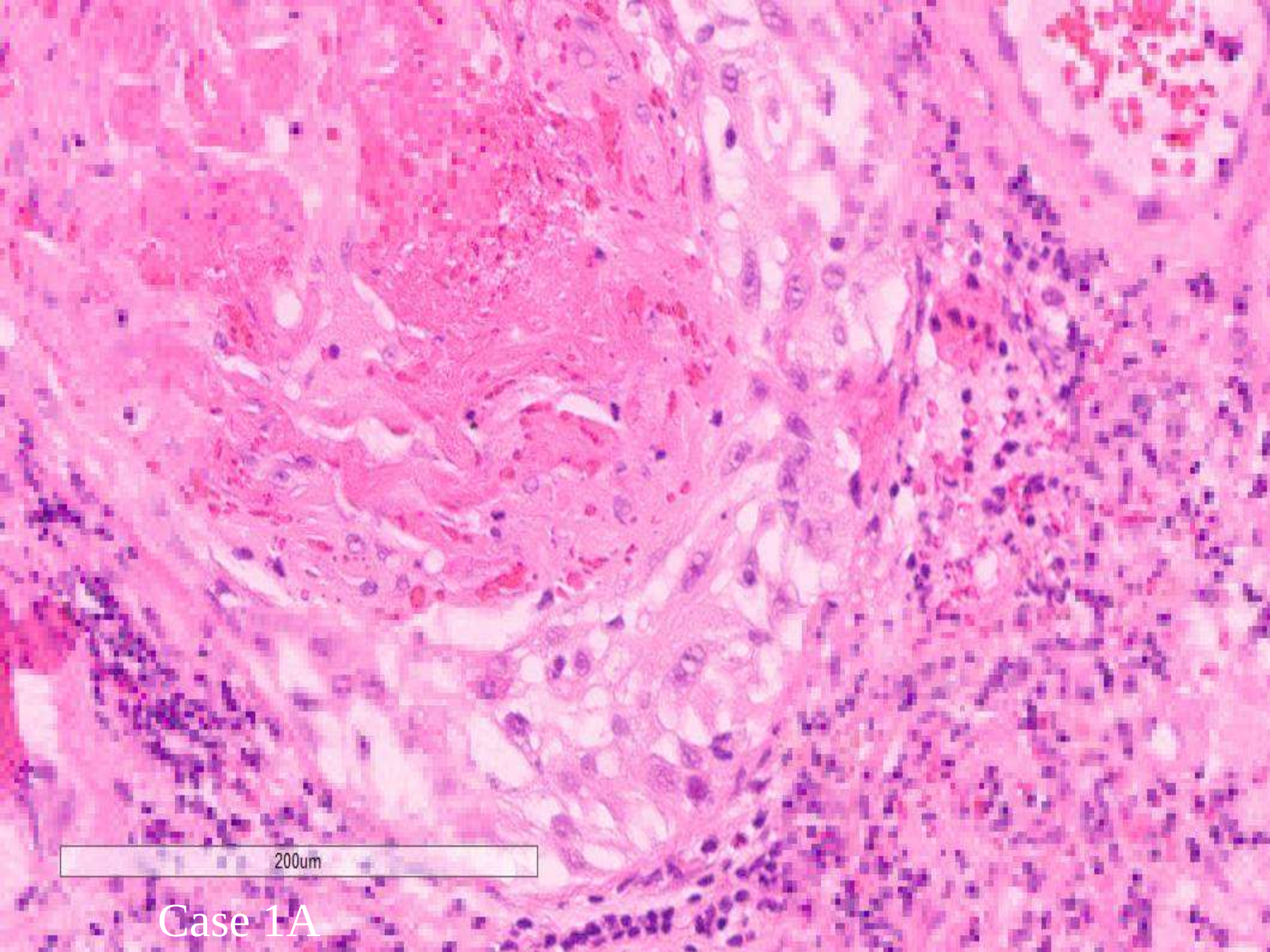
Spcimen A


200um


200um



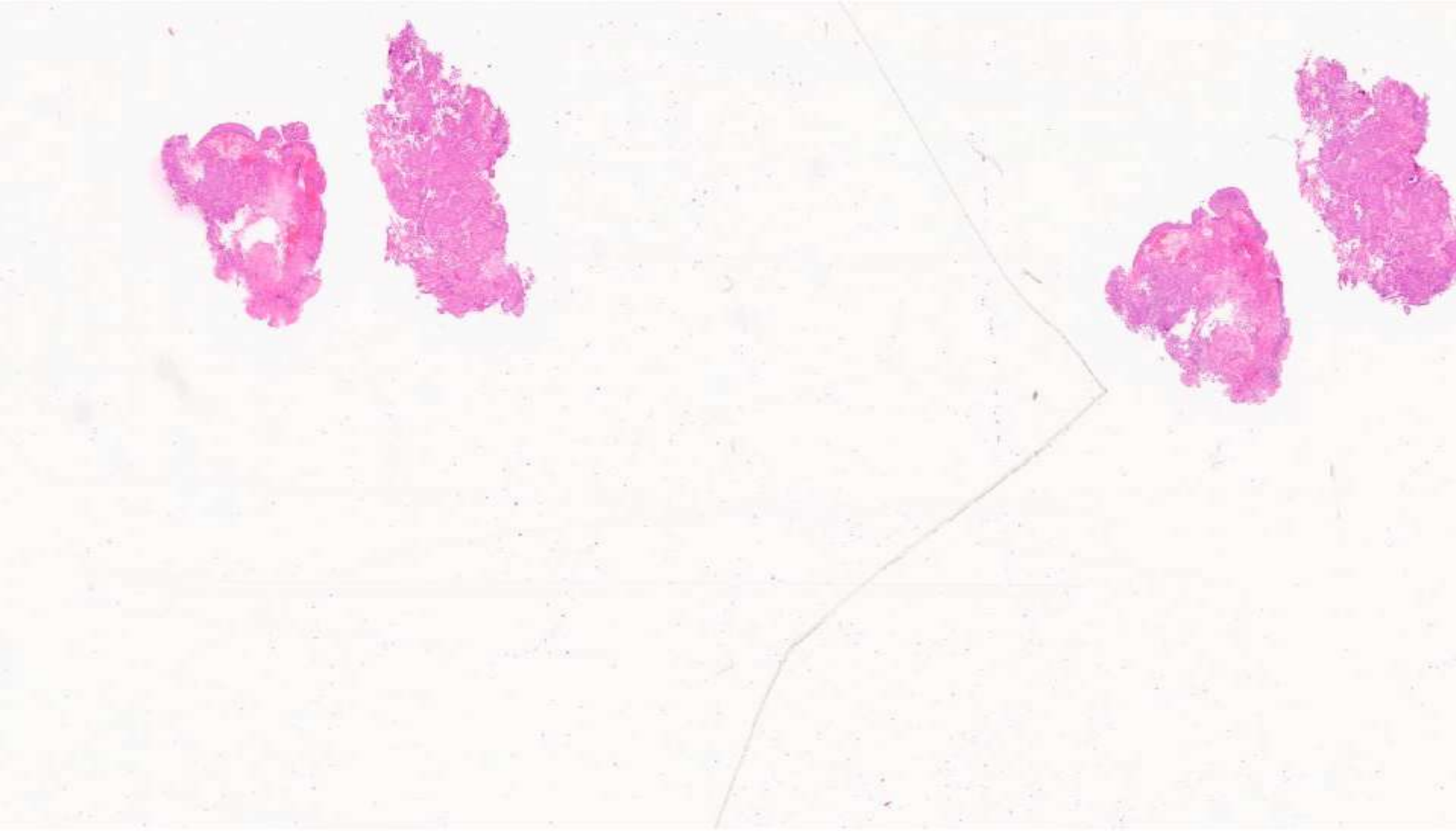
Case 1A



Case 1A

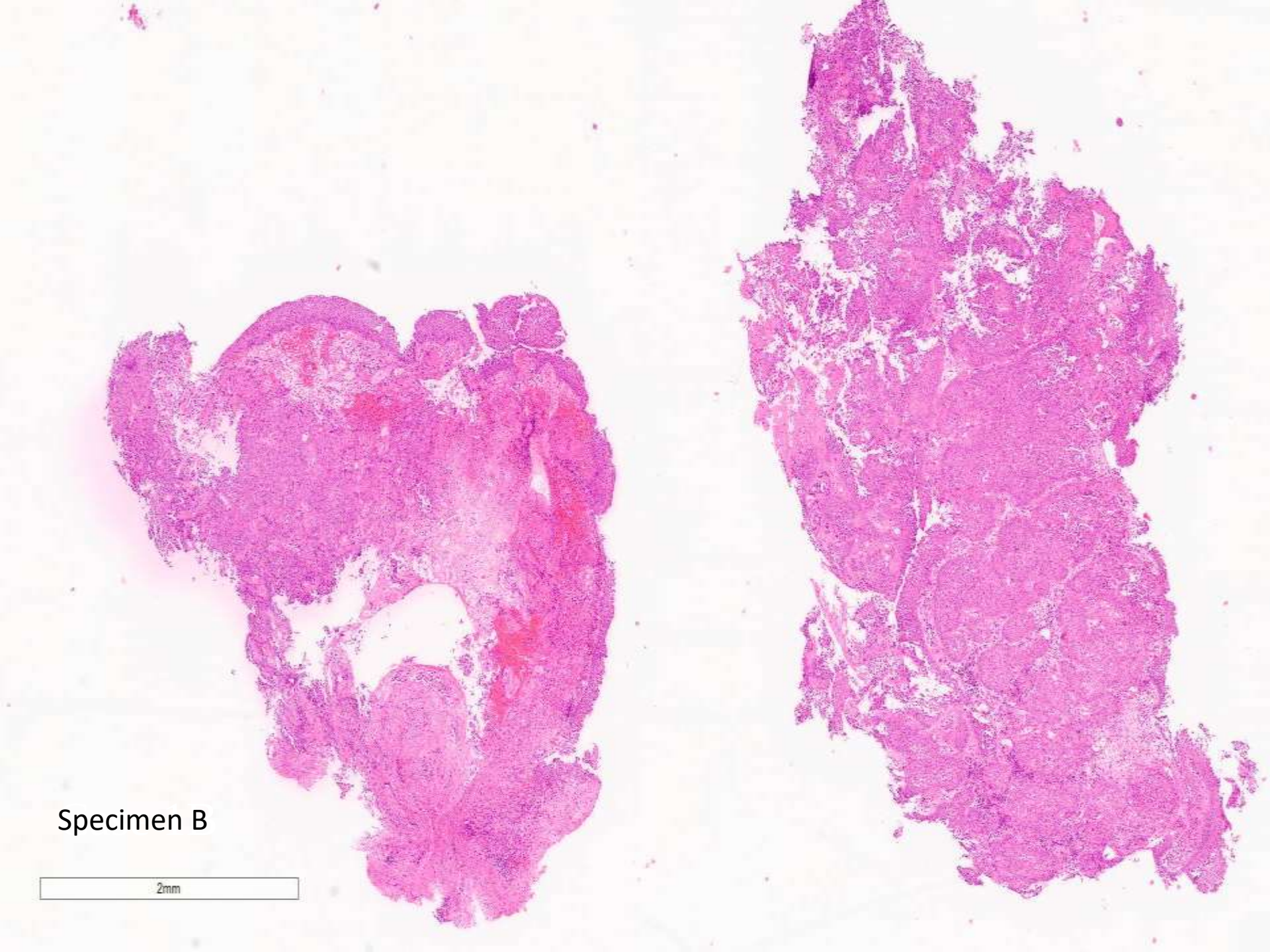
Diagnosis (specimen A)

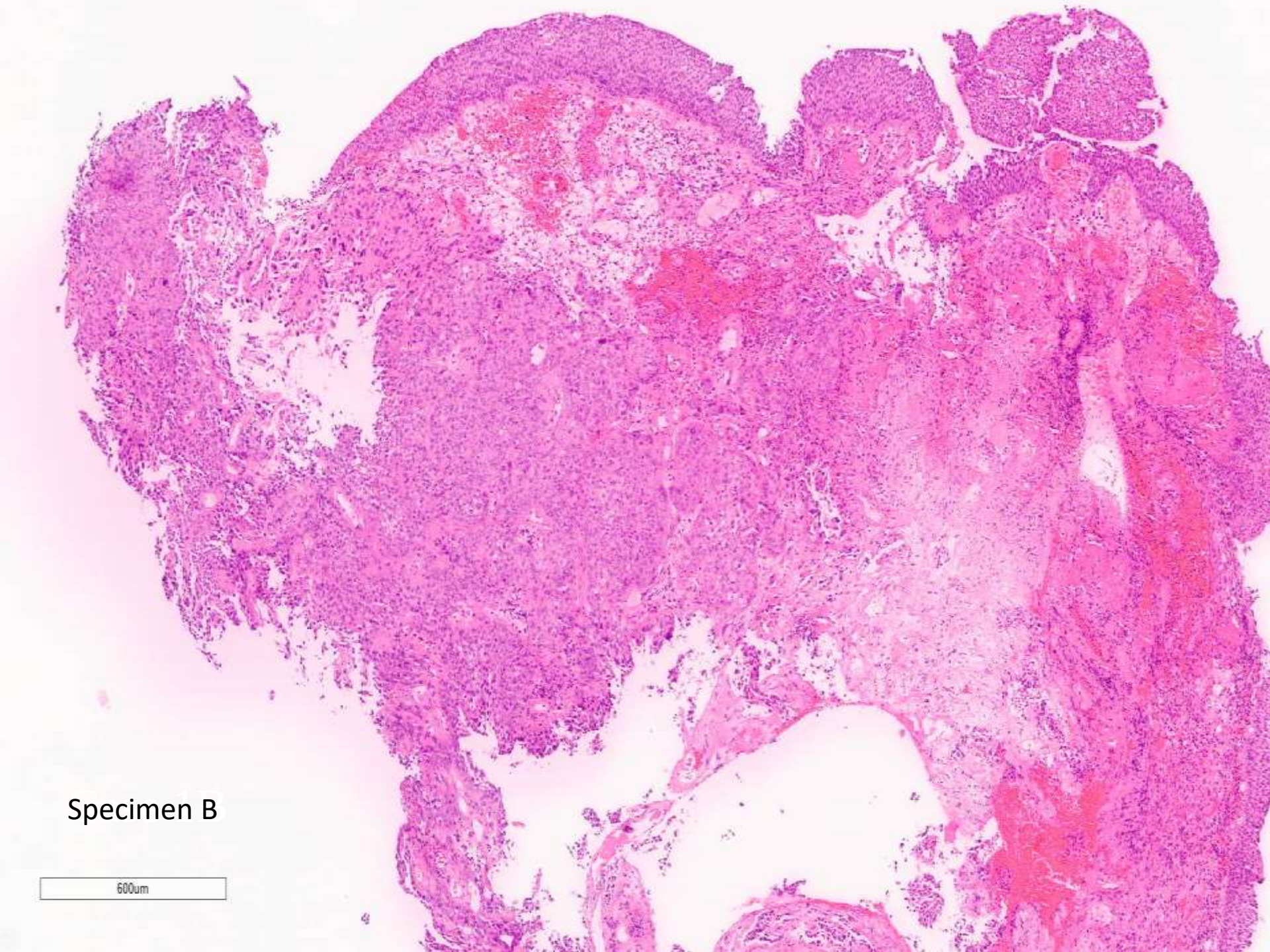
Radiation-induced hyperplasia/[pseudocarcinomatous hyperplasia]

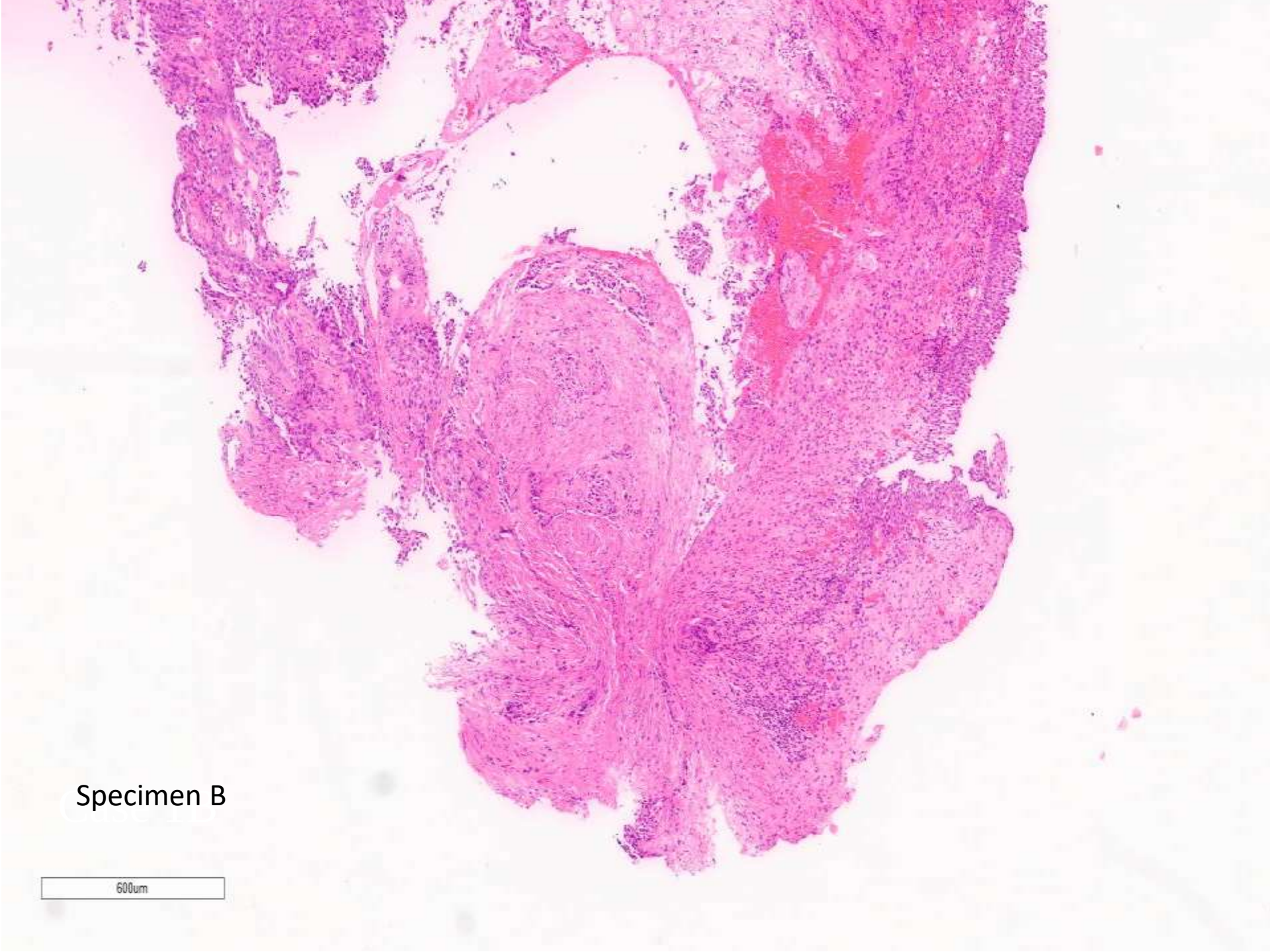


Specimen B

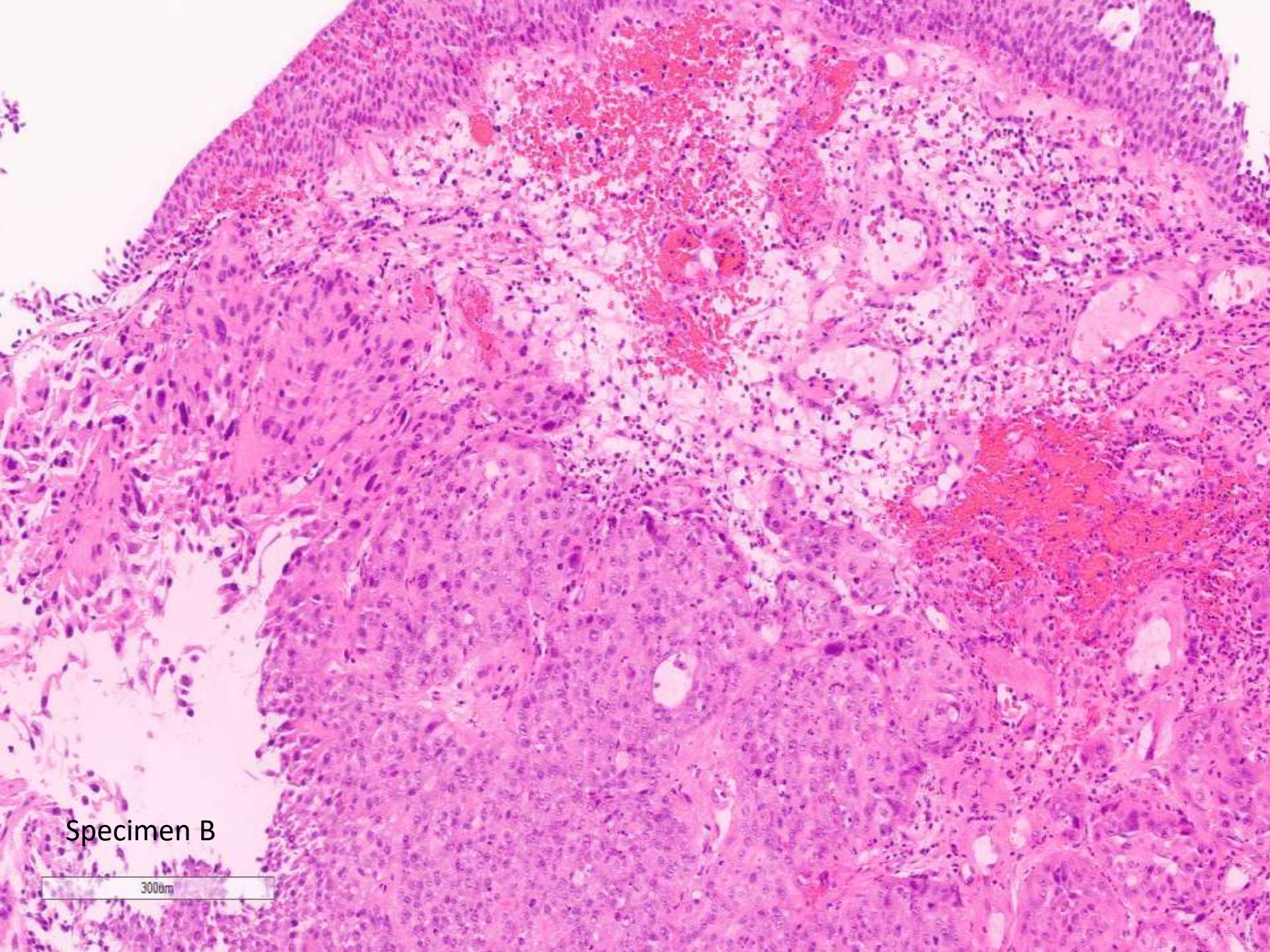
5mm

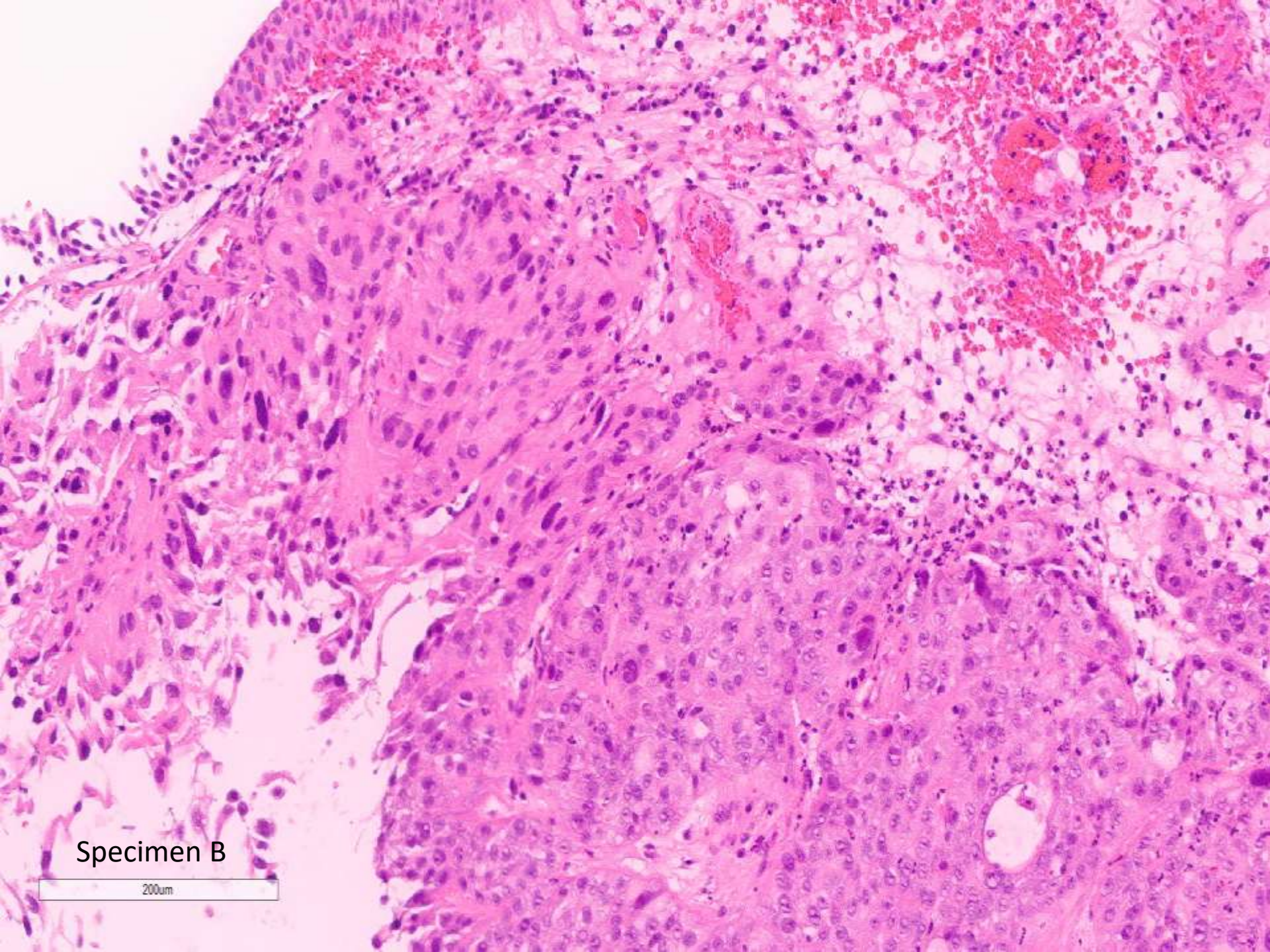

Specimen B
2mm

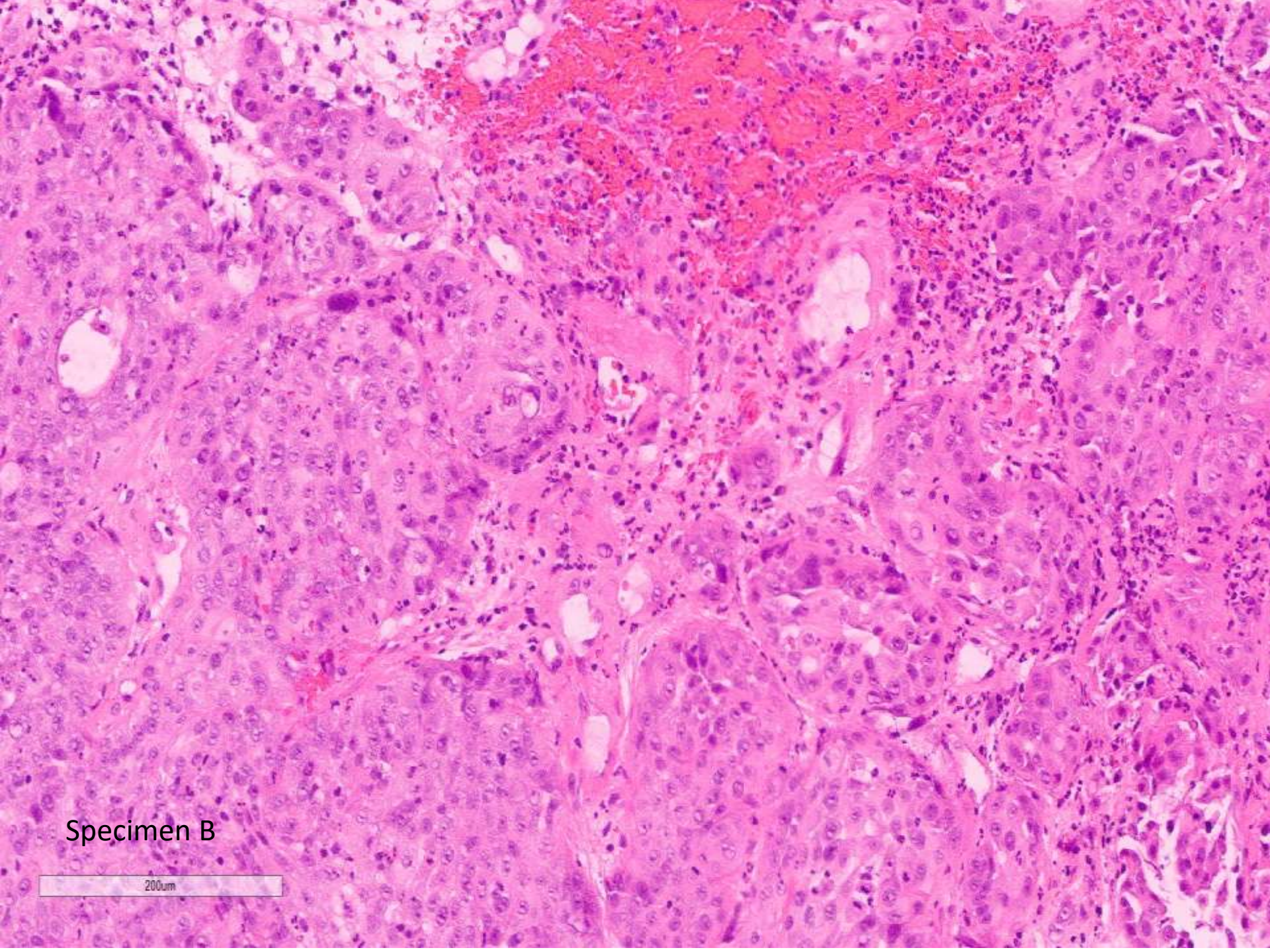

Specimen B
600um

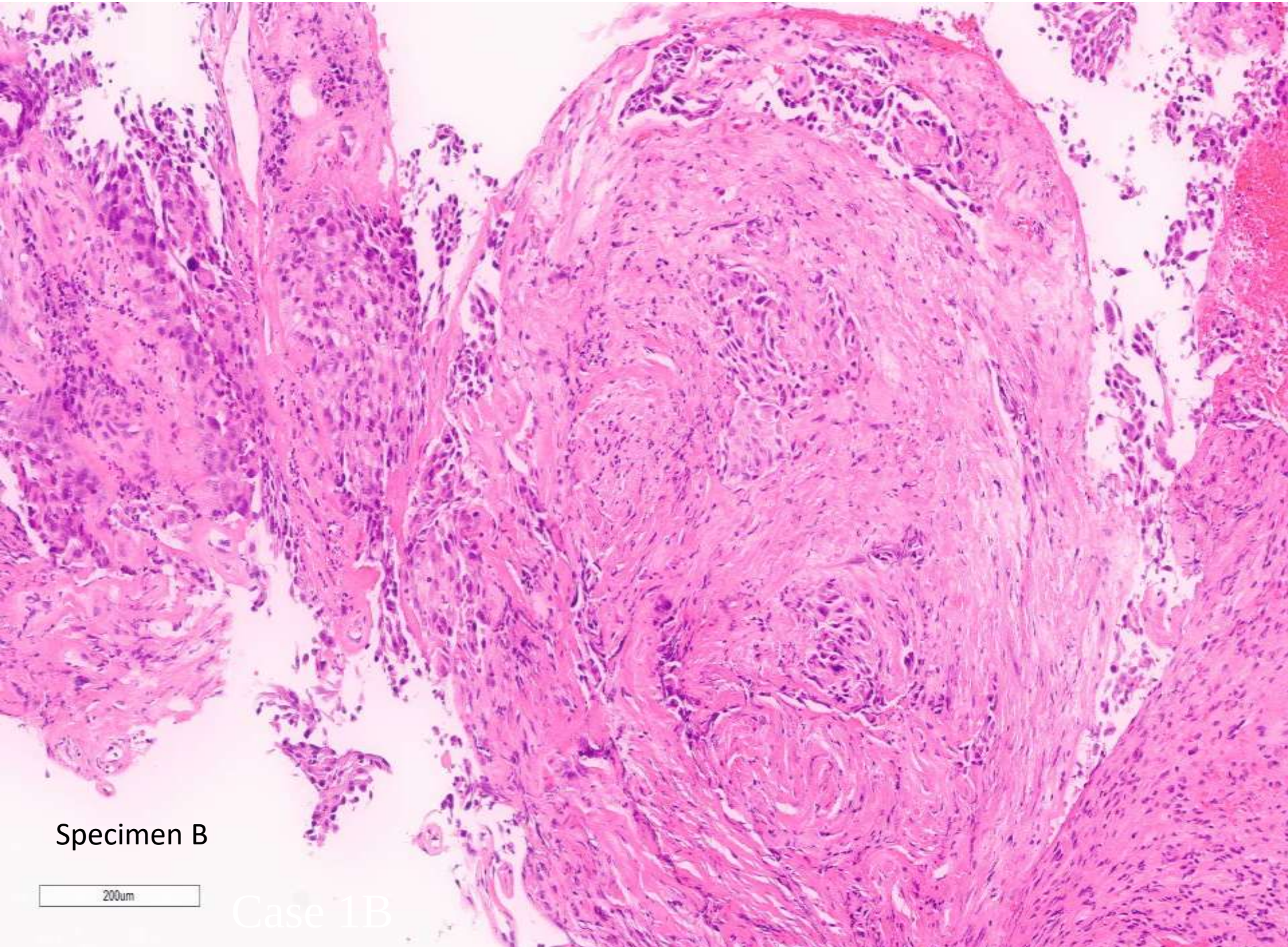


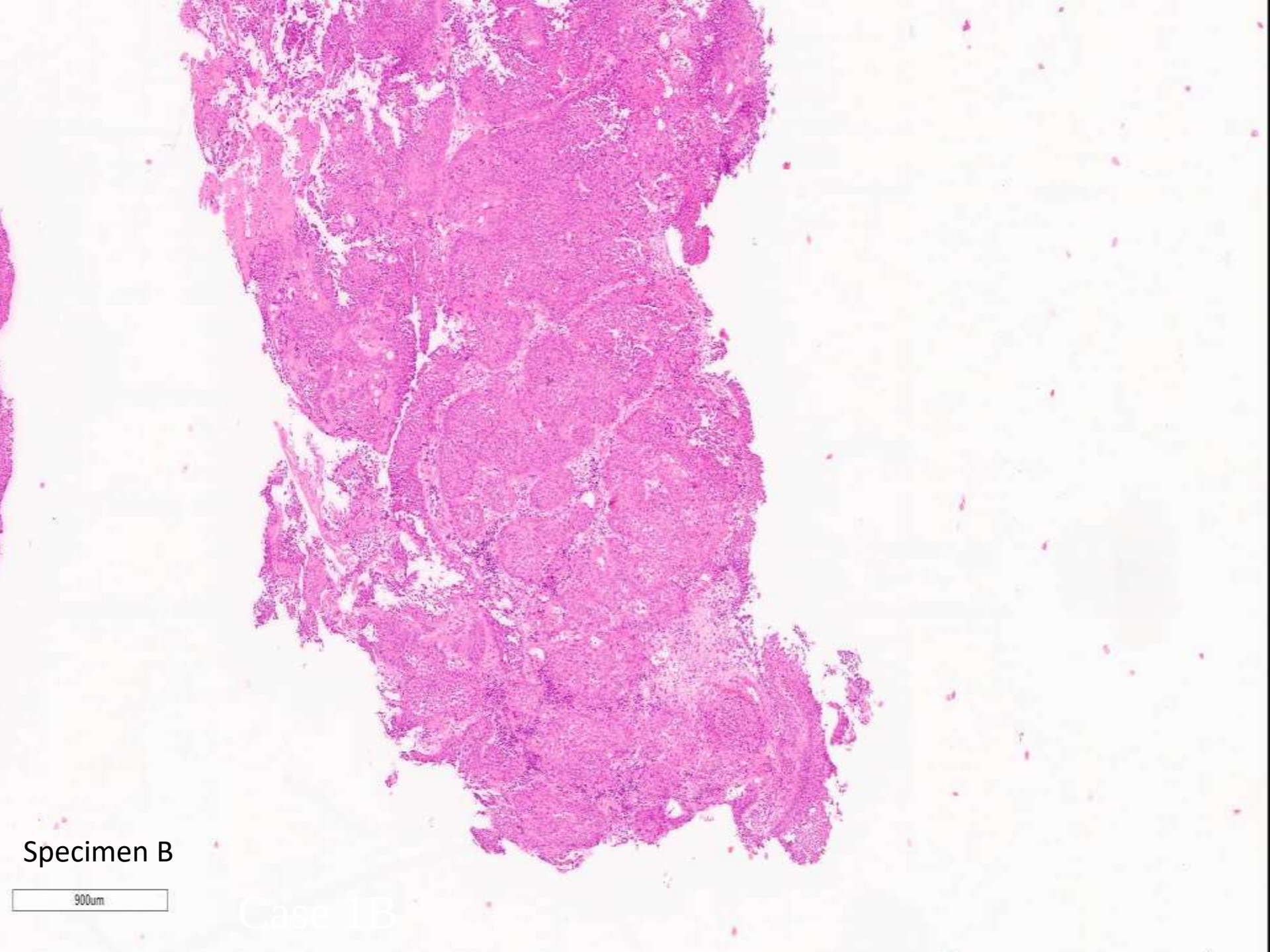
Specimen B

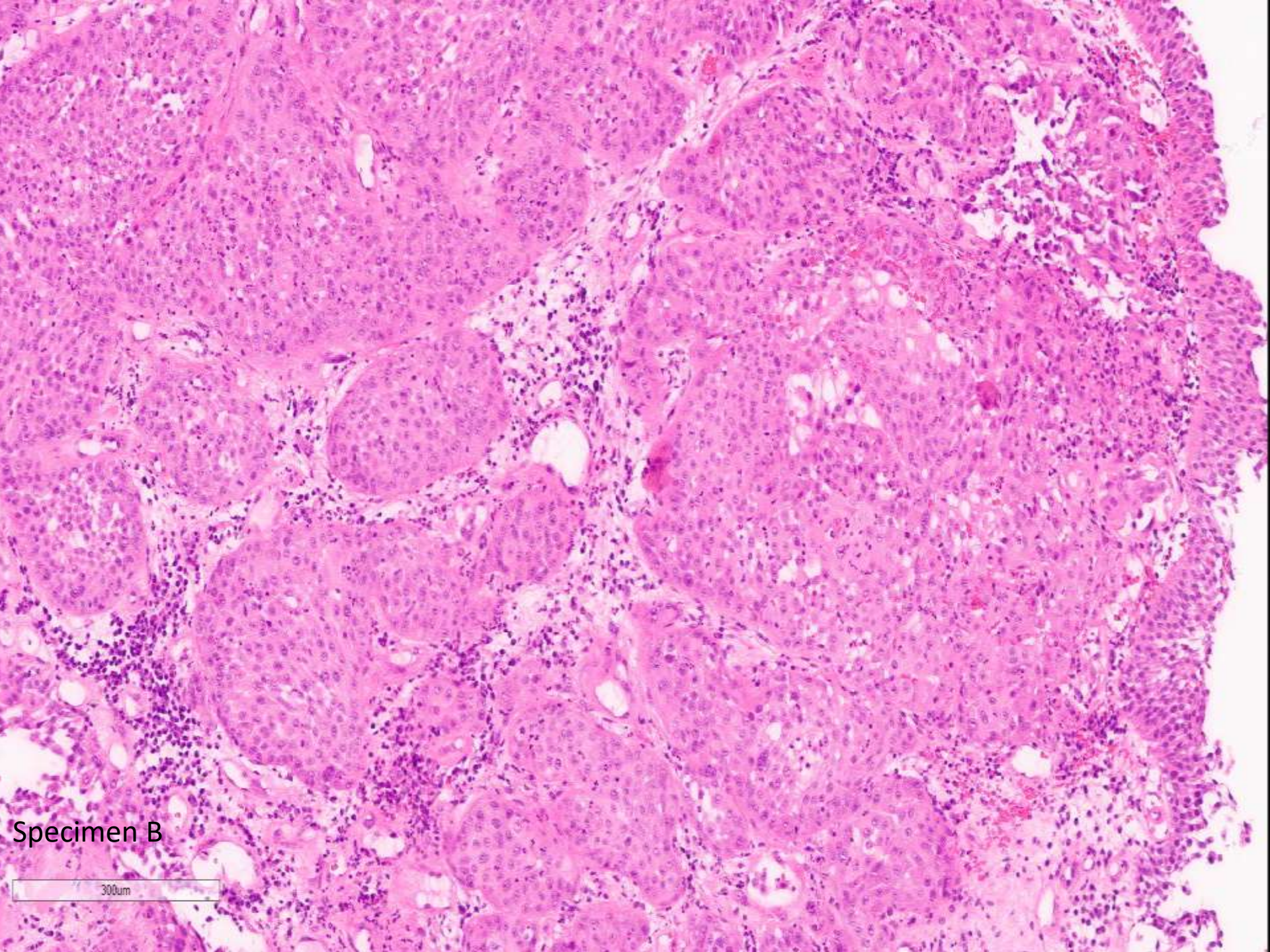

Specimen B
300um

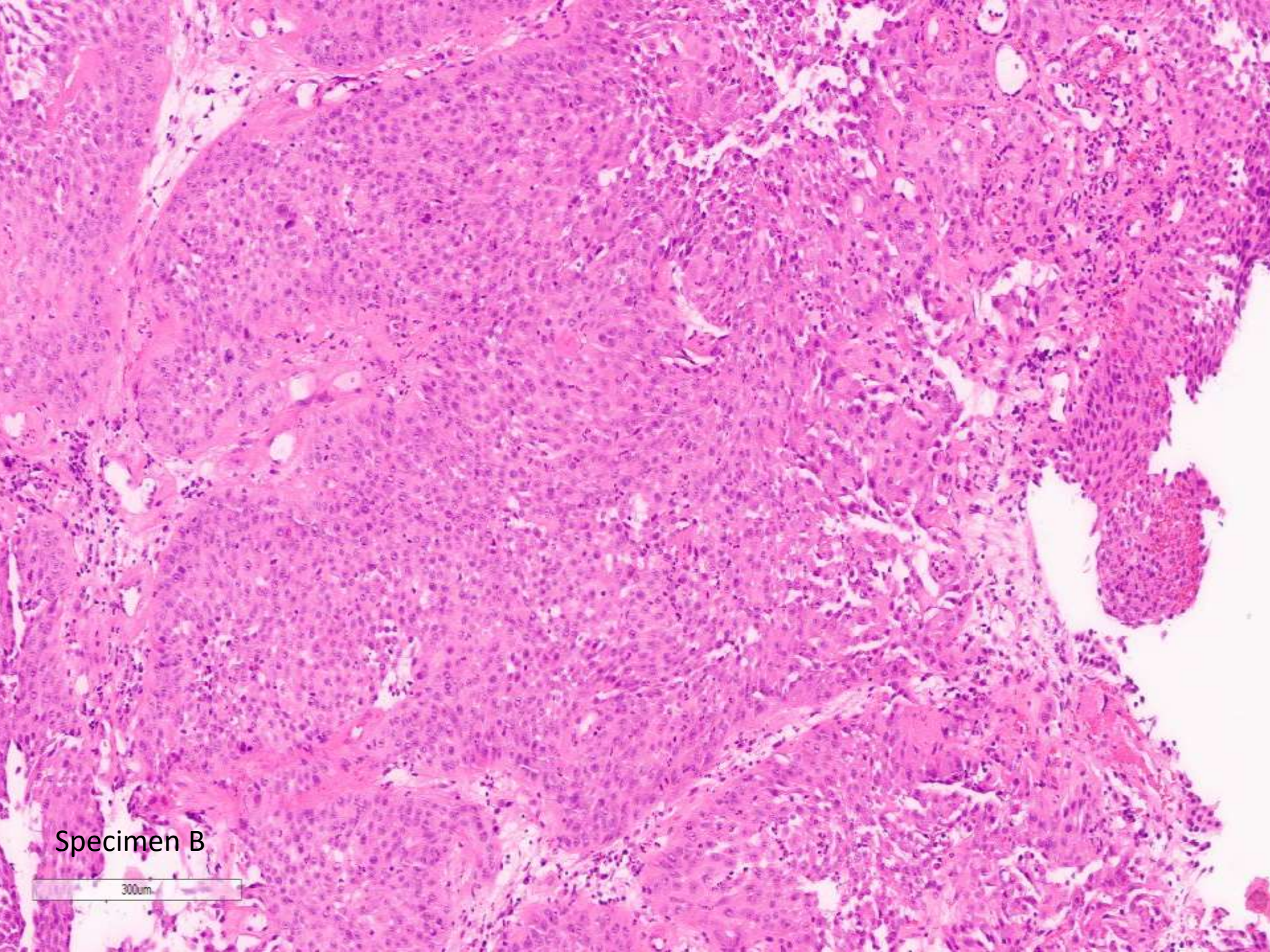

Specimen B
200um

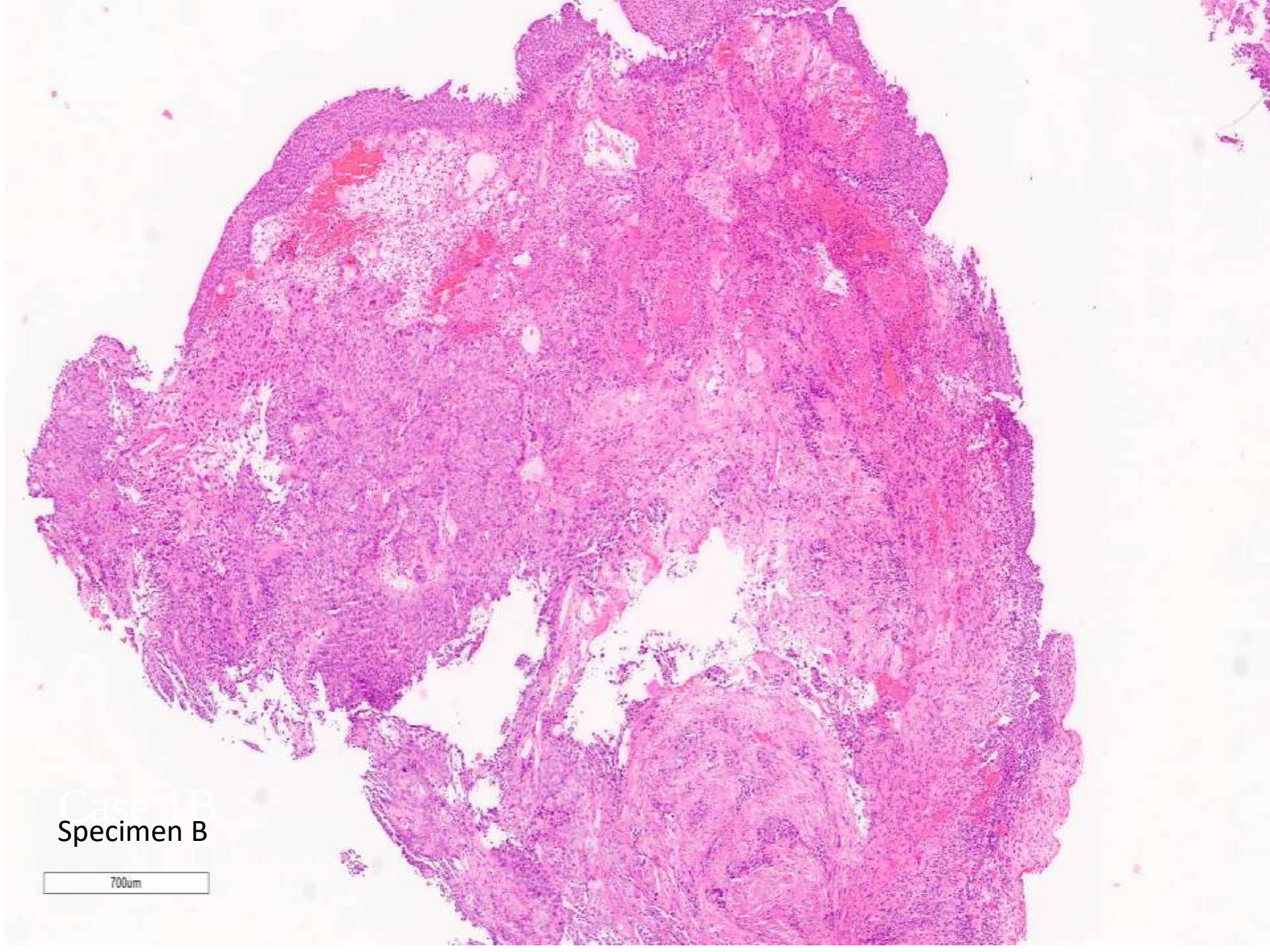

Specimen B
200um

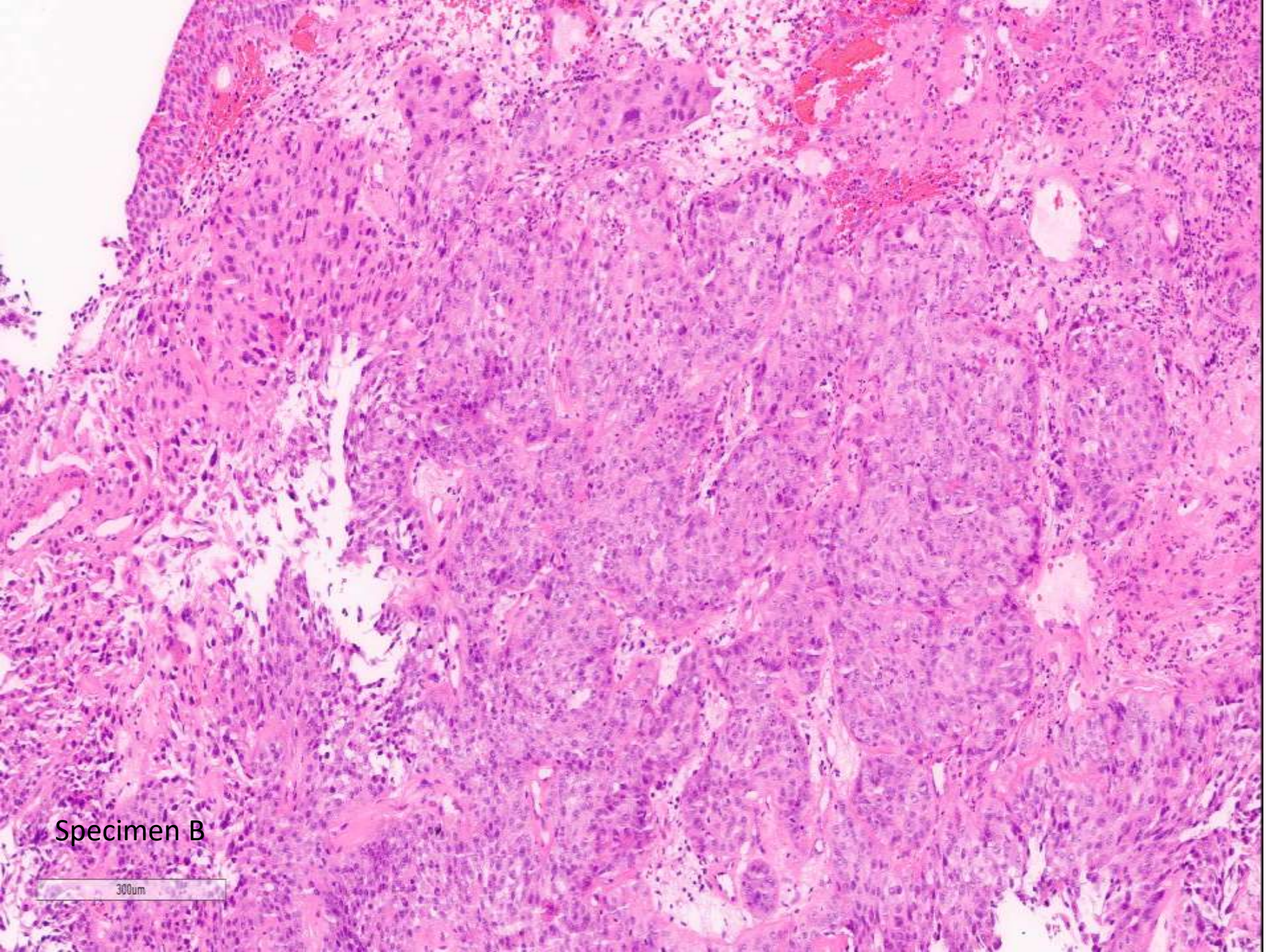

Specimen B
200um
Case 1B

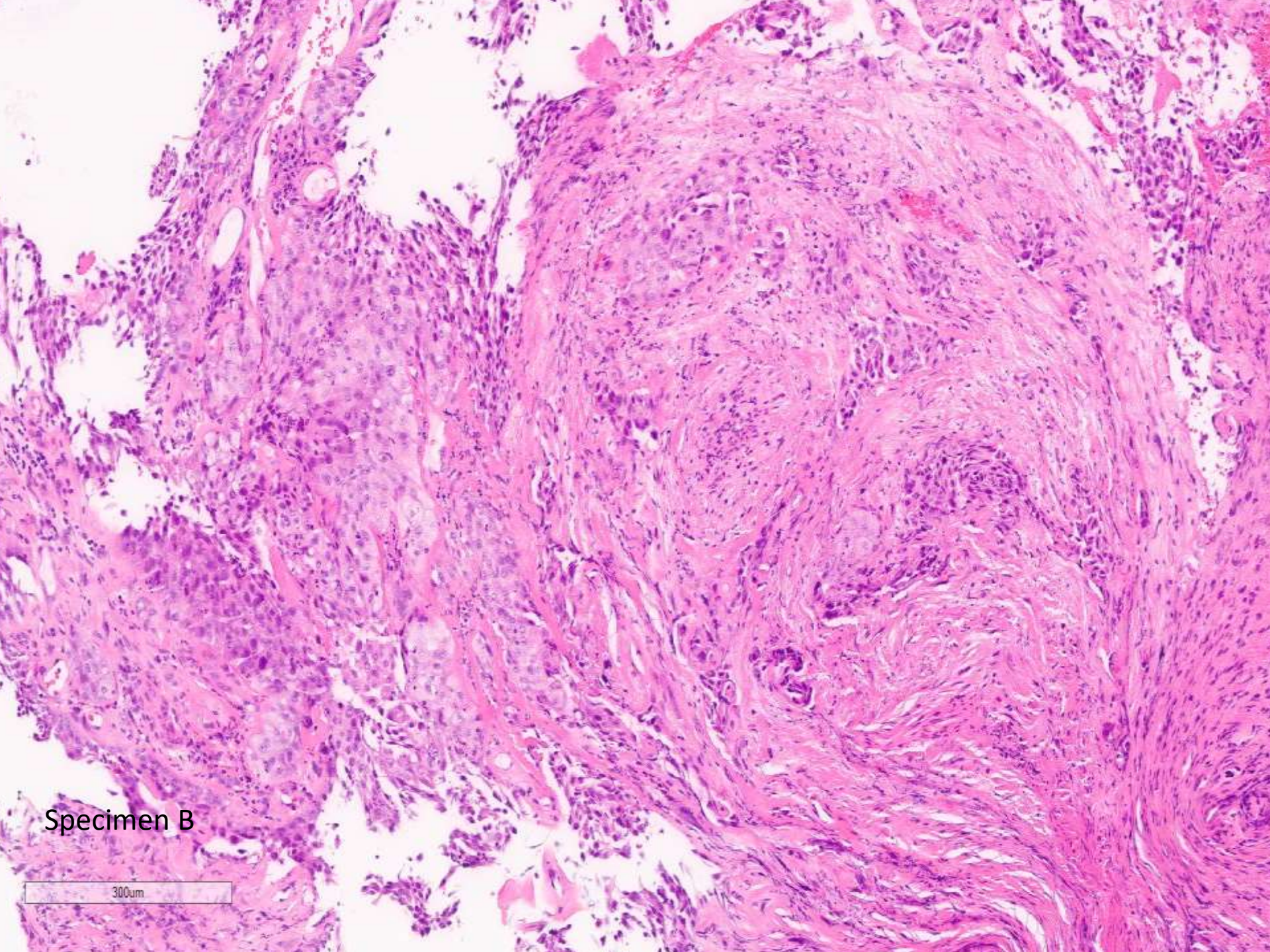

Specimen B
900um


Specimen B
300um


Specimen B
300um


Case 1B
Specimen B
700um


Specimen B
300um


Specimen B
300um

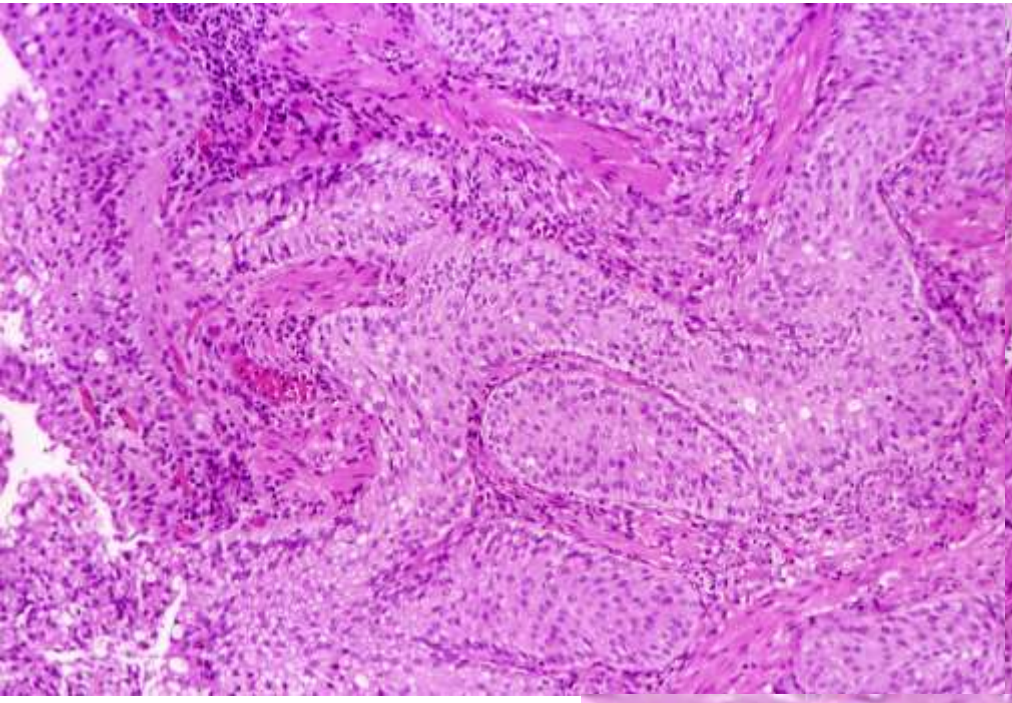
Diagnosis (specimen B)

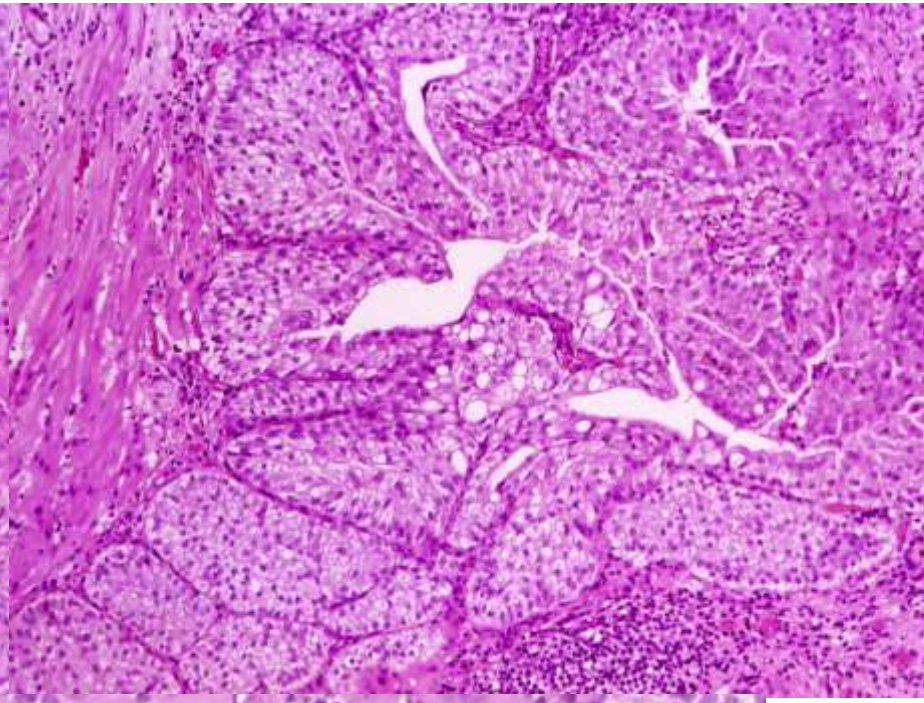
Invasive urothelial carcinoma (has some nested features)

Microcystic/small tubular variant urothelial carcinoma versus cystitis glandularis/von Brunn's nest proliferation

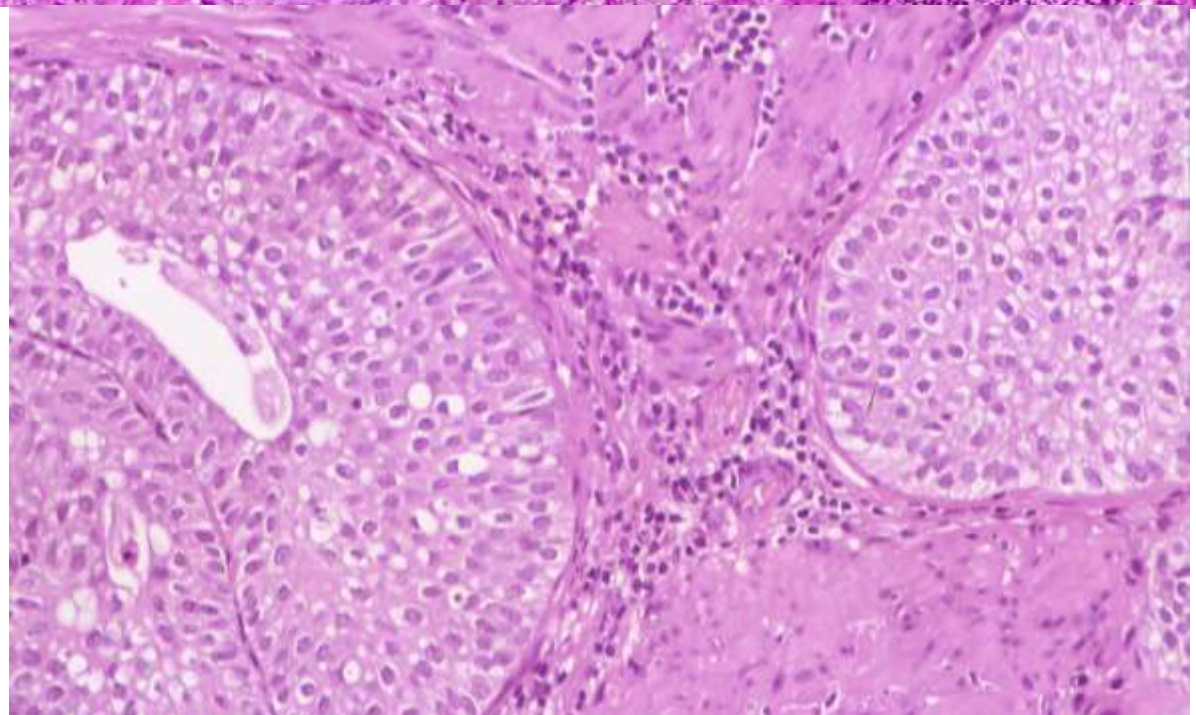
Features favouring carcinoma:

- Haphazard growth/infiltrative pattern
- Cytological atypia
- Variation is size, shape and spacing of microcysts/tubules





Large nested urothelial carcinoma



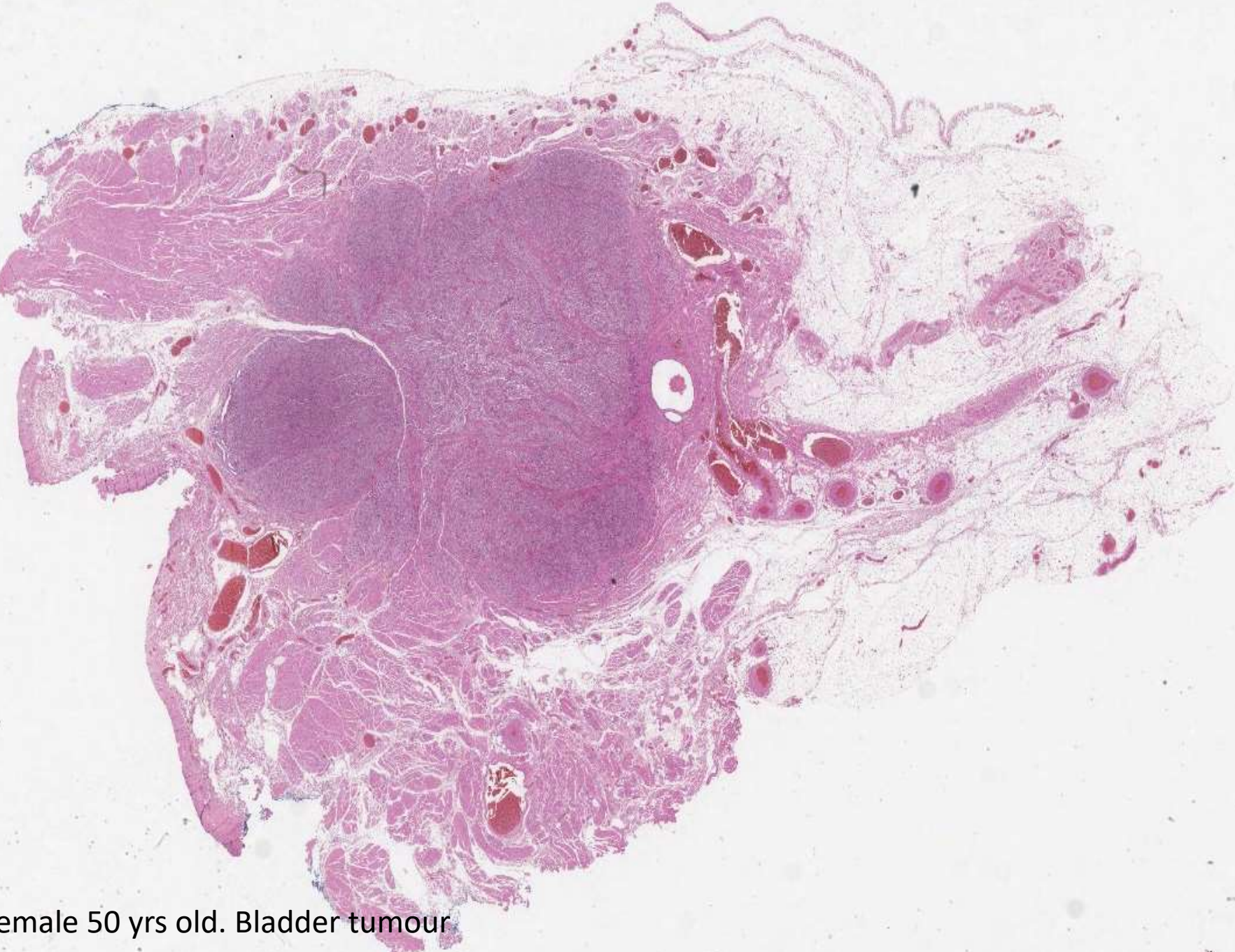
Large cell nested pattern of urothelial carcinoma (UC): 17 cases of a novel variant

Cox RM, Epstein JI

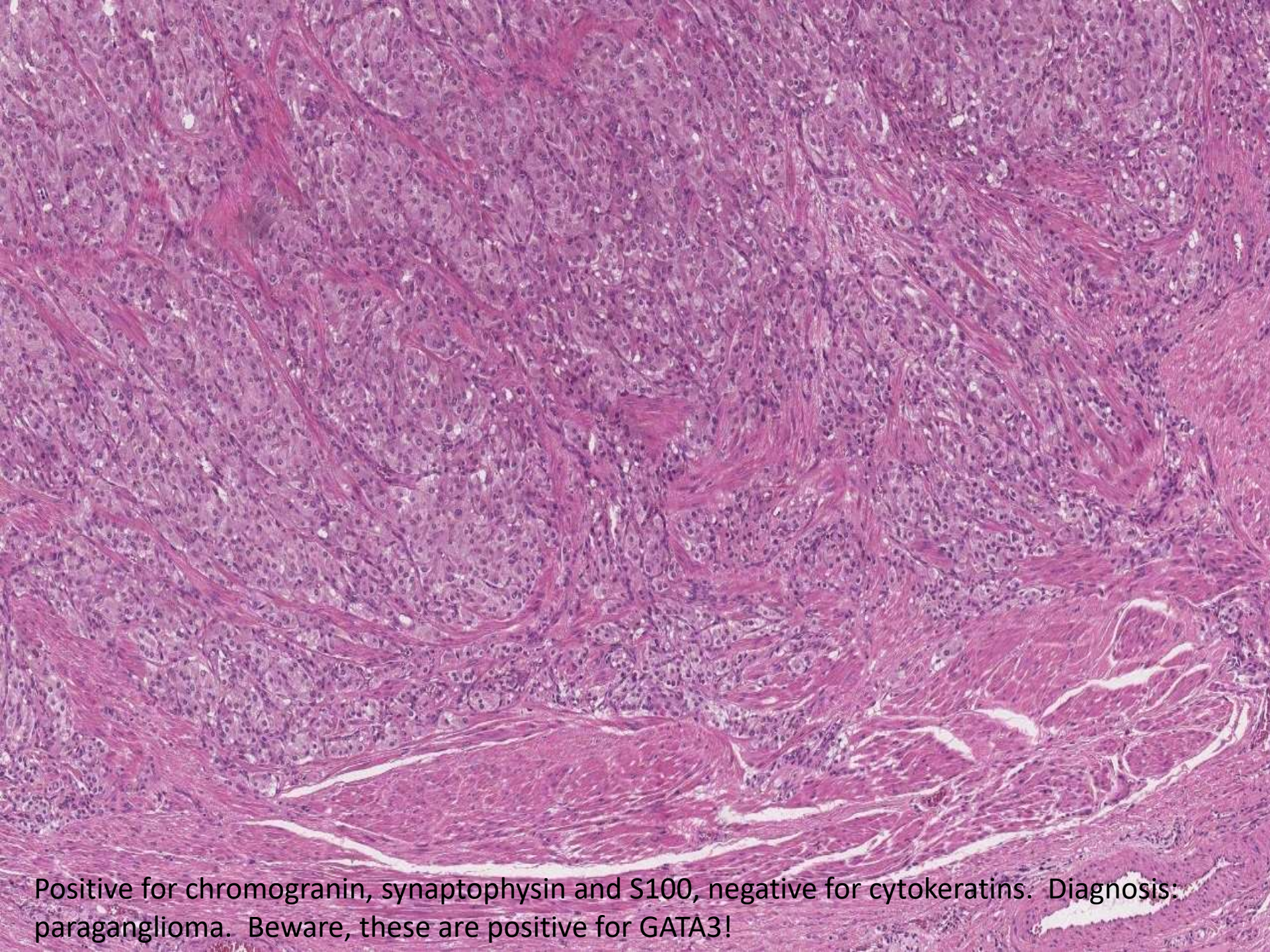
- Large irregular but cytologically bland infiltrative nests
- 14/17 cases had a low grade surface papillary component; 1 had a high grade surface component
- 15/17 invaded muscularis propria
- 14/17 cases had a desmoplastic stromal response
- 3/15 with follow up developed metastases
- Distinguished from inverted growth pattern Ta urothelial carcinoma by (1) muscularis propria invasion and/or (2)irregularly infiltrating nests and/or (3) a stromal reaction to the nests

Differential diagnosis with nephrogenic adenoma

- A peripheral layer of urothelial cells in tubules is not a feature of nephrogenic adenoma (NA is lined by single layer of cuboidal, flattened or hobnail cells)
- Absent to minimal ('degenerative') cytological atypia, no infiltrative pattern and absent mitoses in nephrogenic adenoma
- NA is PAX8 positive (however, some urothelial lesions are also PAX8 positive!). A lesion that is PAX8 negative is very unlikely to be nephrogenic adenoma
- Beware that 40% of nephrogenic adenomas are GATA3 +ve, but they would be negative for high MW cytokeratins and p40



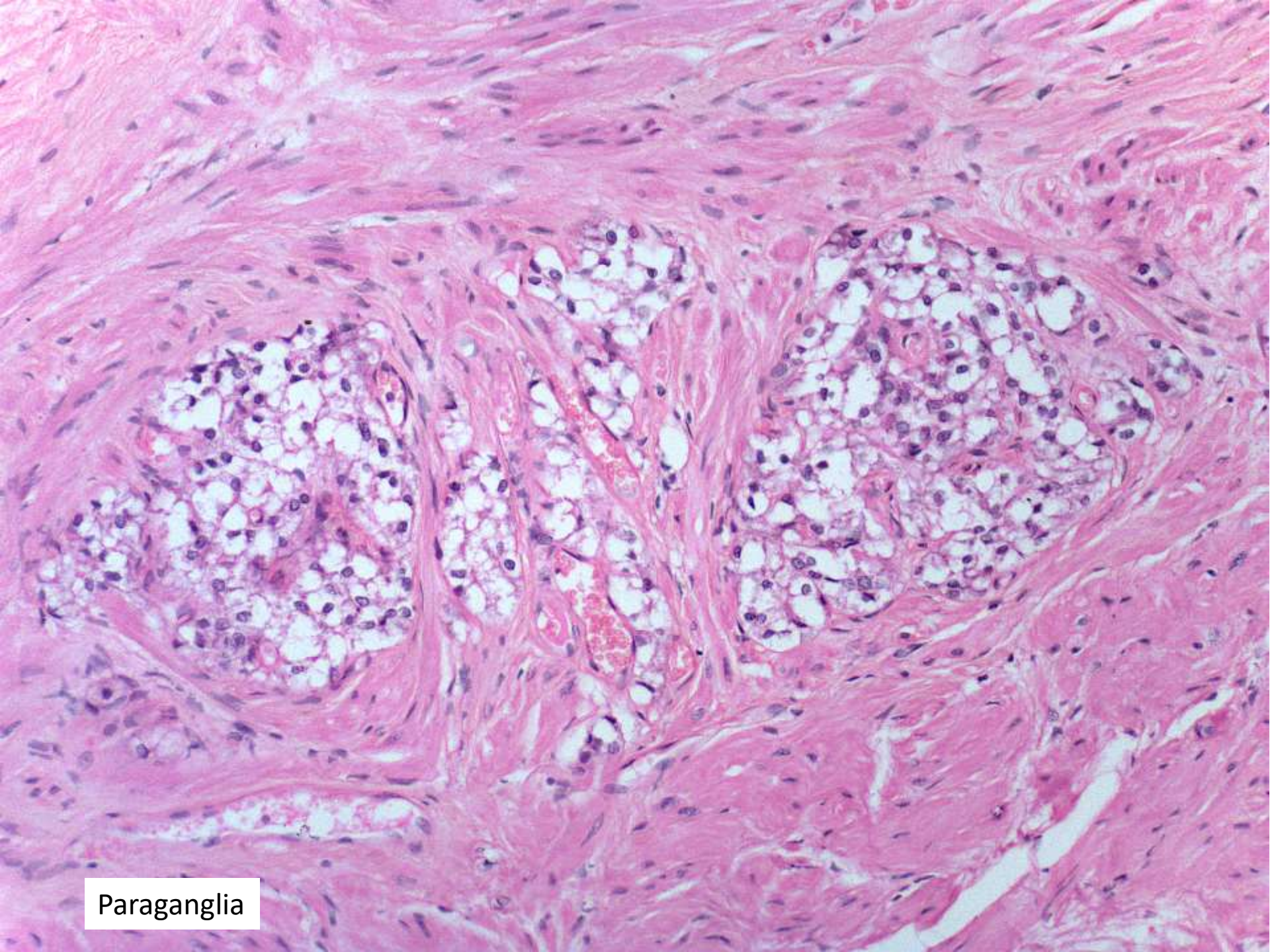
emale 50 yrs old. Bladder tumour



Positive for chromogranin, synaptophysin and S100, negative for cytokeratins. Diagnosis: paraganglioma. Beware, these are positive for GATA3!

Paraganglioma

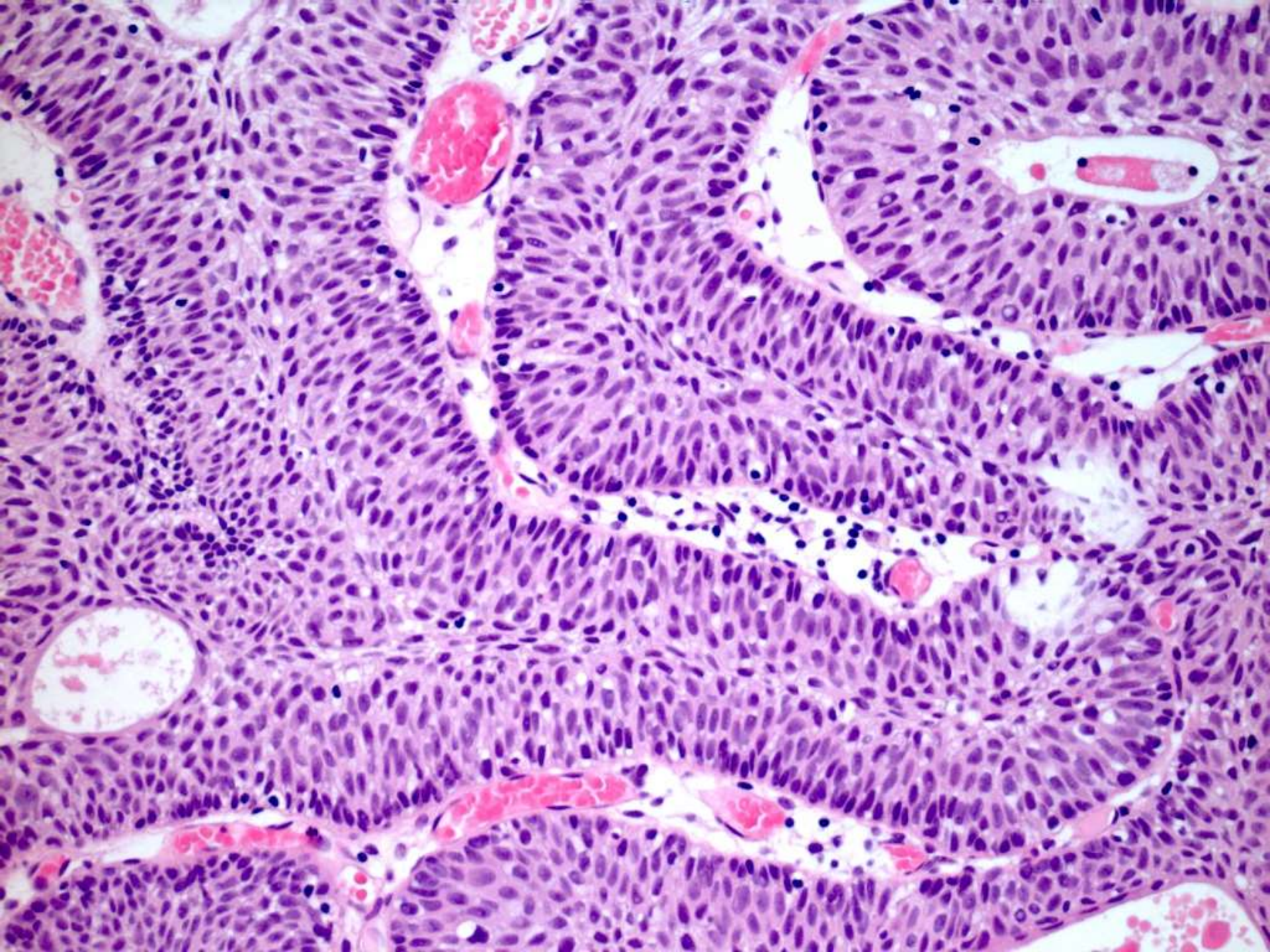
- Mimics urothelial carcinoma due to nested, sometimes ‘pleomorphic’ appearance
- GATA3 positive, like urothelial carcinoma !! (but cytokeratins –ve; neuroendocrine markers +ve)
- 15% have associated hereditary paraganglioma/phaeochromocytoma syndrome (SDHB immuno looking for loss of expression is a good screen for this)

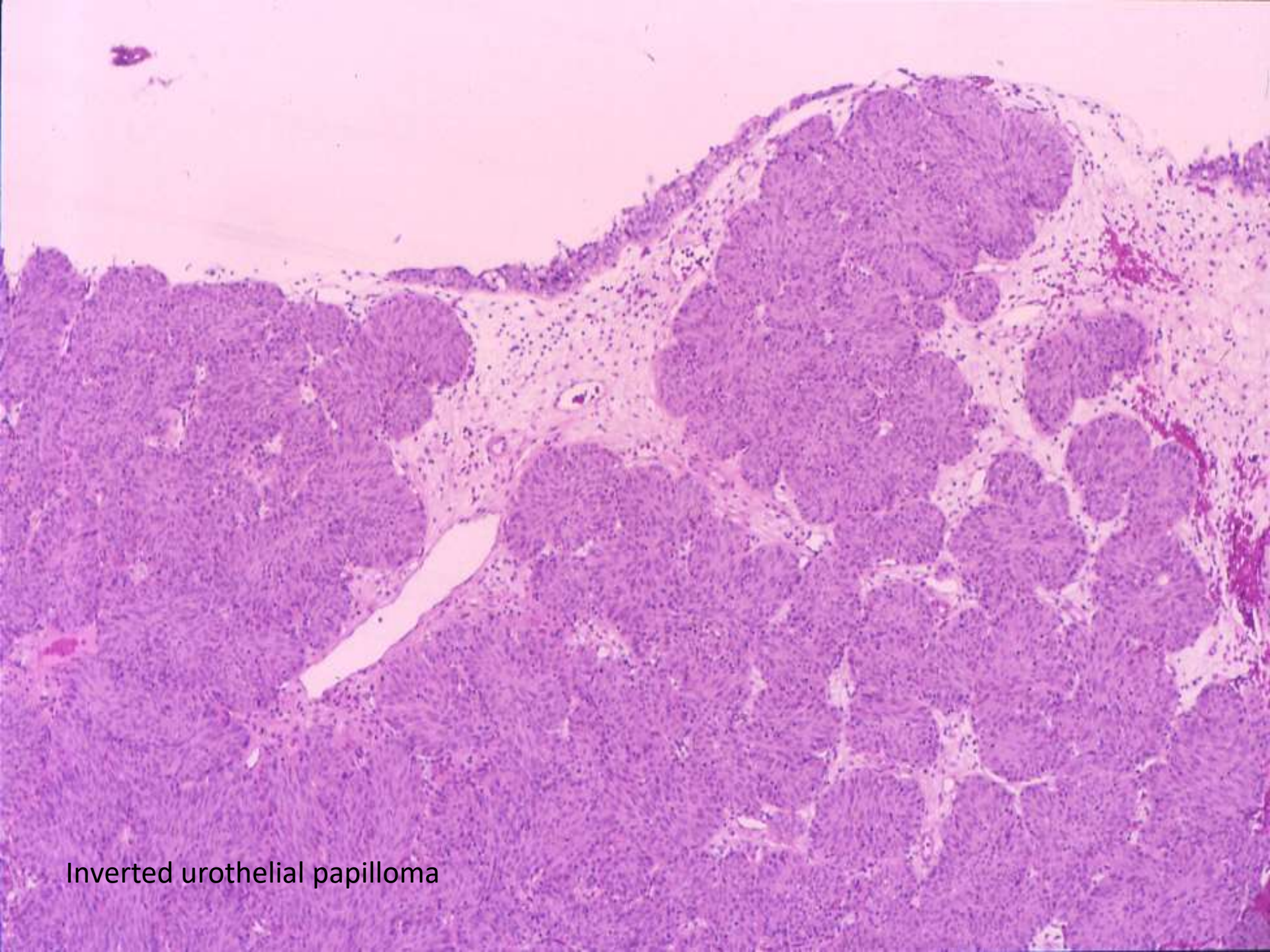

Paraganglia

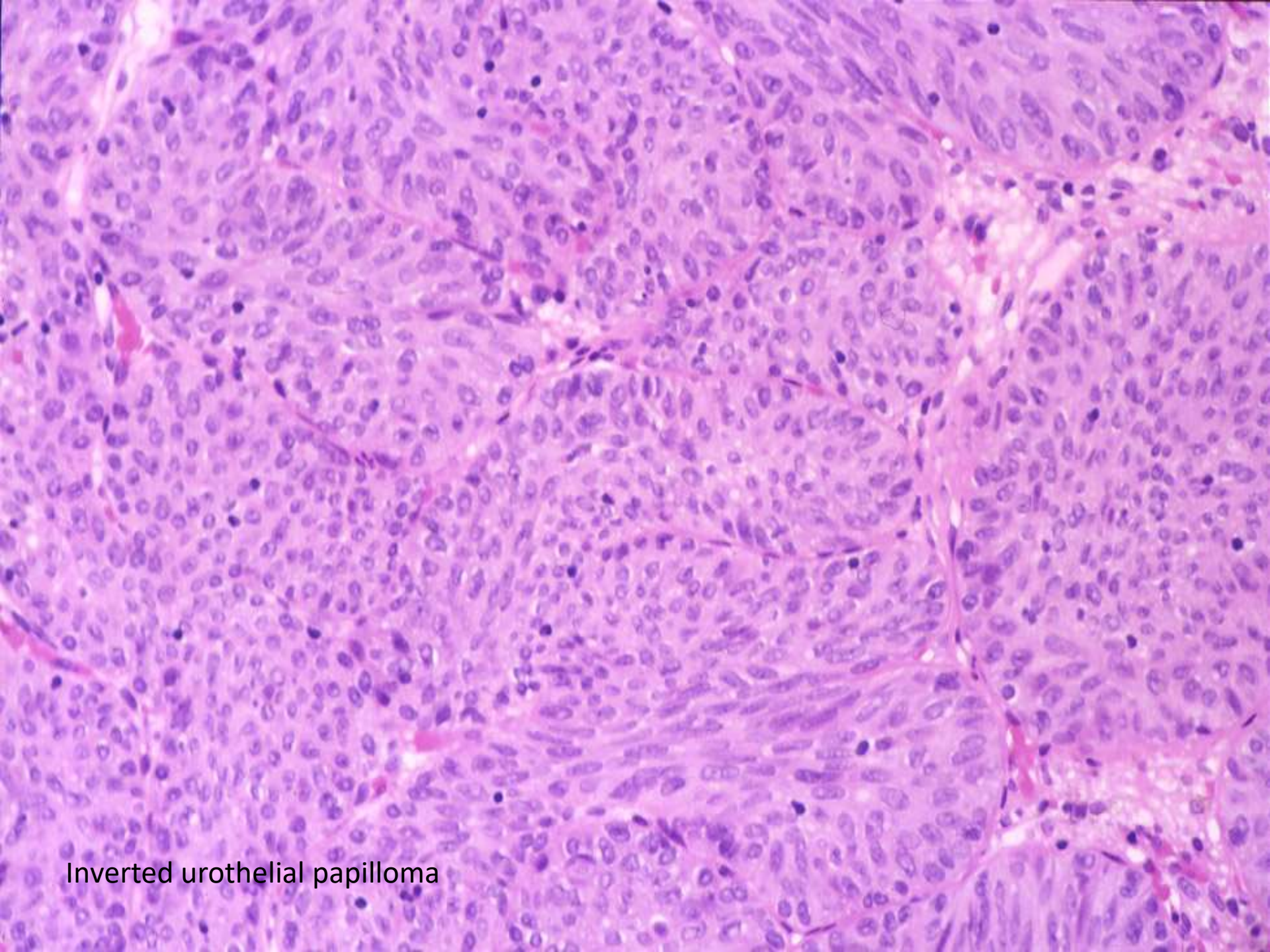
Inverted urothelial papilloma

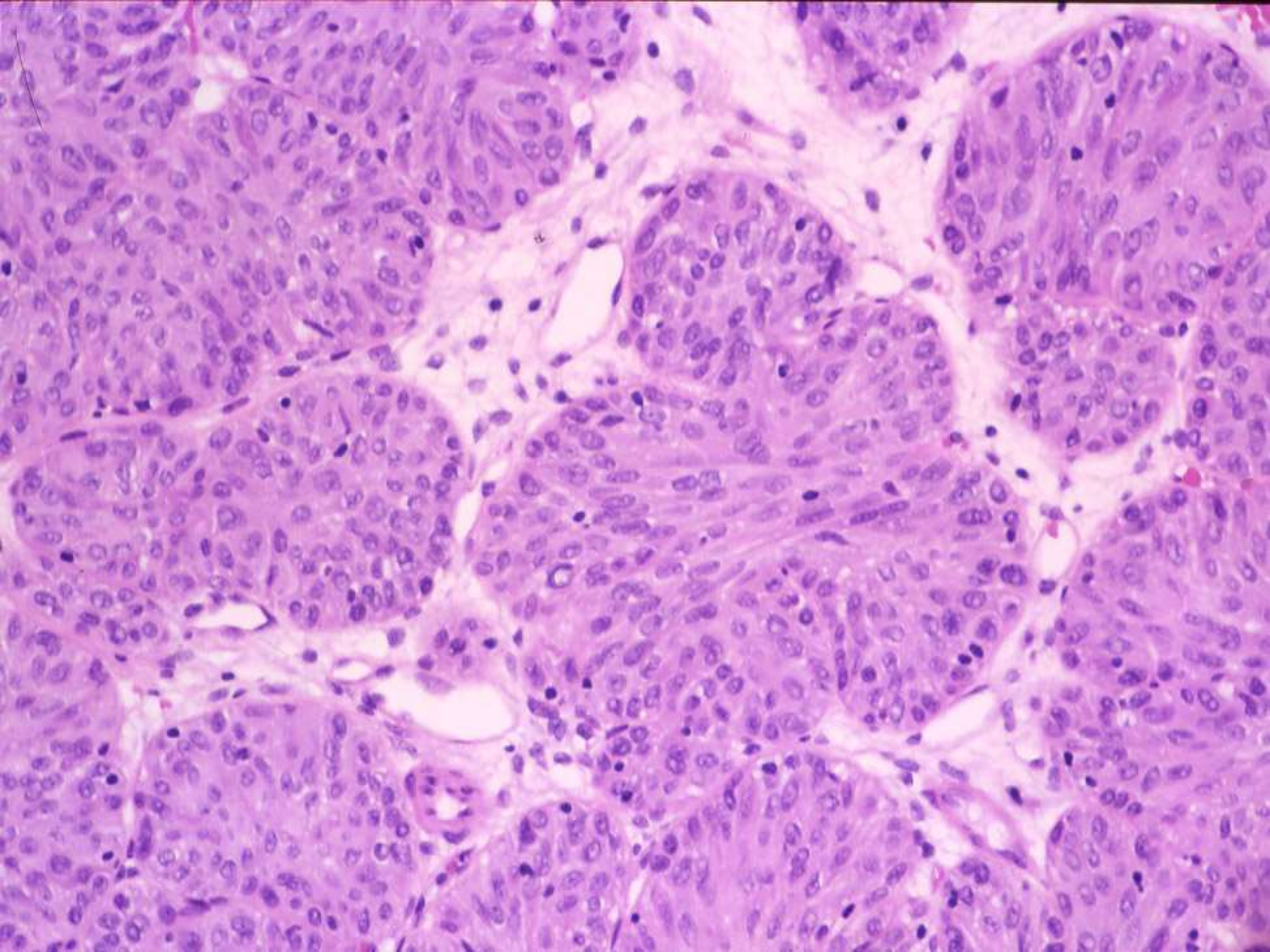
- Rare (<1% urothelial lesions)
- 10-94 years (peak 50-60 years)
- Solitary, pedunculated or solitary
- Up to 8 cm
- Benign
- Some cystoscopic follow up would generally be undertaken
- Differential diagnoses: PUNLMP with inverted growth pattern; inverted urothelial carcinoma

Inverted papilloma: trabeculae are typically uniform in width and narrow




Inverted urothelial papilloma

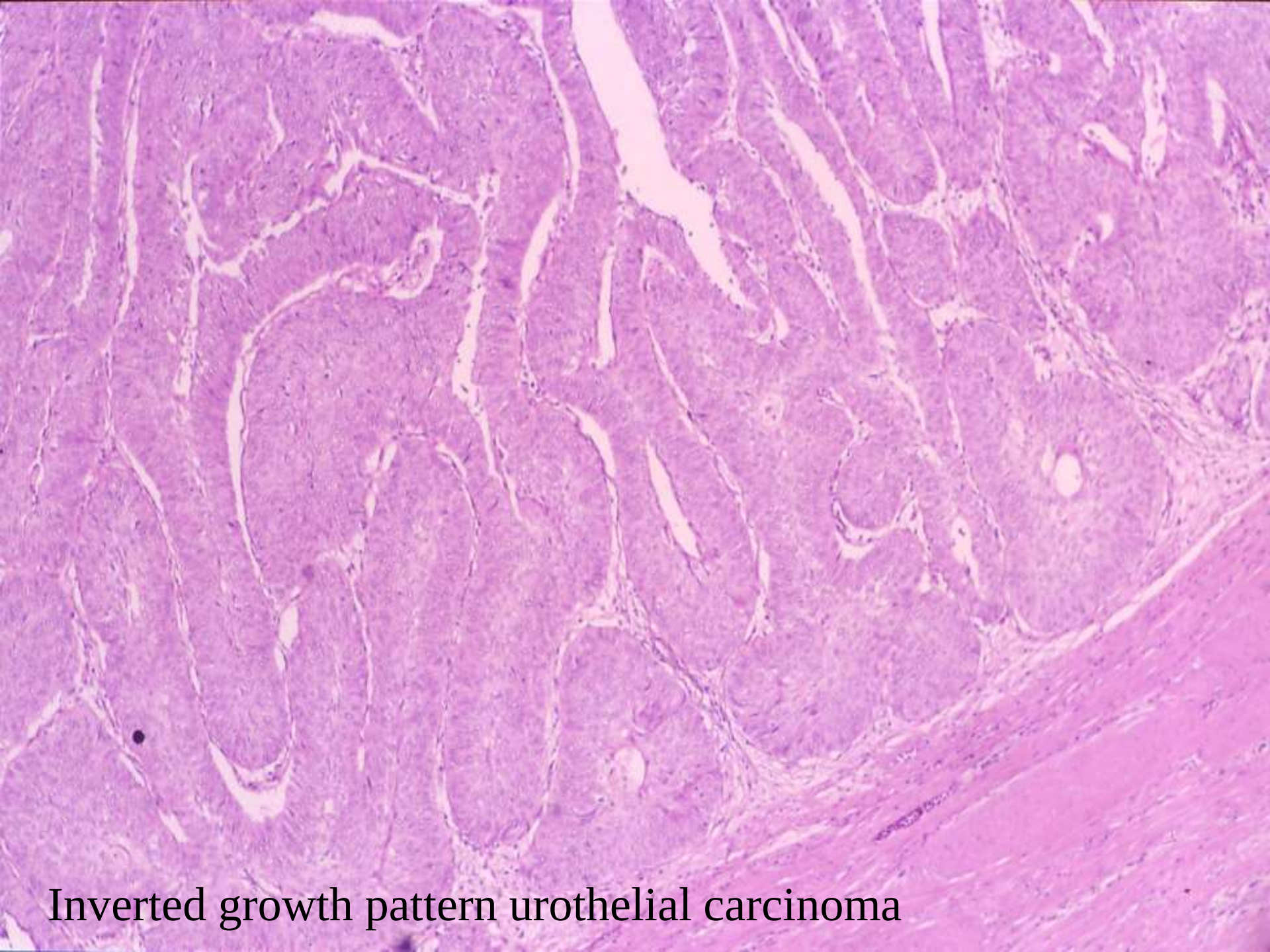

Inverted urothelial papilloma



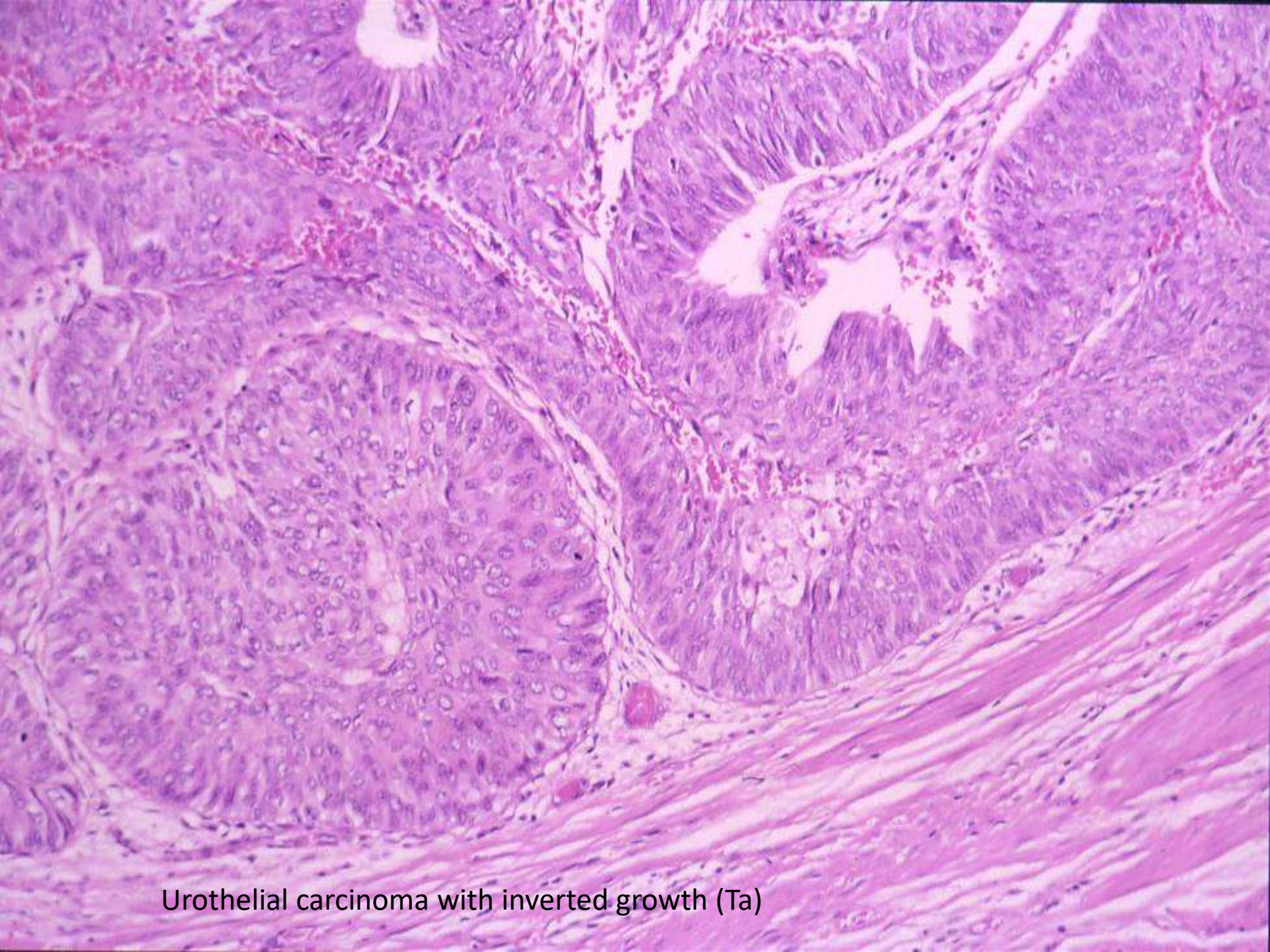
Biopsy interpretation of the bladder

Epstein KI, Reuter VE, Amin MB

"Inverted urothelial papillomas may have focal polypoid exophytic growth, yet lack true papillae…Exceptionally classic inverted papillomas have one or two, apparently true fronds, in these cases a diagnosis of inverted papilloma is still acceptable as the fronds may represent a tangential sectioning off a polypoid growth. In rare cases benign inverted urothelial papilloma may be found with areas typical of exophytic urothelial papilloma…..there is no data on the behaviour of these hybrid lesions.. It is typically recommended that they be followed as if they had an exophytic papilloma with repeated periodic cystoscopic examinations"



Inverted growth pattern urothelial carcinoma

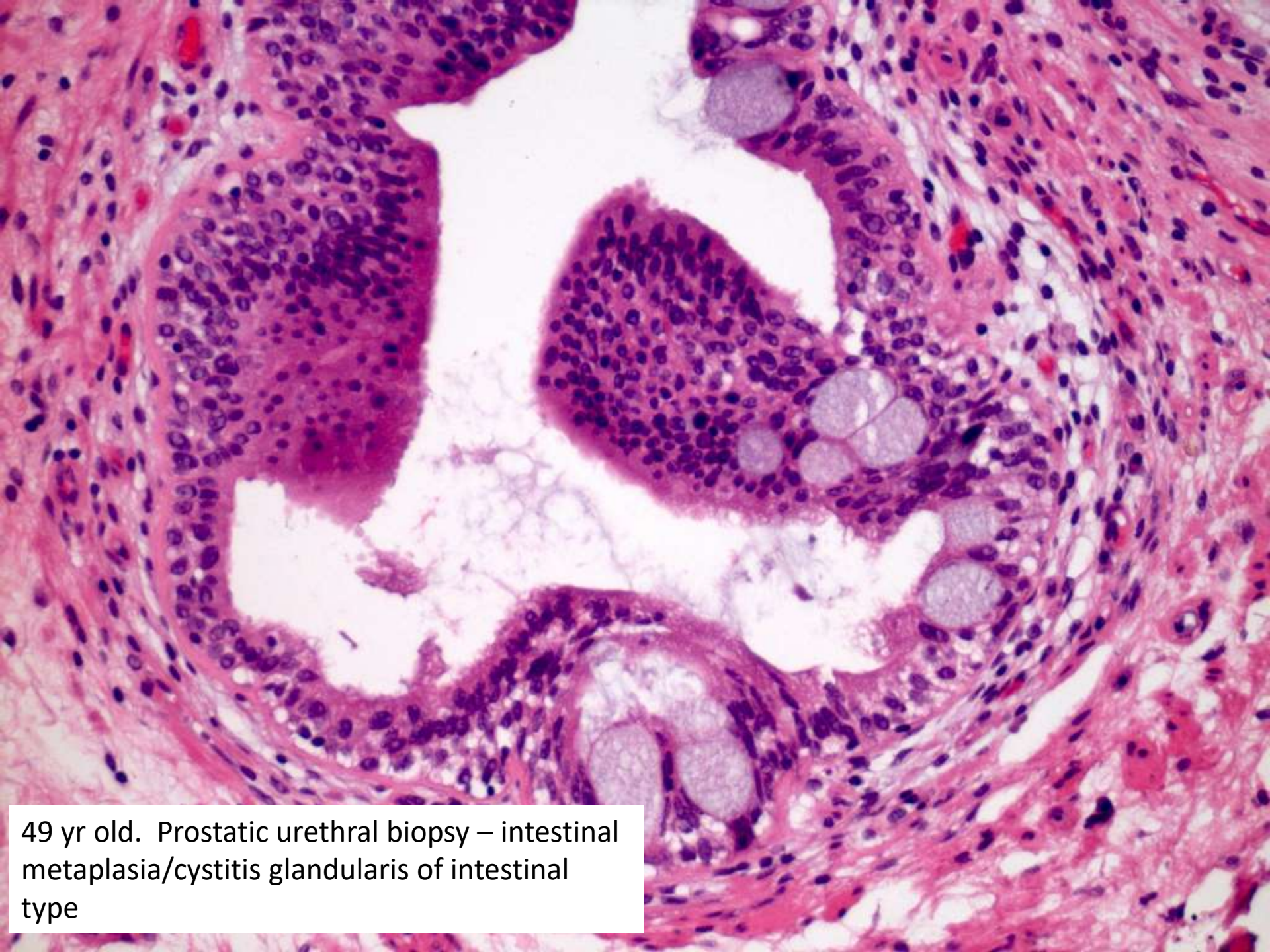


Urothelial carcinoma with inverted growth (Ta)

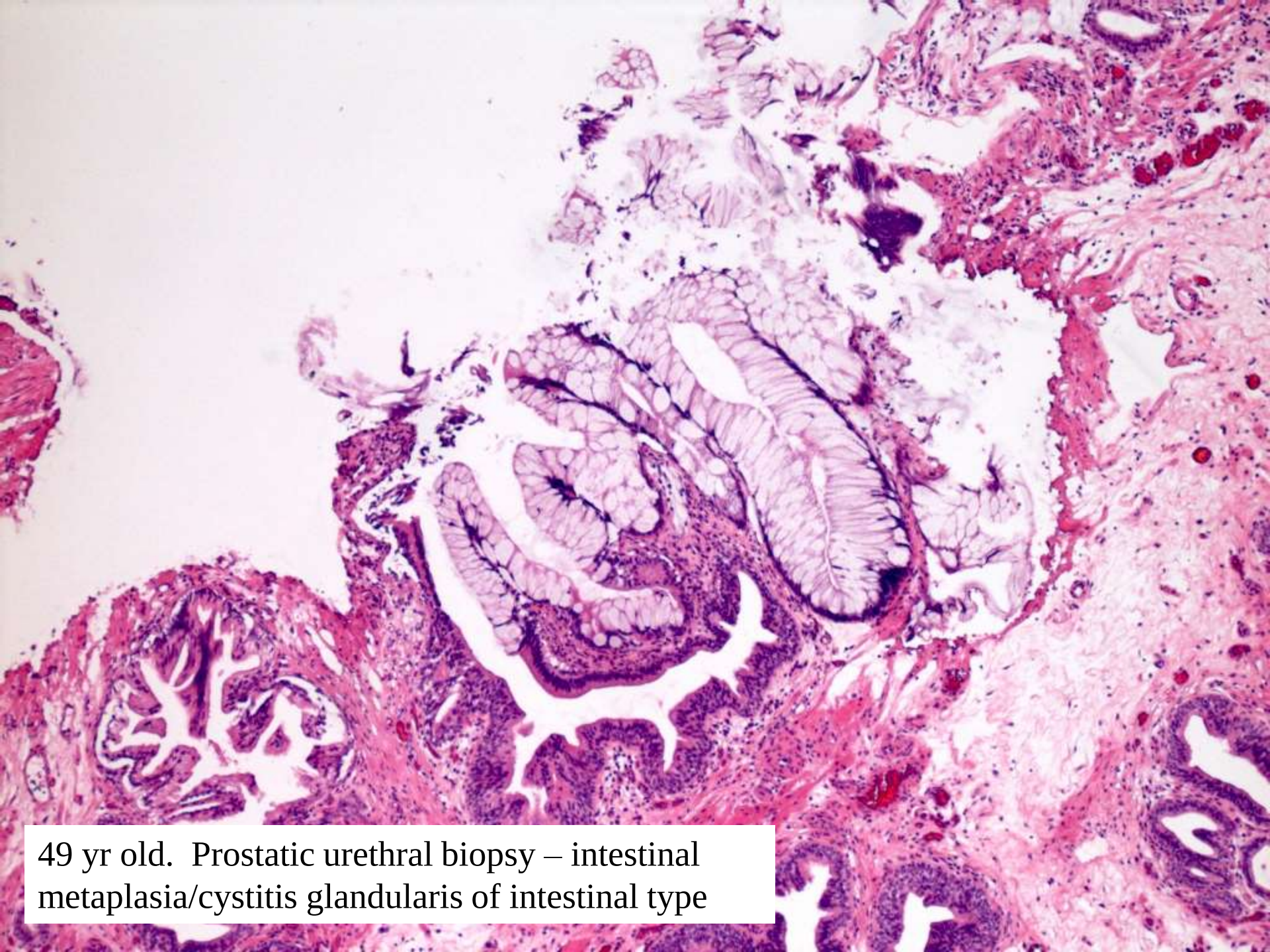
Inverted papilloma vs inverted urothelial carcinoma

Features supporting inverted papilloma:

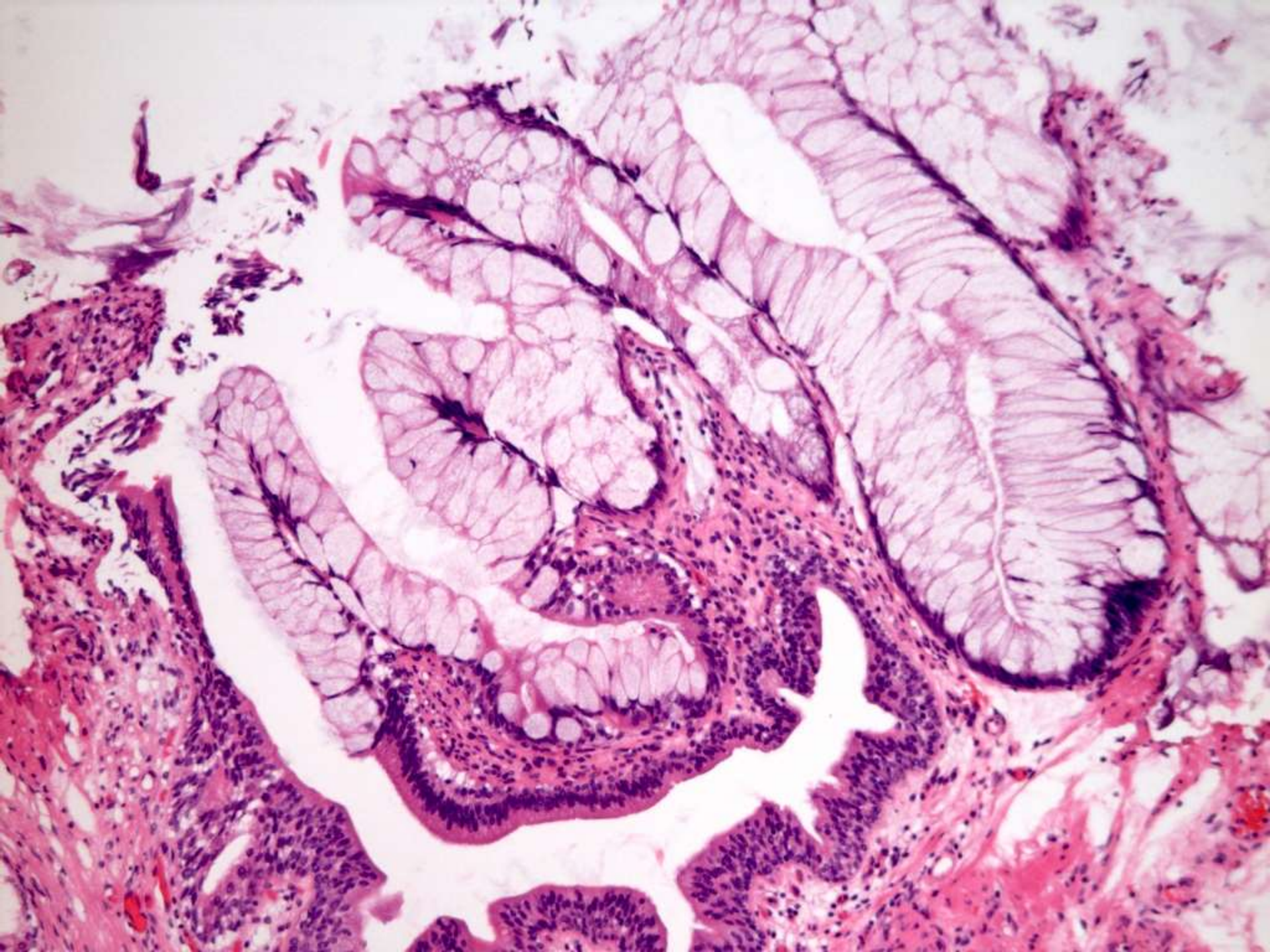
- Usually dome shaped, usually solitary with absent to minimal exophytic component
- Well demarcated from surrounding tissue
- Absent atypia is usual (occasional cases may have some degenerate atypia)
- Relatively slender cords and trabeculae of even width and absence of solid areas
- Peripheral palisading and central spindling in trabeculae
- Destructive invasion absent
- Absence of large rounded nests

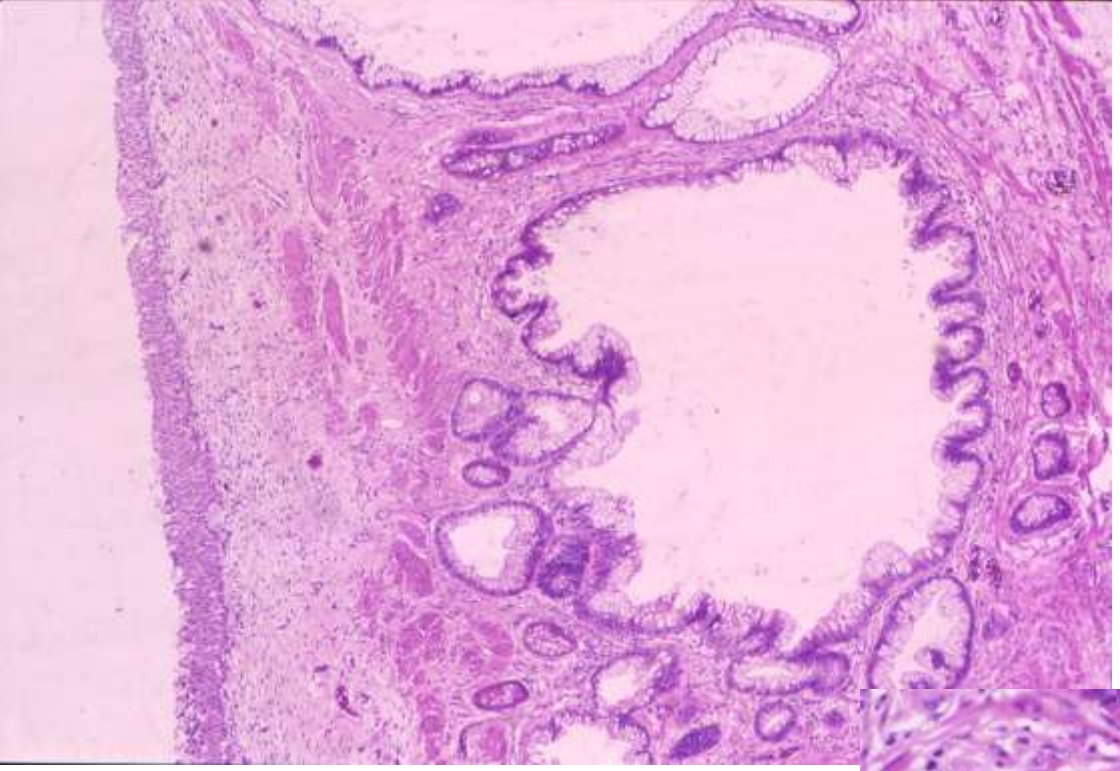


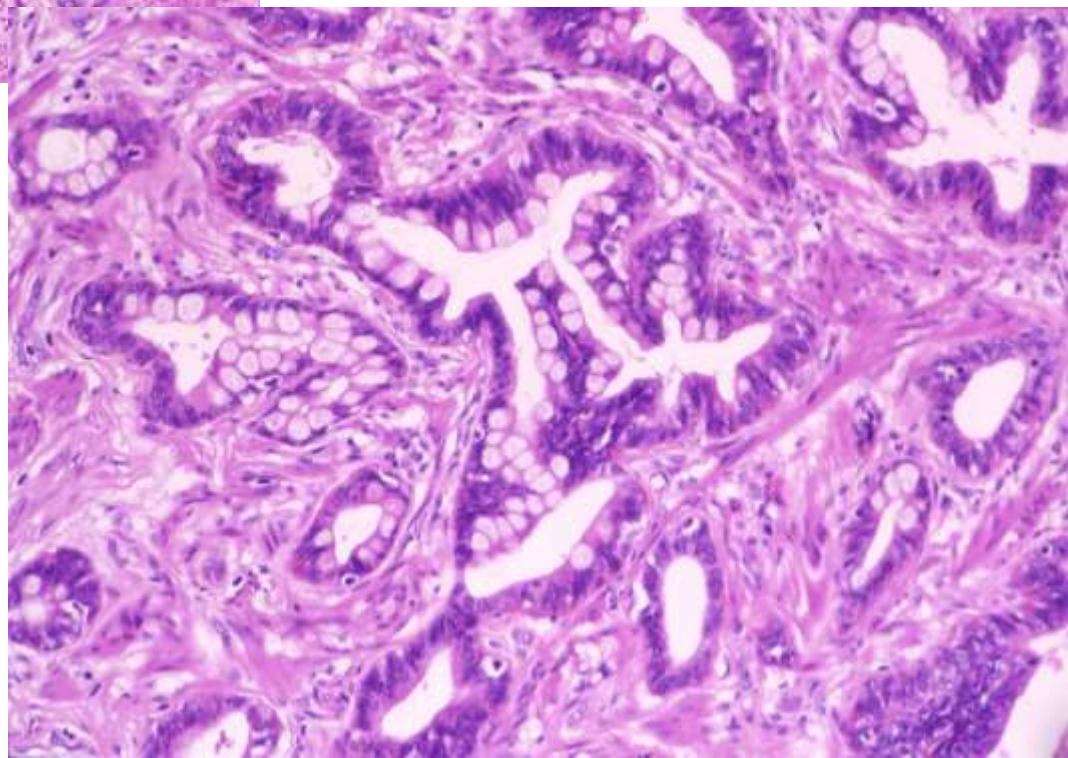
49 yr old. Prostatic urethral biopsy – intestinal metaplasia/cystitis glandularis of intestinal type



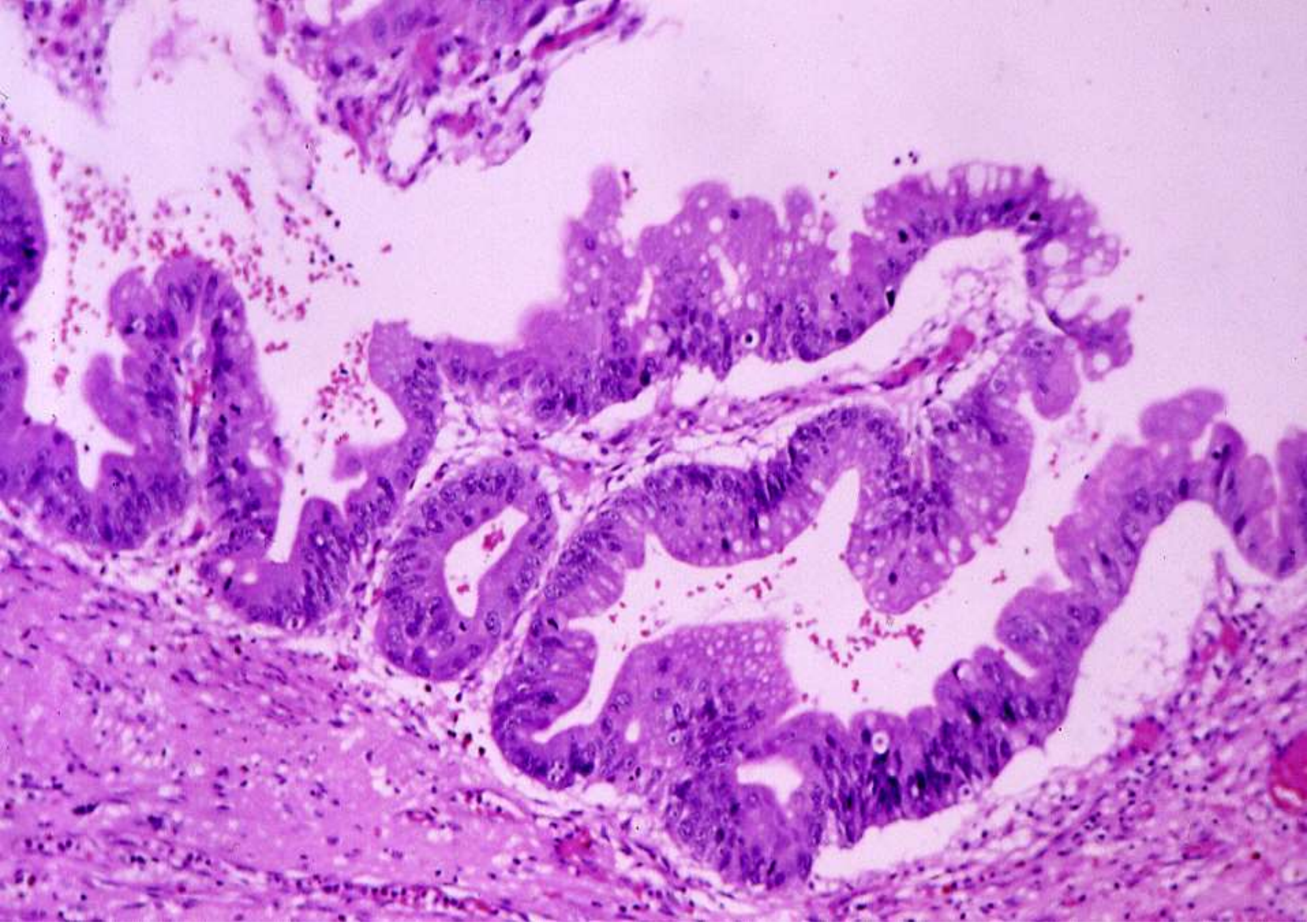
49 yr old. Prostatic urethral biopsy – intestinal metaplasia/cystitis glandularis of intestinal type





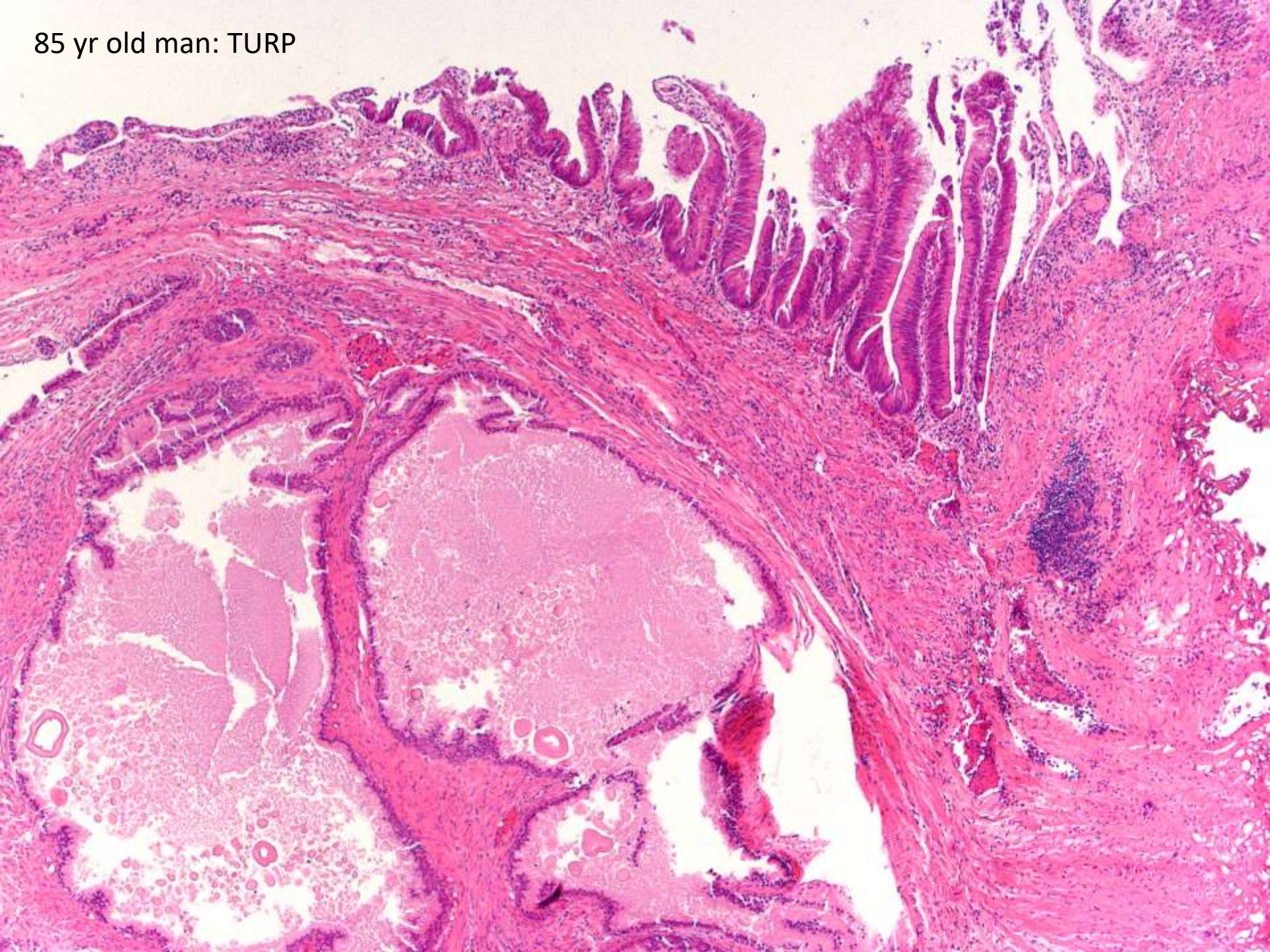


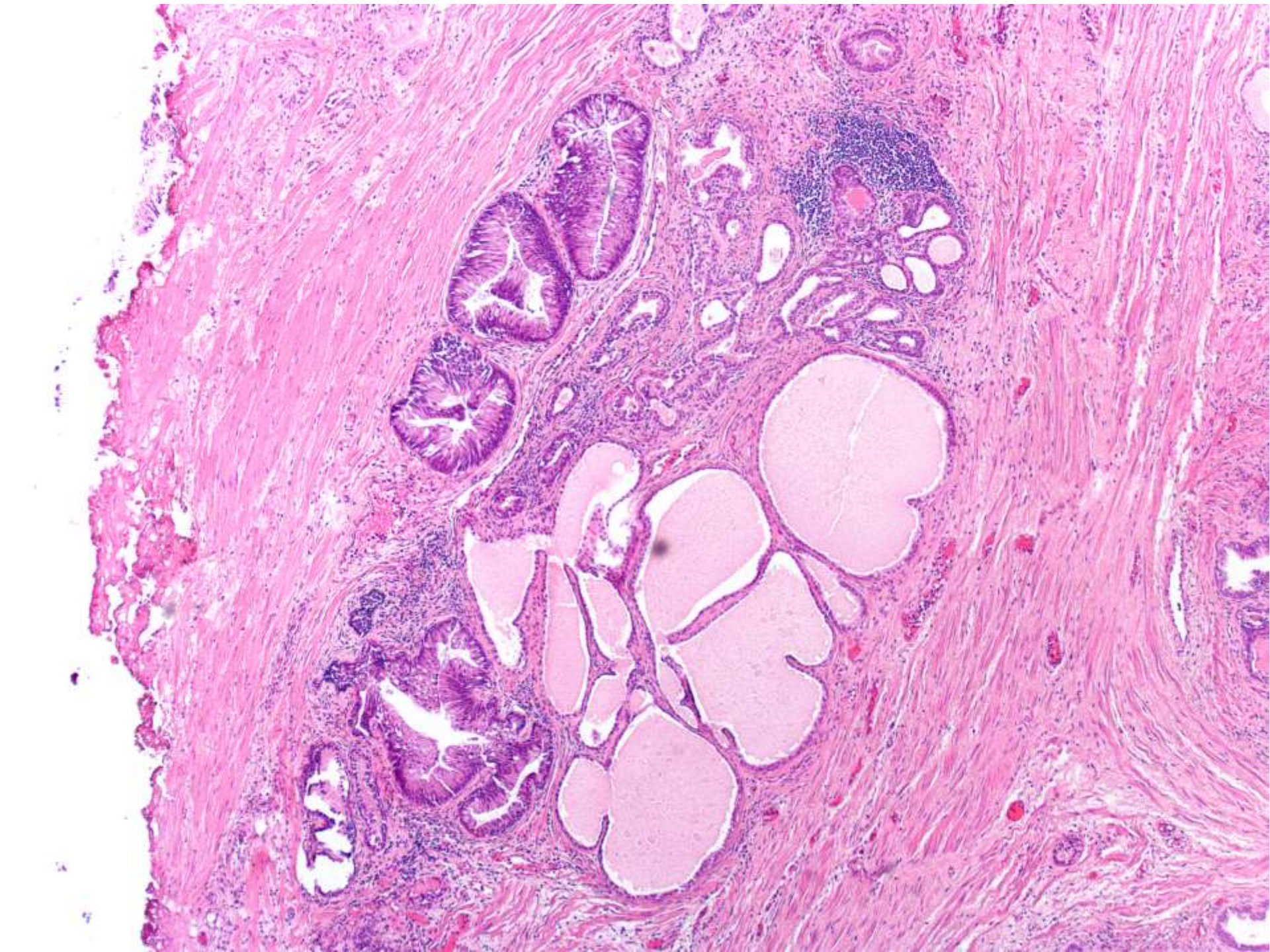
Intestinal metaplasia/cystitis glandularis of intestinal type

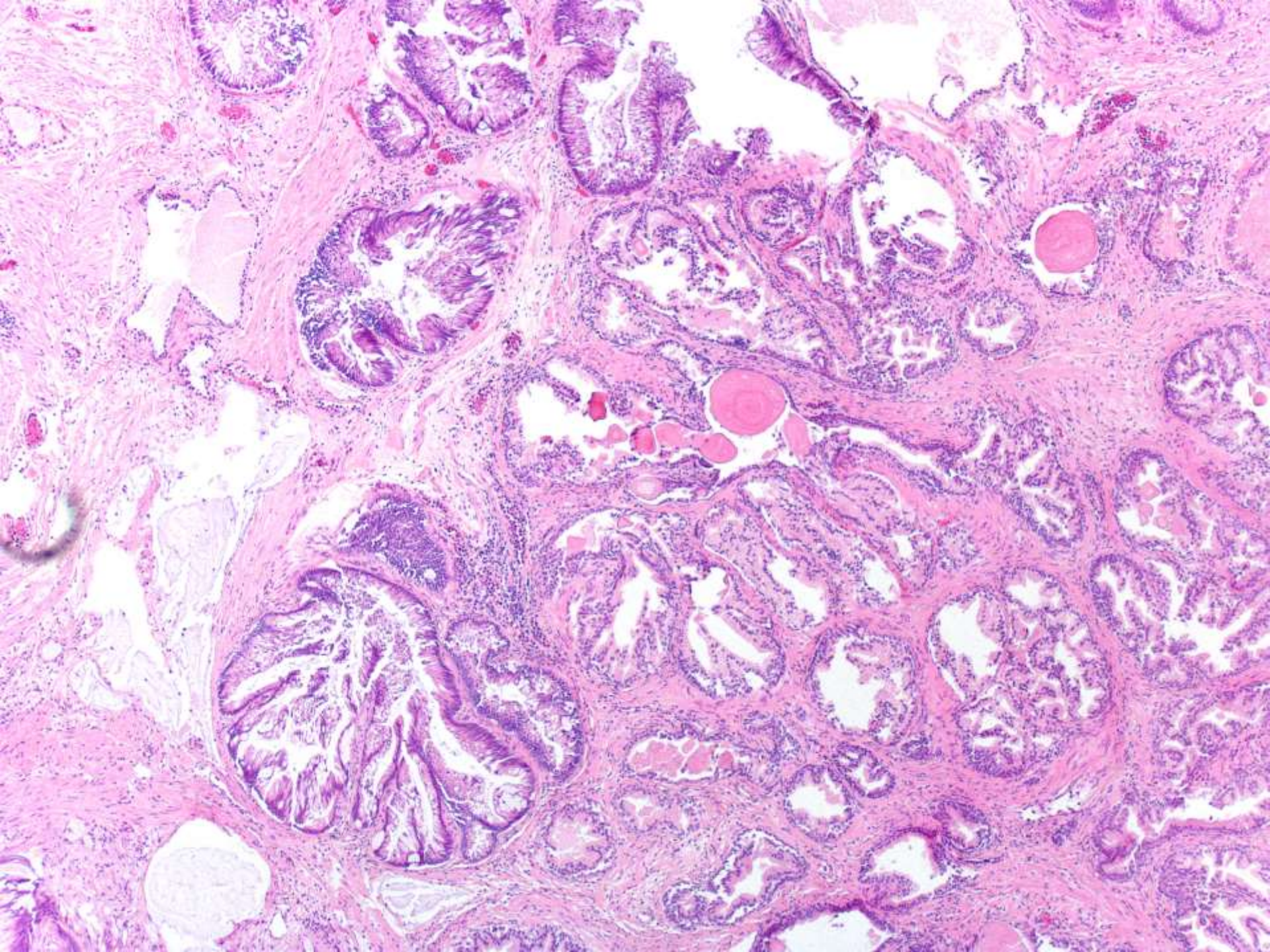


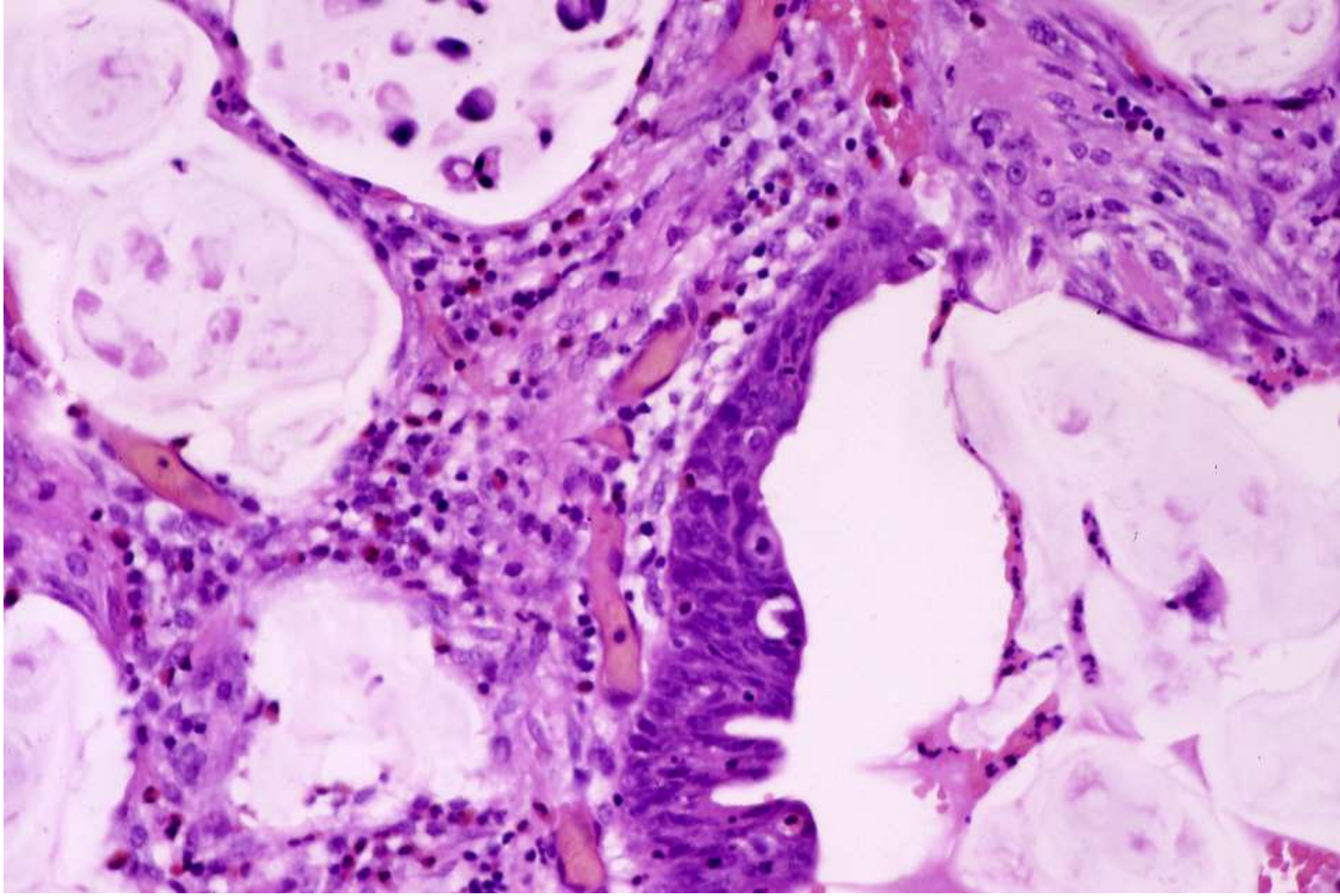
Bladder: intestinal metaplasia with dysplasia

85 yr old man: TURP

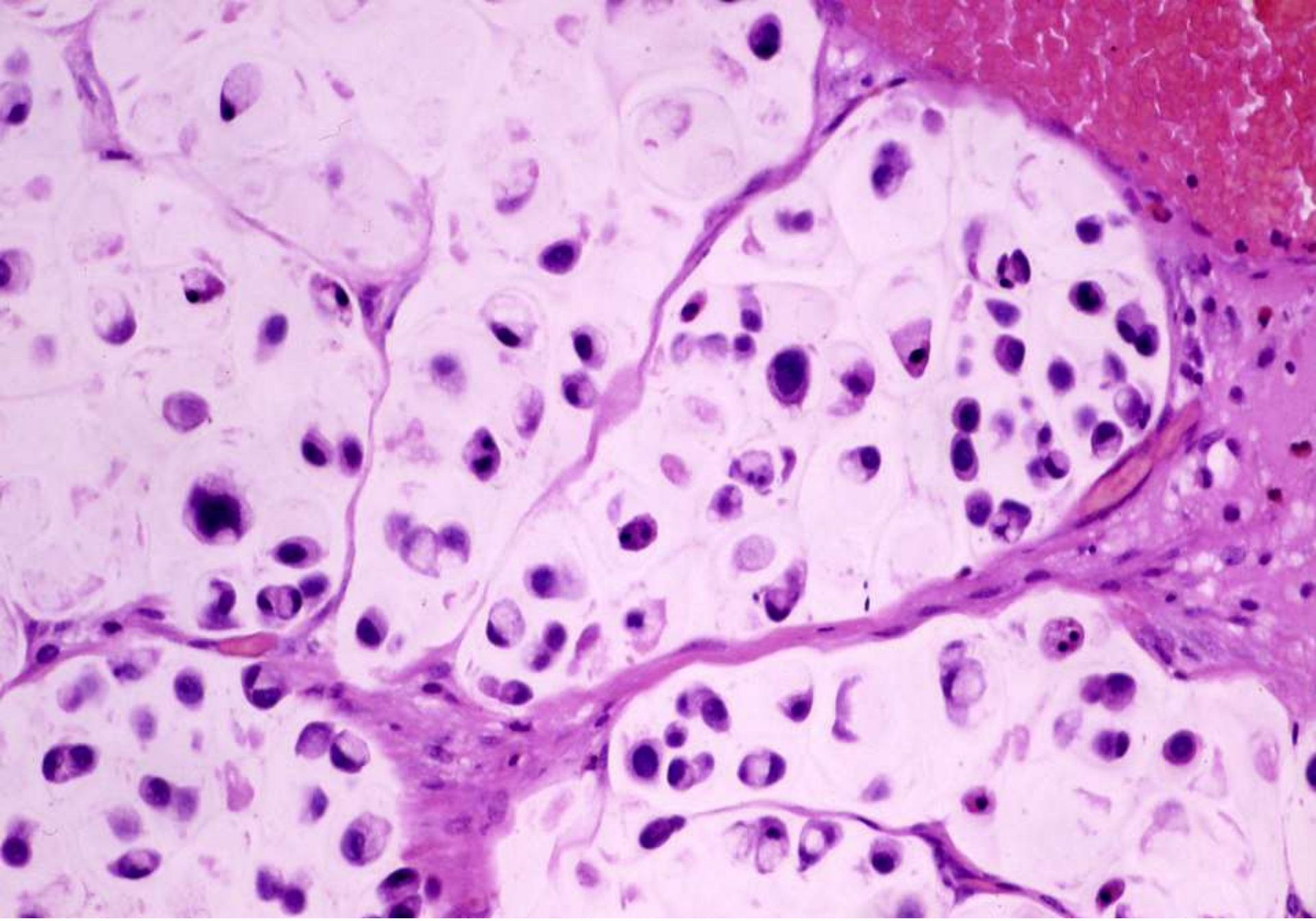








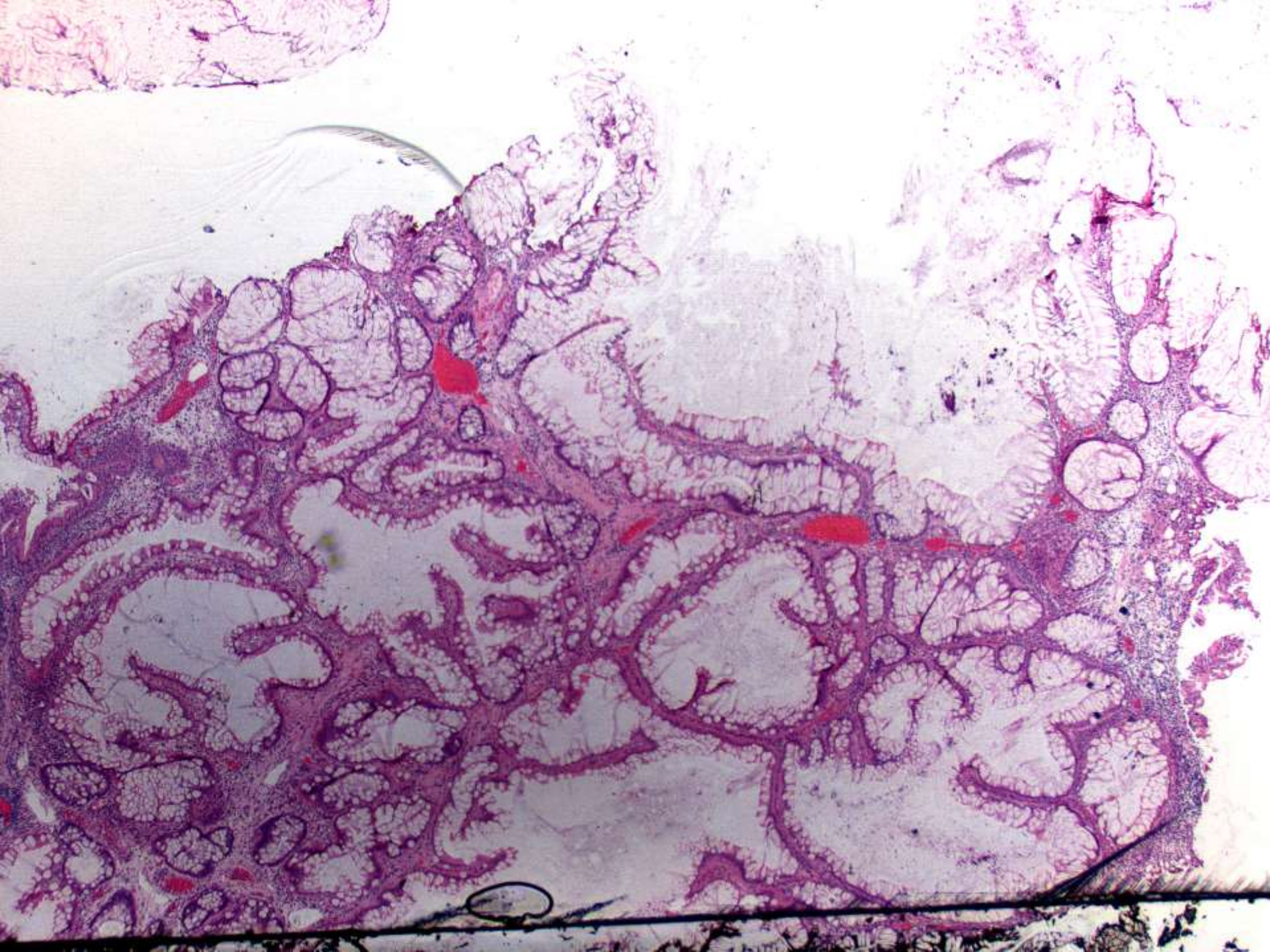
Bladder: invasive signet ring adenocarcinoma arising from intestinal metaplasia with dysplasia

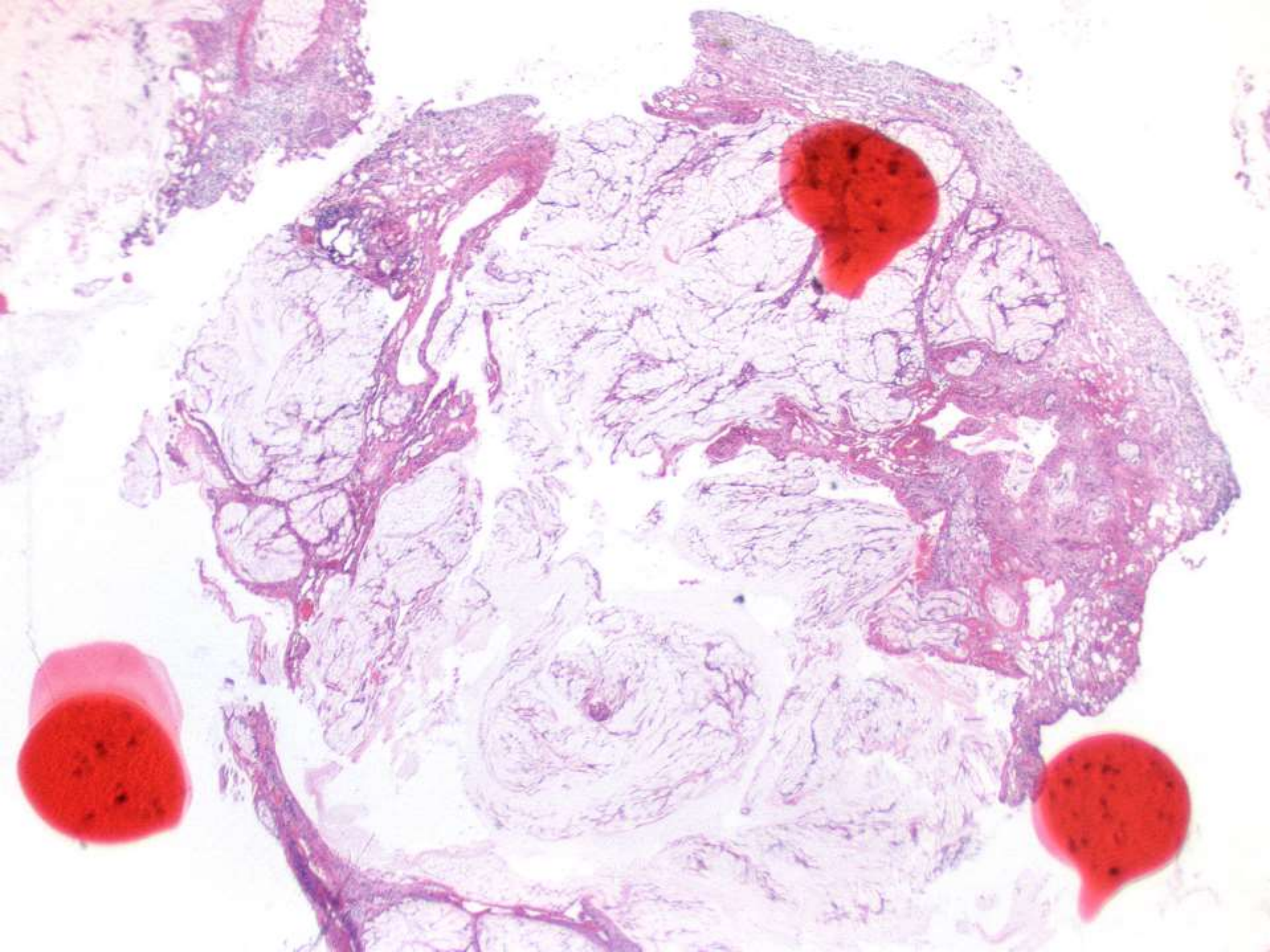


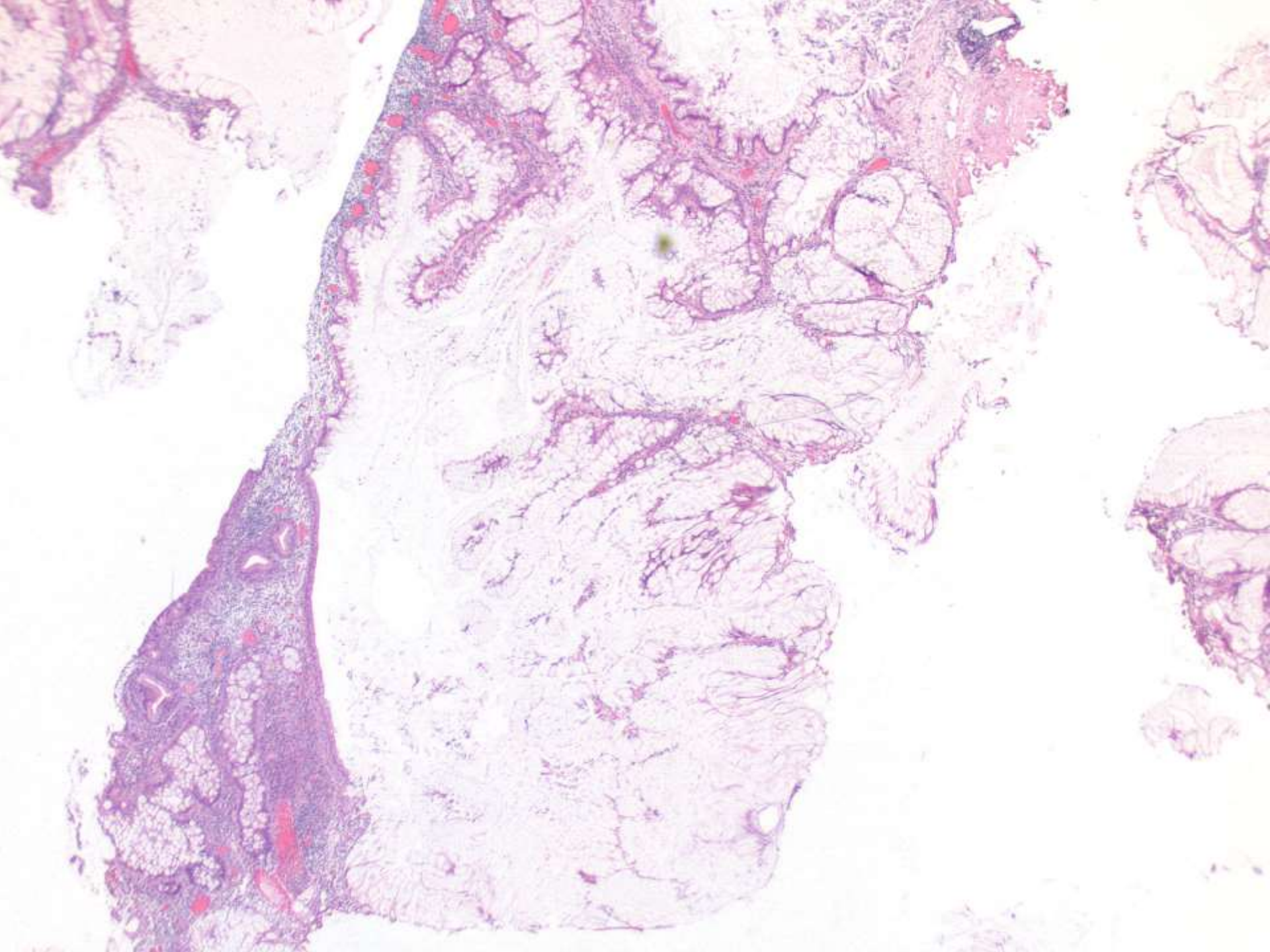
Signet ring adenocarcinoma

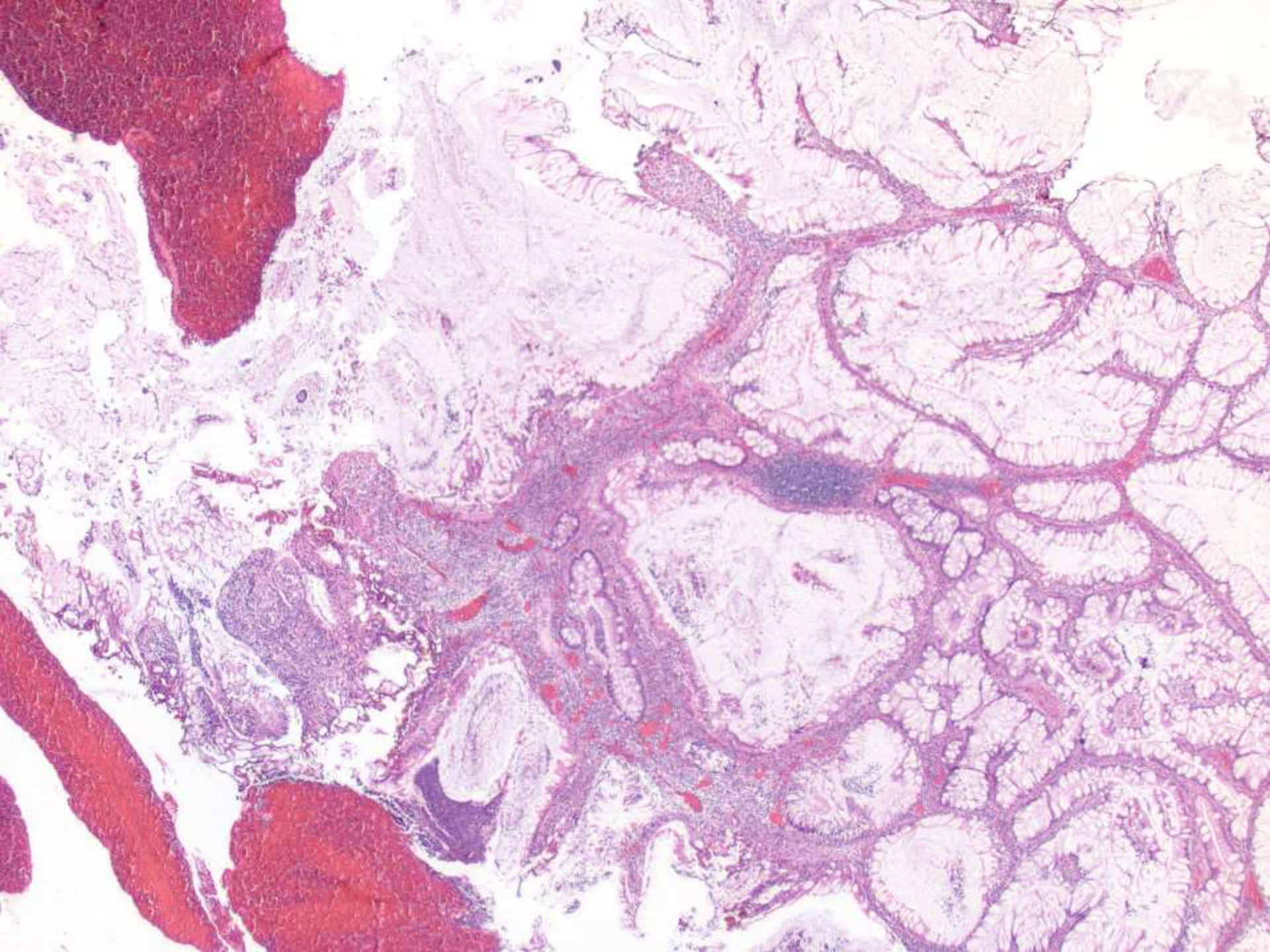
Case: history

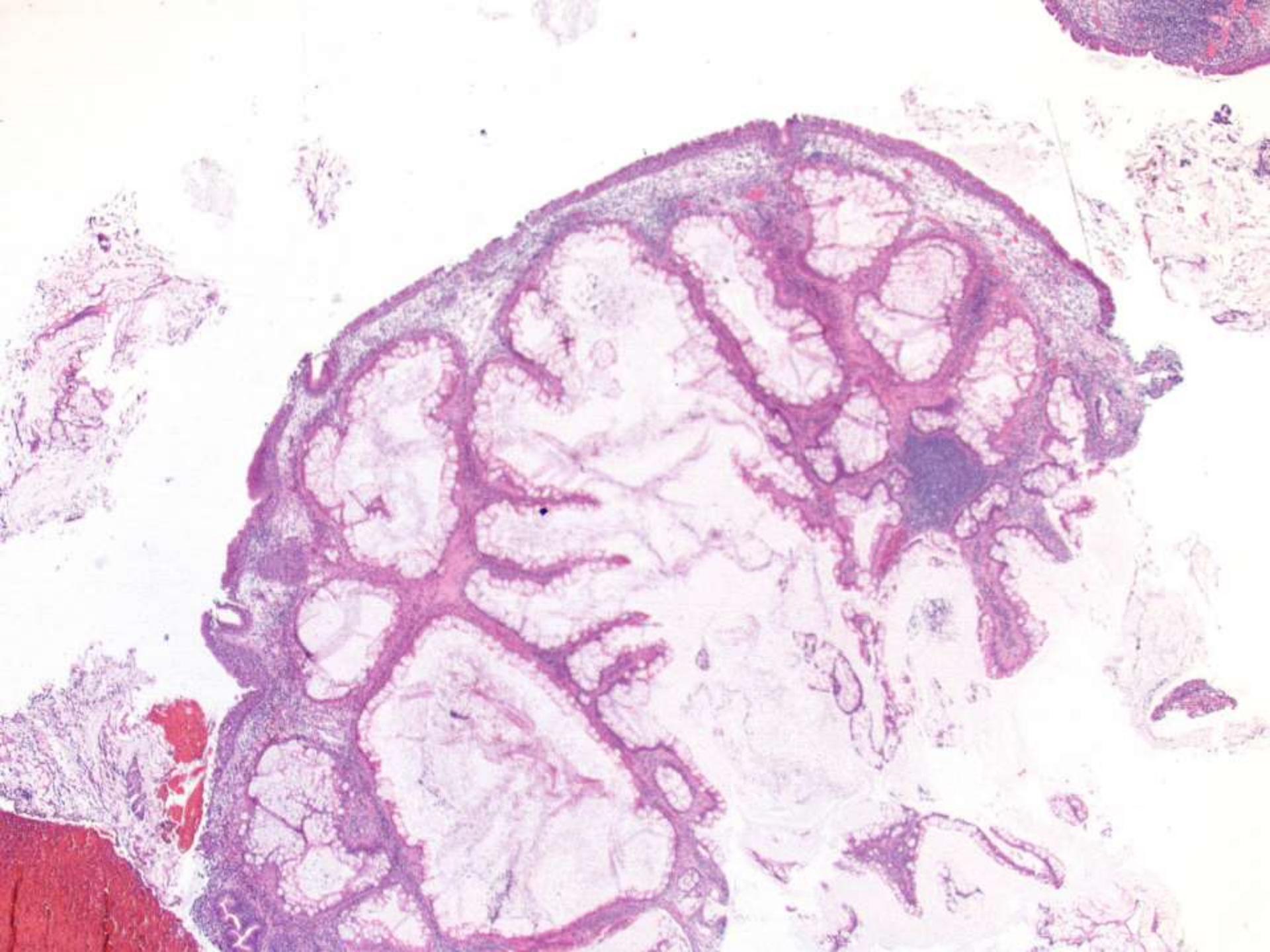
- Female 50 years old
- Bladder TUR
- No macroscopic description but all processed in 1 block
- Clinical information given: “posterior, lateral wall bladder lesion, looks solid”

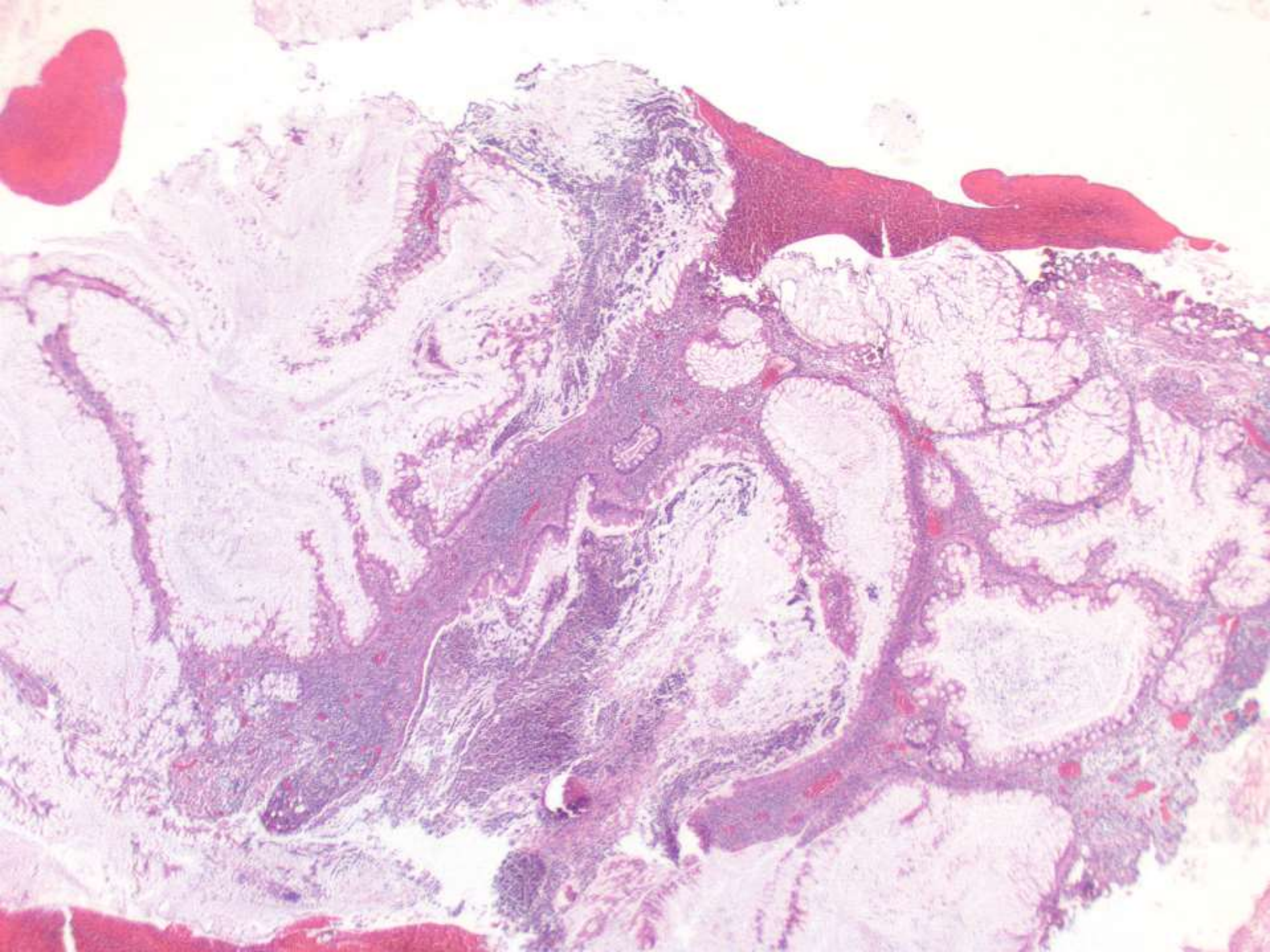


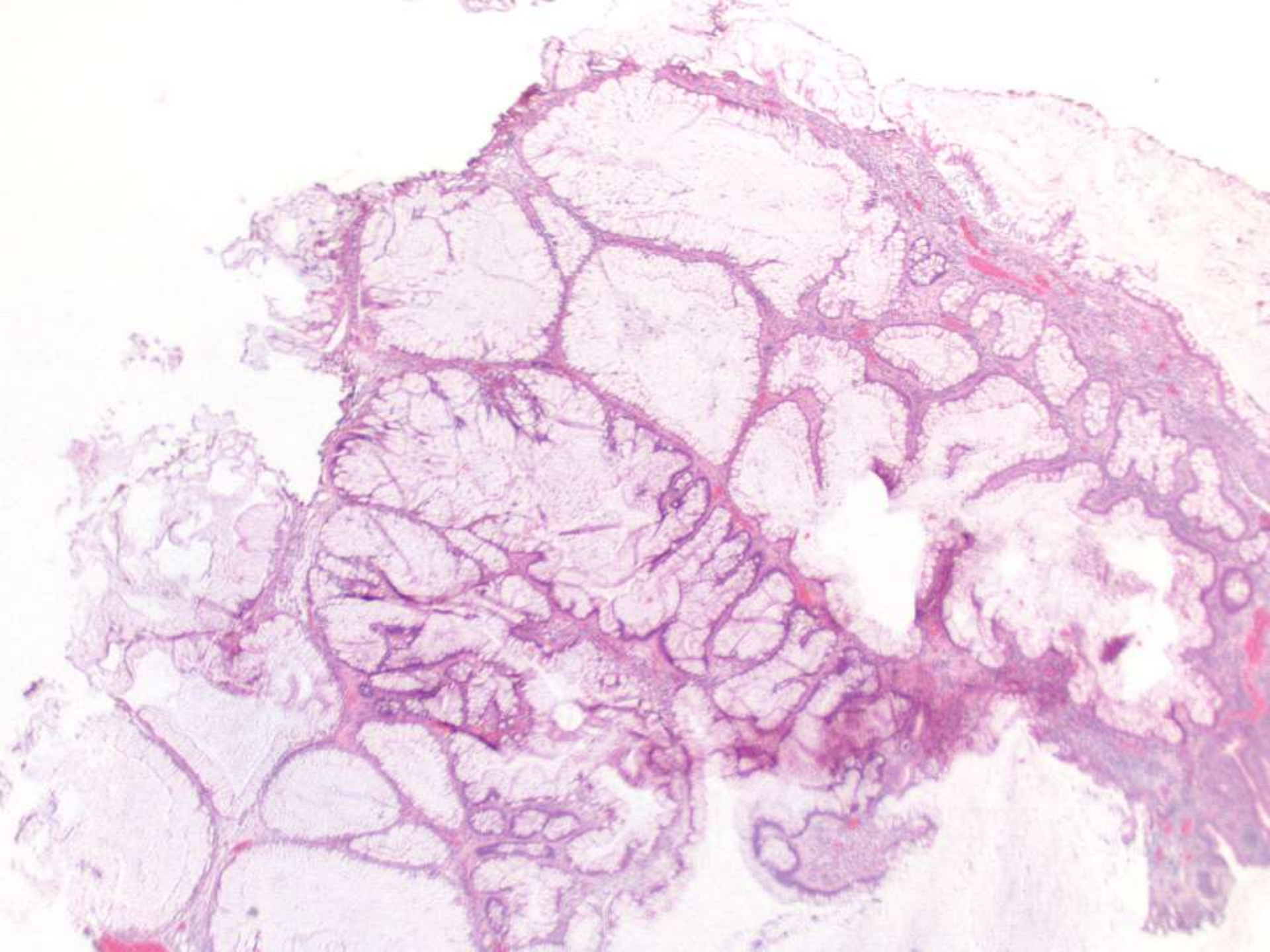


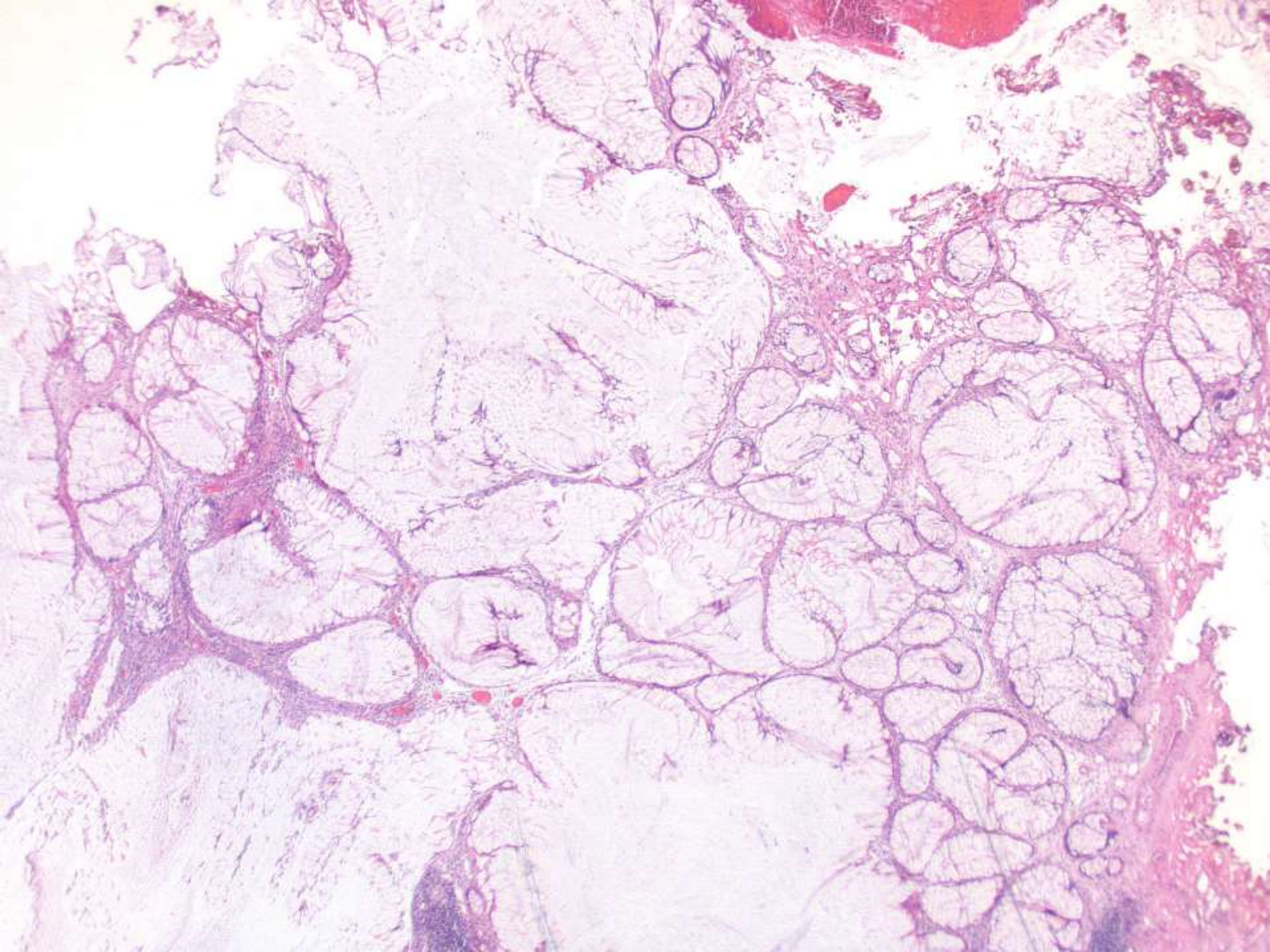


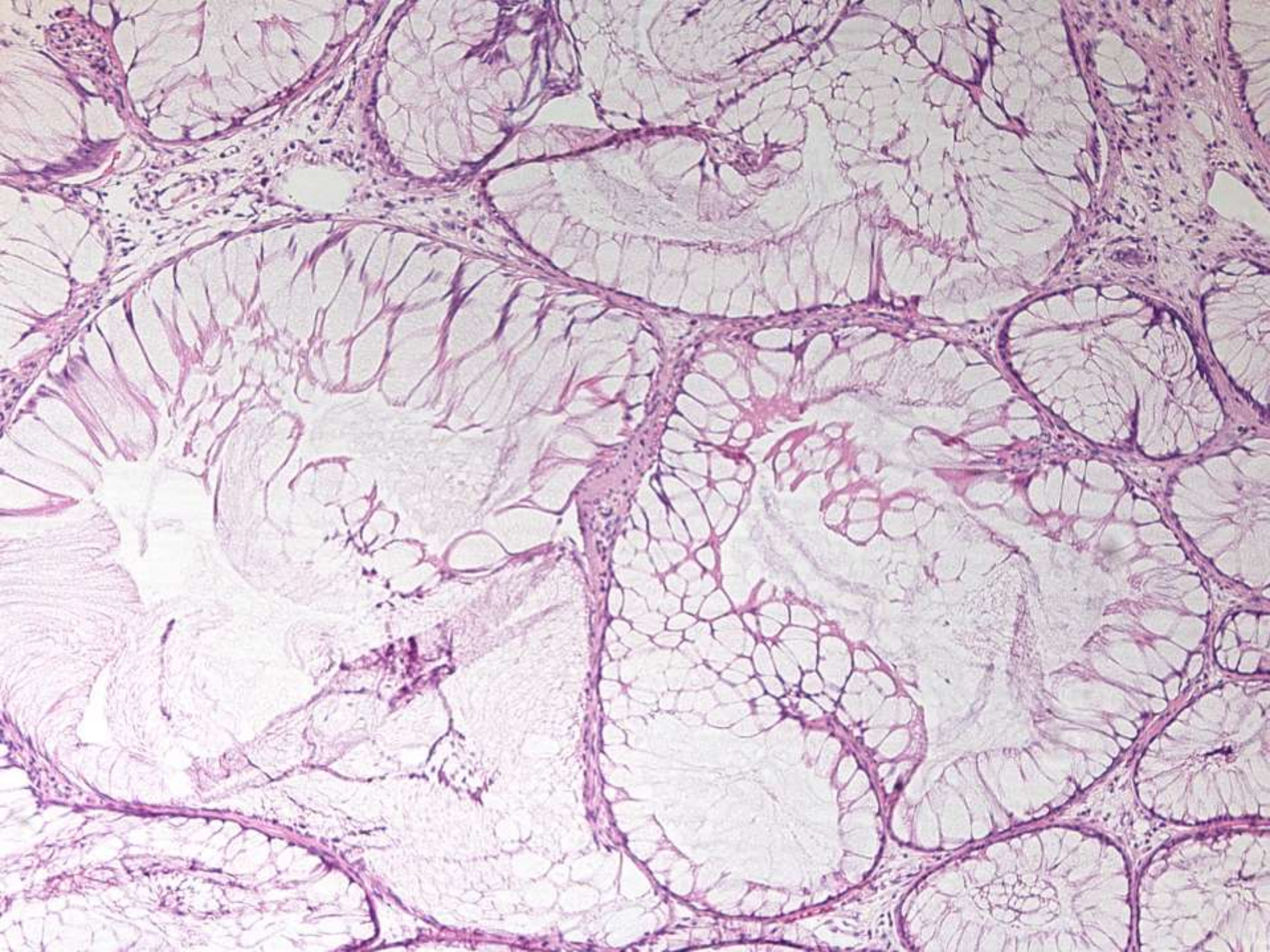


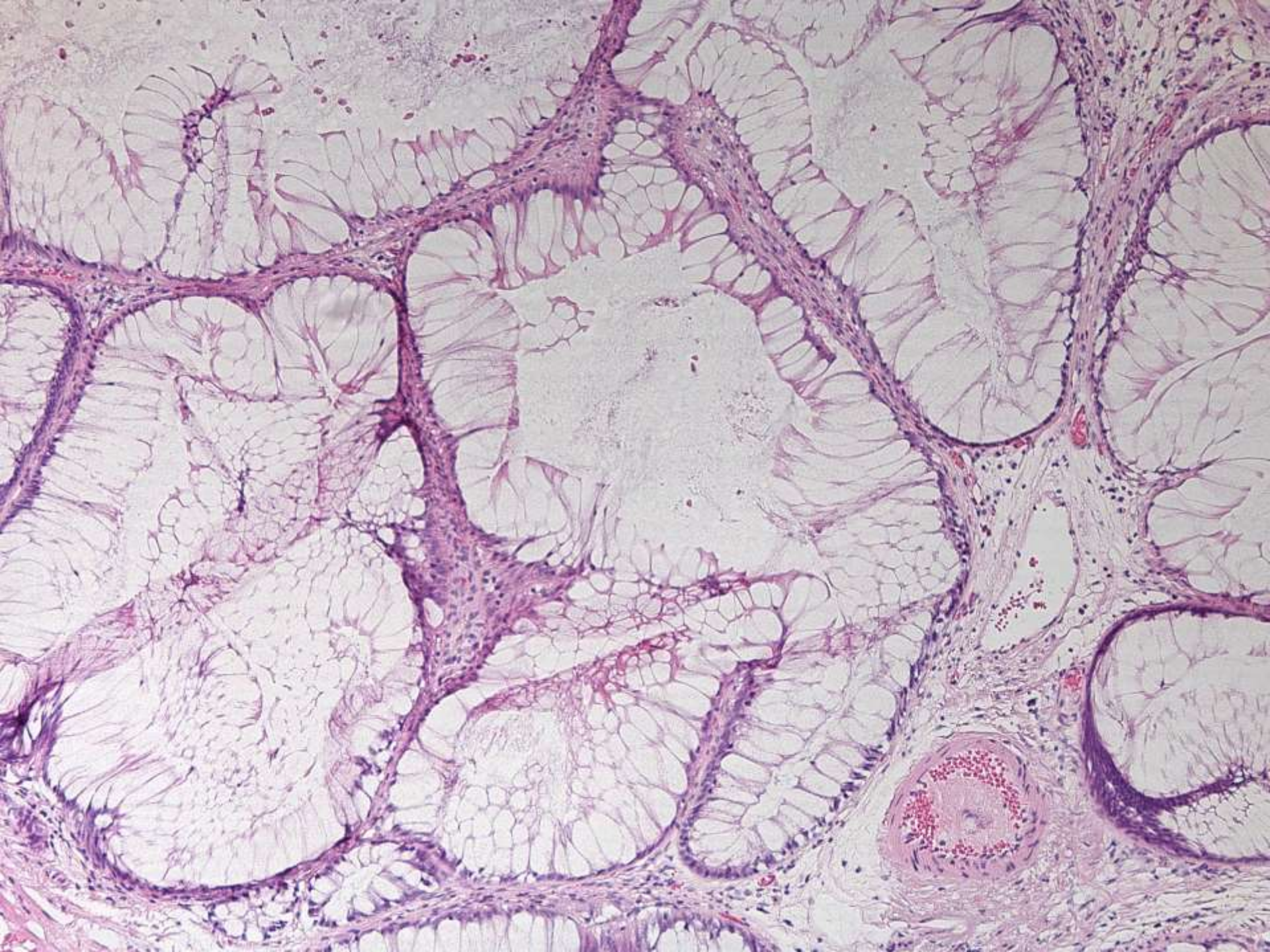


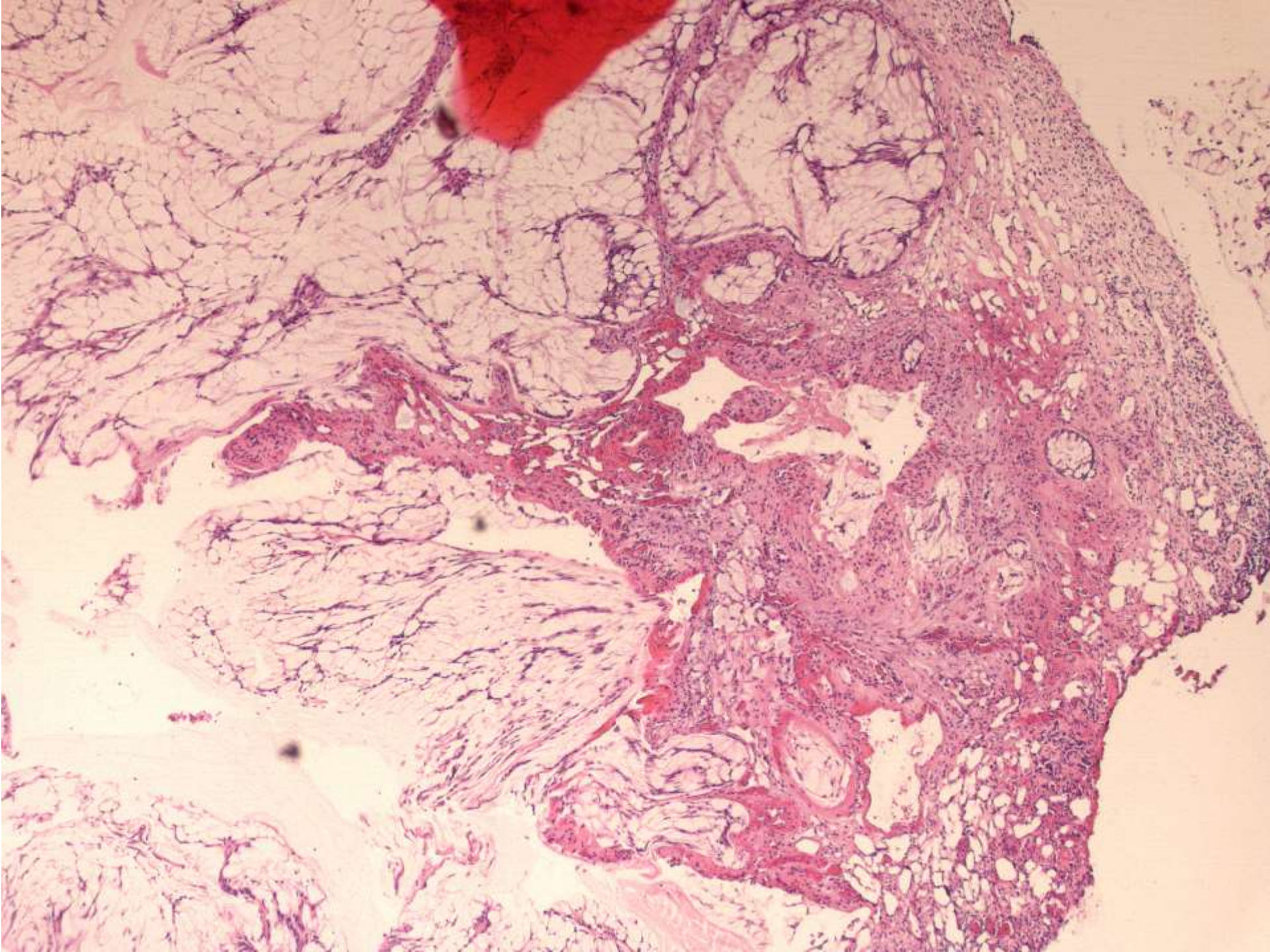


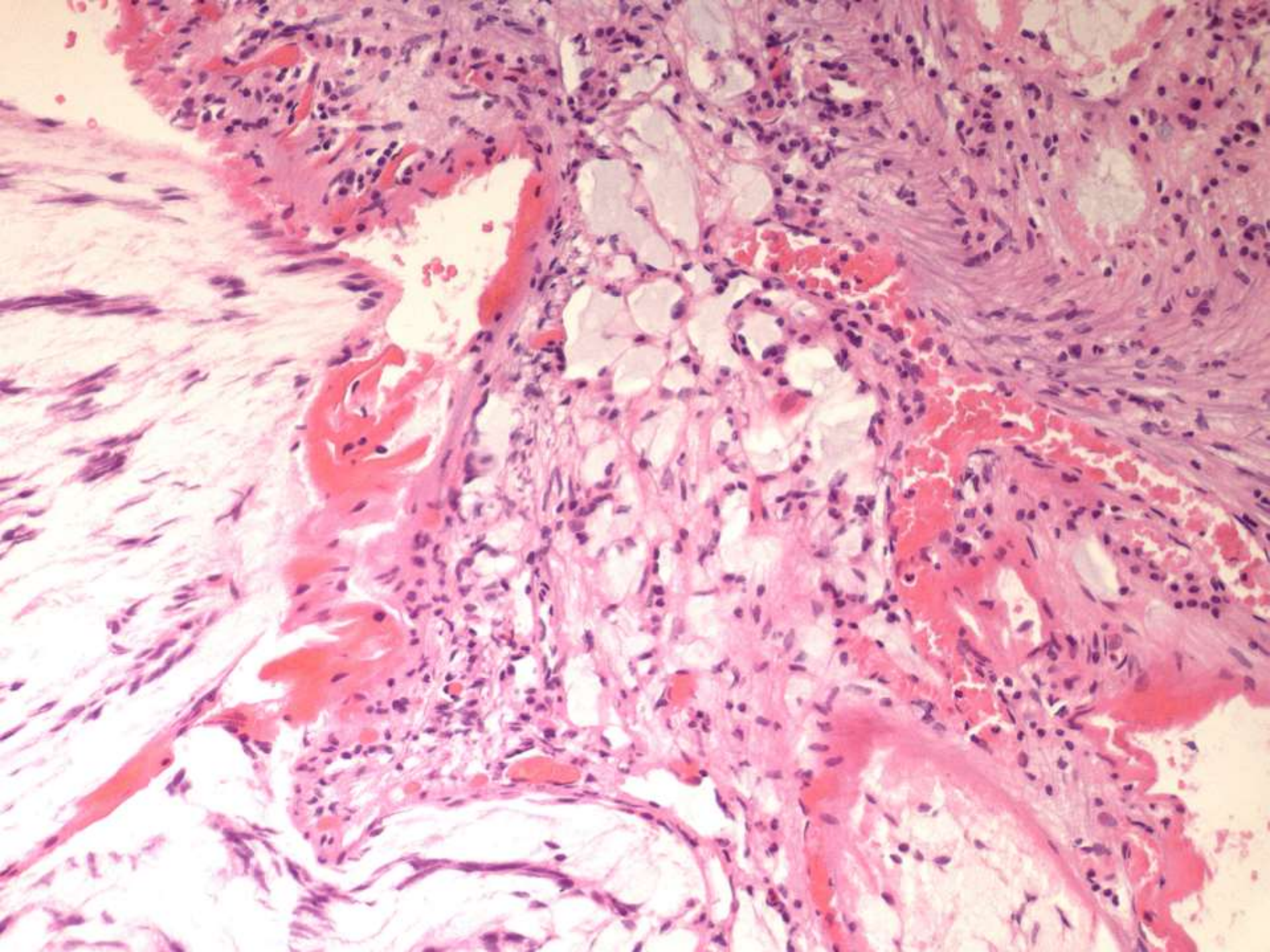


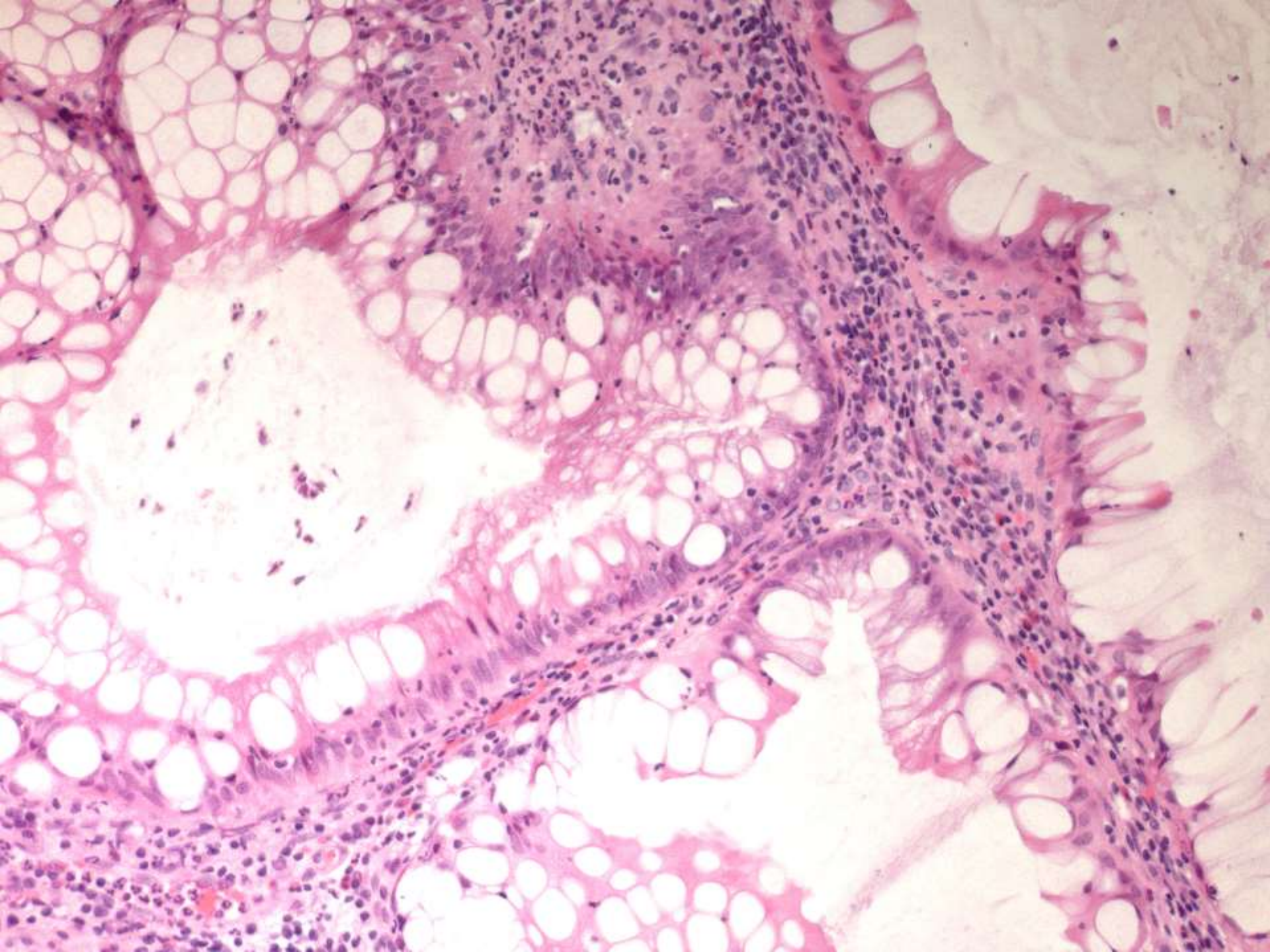


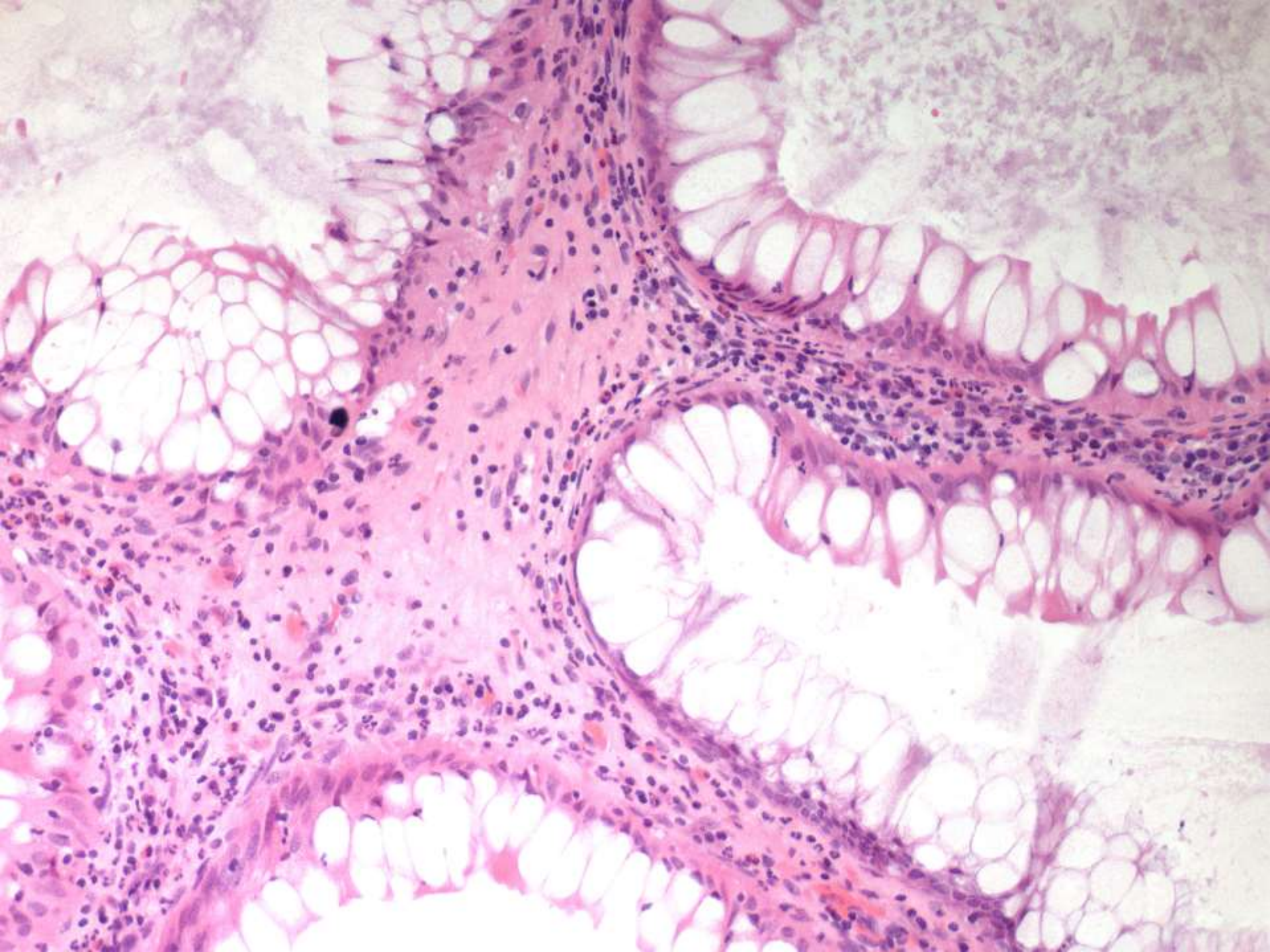


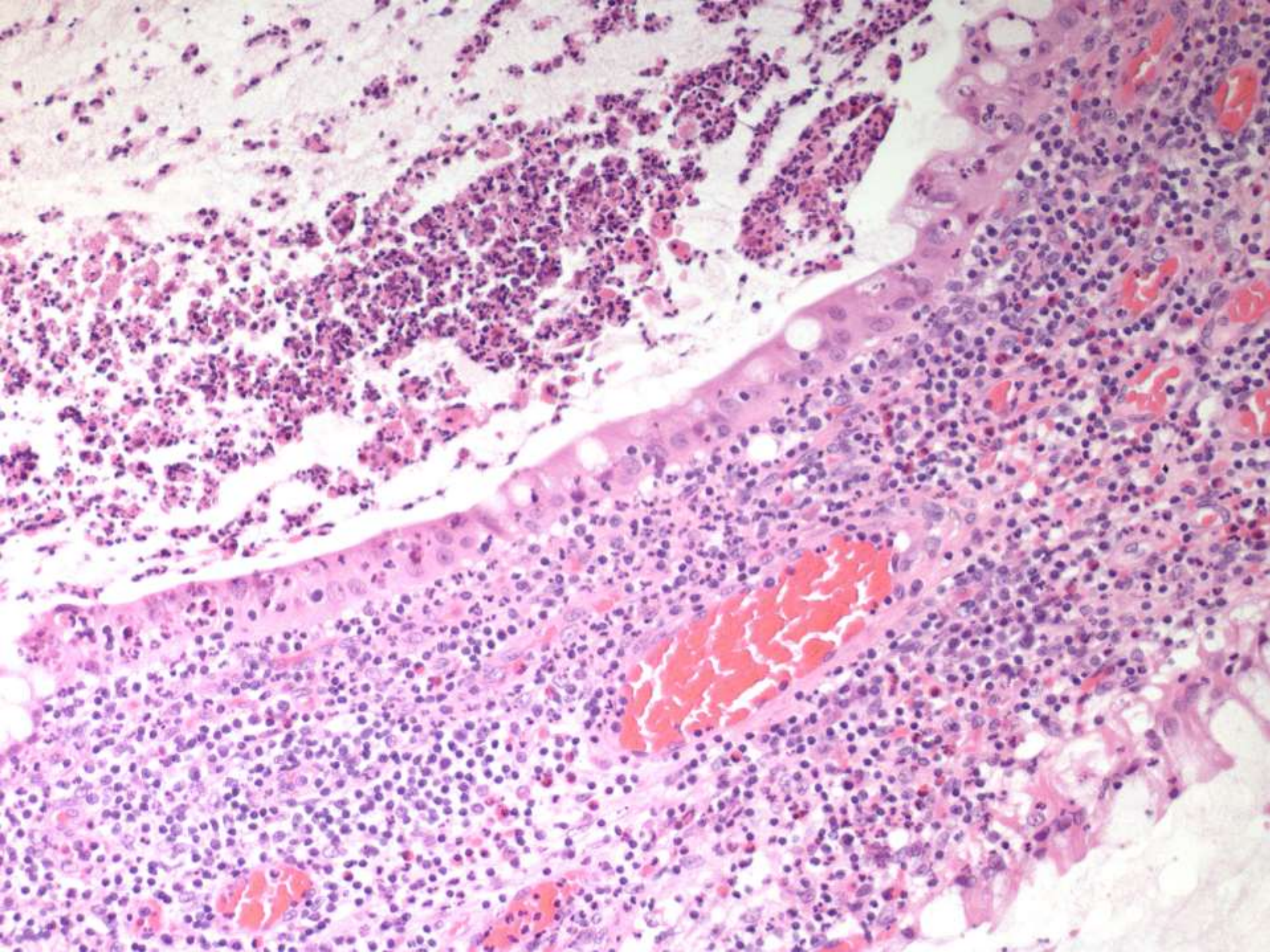












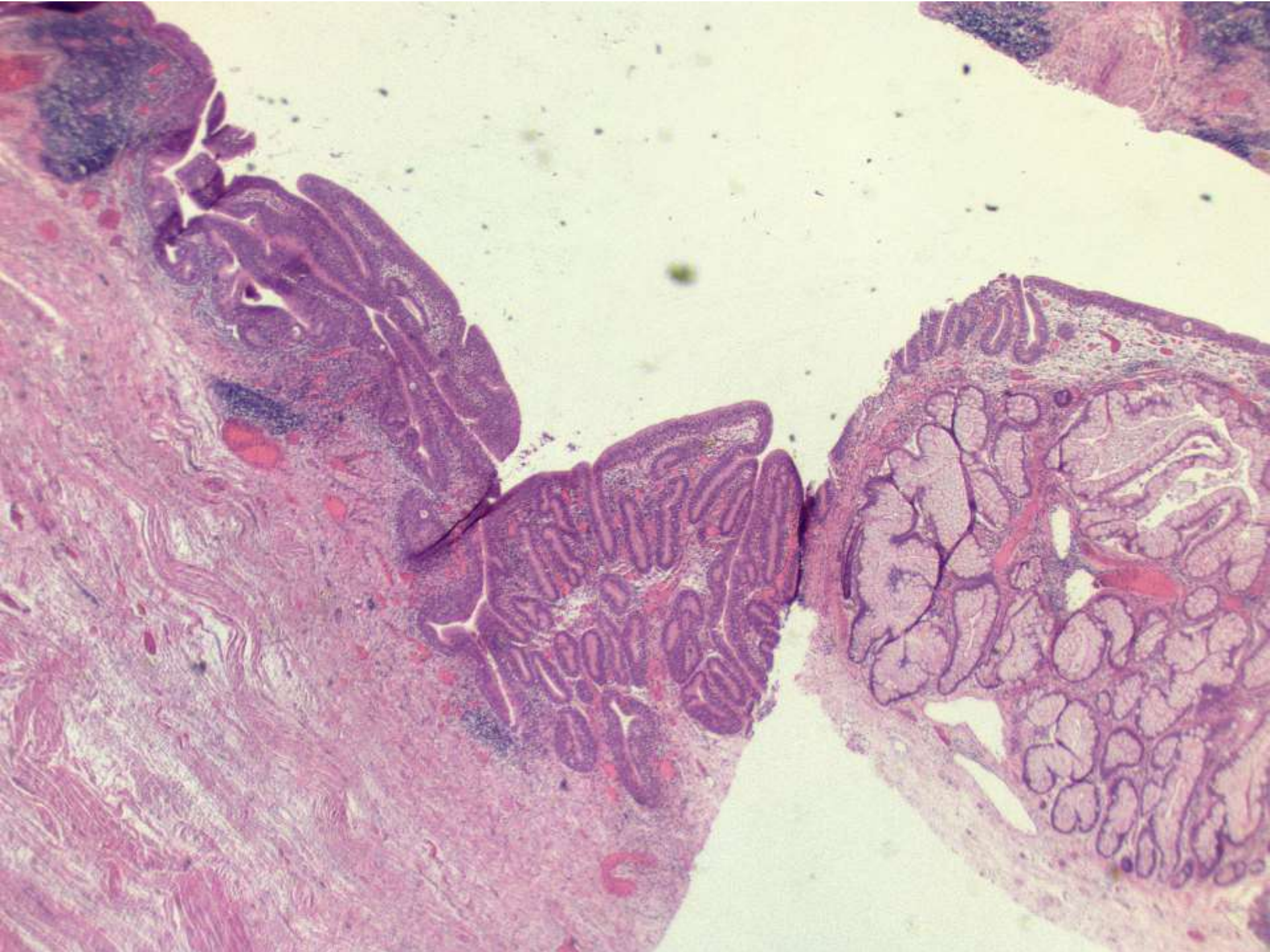
Diagnosis that was actually made for this biopsy:

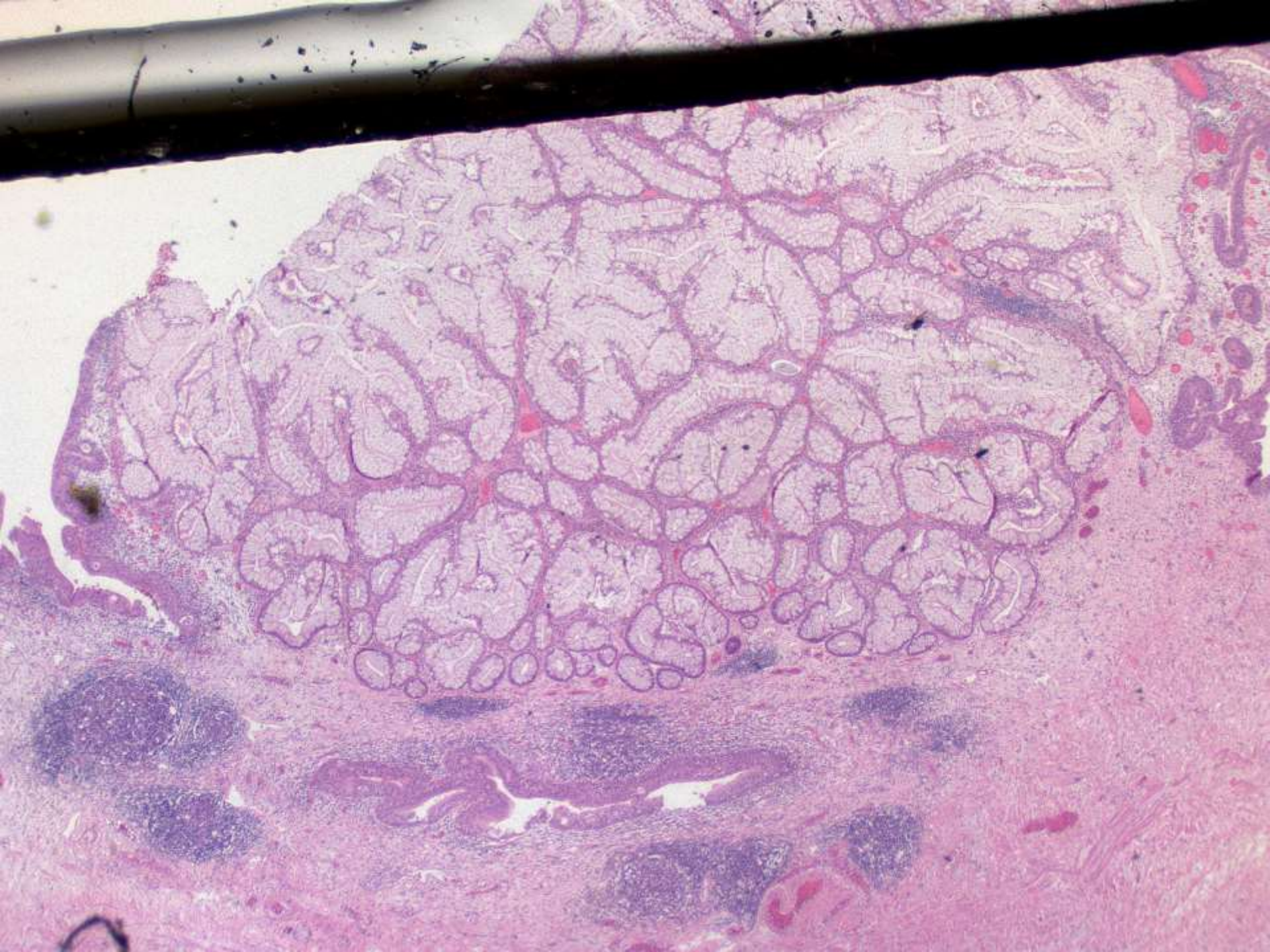
- Invasive moderately differentiated adenocarcinoma
- ? Primary ? Spread/metastasis from elsewhere – please correlate with radiology

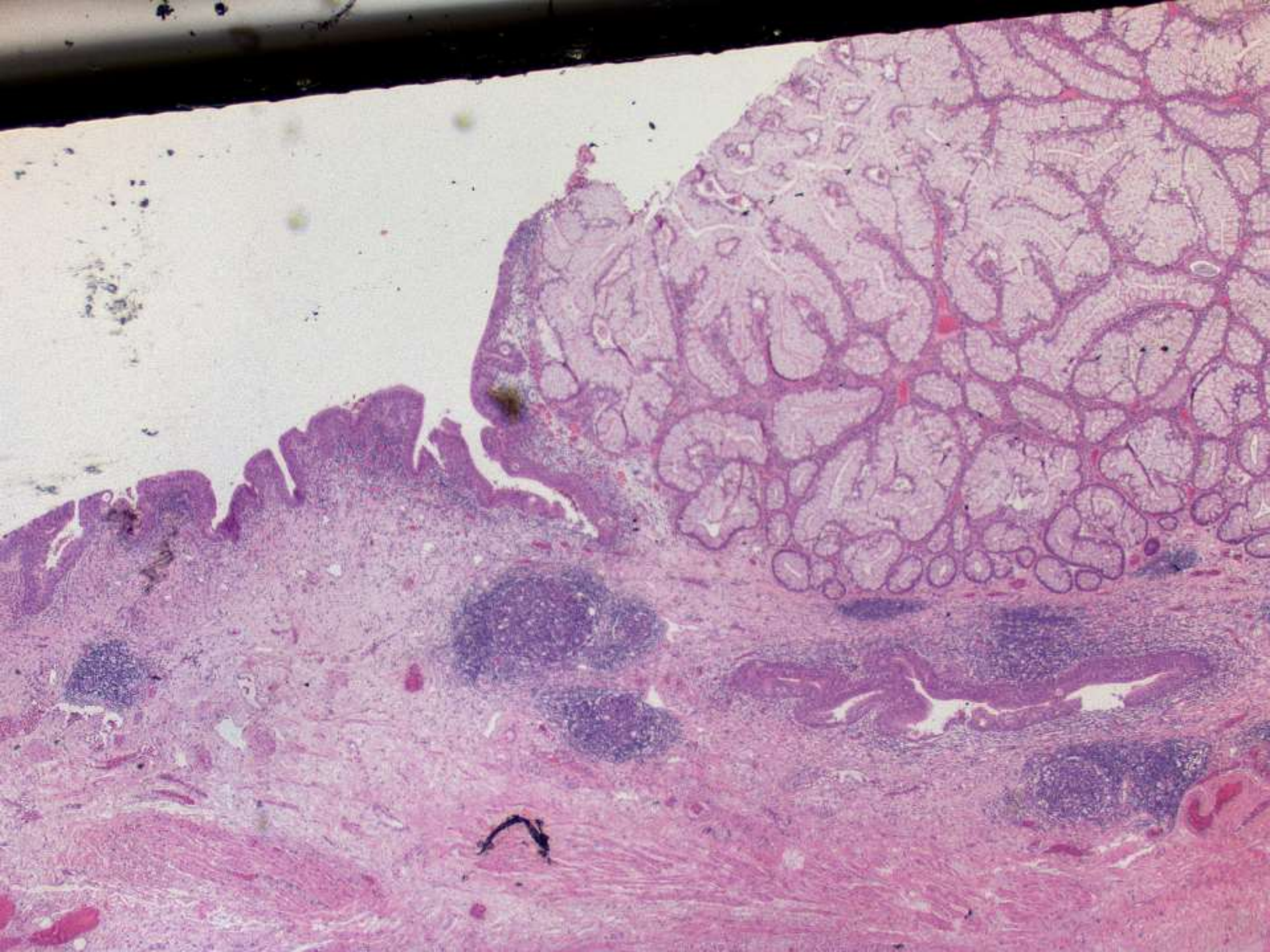
7 weeks later

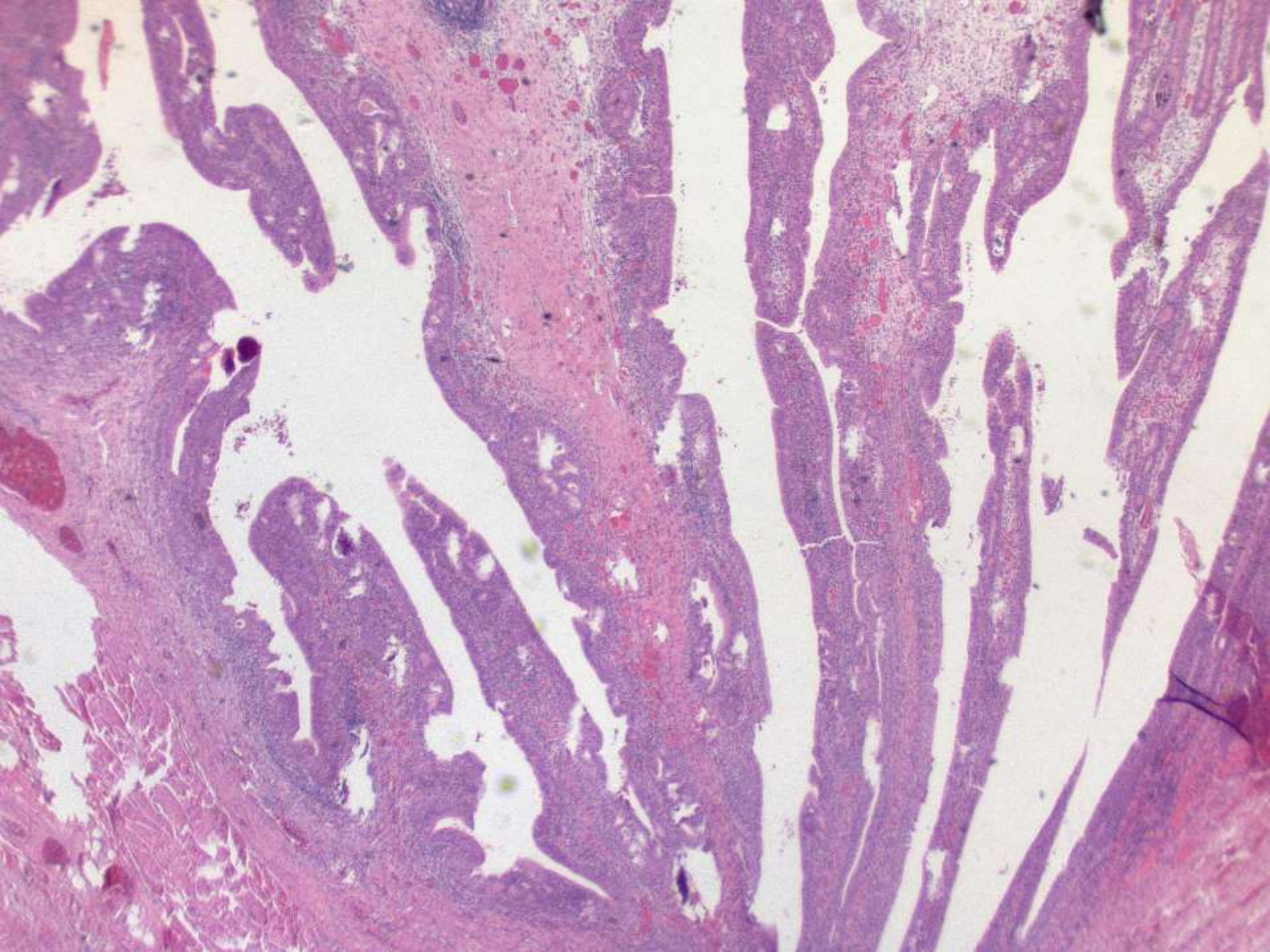
- Patient had an anterior pelvic clearance
- Fibroid uterus with minimal abnormality in bladder macroscopically – slight nodularity of bladder mucosa (right posterior lateral)

Bladder from ant
Pelvis clearance



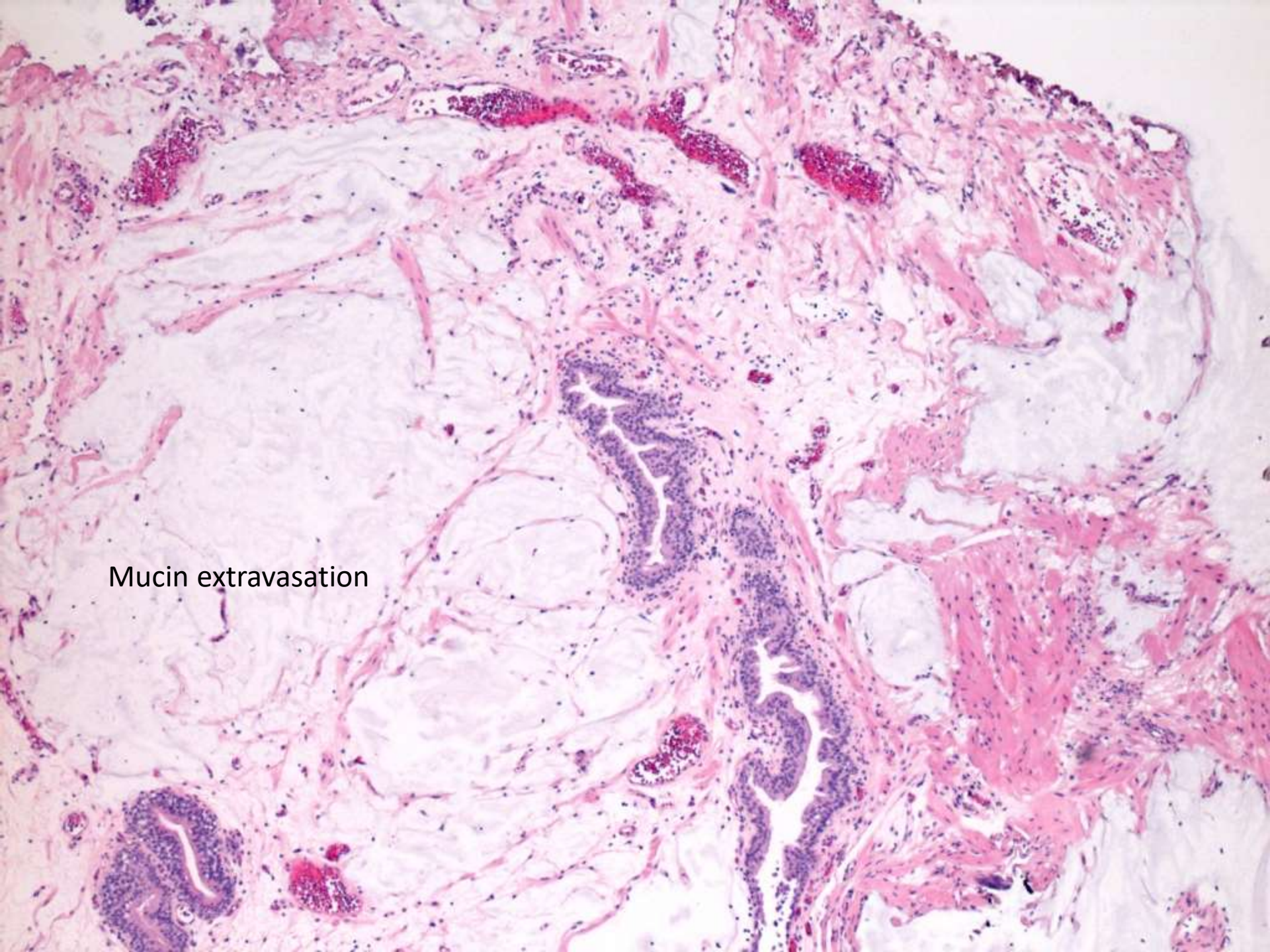




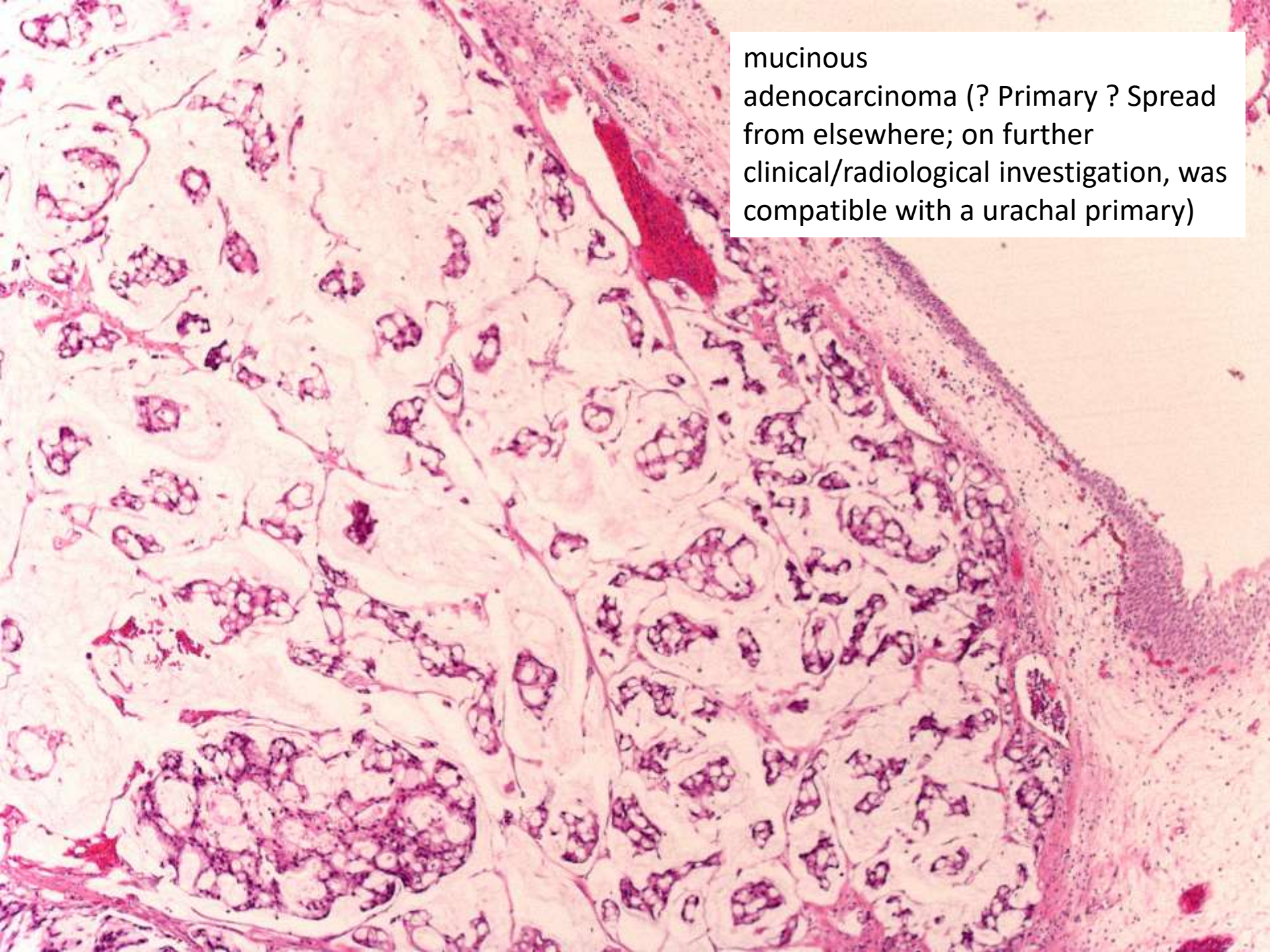


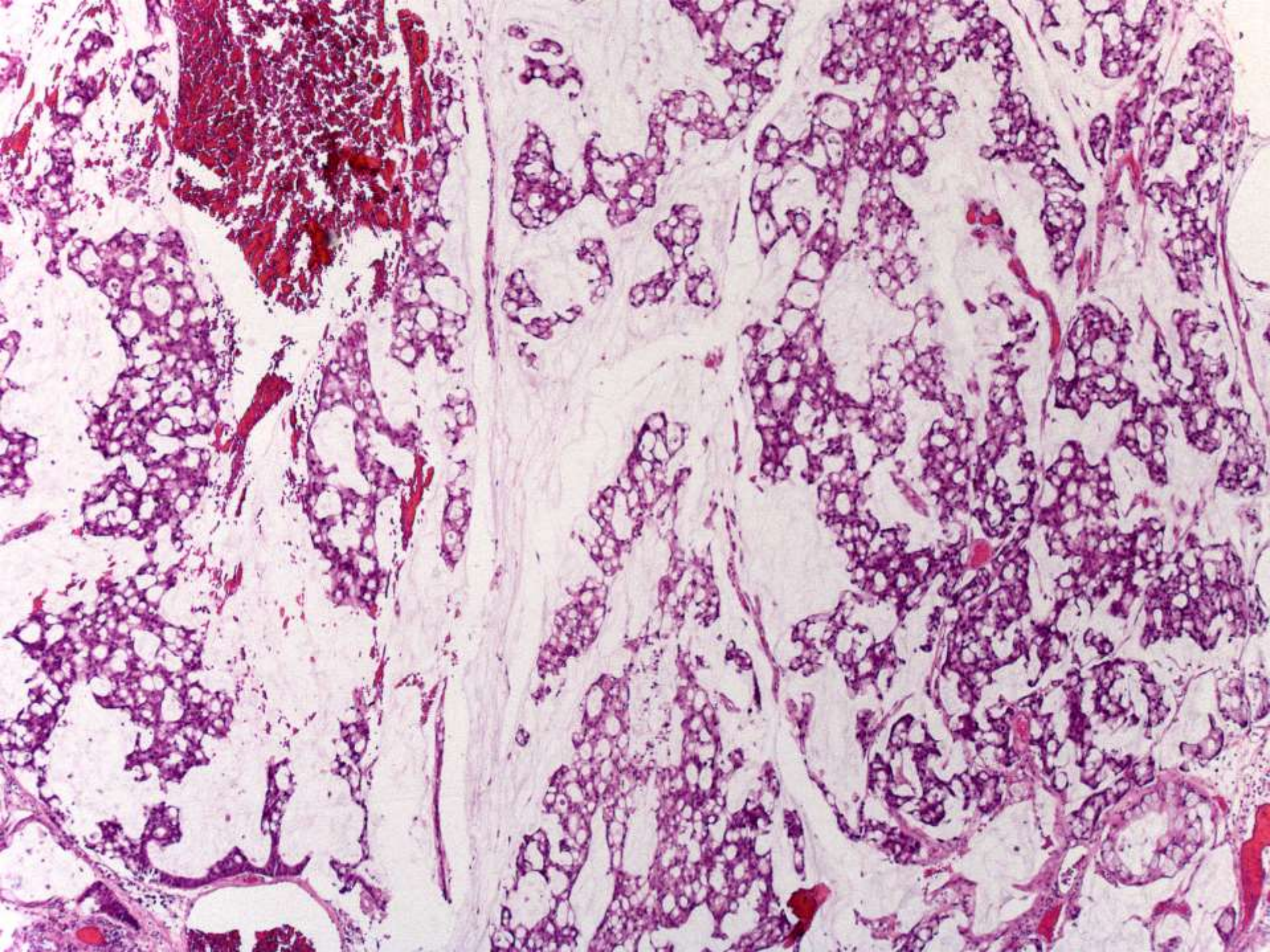
Florid cystitis glandularis with mucin extravasation Young and Bostwick 1996. Am J Surg Pathol

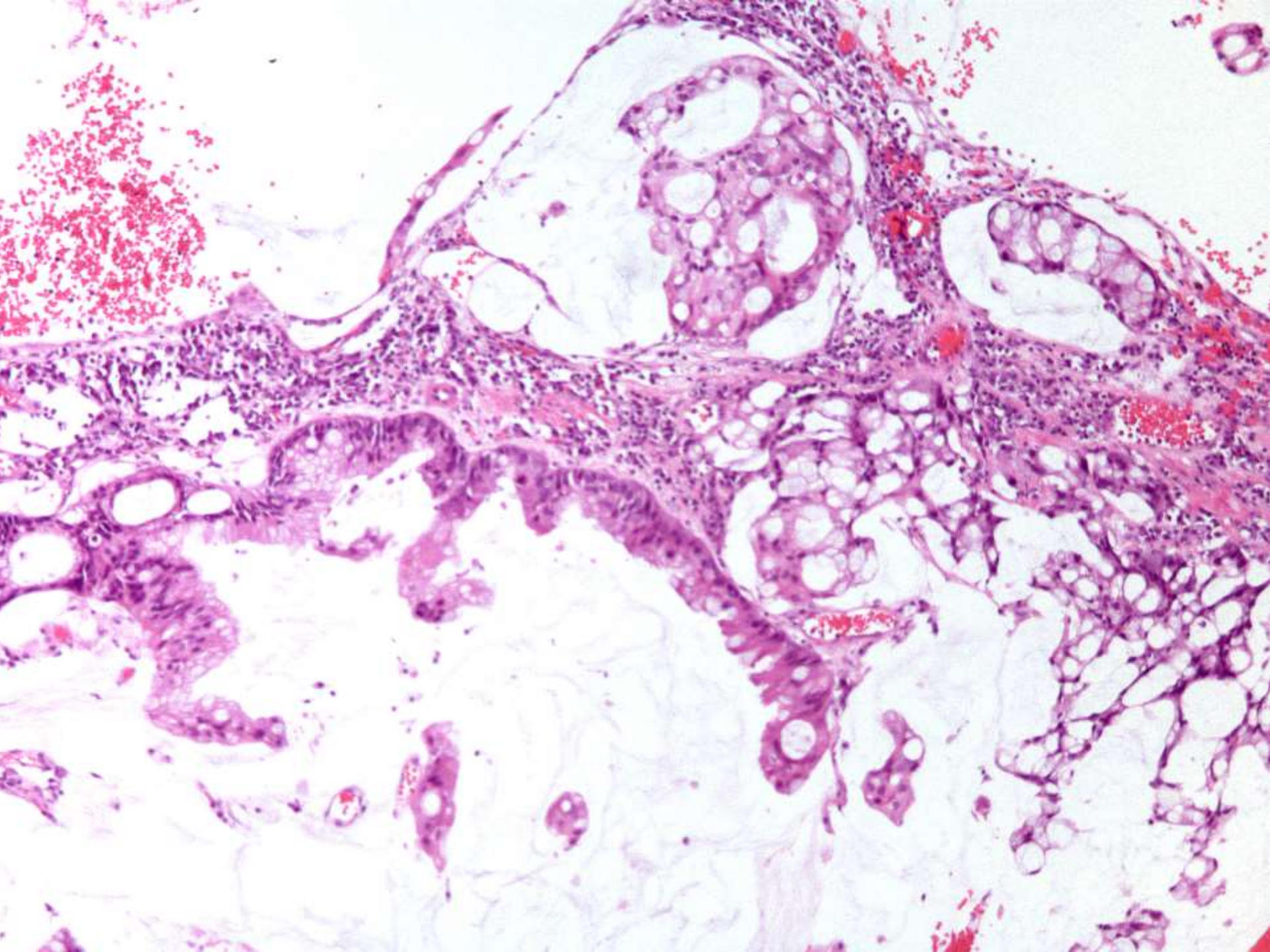
- A significant clinical, radiological and histological mimic of mucinous adenocarcinoma
- Clues to benign disease are:
  - orderly arrangement of epithelium
  - lack of cytological atypia
  - lack of in-situ lesions, no signet ring cells
  - lack of desmoplasia
  - lack of atypical cells floating in mucin

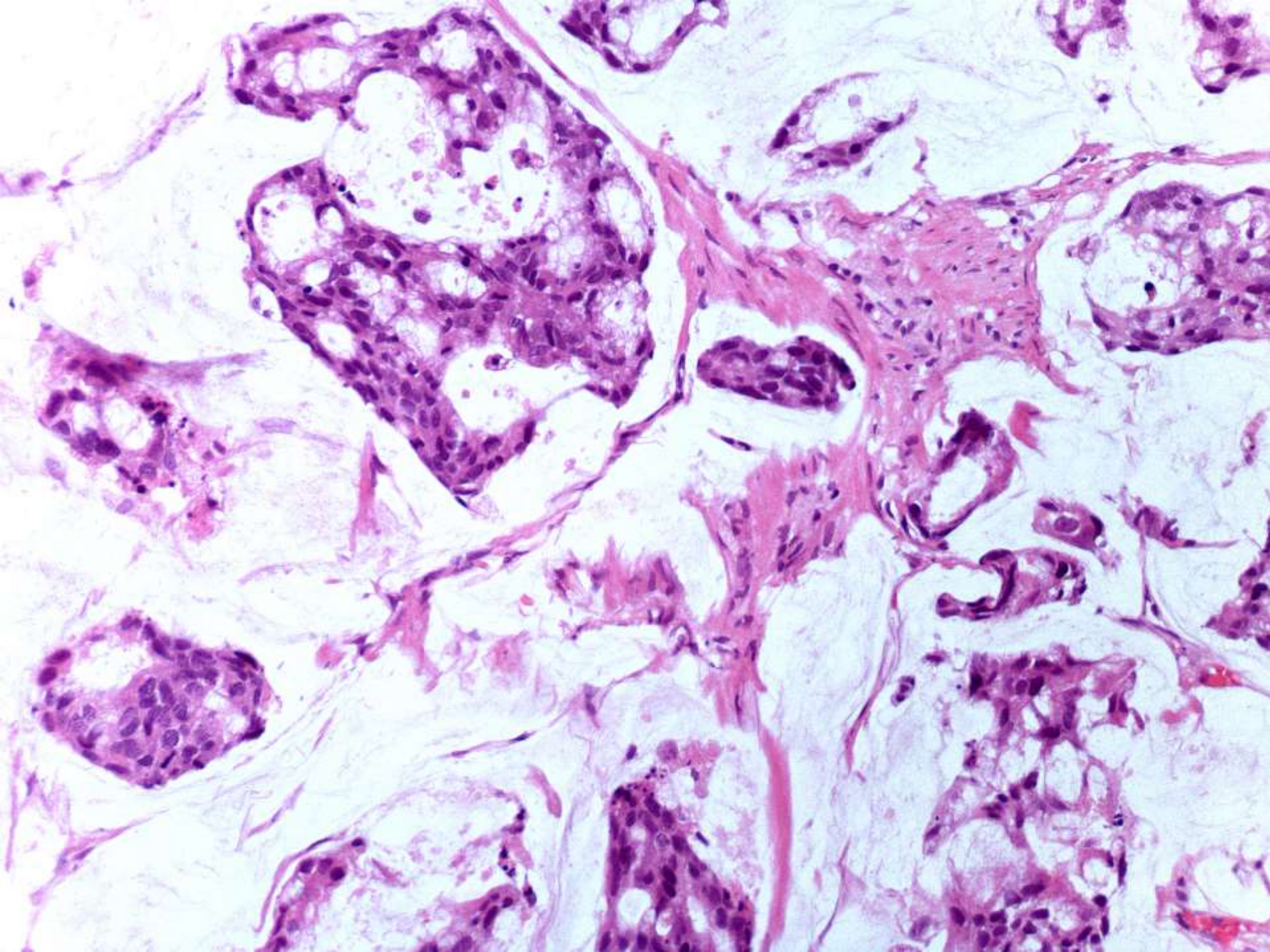

Mucin extravasation

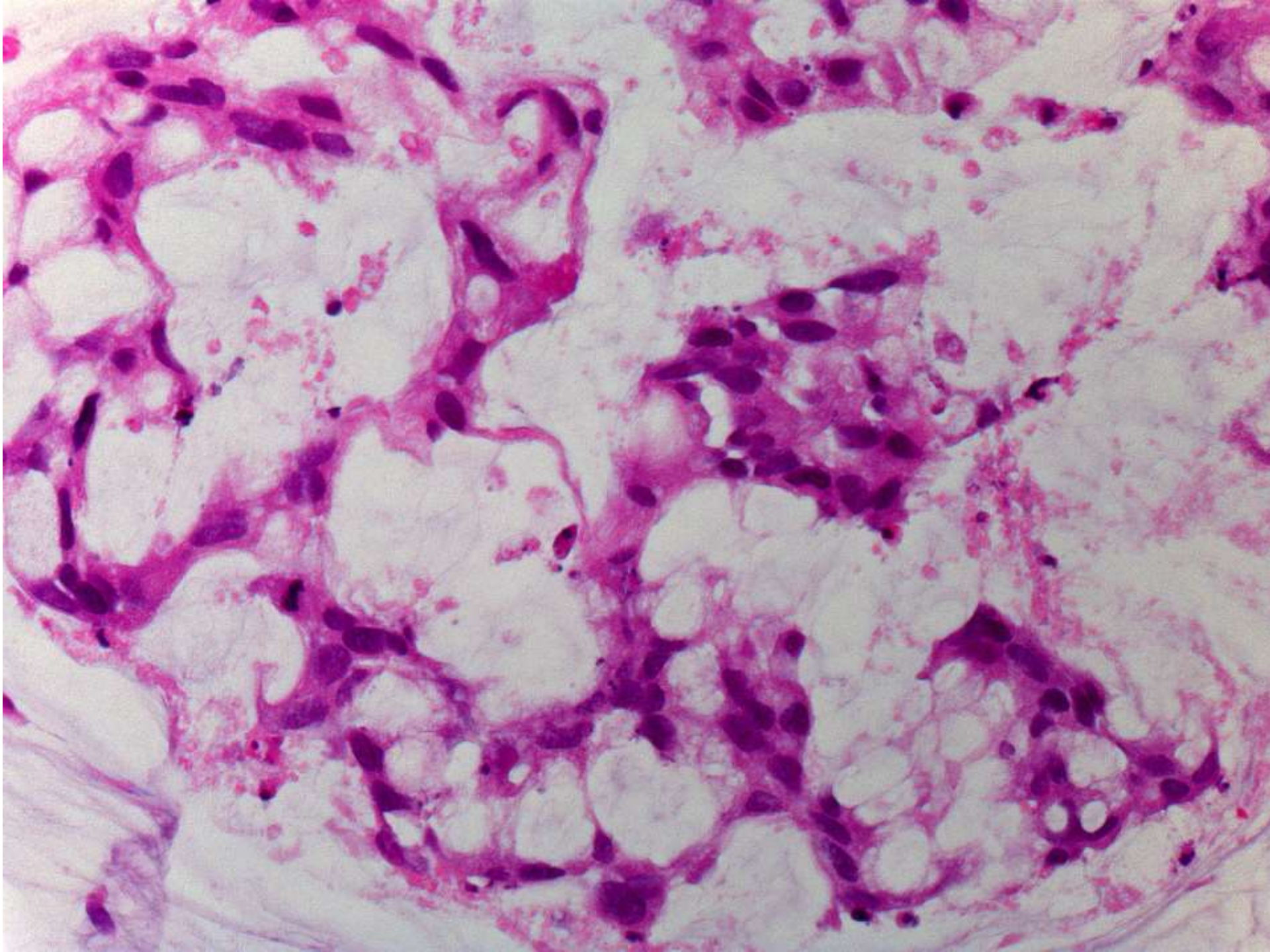
- Male 62 years old
- Solid tumour – dome of bladder
- 4 cm size ?adenocarcinoma
- ?TCC. Appeared muscle invasive


mucinous
adenocarcinoma (? Primary ? Spread from elsewhere; on further clinical/radiological investigation, was compatible with a urachal primary)



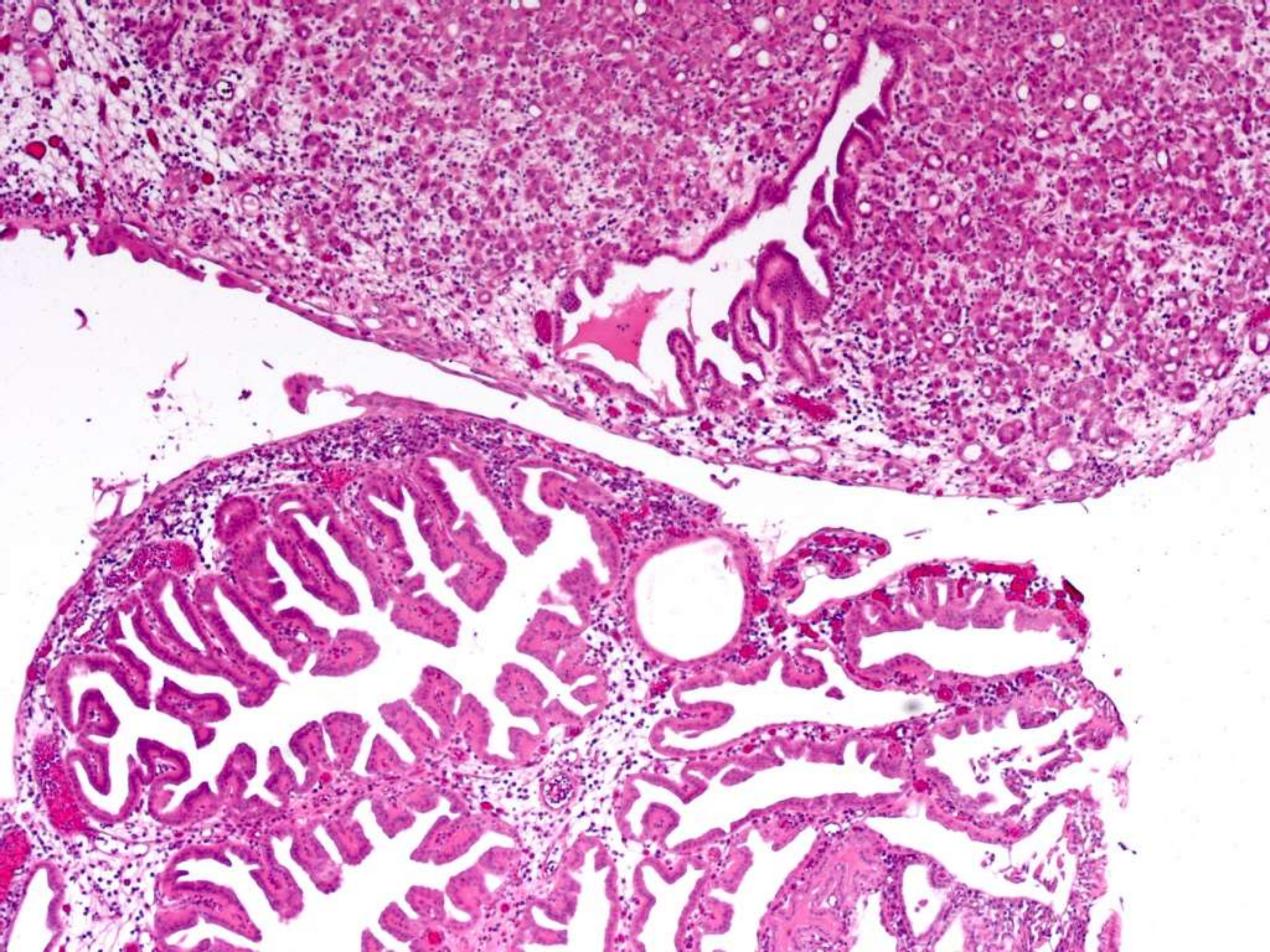


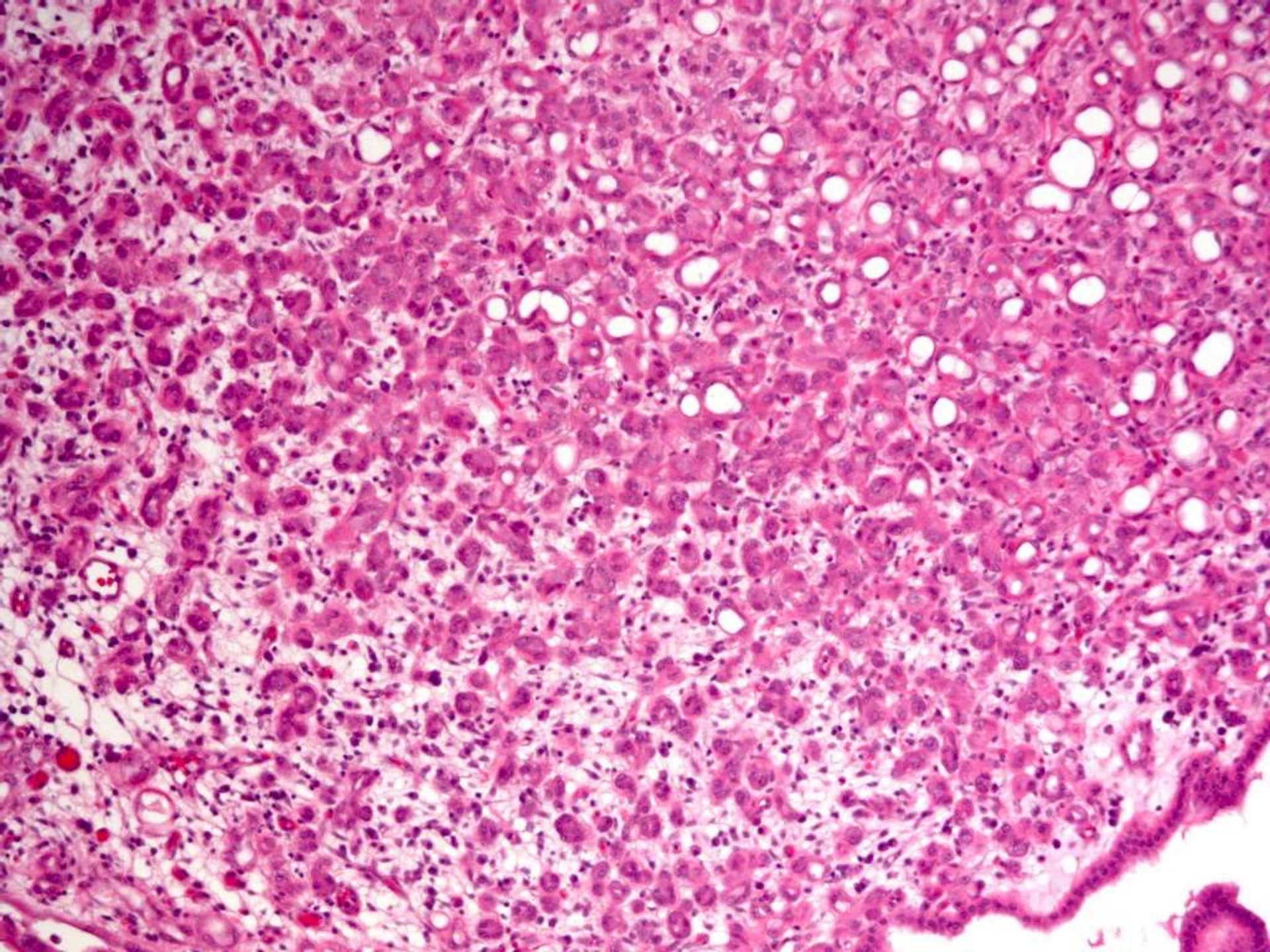


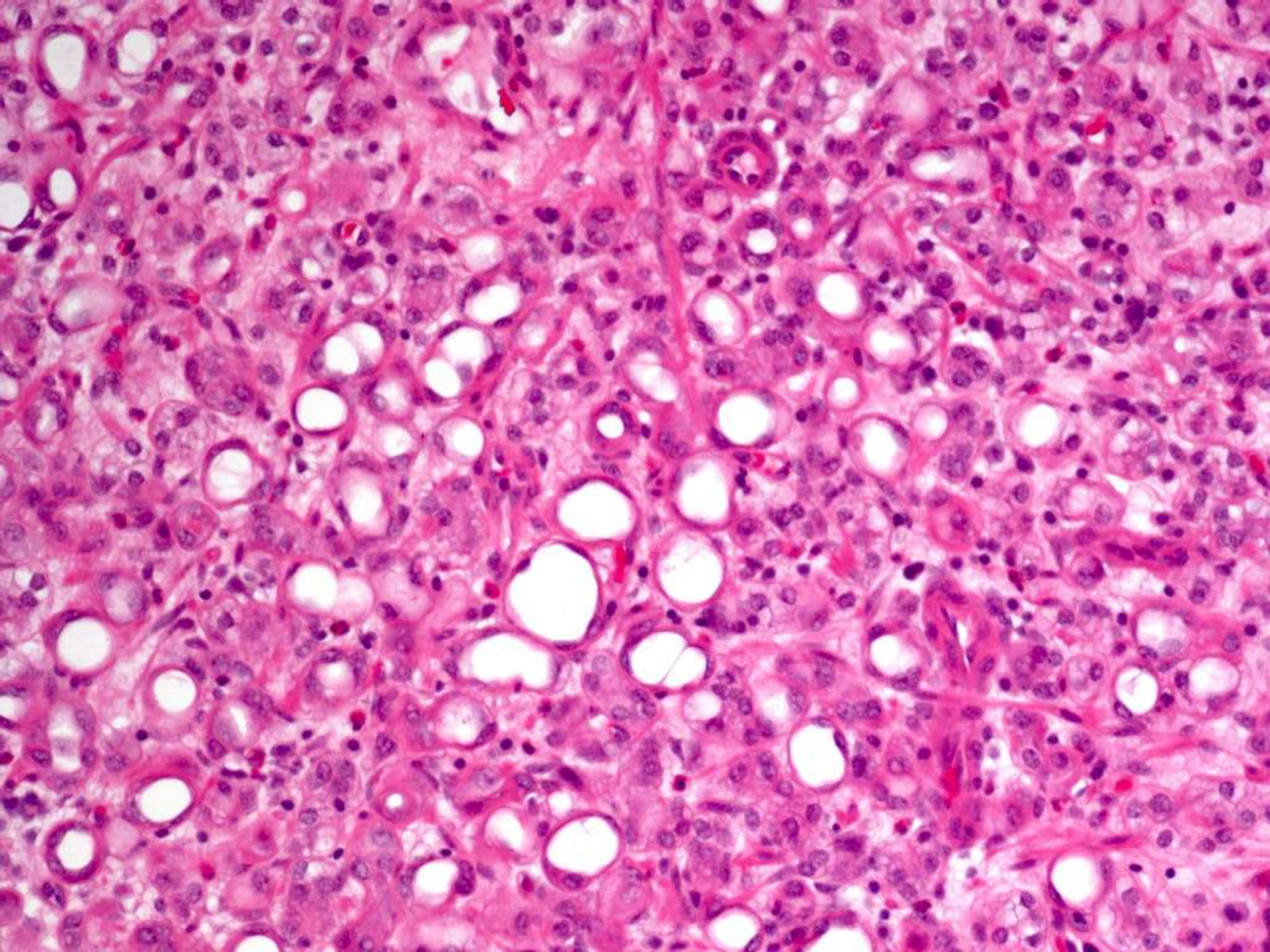


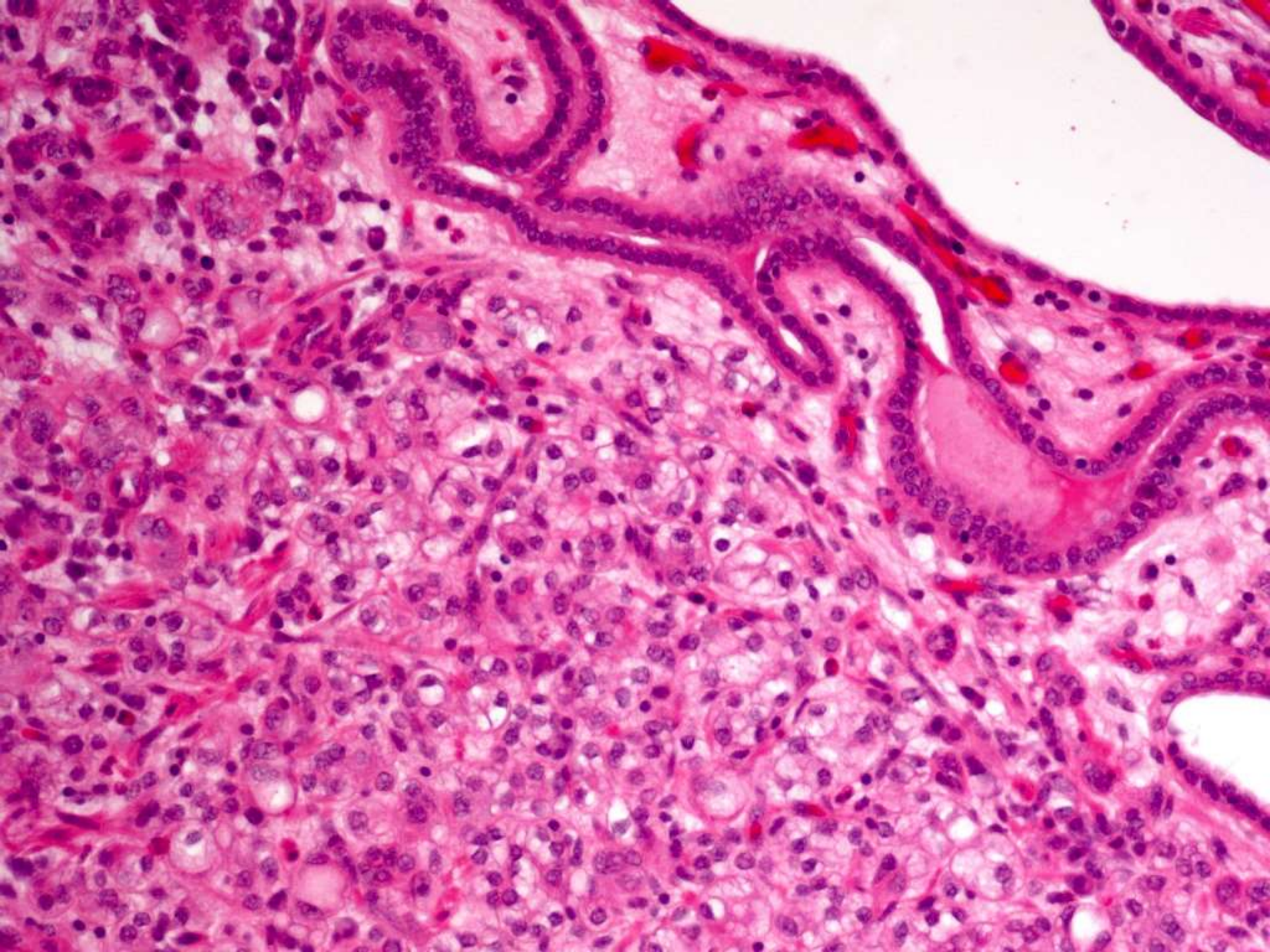
Nephrogenic adenoma

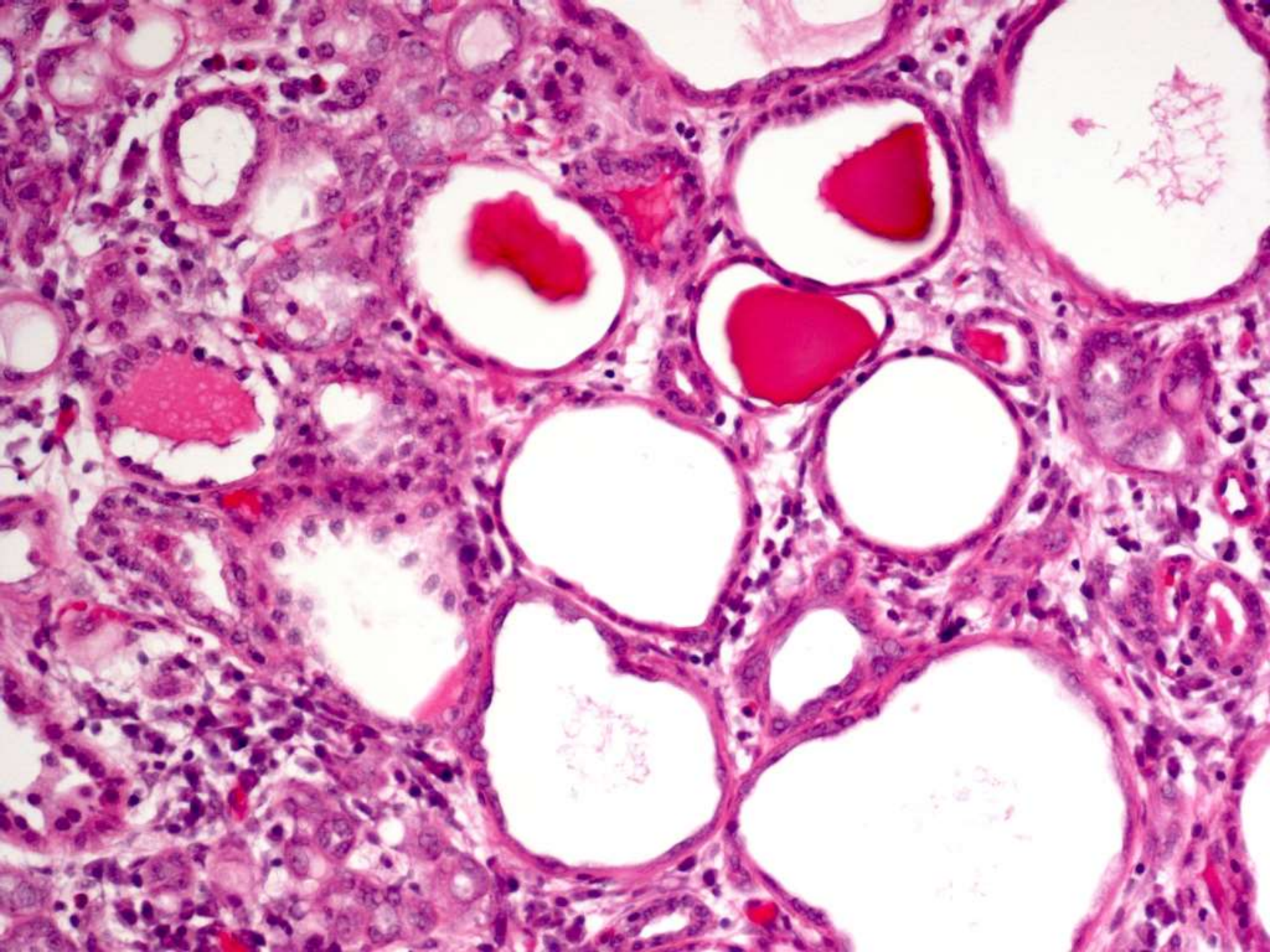
- Typically occurs in setting of injury (prior surgical manipulation, stones or chronic urinary tract infection, occasionally immunosupressed patients)
- <1cm but 10% are 4cm or greater
- No deep invasion of detrusor muscle (can involve muscularis mucosae or fibromuscular stroma of prostate, superficial muscularis propria)
- Mitoses absent to exceptionally rare. No necrosis.
- Low MiB-1 index low (<5%, typically 1-2%)
- Lack of prominent solid growth. Prominent nucleoli in 20% cases, mild degenerative nuclear atypia noted in several series
- Small tubules with mucin mimic signet ring cells
- Residual/recurrent NA in subsequent biopsies in up to 37% cases, but no progression

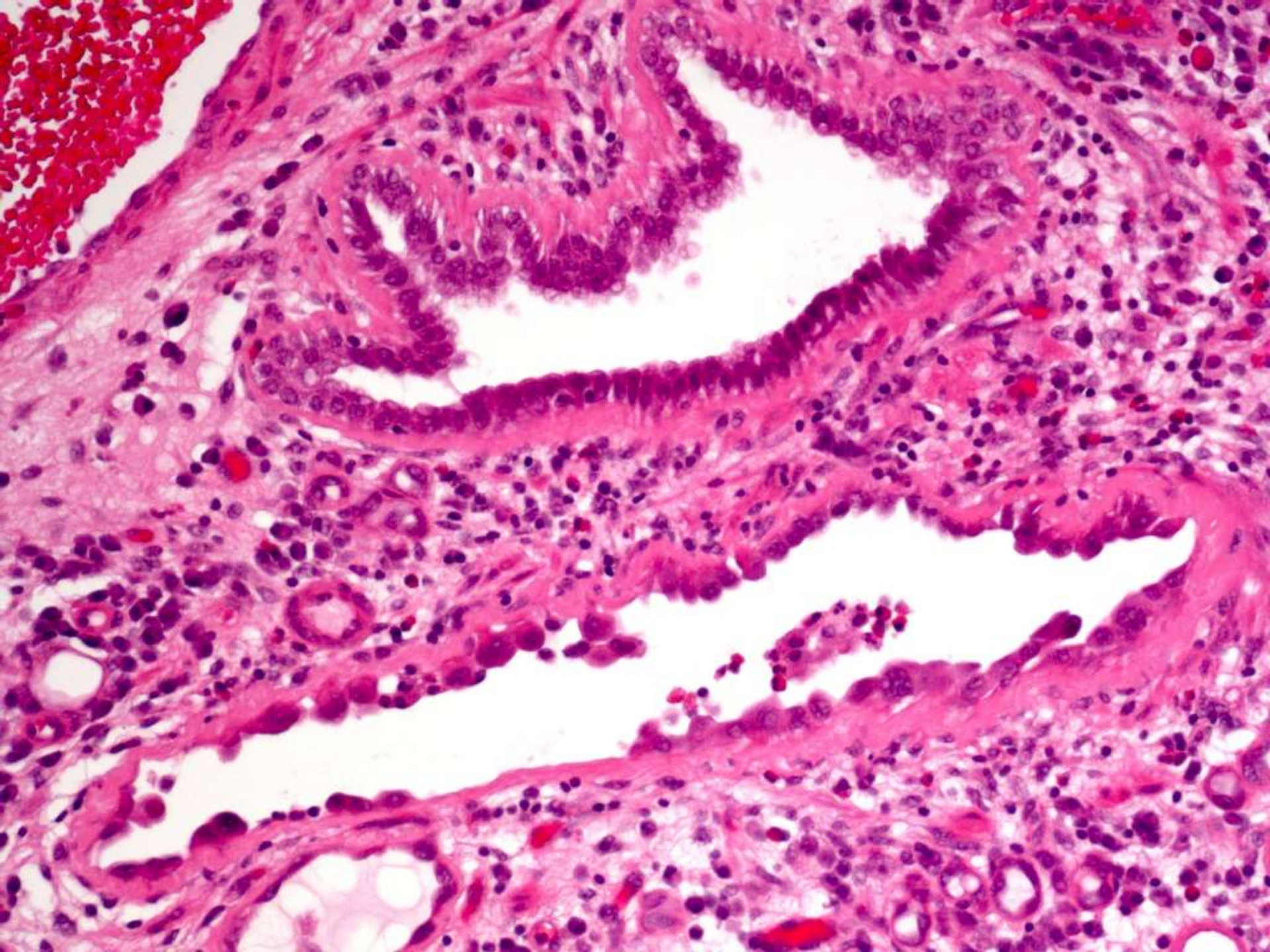


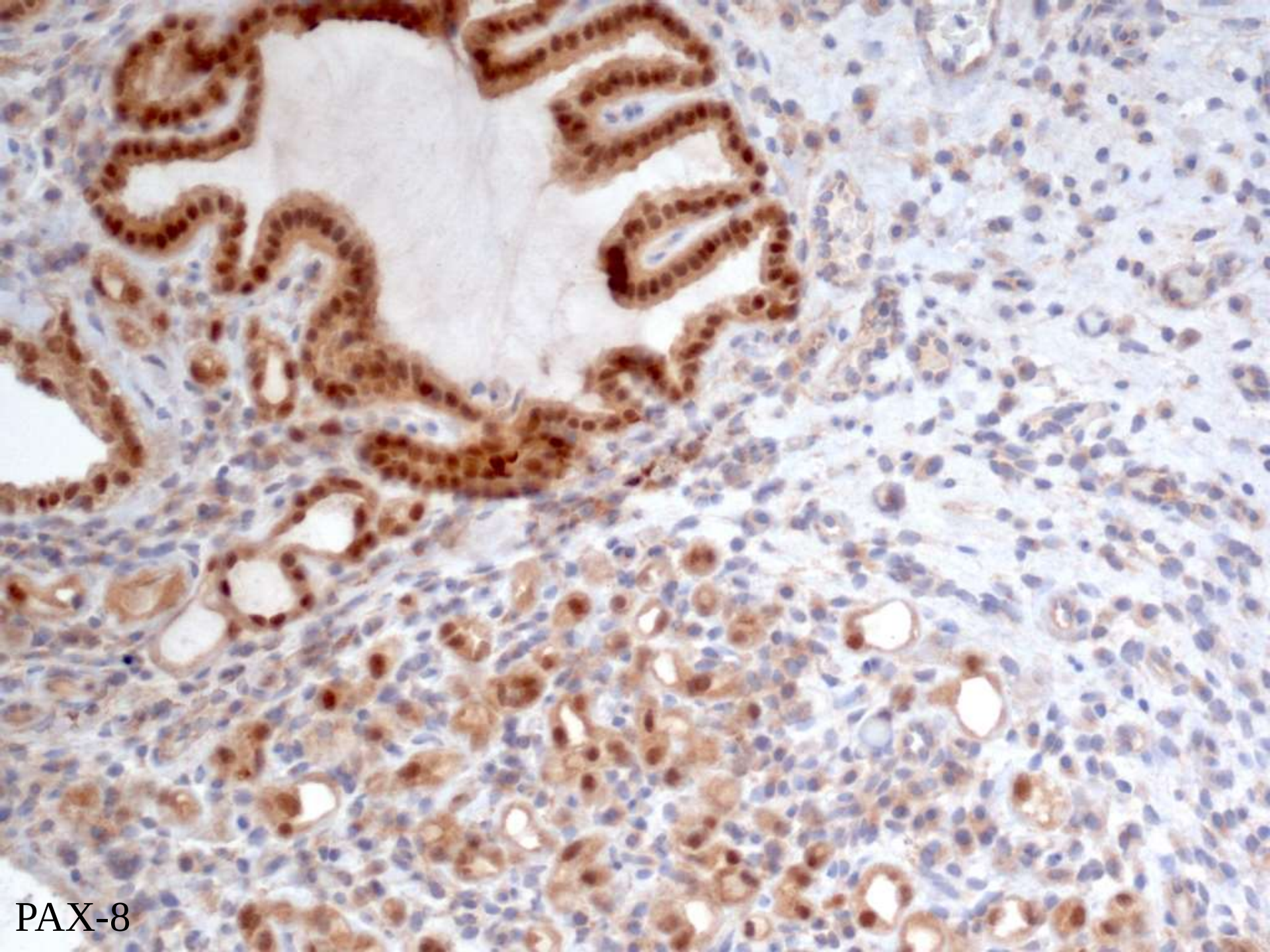


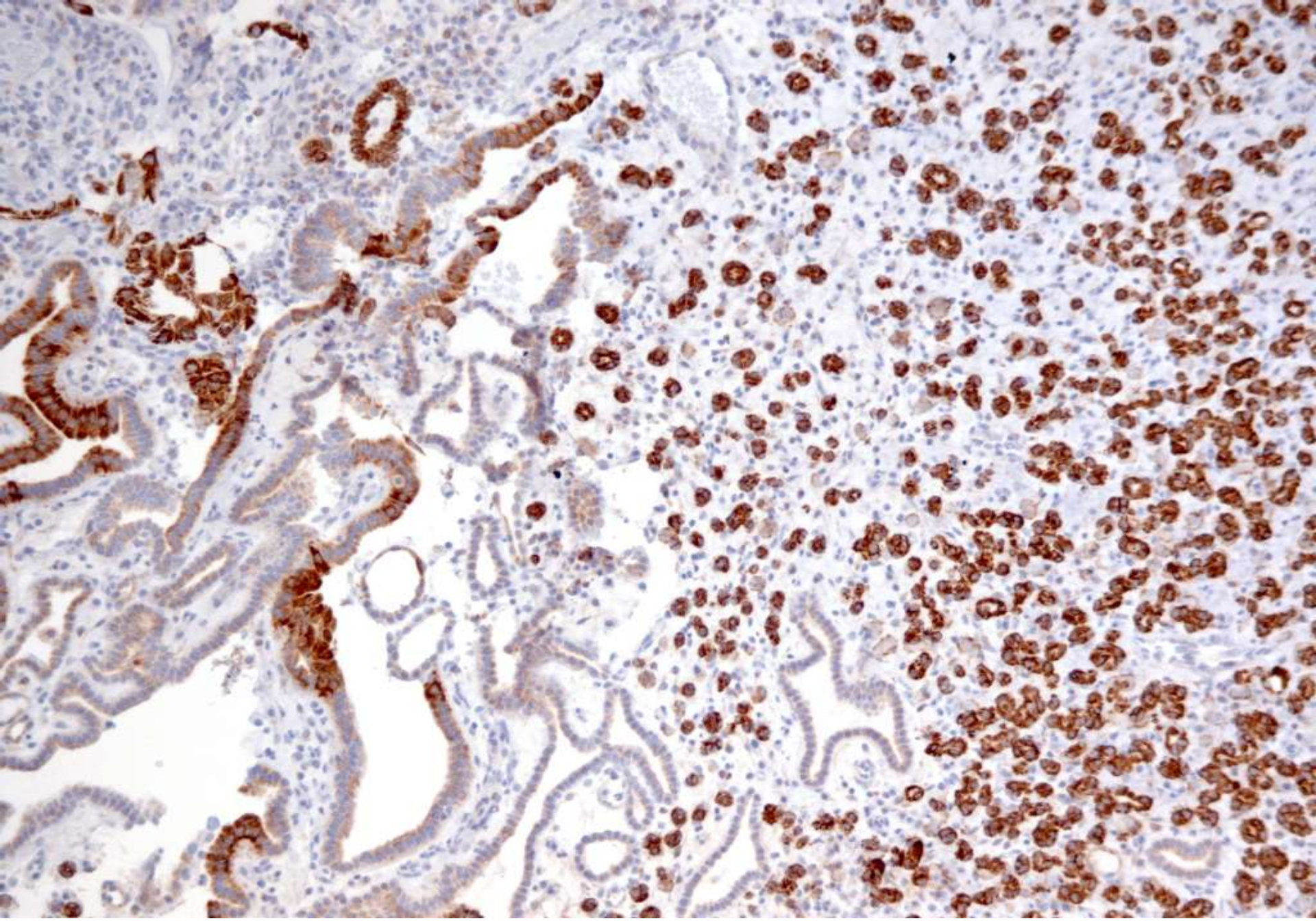




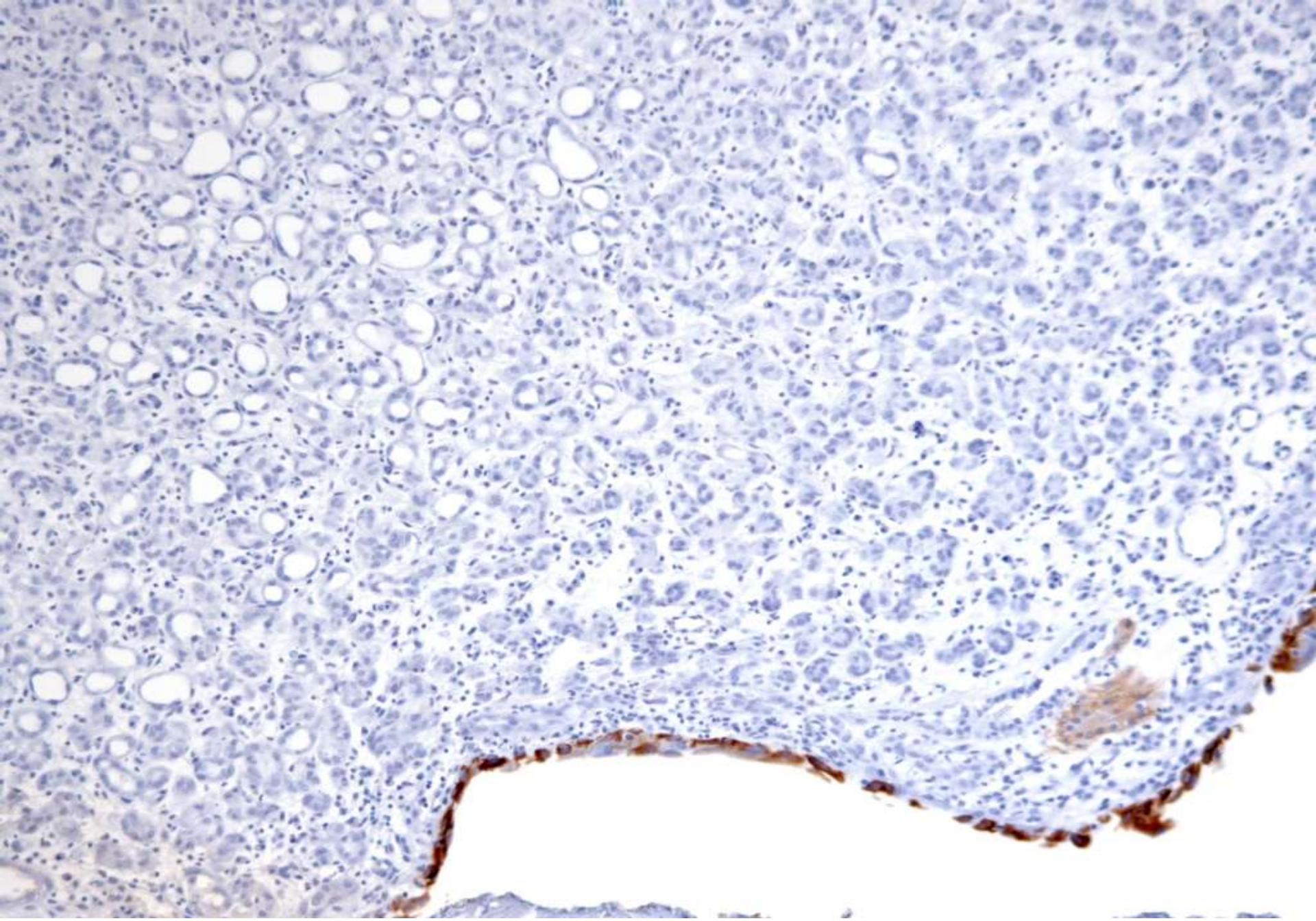





PAX-8



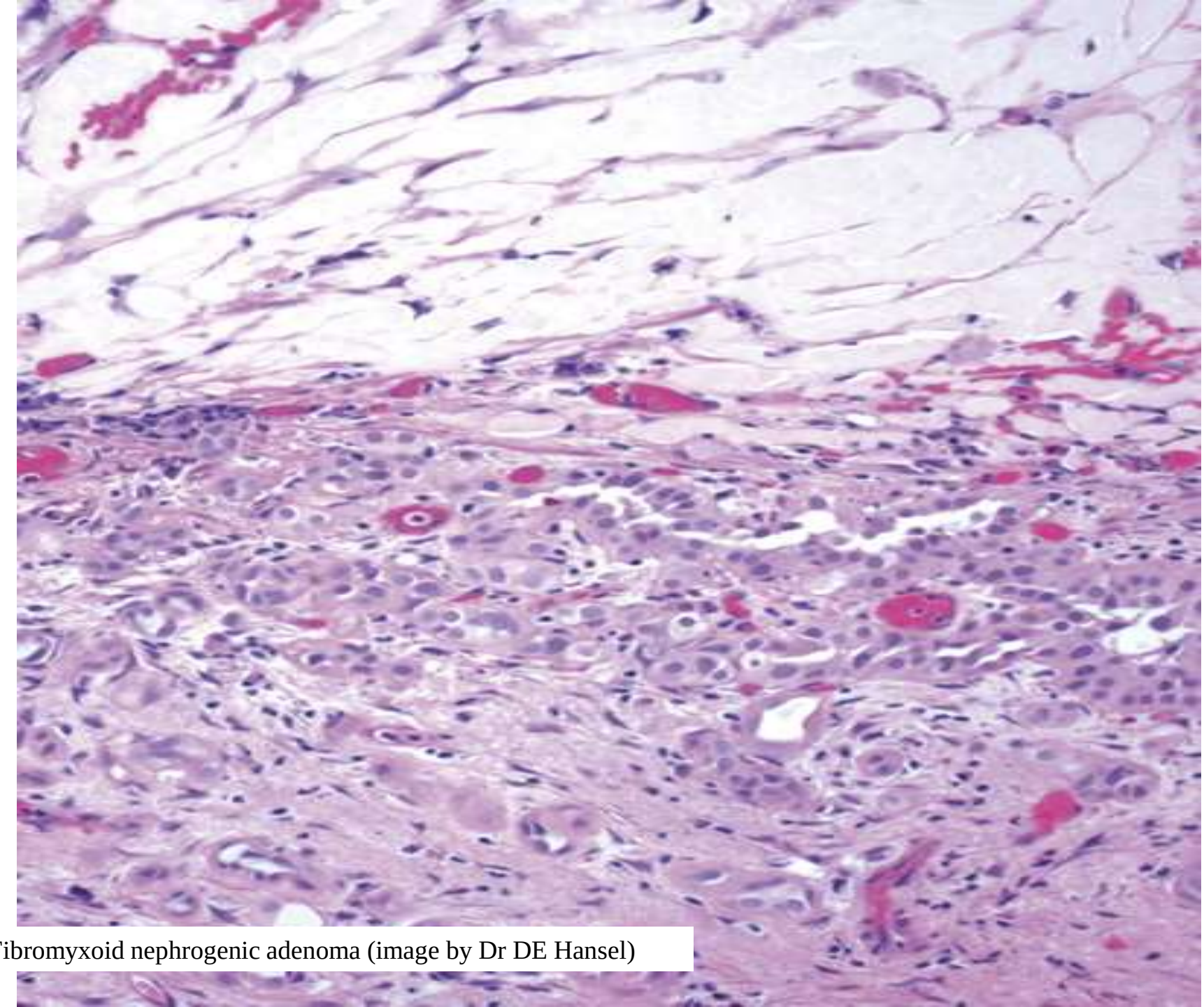
AMACR (racemase)



34ßE12

To avoid confusion with prostatic adenocarcinoma, be aware that in nephrogenic adenoma:

- CK7 and PAX8 are typically positive (unlike prostatic adenocarcinoma), though PAX8 is not specific for NA – correlate with morphology!
- NKX3.1 is negative (unlike prostate tissue/prostate cancer);is typically PSA negative but can be weakly positive;
- [like prostatic adenocarcinoma is typically 34ßE12 and p63 negative; urothelial carcinoma often +ve for these; is positive for racemase (AMACR) in approx 50% cases, like prostatic cancer]
- [beware: GATA3 is positive in 40% cases of nephrogenic adenoma – not by itself useful in distinction from urothelial carcinoma!]



Fibromyxoid nephrogenic adenoma (image by Dr DE Hansel)

Case: history

- Male 71
- Known Ca prostate treated with DXT. Urethral stricture dilated and mucosa for histology
- Five pieces ranging from 5 mm to 33 mm