VÅRMÖTE I PATOLOGI

NPM 2025

19–21 MAY

NORDIC PATHOLOGY MEETING

Fun with Colorectal Polyps and a few Non-Heriditary Polyposes

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Disclosures

- Consultation for Olympus
- Consultant for Johnson and Johnson
- Consultant for Merck
- Received honorarium and travel expense money from ARUP Laboratories

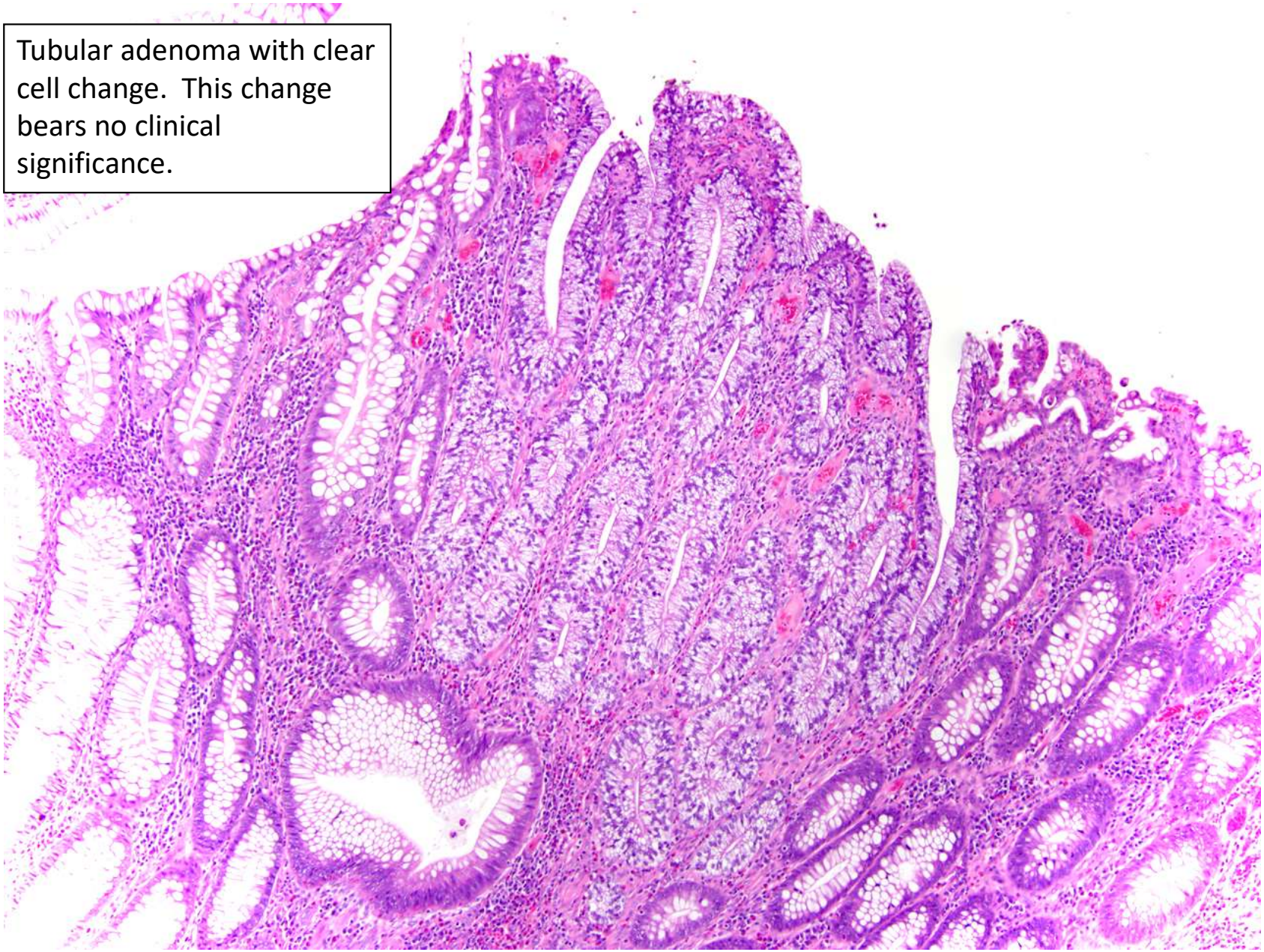
Objectives

- To discuss some unusual aspects of colorectal adenomas.
- To return to basics and discuss the difference between traditional serrated and sessile serrated adenomas.
- To discuss several non-hereditary polyposes.

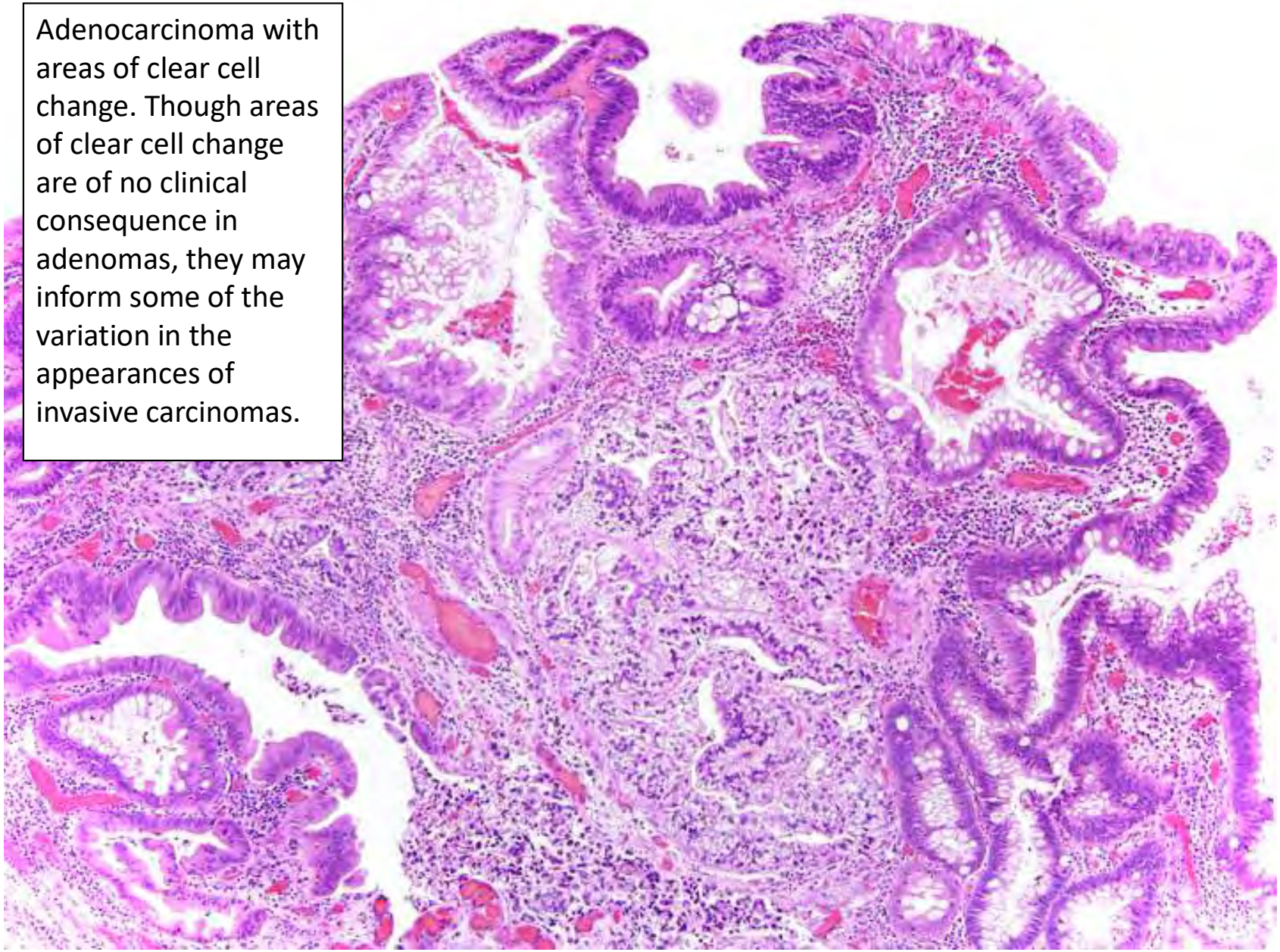
Peculiar Changes in Adenomas

- Clear cell change
- Squamous morules

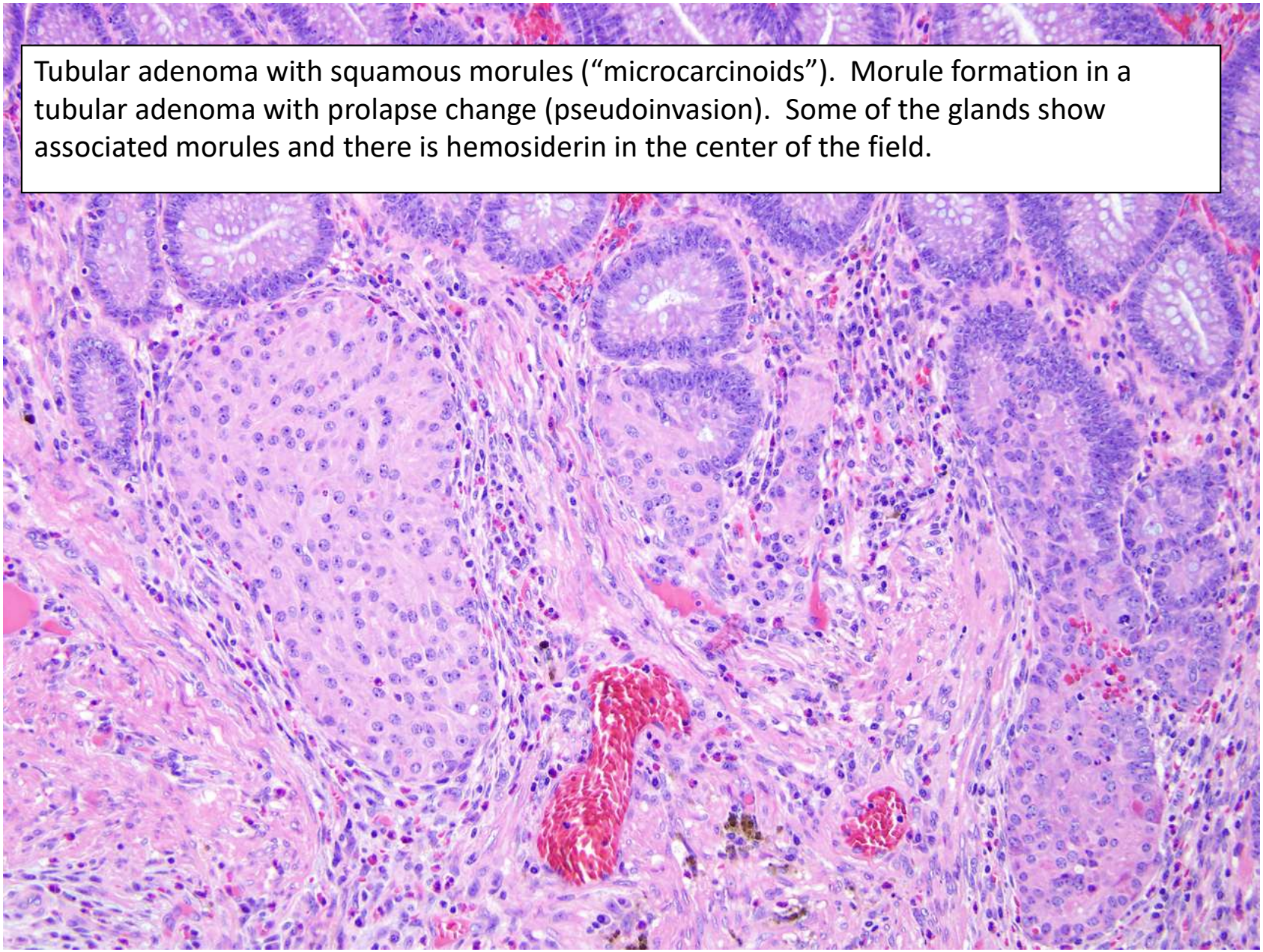
Tubular adenoma with clear cell change. This change bears no clinical significance.



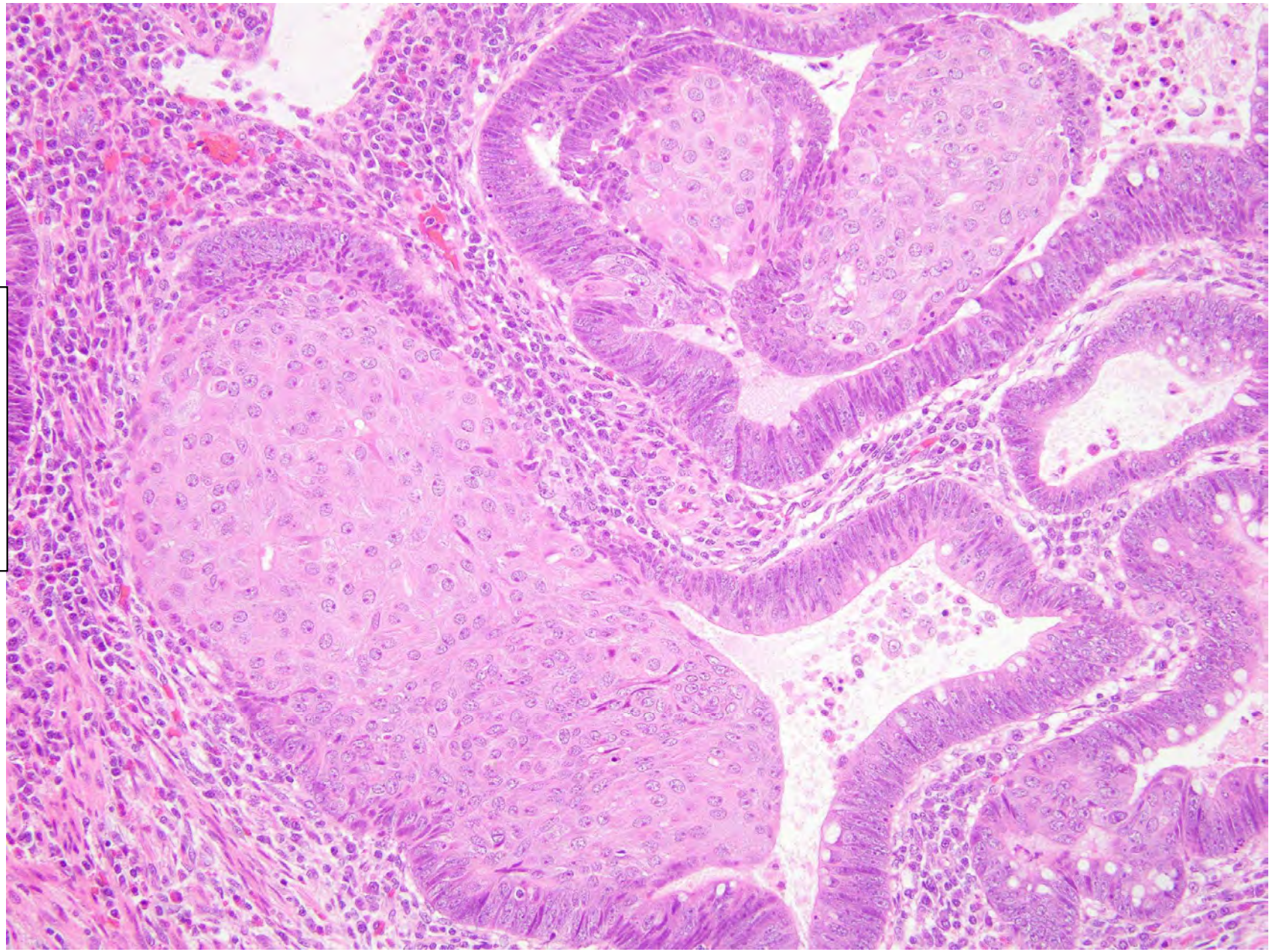
Adenocarcinoma with areas of clear cell change. Though areas of clear cell change are of no clinical consequence in adenomas, they may inform some of the variation in the appearances of invasive carcinomas.

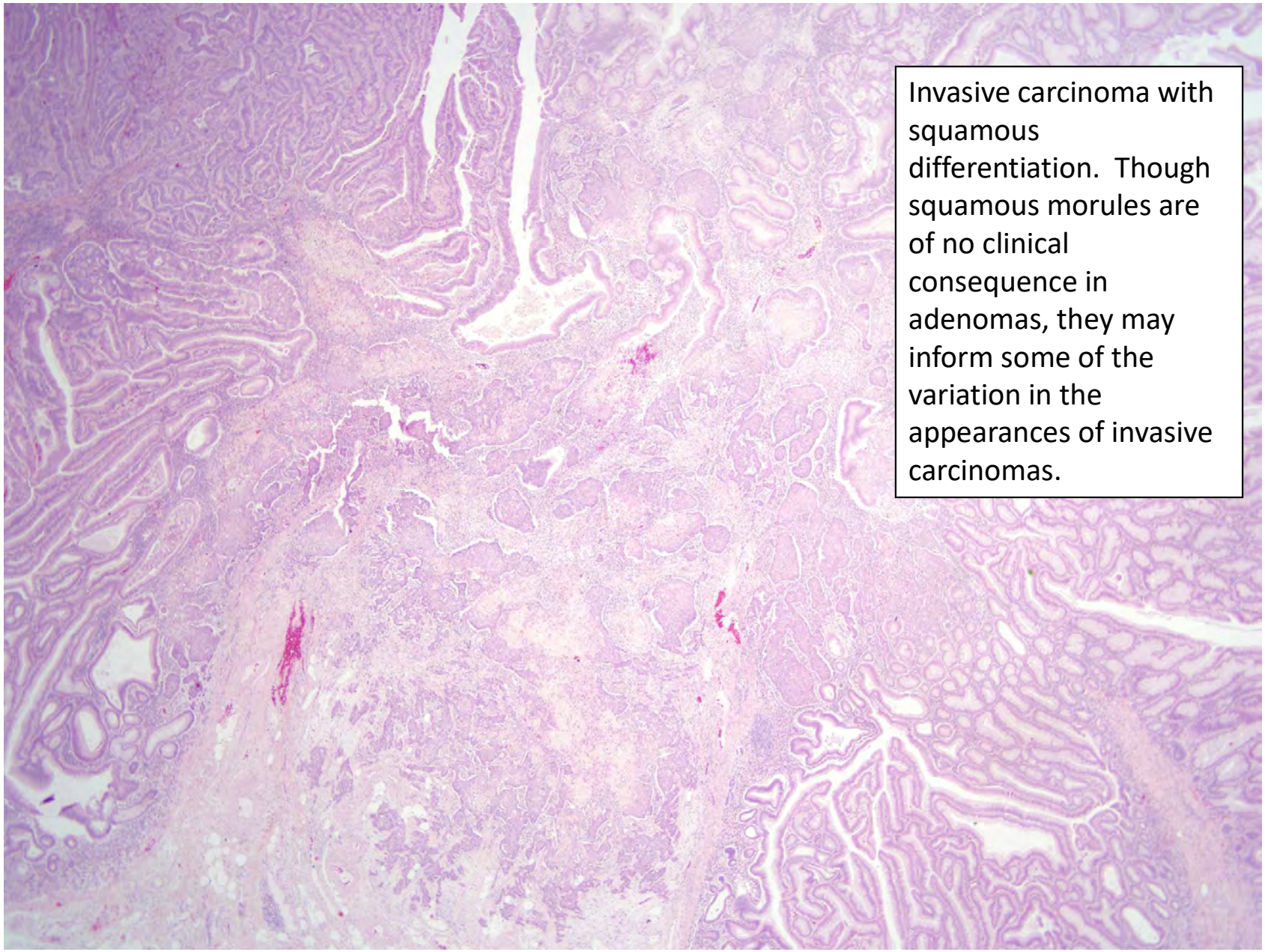


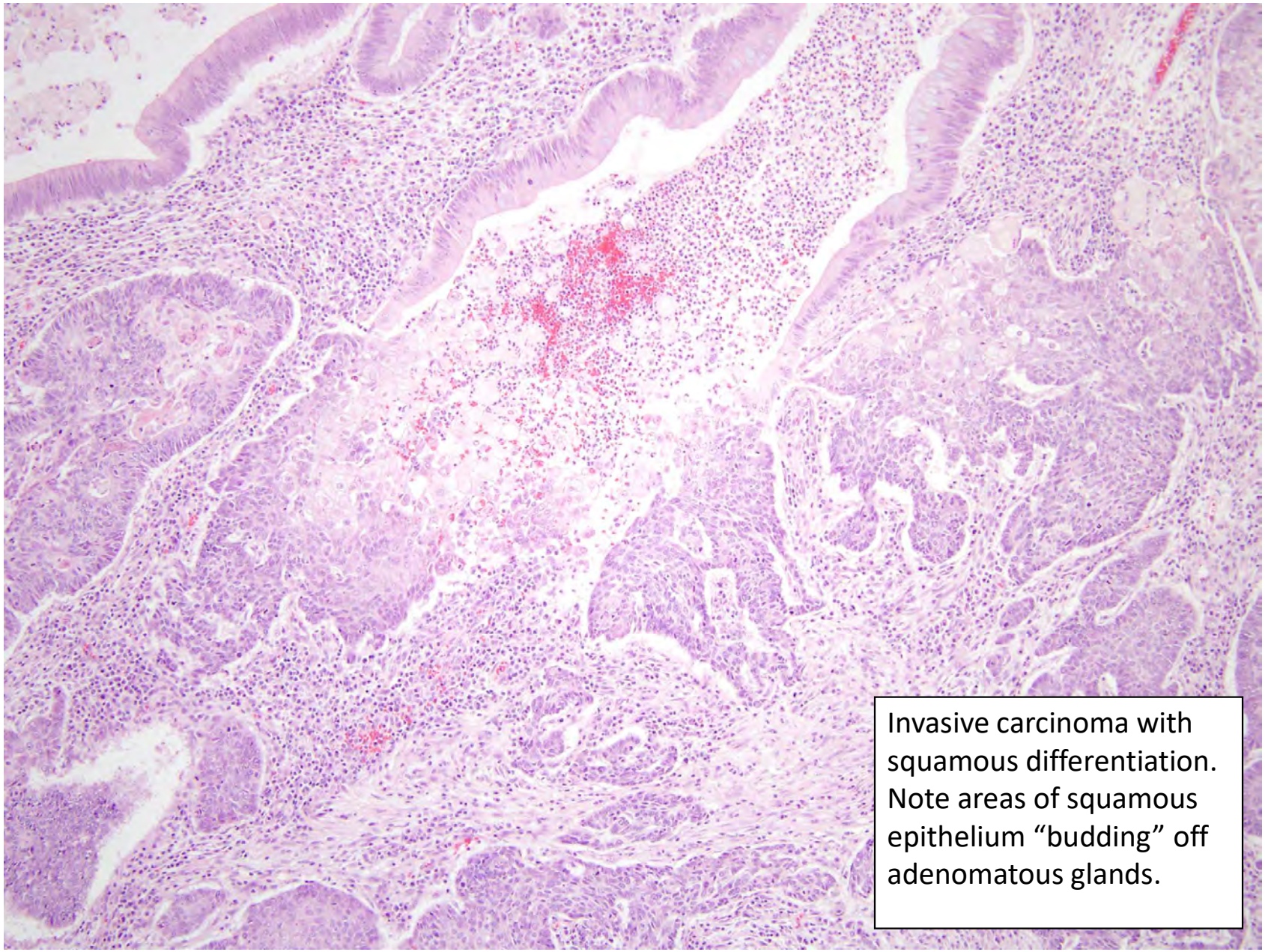
Tubular adenoma with squamous morules (“microcarcinoids”). Morule formation in a tubular adenoma with prolapse change (pseudoinvasion). Some of the glands show associated morules and there is hemosiderin in the center of the field.

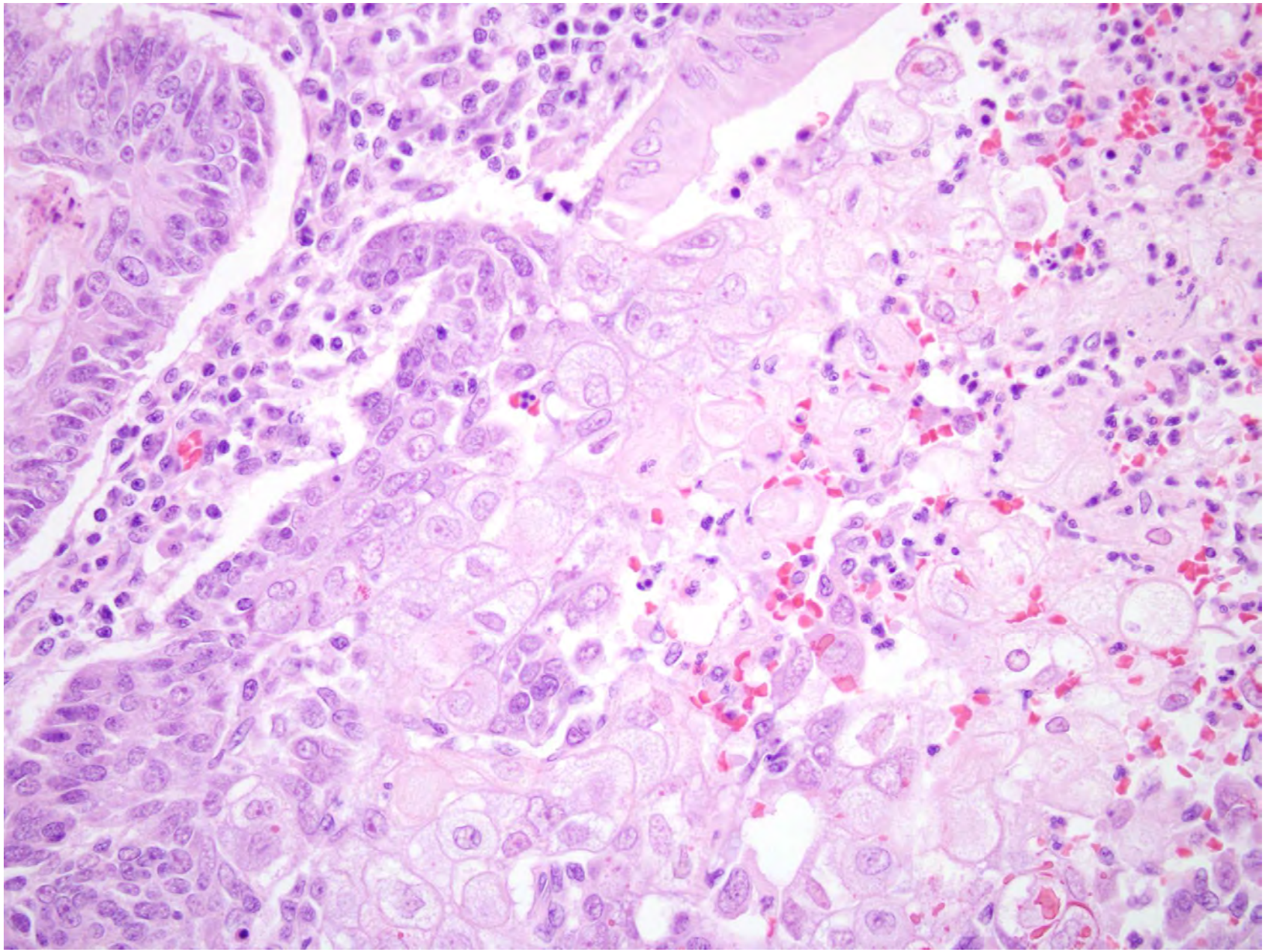


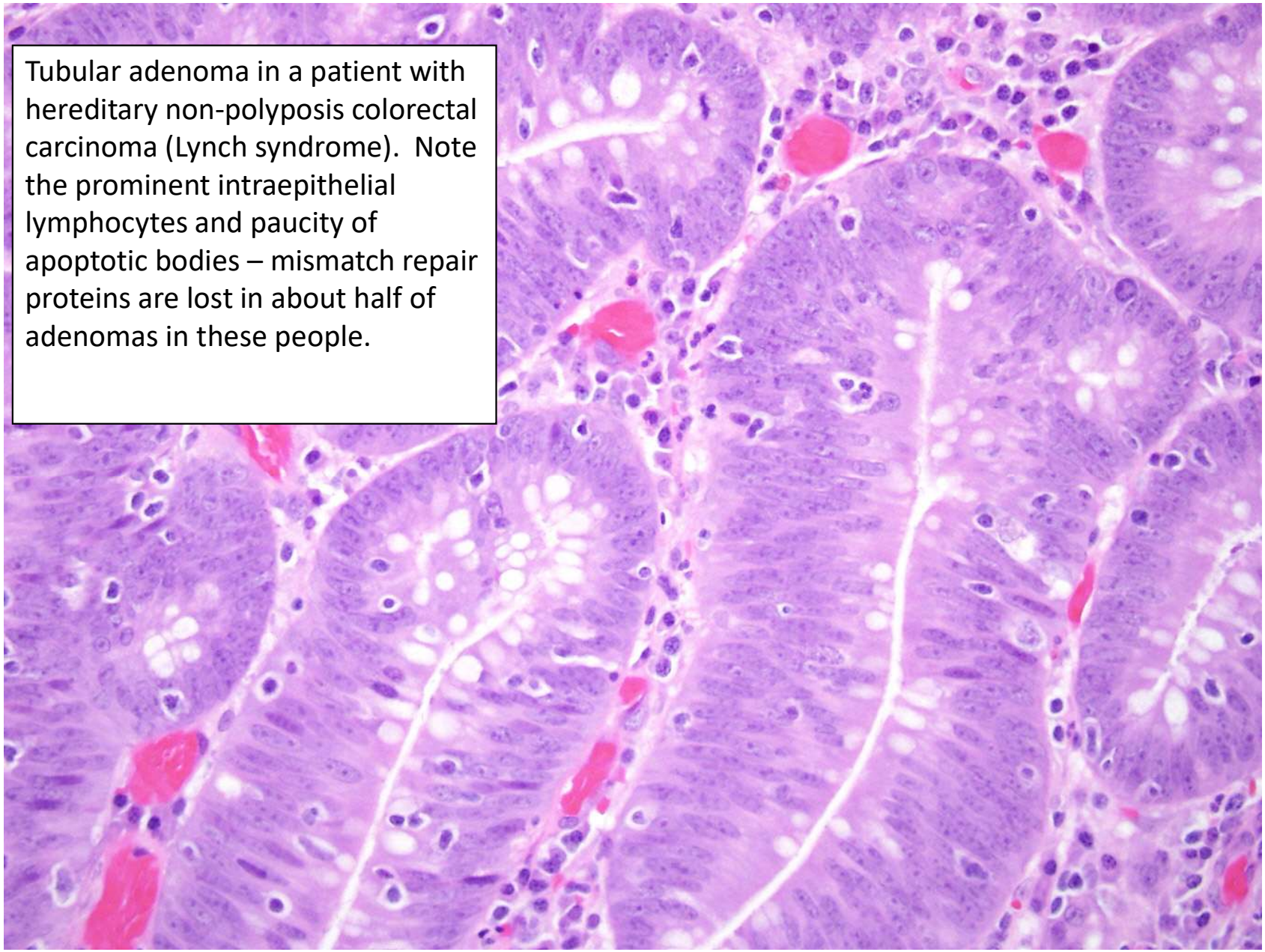
Tubular adenoma with squamous morules. Some observers regard these as “microcarcinoids”- They express both CK5/6 and endocrine markers in some cases




Invasive carcinoma with squamous differentiation. Though squamous morules are of no clinical consequence in adenomas, they may inform some of the variation in the appearances of invasive carcinomas.


Invasive carcinoma with squamous differentiation. Note areas of squamous epithelium “budding” off adenomatous glands.

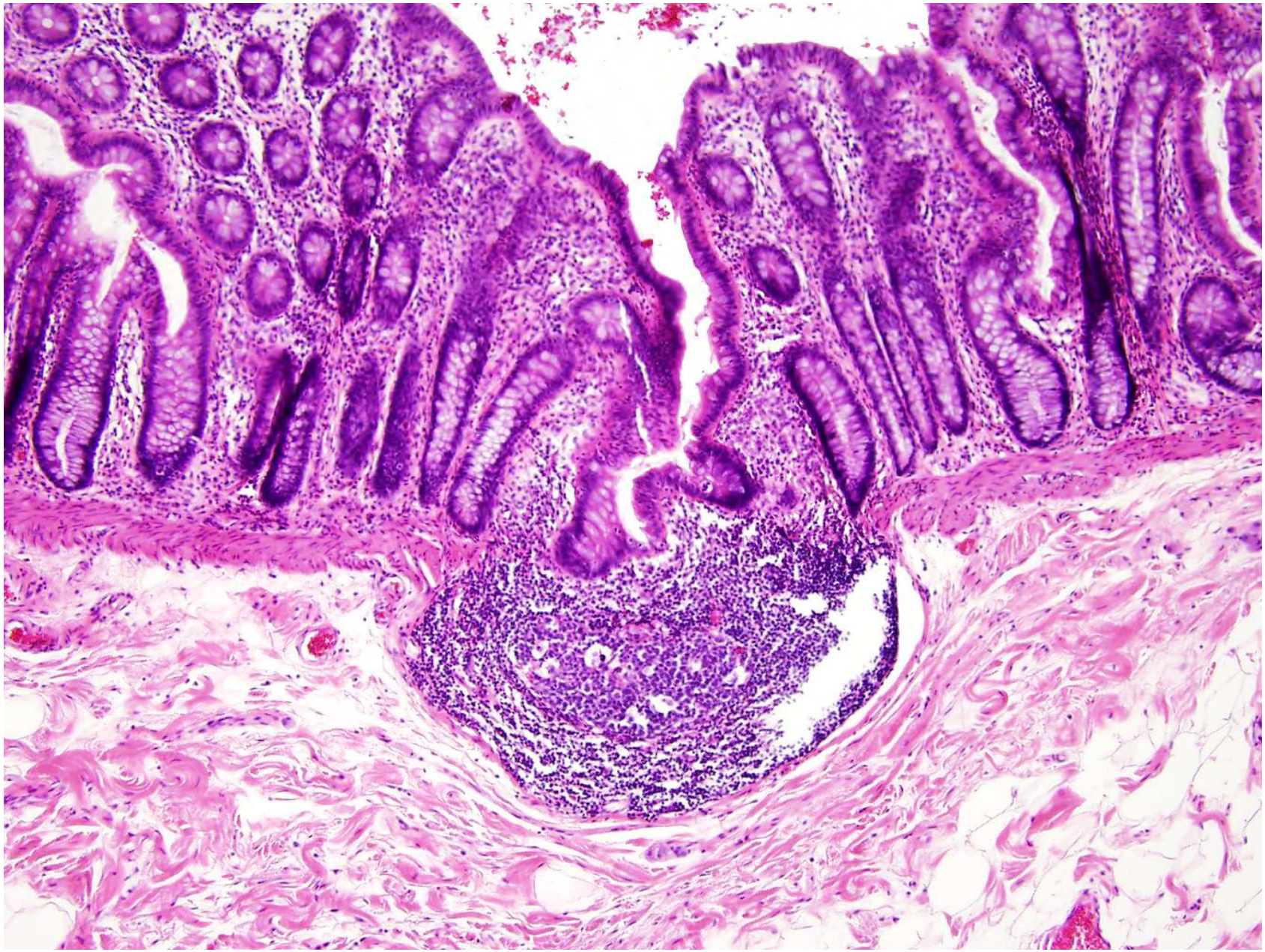


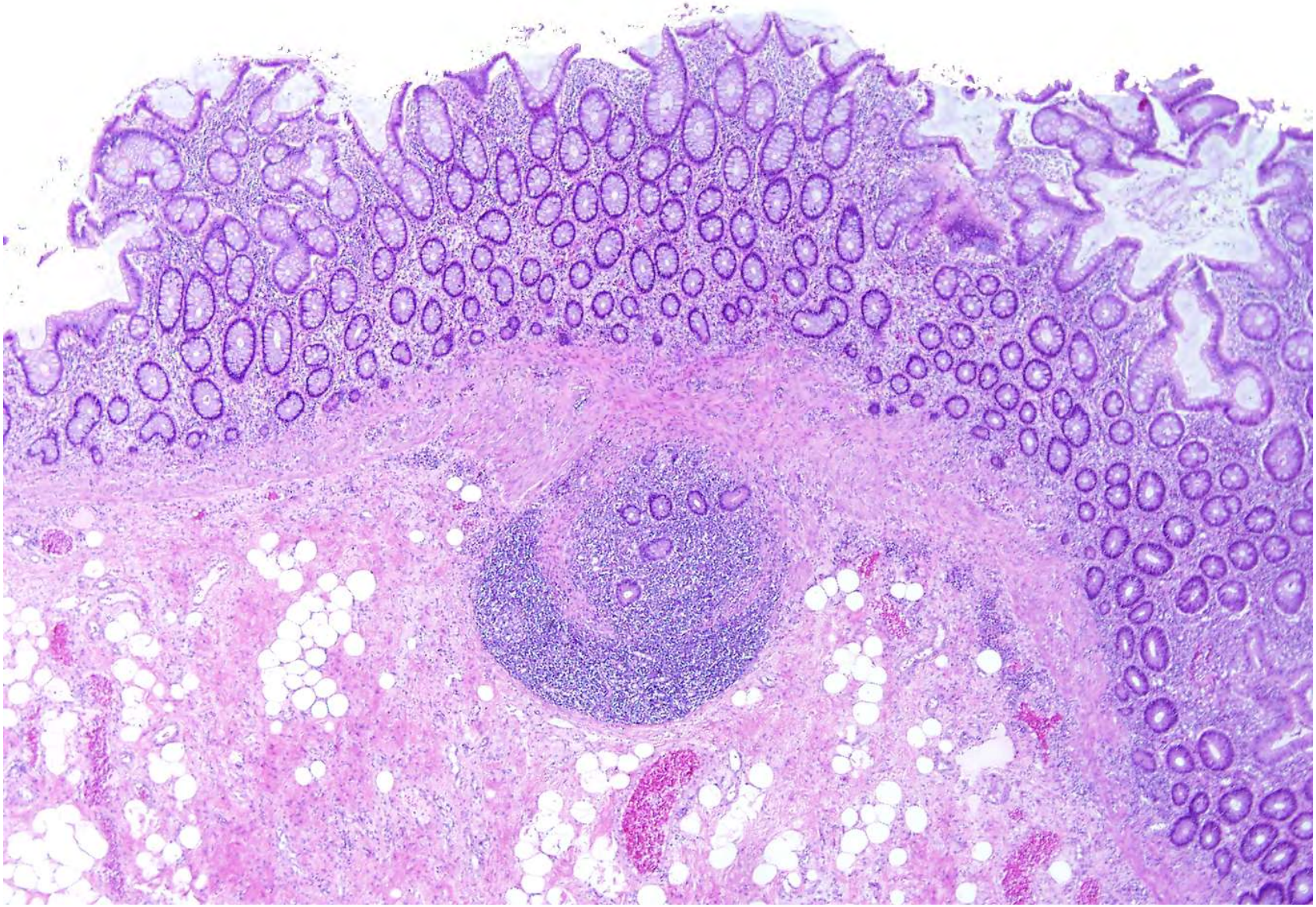


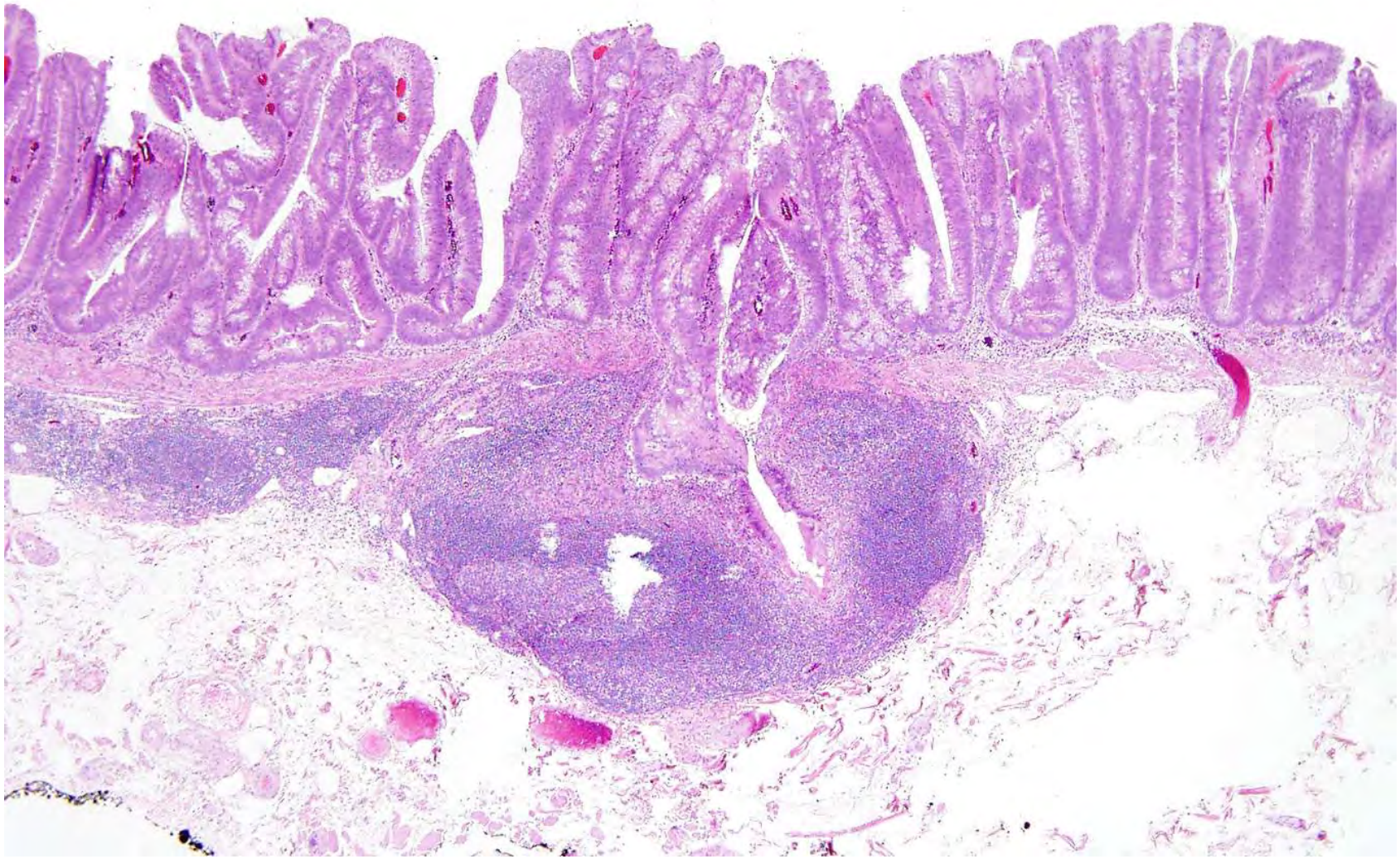
Tubular adenoma in a patient with hereditary non-polyposis colorectal carcinoma (Lynch syndrome). Note the prominent intraepithelial lymphocytes and paucity of apoptotic bodies – mismatch repair proteins are lost in about half of adenomas in these people.

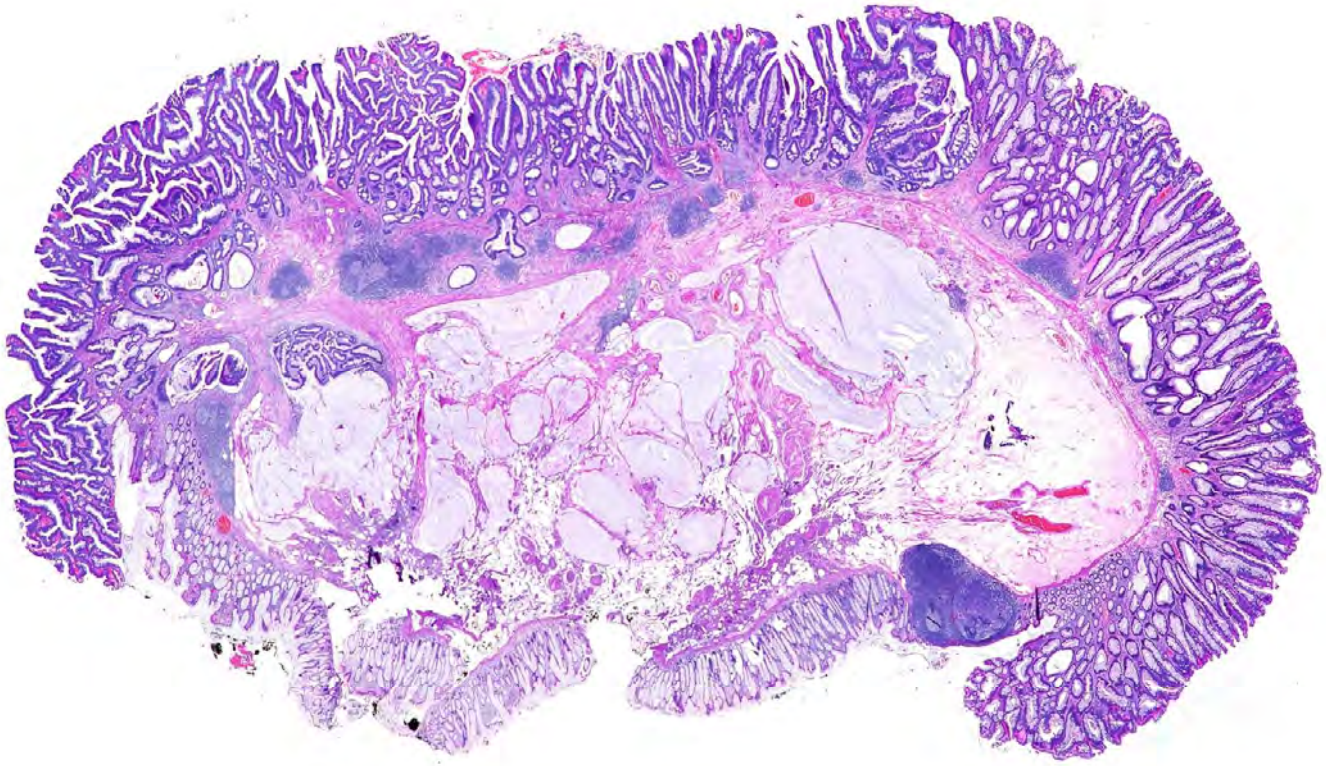
“Pseudoinvasion”

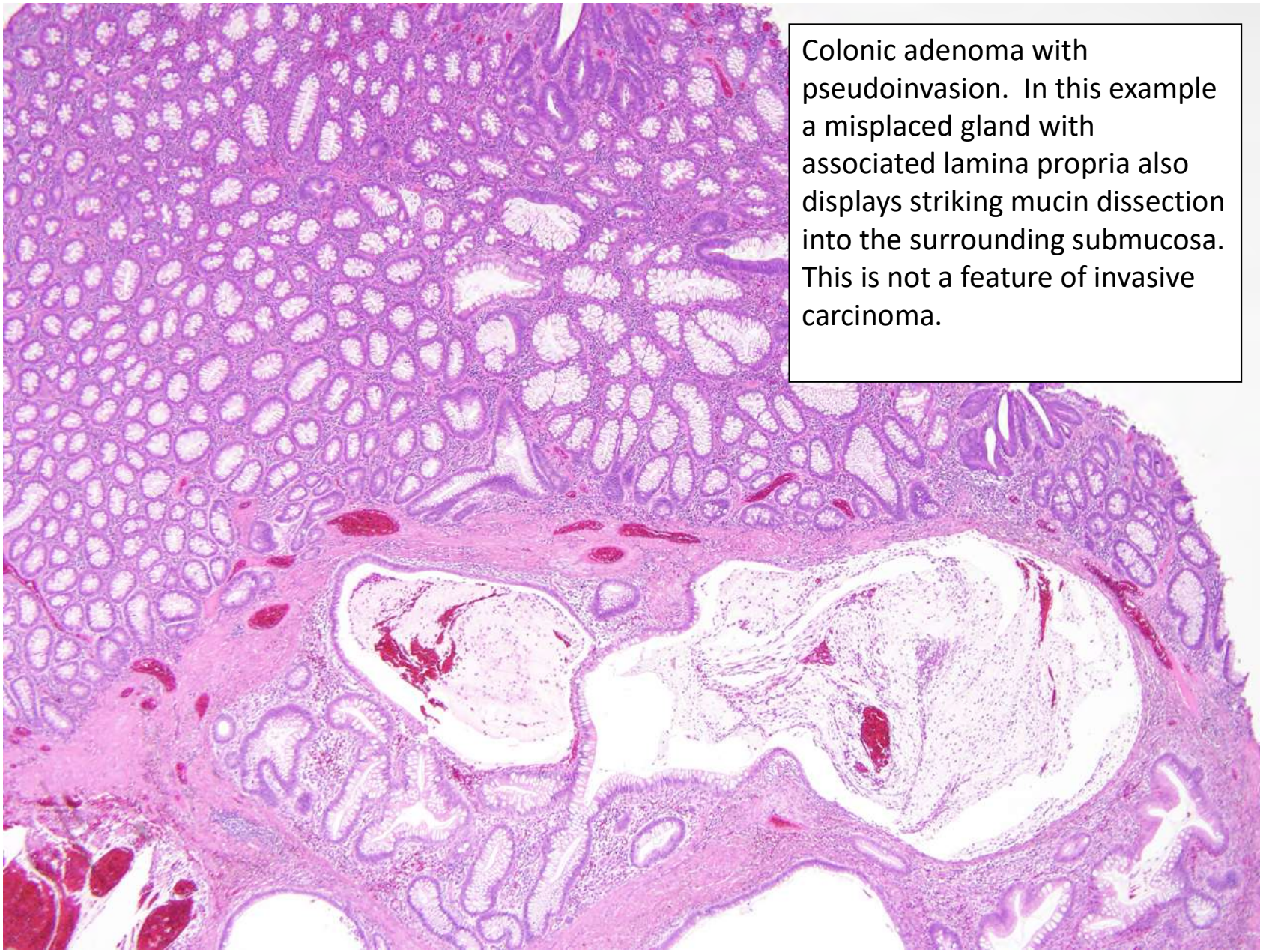
- Usually in sigmoid colon and easy to interpret
- Accompanying hemosiderin
- A few issues with confusion with cancer



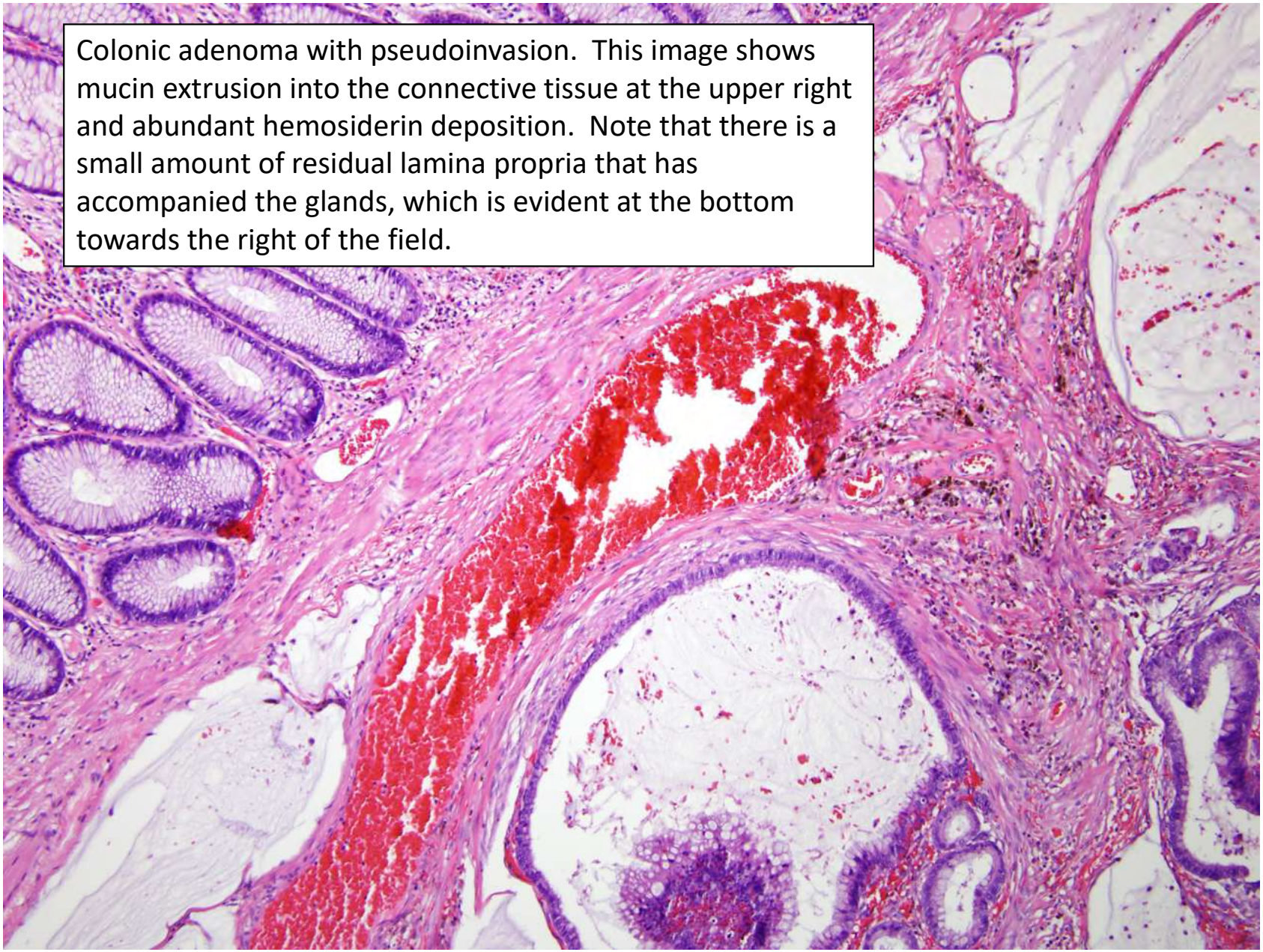




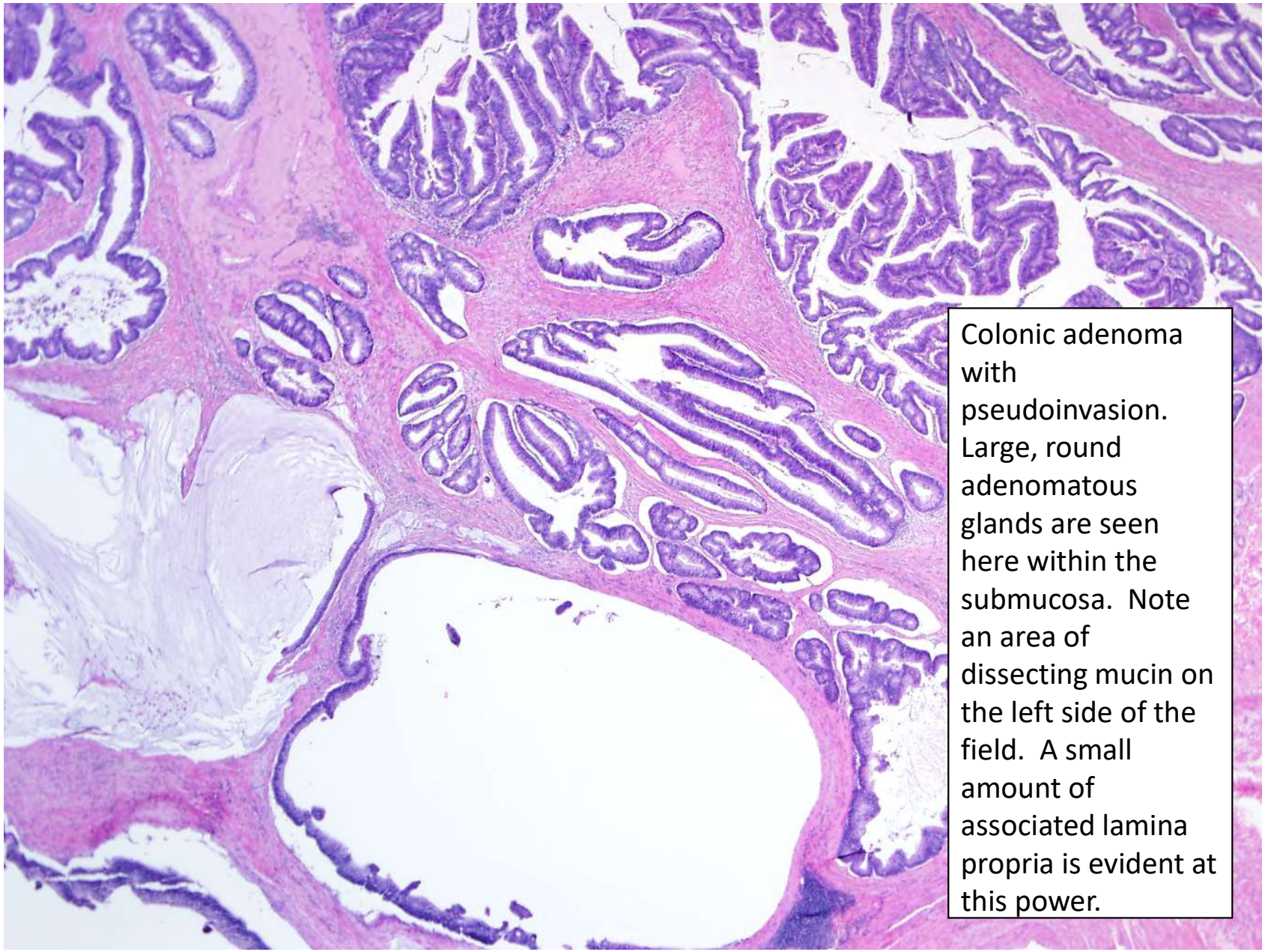




Colonic adenoma with pseudoinvasion. In this example a misplaced gland with associated lamina propria also displays striking mucin dissection into the surrounding submucosa. This is not a feature of invasive carcinoma.

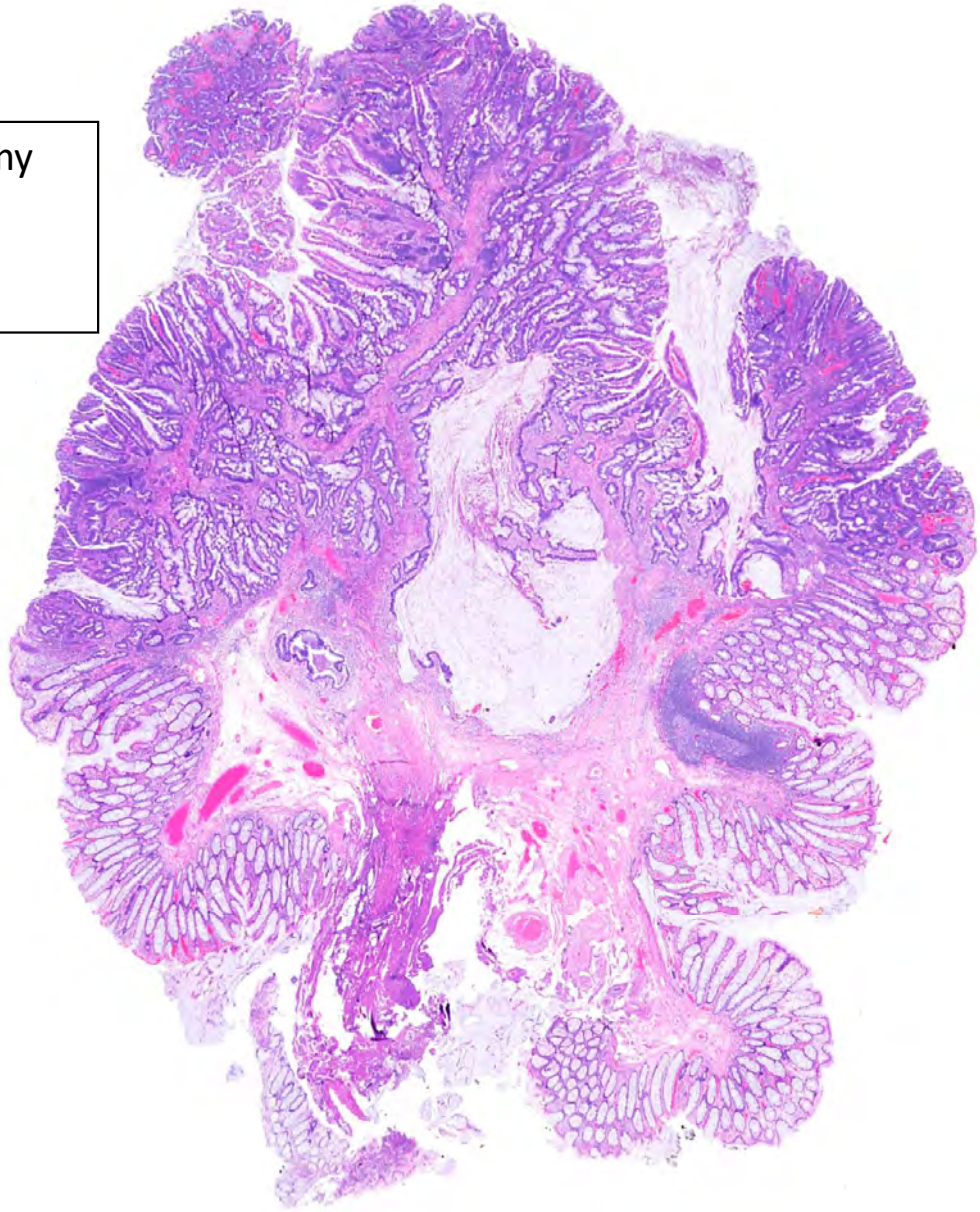


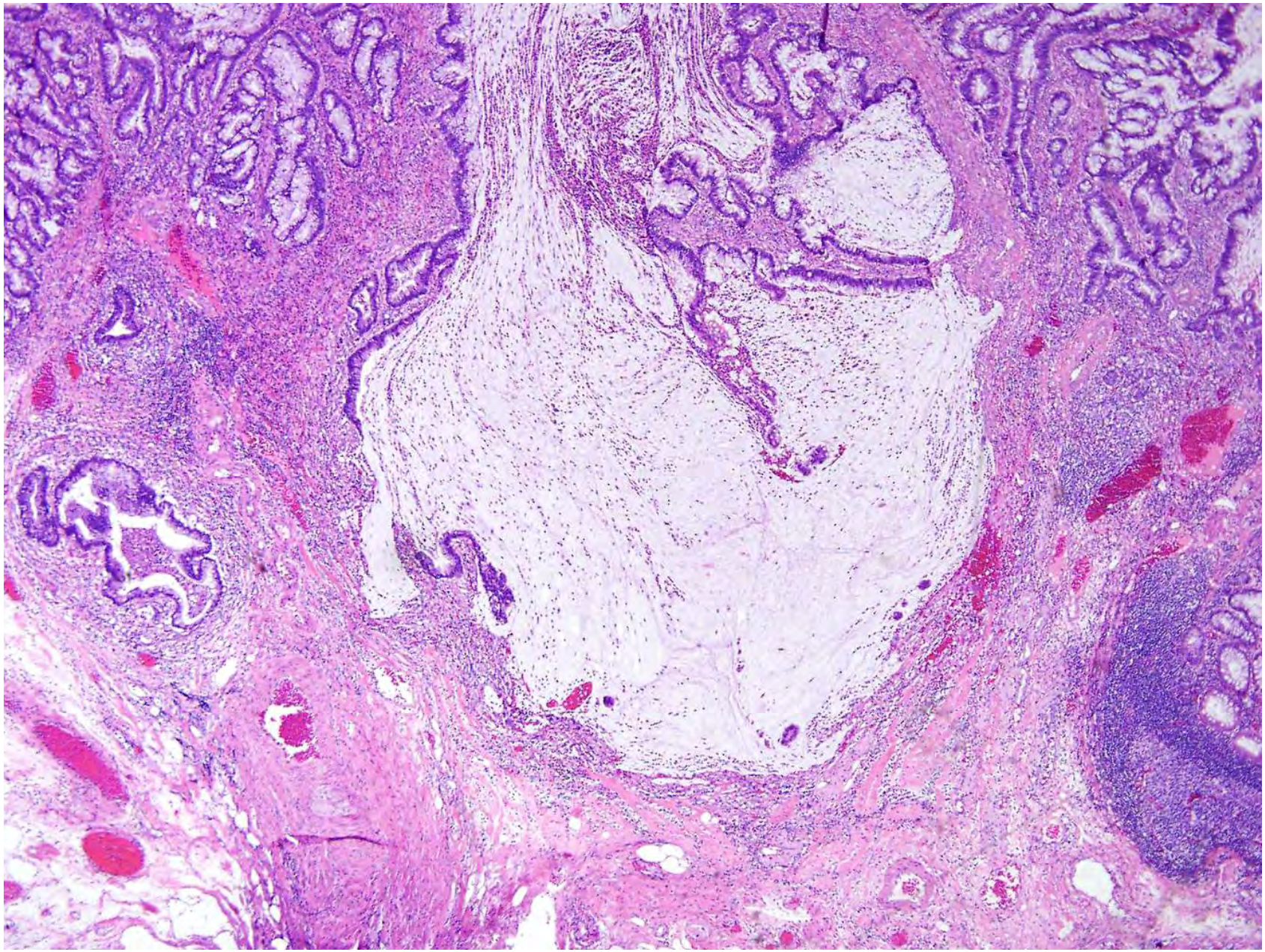
Colonic adenoma with pseudoinvasion. This image shows mucin extrusion into the connective tissue at the upper right and abundant hemosiderin deposition. Note that there is a small amount of residual lamina propria that has accompanied the glands, which is evident at the bottom towards the right of the field.

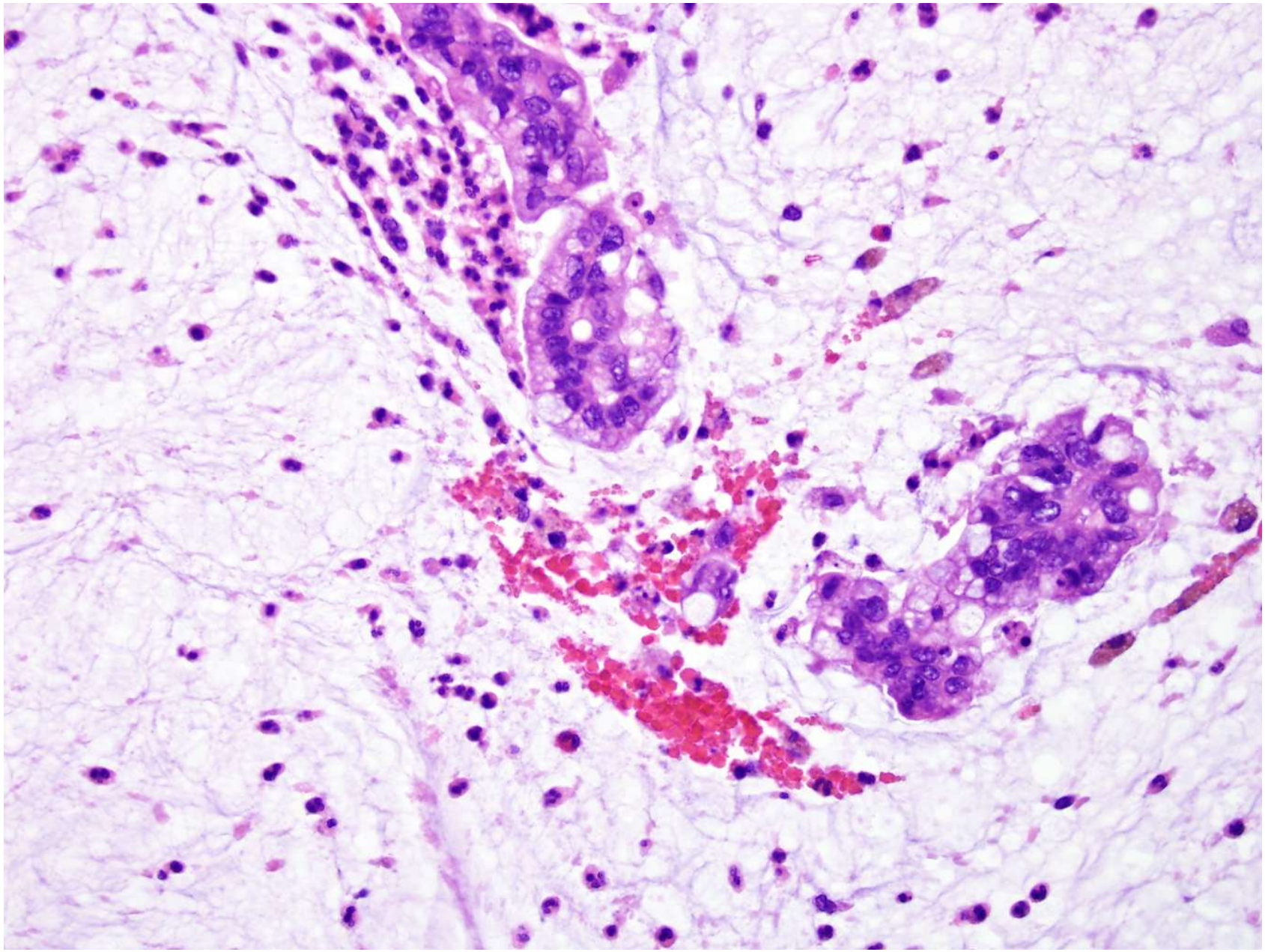


Colonic adenoma with pseudoinvasion. Large, round adenomatous glands are seen here within the submucosa. Note an area of dissecting mucin on the left side of the field. A small amount of associated lamina propria is evident at this power.

Pseudoinvasion (my opinion) with dramatic mucin extrusion







Just When We thought it was Safe to Come out of the Water

- More recently recognized sneaky carcinomas

Adenoma-like adenocarcinoma

Pushing growth pattern

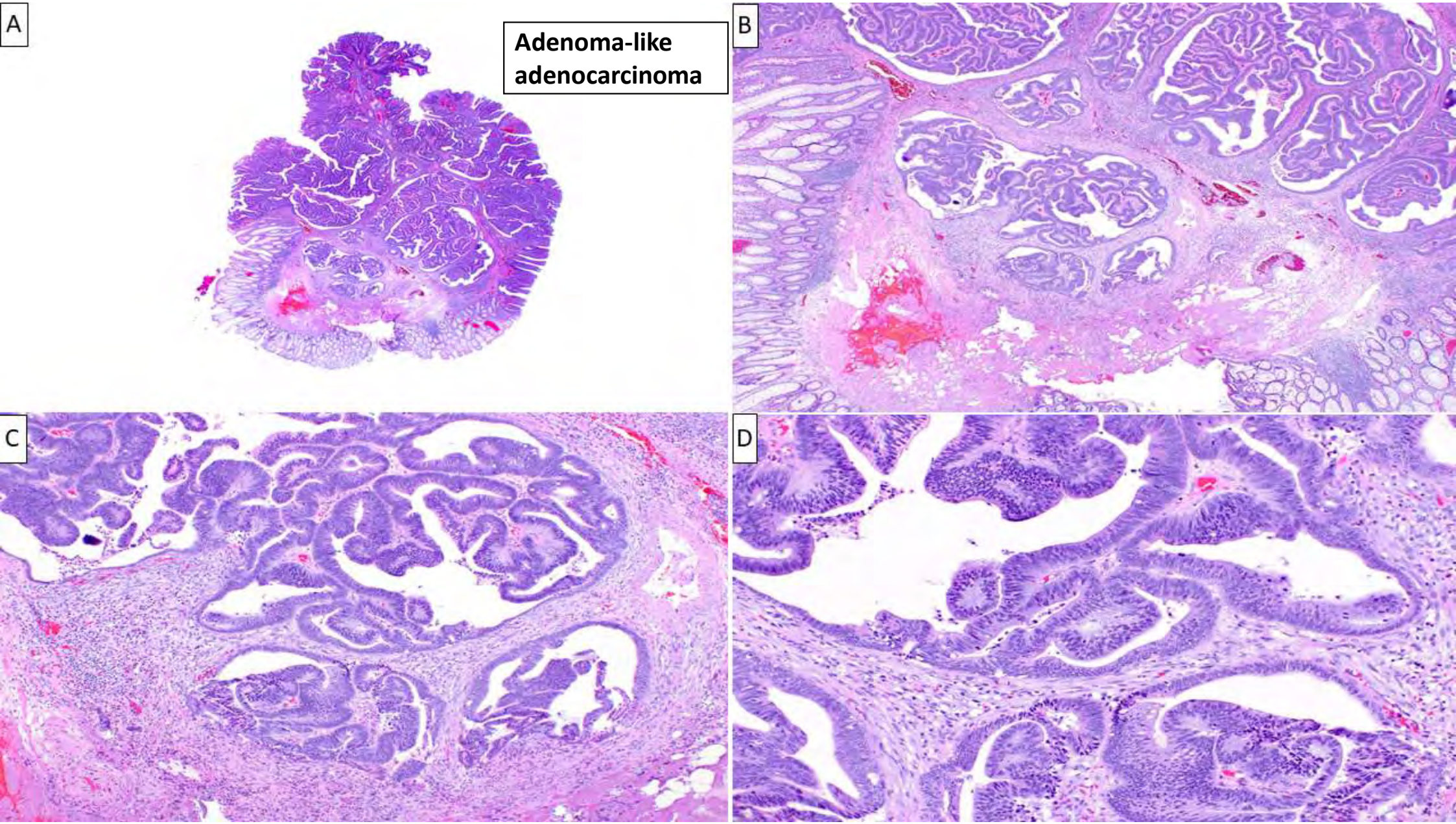
Spindled lamina propria

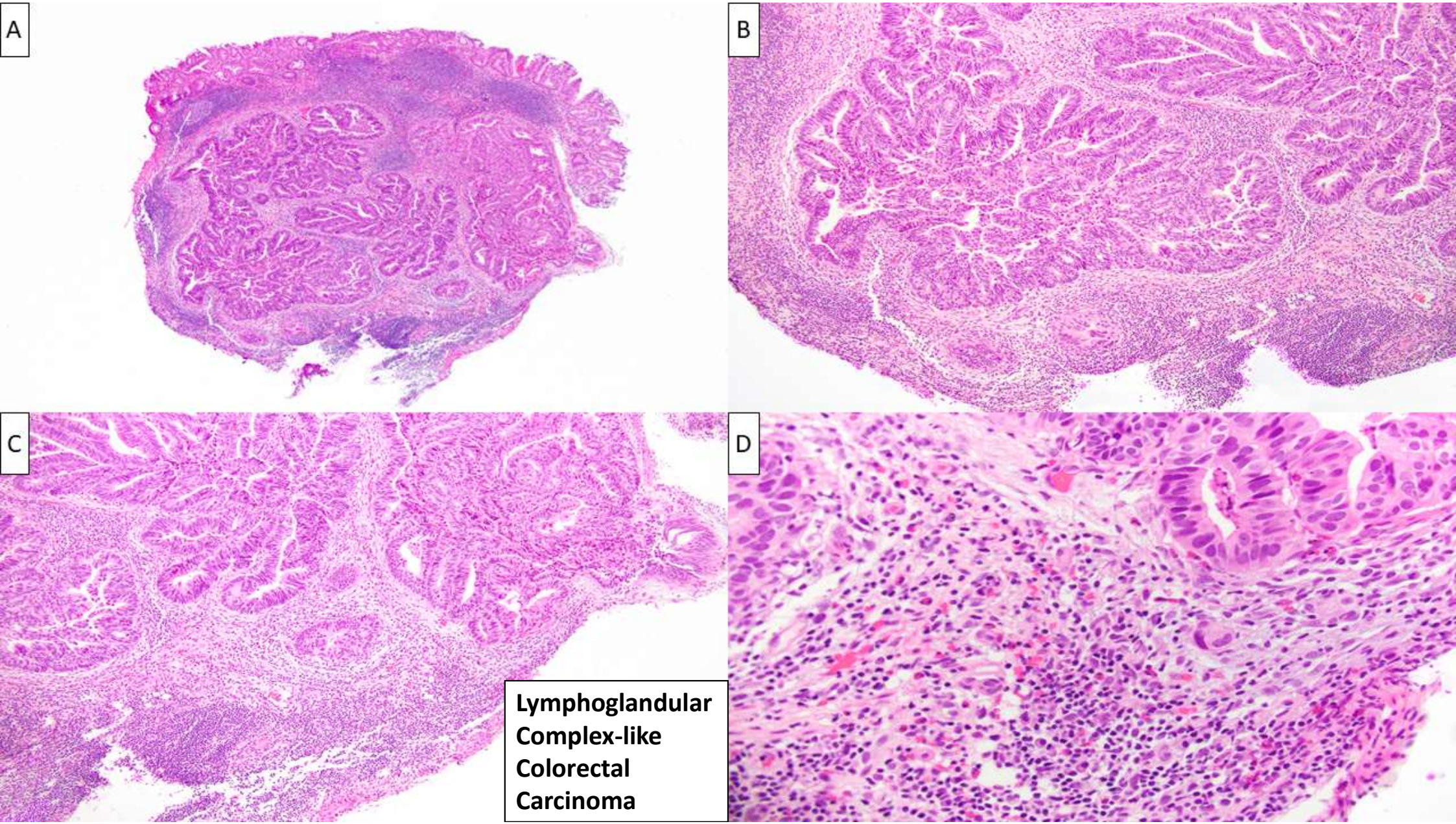
Lymphoglandular Complex-like Colorectal Carcinoma

Similar to mucosal prolapse but haphazard gland distribution, angulation, fusion, and solid nests

Gonzalez RS, Cates JM, Washington MK, Beauchamp RD, Coffey RJ, Shi C. Adenoma-like adenocarcinoma: a subtype of colorectal carcinoma with good prognosis, deceptive appearance on biopsy and frequent KRAS mutation. Histopathology. 2016;68(2):183-90.

Yilmaz O, Westerhoff M, Panarelli N, Hart J, Groisman G, Ruz-Caracuel I, et al. Lymphoglandular Complex-Like Colorectal Carcinoma-A Series of 20 Colorectal Cases, Including Newly Reported Features of Malignant Behavior. Am J Surg Pathol. 2024;48(1):70-9.


A
Adenoma-like adenocarcinoma
B
C
D


A
B
C
D
Lymphoglandular Complex-like Colorectal Carcinoma

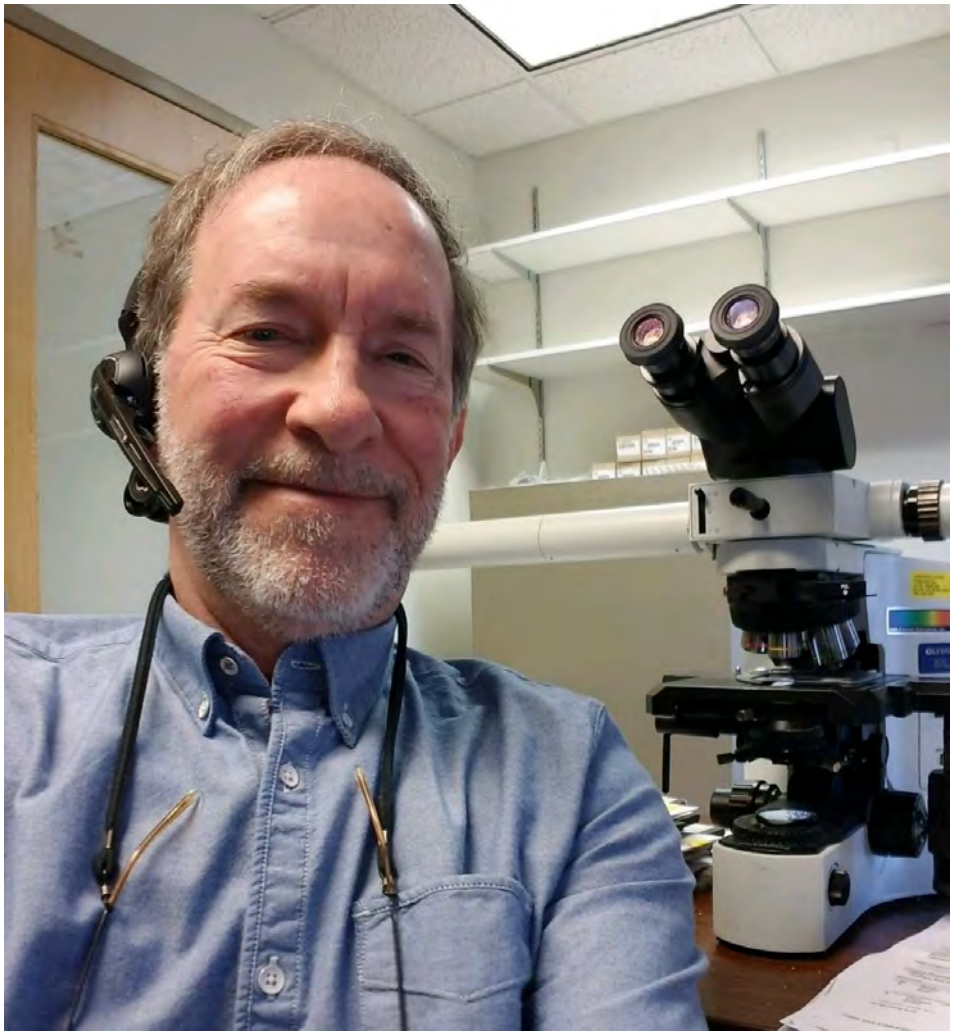
Serrated Polyps are the GI Story of the Turn of the Millennium

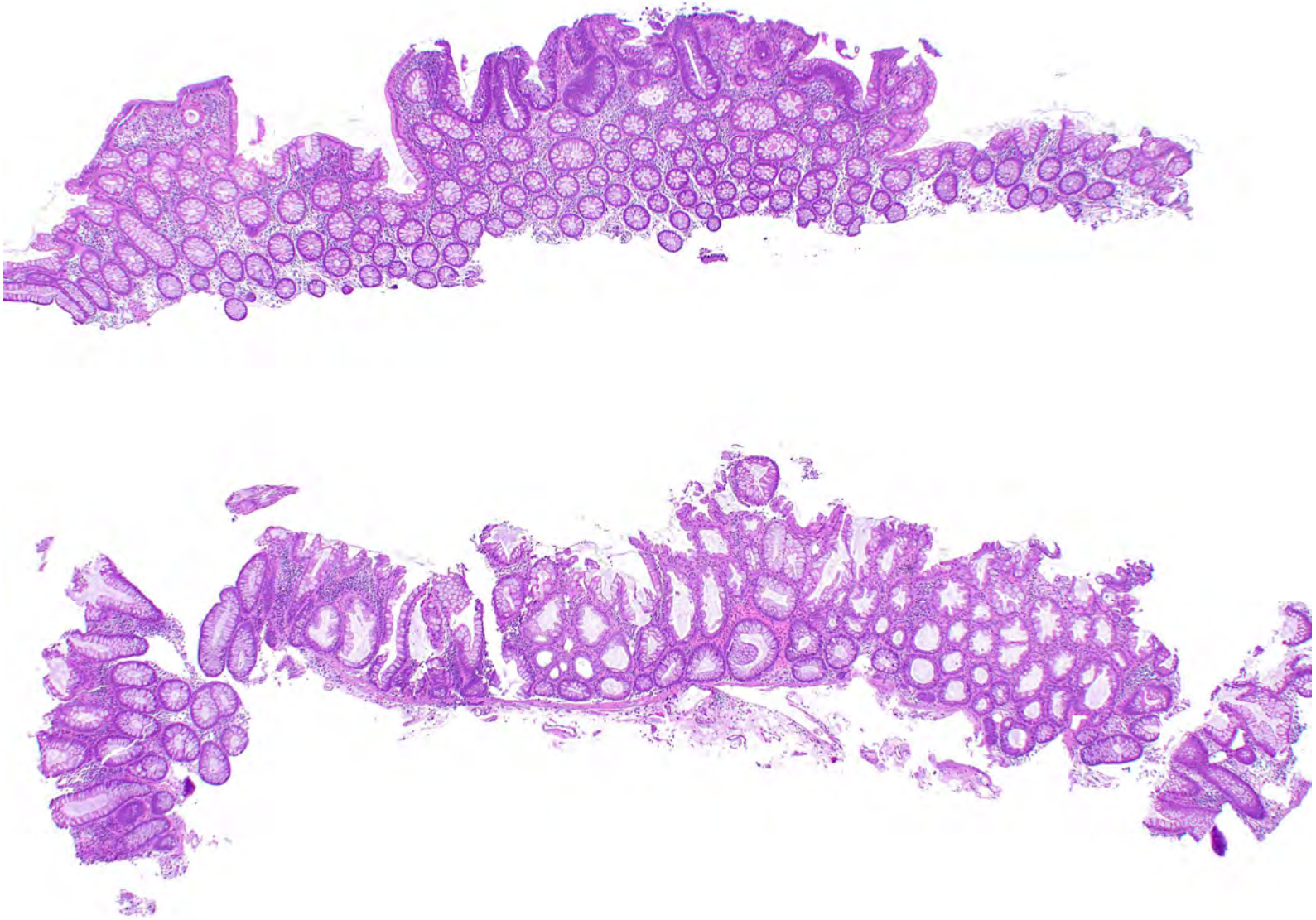
- Will just use the term adenoma for this discussion – do what you like at your place when reporting (I just give all three terms so everyone can understand and also no one explains to me that now we are supposed to say “lesion”).
- The term was coined by Torlakovic and Snover in 1996 – they called it “adenoma” because it is a precursor.
- No one really believed them until 2002-2003

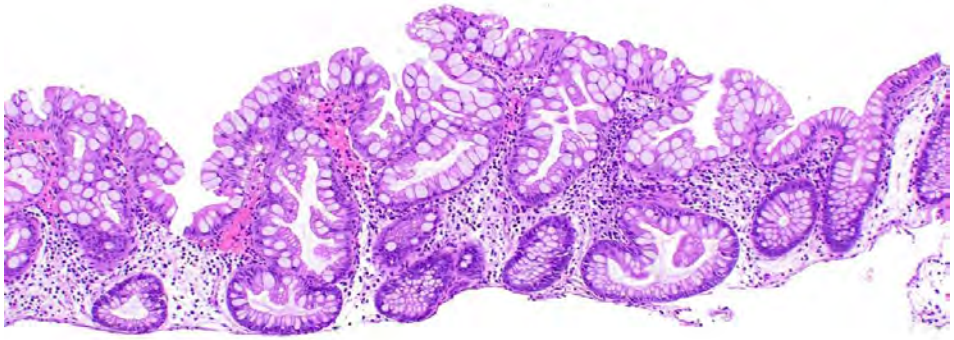
- Torlakovic E, Snover DC. Serrated adenomatous polyposis in humans. Gastroenterology. 1996;110(3):748-55.
- Torlakovic E, Skovlund E, Snover DC, Torlakovic G, Nesland JM. Morphologic reappraisal of serrated colorectal polyps. Am J Surg Pathol. 2003;27(1):65-81.

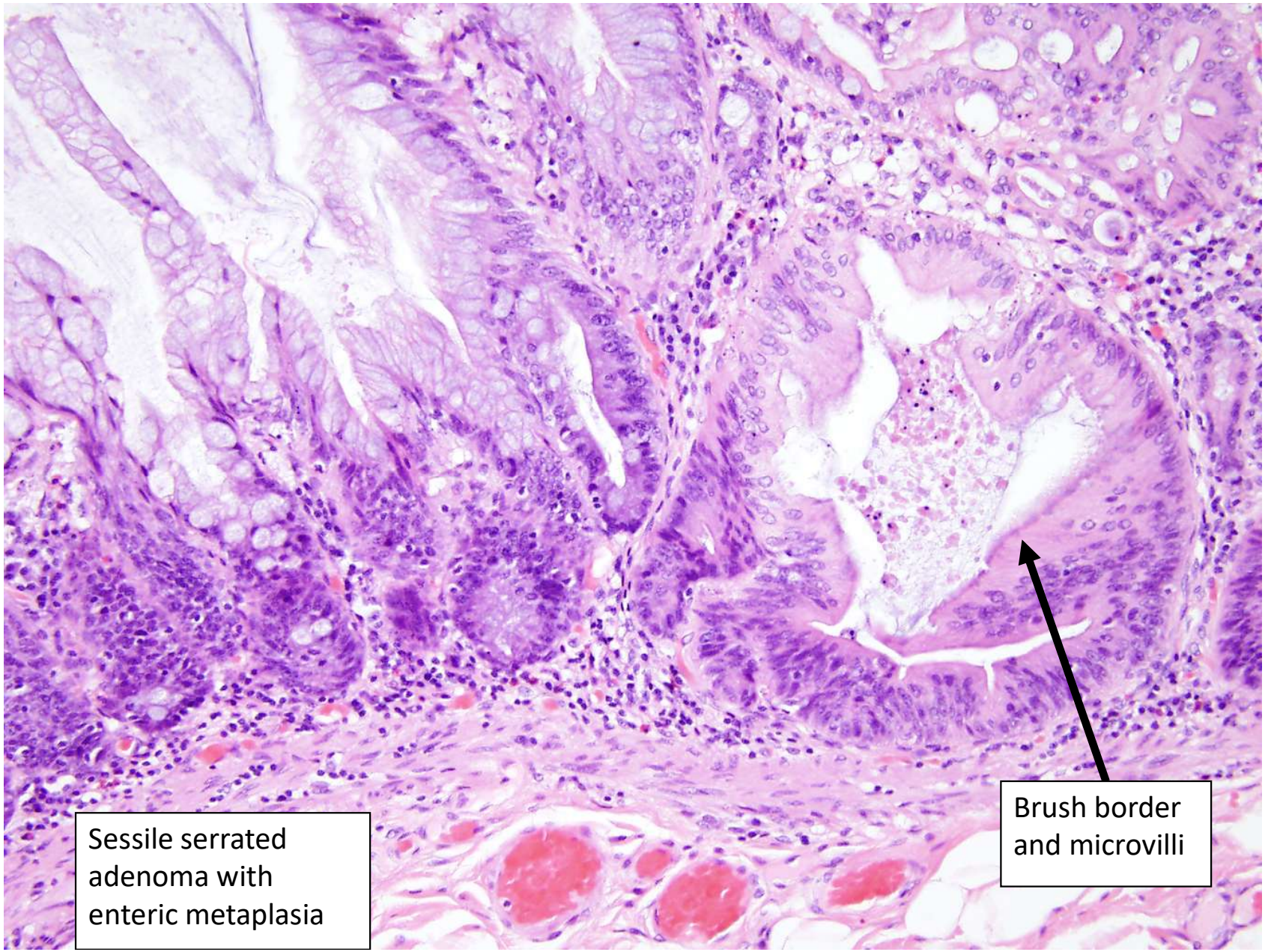
Emina Torlakovic

Dale Snover



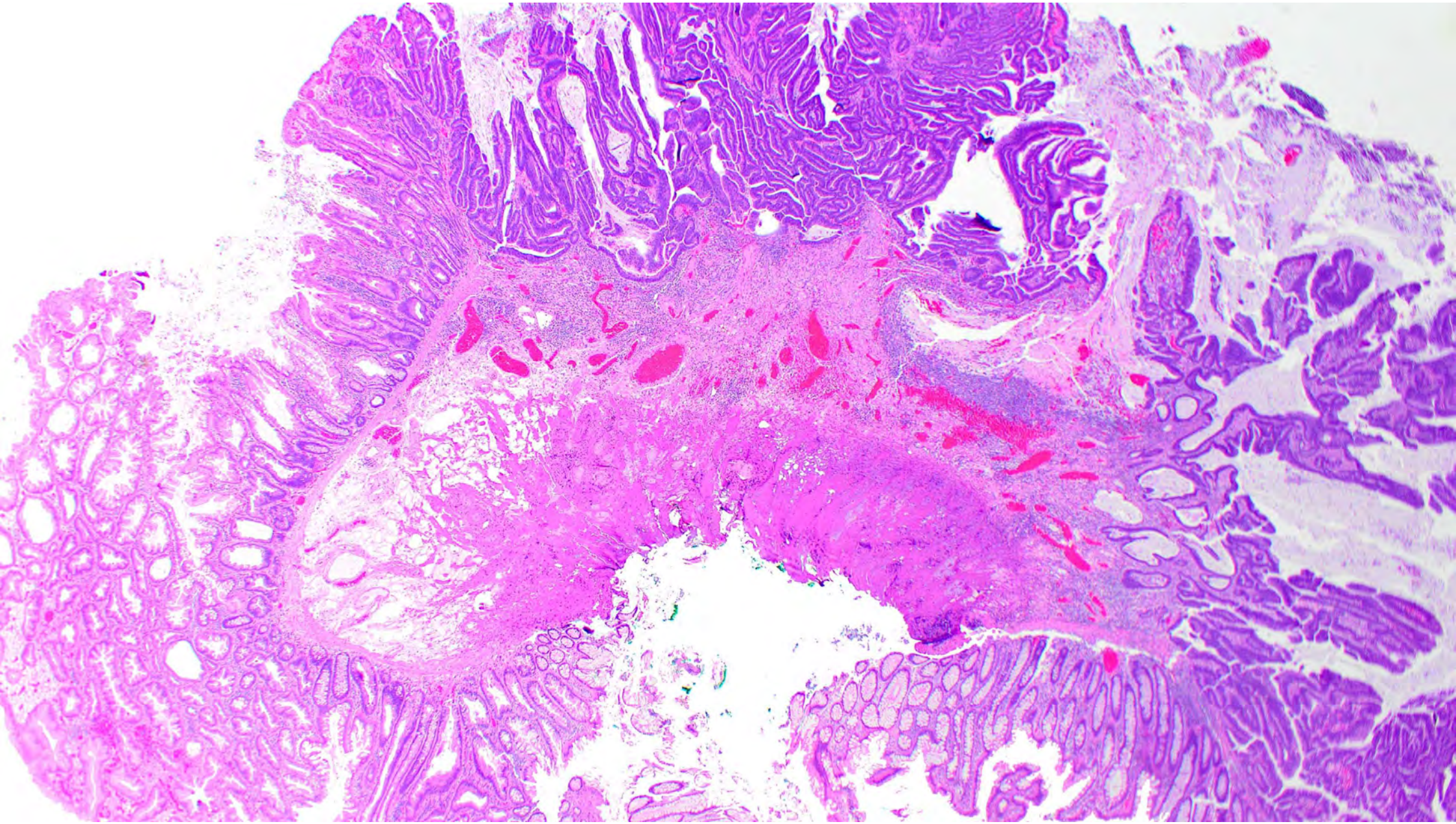


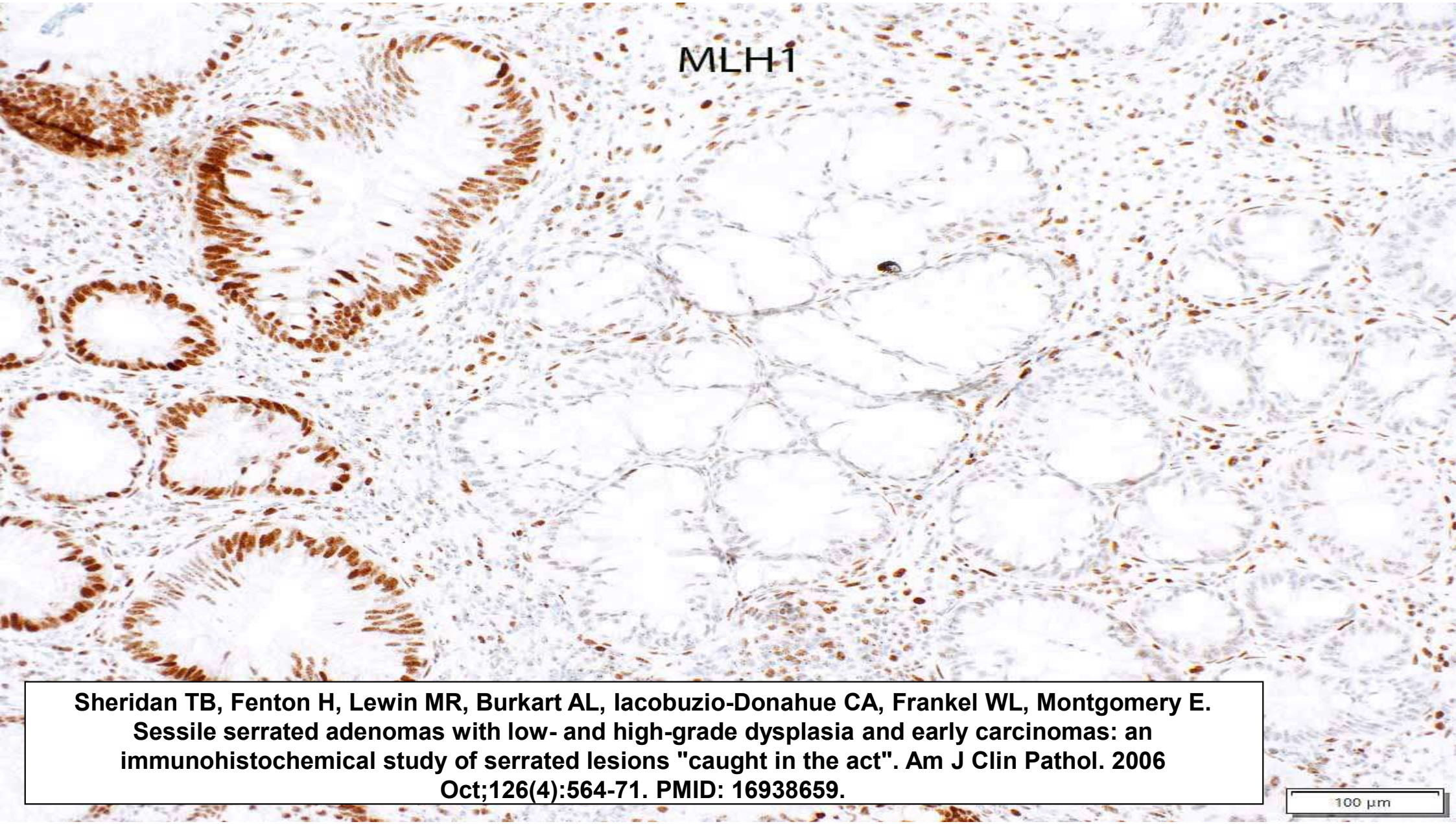



Sessile serrated adenoma with enteric metaplasia
Brush border and microvilli

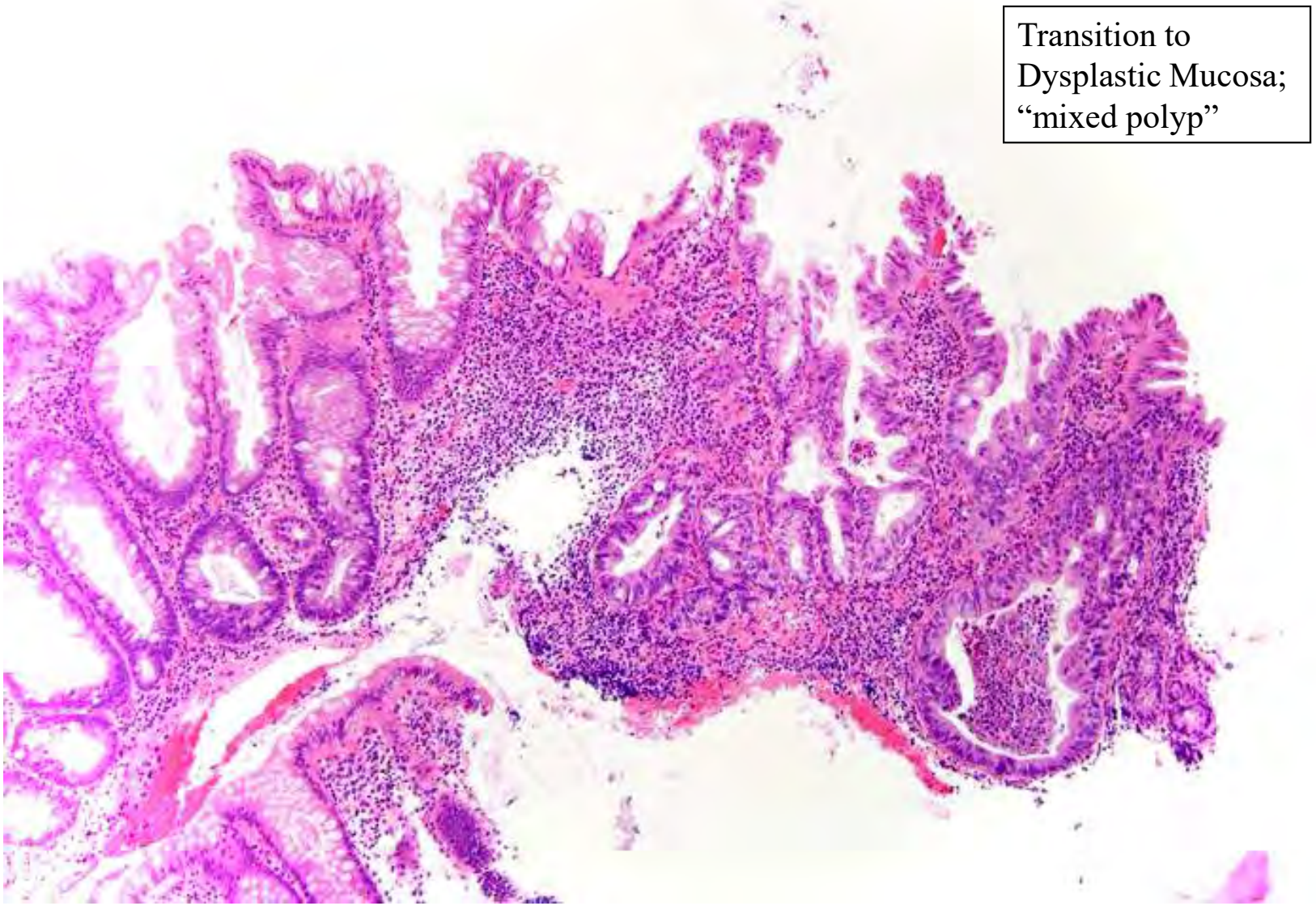
Mixed Polyps

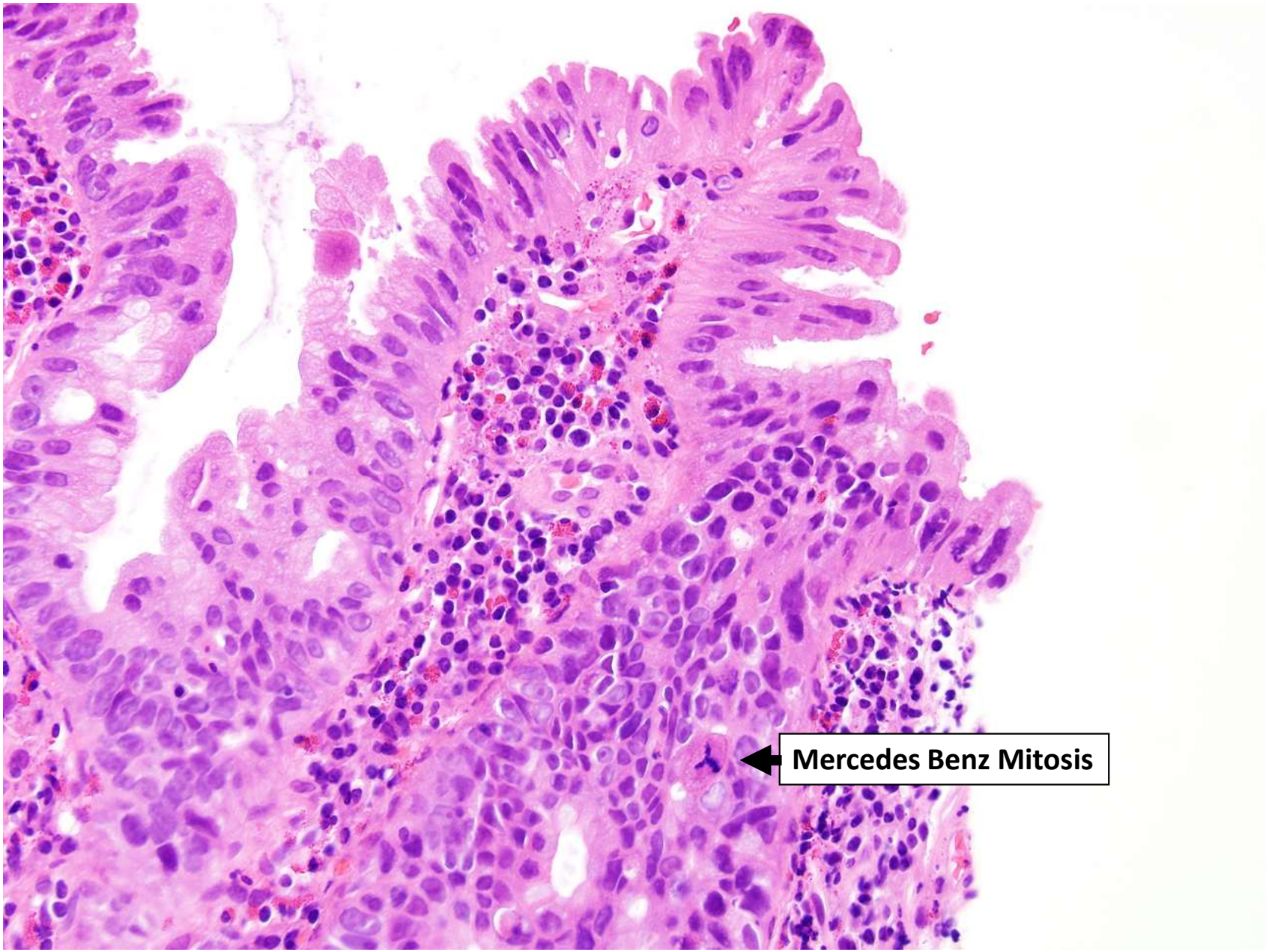
- We know know that “mixed” polyps are generally sessile serrated adenomas that are progressing

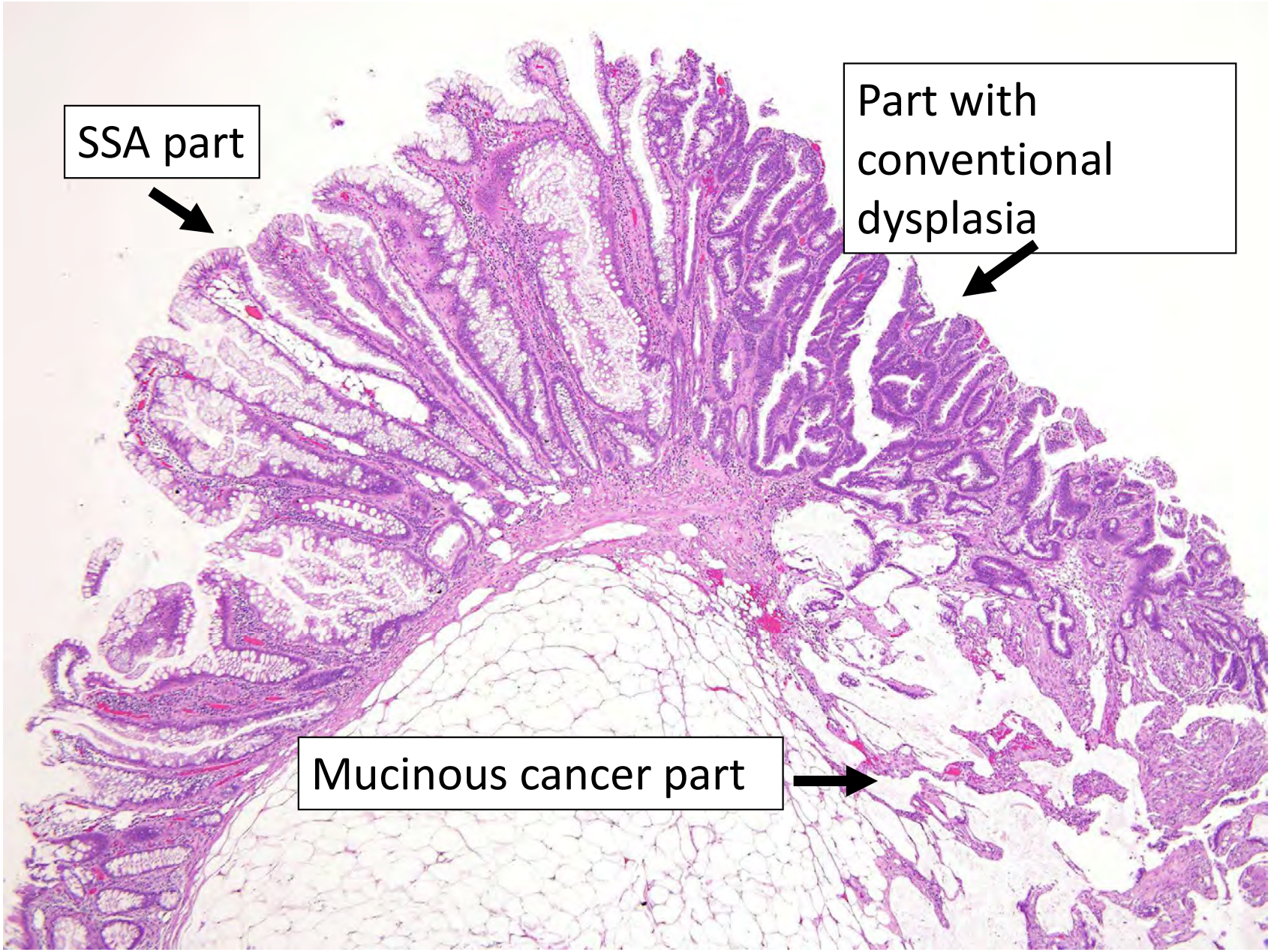




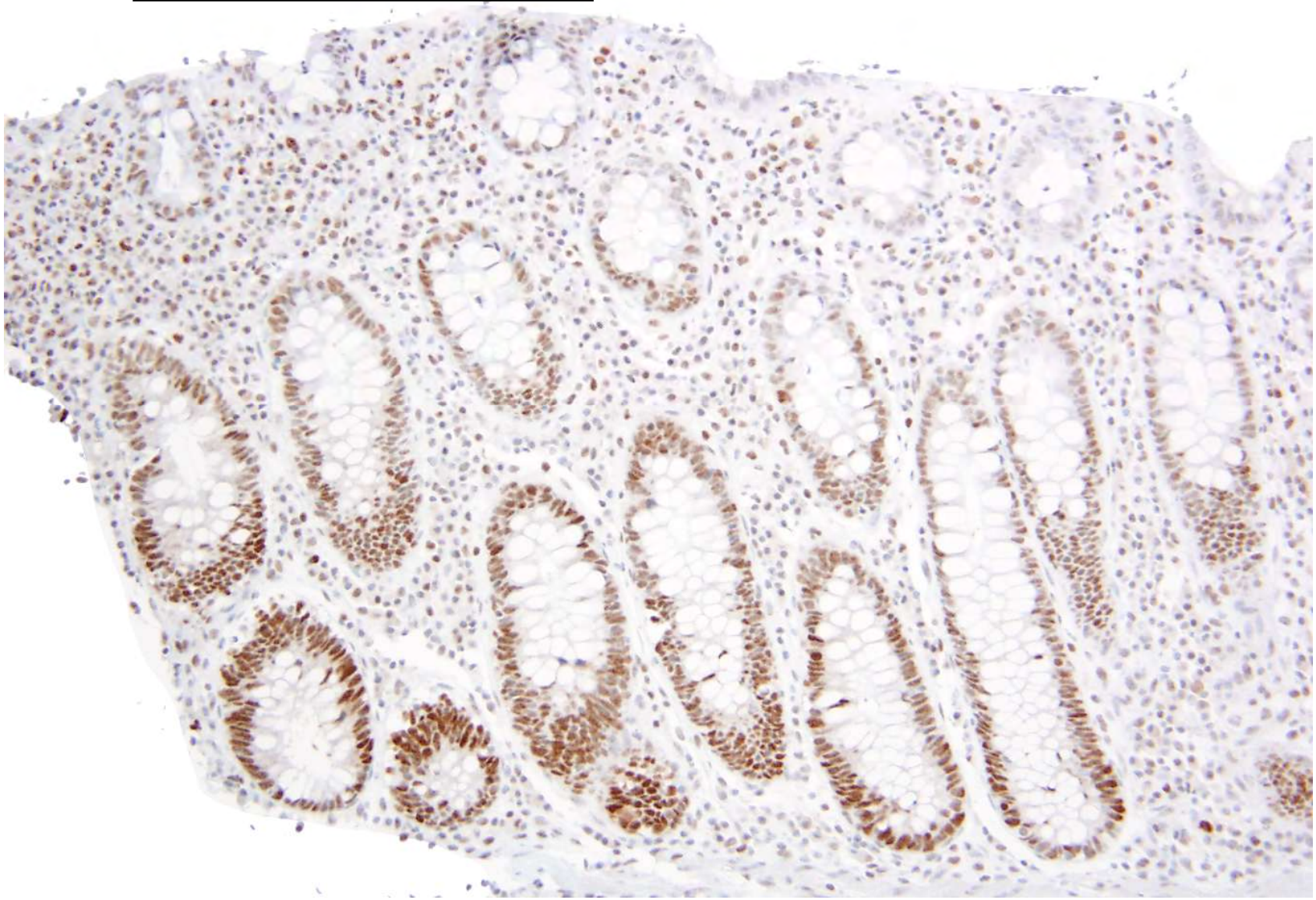
Sheridan TB, Fenton H, Lewin MR, Burkart AL, Iacobuzio-Donahue CA, Frankel WL, Montgomery E. Sessile serrated adenomas with low- and high-grade dysplasia and early carcinomas: an immunohistochemical study of serrated lesions "caught in the act". Am J Clin Pathol. 2006 Oct;126(4):564-71. PMID: 16938659.

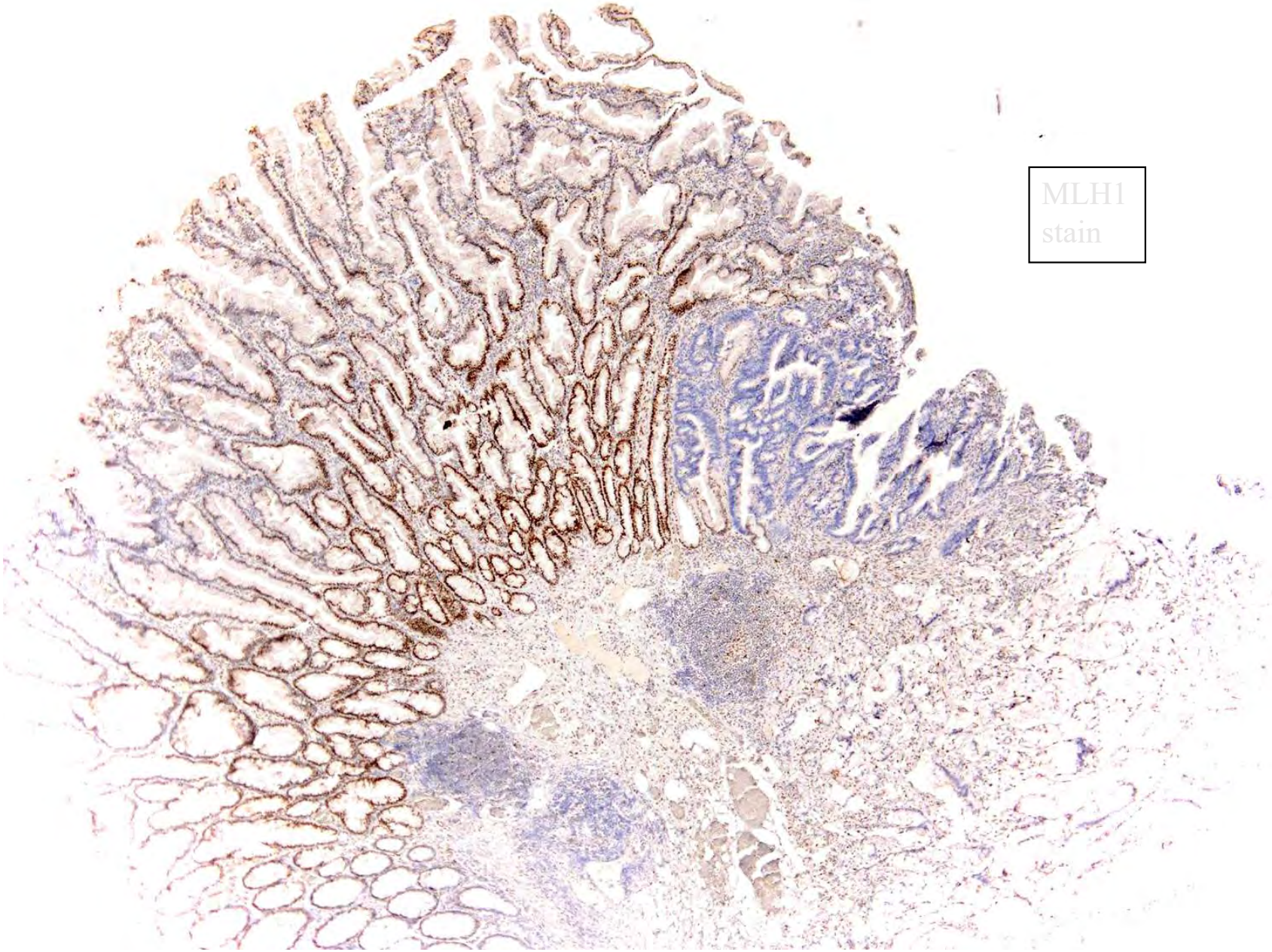

Transition to
Dysplastic Mucosa;
“mixed polyp”

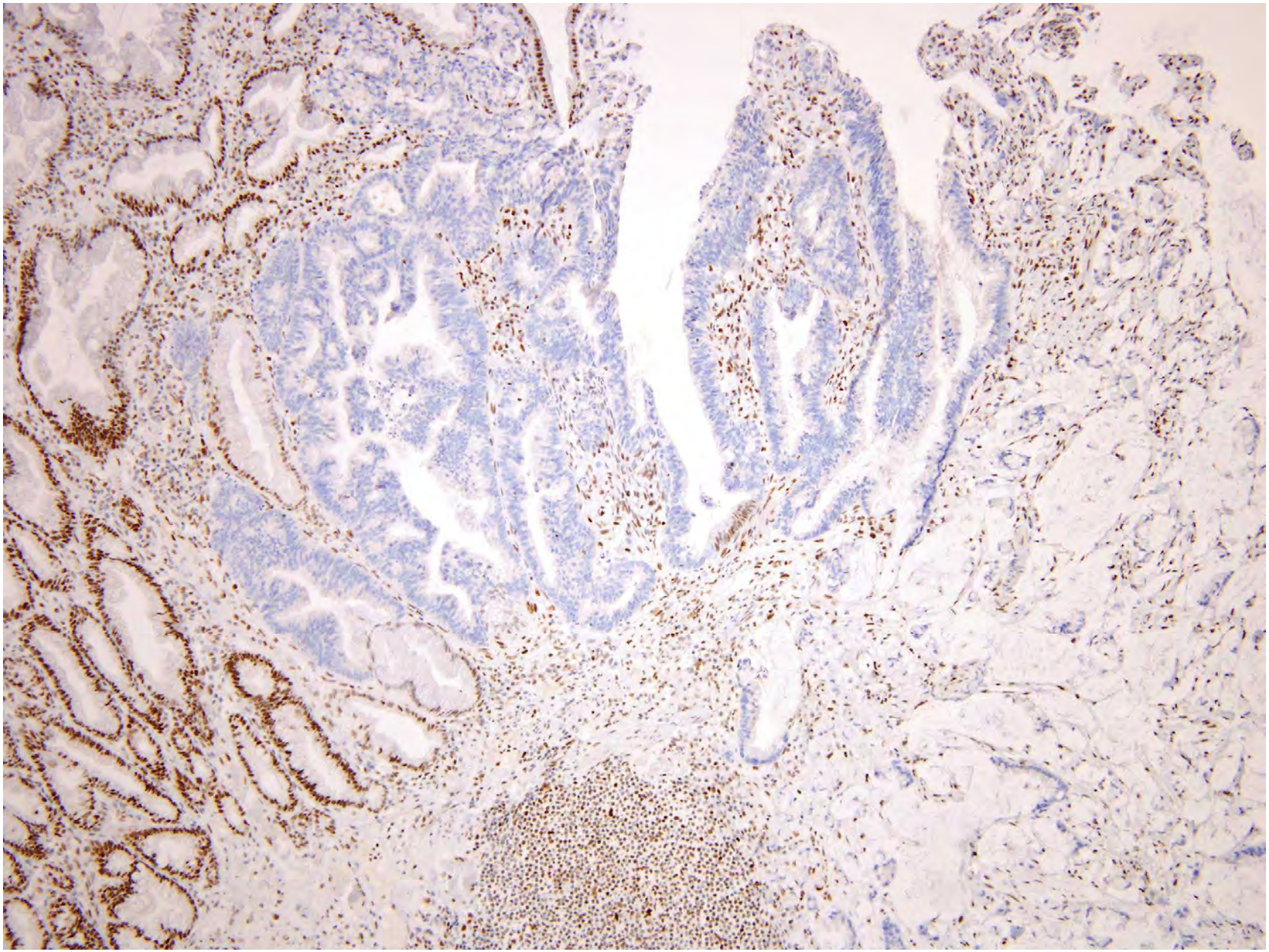

Mercedes Benz Mitosis


SSA part
Part with conventional dysplasia
Mucinous cancer part

MLH1 stain, normal colon




MLH1
stain



What is the difference between a sessile serrated adenoma and a traditional serrated adenoma?

- Longacre TA, Fenoglio-Preiser CM. Mixed hyperplastic adenomatous polyps/serrated adenomas. A distinct form of colorectal neoplasia. Am J Surg Pathol. 1990 Jun;14(6):524-37. PMID: 2186644.
- Yantiss RK, Oh KY, Chen YT, Redston M, Odze RD. Filiform serrated adenomas: a clinicopathologic and immunophenotypic study of 18 cases. Am J Surg Pathol. 2007 Aug;31(8):1238-45. PMID: 17667549.

Teri Longacre

Cecilia Fenoglio-Preiser

Rhonda Yantiss

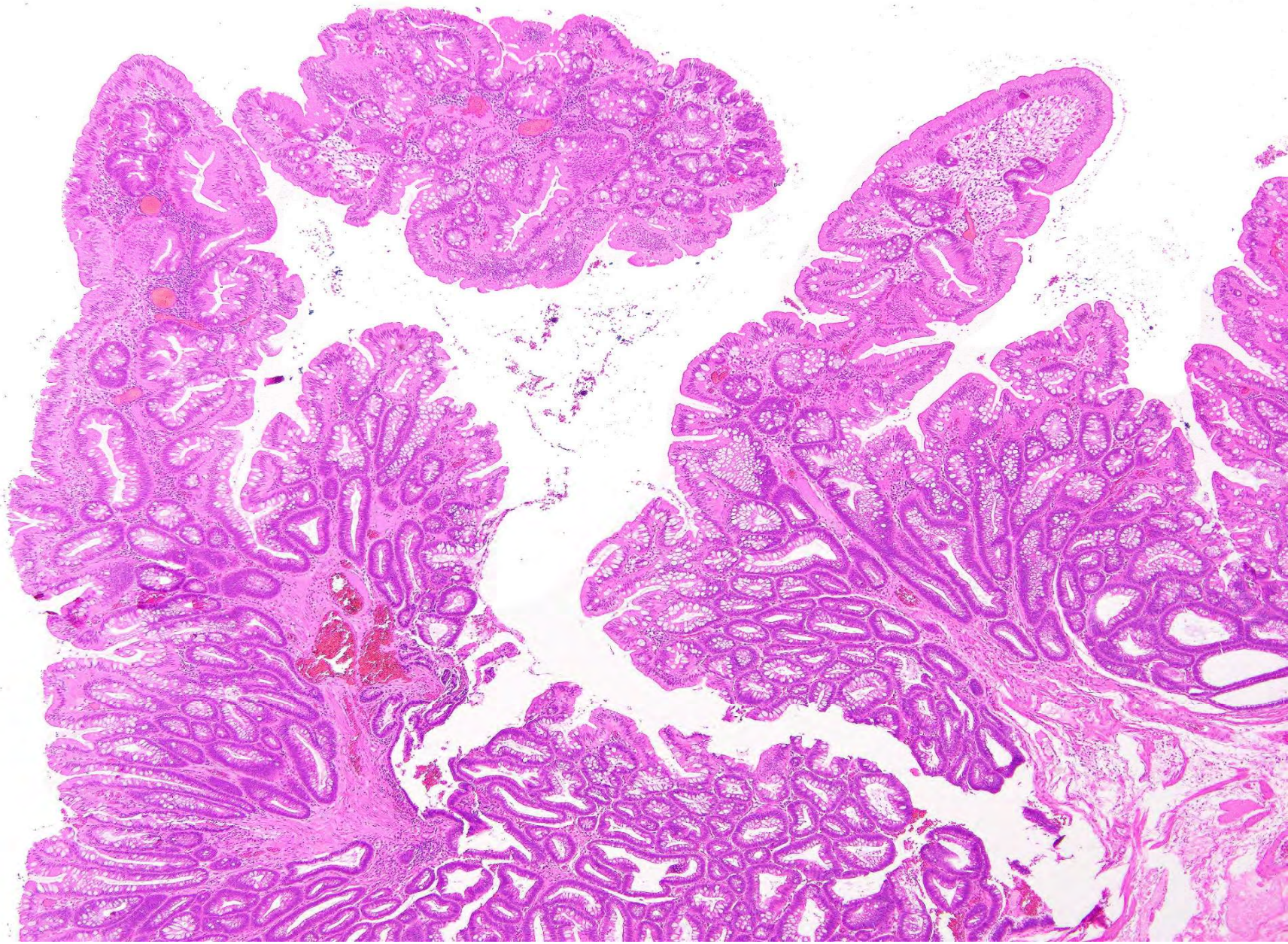
Sessile Serrated Adenoma

- Looks like HP
- Lacks conventional dysplasia
- Right side 70%+

Traditional Serrated Adenoma

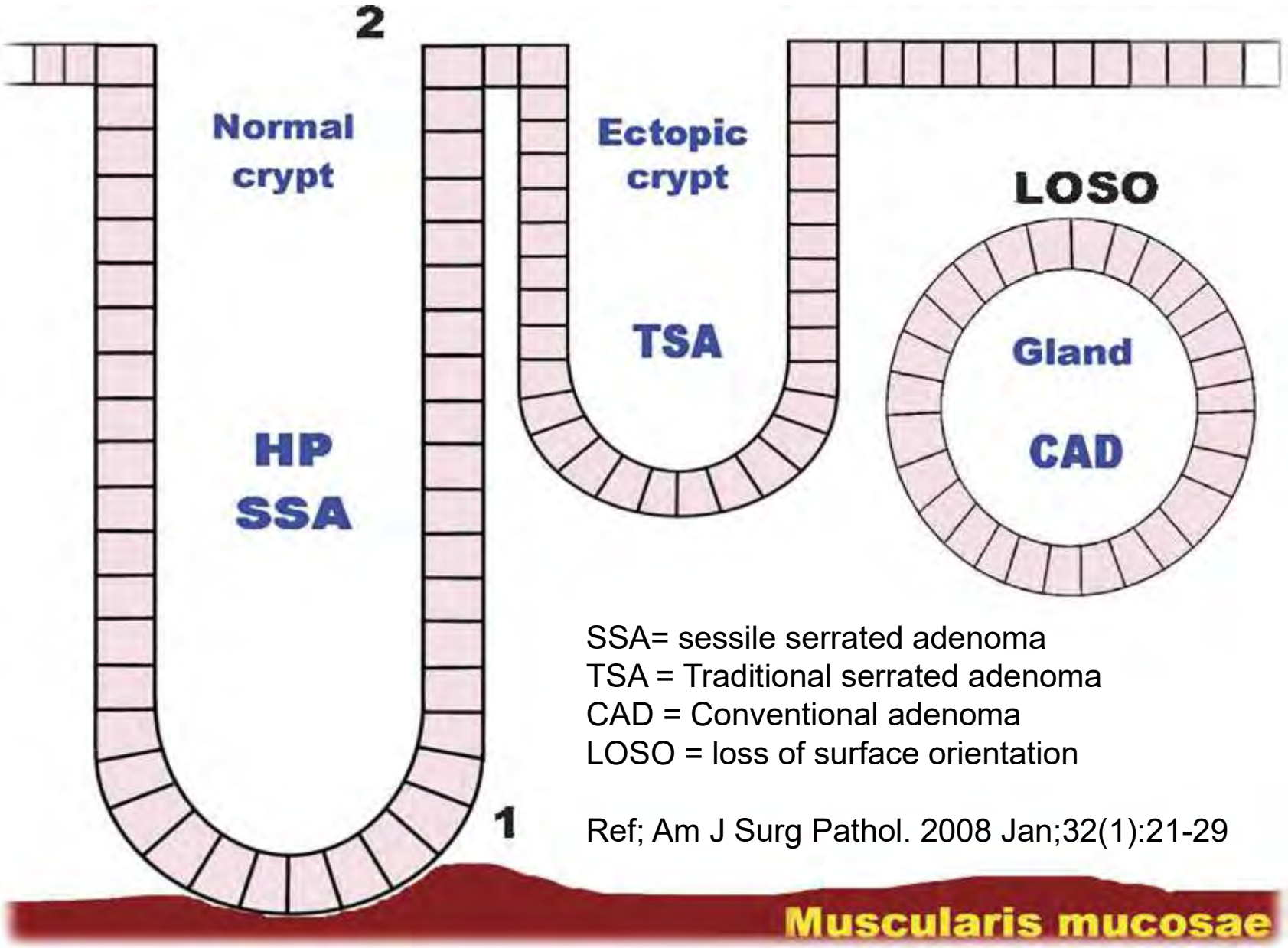
- Has pink cytoplasm and serration
- Has “pencillate” elongated nuclei that are slimmer and less hyperchromatic than those in tubular adenoma
- Left side 70%+

Traditional Serrated Adenoma



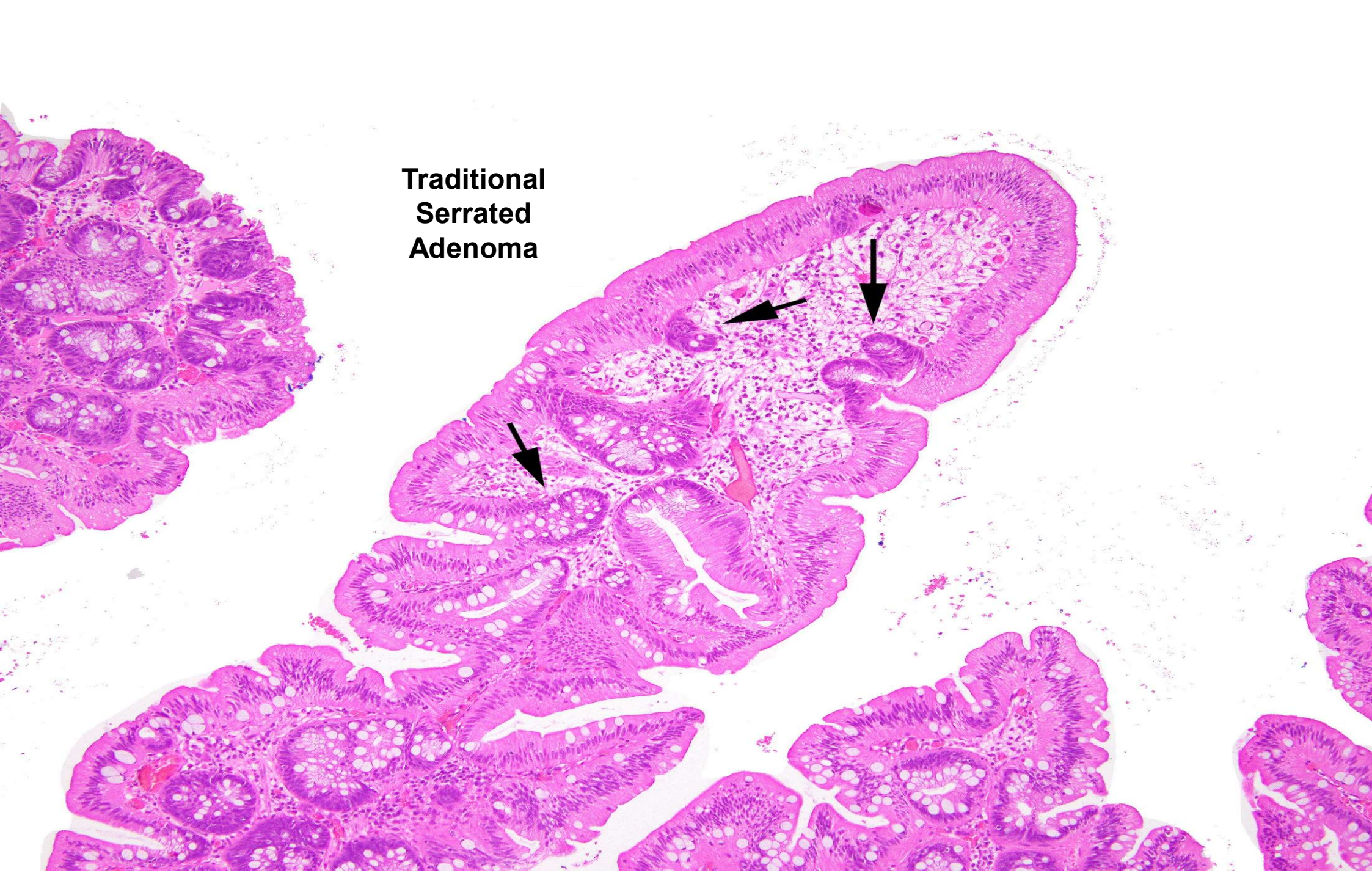
More Torlakovic and Snover

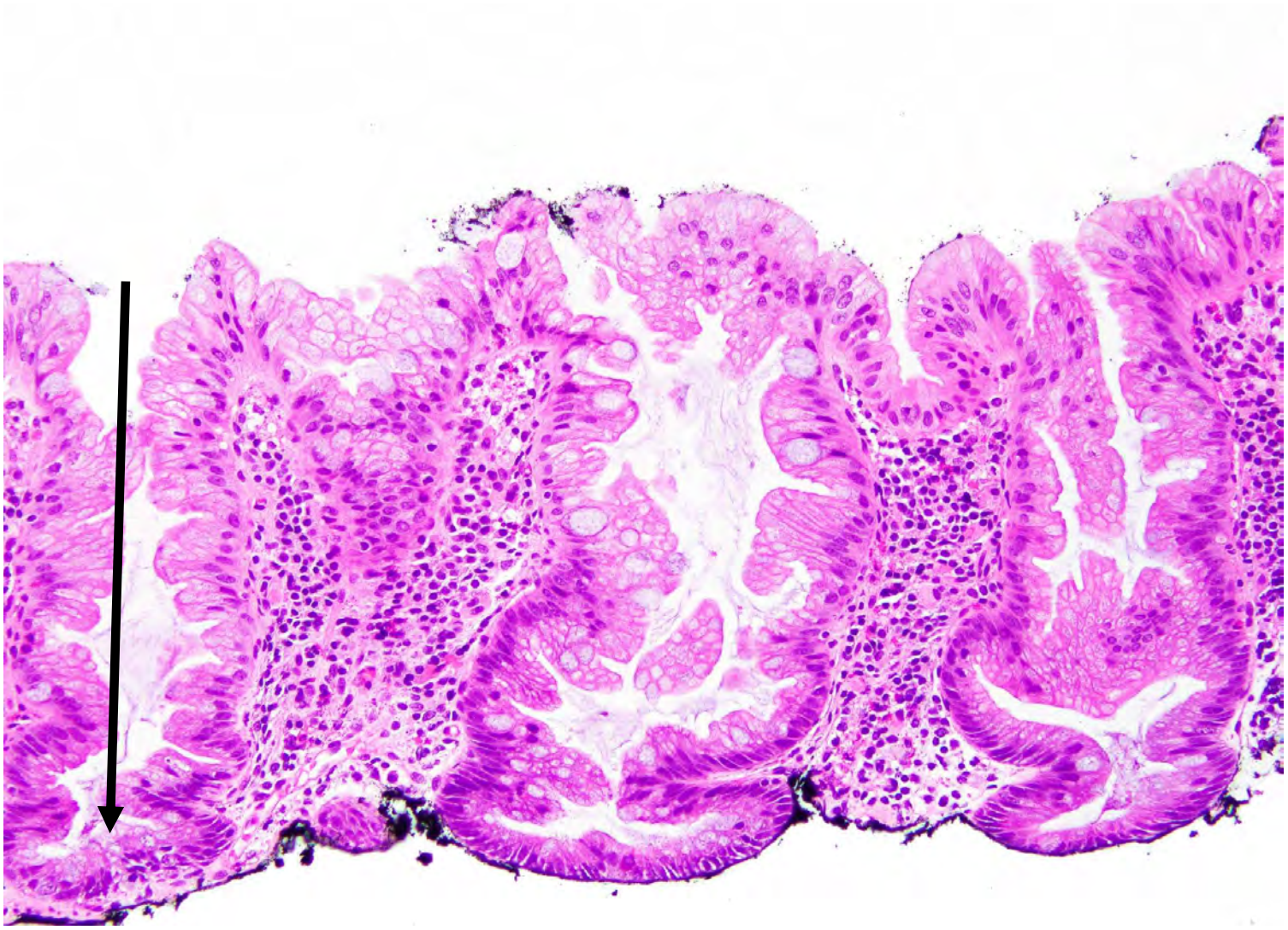
- Characteristic architecture for traditional serrated adenoma (“ectopic crypt formation”) and more features to help in DDX
- Torlakovic EE, Gomez JD, Driman DK, Parfitt JR, Wang C, Benerjee T, Snover DC. Sessile Serrated Adenoma (SSA) vs. Traditional Serrated Adenoma (TSA).Am J Surg Pathol. 2008 Jan;32(1):21-29.



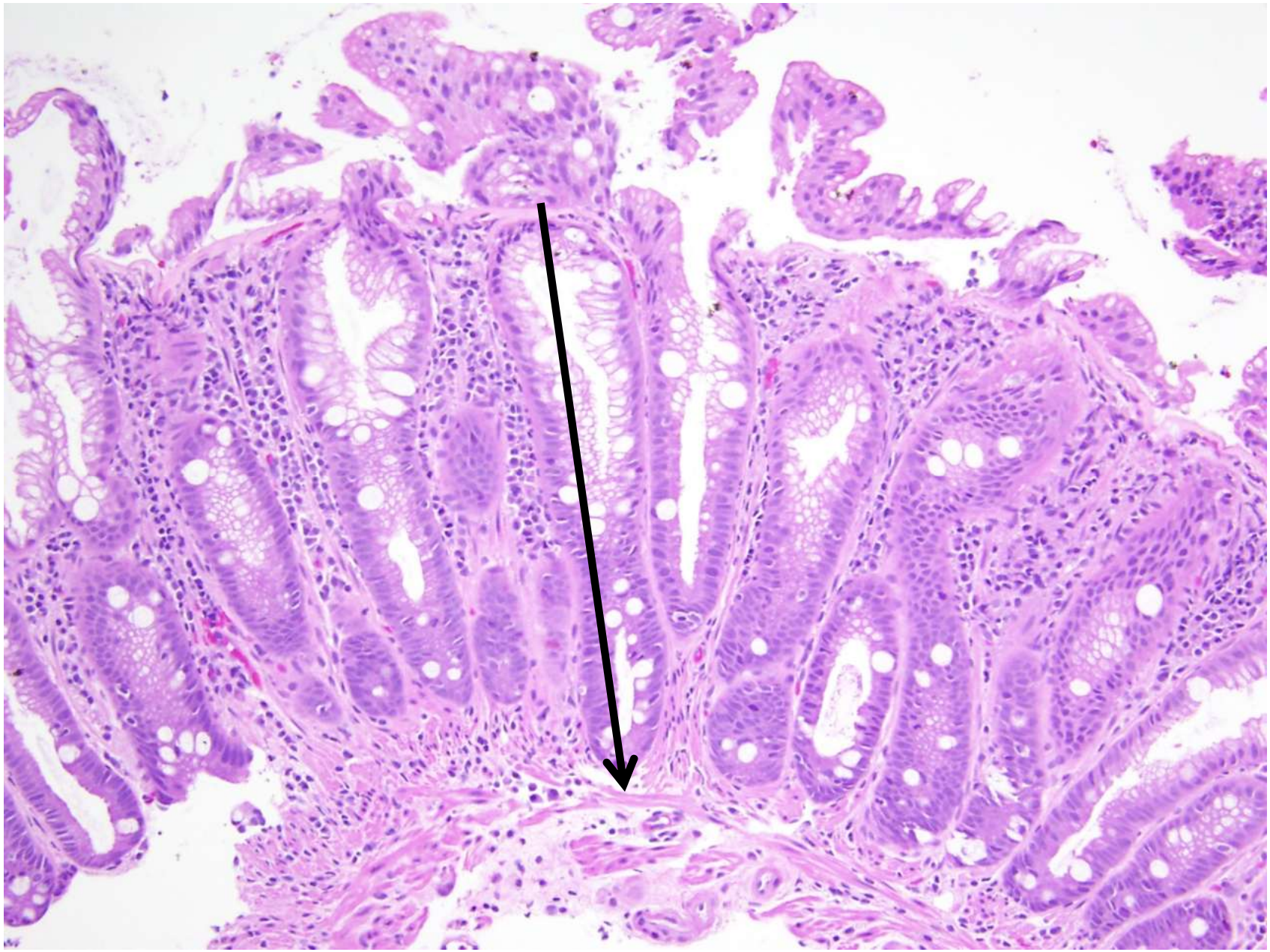
SSA= sessile serrated adenoma
TSA = Traditional serrated adenoma
CAD = Conventional adenoma
LOSO = loss of surface orientation

Ref; Am J Surg Pathol. 2008 Jan;32(1):21-29

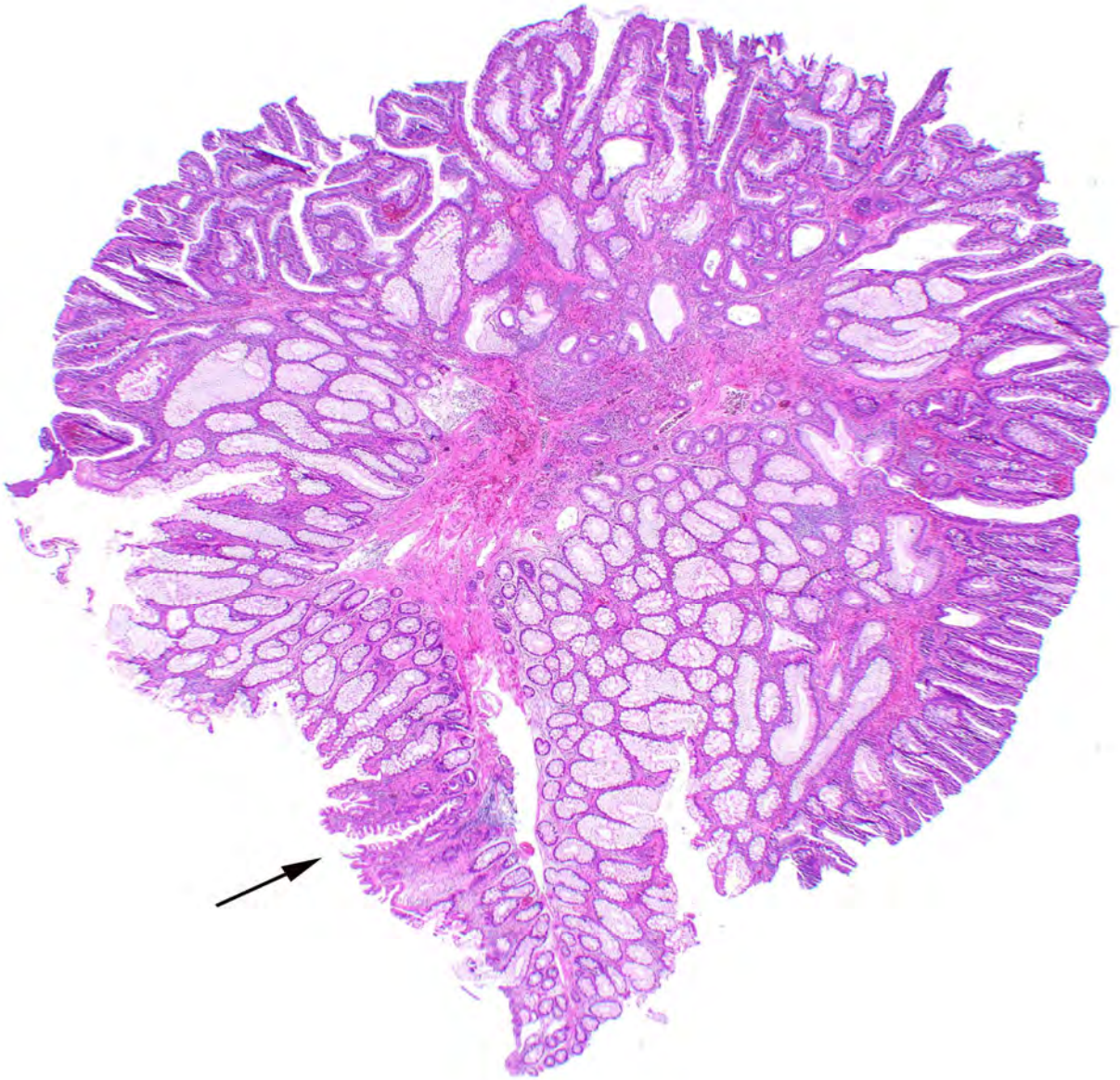

Traditional
Serrated
Adenoma



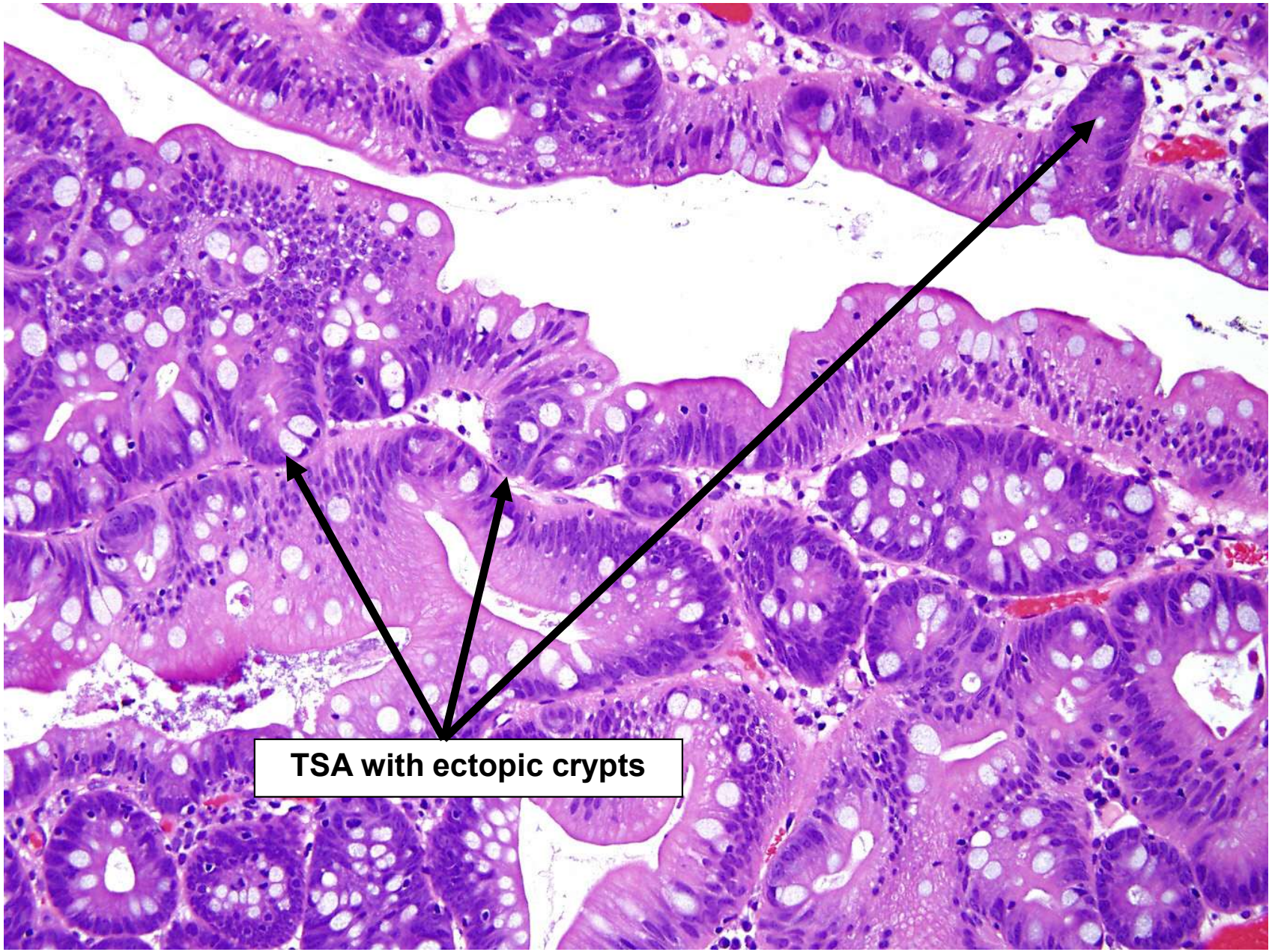
Sessile serrated adenoma — one can make a line from the lumen to the muscularis mucosae in perfectly embedded zones



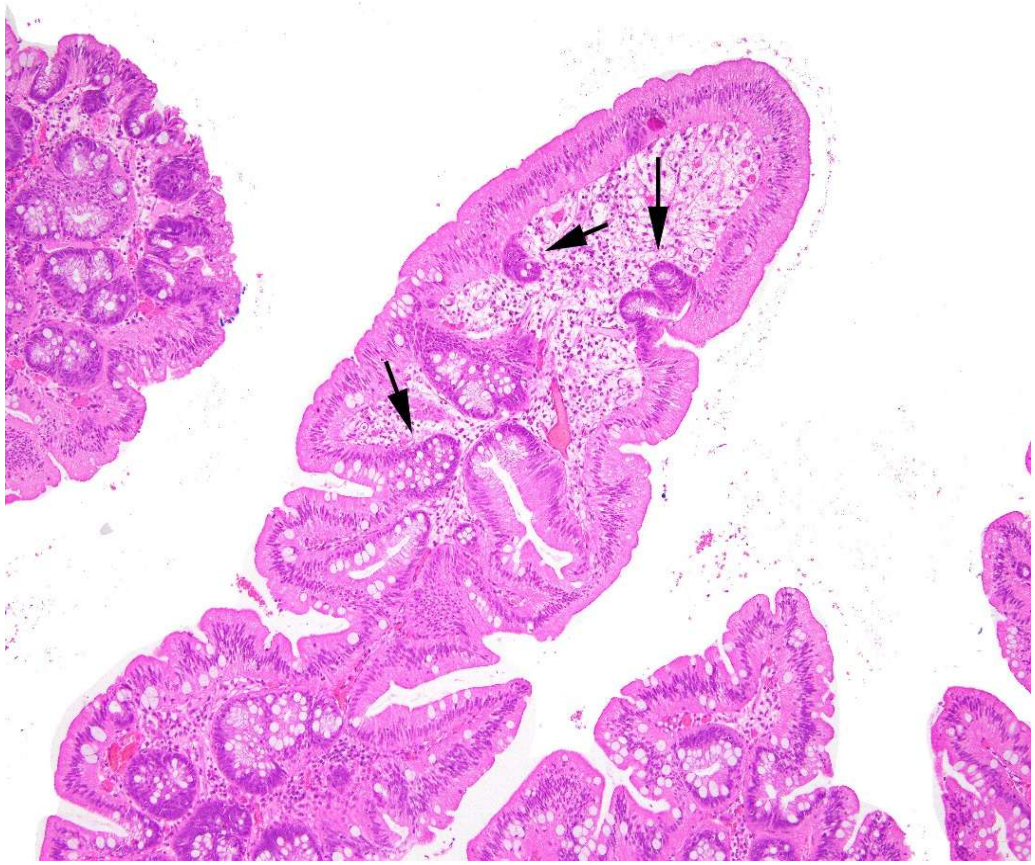
Hyperplastic polyp - one can make a line from the lumen to the muscularis mucosae

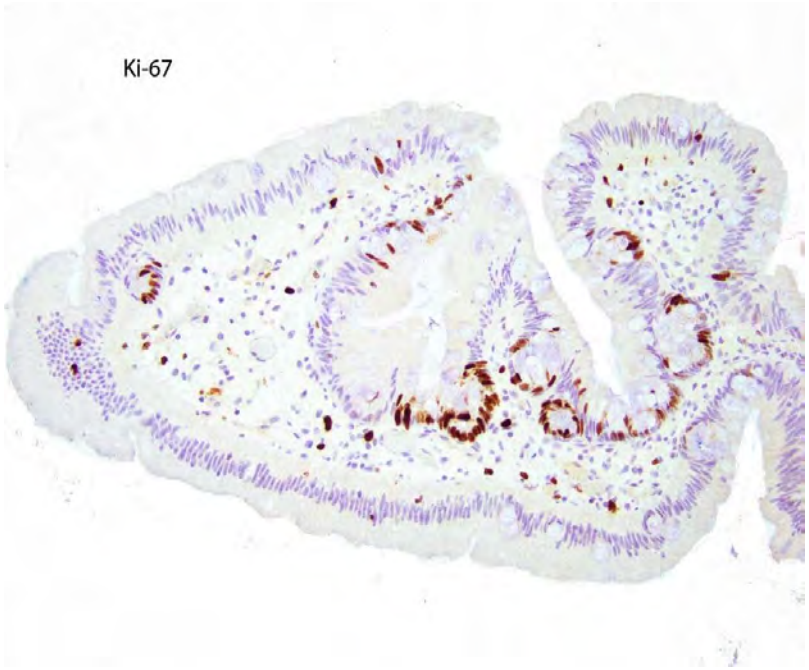


Tubular adenoma – completely disorganized tubules (note the interloper hyperplastic polyp in the stalk with well-aligned architecturally normal crypts)


TSA with ectopic crypts

Proliferation in Traditional Serrated Adenoma



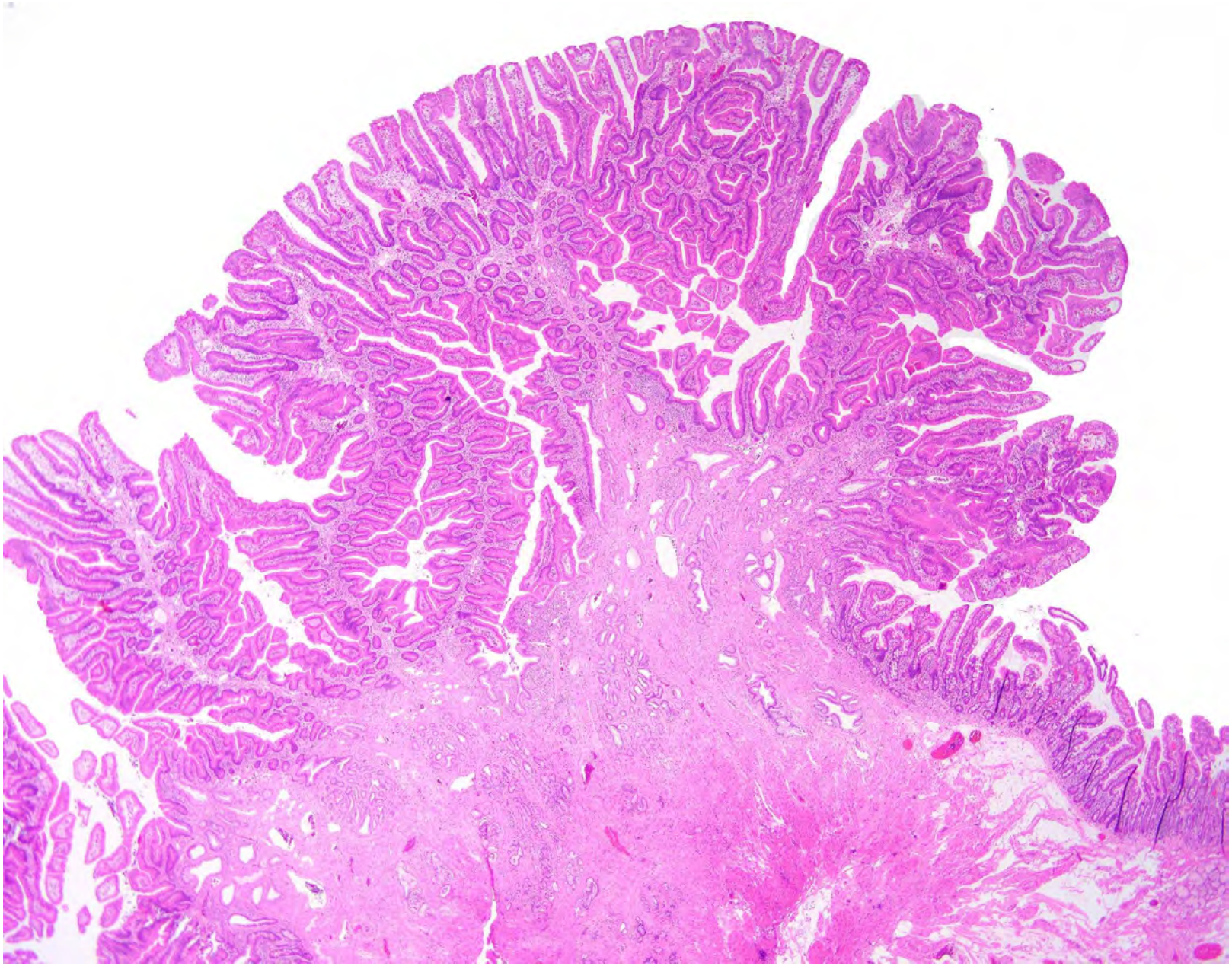


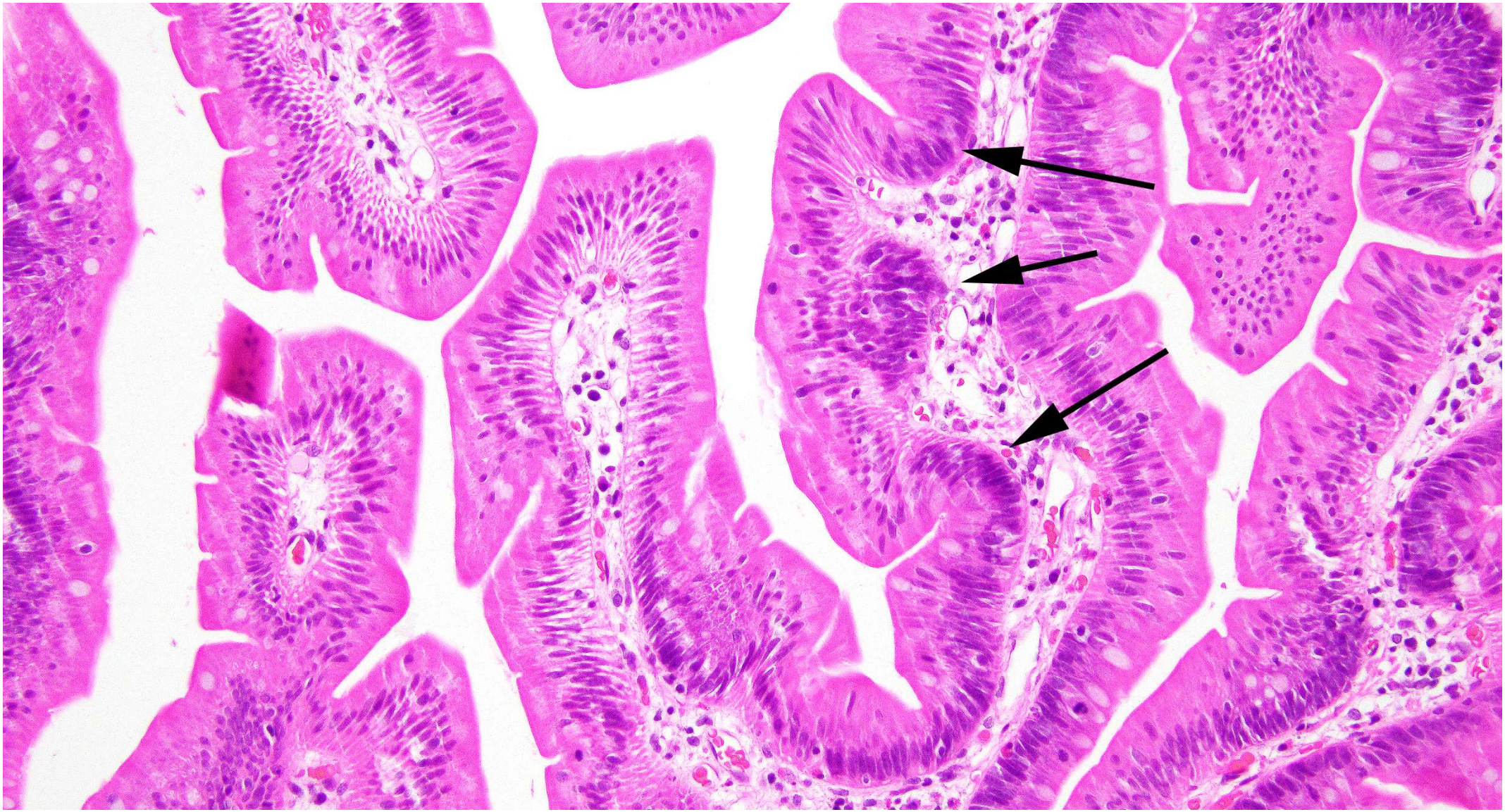
Traditional Serrated Adenoma of Small Bowel

- More common than we have noticed
- Similar molecular profile to that of colorectal lesions
- Sporadic and FAP-associated
- *BRAF*-serrated pathway does not contribute to their pathogenesis

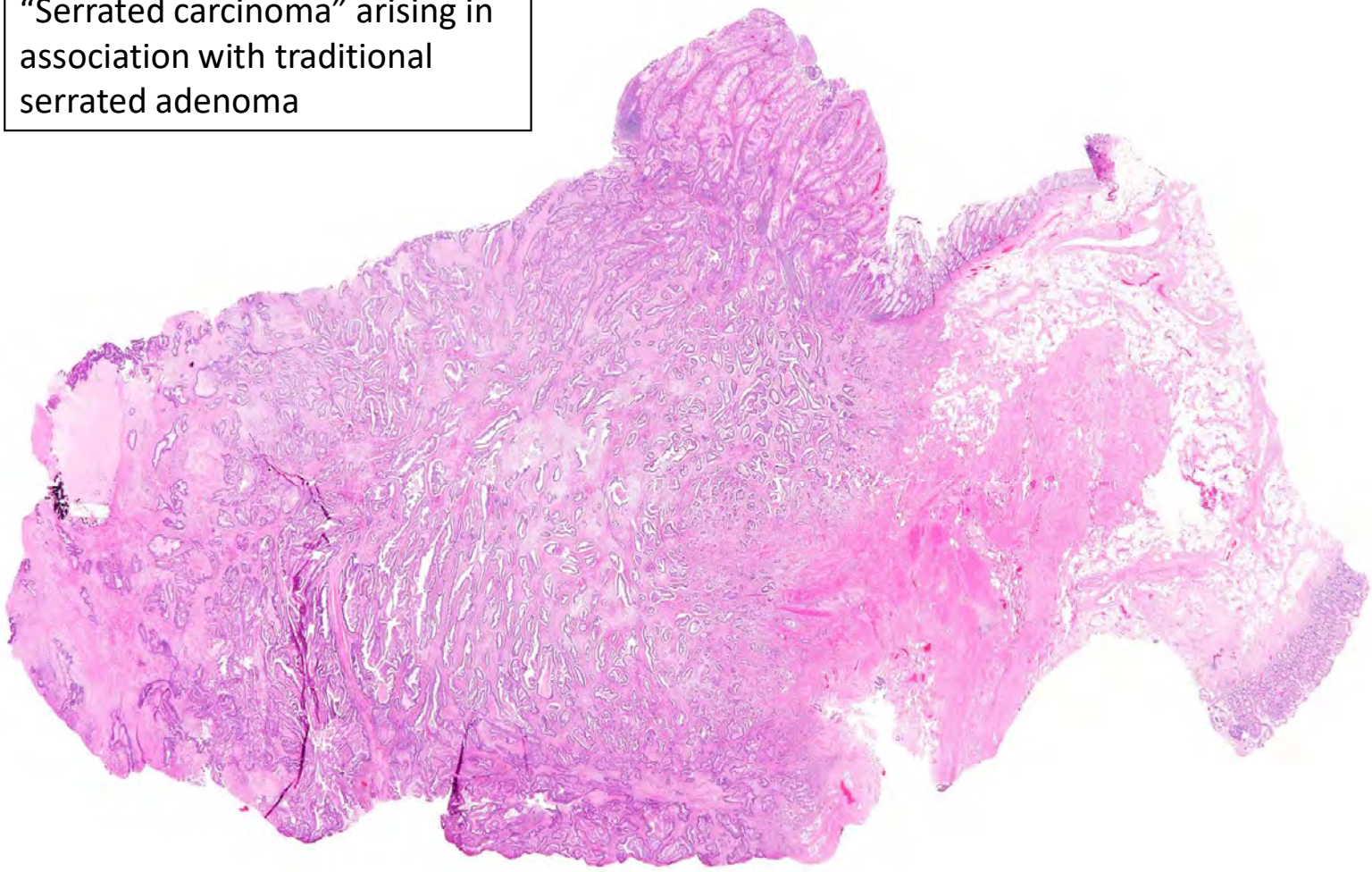
- Rosty C, Campbell C, Clendenning M, Bettington M, Buchanan DD, Brown IS. Do serrated neoplasms of the small intestine represent a distinct entity? Pathological findings and molecular alterations in a series of 13 cases. Histopathology. 2015 Feb;66(3):333-42.
- Alruwaii ZI, Chianchiano P, Larman T, Wilentz A, Wood LD, Montgomery EA. Familial Adenomatous Polyposis-associated Traditional Serrated Adenoma of the Small Intestine: A Clinicopathologic and Molecular Analysis. Am J Surg Pathol. 2021 Dec 1;45(12):1626-1632. PMID: 34232600.

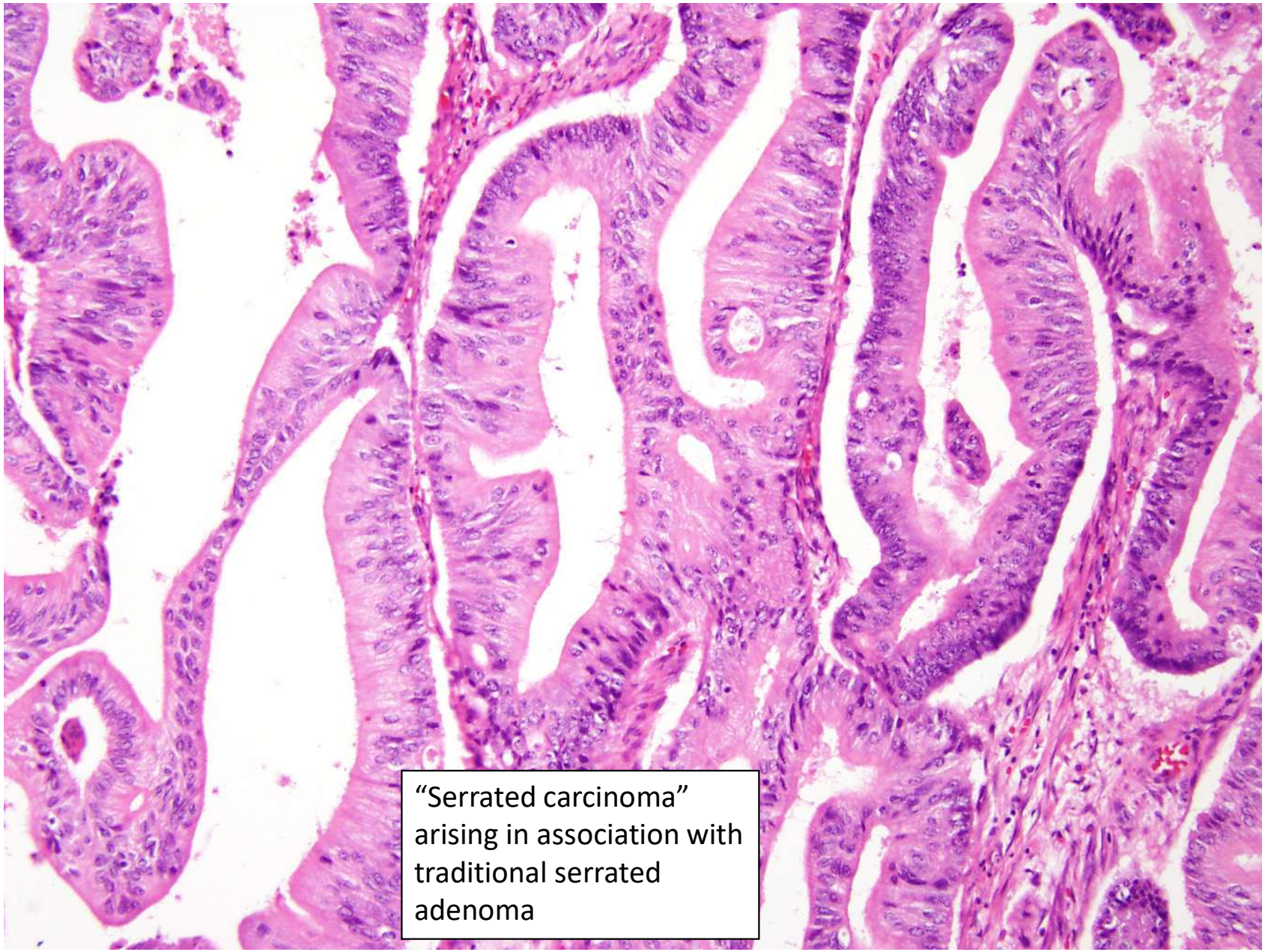
Small intestinal polyp





“Serrated carcinoma” arising in association with traditional serrated adenoma




“Serrated carcinoma” arising in association with traditional serrated adenoma

Genes in TSA

- Mixed bag:
- Both *KRAS* and *BRAF* mutations
- No loss of MLH1 in advanced lesions
- P16 loss in advanced areas (high grade dysplasia) of *BRAF* mutant cases – ? precursor for aggressive *BRAF* mutant MSS cancers

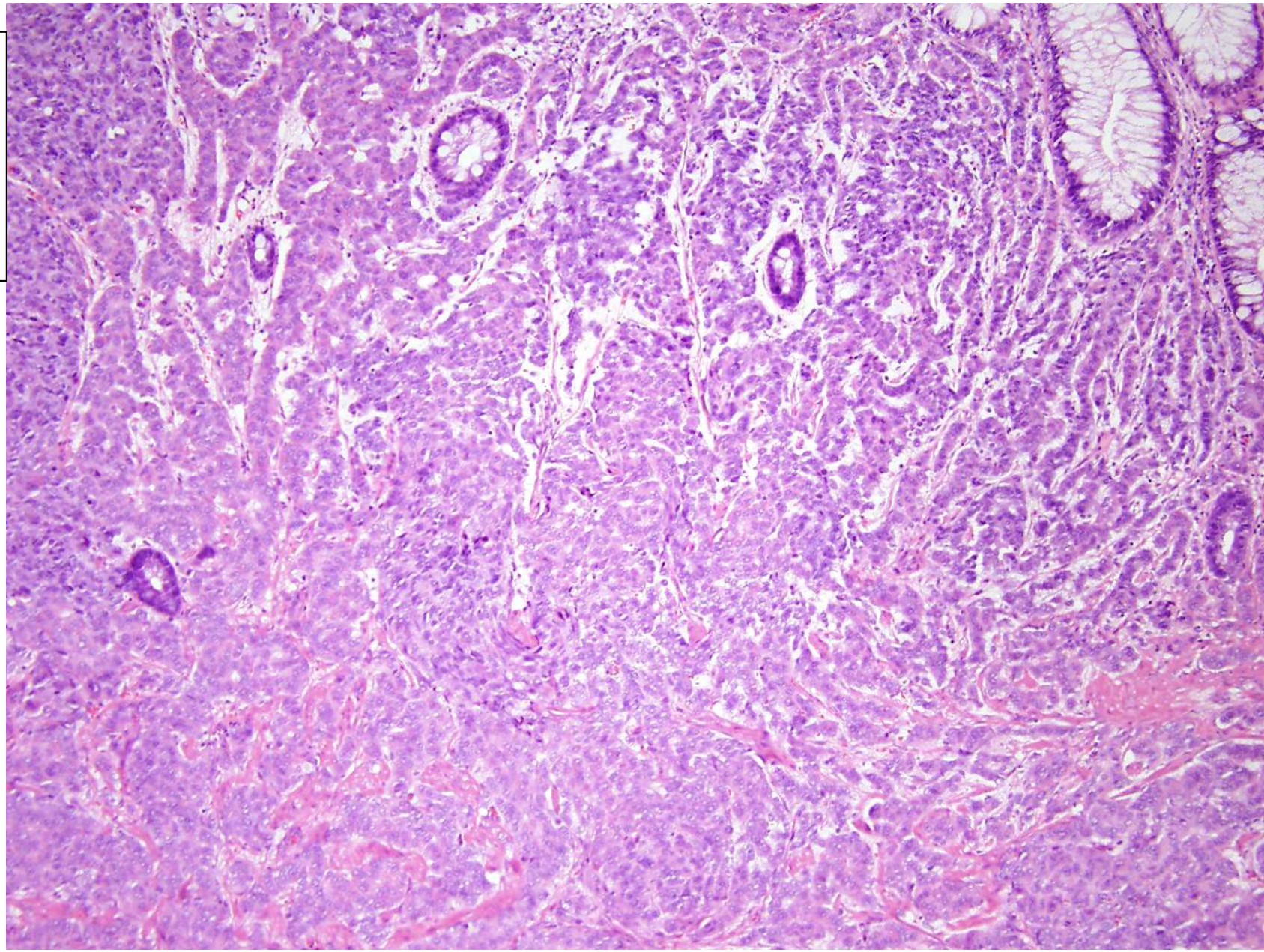
- Bettington ML, Walker NI, Rosty C, Brown IS, Clouston AD, McKeone DM, Pearson SA, Klein K, Leggett BA, Whitehall VLj. A clinicopathological and molecular analysis of 200 traditional serrated adenomas. Mod Pathol. 2015 Mar;28(3):414-27.
- Fu B, Yachida S, Morgan R, Zhong Y, Montgomery EA, Iacobuzio-Donahue CA. Clinicopathologic and genetic characterization of traditional serrated adenomas of the colon. Am J Clin Pathol. 2012 Sep;138(3):356-66.

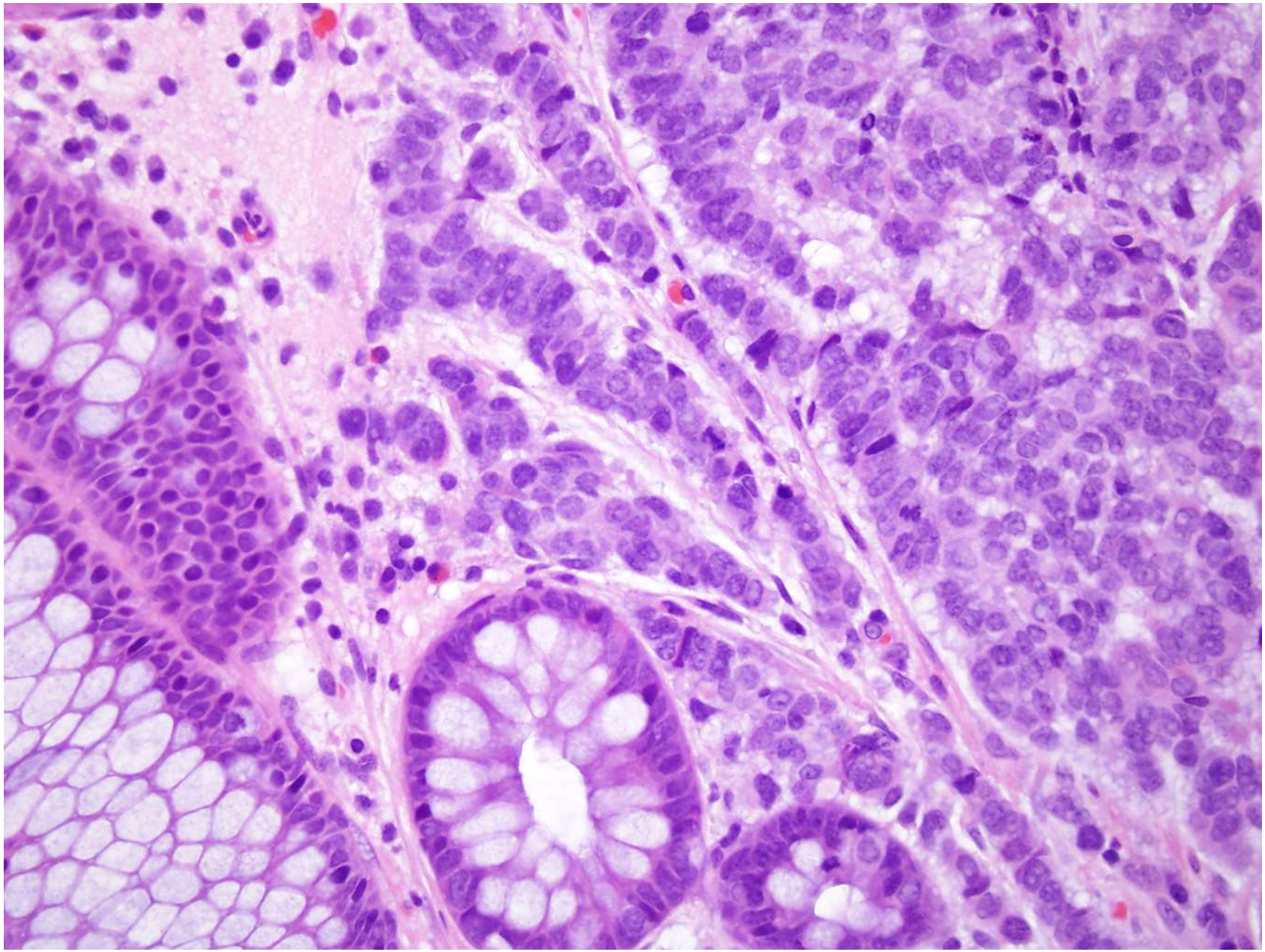
Colorectal well differentiated neuroendocrine tumors

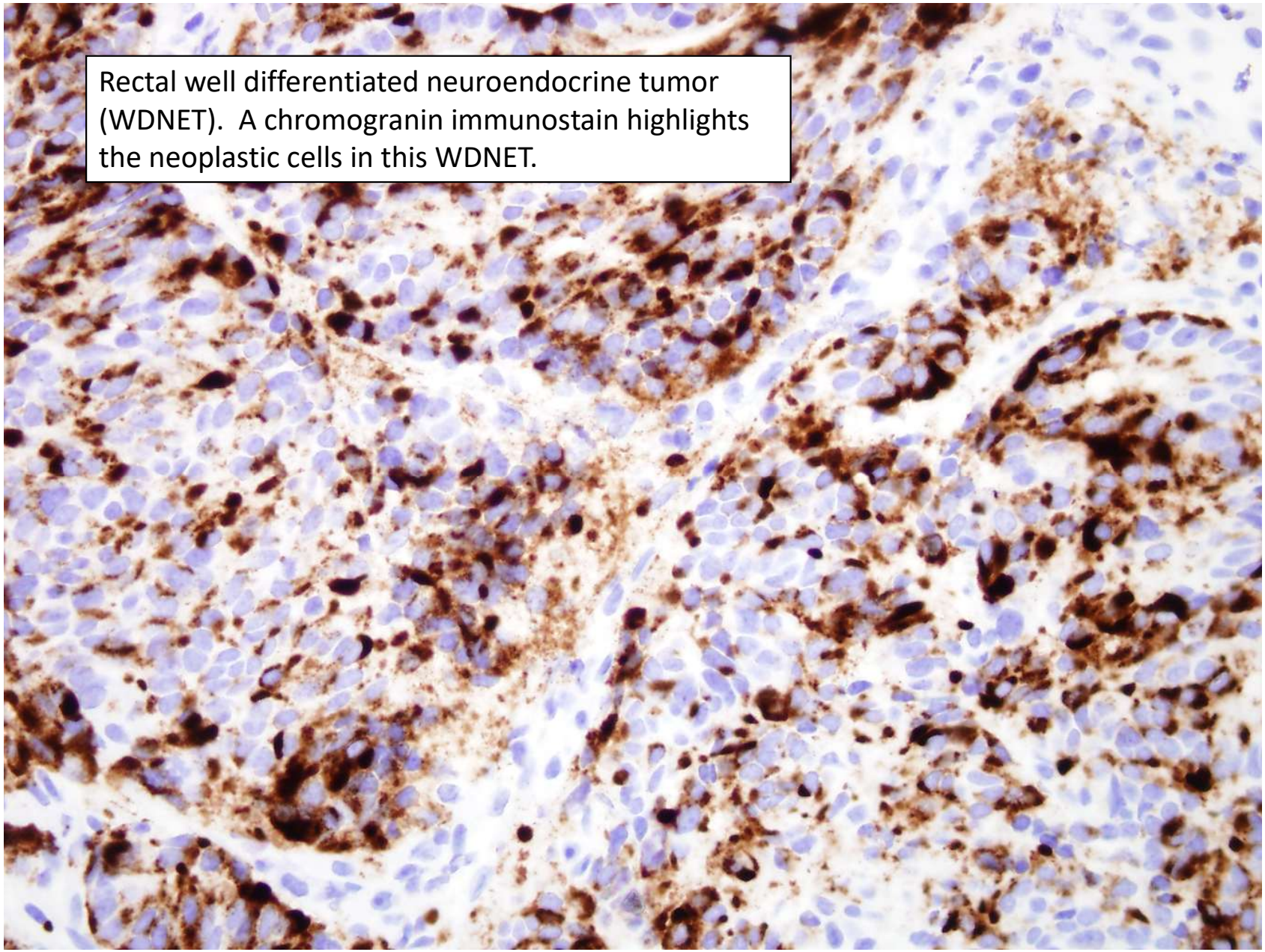
- Most are rectal, small and indolent, with a 5-year survival rate of about 90%.
- Tumor size and muscularis propria invasion are the key predictors of malignant behavior in NETs.
- Rectal WDNETs larger than 2.0 cm or showing locoregional lymph node involvement are managed as per rectal adenocarcinomas
- Small tumors (1-2 cm) confined to the mucosa and submucosa are managed by endoscopic polypectomy.
- Patients with small tumors (1-2 cm) showing muscularis propria invasion but without lymph node metastases on endoscopic ultrasound are managed with transanal excision.
- About (10%) of GI tract NETs arise in the proximal colon (mostly the cecum); larger, more aggressive tumors.
- L cell types are considered indolent (glucagon like peptide (GLP) or PP/PYY producing tumors)
- Those that express chromogranin (rather than synaptophysin only) are slightly more aggressive.

Kim J, Kim JY, Oh EH, Yoo C, Park IJ, Yang DH, Ryoo BY, Ryu JS, Hong SM. Chromogranin A Expression in Rectal Neuroendocrine Tumors Is Associated With More Aggressive Clinical Behavior and a Poorer Prognosis. Am J Surg Pathol. 2020 Nov;44(11):1496-1505. PMID: 32735108.

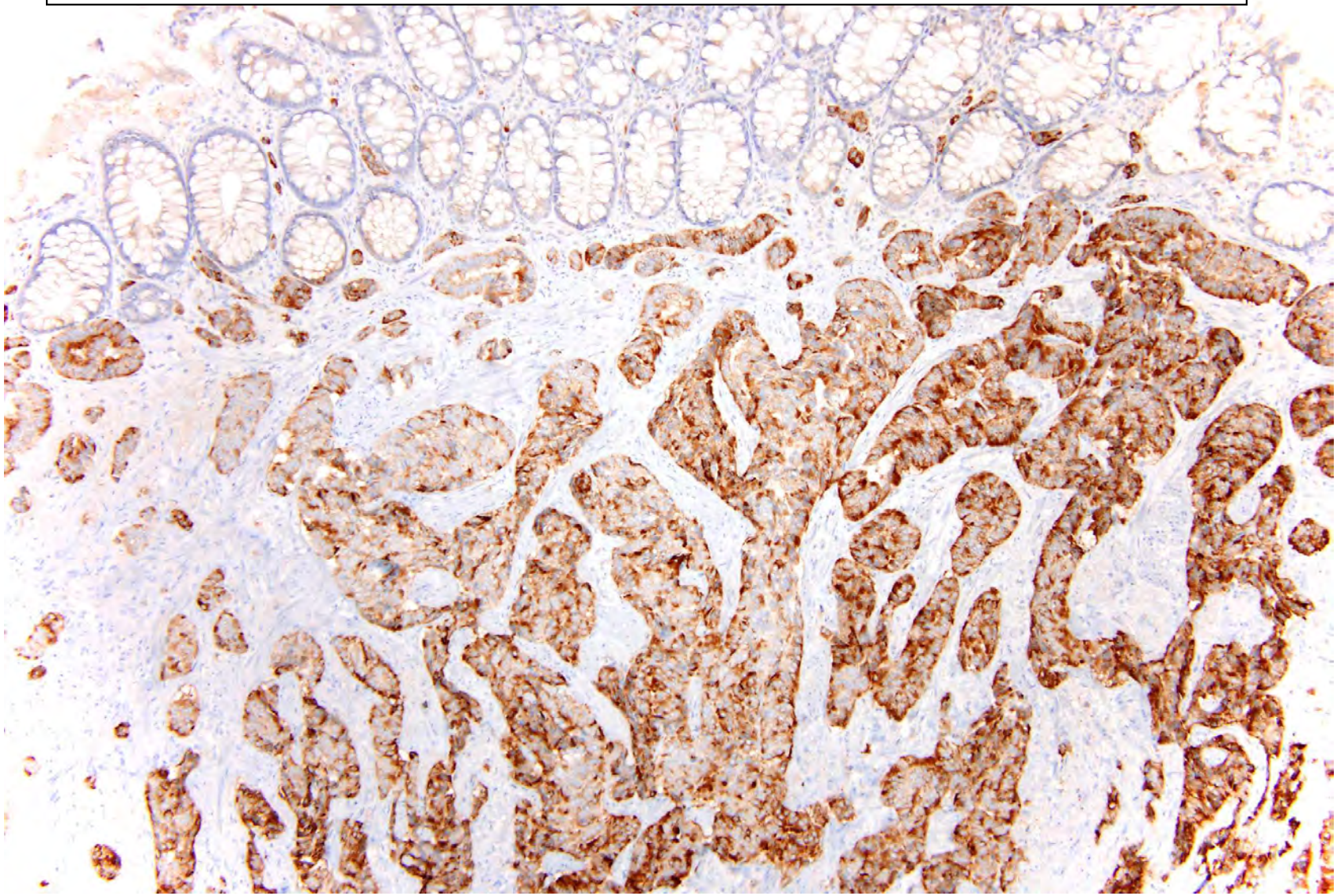
Rectal well differentiated neuroendocrine (carcinoid) tumor (WDNET). The tumor grows in cords, similar to neuroendocrine neoplasms in other organs.






Rectal well differentiated neuroendocrine tumor (WDNET). A chromogranin immunostain highlights the neoplastic cells in this WDNET.

Rectal well differentiated neuroendocrine tumor (WDNET). This particular example was immunoreactive with prostatic acid phosphatase (PAP), a potential pitfall when rectal invasion from known prostatic carcinoma is a consideration.



Malignant Polyps- Background

- When carcinomas arise in adenomas of the colon, invasion of the lamina propria is considered biologically equivalent to high-grade dysplasia (since the lamina propria of the colon is believed to lack lymphatic access, "intramucosal carcinoma" in the colon is thus staged as Tis rather than T1), so some observers do not report this invasion either.

- We report intramucosal carcinoma in adenomas as such and always include a note stating that it is biologically equivalent to high-grade dysplasia (Tis) and that complete polypectomy should be adequate management.

- We report our findings this way in case additional sampling discloses deeper invasion.

Background

- Polyps containing invasive carcinoma comprise about 5% of all adenomas.

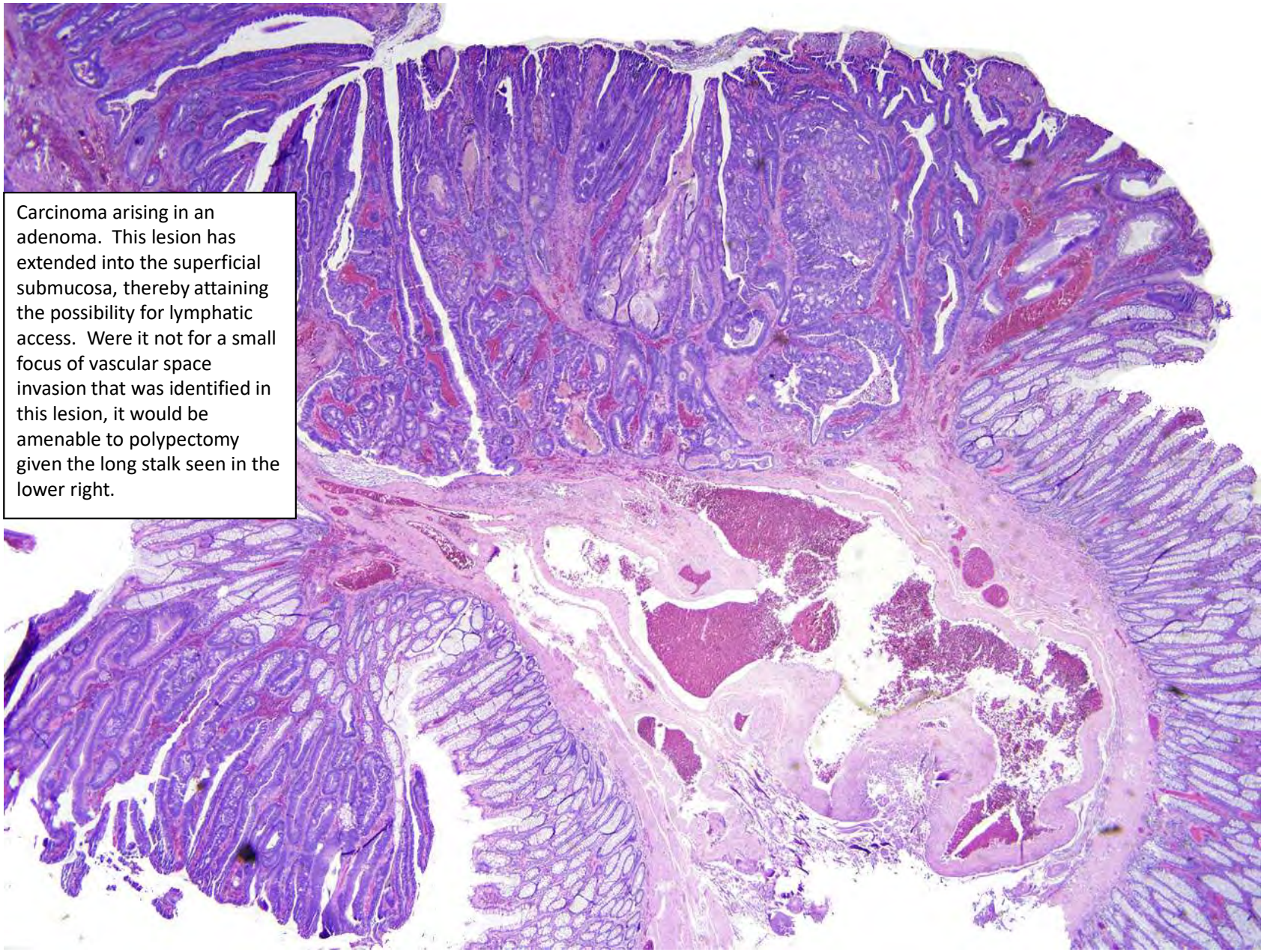
- The chance that any given adenoma contains invasive carcinoma increases with polyp size, and the incidence of invasive carcinoma in adenomas >2 cm ranges from 35% to 53%.

What most US colleagues report in a malignant polyp

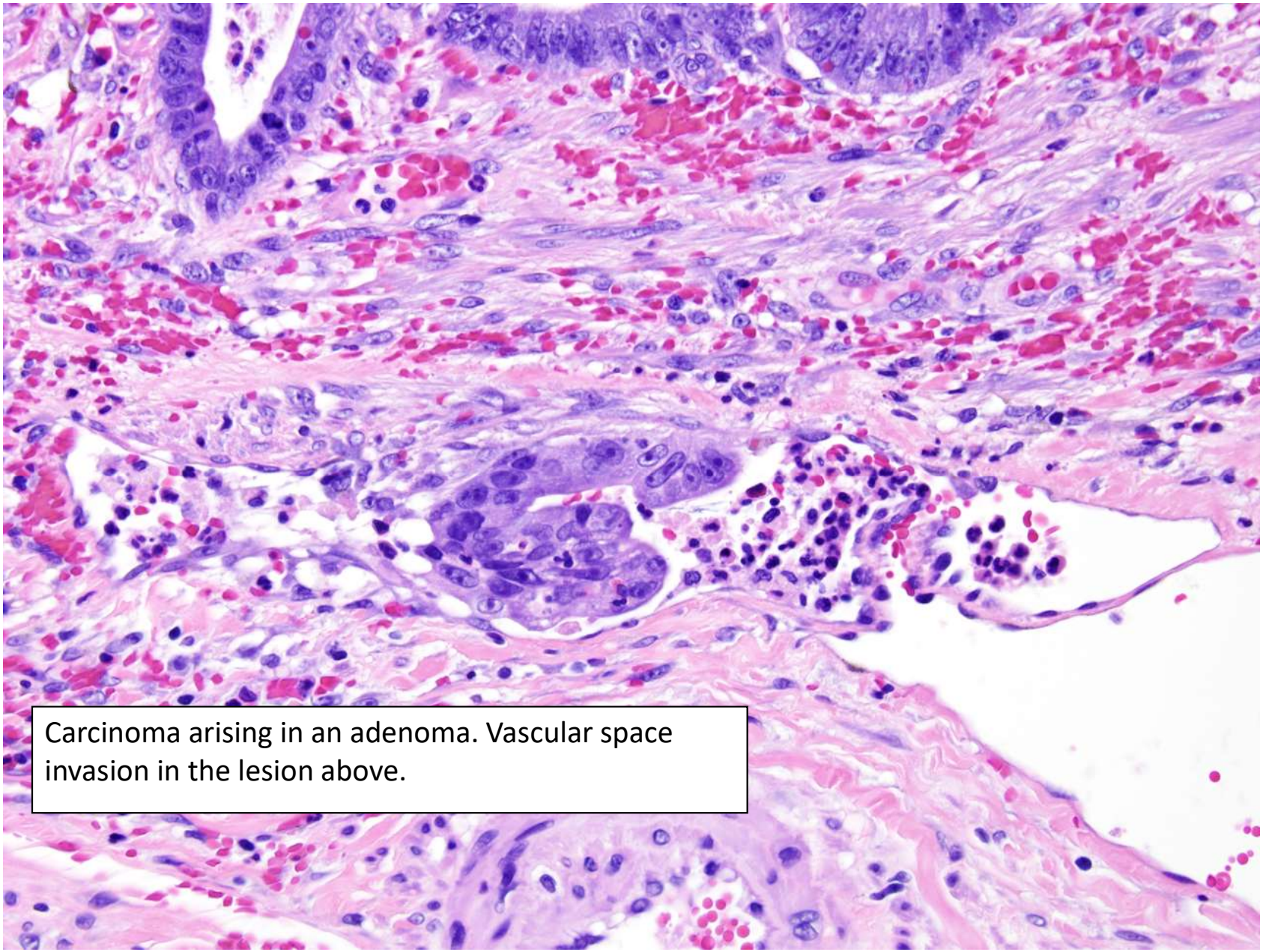
- Whether there is a poorly differentiated component
- Whether there is vascular space invasion
- Whether the polyp is out (usually we want to see a clearance of 2mm or more.)

In the less lazy parts of the world

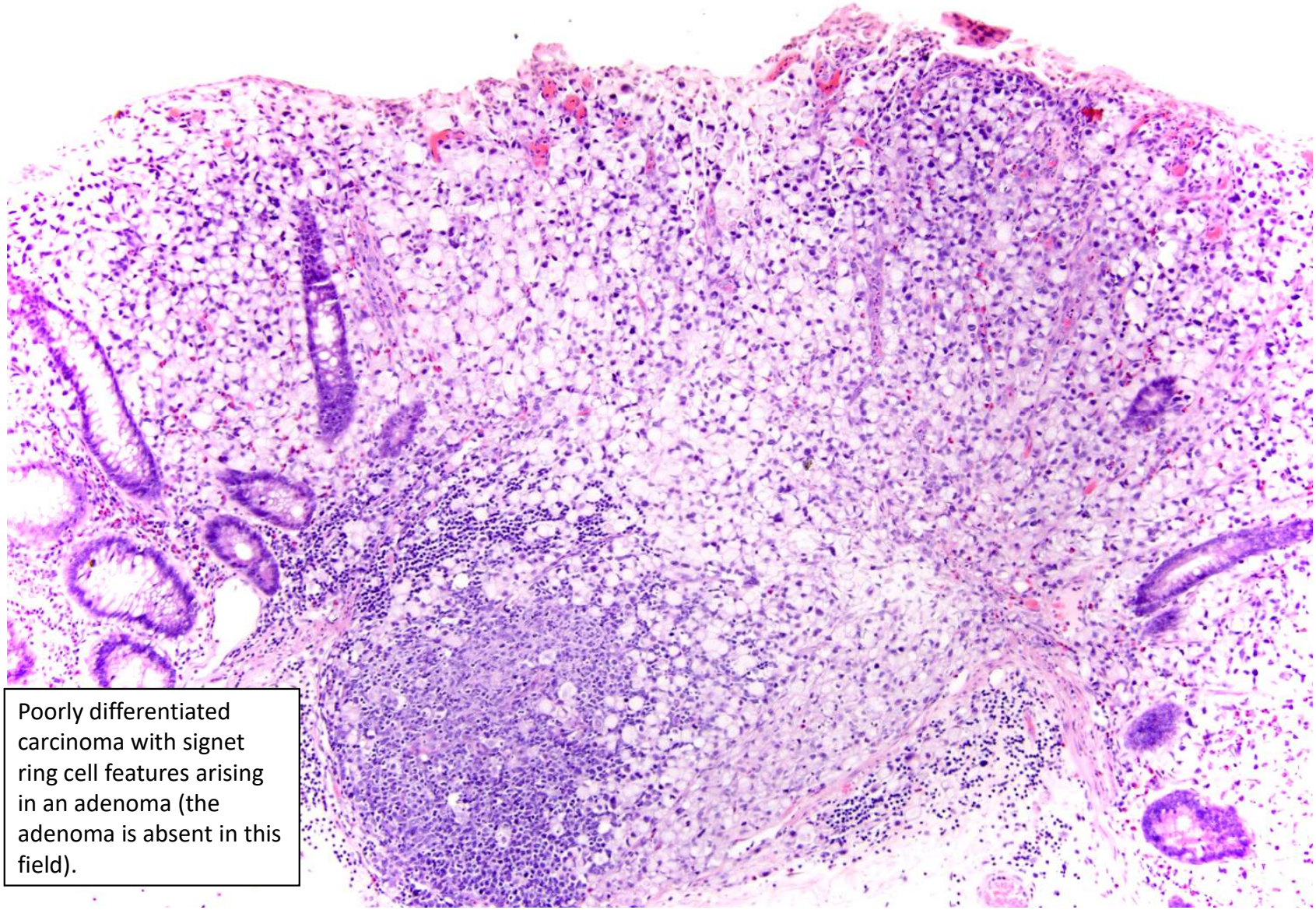
- Polyp configuration (as if the endoscopist did not know)
- Haggitt or Kikuchi level of invasion
- Depth and width of invasion
- Histologic grade
- Vascular invasion
- Tumor budding
- Status of excision margins (1 mm suggested as the “cutoff point”)



Carcinoma arising in an adenoma. This lesion has extended into the superficial submucosa, thereby attaining the possibility for lymphatic access. Were it not for a small focus of vascular space invasion that was identified in this lesion, it would be amenable to polypectomy given the long stalk seen in the lower right.



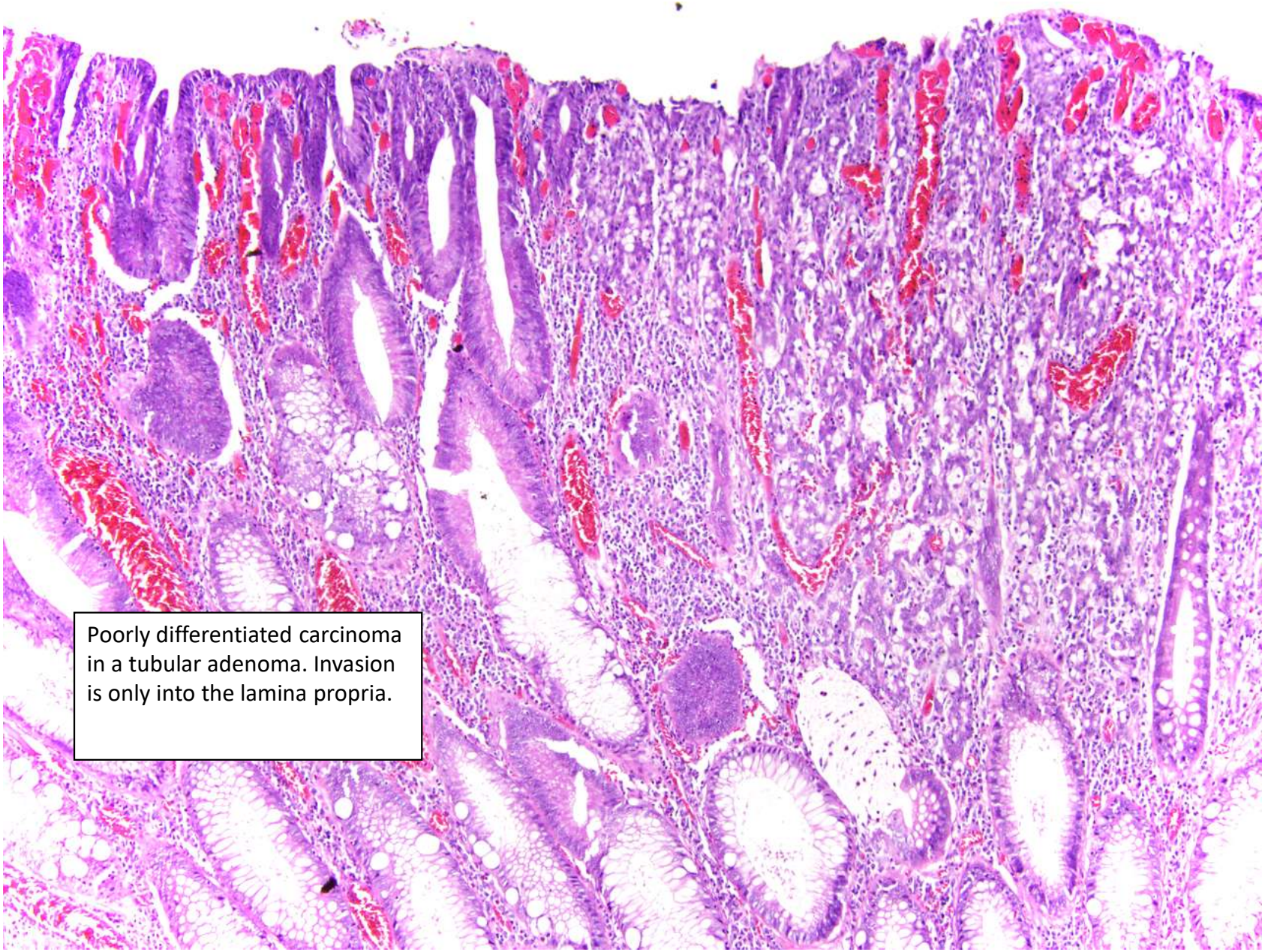
Carcinoma arising in an adenoma. Vascular space invasion in the lesion above.

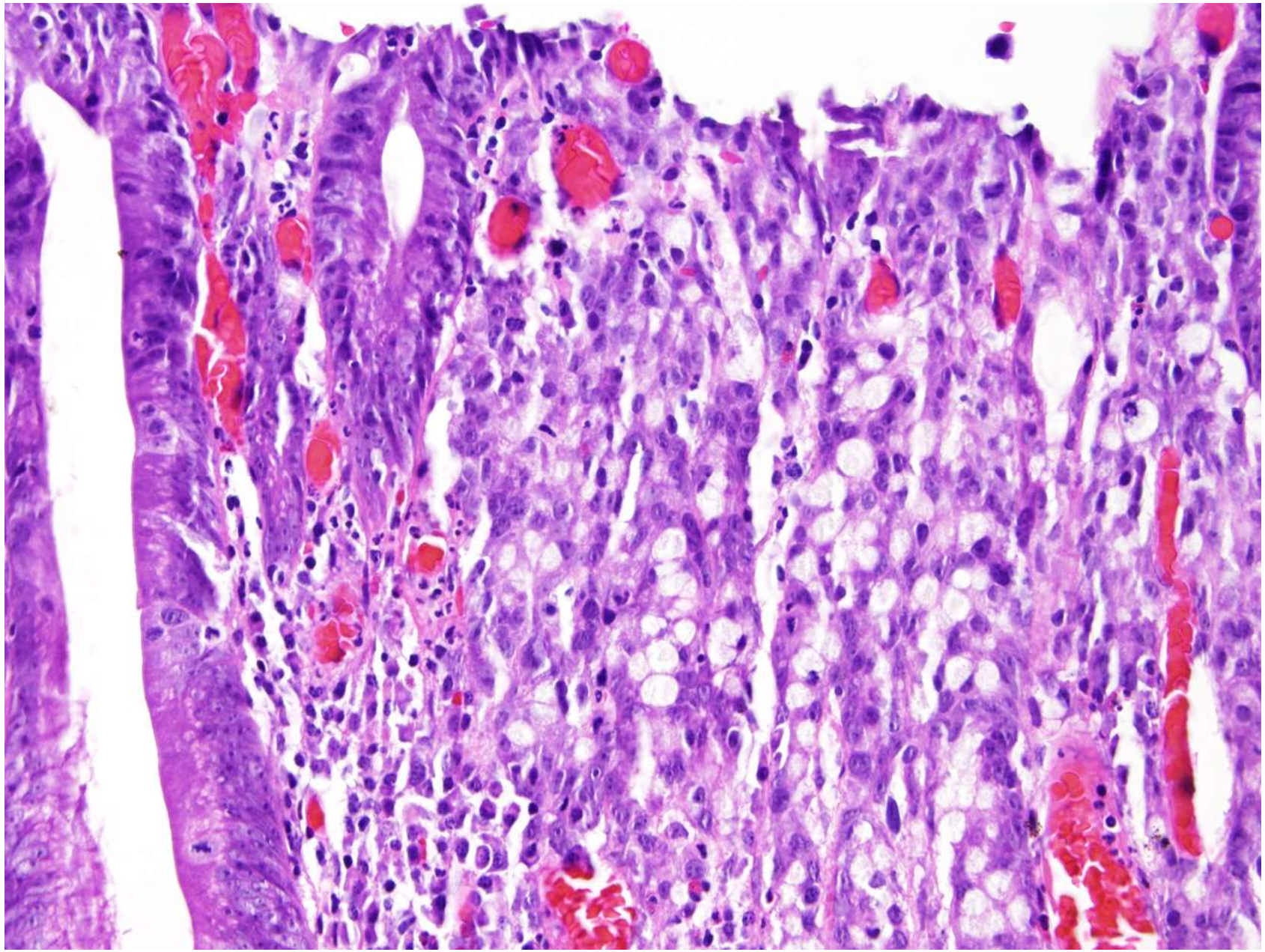


Poorly differentiated carcinoma with signet ring cell features arising in an adenoma (the adenoma is absent in this field).

Invasion into the lamina propria is always Tis?

- What about poorly differentiated carcinoma with invasion restricted to lamina propria
- Rarely encountered presumably because such lesions quickly invade into the submucosa


Poorly differentiated carcinoma in a tubular adenoma. Invasion is only into the lamina propria.

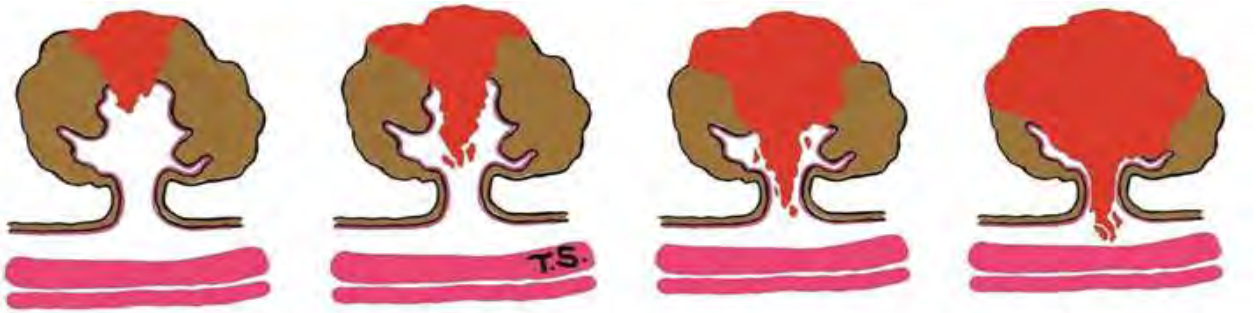


Can lamina propria invasion of poorly differentiated carcinoma be managed conservatively?

- Lewin MR, Fenton H, Burkart AL, Sheridan T, Abu-Alfa AK, Montgomery EA. Poorly differentiated colorectal carcinoma with invasion restricted to lamina propria (intramucosal carcinoma): a follow-up study of 15 cases. *Am J Surg Pathol.* Dec 2007;31(12):1882-1886.
- Shia J, Klimstra DS. Intramucosal poorly differentiated colorectal carcinoma: can it be managed conservatively? *Am J Surg Pathol.* Oct 2008;32(10):1586-1588; author reply 1588-1589.
- ANSWER – CASE BY CASE BASIS

Back to the basics of malignant polyps

Substaging pT1



Level 1:
invasion of the submucosa but limited to the head of the polyp

Level 2:
invasion extending into the neck of polyp

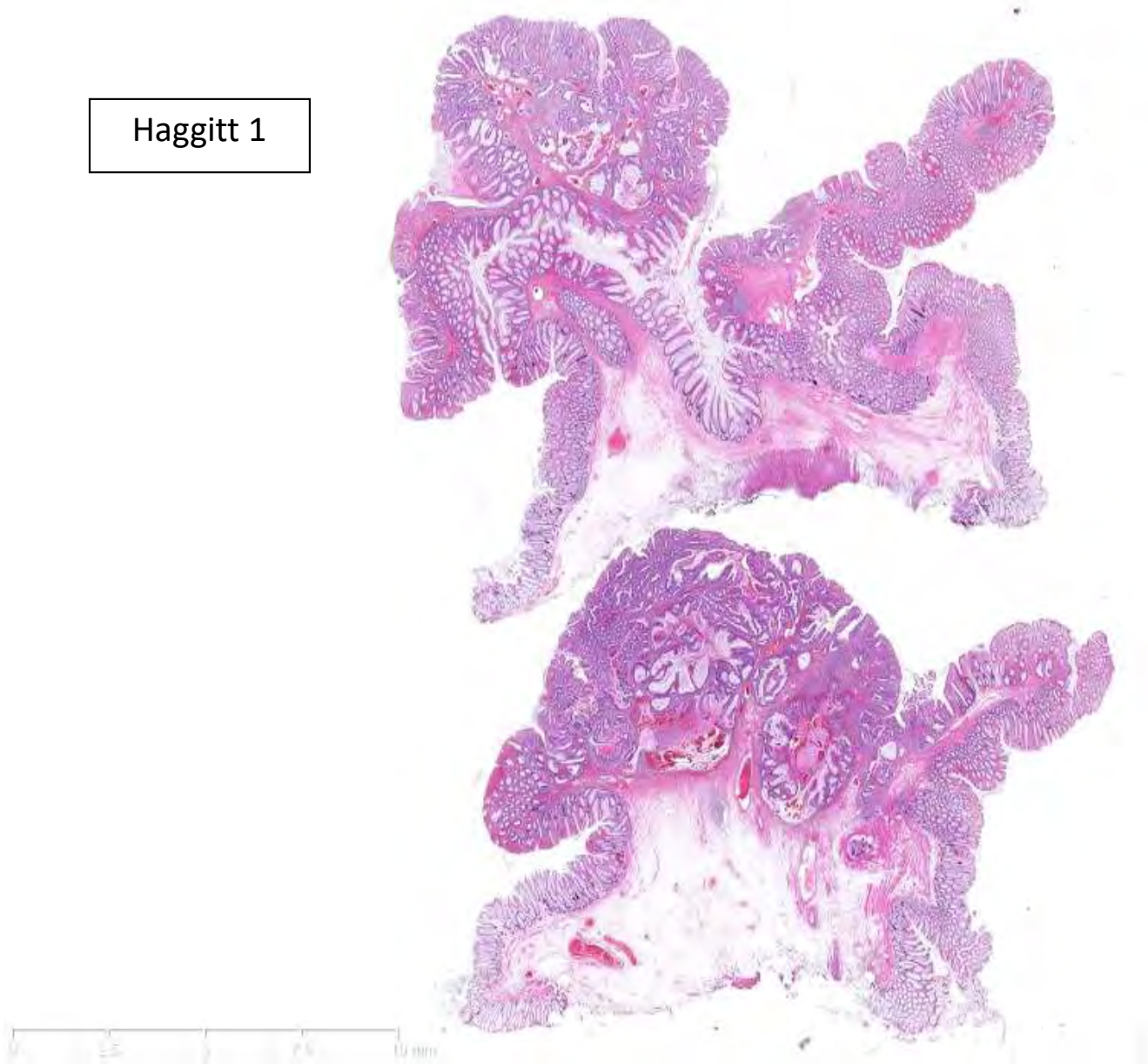
Level 3:
invasion into any part of the stalk

Level 4:
invasion beyond the stalk but above the muscularis propria

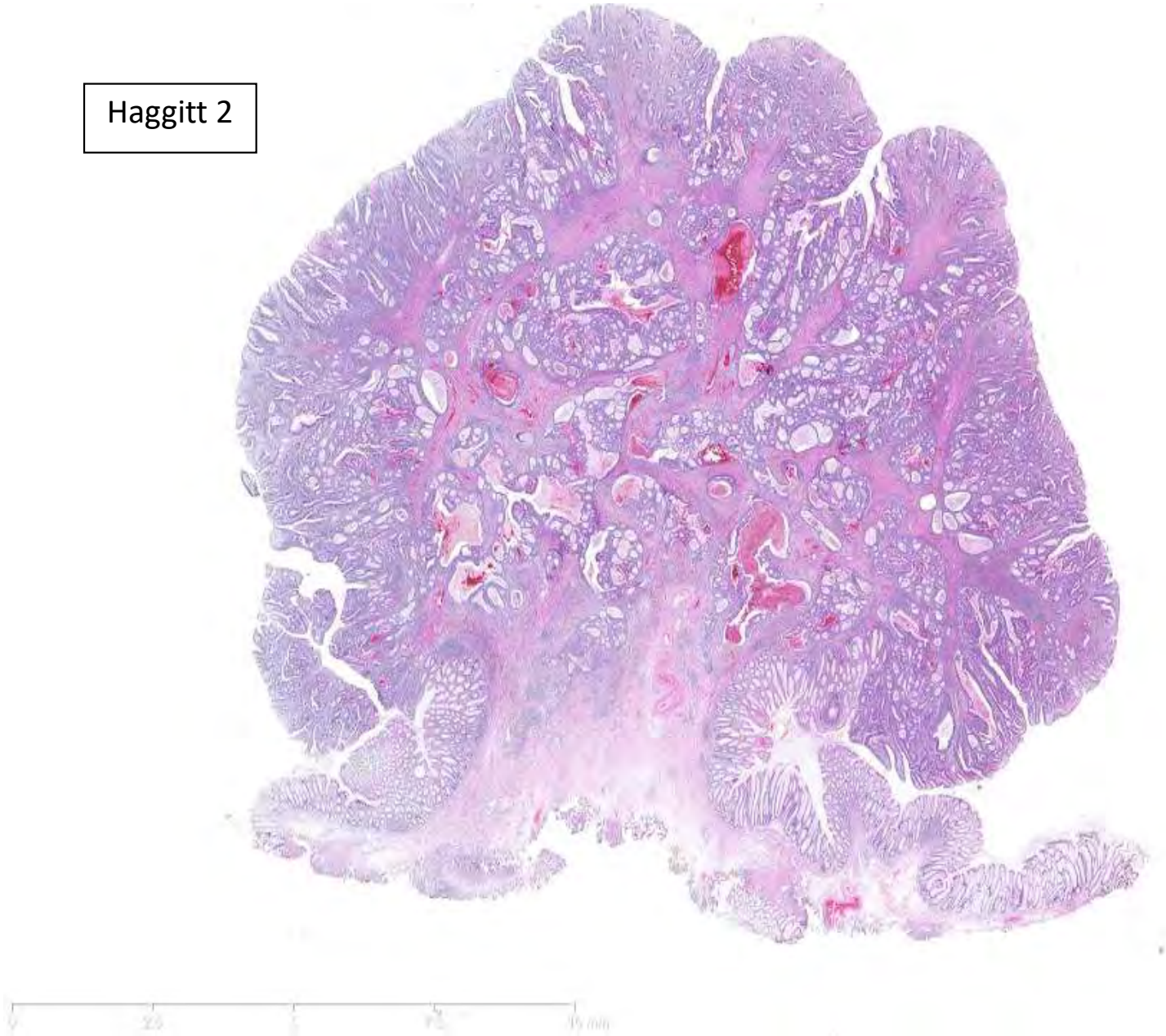
Haggitt's Classification	Number of Cases	Nodal Involvement
Level 1/2	42	0
Level 3	24	6 (25%)
Level 4	185	27 (15%)

Haggitt substaging is recommended for pedunculated lesions (42-85%)!

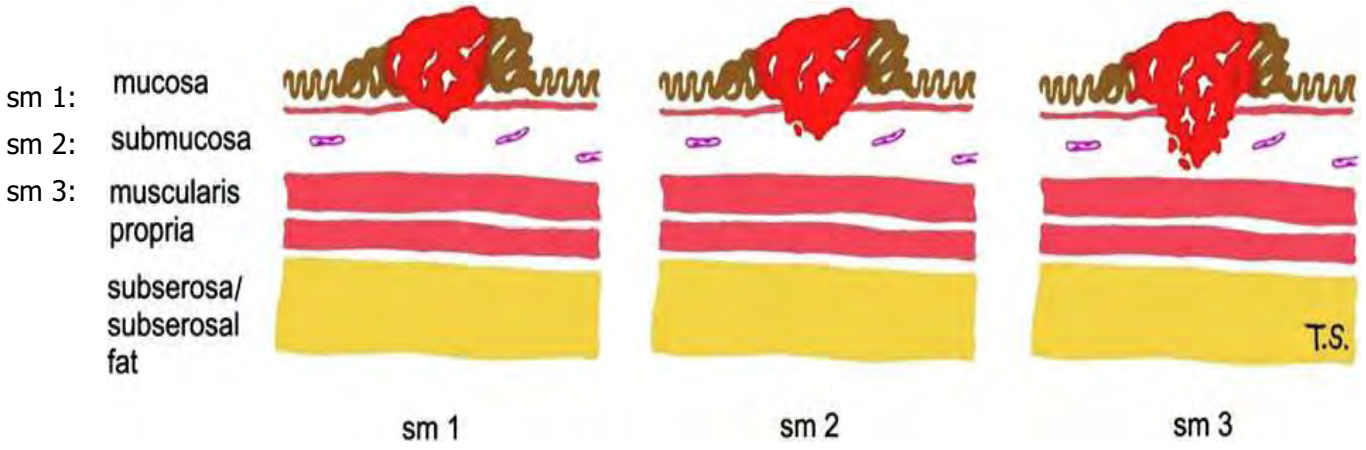
Haggitt 1



Haggitt 2



Substaging pT1



sm 1	sm 2	sm 3
Superficial third of the submucosa 1-3% N positive	**Middle third of the submucosa 8% N positive**	**Deep third of the submucosa 23% N positive**

Kikuchi substaging is recommended for non-polypoid lesions (15-58%)! But you only know where the bottom is in a resection!!!!!

Nascimbeni et al., Dis Colon Rectum 2002
Quirke & Vieth et al., Virchows Arch 2011

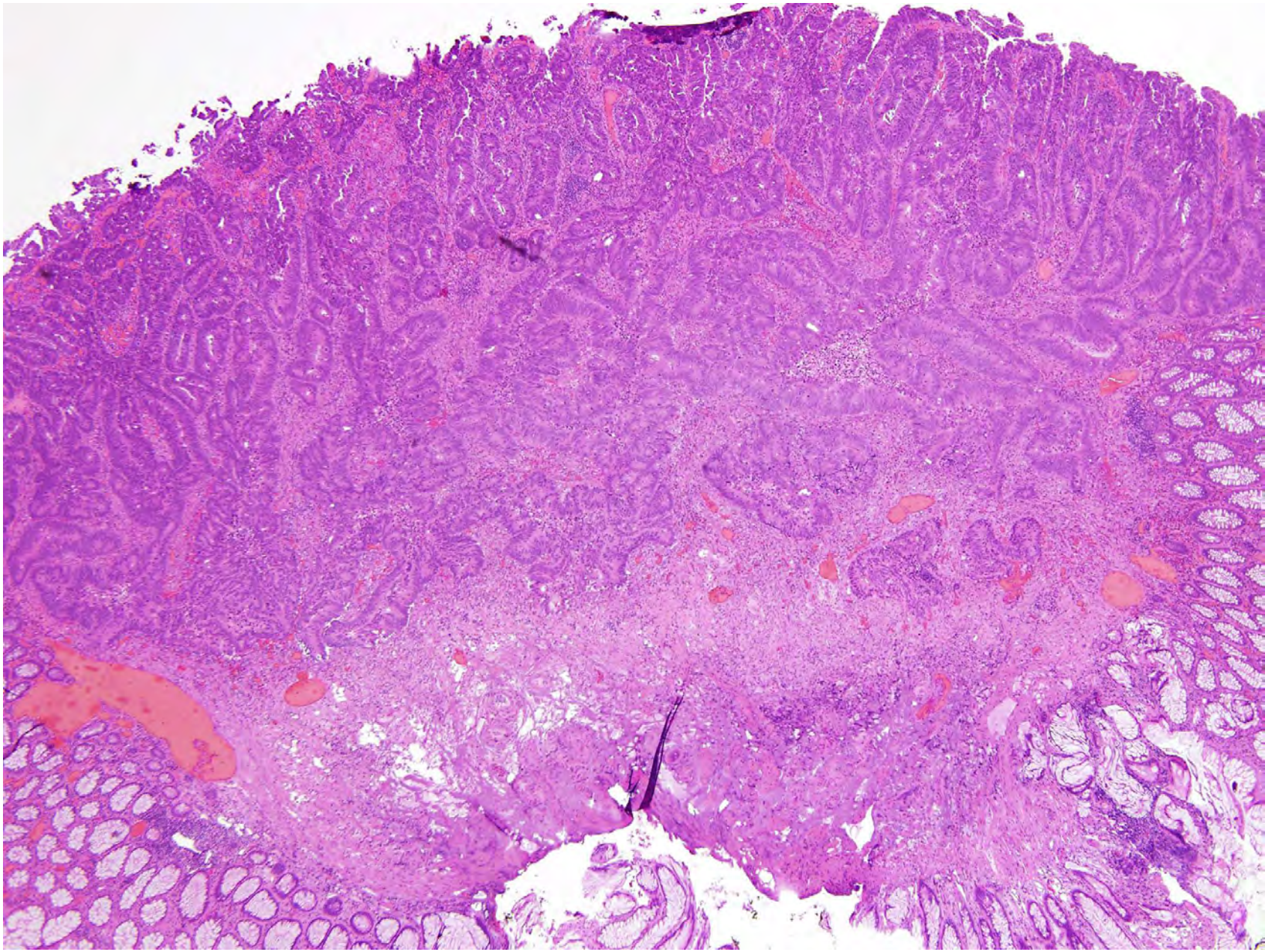
Relationship between the rate of lymph node metastasis and SM depth in early colorectal cancer

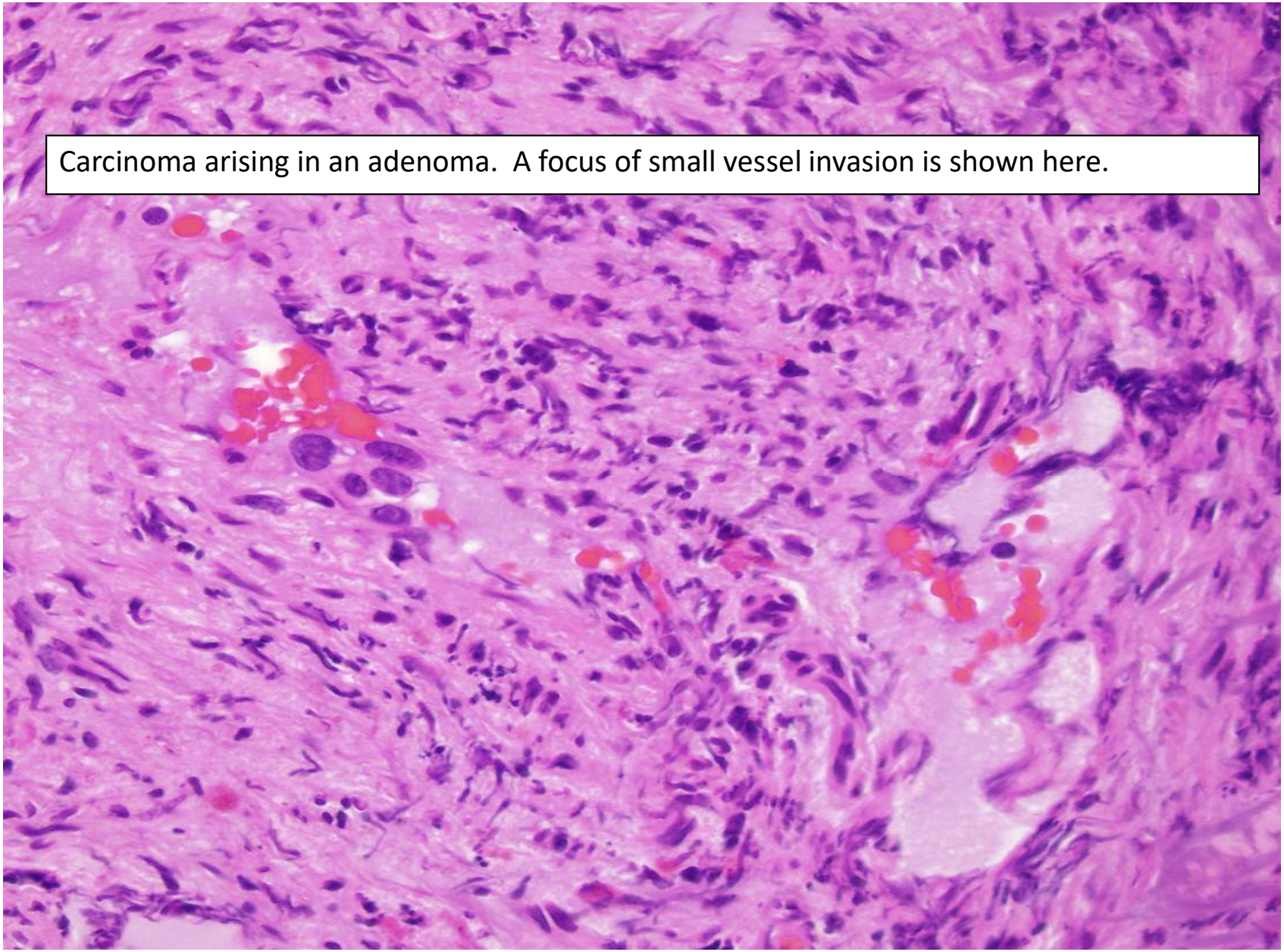
Fujimori et al. Digestion 79 (Suppl): 40-51, 2009

Depth of Invasion into SM	Polypoid Lesions (Ip Type)		Flat Lesions (Non-Ip Type)	
	N (-)	N (+)	N (-)	N (+)
Head Invasion	50	3 (6%)	-	-
< 500 µm	10	0	65	0
500-1000 µm	7	0	58	0
1000-1500 µm	10	1 (9%)	46	6 (12%)
1500-2000 µm	6	1 (14%)	72	10 (12%)
2000-2500 µm	9	1 (10%)	71	13 (15%)
2500-3000 µm	4	0	63	8 (11%)
3000-3500 µm	7	2 (22%)	67	5 (7%)
< 3500 µm	28	2 (7%)	205	35 (15%)
Total	131	10 (7%)	647	77 (11%)

Important especially for mucosal resections and submucosal dissections

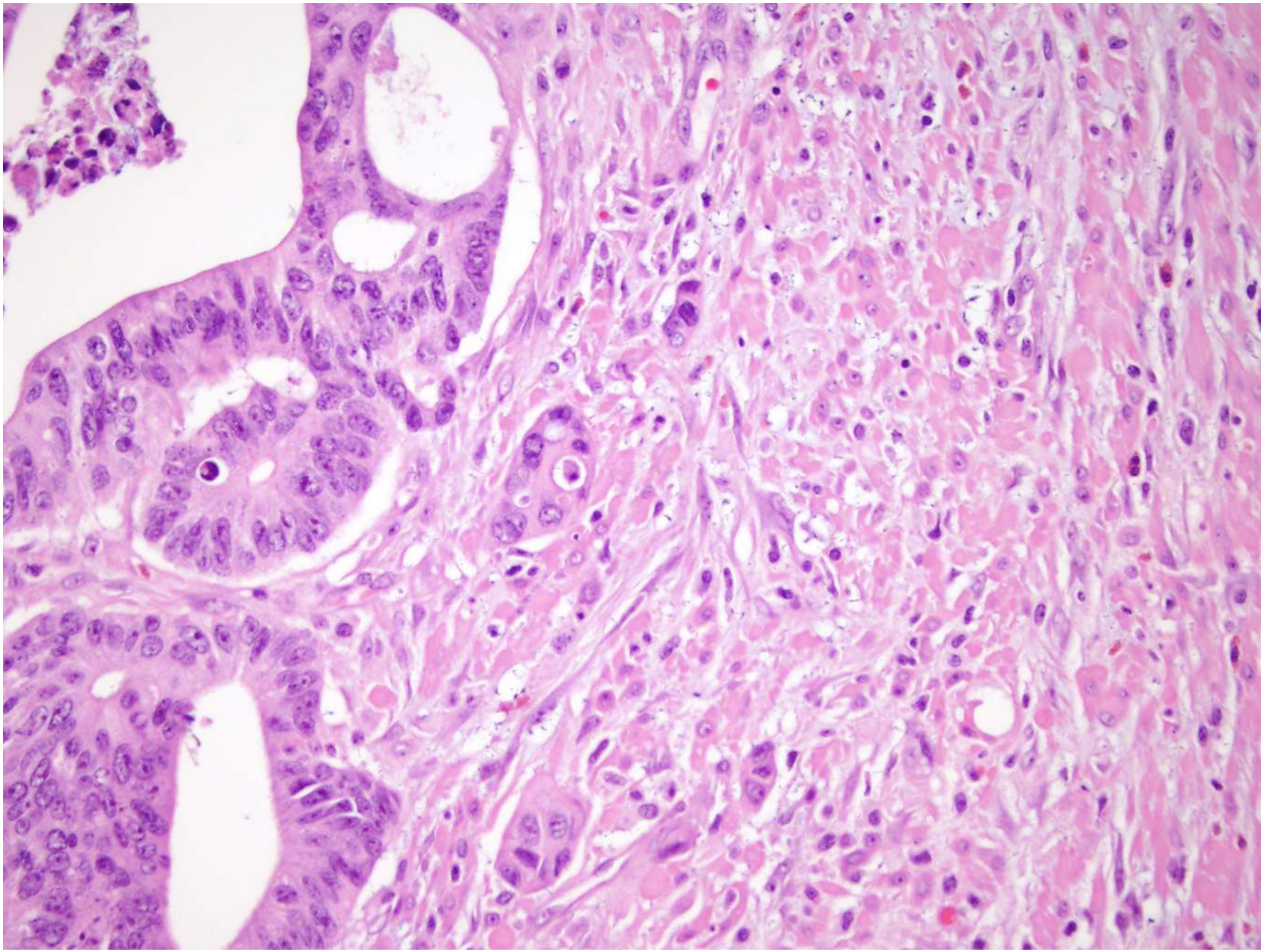
Issue when measuring depth –
The lesion obscures the muscularis mucosae





Carcinoma arising in an adenoma. A focus of small vessel invasion is shown here.

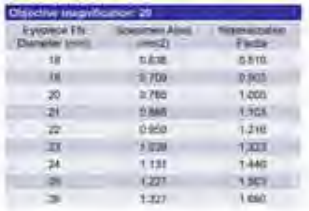
Tumor budding can be defined as the presence of isolated tumor cells, singly or in clusters of <5 cells at the advancing tumor front.



Budding Pains

Lugli A, Kirsch R, Ajioka Y, Bosman F, Cathomas G, Dawson H, El Zimaity H, Fléjou JF, Hansen TP, Hartmann A, Kakar S, Langner C, Nagtegaal I, Puppa G, Riddell R, Ristimäki A, Sheahan K, Smyrk T, Sugihara K, Terris B, Ueno H, Vieth M, Zlobec I, Quirke P. Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. Mod Pathol. 2017 Sep;30(9):1299-1311. PubMed PMID: 28548122.

1 **Define the field (specimen) area for the 20x objective lens of your microscope based on the eyepiece field number (FN) diameter**



2 **Select the H&E slide with greatest degree of budding at the invasive front**

3 **Scan 10 individual fields at medium power (10x objective) to identify the "hotspot" at the invasive front**

For surgical resection specimens, scan 10 fields

For pT1 endoscopic resections (usually <10 fields available), scan all

4 **Count tumor buds in the selected "hotspot" (20x objective)**

Selected hotspot indicated in red

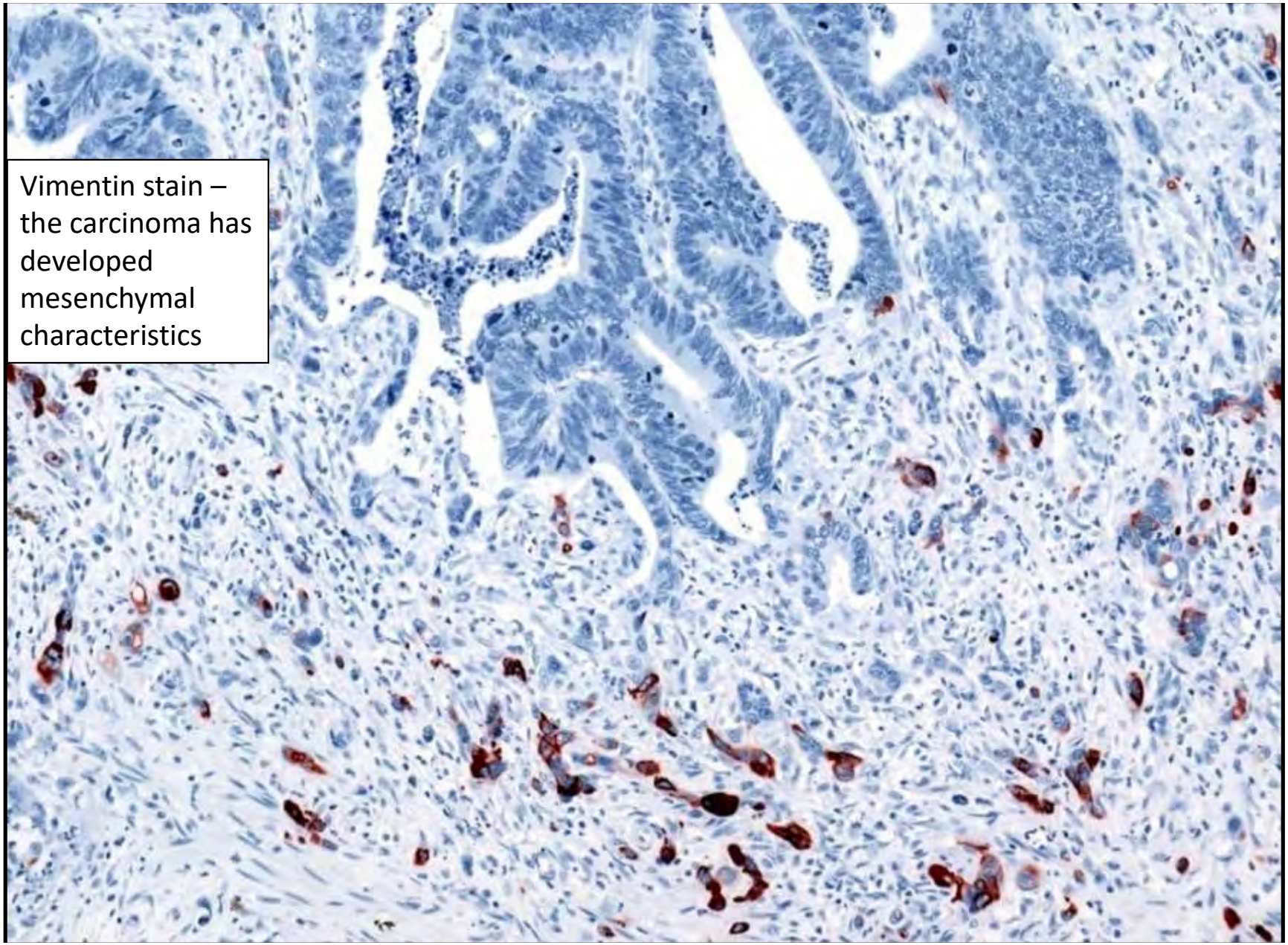
5 **Divide the bud count by the normalization factor (figure 2) to determine the tumor bud count per 0.785mm²**

Select the budding [Bd] category based on bud count and indicate the absolute count per 0.785mm² (see reporting example)

$$\text{Tumor bud count per 0.785 mm}^2 = \frac{\text{Bud count (20x objective)}}{\text{Normalization factor*}}$$

Bd1 (low):	0–4 buds	per 0.785 mm²
Bd2 (intermediate):	5–9 buds	
Bd3 (high):	≥10 buds	

Reporting example:
Tumor budding: Bd3 (high), count 14 (per 0.785 mm²)


Vimentin stain – the carcinoma has developed mesenchymal characteristics

Do we need to stain for endothelial markers to search for vascular invasion?

- The vintage Cooper studies noted that patients whose lesions were even “suspicious for vascular invasion” tended to behave as though vascular invasion.
- We do not always stain but there is nothing wrong with this practice.

What we do at our place

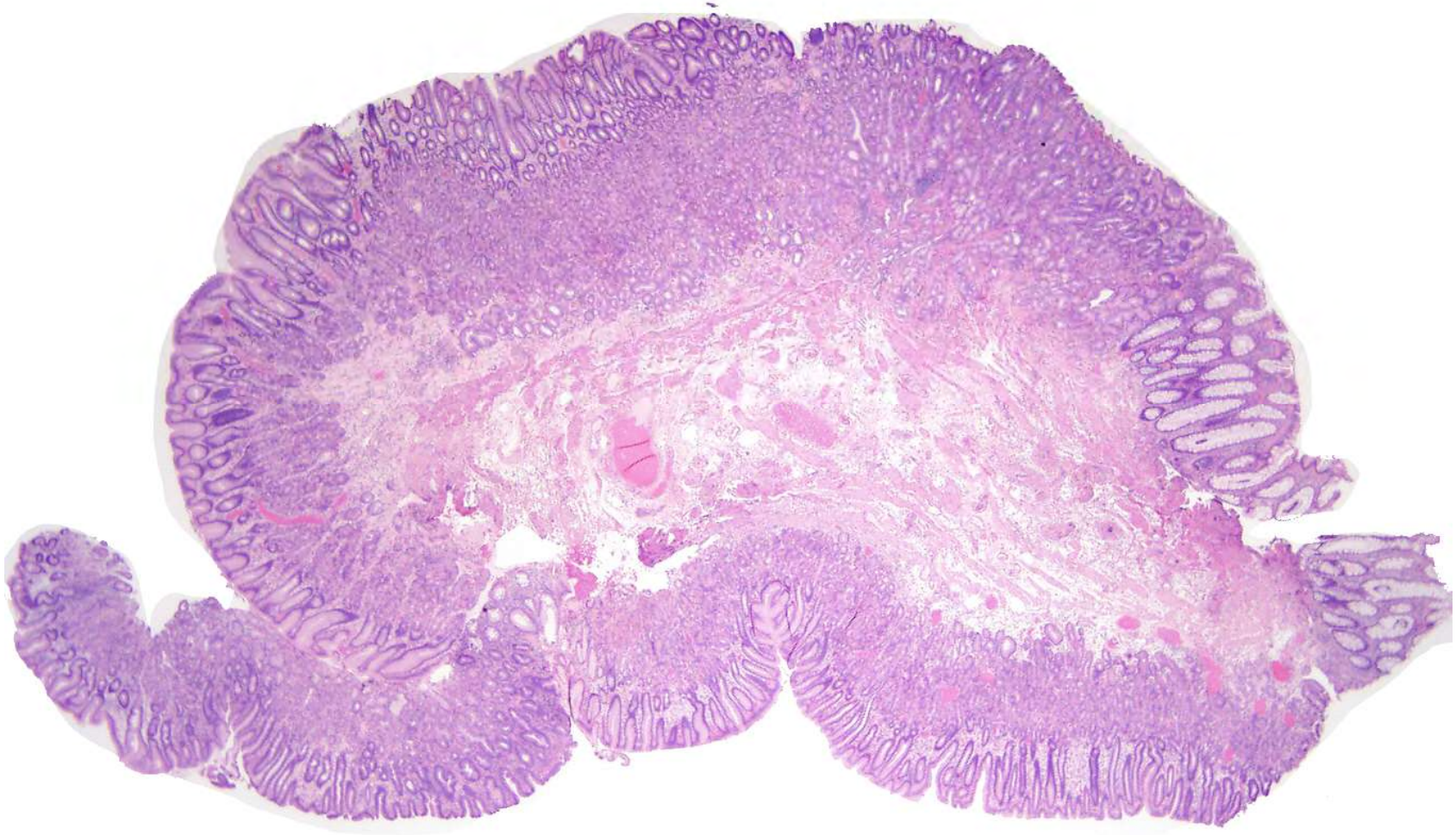
- The old fashioned 3 things (is there vascular invasion, is there a poorly differentiated component, is the lesion out and a measurement is made.
- Budding reported either as such or as a poorly differentiated component
- Occasional staining for keratins or endothelial cells
- Measure depth from the muscularis mucosae in endoscopic submucosal dissections

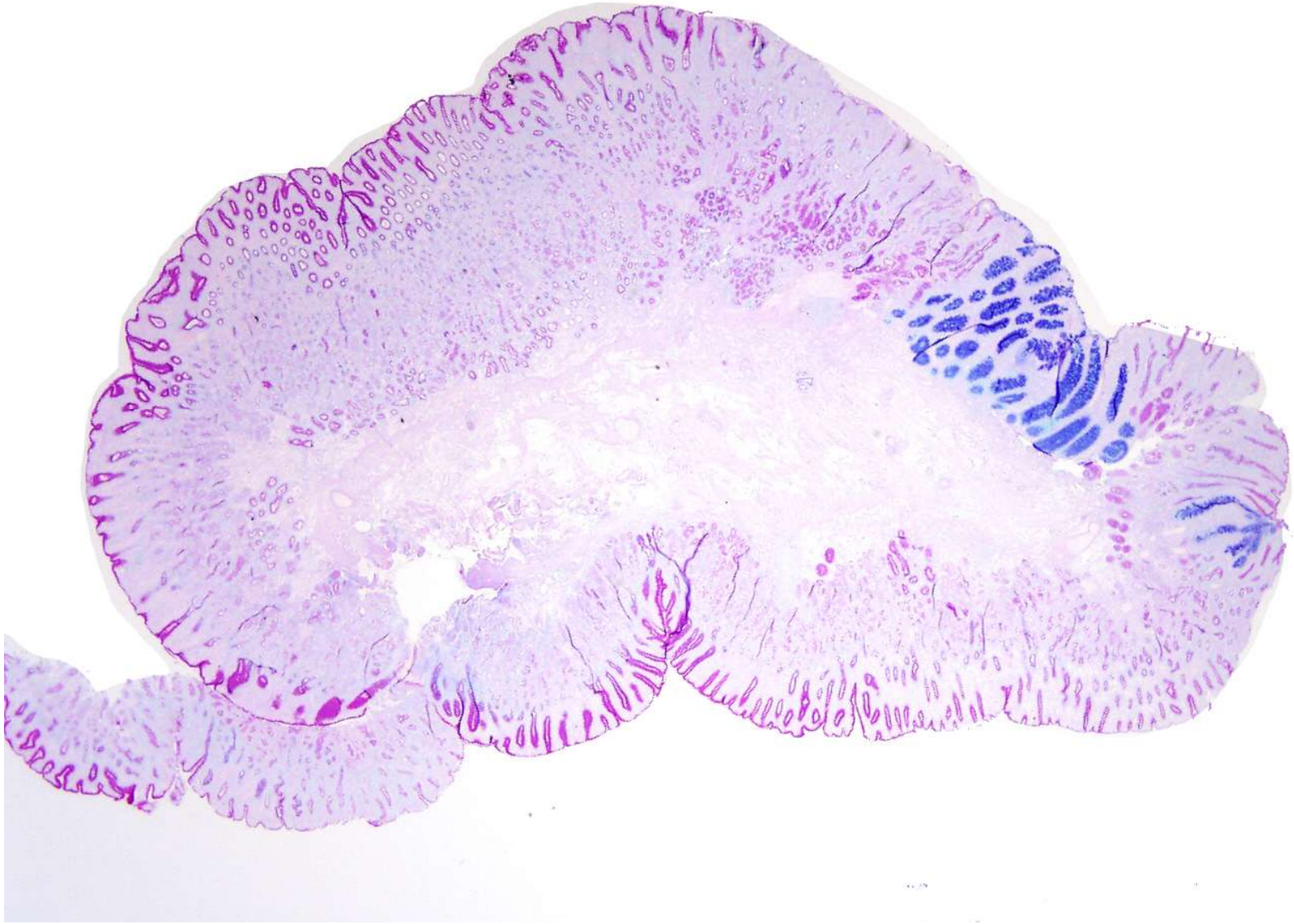
Peculiar NON-hereditary lesions

- Cronkhite Canada syndrome
- Mucosal prolapse
- Cap polyposis
- Polyps associated with portal hypertension

Bleeding per rectum and a rectal polyp

Mannan AASR, Vieth M, Khararjian A, et al. The outlet patch: gastric heterotopia of the colorectum and anus. *Histopathology*. 2018;73(2):220-229.





General Features of Cronkhite-Canada Syndrome

- Acquired, nonfamilial form of diffuse gastrointestinal polyposis

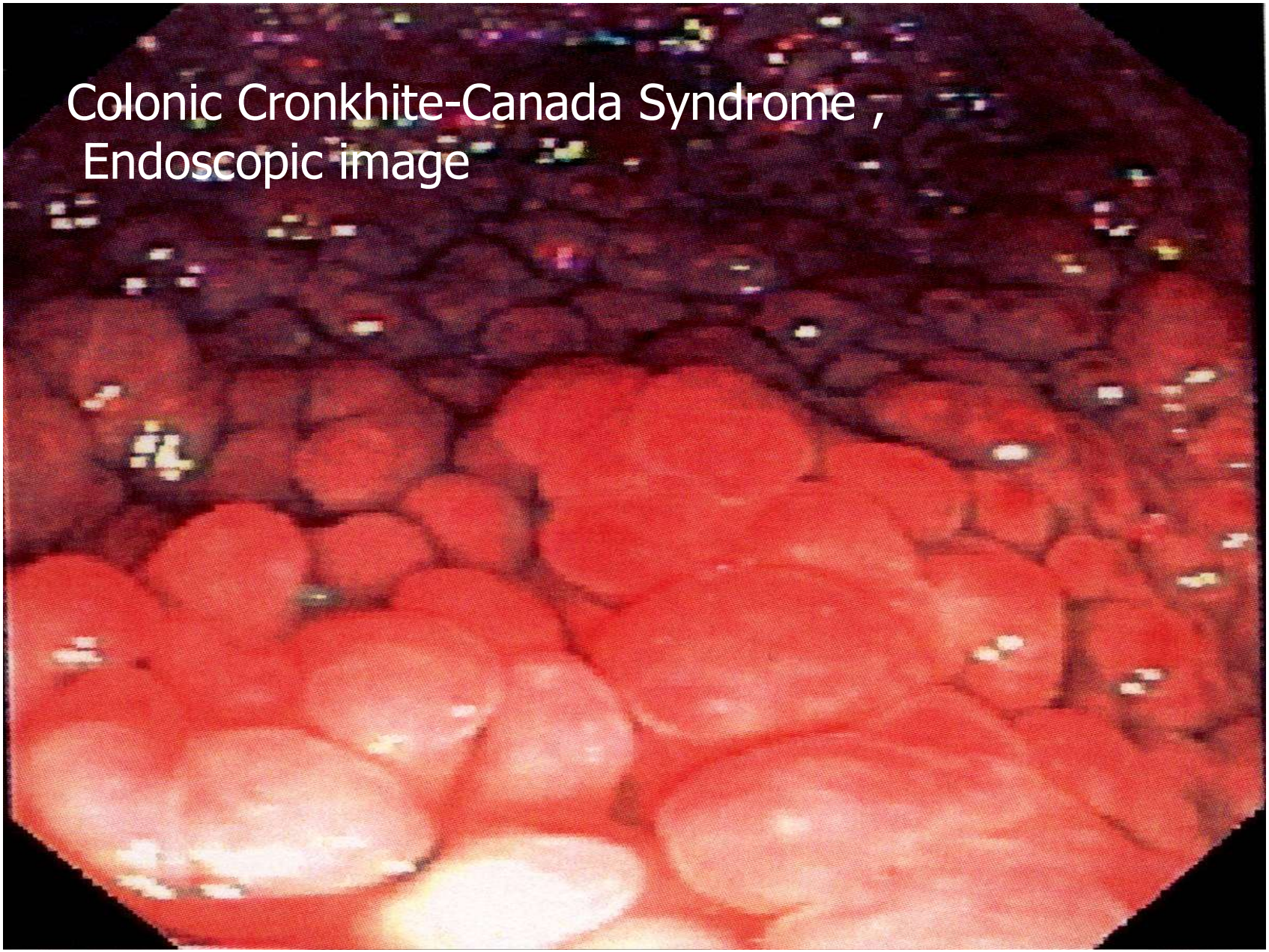
- Other common features include:
  - Skin pigmentation
  - Dystrophic changes of fingernails
  - Alopecia
  - Diarrhea
  - Malnutrition
  - Nonspecific impairment of immune system

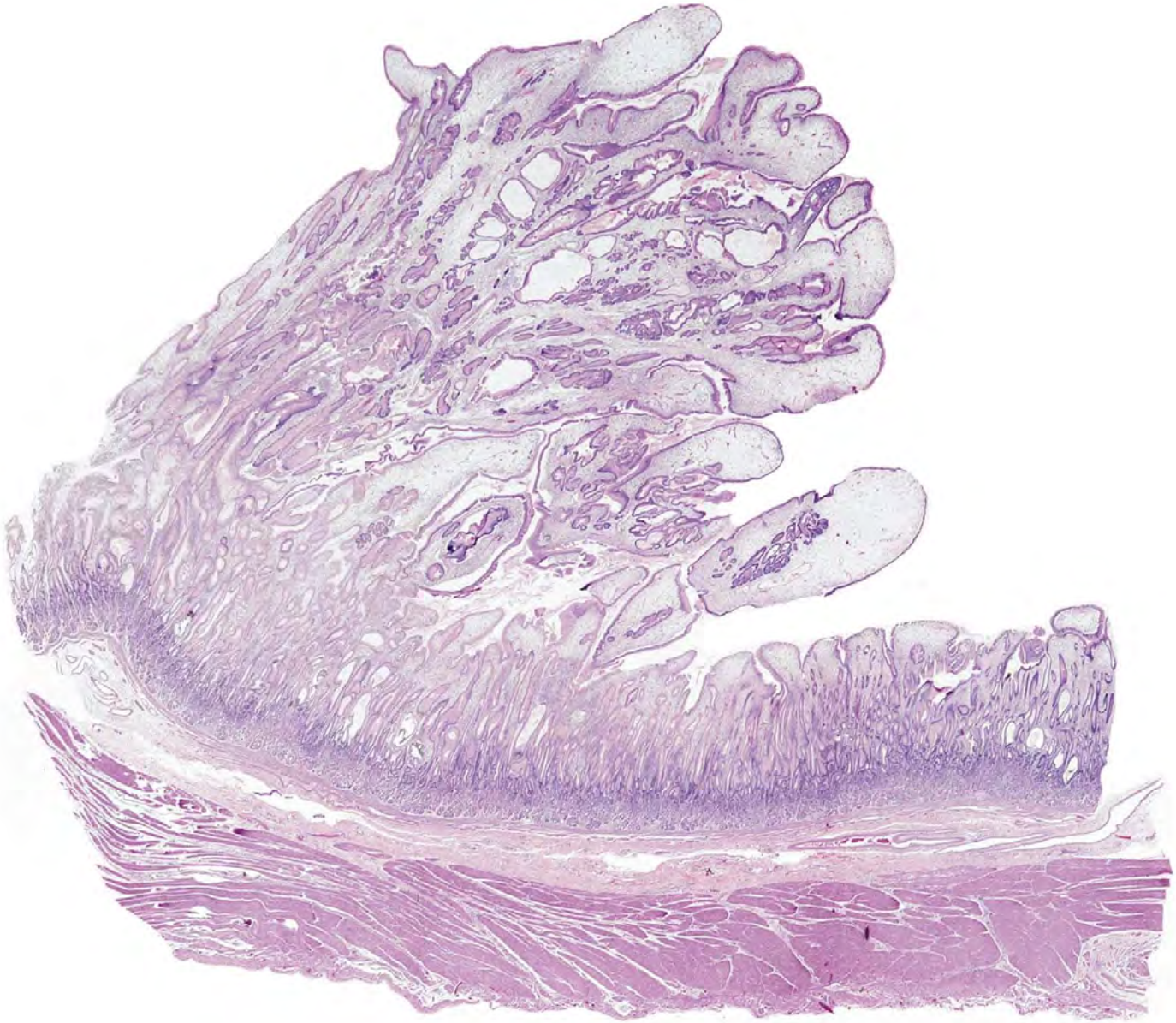
Clinical Features of Cronkhite-Canada Syndrome

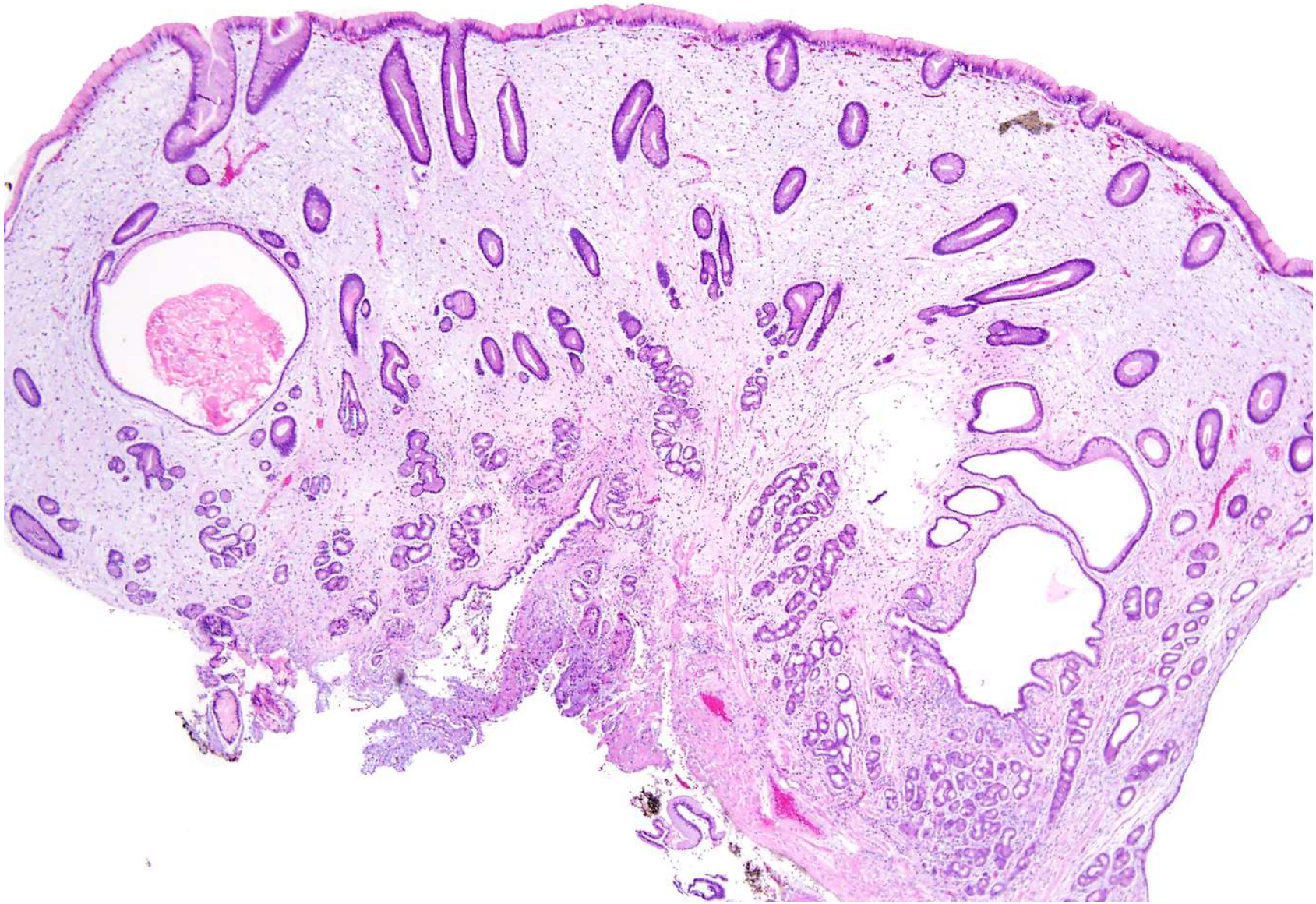
- Average age of onset 62 years
- Present with acute and rapidly progressive illness of diarrhea, protein-losing enteropathy, weight loss and skin abnormalities
- Lab findings include hypoalbuminemia, hypocalcemia, anemia and severe electrolyte deficiencies
- In the past - Poor prognosis due to severity of malabsorption (mortality rate 60%)
- **Recent improved supportive care allows most patients to survive**

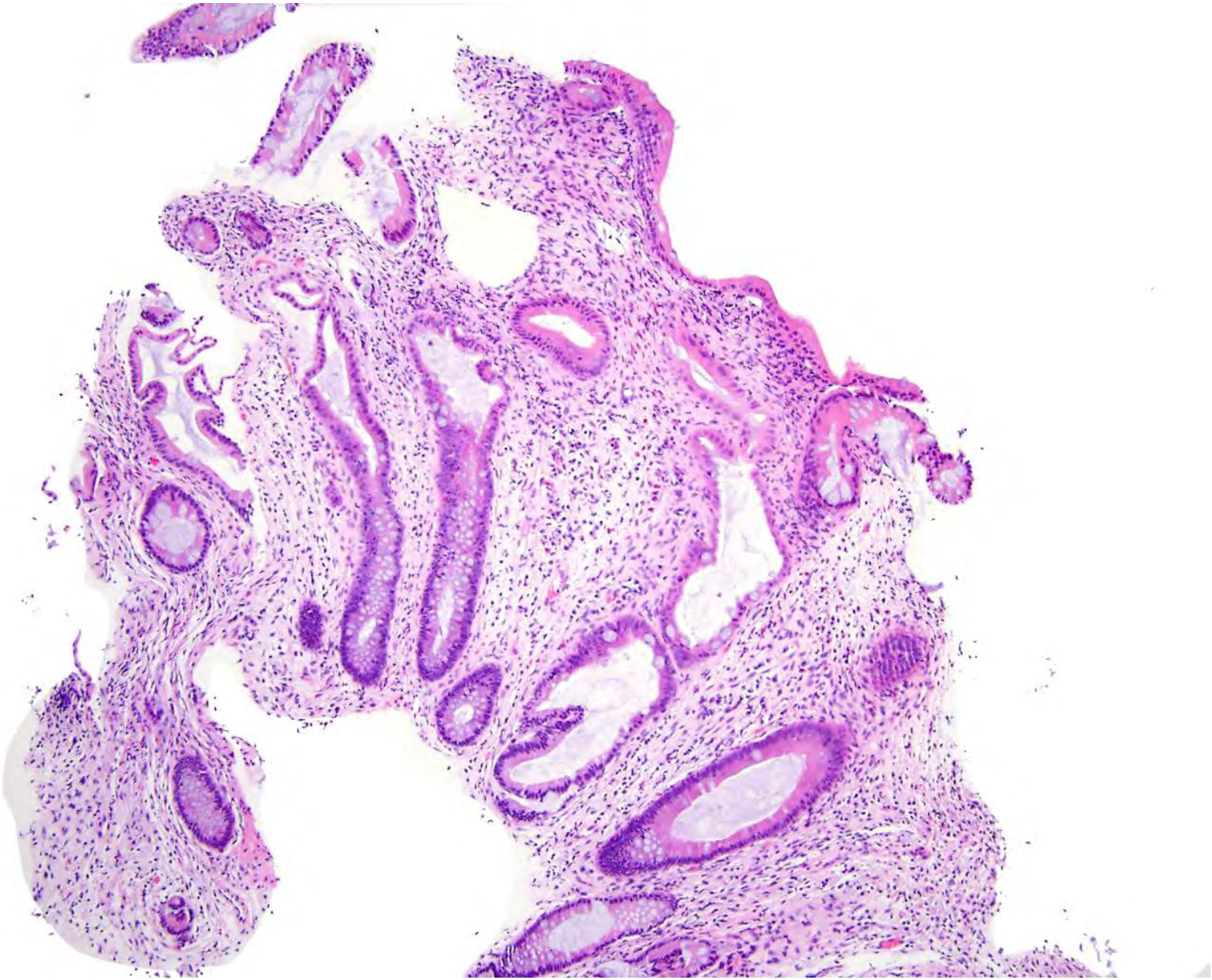
Pathologic Features of Cronkhite-Canada Syndrome

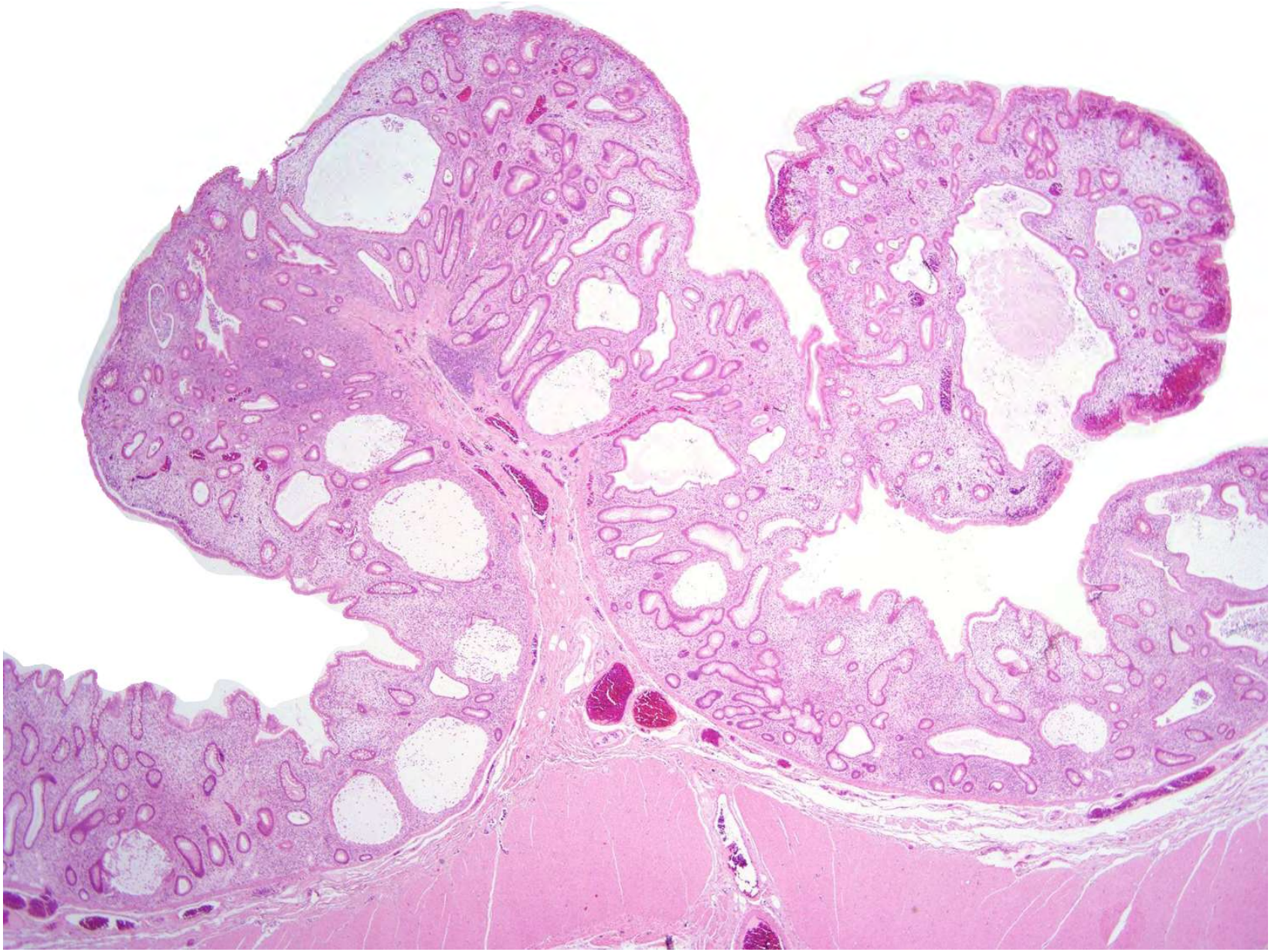
- Gastrointestinal polyps found in almost all patients
- Polyps typically located anywhere from stomach to rectum
- Histologically similar to juvenile (retention) polyps, but not pedunculated as in JPS
- Differences from Juvenile polyposis:
  - Intervening mucosa is also abnormal
  - Edema, congestion and inflammation


Colonic Cronkhite-Canada Syndrome ,
Endoscopic image



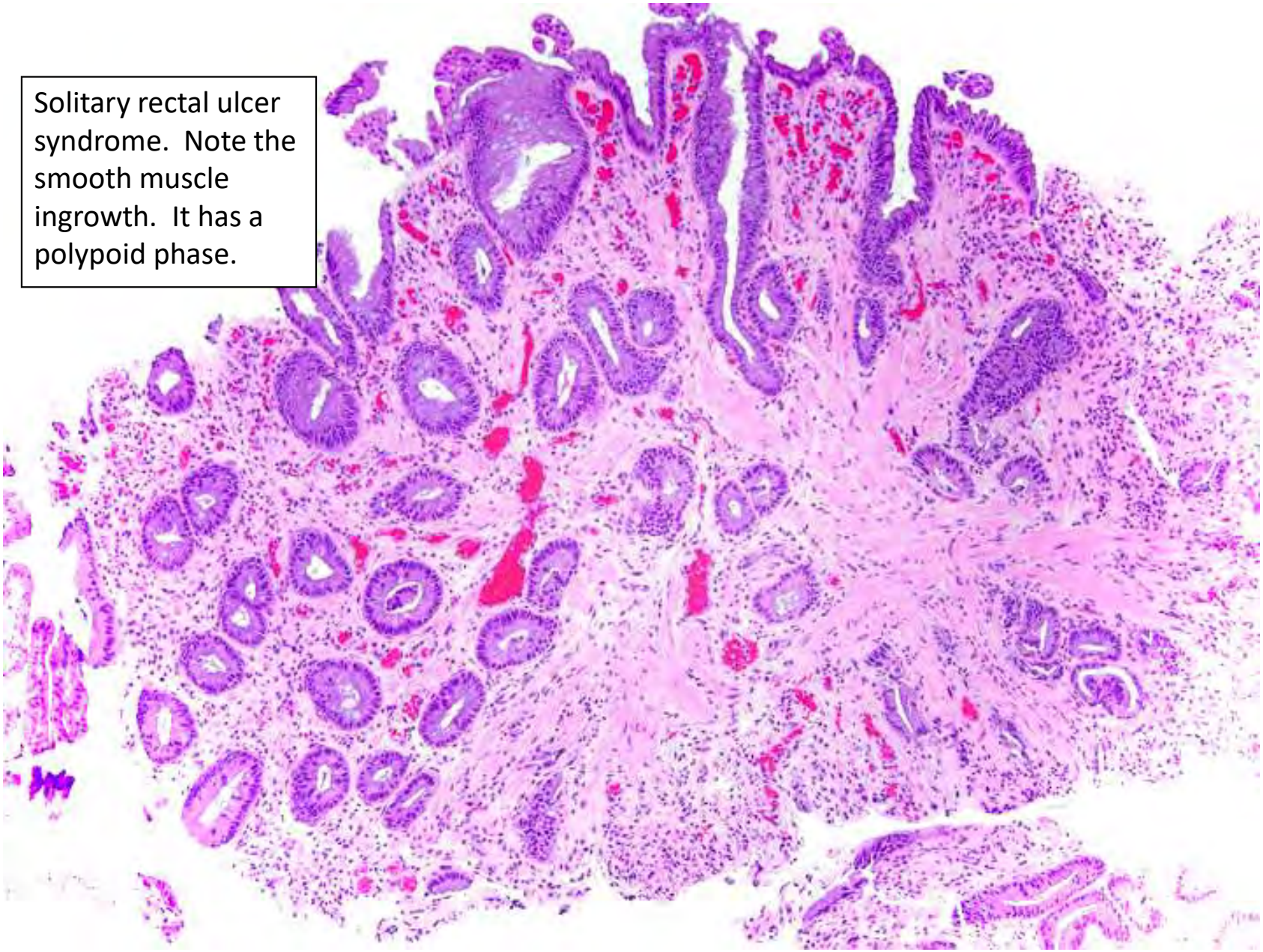


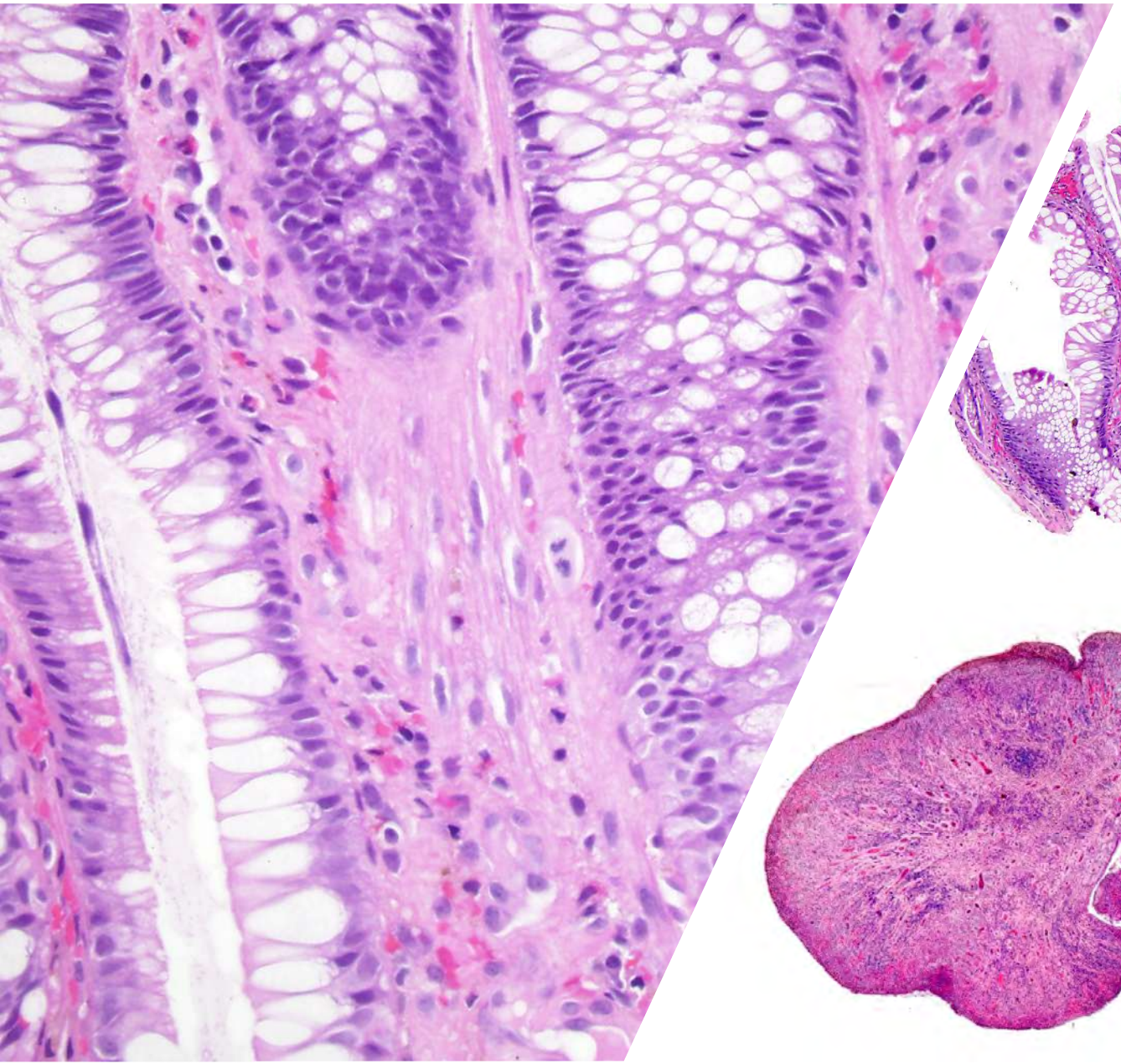


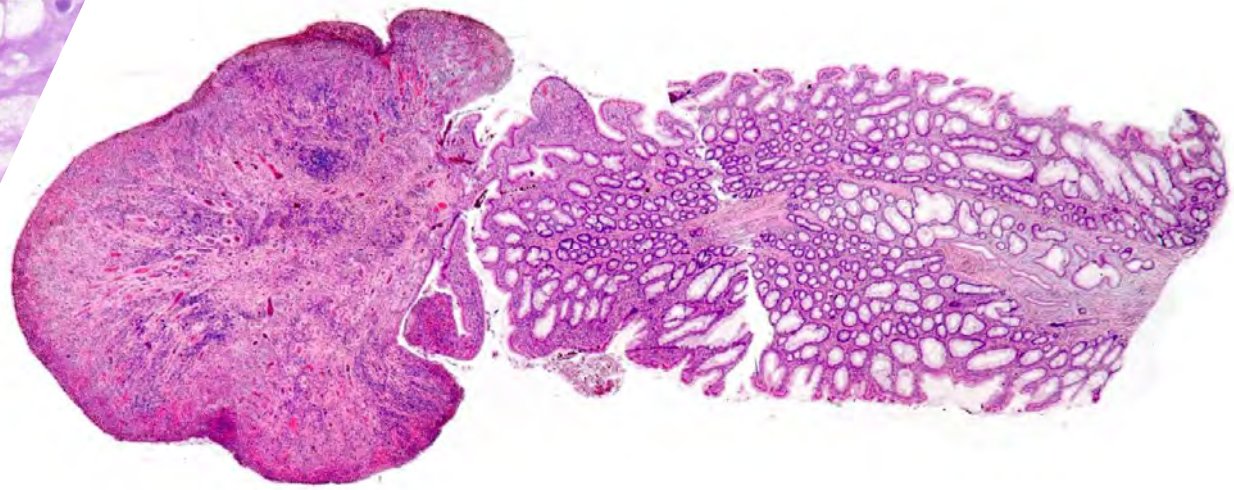


Mucosal prolapse polyps

Solitary rectal ulcer syndrome. Note the smooth muscle ingrowth. It has a polypoid phase.



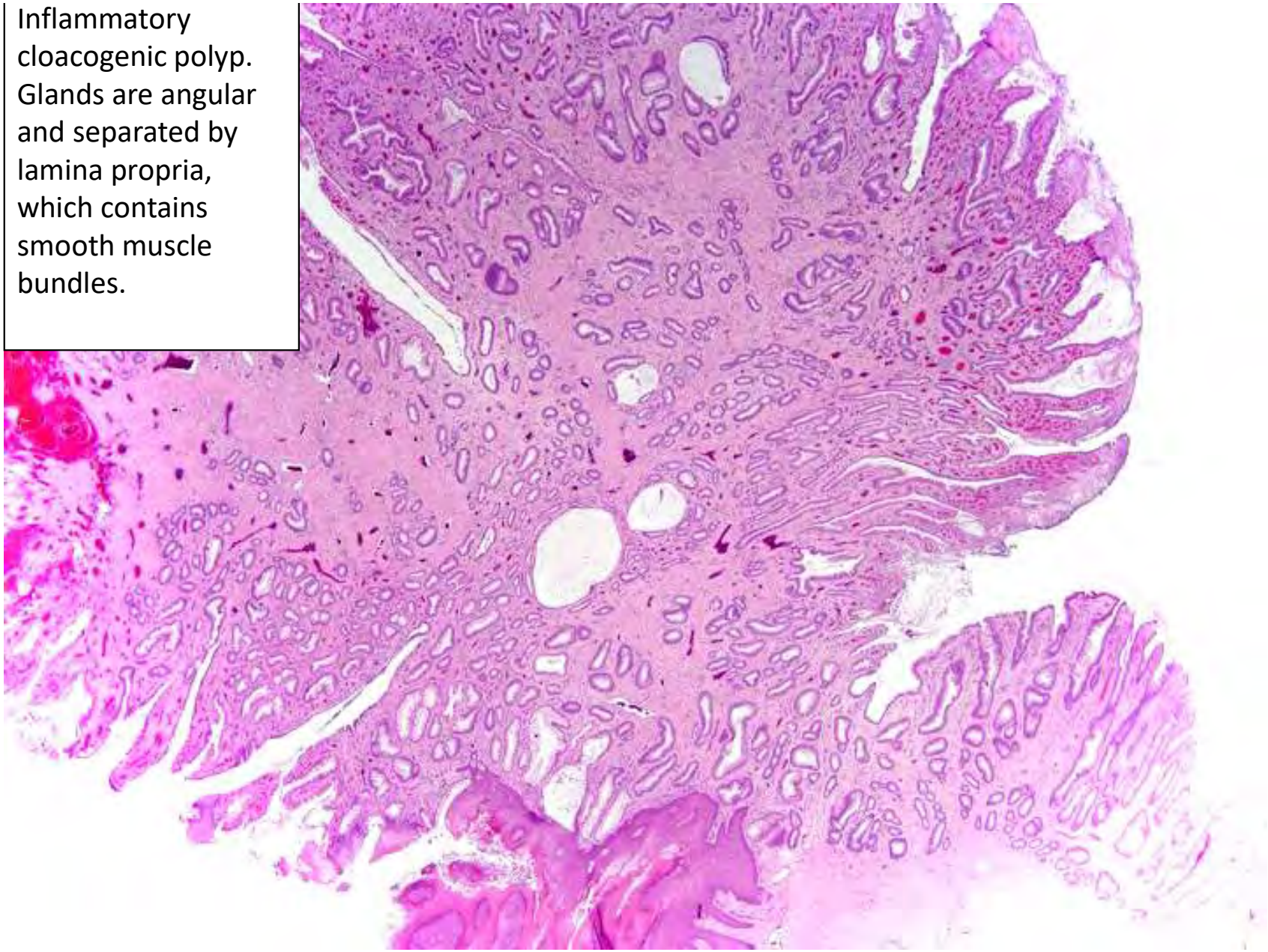


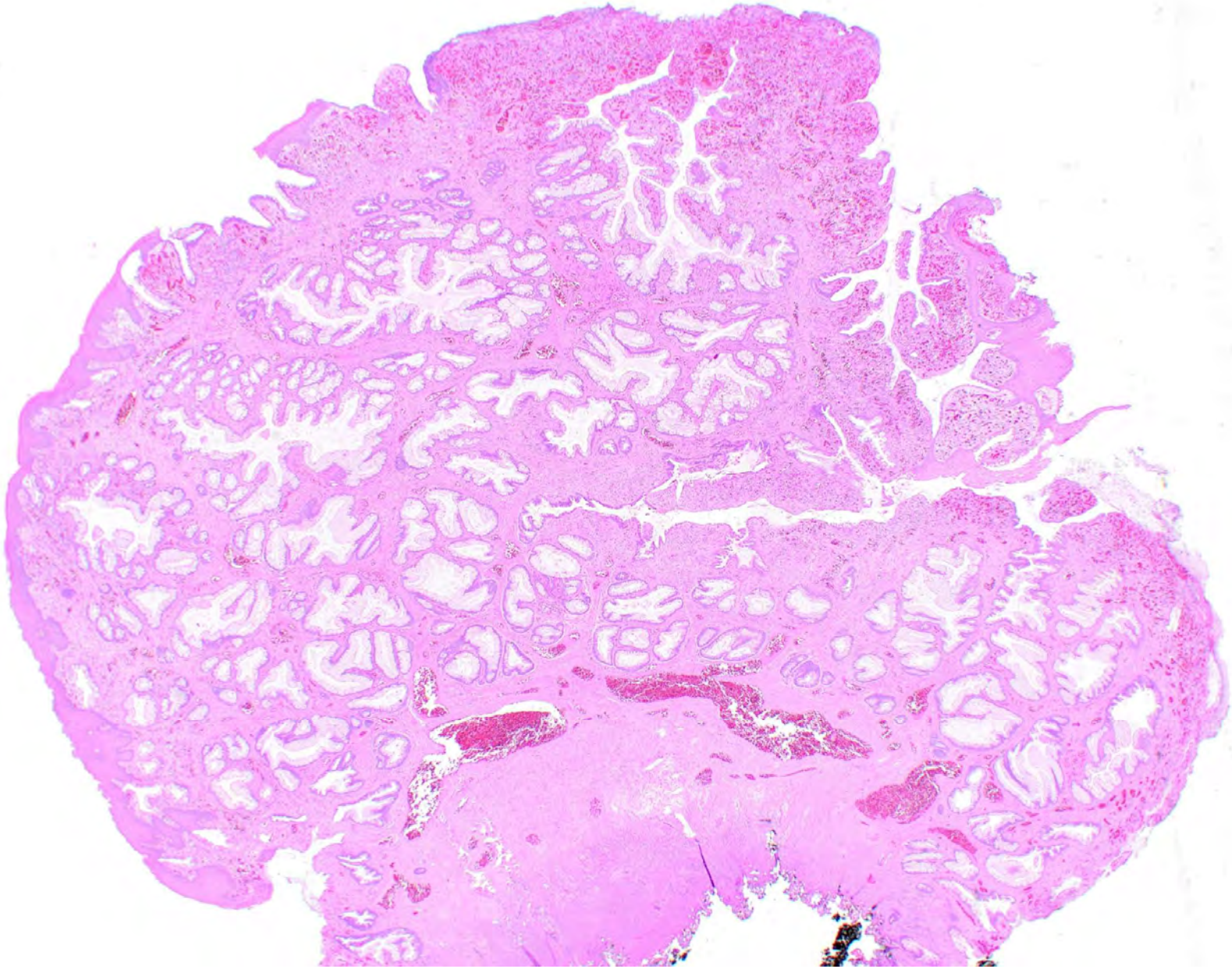


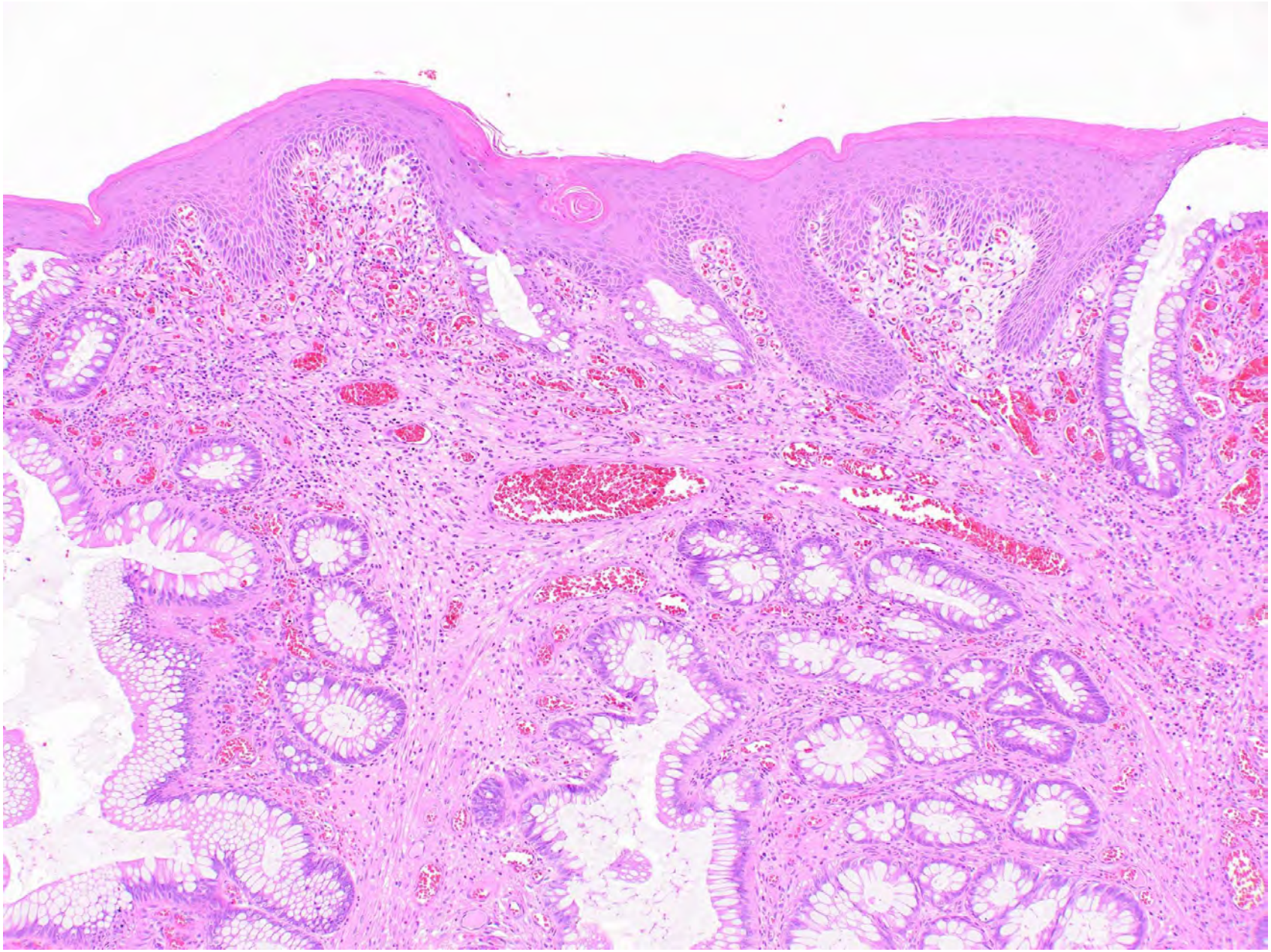
Ano-rectal prolapse

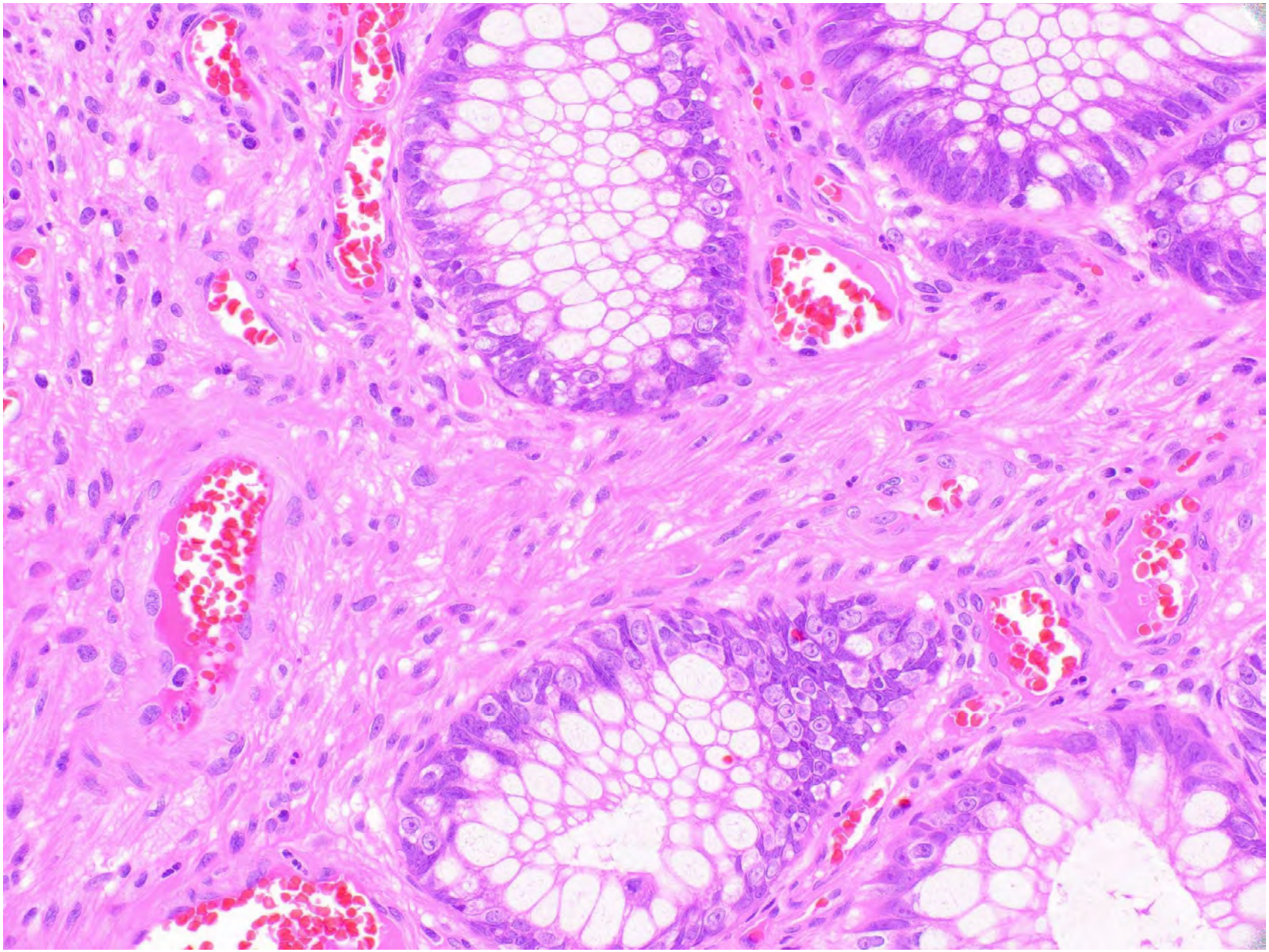
- Termed “inflammatory cloacogenic polyp years ago
- Ref; Lobert PF, Appelman HD. Inflammatory cloacogenic polyp. A unique inflammatory lesion of the anal transitional zone. *Am J Surg Pathol*. 1981;5(8):761-766.

Inflammatory cloacogenic polyp. Glands are angular and separated by lamina propria, which contains smooth muscle bundles.



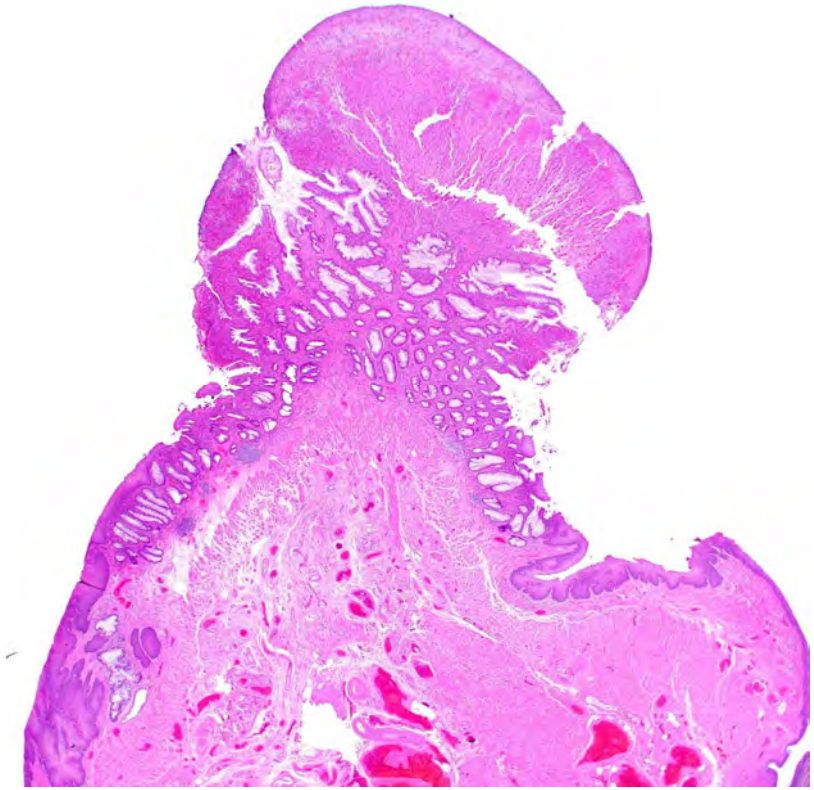




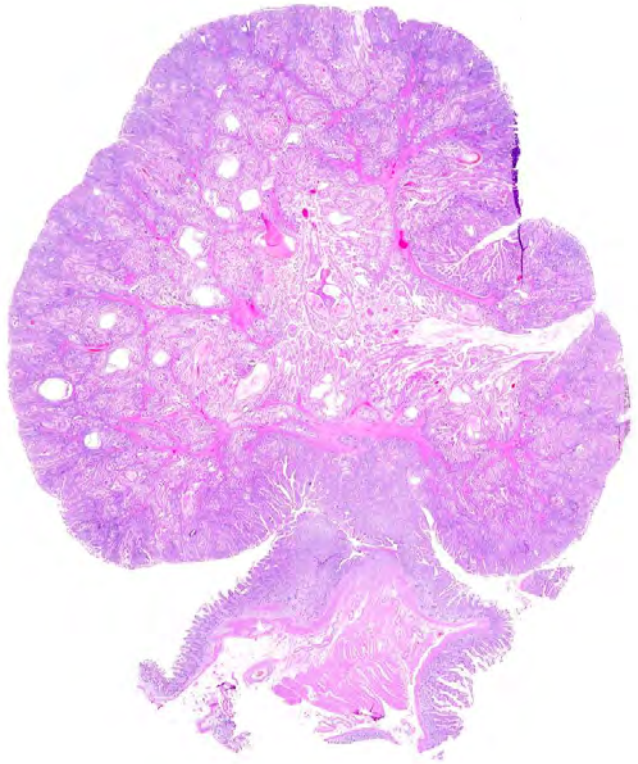


Comparing Mucosal Prolapse Polyps and Peutz Jeghers Polyp

Prolapse

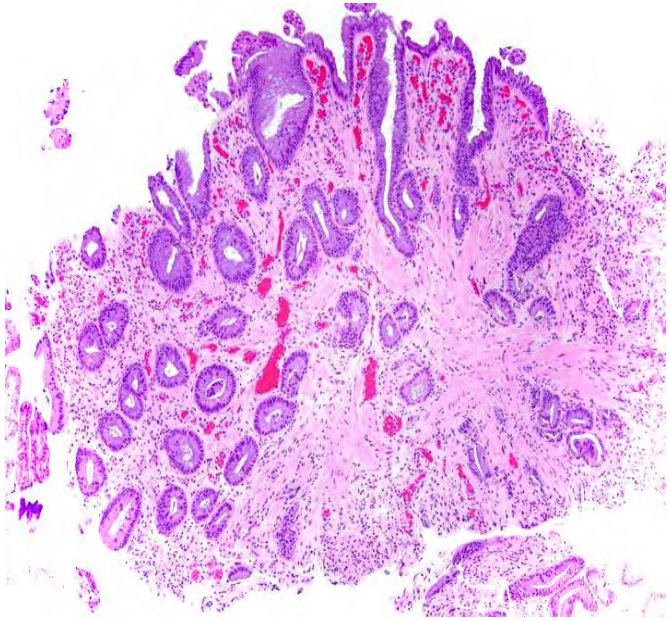


PJ



Comparing Solitary Rectal Ulcer and Peutz Jeghers Polyp

Prolapse



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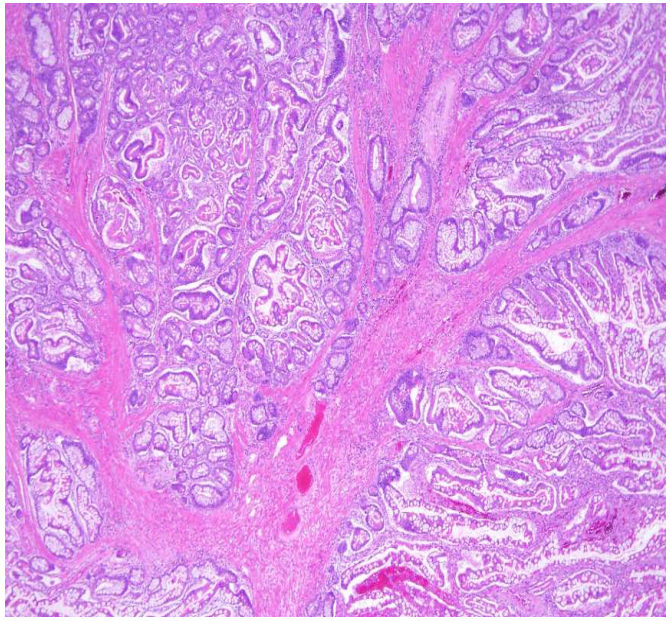
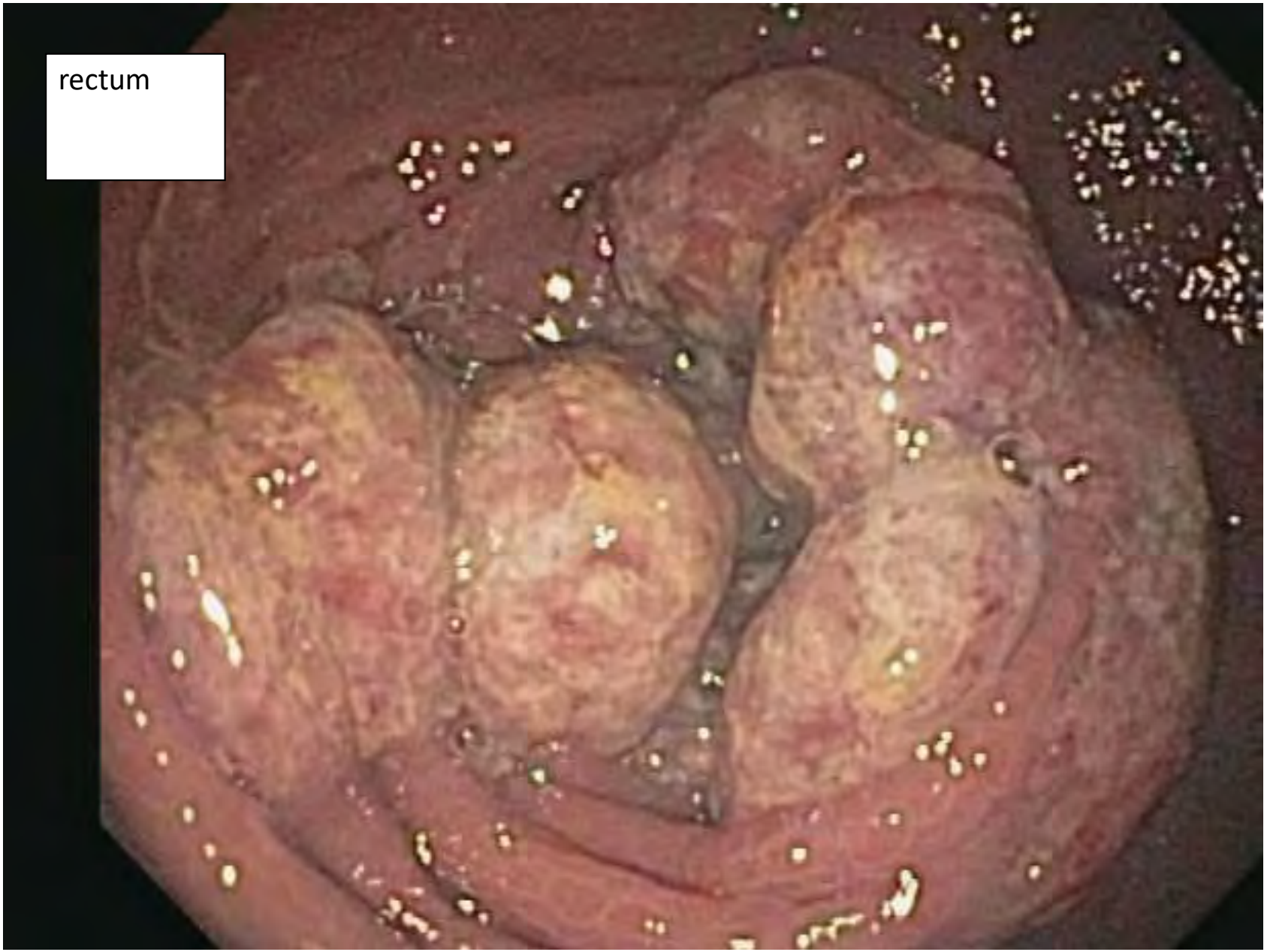
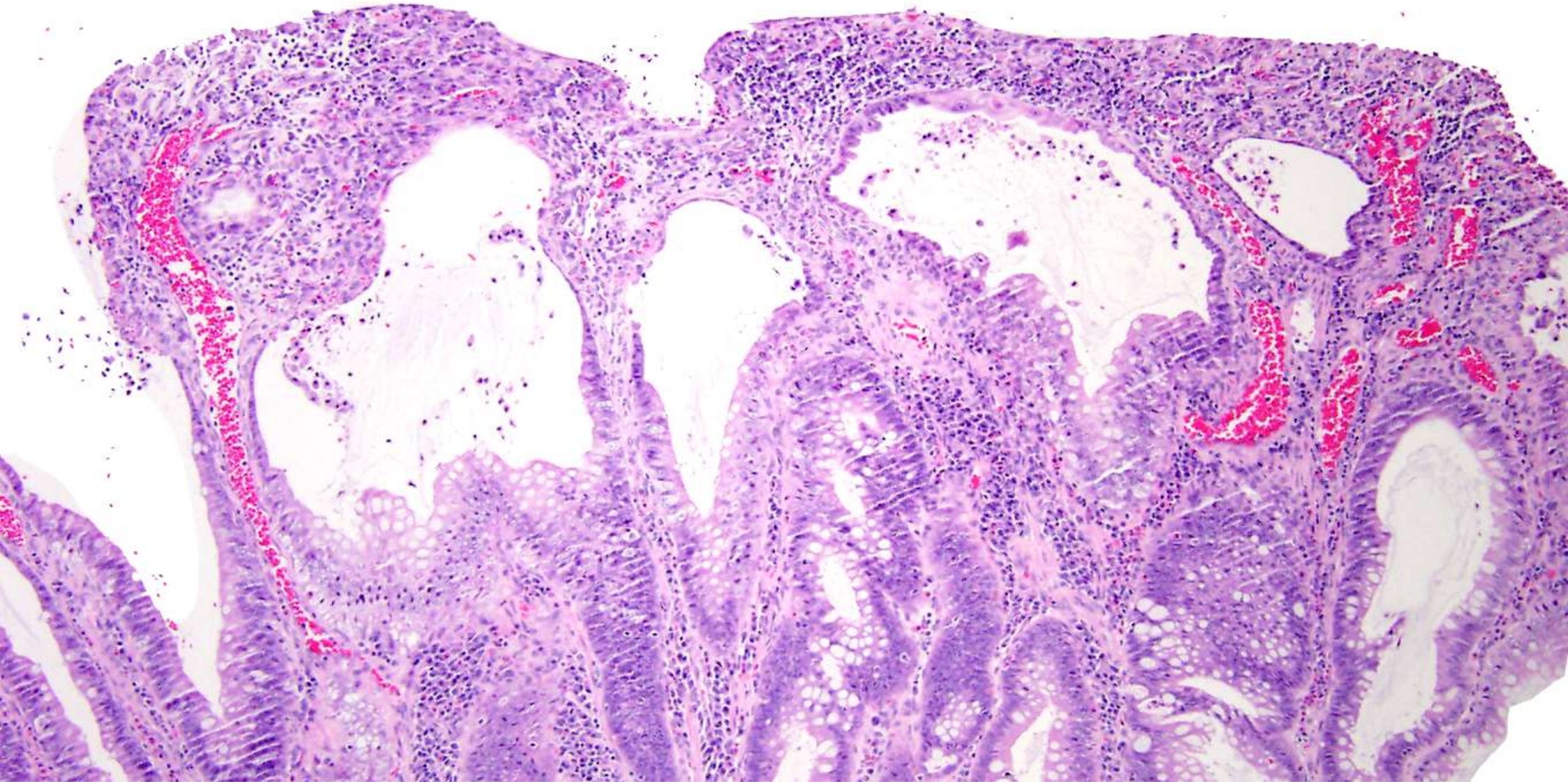
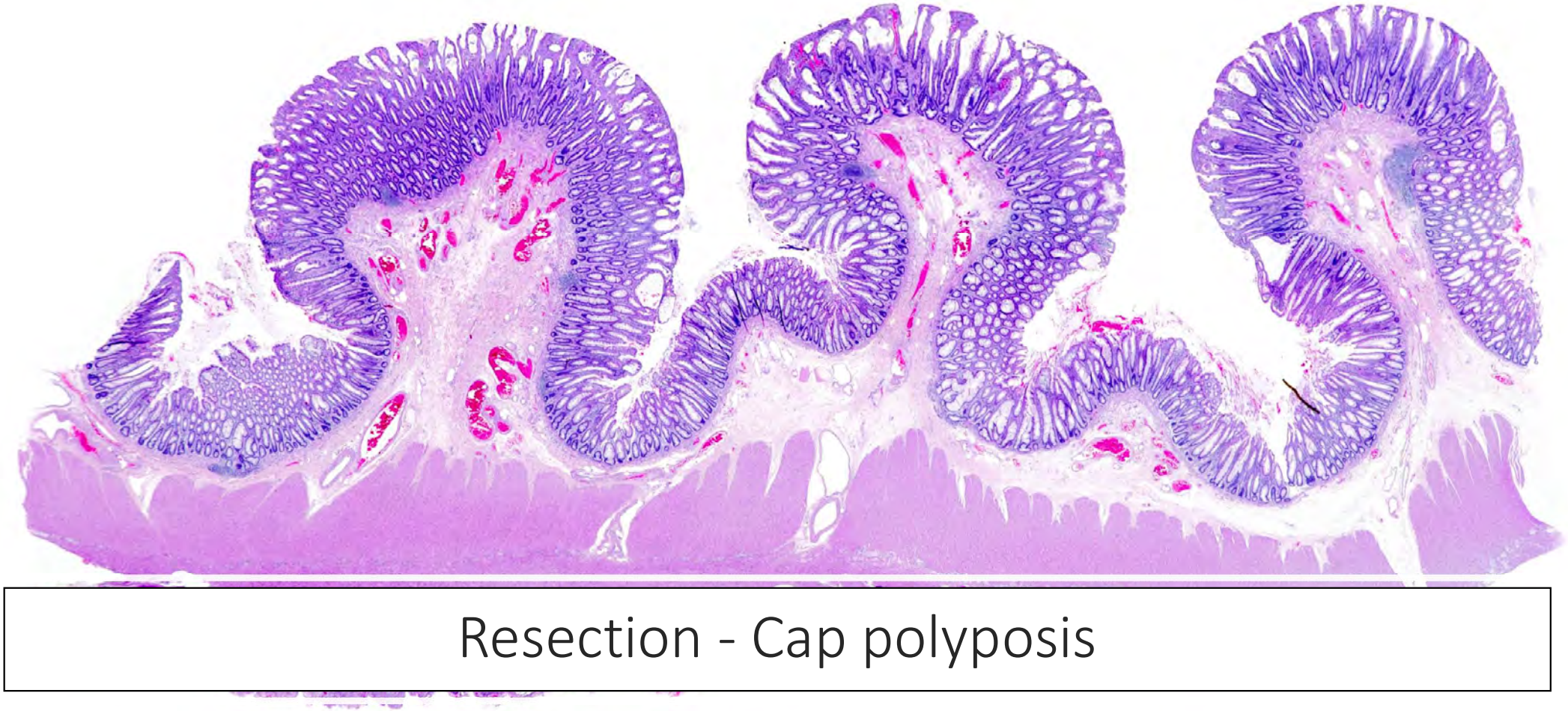


Case

- Middle aged women with horrible mucoid diarrhea and numerous distal colorectal polyps. She finally required distal resection to reduce symptoms


rectum

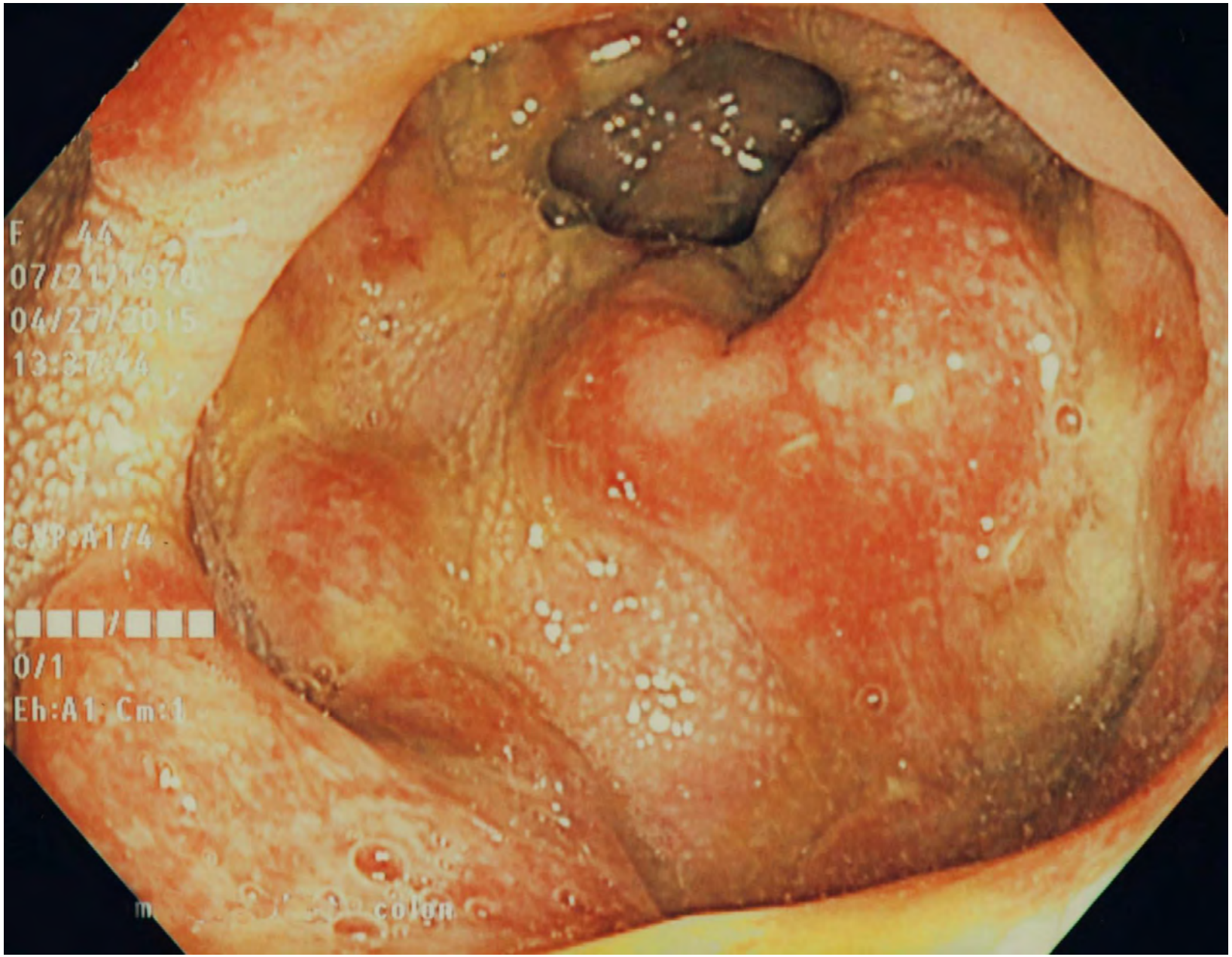




Resection - Cap polyposis

Another Odd One

- Cap polyposis (not hereditary – cause unknown)
- ? A type of mucosal prolapse syndrome
- Mucoid hemorrhagic diarrhea, multiple polyps covered with caps of inflammatory exudate
- Female predominance, 5-6th decade of life
- Surgery often needed to control symptoms
- MANY PATIENTS ARE BELIEVED TO HAVE ULCERATIVE COLITIS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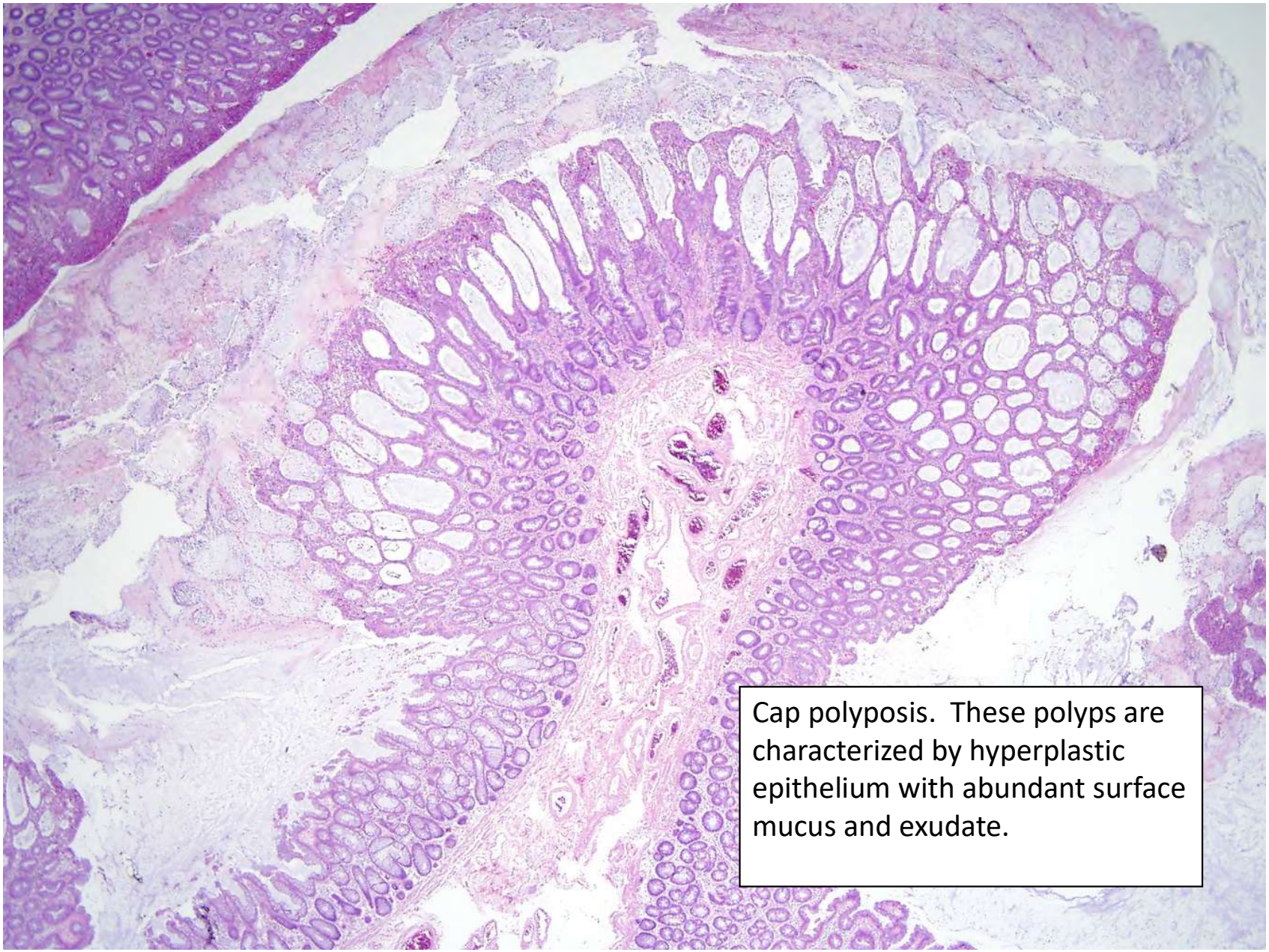
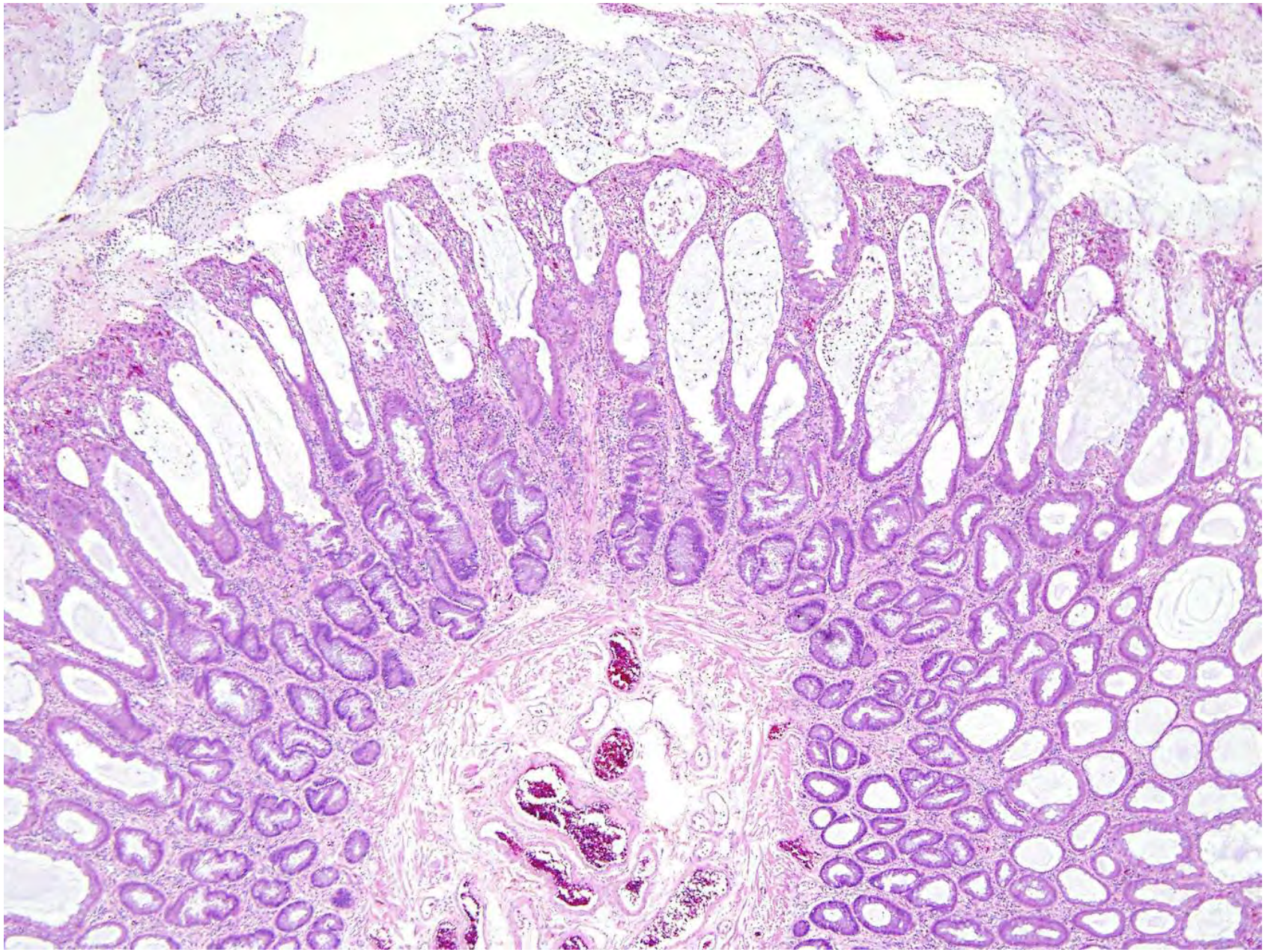
colon



Cap polyposis. These polyps are characterized by hyperplastic epithelium with abundant surface mucus and exudate.



Summary

- We have discussed some general concepts concerning common and rare colonl polyps.
- We have noted some non-hereditary polyposes that can cross our desks

VÅRMÖTE I PATOLOGI

NPM 2025

19–21 MAY

NORDIC PATHOLOGY MEETING