Esophagus – Focus on Barrett's Esophagus

Barrett Esophagus - Epidemiology

- 5th and 6th decade
- M:F - 2:1 -4:1
- White: African-American - 10:1 - 20:1
- Risk of cancer – about 0.5%/year – pooled data mostly US

New study from Denmark

- Hvid-Jensen F, Pedersen L, Drewes AM, Sørensen HT, Funch-Jensen P. Incidence of Adenocarcinoma among Patients with Barrett's Esophagus. N Engl J Med. 2011 Oct 13;365(15):1375-83.
- Annual risk of progression to adenocarcinoma – 0.12%
- Therefore surveillance pointless (at least in Denmark)

Denmark

- Life expectancy (WHO)

M 77y/ F 81y

Obese population estimate:

7%

United States

- Life expectancy

M 76y/ F 81y

Obese population estimate:

33%

Prevalence of BE – Swedish Study

- Columnar lined esophagus in about 10.3%
- BE found in [1.6%] [with goblet cells]
- Alcohol, smoking were risk factors
- *[Gastroenterology 2005; 129: 1825]*

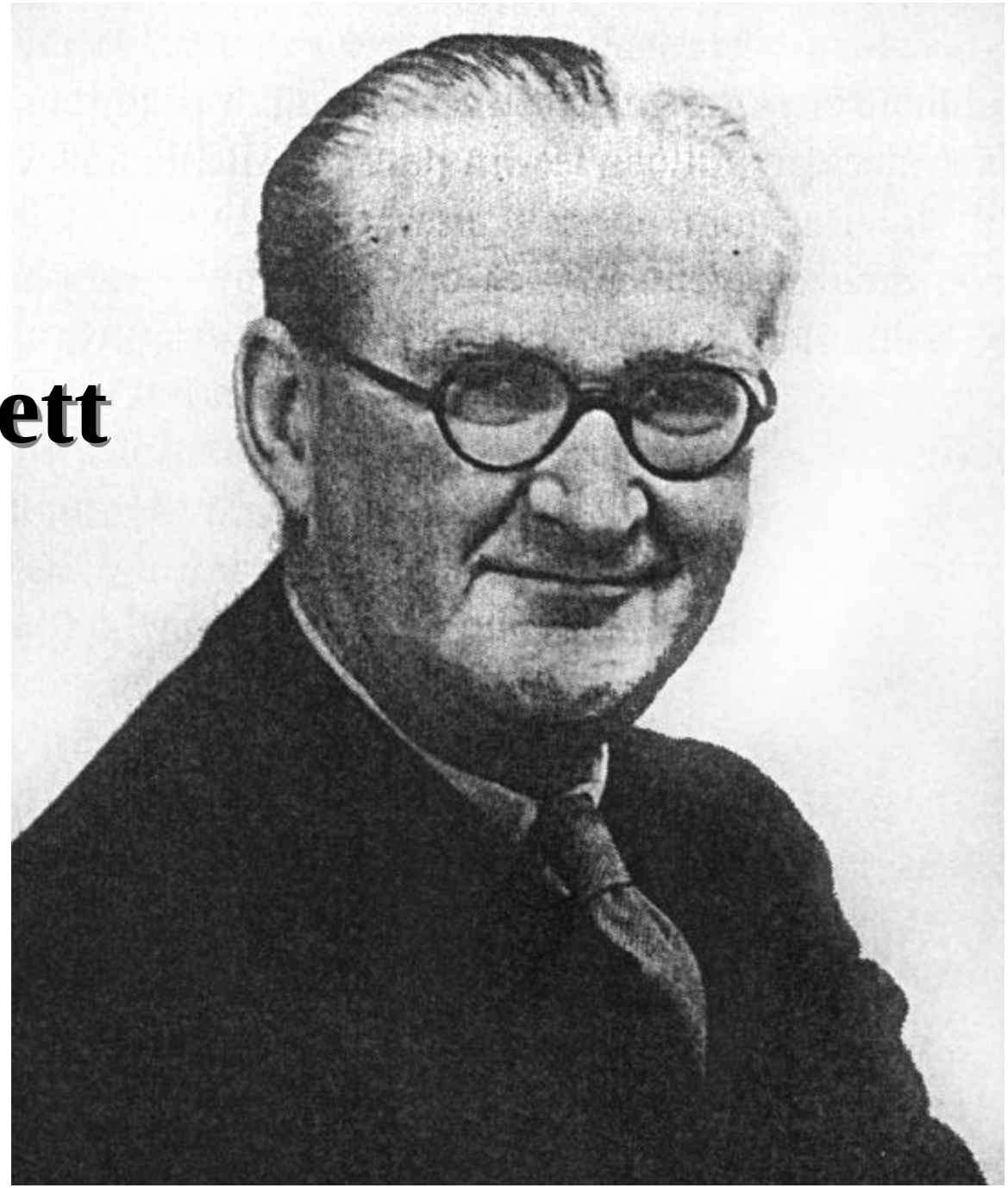
Prevalence of Barrett's USA VA in the Midwest

- 101 men, 9 women, 73% white
- BE found in 27 (25%); 7% LSBE and 17%SSBE
- Risks: Obesity, smoking, alcohol, FH of GERD

CHRONIC PEPTIC ULCER OF THE ŒSOPHAGUS AND 'ŒSOPHAGITIS'

By N. R. BARRETT, London

Norman Barrett

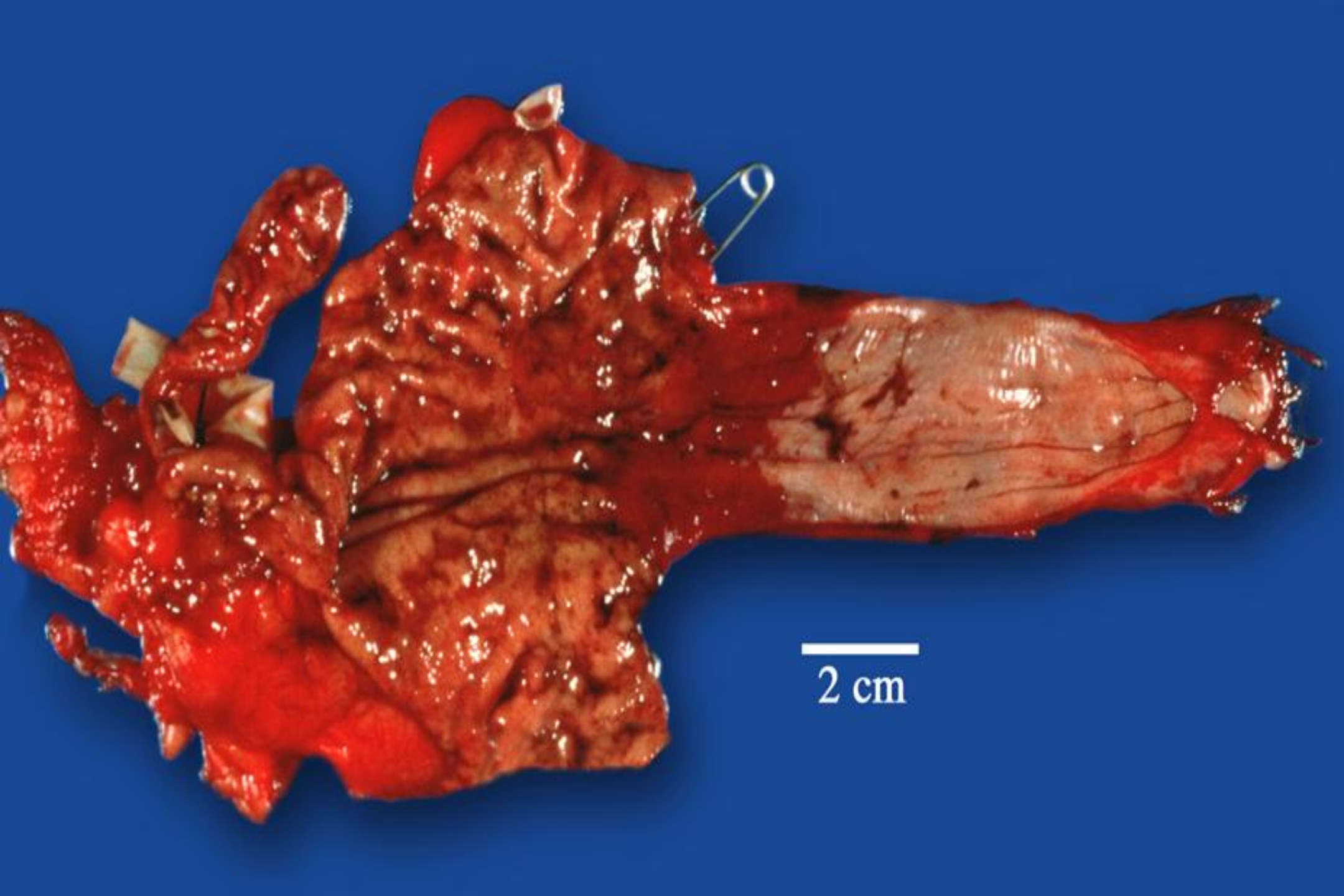


Barrett's Esophagus

- Barrett NR. Chronic peptic ulcer of the oesophagus and "oesophagitis". Br J Surg 1950; 38:174-82.
- Barrett NR. The lower oesophagus lined by columnar epithelium. Surgery 1957; 41: 881-94.

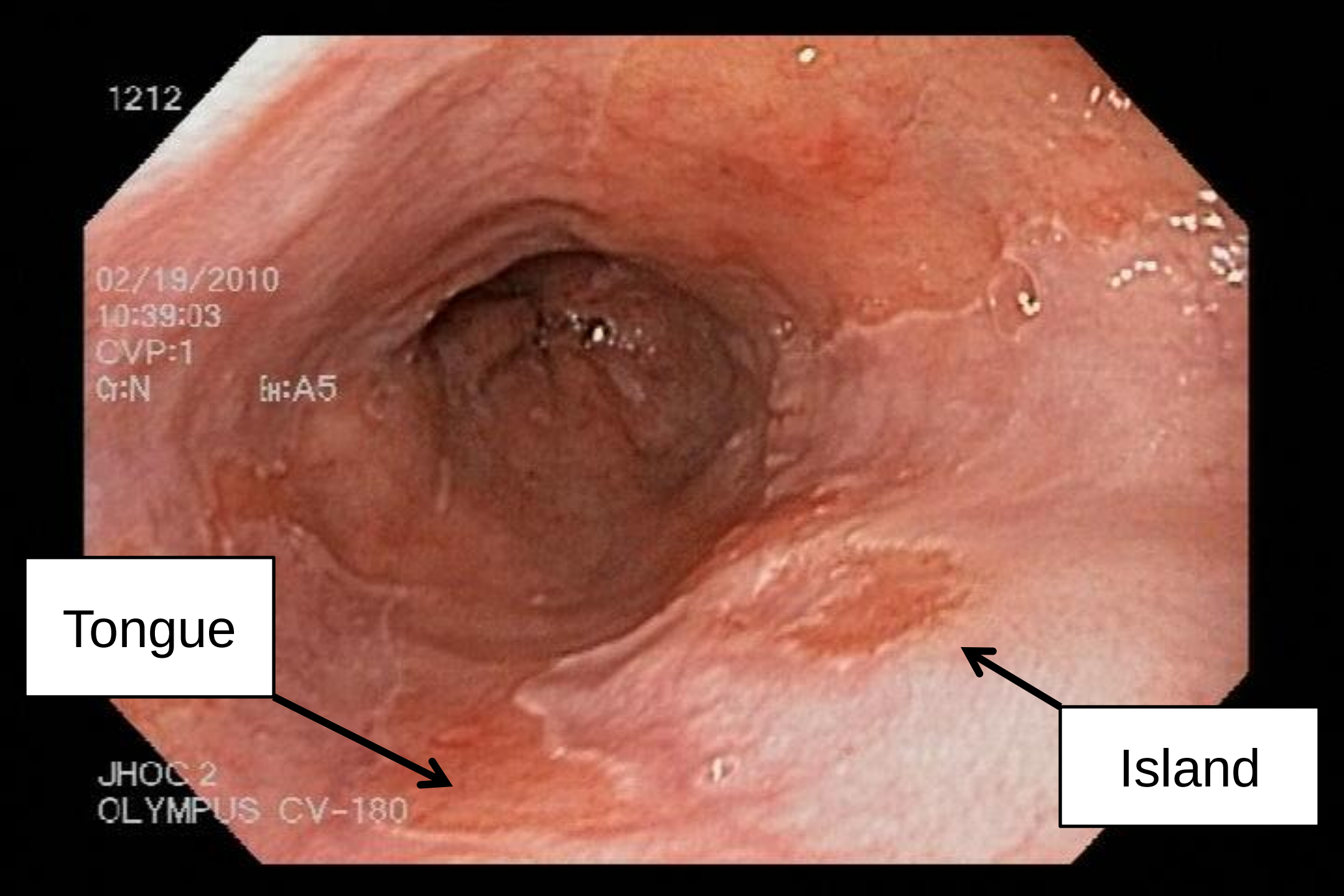
Complications of Barrett's Esophagus - Then versus Now

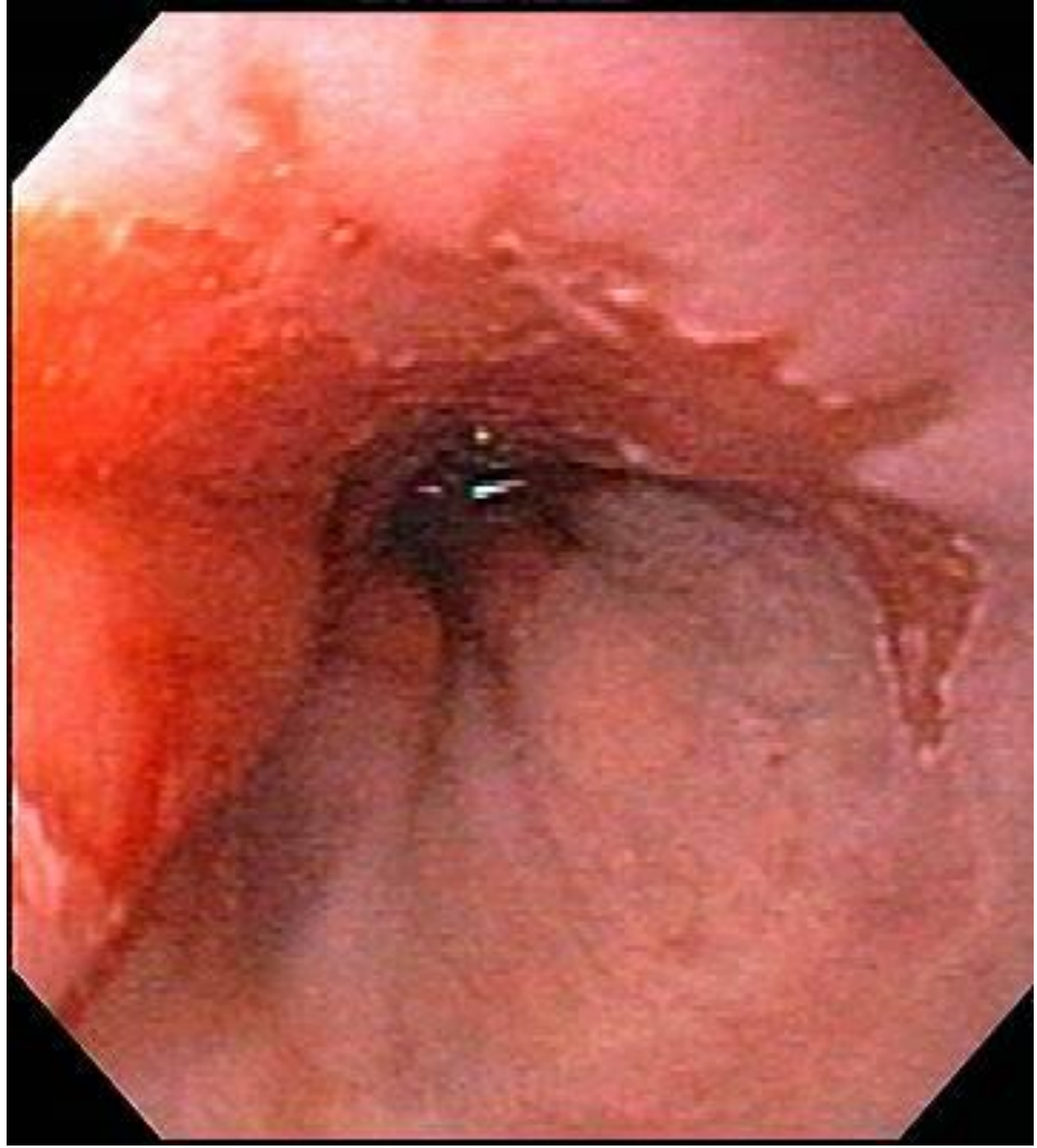
- Then - severe erosive esophagitis and strictures
- Now - in proton pump inhibitor era, ulcers readily healed
- Esophageal reflux now established as a pre-neoplastic process
- Objective now - endoscopic surveillance

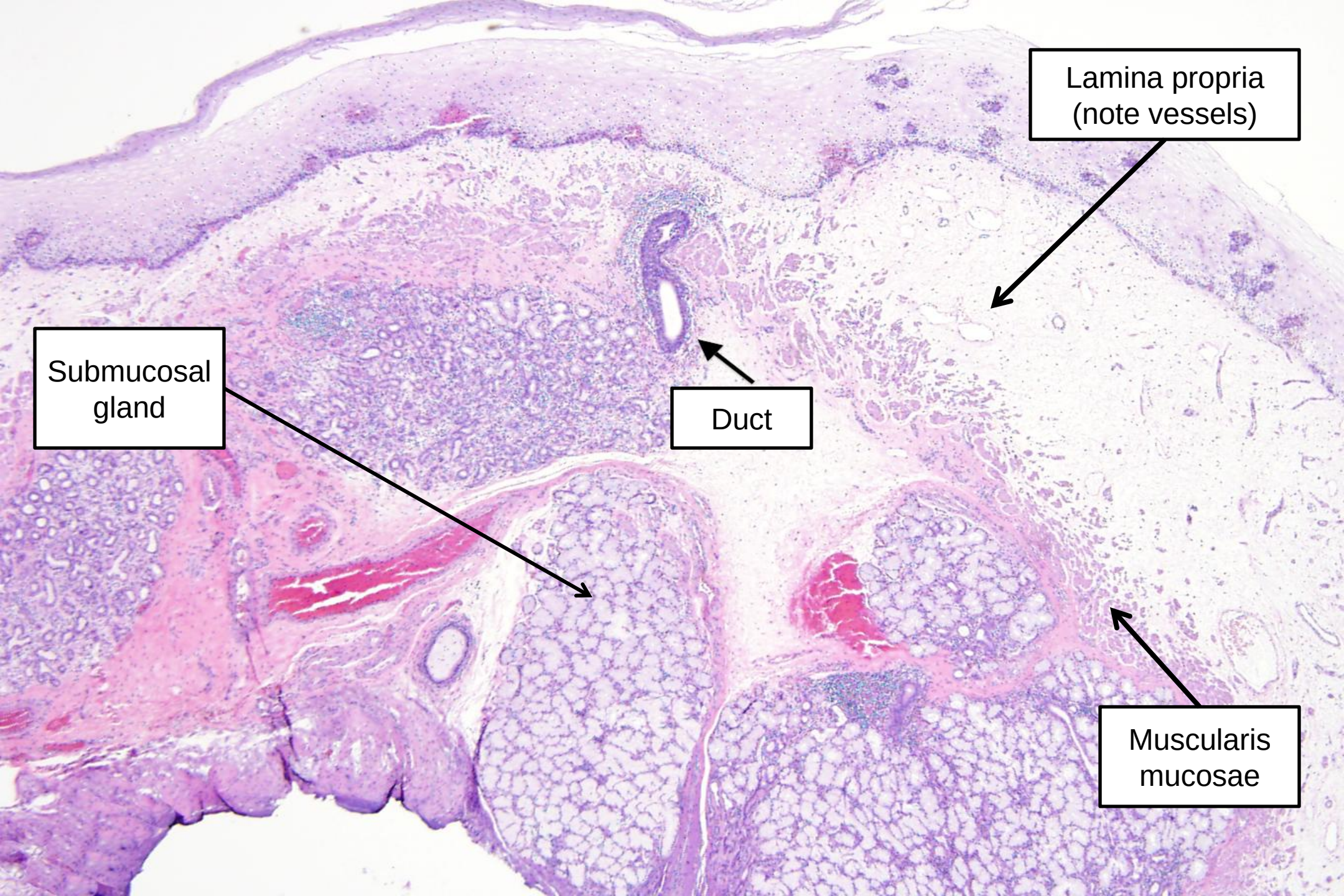

2 cm

American College of Gastroenterology Criteria for Barrett's Esophagus

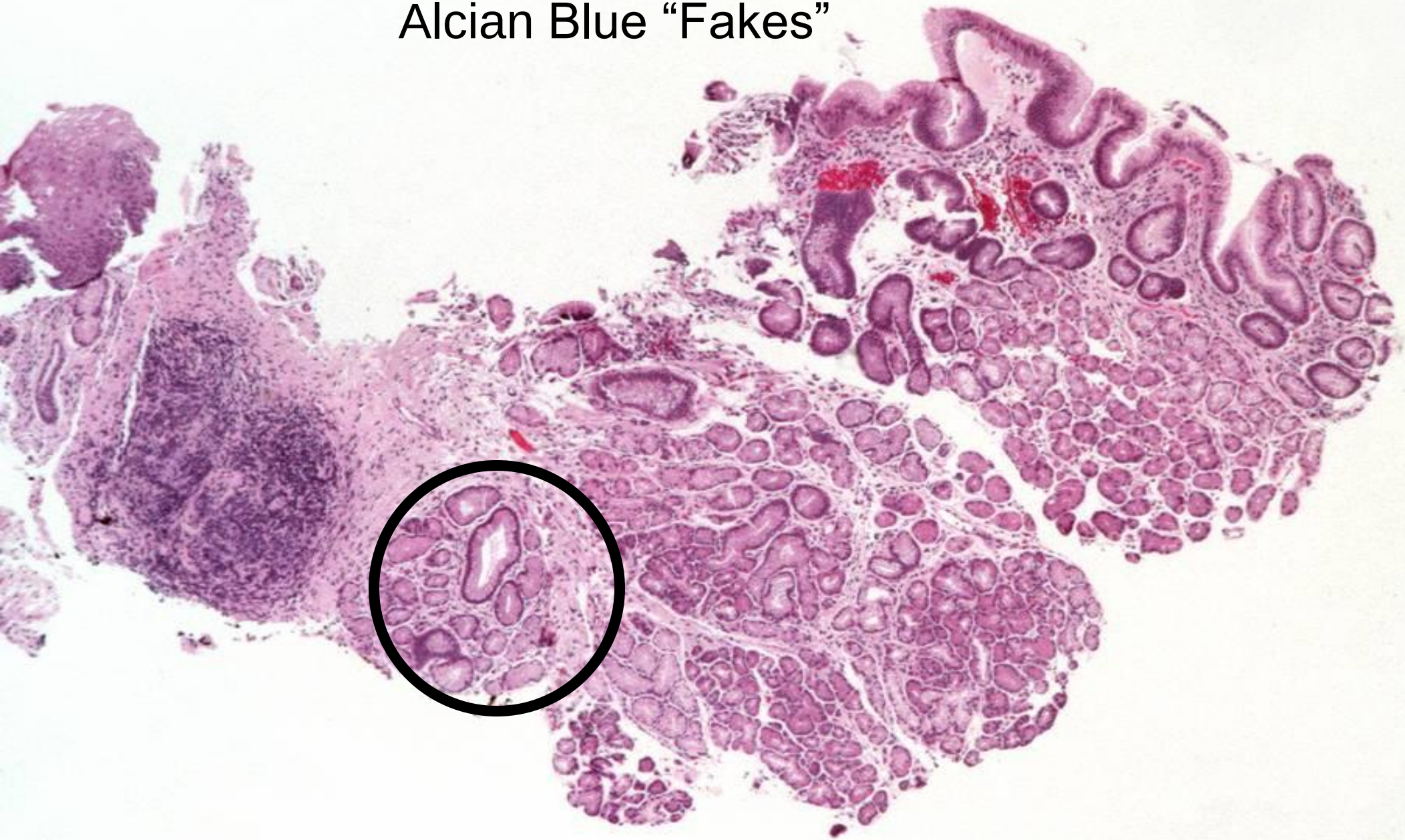
- Barrett's mucosa is a change of the esophageal epithelium of any length that
- 1) can be recognized at endoscopy and
- 2) is confirmed to have intestinal metaplasia on biopsy


1212
02/19/2010
10:39:03
CVP:1
Cr:N
EH:A5
JHOC 2
OLYMPUS CV-180
Tongue
Island

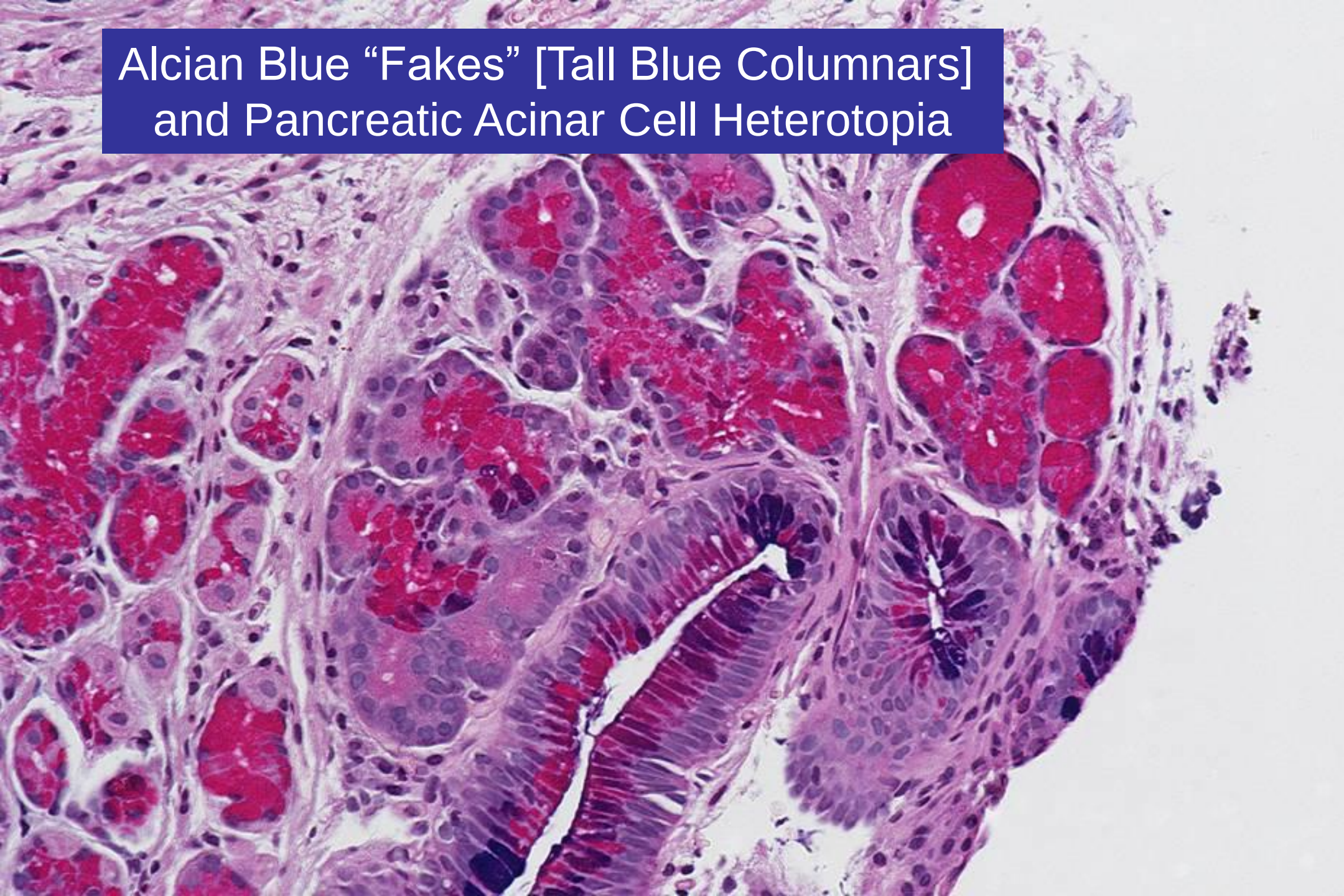


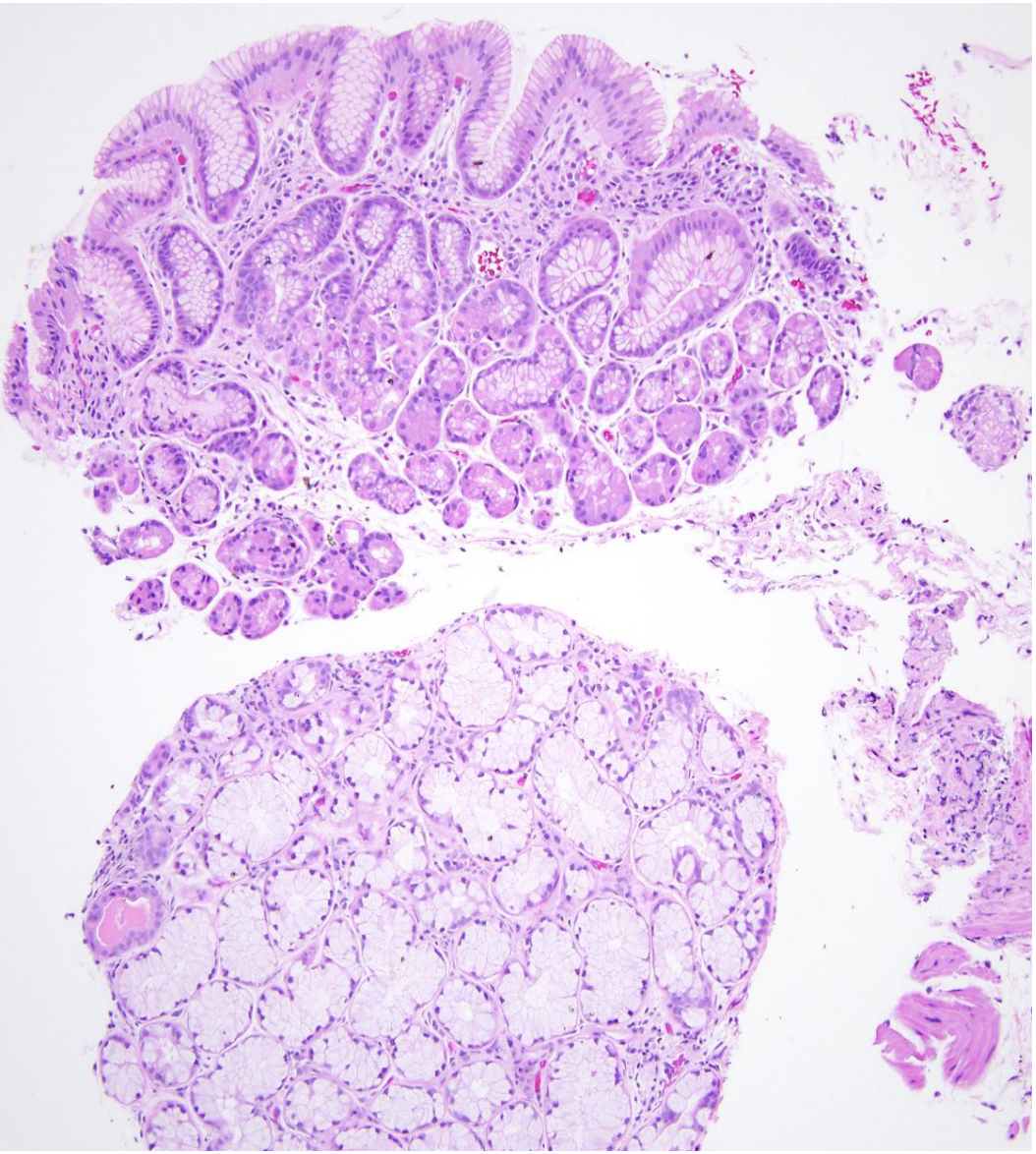

Lamina propria
(note vessels)
Submucosal
gland
Duct
Muscularis
mucosae

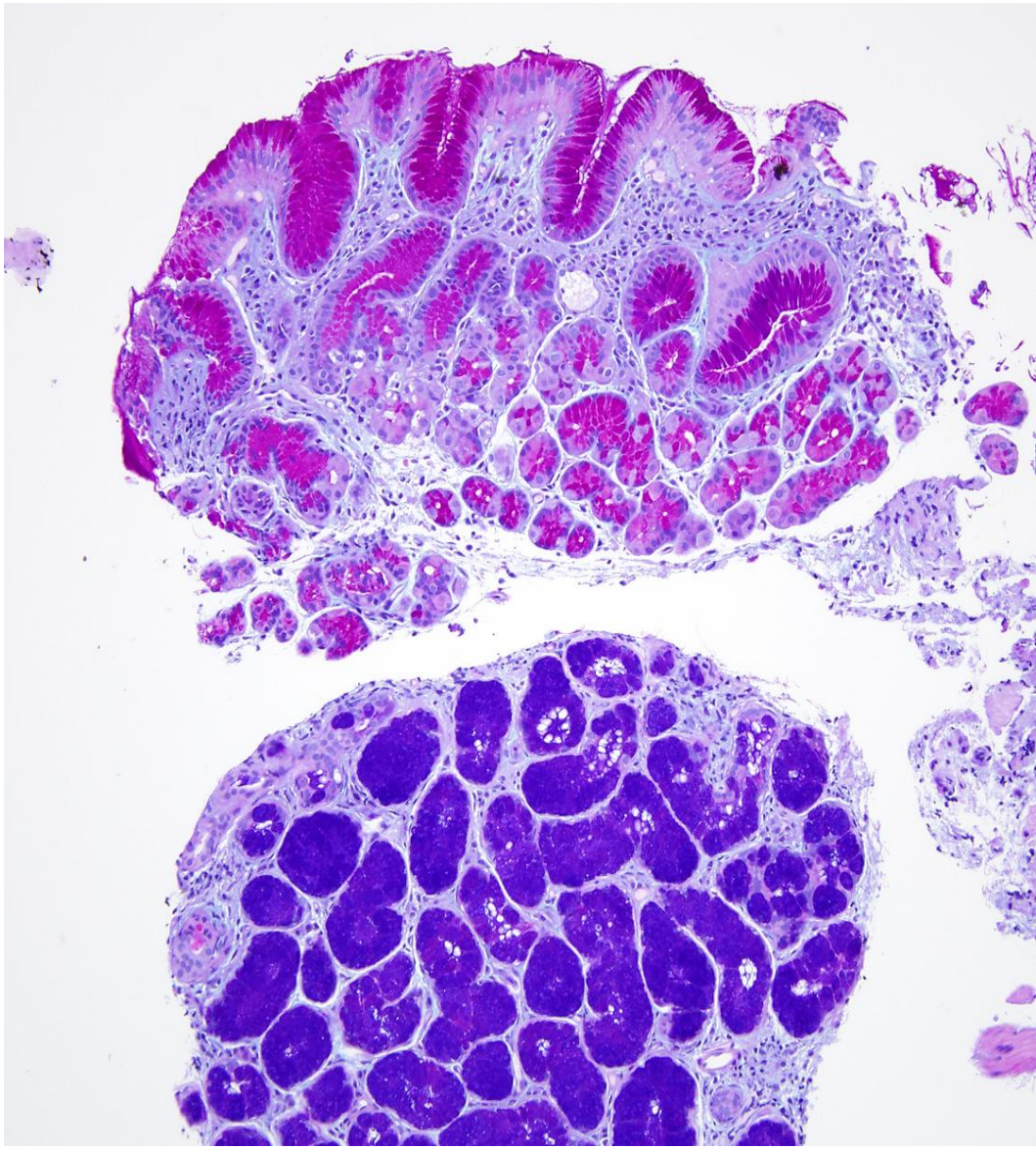
Alcian Blue “Fakes”



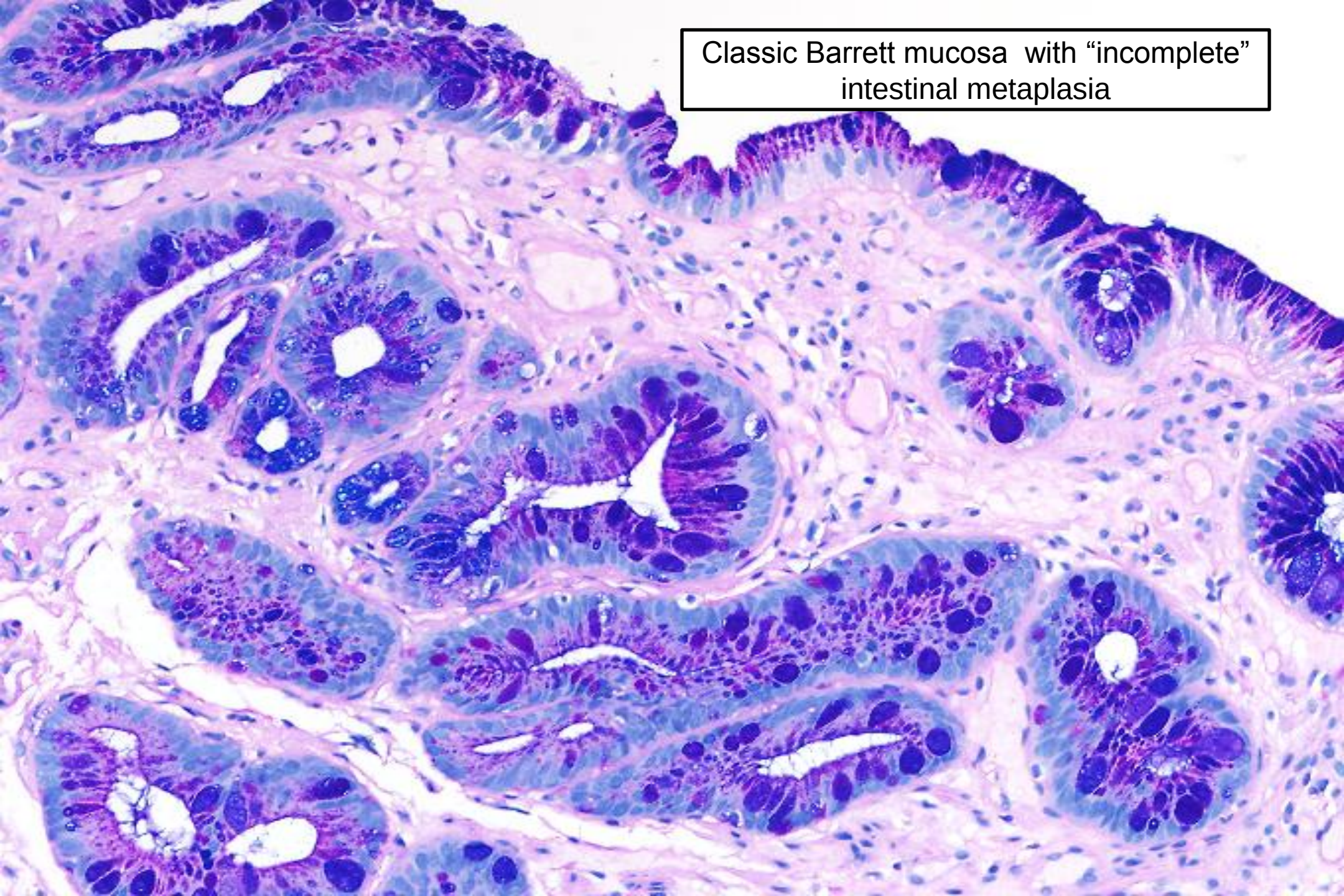
Alcian Blue “Fakes” [Tall Blue Columnars] and Pancreatic Acinar Cell Heterotopia

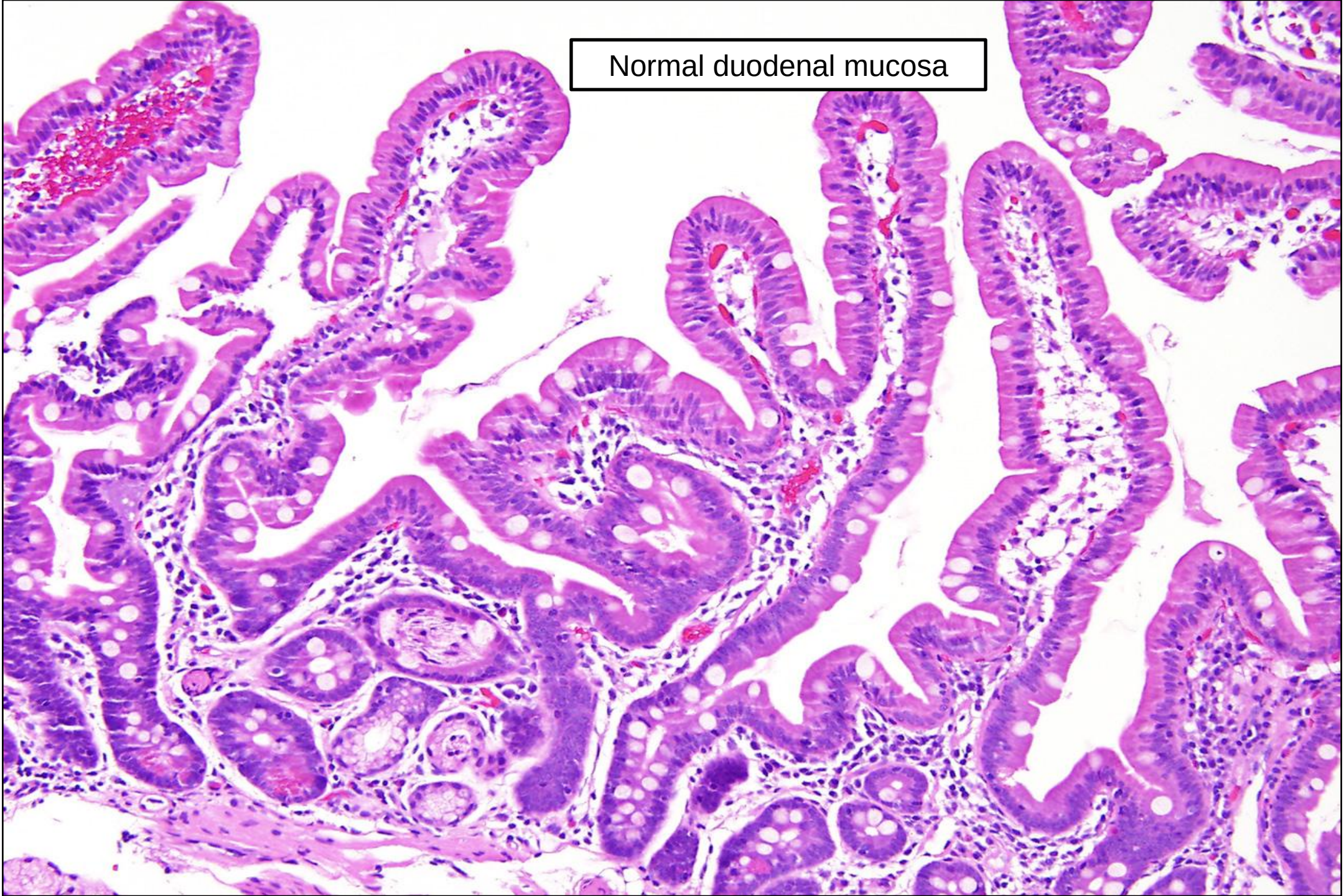


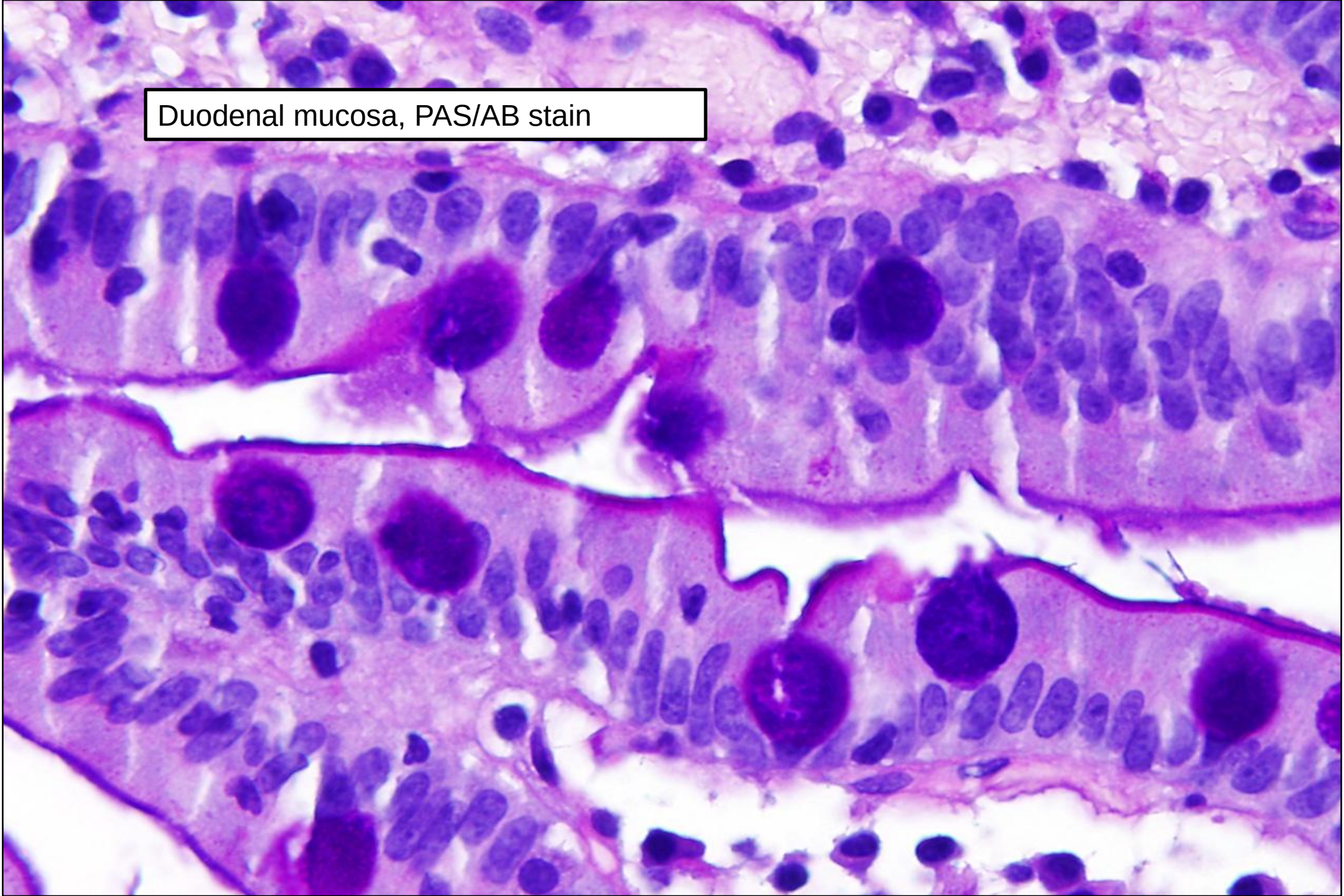




This biopsy is from esophagus – Submucosal glands are present (very purple on Alcian blue)

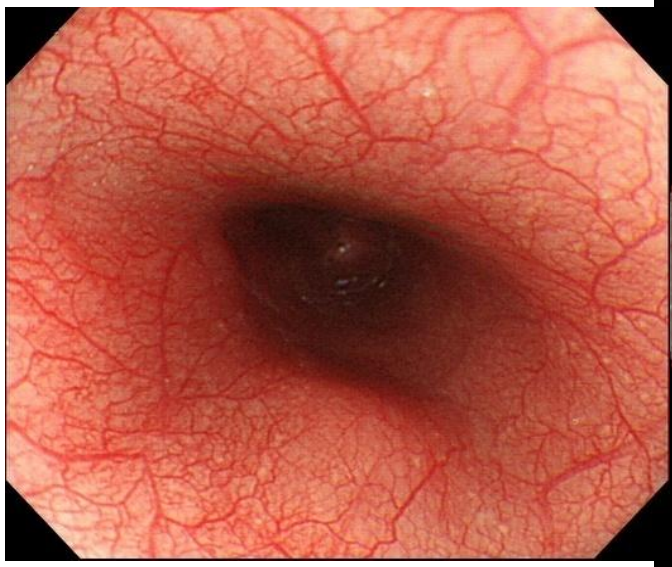

Classic Barrett mucosa with “incomplete” intestinal metaplasia


Normal duodenal mucosa


Duodenal mucosa, PAS/AB stain

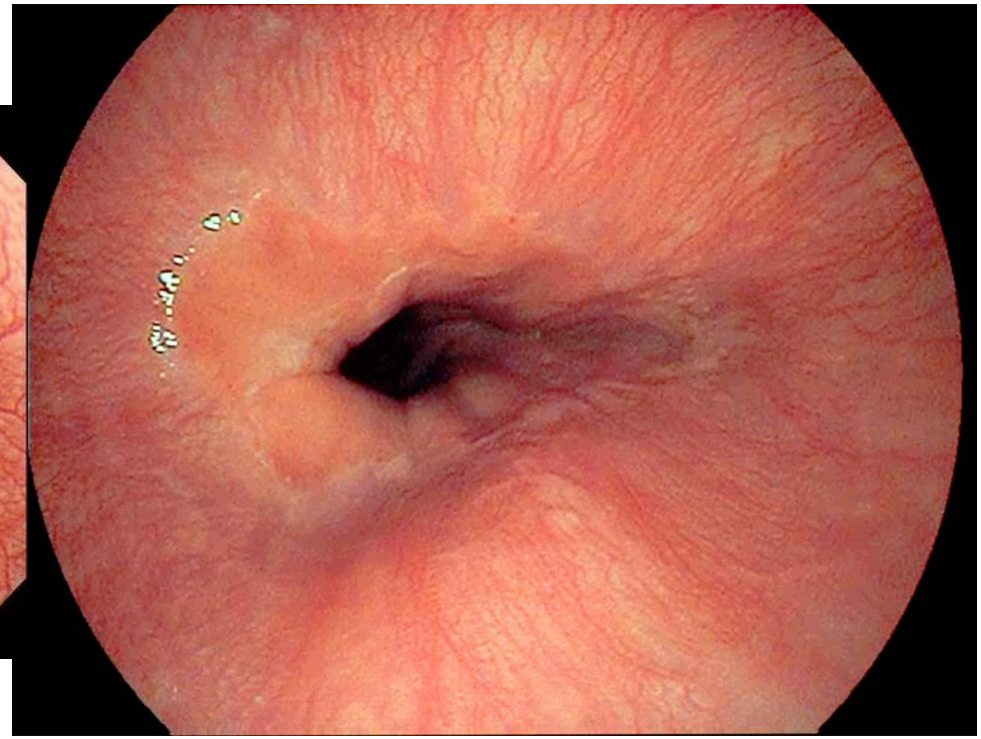
Endoscopic Features Middle Esophagus

Network pattern



Endoscopic Features of Lower Esophagus

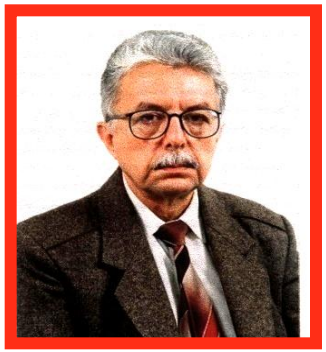
Palisade pattern



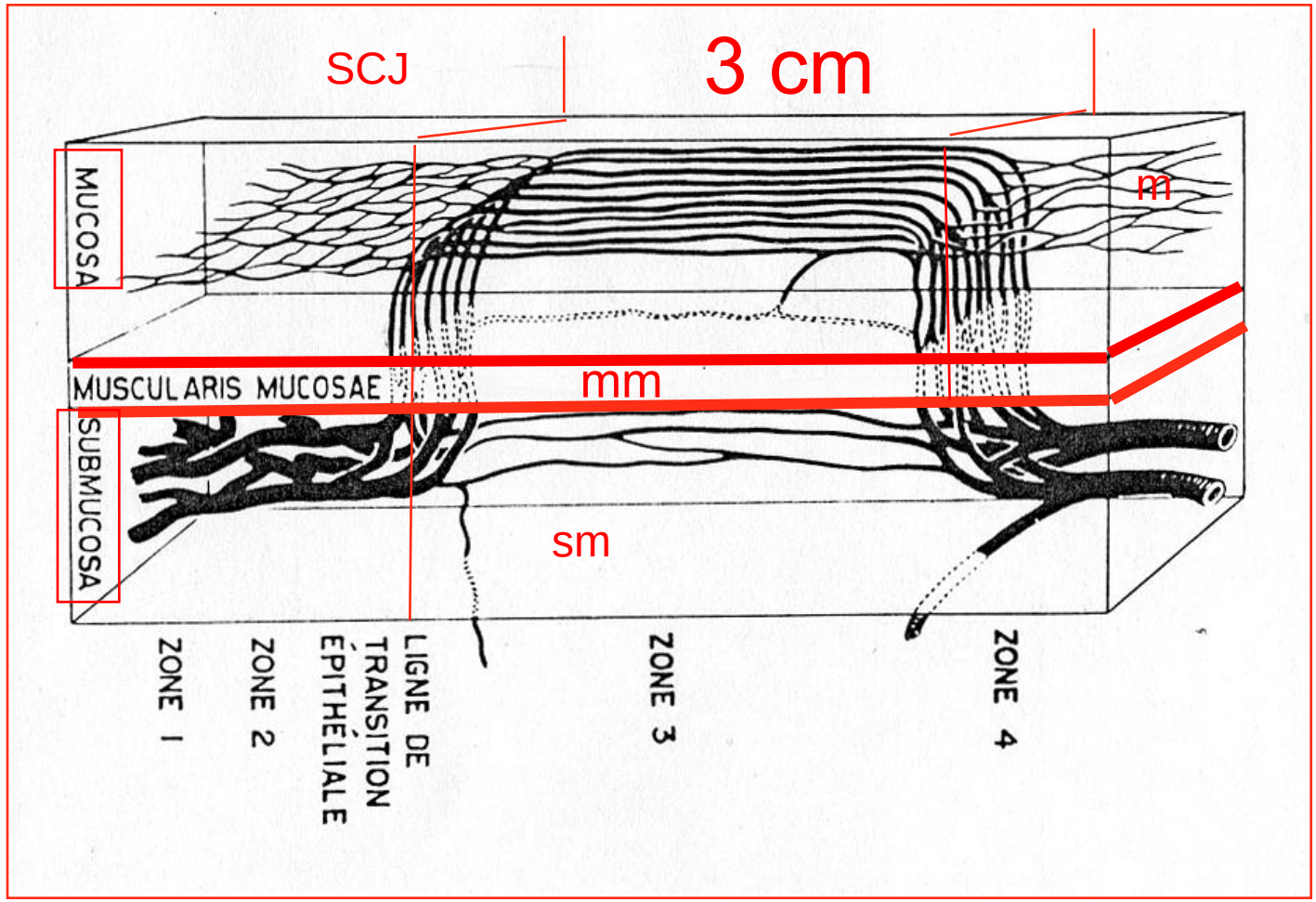
De Carvalho. Acta Anat 1966
Hoshihara et al. Gastroenterol Endosc 1986
Takubo et al. Esophagus 2003, Arch Pathol Lab Med 2005
Hoshihara et al. Esophagus 2006

Hoshihara Y (Left)

Scheme of Palisade Vessels (from Original Paper)

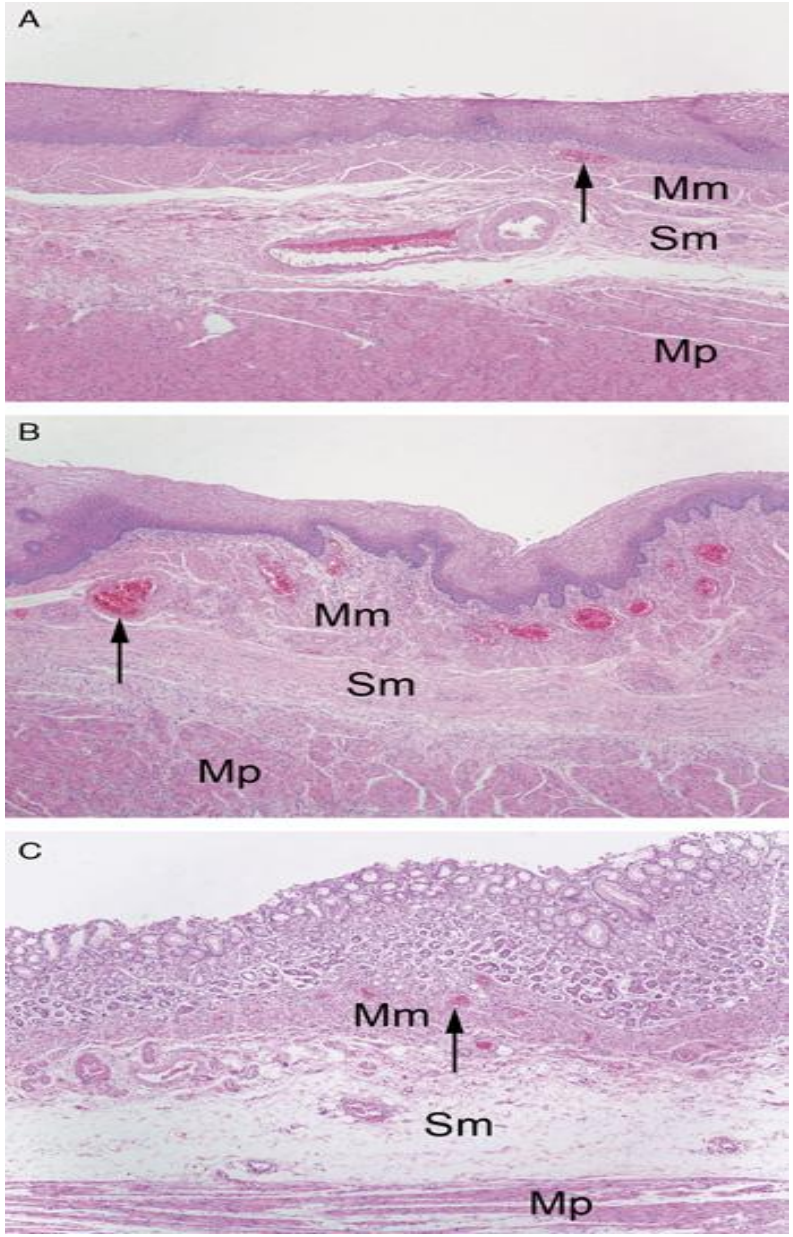


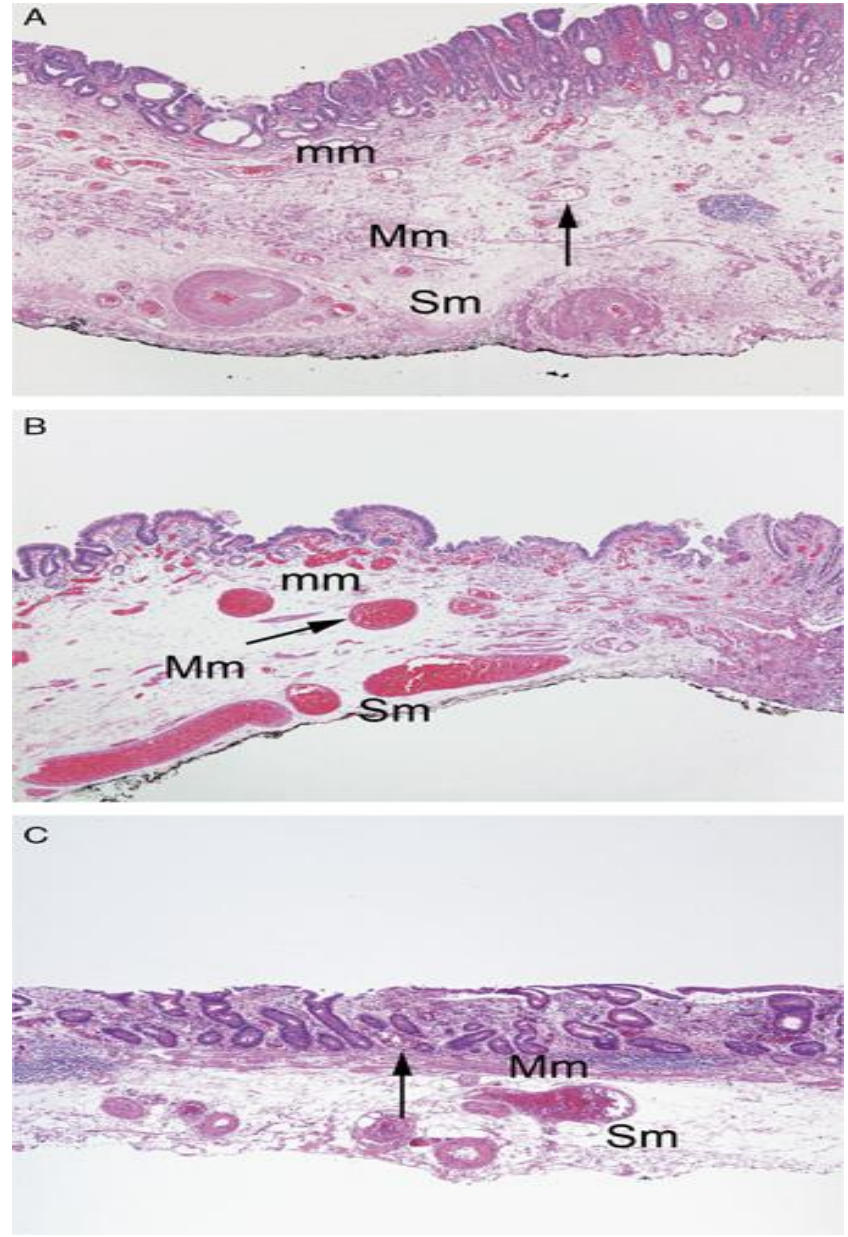
De Carvalho CAF

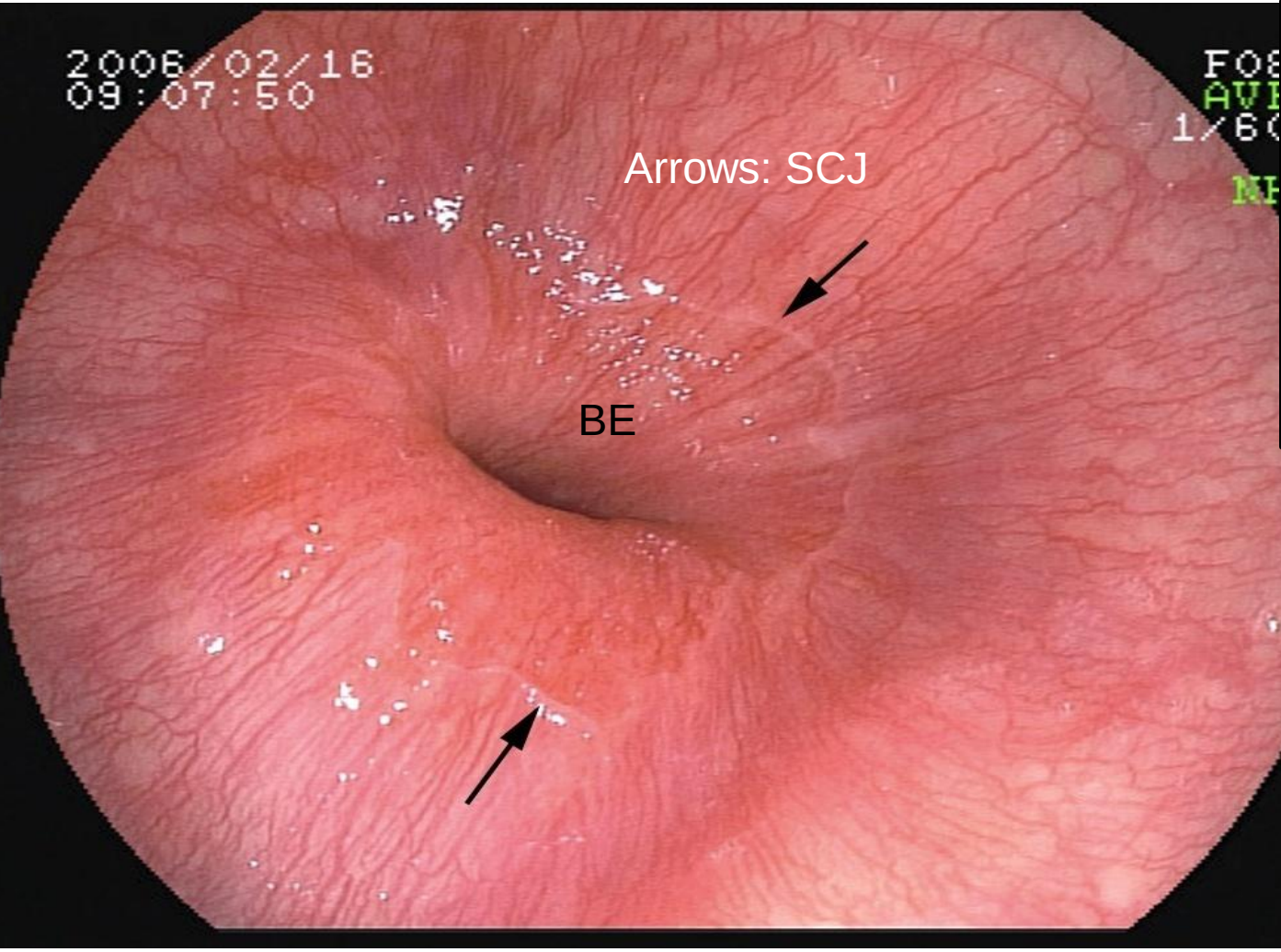


De Carvalho CAF. Sur l'angio-architecture veineuse de la zone de transition oesophago-gastrique et son interpretation fonctionnelle. Acta Anat 1966;**64**:125-162 (in French with English and German abstracts)

Aida J, Vieth M, Ell C, May A, Pech O, Hoshihara Y, Kumagai Y, Kawada K, Hishima T, Tateishi Y, Sawabe M, Arai T, Matsuura M, Takubo K. Palisade vessels as a new histologic marker of esophageal origin in ER specimens from columnar-lined esophagus. Am J Surg Pathol. 2011 Aug;35(8):1140-5.







Endoscopic Features of Barrett's Esophagus

(Definition of Barrett's esophagus by the Japan Esophageal Society 2000, Takubo et al. Esophagus 2003, Arch Pathol Lab Med 2005).

(De Carvalho. Acta Anat 1966, Hoshihara et al. Gastroenterol Endosc 1986).

Endoscopic Barrett's Esophagus Based on Japanese Definitions of Barrett's Esophagus and EGJ

Palisade vessels are seen through columnar epithelium (BE)

Histologic examination is unnecessary as well as Plaque C & M Classification

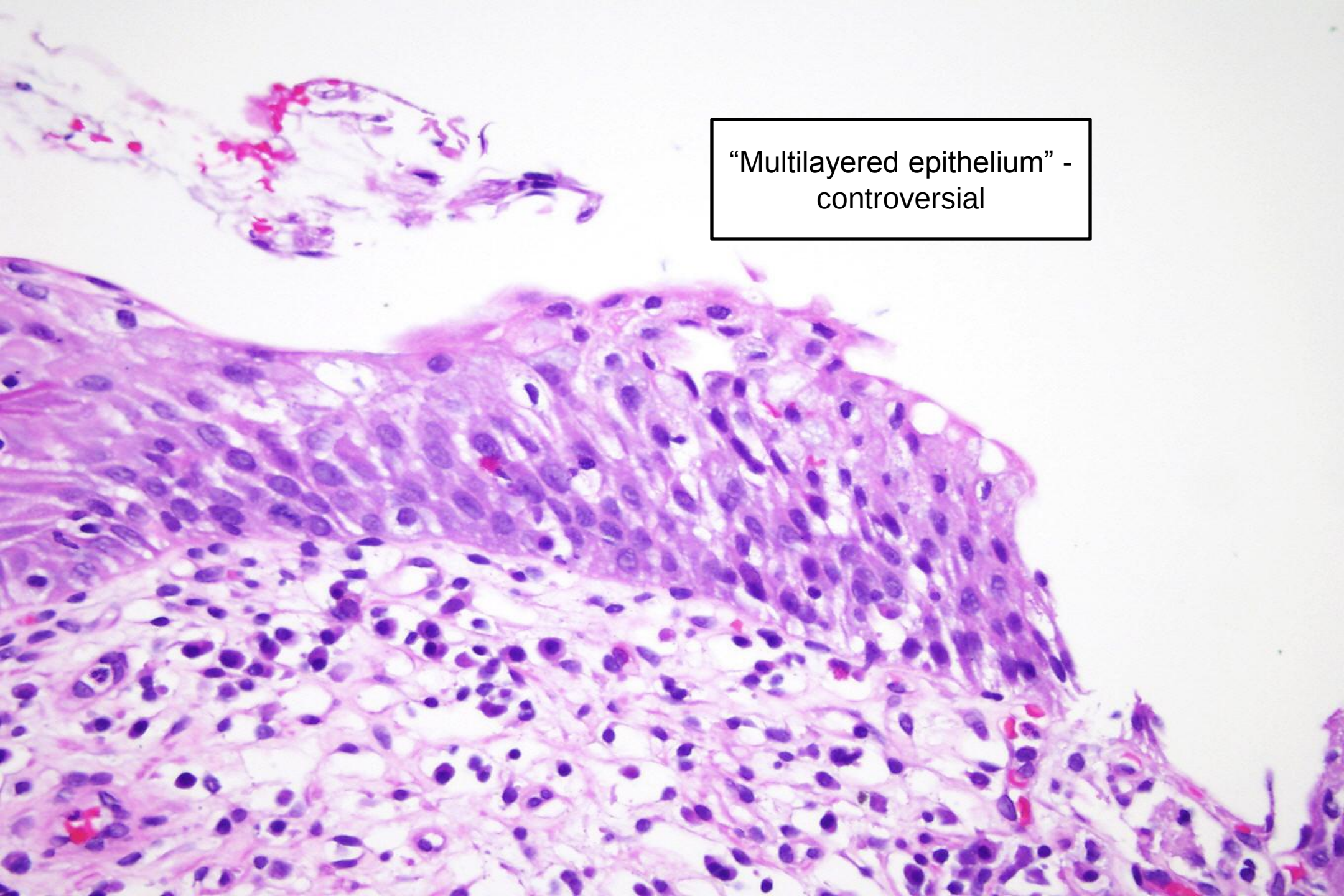
Risk for Progression To Cancer

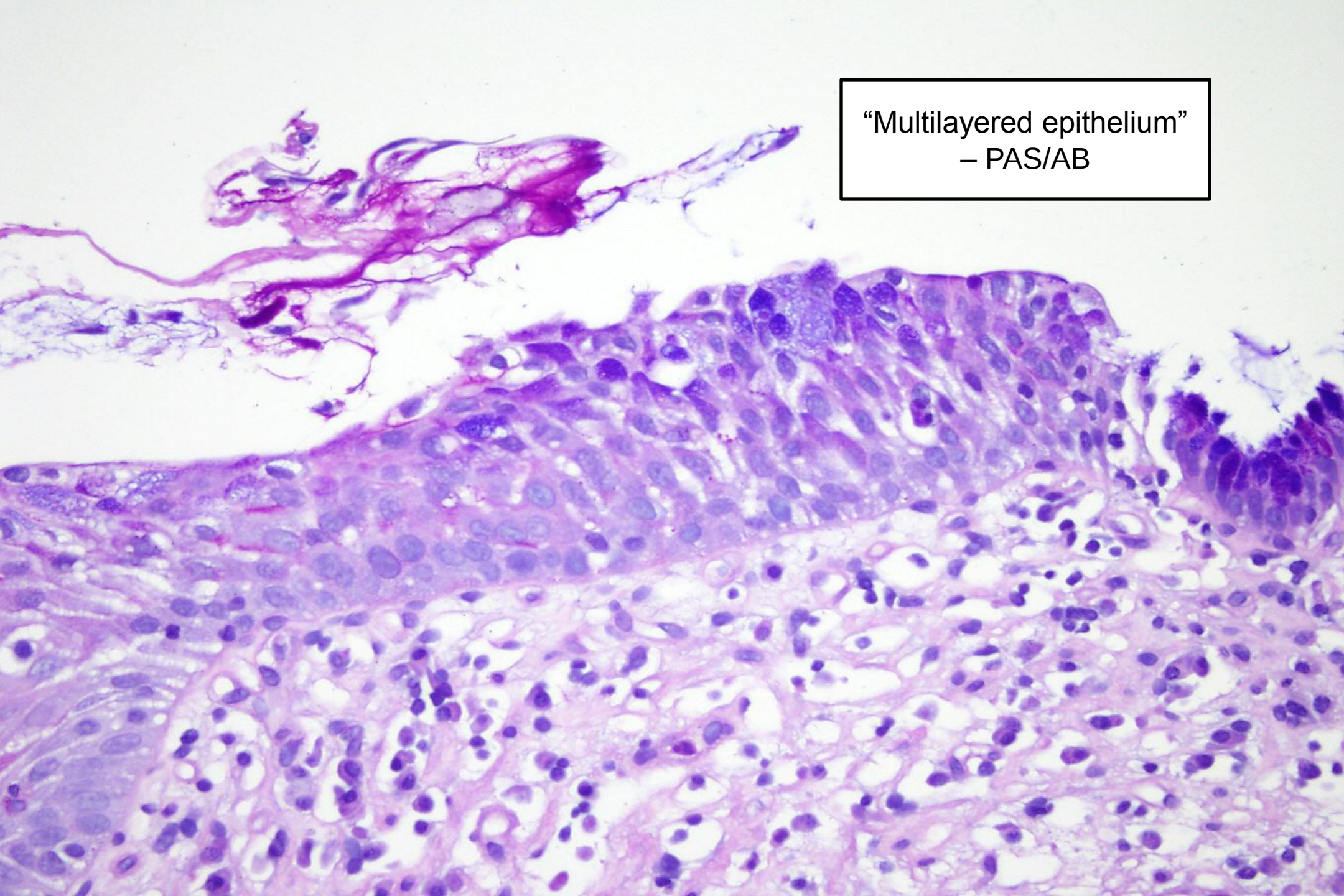
- Sharma et al. Gut 2000; 46: 9-13
- 177 SSBE patients were compared to 76 with CIM using ACG criteria
- Follow-up of 78 SSBE – 9 dysplasias [7 LGD, 2 HGD]
- Follow-up of 34 CIM patients - 1 dysplasia [LGD]
- P = 0.0077

?US/Germany/France,etc Will Stop Requiring Goblet Cells?

- Example: Takubo et al Hum Pathol 2009;40:65-74 used German cases and found that intestinal metaplasia accompanied only 43% of early esophageal adenocarcinomas and believed that most cases arose in association with cardiac type mucosa.
- Stay tuned!
- ACC did not remove the requirement for goblet cells in 2008; AGA will not in upcoming position paper – 2010 but changed definition to leave the door open.


“Multilayered epithelium” - controversial


“Multilayered epithelium” - controversial


“Multilayered epithelium”
– PAS/AB

Dysplasia

- Neoplastic Epithelium Confined within the basement membrane of the gland within which it arose.

Diagnostic Categories

- Negative for dysplasia
- Indefinite for dysplasia
- Dysplasia, low-grade
- Dysplasia, high-grade
- Intra-mucosal carcinoma

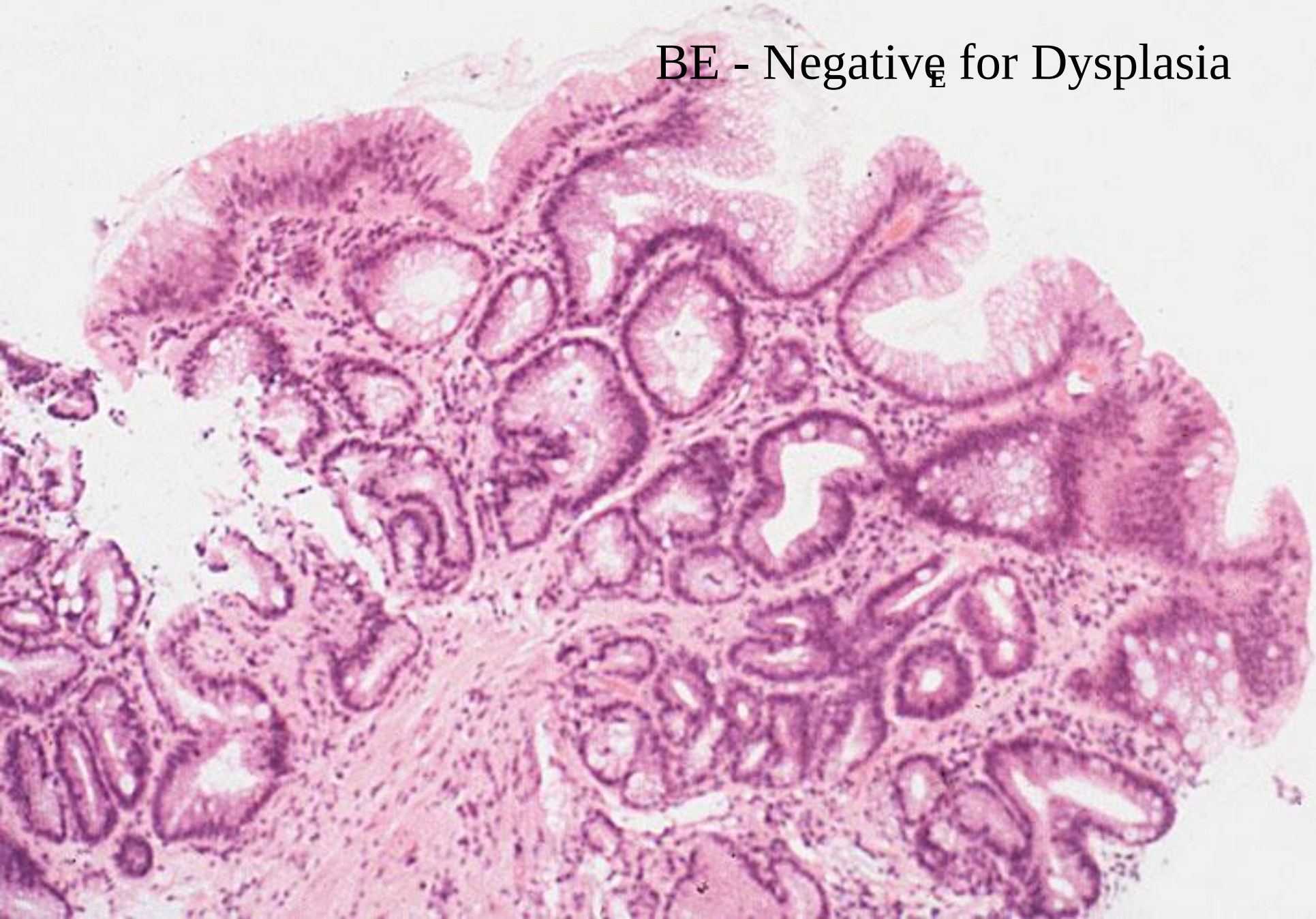
Grading Dysplasia in Barrett's - Algorithm

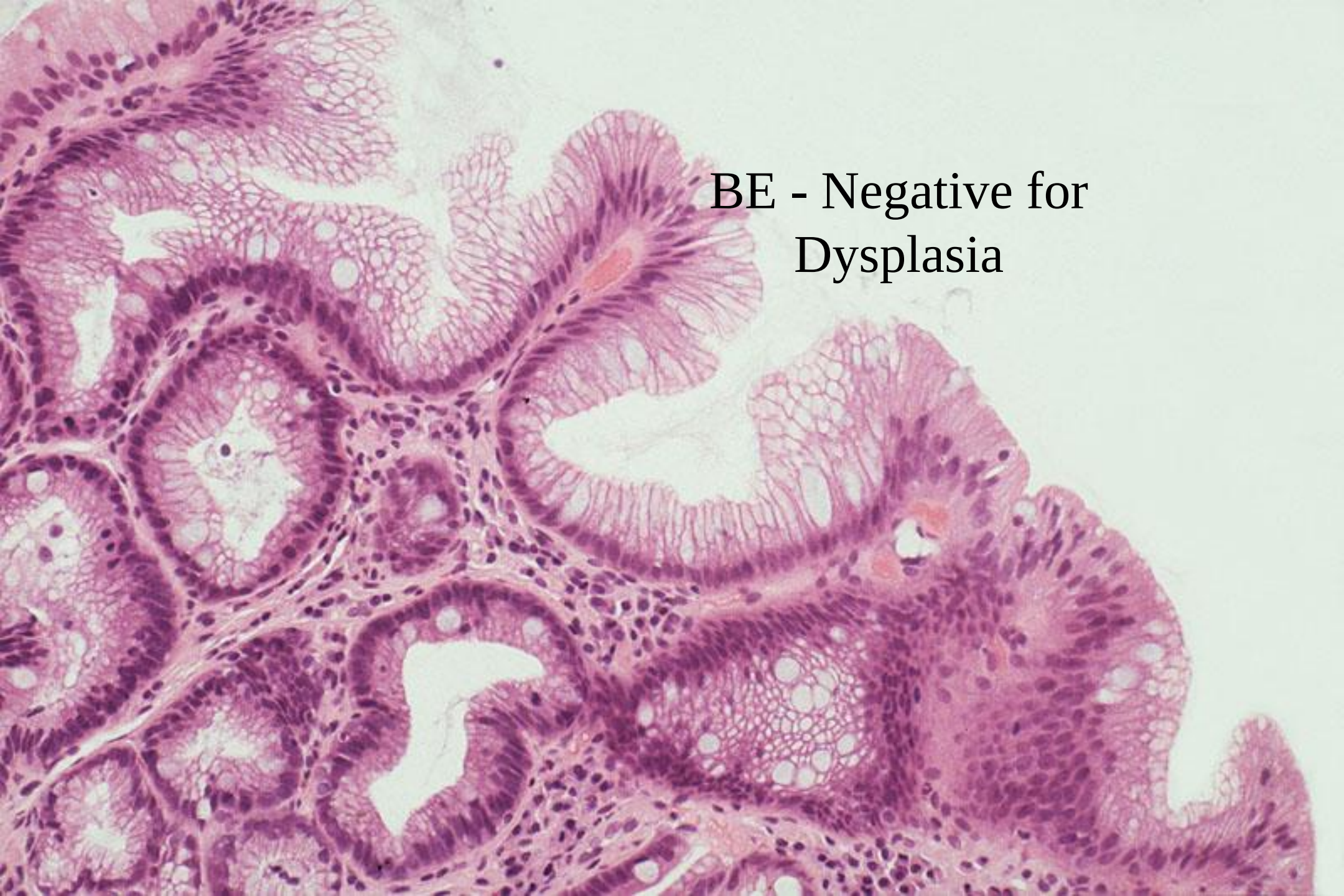
- SURFACE MATURATION [COMPARED TO UNDERLYING GLANDS]
- ARCHITECTURE
- CYTOLOGIC FEATURES
- INFLAMMATION

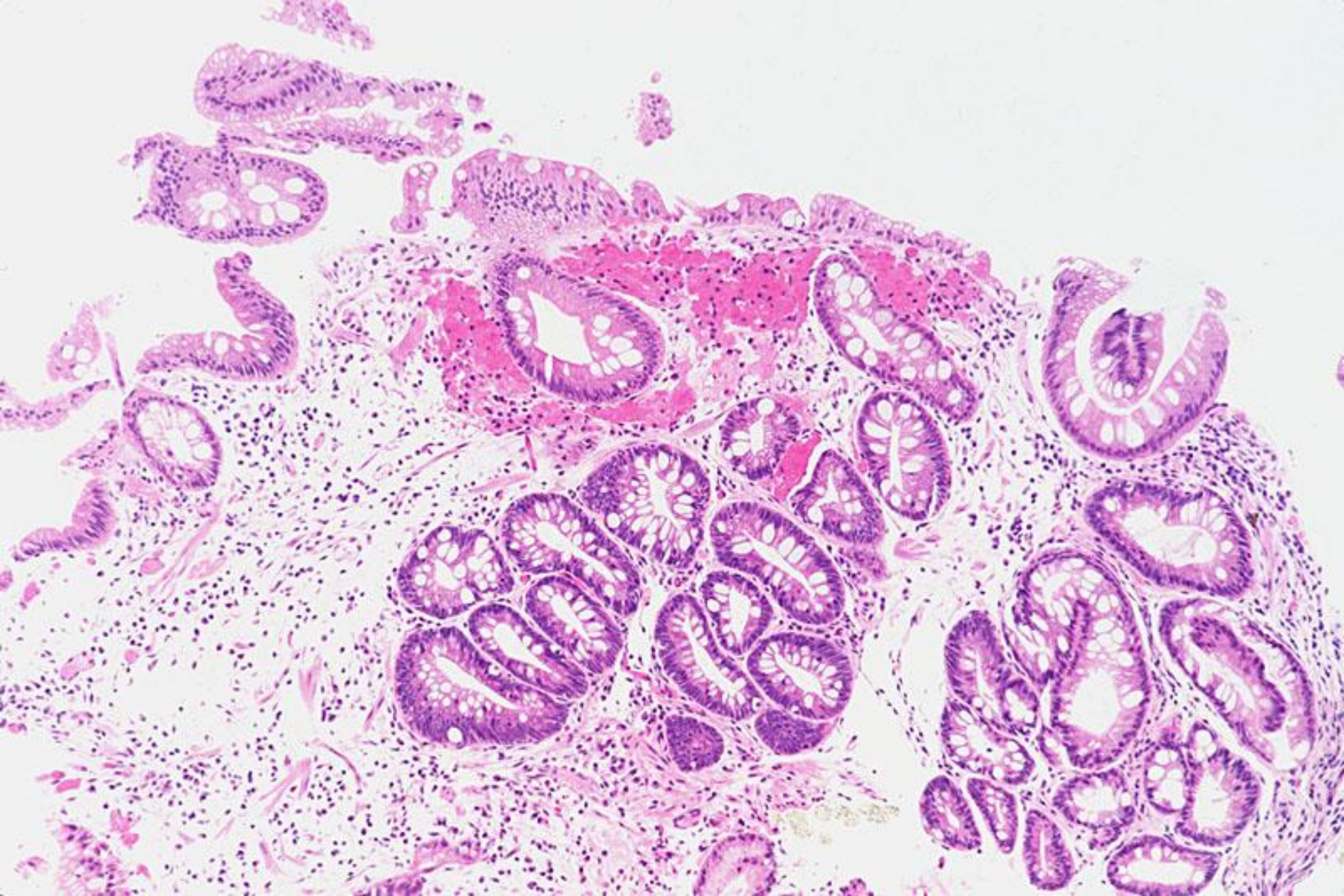
BE - Negative for Dysplasia

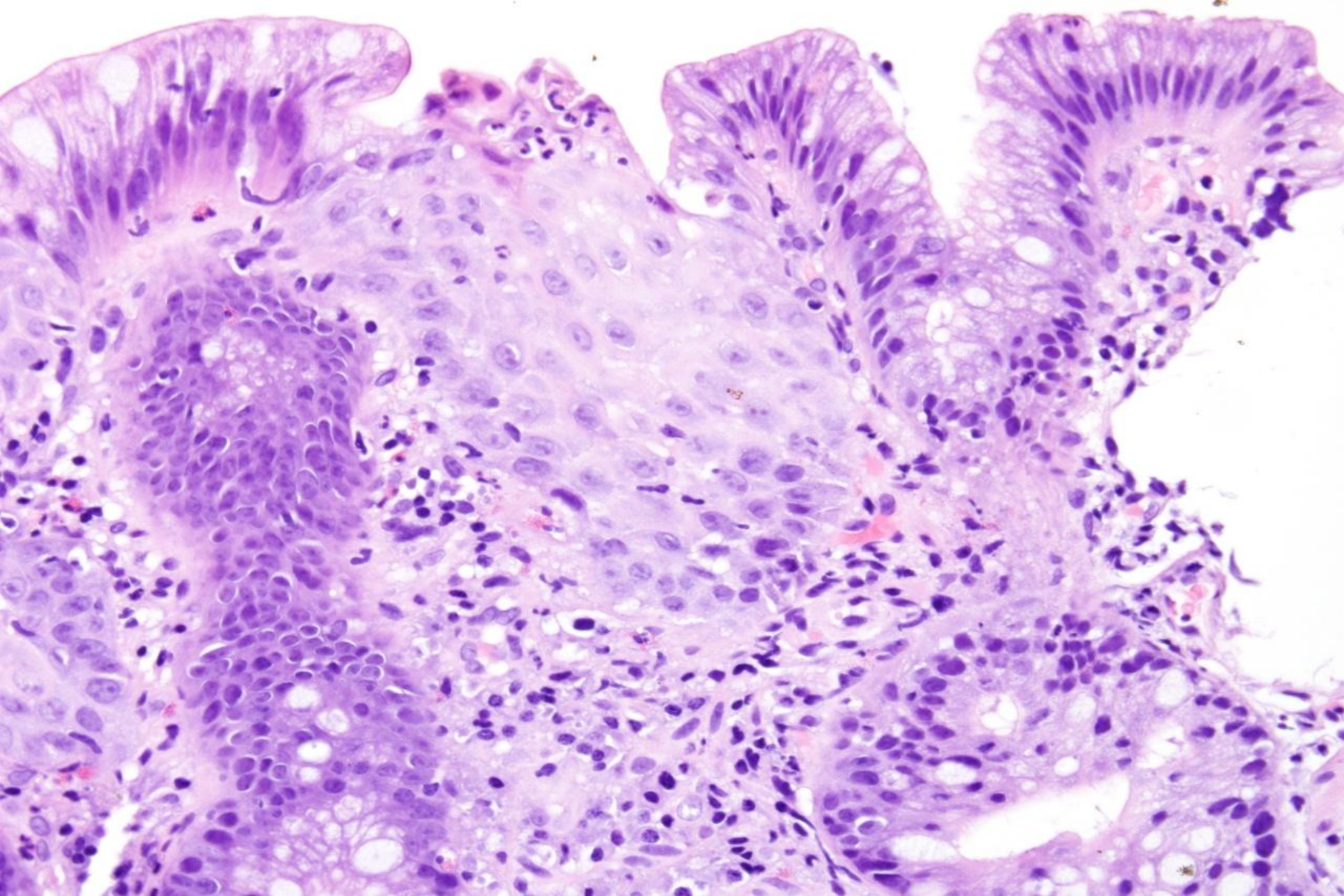
- Surface - More mature than glands
- Architecture - Abundant lamina propria
- Cytology - Normal with mitoses confined to deeper glands. Nuclei with smooth nuclear membranes. Normal nuclear polarity
- Inflammation - Variable

BE - Negative for Dysplasia




BE - Negative for
Dysplasia





Indefinite for dysplasia

Originally defined in IBD and diagnosed by answering the questions…

a) Is this epithelium unequivocally benign or reactive?

b) Is this epithelium unequivocally neoplastic/adenomatous

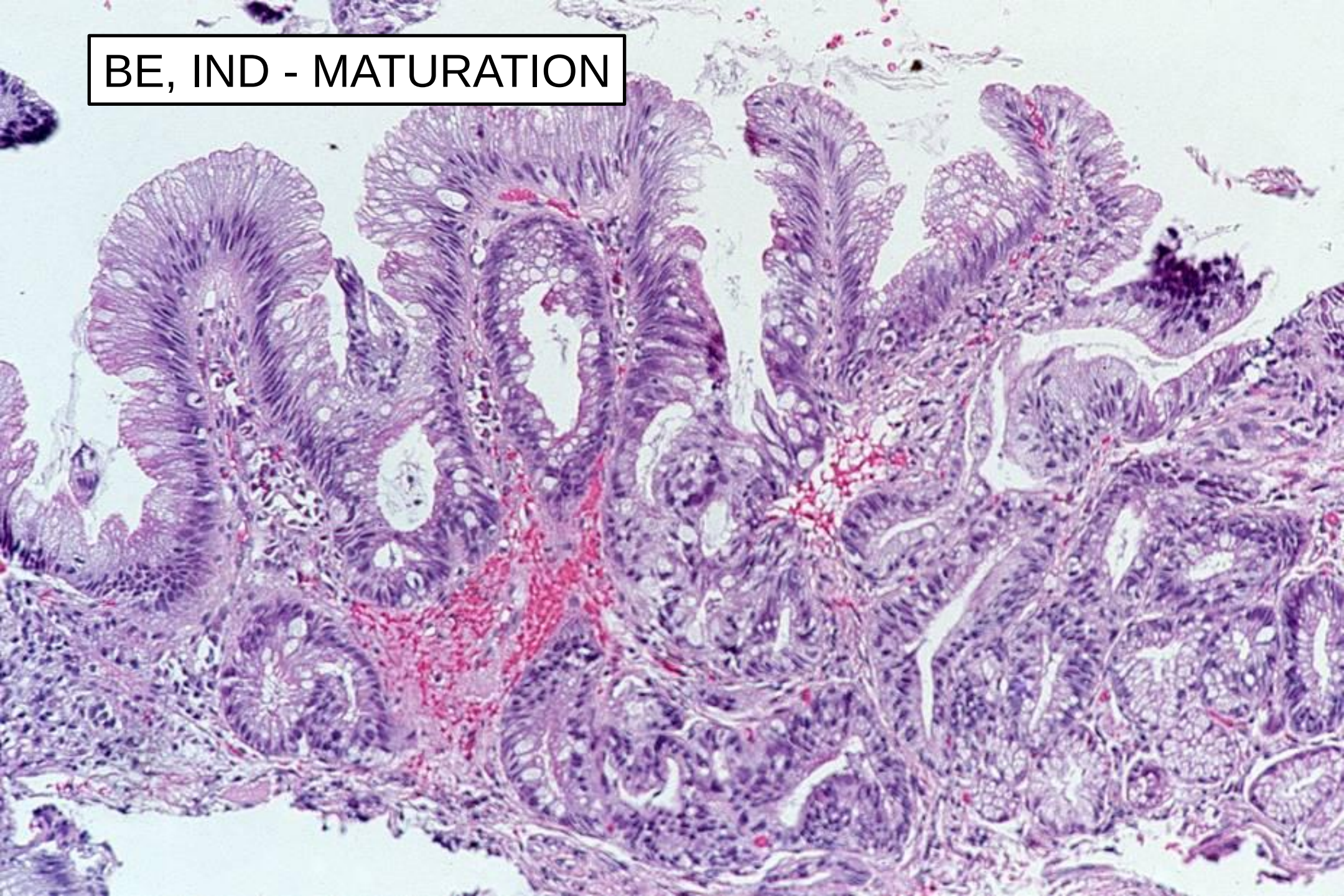
The answer “NO” to both questions = IFD

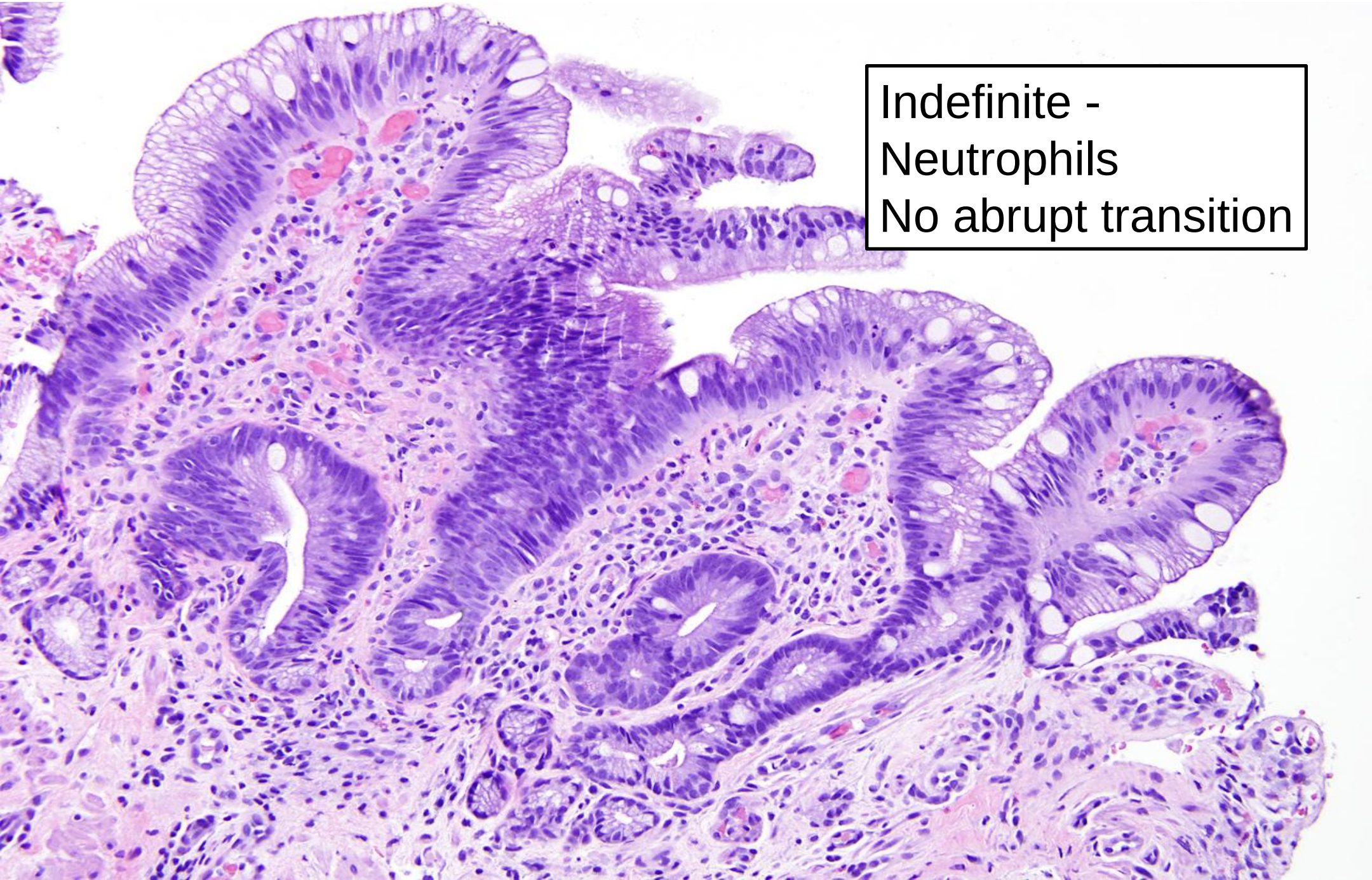
But…..

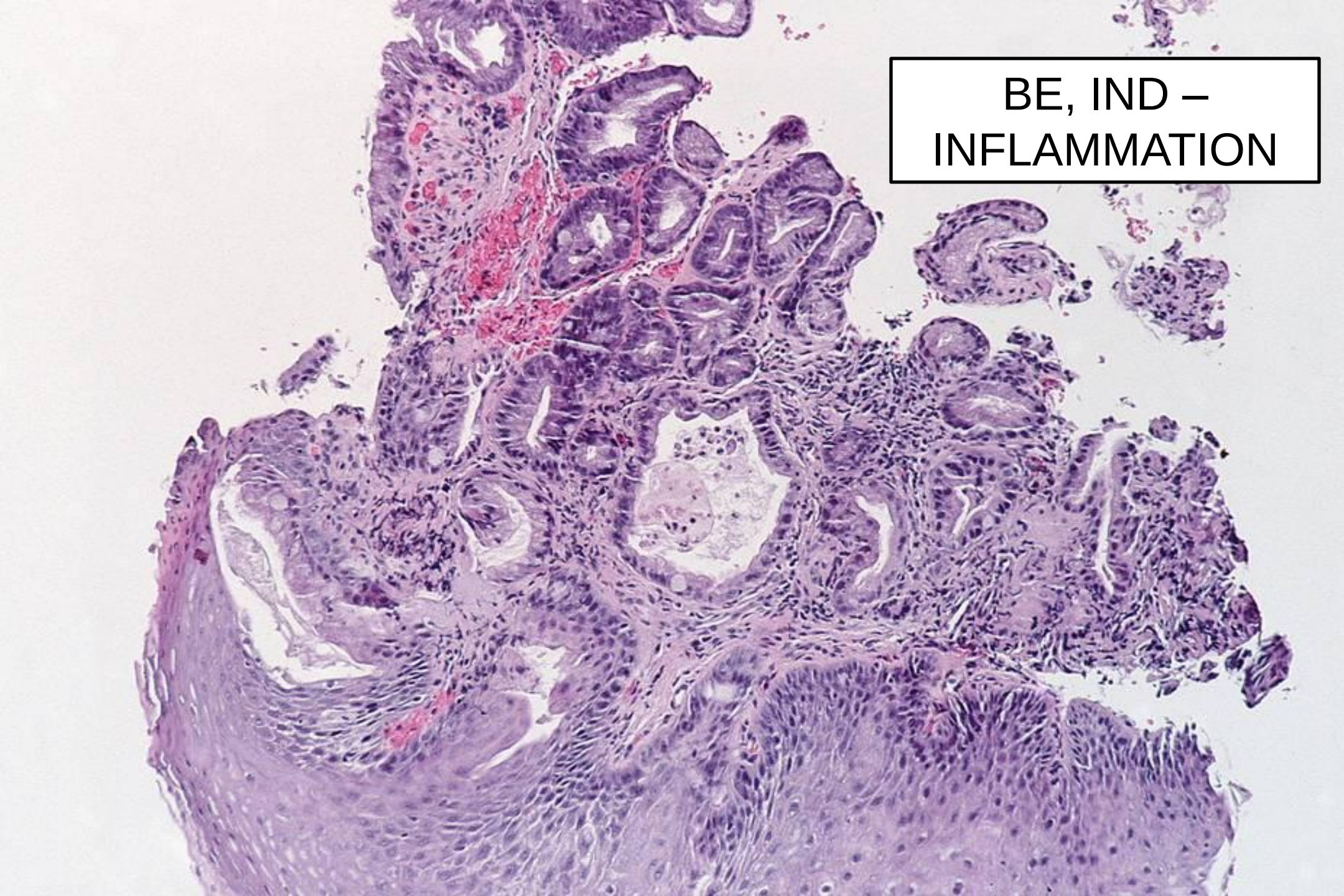
- Montgomery 2001 – study on dysplasia in BE
- Deliberately defined any epithelium that looked dysplastic in the bases of the pits but had surface maturation as IFD
- i.e. impossible to have dysplasia with maturation
- Rationale – maturation is a major feature of regenerating mucosa, so will exclude all reactive changes.

BE, Indefinite for Dysplasia

- Surface – often more mature than glands
- Architecture - slight glandular crowding
- Cytology - hyperchromasia, nuclear membrane irregularities, increased mitoses in deep glands. Maintained nuclear polarity
- Inflammation - Frequently a factor
- **I like to see an abrupt transition to be sure something is dysplastic – and thus clonal – no fully validated reason**

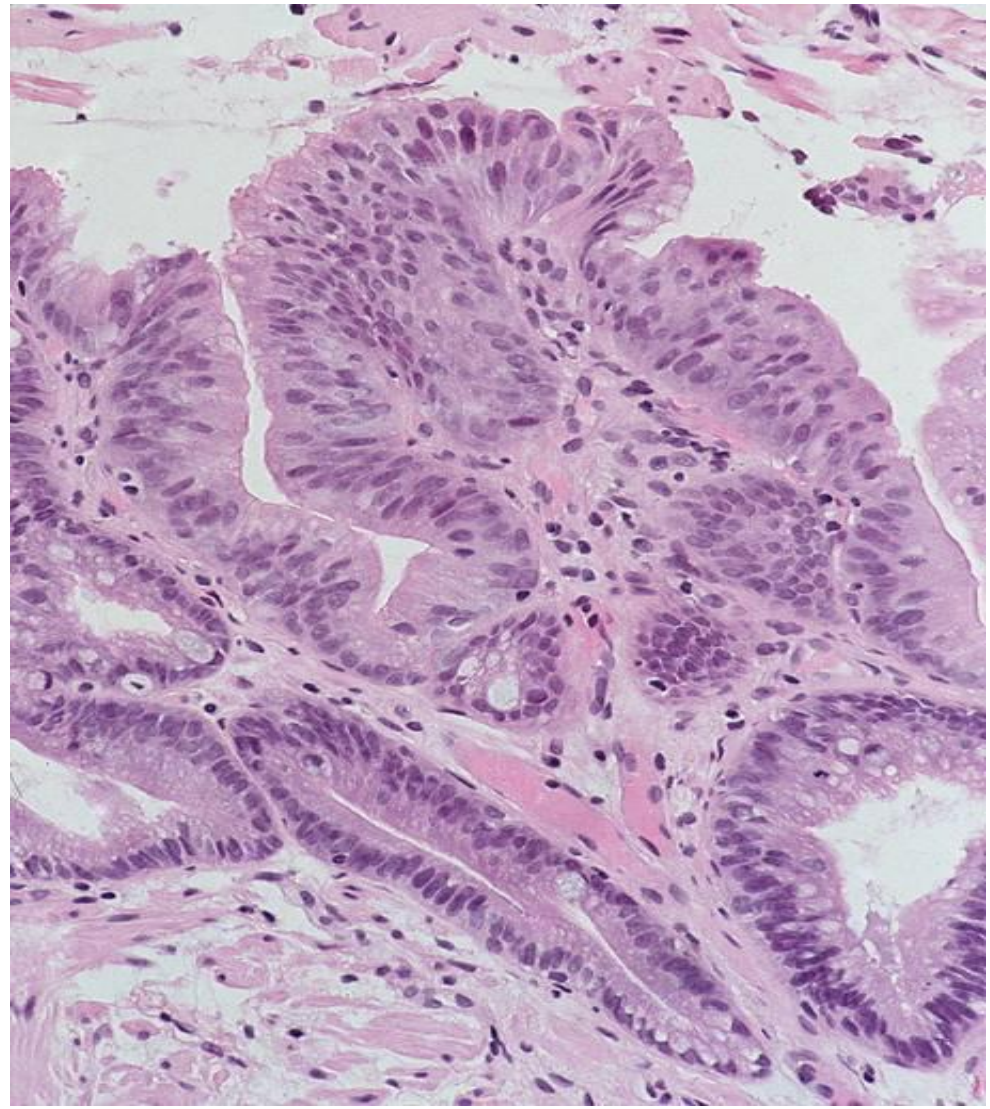

BE, IND - MATURATION


Indefinite -
Neutrophils
No abrupt transition

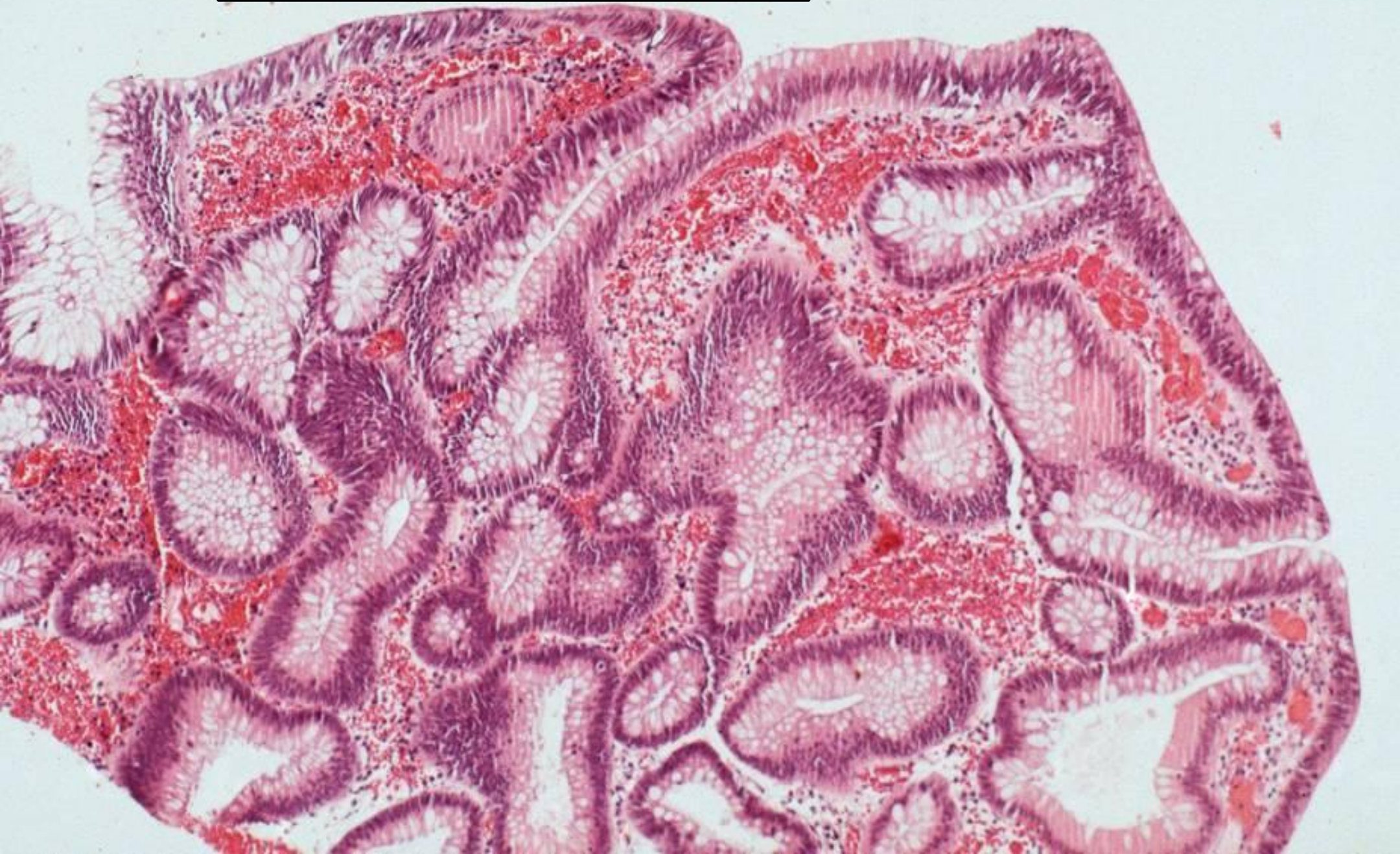

BE, IND –
INFLAMMATION

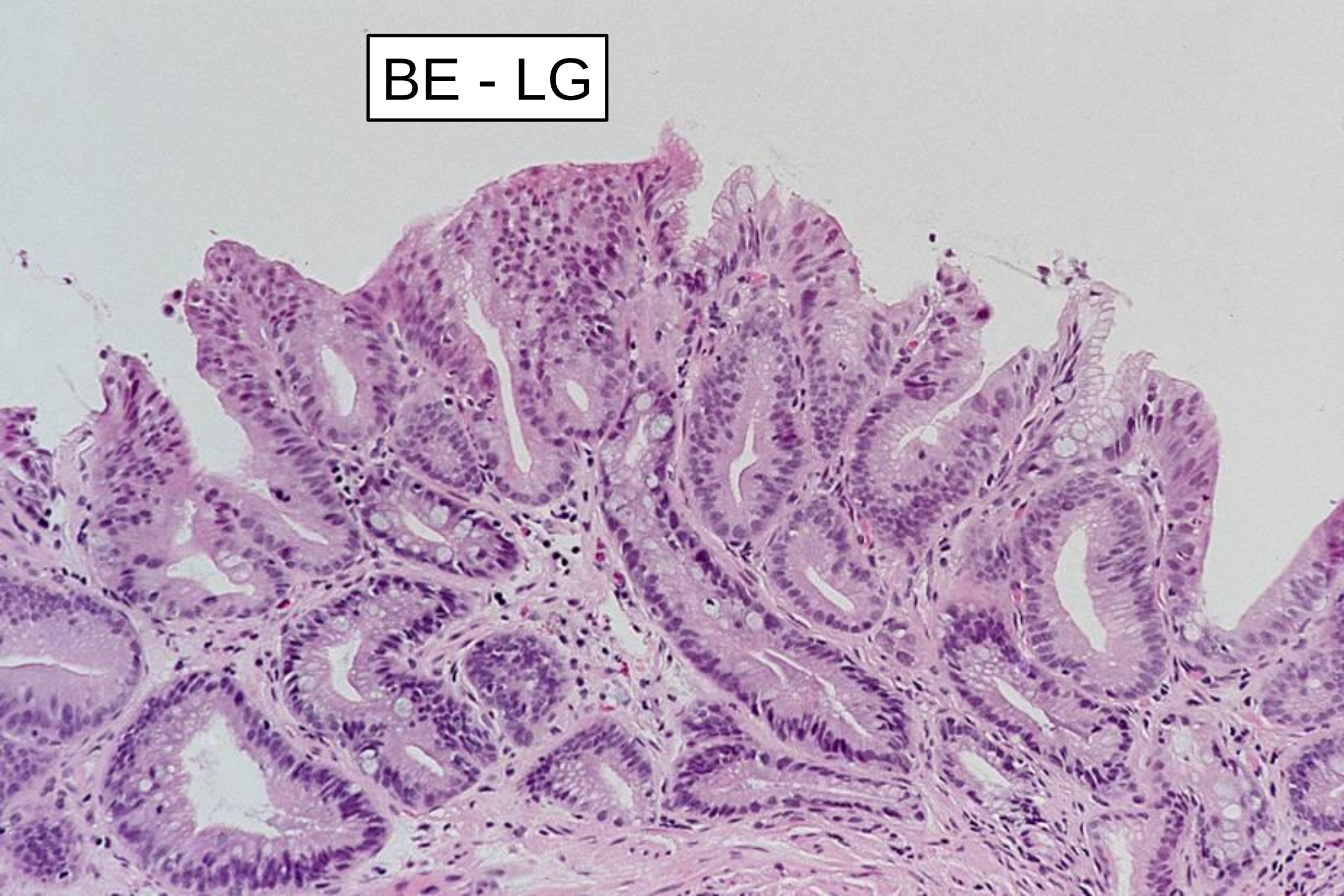
Low Grade Dysplasia

- Clearly neoplastic
- Minimal loss of nuclear polarity
- Surface involved
- Only mild architectural crowding.



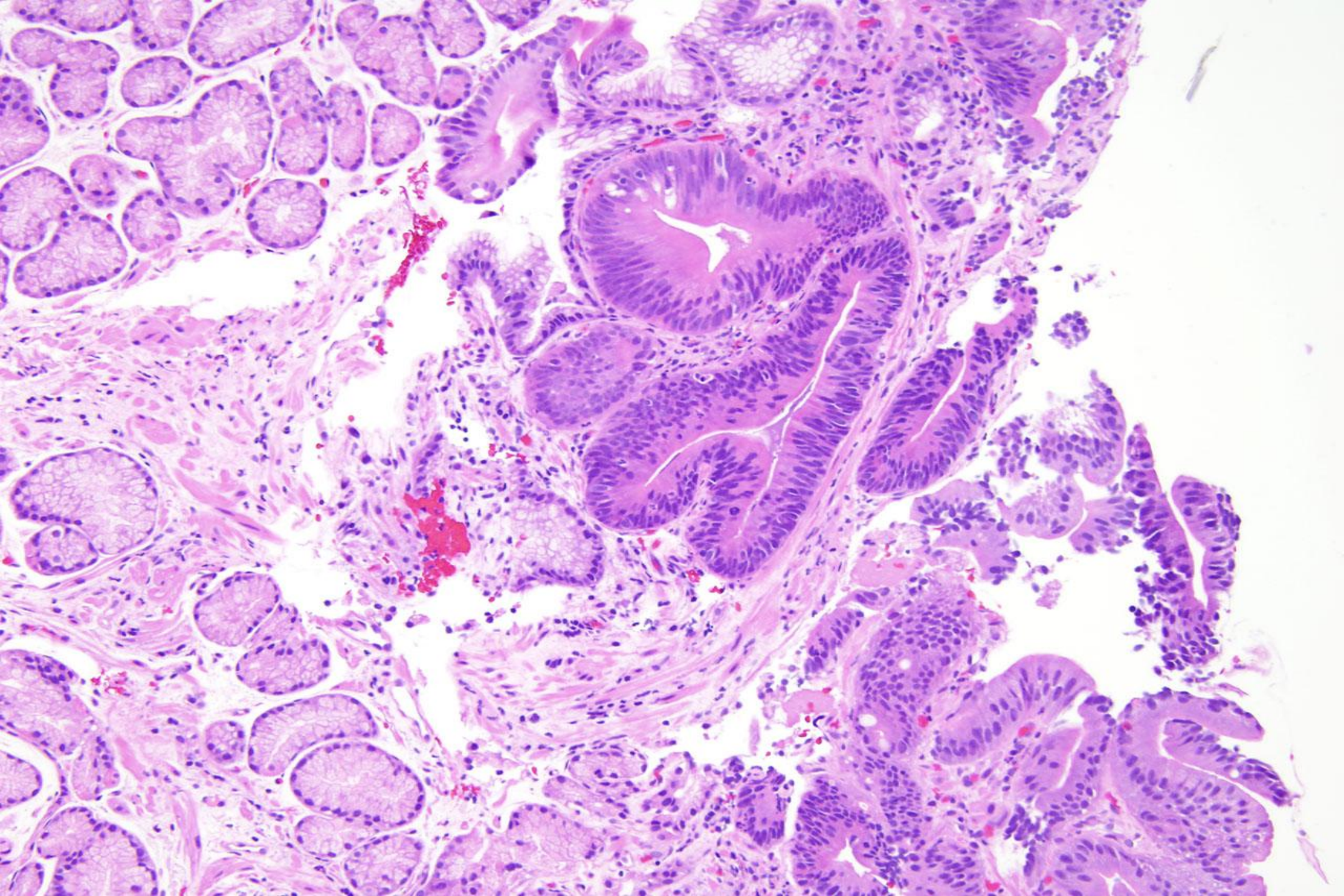
BE, LG - ADENOMA-LIKE

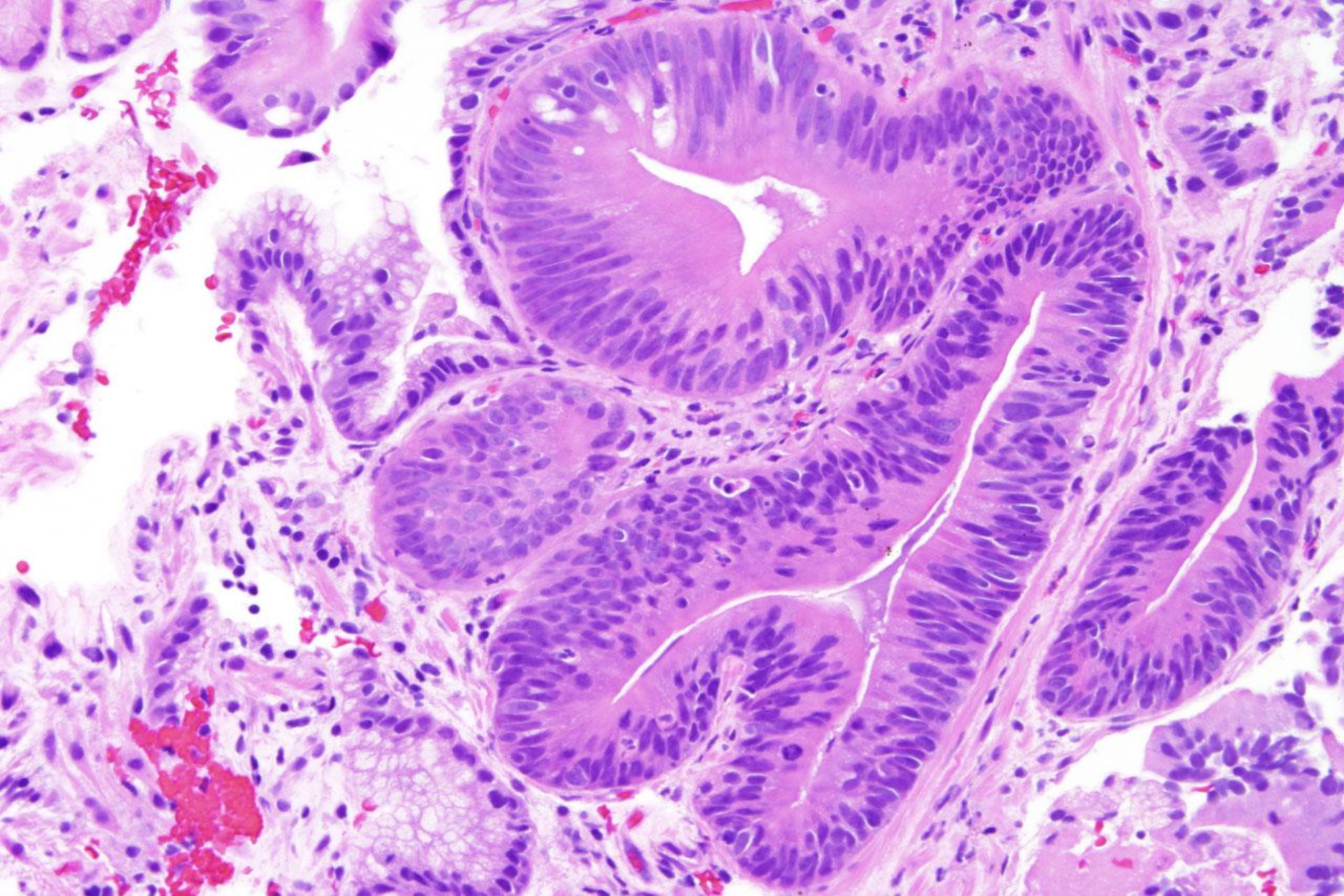


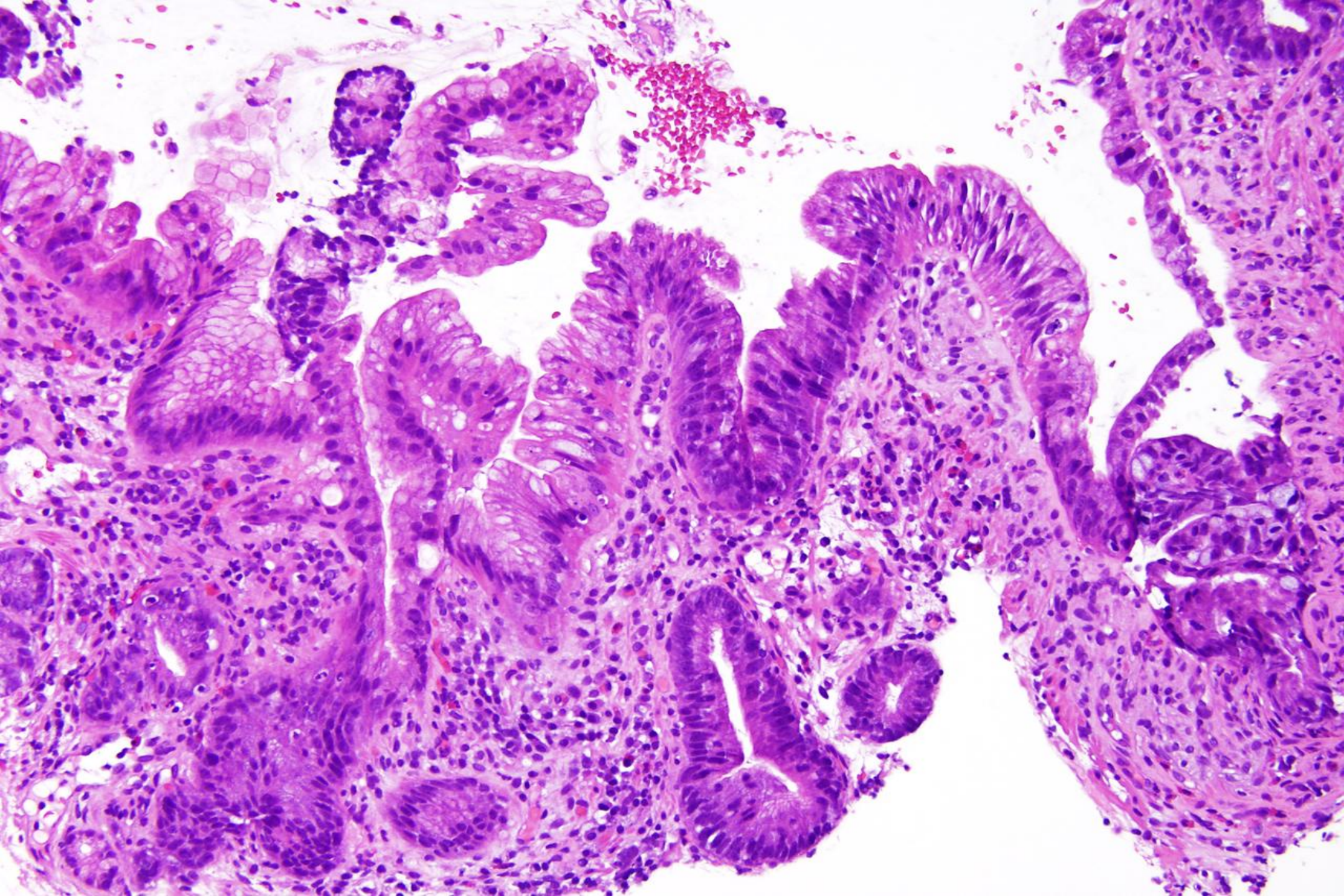

BE - LG

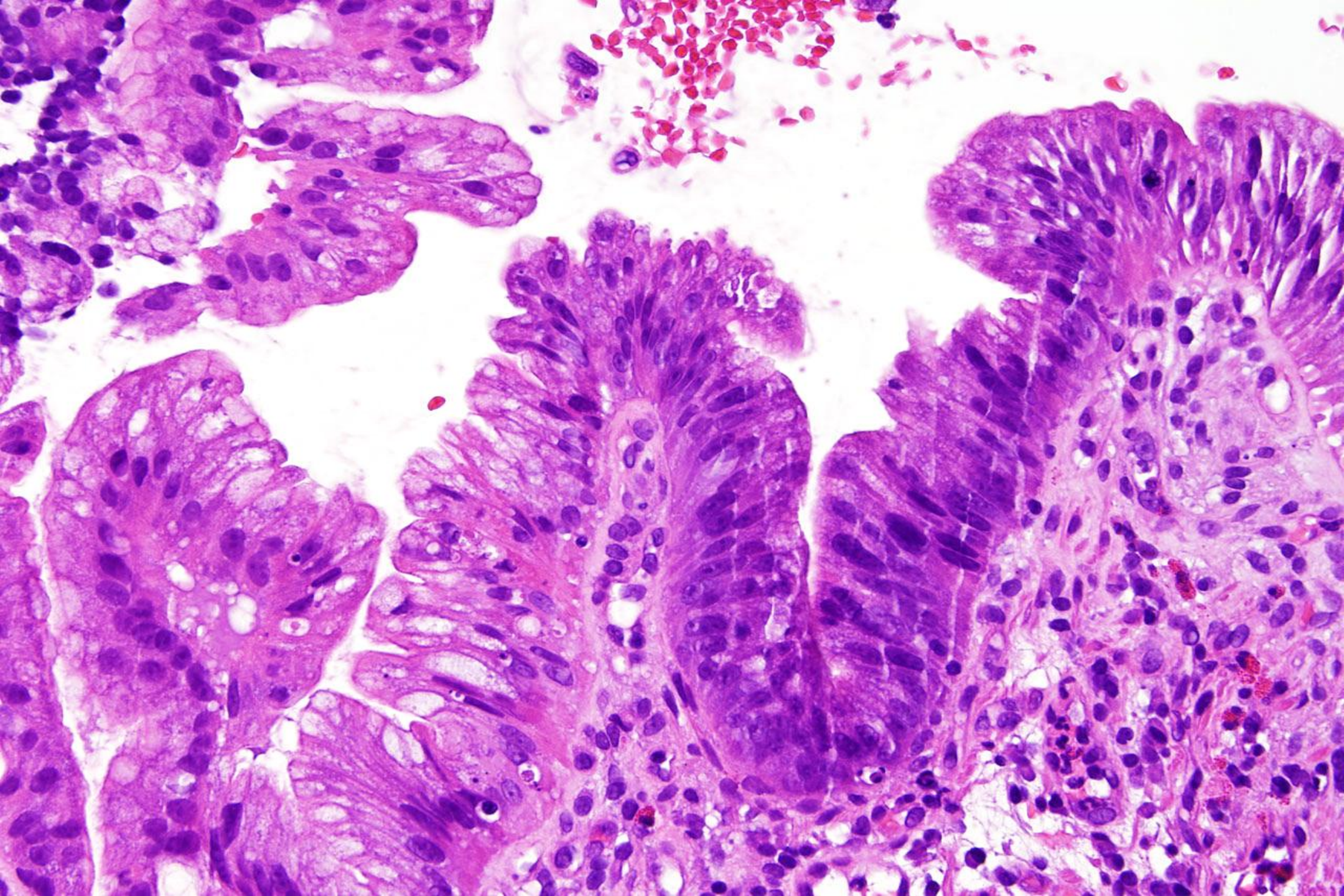
Where is the “Minimum

- Abrupt transition – appears divergent and clonal compared to adjacent epithelium
- But without inflammation in the specific “abnormal” focus

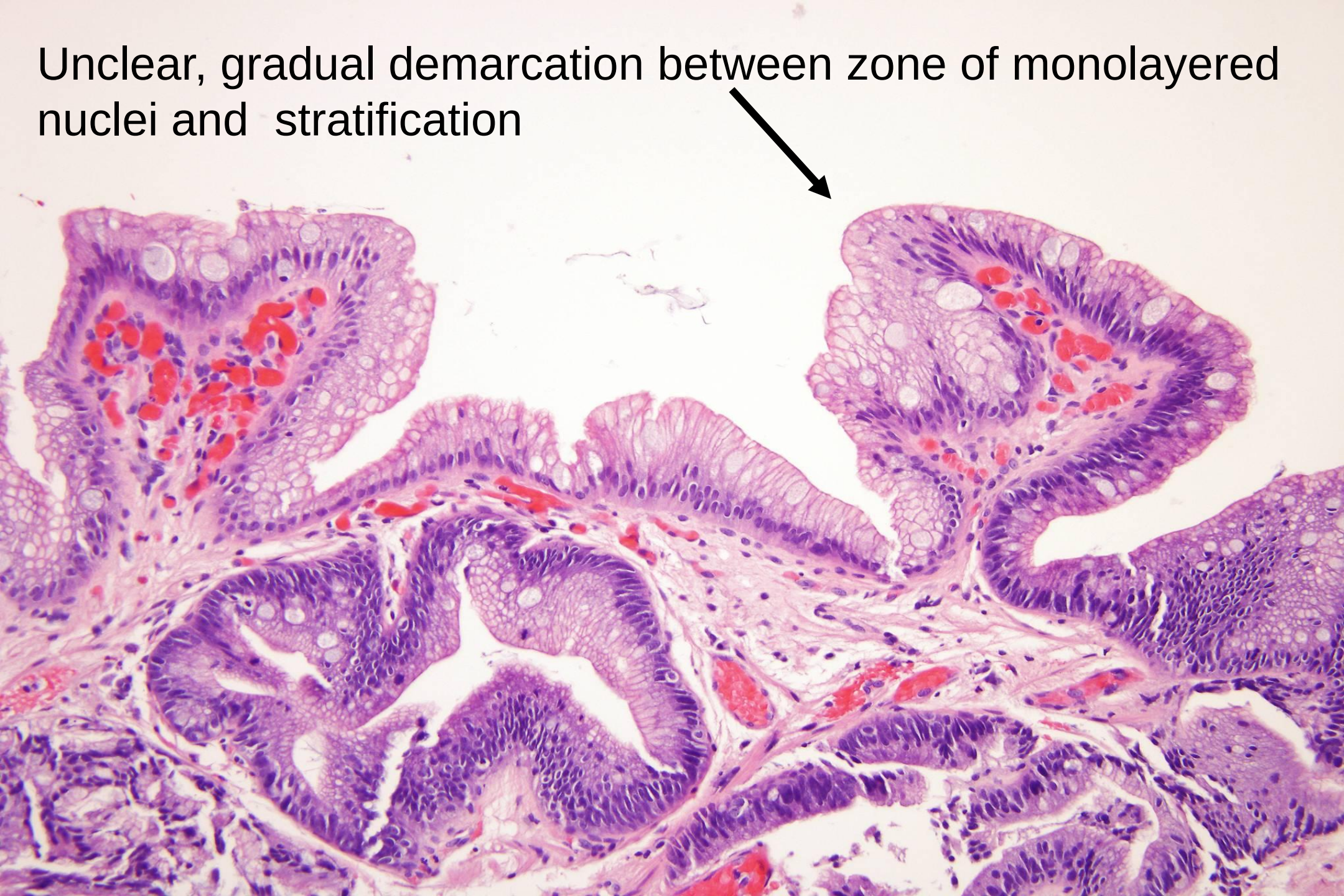


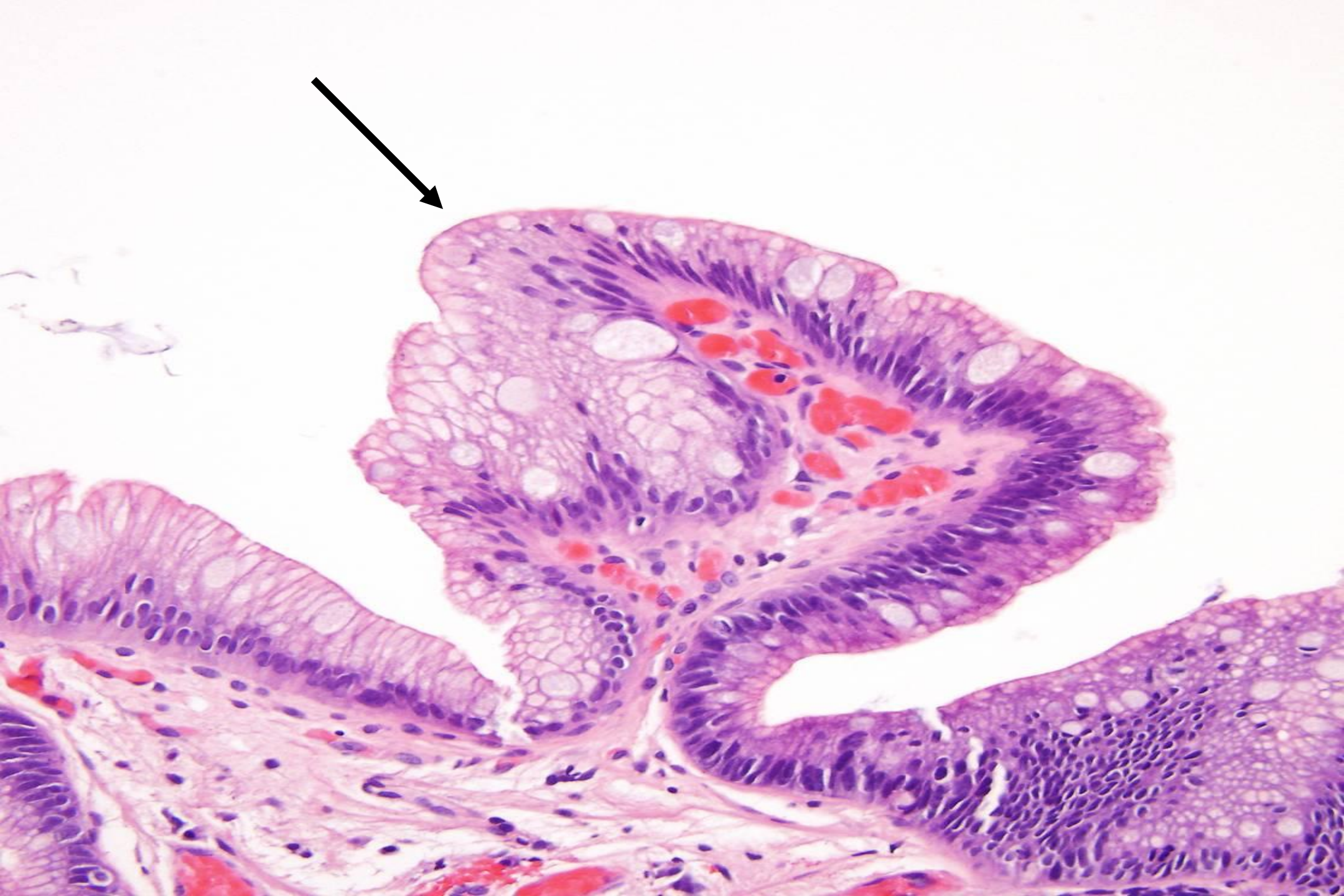


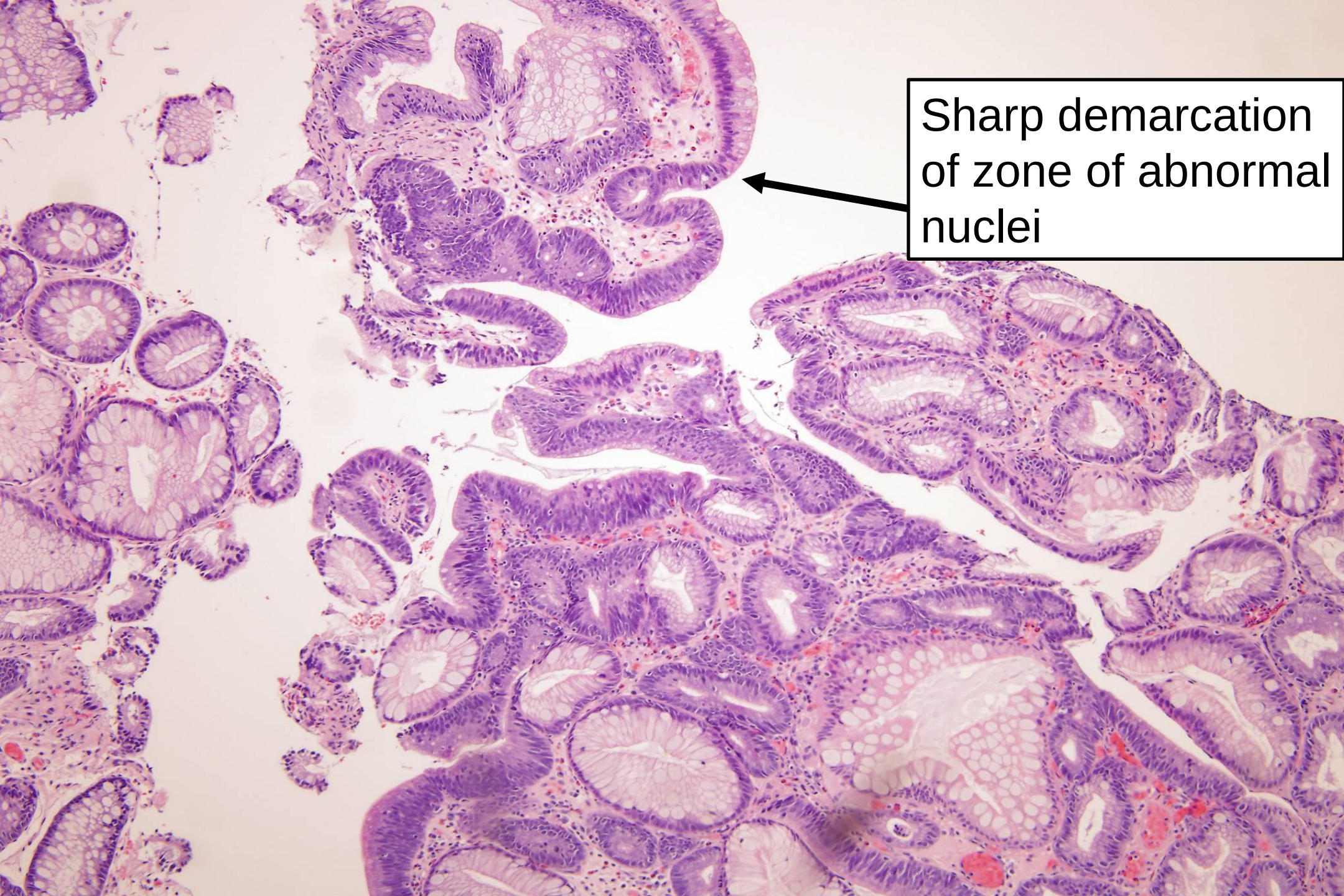


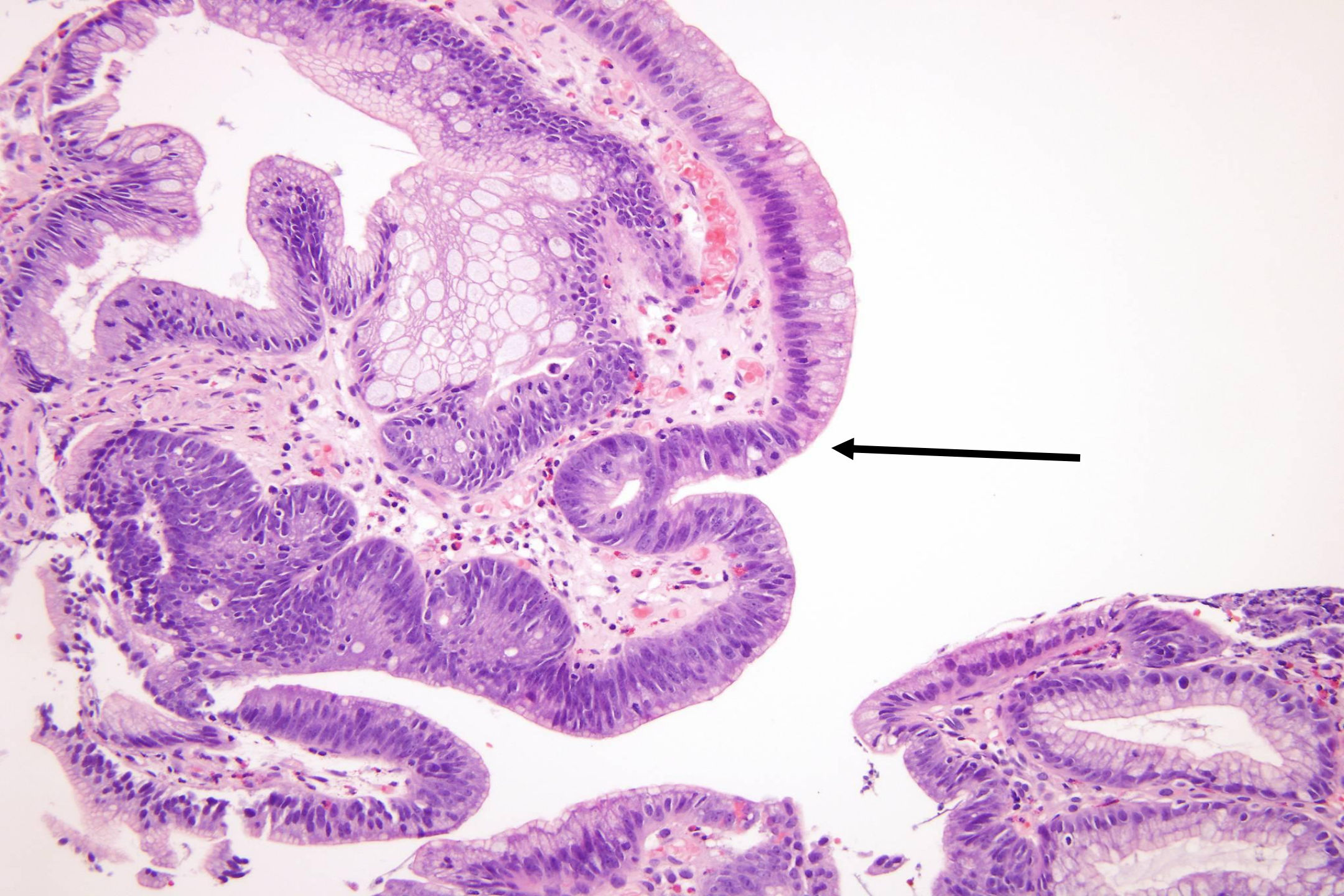


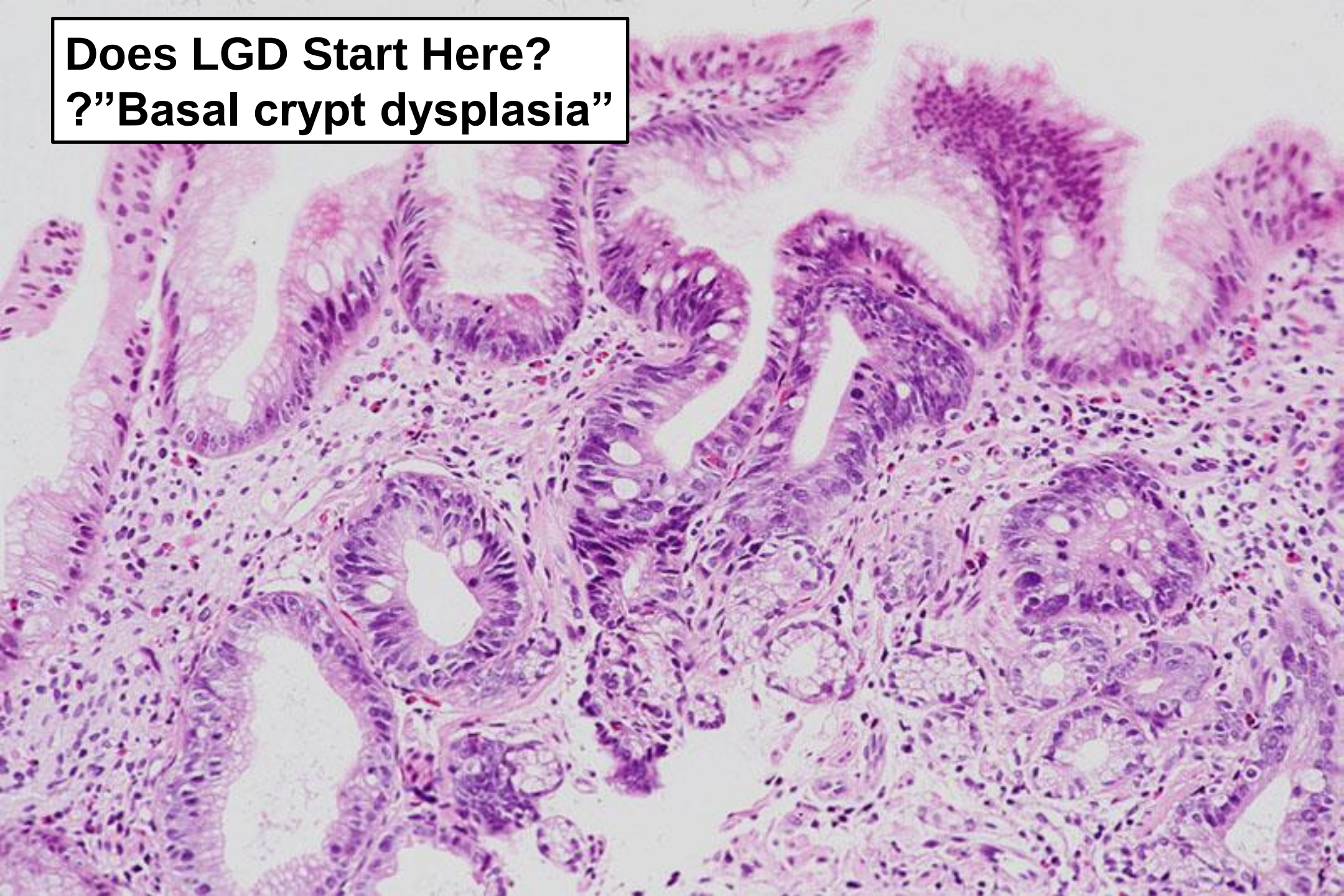
Unclear, gradual demarcation between zone of monolayered nuclei and stratification



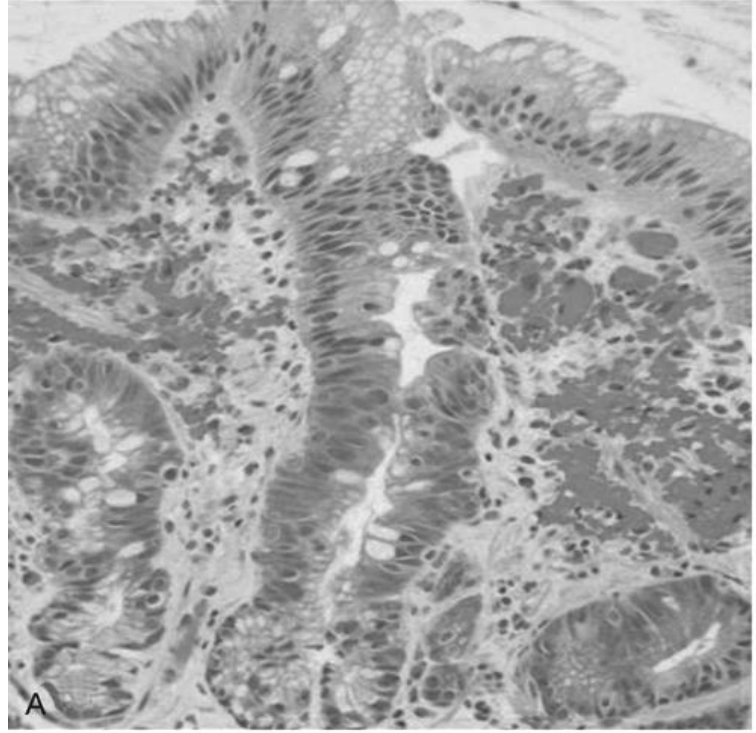


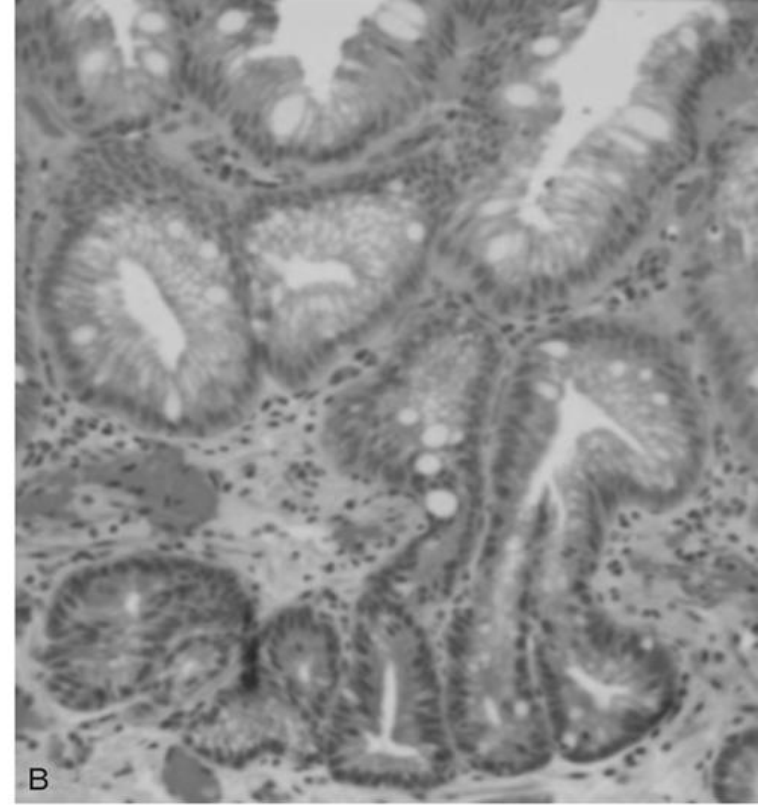

Sharp demarcation of zone of abnormal nuclei




Does LGD Start Here?
?"Basal crypt dysplasia"

- Lomo LC, Blount PL, Sanchez CA, Li X, Galipeau PC, Cowan DS, Ayub K, Rabinovitch PS, Reid BJ, Odze RD.
  Crypt dysplasia with surface maturation: a clinical, pathologic, and molecular study of a Barrett's esophagus cohort.
  Am J Surg Pathol. 2006 Apr;30(4):423-35.


A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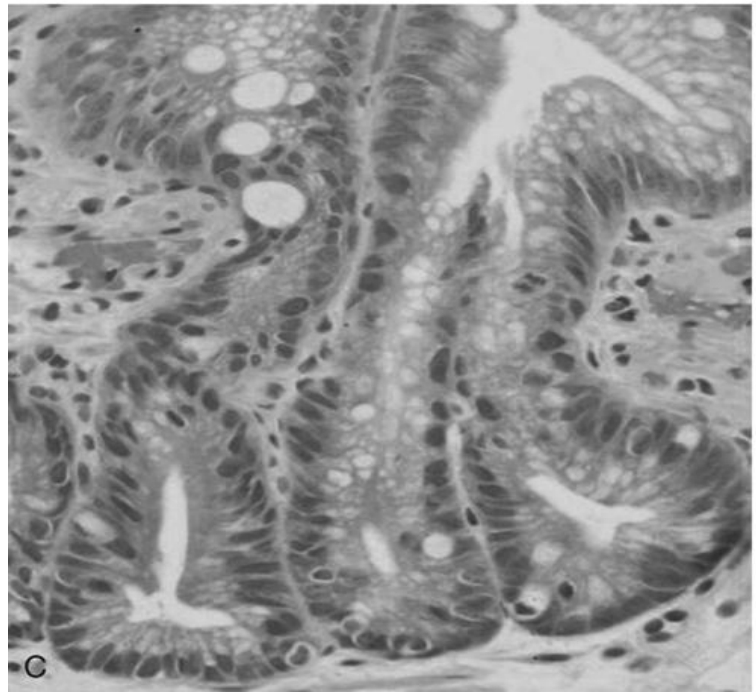
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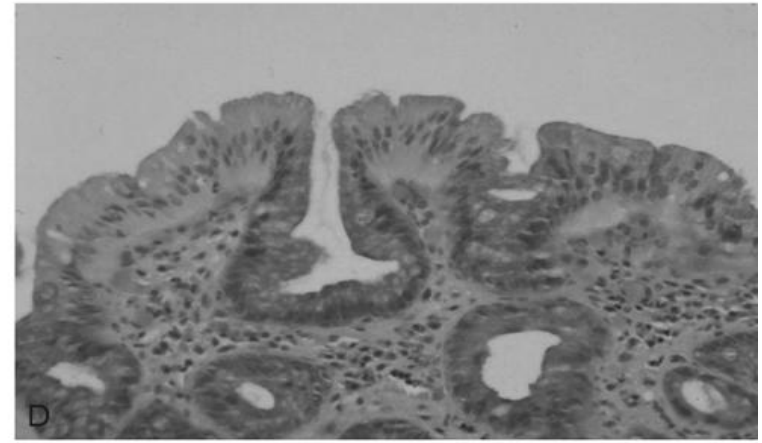
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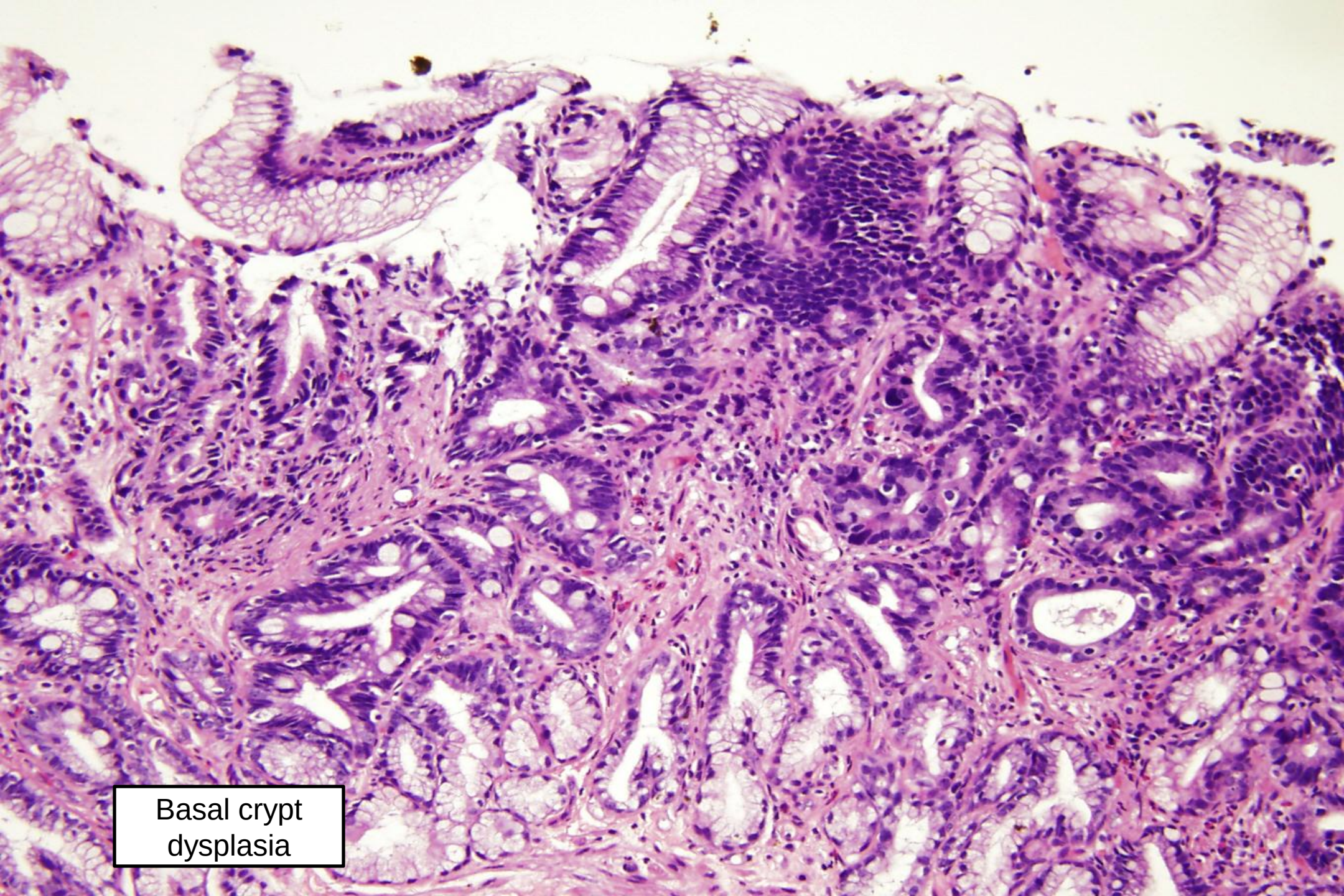
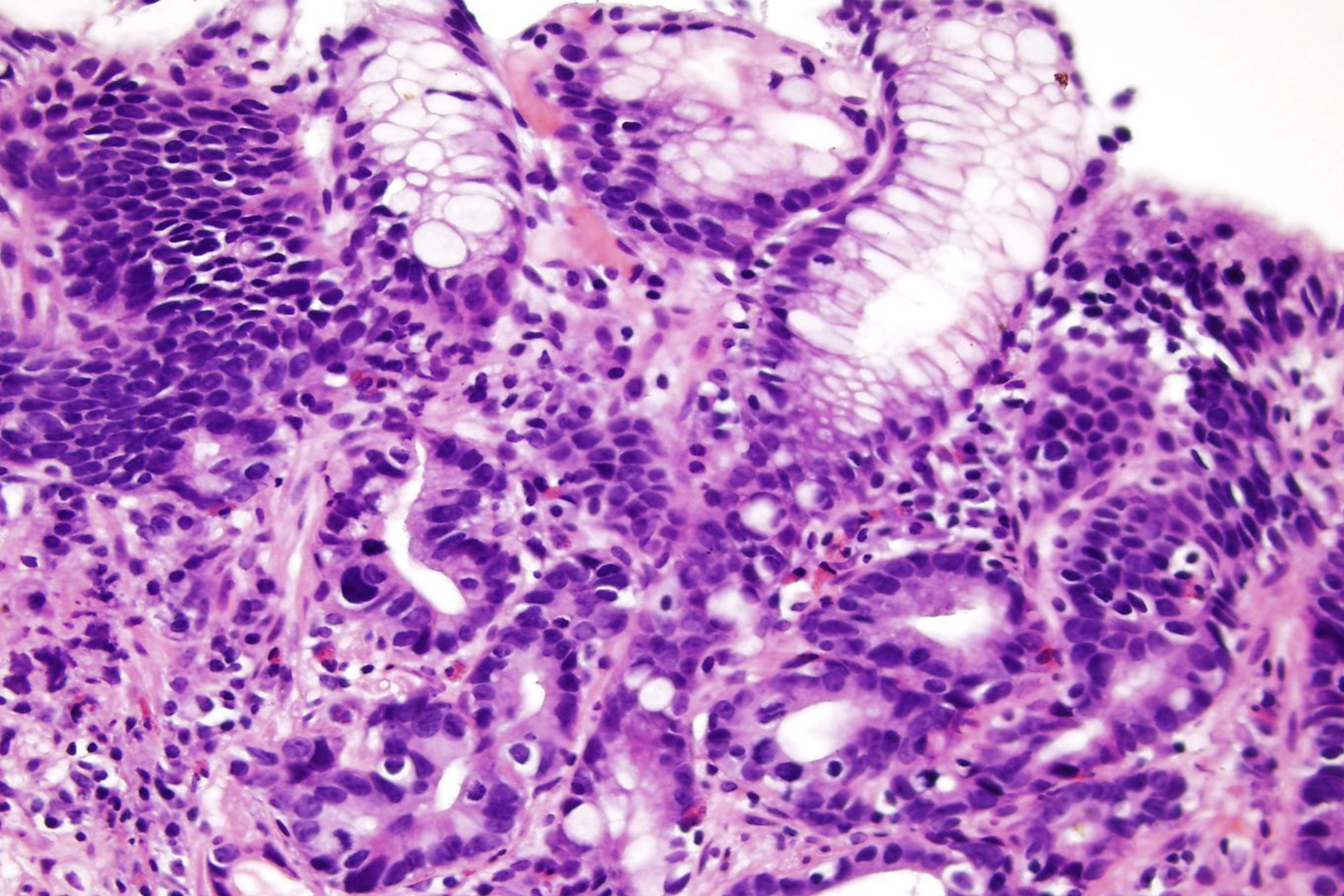
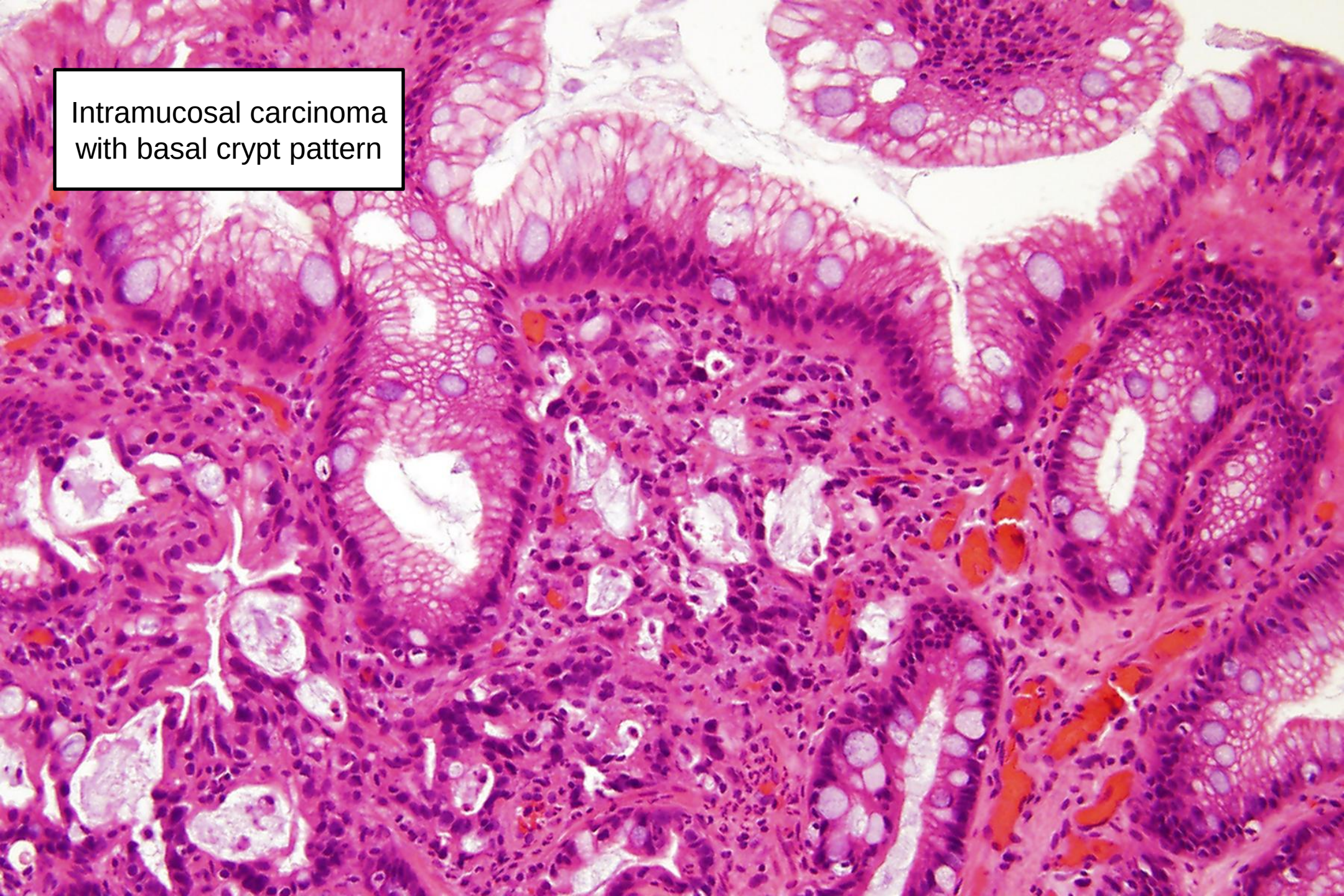
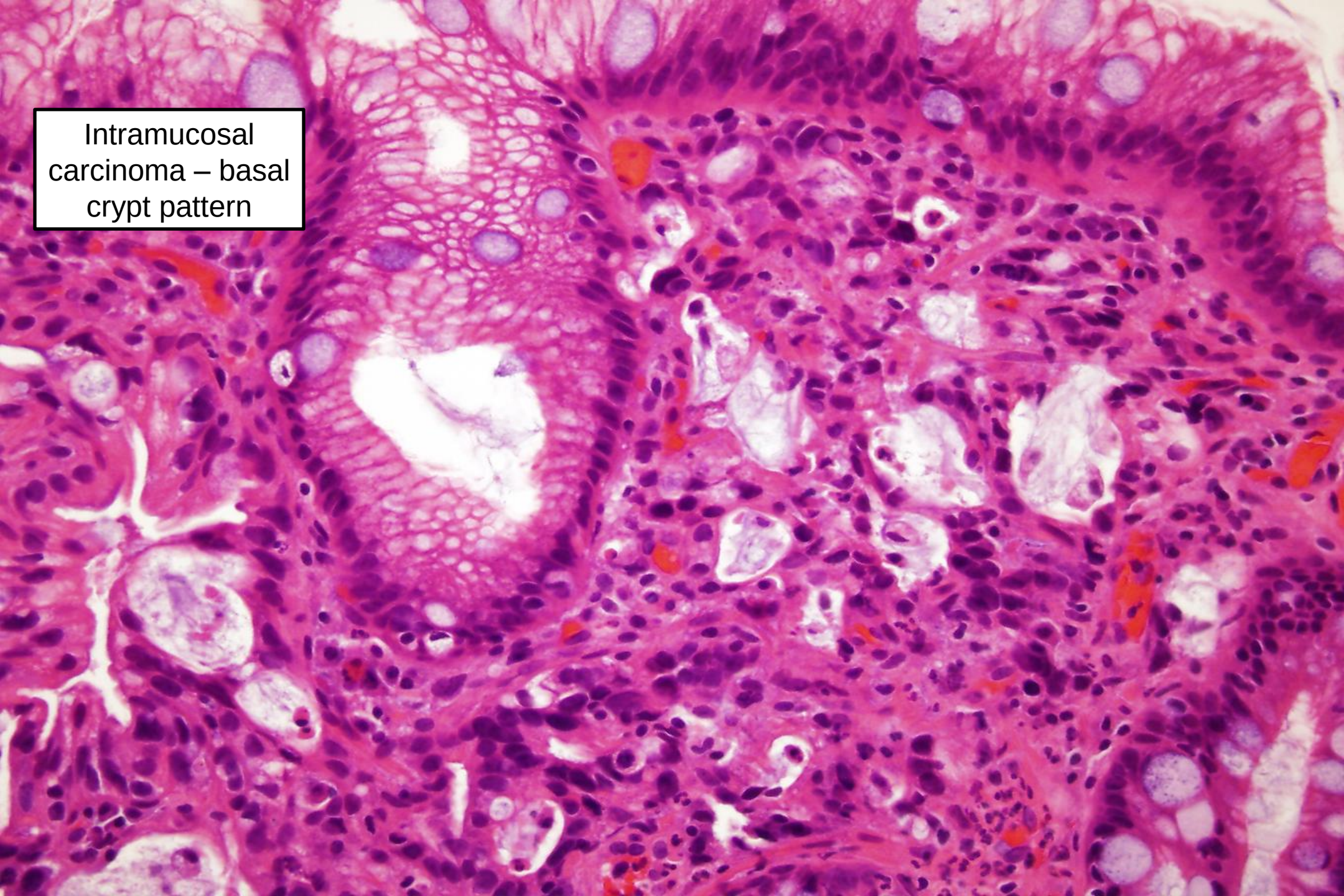

Basal crypt
dysplasia

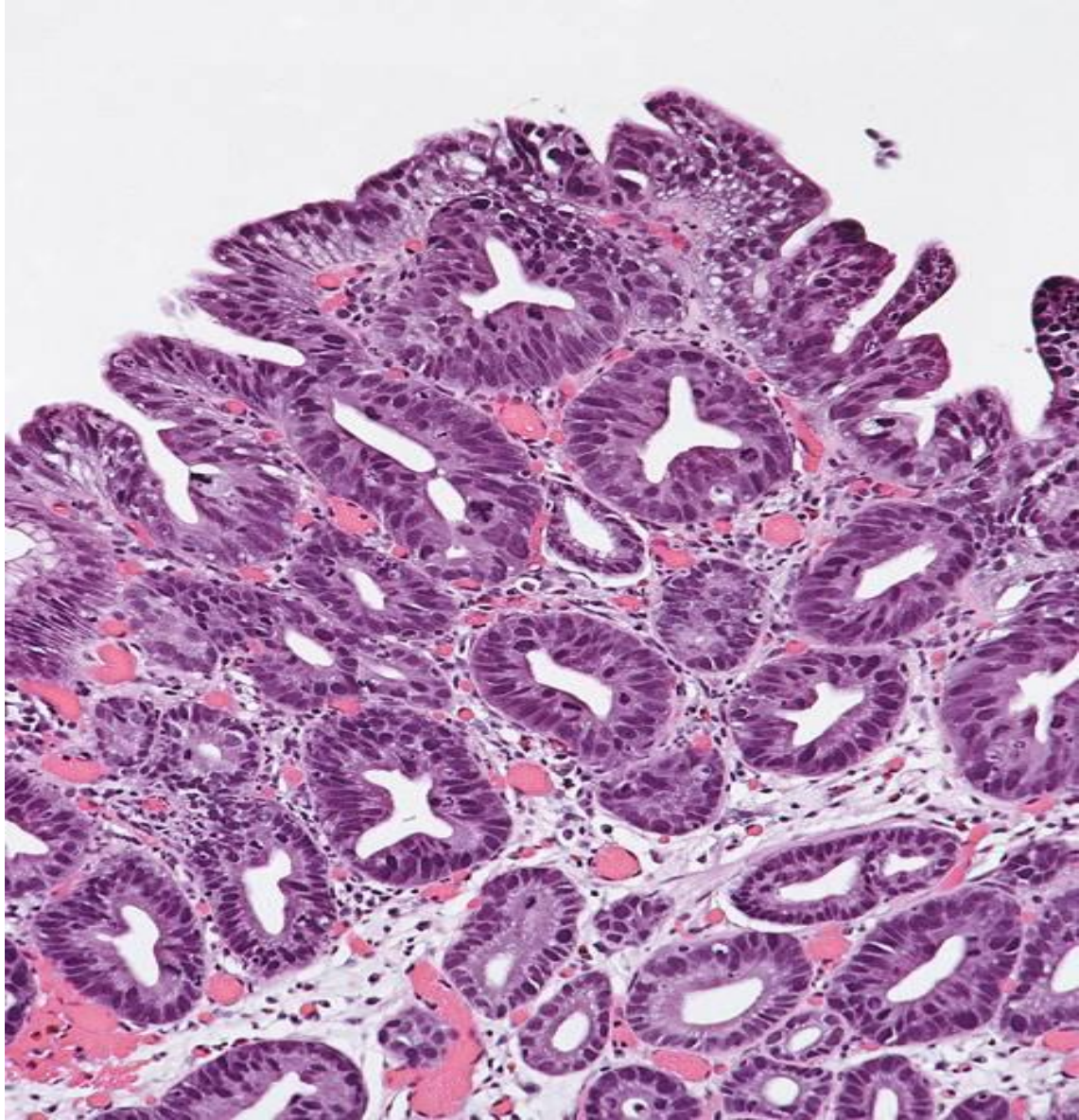


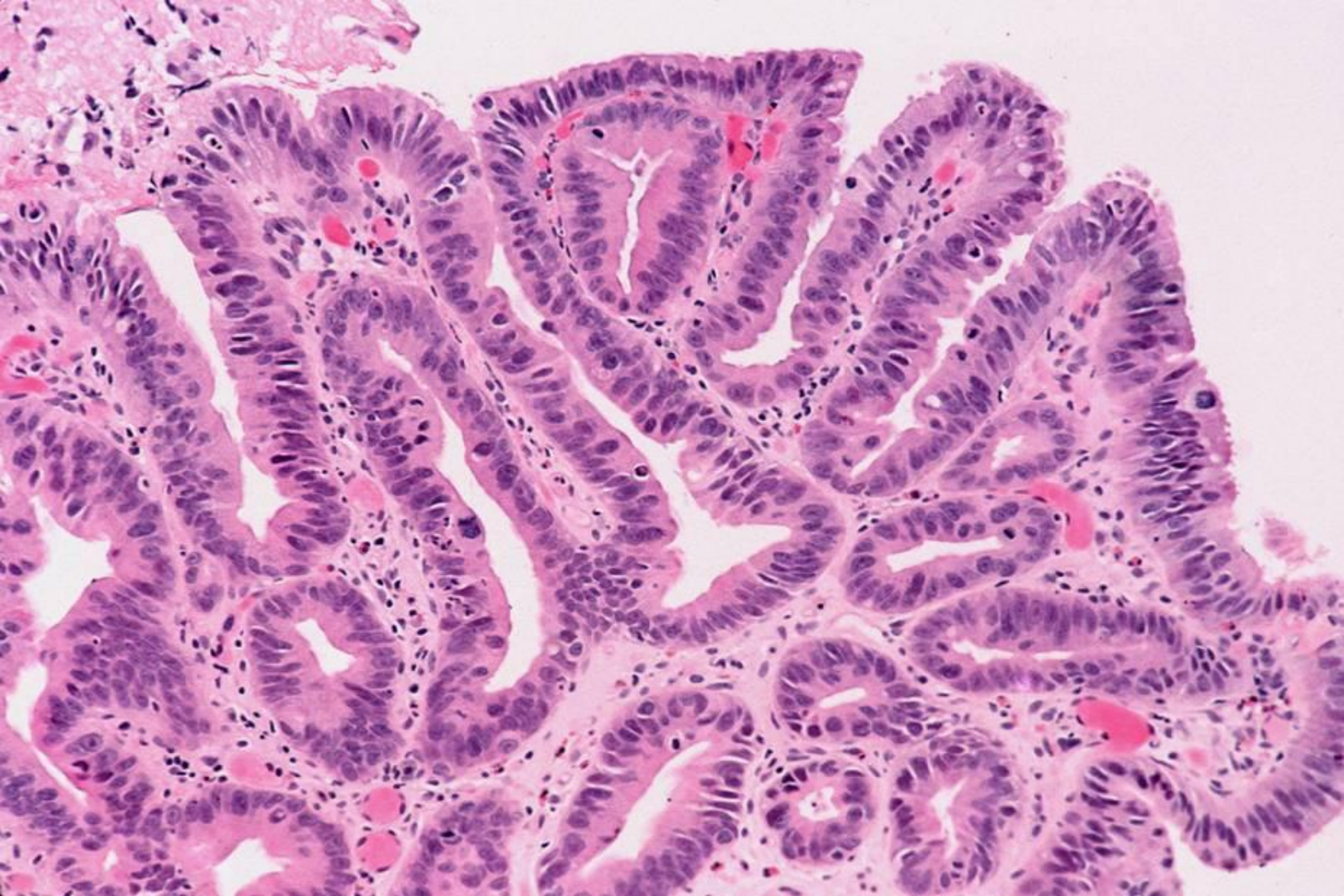

Intramucosal carcinoma
with basal crypt pattern

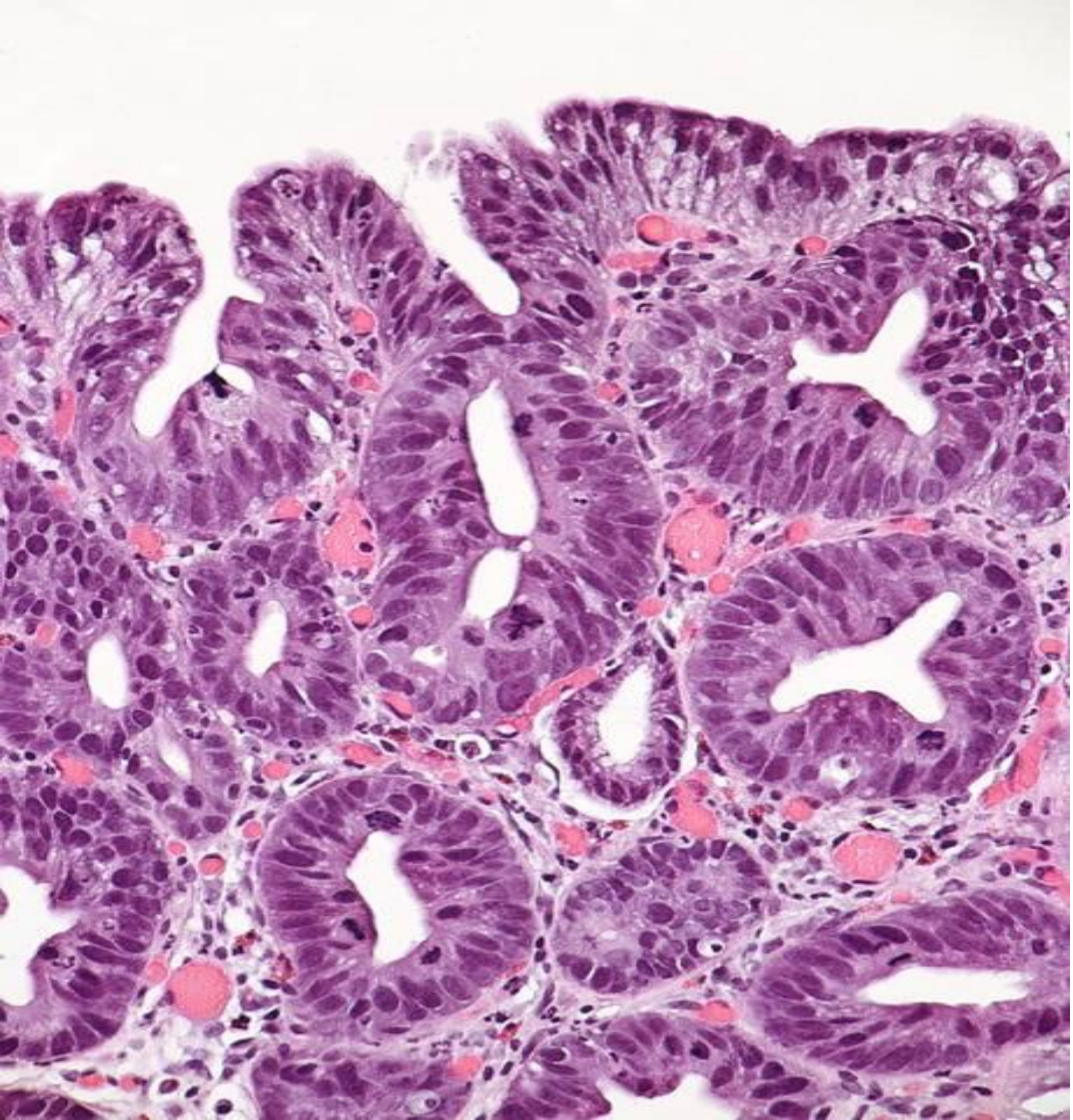

Intramucosal carcinoma – basal crypt pattern

High-Grade Dysplasia

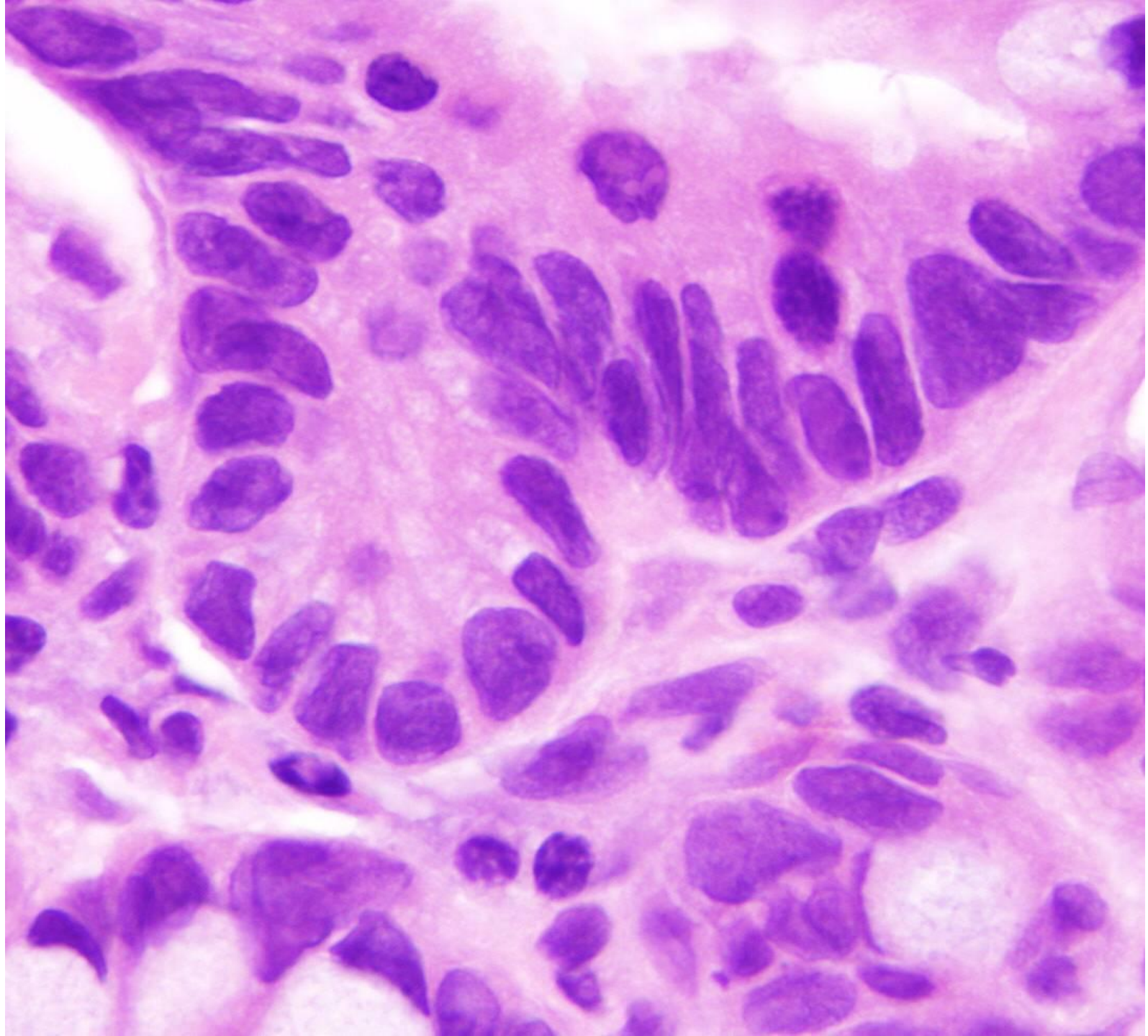
- Surface - No maturation
- Architecture - Crowded glands overrunning lamina propria
- Cytology - Nuclear membrane irregularities, extending to surface and loss of nuclear polarity
- Inflammation - Typically not abundant

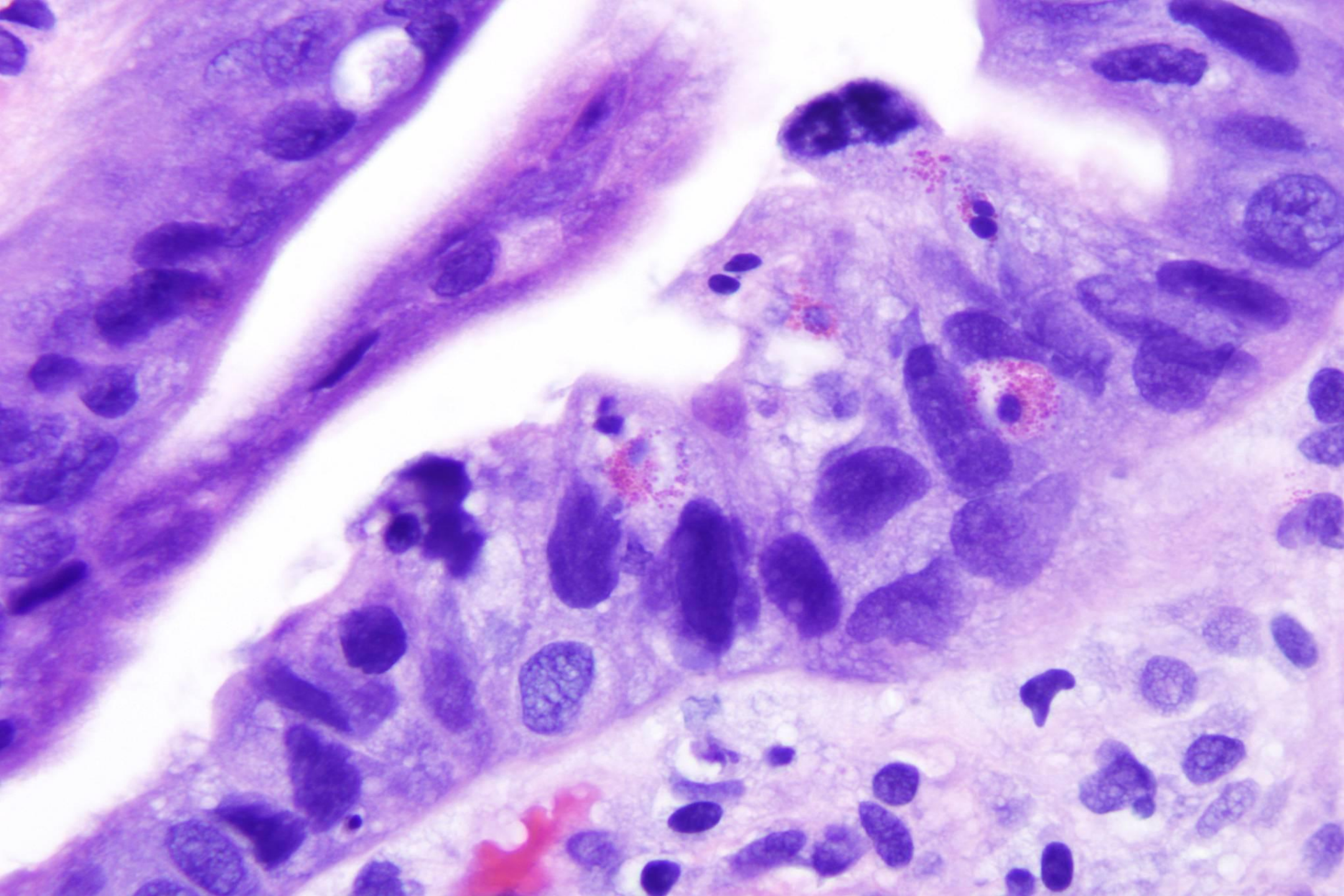






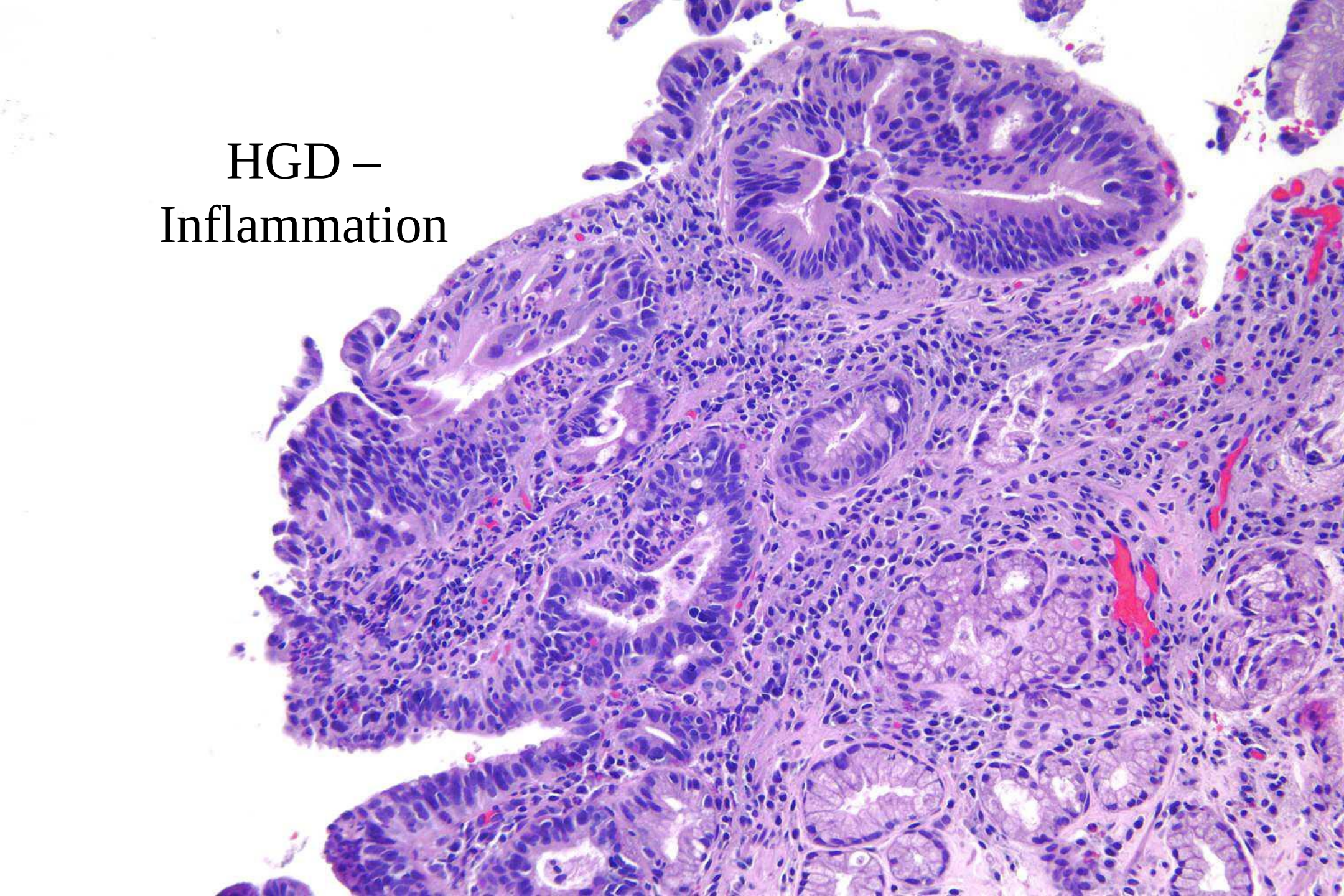
High-Grade Dysplasia

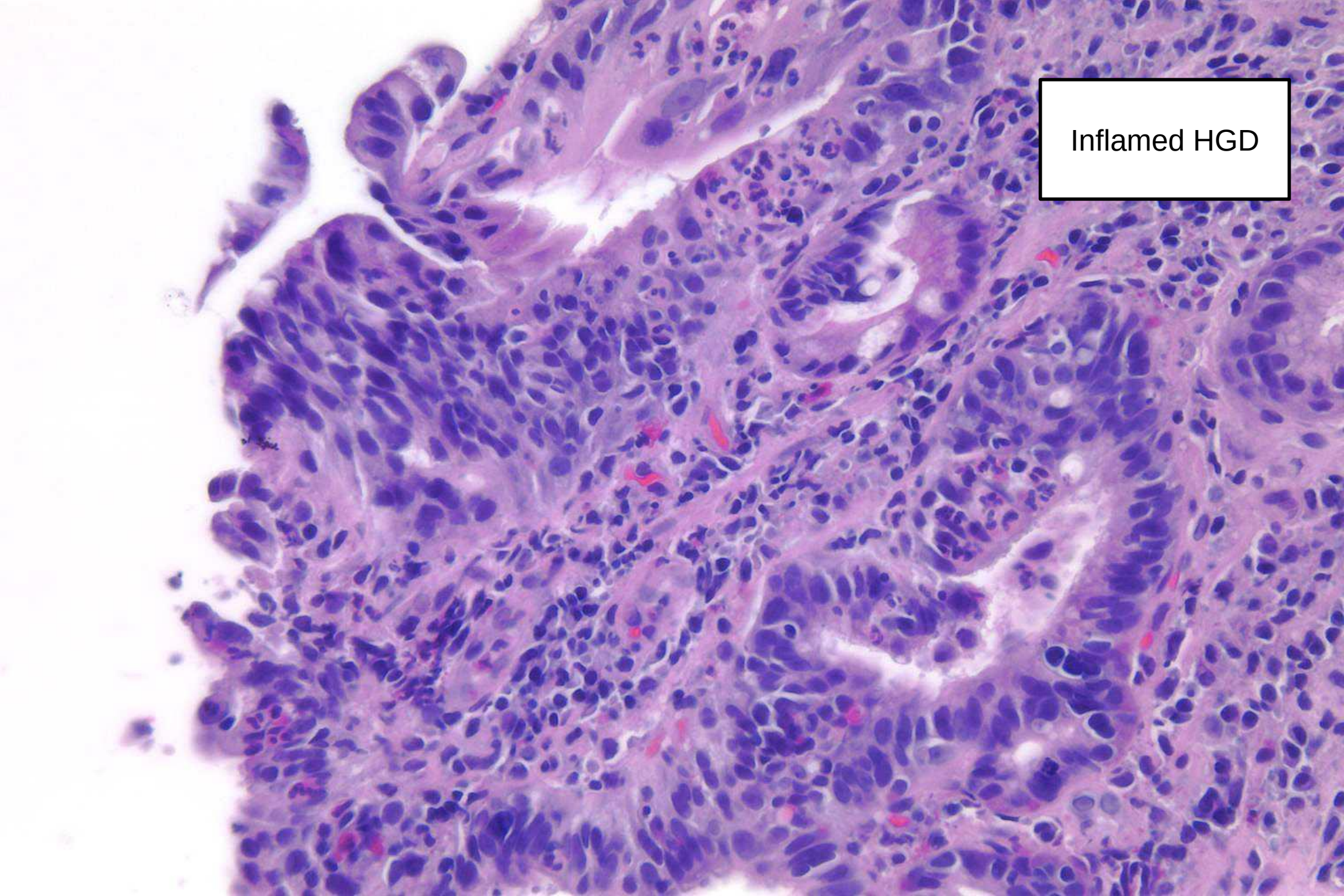


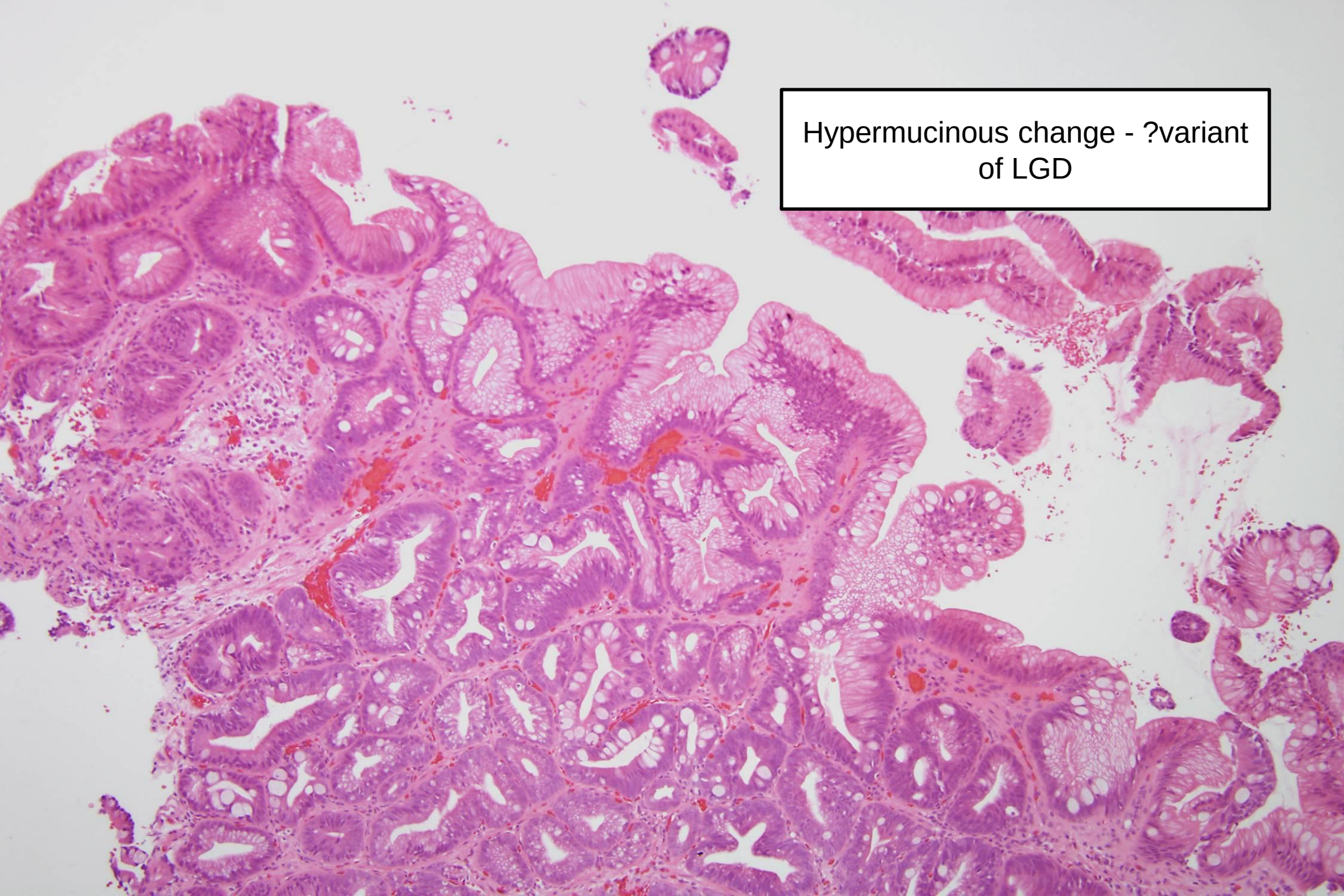


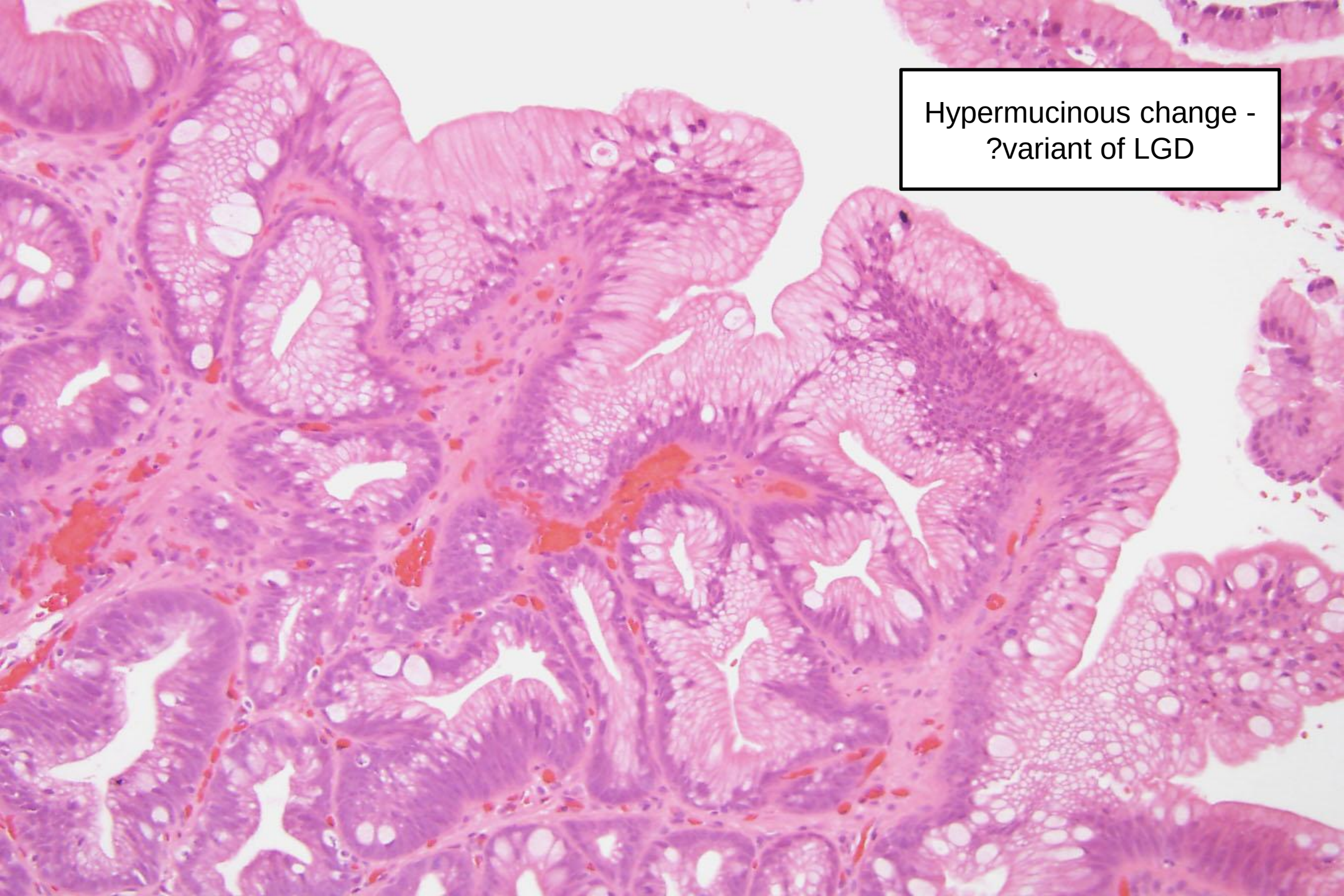
“Funny” Dysplasia Cases

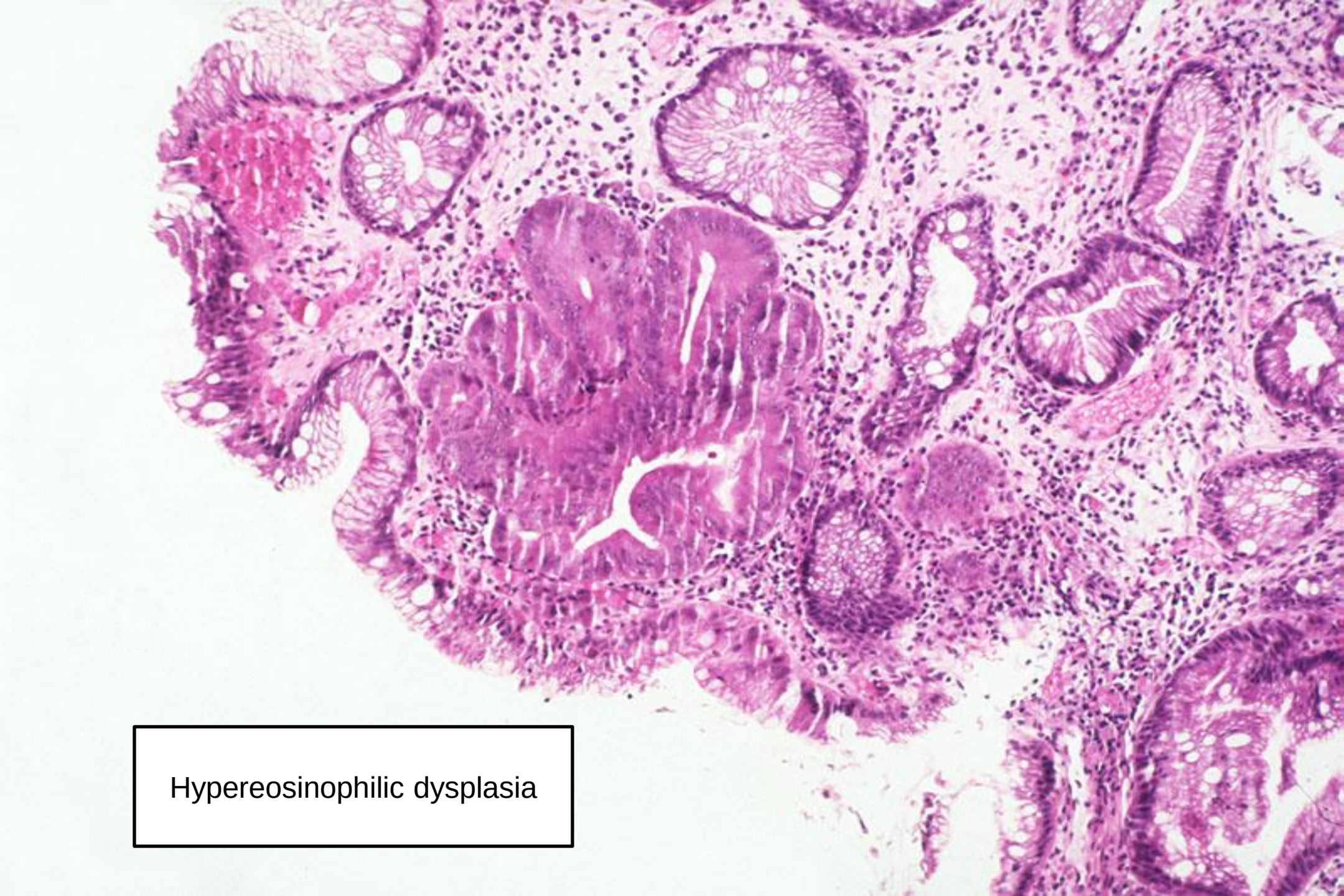
HGD –
Inflammation



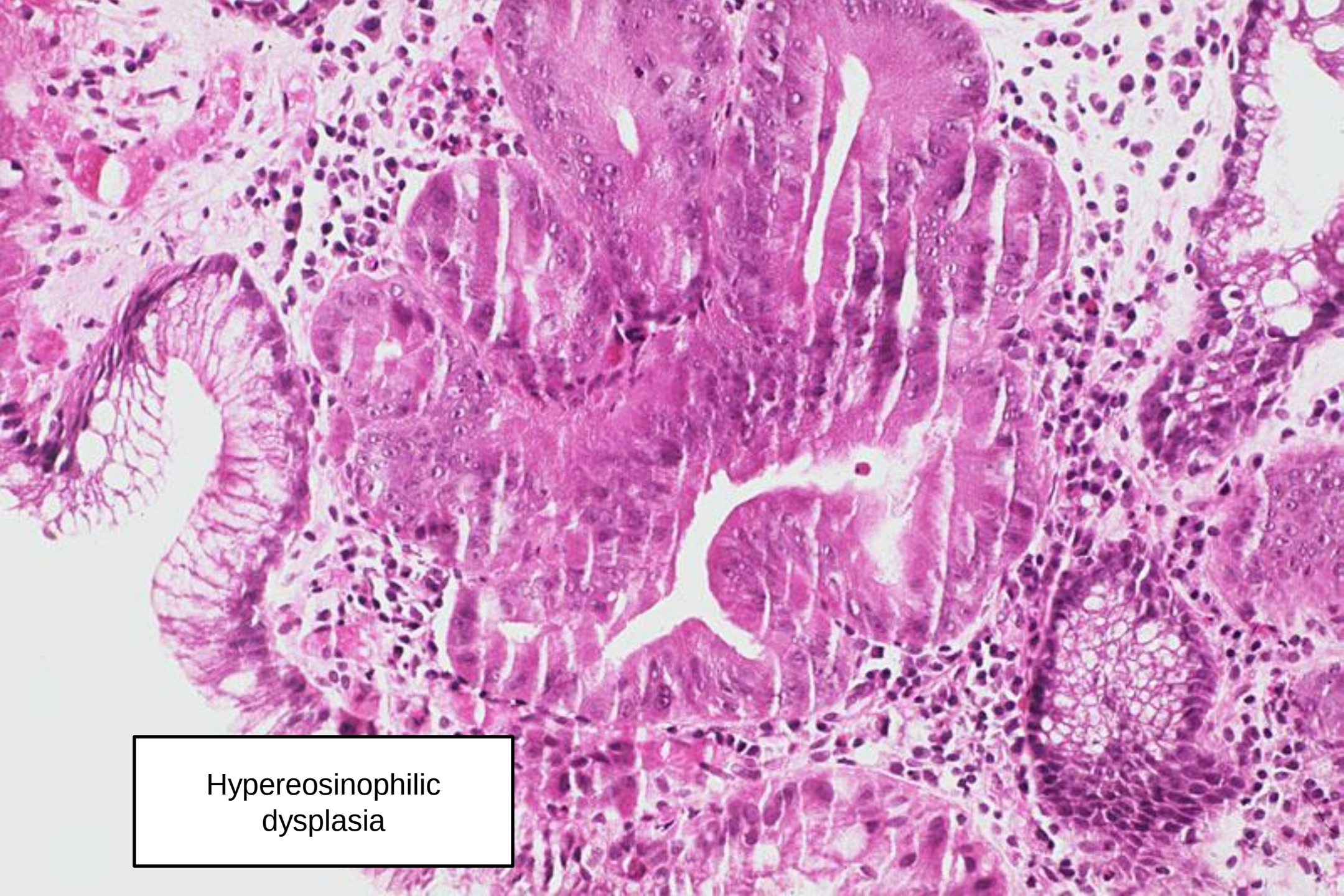

Inflamed HGD

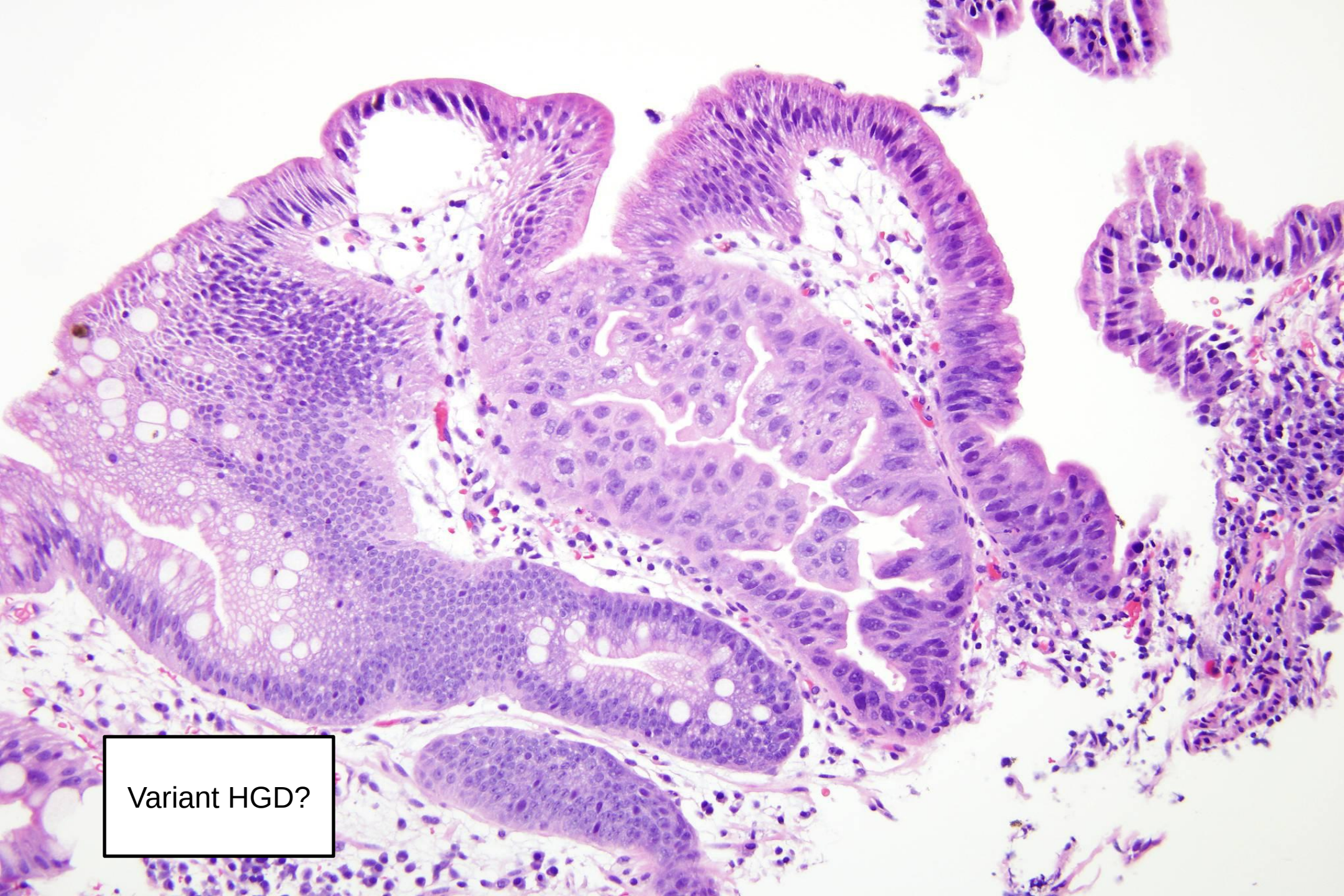

Hypermucinous change - ?variant of LGD

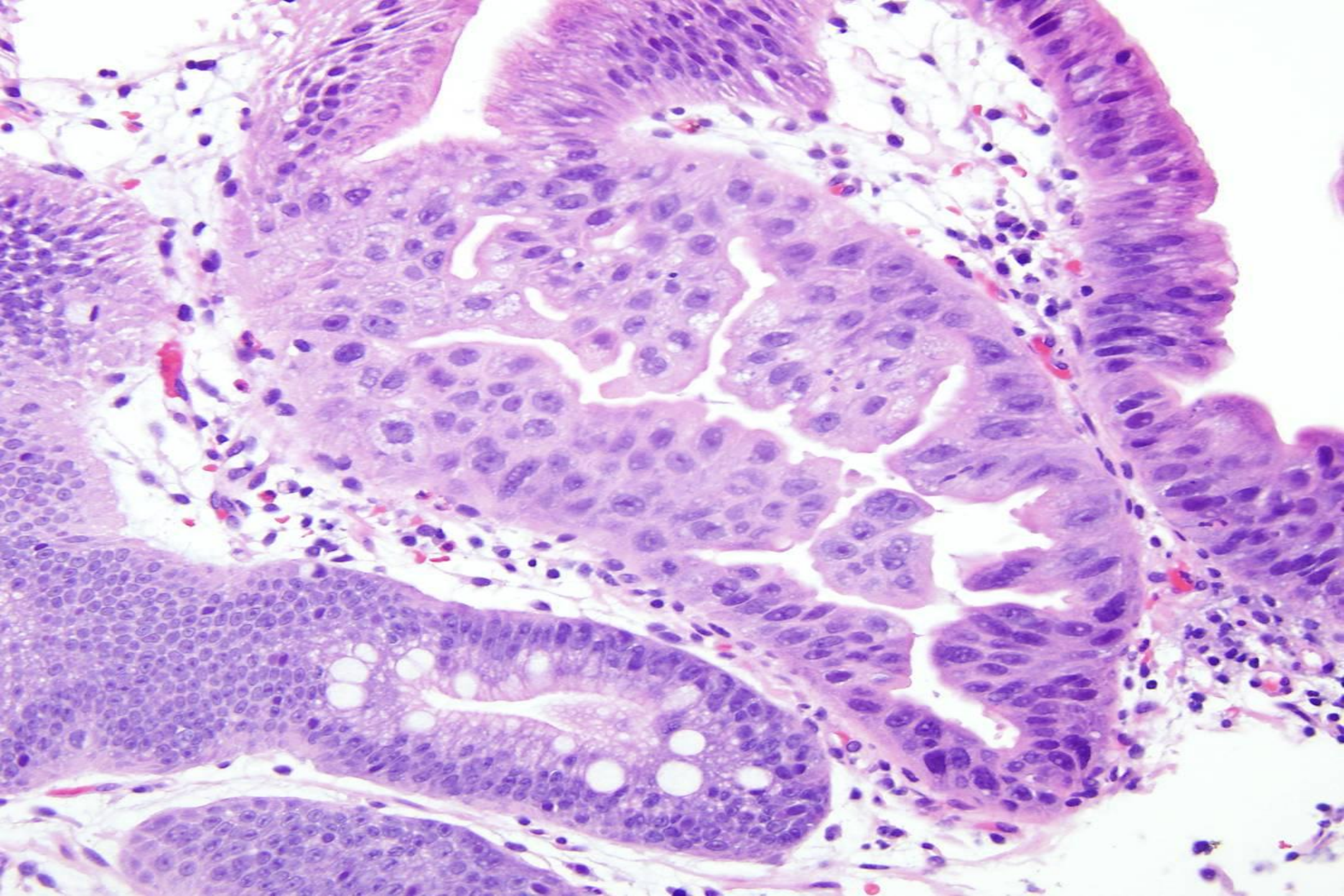

Hypermucinous change -
?variant of LGD

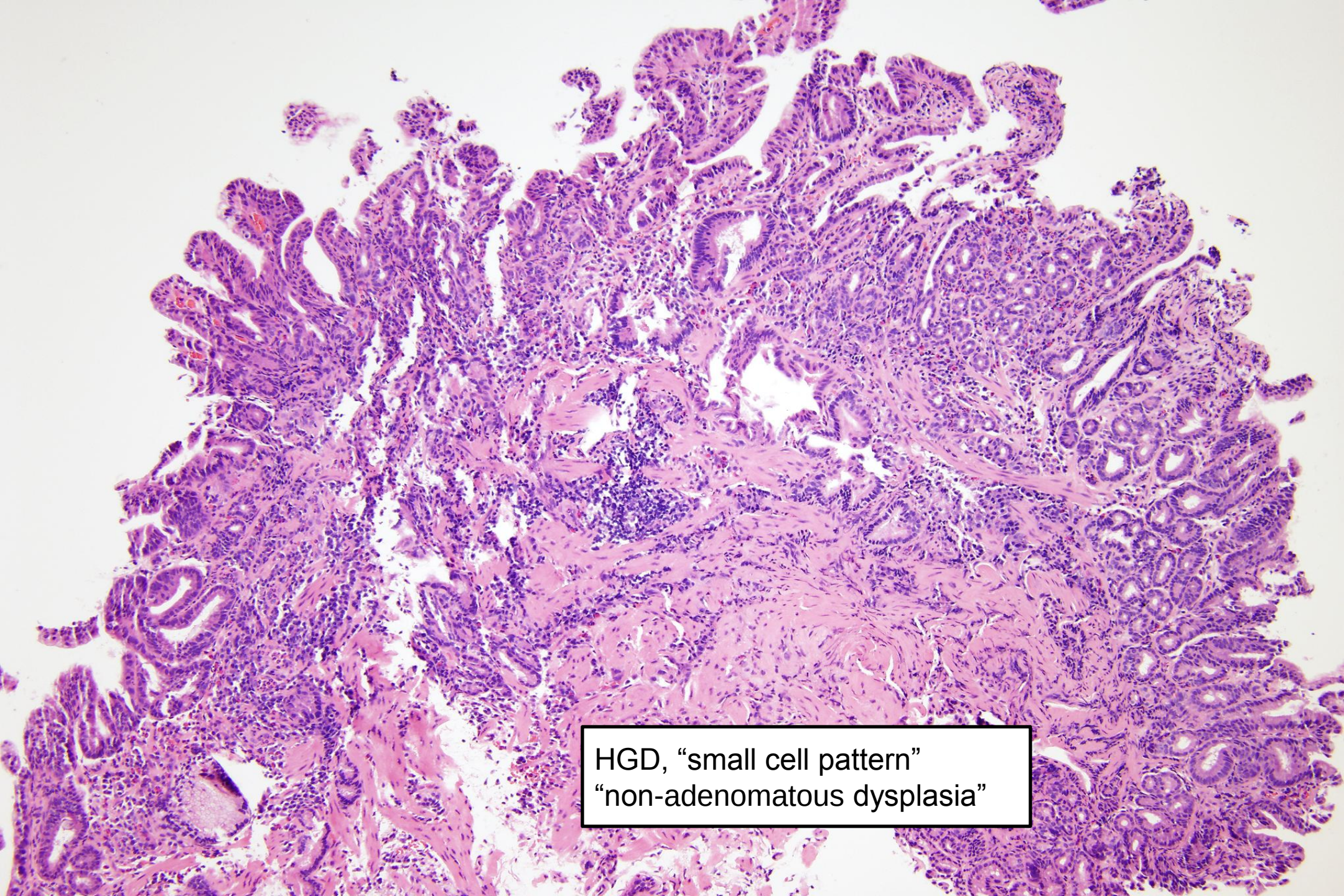


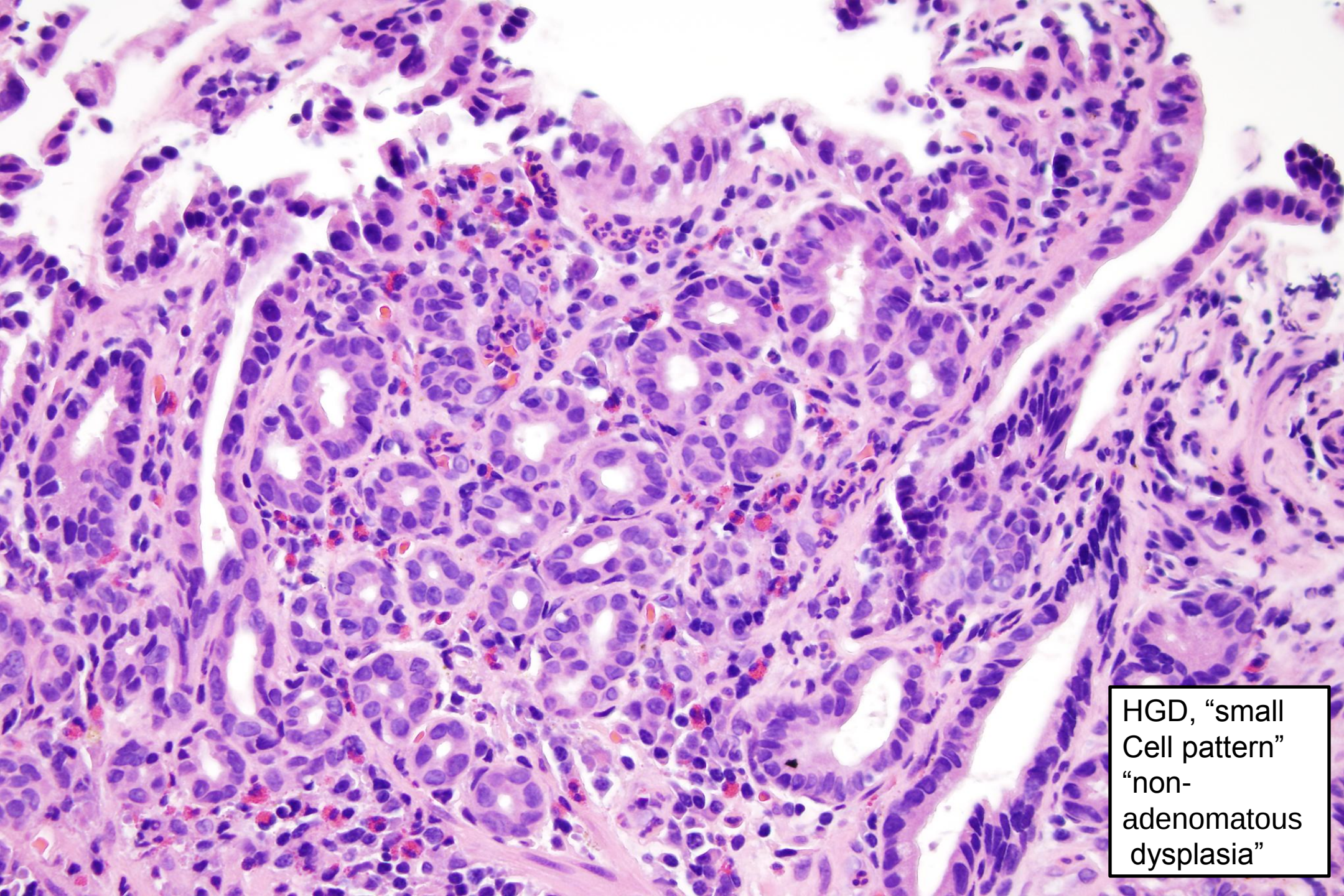
Hypereosinophilic dysplasia

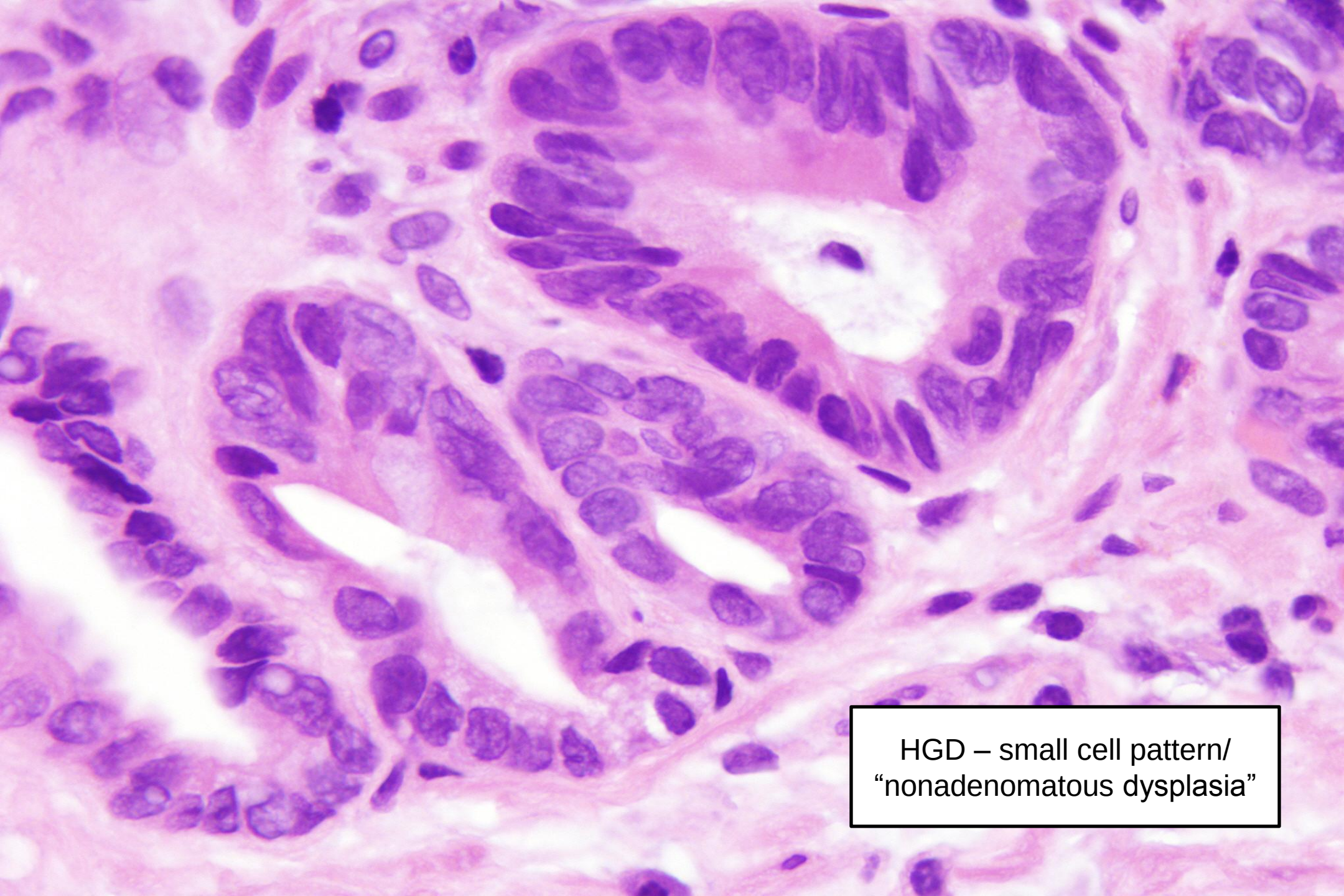

Hypereosinophilic
dysplasia


Variant HGD?



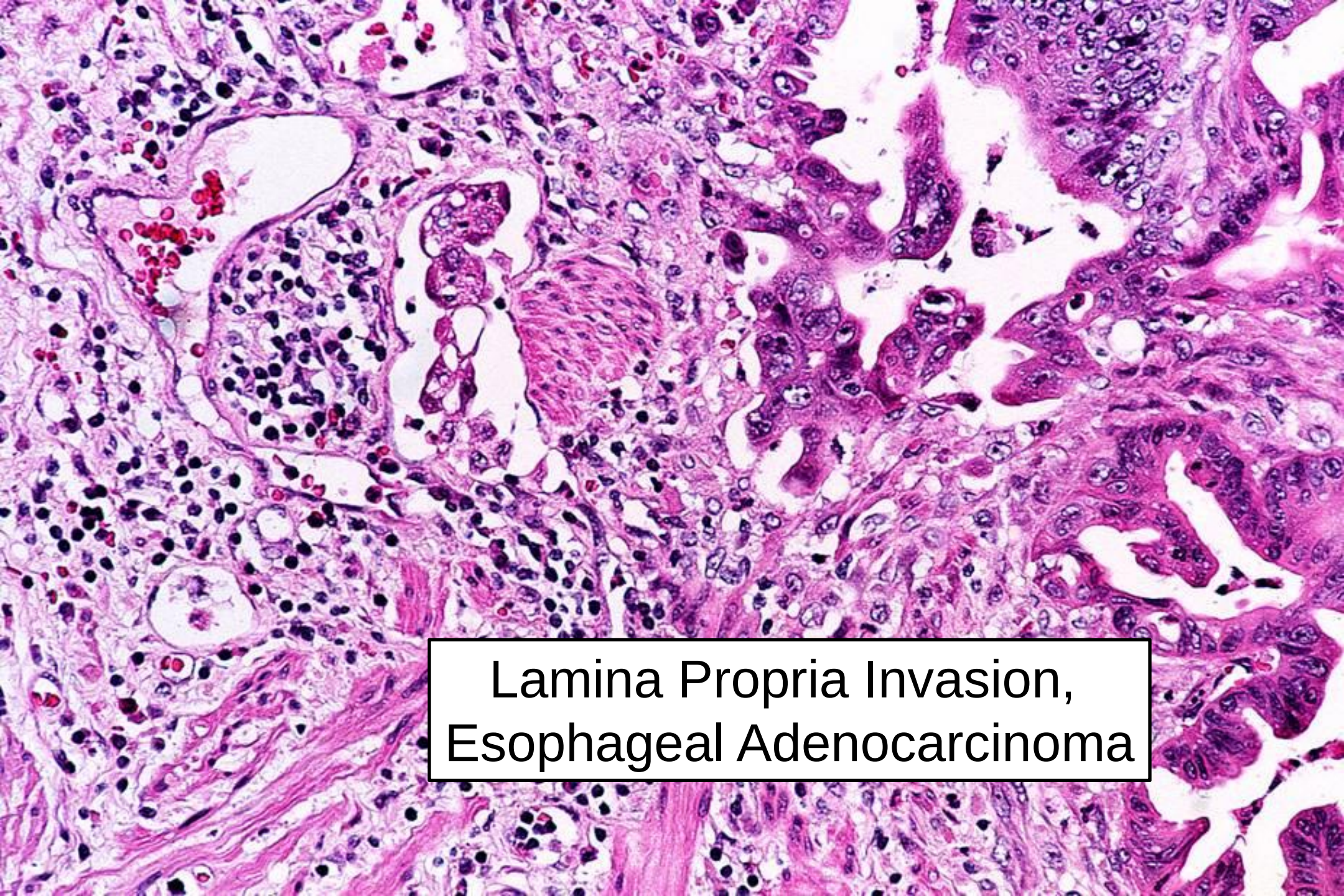

HGD, “small cell pattern”
“non-adenomatous dysplasia”

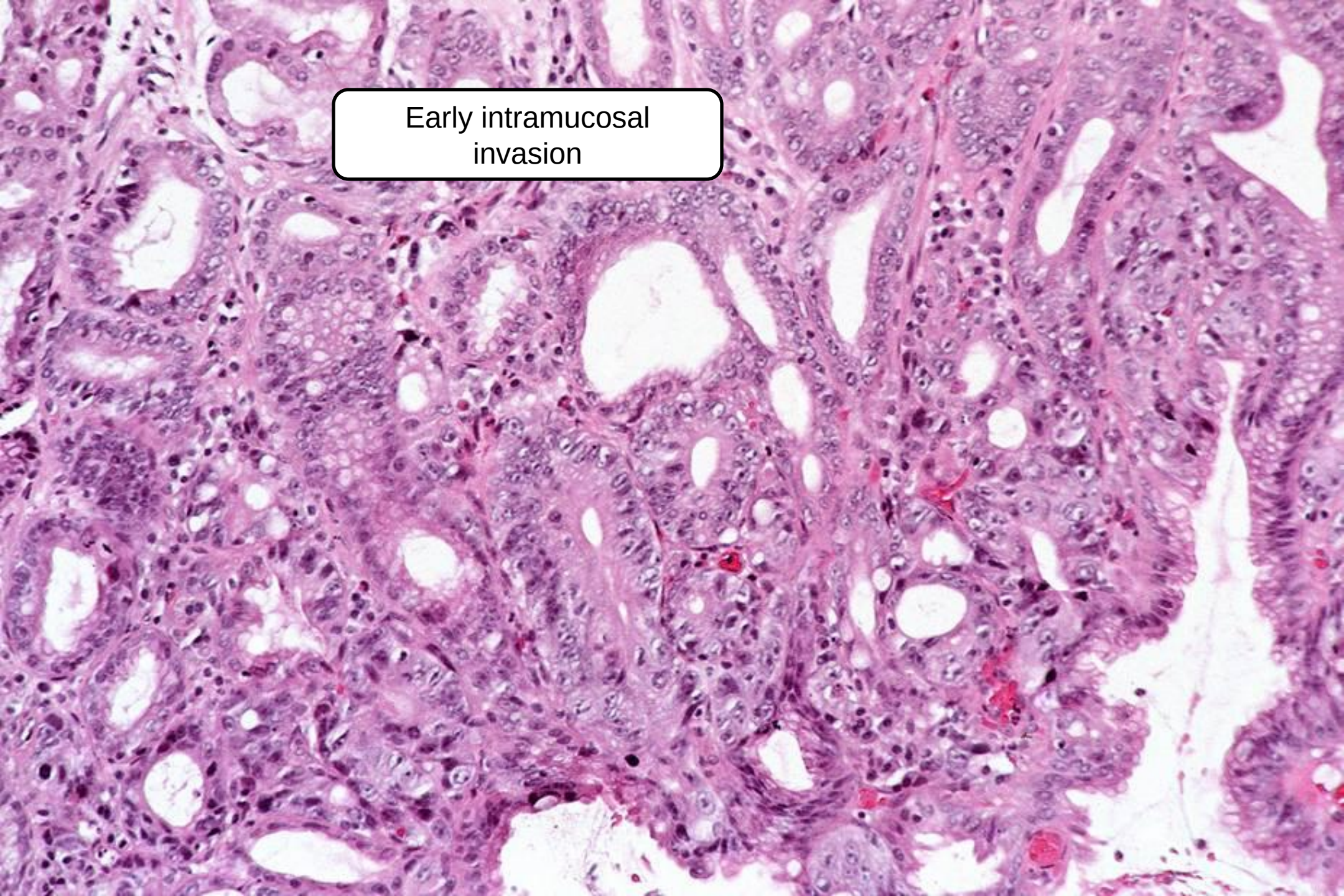

HGD, “small
Cell pattern”
“non-
adenomatous
dysplasia”

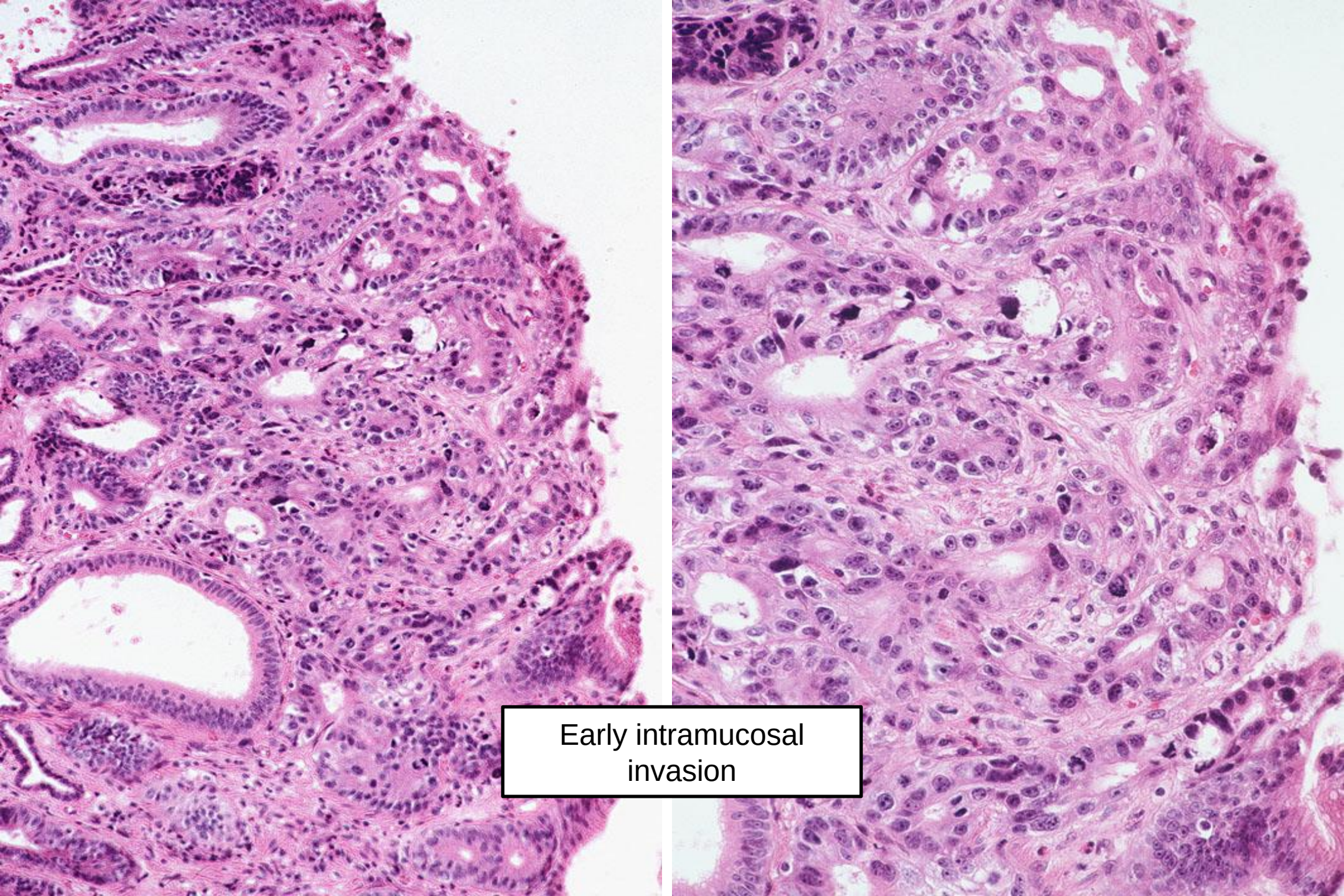

HGD – small cell pattern/
“nonadenomatous dysplasia”

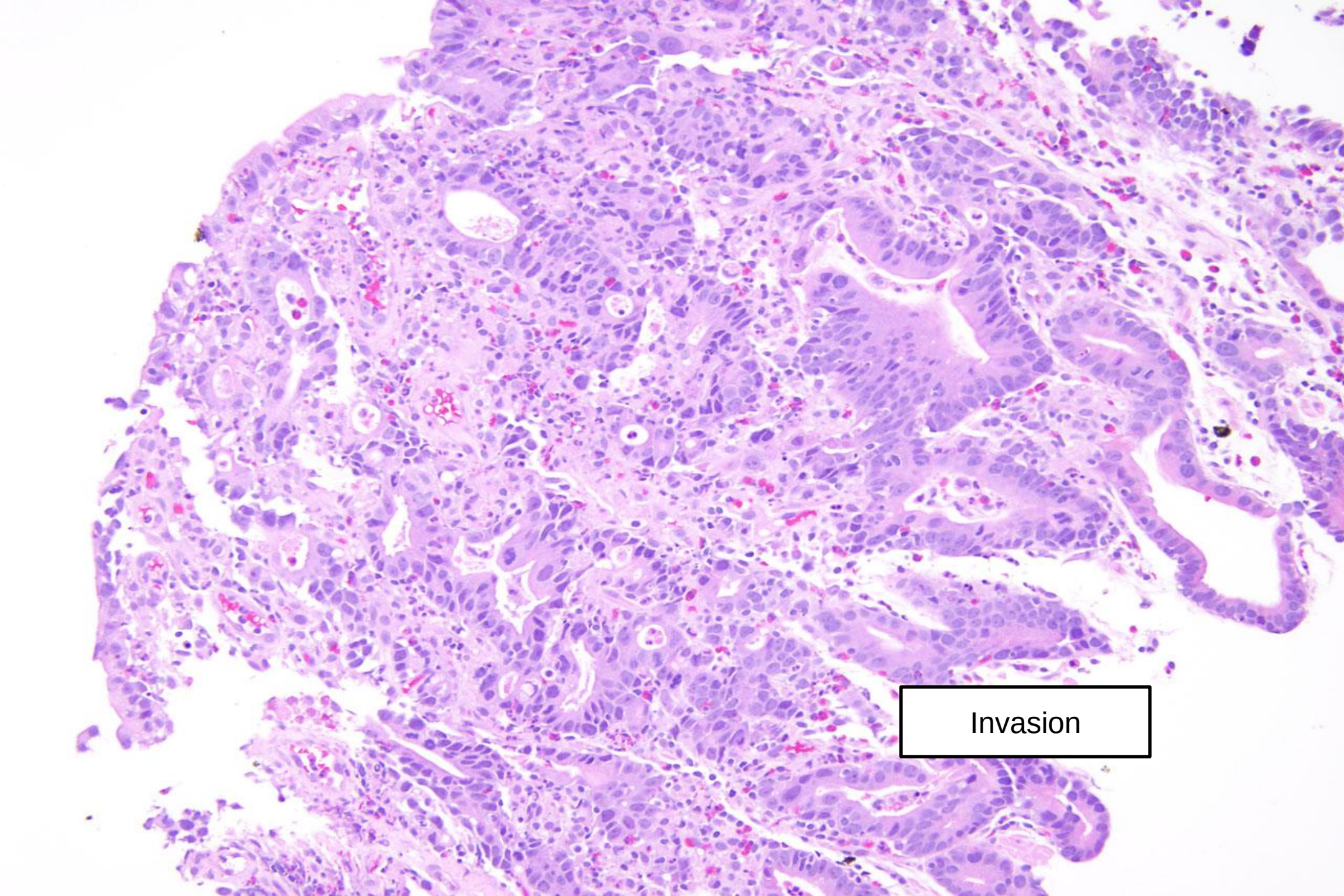
Intramucosal Carcinoma

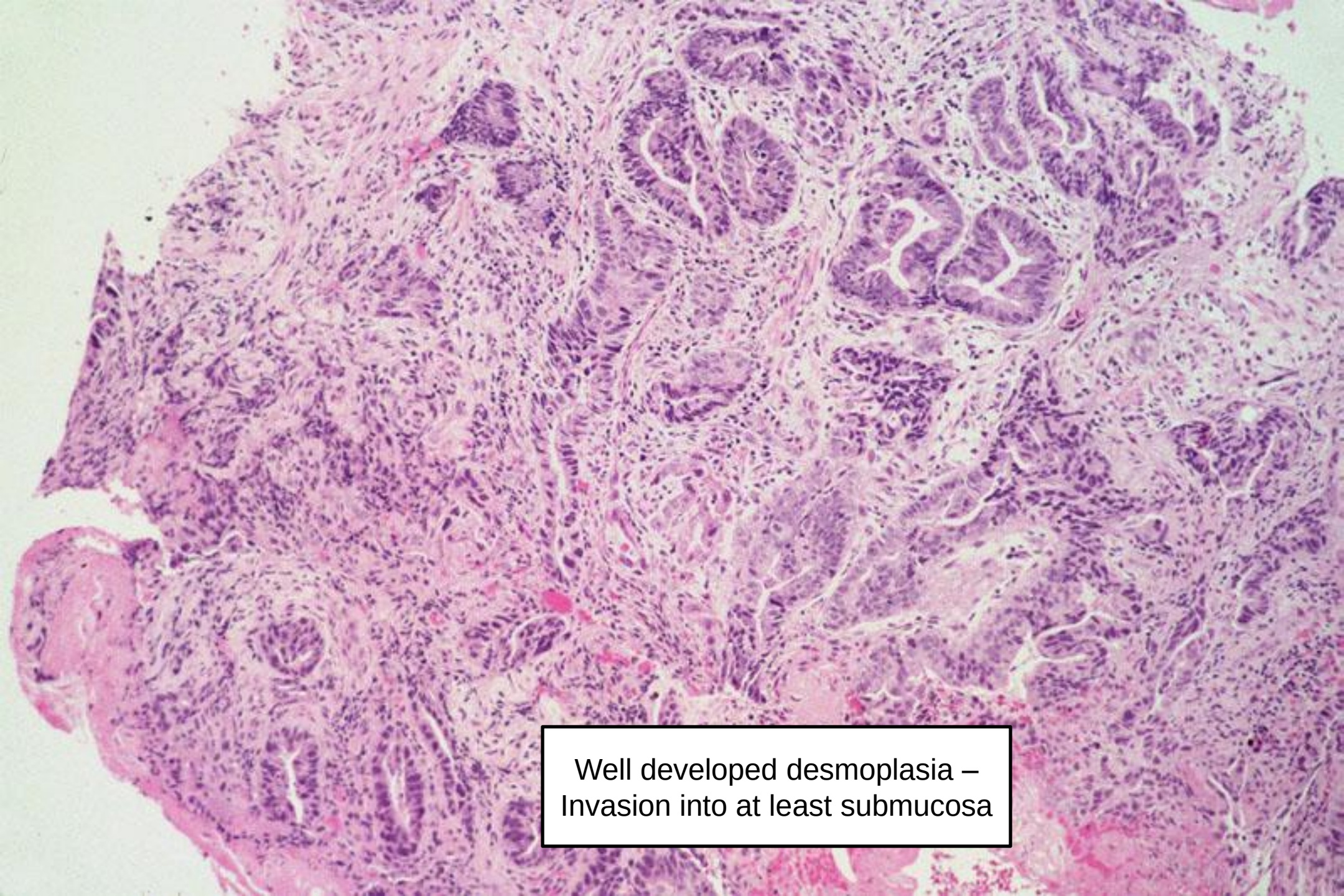
- Surface - No maturation
- Architecture - Effacement of lamina propria and syncytial growth pattern of glands. Back-to-back microglands, “dirty necrosis” in glands, DESMOPLASIA not yet developed
- Cytology - as in HG –but often with nucleoli
- Inflammation - variable

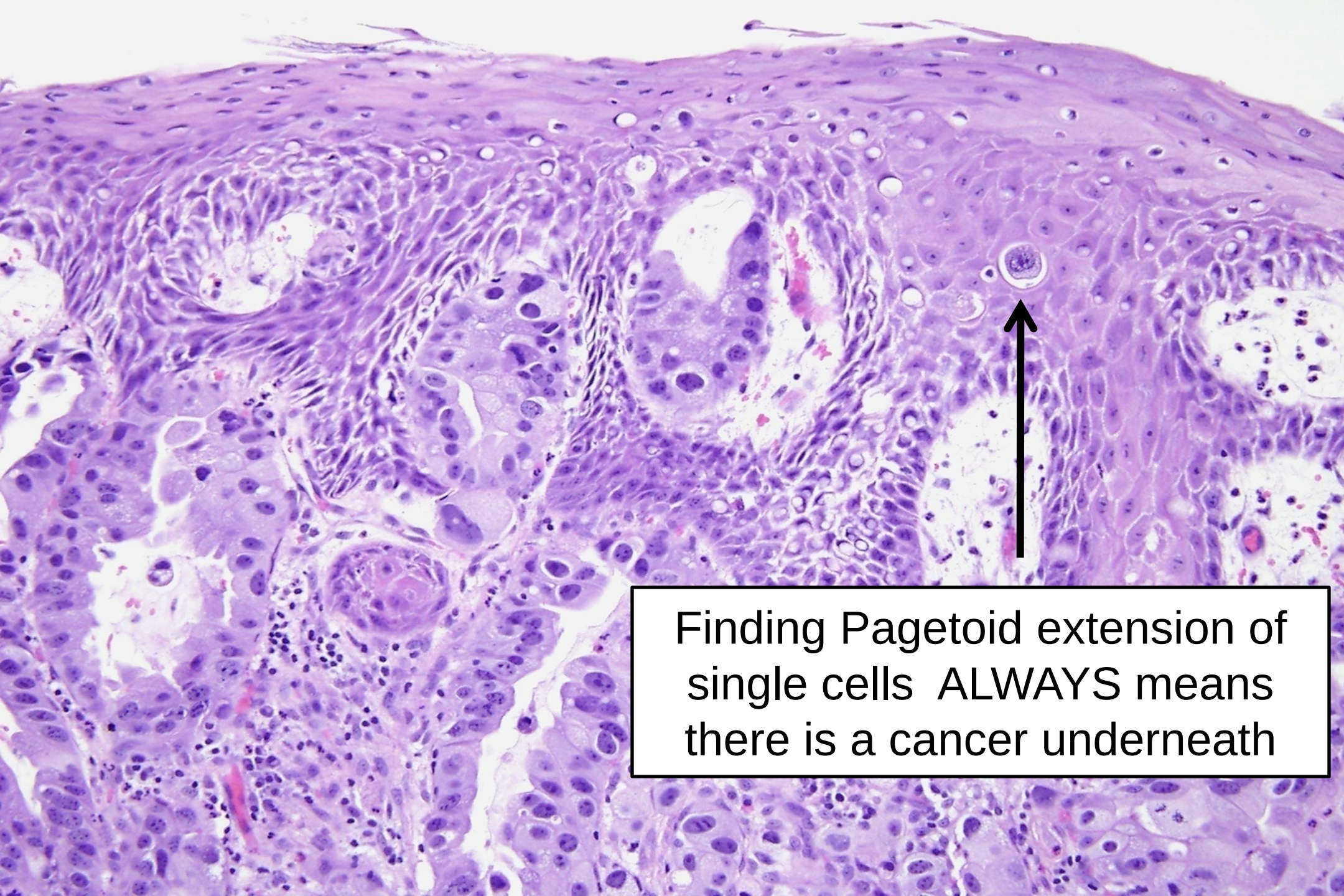

Lamina Propria Invasion,
Esophageal Adenocarcinoma


Early intramucosal invasion


Early intramucosal
invasion


Invasion


Well developed desmoplasia –
Invasion into at least submucosa


Finding Pagetoid extension of single cells ALWAYS means there is a cancer underneath

Alternate Approach; University of Michigan

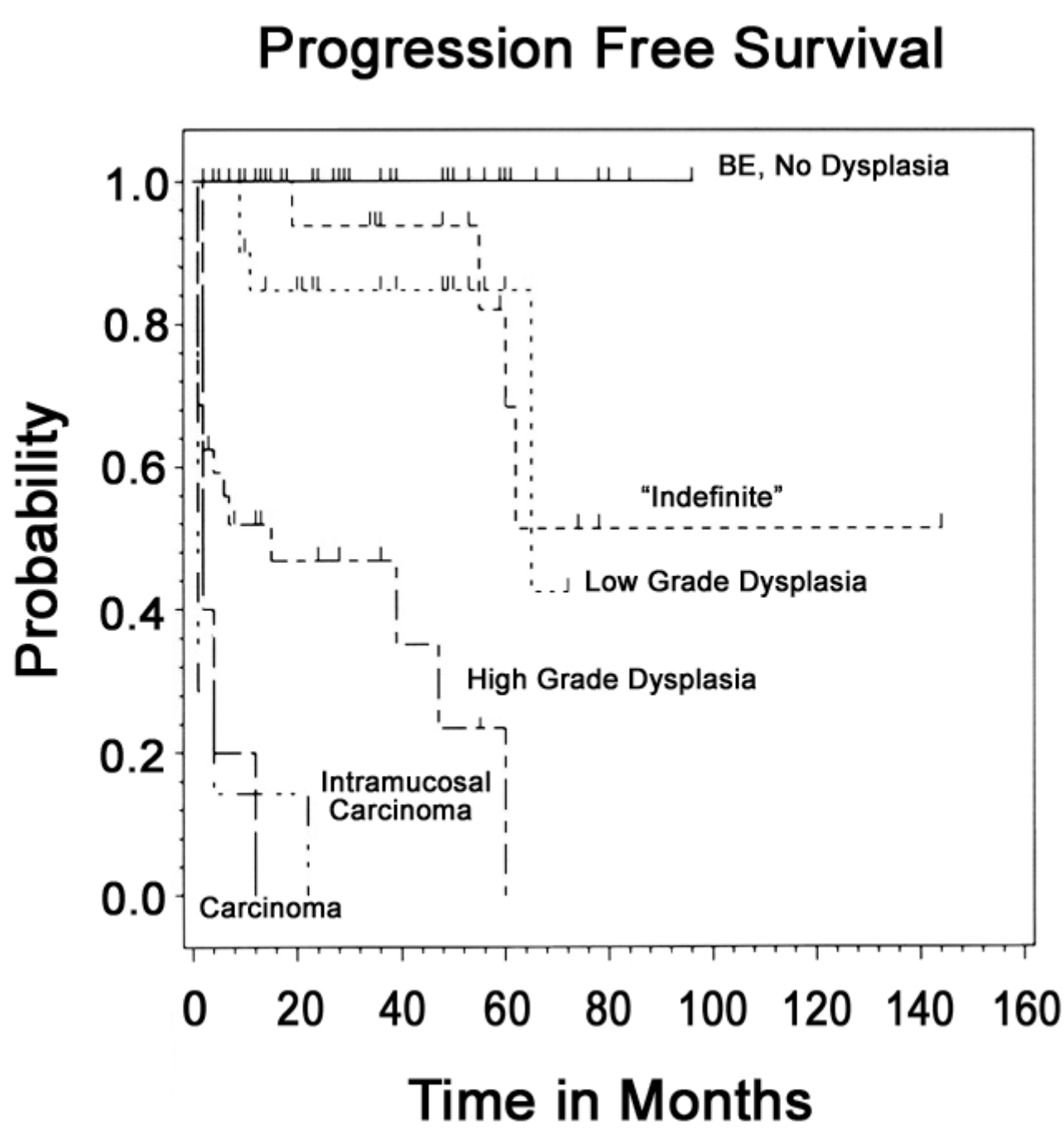
- Zhu et al; Am J Clin Pathol 2009; 132:94-100.
- Classified HGD as “regular” or “suspicious” (“HGD/S”)

The S Factors

- Cribriform/solid growth
- Dilated tubules/necrotic debris
- Ulcerated HGD
- PMNs in dysplasia
- Invasion of squamous epithelium

Impact of “S” Factors on Finding Invasion (T1 or more) at Esophagectomy

- No S factors – No cancers
- One factor – 39%
- Two factors – 83%
- Three factors – 87%
- Four factors – 88%
- Invasion into overlying squamous – 100%


Progression Free Survival
Probability
1.0
0.8
0.6
0.4
0.2
0.0
BE, No Dysplasia
"Indefinite"
Low Grade Dysplasia
High Grade Dysplasia
Intramucosal Carcinoma
Carcinoma
0
20
40
60
80
100
120
140
160
Time in Months

“Modern” View

- Once you remove the people who already have cancer, the progression rate is closer to 20-30% in HGD
- In our hospital, if esophagectomy was done for HGD in patients on “Seattle protocol”, there were no cancers
- If esophagectomy done for HGD in patients NOT on protocol, we found 33% had a missed cancer
- OVERALL - Risk of progression to cancer about 6%/year in patients with high grade dysplasia

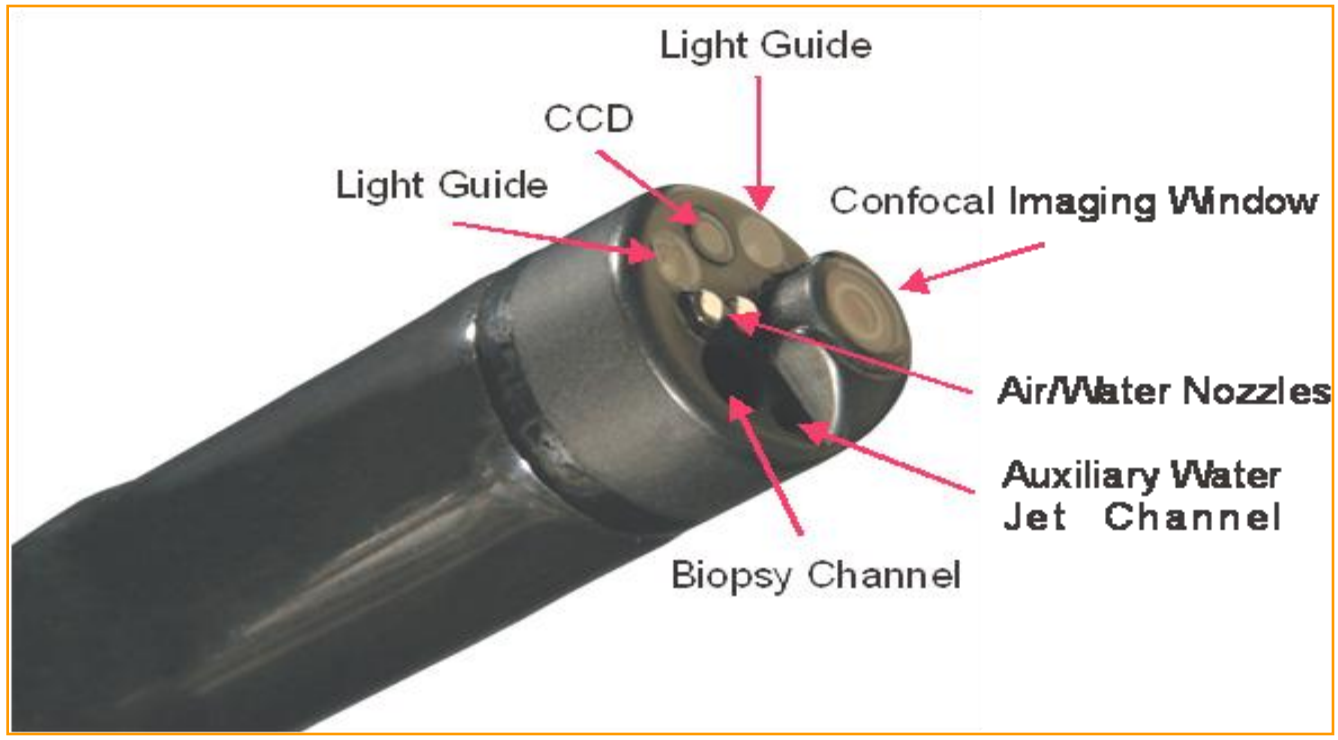
SEER Data

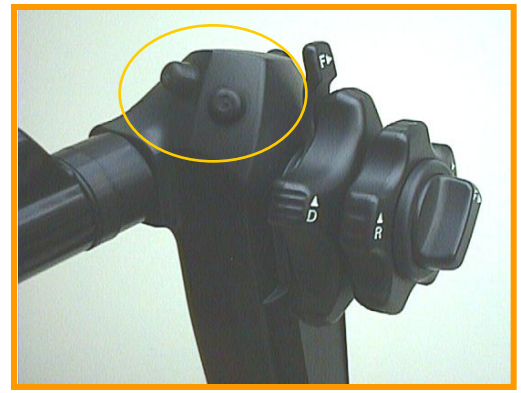
- Patients with early esophageal cancer(T0, T1) managed with endoscopic therapy have equivalent long-term survival compared to those treated with surgical resection.
- Das A, Singh V, Fleischer DE, Sharma VK. A comparison of endoscopic treatment and surgery in early esophageal cancer: an analysis of surveillance epidemiology and end results data. Am J Gastroenterol. 2008 Jun;103(6):1340-5.

Then and Now – Paradigm Shift

- In the past esophagectomy was recommended for HGD BUT there was really nothing better to offer people
- Now we know that radiofrequency ablation (BARRX) is a fantastic option with little risk (about 6%) for strictures
- Ref; Shaheen NJ, Sharma P, Overholt BF, Wolfsen HC, Sampliner RE, Wang KK, Galanko JA, Bronner MP, Goldblum JR, Bennett AE, Jobe BA, Eisen GM, Fennerty MB, Hunter JG, Fleischer DE, Sharma VK, Hawes RH, Hoffman BJ, Rothstein RI, Gordon SR, Mashimo H, Chang KJ, Muthusamy VR, Edmundowicz SA, Spechler SJ, Siddiqui AA, Souza RF, Infantolino A, Falk GW, Kimmey MB, Madanick RD, Chak A, Lightdale CJ. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med. 2009 May 28;360(22):2277-88.
- We are developing better ways to target biopsies to detect neoplasia as well

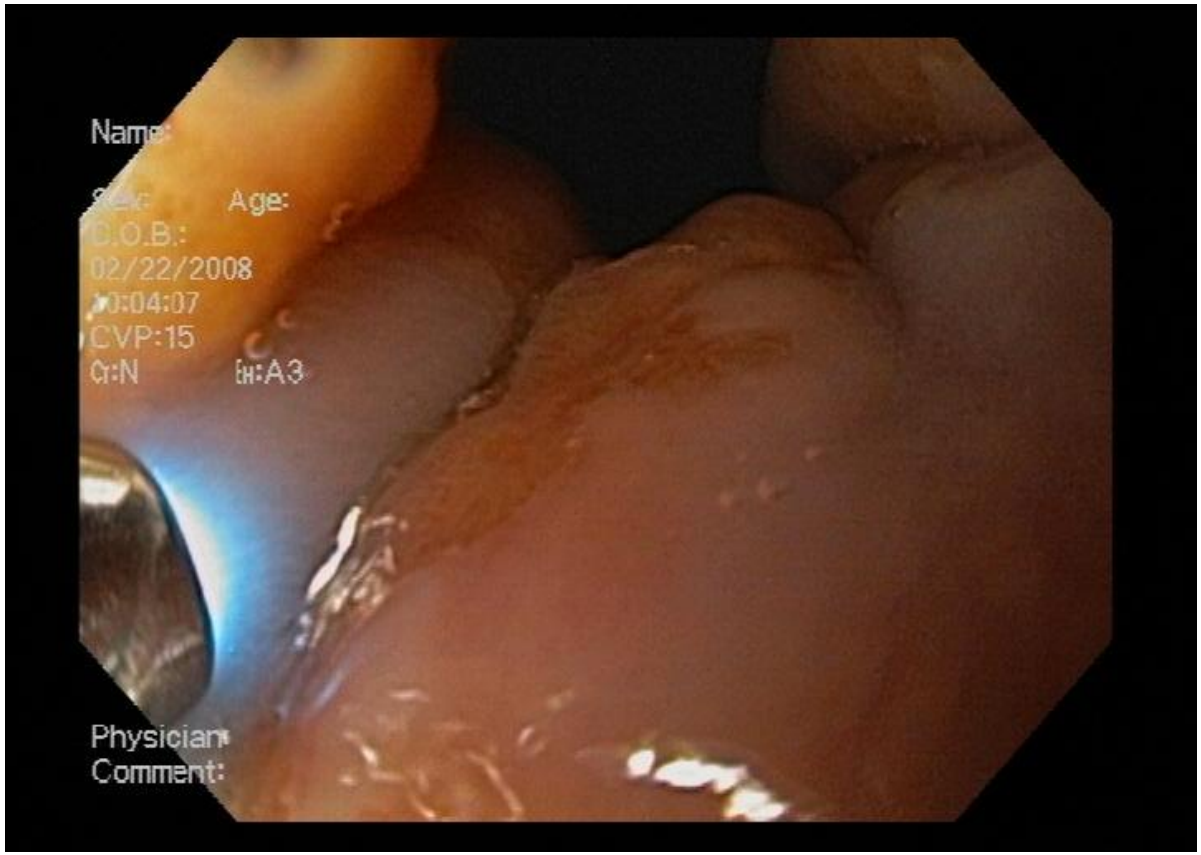
Confocal Endomicroscope



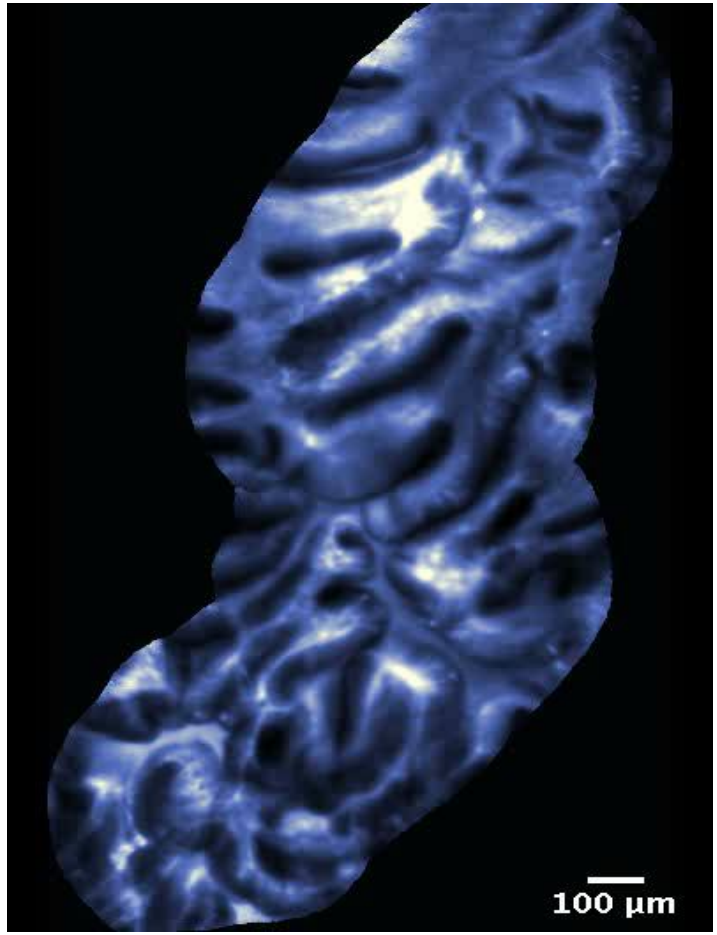


Pentax, Japan & Optiscan, Australia

Confocal Miniprobe

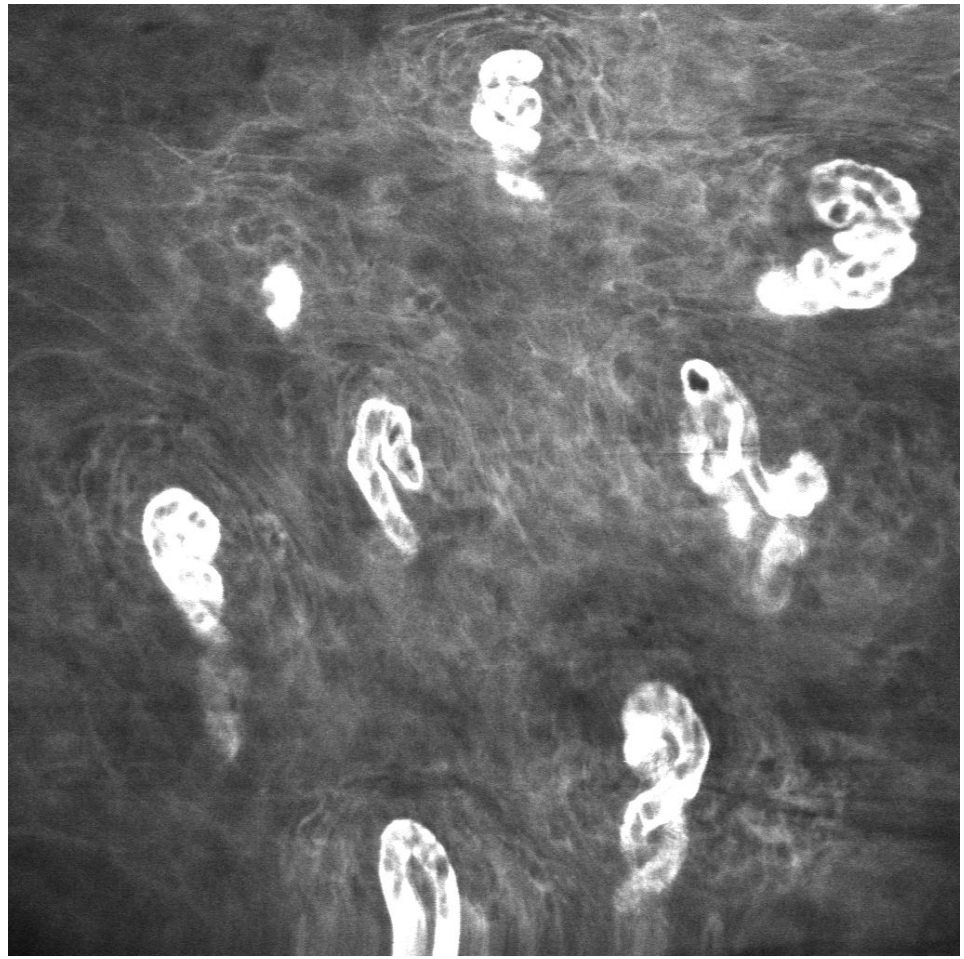


probe works with any endoscope



Cellvizio-GI

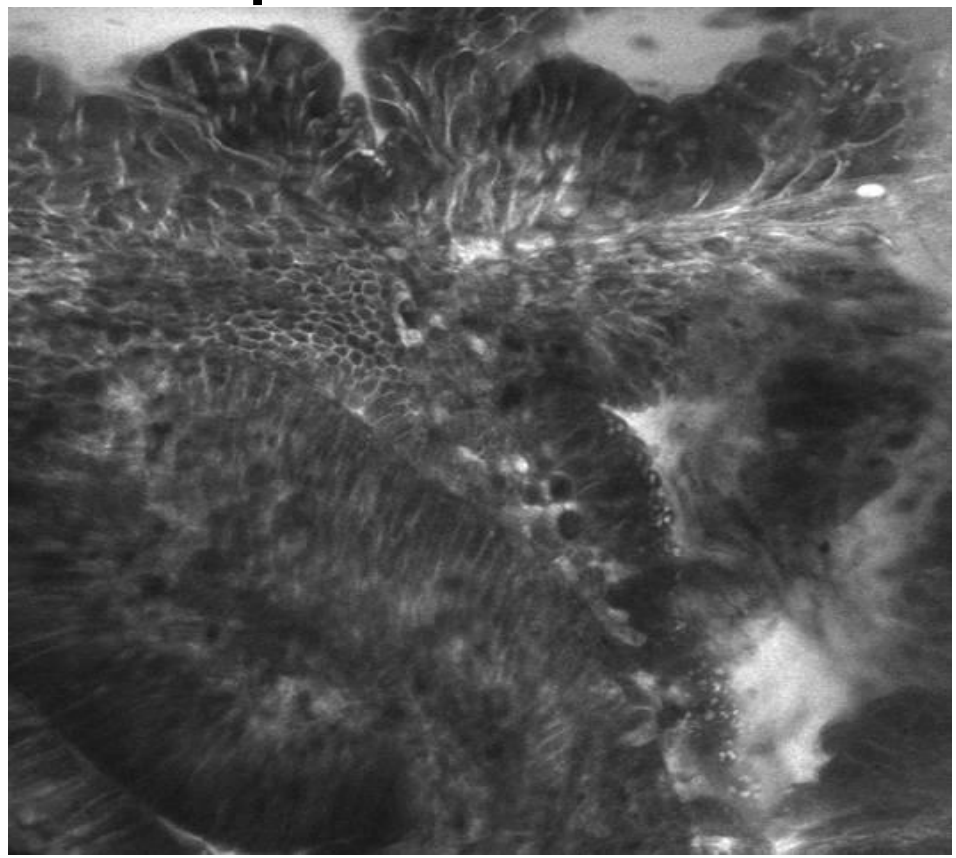
Confocal laser endomicroscopy (CLE)



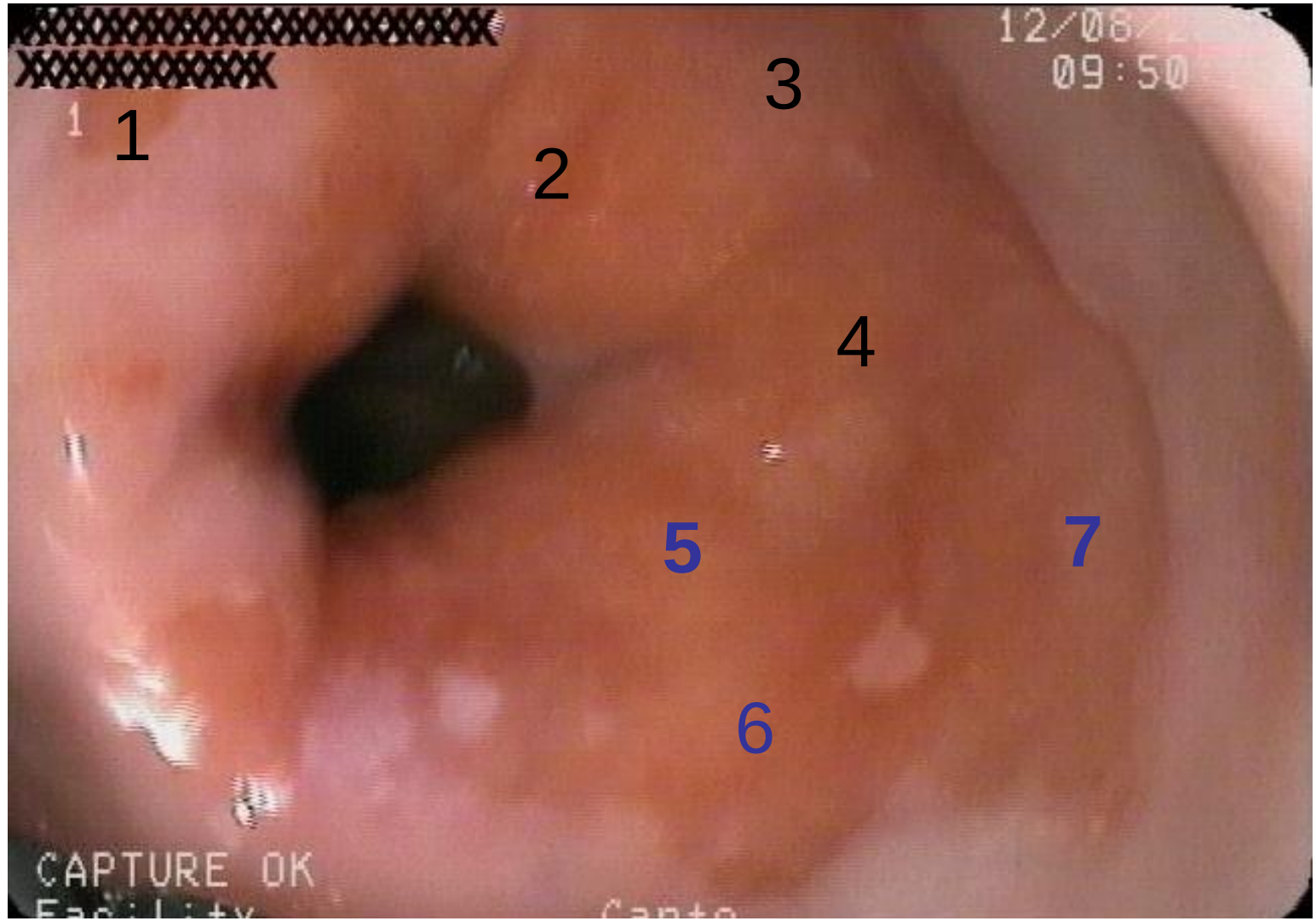
CLE helps choose biopsy sites

BE, no dysplasia

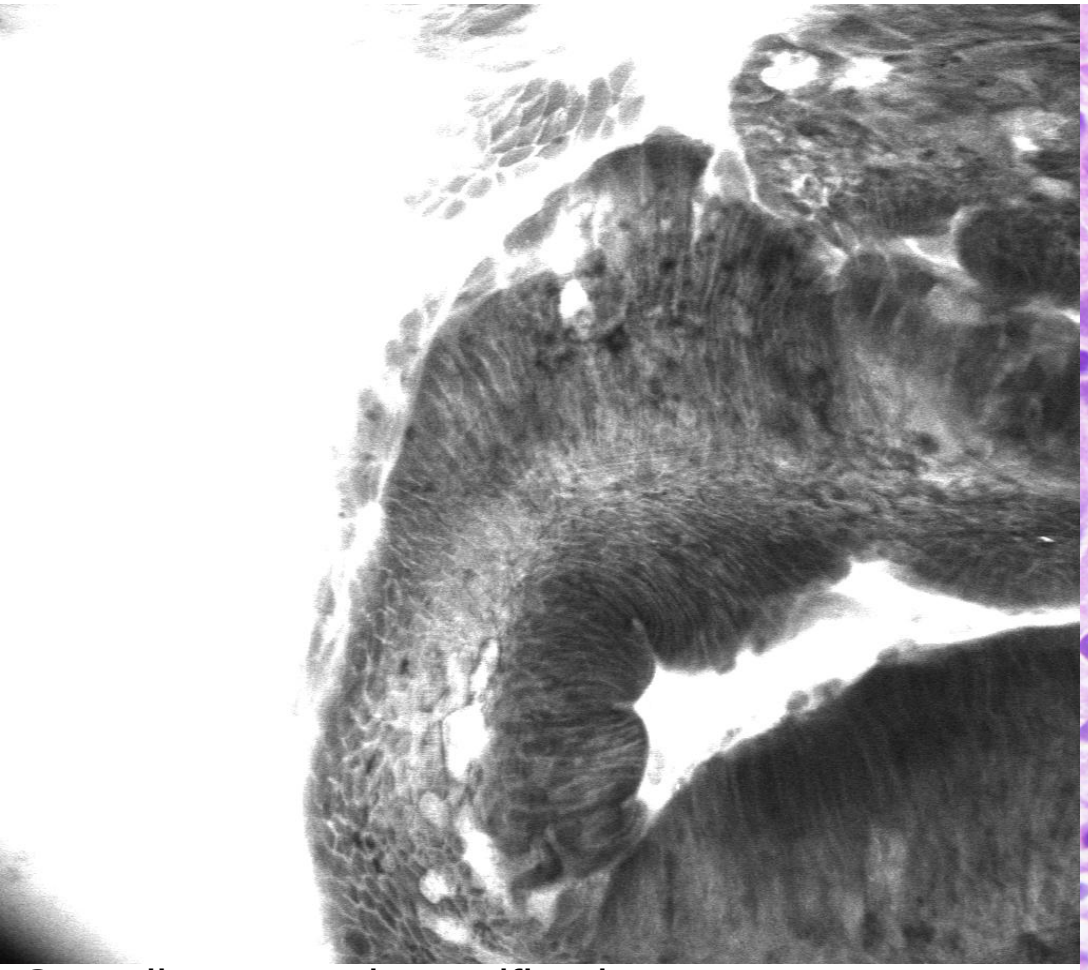
BE neoplasia

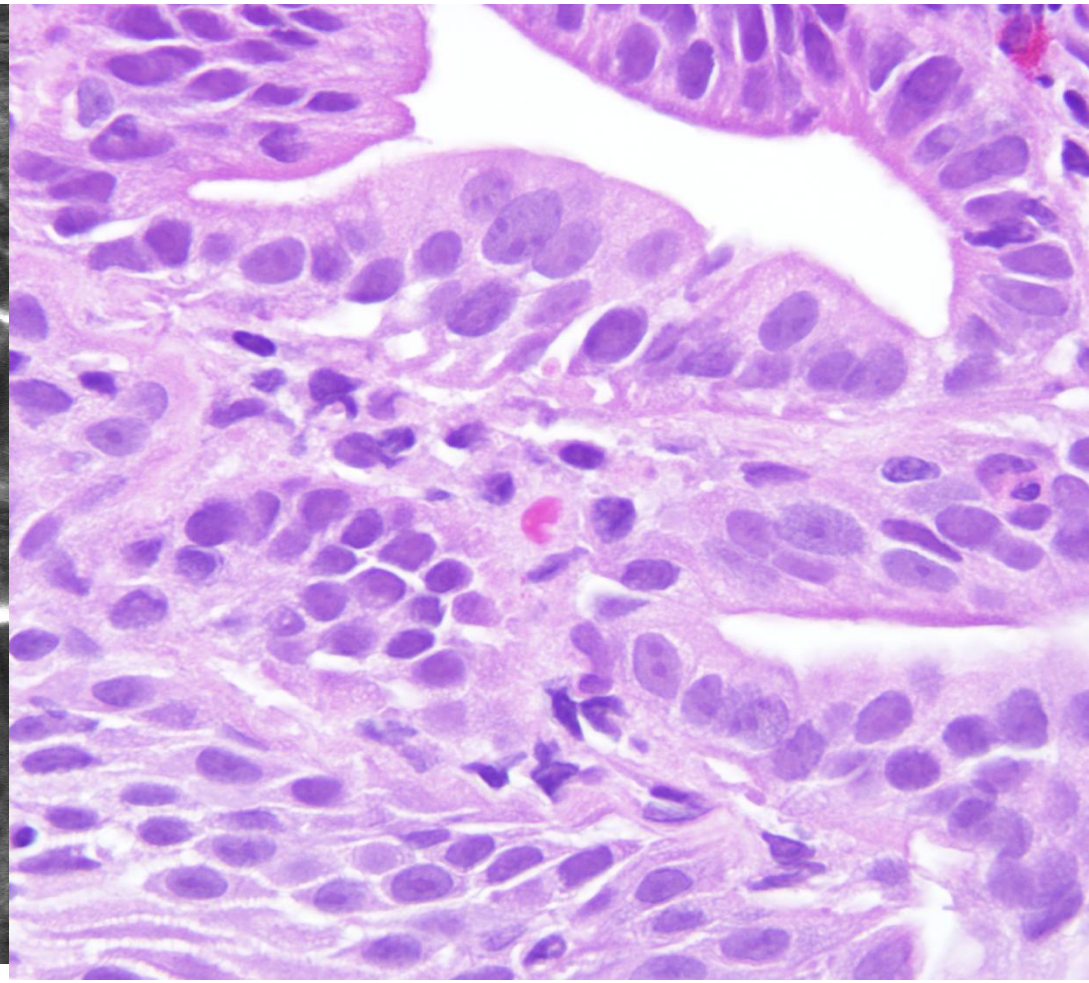


Routine BE Surveillance
Localize Neoplasia, Smarter Biopsies



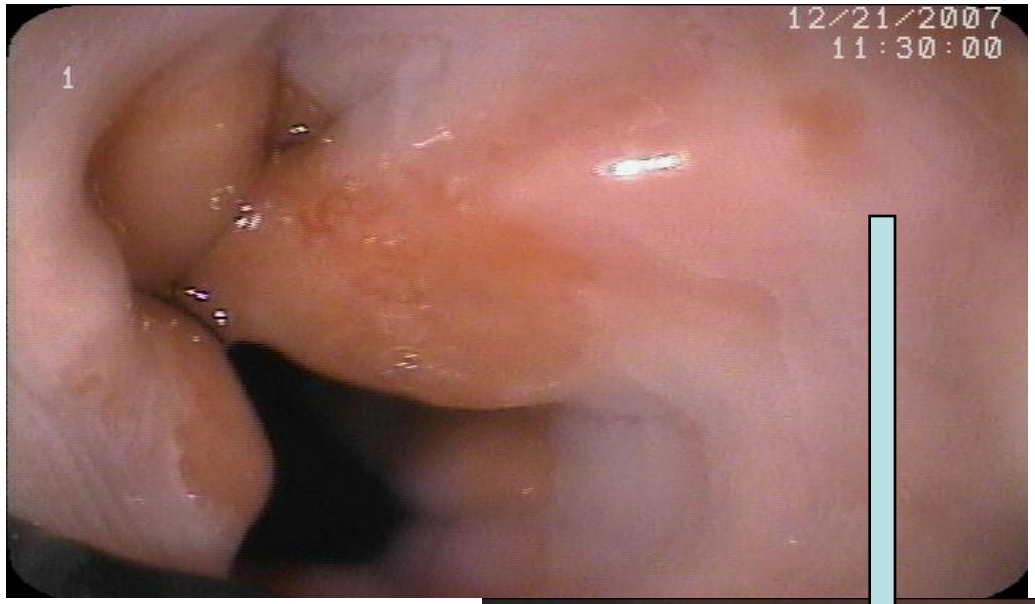
Confocal Site 5
HGD in Flat BE Mucosa

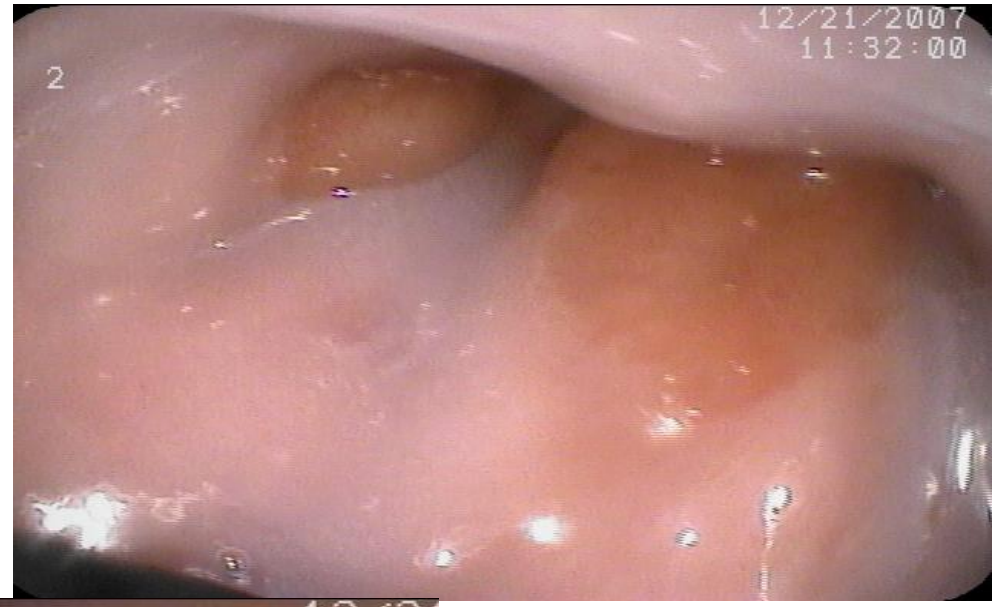


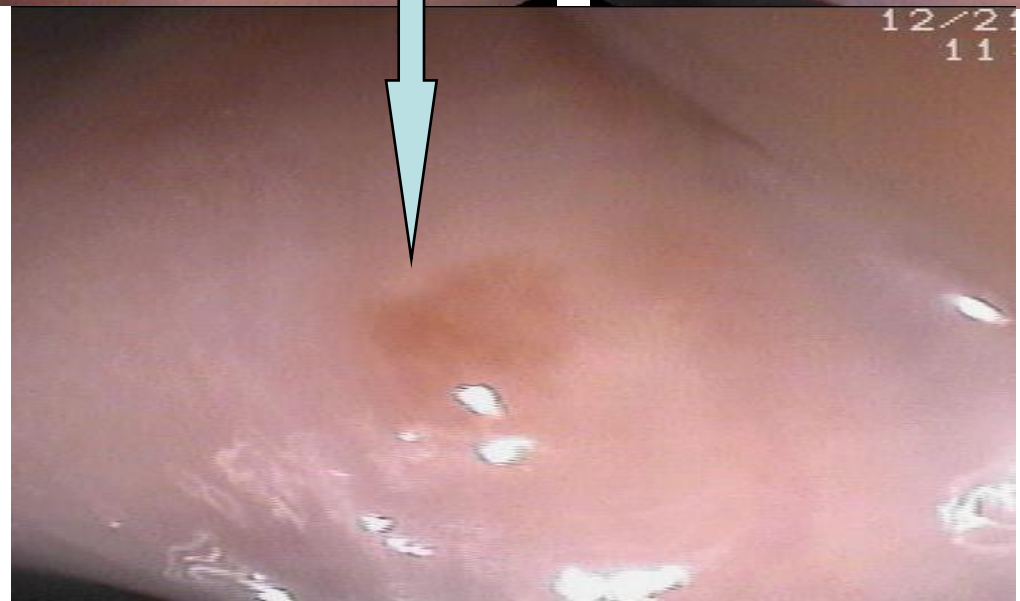


Crowding, pseudostratification

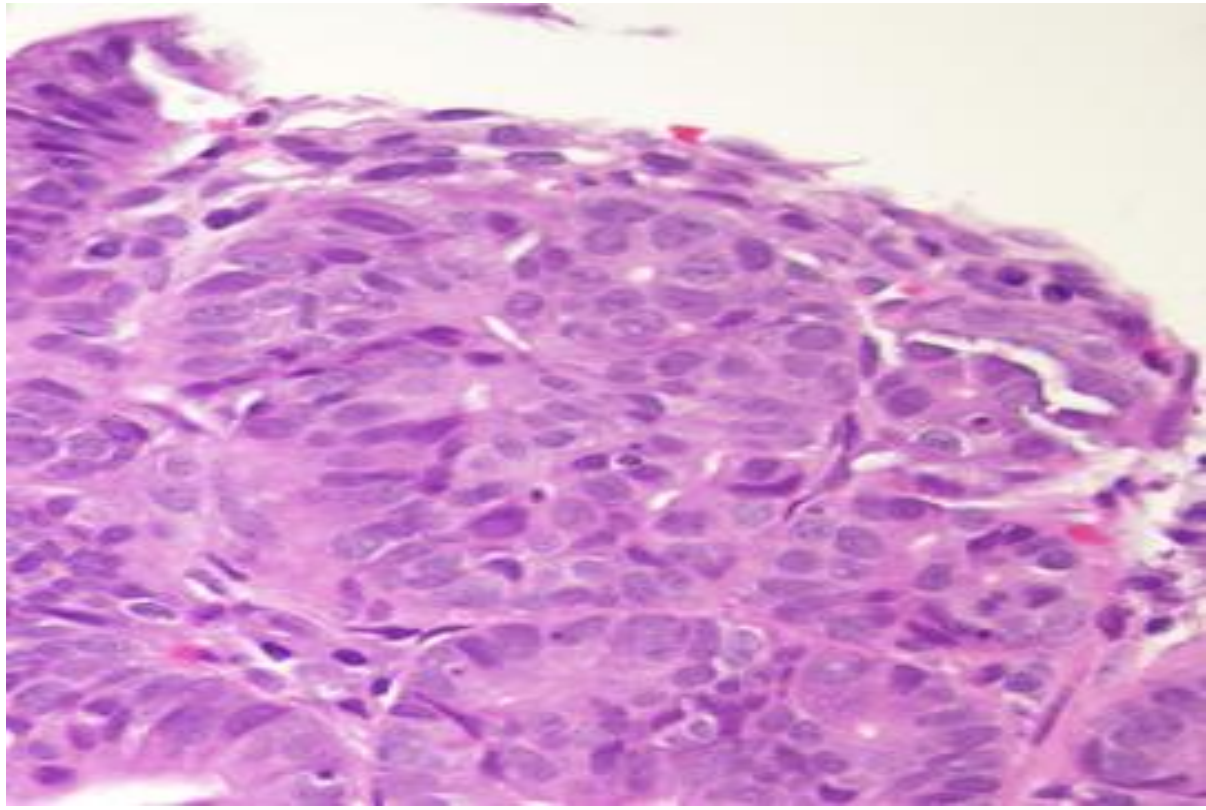
BE Routine Surveillance





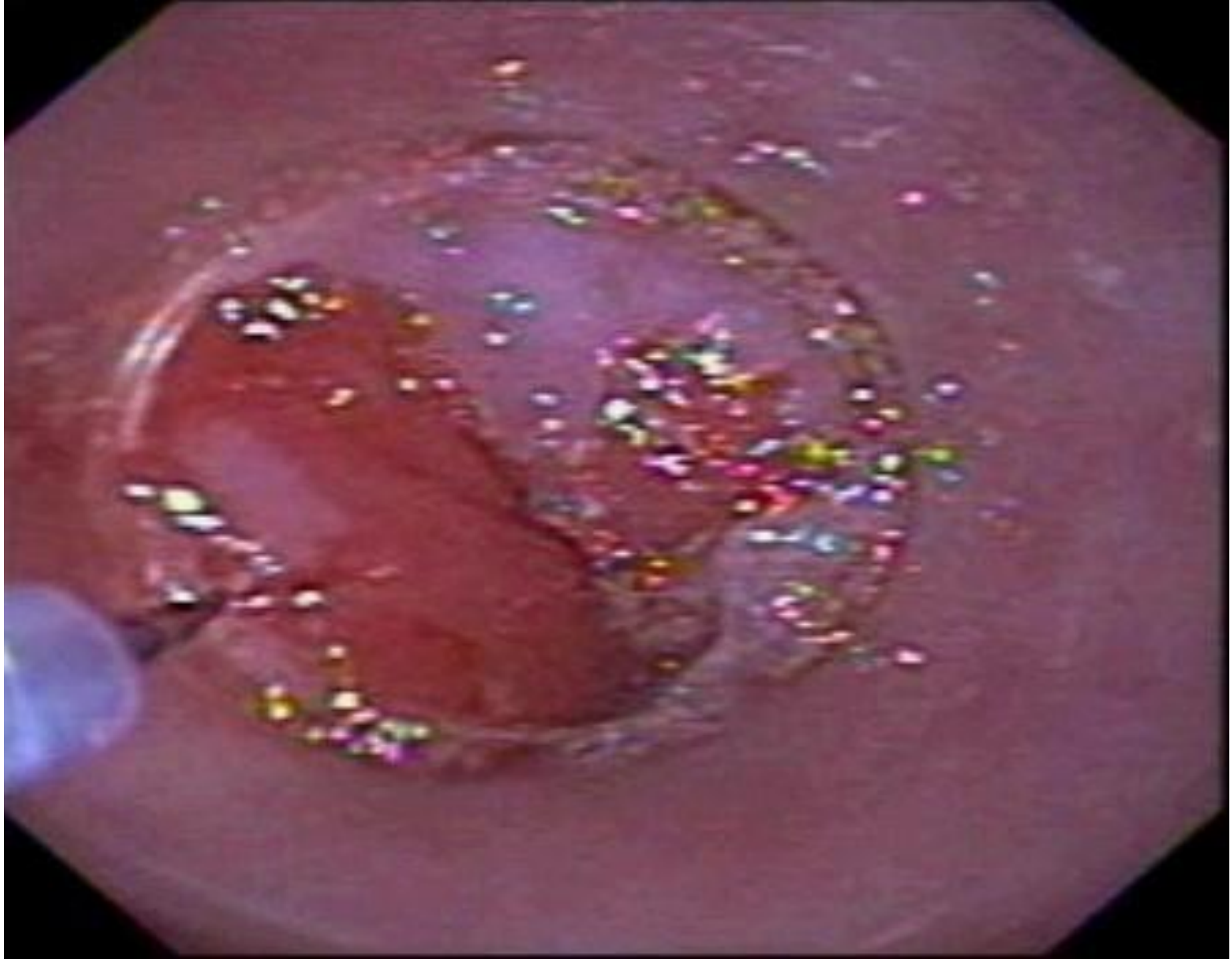


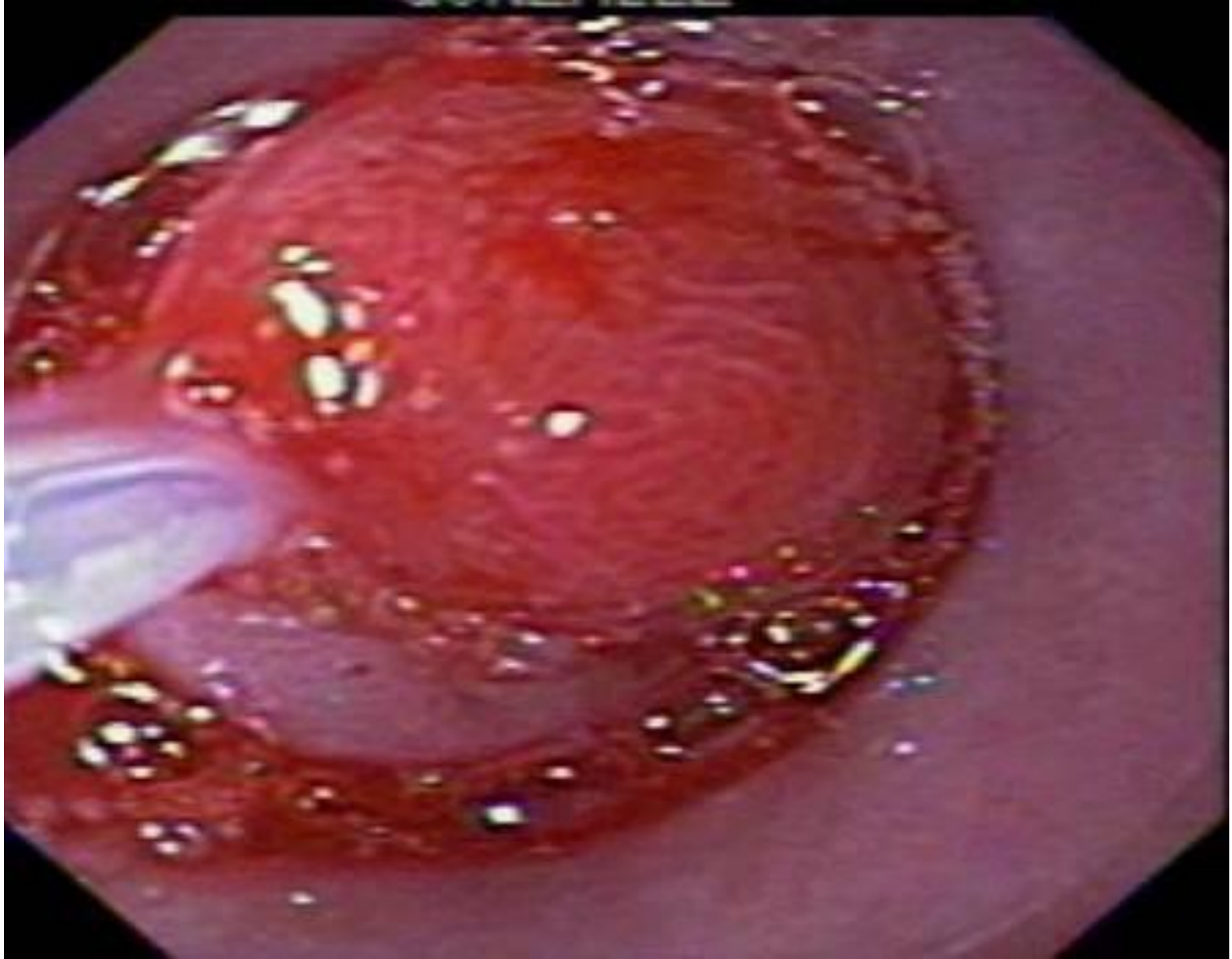
In Vivo Diagnosis of BE HGD

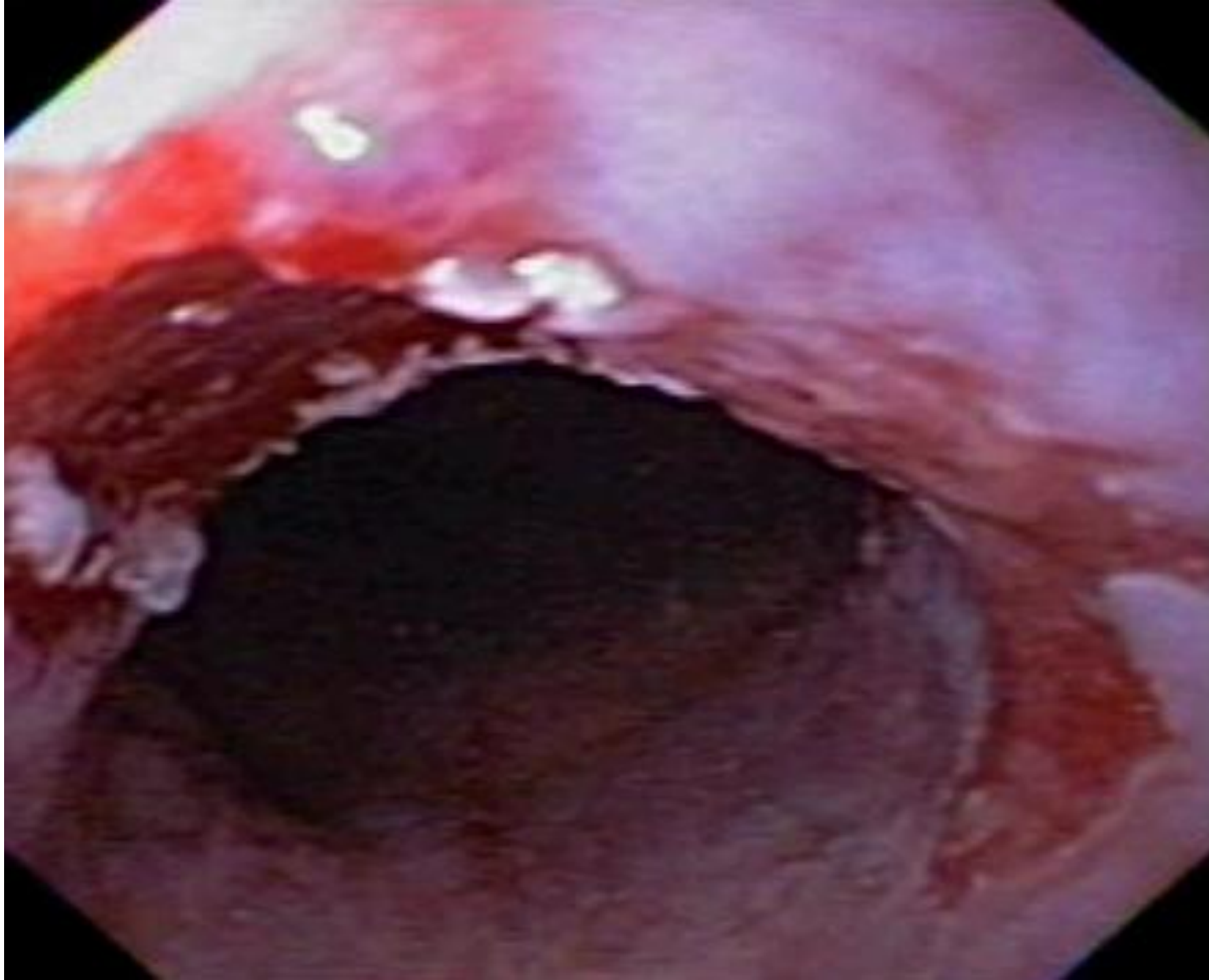


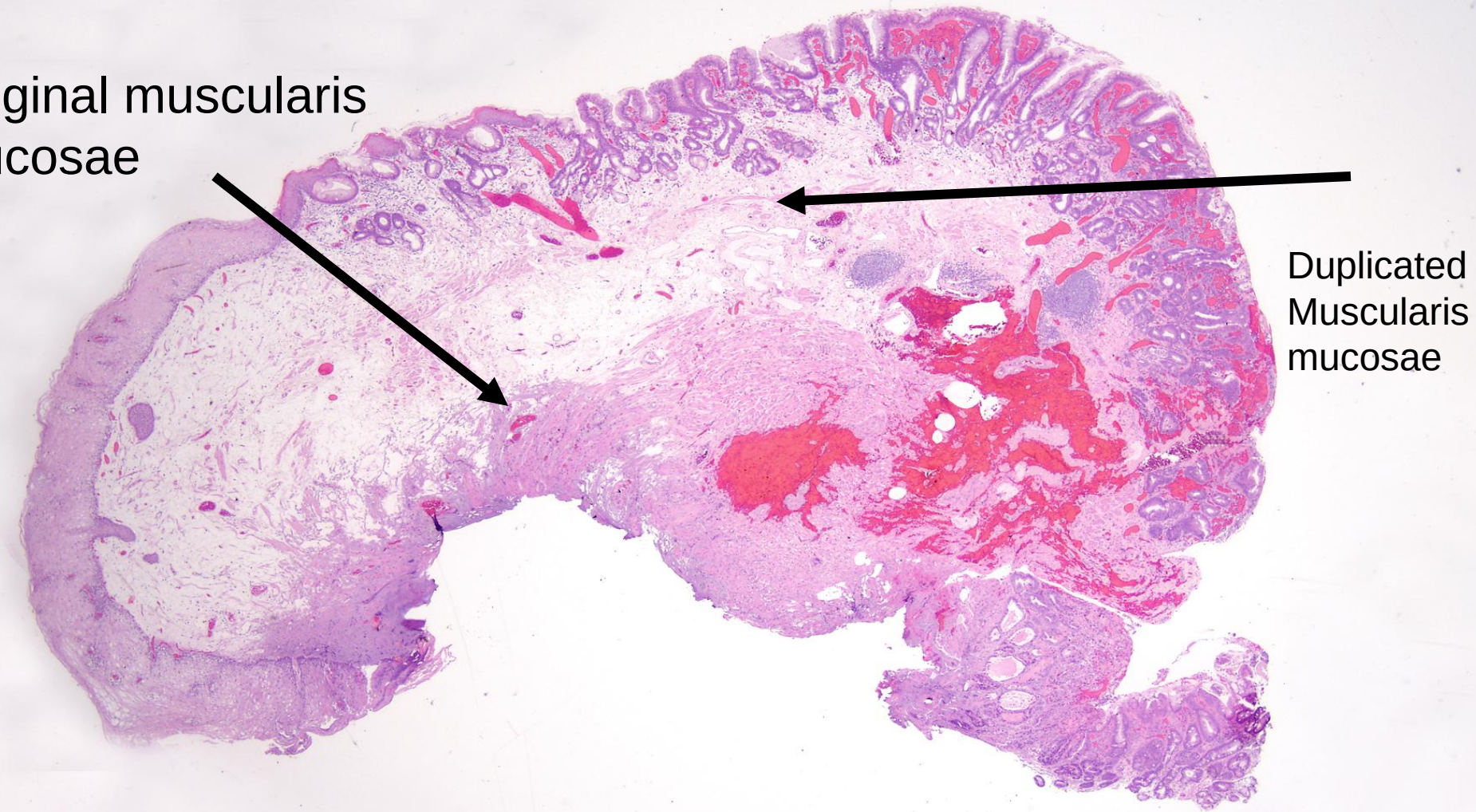
Example case

- A 65 year old man shown to have HGD in Barrett’s mucosa was offered surgery but preferred to under an endoscopic mucosal resection

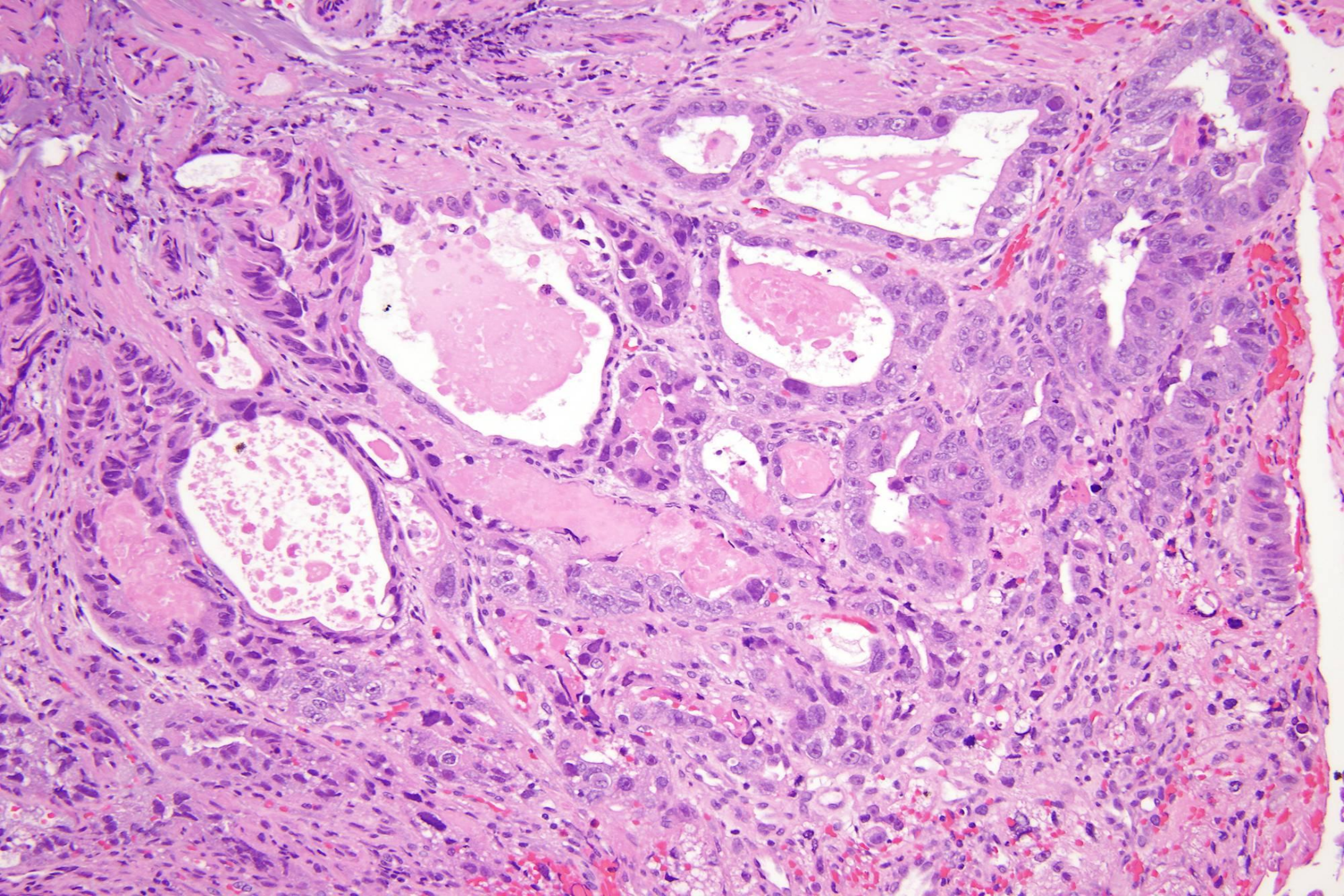


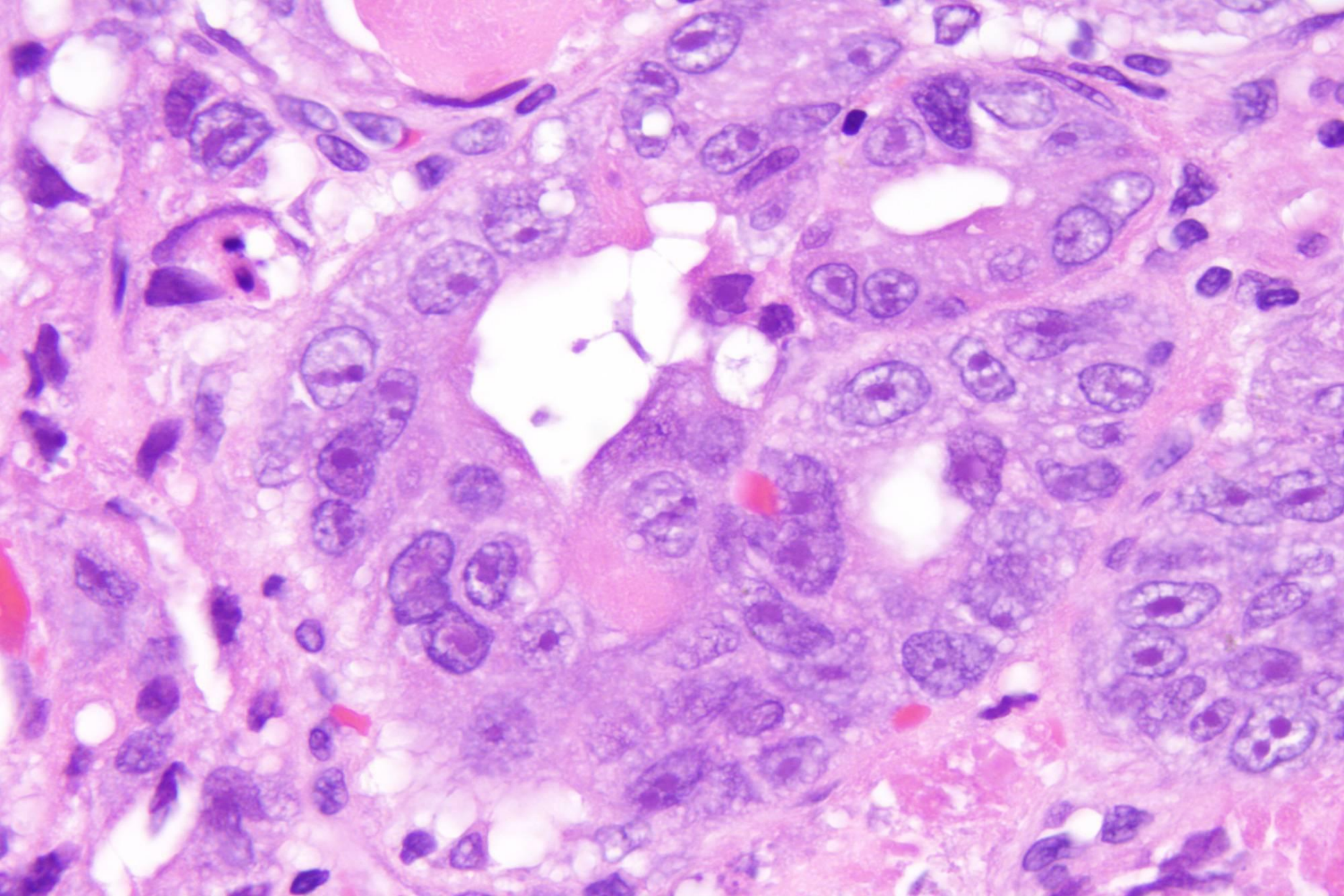


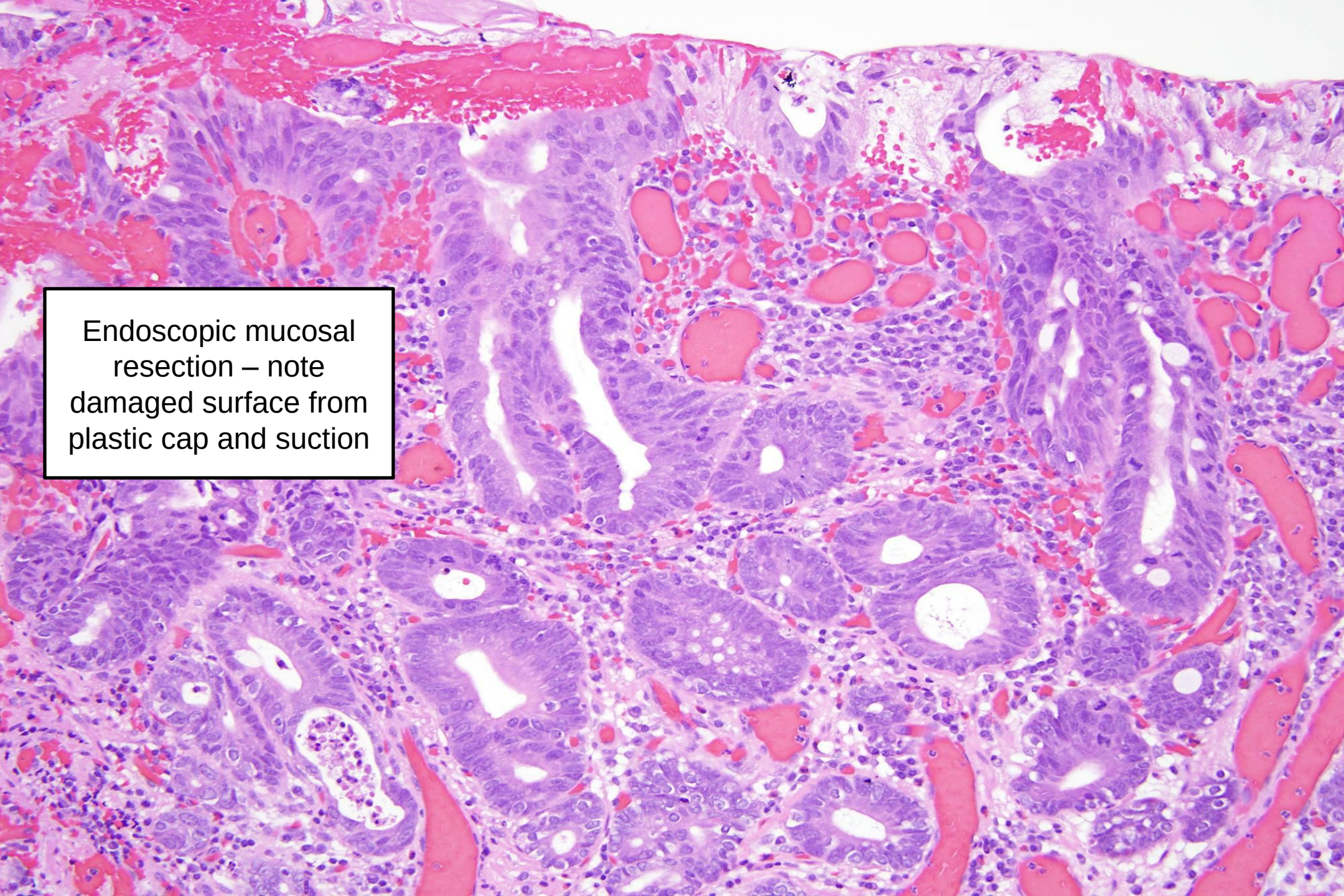


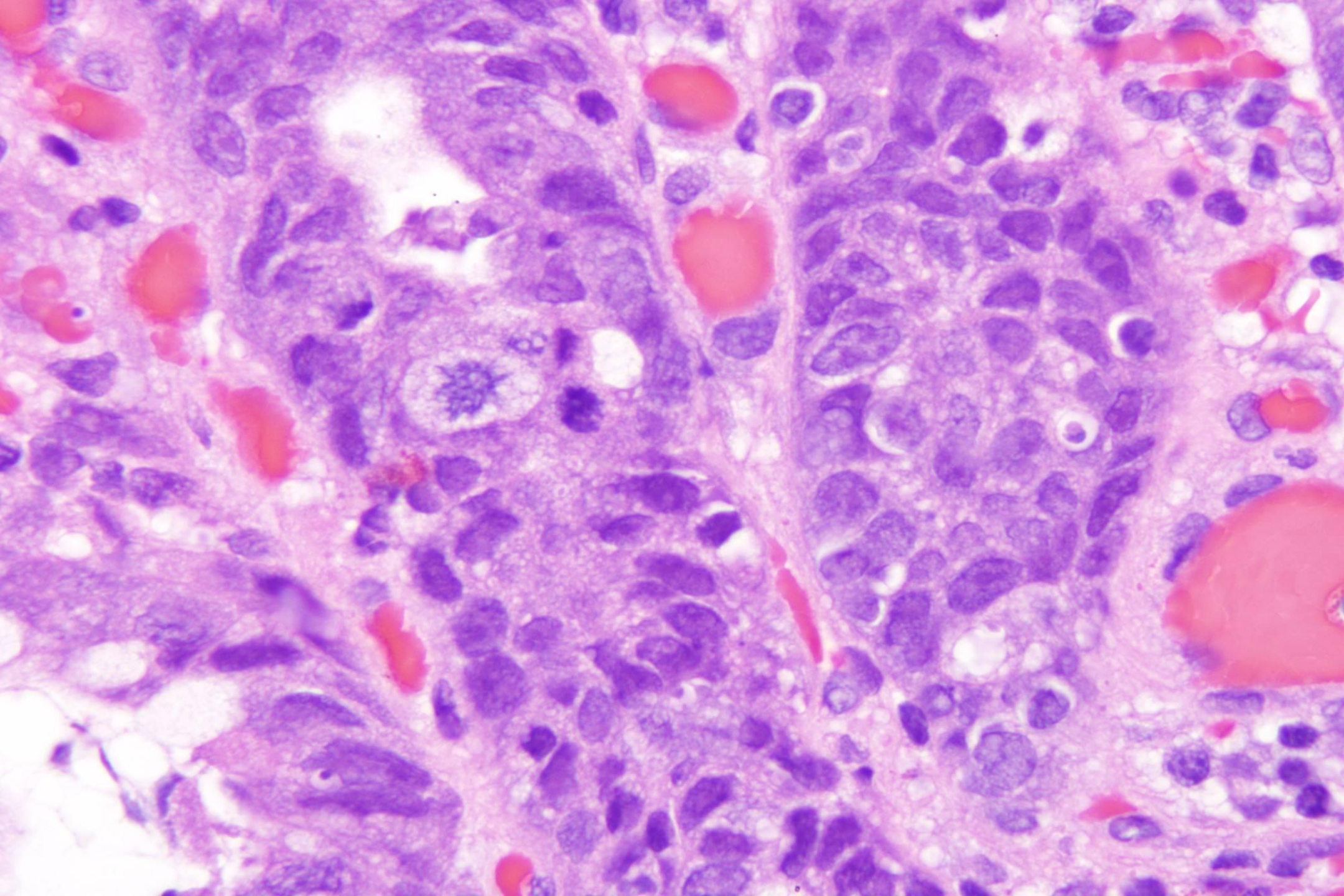


Endoscopic Mucosal Resection [EMR] showing duplicated muscularis mucosae [Ref; Abraham et al. Am J Surg Pathol 2007; 31:1718.]





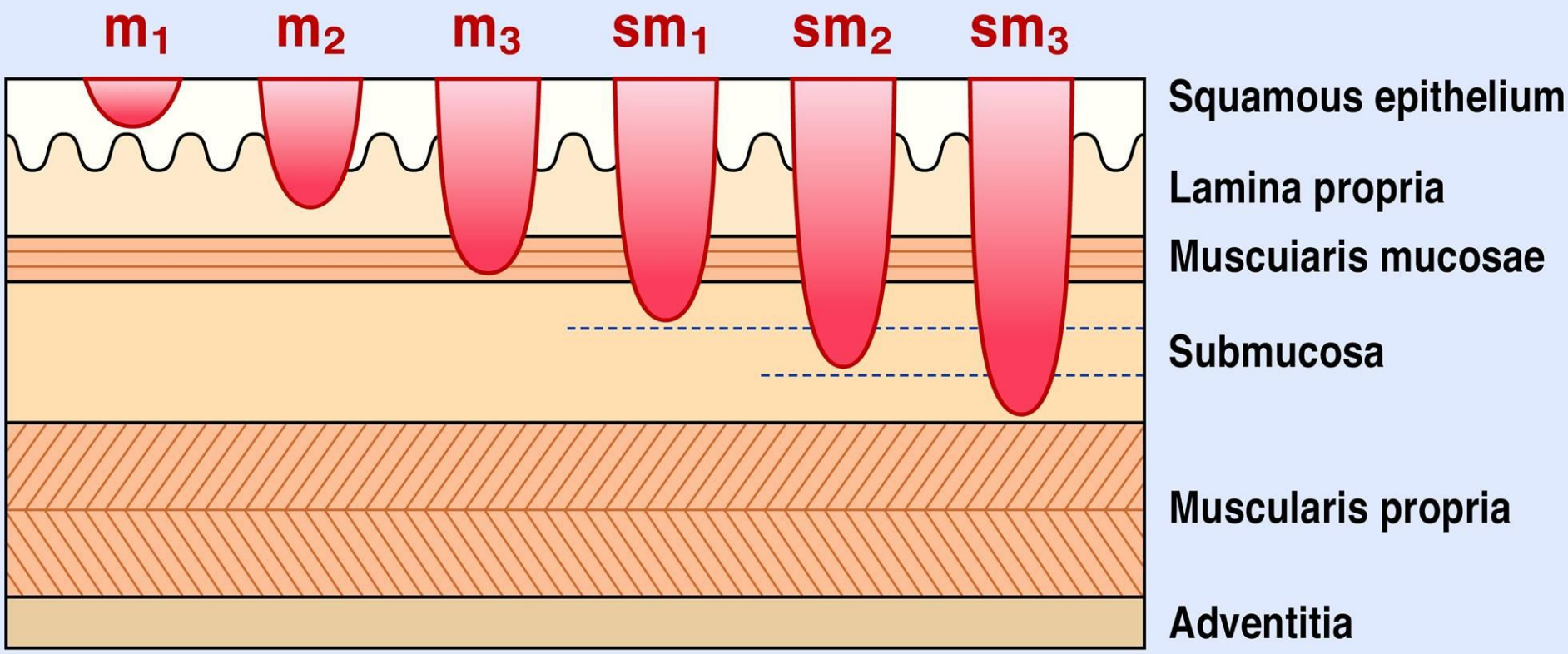

Endoscopic mucosal resection – note damaged surface from plastic cap and suction



Patient

- Patient was followed with photodynamic therapy
- Free of columnar metaplasia as of summer 2011 (8 years)

Subclassification of Depth of Invasion by Superficial Carcinoma Proposed by the Japan Esophageal Society



(Japanese Society for Esophageal Diseases, 1995 : Takubo K, et al. Superficial Carcinoma of the Esophagus in Japan : Curable Lesion. In Superficial Esophageal Neoplasms, Imamura M ed. Springer-Verlag, Tokyo, 2000)

Relationships among Depths of Invasion and Vessel Invasion and Lymph Node Metastasis in Superficial SQUAMOUS Carcinoma

Depth	No. Cases	Vessel Invasion (%)	Lymph Node Metastasis (%)
m1	54	0 (-)	0 (-)
m2	42	2 (5%)	0 (-)
m3	37	13 (35%)	3 (8%)
sm1	24	13 (54%)	4 (17%)
sm2	58	42 (72%)	16 (28%)
sm3	75	68 (91%)	37 (49%)

Makuuchi H et al. Rinsho-Shokakinaika (Clin Gastroenterol) 12:1749-1756, 1997; Endo M et al. Endoscopic treatment for early carcinoma of the esophagus. Shokaki-Shinyo Practice. Bunkodo, Tokyo,1998

Studies – Early Esophagus Adenocarcinomas	Depth	Outcome
Liu. Am J Surg Pathol 2005; 29: 1079	Lamina propria	No mets
Liu. Am J Surg Pathol 2005; 1079	MM or superficial SM	22% mets
Westertwerp. Virchow's Arch 2005;446:497	M1-M3, SM1	1/79 LN mets, 83% 5 yr surv
Westertwerp. Virchow's Arch 2005;446:497	SM2, SM3	44% LN mets; 42% 5 yr surv
Kaneshiro Am J Surg Pathol 2011; 35:697	M1-M3 SM1	0.7% LN mets 8.6% LN mets

Comments on AJCC STAGING

7th Edition !!!!!!!!!!

- **TNM classification of oesophageal carcinomas, 7th Edition**
- **TNM classification[1,2]**
- T – Primary Tumour
- TX Primary tumour cannot be assessed
- T0 No evidence of primary tumour
- Tis Carcinoma in situ/ high-grade dysplasia
- ***T1 Tumour invades lamina propria, muscularis mucosae, or submucosa***

T1a Tumour invades lamina propria or muscularis mucosae

T1b Tumour invades submucosa

T2 Tumour invades muscularis propria

T3 Tumour invades adventitia

T4 Tumour invades adjacent structures

T4a Tumour invades pleura, pericardium, or diaphragm

T4b Tumour invades other adjacent structures such as aorta, vertebral body, or trachea

- N – Regional Lymph Nodes
- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis

N1 Metastasis in 1 to 2 regional lymph nodes

N2 Metastasis in 3 to 6 regional lymph nodes

N3 Metastasis in 7 or more regional lymph nodes

M – Distant Metastasis

M0 No distant metastasis

M1 Distant metastasis

Modifications between the 6th and 7th TNM editions

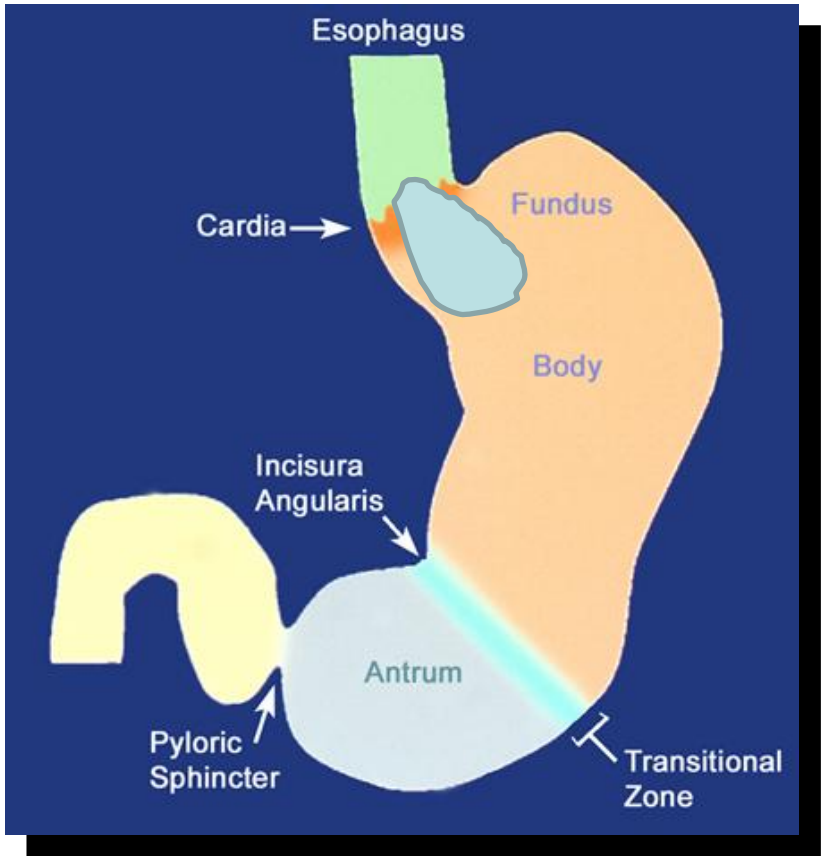
- T1 and T4 are subdivided to provide greater detail for imaging and management
- Regional lymph nodes (N) are subdivided by number involved rather than by their location
- Distant metastasis (M) has been simplified to M1 rather than subdivided by location.

Gastroesophageal (GE) junction carcinomas

- The staging of carcinomas of the oesophagogastric/gastroesophageal junction is based on the following TNM rule: ***a tumour the epicenter of which is within 5 cm of the GE junction and also extends into the oesophagus, is classified and staged using the oesophageal carcinoma scheme. Tumours with an epicenter in the stomach greater than 5 cm from the GE junction or those within 5 cm of the oesophagogastric junction without extension in the oesophagus are classified and staged using the gastric carcinoma scheme.***

Staging GE Junction

Esophagus scheme



Stomach scheme