

Inflammatory Bowel Disease (IBD)-Associated Dysplasia: Old and New

Xiuli Liu, MD, PhD

Professor

Department of Pathology, Immunology, and
Laboratory Medicine

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Objectives

- Clinical significance of dysplasia in IBD
- Schema to evaluate IBD surveillance colonic biopsy
- Variants of IBD dysplasia

IBD Dysplasia

- Interpretation should be put into a clinical/endoscopic context
 - as the management is different even with the morphology
- Detection of dysplasia by surveillance colonoscopy reduces mortality due to CRC in IBD patients
- Surveillance **colonoscopy**
 - Starts 8 years after the onset of disease in pan-colitis
 - May start at the time of IBD diagnosis in patients with PSC
 - May start at the time of PSC diagnosis in patients with IBD
- Biopsy protocol:
 - 4 biopsies every 10 cm, in addition to visible lesions
 - Targeted biopsy

Cumulative Incidence of CRC in IBD

Cumulative incidence of CRC (%)										
Years from dysplasia diagnosis	1	2	3	4	5	6	7	8	9	10
No dysplasia	0.1	0.2	0.4	0.6	0.7	0.9	1.1	1.1	1.4	1.5
Adenoma	1.4	1.4	1.4	1.4	3.2	3.2	3.2	3.2	6.5	6.5
Indefinite for dysplasia	6.3	10.7	10.7	18.8	24.9	24.9	24.9	24.9	28.9	28.9
LGD	9.9	11.8	18.4	19.7	21.2	24.7	29.0	29.0	29.0	32.8
HGD	41	44.7	54.3	54.3	-	-	-	-	-	-

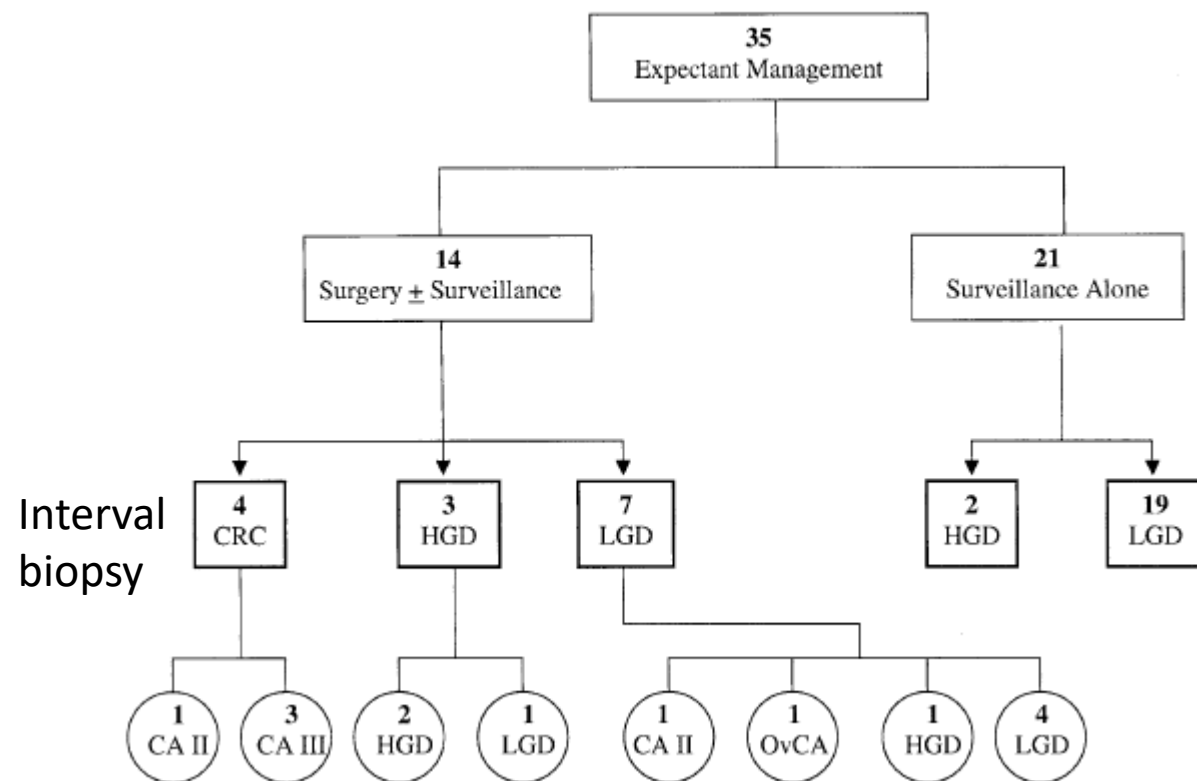
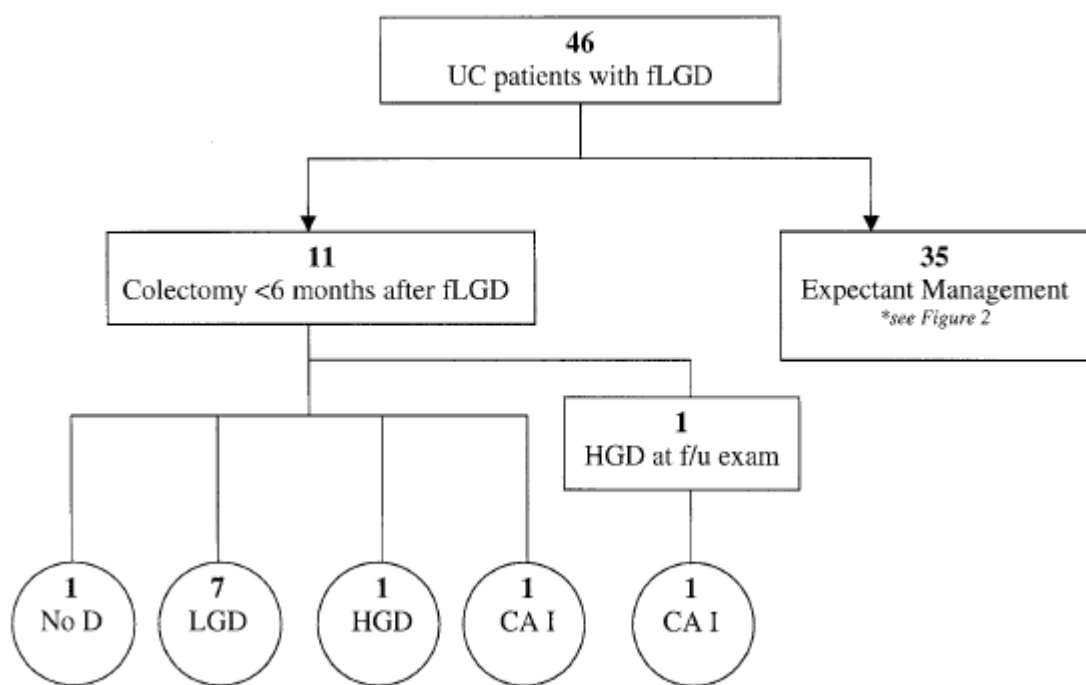
IBD-Associated Dysplasia

- Definition: neoplastic epithelium confined within basement membrane of gland within which it arose
- Diagnosis is based on H&E stained sections

Marker and precursor of CRC

Morson BC and Pang LSC, 1967
Riddell RH, et al., 1983

Dysplasia in IBD: clinical significance



Progression from fLGD to advanced neoplasia at 5-years:
 to CRC: 5/35 (14.3%)
 to HGD: 6/35 (17.1%)

Schema for Grading Dysplasia in IBD

- Negative for Dysplasia
- Positive for Dysplasia
 - Low grade
 - High grade
- Indefinite for Dysplasia

Traditional Approaches to IBD Surveillance Colonic Biopsy

- **Low magnification assessment:**
 - surface maturation (key)
 - architectural complexity
- **High magnification assessment:**
 - cytologic changes in area with no surface maturation

Cytologic Features of Dysplasia

- Nuclear features:
 - Nuclear enlargement, increased N/C ratio
 - Nuclear hyperchromasia
 - Stratification
 - Pleomorphism, loss of polarity
 - Nucleolar enlargement
 - Abnormal mitoses
 - Lack of surface maturation

Nuclear features are the key for the diagnosis of dysplasia

Architectural Features of Dysplasia

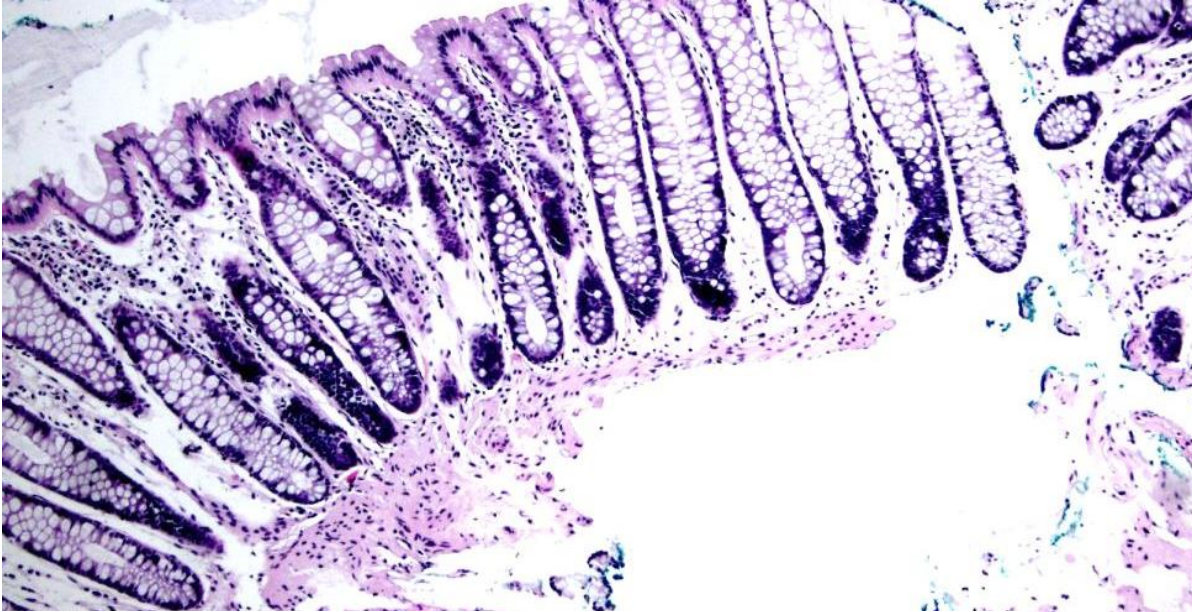
- Best evaluated at low magnification
- Crowding
- The irregularity of gland lumen (papillation into the lumen; cribriform)
- Villiform/papillary configuration of surface epithelium

Grading Dysplasia in IBD

Diagnosing and grading dysplasia based on the degree of cytologic and/or architectural abnormality

Negative for Dysplasia

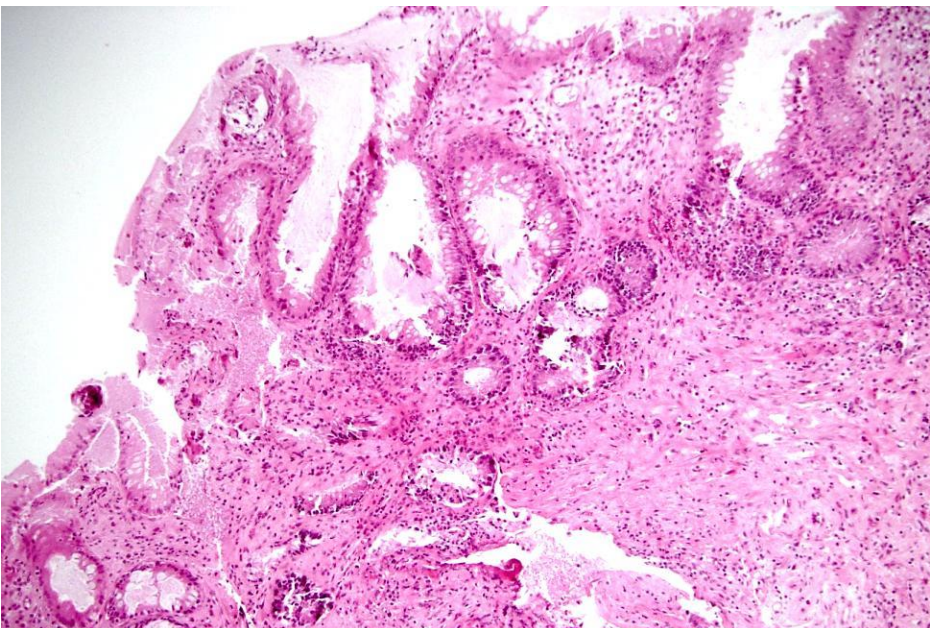
- **Normal histology (after treatment)**
- **Quiescent colitis with only architectural distortion**
- **Chronic inactive colitis with reactive/regenerative changes**
- **Chronic active colitis with reactive/regenerative changes**
 - Loss of mucin
 - Surface maturation
 - Lack of nuclear enlargement, hyperchromasia, or pleomorphism



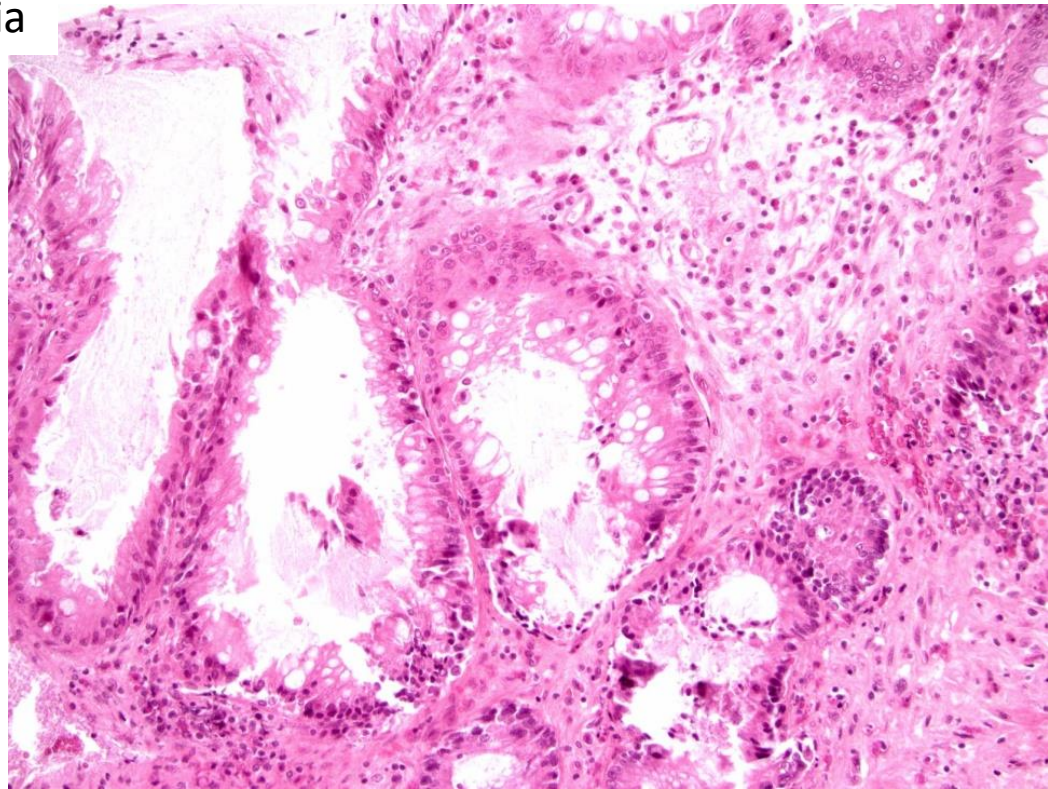
Normal colonic mucosa, negative for dysplasia

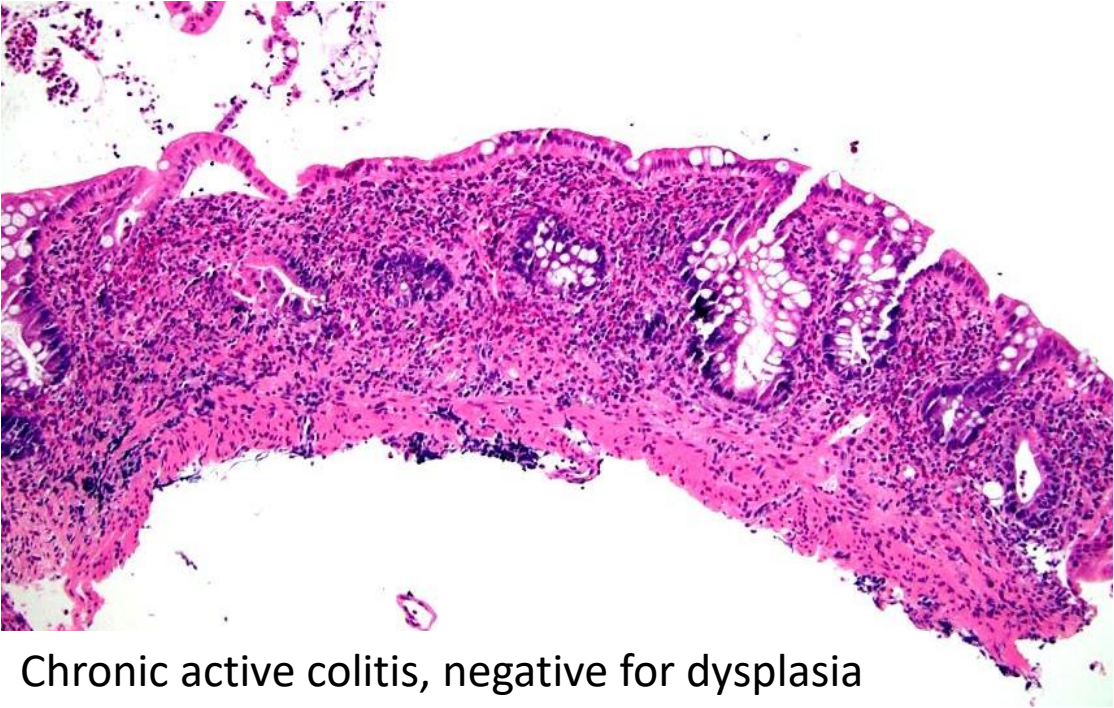


Quiescent colitis, negative for dysplasia

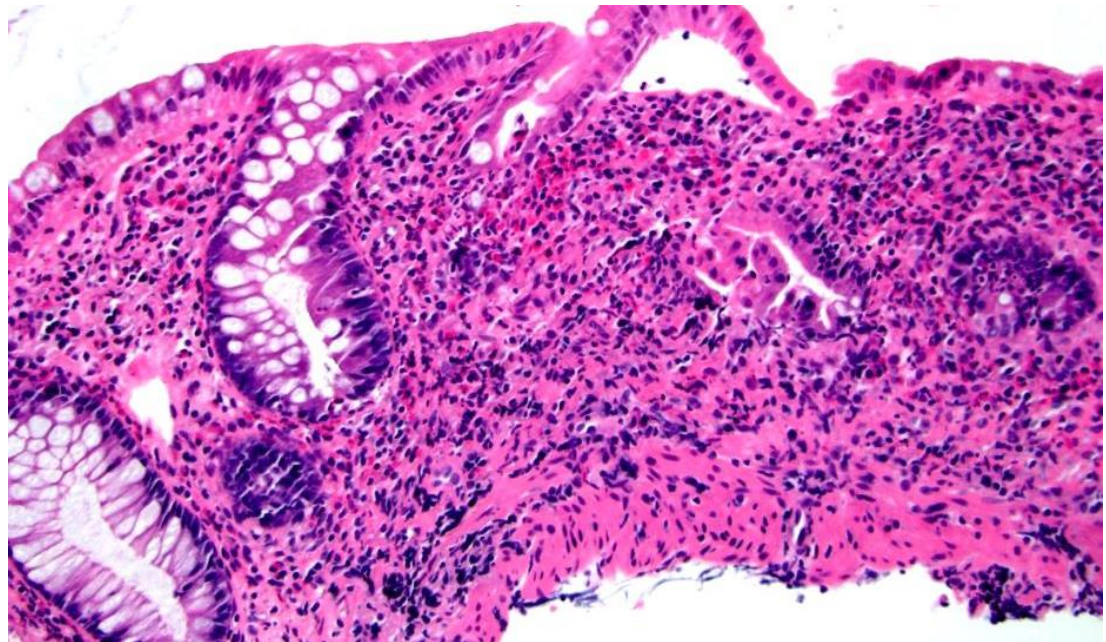


Chronic inactive colitis, negative for dysplasia

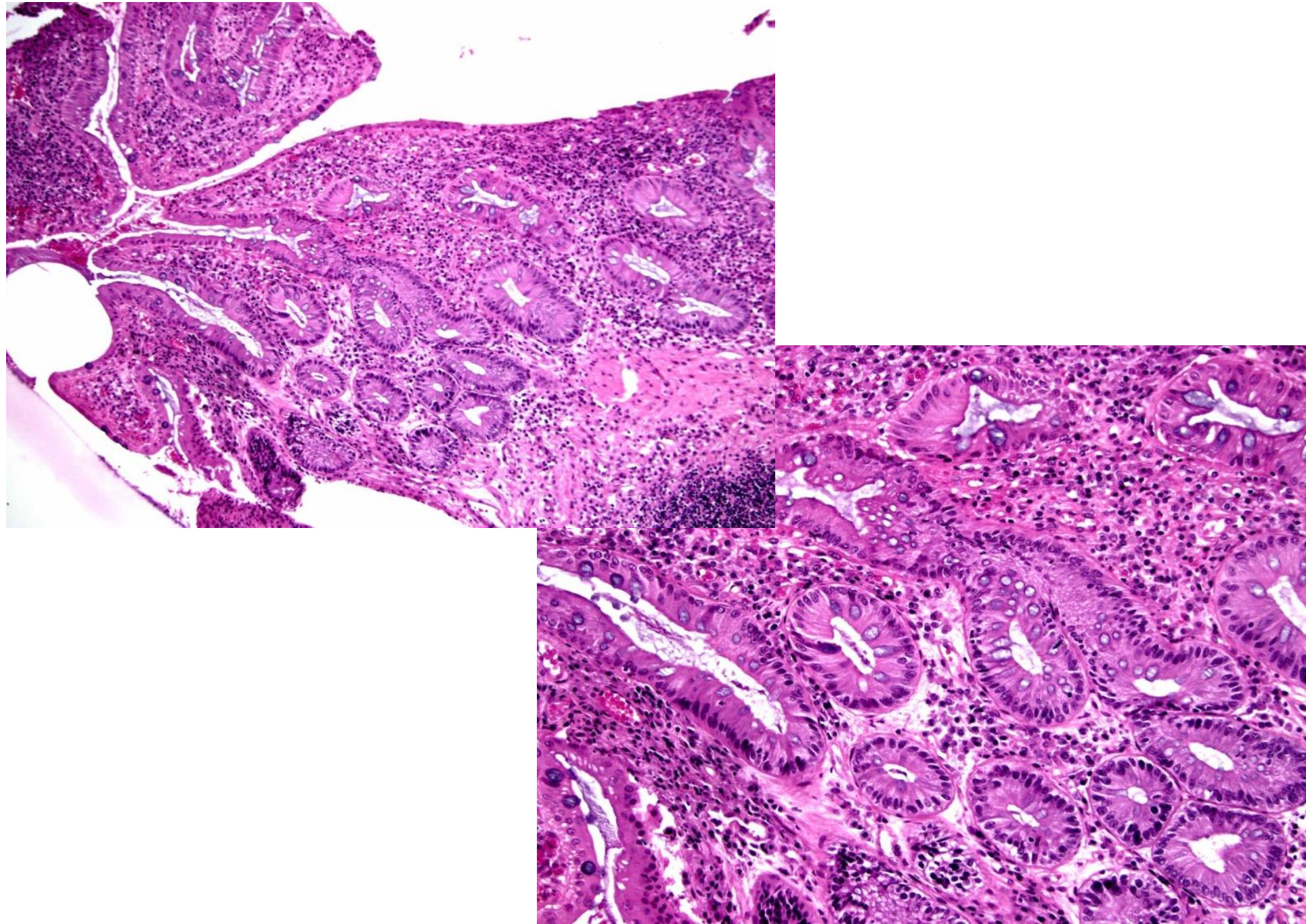




Chronic active colitis, negative for dysplasia



Chronic colitis with minimal activity, negative for dysplasia



Low-Grade Dysplasia in IBD

- **Usually apparent at low power**
 - A distinct focus of dark glands without surface maturation
 - Some may look like adenoma
 - Some may not resemble adenoma
 - Abrupt transition from non-neoplastic to neoplastic
 - Usually minimal inflammation
- **Cytologic features of dysplasia**
 - Enlarged dark nuclei
 - Stratification (less than ½ full-thickness of the epithelium)
 - No loss of nuclear polarity
 - No significant pleomorphism
- **Architectural irregularities**
 - Villiform/papillary surface epithelium
 - No cribriform

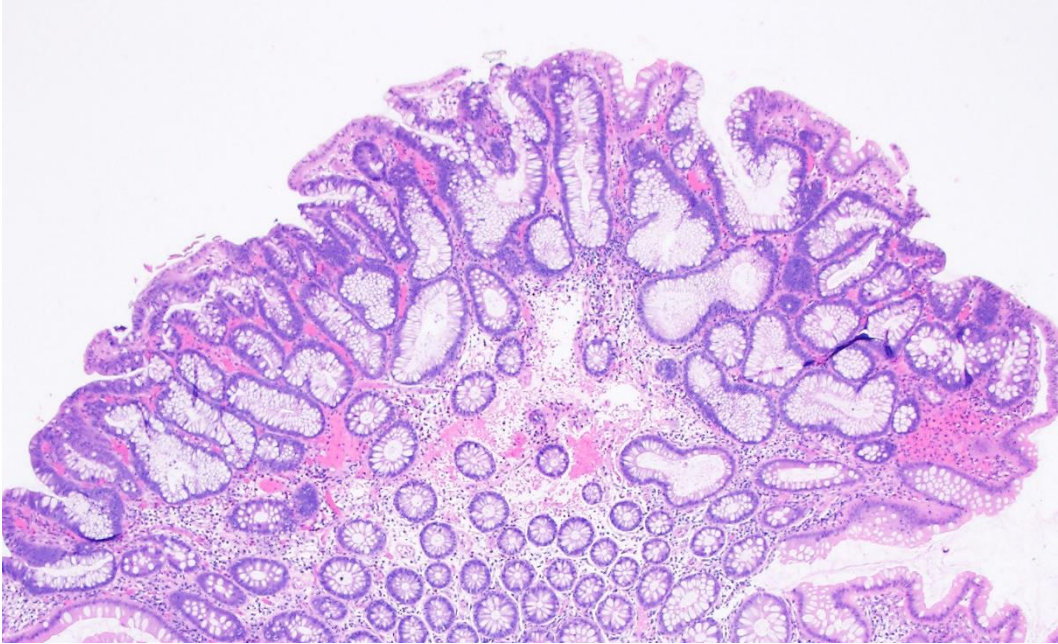
IBD-Associated Dysplasia: conventional dysplasia

- Most readily recognized dysplasia in IBD
- Intestinal type: adenomatous nuclei
- Architectural: tubular, villous, tubulovillous
- Polypoid or flat

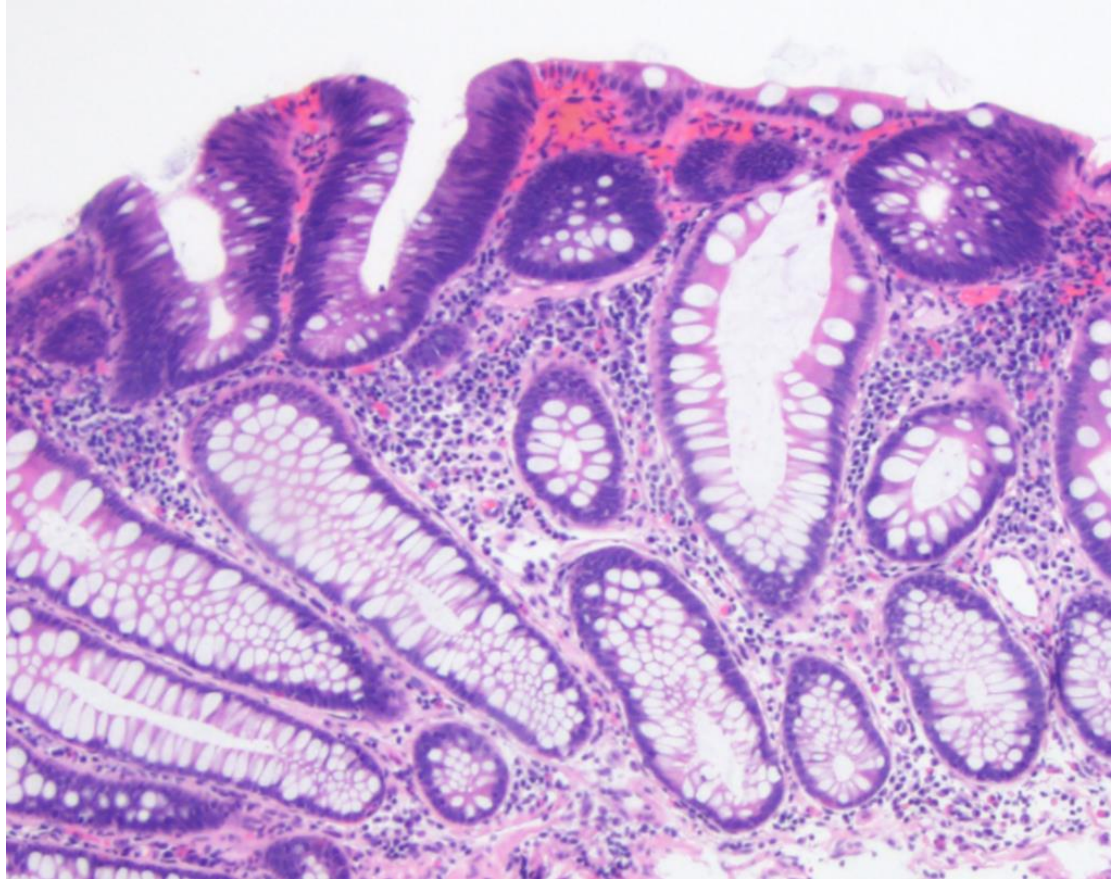
- Can be pure or mixed with non-conventional dysplasia

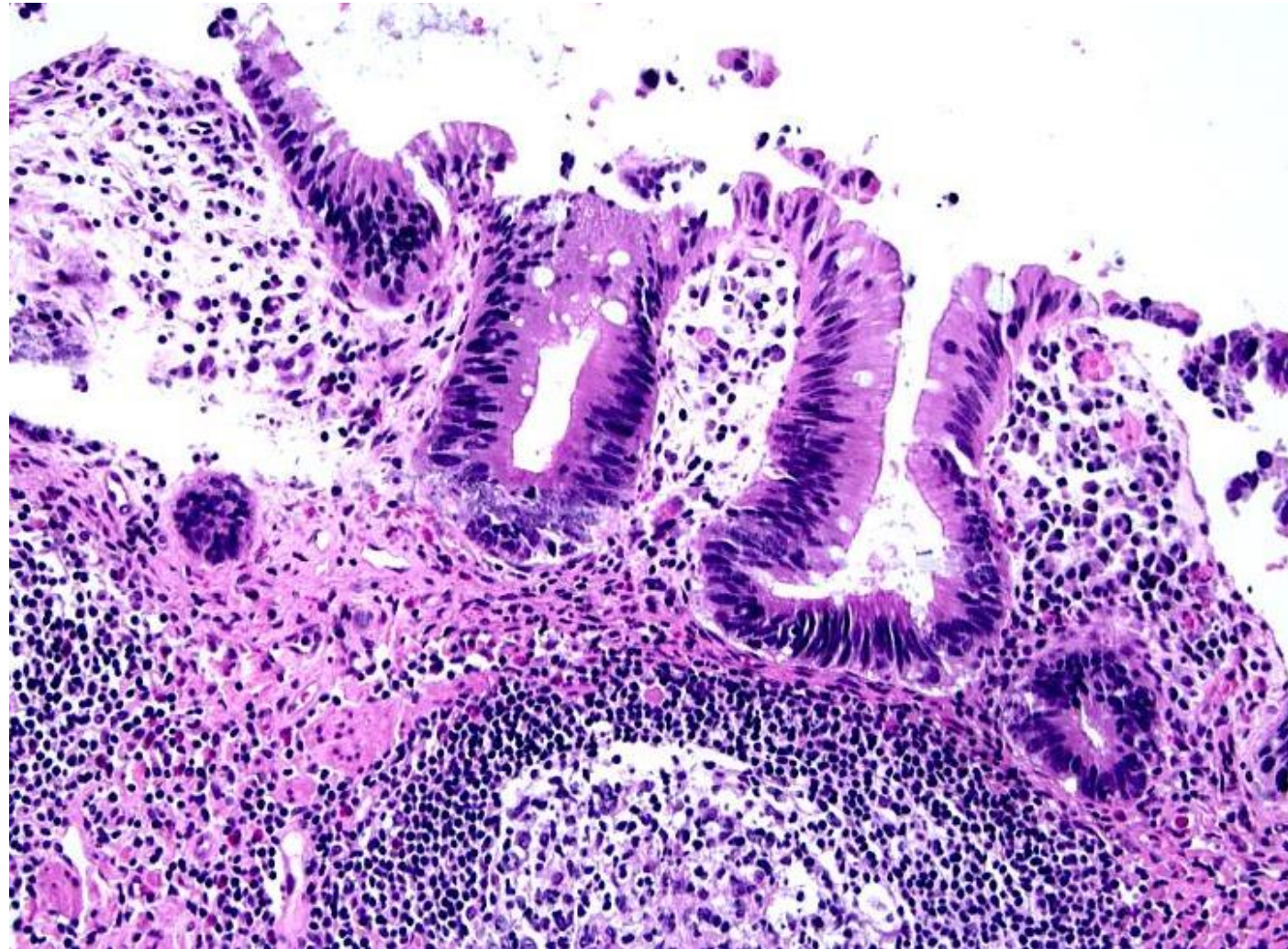
- Adenocarcinoma arising less likely to be poorly differentiated

Positive for low-grade dysplasia,
conventional type, polypoid



Positive for low-grade dysplasia,
conventional type, flat or early polypoid?





Positive for low-grade dysplasia, conventional, flat



Positive for low-grade dysplasia, conventional, flat

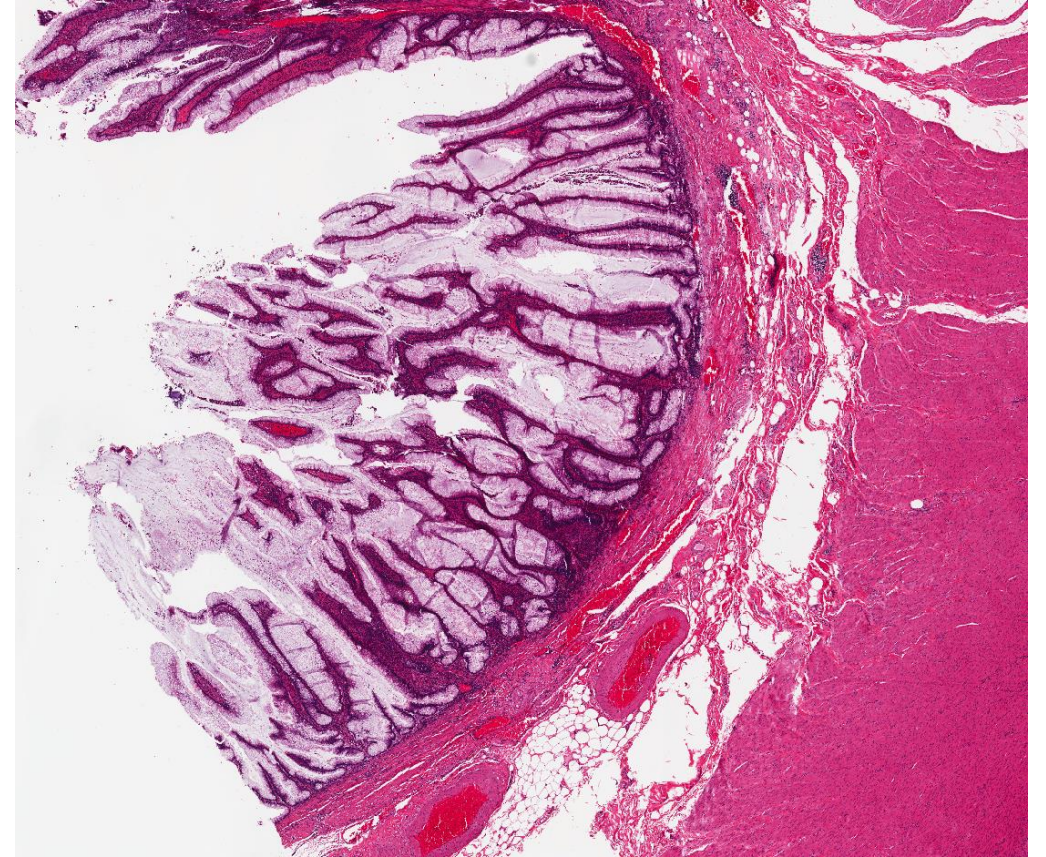
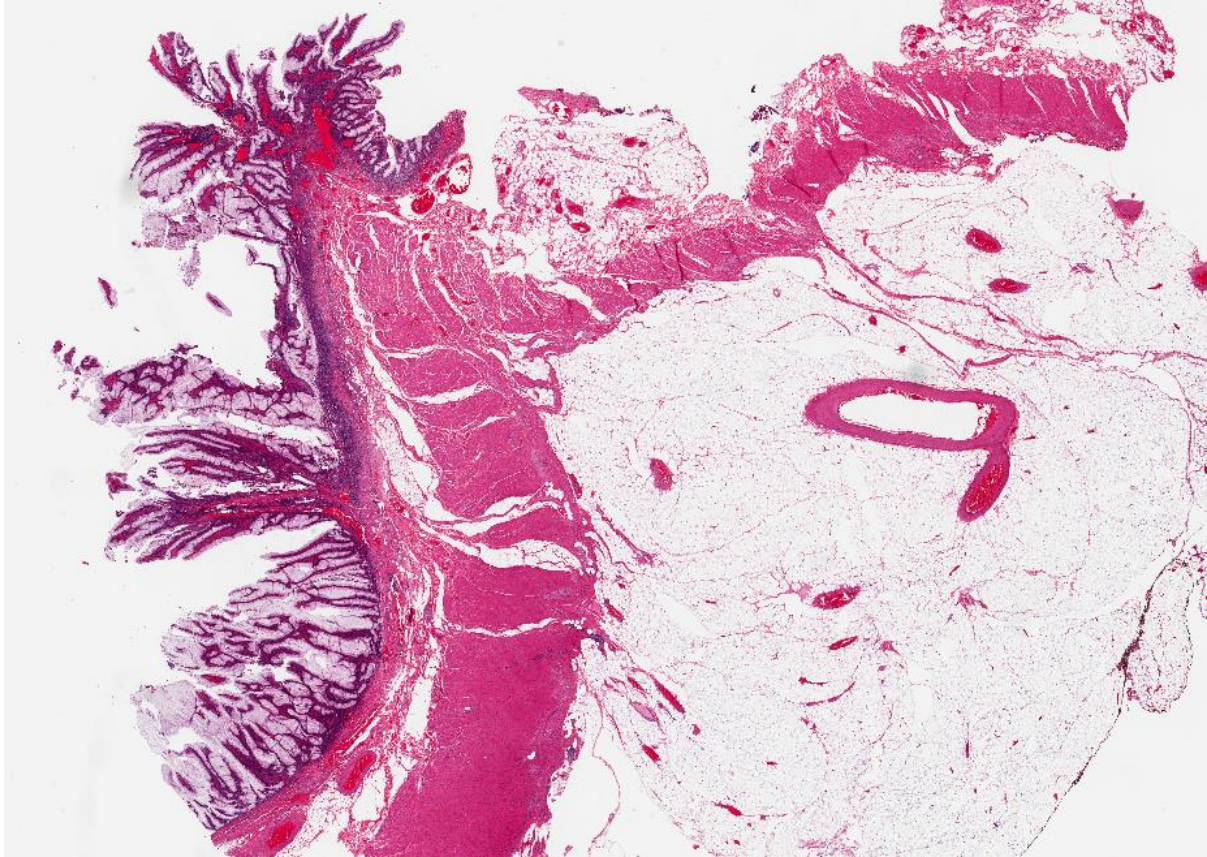
IBD-Associated Dysplasia subtype: non-conventional dysplasia

- Hypermucinous
- Serrated lesions
 - Sessile serrated polyp/adenoma (SSP/A-like dysplasia) or sessile serrated lesion-like dysplasia (SSL-like)
 - Traditional serrated adenoma-like dysplasia (TSA-like)
 - Serrated dysplasia not otherwise specified (Serrated, NOS)
- Goblet cell-deficient dysplasia (GCD, eosinophilic)
- Terminal epithelial differentiation (TED, also known as crypt dysplasia)
- Dysplasia with Paneth cell differentiation (DPCD)
- Dysplasia with pyloric gland differentiation
- Dysplasia with neuroendocrine cell differentiation
- Mixed

Variants of IBD-Associated Dysplasia

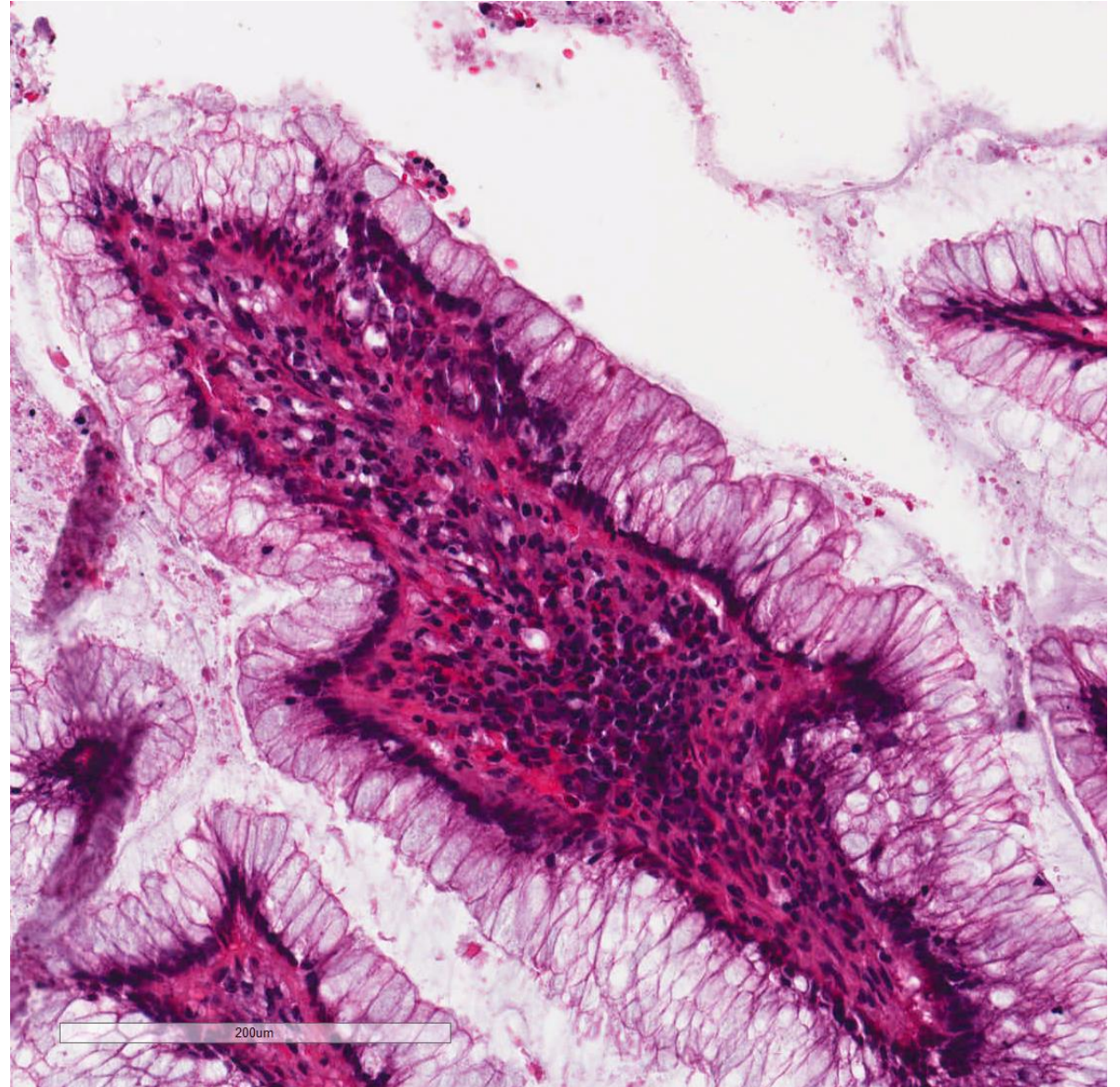
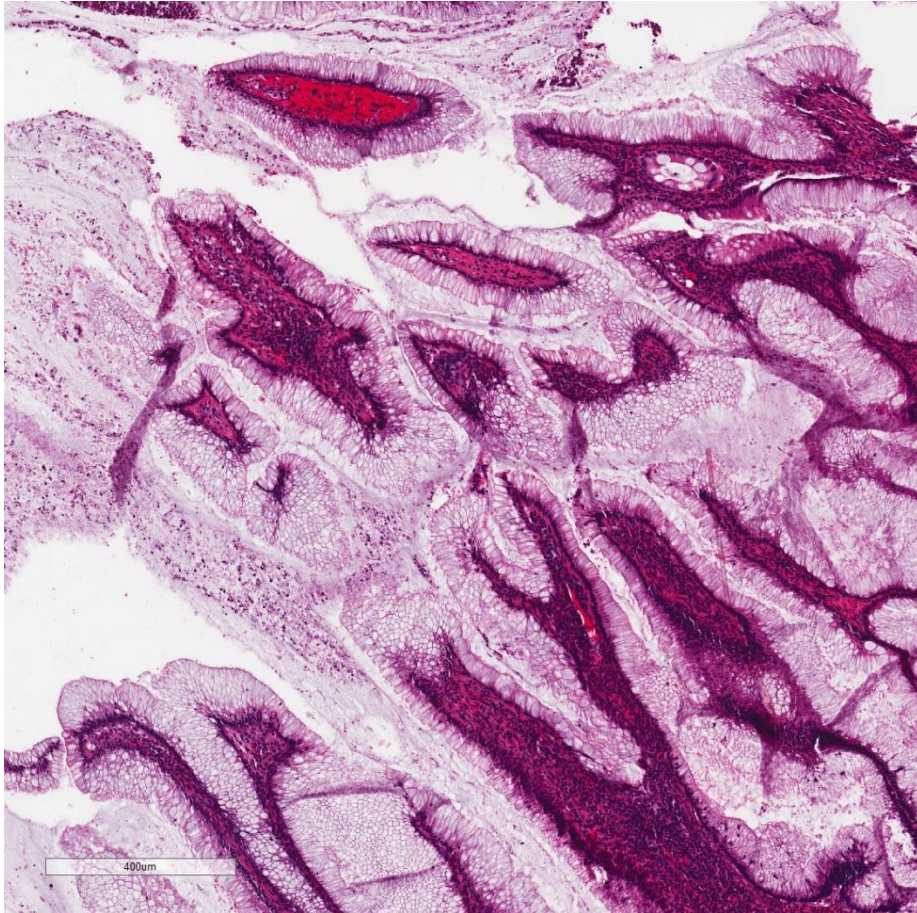
Entity	Architecture	Cytology	Unique features	Endoscopic
Conventional	Tubular, tubulovillous, villous	Pencil-shaped hyperchromatic, stratified	Resembling sporadic colonic adenoma	Polypoid or flat
Hypermucinous	Villous, focally serrated	Mucin rich with uniform minimal to mild nuclear atypia	Monotonous and mucin-rich cells	Flat or polypoid
SSA-like	Serrated architecture	Basally located small round-to-oval or slightly elongated and slightly stratified nuclei, with surface maturation	L shaped or T-shaped crypts	Polypoid or flat
TSA-like	Serrated architecture	Enlarged or slightly elongated, hyperchromatic and slightly stratified nuclei at the base and with abundant eosinophilic cytoplasm	Eosinophilic cytoplasm Aberrant crypts	Polypoid or flat
Serrated, NOS	Serrated architecture		Not SSA or TSA like	Polypoid or flat
GCD	Tubular structure	Enterocyte-type cells with eosinophilic cytoplasm and oval-to-slightly enlarged or elongated and hyperchromatic nuclei	Nuclei not overtly stratified No or few goblet cells	Flat (most often) or polypoid
TED	Tubular or slightly tubulovillous	Enterocyte-type cells and goblet cells nuclei being small, round-to-oval, hyperchromatic nuclei	Nuclear hyperchromasia Nuclei not stratified Not inflamed	Flat
DPCD	Tubular or tubulovillous	Elongated, hyperchromatic nuclei and clusters of Paneth cells	Clusters of Paneth cells	Flat or polypoid
Pyloric differentiation	Tubular or tubulovillous, or villous	Pyloric glandular epithelium with oval-to-slightly enlarged	Arising from pyloric gland metaplasia	Flat or polypoid

IBD-Associated Dysplasia Subtype: hypermucinous

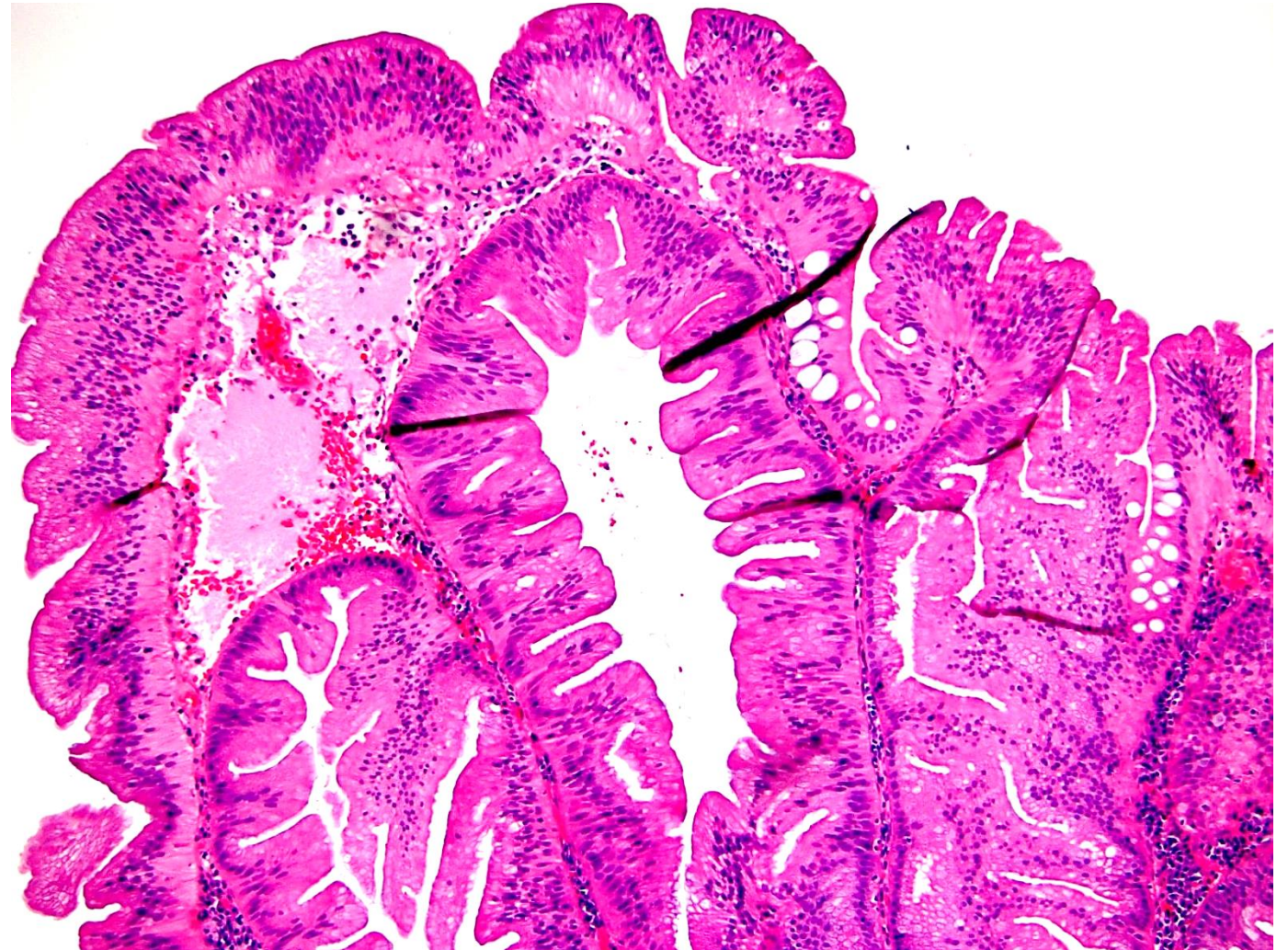


- Villous or focally serrated
- Flat or polypoid
- Mucin-rich
- Minimal to mildly nuclear atypia

IBD-Associated Dysplasia Subtype: hypermucinous

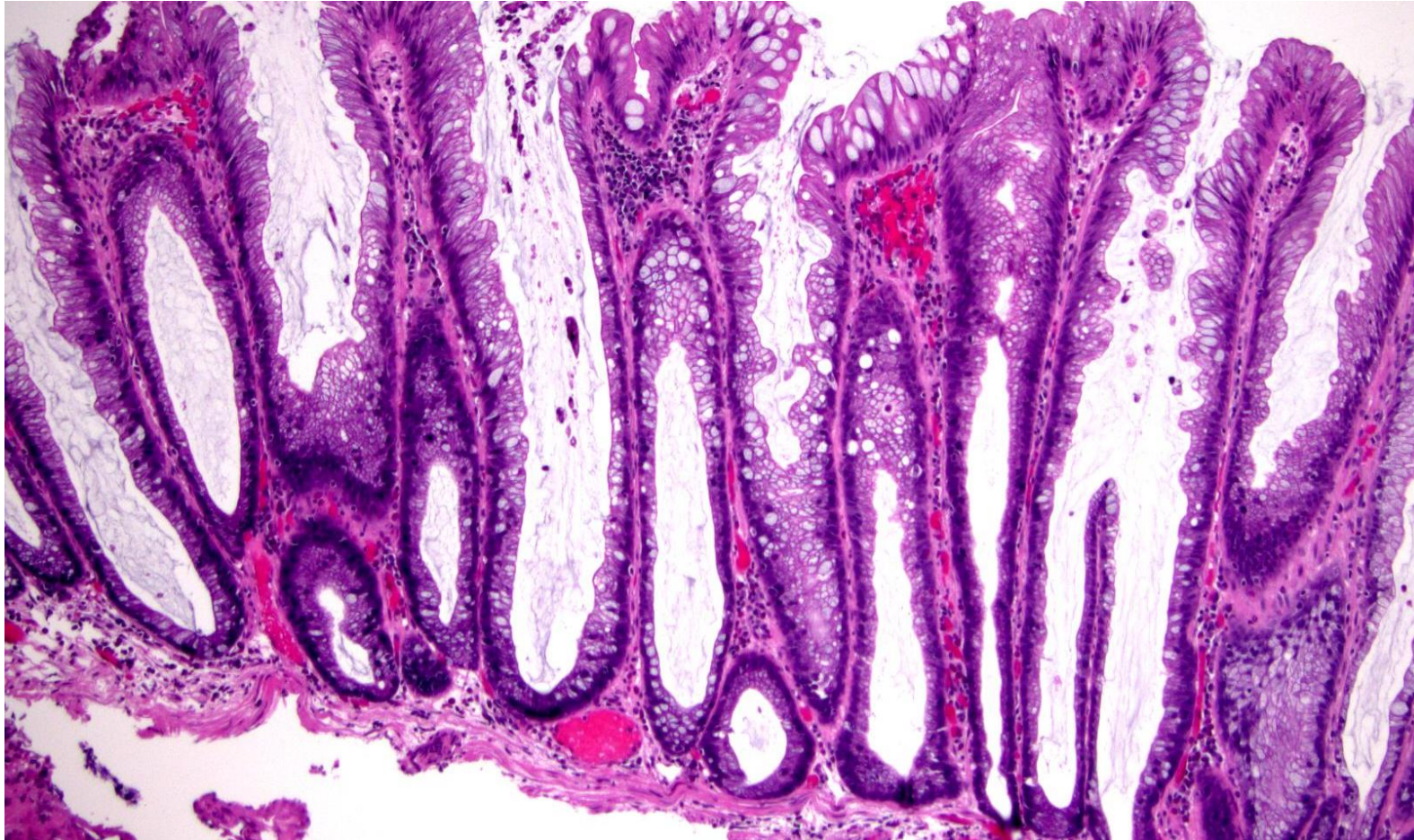


IBD-Associated Dysplasia Subtype: TSA-like

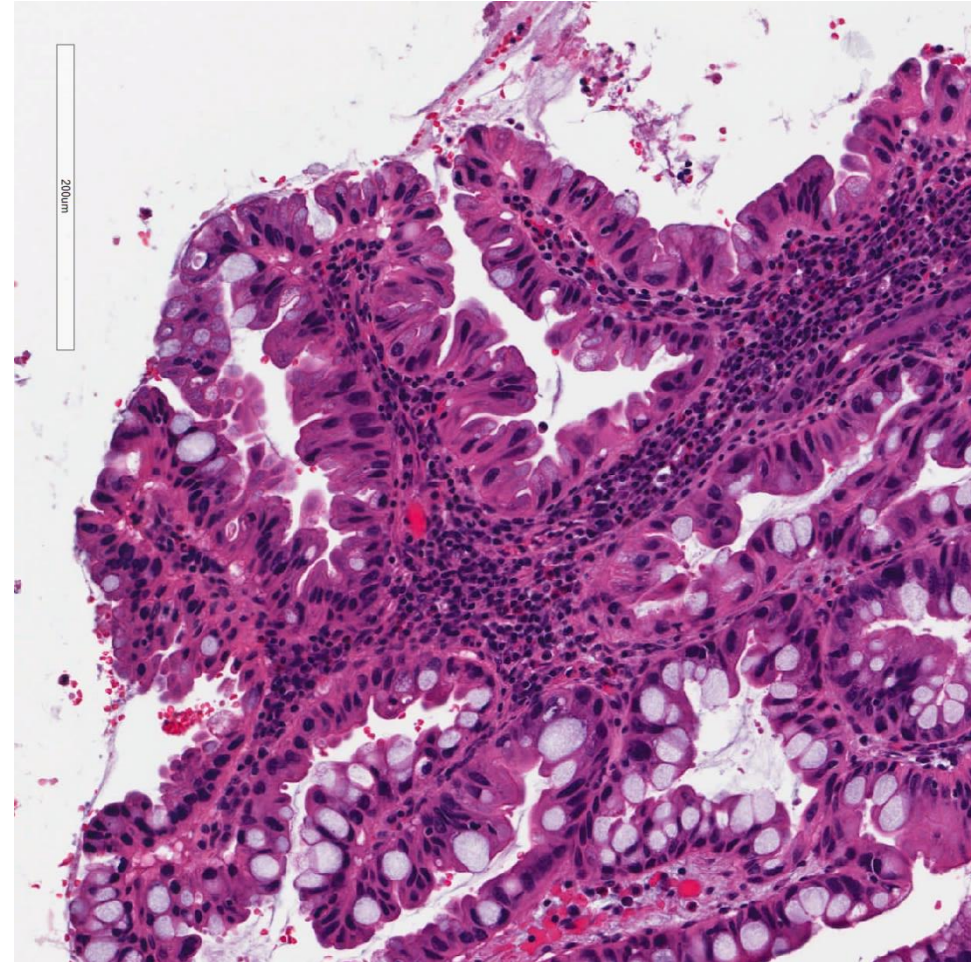
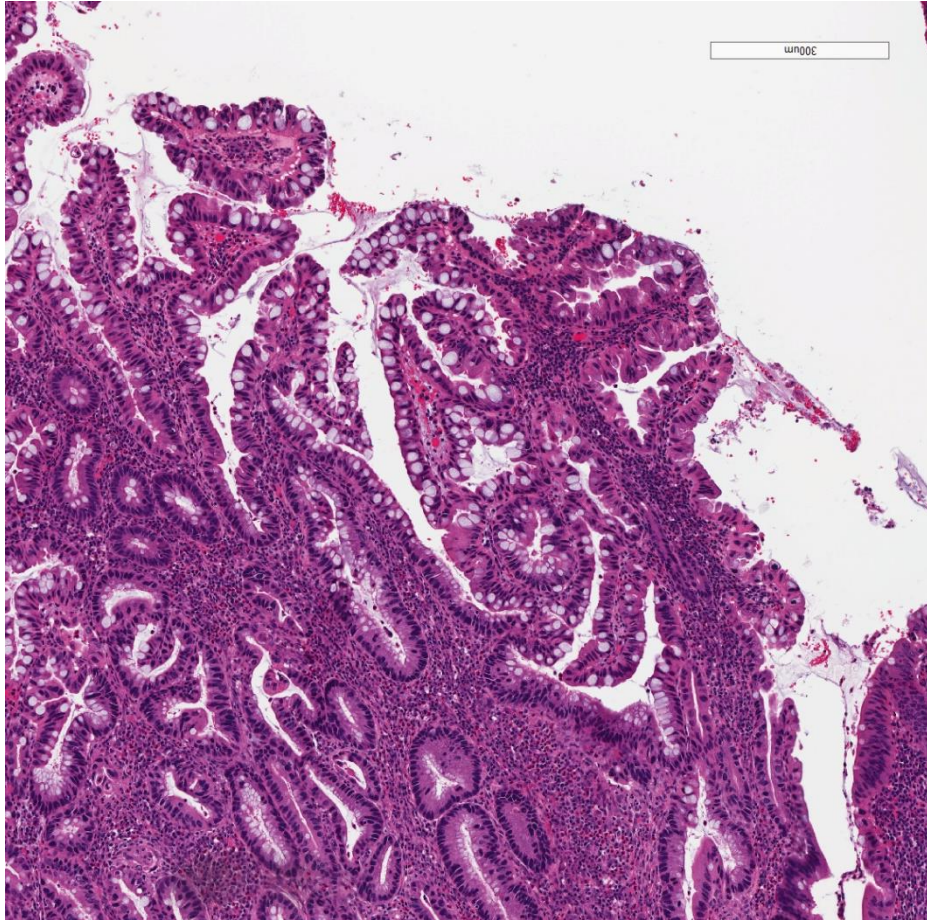


- Tubulovillous/villous lesion
- Serration
- Ectopic crypts
- Elongated nuclei with intensely eosinophilic cytoplasm

IBD-Associated Dysplasia Subtype: SSA/P-like

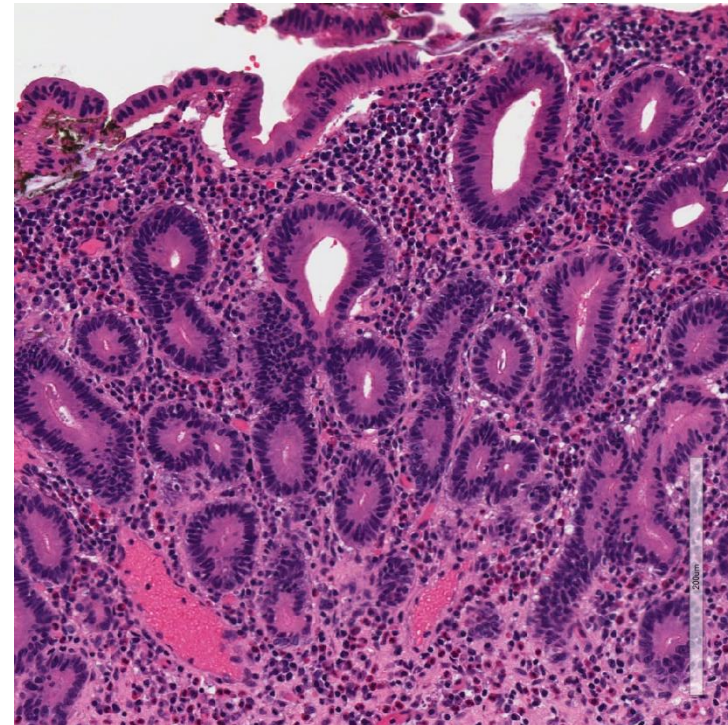
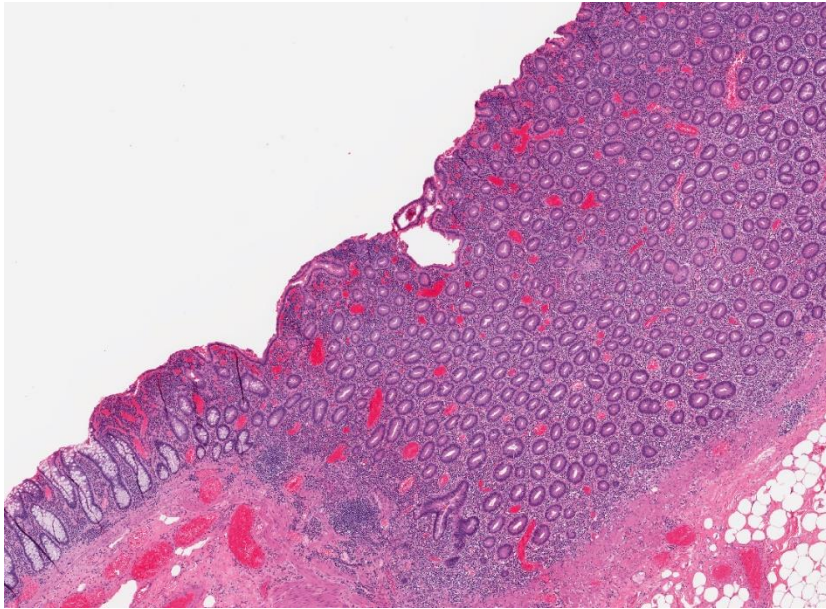


IBD-Associated Dysplasia Subtype: Serrated lesions, NOS



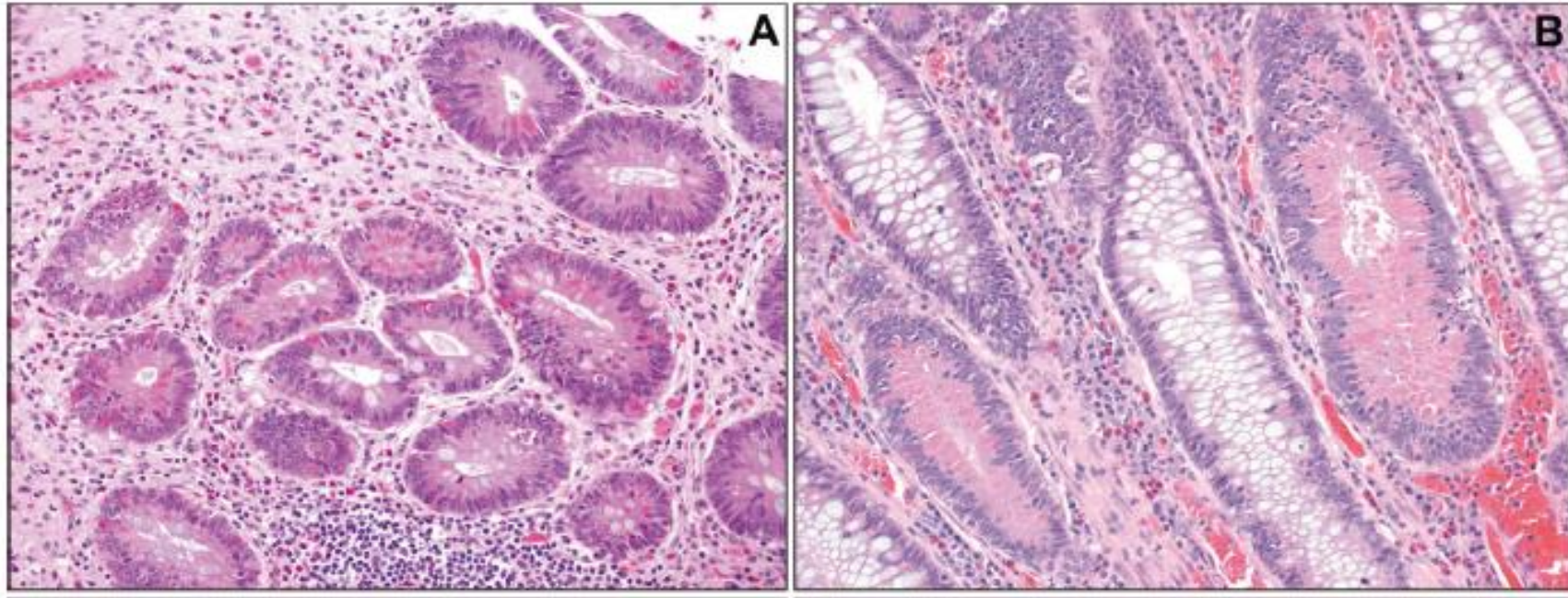
Serrated architecture without definite features of TSA or SSP/A
Mixed enterocytes and goblet cells with mild degree of nuclear atypia

IBD-Associated Dysplasia Subtype: goblet cell-deficient dysplasia



Mildly elongated, enlarged, and hyperchromatic nuclei
Near complete loss or complete loss of goblet cells
No obvious Paneth cells present

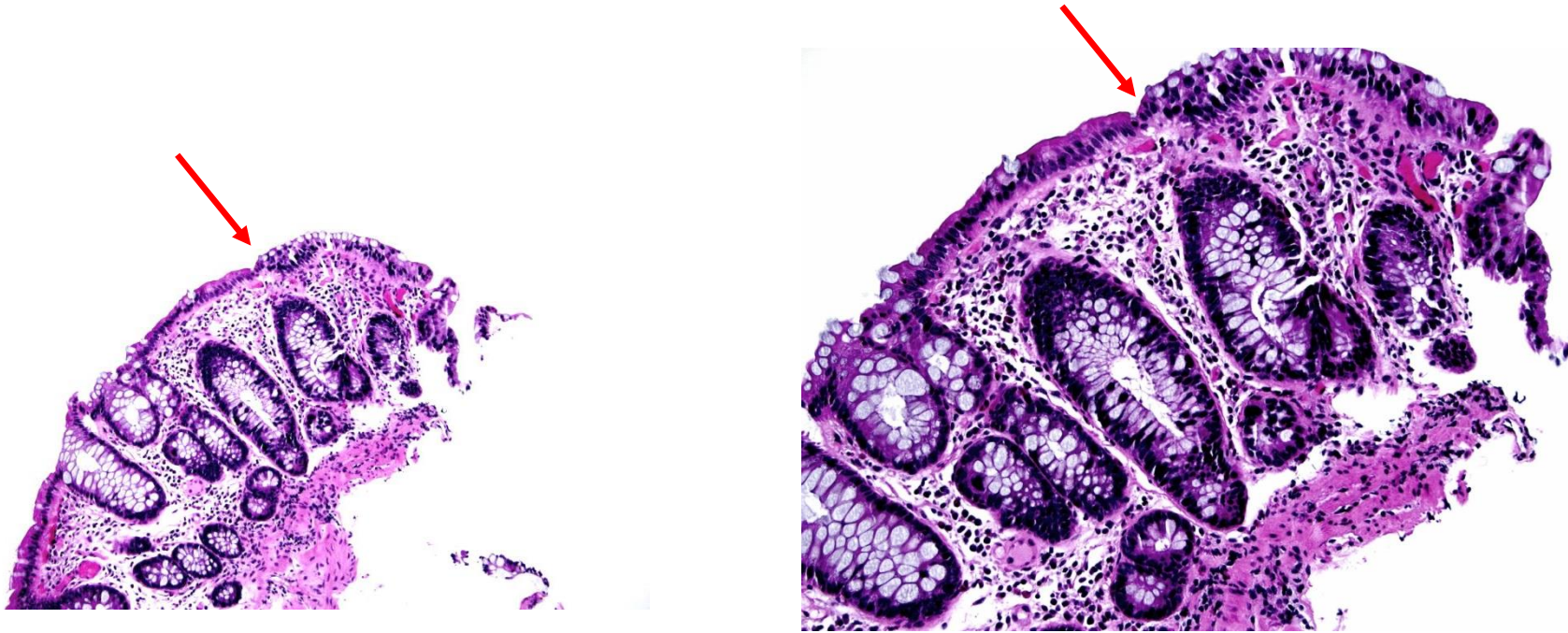
IBD-Associated Dysplasia Subtype: dysplasia with Paneth cell differentiation



Elongated, hyperchromatic nuclei and increased Paneth cell differentiation present in clusters in crypts

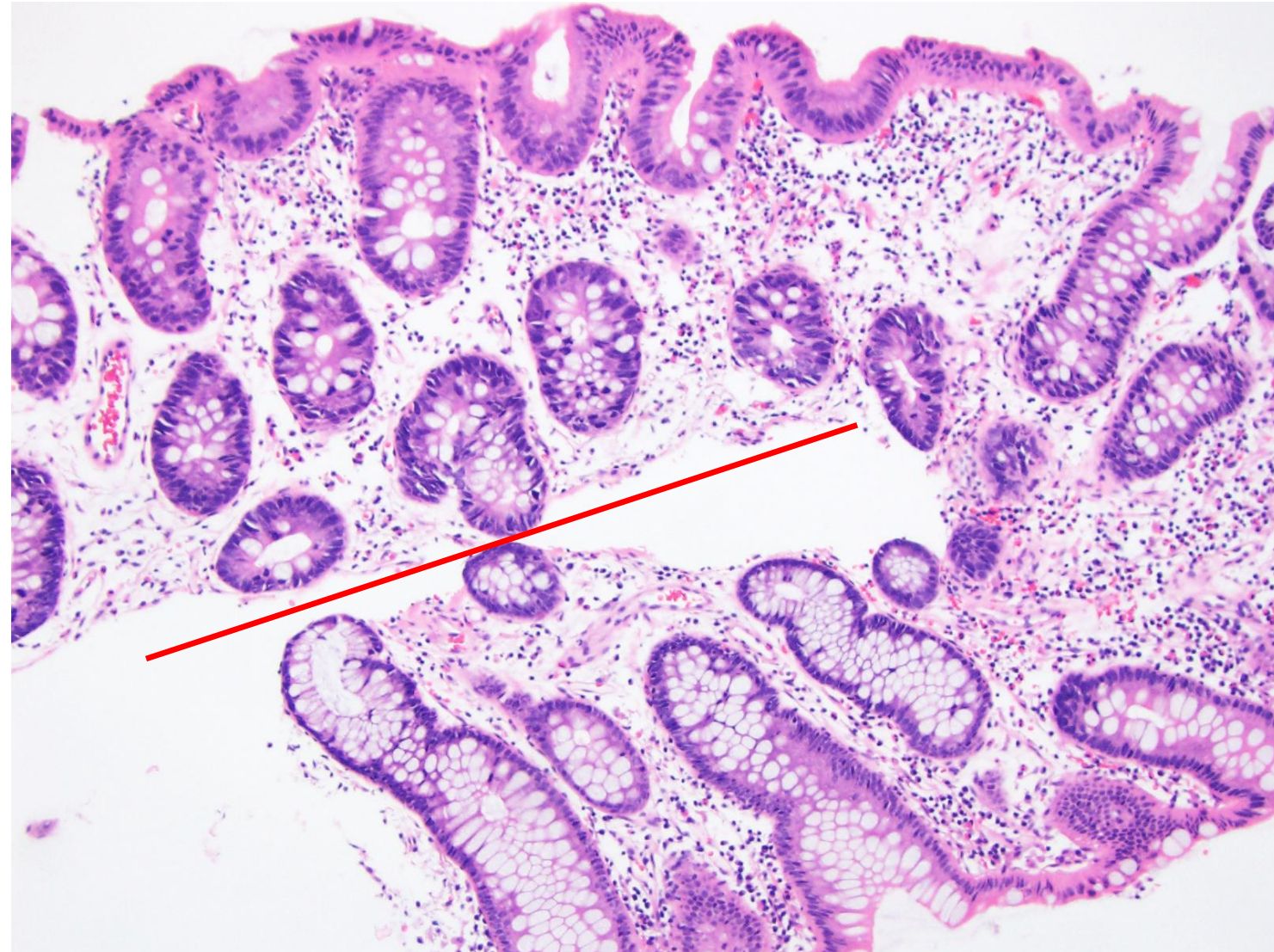
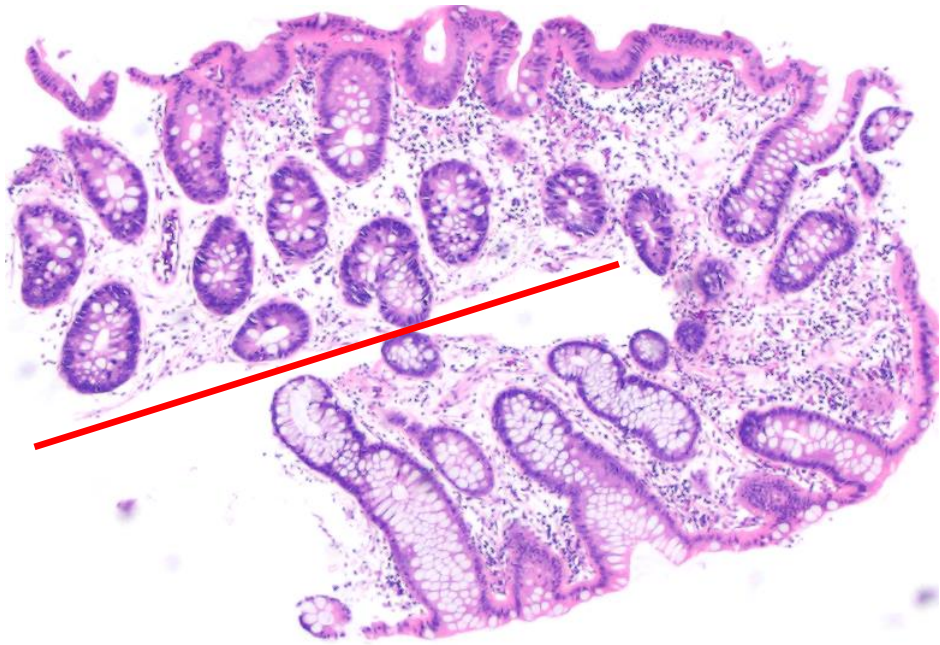
Despite some loss, goblet cells are easily identified

IBD-Associated Dysplasia subtype: terminal epithelial differentiation/crypt cell dysplasia



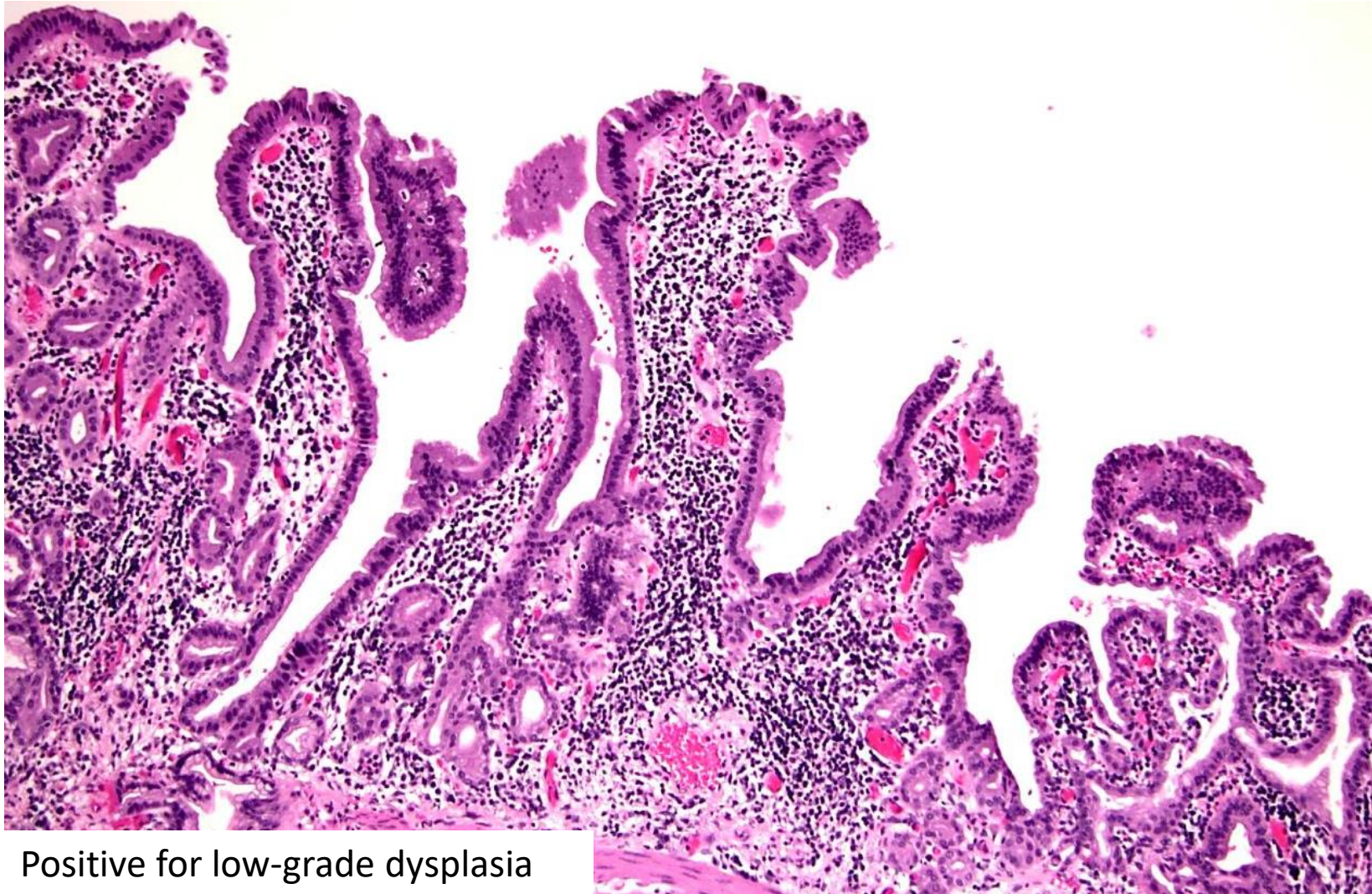
Mildly enlargement and hyperchromasia of slightly irregular, but mostly non-stratified nuclei involving surface and crypts
Absence of inflammation, epithelial injury

IBD-Associated Dysplasia Subtype: terminal epithelial differentiation/crypt cell dysplasia

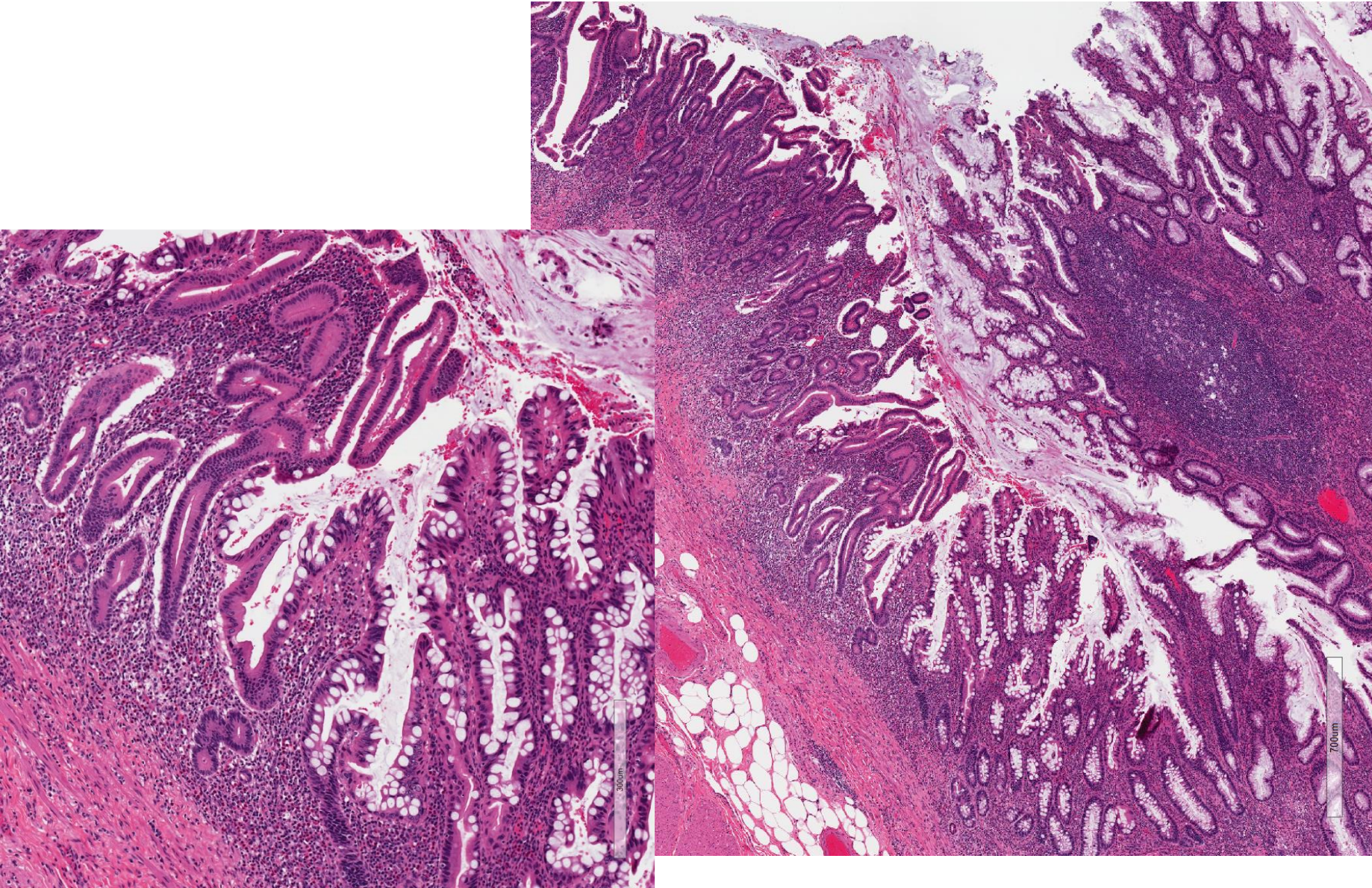


Features:
Mildly enlargement and hyperchromasia of slightly irregular, but mostly non-stratified nuclei involving surface and crypts
Absence of inflammation, epithelial injury

IBD-Associated Dysplasia Subtype: dysplasia with pyloric differentiation



IBD-Associated Dysplasia Subtype: mixed



Goblet cell deficient

Serrated, NOS vs
TED

Flat conventional

Hypermucinous

High-Grade Dysplasia in IBD

- Greater degree of architectural abnormalities

Extensive papillary extension into the lumen, **cribriform glands**

Villiform or papillary surface epithelium

- Greater degree of cytologic abnormalities

Enlarged, round or irregular, **pleomorphic (most objective criteria)**, dark nuclei

Full thickness stratification to the luminal surface

Loss of polarity (most objective criteria)

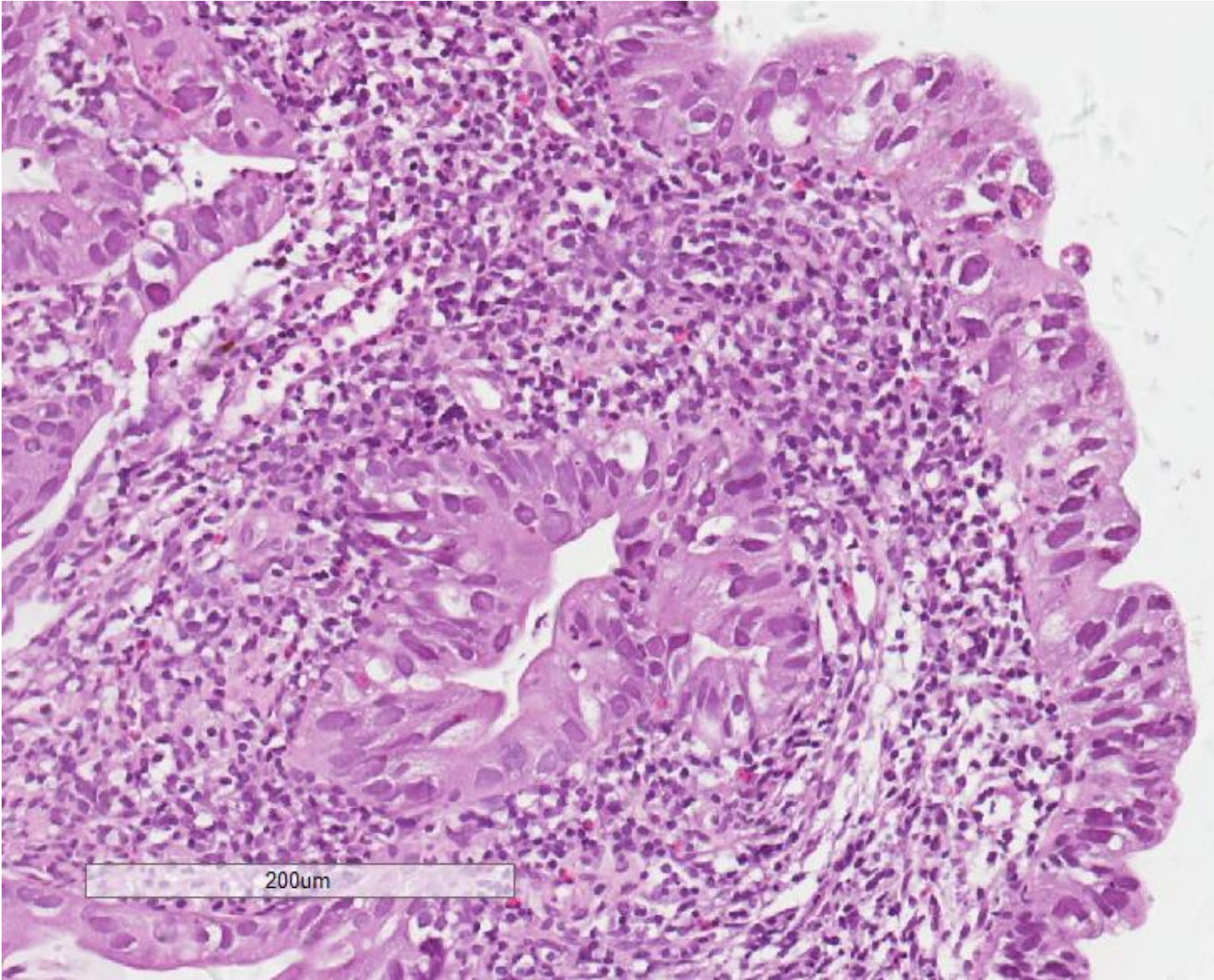
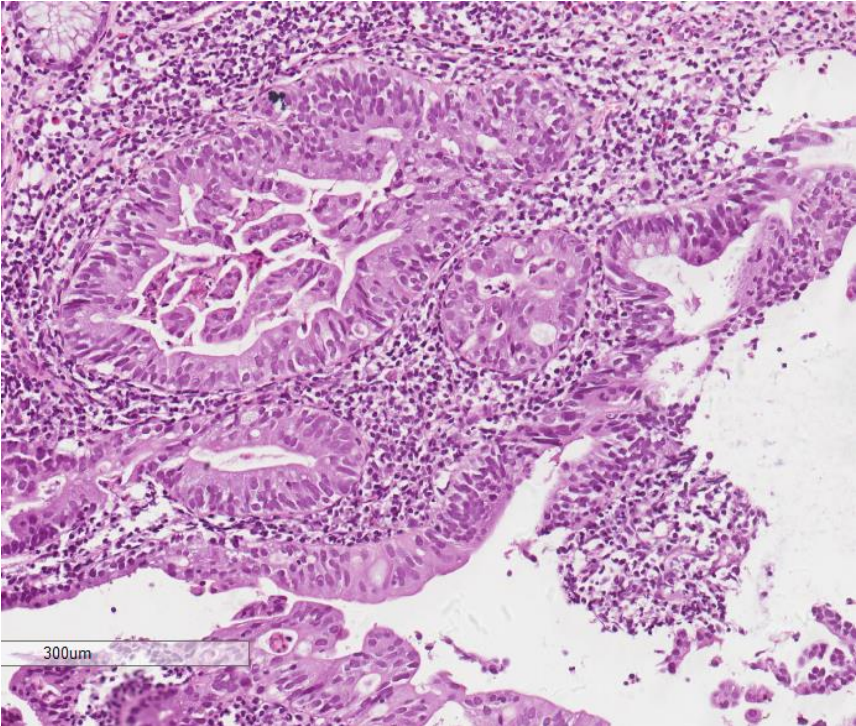
Nucleolar enlargement

Numerous mitoses, abnormal mitosis

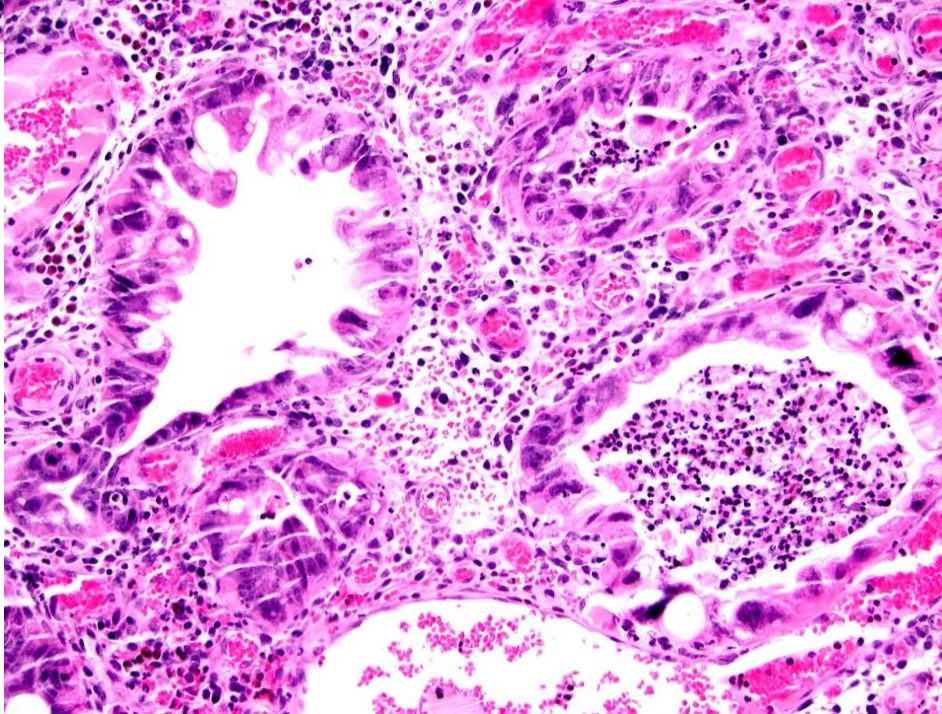
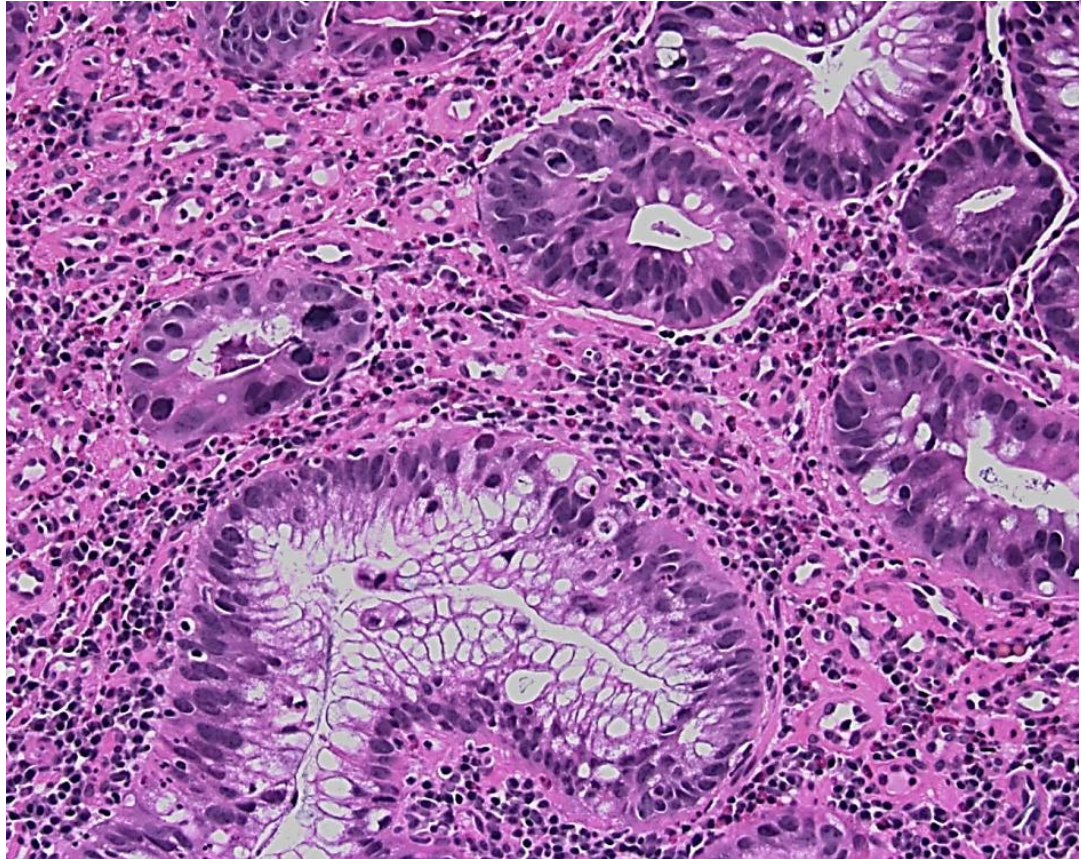
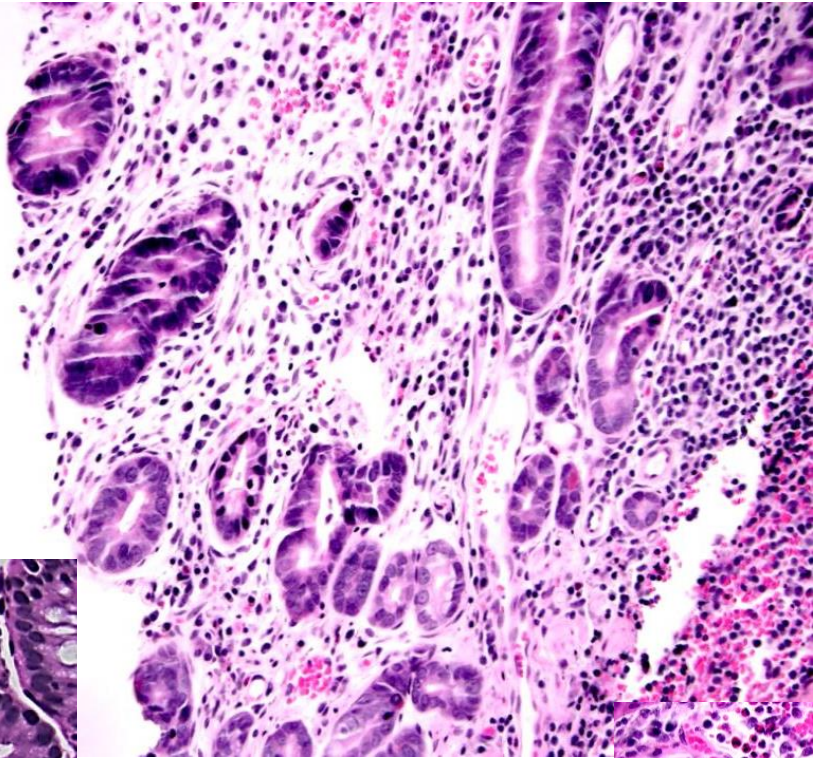
Lack of surface maturation

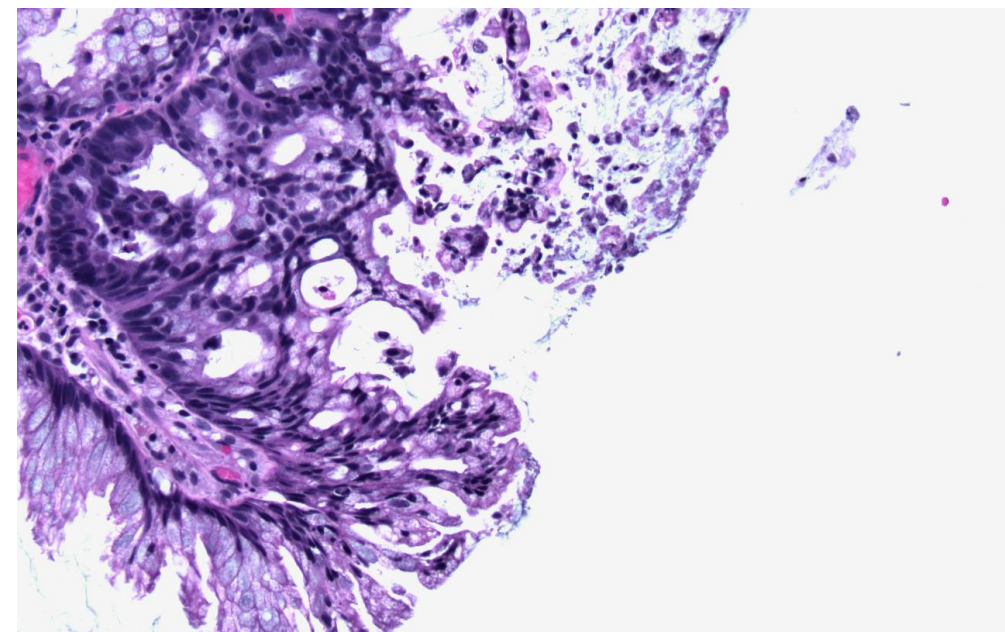
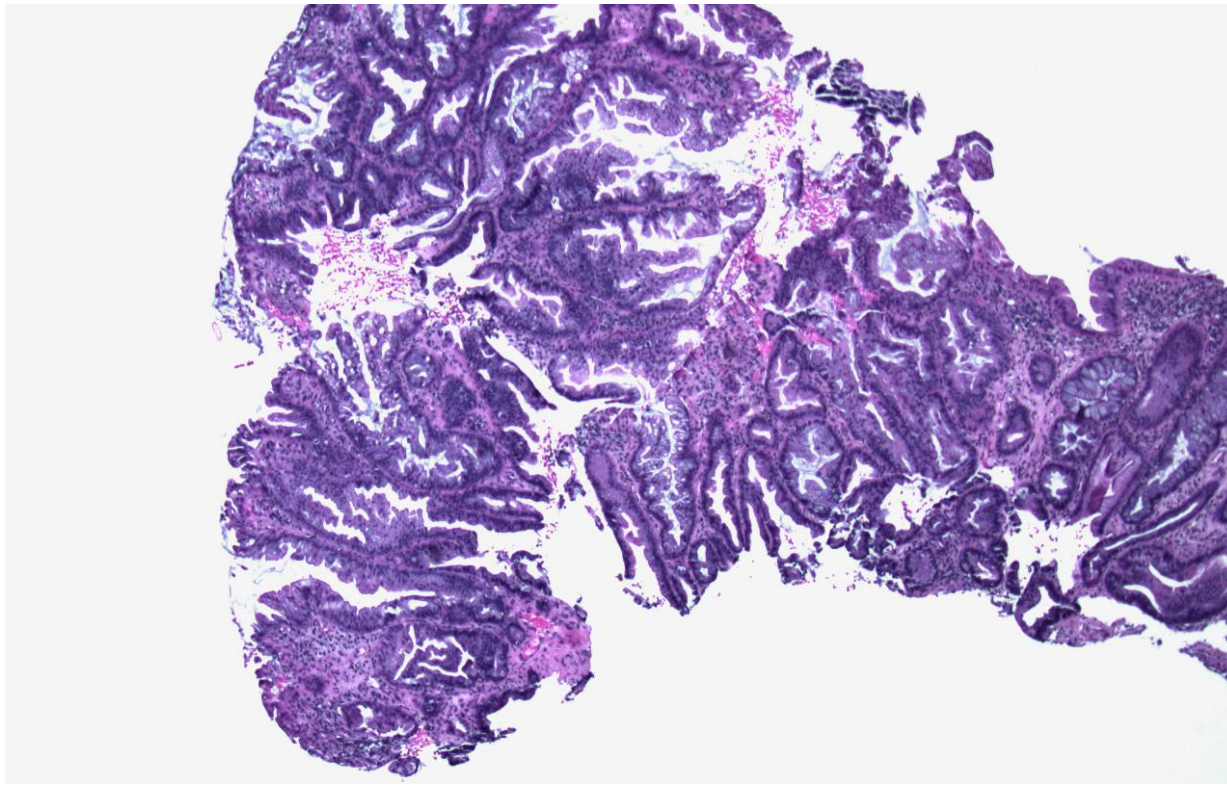
HGD is diagnosed if either one is sufficiently prominent

Positive for high-grade dysplasia



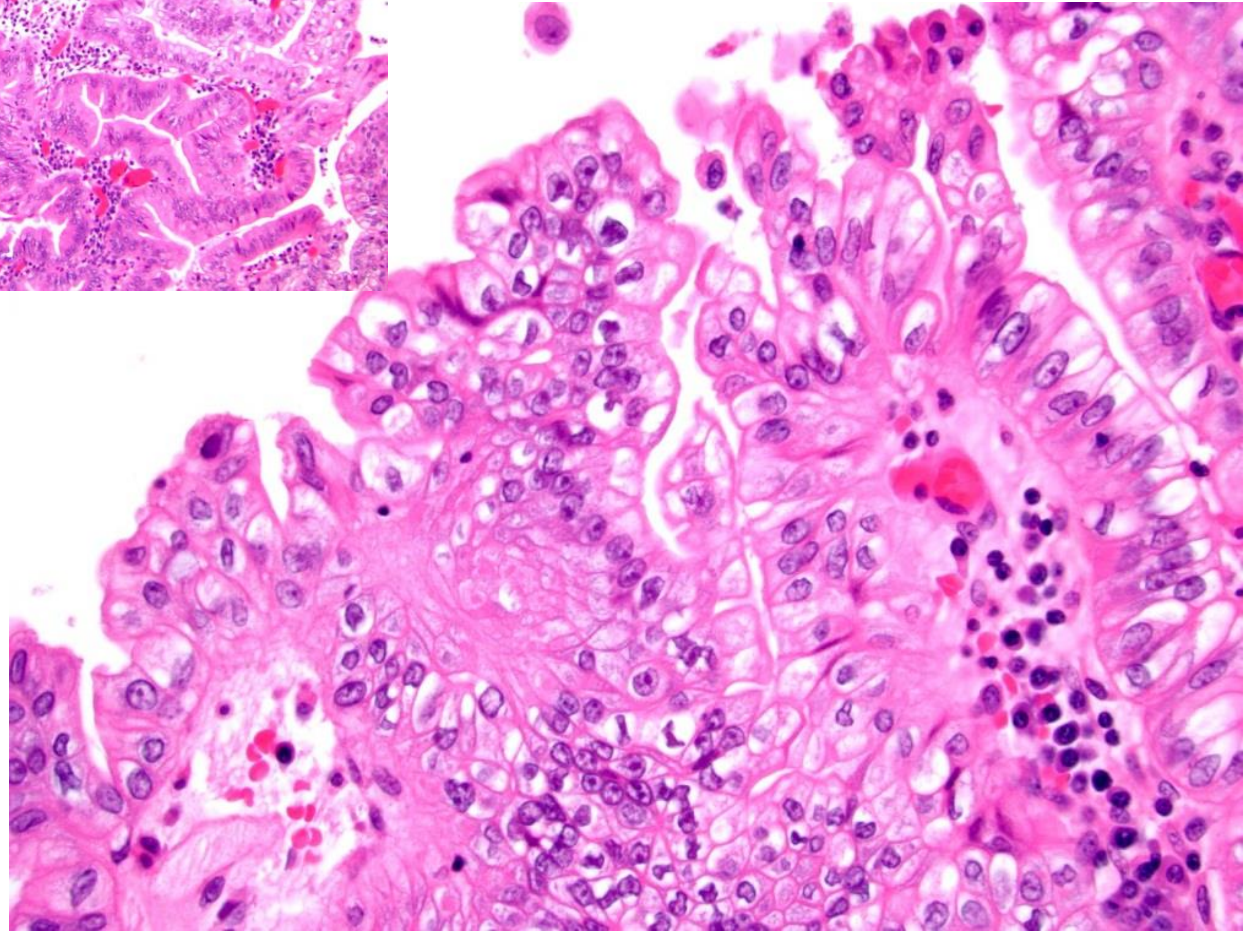
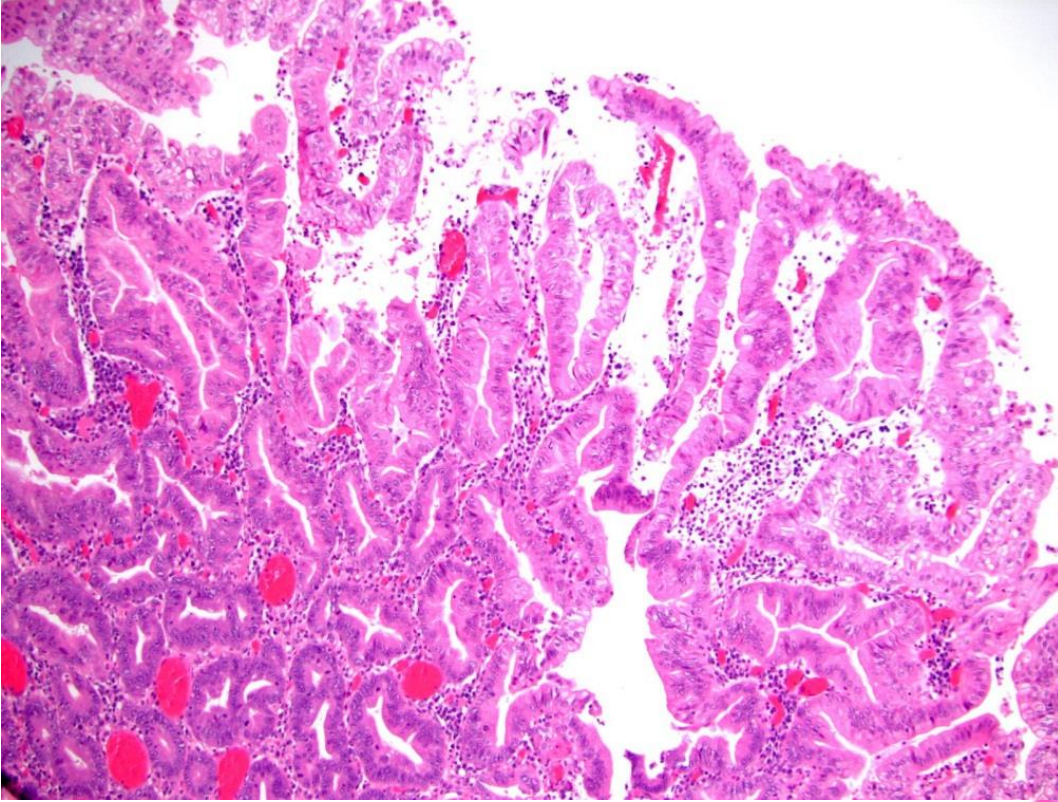
Positive for high-grade dysplasia



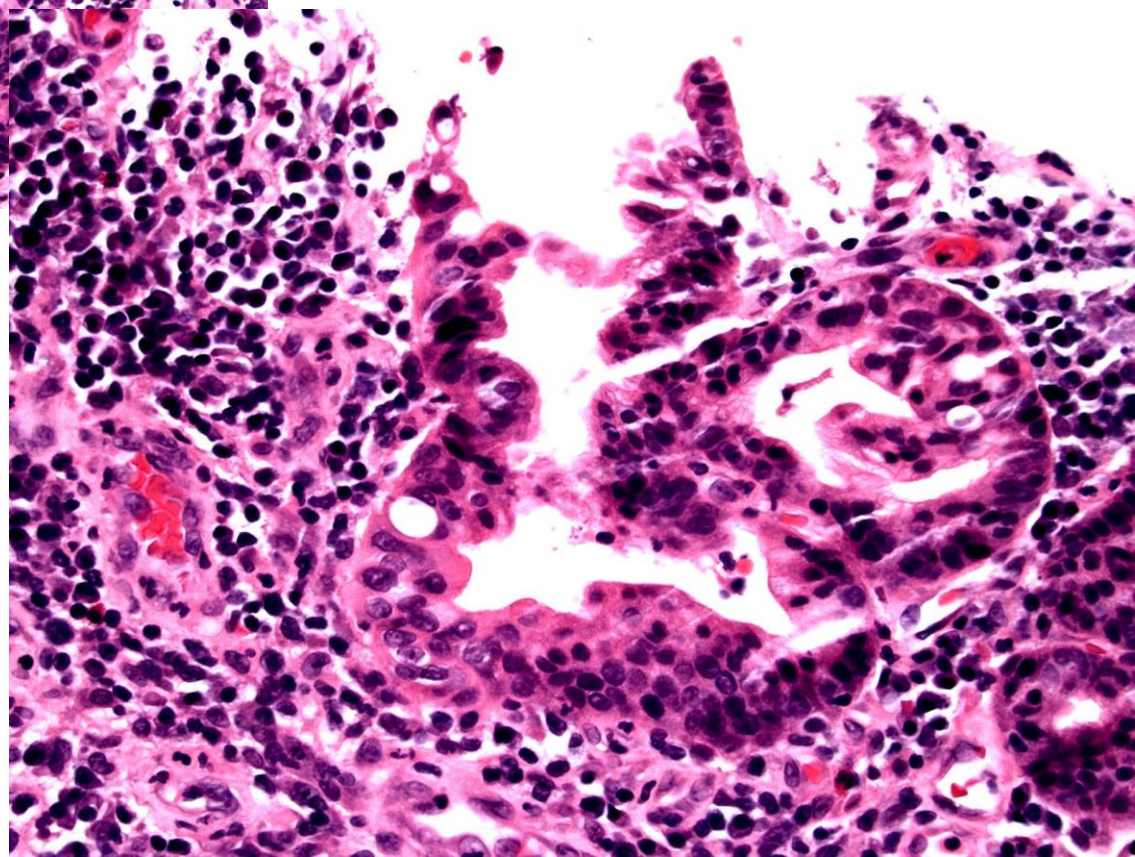
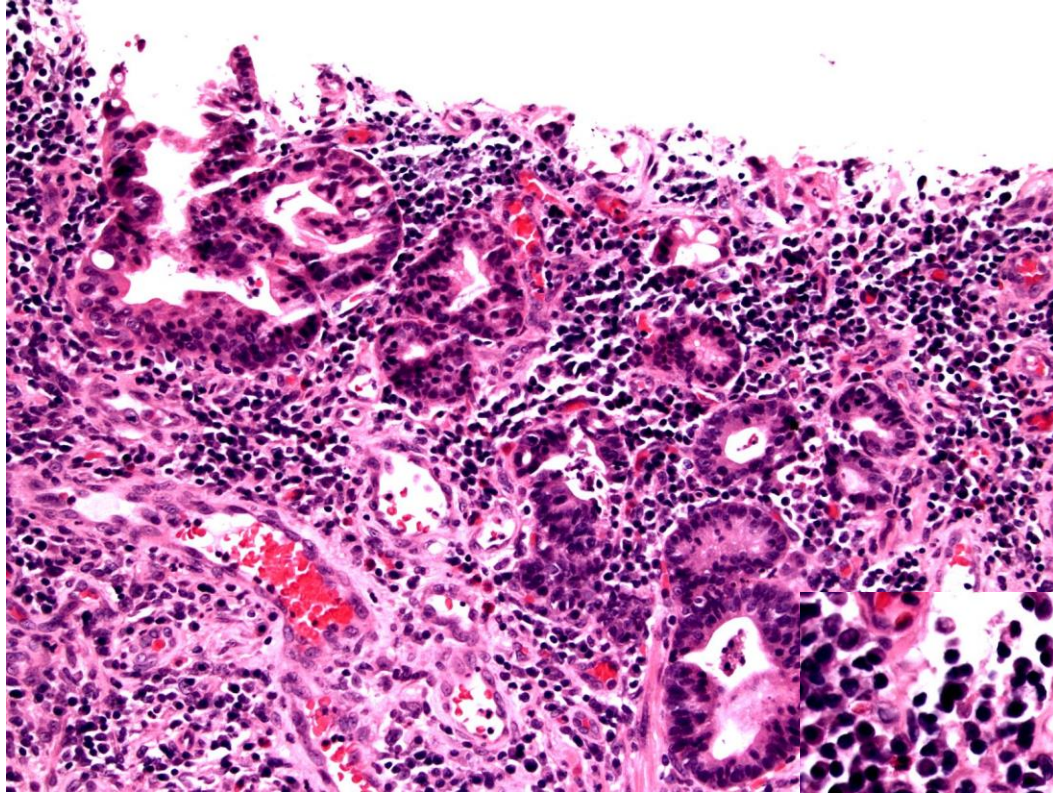


Positive for high-grade dysplasia

Positive for high-grade dysplasia



Positive for high-grade dysplasia



Indefinite for Dysplasia in IBD

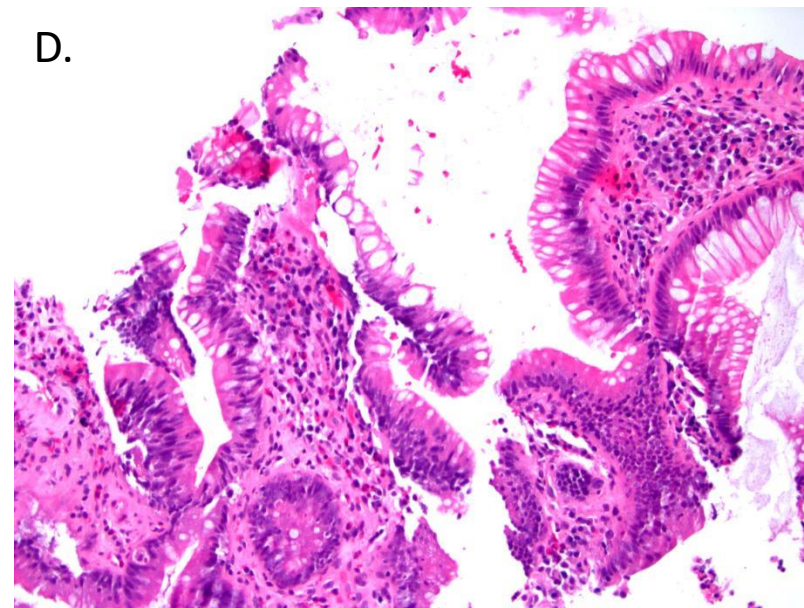
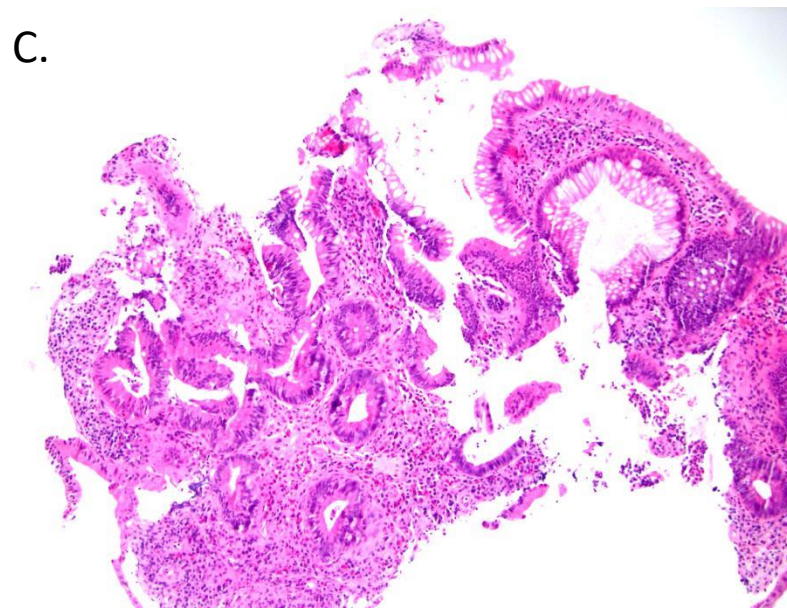
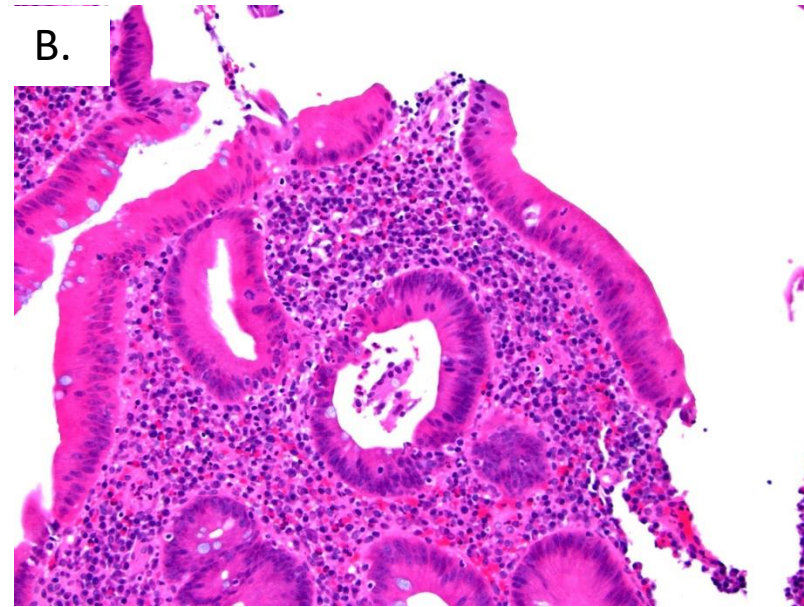
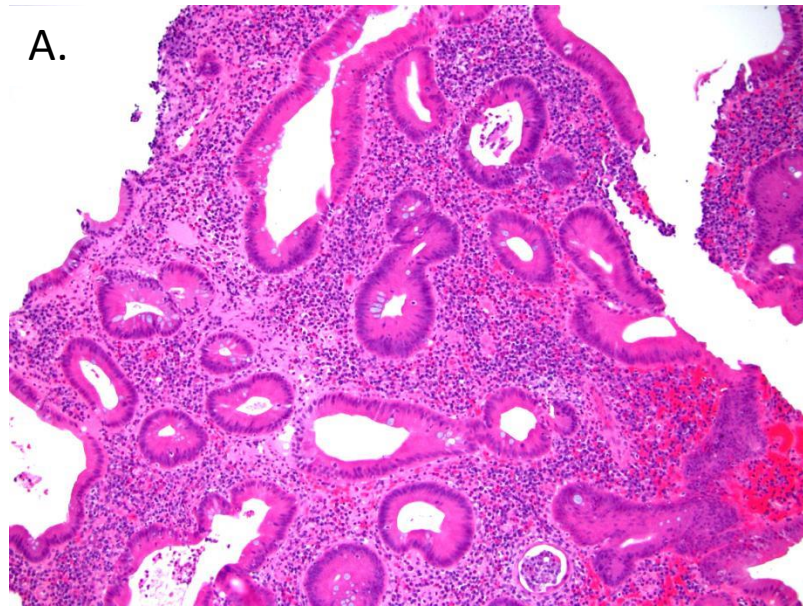
- Sincerely concerning but not unequivocally neoplastic (quantitatively/qualitatively fall short)
- The presence of obscuring inflammation, biopsy artifacts, tangential section, staining quality
- Mildly hyperplastic changes should not be labeled as indefinite for dysplasia

Conceptually, three categories:

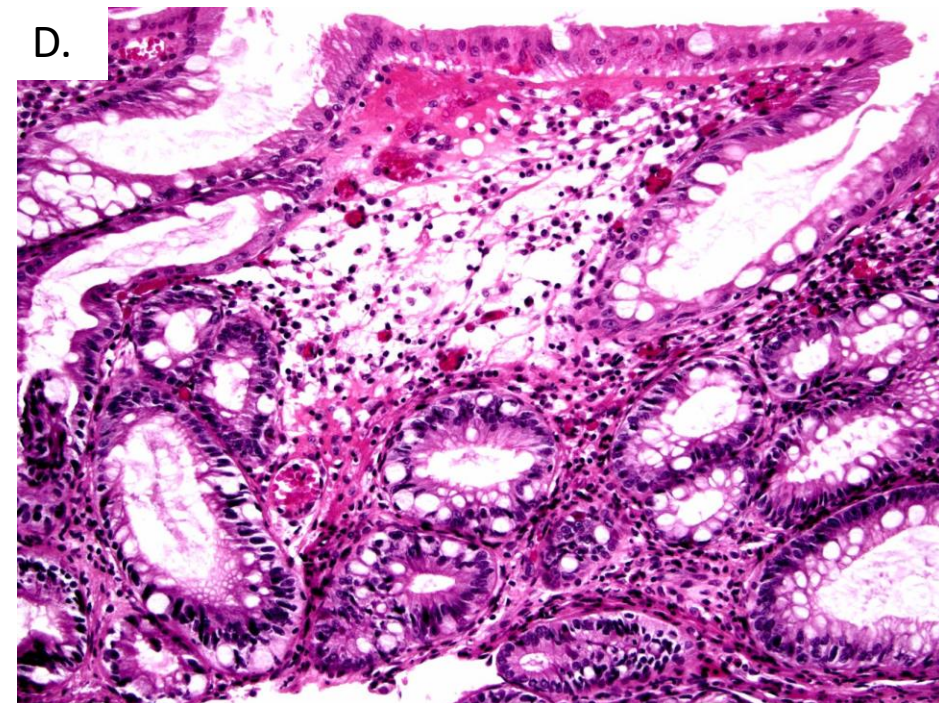
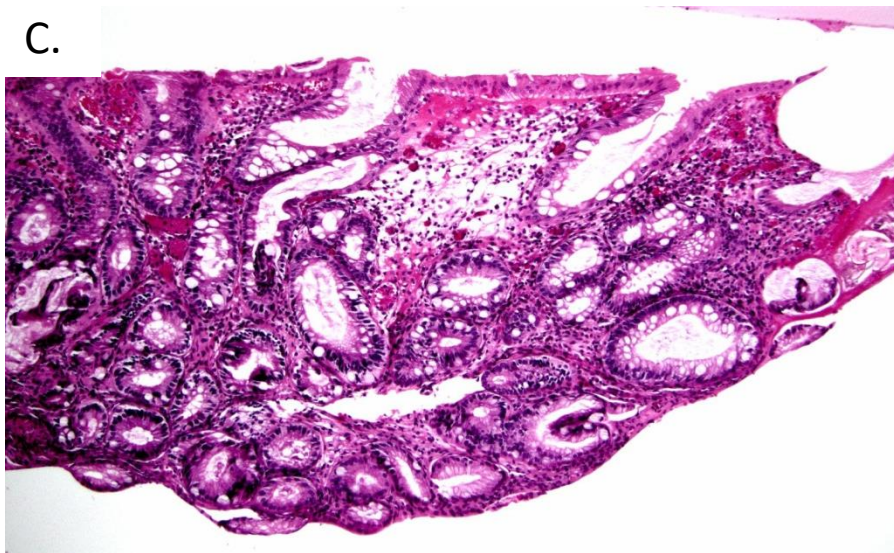
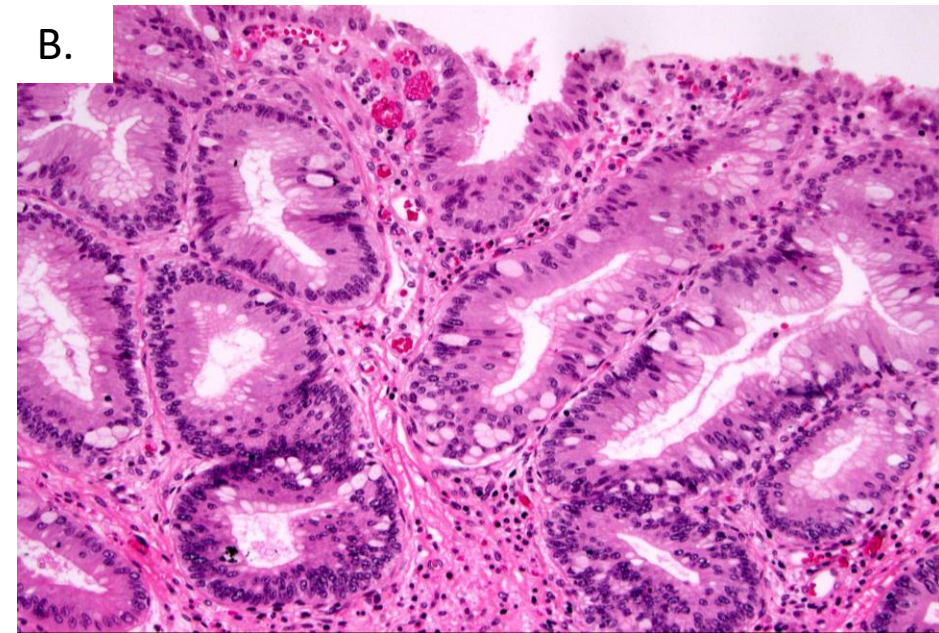
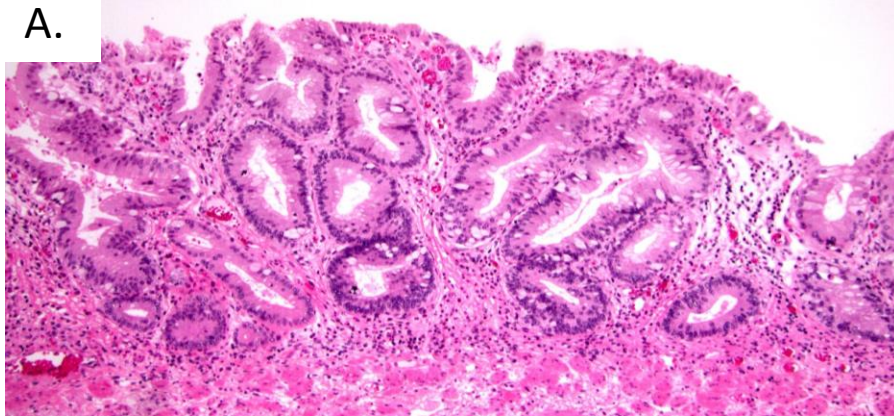
Indefinite for dysplasia, favor reactive

Indefinite for dysplasia, favor dysplasia

Indefinite for dysplasia, cannot tell

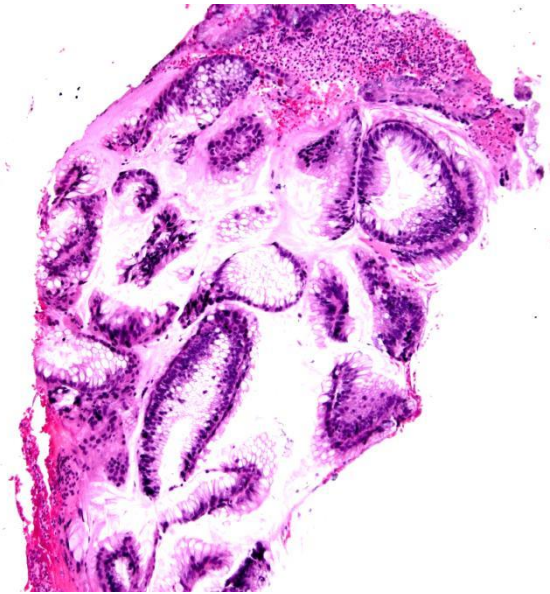


Epithelial changes indefinite for dysplasia, probably negative (A-D)

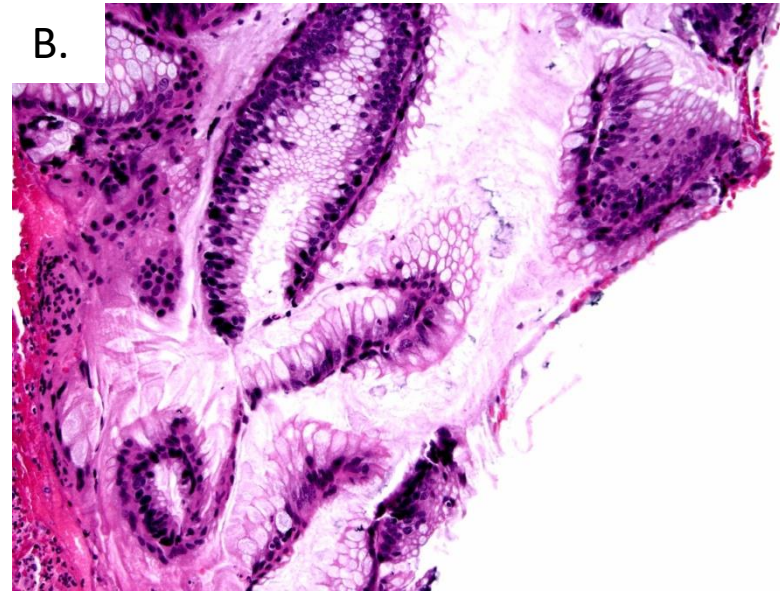


Epithelial changes indefinite for dysplasia, unknown (A-D)

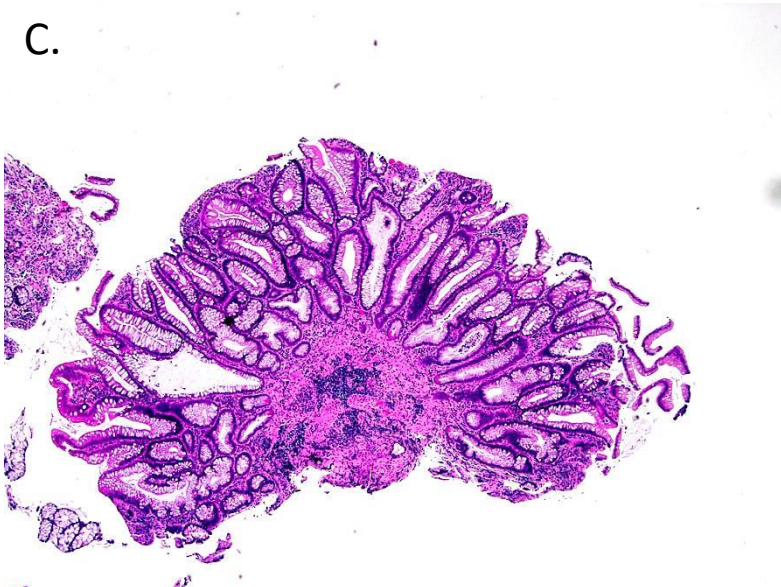
A.



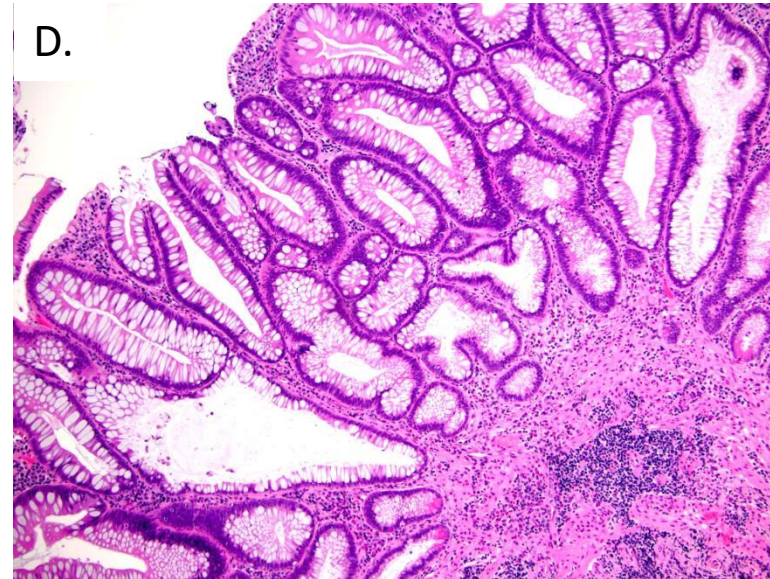
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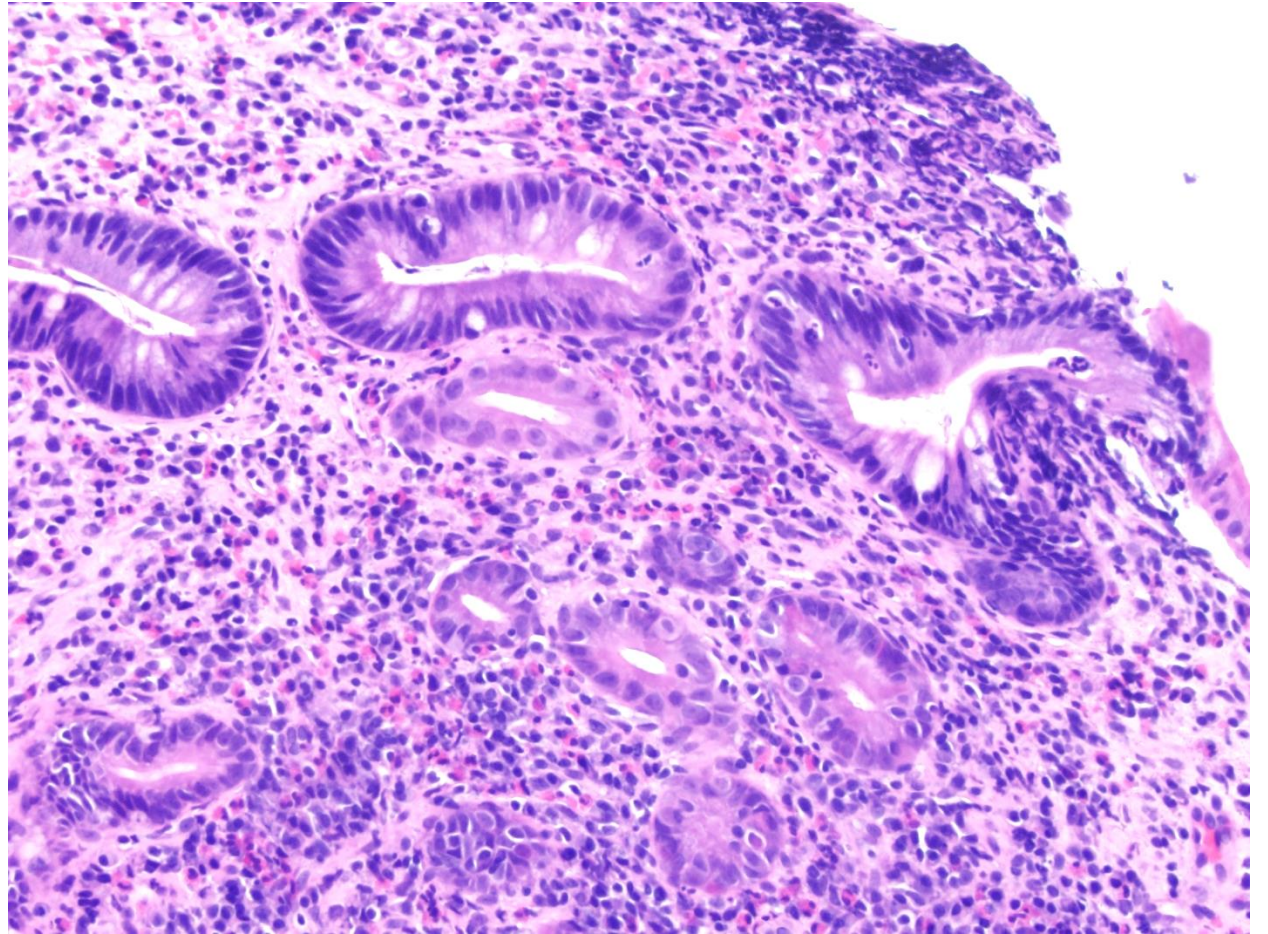
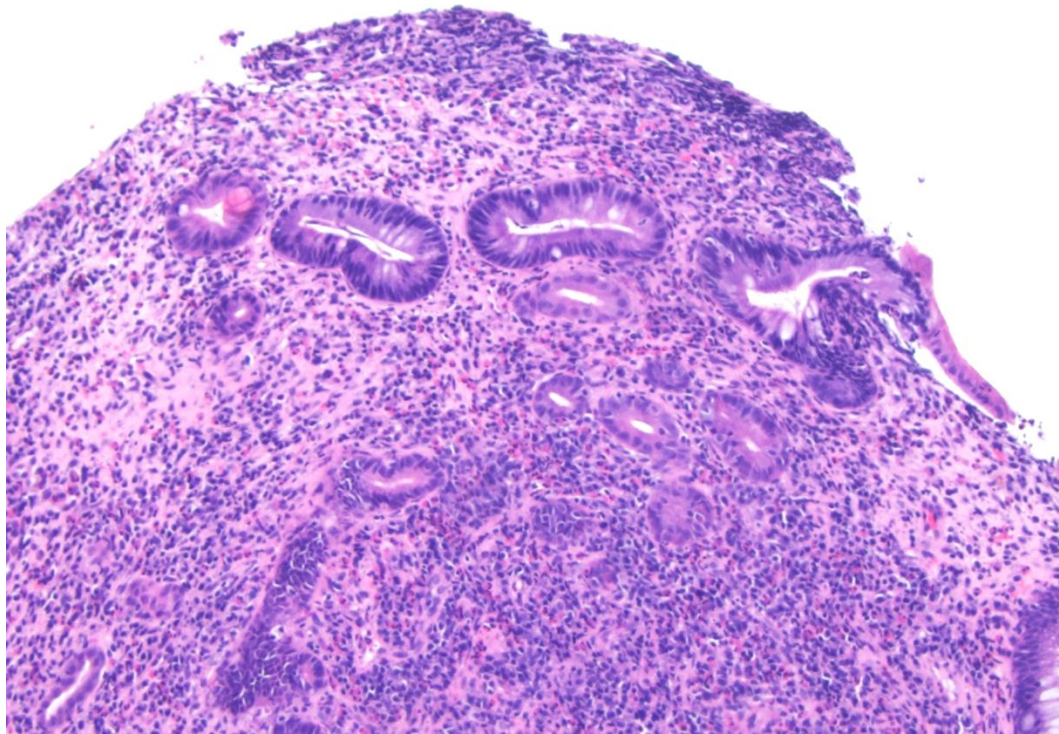
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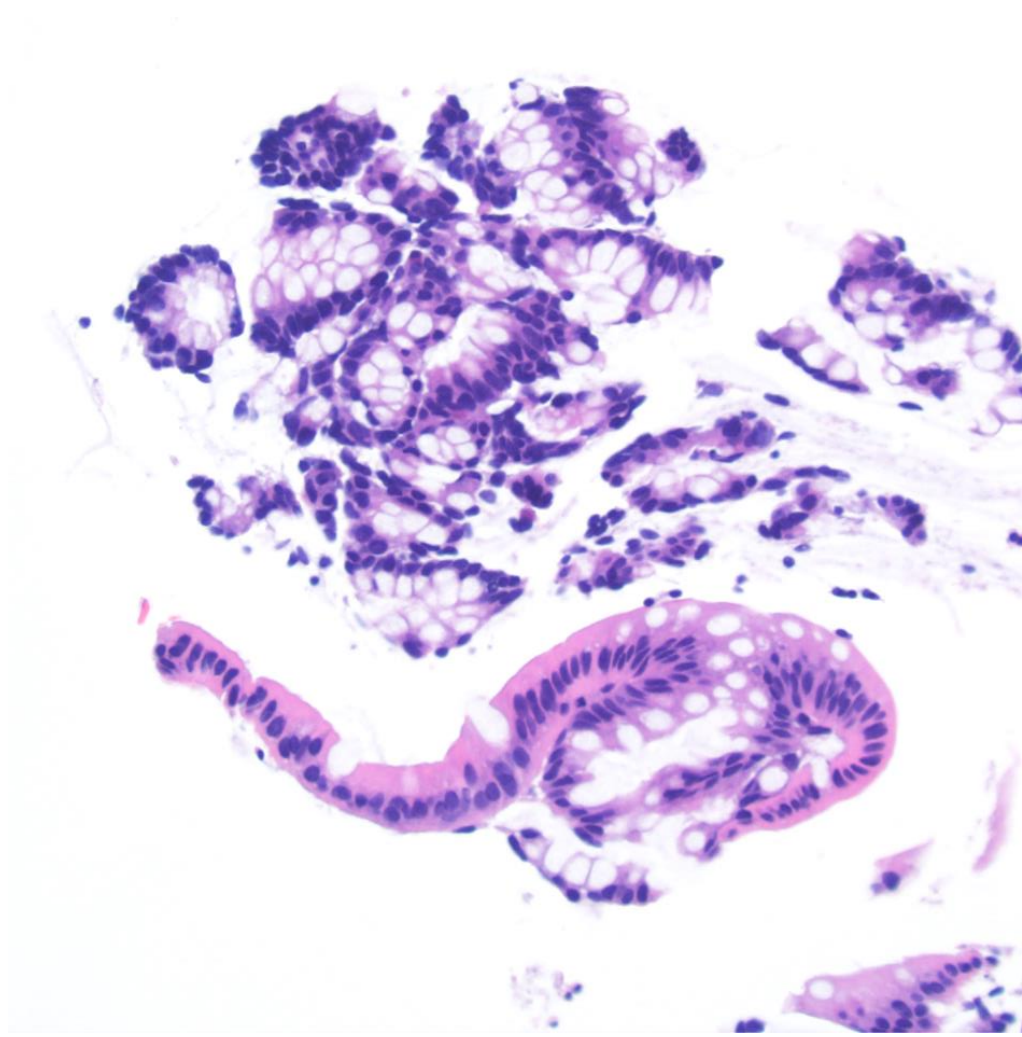
D.



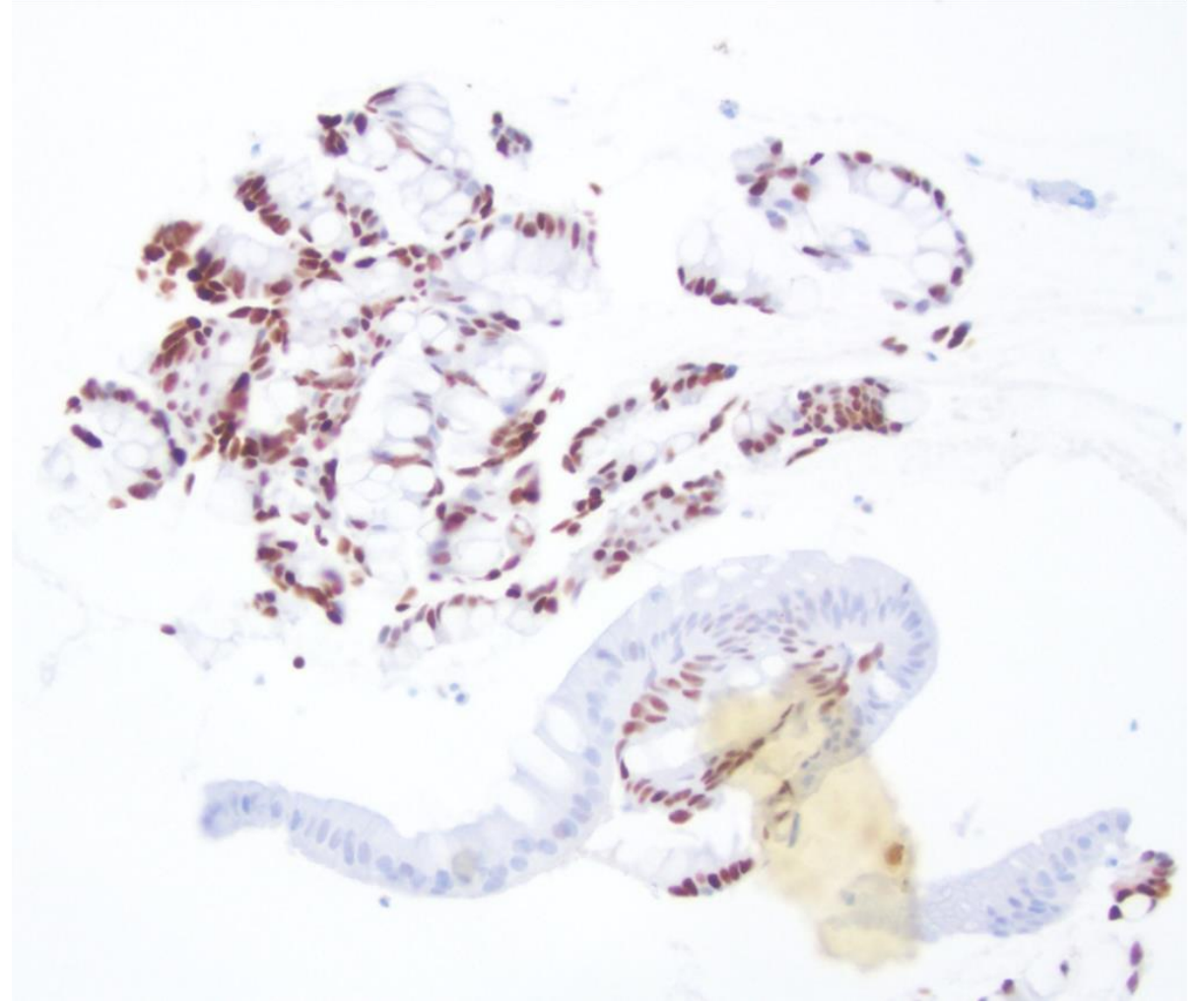
Epithelial changes indefinite for dysplasia, probably positive (A-D)



Epithelial changes indefinite for dysplasia, cannot tell; tangential section



p53



Epithelial changes indefinite for dysplasia, detached atypical epithelium, probable low-grade dysplasia

Dysplasia Interpretation in IBD

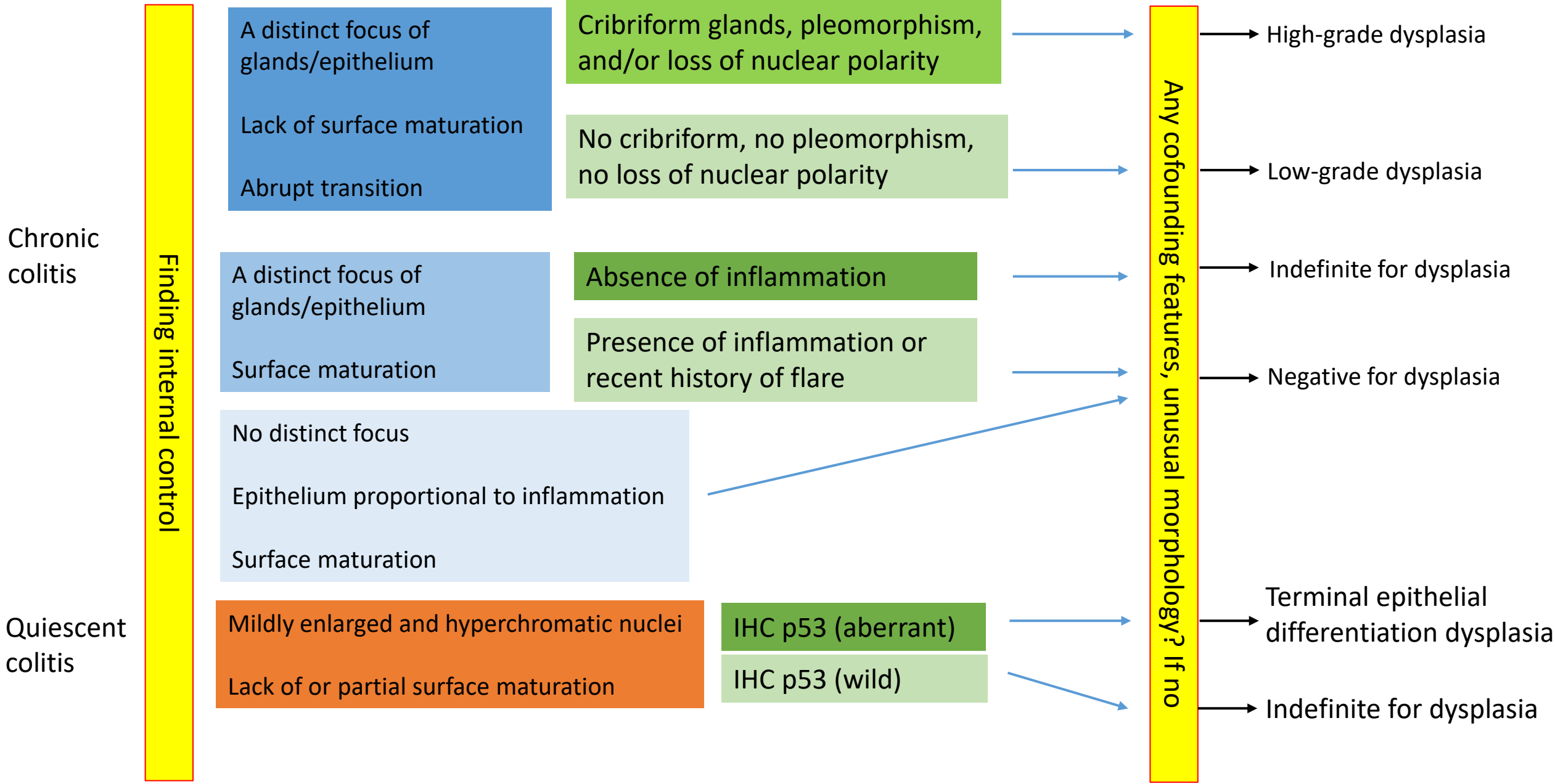
Endoscopic appearance			Endoscopic resectability
Invisible			Resectable
Visible	Polypoid	Pedunculated	
		Sessile	
Nonpolypoid	Superficial elevated	Unresectable	
	Flat		
	Depressed		

Histology grade
LGD
HGD

Histology variant		
Conventional (intestinal type)		
Non-conventional	Hypermucinous	
	Serrated	TSA-like
		SSP/A-like
		Serrated, NOS
	Goblet cell-deficient	
	Dysplasia with Paneth cell differentiation	
	Terminal epithelial differentiation/crypt cell dysplasia	
	Dysplasia with pyloric differentiation	
	Dysplasia with neuroendocrine cell differentiation	
	Mixed	Conventional/non-conventional Non-conventional

Clinically relevant; management primarily depends on visibility and resectability

Colonic Surveillance Biopsies: practical approaches



Terminology for Reporting

Location of biopsy	Endoscopic finding	Pathologic diagnosis	Implications
Outside of colitis region	Polyp or sessile lesions	Sporadic adenoma, hyperplastic polyp, or sessile serrated polyp	Complete removal with routine IBD annual surveillance
Inside of colitis region	Polyp (resectable)	Polypoid LGD or HGD	Complete removal with intensified surveillance
	Polyp (unresectable) on conventional colonoscopy	Polypoid LGD or HGD (should be confirmed by another GI pathologist)	IBD expert referral with chromoendoscopy or colonoscopy of high resolution: <ol style="list-style-type: none"> i. Resectable LGD or resectable HGD: complete removal with intensified surveillance ii. Unresectable LGD: colectomy indicated iii. Unresectable HGD: colectomy
	Visible but unresectable mass/lesion (elevated, flat, depressed) or invisible on conventional colonoscopy	LGD, HGD, or invasive adenocarcinoma (should be confirmed by another GI pathologist)	Focal LGD: intensified surveillance or referral to an IBD center for a repeat colonoscopy with high resolution and/or chromoendoscopy or colectomy (depending on clinical and endoscopic suspicion) HGD: colectomy Invasive adenocarcinoma: colectomy
	Sessile lesion	Sessile serrated polyp	Complete removal with routine IBD annual surveillance

Summary

- Clinical significance of dysplasia in IBD
- Schema to evaluate IBD surveillance colonic biopsy
- Variants of IBD dysplasia