Inflammatory Bowel Disease
The basics and practical issues

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Inflammatory Bowel Disease

- Basic Pathology of Inflammatory Bowel Disease
- Initial diagnosis on endoscopic biopsies
- Evaluation and reporting on follow-up biopsies
- Evaluation of surgical specimens
- Reporting systems for IBD mucosal biopsies
- Mimics of IBD
- Dysplasia in IBD

Basic Pathology of IBD

- Lifelong disorders predominantly present in developed countries.
- Pathogenesis involves Interaction between genetic and environmental factors
- Covers two specific diseases: ulcerative colitis (UC) and Crohn’s disease (CD).

Clinical Features

- Both disease tend to arise in early adulthood,
- But can arise at any age from early childhood onward.
- Chronic diarrhea characteristic
- Bloody diarrhea typical of UC;
- Abdominal pain and weight loss are also typical.

Macroscopic Features : UC

- Typically demonstrates **diffuse and continuous** mucosa-based inflammation, involving the rectum, and extending to a variable degree proximally.
- Colonic mucosa typically shows diffuse erythema, granularity, hemorrhage, superficial ulcers, epithelial denudation, and inflammatory (“pseudo”) polyps.
- The **transition** between inflamed and uninflamed mucosa is usually sharply defined; skip lesions are not a feature of classic UC.
- **Exceptions** may include recent onset disease, especially in pediatric patients, quiescent or treated colitis, fulminant colitis or toxic megacolon, and distal colitis with a cecal and/or periappendiceal patch of inflammation.

Macroscopic Features : CD

- CD is **transmural and segmental** inflammatory disease involving the distal ileum in at least 70% of patients
- Up to 30% of CD patients may have disease predominant in or limited to the colon
- The rectum is usually spared, or relatively less inflamed than proximal colon.
- The involved mucosa shows aphthous erosions and long, serpentine, linear, and longitudinally oriented ulcers that produce a cobblestoned appearance.
- Strictures and/or wall thickening and fibrosis, deep fissures and/or fistulae, and, most characteristically, mesenteric fat wrapping are typical features of CD.

Microscopic Features : UC

4 components of histological features

- Mucosal architecture
- Lamina propria cellularity
- Neutrophil granulocyte infiltration
- Epithelial abnormality

Microscopic Features : UC

Normal crypts are straight, parallel and extend from immediately above the muscularis mucosae to the surface

- Chronic inflammation causes crypt **architectural abnormalities**:
- **Crypt distortion** (crypts that are no longer parallel, vary in diameter and/or are dilated).
- **Branching** (represents regeneration, branching of more than 10 % of crypts or presence of more than two branched crypts in a well-oriented biopsy specimen with at least 2 mm of muscularis mucosae is abnormal.
- **Atrophy** (defined as shortened crypts, accompanied by an increased layer of lamina propria stroma beneath)
- **Decreased crypt density** (separation of adjacent crypts by lamina propria equivalent to or greater than one crypt diameter)
- Also changes of surface topography (surface irregularity).

Microscopic Features : UC

- Normally, the **lamina propria** shows has the lowest cell density of mononuclear inflammatory cells in the lower third.
- In UC there is increased and/or altered distribution of cell types normally present in the colorectal mucosa.
- A homogeneous increase in cellularity occurs throughout the lamina propria, for which the term **transmucosal** is used, and this can be best appreciated in the lower third.
- **Basal plasmacytosis**: plasma cells are predominantly observed between the base of the crypts and the muscularis mucosae
- This feature is helpful in differentiating between a first attack of UC (63 %) and infectious colitis (6 %), but not from CD

Microscopic Features : UC

- **Neutrophils**, which reflect disease activity, are present in the lamina propria and/or invade the surface or crypt epithelium
- **Cryptitis** (presence of neutrophils within crypt epithelium)
- **Crypt abscesses** (presence of neutrophils within crypt lumina)
- Crypt abscesses are more common in UC (41 %) than in CD (19 %).

Microscopic Features : UC

Epithelial abnormalities include surface epithelial damage, mucin depletion, and metaplastic changes

- **Surface epithelial damage**, such as flattening, focal cell loss, erosions, and ulcers reflect the activity of disease.
- **Mucin depletion**, defined as reduction in the number of goblet cells and/or reduced quantity of intracellular mucin. Severe, widespread goblet cell depletion is a classic feature of active UC. But is a weak distinguishing feature in UC as it also occurs in other reactive processes.
- **Paneth cell metaplasia** (in the left colon) is a feature of chronicity

Microscopic Features : UC

Early stage disease

- Preserved crypt architecture and absence of a transmucosal inflammatory infiltrate do not rule out early stage UC
- Distinction from infectious colitis (acute self-limiting colitis) is a major concern.
- Focal or diffuse basal plasmacytosis is the earliest diagnostic feature with the highest predictive value for diagnosis and can be identified in 38 % of patients within 2 weeks after presentation

Microscopic Features : UC

Longstanding disease

- There is widespread architectural crypt distortion and increased cellularity of the lamina propria
- Confusing features such as patches of normal mucosa, discontinuous inflammation and rectal sparing can occur
- With time, (especially with treatment), the extent of involvement of the colon tends to decrease, In parallel, the distribution pattern may change from diffuse (continuous) to patchy (discontinuous)

Microscopic Features : UC

Quiescent disease

- The mucosa may still show features reflecting sustained damage, e.g, architectural abnormalities and reduced crypt density.
- The inflammatory infiltrate is of variable density, and as a result, the lamina propria may either appear hyper- or hypocellular.
- Neutrophils are not observed in quiescent disease.

Microscopic Features : Crohn's Disease

- **Chronic active ileitis** is histologically defined by the presence of acute and chronic injury characterized by neutrophils in the epithelium and/or lamina propria with cryptitis, crypt abscesses, erosions, or ulcers in combination with full thickness, dense lymphocytic inflammation and plasmacytosis.
- These, as well as an irregular villous architecture, are features in favour of a diagnosis of CD in endoscopic ileal biopsy samples.
- When the ileitis is in continuity with proximal colitis, the features should be used with caution, because they occur also in backwash ileitis in UC.

Microscopic Features : Crohn's Disease

- **Focal (discontinuous) chronic inflammation** implies increased cellularity of the lamina propria (with lymphocytes and plasma cells), of variable density throughout the biopsy specimen.
- One or more circumscribed foci with increased mononuclear cell density can be found against a background of normal mucosa or mucosal samples with variable intensity of inflammation.
- Normal lymphoid aggregates are not considered as focal inflammation.
- In a biopsy, the inflammation may extend into the submucosa.

Microscopic Features : Crohn's Disease

- The presence of neutrophils in the lamina propria or in the epithelium, including cryptitis and crypt abscesses, indicates active disease and signifies epithelial damage.
- An epithelioid cell **granuloma** is a discrete collection of at least five epithelioid cells (activated histiocytes with homogeneous slightly eosinophilic cytoplasm), with or without multinucleated giant cells.
- In CD, granulomas are often poorly delimited.
- Only granulomas **not related to crypt injury** should be regarded as a feature in support of CD.
- Infection may also give rise to granulomas and should always be excluded.

Microscopic Features : Crohn's Disease

- The chronic inflammatory process induces alterations in mucosal architecture. These are generally less prominent than in UC and focal or discontinuous.
- Pyloric (pseudopyloric) gland metaplasia is related to mucosal ulceration and repair and may be observed in ileal biopsies from patients with CD.
- **Transmural lymphoid aggregates** (identifiable only in resection specimens and usually not in ulcerated areas) and granulomas are features supporting a diagnosis of CD.

Microscopic Features : Crohn's Disease

- A single feature is not regarded as sufficient for a reliable diagnosis of CD.
- Most expert clinicians and pathologists agree that the **presence of granulomas and at least one other feature** establishes a diagnosis of CD.
- The second feature can be either inflammation or, more specifically, architectural abnormalities.
- Granulomas is not a prerequisite for a diagnosis of CD. (Granulomas are more often observed in children and adolescents than in adults.)

Microscopic Features : Crohn's Disease

Additional useful features:

- focal chronic inflammation without crypt atrophy,
- focal cryptitis,
- aphthous ulcers,
- disproportionate submucosal inflammation,
- neural hypertrophy (nerve fibre hyperplasia),
- increased number of intraepithelial lymphocytes and in the colon proximal location of ulceration
- architectural distortion.

Microscopic Features : Crohn's Disease

- When multiple biopsies are available, ileal involvement, colonic inflammation with a decreasing gradient from proximal to distal, as well as the absence of features highly suggestive or diagnostic for UC (such as diffuse inflammation, crypt irregularity and reduced crypt density), also support a diagnosis of CD.
- Biopsies from the upper gastrointestinal tract can provide additional diagnostic clues, particularly in children and adolescents.

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Initial diagnosis on endoscopic biopsies

- In patients with suspected IBD, histological examination should be performed **before initiation of treatment**.
- Detailed clinical information and proper biopsy techniques (location and quantity) are key determinants of reliable pathologic diagnosis.
- **Information** regarding symptoms and duration, endoscopic pattern and extent of disease, and laboratory study results (stool and microbiology) should be available.
- At first diagnosis, at least 2 **biopsies from five different intestinal sites**, including terminal ileum, rectum, and both diseased and normal appearing mucosa, should be submitted in separate containers.
- **Specimens** should be well fixed, properly embedded and oriented, with multiple step sections.

Initial diagnosis on endoscopic biopsies

Histologic criteria for the diagnosis of chronic colitis:

- Diffuse, transmucosal plasma cell-rich inflammation, expansion of the lamina propria between and below crypts, and, most characteristically, basal plasmacytosis.
- Altered crypt architecture (e.g. distortion, branching, atrophy, villiform change) often present, +/- Paneth cell metaplasia from the mid transverse colon to the rectum.
- Intraepithelial neutrophils are a hallmark of disease activity and are almost always present in biopsies obtained at symptom onset, often with epithelial injury (e.g., cryptitis, crypt abscess, erosion, ulcer).

Initial diagnosis on endoscopic biopsies

Although generally reliable, the above features lack sensitivity and specificity for IBD in certain scenarios:

- early/acute phases of disease,
- fulminant colitis,
- pediatric patients

as the histologic features of chronic injury may not be as apparent in these situations.

Initial diagnosis on endoscopic biopsies

- Conversely, prolonged infections can lead to chronic mucosal injury (e.g., basal plasmacytosis, crypt architectural distortion, and Paneth cell metaplasia).
- Importantly, certain rare or newly described entities (e.g., Behçet's disease and immune checkpoint inhibitor-induced colitis) can present with an IBD-like histologic pattern.

Initial diagnosis on endoscopic biopsies

Histopathologic evaluation and reporting in inflammatory bowel disease A consensus paper sponsored by the Rodger C. Haggitt Gastrointestinal Pathology Society *Modern Pathology (2026)*

“Pathologists may comment on the likelihood of an actual IBD diagnosis, which may depend on available clinical data, but we generally recommend a descriptive diagnosis of chronic colitis or chronic active colitis in most circumstances and certainly in ambiguous cases or in settings of limited clinical data.”

Initial diagnosis on endoscopic biopsies

Subtyping of IBD on biopsies (as UC or CD):

- Requires sufficient clinical, laboratory, imaging, and endoscopic data.
- For CD, that includes evaluation of the upper GI tract in children as well as in adults with upper GI symptoms.
- Histological evaluation of lower GI tract biopsies obtained at disease onset, prior to the initiation of medical therapy
- Typically UC is continuous, diffuse, and mucosa-based, circumferentially extending to a variable length of colon proximal to and involving the rectum

Initial diagnosis on endoscopic biopsies

Subtyping of IBD on biopsies (as UC or CD), caveats :

- 10% of UC patients have **isolated cecal/periappendiceal inflammation** accompanied by more distal colitis with sparing of the intervening mucosa.
- **Crypt rupture** in cases of UC can elicit granulomatous (“cryptolytic”) inflammation that is intimately associated with the epithelium and often contains neutrophils.
- In contrast, CD granulomas, which are not crypt rupture related, are often located in upper levels of mucosa, in-between crypts.

Initial diagnosis on endoscopic biopsies

Subtyping of IBD on biopsies (as UC or CD), caveats :

There are situations in which UC can be patchy and/or relatively spare the rectum:

- In children
- In patients with concomitant primary sclerosing cholangitis (PSC), (frequent ileal inflammation, relative rectal sparing)
- After therapy-induced preferential histologic healing

Initial diagnosis on endoscopic biopsies

Subtyping of IBD on biopsies (as UC or CD):

Histologic features of CD in lower GI biopsies:

- Granulomas (present in up to 25% of patients),
- Chronic ileitis,
- Segmental pattern of inflammation with skip lesions
- Relative rectal sparing, or only patchy active and/or chronic inflammation without crypt destruction.

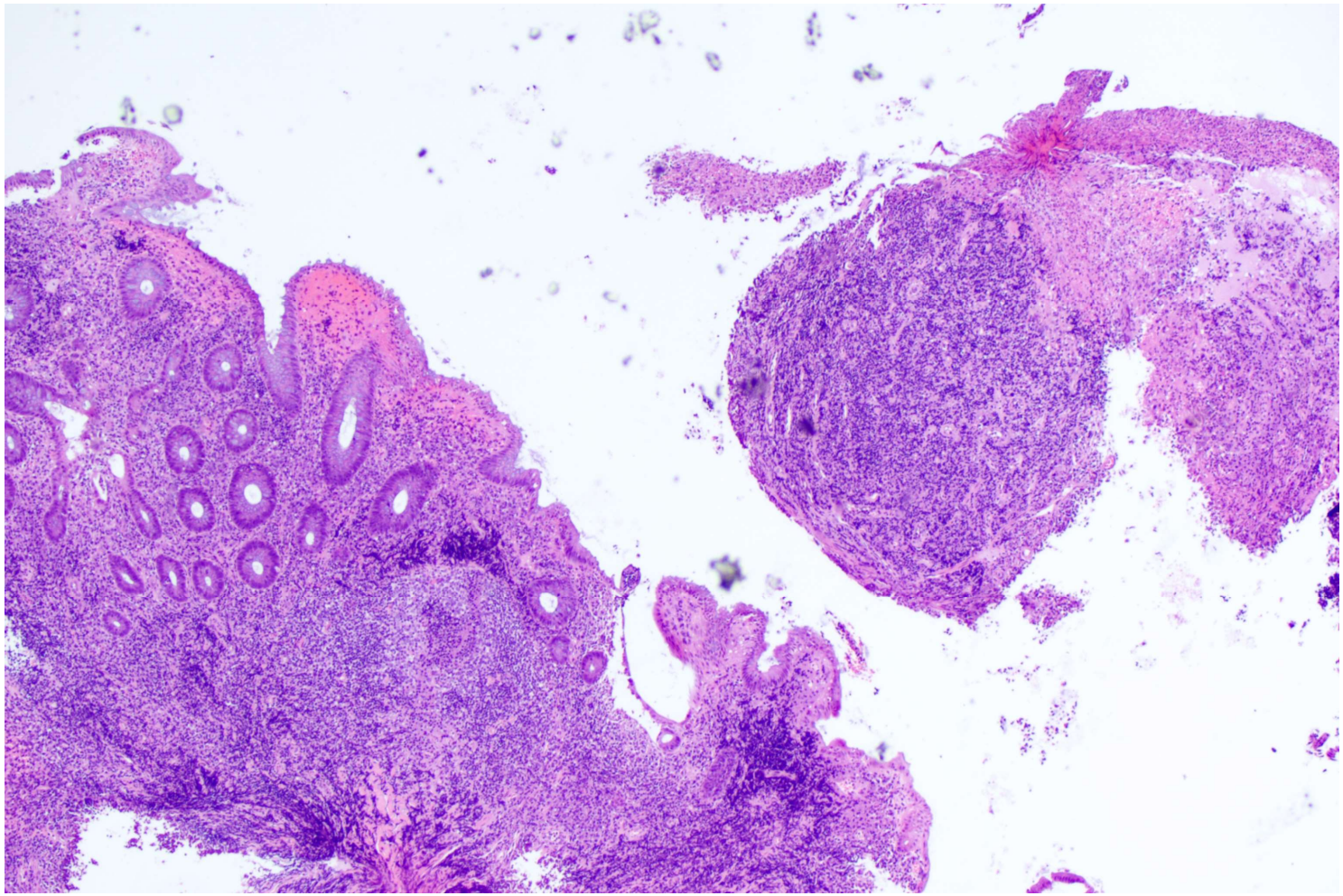
Assessment of the distribution of mucosal injury (i.e., segmental versus continuous) requires evaluation of biopsy specimens that follow specific protocols

Initial diagnosis on endoscopic biopsies

- Some authors use the term “IBD, unclassified” **(IBDU**) for cases of chronic colitis that cannot be subtyped, but this is not universally accepted.
- Reason: possible confusion with “**indeterminate colitis**,” a term specifically reserved only for resection specimens that show overlapping features between UC and CD, such that differentiation is not possible, despite adequate clinical and histologic data.

Initial diagnosis on endoscopic biopsies

- For cases of chronic colitis that cannot be subtyped, the descriptive term “**chronic active colitis**” is considered more appropriate by some, particularly in certain scenarios that preclude confident subclassification of IBD based on biopsy evaluation.
- Examples: cases of chronic active colitis without a complete set of biopsies, diffuse colitis with numerous granulomas related to crypt rupture, or predominantly right-sided chronic colitis.
- Regardless of the term used, **accompanying qualifiers** or notes following the diagnosis can contain additional information.



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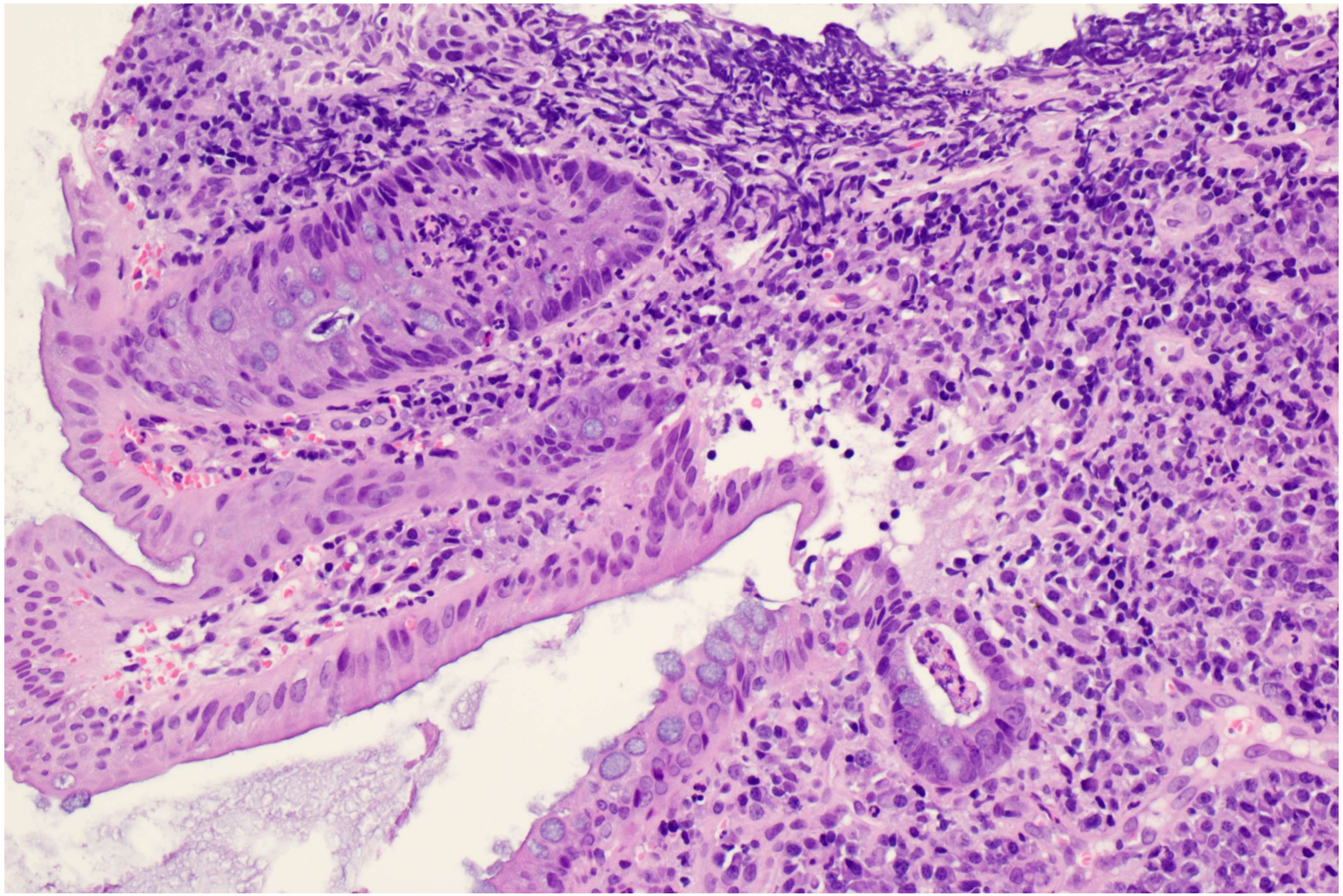
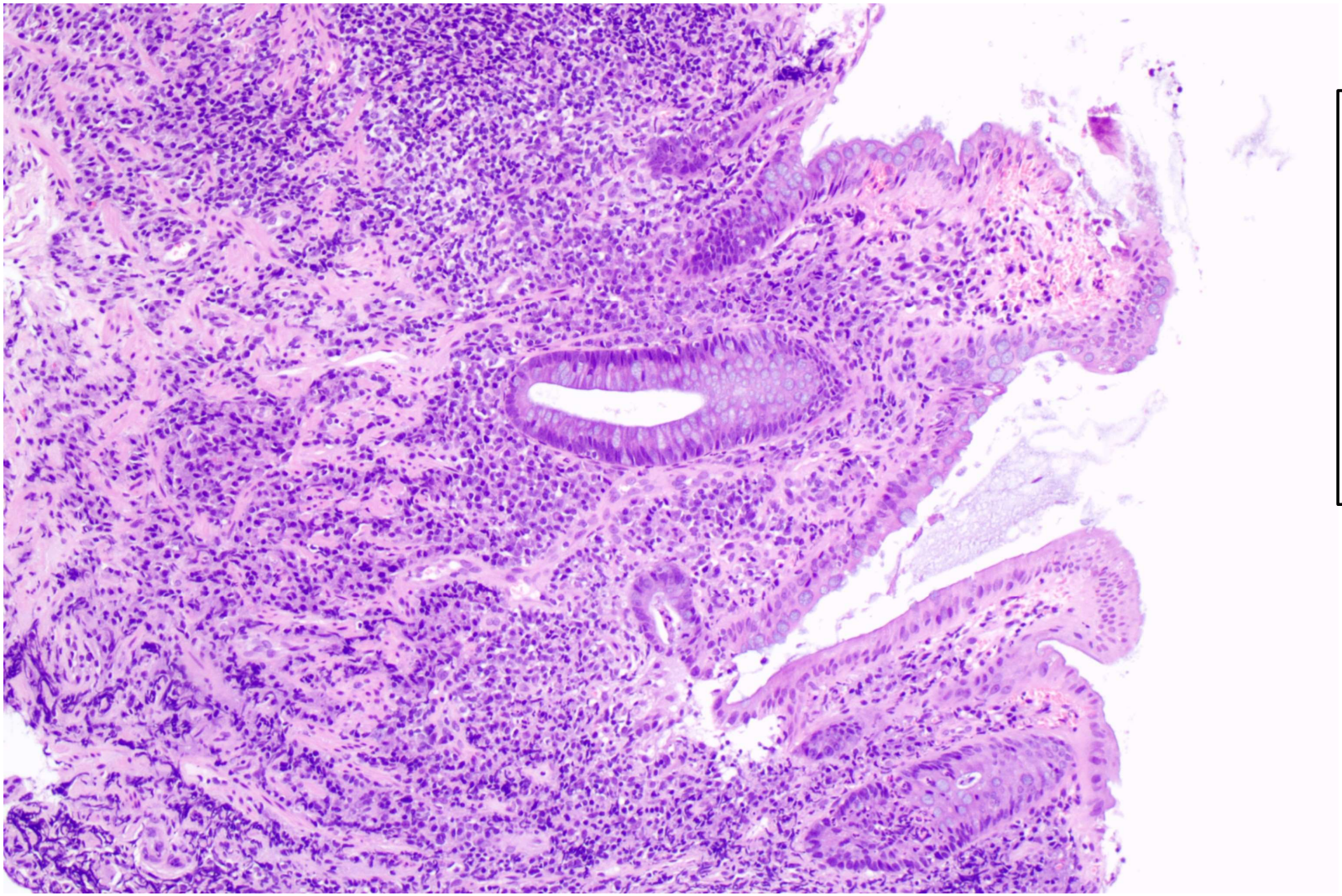
Rectal biopsy

- Villiform surface
- Transmucosal Chronic inflammatory cells
- Crypts apparently shortened
- Ulceration



- Crypt abscess
- Cryptitis
- Goblet cell depletion



- Transmucosal lymphoplasmacytic infiltrate
- Decreased crypt density
- Basal plasmacytosis

What is your diagnosis?

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Reporting on follow-up biopsies of IBD

Purposes:

- Monitoring of disease activity
- Evaluation of treatment effectiveness in clinical trials
- Evaluation for possible dysplasia or neoplasia
- Find out reason for treatment resistance, such as opportunistic infection

Reporting on follow-up biopsies of IBD

- Poor correlation between clinical symptoms, endoscopic appearance, and histologic findings in patients with IBD.
- Histologic activity, defined as the presence of neutrophilic inflammation, provides critically important information during the evaluation of disease outcomes.

Reporting on follow-up biopsies of IBD

- Segmental, patchy distribution of inflammation in CD practically necessitates sampling of **at least 5 intestinal segments** (ileum, right colon, transverse colon, left colon, and rectum).
- Microscopic heterogeneity may also be present in UC, particularly after treatment, and thus increasing the number of biopsy tissue fragments obtained (**2-3 vs. 1) per anatomic location**, ensures more accurate histologic assessment of disease activity.

Reporting on follow-up biopsies of IBD

- It is recommended that the **most severely inflamed** tissue fragment in each specimen container should determine what is reported.
- However, patchy distribution or severity of inflammation may be helpful histologic findings, and their presence should be noted.
- For ulcerative colitis, cumulative data suggest that residual histologic inflammation increase the risk for adverse patient outcomes.
- In contrast to UC, data regarding the potential benefit of achieving histologic remission in CD are less convincing.
- However, the nature of CD (patchiness and inflammation present deeper in the gut wall, where inflammation may be considerable) may hinder accurate assessment of disease activity in endoscopic mucosal biopsies.

Reporting on follow-up biopsies of IBD: UC

- In recent years, formal **systems for scoring** different histologic aspects in IBD have been proposed.
- These were designed as research tools, and frequently used in randomized control trials (RCTs) evaluating treatment efficacy.
- The best-established systems include the Geboes score (**GS**), Robarts Histopathology Index (**RHI**), and Nancy Histological Index (**NHI**). All 3 provide semiquantitative measures of neutrophilic inflammation and have been endorsed for use in clinical trials by expert panels.

Reporting on follow-up biopsies of IBD: UC

- The NHI was specifically developed with the goal of being simple, easy to use and largely reproducible.
- A grade (0-4) is assigned for each site biopsied, based on the most severely affected tissue fragment.
- A score of ≤1 represents histologic remission (i.e., absence of neutrophils).

Reporting on follow-up biopsies of IBD: UC

- In actual practice, whether histological scoring is required depends on needs of the corresponding multidisciplinary disease management team,
- But descriptive **indications of disease activity**, such as mild (rare neutrophils), moderate (numerous neutrophils in clusters or crypt micro-abscesses) and severe (erosions and/or ulcers) are almost equivalent to the NHI system and therefore also sufficient and should be clearing stated in the report.
- The presence of erosions/ulcers, equivalent to NHI grade 4 may be helpful to clinicians as they navigate management and should also be included.

Reporting on follow-up biopsies of IBD: CD

- Some histopathologic scores have been developed with the aim of being more applicable to **Crohn's Disease:**
- **GHAS (**Global Histological Activity Score) evaluates histologic features of disease activity and chronic injury, but in addition records the presence of granulomas and quantifies the number of affected biopsy fragments
- The **IBD-DCA** (Inflammatory Bowel Disease Distribution, Chronicity, Activity) score, was developed by international consensus to report overall measure of disease distribution at each anatomic site biopsied, rather than reporting the most severe degree of involvement. Biologic validation is still lacking for this method.
- Despite these specifications, consensus panels have proposed that NHI, GS, and RHI can also be used in CD.

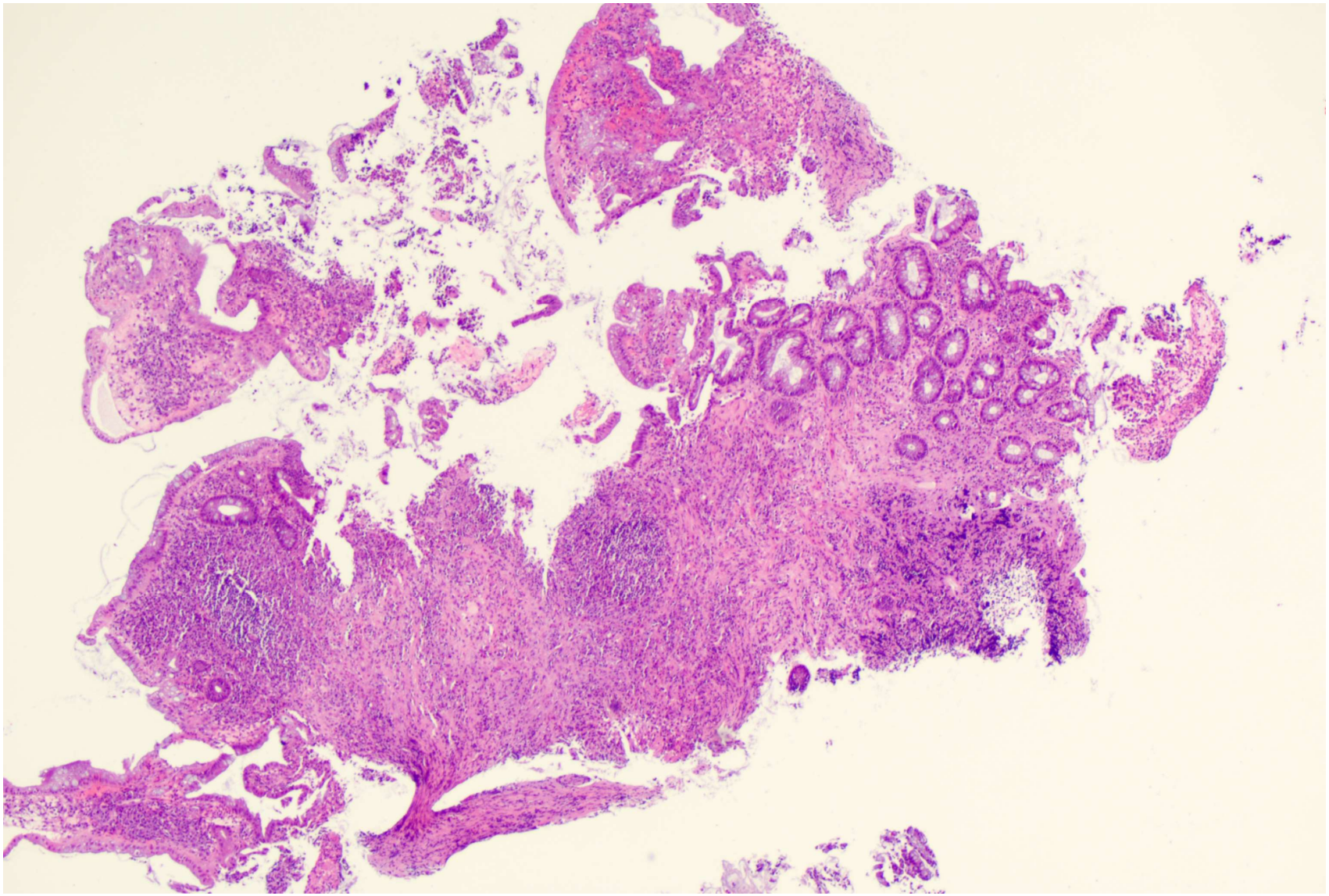
Reporting on follow-up biopsies of IBD

- **Histologic remission** is defined by most authors as the complete absence of mucosal neutrophils, including both in the epithelium and lamina propria.
- In practical terms, the NHI authors explicitly stated that this is equivalent to “no neutrophils in the biopsy specimen”.
- A consensus interpretation of the GS requires no neutrophils in the epithelium and no more than one extravascular neutrophil in the lamina propria.
- **Histologic improvement** is a softer target of treatment and may be defined as a 1-point reduction in the NHI score.

Reporting on follow-up biopsies of IBD

Superimposed infections

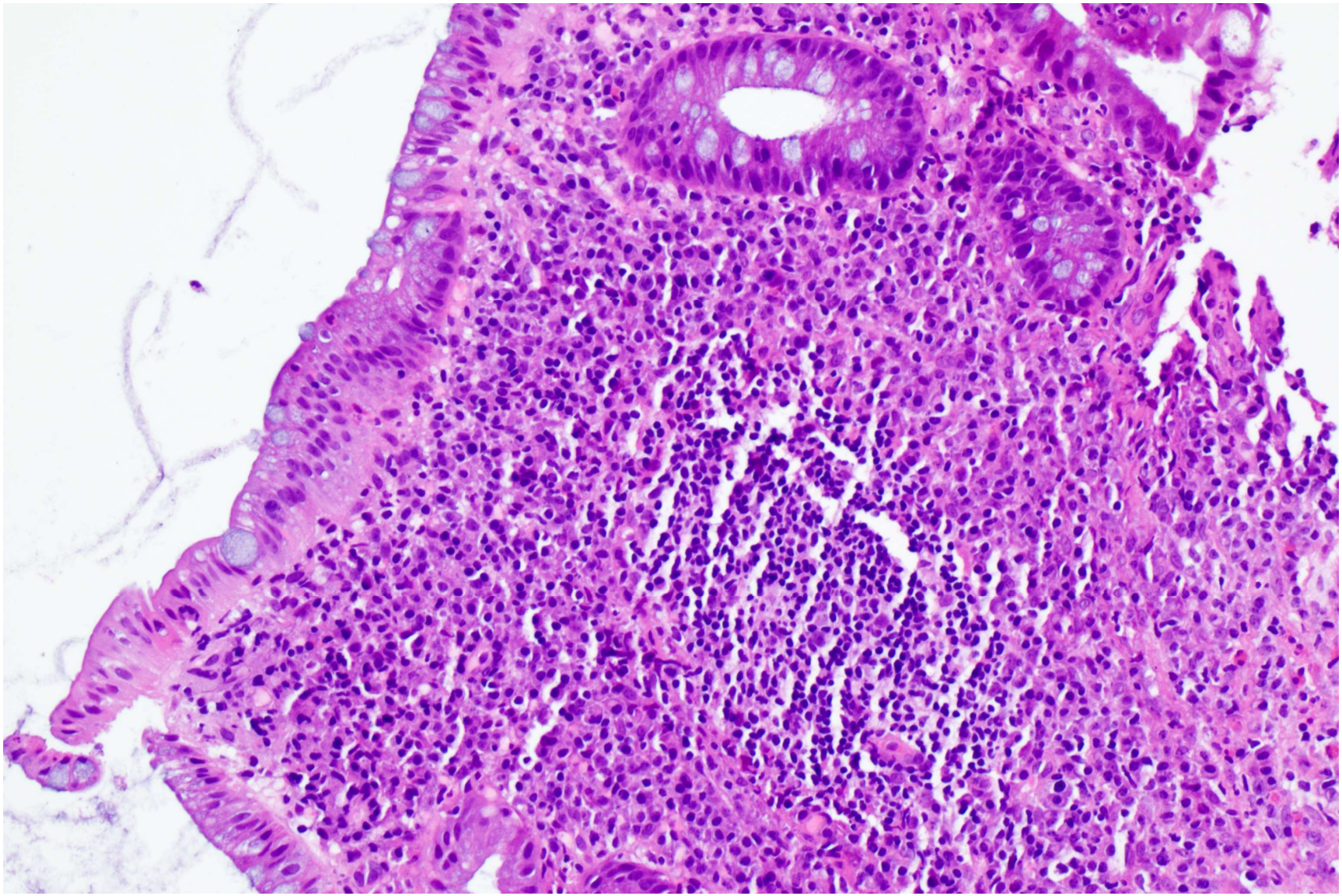
- **CMV** can be reactivated in IBD, especially in older patients and those requiring immunomodulators and corticosteroids.
- IHC is recommended for patients with severe colitis refractory to immunosuppression, especially in steroid-dependent patients, and in biopsies with prominent granulation tissue and/or large ulcers.
- Semi-quantitative assessment of IHC stains helps guide clinical management since certain cutoffs are associated with greater colectomy risk, whereas rare inclusions may indicate bystander effect in severely active IBD. But formal grading is premature at this time.

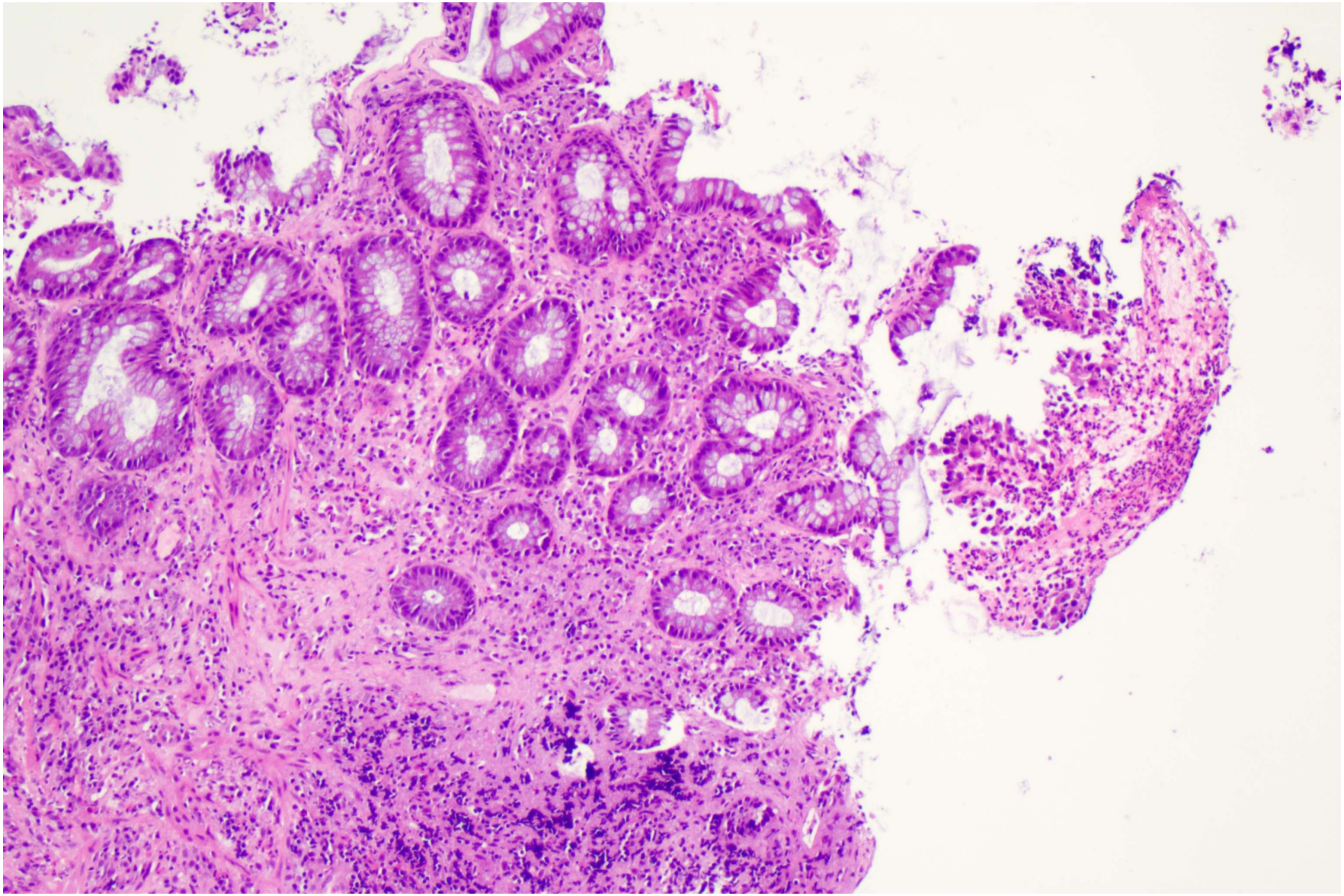


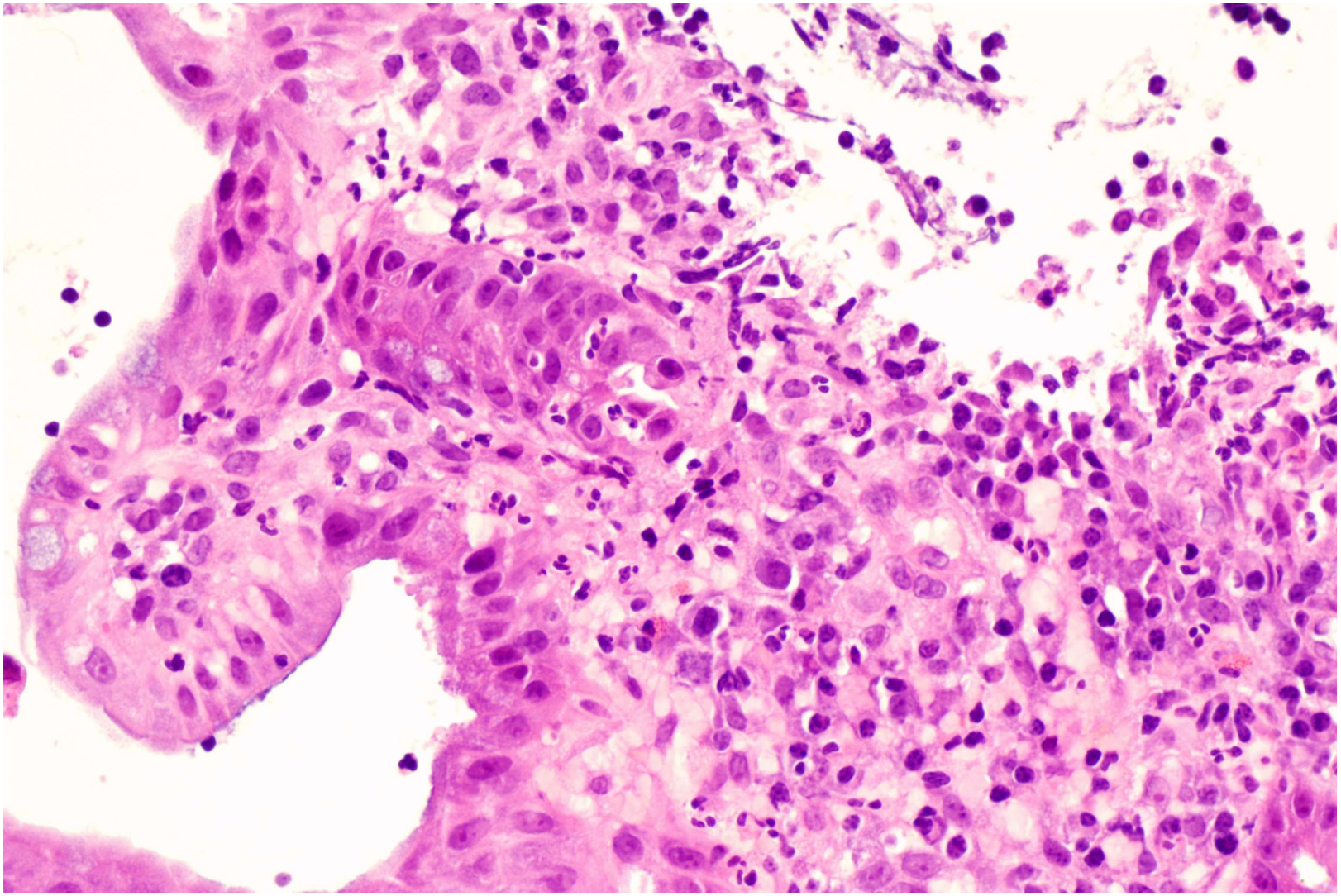
M/36

- Known UC
- On Steroid Enema
- FU biopsy

- Crypt distortion
- Patchy chronic inflammation
- Ulcer







How would you report on this case and any additional work up?

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Reporting on surgical specimens

- Approximately 20% of UC and up to 70% of CD patients ultimately require surgical intervention
- Indications include refractory disease, strictures or fistulae, and neoplasia.
- Pathological examination should **aim** at confirmation of diagnosis, evaluation for subtype, degree and extent of inflammation, and assessment for dysplasia and carcinoma.

Reporting on surgical specimens

- Surgical management of **UC** is usually reserved for patients with: 1) severely active, medically refractory disease, 2) fulminant colitis and/or toxic megacolon, 3) free perforation, or 4) neoplasia.
- Typically involves total proctocolectomy with end ileostomy or ileal pouch-anal anastomosis (IPAA)
- Indications for surgery in **CD** patients include: 1) severe, refractory colitis, 2) symptomatic stricture that is not amenable to medical or endoscopic treatment, or cannot be adequately surveilled endoscopically, 3) free perforation, 4) abscess, drainage, or enteric fistula that does not respond to medical therapy, 5) hemodynamic instability due to hemorrhage, and 6) neoplasia.
- Surgical specimens are more variable in CD.

Reporting on surgical specimens

- Regardless of specimen type, the general approach begins with review of the **clinical information** regarding the indication for resection, endoscopic findings and/or imaging results, mention of fistula, abscess or stricture, previous history of bowel resection, and prior diagnosis of neoplasia.
- Evaluation of the specimen should **document**: dimensions, orientation, and segments included; appearance, distribution, and severity of mucosal inflammation; wall thickness and stiffness; quality of serosa and mesentery as well as the presence of any adhesions or creeping fat; location and extent of any strictures, fissures, fistulae or abscesses; size, location, and extent of any polyps, plaques, or masses; and status of resection margins

Reporting on surgical specimens

Block taking:

- In general, 1-2 full-thickness sections per 10 cm or approximately 2 tissue blocks per colonic segment with 2 sections in each block, in addition to areas of diagnostic interest, including visible lesions.
- Representative sections of proximal and distal margins, terminal ileum, ileocecal valve, appendix, and lymph nodes are also recommended.
- In cases of known or suspected dysplasia, the protocol should double the number of sections, again focusing on areas of interest and visible lesions, with the latter entirely submitted or extensively sampled, and more generously sample lymph nodes.
- If obvious carcinoma is present, standard sectioning for tumors with harvesting of all regional lymph nodes should apply.

Reporting on surgical specimens

Subtyping IBD in resection specimen

- The pathologic distinction between UC and CD requires correlation with clinical, endoscopic, imaging, and laboratory findings.
- **UC** inflammation is classically mucosa-limited, and while it can often involve muscularis mucosae and even occasionally extend to the superficial submucosa, transmural inflammation and fibrosis are not typically present.
- **CD** is characterized by patchy, discontinuous, transmural inflammation and occasional nonnecrotic, noncryptolytic epithelioid granulomas. Deep fissuring ulcers that extend into muscularis propria, transmural chronic inflammation with linear arrays of lymphoid aggregates along the muscularis propria-subserosa border (away from ulcers), transmural fibrosis, neuromuscular hypertrophy, and fistulae favour CD over UC.

Reporting on surgical specimens

Subtyping IBD in resection specimen

- **Exception** : cases of fulminant UC may exhibit knife-like deep fissures that are largely composed of granulation tissue, as well as transmural inflammation and fibrosis.

Reporting on surgical specimens

Subtyping IBD in resection specimen

- Definitive distinction between UC and CD cannot be established with certainty in approximately 5-10% of IBD resection specimens that show overlapping features and which are often classified as "**indeterminate colitis**" (IC)
- This is a provisional label assigned until the natural history of the disease becomes evident: most patients ultimately prove to have UC.
- The term **"IBD, type indeterminate"** is advocated by Rodger C. Haggitt Gastrointestinal Pathology Society to replace the term indeterminate colitis.
- It should be restricted to IBD resection specimens for which the constellation of findings (current gross and histologic features, prior biopsy results, as well as clinical, endoscopic and radiologic data) cannot reliably distinguish between UC and CD, after uncommon, but well-known, variants of each have been excluded.

Reporting on surgical specimens: Margin status

Crohn's Disease

- Surgical resection is an important component of the clinical management in CD, but it is not curative, with up to 90% of patients experiencing endoscopic recurrence within 1 year and up to 35% of those requiring a second resection within 10 years.
- Employing conservative surgical approaches to preserve maximal intestinal length relies on the histologic evaluation of disease involvement at the resection margin.
- Histologically positive resection margins, regardless of the actual definition, are associated with increased overall, clinical, anastomotic, and surgical recurrence.

Reporting on surgical specimens: Margin status

Crohn's Disease

- The presence of **granulomas**, whether at initial diagnosis, on the resection margin, or in lymph nodes, has also been correlated with increased rates of CD recurrence in some studies.
- Many studies have reported that submucosal and/or myenteric **plexitis** at the proximal resection margin is associated with increased risk of postoperative clinical or endoscopic CD recurrence.

Reporting on surgical specimens: Margin status

Ulcerative Colitis

Active inflammation at the distal resection margin of proctocolectomy specimens is associated with complications of the subsequently created pouch, such as anastomotic leak, stricture, intra-abdominal abscess/infection, fistula, bowel obstruction, or pouchitis in some studies.

Pouchitis

- The most common complication of IPAA
- primary or secondary, due to an identifiable etiology such as ischemia or pathogenic infection
- Histologic evaluation of endoscopic biopsies should systematically assess the presence and degree of active and chronic inflammation, granulomas, and neoplasia, as well as features suggesting secondary etiology

Pouchitis

- **Crohn-like disease of the pouch (CLDP)**: non-necrotic, noncryptolytic granulomas in the pouch, pre-pouch ileum or rectal cuff; segmental inflammation, skip lesions, longitudinal ulcers, fistulae or strictures in the pouch or pre-pouch small bowel; late development of fistulae or abscess (6-12 months after stoma closure); and pre-pouch ileitis.
- Subclassified into inflammatory, fibrostenotic/stricturing, or fistulizing/penetrating phenotypes
- Diagnosis requires correlation of clinical, endoscopic, imaging and histological features, in the context of reviewing the original pathology diagnosis of the resection material.
- Non-healing ulcers or persistent strictures or fistulas in the pouch should also raise the differential diagnosis of neoplasia.

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Geboes score (GS) and the derived Robarts histopathological index (RHI).

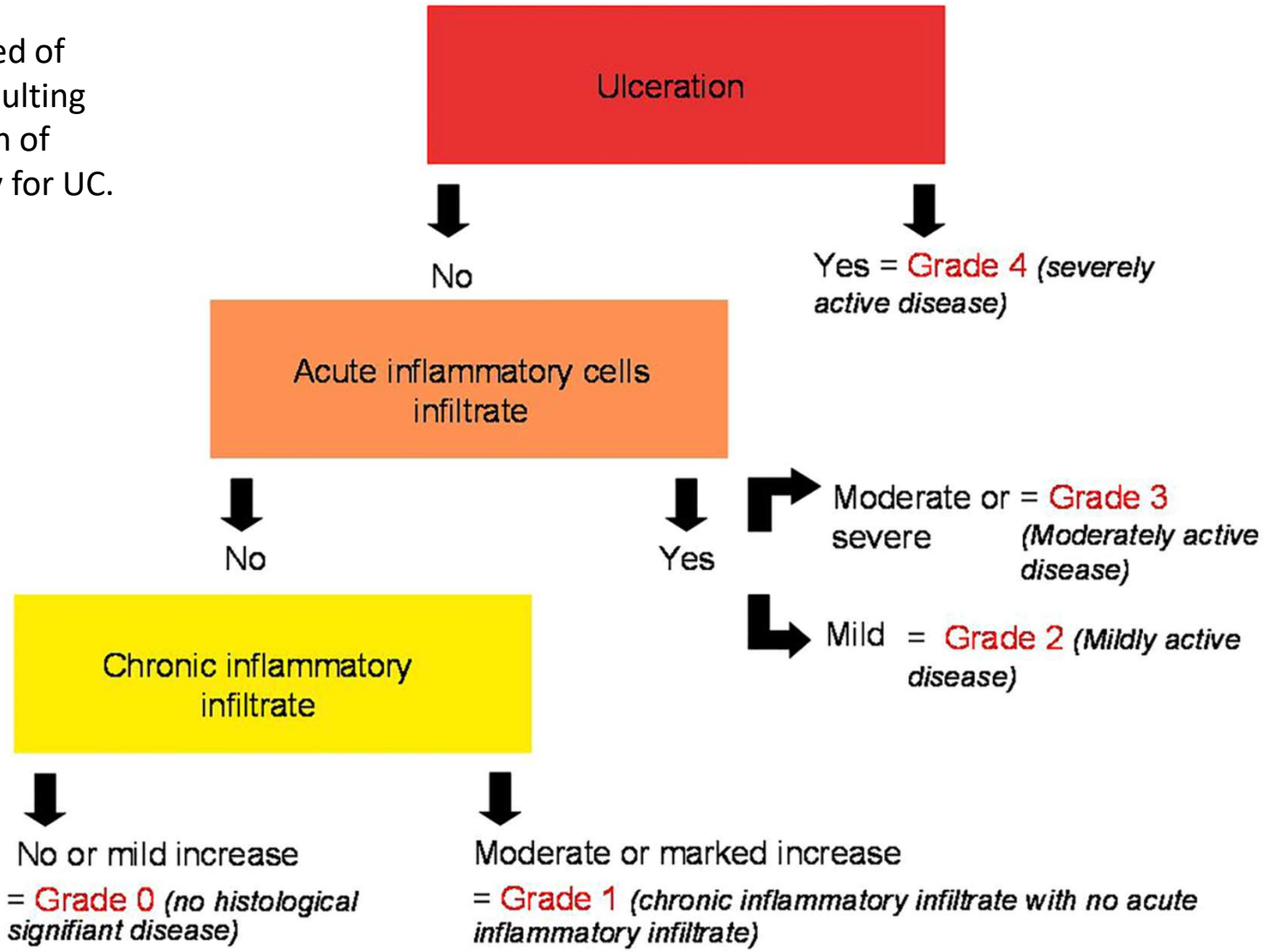
GS	Morphology	RHI
Grade 0: Architectural changes	0.0 No abnormality	0
	0.1 Mild abnormality	0
	0.2 Mild/moderate diffuse or multifocal abnormalities	0
	0.3 Severe diffuse or multifocal abnormalities	0
Grade 1: Chronic inflammatory infiltrate	1.0 No increase	0
	1.1 Mild but unequivocal increase	1
	1.2 Moderate increase	2
	1.3 Marked increase	3
Grade 2A: Eosinophils in lamina propria	2A.0 No increase	0
	2A.1 Mild but unequivocal increase	0
	2A.2 Moderate increase	0
	2A.3 Marked increase	0
Grade 2B: Neutrophils in lamina propria	2B.0 No increase	0
	2B.1 Mild but unequivocal increase	2
	2B.2 Moderate increase	4
	2B.3 Marked increase	6
Grade 3: Neutrophils in epithelium	3.0 None	0
	3.1 <5% crypts involved	3
	3.2 <50% crypts involved	6
	3.3 >50% crypts involved	9
Grade 4: Crypt destruction	4.0 None	0
	4.1 Probable–Local excess of neutrophils in part of the crypts	0
	4.2 Probable–Marked attenuation	0
	4.3 Unequivocal crypt destruction	0
Grade 5: Erosions and ulcerations	5.0 No erosion, ulceration or granulation tissue	0
	5.1 Recovering epithelium + adjacent inflammation	5
	5.2 Probable erosion—focally stripped	5
	5.3 Unequivocal erosion	10
	5.4 Ulcer or granulation tissue	15

Nancy index.

Grade	Morphology
0	No or only mild increase in chronic inflammatory cells
1	Moderate or severe increase in chronic inflammatory cells (lymphocytes, plasma cells, and eosinophils) defined as presence of an increase in chronic inflammatory cells that is easily apparent
2	Mild increase in neutrophils defined as few or rare neutrophils in lamina propria or in the epithelium that are difficult to see
3	Moderate or severe increase neutrophils defined as presence of multiple clusters of neutrophils in lamina propria and/or in epithelium that are easily apparent
4	Ulcers or erosions defined as loss of colonic crypts replaced with “immature” granulation tissue (disorganized blood vessels with extravasated neutrophils) or the presence of fibrinopurulent exudate

Histological remission = 0; histological response ≤ 1.

Algorithm of the **Nancy histological index** composed of three histological items resulting in a five-grade classification of histological disease activity for UC.



IBD-DCA score.

Parameter	Morphology
Distribution [D]	0 Normal
	1 <50% of tissue affected per same biopsy site
	2 >50% of tissue affected per same biopsy
Chronic features [C]	0 Normal
	1 Crypt distortion and/or mild lymphoplasmacytosis
	2 Marked lymphoplasmacytosis and/or basal plasmacytosis
Activity features [A]	0 Normal
	1 Two or more neutrophils in lamina propria in one high-power field [HPF] and/or intraepithelial neutrophils [any number] 2 Crypt abscesses, erosions, ulcers

Comparison Between Histologic Indices in Inflammatory Bowel Disease

Index	Indication	Advantages	Disadvantages	Implementation in Clinical Trials	Implementation in Clinical Practice
Geboes Score	Ulcerative colitis and likely Crohn disease	Evaluates a broad spectrum of histologic features, most commonly used	Complex score, not designed to be responsive	Yes	Difficult
Robarts Histopathology Index	Ulcerative colitis and likely Crohn disease	Designed to be responsive with a large dynamic range, commonly used	Requires calculation to arrive at the score	Yes	Unknown, likely not too difficult
Nancy Index	Ulcerative colitis and likely Crohn disease	Simple to score, commonly used	Captures only limited information	Yes	Easy
Global Histologic Disease Activity Index	Crohn disease	Most commonly used index in Crohn disease	Complex score, not designed to be responsive	Yes	Difficult
Harpaz Index	Ulcerative colitis	Simple to score	Captures only limited information	No	Easy
Chicago/Rubin Index	Ulcerative colitis	Simple to score	Captures only limited information	No	Easy
IBD-DCA* Score	Ulcerative colitis and Crohn disease	Relatively simple to score	Captures only limited information, limited data	No	Unknown, likely not too difficult

*Inflammatory Bowel Disease—Distribution, Chronicity, Activity.

Inflammatory Bowel Disease

- Basic Pathology of Inflammatory Bowel Disease
- Initial diagnosis on endoscopic biopsies
- Evaluation and reporting on follow-up biopsies
- Evaluation of surgical specimens
- Reporting systems for IBD mucosal biopsies
- Mimics of IBD
- Dysplasia in IBD

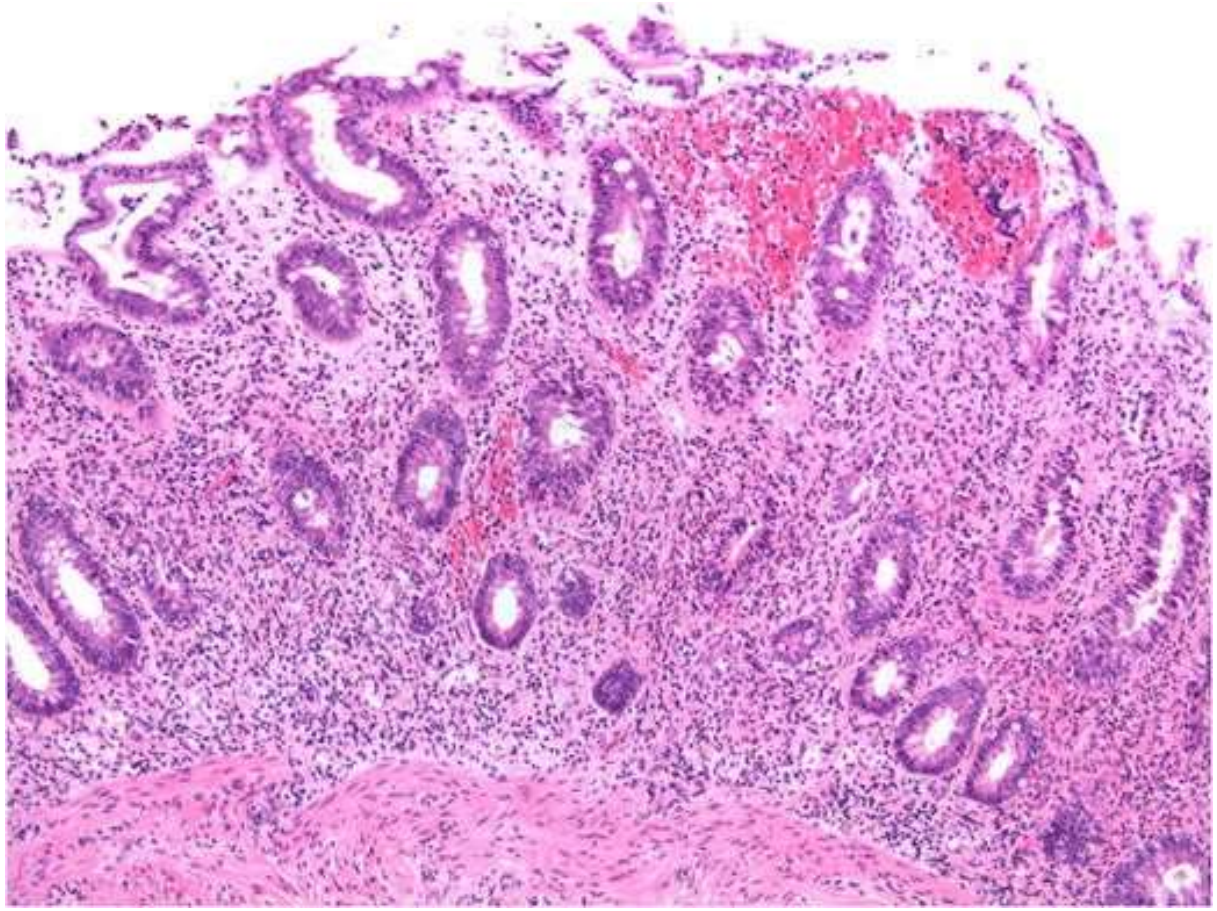
Mimics of IBD

- Infectious Colitis
- Drug induced mucosal damage (DIMI)
- Ischaemic enterocolitis
- Radiation enterocolitis
- Behcet's syndrome
- Segmental colitis associated with diverticulosis (SCAD)
- Microscopic colitis (MC)
- Malignant lymphoma and other tumours
- Endometriosis

Infectious Colitis

Histologic patterns of gastrointestinal infections

1. Infections producing essentially no histologic changes, or very minimal histologic changes (e.g. *Vibrio* species)
2. Infections that typically cause a nonspecific ‘acute infectious colitis’ or ‘acute self-limited colitis’ pattern (e.g. *Campylobacter*)
3. Infections that produce more specific or even diagnostic morphologic features (e.g. those with granulomas, pseudomembranes, or inclusions)



Campylobacter-associated infective colitis.

- Florid acute inflammation, in the crypt epithelium and in the lamina propria.
- Superficial mucosal oedema.
- Mucin depletion
- No significant crypt architectural distortion
- Predominance of acute inflammatory changes over chronic inflammatory changes that help differentiate infective, particularly bacterial, colitis from chronic inflammatory bowel disease

Infections mimicking IBD

- **Salmonella Species –** cause of food poisoning to typhoid fever
- Typhoid fever
  - Can produce bowel wall thickening, hyperplastic Peyer's patches, aphthoid ulcers overlying Peyer's patches, linear ulcers, full thickness ulceration, necrosis, perforation and toxic megacolon.
  - Histologically, Peyer's patches become hyperplastic, followed by inflammation and ulceration of the overlying epithelium.
  - The lymphoid follicles are then infiltrated and obliterated by macrophages. Mononuclear cells are the predominant inflammatory cells, whereas neutrophils are often less prominent.
  - Architectural distortion severe enough to mimic IBD

Infections mimicking IBD

- **Salmonella Species** – cause of food poisoning to typhoid fever
- Non-typhoid fever infection
  - Gross and histologic findings are often milder, The pathologic features are most often those of AITC,
  - But severe cases may have significant crypt distortion.

Distinction from IBD

- Crypt distortion is generally more pronounced in IBD than in salmonellosis, but there may be considerable overlap;
- Shorter duration of symptoms favours infection.
- Stool cultures are the very helpful, and blood cultures may also be helpful in cases of sepsis.

Infections mimicking IBD

- **Shigella Species**
- *Shigella dysenteriae* is the most virulent and most common in underdeveloped countries whereas *S. sonnei* is more common in developed countries.
- Symptoms: Fever, abdominal pain, Diarrhea, initially watery, followed by bloody, mucoid, and/or purulent diarrhea
- Left colon is often most severely affected, Initially, the distribution of colitis is often contiguous, mimicking ulcerative colitis. As infection resolves, involvement may be more patchy. The mucosa is hemorrhagic, and variably ulcerated.
- Early shigellosis typically has features of acute infectious colitis.
- As disease continues, mucosal destruction occurs, along with an expanded lamina propria containing many neutrophils and mononuclear cells. Marked architectural distortion can occur.
- **Clinical history** (particularly duration of symptoms and history of travel) may be very helpful in making a diagnosis. **Stool cultures** may also be very useful.

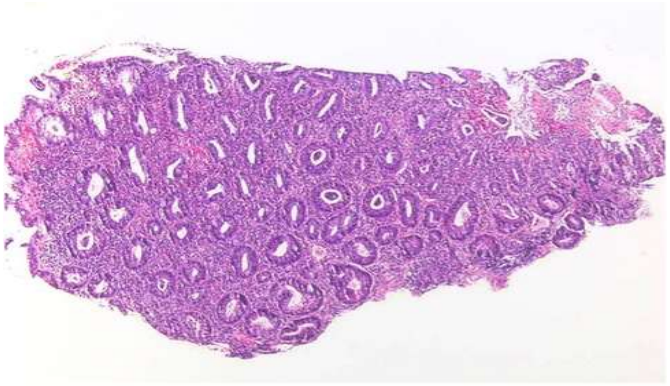
Infections mimicking IBD

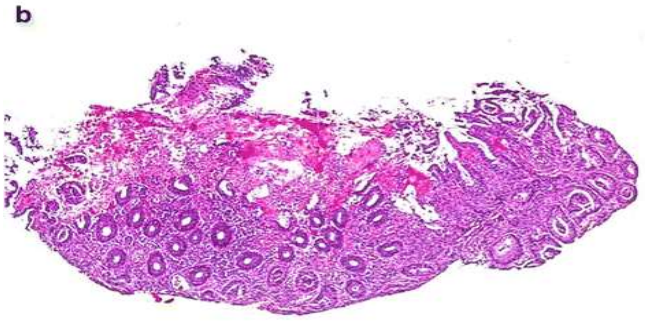
- **Yersinia Species**
- Most common cause of bacterial enteritis in Northern and Western Europe
- Found in a wide range of foods, including chicken, fish, shellfish, dairy products, beef, lamb, poultry, and pork products, as well as water.
- May cause diarrhea, abdominal pain, diarrhea, majority of infections are self-limited,
- Chronic infections have also been well documented
- Involves the ileum, right colon, and appendix preferentially,
- The involved bowel has an edematous, thickened wall with nodular inflammatory masses centred on Peyer's patches. Linear and/or aphthoid ulcers may be present as well.
- Either suppurative or **granulomatous** inflammation can be seen
- Architectural distortion, transmural lymphoid aggregates, and mural fibrosis may closely **mimic Crohn's disease**

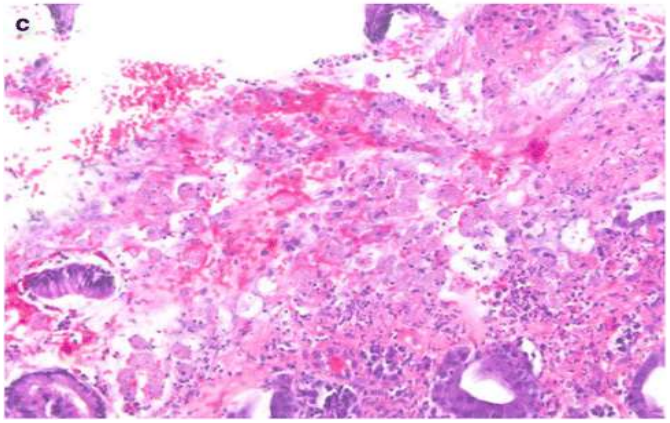
Infections mimicking IBD

- ***Entamoeba Histolytica***

- Infection is typically acquired through contaminated food or water
- Symptoms can be nonspecific, but in severe cases cramping abdominal pain, fever, and bloody or mucoid diarrhea can occur
- Cecum is most commonly involved, but any level of the large bowel can be affected.
- Endoscopically, small ulcers are the most common lesion, which may coalesce to form large ulcers, which undermine adjacent mucosa, classic '**flask-shaped**' lesion.
- Microscopic changes may be subtle. The earliest lesion is a mild neutrophilic infiltrate. In more advanced disease there may be deep ulcers (extending at least into the submucosa.
- Organisms may be found at the surface of the bowel, or within the ulcer beds. Abundant necroinflammatory debris is a frequent finding, and amoebae are generally found within it.
- Invasive amoebae are occasionally seen deep in the wall of the bowel. Gland distortion may be seen in adjacent mucosa.
- The presence of **ingested RBC** is pathognomonic of *E. histolytica*.







Sigmoid colon biopsy from a young man who presented with symptoms and endoscopic signs suggestive of chronic inflammatory bowel disease

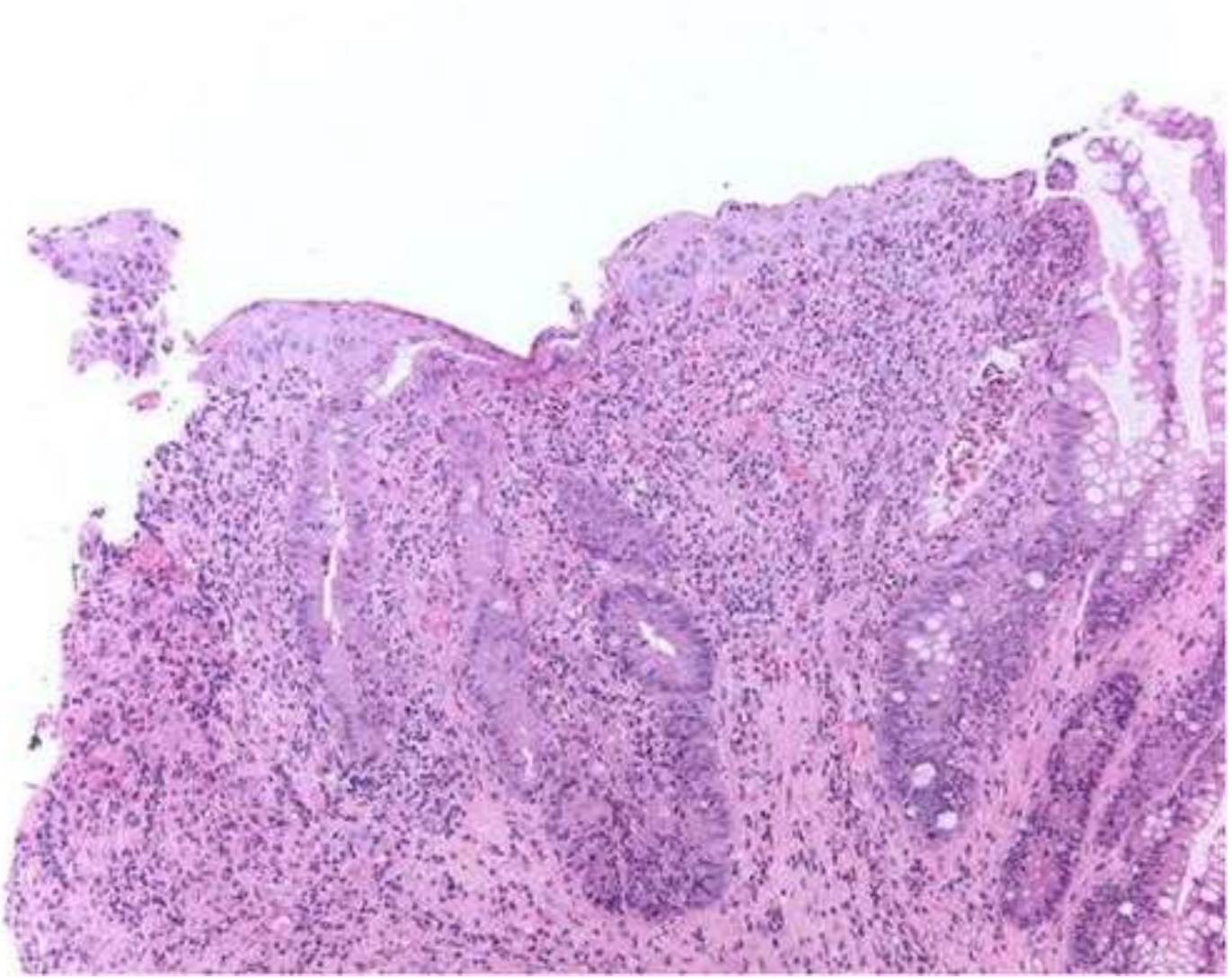
a. Chronic inflammatory changes and crypt architectural distortion, with a small amount of fibrinous exudate (top right)

b. Deeper section shows much more extensive exudate

c. High power of this fibrinous exudate and shows innumerable amoebic organisms. Intracellular red cells can be identified (bottom left).

Infections mimicking IBD

- **Lymphogranuloma venereum** caused by Chlamydia trachomatis
- Chronic ulcerative disease transmitted via anal inoculation
- Endemic disease in tropical and subtropical regions with increased incidence in the western population, especially **men who have sex with men**
- Most common presentation is proctitis syndrome: painful hemorrhagic proctitis, often mimicking inflammatory bowel disease
- Findings are usually restricted to rectum and anus
- Intense lymphohistiocytic infiltrate with prominent plasma cells and lymphoid aggregates, only mild to moderate acute inflammation,
- Minimal basal plasmacytosis and crypt distortion, only rare granulomas and Paneth cell metaplasia



Anorectal junction biopsy from a young man with clinical, radiological and endoscopic features suggestive of anorectal Crohn's disease

•M/E: Intense lymphohistiocytic infiltrate with prominent plasma cells and lymphoid aggregates, mild acute inflammation, minimal basal plasmacytosis and crypt distortion.

In fact, this was an MSM, HIV-positive man with anorectal LGV.

Drug-induced Colitis mimicking IBD

- The GIT has a somewhat limited repertoire of response to insults. Therefore, various drugs can yield the same histological patterns, and these can also overlap with non-drug mucosal injuries.
- A single drug can induce a variety of histopathological patterns of injury.
- **Proving a causal role between a drug and GI damage** requires, ideally, objective evidence of disease, a temporal association between the introduction of the medication and clinical presentation, resolution of symptoms upon cessation of the drug, recurrent symptoms upon reintroduction, and exclusion of all other possible causes.
- Histology in isolation often does not provide a definitive diagnosis of DIMI , a **multidisciplinary approach** is essential.

Histological Features and Patterns of Drug injury in the GIT :

- Focal or diffuse acute (active) colitis
- Chronic colitis (active or inactive)
- Apoptotic excess
- Dilated damaged crypts with apoptosis
- Coeliac disease-like pattern
- Microscopic colitis pattern
- Ischaemic colitis pattern
- Pseudomembranous colitis
- Erosions and ulcers
- Crystal deposition
- Pseudomelanosis coli
- Eosinophilia
- Malakoplakia
- Epithelial atypia

Drug-induced Colitis mimicking IBD

The three patterns of drug-induced colitis:

1. UC-like pattern with diffuse inflammation and ulceration. NSAID-related ulcers are found mainly in the right colon and are more common in elderly patients , while those associated with gold salts are responsible for limited damage to the rectum.
2. CD-like pattern, either with granulomas (associated with the use of diclofenac, naproxen, clofazimine or etanercept [77]) or without granulomas (in patients on immunosuppressive treatment or NSAIDs [78]).
3. A pattern similar to graft versus host disease, observed in patients taking mycophenolate.

Drug-induced Colitis mimicking IBD

Immune checkpoint inhibitors (ICI)-induced enterocolitis

- Monoclonal antibodies that target immune checkpoint proteins, such as cytotoxic T-lymphocyte associated protein (**CTLA**) (e.g., ipilimumab), programmed cell death protein 1 (**PD-1**) (e.g., nivolumab and pembrolizumab).
- ICI-induced enterocolitis resembles IBD at presentation by causing abdominal pain and diarrhoea, often with blood and mucus.
- Time to onset of symptoms is typically 6–8 weeks for anti- CTLA-4 agents and 3–6 months for anti-PD-1 therapy.
- Involvement of the colon can be diffuse (typical of anti-CTLA-4 agents), resembling UC, or may be segmental, resembling CD (more typical of anti-PD-1 agents).

Drug-induced Colitis mimicking IBD

Immune checkpoint inhibitors (ICI)-induced enterocolitis: Histological clues :

- Crypt epithelial cell apoptosis
- Atrophic crypts
- Intra-epithelial lymphocytosis (more than 10 intraepithelial lymphocytes within 100 surface epithelial cells)
- A mild (rather than moderate/severe) degree of CAD
- Less frequent basal plasmacytosis
- Lesser degree of cryptitis and crypt abscesses compared to UC.

A triad of active colitis, IELs and increased epithelial apoptosis occurs in about one third and may suggest ICI colitis.

Nevertheless, drug history is essential for diagnosis.

Drug-induced Colitis mimicking IBD

Phosphoinositide-3-kinase inhibitors

Idelalisib is a selective inhibitor of the delta isoform of phosphoinositide-3-kinase (PI3Kδ)

Can cause a continuous or focal colitis affecting either the entire colon or the left side.

Symptoms include watery, non-bloody diarrhoea (46% of patients), abdominal cramping, nausea, vomiting, and weight loss, with an average time to onset of 15 months.

Histologically, there may be overlap with IBD with cryptitis and crypt abscesses, erosions/ulcers, mild crypt architectural abnormalities, and Paneth cell metaplasia.

The most frequently observed histological features in **idelalisib-induced colitis** may also help discriminate from IBD, namely:

- An increase in IELs, comprising a mixture of small mature lymphocytes, and ‘activated’ lymphocytes with larger size, nucleomegaly, and irregular nuclear contours.
- Crypt epithelial cell apoptosis. 50% of cases show large “exploding’ apoptotic epithelial cells in crypts. Sometimes, this occurs without significant inflammation and may resemble GVHD.

Drug-induced Colitis mimicking IBD

Mycophenolate mofetil (MMF)

- Can cause nausea, vomiting, constipation, dyspepsia and watery or occasionally bloody diarrhea.
- Colonoscopy is often normal, but can show erosions, ulcers or patchy erythema, usually spares the rectum.
- Histologically it can cause lymphoplasmacytic lamina propria inflammation, Paneth cell metaplasia, and crypt loss.
- A ‘CD-like’ pattern of mucosal changes may occur, with patchy dense inflammation, erosions/ulcerations and lymphoid hyperplasia. An acute self-limited colitis or FAC can also occur.
- Increased crypt epithelial cell **apoptosis** is almost always prominent, GVHD-like.
- **Cystically dilated crypts** lined by flattened or atrophic epithelial cells also characteristic.

Drug-induced Colitis mimicking IBD

Nonsteroidal anti-inflammatory drugs

- Incidence of adverse effects approaches 70% with long term treatment.
- In the **stomach**, NSAIDs can cause reactive gastropathy or superficial mucosal necrosis.
- NSAID-induced **enteropathy** is increasingly common. It can be patchy with active inflammation, mucosal architectural distortion and pyloric metaplasia thus simulating CD.
- **Diaphragm disease** is a long-term complication usually affecting the small bowel. It is highly characteristic but not pathognomonic of NSAID injury.
- NSAIDs cause a broad spectrum of damage in the **colon** including IBD-like patterns. Histology microscopic colitis, eosinophilic colitis, ischaemic-type colitis and chronic colitis.

Drug-induced Colitis mimicking IBD

Other drugs

Colitis with clinical, endoscopic and histological features indistinguishable from IBD (predominantly UC) has also been reported following administration of **rituximab**, an anti-CD20 monoclonal antibody used in the treatment of conditions including B-cell malignancies and rheumatoid arthritis.

Segmental colitis associated with diverticulosis (SCAD)

- Histologically characterized by a transmucosal chronic inflammation associated with crypt distortion, basal plasmacytosis or granulomas
- May mimic UC and CD histologically
- Restricted to the mucosa of the interdiverticular area of the colonic segment that is affected by diverticular disease.
- Rectum is typically spared
- For a correct diagnosis, it is fundamental to know the endoscopic findings, the exact biopsy site and to compare the morphology of the affected area and the rectum in the differential diagnosis with IBD

Behcet's Disease

- A multi-systemic inflammatory disorder of an unknown etiology and shows a chronic recurrent clinical course.
- It is characterized by oral and genital ulcerations, ocular lesions, skin manifestations, arthritis, vasculitis, and gastrointestinal involvement.
- GI involvement (intestinal BD) in 3-60%, usually appear 4.5–6 years after the onset of the oral ulcers., the most common location of intestinal BD being the ileocecal area.
- The lesions are most commonly found in the terminal ileum, particularly in the area of lymphoid aggregates and Peyer's patches, and the cecum, and less frequently in the colon.
- Localised single or multiple ulcers in the ileocecal region.
- Histologically, **vasculitis** of the small veins and venules is common in cases of intestinal BD. It is characterized by a lymphocytic infiltrate. However, chronic **nonspecific** (sometimes transmural and granulomatous) inflammation with a normal intervening mucosal area may mimic CD.
- One must rely on the clinician to suggest the diagnosis

Inflammatory Bowel Disease

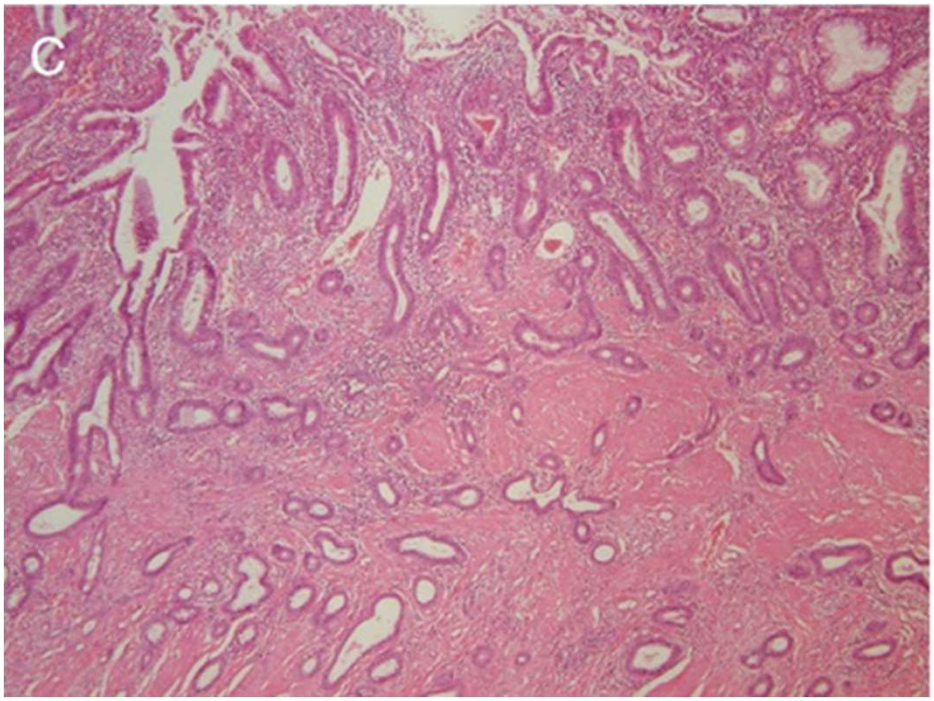
- Basic Pathology of Inflammatory Bowel Disease
- Initial diagnosis on endoscopic biopsies
- Evaluation and reporting on follow-up biopsies
- Evaluation of surgical specimens
- Reporting systems for IBD mucosal biopsies
- Mimics of IBD
- Dysplasia in IBD

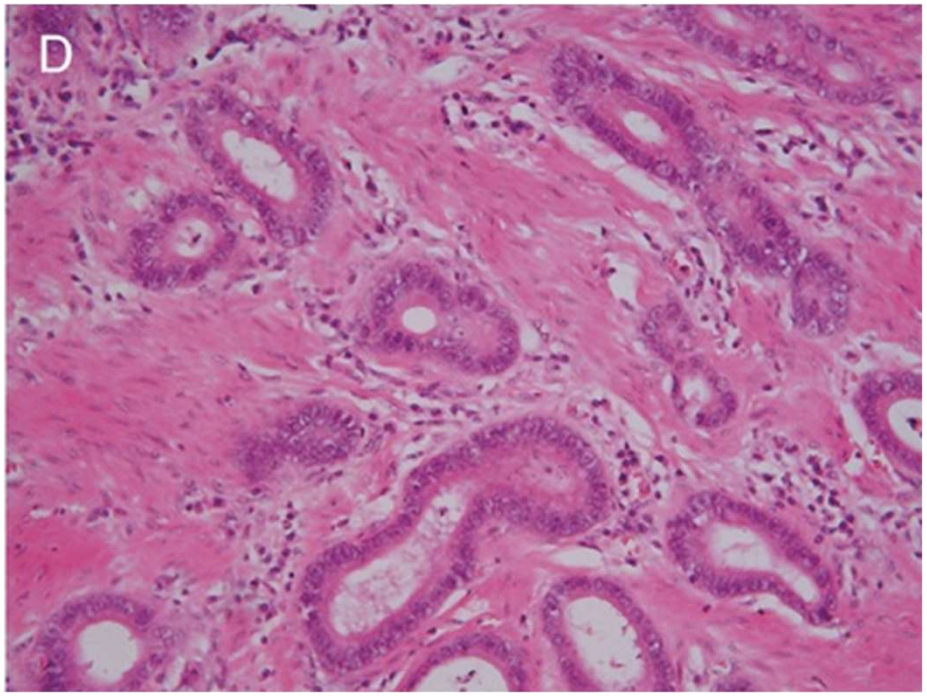
Dysplasia and Carcinoma associated with IBD

- Estimated risk of Colorectal Carcinoma of 1% at 10 years and 7% at 30 years
- Even higher in patients with IBD and concomitant primary sclerosing cholangitis (PSC).
- The pathogenesis of neoplasia in IBD is multifactorial: altered microbiome and repeated bouts of inflammation-induced injury result in genetic and epigenetic changes in patients with long-standing disease.
- Crypt stem cells develop **mutations (often in TP53 and/or KRAS**) that allow a selective growth advantage in the setting of chronic injury. These abnormal cells then recolonise injured mucosa, creating a **'field effect**'
- TP53 mutations and aneuploidy, can be detected in the injured mucosa, even in the absence of recognisable dysplasia
- Some IBD-associated CRC patients show hypermutation linked to defects in mismatch repair (e.g. MLH1) or proofreading (e.g. POLE) mechanisms.

Colitis-associated carcinoma (CAC)

- CAC often **lacks APC mutations**, in contrast to many sporadic lesions in which APC mutations occur early in the adenoma-to-carcinoma sequence.
- **TP53** is the most commonly identified mutation. It occurs earlier in the neoplastic process.
- Higher rates of **aneuploidy**, IDH1 mutations, MYC amplification, and chromosomal instability.
- Often shows mucinous and signet ring morphology, with a subset of cases showing a unique **low-grade tubuloglandular** morphology.
- **Loss of SATB2** immunohistochemical (IHC) expression can be seen, with one study showing loss in 50% of CAC and 40% of associated dysplastic lesions.





LGTGA (low-grade tubuloglandular adenocarcinoma**)**

- Similarity of well-differentiated invasive glands to overlying low-grade dysplastic colonic crypts
- Paucity of desmoplastic stromal reaction.
- Frequent coexpression of CK7 and CK20, and frequent silencing of hMLH1.

Dysplasia in IBD

Conventional Dysplasia

- Resembles the dysplasia seen in sporadic colorectal adenomas.
- Typically involves the crypts uniformly and extends to the surface epithelium.
- **Low-grade dysplasia**: Mildly enlarged, elongated, hyperchromatic, stratified and crowded nuclei that are mostly confined to the basal half of the cell cytoplasm. Surface involvement of the mucosa is key to the diagnosis.
- **High-grade dysplasia:** Dysplastic cells show markedly enlarged, often pleomorphic, round, hyperchromatic nuclei, often with prominent nucleoli, loss of nuclear polarity and full-thickness stratification of nuclei. It is often, but not necessarily accompanied by architectural atypia.

Dysplasia in IBD

Nonconventional Dysplasia

- Recently, several new patterns of dysplasia have been described.
- Show clinicopathological differences from conventional dysplasia.
- Often under-recognized
- Harbor an increased risk of developing advanced neoplasia compared with conventional dysplasia

Dysplasia in IBD

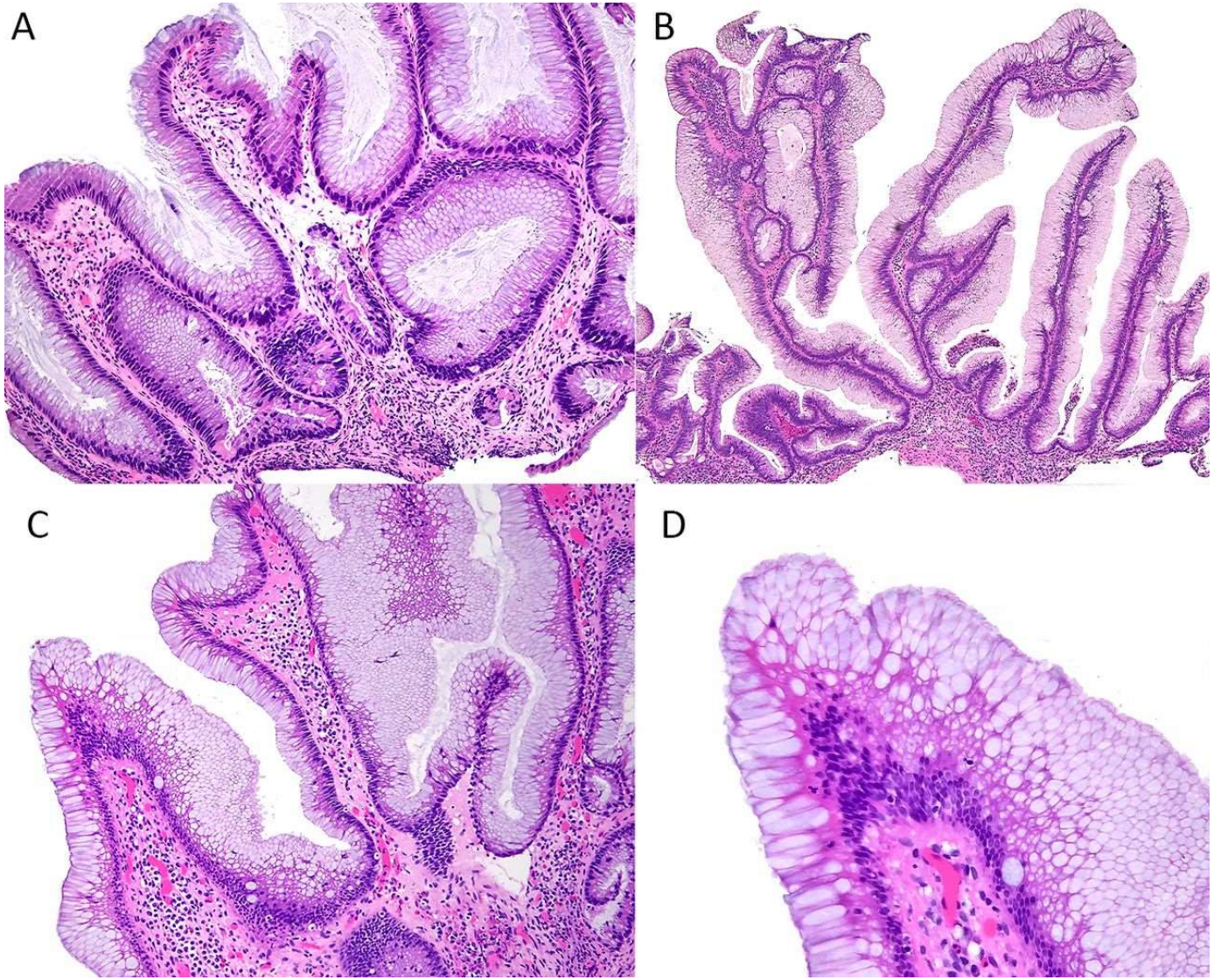
Nonconventional Dysplasia

- Hypermucinous Dysplasia
- Goblet Cell Deficient Dysplasia
- Basal crypt dysplasia
- Crypt cell Dysplasia
- Dysplasia with increased Paneth cell Differentiation
- TSA-like
- SSA-like
- Serrated dysplasia, not otherwise specified

Dysplasia in IBD

Hypermucinous Dysplasia

- Also referred to as gastric dysplasia
- Initially described as a polypoid lesion in the distal colon, may also be endoscopically invisible and occur throughout the colon
- Villous or tubulovillous architecture, lined by tall, mucinous columnar epithelial cells with a **gastric foveolar-like** morphology.
- The degree of cytological atypia often decreases at the villous tip surface and can have a **deceptively benign appearance**.
- Often has aberrant p53 expression, aneuploidy, high prevalence of KRAS mutations. Often found adjacent to mucinous adenocarcinoma.

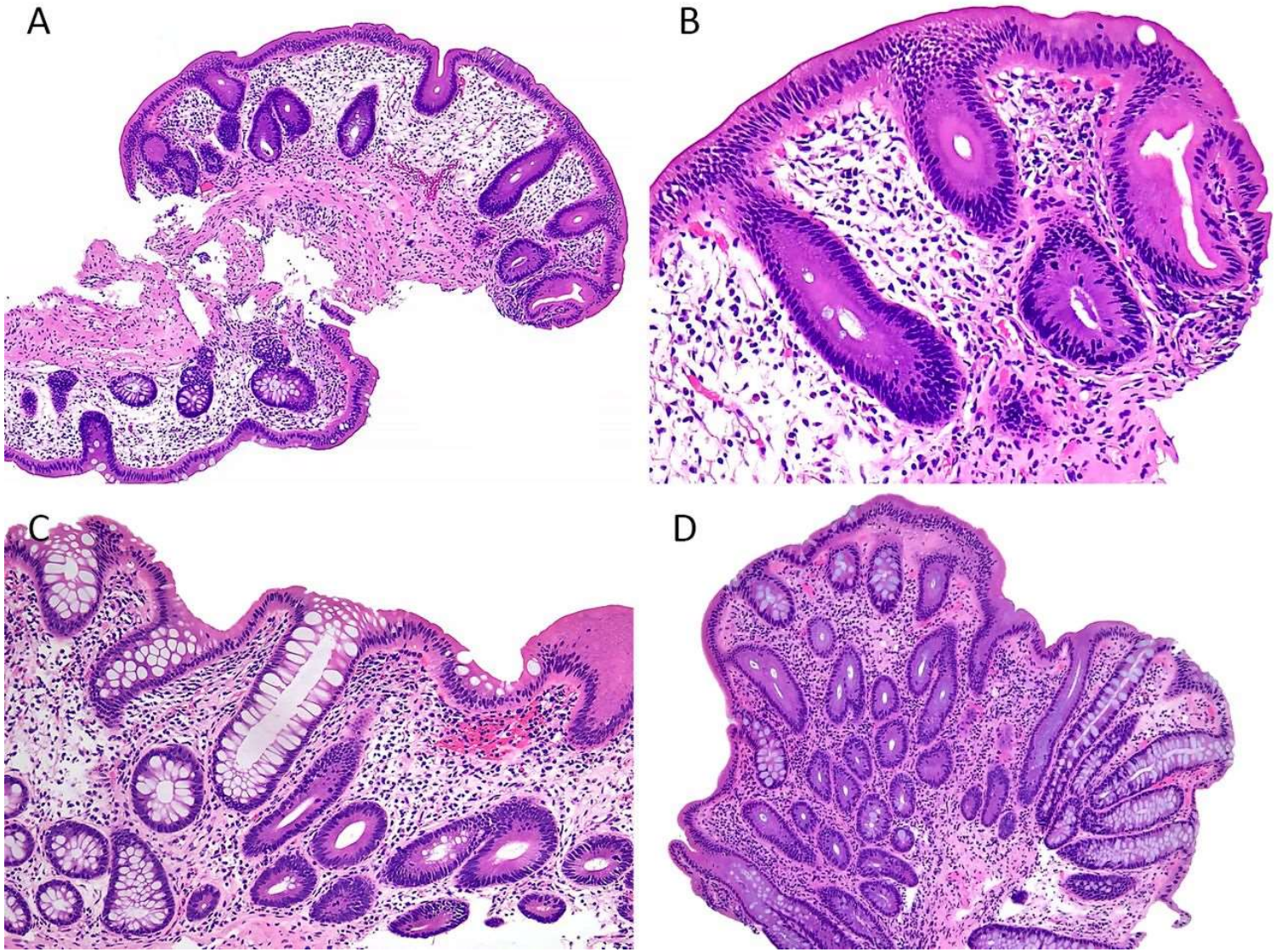


Hypermucinous Dysplasia

Dysplasia in IBD

Goblet Cell Deficient Dysplasia

- Often endoscopically invisible
- Tubular growth pattern without architectural complexity
- Nuclei are mildly hyperchromatic and penicillate to oval in shape.
- Goblet cells are absent or markedly reduced, leading to a **distinctly eosinophilic cytoplasm**
- High rates of advanced neoplasia within the same segment of the colon on follow-up
- Various mutations in TP53, KRAS and PIK3CA have been identified
- Must be distinguished from loss of goblet cells that typically occur in damaged mucosa.
- May consider a diagnosis of indefinite for dysplasia in the setting of active inflammation.

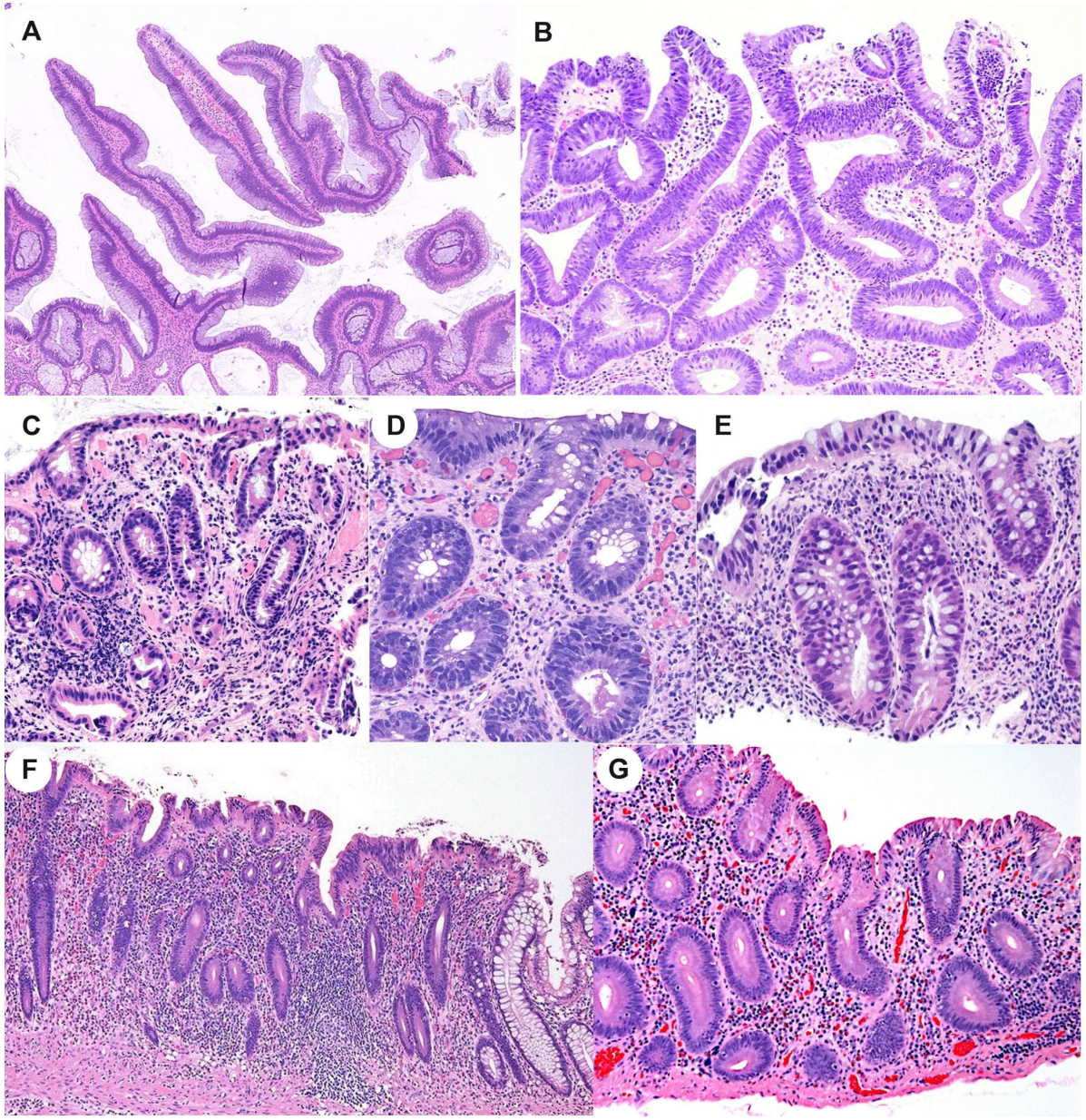


Goblet Cell Deficient Dysplasia

Dysplasia in IBD

Crypt cell atypia/dysplasia

- Also termed dysplasia with terminal differentiation
- Not to be confused with basal crypt dysplasia
- Dysplastic epithelium characteristically shows non-crowded, flat, tubular growth pattern
- Crypts are lined by enterocytes and interspersed goblet cells in roughly comparable proportions
- The cell nuclei are typically enlarged, hyperchromatic, round to slightly ovoid, usually contain dense or clumpy chromatin and may sometimes also contain prominent nucleoli.
- The atypical cells of this lesion **extend to the surface epithelium** with very little, or no, reduction in nuclear size and atypia.



Conventional dysplasia:
resembles sporadic tubulovillous or tubular adenoma

Crypt cell dysplasia

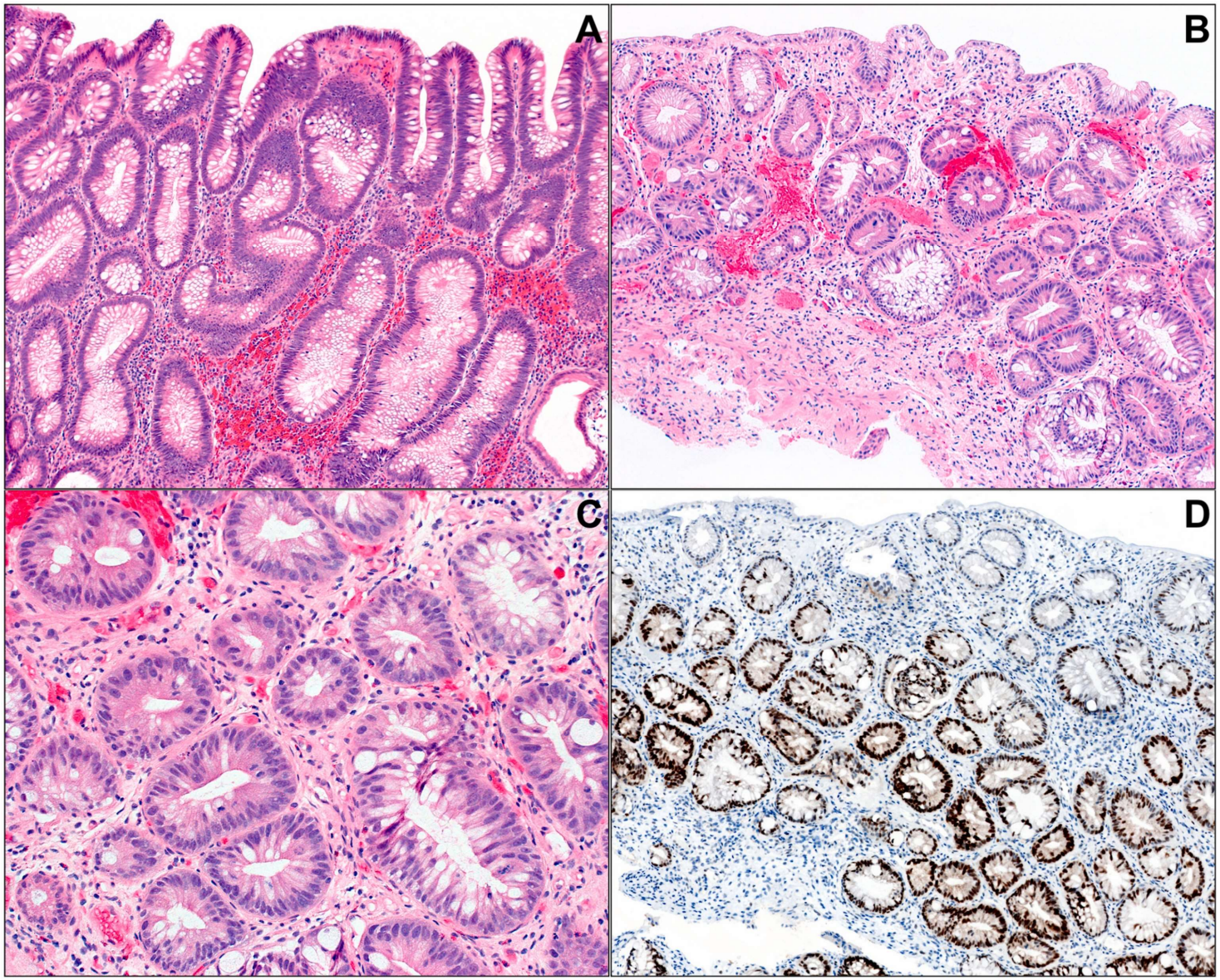
Goblet cell deficient dysplasia

Dysplasia in IBD

Basal crypt dysplasia

- More common in pediatric IBD patients than adult IBD patients.
- Most cases occur in ulcerative colitis, typically in patients with long-standing disease.
- Often flat, invisible endoscopically, and lacks significant architectural atypia.
- Characterized by mildly enlarged, crowded, hyperchromatic, round to oval or slightly elongated nuclei confined to the basal portions of the crypts without surface involvement.
- Histologically low grade
- Aberrant **p53** and aneuploidy, found next to high-grade dysplasia or carcinoma
- Advised to use p53 as adjunct in diagnosis

Conventional Dsyplasia



Basal Crypt Dysplasia, low-power view

Basal Crypt Dysplasia. Medium-power view

Strong, diffuse nuclear p53 immunoreactivity (overexpression pattern) in dysplastic crypts

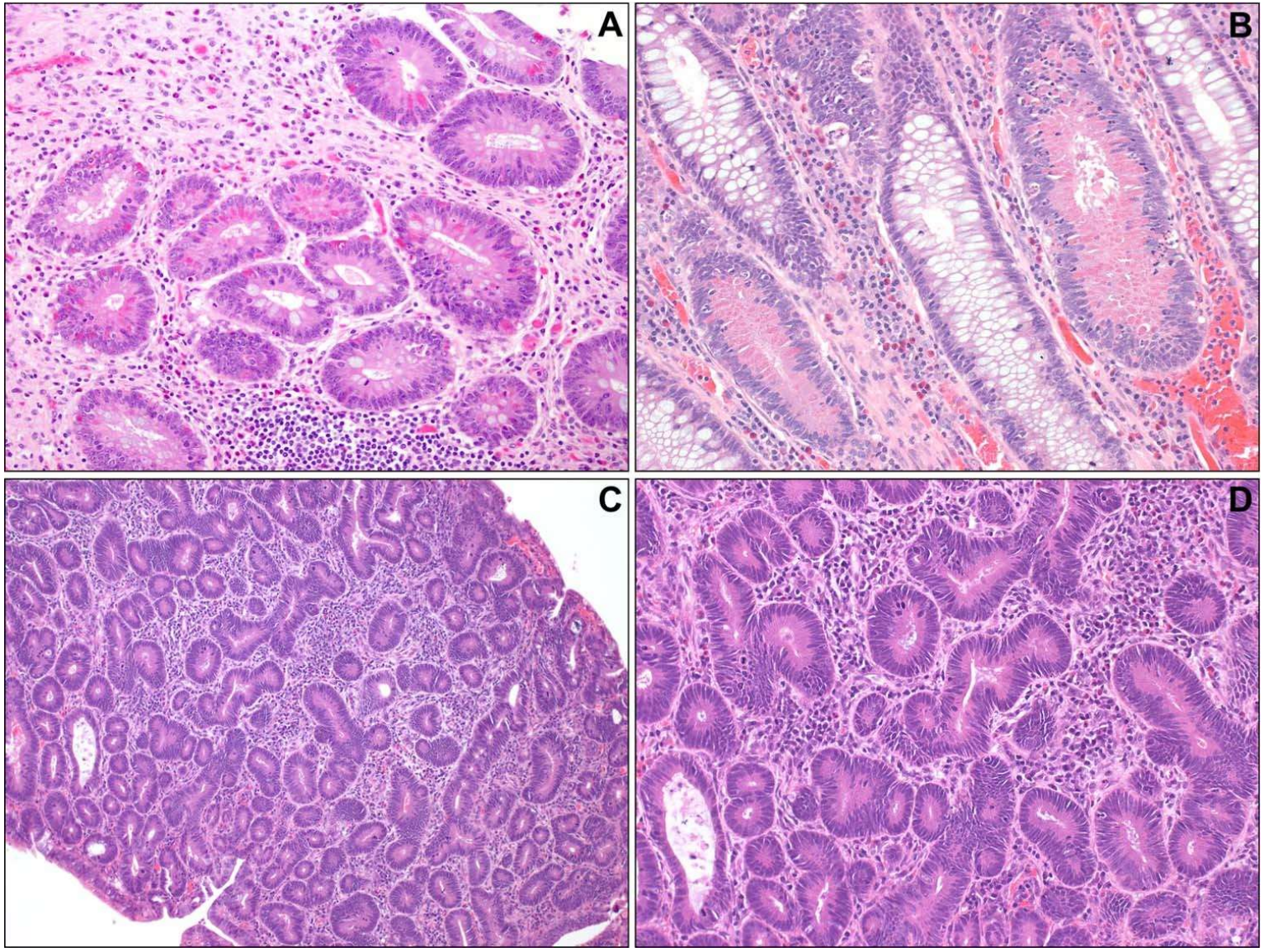
Dysplasia in IBD

Dysplasia with increased Paneth cell differentiation

- Often presents as a polypoid lesion.
- Morphologically resembles conventional adenomatous dysplasia but with increased Paneth cells involving at least two sequential crypts in two separate foci.
- Comparatively low rate of aneuploidy
- Lower risk of progression to advanced neoplasia, equivalent to a low-risk dysplastic lesion.

Dysplasia with increased Paneth cell differentiation

Goblet cell Deficient Dysplasia



Dysplasia in IBD

Serrated Dysplasia/Lesion

- Serrated dysplastic lesions in IBD are usually polypoid.
- more common in patients with long-standing IBD
- Include SSL-like lesion, TSA-like lesion and serrated lesion NOS

- The short-term risk of neoplastic progression of these lesions appears to be low.

Dysplasia in IBD

TSA-like dysplasia/lesion

- A serrated lesion, often with tubulovillous or villous architecture.
- The nuclei are hyperchromatic and pencillate. The cells have abundant eosinophilic cytoplasm.
- Ectopic crypt foci are commonly present.
- Aberrant p53 IHC staining was identified in 48% of lesions in one study
- No aneuploidy detected
- harbour KRAS or BRAF mutations.

Dysplasia in IBD

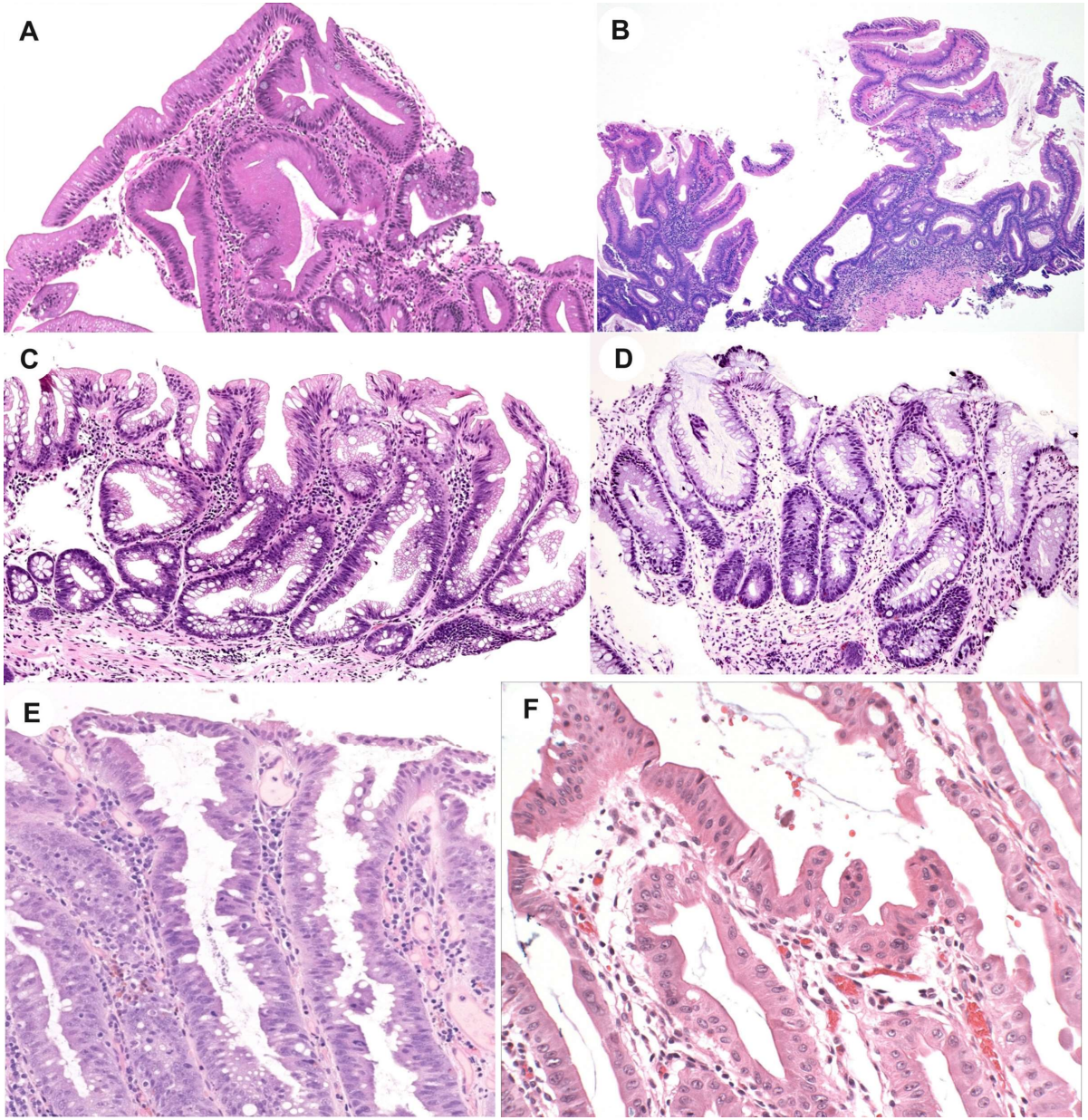
SSL-like dysplasia/lesion

- Often seen in the right colon.
- Has similar serrated/hyperplastic morphology with abnormal basal crypt dilatation as seen in sporadic lesions.
- While a subset of these lesions harbour BRAF mutations, other studies have shown an increased number of KRAS mutations.

Dysplasia in IBD

Serrated dysplasia/lesion, NOS

- Complex serrated profile without features of TSA-like dysplasia or SSL-like dysplasia
- Shows varying degrees of cytologic or architectural atypia,
- More commonly low grade dysplasia

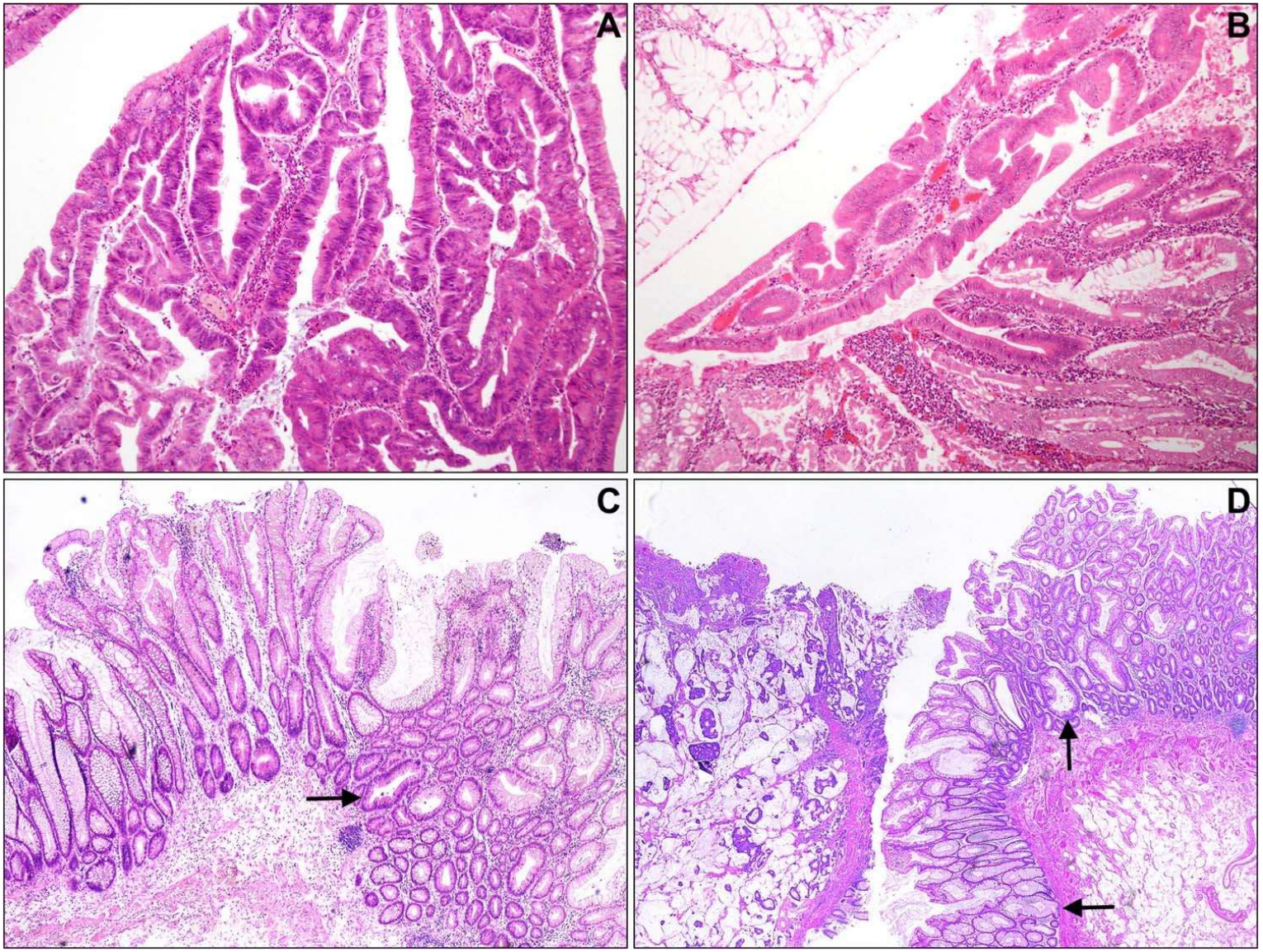


Traditional serrated adenoma (TSA)-like dysplasia

Sessile serrated lesion (SSL)-like dysplasia

Serrated dysplasia NOS

TSA-like lesion: elongated nuclei with intensely eosinophilic cytoplasm and ectopic crypts



TSA-like lesion, with hyper-mucinous dyplsia in tope left corner

SSL-like lesion: serration and dilation at the crypt base and surface

SSL-like lesion: Dilated L-shaped crypts at the interface with muscularis mucosa. Mucinous Ca on left side.

Morphological, prognostic and molecular features of non-conventional dysplasia

	Hypermucinous	Goblet cell deficient	Basal Crypt dysplasia	Dysplasia with Paneth-cells	TSA like	SSA like
Histological subtype	Gastric	Intestinal	Intestinal	Intestinal	Serrated	Serrated
Architecture	Villous or tubulovillous	Tubular	Preserved	Tubular	Villous or tubulovillous	Tubular
Morphological features	Columnar, mucinous epithelium (foveolar-like), with mild nuclear atypia most prominent in crypts	Absent or markedly reduced goblet cells with prominent eosinophilic cytoplasm	Mildly enlarged, hyperchromatic, round to oval, irregular nuclei, without overt surface involvement	Increased Paneth cells involving at least two sequential crypts in two different foci	Columnar cells lined by elongated hyperchromatic pencillate nuclei, abundant eosinophilic cytoplasm, and ectopic crypt foci	Abnormal dilatation of basal crypt as seen in sporadic lesions (lateral spread)
Endoscopic appearance	Mostly polypoid	Often invisible	Usually invisible	Often polypoid	Often polypoid	Often polypoid
Suspected risk of developing HGD/CRC	High	High	High	Similar to conventional	Similar to conventional	Similar to conventional
Molecular	KRAS Aneuploidy TP53	TP53, KRAS, PIK3CA, Aneuploidy	Aneuploidy TP53		KRAS BRAF	BRAF KRAS

Dysplasia in IBD - Reporting

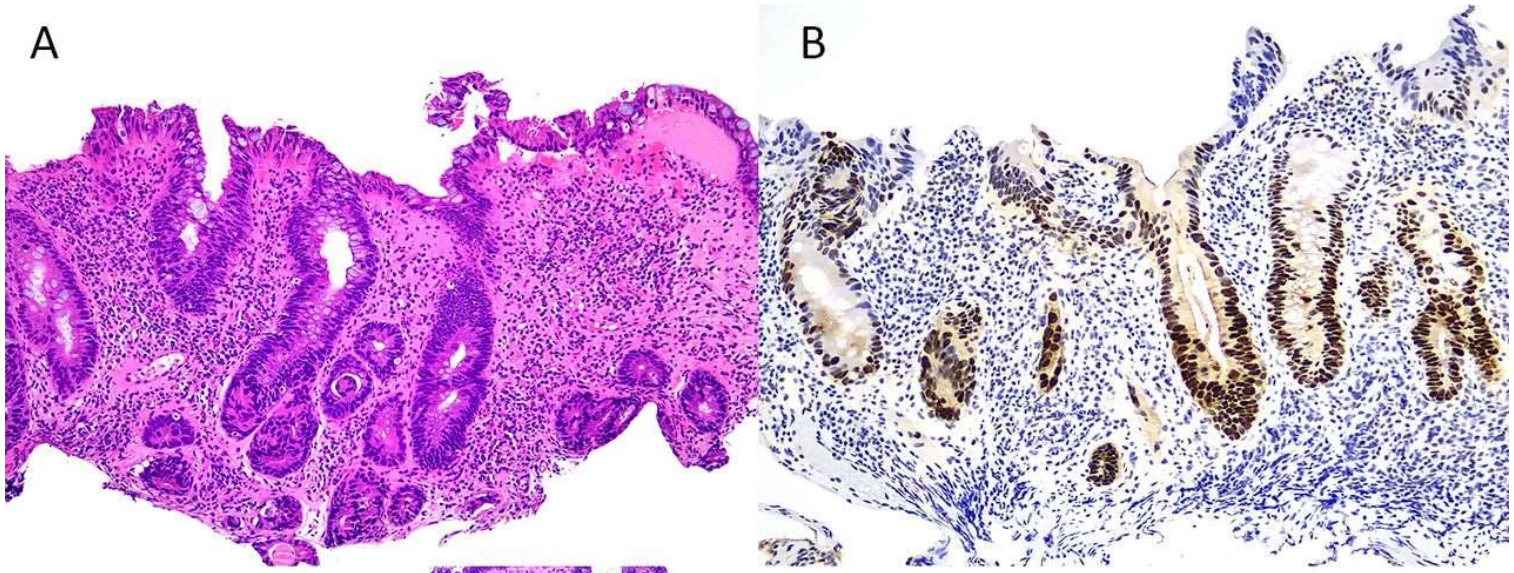
Riddell system:

- Negative for dysplasia
- Indefinite for dysplasia
- Positive for dysplasia
  - ➢Low-grade dysplasia
  - ➢High-grade dysplasia

Indefinite for dysplasia

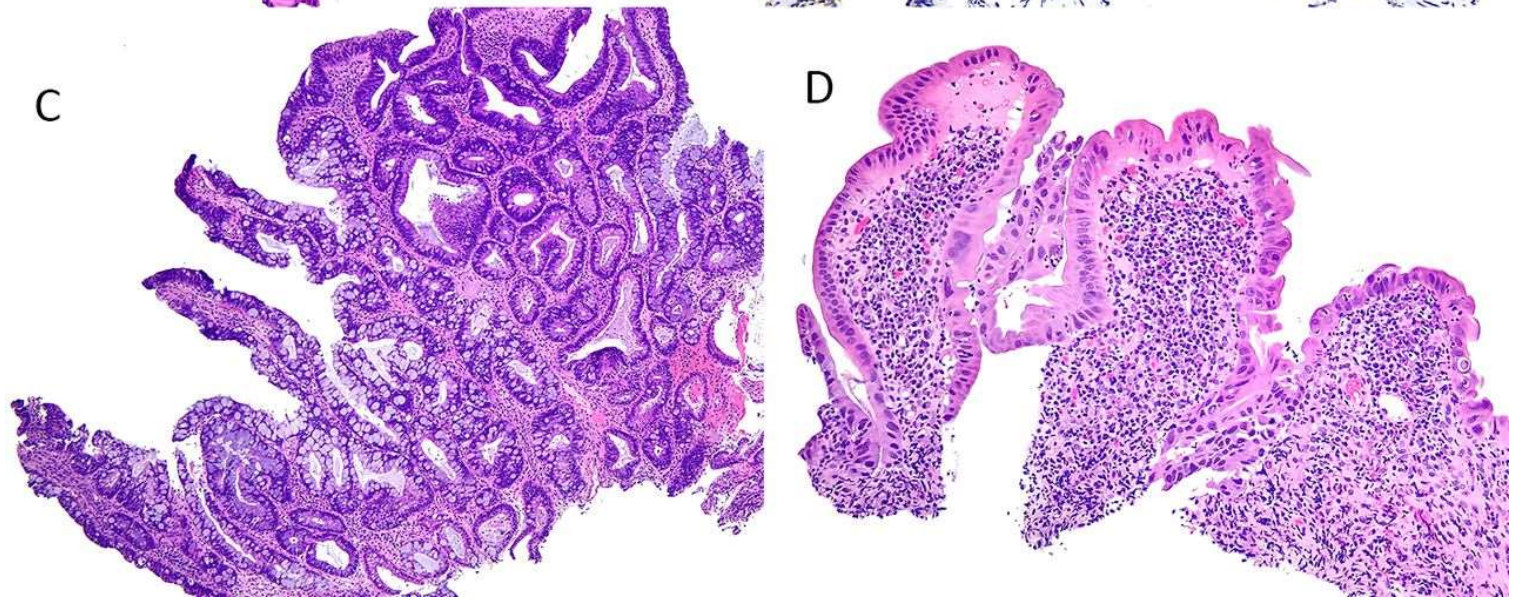
- Applied to epithelial changes that appear to exceed the limits of ordinary regeneration but are insufficient for an unequivocal diagnosis of dysplasia
- Often used in atypical mucosa with exuberant inflammation, in which a reactive/regenerative process remains within the differential diagnosis.
- Early repeat biopsy is often required to assess the changes more accurately.

Conventional adenomatous dysplasia



P53 IHC

Conventional adenomatous dysplasia with increased goblet cells

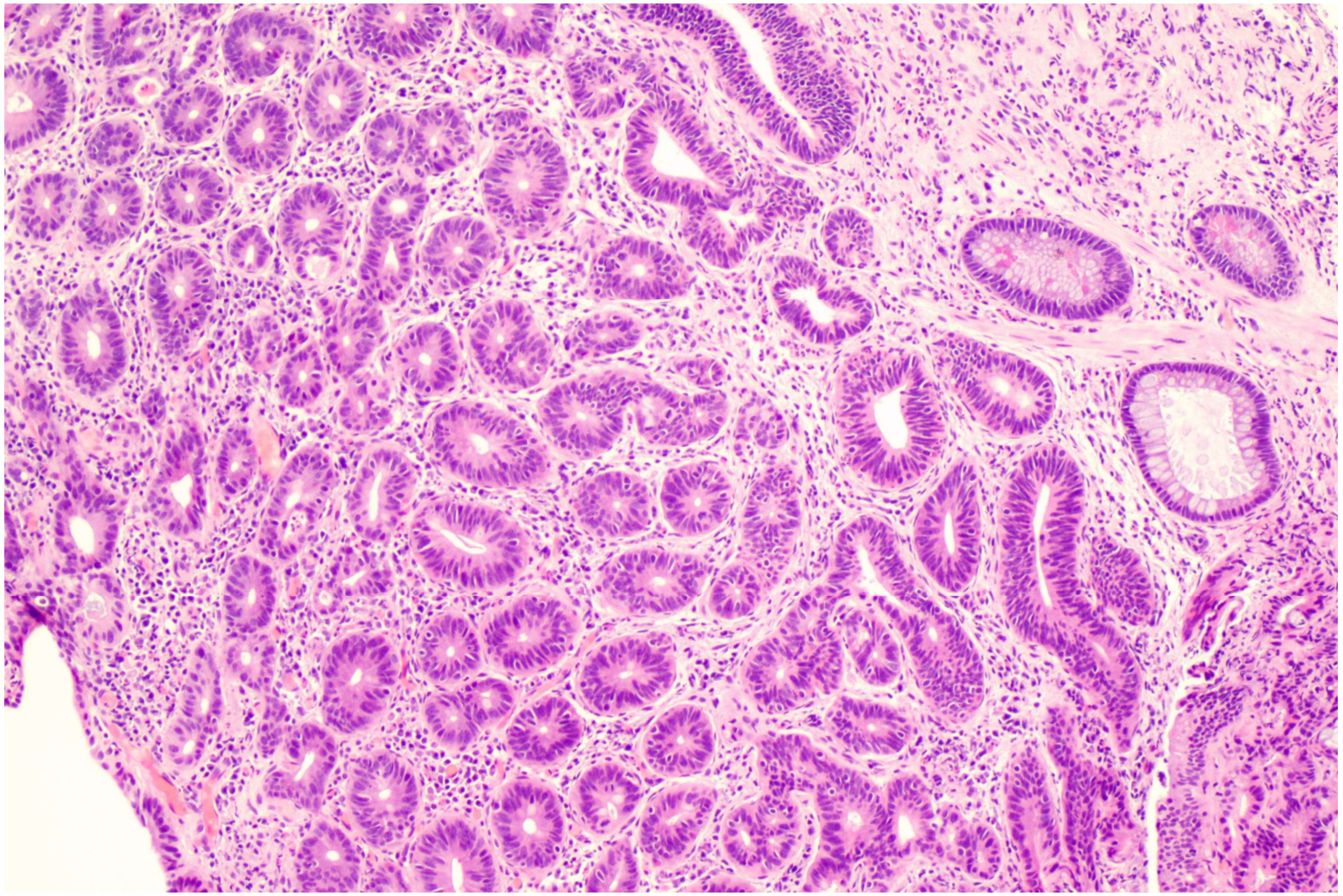


Indefinite for dysplasia

Dysplasia in IBD - Reporting

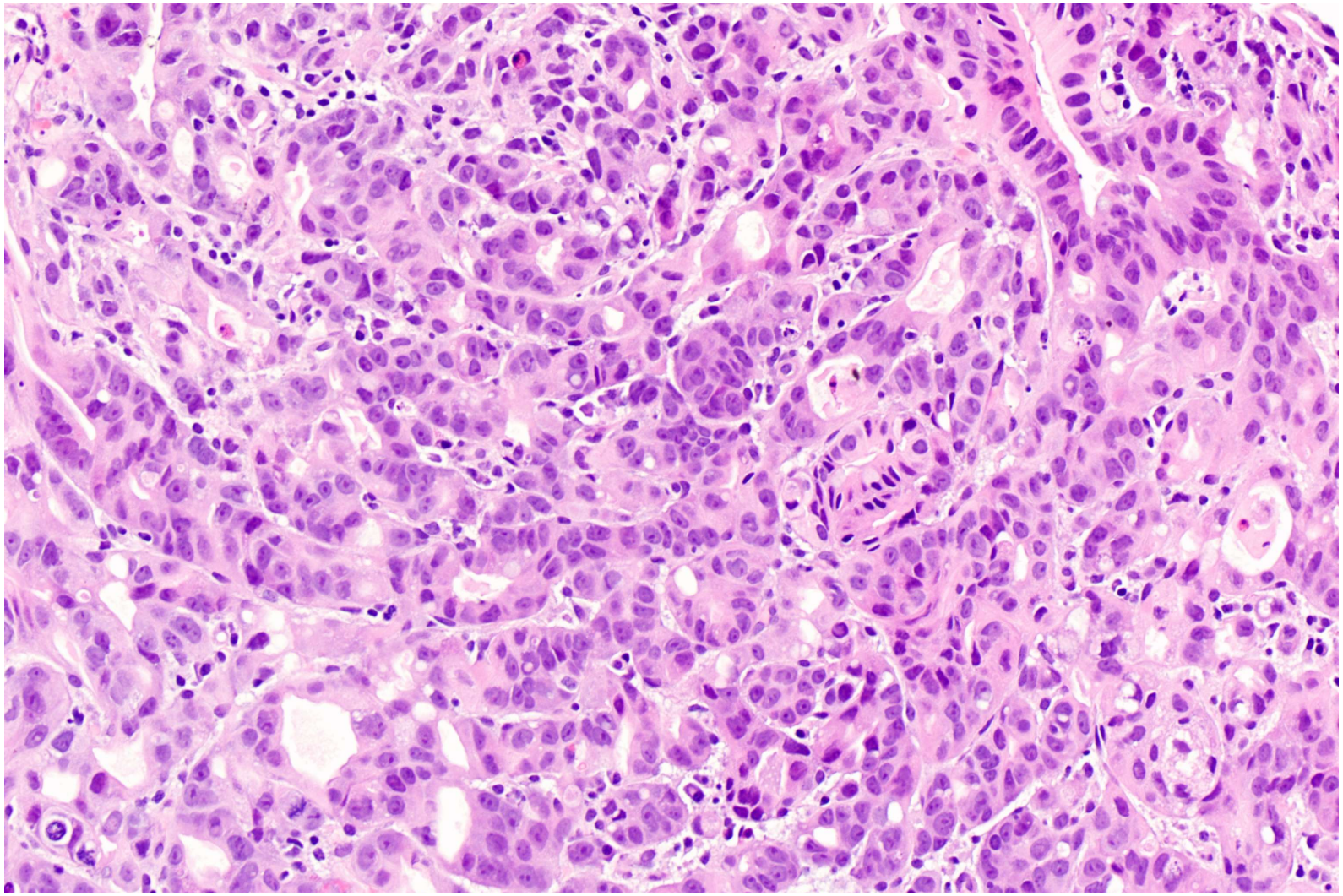
For basal crypt dysplasia

- When aberrant p53 staining is present, basal crypt dysplasia should be reported as “(at least) low-grade dysplasia, basal crypt variant,” with a comment highlighting its frequent association with synchronous/metachronous neoplasia (including advanced neoplasia).
- If p53 staining shows a wild-type pattern but morphologic suspicion remains high, a descriptive diagnosis such as “basal crypt atypia” or indefinite for dysplasia (IND) is appropriate, accompanied by a recommendation for follow-up colonoscopy consistent with standard practice for IND cases.

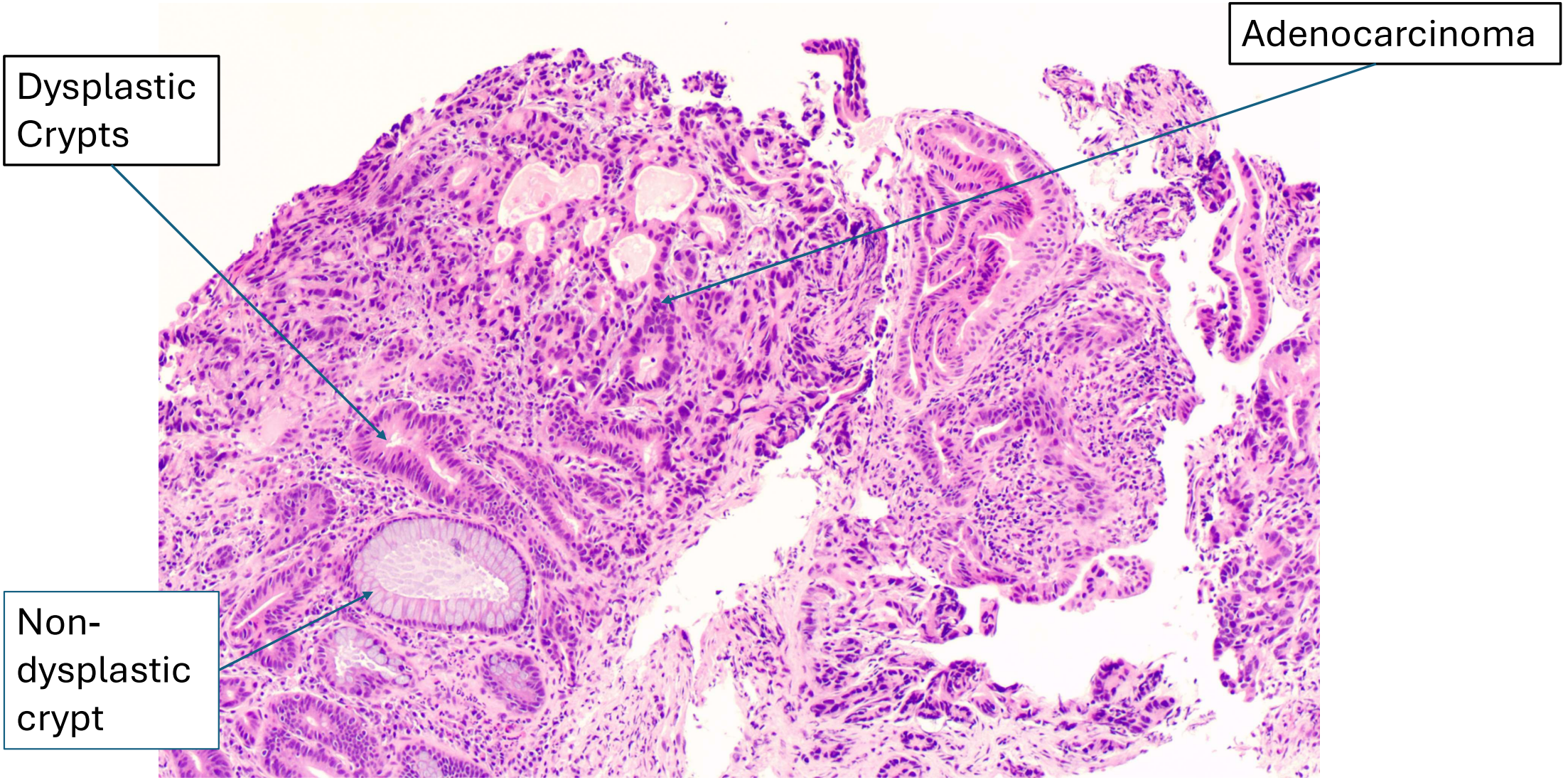


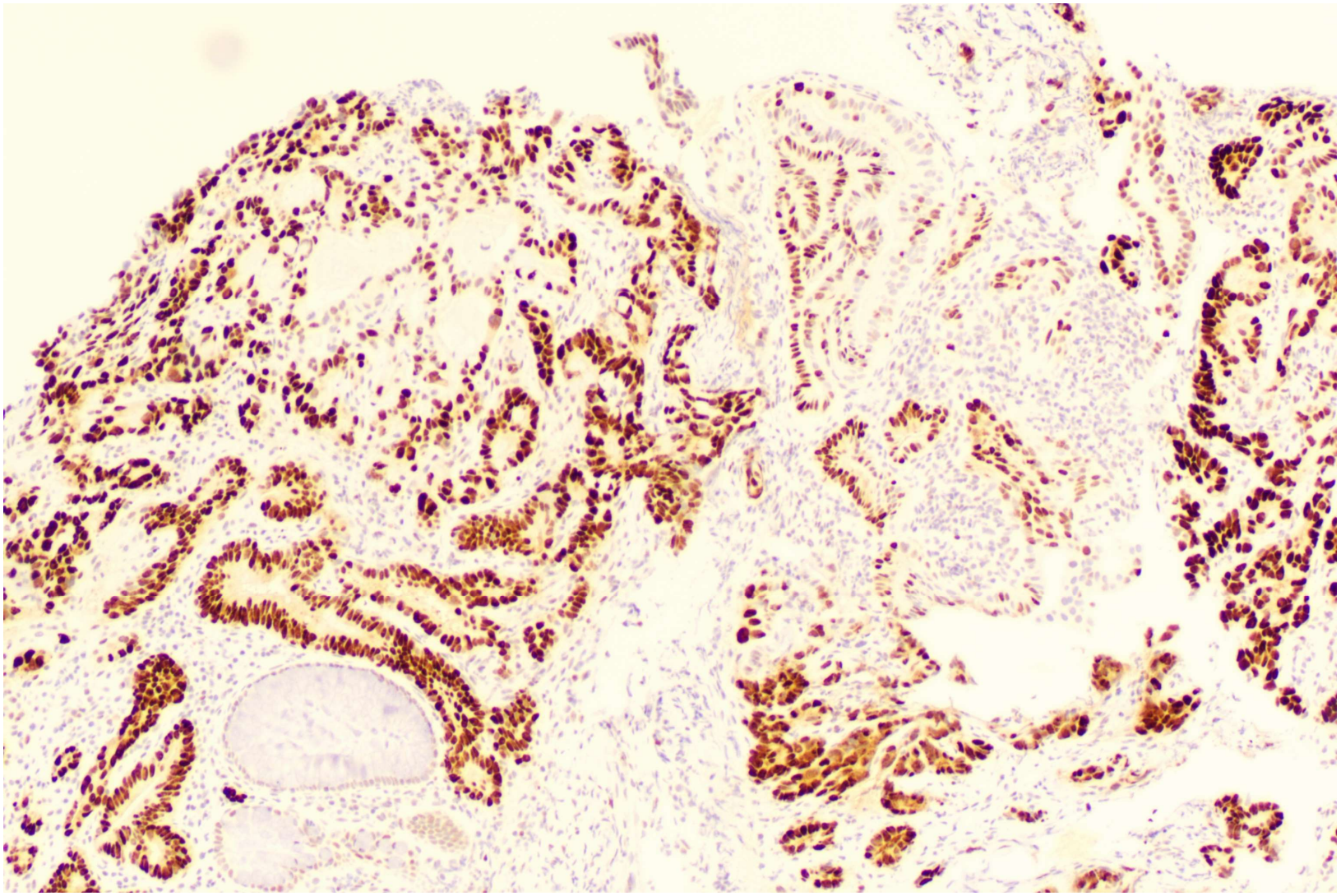
Second patient, rectal Bx 6 years later

Dysplasia

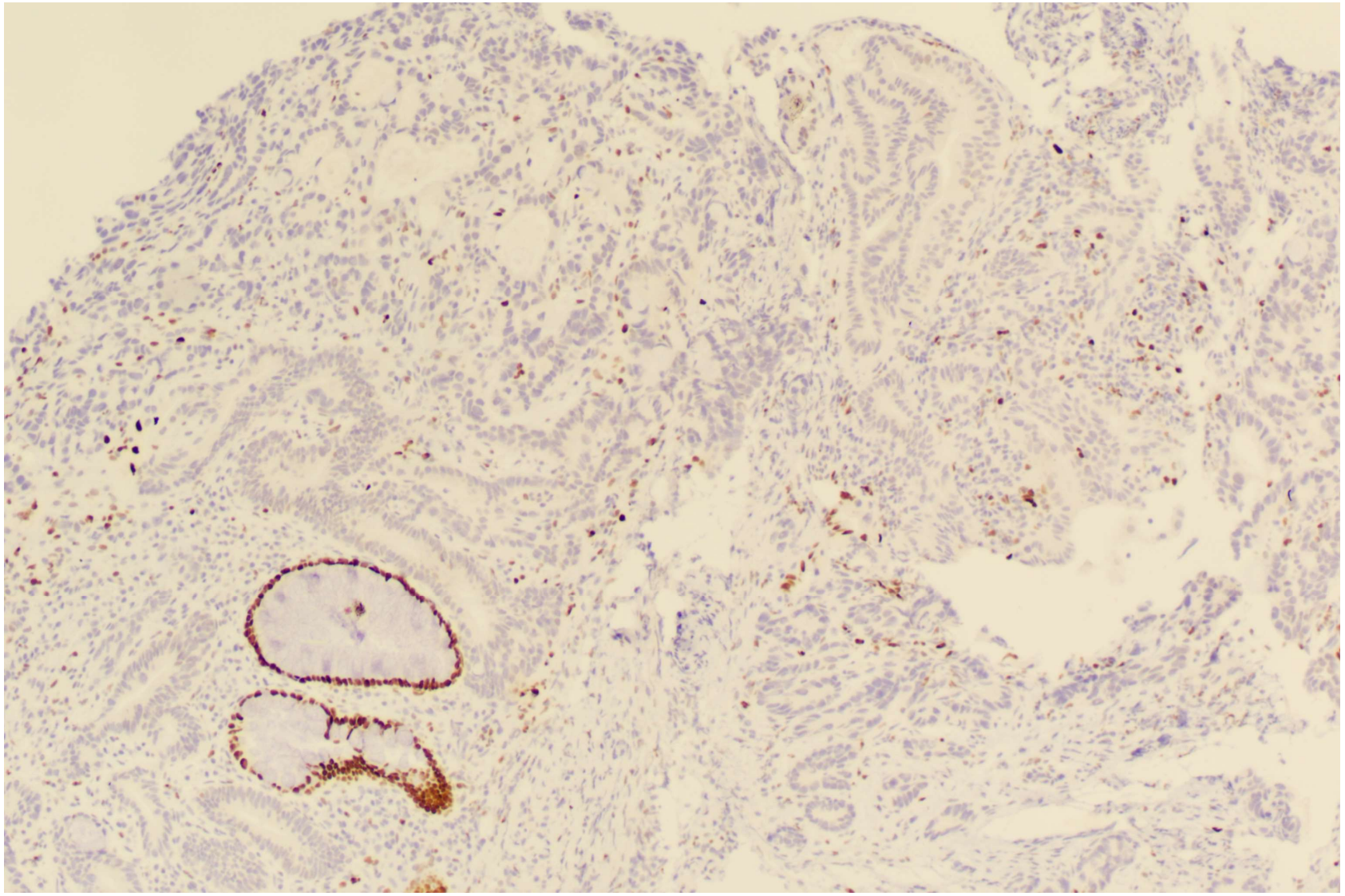


Adenocarcinoma

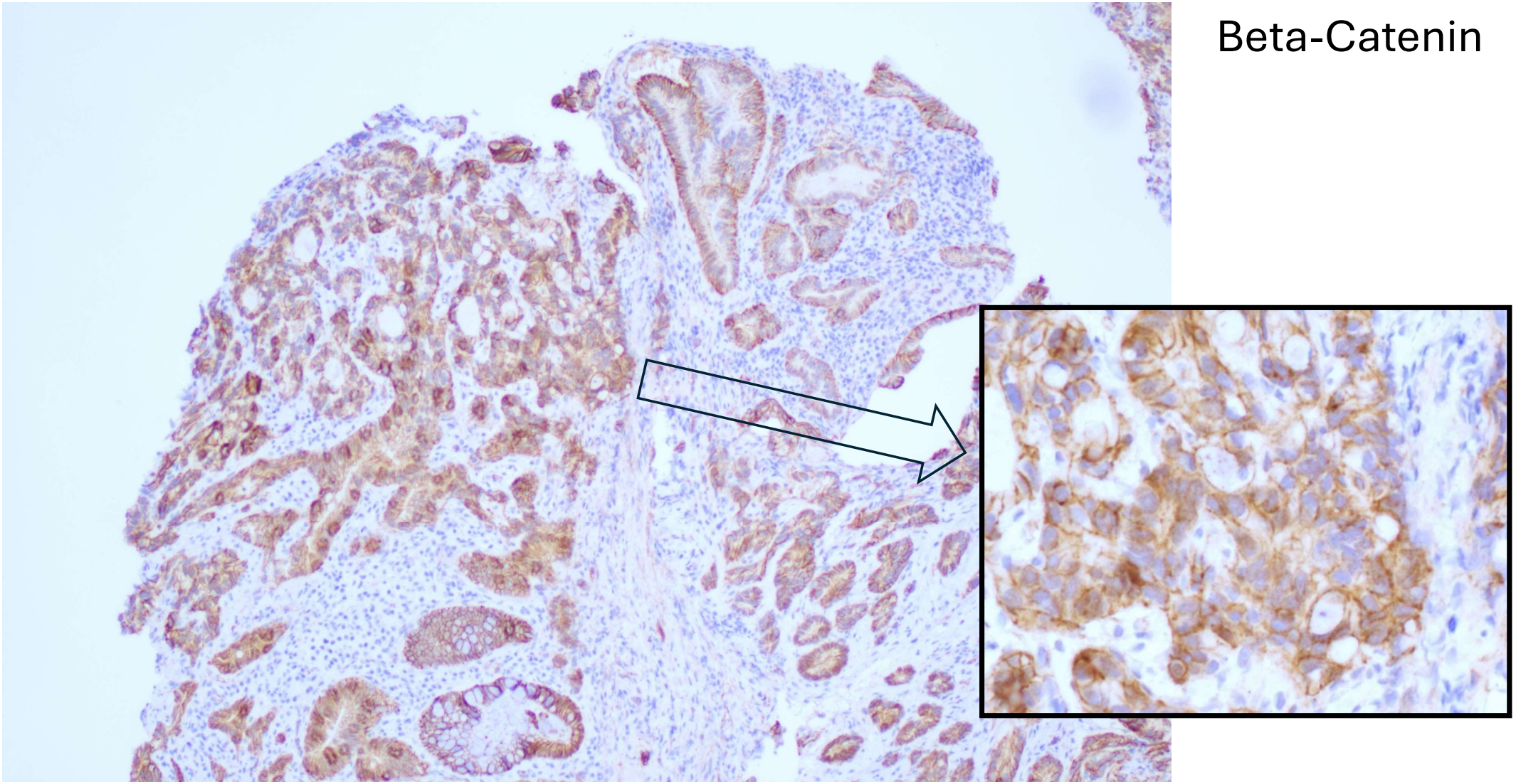

Adenocarcinoma
Dysplastic Crypts
Non-dysplastic crypt



p53



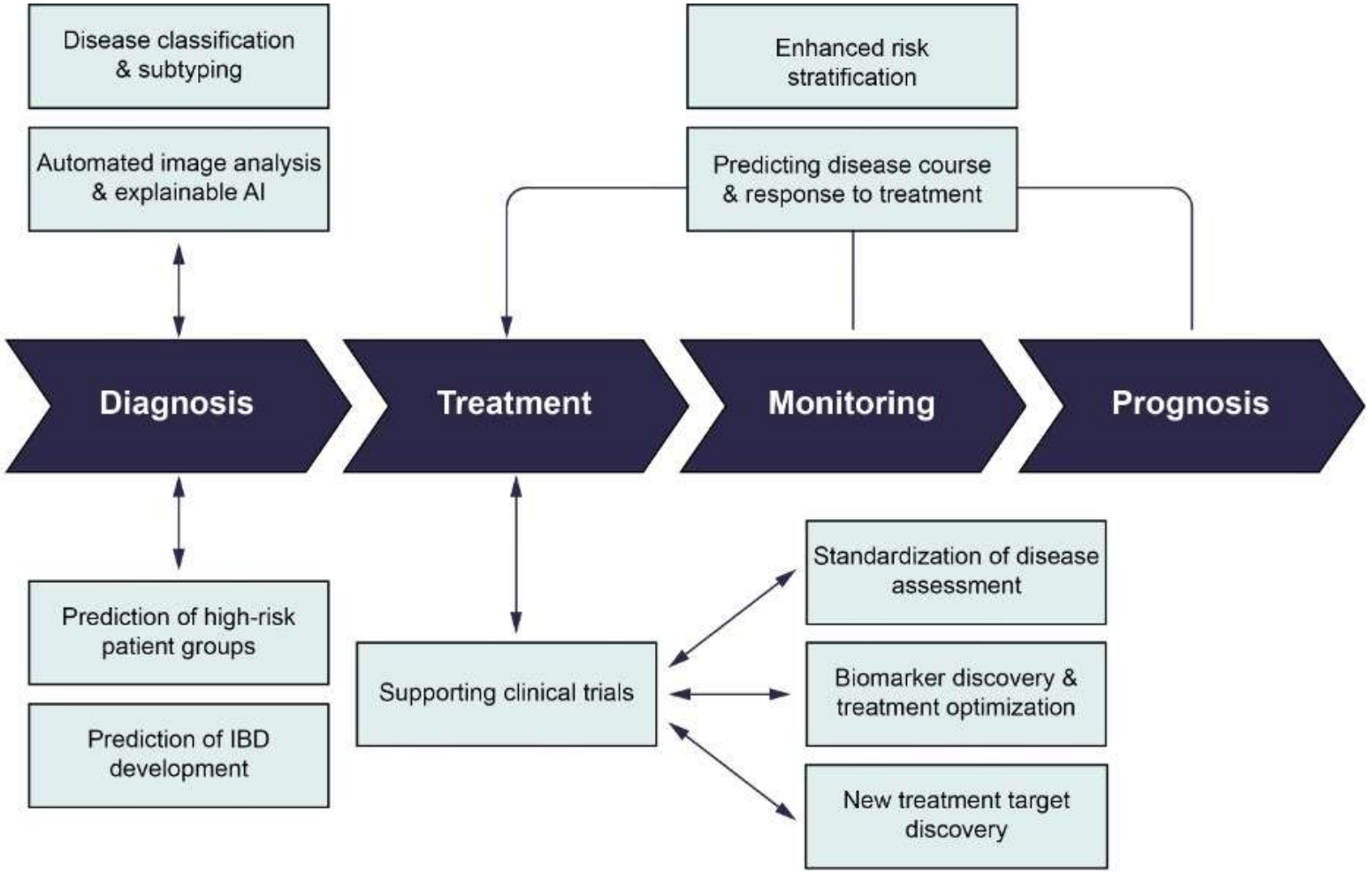
SATB2


Beta-Catenin

Colitis-associated Adenocarcinoma with conventional dysplasia

Revolutionizing Inflammatory Bowel Disease Histology Assessment Through Artificial Intelligence

College of American Pathologists



Opportunities where AI application can revolutionize histological disease assessment in IBD.

Thank you