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Position Paper

Pattern-based histologic approach in colitis with chronic architectural damage: GIPAD recommendations

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ABSTRACT

Histologic evaluation of colonic biopsies in patients with chronic diarrhea or long-standing colitis is frequently performed in the setting of incomplete clinical, endoscopic, or laboratory information. In this context, overlapping morphologic features across different etiologies often lead to nonspecific or misleading diagnoses, such as "chronic colitis," with potential implications for patient management.

To improve diagnostic clarity and clinicopathologic communication, the Italian Group of Digestive Disease Pathology (GIPAD) developed a structured, pattern-based histologic approach for the interpretation and reporting of adult colitis with chronic architectural damage, based on multidisciplinary discussion and critical appraisal of the literature. Distinct histologic patterns are described and correlated with relevant differential diagnoses.

Major patterns of colitis with chronic architectural damage are identified, and for each pattern, key morphologic features and principal differential diagnoses—including inflammatory bowel disease and other conditions such as drug-related injury, ischemia, infection, diversion colitis, and immune-mediated disorders—are discussed.

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A pattern-based histologic approach provides a practical framework for reporting colitis with chronic architectural damage. This strategy narrows differential diagnoses, avoids nonspecific terminology, and supports clinical decision-making, while preserving the primacy of integrated clinicopathologic diagnosis when sufficient information is available.

1. Introduction

The histologic assessment and interpretation of endoscopic colonic biopsies is of crucial importance for patients who experience chronic diarrhea or long-standing symptoms of colitis.

Endoscopic biopsies must be evaluated and interpreted within the appropriate clinical context: providing detailed clinical indications is not merely helpful but essential for meaningful interpretation. A multidisciplinary approach is imperative for differentiating between different forms of chronic colitis, including inflammatory bowel disease (IBD). Collaboration among clinicians and pathologists ensures that all relevant clinical, histological, and imaging data are considered, leading to more accurate differentiation between types of chronic colitis and supporting optimal patient management.

The diagnosis should be supported and confirmed by a combination of medical history, drug history, laboratory data (including stool tests), imaging, endoscopic appearances, histology, and follow-up [1,2].

In real life, however, pathologists are often asked to assess endoscopic colonic biopsies with incomplete clinical information or with an insufficient or inappropriate number of biopsies. In the setting of an incomplete clinical picture, diagnosis can be challenging, as histology may show features that do not conform to a specific diagnostic entity [3].

The differential diagnosis of chronic inflammatory conditions that may affect the large bowel is wide, and it may represent a significant challenge [4]. When the histologic or clinical features of a colonic inflammatory process are neither clear nor defined, pathologists tend to adopt the inappropriate diagnosis of *chronic colitis*. This diagnosis can, however, be misleading as it forces the clinician to consider a wide range of possible differential diagnoses, including IBD, long-standing infections, chronic ischemia, and drug-induced chronic colitis [5].

In routine clinical practice, in most cases of *chronic colitis,* a diagnosis of IBD, in particular ulcerative colitis (UC), will eventually be reached. However, most is not all, making this diagnosis easily equivocal and could potentially be misunderstood by clinicians, causing management delays and incorrect treatments with potential dire consequences [6,7].

The Italian Group of Digestive Disease Pathology (Gruppo Italiano Patologi Apparato Digerente - GIPAD) proposes a *pattern-based histologic approach* in reporting histologic damage in a biopsy setting. This paper will focus on colitis with chronic architectural damage. The pattern-based histologic approach for colitis *without* chronic damage has been discussed in a different manuscript entitled: Pattern-based histologic approach in colitis without chronic architectural damage: GIPAD recommendations [8]. The two papers will focus on the adult population and on the first diagnosis of disease. Hence, the pediatric population and follow-up considerations will not be discussed.

2. Definition of chronic colitis

The definition of chronic colitis is often misconstrued as there is still some confusion among pathologists concerning the term 'chronic'. As a result, the diagnosis of chronic colitis is often used inappropriately.

The fundamental point is that the presence of chronic inflammation of the lamina propria alone is not a sufficient parameter for a diagnosis of chronic colitis. Indeed, according to the literature, 'chronic colitis refers to a descriptive clinical-pathological term characterized by the evidence of *chronic injury to the mucosa* [7]. and we, as GIPAD, fully endorse this definition.

The most reliable features of chronic mucosal damage are crypt architectural distortion, including crypt branching, crypt atrophy, a villiform/irregular mucosal surface of colonic mucosa, basal plasmacytosis, and metaplastic epithelial changes (e.g., Paneth cell metaplasia, pseudo-pyloric metaplasia) [7,9–10] Regardless of the inflammatory pattern of injury, the identification of one or more of these histological features in the mucosa of inflamed colonic biopsies should orient pathologists towards a chronic pathological process. These features of chronicity can be found in colitis of different etiologies, and they usually start developing, in most scenarios, after months of repeated mucosal injury [10,11]. For this reason, the duration of symptoms and, therefore, the timing of biopsies are crucial factors for the identification of chronic injury.

Crypt architectural distortion is best evaluated at low power and includes crypt branching and crypt irregularity, with angulated glands, showing abnormal size or shape, or glands that are not vertically oriented. At least two altered crypts in the same biopsy should be identified to define architectural distortion. It is worth noting that poor orientation of samples and the presence of lymphoid aggregates may lead to misinterpretation of architectural distortion and crypt atrophy [1,7].

Crypt atrophy consists of a reduction of the total area of the mucosa occupied by the crypts, usually due to a combination of widening of the lateral spaces between crypts and between the base of the crypts and the muscularis mucosae (crypt shortening) [1,7]. Crypt atrophy is an important feature in the evaluation of chronic mucosal damage, but its interpretation requires careful consideration as atrophy should be interpreted with caution in the presence of intense inflammation, as a dense inflammatory infiltrate can mimic atrophy. Therefore, the assessment of atrophy is most reliably performed in the context of quiescent or long-standing disease, where confounding factors such as active inflammation are minimized.

A villous architecture of the mucosal surface is characterized by an undulated (rather than flat) silhouette at the luminal border of colorectal mucosa, due to dilation and separation of crypts, sometimes with a true villiform architecture [1,7].

Basal plasmacytosis consists of a patchy or diffuse band-like increase in plasma cells, with scattered eosinophils, in the deep lamina propria, usually between the crypt bases and the muscularis mucosae. In normal mucosa, plasma cells are most densely distributed in the upper third of the lamina propria, with their numbers gradually decreasing toward the lower basal third. Notably, basal plasmacytosis is one of the earliest features of IBD, and it can be detected within the first weeks after symptom onset [11]. In addition, basal plasmacytosis is considered a predictive feature of relapse as it may be detected just before an inflammatory flare-up of disease [12].

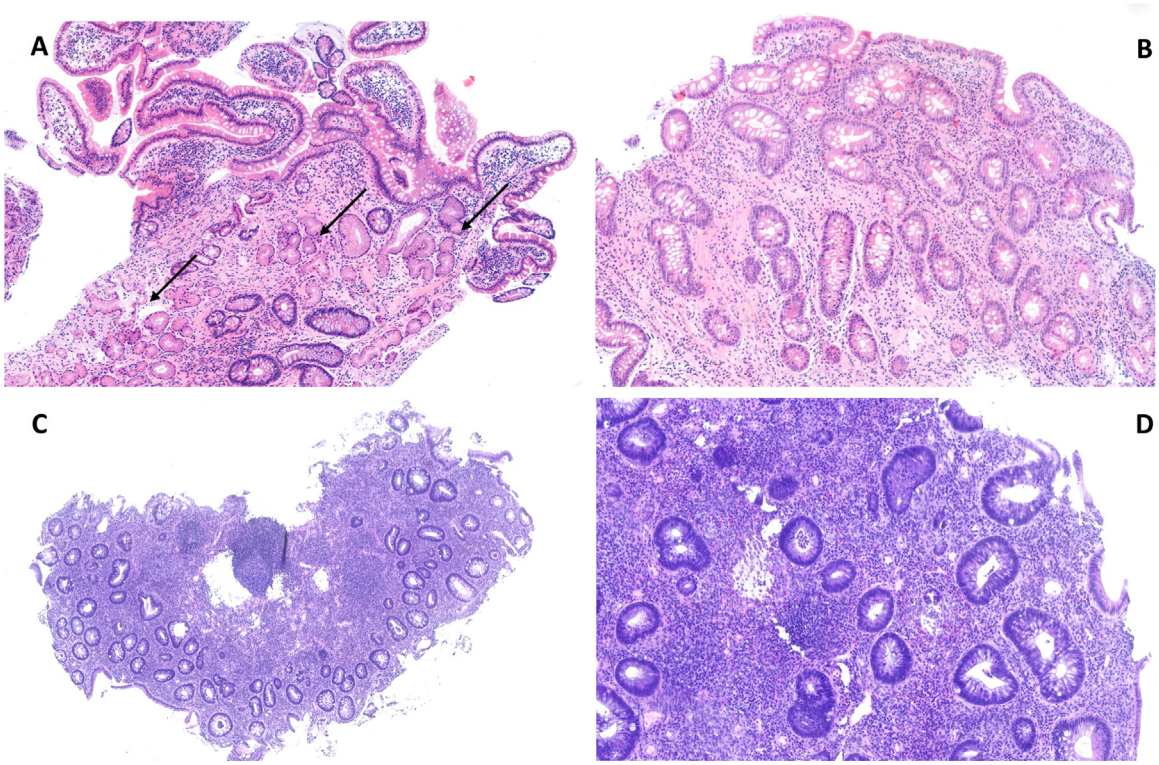

Fig. 1. Focal and diffuse active chronic colitis patterns. (A, B) Focal active chronic colitis in Crohn's disease, with architectural distortion and activity. Pseudopyloric metaplasia can be seen in panel A (arrows). (C, D) diffuse active chronic colitis in ulcerative colitis, characterized by mixed inflammatory infiltrate in lamina propria, associated with basal plasmacytosis, crypts architectural distortions, cryptitis and crypt microabscesses. Hematoxylin & eosin stain; original magnification: 40 × (A, C), 200 × (B), 100 × (D).

Paneth cell metaplasia is defined by the presence of Paneth cells in the left colon-rectum distal to the splenic flexure. Paneth cells are numerous throughout the small bowel mucosa and the right colon, and their number decreases towards the left colon. Their presence in the distal colon (descending colon, sigma, and rectum) is always a sign of chronic destruction and regeneration of the mucosa [13].

Pseudo-pyloric metaplasia is characterized by the replacement of the normal intestinal epithelium by gastric pyloric-like glands. Pseudo-pyloric metaplasia is more common in the small bowel in the setting of chronic ileitis, but it can occasionally be found in the colon, particularly in the setting of IBD. Similarly, this type of metaplasia is a sign of chronic regeneration acting as an adaptive response to chronic injury or inflammation.

3. Diffuse active chronic colitis pattern

3.1. Morphology of diffuse active chronic colitis pattern

The diffuse active chronic colitis pattern, as the name implies, is characterized by the presence of diffuse features of chronic mucosal injury associated with neutrophilic (acute/active) and lympho-plasmocytic (chronic) inflammation (Fig. 1). The inflammatory infiltrate can be mild, moderate, or severe, and it is usually composed of a mixture of lymphocytes, plasma cells, monocytes, eosinophils, and neutrophils. Active inflammation is present in the form of cryptitis, crypt abscesses, erosions, and ulcers. Mucosal edema and reactive epithelial changes may also be seen.

The diffuse active chronic colitis pattern may involve the entire colon in the form of pan-colitis, or it can be present in selected segments of the bowel, for example, the rectum.

Histologically, the features of diffuse active chronic colitis pattern should be similar within and between fragments from the same site, and the involvement between different bowel segments is usually continuous.

3.2. Differential diagnosis of diffuse active chronic colitis pattern (Tab. 1)

The most typical etiology responsible for this pattern is *IBD*, particularly *UC*.

The main histological features that favor a diagnosis of UC are diffuse architectural distortion, basal plasmacytosis (and this is indeed an important feature), and mucin depletion. While the presence of basal plasmacytosis strongly suggests a UC diagnosis, its absence renders the diagnosis of untreated UC unlikely. The diagnosis of IBD should be based on a combination of clinical, laboratory, endoscopic, imaging, and histological investigations. Thus, biopsy samples should be accompanied by the patient's clinical history and the endoscopic findings at least. If an IBD is suspected, European guidelines recommend sampling at least two biopsies from each colonic segment, including biopsies from the terminal ileum and the rectum [1,14]. Numerous other entities can show *some* elementary lesions, like UC, but it is the association with other clinical-histological features that point to the correct diagnosis (Table 1).

Drugs can cause a wide range of alterations, including a diffuse active chronic colitis pattern (e.g., associated with non-steroidal anti-inflammatory drugs [NSAIDs] and immunomodulatory drugs).

The correlation with patient history and a scrutiny of the histologic features is imperative. *Immune-checkpoint inhibitor (ICI)* therapy can occasionally cause colitis, which may show different histological patterns of injury, ranging from mild acute colitis, IBD-like colitis, microscopic colitis, and features of apoptotic enteropathy [15]. The mucosa most commonly shows a mixed inflammatory infiltrate within the lamina propria, foci of active cryptitis, and crypt microabscesses. Crypt apoptotic cells may be prominent,

Table 1
Differential diagnosis in diffuse active chronic colitis pattern.

Etiology		Affected colonic tract	Additional histological findings	Diagnostic tests
IBD	UC	Any	Diffuse architectural distortion, basal plasmacytosis, mucin depletion.	Clinical integration, endoscopy
Diversion proctocolitis		Any diverted segment	Numerous and large lymphoid follicles, vascular damage (lymphocytic phlebitis)	Clinical integration, endoscopy
Drugs	ICI	Any	Apoptoses in crypt epithelial cells; increased IELs in crypts; histologic alterations may extend to the ileum and the upper digestive tract	Clinical integration
	MFA	Any	Degenerated and dilated crypts layered by flat eosinophilic epithelium, with apoptoses in the crypt epithelium. Numerous eosinophils within the lamina propria.	Clinical integration,
Infection	CMV	Any	CMV cytopathic alterations in stromal, endothelial, and epithelial cells	Clinical integration, serology
Vascular diseases	Ischaemia (long-standing)	Any	Mucosal hyalinising fibrosis; glandular dropout; microthrombi; hemosiderin-laden macrophages	Clinical integration, endoscopy

Abbreviations: IBD: inflammatory bowel disease; UC: ulcerative colitis; SCAD: segmental colitis associated with diverticulosis; ICI: immune checkpoint inhibitor; IEL: intraepithelial lymphocytes; MFA: Mycophenolate.

and neutrophilic infiltration is common. More severe cases may result in erosions, ulcers, marked crypt atrophy with attenuation of the epithelium with luminal debris. The distribution of changes is often continuous, although in some cases it may be patchy. Recently, some studies have demonstrated that ICI colitis may show features of chronicity such as crypt distortion, basal plasmacytosis, and intraepithelial lymphocytes [16]. Histological distinction between IBD and ICI colitis is difficult without supporting clinical history. However, the presence of prominent apoptosis, atrophic or dilated crypts with attenuated epithelium, and intraepithelial lymphocytosis may support a diagnosis of ICI colitis.

Mycophenolate may also be associated with an active chronic colitis pattern, which could be either diffuse or focal, and it can often mimic IBD. Histologically, the glandular architecture appears mildly to moderately distorted, with focal crypt branching, crypt atrophy, mucin depletion, and Paneth cell metaplasia. Mycophenolate colitis can show features not typical of IBD, which would help with the differential diagnosis, such as prominent apoptoses, degenerated and dilated crypts with flattened atypical epithelium, and increased eosinophils within the lamina propria. The lamina propria is usually inflamed, but the severity of inflammation has been described as less severe than true IBD [15,17,18].

Diversion proctocolitis is a condition affecting intestinal segments excluded from the fecal stream. It occurs after surgical intervention, often in an IBD context but also in other clinical settings, for instance, diverticular disease, motility disorders, and neoplasia. This inflammatory condition may take weeks or months to develop, and it is likely due to an alteration of the microbiome and a lack of energy sources, including short-chain fatty acids. Histologically, it is characterized by diffuse chronic mucosal injury, including distortion of the crypt architecture, mild mucin depletion, and glandular atrophy, along with inflammation. In addition, diversion colitis features numerous large lymphoid follicles with germinal centers. There may be signs of activity, including active cryptitis, crypt abscess, erosions and ulcers, and vascular damage such as lymphocytic phlebitis [14,19–22]. Granulomas are uncommon but may be found, especially in the setting of resections for Crohn's disease (CD). The histology of diversion colitis can mimic IBD, regardless of the underlying etiology, and a reliable distinction is difficult. Features of IBD and diversion can also co-occur. Hence, a first diagnosis of IBD in diverted colonic segments is not advisable [4].

Ischemic colitis can show diffuse inflammatory involvement of the colon with associated crypt atrophy and distortion. However, basal plasmacytosis is absent, and instead, one can appreciate typical features such as hyalinization and fibrosis of the lamina propria and crypt dropout. Ischemic-like pattern with chronic damage will be discussed later in the text.

Several *infectious diseases*, induced by viruses, bacteria, and parasites, can lead to diffuse chronic colitis with activity. Sexually transmitted infectious agents such as chlamydia, gonorrhea, and syphilis can cause diffuse active inflammation of the distal rectum, associated with chronic mucosal damage. Pathologists should keep this differential in mind when rectal biopsies show marked lymphocytic inflammation, with prominent plasma cells, but with less pronouncedbasal plasmacytosis (as inflammation is generally diffuse within the lamina propria). Indeed, the presence of basal plasmacytosis favors IBD/UC over infections. If this etiology is suspected by the pathologist, it should be communicated to the treating physician, as key clinical aspects may not have been adequately investigated.

Cytomegalovirus (CMV) colitis can histologically resemble IBD, having diffuse architectural distortion, chronic inflammation, superficial erosions, and cryptitis. The detection of CMV cytopathic alterations in stromal, endothelial, and epithelial cells is a reliable marker of a CMV infection and should be confirmed by immunohistochemical staining or polymerase chain reaction (PCR) techniques. Notably, CMV reactivation can also occur in patients with IBD, particularly those receiving long-term corticosteroid or immunosuppressive therapy.

4. Focal active chronic colitis pattern

4.1. Morphology of the focal active chronic colitis pattern

The focal active chronic colitis pattern is characterized by the presence of the above-mentioned features of chronicity associated with focal or segmental signs of neutrophilic activity, such as crypt abscesses, cryptitis, or the presence of neutrophils in the lamina propria (Fig. 1). Endoscopic findings can vary, ranging from macroscopically unremarkable mucosa to erythematous, granular, friable, and edematous mucosa with or without isolated aphthous or linear ulcers. Moreover, reparative alterations (e.g., strictures, atrophic appearance of mucosa) may occur.

4.2. Differential diagnosis of focal active chronic colitis pattern (Tab. 2)

Crohn's Disease (CD) can affect any segment of the digestive tract, although the distal ileum and right colon are the most involved sites. Endoscopically, colorectal mucosa classically shows a discontinuous, patchy pattern of inflammation (the so-called *skip lesions*). In the early phase of the disease, sparse, small mucosal aphthous ulcers may be detected in the large bowel and/or terminal ileum. As the disease progresses, linear or serpiginous deeper lesions may be identified, occasionally with accompanying inflammatory polyps or pseudopolyps. Histologically, these macroscopic alterations correspond to focal/discontinuous chronic inflammation with or without neutrophilic infiltrate, associated with focal architectural changes and granulomas. Sometimes, these histologic al-

terations can be noted only in one of the multiple (generally 2) samples taken from the same colonic site, reflecting the patchy distribution of CD. The presence of non-cryptolytic, non-caseating, epithelioid granulomas is highly suggestive of CD, mostly when associated with at least another above-mentioned histologic feature. Granulomas, however, may be found in about half of adult cases at onset and in only 18% of subsequent biopsies, while tending to be more frequent in children, with the same frequency in both the early and late phases (67–54% of cases). In difficult cases, the involvement of the terminal ileum and the presence of a proximal-to-distal gradient of histologic changes may be useful to achieve the correct diagnosis [1,23–24] Children and adolescents may show a different phenotype, especially at onset. Pediatric CD is characterized by more colonic and less ileal involvement compared to adults, and a more frequent detection of granulomas. Moreover, the finding of focal inflammation with or without granulomas in the upper gastrointestinal tract can be useful to identify CD in unusual pediatric cases [1,4,7]. A possible cause of focal active chronic colitis, which mimics CD, is intestinal endometriosis, which should be considered in non-menopausal women with a history of endometriosis. This possibility is a diagnostic challenge when no endometrial glands/stroma are present in the biopsy specimens and often requires pelvic imaging to reach a correct diagnosis [25].

An *unusual presentation of UC* may present discontinuous involvement of the colonic mucosa with skip lesions. This presentation is most seen in children, in patients with associated primary sclerosing cholangitis (PSC), or in treated patients with long-standing disease of any age. Children may present with pancolitis and relative rectal sparing. Patients with UC-PSC can also show features of pancolitis, usually more active in the right colon [26]. In unusual cases, UC can also involve the rectum only and the appendix/caecal patch with no involvement of the remaining colonic mucosa. It is important to recognize these atypical histological variants of UC to avoid a diagnosis of CD. In long-standing UC patients, the colonic mucosa may present areas of inflammation and architectural distortion alternated with areas of quiescent colitis with mild or no architectural alteration, and this phenomenon is usually secondary to treatments. It is important, therefore, to have a detailed report of what treatment the patient with known UC is undergoing, to prevent a possible, erroneous change in diagnosis to CD [1,23].

Diverticular colitis/segmental colitis associated with diverticulosis (SCAD) can show both diffuse crypt distortion/atrophy and basal plasmacytosis, associated with active inflammation in the form of cryptitis and crypt abscesses. Inflammation usually involves the mucosa in the interdiverticular region without necessarily involving diverticular orifices. Paneth cell metaplasia can also be present. Correlation with endoscopic findings and correct sampling is essential, although in severe cases, linear ulcers and cobblestone appearance of mucosa may resemble CD. The histological abnormalities in SCAD are usually restricted to biopsies obtained from an area affected by diverticulosis, whereas other biopsies (notably those from the rectum, making rectal biopsies essential for differential diagnosis) are spared. In this regard, UC, especially after treatment, can show rectal sparing, though in this case, clinical history can facilitate the correct diagnosis [4,14,27].

Especially in long-standing cases, some *infectious colitides* can be characterized by a focal active chronic pattern, with crypt distortion and withering and mild activity with band-like distribution localized mainly in the superficial part of the lamina propria and in the perivascular area [4,14,28]. Colitis associated with *Yersinia* and *Mycobacterium* infection is usually localized to the ileocecal region, appendix, and right colon. Typical histological alterations may include mucosal erosions, cryptitis, architectural disarray, and pyloric gland metaplasia, but the most striking sign consists of granulomas. In contrast to CD-related non-caseating granulomas, yersiniosis and tuberculosis granulomas typically have central necrosis and a lymphoid cuff. Moreover, in tuberculous colitis, acid-fast stains may reveal the presence of microorganisms in granulomas. Nevertheless, in most cases, differential diagnosis with CD can be challenging, and only a combination of endoscopy, mycobacterial culture, imaging, and medical history can help make the correct diagnosis [4,14].

Vascular diseases, especially long-standing ischemia, may show a focal active chronic pattern, demonstrating non-specific (superficial erosions, architectural changes, mild-moderate inflammation, pyloric gland, and Paneth cell metaplasia) and specific changes (mucosal hyalinizing fibrosis, glandular dropout, microthrombi, and hemosiderin-laden macrophages). These alterations more frequently affect the left colon, followed by the transverse colon, right colon, while the rectum is generally not involved as much. Endoscopic aspects of long-standing ischemia (pseudopolyps, strictures, decreased haustrations, and granular mucosa) are less informative, as they can resemble IBDs, particularly CD [4,14,29].

Behçet's disease, a vascular disease characterized by recurrent gastrointestinal, oral, and genital ulcers, may show focal activity with prominent architectural distortion on ileocolonic biopsies, especially in those taken in the ileocecal region. Architectural changes are unusual and usually located close to ulcers. While both conditions may show overlapping features, granulomas strongly favor a diagnosis of CD, while neutrophilic vasculitis favors Behçet's. Medical history in combination with a careful clinical examination can help differentiate between Behçet's disease and CD [4,14,29].

Various *drugs* can cause focal active colitis with features of chronicity. ICI can trigger colitides characterized by both focal activity (cryptitis and crypt abscesses) and chronic changes (crypt distortion and Paneth cell metaplasia). At endoscopic examination, the mucosa may appear erythematous with erosions and ulcerations, and the distribution of lesions may occasionally affect only a tract of colorectum or have a discontinuous distribution. For these reasons, ICI-induced colitis may closely mimic CD, both endoscopically and histologically. If present, apoptoses and an increase of intraepithelial lymphocytes in crypts can lean towards ICI colitis. Medical history, combined with histology, can lead to the correct diagnosis [4,14,30].

Radiation-induced acute colitis may develop within 2 weeks following irradiation and usually demonstrates architectural distortion with or without crypt atrophy, goblet cell depletion, and Paneth cell metaplasia, features that can be shared with IBDs. The presence of lamina propria fibrosis, stromal hyalinization, vascular ectasia, and nuclear atypia in epithelial cells and fibroblasts favors radiation damage. On the other hand, the presence of basal plasmacytosis and granulomas favors UC and CD, respectively. A previous clinical history of irradiation can easily help in differential diagnosis and must be provided by the clinician in every case [4,14,31].

Solitary rectal ulcer syndrome (SRUS) is a condition related to disorders of defecation, typically affecting young adults. The lesions are localized on the anterolateral wall of the rectum or can be circumferential. Biopsy samples show gland architectural alterations, such as elongation, dilation, and distortions of crypts, which can become angulated and diamond-shaped, surface erosions with neutrophilic inflammation, and hypertrophic muscularis mucosa with splayed fibers extending between glands [4,14,32]. Unlike IBD, inflammation is typically minimal and limited to the superficial lamina propria. The key distinguishing feature is fibromuscular hyperplasia extending between crypts, best seen on trichrome stain but also recognizable on H&E. Prolapse changes are usually most prominent in the distal rectum, although they can occur elsewhere in association with a polyp or surgical anastomosis. Correlation with endoscopic findings is critical: a solitary lesion, polypoid mucosa, or anterior rectal involvement in a patient with

Table 2
Differential diagnosis in focal active chronic colitis pattern.

Etiology		Affected colonic tract	Additional histological findings	Diagnostic exams
IBD	CD	Any	Presence of non-cryptolytic noncaseating epithelioid granulomas; histologic alterations may extend to the ileum and upper digestive tract	Clinical integration, endoscopy
	UC after treatment	Any. Most frequently left colon	Presence of consistent basal plasmacytosis	Clinical integration, endoscopy
SCAD		Sigma	Alterations are limited to sigma; it can be indistinguishable from treated UC	Clinical integration, endoscopy
Infection	Yersiniosis	Ileocecal region, appendix, right colon	Suppurative granulomas with a lymphoid cuff	Clinical integration, serology, microbiological culture, and imaging
	Tuberculosis	Ileocecal region, appendix, right colon	Caseating granulomas with a lymphoid cuff; microorganisms may be positive to acid-fast stains	Clinical integration, serology, microbiological culture, and imaging
Vascular diseases	Ischaemia (long-standing)	Left colon, transverse colon, right colon, rectum (rarely)	Mucosal hyalinising fibrosis; glandular dropout; microthrombi; hemosiderin-laden macrophages	Clinical integration, endoscopy
	Behçet's disease	Ileocecal region	Architectural alterations are only adjacent to ulcers, vasculitis	Clinical integration
Drugs	ICI	Any	Apoptoses in crypt epithelial cells; increased IELs in crypts; histologic alterations may extend to the ileum and the upper digestive tract	Clinical integration
Radiation	Irradiated segments	Usually sigma and rectum	Lamina propria fibrosis; stromal hyalinisation; vascular ectasia; nuclear atypia (p53-) in epithelial cells and fibroblasts	Clinical integration
SRUS		Rectum	"Diamond-shaped crypt"; hypertrophic muscularis mucosa with splayed fibers extending between glands	Clinical integration, endoscopy

Abbreviations: IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; SCAD: segmental colitis associated with diverticulosis; ICI: immune checkpoint inhibitor; IEL: intraepithelial lymphocytes; SRUS: solitary rectal ulcer syndrome.

chronic constipation or straining strongly favors prolapse over IBD (Table 2).

5. Non-active colitis with chronic damage

5.1. Morphology of the non-active chronic colitis pattern

The non-active colitis with chronic damage pattern is characterized by architectural distortion of the crypts, a hallmark of chronic mucosal damage, without neutrophilic (active) inflammation. In addition to architectural distortion, all features of chronic damage can be variably found, depending on etiology (e.g., basal plasmacytosis, Paneth cell metaplasia, etc.)

This pattern may be seen throughout the colon or localized to certain segments, but unlike the diffuse active pattern, there is no concurrent neutrophilic activity to suggest an active flare. It may represent a quiescent phase of an established IBD, particularly in patients under treatment.

5.2. Differential diagnosis of the non-active chronic colitis pattern (Tab. 3)

The non-active chronic colitis pattern most commonly represents *treated or quiescent IBD*. In the context of IBD, this pattern can be seen during clinical remission, especially in patients receiving effective immunosuppressive therapy or biologic drugs. Histological features of chronicity—architectural distortion, basal plasmacytosis, and Paneth cell metaplasia—persist despite the resolution of acute inflammation. Careful comparison with prior biopsies is essential to assess changes over time.

All conditions associated with architectural distortion, including several non-IBD conditions, can show chronic mucosal changes without active inflammation. This is true for many causes which show both active and non-active disease and some have already been mentioned in the previous paragraph. In particular, *SCAD* [4,23,27]. and *diversion colitis* may show a non-active chronic colitis pattern [4,20–23]. Similarly, ischemic and radiation colitis [4,27], as well as mucosal prolapse (including solitary rectal ulcer syndrome and localized prolapse changes elsewhere in the colon) [4,32], can present with a non-active chronic colitis pattern histologically. *Post-infectious colitides* and *drug-related injury* [4,15,18]. may also show chronic changes with little to no inflammation (Table 3).

Finally, *microscopic colitis* may occasionally show architectural distortion and a chronic non-active inflammatory infiltrate, but in general, architecture is preserved, and thus this entity not discussed further [8]. Furthermore, the diagnosis of microscopic colitis requires characteristic histologic features: a thickened subepithelial collagen band in collagenous colitis and increased intraepithelial lymphocytes in lymphocytic colitis.

6. Ischemic-like pattern with chronic damage

6.1. Morphology of the ischemic-like pattern with chronic damage

Chronic ischemic damage in the colonic mucosa can be the consequence of different conditions related to the patient's health or exogenous factors (drugs and medications) [33]. This pattern is more frequently seen in elderly patients with comorbidities and subjects with chronic illnesses, including vascular diseases and diabetes, with a possible additional detrimental impact of prolonged pharmacological therapies [2,34]. In young-adults, the ischemic pattern more often refers to drug-induced damage and drug abuse [35]. Colitis with an ischemic pattern includes various levels of damage that vary from minimal, focal, and superficial to diffuse, deep, and irreversible [36]. Morphologic alterations in the chronic setting include typical ischemic type changes, such as small and atrophic crypts, lined by small, irregular cells with eosinophilic cytoplasm, dark nuclei, and evident nucleoli in a hyalinized stroma with inconspicuous inflammation [10,35]. with associated architectural changes and possible pseudopyloric metaplasia as features of chronicity (Fig. 2).

6.2. Differential diagnosis of the ischemic-like pattern with chronic damage

Causes of ischemic-pattern colitis include different chronic conditions that result in a prolonged (not sudden) decrease of colonic perfusion, such as atherosclerosis or thromboembolic events (e.g., in atrial fibrillation). In these cases, visible epithelial and mesenchymal modifications, but not prominent inflammation, are seen.

Table 3
Differential diagnosis of the non-active chronic colitis pattern.

Etiology	Affected colonic tract	Additional histological findings	Diagnostic exams
IBD (quiescent UC or CD)	Any	Architectural distortion, basal plasmacytosis, Paneth cell metaplasia	Clinical history, comparison with prior biopsies
Diverticular-associated (segmental) colitis	Interdiverticular mucosa, usually sigmoid	Chronic inflammation; rectal sparing	Endoscopy, anatomical distribution
Diversion colitis (inactive)	Diversion segments	Numerous lymphoid follicles with germinal centers	Clinical history of fecal stream diversion
Ischemic colitis (chronic phase)	Any, usually watershed zones	Crypt distortion, mucosal atrophy, lamina propria fibrosis, hyalinization	Endoscopy, clinical context
Radiation colitis (chronic phase)	Irradiated segments	Crypt distortion, lamina propria fibrosis, hyalinization	Radiation history, endoscopy
Mucosal prolapse	Distal rectum or associated with polyp/anastomosis	Marked crypt distortion, fibromuscular hyperplasia between crypts, superficial inflammation	Trichrome/elastin stains, endoscopy (solitary lesion, polypoid mucosa, straining history)
Post-infectious colitis	Any	Residual architectural changes, mild chronic inflammation, absence of basal plasmacytosis	Clinical history of recent infection
Drug-related injury (e.g., ICI, mycophenolate)	Any	Architectural abnormalities, may lack active inflammation	Clinical context, drug history
Microscopic colitis (rare mimic)	Any	Occasional architectural distortion, usually preserved architecture, sub-epithelial collagen or increased IELs	Histological criteria, clinical suspicion

Abbreviations: IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; ICI: immune checkpoint inhibitor; IEL: intraepithelial lymphocytes.

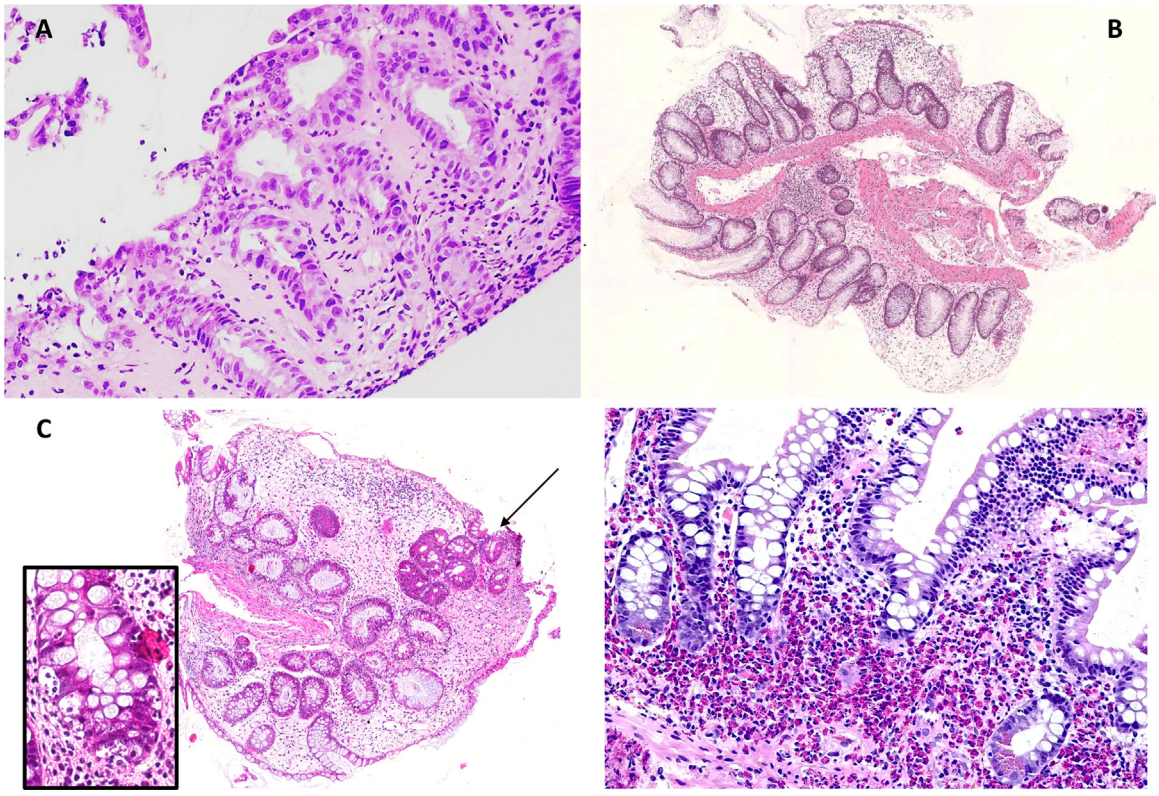

Fig. 2. Other patterns with chronic damage. (A) Chronic ischemic-like pattern, characterized by neutrophilic activity in superficial epithelium, minimal mixed inflammatory infiltrate in lamina propria, and hyalinized stroma. (B, C) Apoptotic-like pattern, demonstrating mild chronic inflammation of lamina propria, crypt architectural distortions, and diffuse apoptotic bodies in glandular crypts (arrow and inset). (D) Eosinophilic-like pattern with prominent and confluent eosinophils. Hematoxylin & eosin stain; original magnification: 200 × (A, C, D) and 40 × (B).

The presence of eosinophils associated with atrophic modifications has been associated with the use of hypotensive and vasoconstrictor drugs or chemotherapeutics. Invasive endoscopic procedures and vascular or abdominal surgery can lead to ischemic damage to the mucosal wall at different depths, resulting in scars. Colonic volvulus, chronic infections, or chronic inflammation affecting the large bowel can be a cause of an ischemic pattern of colopathy. *Radiotherapy damage* may include ischemic and chronic aspects consisting of crypt atrophy, distortion of their shape, and regenerative aspects of the epithelium [37]. Obliterated capillary vessels may also be observed. Scar tissue with reactive fibrosis is typical of the chronic phases of ischemic colitis and can develop after radiotherapy. It is observed in the mucosal lamina propria and in the submucosa, and where it may become exuberant, leading to mucosal polyps or luminal stenosis, with minimal chronic inflammation.

7. Eosinophilic-like colitis pattern with chronic damage

7.1. Morphology of the eosinophilic-like colitis pattern with chronic damage

Eosinophil counts vary significantly depending on the gastrointestinal tract, with an increase from the esophagus to the duodenum, a peak in the cecum and ascending colon, and a de-

crease in the distal segments of the colon, apart from the sigmoid colon, where a moderate presence of eosinophilic granulocytes is observed. (3841). Nevertheless, studies in the literature are often difficult to compare, as eosinophil counts are expressed as wide ranges per high-power field (HPF) with different microscopic field numbers, rather than per mm^2 [41]. They are distributed in the submucosa and within the crypt epithelium, with possible formation of eosinophilic abscesses (Fig. 2). At times, it is possible to observe eosinophil degranulation. Increased eosinophils in the mucosal lamina propria are observed in the acute phases of mucosal damage but may persist for a long time and therefore also characterize chronic mucosal damage also [34–41].

7.2. Differential diagnosis of the eosinophilic-like colitis pattern with chronic damage

Most cases of eosinophilic colitis in adults are due to *drugs*, including NSAIDs, antiplatelet agents, and hormone therapy. Knowledge of a patient's medical history regarding recent drug intake helps the pathologist suggest this diagnosis [42]. Increased eosinophils in endoscopic biopsies of the ileo-colonic mucosa must be placed in differential diagnosis with allergies or hypersensitivity to exogenous foods (*milk-protein proctocolitis* in infants) or other substances, including drugs for colonoscopy preparation and parasitic helminthic infections, including *Strongyloides stercoralis, Enterobius vermicularis*, and *Trichuris trichiura* (whipworm) [42]. Liver transplant recipients maintained on *immunosuppressive therapy* with tacrolimus can develop colonic eosinophilia that reduces when immunosuppression is reduced [43]. Some cases of eosinophilic colitis have been described in the course of *Churg-Strauss disease*, in which colonoscopy revealed multiple erosions in the epithelium and increased eosinophilic infiltration, typically perivascular, but this tends to decrease after therapy with high doses of corticosteroids and cyclophosphamide [43]. It is worth noting that, although the eosinophilic infiltrate may be striking, it is frequently observed in chronic or relapsing UC and does not necessarily indicate another pathology such as eosinophilic colitis. Accurate diagnosis relies on evaluating the constellation of histological changes in conjunction with clinical context, rather than on any single feature.

Where no underlying pathology is identified, the rich eosinophilic infiltration in the colonic mucosal lamina propria is clinically referred to as *primary eosinophilic colitis* [44]. In this condition, histologically, we observe an increase of eosinophils, either diffusely or in clusters, in the absence of clear causes. Primary eosinophilic colonic disorders represent a spectrum of inflammatory disorders in which eosinophils infiltrate the intestine, only partly mediated by IgE [45]. In some cases, eosinophilic colitis occurs independently of blood hyper eosinophilia. One must stress that this is a clinical diagnosis (not a histopathology one), proposed only in the correct setting and when all other causes of increased eosinophil counts have been excluded.

8. Apoptotic-like colopathy pattern with chronic damage

8.1. Morphology of the apoptotic-like colopathy pattern with chronic damage

Although uncommon, an apoptotic pattern of ileocolonic mucosal damage can be observed in several clinical conditions. It is characterized by the detection of diffuse apoptotic bodies, such as pieces of degenerating dust and cellular debris of variable size, within the crypt epithelium, associated with histological signs of chronic damage, such as crypt rarefaction/loss combined with regenerative aspects of the epithelium and mucin depletion (Fig. 2). The correct diagnosis requires correlation between the histological features and clinical history as possible causes include drug induced lesions (e.g. mycophenolate), history of haematopoietic stem cell transplantation, immunodeficiencies or viral infections [46]. In these conditions, inflammation varies from mild to severe, with erosions or ulceration and includes plasma cells, eosinophils, and lymphocytes, which in some cases are intraepithelial (on the superficial epithelium) showing a *celiac disease-like pattern* [47]. In some cases, a mosaic distribution of inflammation is observed, with surface scalloping mucosal damage at endoscopy [48].

8.2. Differential diagnosis of the apoptotic-like colopathy pattern with chronic damage

In biopsies from patients with *graft-versus-host disease (GVHD),* apoptotic bodies are primarily detected in the deep crypts of the colon, sometimes contained in cytoplasmic vacuoles, and, in severe forms, they organize in clusters and form apoptotic abscesses [46]. If GVHD persists, chronic architectural features may also be seen, such as crypt distortion and atrophy of the crypts up to complete crypt loss, and with aggregates of neuroendocrine cells in the lamina propria [49–50]. *Common variable immunodeficiency (CVID)* leads to an apoptotic-like pattern colopathy, characterized by intraepithelial lymphocytosis, more pronounced in the deep portion of the crypts and intermingled with apoptotic bodies, and prominent lymphoid aggregates lacking plasma cells [51]. *Autoimmune enterocolopathy* refers to a specific condition affecting the small intestine predominantly, characterized by villous atrophy, increased apoptosis in the crypts, neutrophilic cryptitis and microabscesses, increased intraepithelial lymphocytes and Paneth cell metaplasia, mainly in the distal colon [52].

9. Conclusions

In conclusion, our main message is that *chronic colitis* is defined by the presence of histological chronic mucosal injury and not as sole chronic-type inflammation. Features of chronic mucosal injury include crypt architectural distortion (e.g., crypt branching, crypt atrophy, a villiform/irregular mucosal surface), basal plasmacytosis, metaplastic epithelial changes (e.g., Paneth cell metaplasia, pseudo-pyloric metaplasia), and fibrosis [9,10,18]. A mere diagnosis of *chronic colitis* is not specific, as it may be misinterpreted by clinicians; furthermore, it does not provide useful information for possible differential diagnosis.

Histological features of chronicity can be encountered in numerous pathological conditions, including IBD colitis and non-IBD colitis, and the differential diagnosis requires an accurate histological and clinical assessment and a multidisciplinary approach. In some cases, a definite diagnosis cannot be reached due to a lack of clinical information, insufficient sampling, or overlapping histologic features.

With this in mind, we, as GIPAD, propose a *pattern-based histological approach* in reporting chronic histological damage in the biopsy setting, especially for cases in which reaching a final diagnosis is challenging. This approach could narrow the range of possible differential diagnoses, assisting clinicians in ensuring the best management for patients. For instance, a report may state: "Colitis with a diffuse active chronic pattern (GIPAD 2026), suggestive/supportive of the clinical impression of ulcerative colitis." Alternatively, if clinical information is lacking, the report could read: "Colitis with a diffuse active chronic damage pattern (GIPAD 2026); clinical correlation for possible ulcerative colitis is required."

It is important to emphasize that this diagnostic approach, based on histological patterns, must not preclude the formulation of an accurate diagnosis. Providing clinical indications is a prerequisite for accurate histological interpretation, and pathologists

should clearly document in their report whether relevant clinical data were available, and specify which clinical information was considered during the assessment. This practice would ensure that histological findings are evaluated in the proper clinical context, supporting precise diagnosis and effective communication between pathologists and clinicians.

However, whenever clinical, histological, and endoscopic features are fully consistent with a specific pathological entity, the pathologist should provide a definitive diagnosis. Otherwise, the histological pattern should be stated, together with appropriate diagnostic proposals or differential diagnoses. Ultimately, pattern-based interpretation should serve as a supportive framework, rather than a substitute for integrative clinicopathological diagnosis, in those cases when important pieces of the puzzle are missing (e.g., no clinical information, incomplete endoscopic details or sampling amongst others).

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Declaration of competing interest

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