

Position Paper

Pattern-based histologic approach in colitis without chronic architectural damage: GIPAD recommendations



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ARTICLE INFO

Article history:

Received 28 January 2026

Accepted 10 April 2026

Available online 2 May 2026

Keywords:

Apoptotic colitis

Crohn disease

Eosinophilic colitis

Inflammatory bowel disease

Ischemic colitis

Ulcerative colitis

ABSTRACT

In patients presenting with intestinal symptoms who undergo colonoscopy with mucosal sampling, the pathologist plays a central role in identifying the underlying etiology in order to guide appropriate clinical management. However, common intestinal symptoms such as diarrhea are shared by a broad spectrum of conditions, including infectious diseases, functional disorders (e.g., irritable bowel syndrome), inflammatory bowel disease (IBD), drug-induced injury, and metabolic disorders (e.g., diabetes mellitus). Although serological biomarkers may support the diagnostic workup, they are frequently insufficient to establish a definitive diagnosis. Moreover, endoscopic examination may fail to detect significant mucosal abnormalities even when histology reveals disease-specific patterns, as occurs in lymphocytic and collagenous colitis (i.e., microscopic colitis). In this complex diagnostic landscape, histomorphological evaluation represents a crucial element, allowing integration of microscopic findings with clinical and endoscopic data to reach an accurate interpretation.

In recent years, accumulating evidence has demonstrated that similar histological patterns of intestinal injury—such as IBD-like architectural and inflammatory changes or eosinophil-rich infiltrates—may be

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<https://doi.org/10.1016/j.dld.2026.04.008>

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associated with different underlying etiologies. This overlap is particularly relevant in patients treated with novel oncologic therapies, including tyrosine kinase inhibitors (TKIs), immune checkpoint inhibitors (ICIs), and emerging treatments such as chimeric antigen receptor T-cell (CAR-T) therapy. In addition, in daily practice, pathology request forms often lack essential clinical, endoscopic, and laboratory information, further increasing the risk of diagnostic misinterpretation and inappropriate disease attribution. To address these challenges, the Italian Group of Digestive Disease Pathology (GIPAD) proposes a pattern-based histological approach for reporting mucosal damage in patients with colitis. In this first paper, we focus on non-chronic patterns of mucosal injury and discuss their principal differential diagnoses, with the aim of supporting standardized reporting and improving clinicopathological correlation.

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1. Introduction

A pathologic diagnosis is a mosaic of elementary lesions, which, once recognized and combined, make up a pattern of damage that may correspond to various etiologies. It is important to remember that the histologic lesions, either as a single elementary lesion (i.e., eosinophils or basal plasmocytosis) or as an overall pattern (i.e., chronic or ischemic-type damage), cannot be attributed to a single/specific etiology but require clinical integration. Indeed, morphology can be affected by drugs (e.g., inflammatory bowel disease - IBD - during treatment) and/or diet (e.g., celiac disease during a gluten-free diet) and/or time of onset of disease (a couple of weeks versus months). Interestingly, bowel prepping for endoscopy can affect histology in intestinal biopsy specimens, and the pathologist must account for this when identifying lesions. Innovative treatments, such as novel cancer treatments, both in terms of new drugs (e.g., Immune Checkpoint Inhibitors - ICI) and new technologies (such as chimeric antigen receptor T-cell (CAR-T) therapy), represent additional potential differential diagnoses of colitis that the pathologist may not be aware of, at the time of histological examination [1].

In routine practice, the pathologist is often asked to submit a 'definite' histologic diagnosis, i.e., to submit an IBD diagnosis or an 'eosinophilic colitis', blinded to clinical, serological, and endoscopic data because they are lacking in the histological request form. Pathologists should resist the temptation of making a 'definitive' diagnosis regardless of the availability of clinical information, as this may pose significant management implications.

A similar pattern-based approach is advocated in other settings, such as liver disease [2] and lung disease [3], to name but a few. Similarly, a morphologic pattern of damage has been recently proposed in very early onset (VEO)-IBDs and showed clinical utility in differentiating monogenic disease from 'true' IBD [4,5]. In this pediatric context, reporting a histologic pattern of mucosal damage is advocated rather than a 'definitive' diagnosis so as not to potentially misdiagnose a monogenic cause of intestinal symptoms (with important prognostic and treatment implications). Such a pattern-based approach is helpful in daily clinical practice for intestinal mucosa biopsies from adult patients as well.

The Italian Group of Digestive Disease Pathology (Gruppo Italiano Patologi Apparato Digerente - GIPAD), aims to contribute to this issue by proposing a 'pattern-based histological approach' in reporting histological damage in the biopsy setting.

To simplify the approach to the histologic pattern of mucosal damage, we first describe the morphologic features in a 'normal/healthy' intestinal mucosa. No mention will be made of acute or chronic conditions in terms of time from the onset of symptoms, as these data are often missing from the pathology request form, or of the type of inflammatory infiltrate, as this may be subjective and may vary from patient to patient. Instead, two major lesion classes will be described: i) a class with no major architectural gland alterations, such as glandular distortion and atrophy,

and ii) a class based on the presence of major architectural gland alterations.

In this paper, we will describe the morphology of 'normal/healthy' intestinal mucosa and the histologic pattern of mucosal damage with no architectural alterations (non-chronic pattern). The histologic pattern of mucosal damage with architectural alterations (chronic damage pattern) will be described in a subsequent contribution [6].

2. Definition and morphology of 'normal intestinal mucosa' (Fig. 1)

A baseline of what constitutes 'normal/healthy intestinal mucosa' is important to compare and describe minimal lesions and/or patterns of disease. In this paragraph, therefore, we describe criteria to define 'normal/healthy' intestinal mucosa by analyzing all the mucosal compartments. The colonic mucosa is composed of epithelial crypts, the connective tissue of the lamina propria with accompanying immune (inflammatory) infiltrate, interposed between the crypts, and a thin band of smooth muscle tissue, the muscularis mucosae [7].

2.1. Glandular epithelium

From an architectural perspective, colonic crypts appear indistinguishable between the right and left colon, while variations are present in terms of cell types. Crypts are arranged as parallel, homogeneously sized, regularly aligned tubules that are evenly spaced, and their bases rest directly on the muscularis mucosae [8]. When observed in a longitudinal section, the crypts may resemble test tubes in a rack, whereas in cross-section, they can resemble a field of daisies.

Crypts are lined by a single layer of columnar cells, either absorptive cells, most represented in the right colon, or mucus-secreting goblet cells, most represented in the left colon [9]. Additionally, colonic crypts may contain Paneth cells, endocrine cells, and very rare intraepithelial lymphocytes, eosinophils, and mast cells. It is crucial to distinguish Paneth cells from endocrine cells, as endocrine cells are normally present throughout the entire colon, whereas Paneth cells are considered a normal finding only in the right colon and transverse colon. When identified in the left colon, metaplastic Paneth cells are regarded as a histological marker of chronic injury [10]. Paneth cells contain large eosinophilic granules and are in direct contact with the luminal side of the crypts, playing an immunological role in defending against intraluminal pathogens. In contrast, endocrine cells contain small, fine, reddish granules and are in direct contact with the crypt basal membrane, allowing them to release their hormonal content into the surrounding capillaries [11].

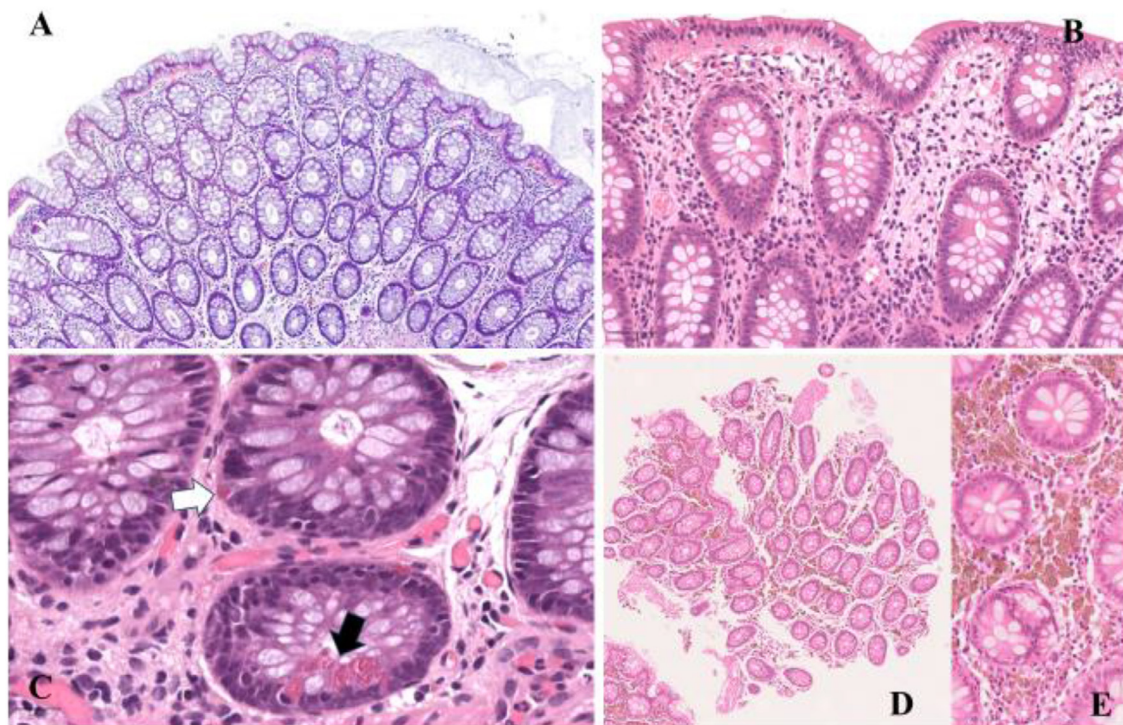


Fig. 1. 'Normal mucosa'. A: 'Normal' intestinal mucosa with different compartments; B: Normal glandular architecture and immune-cell composition; C: Glandular cellular component with Paneth cells (white arrows) and endocrine cells (black arrow) - Paneth cells are considered 'normal' in the ascending and transverse colon; D,E: Pseudomegacolon.

2.2. Inflammatory cellular component

The lamina propria of the normal colonic mucosa contains various immune elements, including lymphocytes, macrophages, eosinophils, mast cells, and some plasma cells, predominantly IgA-secreting. Even *rare* neutrophilic granulocytes in the lamina propria are considered normal, especially in proximity to small capillaries [12]. The cellularity of the lamina propria exhibits a different distribution gradient across colonic segments, with a higher cellular concentration in the right colon compared to the left colon; a further gradient is observed from the luminal surface, degrading down towards the muscularis mucosae. Moreover, lymphoid aggregates can be observed throughout the colon, similar to those in the small intestine, contributing to intestinal immune system function [13]. A gradient of eosinophils is also seen from right to left with seasonal and geographic variability [14].

As previously described, some of these immune cells, particularly lymphocytes, may also localize within the colonic glandular epithelium. Specifically, a count of fewer than 5 intraepithelial lymphocytes (IELs) per 100 epithelial nuclei is considered normal [15] (the epithelium over lymphoid aggregates may contain more intraepithelial lymphocytes as well as specialized M-cells, which function as antigen-presenting cells). In contrast, the presence of intraepithelial neutrophils is always a histological feature of pathology.

Finally, another cell type that can be found in the colonic mucosa is the muciphage. These cells are more commonly observed in rectal mucosa and consist of macrophages with abundant foamy/mucinous cytoplasm. Their primary function is to "clear" extravasated mucin resulting from nonspecific mucosal damage [16].

2.3. Stromal component

The lamina propria also contains a stromal component that provides support for the crypts. It consists of loose connective tissue

rich in capillaries and lymphatic vessels, where two types of mesenchymal cells can be observed: pericrypt myofibroblasts and subepithelial myofibroblasts. Another mucosal mesenchymal component is the muscularis mucosae, a thin band of smooth muscle tissue, whose presence in biopsy samples is essential for the accurate histological assessment of crypt regularity versus distortion/atrophy [17].

2.4. Differential diagnosis in normal intestinal mucosa

In the setting of endoscopic biopsies showing normal/healthy colonic mucosa, the primary objective of the differential diagnostic process is to describe normal histology. For this purpose, it is crucial to recognize certain histologic alterations that may result from bowel preparation and/or endoscopic trauma. These include epithelial desquamation, acute hemorrhagic foci, edema, pseudolipomatosis, decreased intracellular mucus, and increased mitotic activity [18].

One of the most common errors in bowel biopsies is the use of the term "mild chronic inflammatory infiltrate" in normal colonic mucosa samples. This terminology can be misinterpreted as a diagnosis of 'chronic colitis', and this may mislead the clinician and confuse patient management. Therefore, it is crucial not to be overly influenced by the presence of inflammatory cells, particularly in the right colon, where their concentration is naturally higher than in the left colon. Additionally, identifying the specific types of inflammatory cells present—such as plasma cells and neutrophils versus lymphocytes and eosinophils—can provide valuable diagnostic clarity [12–15].

Two additional potential diagnostic pitfalls may arise when evaluating the normal architectural configuration of the crypts. The first involves the misinterpretation of crypt branching. Crypt branching is considered pathologic when it affects the lower two-thirds of the mucosa. However, anatomic variants of the colonic mucosa exist in which surface undulations are present, and the

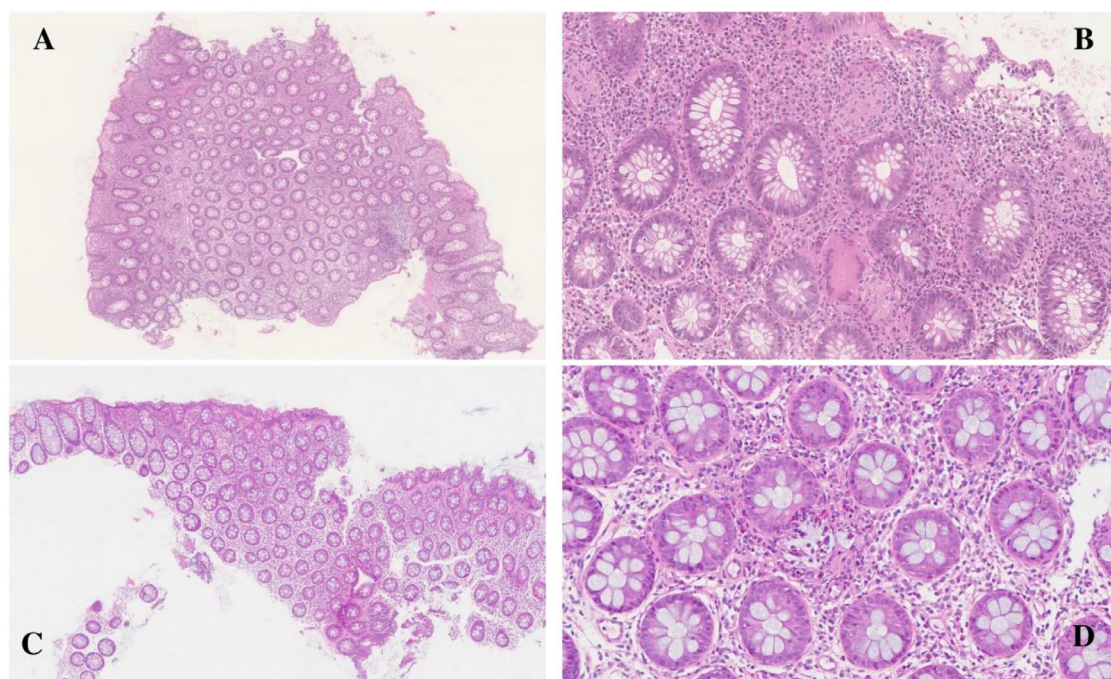


Fig. 2. Diffuse active and focal active non-chronic colitis pattern. A, B, Diffuse active colitis with granulomata, infectious etiology; C, D: Focal active colitis, infectious etiology.

underlying crypts may exhibit branching in the upper third of the mucosa [19]. This should not be regarded as a histological feature of mucosal damage. The second pitfall may arise when observing crypts close to mucosal lymphoid aggregates, as they may appear branched. Pigment in macrophages can be the only minimal lesion observed in patients with inappropriate and long-term use of laxatives and can lead to a ‘pseudomelanosis coli’ appearance, detectable both at endoscopy and at histology [9].

2.5. Elementary lesions

Having described normal mucosa, it is important to identify elementary lesions which may be seen in biopsy tissue and, for further reference, to distinguish between acute-type lesions and chronic-type lesions.

Acute/active-type elementary lesions: inflammatory infiltrate with neutrophils, polymorphonuclear neutrophils infiltrating the crypt epithelium (cryptitis) and crypt abscesses, erosions and ulcers, lamina propria edema

Chronic-type elementary lesions: crypt branching and architectural distortion, mucosa surface irregularity (e.g., villous architecture in colonic biopsies), Paneth cell metaplasia in left-sided colonic and rectal biopsies, pseudopyloric metaplasia mostly in ileal biopsies, basal plasmocytosis.

3. Diffuse active non-chronic colitis pattern

3.1. Morphology: Diffuse active non-chronic colitis pattern (Fig 2, a-b)

The diffuse active non-chronic colitis pattern (DAC-type pattern) of colitis is characterized by active, neutrophilic inflammation of the lamina propria with lamina propria edema, cryptitis, cryptic abscesses, erosions, and ulcerations combined in various ways; by definition, no signs of chronic damage are observed [20]. In some cases, the lamina propria appears more hemorrhagic, while in others, pseudomembranes and/or ischemic changes (see later paragraph) may be associated [20]. Lesions can be patchy or diffuse in distribution and may predominantly involve the right colon

or the rectum in certain instances (e.g., *Salmonella* or *Yersinia* in the cecum area). If biopsies are performed several weeks after disease onset, partial histologic resolution characterized by sparse neutrophilic inflammation, reactive epithelial changes, and mucosal edema can be observed.

3.2. Differential diagnoses of diffuse active pattern (Table 1)

Most DAC-pattern colitides are caused by *infections*, though it is generally not possible to identify a specific etiology on biopsy histology, and clinical integration with serological data and stool culture is mandatory to reach a definite diagnosis. Rarely, some specific features that enable the identification of etiology may be seen. Cytomegalovirus (CMV) must always be looked for, especially in elderly or (immune)compromised patients. CMV inclusions, which can be confirmed using immunohistochemistry, may be found in the lamina propria (endothelial and stromal cells) and are often seen in ulcers/granulation tissue. *Salmonella* infection, though rarely biopsied, is mainly localized in the right segments (ileum, right colon, cecal appendix); histological findings consist of DAC, hyperplasia of Peyer’s patches, ulcerations, and necrosis with a sometimes-prominent mononuclear cell in the lamina propria. *Campylobacter* infection-associated lesions are also more frequently found in the right colon with a DAC pattern and possible histiocytic aggregates that resemble granulomas. *Shigella* infection, on the other hand, is generally associated with a DAC-pattern mainly located in the left colonic segments. Pseudomembranes may be seen at onset, while late phases of infection can pose difficulties in distinguishing from Crohn’s disease, as they may be characterized by segmental inflammation with architectural distortion. A typical pseudomembranous pattern, with associated DAC-pattern, is seen in *Clostridium difficile* infection and is characterized by ballooning crypts and volcano-type exudate (eruptive fibrino-granulocyte exudates that resemble an erupting volcano) [19,21].

A differential diagnosis that can pose difficulty for the pathologist is the *distinction between IBD and infectious causes*, as a DAC pattern can be observed in IBD patients at onset. Generally, ul-

Table 1
Differential diagnosis in Diffuse Active non-chronic Colitis pattern.

Etiology		Mucosal Damage Extension	Additional histological findings	Diagnostic tests
Infection	CMV	Pancolic	Ulcers and granulation tissue; CMV immunostaining	Serology
	Salmonella	Right colon	Peyer's patches hyperplasia; ulceration, necrosis	Serology
	Campylobacter	Right colon	Histiocytic aggregates	Serology
	Shigella	Left colon	Onset: pseudomembranes	Serology
IBD at onset	Clostridium	Pancolic	Late phase: IBD-like pattern (Crohn's Disease like)	Serology
	UC	Pancolic	Ballooning crypts; volcano-type exudate	Serology
			Dense transmural lymphoplasmacytic infiltrate in true UC	Serology
Drugs		Pancolic	-	Clinical integration

Abbreviations: CMV: Cytomegalovirus; IBD: Inflammatory Bowel Disease; UC: Ulcerative Colitis.

Table 2
Differential diagnosis in Focal Active (non-chronic) Colitis pattern.

Etiology	Mucosal Damage Extension	Additional histological findings	Diagnostic tests
Bowel prep for colonoscopy	Focal/pancolic	None	Clinical integration
IBS	Focal/pancolic	None	Clinical integration
Infection	Focal/ Pancolic	None	Clinical integration
Drugs	Focal/pancolic	Isolate apoptoses	Clinical integration
IBD at onset	Pancolic	Moderate lymphoplasmacytic infiltrate with/without chronic glandular damage	Clinical integration

Abbreviations: IBD: Inflammatory Bowel Disease; IBS: Inflammatory Bowel Syndrome; UC: Ulcerative Colitis.

cerative colitis (UC) shows an accompanying dense, transmucosal, lymphoplasmocellular inflammatory infiltrate in the lamina propria [21].

DAC may be related to *drugs* such as fenemates, etodolac, diclofenac, naproxen, carbamazepine, and rituximab [22,23]. In particular, non-steroidal anti-inflammatories (NSAIDs) may cause a DAC-pattern with inflammation both in the ileum and colon (more often right colon), often associated with erosions and ulcers. The presence of ulcers with an adjacent near normal-looking mucosa suggests a NSAID injury, while sometimes active inflammation, cryptitis, apoptoses, and regenerative epithelial injury may be seen [22,23].

4. Focal active non-chronic colitis pattern

4.1. Morphology: Focal active non-chronic colitis pattern (Fig 2, c-d)

The focal active colitis (FAC) pattern is the focal/isolated presence of polymorphonuclear neutrophils infiltrating the crypt epithelium (cryptitis), involving one or a few single crypts in the absence of significant lamina propria inflammation (except for surrounding the involved crypts) or chronic glandular damage.

Focal active inflammation involving isolated glands, in an otherwise unremarkable context, in patients with a silent clinical history, is a relatively frequent event [24]. FAC is related to different clinical scenarios and different etiologies requiring correlation with drug history, clinical, and laboratory findings [25].

4.2. Differential diagnoses of focal active pattern (Table 2)

The FAC pattern is a frequently encountered pattern that may pose considerable difficulties for the treating physician, as multiple clinical conditions correlate with this histopathological pattern

[25,26]. In some cases, FAC may be a facet of irritable bowel syndrome or seen in patients who are particularly sensitive to bowel prep for colonoscopy (sometimes with aphthous erosions [22,23]). In other cases, however, a FAC pattern is associated with a precise etiology.

Infectious colitis may present with a FAC pattern, either in the first days of infection, associated with edema and ulcerations, or during the resolution of inflammation. Correlation with the onset of symptoms (diarrhea) and serological data and stool cultures are necessary for diagnosis [26]. *Drug-related FAC* is often seen in NSAID use, and the presence of occasional apoptoses can orient a causal diagnosis [23]. An *IBD-related FAC* pattern is more often seen in children, especially in Crohn's disease, where some degree of chronic glandular damage and at least a moderate lymphoplasmacellular infiltrate should help. A FAC pattern can be observed in UC that is partially responsive to therapy, but usually, alterations from chronic damage are also seen. Of note, some cases of UC at onset in children show a FAC pattern without architectural distortion, and this diagnosis requires close interaction with clinical colleagues [21,26].

5. Ischemic-like colitis pattern

5.1. Morphology: Ischemic-like colitis pattern (Fig 3, a-b)

The ischemic-like colitis (IC) pattern typically shows a preserved glandular architecture with withering of crypts, characterized by small (microcrypts) and fading glands, lined by reactive epithelium. The more superficial/luminal aspects of the crypts are generally involved first in early lesions, and these may progress to complete crypt loss with erosions as damage is more severe. Cytologically, irregular enterocytes with eosinophilic cytoplasm and dark nuclei, as well as depletion of mucin, are present. Erosions may be identified adjacent to these areas, and the lamina propria may show hemorrhages and edema associated with pseudo-detachment of the superficial luminal epithelium. Generally, inflammation is mild to moderate with/without cryptitis, and reduction of inflammation is seen the further away the samples are taken from the involved areas. One important feature that is usually seen in conjunction with crypt withering is lamina propria fibrosis [21]. In severe cases, ulceration and pseudomembranes are present, as well as transmural necrosis, which is not appreciable in intestinal biopsy samples. In some cases, chronic glandular damage with architectural changes may be seen in the case of chronic recurrent ischemic colitis; this aspect will be discussed in the subsequent paper [6].

The IC-pattern does not imply an etiological diagnosis; this pattern may be seen in true ischemic causes but also in other non-ischemic cases, such as infectious or drug-induced colitis. This pattern is frequently related to 'acute transient (reversible) ischemic

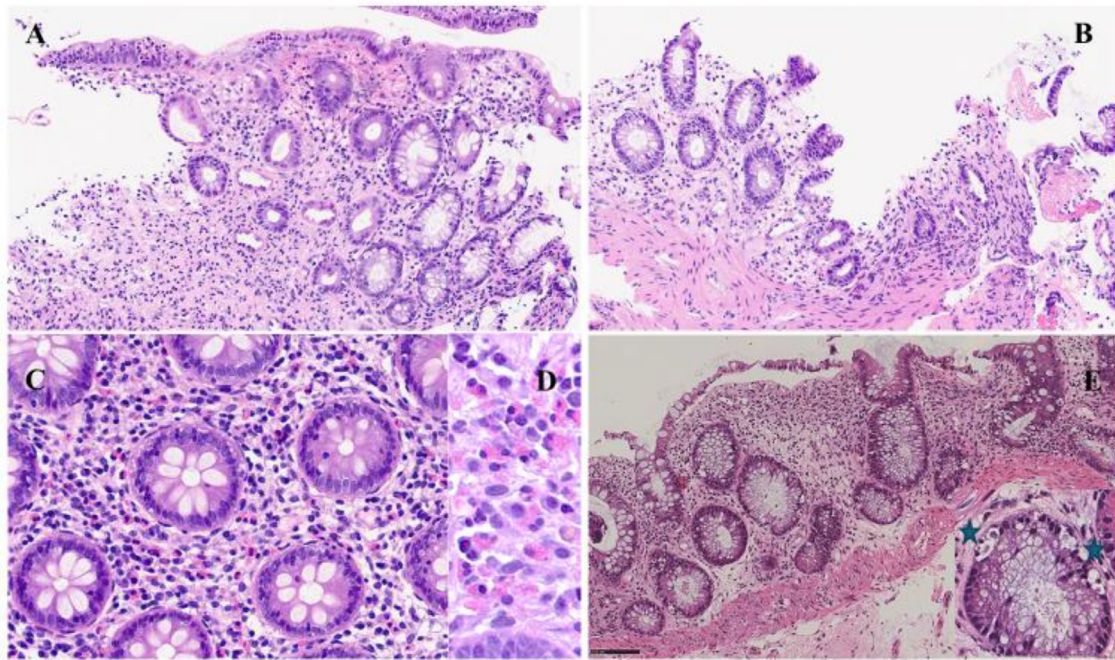


Fig. 3. Non-active colitis without chronic damage: A, B: Ischemic-like colitis pattern; C,D: Eosinophil-like colitis pattern; E: Apoptotic-like pattern with apoptotic bodies (onset).

colitis and 'acute severe (irreversible) ischemic colitis', according to both Boley [27] and Marston [28] classifications.

Acute transient lesions are related to non-occlusive ischemia or vasospasm induced mainly by medications and infections and are characterized, in the early phase, by mucosal and submucosal edema, hemorrhage, and detachment of the surface epithelial layer from the underlying basement membrane, whereas the late phase (reperfusion) is characterized by neutrophilic inflammatory infiltrates and cryptitis [27].

Acute severe lesions are generally related to occlusive ischemia for arterial and venous thrombosis, vasculitis, small and medium vessel disorders (amyloidosis, diabetes mellitus, radiation), hypercoagulable states (congenital and acquired), and intestinal occlusion (cancer-related obstruction, hernias, volvulus, etc.) [21,28]. Some infections, such as *Escherichia coli*, may also lead to coagulative disorders and severe colonic lesions. Acute severe (irreversible) ischemic colitis is characterized by an early phase, with mucosal erosions, ulceration, and necrosis, sparing of the deeper crypts, lamina propria hemorrhage and fibrosis, whereas transmural necrosis and edema with fibrinous serositis arise in the late phase [9].

5.2. Differential diagnosis of ischemic-like colitis pattern (Tables 3 and 4)

Classifying the IC-pattern according to the extension of mucosal damage (i.e., pan-colic vs localized) and co-existence of other 'minimal lesions' can help delineate different etiologies. A location-based differential is a useful approach for these types of lesions.

Localized/segmental damage is due to local perfusion deficiency, such as occurs in thrombo-embolic and cardiac diseases, cardiovascular surgery, and in abdominal aortic aneurysms, and affects the intestinal segment vascularized by the altered arterial vessel [29].

Sigma-restricted lesions may be related to diverticular disease due to motility alterations leading to mucosal traction and possible infection [21,30]. Notably, the IC pattern is described in uncomplicated diverticular disease, whereas complicated disease, showing chronic damage and IBD-like morphology, is also possible [6,31].

In the presence of an ischemic pattern of colitis limited to the sigmoid tract, non-complicated diverticular disease is a possibility and should be suggested only if diverticulae are described at endoscopy.

Rectum-restricted damage is generally seen in mucosal prolapse syndrome with related solitary rectal ulcer syndrome (SRUS), or over hemorrhoids, diagnosis of which requires endoscopic correlation. Ischemic pattern lesions with erosions or ulcers, often combined with thickening of the subepithelial layer, are observed in the earliest phase of SRUS, showing hyperplastic smooth muscle fibers extending upward from a thickened muscularis mucosae with vascular congestion, hemorrhage, and edema. In the late phase, crypt dilatation and elongation with mucin depletion and a hyperplastic or serrated architecture (limited to the upper half of glands) can be observed, as well as diamond-shaped crypts in the basal half (distorted by the muscularized lamina propria). Cloacogenic polyps, inflammatory cap polyps, and inflammatory myoglandular polyps share features of the ischemic pattern but represent a distinct category, as they are endoscopically categorized as 'polyps' [5].

The acute phase of radiation-induced colitis usually presents with ischemic-type features and requires knowledge of previous radiation treatment for diagnosis. Epithelial flattening and dilated crypts with mucin-depleted enterocytes, exhibiting bizarre nuclei mimicking dysplasia and increased apoptoses with mild to moderate inflammatory infiltrate and small-vessel ectasia in the lamina propria are often seen. Foci of ulceration, prominent hyalinization of the lamina propria, and vascular fibrinoid necrosis can be observed in severe cases. Diffuse fibrosis and glandular atrophy with scattered lymphocytes and plasmacells are observed in the chronic stage [21]. Diagnosis is based on the clinical context.

Diffuse/pan-colic lesions stem from diffuse microvascular damage due to vasculitis or vascular spasm, related to iatrogenic factors (drugs), environmental factors (infections), coagulopathies (congenital or acquired), and autoimmune disorders targeting small vessels.

Theoretically, all *drugs* can lead to a pan-colic ischemic pattern of damage, but the most frequent are diuretics, antibiotics, anti-hy-

Table 3
Differential diagnosis in Ischemic-like colitis pattern, localized damage.

Mucosal Damage Extension	Etiology	Additional histological findings	Diagnostic tests
Localized/segmental	Thrombo-embolic and cardiac diseases, Cardiovascular surgery, Abdominal aortic aneurysms		Clinical Integration
Sigma-restricted Rectum-restricted	Not-complicated diverticular disease Solitary rectal ulcer syndrome (SRUS)	Early phase: hyperplastic smooth muscle fibers extending upward from a thickened muscularis mucosae with vascular congestion, hemorrhage, and edema. Late phase: crypt dilatation and elongation with mucin depletion and hyperplastic or serrated architecture	Endoscopy Endoscopy
	Hemorrhoids Radiation (acute phase)	Mucin-depleted enterocytes, with bizarre nuclei mimicking dysplasia and increased apoptoses	Endoscopy Clinical Integration

Table 4
Differential diagnosis in Ischemic-like colitis pattern, pancolic damage.

Mucosal Damage Extension	Etiology	Additional histological findings	Diagnostic tests
Pancolic	Drugs Be careful of immune checkpoint inhibitors (ICI) and tyrosine kinase inhibitors Primary Gut Infection Autoimmune Disease		Clinical Integration
	Thrombotic microangiopathy	SLE: lymphocytic inflammatory infiltrate within the vessel wall and vascular intimal thickening, thrombosis, and fibrinoid necrosis BD: deep, well-delineated, punched-out ulcers characteristically overlining lymphoid aggregates Microvascular endothelial cell injury and thrombosis	Clinical and serological integration
	Hereditary coagulative disorders Acute hypoperfusion (hypovolemic shock)	Biopsy sampling uncommon	Clinical integration Clinical integration

Abbreviations: BD: Behçet's disease; SLE: Systemic lupus erythematosus.

pertensive drugs, digoxin, NSAIDs, and pseudoephedrine [22]. Recently, chemotherapy, immune checkpoint inhibitors (ICI), and tyrosine kinase inhibitors (TKs) have been shown to be associated with a pan-colic ischemic pattern [1,32]. Of note, oral contraceptives have been reported to cause focal and segmental colitis with aphthous ulcers on a background of normal mucosa and rectal sparing. The presence of crystals on the surface epithelium or in the lamina propria can suggest specific drugs, such as ion-exchange resins, with peculiar morphologic features [22,23].

Primary gut infection, both from bacteria and virus, can lead to a pan-colic ischemic pattern of damage. Generally, endoscopy and biopsy are performed in the post-acute phase, when patients have persistent symptoms and a differential with IBD is required. An ischemic pattern of damage can be associated with mild to moderate inflammatory infiltrate with neutrophils and cryptitis with deposits of fine nuclear debris in the sub-epithelial zone, reactive hyperplastic changes, and patchy or diffuse mucin depletion [21,33].

Autoimmune diseases such as systemic lupus erythematosus (SLE) and Behçet's disease, involving small vessels, can lead to a pan-colic ischemic pattern of damage. Vasculitis in SLE affects small venules and arteries with lymphocytic inflammatory infiltrate within the vessel wall and vascular intimal thickening, thrombosis, and fibrinoid necrosis. Behçet's disease is characterized by deep, well-delineated, punched-out ulcers characteristically overlining lymphoid aggregates with an IC-pattern in the un-involved mucosa. Rarely can the pathologist suggest such diagnoses on biopsy samples, as vessel damage is not easily appreciated. Therefore, in the presence of an IC-pattern of damage, an autoimmune etiology requires clinical and serological integration [9]. Similar considerations are true for other diseases involving vessels in the bowel wall, such as Thrombotic microangiopathy, which is char-

acterized by microvascular endothelial cell injury and associated thrombosis [34].

Rarely, pan-colic damage can be associated with hereditary coagulative disorders and acute hypoperfusion, such as occurs in hypovolemic shock, though intestinal biopsy sampling is uncommon due to dramatic clinical onset [30].

6. Non-active colitis without chronic damage

Many diverse patterns are present within this family of disorders depending on inflammatory cell type present, distribution or other factors such as apoptoses.

6.1. Microscopic colitis

6.1.1. Morphology: Microscopic colitis – lymphocytic and collagenous colitis (Fig. 4)

Lymphocytic colitis (LC) is defined by 20 or more intraepithelial lymphocytes (IELs) on 100 enterocytes in the superficial epithelium, associated with mild degenerative and/or regenerative changes such as vacuolization, flattening, and mucin depletion. The lamina propria shows increased inflammatory cells, mainly lymphocytes and plasma cells, and only rarely eosinophils and neutrophils [35]. Little or no crypt architectural distortion is seen. IEL count should be performed on H&E, and CD3 immunostaining is not required routinely [35].

In *collagenous colitis* (CC), the presence of a thickened amorphous hyaline eosinophilic collagen band, >10 μ m thick, immediately beneath the superficial epithelium of the mucosa is the defining feature. The collagen band is typically extensive and pronounced, with trapped blood cells, inflammatory cells, and capil-

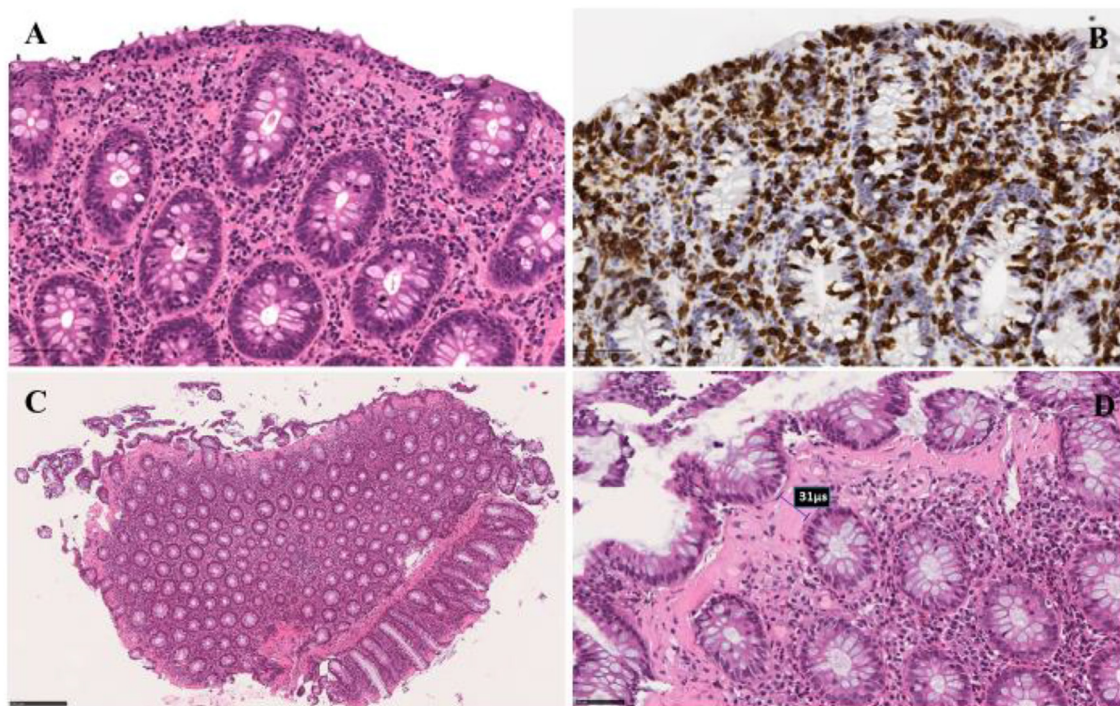


Fig. 4. Non-active colitis without chronic damage: Microscopic colitis. A, B: Lymphocytic colitis (A Hematoxylin/Eosin; B: CD3 immunostaining); C, D: Collagenous Colitis.

laries embedded in its thickness. The overlying epithelium is often missing or detached, while mucosal architecture is preserved. The thickness of the collagen band can be empirically evaluated by taking the diameter of a lymphocyte, which is typically about 7 μm in diameter, as reference. An increased number of IELs may be seen [35] in the surface epithelium, and a predominantly mononuclear inflammatory infiltrate is present in the lamina propria, with possible active crypt inflammation and occasional crypt abscess formation. In most cases, the diagnosis can be established on H&E-stained slides; in doubtful cases, collagen stains (such as Masson) may be helpful [21,33].

Importantly, when both a $> 10 \mu\text{m}$ thick collagen band and increased IELs (>20 IELs) are present, a diagnosis of CC should be submitted [21,33].

Microscopic colitis in its 2 forms (LC and CC) is characterized by a clinical history of chronic watery, non-bloody, diarrhea of at least 1-month duration and normal endoscopic appearance of the ileo-colic mucosa [21,33]. The pathogenesis of microscopic colitis is likely to be multifactorial, comprising abnormal immune response, impaired intestinal barrier function, autoimmunity disorders, and myofibroblast dysfunction [36]. Smoking and several drugs, in particular NSAIDs, have also been associated with the development of this disease, both as primary etiology and as a trigger [23]. Other drugs associated with microscopic colitides include frequently used angiotensin receptor blocking (ARB) drugs (such as olmesartan) used to treat hypertension, antidepressants, ticlopidine, and more recently, anti-cancer ICI therapy [1,23,32]. A complete drug history by the clinician is fundamental for correct cause identification. LC is also associated with other autoimmune diseases, particularly thyroiditis (19%), rheumatoid arthritis (4%), fibromyalgia (5%), celiac disease (3%), and lymphocytic gastritis (1%) [9,36].

Recently, incomplete forms of LC and CC and variants have been described. Biopsies from patients with clinical features of microscopic colitis (chronic watery diarrhea) but not completely fulfilling the morphologic criteria for LC or CC (incomplete forms of microscopic colitis) are sometimes seen. In this setting, histology may show an increased number of IELs, but these are <20 per 100 ep-

ithelial cells (incomplete lymphocytic colitis). In other instances, a focally thickened collagen band ($<10 \mu\text{m}$ thick) is seen (incomplete collagenous colitis) in the presence of increased inflammatory infiltrate in the lamina propria. In this setting, to avoid over-diagnosis, a clinicopathological correlation is vital, and a definitive diagnosis of incomplete LC or incomplete CC should be made only in the appropriate clinical context [35].

6.1.2. Differential diagnoses of microscopic colitis (Table 5)

Both LC and CC may pose diagnostic difficulties as other entities may show IEL increase or collagen increase. In particular, Crohn's disease may show an increase in IELs, while UC often shows subepithelial collagen layer thickening [9]. In both scenarios, architectural distortion usually permits an IBD diagnosis. Focal IEL increase can be seen in resolving diffuse active colitis and can be found in diverticular disease and should not lead to a LC diagnosis, which requires a diffuse increase in superficial IELs. For CC, possible mimickers include mucosal prolapse and ischemic-colitis pattern, but these latter entities show fibrosis of the lamina propria and not collagen limited to the submucosal area. Amyloid deposits may be localized along the basement membranes of crypts and blood vessels in contrast to the submucosal position in CC [35].

6.2. Eosinophilic-like colitis pattern

6.2.1. Morphology: Eosinophilic-like colitis pattern (Fig 3, c-d)

The eosinophilic-like pattern (Eos-pattern) is defined by inflammatory infiltrates exclusively or predominantly composed of eosinophils, usually without destruction of the crypts and with no signs of chronic glandular damage [37].

In the colon, eosinophils, like other inflammatory cells, follow a decreasing distribution gradient according to the length of the viscera, from the cecum to the rectum [12,13]; consequently, the evaluation of the eosinophil infiltrate must be carried out considering the anatomical site of the biopsy. The eosinophil count in the large bowel mucosa in normal conditions is variable, however, there is currently no universally accepted range. Furthermore, there is a

Table 5
Differential diagnosis in Non-active colitis without chronic damage.

Microscopic colitis	Etiology	Histological findings	Diagnostic tests
Lymphocytic colitis	Drugs	-	Clinical integration
	Autoimmune Disease	-	Serological integration
	Lymphocytic gastritis	-	
	Infection	Focal <20 IEL increase	Serological integration
Collagenous colitis	Diverticular Disease	Focal <20 IEL increase	Endoscopy
	Drugs		Clinical integration
	Mucosal prolapse	Fibrosis in lamina propria	Endoscopy

Abbreviation: IEL: Intraepithelial Lymphocytes.

Table 6
Differential diagnosis in Eosinophilic-like colitis.

Etiology	Histological findings	Diagnostic tests
Drugs	-	Clinical integration
IBD	-	Clinical integration
Collagen disease	-	Serological integration
Helminths/protozoa	Focal eosinophilic infiltrate increased	Serological integration
Allergic colitis	-	Clinical integration
Mastocytosis	Mastocytes CD117+/Tryptase+ Cyclin D1 and CD1a	Clinical integration
Langerhans cell histiocytosis		Clinical integration
Primary eosinophilic gastrointestinal disorders	Dense eosinophilic infiltrate in the full thickness of intestinal wall	Clinical, serological, genomic integration

recognized variability concerning differences in geographical area and season [37]. Despite the difficulties in evaluating minor increases in eosinophil counts, abnormal findings include markedly increased eosinophil counts, eosinophil crypt abscesses, extensive degranulation, and minimal active and chronic inflammation [38].

6.2.2. Differential diagnoses of eosinophilic-like colitis (Table 6)

The Eos-pattern is seen in numerous conditions, and definitive diagnosis is based on clinical and serological correlation [39]. Eosinophils can be increased in IBD, both at onset (the absence of architectural distortion makes diagnosis particularly difficult) and in the quiescent phase, and should not be misinterpreted as an Eos-pattern [38,39]. The Eos-pattern may be a sign of adverse drug reaction. The most common drugs that can show an increase in lamina propria eosinophils are 5-aminosalicylates, NSAIDs, clozapine, carbamazepine, diclofenac, enalapril, rifampicin, and ticlopidine, amongst others [22,23]. A fair number of collagen pathologies are related to the increase in Eos-pattern colitis, such as lupus erythematosus, scleroderma, dermatomyositis, and polymyositis, and clinical correlation is fundamental. When the eosinophilic infiltrate is focal, tissue levels should be requested, and these may help in identifying parasites, in particular helminths (such as *Strongyloides stercoralis*, *Schistosoma*, *Trichuris trichiura*) [40], though identification on biopsy samples is difficult. In children, especially in babies (under 1 year of age) with diarrhea, an abundant eosinophilic infiltrate of the lamina propria, in the absence of signs of chronicity, is often seen in allergic colitis (e.g., to cow's milk) [38,41,42].

Important conditions that should always come to mind when eosinophils are abundant are systemic mastocytosis and Langerhans cell histiocytosis, which can cause an increase in the number of eosinophils in the lamina propria, often with a subepithelial disposition (for mastocytosis). In these cases, an accurate assessment of the types of cells present in the lamina propria as well as immunohistochemistry can aid in diagnosis (CD117, CD25, and mast cell tryptase for mastocytes and Cyclin D1 and CD1a for Langerhans cells [9]).

Finally, primary eosinophilic gastrointestinal disorders represent a broad spectrum of pathological conditions of the gastrointestinal

tract in which an abnormal increase in eosinophilic infiltrates in the bowel wall is observed, in the absence of known causes, but diagnosis requires clinical exclusion of all possible known causes of eosinophilia and is not a tissue diagnosis, in both adults and children [38,41,42].

6.3. Apoptotic-like colitis pattern

6.3.1. Morphology: Apoptotic-like colitis pattern (Fig 3, e)

Apoptotic-like pattern (Apop-like) is characterized by apoptotic bodies (i.e., small nuclear fragments) within glandular epithelium in a scant inflammatory background. Isolated apoptoses can be found in normal intestinal mucosae, and no consensus exists concerning the number of apoptotic bodies in gland/consecutive glands to define apoptotic colitis [43]. Glandular atrophy and distortion can vary from very focal/mild to severe [44]. In this paper, we discuss Apop-like without chronic damage, whereas Apop-like with chronic damage is described in the second paper [6].

6.3.2. Differential diagnoses of apoptotic-like colitis (Table 7)

Historically, Apop-like has been associated with Graft Versus Host Disease (GVHD), an important complication of hematopoietic stem cell and, less frequently, solid transplantation. In this context, GI involvement occurs in up to 50% of patients with clinical and morphological differences according to the type of and time from transplantation [45]. In particular, Apop-like without chronic damage can be observed in GVHD, Grade 1–2, characterized by glandular apoptosis without glandular loss/distortion [43]. The apoptotic bodies appear first in the proliferative compartment, i.e., in deep glands, with an ‘exploding crypt cells’ aspect. Additional features, like smaller glands with atrophic, hyper-eosinophilic epithelium (apoptotic crypt), clusters of five or more apoptotic bodies (apoptotic microabscess), can be observed in more severe cases [44]. However, in a post-transplant setting, several other causes are associated with Apop-like colitis without chronic damage, most frequently CMV infection and mycophenolate mofetil (MMF) toxicity, both requiring a different therapeutic approach with respect to GVHD. Concerning CMV infection, decreasing/cessation of steroid/MMF administration is required, while

Table 7
Differential diagnosis in Apoptotic-like colitis.

Etiology		Histological findings	Diagnostic tests
Graft Versus Host Disease (GVHD)	Grade 1–2	-	Clinical integration
Cytomegalovirus (CMV)		-	Immunohistochemistry
Mycophenolate mofetil (MMF)		>15 eosinophil per 10 HPF, lack of naked neuroendocrine cell clusters, apoptotic microabscesses	Clinical integration
Non-tuberculosis Mycobacteria		-	Serological integration
Drugs		Superficially restricted mucosal apoptosis in bowel preparatory regimen Apoptosis with intraepithelial lymphocytosis and neutrophilic cryptitis in Idelalisib	Clinical integration
Monogenic Disease	Pediatric setting	-	Clinical integration

for MMF toxicity, steroids should be administered. With respect to GVHD, eosinophilic count >15 per 10 HPF, lack of ‘naked’ neuroendocrine cell clusters, and apoptotic microabscesses favour an MMF etiology [46].

In other morphological contexts, like IBD, CMV infection can be suspected by typical cytonuclear alterations, while in GVHD, viral infection can be undetectable as histologic features overlap. For this reason, CMV IHC is strongly encouraged in all suspected GVHD cases, even if no viral nuclear inclusions are identified [43,44]. Unfortunately for the pathologist, GVHD can co-occur with MMF toxicity and/or CMV infection; for these reasons, a definitive diagnosis of GI GVHD depends on clinical, histological, and laboratory integration [43–46]. Finally, Apop-like can be observed up to 20 days after transplantation, in relation to the pre-transplantation conditioning regimen alone [43].

Other infections, such as adenovirus, non-tuberculous mycobacteria [44,45], and drugs [22,23], are associated with Apop-like colitis without chronic damage. In this context, peculiar features can predict association with specific drugs, such as superficially-restricted mucosal apoptoses in bowel preparatory regimen, and apoptoses with intraepithelial lymphocytosis and neutrophilic cryptitis in Idelalisib [44].

Most recently, Apop-like colitis without chronic damage has been described in ICI therapy with particular reference to CTLA-4 inhibitors, whereas other inhibitors, such as anti-PD1/PD-L1, are associated with Apop-like colitis with chronic damage. Interestingly, mucosal injury can arise months after stopping ICI administration, making clinical integration critical [32].

Finally, Apop-like colitis without chronic damage has been reported in a patient affected by Hodgkin Lymphoma under therapy with Brentuximab, an anti-CD30 targeted antibody-drug conjugate [47].

In the pediatric setting in children <6 years of age, Apop-like colitis has been described in Monogenic Diseases, mendelian-inherited diseases related to primary immunodeficiencies, showing clinical features of IBD at early onset (i.e., Very early onset-Inflammatory bowel disease-VEO-IBD) [4,5,48]. In a multicenter study, Apop-like pattern was identified in 1 out of 63 children with a clinical diagnosis of VEO-IBD [5]. According to dramatic differences in clinical management, prognosis, and therapy, Apop-like colitis pattern diagnosis is particularly recommended in this setting [48–50].

7. Conclusion

In a ‘perfect/ideal world’, each pathology request form (regardless of disease and/or the organ affected) should include all clinical and treatment information, serological profile, as well as endoscopic and radiologic findings of the patient. In intestinal disease clinical integration is crucial, due to the overlapping histological features shared between different colitides, both in the pediatric

and adult setting. We therefore underscore the critical role of comprehensive clinical information in the interpretation of histopathological specimens and highlight the responsibility of submitting clinicians to clearly communicate the indication for biopsy to the pathologist. Similarly, it is responsibility of the reporting pathologist to include all clinical information and use this information to interpret pathological findings.

The pattern-based approach to reporting the pathology of intestinal biopsies represents a structured, reproducible, and clinically meaningful strategy for diagnosing a wide range of gastrointestinal disorders. By focusing on recognizable histologic patterns based on elementary lesions, this method enhances diagnostic accuracy, promotes consistency among pathologists, and facilitates clearer communication with clinicians. A further advantage is improved diagnostic efficiency, particularly for non-specialist pathologists. As already mentioned, the critical issue underlined by many pathologists is the lack of clinical details that are necessary for correct diagnostic interpretation. The pattern-based approach is particularly useful in situations where these are limited or unavailable. In such cases, relying on histologic patterns allows the pathologist to generate a focused differential diagnosis and guide further clinical correlation despite the lack of comprehensive background information.

The various morphologic patterns described in this manuscript constitute the descriptive and analytical foundation of the evaluation. It should be clearly stated that these histological patterns represent the technical instruments through which tissue alterations are characterized and interpreted, ultimately guiding the formulation of a diagnostic conclusion. Accordingly, the report must conclude with a well-defined diagnostic proposal, reflecting the pathologist’s final interpretative responsibility and clinical judgment.

Overall, while not a substitute for comprehensive pathological assessment, the pattern-based approach serves as a valuable tool that enhances diagnostic clarity, supports clinical decision-making, and ensures greater consistency in intestinal biopsy interpretation.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

Author Contributions

Conceptualization, Iacopo Panarese (IP), Paola Spaggiari (PS), Luca Albarello (LA), Matteo Fassan (MF) and Paola Parente (PP); methodology and validation, Giovanni Arpa (GA), Alessandro Gambella (AG), Federica Grillo (FG), Alessandro Vanoli (AV), Luca Mastracci (LM), Carla Giordano (CG), Francesco Vasuri (FV), Rossano Ambu (RA), Claudia Mescoli (CM), Graziana Arborea (GA), Fabrizio Bossa (FB), Edoardo Vincenzo Savarino (EVS), Alessandro Caputo (AC), Luca Reggiani-Bonetti (LRB), Francesca Rosini (FR), Antonio

Di Sabatino (ADS); resources, PP; data curation, writing – original draft preparation, IP, PS, LA, GA, AC, LRB, FR, PP, writing – review and editing, AG, FG, AV, LM, CG, FV, RA, CM, GA, FB, EVS, ADS, MF; supervision, PP; project administration, PP. All authors have read and agreed to the published version of the manuscript.

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