Non-neoplastic colorectal disease biopsies: evaluation and differential diagnosis

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ABSTRACT

A wide variety of non-neoplastic conditions may be encountered on colorectal biopsy encompassing idiopathic, infectious, vascular and immune-mediated aetiologies. Although interpretation of such biopsies may be challenging, appreciation of the dominant pattern of injury and subsequent host response may allow for a more focused histological diagnosis in the correct clinical and endoscopic setting. This article aims to provide a systematic, methodical approach to the assessment of such biopsies, concentrating mainly on diagnoses other than inflammatory bowel disease.

INTRODUCTION

Non-neoplastic colorectal disease forms a considerable portion of the daily workload for practising pathologists and endoscopic operators alike and represents a major worldwide health and economic issue.[1] Depending on geographical location, the annual incidence of idiopathic inflammatory bowel disease (IBD) ranges from 5 to 24.3 cases/100 000 person-years.[2] However, when considering examples of non-IBD colitides, the incidence of microscopic colitis ranges from 5.2 to 10.8 cases/100 000 person-years in northern Europe and North America, and the incidence of ischaemic colitis ranges from 4.5 to 44 cases/100 000 person-years with a marked age-related increase.[3 4] These examples do not take into account numerous other potential causes of colitis, a number of which are described herein.

Given the limited range of macroscopic reaction patterns that the colonic mucosa may demonstrate on endoscopy, gastrointestinal endoscopic biopsy is an important diagnostic tool.[5 6] However, the limited endoscopic spectrum of patterns may be reflected by the microscopic findings, which often demonstrate significant overlap between various subtypes and aetiologies of colitis. This results in the need for a description of the pattern of injury, rather than a precise suggestion of the underlying aetiology.

The purpose of this review is to revisit the histopathological characteristics of colitis, focusing primarily on aetiologies other than IBD. The aim is to use the predominant pattern of injury seen within the biopsy, together with the endoscopic impression and clinical history, to enable the reporting pathologist to suggest a range of aetiologies with a differential diagnosis or, in some cases, to suggest a specific diagnosis. Such is the scope of IBD that it is not possible to ignore it. Therefore, consideration will be given to Crohn's disease and ulcerative colitis, particularly in relation to patterns of injury with which they are less frequently associated. To offer a user-friendly practical document we use a standard approach: first an appreciation of normal findings and variants of normality within the colonic mucosa (an example of which is provided in figure 1), followed by identification of abnormalities by microscopic low power impression, assessment of architecture and other indicators of chronic injury in conjunction with any additional features.

Figure 2 outlines a non-exhaustive list of differential diagnoses to consider when confronted with a predominant morphological pattern. It should be noted that there is a distinction to be made between conditions in which these features are frequently encountered (highlighted in bold within the algorithm) and those conditions which warrant consideration only when the former have been excluded.

ESTABLISHING NORMAL MUCOSAL PATTERNS AND THRESHOLDS FOR THE PATHOLOGICAL

Neutrophil-predominant inflammation

- Neutrophils have an essential role in protecting injured epithelium and, while the presence of two or three intraepithelial neutrophils may reflect bowel preparation or similar factors, any higher number should prompt a search for other features that could indicate an abnormality.[7 8]
- The presence of neutrophils exceeding the small number described above indicates an acute inflammatory process, or 'activity' in the setting of a chronic process, and encompasses cryptitis, crypt abscess formation and neutrophils in the surface epithelium. In addition, evaluation of a biopsy with neutrophil-predominant inflammation should contain further information regarding extent (focal/segmental vs diffuse) and distribution (within sites and between sites). Distribution of chronic changes is particularly important when considering a differential diagnosis of untreated IBD, with Crohn's disease tending to be more irregular within sites and between sites.[9] There is some evidence that acute cryptitis is more likely to be focal in Crohn's disease than in ulcerative colitis, although reports conflict as to the discriminant value of this feature.[7] There is also evidence that extensive crypt abscess formation is more likely in ulcerative colitis than in Crohn's disease.[7]
- Focal, isolated neutrophilic crypt and/or epithelial injury in the absence of other changes (often referred to as focal active colitis) is a descriptive

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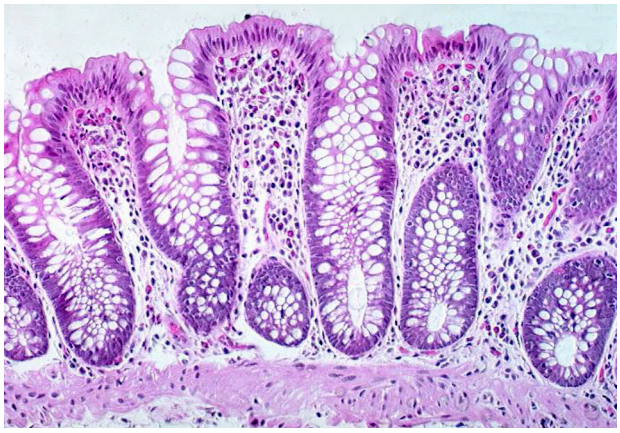

Figure 1 Normal colonic mucosa. The plasma cell gradient, decreasing from the epithelium to the base of the crypts, can be appreciated in this biopsy from the right colon.

and non-specific finding. It may reflect many underlying processes including bowel preparation, infectious colitis (that may be resolving), drug-mediated colopathy, ischaemic colitis and IBD.[10 11]

Pseudomembranes

- This is an abnormal finding and an underlying cause should always be sought.
- Pseudomembranes are defined as a spray of nuclear debris, neutrophils, fibrin and mucin erupting out of the upper portion of the crypts, which coalesce to form a linear, inflammatory pseudomembrane covering the luminal epithelium.[12]

Subepithelial collagenosis

- A thin, regular subepithelial collagen band composed of type IV collagen is normally present and should not exceed 5 µm in depth.[13] In practice, one should be careful not to overinterpret extension of the cytoplasm with cellular displacement as collagen. Collagen band thickness should be assessed only in well-orientated sections.
- Subepithelial collagenosis is defined as thickening of the subepithelial collagen plate. In diseases characterised by subepithelial collagenosis, the plate is more than 10 µm in thickness and may be as much as 100 µm.[13] The thickened collagen plate consists of Type I, III, IV and VI collagens, contrasting with the plate in normal mucosa which comprises type IV only.[14] As a confirmatory measure, trichrome and tenascin stains can be used to highlight the collagen layer. However, this is rarely necessary in our experience.

Intraepithelial lymphocytosis

- Intraepithelial lymphocytes (IELs) are present normally within the colonic mucosa. The usual number is less than 5 IELs per 100 epithelial cells, and may be slightly higher in the right colon.[9]
- Intaepithelial lymphocytosis has been defined as a count exceeding 20 IELs/100 epithelial cells based on H&E analysis.[13 15] IELs should not be counted in epithelium overlying mucosa-associated lymphoid tissue as they are normally present in larger numbers in this area.[16] IELs are CD3-positive T-cells.[17] Fiehn *et al* have since suggested that if CD3 immunohistochemistry is used the threshold for intraepithelial lymphocytosis should be increased as more cells will be detected. In their study, 53% of cases diagnosed as normal (ie, less than 5 IELs/100 epithelial cells) on H&E demonstrated an increased number of IEL's on CD3 stain. While most of these increases were minimal (5–9 IELs/100 epithelial cells), one patient had more than 20 IELs/100 epithelial cells on CD3 stain.[18]

Histiocytic and granulomatous inflammation

- Macrophages can be difficult to identify, unless they contain phagocytosed mucin (muciphages), a normal finding particularly within the rectum.
- A granuloma is defined as a collection of at least five epithelioid histiocytes.[7] Once identified, the cause of granulomatous inflammation often requires clinicopathological correlation, follow-up and potentially further systemic investigations. The presence of granulomas and a description regarding their nature (eg, necrotising vs non-necrotising), and other findings should be provided, as this can provide a clue to the underlying aetiology. This allows the clinician to consider the causes of granulomatous inflammation, should

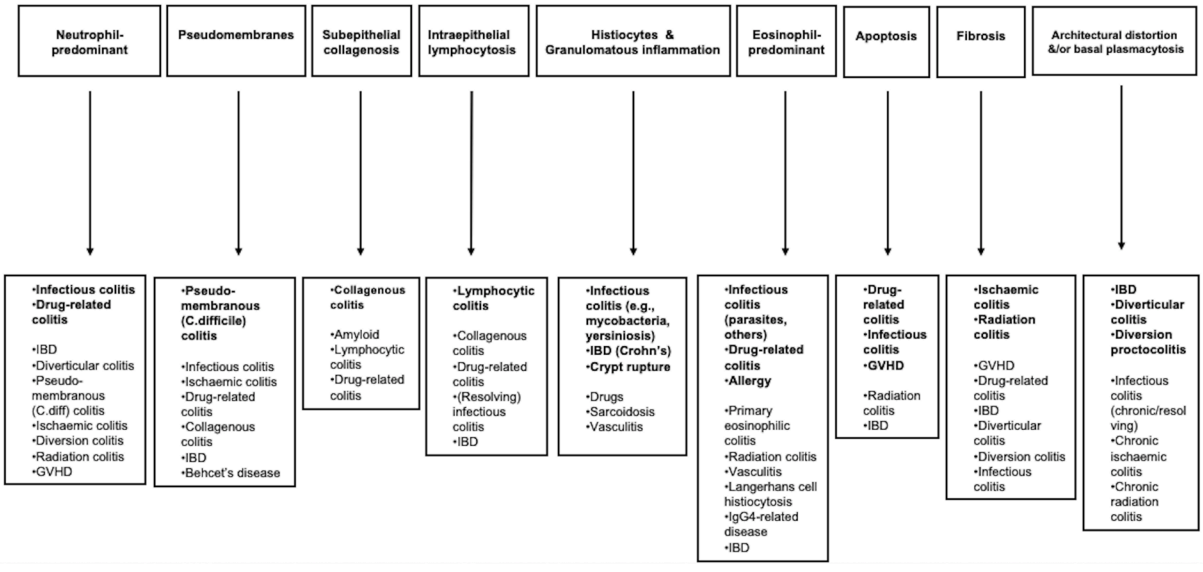

Figure 2 Summary of differential diagnoses on the basis of histological features. GVHD, graft-versus-host disease; IBD, inflammatory bowel disease.

no specific features (such as infectious organisms) be identified on H&E or special stains.[19] Recognition of cryptolytic granulomas (collections of epithelioid histiocytes adjacent to ruptured crypts) is important, as the implications for aetiology and management may be different.[20]

Eosinophil-predominant inflammation

- Eosinophils are normally present within the lamina propria; however, there is limited data on what levels are considered within normal limits. In some reports they are more numerous in the right colon than elsewhere and there is even some evidence suggesting that numbers vary seasonally and geographically.[21 22] Matsushita *et al* compared eosinophil counts among adults of differing races and found that there was little contrast in number or distribution of eosinophils within the colon between Japanese, Japanese American and Caucasian groups.[23] Across the three groups, they found samples from the caecum/ascending colon/transverse colon to contain anywhere between 1–163 eosinophils/mm^2, while samples from the descending colon/sigmoid/rectum exhibited 0–106 eosinophils/mm^2. In a paediatric population with normal histology, Silva *et al* demonstrated that the highest numbers of eosinophils were seen within the caecum (range 2–125 eosinophils/mm^2) and gradually decreased from the proximal colon to the rectum (range 0–44 eosinophils/mm^2).[24]
- Mild increases in the number of eosinophils can be difficult to appreciate. The loss of a decrescendo from right to left colon might suggest that the eosinophil count is increased (D Antonioli, private communication). However, in the majority of eosinophil-predominant inflammatory processes, there will be a marked increase in eosinophils (both within the lamina propria and the epithelium), eosinophilic crypt abscesses, degranulation of eosinophils and extension of eosinophils into the underlying muscularis mucosae.[25 26]

Apoptosis

- Apoptosis is morphologically recognised by the presence of the 'apoptotic body', characterised by condensation and fragmentation of the nuclear chromatin.[27] This occurs principally in the superficial part of the crypt, where apoptosis represents physiological turnover of senescent cells. Koornstra *et al* published a systematic review appraising 53 papers which investigated the percentage of apoptosis in varying scenarios. Five of these included counts made on normal mucosa. Expressed as a mean percentage of apoptotic cells of the total number of epithelial cells the apoptotic index ranged from 1.3% to 2.75%.[28] This is in contrast to deep crypt apoptosis in the lower proliferative zones, which is the result of genomic injury.[28] This is much more intermittent with a mean frequency of less than one apoptotic cell per crypt.[29 30]
- An explanation for any increase in apoptotic activity exceeding this within the proliferation zones should be sought by the reporting pathologist, remembering also that bowel preparation is one cause of this pattern of mucosal damage.[7]

Fibrosis

- Fibrosis is an abnormal finding and an underlying cause should always be sought.
- The progressive intramural deposition of collagen (particularly type I) and other extracellular matrix components is the result of local chronic inflammation.[31] Dependent on the aetiology and severity, this may be limited to the mucosa or may extend to the full thickness of the bowel wall resulting in stricture formation and may be accompanied by hypertrophy of the muscular layers as the gut attempts to overcome the resistance to peristalsis caused by fibrosis.[32]

Architectural distortion and basal plasmacytosis

- Crypts in normal mucosa are orientated parallel to each other and are evenly spaced by the intervening lamina propria. The crypts stretch from the epithelial surface to the muscularis mucosae and are lined by columnar epithelium with abundant goblet cells, the latter being more prominent in the rectum.[16] The normal inflammatory component within the lamina propria demonstrates a gradient, being denser towards the surface and petering out towards the base of the crypts. The inflammatory gradient is less well established in the right colon which also naturally contains more inflammatory cells than the left, particularly plasma cells.[7 33] This anatomic variation can cause interpretative difficulties, especially if the exact site of origin of the biopsy is not known to the pathologist.
- Architectural distortion and basal plasmacytosis often occur in unison, acting as barometers of chronic injury. Basal plasmacytosis is defined as an increase in the density of plasma cells at the base of the mucosa, either adjacent to the crypt base or between the crypt base and the muscularis mucosae. It is the strongest indicator of IBD and is uncommon in non-IBD colitides.[34] That being said, it can also result from long-standing infectious colitis and other chronic colitides such as diverticular colitis and diversion colitis. In the right colon, plasma cells occur in greater number and do not necessarily adhere to the usual inflammatory gradient. Architectural distortion encompasses variation in size and shape of crypts, crypt branching, and altered crypt orientation (loss of parallelism) and is often accompanied by crypt atrophy (shortening and wider spacing of crypts) or crypt drop-out. However, there are a number of caveats to consider. In particular, poor orientation can cause the crypts to appear irregular. Therefore, assessment of crypt architecture should be confined to well-orientated sections. Also, crypts in the vicinity of mucosa-associated lymphoid tissue cannot be assessed reliably for architectural changes. Furthermore, rectal mucosal crypts are often more irregular than those in the colon and assessment of apparently abnormal architecture at this site should be correlated with other findings.[7 16]

PATTERN-BASED DIFFERENTIAL DIAGNOSES FOR CONSIDERATION

Cautionary advice

It is always prudent to consider a procedure related cause for those cases which show mild, non-specific mucosal abnormality. Bowel preparation and subsequent endoscopy is an invasive procedure, which has the potential to traumatise the mucosa. These can result in occasional intraepithelial neutrophils (particularly along the surface epithelium), mucin depletion, petechial haemorrhage and oedema within the lamina propria, increased crypt apoptosis and pseudolipomatosis.[7]

Taking into account the normal mucosal variation and individual elementary features, we have developed figures 3 and 4 to provide a broad practical diagnostic approach with diagnoses at each stage listed in order of decreasing frequency. It should be noted that this algorithm is not all-encompassing and merely

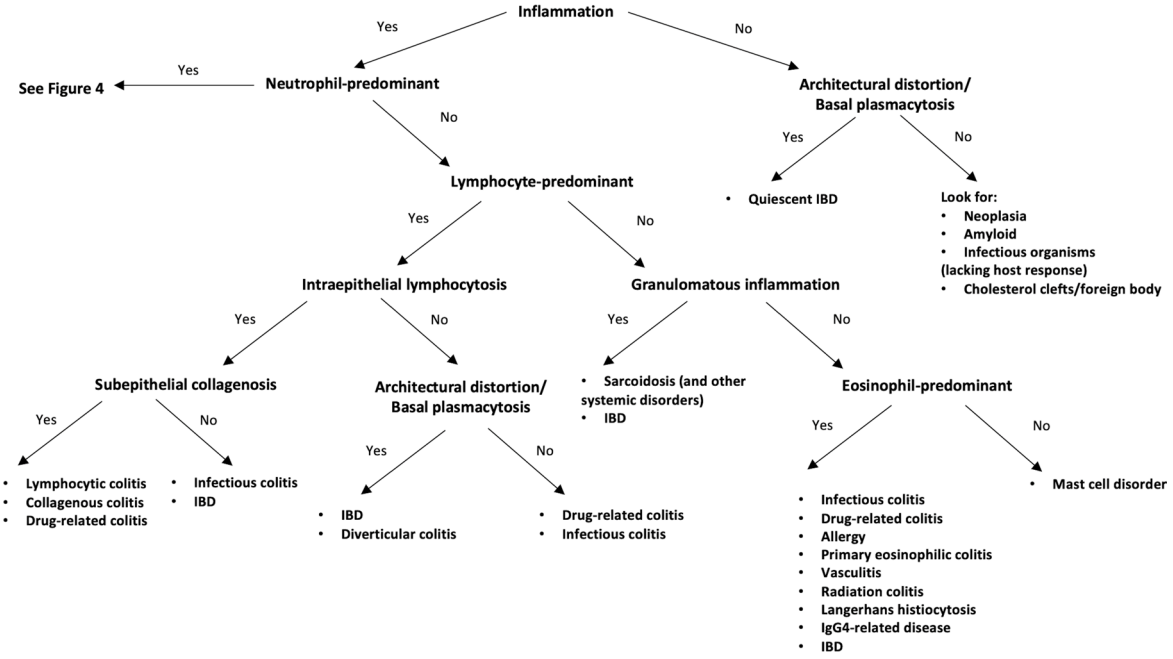

Figure 3 Diagnostic work flow for cases characterised by non-neutrophilic inflammation. IBD, inflammatory bowel disease.

highlights the most likely diagnoses when the features in question are present; each case is unique and should be approached with the specific clinical and endoscopic presentation in mind.

Infectious colitis

This diagnosis requires consideration particularly in the immunocompromised, those who have been travelling, and in cases of isolated proctitis. Infections can cause a wide variety of morphological patterns depending on the organism and clinical setting, and the following considerations comprise only a minority of these. A comprehensive discussion is outside the scope of this review. Even utilising light microscopy and clinical investigations, the causative pathogen is often not identified.

Broadly speaking, bacterial infections such as *Salmonella*, *Shigella and Campylobacter* cause neutrophil-predominant inflammation, seen within figure 5,[35] while eosinophil-predominant inflammation is more indicative of parasitic organisms such as helminths.[36] Granulomatous inflammation can be seen with *Mycobacterium tuberculosis*, *Yersinia enterocolitica* and occasionally in cases of schistosomiasis, secondary to the presence of schisto ovum. Mycobacterium avium intracellulare typically produces aggregates of foamy macrophages.[37] *Pseudomembrane* formation can be seen with *Clostridium difficile* and, less often with *Strongyloides stercoralis* and *Escherichia coli*.[38 39] The enterohaemorrhagic variant of *E. coli* demonstrates an ischaemic-like pattern including hyaline fibrosis of the lamina propria[40] and the same has been reported with *Klebsiella oxytoca* infection.[41]

Viral organisms also cause infectious colitis. Cytomegalovirus can be associated with an increase in apoptosis,[30] as can

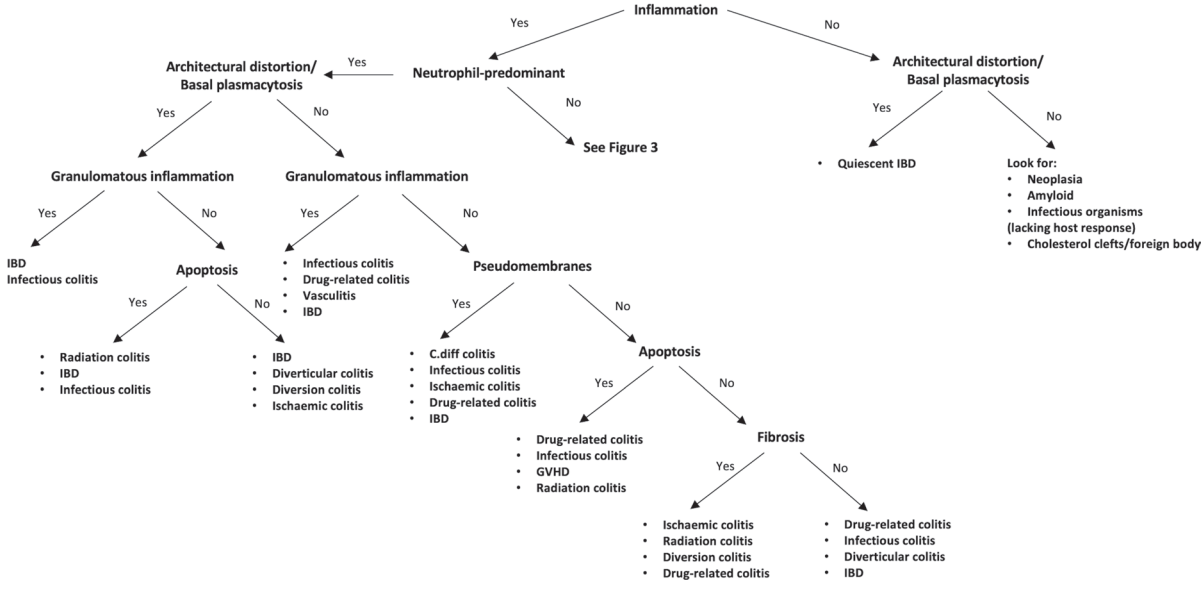

Figure 4 Diagnostic work flow for cases characterised by neutrophilic inflammation. GVHD, graft-versus-host disease; IBD, inflammatory bowel disease.

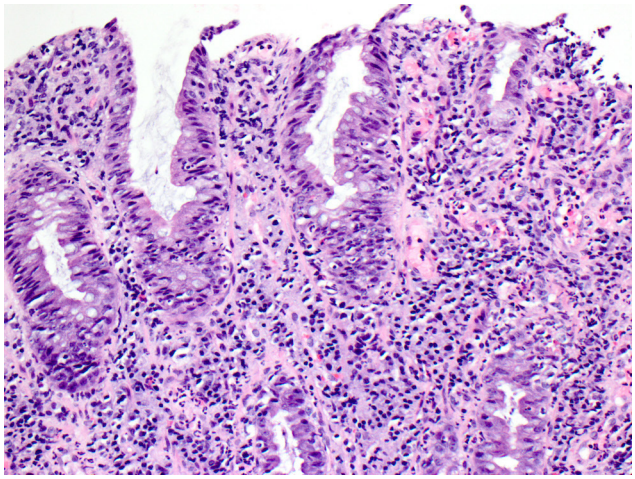

Figure 5 An example of infectious colitis. The histology shows marked neutrophil-predominant inflammation.

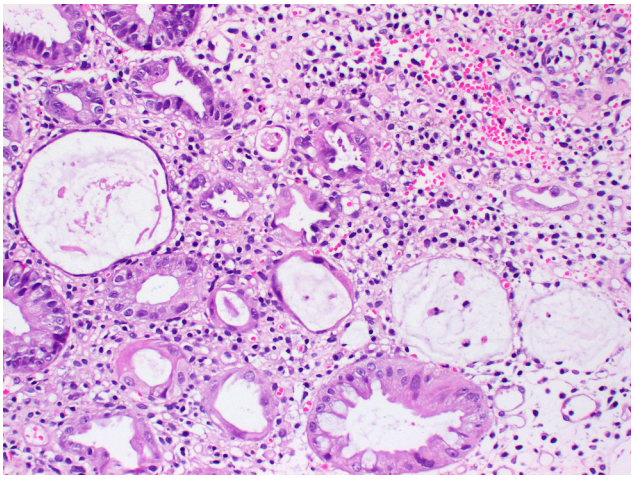

Figure 6 Drug-induced injury secondary to methotrexate. The histology shows crypt distortion and significant crypt epithelial damage; the lamina propria contains a mixed inflammatory infiltrate.

helminths.[42] Fungal infections are rare in the Western hemisphere, except in immunosuppressed patients. Unless protracted, infectious colitis should be distinguishable from IBD by the absence of architectural distortion and basal plasmacytosis.

Drug-related colitis

A wide range of aetiological agents can produce a spectrum of morphological patterns, a discussion of which is beyond the scope of this review.[43] There are well-known colitis-inducing drugs such as mycophenolate mofetil, which causes apoptosis thereby mimicking graft-versus-host disease (GVHD), and non-steroidal anti-inflammatory drugs (NSAIDs), which can cause eosinophil-predominant inflammation, ischaemic-like colitis with fibrosis or collagenous/lymphocytic colitis represented by the presence of subepithelial collagenosis and/or IELs.[44] Novel drugs such as ipilumimab and tumour necrosis factor inhibitors can cause any combination of neutrophil-predominant inflammation, apoptosis and crypt distortion.[43] Reports of anti-PD1-induced colitis have been increasing since 2017, adding the likes of pembrolizumab and nivolumimab to the list.[45–47] These may demonstrate a neutrophil-predominant pattern of injury but the spectrum of changes that they induce is wide. Indeed, many of these newer drugs, and others, are capable of producing a large variety of changes. Therefore, attribution of a particular histological pattern to an individual drug is rarely possible without the clinical history—and even then is often difficult. A case of methotrexate induced injury is shown in figure 6.

Before making the diagnosis of a first presentation of IBD on a biopsy specimen, a review of the patient's clinical and medication history is always advisable, particularly in the setting of oncology and/or organ transplantation.

Diverticular colitis

Diverticular disease is a common condition, particularly in the Western hemisphere. There are several complications associated with diverticular disease such as haemorrhage, inflammation of the diverticulum itself (diverticulitis) or of the mucosa adjacent to a diverticulum, abscess, fistula or perforation. In up to 4% of cases, the affected segment demonstrates a chronic colitis.[48] The histological features (architectural distortion, basal plasmacytosis and varying degrees of neutrophil-predominant inflammation) are identical to those seen with IBD, and knowledge of the endoscopic appearance (ie, presence of diverticula with inflammation of the peridiverticular mucosa) and detection of rectal sparing, is essential. It should also be noted that chronic bouts of diverticular disease can cause subepithelial collagenosis.

Collagenous colitis

Collagenous colitis is a disease process characterised by subepithelial collagenosis, however, the diagnosis is not based on this finding in isolation and is most often accompanied by surface epithelial injury/detachment, IELs and increased inflammation within the lamina propria, particularly eosinophils.[49] There may be focal, isolated neutrophilic crypt and/or epithelial injury. There is usually no architectural distortion or basal plasmacytosis.[50] Variants exist, including reports of collagenous colitis with pseudomembrane formation[51–54] and of an association with histiocytic inflammation and giant cells.[55 56]

In addition, some authors propose the existence of an 'incomplete' or borderline form of collagenous colitis in which subepithelial collagenosis is less pronounced (more than 5 µm but less than 10 µm), in the setting of a history of chronic watery diarrhoea. In such cases entrapment of superficial capillaries by collagenous wrapping may be a useful feature.[57] There is little consensus on the diagnostic criteria for this 'entity' and, consequently, on its clinical significance—if any. It has been suggested that it may represent an early form of collagenous colitis or may reflect undersampling.[58 59] The features should be described and correlation with the clinical picture advised, perhaps avoiding a final diagnostic 'label'. The features of collagenous colitis are highlighted in figure 7. Amyloidosis can be difficult to distinguish from collagenous colitis, but, once considered, can be excluded with a Congo Red stain.[60]

Lymphocytic colitis

Key findings include IELs accompanied by evidence of surface injury or regeneration and increased inflammation within the lamina propria, as seen in figure 8. There may be mild subepithelial collagenosis, but this should not exceed 10 µm.[57] There should be little appreciable architectural distortion. Basal plasmacytosis may occur. Focal neutrophilic crypt and/or epithelial infiltration, including occasional crypt abscess formation may be seen.[61]

Variants include lymphocytic colitis with histiocytic inflammation[56] and a peculiar localisation phenomenon in which the

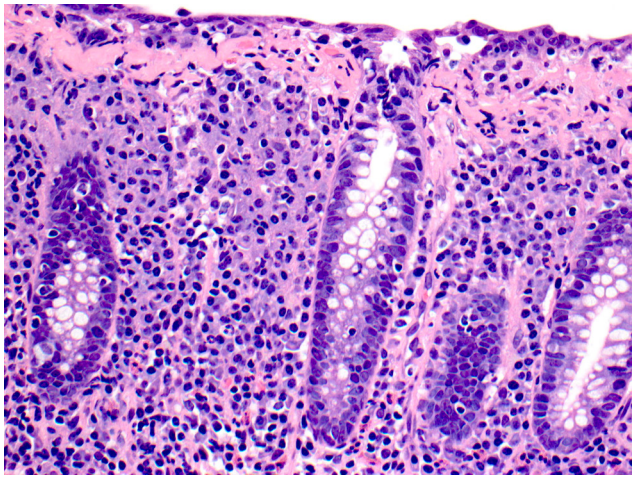

Figure 7 Collagenous colitis. Biopsy showing a distinct, thickened subepithelial collagen plate with disruption of the overlying epithelium.

numbers of IELs are within normal limits along the surface, but are markedly increased within the crypts (so-called cryptal lymphocytic colitis).[62]

The proposed 'incomplete' or 'paucicellular' variant of lymphocytic colitis refers to colonic mucosa in which there are fewer than 20 IELs/100 epithelial cells. Fiehn *et al* have classified incomplete lymphocytic colitis as 10–19 IELs/100 epithelial cells (when accompanied by the other diagnostic criteria of epithelial injury/regeneration and lamina propria inflammation) and 5–9 IELs/100 epithelial cells as nonspecific reactive changes, as the risk of evolution to diagnostic lymphocytic colitis in the latter group is low.[18] The former, sometimes reported as colonic lymphocytosis, is a non-specific finding but may represent a resolving infectious colitis. Its existence as an entity is questionable, and indeed a histology report with this 'diagnosis' might cause confusion rather than assisting patient management.

Experts do not agree on the degree of overlap, if any, between collagenous and lymphocytic colitis. Some authors regard them as the same entity while others consider them to be completely distinct from each other. Most pathologists recognise that there is at least some overlap.

Eosinophilic colitis

Eosinophilic colitis may be regarded as a pattern (rather than a diagnosis), which generates a long list of differential diagnoses. An example is shown in figure 9. In the paediatric population, atopy and allergy is the most common cause of eosinophil-predominant

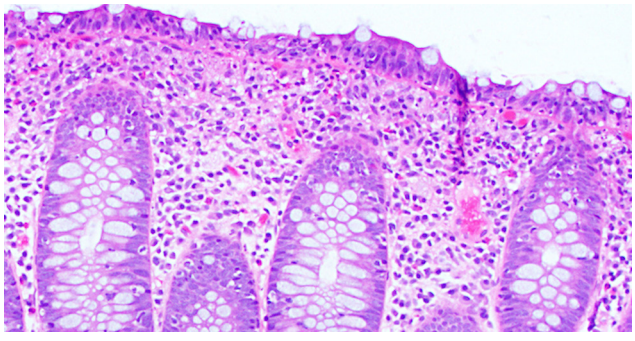

Figure 8 Lymphocytic colitis. This biopsy shows marked intraepithelial lymphocytosis and increased numbers of inflammatory cells within the lamina propria.

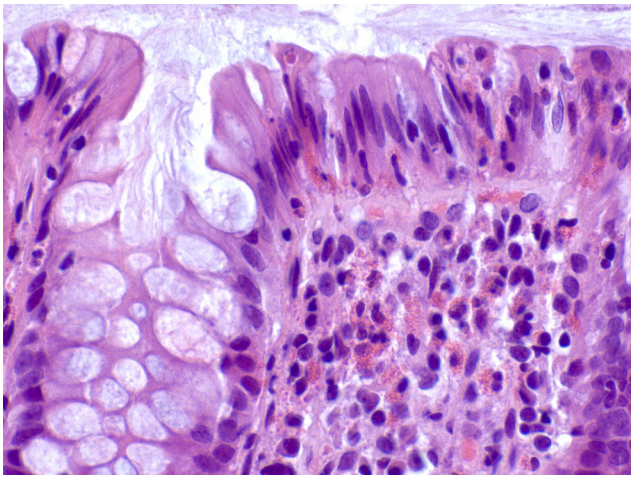

Figure 9 An example of eosinophil-predominant colitis. Clusters of eosinophils, some of which have infiltrated the epithelium, with associated degranulation.

inflammation in the colon.[63] It is important to consider an infectious (particularly invasive parasites) aetiology, especially in patients who are immunosuppressed.[64 65] Numerous medications are associated with eosinophil-predominant inflammation of the colon, including antiepileptics, antipsychotics and anti-inflammatories.[66–68] Emtricitabine/Tenofovir treatment for HIV has also recently been added to the list.[69] Other secondary causes of eosinophil-predominant inflammation are granulomatous polyangiitis with eosinophilia (ie, Churg-Strauss syndrome), Langerhans cell histiocytosis and IgG_4-related disease.

Granulomatous colitis

Granulomatous colitis is a descriptive term with a considerable list of potential causes. These include chronic granulomatous disease, a rare inherited multisystem disorder which presents in children with recurrent infection and failure to thrive as a result of immunodeficiency[9] and is characterised histologically by a mucosal infiltrate composed of eosinophils and macrophages with a conspicuous absence of neutrophils.[70]

There are many secondary causes of granulomatous inflammation such as infections, for example, *Mycobacterium tuberculosis* and *Yersinia enterocolitica* and systemic disorders, for example, sarcoidosis and vasculitides. Figure 10 shows a case of *Mycobacterium tuberculosis* colitis. Generally speaking, sarcoidal granulomas are typically well formed, non-necrotising and lacking a lymphoid cuff whereas vasculitic and infection-mediated granulomas tend to be ill-defined and necrotising,[25] however, in the majority of cases the morphology of the granulomas is unhelpful. Drugs sometimes induce granulomas, but other possibilities should be excluded before considering drugs as a potential aetiology.[71]

The prototypical granuloma-forming pathology seen within the colon is Crohn's disease, and observed more commonly in younger patients. Diverticular disease and in some instances parasitic infections may cause transmural chronic inflammation with prominent granulomas that can result in a clinical and histological picture reminiscent of Crohn's disease.

Pseudomembranous (*C. difficile*) colitis

C. difficile infection is the archetypal cause of pseudomembranous colitis; a case with classic histology is shown in figure 11. It occurs most frequently in hospitalised patients or those in

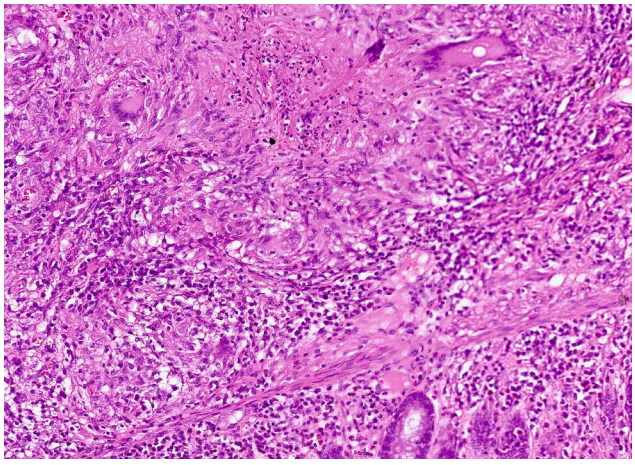

Figure 10 A case of granulomatous colitis characterised by histiocytes and giant cells with caseous necrosis. This patient had *Mycobacterium tuberculosis*.

long-term care homes, as a result of antibiotic therapy, particularly with agents such as clindamycin, cephalosporins and fluoroquinolones.[72] Early in the disease course, pseudomembranes may not be well developed and the mucosa may demonstrate ischaemic-like changes or neutrophil-predominant inflammation only.[73]

There are other causes of pseudomembrane formation (some of which are discussed within this review in more detail) such as collagenous colitis, IBD, ischaemic colitis, other infectious organisms, drugs and Behcet's disease.[74]

Ischaemic colitis

Ischaemic colitis has a large number of causes, both thromboembolic and non-thromboembolic (including vasculitis, vasospasm and hypovolaemia).[75] In many cases, however, the histology is non-specific and the patient comorbid, making a definitive diagnosis of the underlying cause difficult.[76]

Ischaemic colitis can be subdivided into acute (a sudden, profound ischaemic insult which may be either reversible or irreversible) and chronic (repeated ischaemic and reperfusion injury, most commonly due to progressive atherosclerotic disease). Dependent on the mechanism and calibre of vessels involved, the

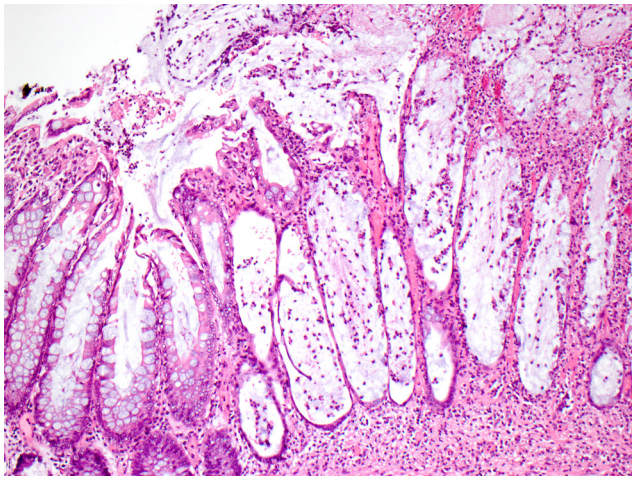

Figure 11 A case of pseudomembranous (*Clostridium difficile*) colitis. The biopsy shows a spray of nuclear debris, neutrophils, fibrin and mucin erupting out of the crypts, forming an inflammatory membrane.

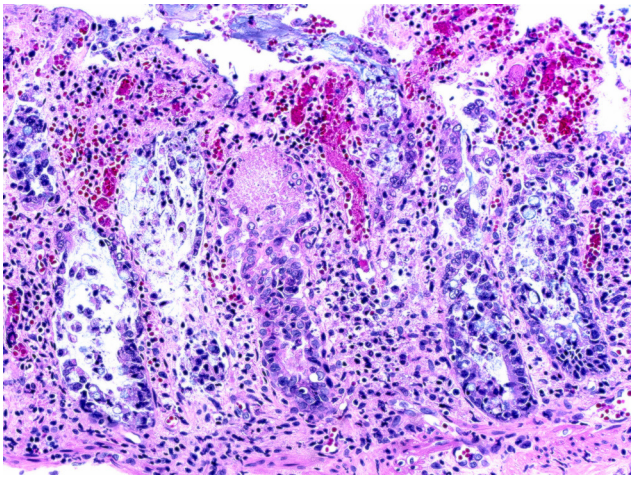

Figure 12 Ischaemic colitis. This biopsy is characterised by mucosal erosion, oedema and haemorrhage with mucin depletion, with formation of 'withering' crypts indicative of acute injury.

depth of injury can vary from mucosal up to transmural with a similarly wide range of severity.[1] In the early phase of ischaemia, there is mucosal erosion, oedema and haemorrhage with mucin depletion, which progresses to superficial necrosis and formation of 'withering' crypts characterised by a degenerate, attenuated epithelial lining and sparing of the deeper parts of crypts. The degree of inflammation is variable and in cases of sudden, complete vascular occlusion there may be full thickness necrosis with limited inflammation. Neutrophil- rich inflammation is the signatory of reperfusion injury and may be associated with pseudomembrane formation. Following the acute episode, there may be deposition of hyaline material and fibrosis. In some cases, there is such marked submucosal fibrosis and/or oedema that a mass lesion is apparent on endoscopy, thereby mimicking malignancy.[77] A case of acute ischaemic colitis is shown in figure 12.

In addition to the changes seen within the spectrum of acute ischaemic colitis, chronic ischaemic colitis may demonstrate features of chronic disease such as architectural distortion and basal plasmacytosis, which can then raise the possibility of IBD.[9] Ischaemic colitis should be differentiated from pseudomembranous (*C. difficile*) colitis, radiation colitis, solitary rectal ulcer syndrome, iatrogenic damage (NSAIDs, resins) and certain forms of infectious colitis which induce an ischaemic-type pattern.

Solitary rectal ulcer syndrome/mucosal prolapse

This is a relatively uncommon condition, seen primarily in younger patients and typically presenting with diarrhoea and rectal bleeding.[1] While the common endoscopic finding is of mucosal ulceration commonly on the anterior wall and predominantly solitary (hence the disease name), 25% of cases demonstrate polyp formation, potentially simulating neoplasia.[78]

Histologically, there is thickening of the mucosa with obliteration of the lamina propria by vertically orientated and splayed muscle fibres and variable fibrosis. The crypts are elongated, dilated and hyperplastic and become 'pinched' at the base, resulting in a characteristic diamond-shaped rather than circular profile.[79] The surface may demonstrate erosion and fibrin formation, reminiscent of a pseudomembrane.[80] Alternatively, lesions which presumably have been traumatised may demonstrate neutrophil-predominant inflammation, and there is the potential for confusion with IBD and ischaemia.[81]

Diversion colitis

Diversion colitis refers to the mucosal abnormalities that develop in a defunctioned segment of colon. It most commonly occurs 3–36 months postsurgery.[9] The pathophysiology of this condition is not entirely clear but it is likely that the sudden loss of the faecal stream leads to alteration of the mucosal flora, with or without superimposed vascular compromise.[1] While the histological findings may vary widely, they often show neutrophil-predominant inflammation and large, hyperplastic lymphoid follicles. Lamina propria fibrosis has also been described.[82] Mild crypt architectural distortion may be seen and the presence of this finding does not necessarily indicate IBD, although there is often a background of underlying IBD that makes precise interpretation of the histological findings difficult.[83] In particular, the relative contributions of diversion and underlying IBD to the histological changes in this setting are almost impossible to determine. Knowledge that the biopsy being reviewed is from a diverted segment is of course necessary for diagnosis.

Radiation colitis

The incidence of radiation-induced colitis increases relative to the cumulative dose of radiotherapy administered to the pelvic region, primarily for treatment of gynaecological and prostate cancers; there are few side effects with doses less than 45 Gy, while doses above 70 Gy can cause significant side effects.[84] The effects can be divided arbitrarily into short-term (acute), occurring within the first few weeks, and long-term (chronic). Acute radiation colitis is manifested by any combination of the following—apoptosis, neutrophil-predominant inflammation and eosinophil-predominant inflammation. Some authors regard the latter as highly characteristic. Crypt withering is also a common observation. Chronic radiation colitis may demonstrate marked stromal fibrosis and vascular abnormalities (figure 13), particularly in the submucosa and deeper layers, and the mucosa may show architectural distortion.[1] Radiation exposure can cause epithelial and fibroblast atypia; the nuclei are enlarged and hyperchromatic (but retain a low nuclear to cytoplasmic ratio), with a 'smudged' or 'blurred' quality, and there is the potential for confusion with neoplasia.[9]

Graft-versus-host disease

The histological hallmark of GVHD is the presence of increased crypt epithelial cell *apoptosis*. In patients with a history of bone marrow/stem cell transplantation (and less frequently in solid organ transplantation), this diagnosis should be considered. In mild cases, there is sparse associated inflammation, which is predominantly mononuclear. In more severe cases apoptosis may be marked, with formation of apoptotic microabscesses (≥5 adjacent apoptotic bodies), epithelial injury (including ulceration) and pronounced neutrophilic infiltrates.[30] Acute cases of GVHD may be graded as 1–4 dependent on severity but in practice the histological features do not correlate well with the clinical picture and grading is therefore not a requisite.[30] Aside from the drug and infectious aetiologies outlined elsewhere in this review, apoptotic colopathy should also merit consideration of common variable immunodeficiency (CVID) and autoimmune enteropathy in the differential diagnosis, particularly when there is no history of transplantation.[85 86] IBD may also cause significant apoptosis on occasion.

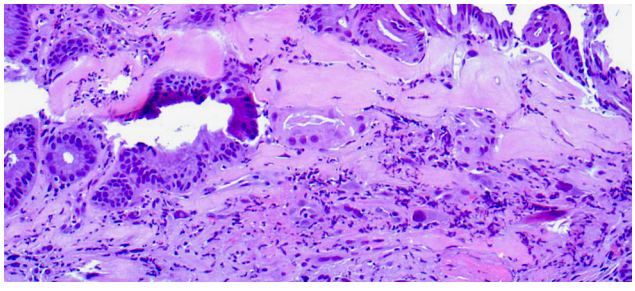

Figure 13 Chronic radiation colitis. There is marked lamina propria fibrosis in a supepithelial distribution which should not be confused with collagenous colitis.

Take home messages

- The colorectal mucosa has a limited range of response to innumerable causes of injury.
- This often leads to significant overlap between various conditions that may produce similar morphological changes, but which have markedly different clinical management.
- Recognition of the dominant pattern of injury and provision of the relevant differential diagnoses may be the limit of the histological interpretation.
- A multidisciplinary approach will help to optimise the accuracy of the diagnosis.

Chronic idiopathic IBD

The characteristic features of established ulcerative colitis and Crohn's disease are the presence of architectural distortion and basal plasmacytosis. These are accompanied by varying degrees of neutrophil-predominant inflammation. In the case of Crohn's disease, there may be granulomatous inflammation. In established cases, the diagnosis is often relatively easy to make. Other patterns of injury seen in IBD may include pseudomembrane formation,[74] IELs[87] and fibrosis, all of which may coexist or predominate and hence make the diagnosis less straightforward. Furthermore, the full spectrum of 'classic' histological findings may be absent early in the course of the disease when neither the clinical presentation nor the endoscopic features are suggestive. The same warning is particularly true in the paediatric population and certainly in treated individuals. A full clinical and endoscopic history is necessary for interpretation.

CONCLUSION

Identifying the aetiology of an abnormality on colorectal biopsy specimens can be difficult. Often, there is significant overlap between various conditions that may produce similar morphological changes. Nevertheless, the management and clinical implications may be very different. Histological assessment may play a crucial role in making or refining the diagnosis. Most importantly, a multidisciplinary approach, integrating the clinical, endoscopic and pathological features, will usually help to optimise the accuracy of diagnosis and the quality of management.

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