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Gut inflammation induced by drugs: Can pathology help to differentiate from inflammatory bowel disease?

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Abstract

Drug-induced mucosal injury (DIMI) in the gastrointestinal tract is important to recognise, partly because cessation of the culprit agent alone may result in resolution of symptoms. An ever-growing list of medications, including newer immunotherapeutic agents and targeted therapies, can cause gastrointestinal inflammation of varying severity. However, the diagnosis of DIMI is challenging, as a single drug can induce a variety of histopathological patterns of injury including acute colitis, chronic colitis, microscopic colitis, apoptotic colopathy, and ischaemic-type colitis. An additional consideration is the potential clinical, endoscopic and histological overlap of DIMI with gastrointestinal mucosal injury secondary to other entities such as inflammatory bowel disease (IBD). We discuss DIMI of the gastrointestinal tract with an emphasis on histological patterns that mimic IBD, histological features which may distinguish the two entities, and the diagnostic role and limitations of the pathologist.

KEYWORDS
crohn's disease, damage, drug-induced, gastrointestinal tract, iatrogenic, inflammatory bowel disease, medication-induced, mucosal injury, ulcerative colitis

CASE

A 73-year-old woman presented with a 6-week history of abdominal cramps, Grade 2 diarrhoea and rectal bleeding. Stool cultures excluded infection. Colonoscopy showed diffuse left sided colitis with oedematous mucosa, erythema, and mucosal friability, raising the possibility of inflammatory bowel disease (IBD). Colorectal biopsies (illustrated in Figure 2b,c) showed active chronic colitis, with diffuse chronic inflammation, cryptitis, crypt abscesses, crypt distortion and crypt atrophy. Basal plasmacytosis, a consistent feature of new IBD, was mild and focal. There were no granulomata. The features were reminiscent of ulcerative colitis (UC), but the patient's age and the absence of convincing basal plasmacytosis raised the possibility of an alternative diagnosis. Additional enquiries revealed a history of advanced lung cancer and pembrolizumab therapy for the past 3 months. The provisional diagnosis was then immune checkpoint inhibitor (ICI) colitis. Pembrolizumab was held and the patient was commenced on oral prednisolone 1 mg/kg daily. Within 48 h symptoms improved to grade 1. Steroids were tapered over the following 6 weeks with complete resolution of symptoms. Although rechallenge with immune checkpoint inhibition was considered, this was ultimately not attempted due to patient preference.

INTRODUCTION

Within the last 2 decades there has been an explosion in the number of new targeted therapeutic agents, particularly in the fields of oncology and haematology. These drugs are often highly effective,

but they are associated with a range of potentially serious side effects including gastrointestinal (GI) abnormalities.

Diagnosis of drug-induced GI mucosal injury is a challenge, complicated by the ability of therapeutic agents to induce more than one pattern of injury. Furthermore, drug-induced mucosal injury (DIMI) can closely mimic other entities such as infectious colitis, graft-versus-host disease (GVHD), ischaemic colitis and IBD. As illustrated by our case, the distinguishing histopathological features are often subtle, few or absent, meaning that communication between clinician and pathologist is essential.

In this review, we will discuss DIMI of the GI tract GI tract (GIT), histological patterns which mimic IBD, histological features which may assist differentiation between IBD and DIMI, and the role and limitations of the pathologist. The list of medications which may mimic IBD is long and ever-expanding; these have been very recently comprehensively reviewed[1,2] and to discuss them all is outside the scope of this review. We select some illustrative examples to address the question of whether pathology can help differentiate between these two aetiologies of gut inflammation.

DEFINITIONS

'Acute colitis' refers to acute onset of diarrhoea or other symptoms in a patient with no prior history and no evidence of a chronic condition.[3] Histologically, acute inflammatory cells predominate and crypt architecture is normal.[4] Acute colitis may represent a genuinely acute and self-limited colitis or may represent the early phase of a chronic condition. Inflammation is designated 'chronic' histologically if there are features such as crypt distortion, crypt atrophy, diffuse lymphoplasmacytic inflammation in the lamina propria, basal plasmacytosis, Paneth cell metaplasia/hyperplasia, and lamina propria fibrosis.[3,5] Chronic inflammation is subcategorised as 'active' if there are superimposed acute ('active') features, for example, cryptitis, crypt abscesses, surface erosion, or ulceration, and otherwise as 'inactive'. Focal active colitis (FAC) usually describes isolated focal acute inflammation of the colonic mucosa with no evidence of chronic inflammation.[6]

WHAT ARE THE ENDOSCOPIC AND HISTOLOGICAL FEATURES OF IBD?

IBD is a chronic idiopathic inflammatory disease of the GIT with a relapsing and remitting course. The term 'IBD' encompasses UC and Crohn's disease (CD).

UC is characterised by mucosal and submucosal large bowel inflammation that begins in the rectum and spreads proximally in a continuous fashion with an abrupt transition to normal. In contrast, CD is transmural and discontinuous and can involve any component of the GIT. Rectal sparing, ileal inflammation and perianal disease favour CD over UC. Typical endoscopic findings in UC include oedematous mucosa, erythema, loss of vascular markings, mucosal granularity, friability, erosions, superficial ulcers, spontaneous bleeding, and inflammatory polyps. Suggestive endoscopic features of CD include aphthous ulcers, deep serpiginous or linear ulcers, a cobblestone pattern, strictures, fissures and fistulae.[7]

Histology can help distinguish UC from CD. Features favouring UC include a diffuse and continuous distribution of chronic changes such as crypt architectural abnormalities, crypt atrophy, villous mucosal surface, lymphoplasmacytic chronic inflammation and basal plasmacytosis together with severe mucin depletion and worsening of abnormalities towards the rectum[5] (Figure 1a). Features favouring CD include focal or patchy chronic inflammation, discontinuous crypt irregularity, granulomata unrelated to crypt injury, and disproportionate submucosal inflammation[5] (Figure 1b). Additional features of CD in resection specimens include transmural lymphoid aggregates, fibrosis, deep fissures and neuronal hyperplasia.[5] Precise differentiation is not always possible, and the term IBD-unclassified is then applicable.

WHAT IS THE ROLE OF HISTOLOGY IN DIFFERENTIATING DIMI FROM IBD?

Proving a causal role between a drug and GI damage requires, ideally, objective evidence of disease, a temporal association between the introduction of the medication and clinical presentation, resolution of symptoms upon cessation of the drug, recurrent symptoms upon reintroduction, and exclusion of all other possible causes. The Naranjo score aims to calculate the probability of an adverse drug reaction.[8]

Endoscopic features of DIMI are non-specific. Although certain clinical and histological clues may arouse suspicion of DIMI, as in this case, these will not always be present. Histology in isolation often does not provide a definitive diagnosis of DIMI and can only

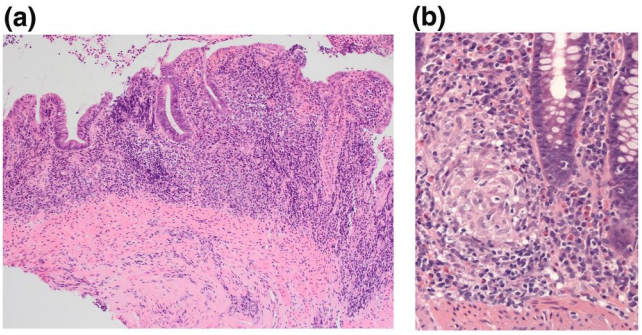

FIGURE 1 Histological features in inflammatory bowel disease (IBD). (a) ulcerative colitis (UC): Severe crypt architectural distortion (CAD) and crypt loss, alongside a diffuse increase in chronic inflammatory cells in the lamina propria, basal lymphoplasmacytosis and mucin depletion are features of chronicity. Extensive changes within and between biopsies favour UC over Crohn's disease. (b) Crohn's disease: Non-cryptolytic epithelioid granulomata are characteristic of Crohn's disease. The lamina propria also shows an increase in chronic inflammatory cells, including plasma cells, lymphocytes and eosinophils

diagnose IBD in the context of the clinical picture. Therefore, a multidisciplinary approach is essential. European Crohn's and Colitis Organisation (ECCO) and the European Society of Pathology (ESP) joint guidance recommends that biopsies for suspected IBD should be accompanied by full clinical information, including a drug history.[5] A major role of the pathologist is to decide if the histology supports the clinical diagnosis and to exclude important differential diagnoses.

WHAT ARE THE HISTOLOGICAL PATTERNS OF DIMI?

The consequences of DIMI in the GIT range from minor asymptomatic histological alterations to fatal events. DIMI can affect any part of the GIT. The GIT has a somewhat limited repertoire of response to insults. Therefore, various drugs can yield the same histological patterns, and these can also overlap with non-drug mucosal injuries. On the other hand, a single drug can also cause more than one pattern of changes. A sound knowledge of the distribution and histology of lesions that different agents induce can help the pathologist to suggest the aetiology.

Histological features and patterns of drug injury in the GIT include[9]:

- focal or diffuse acute (active) colitis
- chronic colitis (active or inactive)
- apoptotic excess
- dilated damaged crypts with apoptosis
- coeliac disease-like pattern
- microscopic colitis pattern
- ischaemic colitis pattern
- pseudomembranous colitis
- erosions and ulcers
- crystal deposition
- pseudomelanosis coli
- eosinophilia
- malakoplakia
- epithelial atypia

Macroscopically there may be strictures, diaphragms, or perforation of colonic diverticula.[9]

The chronic colitis pattern of drug injury can closely mimic IBD, and can cause an UC-like or CD-like pattern, the latter including granulomata.[10] Acute colitis and FAC also have the potential to mimic IBD, in particular CD.

WHICH DRUGS CAN MIMIC IBD AND WHAT HISTOLOGICAL CLUES CAN HELP DISTINGUISH DIMI FROM IBD?

Four representative examples will be discussed, namely ICIs, idelalisib, mycophenolate mofetil (MMF), and non-steroidal anti-inflammatory drugs (NSAIDs) (see also Table 1). We highlight potential differences between IBD and IBD-like DIMI, although we emphasise these features are imprecise and often subtle, or not always present.

Immune checkpoint inhibitors

ICIs are monoclonal antibodies that target checkpoint pathways. They improve survival significantly in patients with various advanced-stage cancers.[11] ICIs promote the survival of cytotoxic T-cells by targeting immune checkpoint proteins that act as negative regulators of T-cell anti-tumour immune response and are expressed on the surface of cytotoxic T-cells, namely cytotoxic T-lymphocyte-associated protein (CTLA-4) (for example, ipilimumab) and programmed cell death protein 1 (PD-1) (for example, nivolumab and pembrolizumab). ICIs that target programmed death ligand 1 also exist (for example, atezolizumab). The interactions increase anti-tumour T-cell activity. Unfortunately, this can simultaneously induce immune-related adverse events affecting the non-neoplastic cells of the skin, luminal GIT, liver, endocrine organs, lungs and other organs.[12]

Diarrhoea is the commonest GI side effect[11,13,14] and is usually transient and mild or moderate but can be severe and even fatal.[15] There is an increased risk of ICI-induced enterocolitis in the setting of dual ICI administration, concurrent NSAIDs or melanoma.[16]

ICI-induced enterocolitis resembles IBD at presentation by causing abdominal pain and diarrhoea, often with blood and mucus. Time to onset of symptoms is typically 6–8 weeks for anti-CTLA-4 agents and 3–6 months for anti-PD-1 therapy.[17] Recurrent anti-PD-1 colitis can commence months after completing treatment.[18]

Colonoscopy findings include normal mucosa (37%), ulceration (27%–40%), and non-ulcerative changes (36%–42%) such as altered vascularity, erosions, exudates, granularity, and erythema.[11] Involvement of the colon can be diffuse, resembling UC, or may be segmental, resembling CD.[19] Ileitis (11%–14%) and ileocolitis (<20%), resembling CD, are less common than pancolitis (23%–40%) or left-sided colitis (31%–43%), which mimic UC.[16] Diffuse changes are more typical of anti-CTLA-4 agents and patchy changes of anti-PD-1 agents.[20] Other CD-like features include aphthous ulcers, anal fistulae, and fissures.[21]

Immune checkpoint inhibitors: Histology

There is a wide spectrum of histological findings in ICI enterocolitis. These include

- acute colitis
- chronic colitis
- lymphocytic colitis

TABLE 1 Drug-induced injury mimicking inflammatory bowel disease (IBD): potentially helpful histological clues

Drug	Clinical features	Endoscopic features	Histological features overlapping with IBD	Histological features distinguishing from IBD
Immune checkpoint inhibitors: Anti-CTLA-4 antibody, for example, ipilimumab and anti-PD-1 antibody, for example, nivolumab	Abdominal pain and diarrhoea, often with blood and mucus History of advanced carcinoma or melanoma	Normal, oedema, altered vascularity, erosions, exudates, erythema, ulceration Pancolitis, left sided colitis > ileitis, ileocolitis	Acute colitis (lamina propria inflammation, focal cryptitis, crypt abscesses (focal or diffuse)) Features of chronicity (basal lymphoplasmacytosis, CAD, Paneth cell metaplasia) Granulomata (cryptogenic)	Increased crypt epithelial cell apoptosis including apoptotic microabscesses Crypt atrophy Increased IELs Features of chronicity typically mild Granulomata rare, usually associated with crypt rupture Predominance or presence of other histological patterns for example, microscopic colitis
Idelalisib	Watery, non-bloody diarrhoea, abdominal cramping, nausea, vomiting, weight loss History of haematological malignancy	Mucosal erythema, congestion, granularity, decreased vascularity, erosions, and ulcers Entire colon or left side	Cryptitis and crypt abscesses, erosions, ulcers, lamina propria inflammation Granulomata (cryptogenic) Features of chronicity	Increased IELs Crypt epithelial cell apoptosis CAD typically mild Granulomata associated with ruptured crypts
Mycophenolate mofetil	Dyspepsia, watery or occasionally bloody diarrhoea, nausea, vomiting History of solid organ transplant, haematopoietic stem cell transplant, autoimmune or inflammatory disease	Normal Erosions Ulceration Patchy erythema	Chronic active/inactive colitis Rarely granulomata	Increased crypt epithelial cell apoptosis Individual damaged crypts 'Empty' oedematous or eosinophil-rich lamina propria Mild or no CAD Ischaemic-like pattern: Mucin-depleted crypts, preserved crypt architecture, minimal lamina propria inflammation, crypt dropout
NSAIDs	Anaemia, melaena, dyspepsia, nausea, vomiting, diarrhoea (+ /− bloody)	Erythema, erosions well-demarcated ulcers surrounded by normal-appearing mucosa Strictures Diaphragms	Focal active colitis IBD-like pattern: Ileitis and patchy colitis with crypt disarray Chronic colitis	Usually CAD and granulomata absent resence of diaphragm disease Other histological patterns for example, microscopic colitis, eosinophilic colitis, ischaemic colitis

Abbreviations: CAD, crypt architectural distortion; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; IELs, intra-epithelial lymphocytes; NSAIDs, non-steroidal anti-inflammatory agents; PD-1, programmed cell death protein = 1.

- collagenous colitis
- GVHD-like colitis
- mixed/overlapping patterns[22,23]

Inflammatory changes are usually diffuse but can be patchy or rarely FAC.[22,24] The 'acute colitis' pattern can include cryptitis, crypt abscesses, intraepithelial neutrophils, and neutrophilic lamina propria infiltration,[17,18,21–23,25–28] often accompanied by crypt dropout, crypt atrophy, and/or crypt epithelial cell apoptosis,[13,17,18] and is the most common presentation of ipilimumab-induced colitis.[22]

A 'chronic active colitis' pattern may also occur, with mononuclear lamina propria infiltrate, basal lymphoplasmacytosis, crypt architectural distortion (CAD) and Paneth cell metaplasia accompanied by acute features[17,18,22,26] (Figure 2a–c), as described in the present case. Features of chronicity are more common in recurrent anti-PD-1 colitis than in new disease[18] and less common when patients are on ipilimumab alone than PD-1 inhibitors alone or dual ICI therapy.[22]

A 'microscopic colitis' pattern of injury occurs in a minority,[18] more often with PD-1 inhibitors than anti-CTLA-4 agents.[22] This shows increased lymphocytes and plasma cells in the lamina propria, an increase in intra-epithelial lymphocytes (IELs) and, occasionally, a dense subepithelial collagen band.[17,22,26] Minor degrees of microscopic colitis-like change are quite common in ICI colitis.

The GVHD-like pattern shows crypt epithelial cell apoptosis with crypt injury and dropout and is commoner in patients on dual ICI therapy.[17,22]

Occasionally, there are ischaemic colitis-type features such as withered crypts, reactive epithelial changes and a fibrotic lamina propria.[14,17,23,26]

Immune checkpoint inhibitors: Histological distinction from IBD and other causes

The active chronic colitis pattern, and, to a lesser degree, the acute pattern, can mimic IBD. Although the left colon is affected in 98% of cases of ICI colitis,[11] anti-CTLA-4 colitis has been described as more evenly distributed throughout the GIT, compared with UC which is more severe distally.[28] Involvement of the ileum may also help differentiate ICI colitis from UC. Histological clues to ICI colitis include:

- crypt epithelial cell apoptosis[25,27,28] (variable definitions, including more than 3 apoptotic bodies within epithelium of 10 crypts,[23]

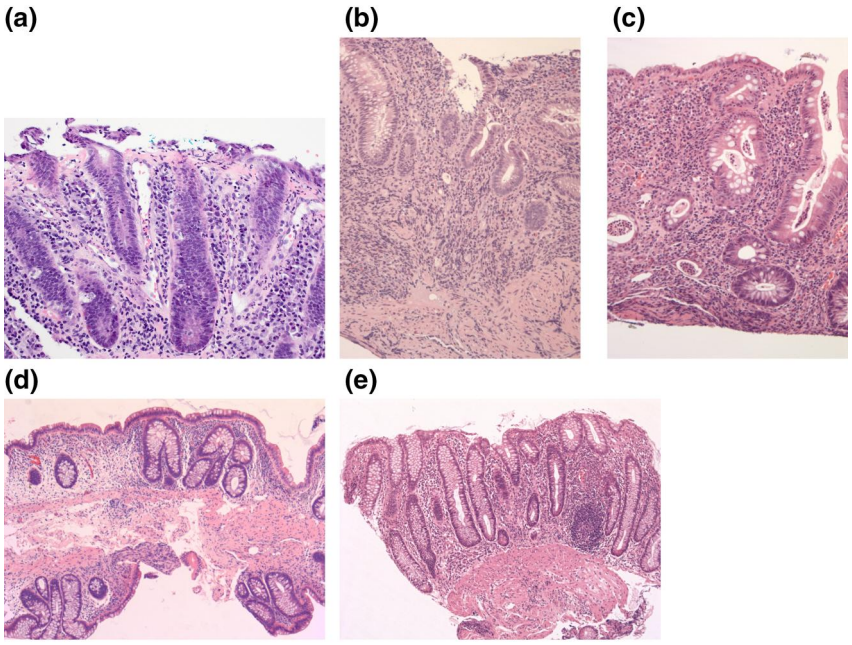

FIGURE 2 Histological features of Drug-induced mucosal injury (DIMI) in the gastrointestinal tract which overlap with inflammatory bowel disease (IBD). (a) immune checkpoint inhibitor (ICI) colitis secondary to Ipilimumab: There is an increase in both acute and chronic inflammatory cells within the lamina propria. An increase in crypt epithelial cell apoptosis and relatively mild degree of crypt architectural distortion (CAD) are subtle features indicating the correct diagnosis. (b) ICI colitis secondary to Pembrolizumab: Histological features overlap with, and may be indistinguishable from, ulcerative colitis (UC), including CAD, crypt loss, a diffuse increase in lamina propria chronic inflammation and basal lymphoplasmacytosis. (c) ICI colitis secondary to Pembrolizumab: ICI colitis secondary to Pembrolizumab. Histological features overlap with, and may be indistinguishable from, UC, including CAD, crypt loss, a diffuse increase in lamina propria chronic inflammation and basal lymphoplasmacytosis. (d) Colitis secondary to mycophenolate mofetil (MMF) resembling IBD: In MMF colitis, CAD, crypt loss and an increase in lamina propria chronic inflammatory cells with loss of the inflammatory gradient can mimic IBD. The features are typically milder than those seen in IBD. MMF colitis is more likely than IBD to show prominent crypt epithelial apoptosis and characteristic dilated damaged crypts. (e) Colitis secondary to NSAIDs: NSAIDs can cause a variety of patterns of inflammation in the colon, including chronic colitis. There is an increase in lamina propria inflammatory cell density and a mild degree of CAD. Typical IBD-like histology is very unusual

more than one apoptotic cell per biopsy,[29] more than 5 apoptotic bodies per 100 crypts[9]). Excess apoptosis can be seen without accompanying inflammation, producing a GVHD-like pattern of injury, or in combination with acute colitis or chronic active colitis[17] (Figure 2a)
- atrophic crypts with attenuation of crypt epithelium,[17,18,30] sometimes with an intraluminal admixture of apoptotic debris and inflammatory cells[13,17,18,23]
- intra-epithelial lymphocytosis (more than 10 intraepithelial lymphocytes within 100 surface epithelial cells)[23,25,27,30,31]
- a mild (rather than moderate/severe) degree of CAD[16,28] (Figure 2a–c), less frequent basal plasmacytosis,[28] fewer lamina propria plasma cells, less subcryptal inflammation, lower overall chronicity scores compared to IBD[23]
- Lesser degree of cryptitis and crypt abscesses compared to UC[28]

A triad of active colitis, IELs and increased epithelial apoptosis occurs in about one third and may suggest ICI colitis.[22] Granulomata have been reported[32] but probably only in association with ruptured crypts[11,26,33] and otherwise suggest an alternative diagnosis, for example, CD.

Severe inflammation, severe CAD and basal plasmacytosis favour IBD, and particularly UC (see Table 1).

Several studies[23,28,30,31] have compared lymphocytic subsets between ICI colitis and IBD with variable results. For example, one study reported similar CD8 + T-lymphocyte counts and immune cell infiltration patterns between UC and ICI colitis,[30] and another described higher CD8 + and CD4 + T-lymphocytes in IBD compared to anti-PD-1 colitis.[23] Analysis of lymphocytic subsets and immune cell infiltration patterns is not currently used in practice for diagnostic purposes.

Immune checkpoint inhibitors: Upper GI tract

ICIs cause a variety of upper GI tract changes. Endoscopic features include erythema, erosions, exudates, and ulcers.[17] Few histological features have any specificity. In the oesophagus, lymphocytic inflammation and ulcerative oesophagitis have been rarely reported.[17] The stomach may show chronic active gastritis, lymphocytic gastritis, focal enhancing gastritis or periglandular inflammation, and may show increased IELs, apoptosis and mucin depletion.[17,25,26,34] The duodenum may show erosion, lymphoplasmacytic inflammation, an increase in IELs, an increase in apoptosis, villous blunting, crypt distortion, neutrophilic cryptitis/villitis, and an increase in eosinophils.[13,17,21,25,26] Granulomata have also been reported in the duodenum and rarely the stomach.[17,21] The ileum can show villous blunting, an increase in IELs, dense lamina propria inflammation, cryptitis/villitis and scattered apoptosis.[25,26]

Many of these changes overlap with other disorders, including CD. The most useful diagnostic feature of CD in the upper GIT is the presence of granulomata[35] that are not related to crypt rupture as they are rare in ICI-induced disease.

Phosphoinositide-3-kinase inhibitors

Idelalisib is a selective inhibitor of the delta isoform of phosphoinositide-3-kinase (PI3Kδ) and is used to treat several B-cell malignancies. It can cause a continuous or focal colitis affecting either the entire colon or the left side.[36] Symptoms include watery, non-bloody diarrhoea (46% of patients), abdominal cramping, nausea, vomiting, and weight loss, with an average time to onset of 15 months.[36]

Histologically, there may be overlap with IBD, with cryptitis and crypt abscesses (>50%), erosions/ulcers (20%–30%), mild crypt architectural abnormalities, and Paneth cell metaplasia (14%). The latter two features correlate with a longer interval between symptom onset and endoscopy.[36] Crypt abscesses containing eosinophils have been described.[37]

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

- An increase in IELs (86%), comprising a mixture of small mature lymphocytes, and 'activated' lymphocytes with larger size, nucleomegaly, and irregular nuclear contours[36]
- Crypt epithelial cell apoptosis (79%). 50% of cases show large 'exploding' apoptotic epithelial cells in crypts. Sometimes, this occurs without significant inflammation and may resemble GVHD[36–38]

As for anti-PD-1 colitis, granulomata can occur in association with ruptured crypts but are otherwise not a feature.[36] Other reported patterns of injury include lymphocytic colitis[37] and ischaemic features.[38]

Idelalisib can also affect the small intestine, causing crypt apoptosis, villous blunting, an increase in IELs, and acute inflammation.[37]

Mycophenolate mofetil

MMF is an antimetabolite immunosuppressant used in haematopoietic and solid organ transplants and autoimmune disease. It blocks the de novo pathway of purine synthesis. GIT toxicity affects up to 45% of patients.[39] The commonest symptoms are nausea, vomiting, constipation, dyspepsia and watery or occasionally bloody diarrhoea.[39,40] Colonoscopy is normal in 47%,[40,41] but can show erosions, ulcers[39,41] or patchy erythema.[40] Abnormalities tend to spare the rectum[41] and may preferentially involve the right colon,[42,43] which may help to differentiate it from UC.

IBD-like features are observed in 13%–100%[40,42–44] of cases, and include CAD,[42,43] predominantly lymphoplasmacytic lamina propria inflammation, Paneth cell metaplasia, and crypt loss[43,45] (Figure 2d). Inflammation and architectural distortion are typically milder than in IBD.[40,41,43,45] A 'CD-like' pattern of mucosal changes may occur,[46,47] with patchy dense inflammation, erosions/ulcerations and lymphoid hyperplasia.[43] An acute self-limited colitis or FAC may mimic very early IBD.[41,42,45]

Despite these examples of overlap, MMF colitis is often histologically distinct from IBD. Increased crypt epithelial cell apoptosis is almost always prominent,[42,43,45] and a GVHD-like pattern with crypt epithelial apoptosis, no or mild crypt disarray, mild to moderate inflammation and no to mild activity may predominate.[40,41,43,45,48] Individual or dilated damaged crypts are also relatively specific and consist of often cystically dilated crypts lined by flattened or atrophic epithelial cells, which may be empty or contain luminal secretions, apoptotic debris or sparse intraluminal neutrophils.[40,42,43,46] These crypts may occasionally be lined by cells with abundant eosinophilic cytoplasm[42] and may show regenerative or bizarre atypia.[40] The lamina propria may be rich in eosinophils[43,48] or 'empty'-appearing due to oedema with patchy foci of neutrophils.[40] Occasionally an ischaemic pattern[41,45] or a mixed pattern with chronic architectural disarray, increased crypt apoptosis, cryptitis and isolated damaged crypts[42] may be apparent. Granulomata are rare.[40]

Histological features of upper GIT MMF toxicity include erosive or ulcerative oesophagitis, reactive gastropathy, duodenal ulcers, GVHD-like features in the small intestine, duodenal villous atrophy, and rare 'Crohn's-like' gastroduodenal or ileal granulomatous inflammation.[40,49]

Nonsteroidal anti-inflammatory drugs

NSAIDs are among the most common medications worldwide,[50] meaning even their rarer complications are seen frequently. NSAIDs are used to treat a wide variety of inflammatory conditions, including arthritides. The method of action of NSAIDs is blockade of cyclooxygenases (COX) 1 and 2, resulting in decrease in prostaglandin synthesis. The incidence of adverse effects approaches 70% with long term treatment.[9]

Common symptoms and signs of NSAID-induced GIT injury include melaena, dyspepsia, nausea and vomiting. Colitis can cause diarrhoea, usually of short duration, which may be bloody.

Endoscopic findings of NSAID-induced injury include erythema, erosions and discrete, punched-out ulcers surrounded by normal-appearing mucosa.[51,52] Abnormalities are usually non-specific and most commonly affect the gastric antrum, duodenal bulb, distal ileum and right colon.[51–53] Detection of NSAID-induced enteropathy is increasingly common, due to a combination of more widespread deployment of balloon-assisted and video capsule endoscopy and use of enteric resistant coating on medications.[51] Wide-based circumferential strictures may occur in the small intestine and colon with long term use.[52,54]

In the stomach, NSAIDs can cause reactive gastropathy or superficial mucosal necrosis.[50,53] Histologically, NSAID-induced enteropathy can be patchy with active inflammation, mucosal architectural distortion and pyloric metaplasia thus simulating CD.[52] Compared with CD, NSAIDs very rarely or never induce granulomata, cause less inflammation and architectural distortion, and do not produce transmural lymphoid aggregates, fissures or fistulae.[51]

Diaphragm disease is a long-term complication usually affecting the small bowel, less commonly large bowel and rarely the stomach.[55] Diaphragm disease comprises submucosal fibromuscular hyperplasia, resulting in often ulcerated, circumferential, thin web-like septa in the lumen.[50,56] Diaphragm disease is highly characteristic but not pathognomonic of NSAID injury. The histological features include submucosal fibrosis and collagen bundles aligned towards the apex of the stricture.[56]

NSAIDs cause a broad spectrum of damage in the colon including IBD-like patterns.[50] Symptoms include bloody diarrhoea and abdominal pain.[50] Endoscopic features include normality, friability, hyperaemia, oedema, erosions and ulcers. Diffuse rectal and colonic mucosal damage can suggest UC while patchy involvement, which is more common, can mimic CD.[50] Ulcers are commonest in the caecum and ascending colon.[54,57] Perforation can occur. Strictures are less common than in the small bowel. Histological patterns include microscopic colitis, eosinophilic colitis, ischaemic-type colitis and chronic colitis.[9,50,52,58] Histology is nonspecific and can show various degrees of inflammation in the lamina propria, crypt disarray, focal IELs,[59] prominent eosinophils or increased basal apoptosis[50] (Figure 2e). Granulomata are very rare.[60] NSAIDs can cause a FAC pattern, often orientated basally in the crypts, associated with basal crypt apoptosis[61] (Table 2). Typical IBD-like histology is very unusual.

As well as causing a drug-induced inflammatory colitis which may mimic IBD, there is evidence that NSAID use may increase the risk of developing IBD.[62–64] There is conflicting evidence linking NSAID use to flares of known IBD.[65]

Other drugs that mimic IBD

Many other medications can cause an enterocolitis with the potential to mimic IBD clinically and pathologically.[53,66–71] Many are reported in the literature to cause de novo IBD, or exacerbation of pre-existing IBD. It is not clear whether these medications truly do trigger the development of IBD in susceptible patients, or represent a drug-induced colitis that closely mimics IBD. Biologic therapies are a prominent example. Anti-tumour necrosis factor-alpha (TNF-alpha) biologic agents are in widespread use for immune-mediated inflammatory disorders and several studies support a tentative association between these drugs, particularly etanercept, and the development of both de novo IBD and of flares of pre-existing IBD.[66,72–77] A CD pattern is typical. Histological features include granulomata, superficial ulceration, crypt abscesses and CAD.[73] However, the apparent progression to IBD or an IBD-like illness on these drugs may be coincidental or might represent an unmasking of underlying disease[78–80] while co-administration of NSAIDs may also confound the assessment. Colitis with clinical, endoscopic and histological features indistinguishable from IBD (predominantly UC) has also been reported following administration of rituximab, an anti-CD20 monoclonal antibody used in the treatment of conditions including B-cell malignancies and rheumatoid arthritis.[81–85] IL-17 inhibitors used in conditions such as psoriasis, for example, secukinumab, may induce or exacerbate IBD,[14,86,87]

TABLE 2 Differential diagnoses for patterns of mucosal injury that histologically overlap with inflammatory bowel disease (IBD)

Histological pattern	Differential diagnosis	
Focal active colitis	Infectious colitis (e.g. *Campylobacter jejuni*, *Salmonella*, *Shigella*, *Escherichia coli*, *Yersinia* and viral), drugs (e.g. NSAIDs, antibiotics, PPIs, sodium phosphate, MMF), IBS, IBD (CD > UC), incidental[61]	
Self-limited/acute colitis	IBD (CD > UC), infectious colitis (e.g. *Campylobacter jejuni*, *Salmonella* species, *Shigella* species, *Escherichia coli*, *Yersinia enterocolitica*, rotavirus, enterovirus, adenovirus, *Entamoeba histolytica*, *Cryptosporidium* spp), ischaemia, radiation, drugs (e.g. MMF, ICIs, idelalisib, NSAIDs, antibiotics)[3,57]	
Chronic (active or inactive) colitis	**Preserved architecture**[3] Drugs (e.g. ICIs, NSAIDs, MMF), IBD (early or resolving), diverticular disease, infectious colitis (late/resolving phase, e.g. *Shigella*, *Treponema pallidum*, *Chlamydia*), microscopic colitis	**Crypt architectural distortion**[3] IBD, drugs (e.g. ICIs, NSAIDs, MMF, TNF-alpha inhibitors, rituximab), longstanding infectious colitis (e.g. *Yersinia* spp, amoebic colitis, *Shigella*, *Salmonella*, *Mycobacterium tuberculosis*), diverticular disease-associated colitis, chronic ischaemia, chronic radiation colitis, mucosal prolapse, diversion colitis
Granulomata	CD (non-cryptolytic), UC (cryptolytic), diversion colitis, diverticular disease-associated colitis (cryptolytic), infection (bacterial e.g. *Mycobacterium tuberculosis*,[a] *Yersinia enterocolitica*,[a] *Bartonella henselae*,[a] lymphogranuloma venereum,[a] *Treponema pallidum*, *Salmonella*, *Campylobacter jejuni*; fungal e.g. Histoplasmosis,[a] cryptococcosis,[a] coccidiodomycosis[a]; parasitic e.g. schistosomiasis), sarcoidosis, medications (e.g. ICIs, idelalisib – cryptolytic), foreign body reaction, lymphoma.[3,119,120]	

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; ICIs, immune checkpoint inhibitors; MMF, Mycophenolate mofetil; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; TNF-alpha, tumour necrosis factor alpha; UC, ulcerative colitis.

[a]usually necrotising/caseating/suppurative granulomata.

although other studies suggest this risk is not statistically significant.[88] There are isolated case reports of development of de novo IBD or flaring of IBD linked to administration of IL-1 antagonists, including anakinra and canakinumab,[70,89] anti-IL-6R antibody tocilizumab,[71,86] CTLA-4-Fc fusion protein abatacept,[90,91] and the anti-vascular endothelial growth factor monoclonal antibody bevacizumab.[92]

Case reports and observational studies describe IBD-like histological changes, including FAC and chronic colitis, in a range of other medications, including tyrosine kinase inhibitors such as dasatinib,[93,94] sunitinib and sorafenib,[95,96] proteasome inhibitor bortezomib,[97] immune modulators such as tacrolimus,[68] azathioprine,[98] leflunomide,[69] hydroxycarbamide[53] treatments for hepatitis C including interferon and/or ribavirin,[99–102] sofosbuvir, simeprevir,[103,104] and gold.[105]

Isotretinoin is a synthetic analogue of vitamin A, approved for treatment of severe recalcitrant nodular acne. Its association with development of de novo IBD is controversial, with no causal relationship established.[106–108] Antibiotics are postulated to predispose to IBD via disruption of the microbiome. Multiple studies have been published describing an association between antibiotic use and later development of IBD (particularly CD) in both children and adults[106–111] with penicillin having the weakest association and metronidazole the strongest.[110]

WHAT HISTOLOGICAL PATTERNS OF DIMI ARE EASILY DISTINGUISHED FROM IBD?

Certain histological patterns of DIMI are distinct from those caused by IBD.

These include:

- apoptotic enteropathy/colopathy
- villous blunting in the small bowel
- ischaemic colitis pattern
- microscopic colitis
- eosinophilic colitis
- haemorrhagic colitis
- pseudomembranous colitis
- crystal deposition

In these cases, the pathologist may have a useful role in helping to exclude IBD (see Table 3).[9,50–53,112] A drug-induced chronic ischaemic colitis pattern of injury in particular can overlap with IBD if there is CAD and Paneth cell metaplasia, but hyalinisation, fibrosis, a relative paucity of chronic inflammatory cells and selective damage to the superficial epithelium of the crypt favour ischaemia.[4,113,114]

WHAT ARE THE FUTURE ROLES FOR THE PATHOLOGIST IN ASSESSMENT OF DIMI?

The Nancy Histological index and the Robarts Histopathology Index (RHI) are validated indexes for UC that evaluate the severity of mucosal changes in biopsies.[115,116] In a recent study of ICI-induced colitis, a Nancy score of 3 or 4 predicted a higher likelihood that infliximab use would be necessary.[117] In another report, a higher RHI was independently associated with a need for biologic use and adverse clinical outcomes in ICI-induced colitis.[118] These data indicate a potential prognostic role for histopathology. Future directions

TABLE 3 Differential diagnoses for selected patterns of mucosal injury histologically distinct from inflammatory bowel disease (IBD)

Histological pattern	Description	Potential causes
Ischaemic colitis	Surface epithelial injury, epithelial mucin loss, atrophic/withered microcrypts and lamina propria hyalinisation, mucosal and submucosal haemorrhage, oedema, necrosis with or without overlying pseudomembranes[3] Chronic ischaemia: can mimic IBD due to features of chronicity (CAD, Paneth cell metaplasia)[3]	Drugs (MMF, NSAIDs, sodium polystyrene sulfonate, capecitabine, cocaine, ergotamine, diuretics, ACE inhibitors, gold compounds exogenous hormones, methysergide), hypotension/shock, cardiac failure or arrhythmias, coagulopathy, atheroembolism, infection (e.g. *Escherichia coli* 0157:H7, *Shigella*, *Clostridium difficile*, cytomegalovirus, angioinvasive fungi or parasites) surgical procedures, vasculitis, trauma[50,57]
Eosinophilic colitis	Various definitions; sheets of eosinophils infiltrating the crypt epithelium and lamina propria with extension through the muscularis mucosae into the submucosa + /− muscularis propria[122,123]	Allergic colitis, eosinophilic gastroenteritis and colitis, vasculitis, (e.g. Churg-Strauss syndrome), parasitic infection (e.g. *Enterobius vermicularis*, *Ascaris lumbricoides*, *Strongyloides stercoralis*, *Schistosomiasis*), medications (e.g. clozapine, carbamazepine, rifampicin, NSAIDs, tacrolimus, gold), mast cell disorders (e.g. systemic mastocytosis), hypereosinophilic syndrome, acute radiation colitis[3,121,122]
Small intestinal villous atrophy	Villous atrophy, an increase in IELs and increased lamina propria lymphocytes and plasma cells + /− increased apoptosis in drug-related	Coeliac disease, IBD, food allergy, medication (e.g. olmesartan, ipilimumab, MMF, NSAIDs, azathioprine), GVHD, tropical sprue, infection (e.g. giardiasis, small bowel bacterial overgrowth, viral, fungal, parasitic), autoimmune enteropathy, CVID, lymphoma[123]
Apoptotic enteropathy	Increased crypt apoptosis (variable definitions: One AB per biopsy piece, total number of ABs at least equal to number of pieces, scattered AB in >1 crypt[124] > 5 ABs per crypt)[125] Apoptotic microabscesses: 5 or more ABs per crypt[126] Dilated damaged crypts (favour GVHD or drugs)	Medications (e.g. MMF, ICIs, antimetabolites [methotrexate, 5-fluorouracil, capecitabine], idelalisib, TNF-alpha inhibitors [etanercept, infliximab], NSAIDs, ARBs, colchicine, taxanes, capecitabine), GVHD, infection (e.g. cytomegalovirus, adenovirus, cryptosporidiosis, HIV), radiation injury, CVID, autoimmune enterocolopathy[126]
Microscopic colitis	Lymphocytic colitis: Surface epithelial damage, increased IELs, expansion of lamina propria chronic inflammatory cells Collagenous colitis: As for lymphocytic colitis, but including a thickened irregular subepithelial collagen plate[127]	Medications (e.g. PPIs, histamine H2 receptor blockers, ticlopidine, flutamide, selective serotonin reuptake inhibitors, acarbose, NSAIDs, ICIs, statins, carbamazepine),[3,9,127] infection (e.g. *Campylobacter jejuni)*, autoimmune disease[127]
Crystal deposition	Deposition of characteristic crystals or crystalline material, in normal GI mucosa or associated with additional features such as erosions, ulcerations, pseudomembranes or necrosis, the latter of which may be transmural[9,50]	Medications (e.g. bisphosphonates, sodium polystyrene sulfonate, sevelamer, iron, cholestyramine)[9,50]
Pseudomembranous colitis	Mixed inflammatory/ischaemic pattern with laminated pseudomembranes composed of fibrin-rich exudate and mucus containing neutrophils and necrotic epithelial cells overlying dilated and damaged crypts; ischaemic features develop with progression[57]	Infection (bacterial e.g. *Clostridium difficile*, *Shigella*, *Escherichia coli;* parasitic e.g. Entamoeba histolytica; viral e.g. cytomegalovirus), drugs (antibiotics e.g. penicillins, clindamycin, cephalosporins, trimethoprim-sulfamethoxazole; alosetron, cisplatin, cocaine, ciclosporin A, dextroamphetamine, docetaxel, 5-fluorouracil, gold, glutaraldehyde, NSAIDs, paraquat, PPIs),[9,57] radiation injury,[57] pseudomembranes seen in other forms of colitis, for example, ischaemic colitis, IBD, microscopic colitis[128]

(Continues)

TABLE 3 (Continued)

Histological pattern	Description	Potential causes
Haemorrhagic colitis	Haemorrhagic oedematous lamina propria, fibrin thrombi within capillaries, ischaemic/regenerative crypts, variable neutrophilic inflammation, pseudomembranes (not the predominant feature if present)[57]	Infection (e.g. *Escherichia coli* O157:H7, *Shigella*, *Klebsiella oxytoca* following antibiotics), non-infectious acute ischaemia, drugs (antibiotics including ampicillin, amoxicillin and erythromycin,[50] alpha-interferon, hyperosmolar medication formulations), acute radiation injury[3,57]

Abbreviations: AB, apoptotic body; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CAD, crypt architectural distortion; CVID, chronic variable immune deficiency; GVHD, graft-versus-host disease; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; ICIs, immune checkpoint inhibitors; MMF, Mycophenolate mofetil; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; TNF-alpha, tumour necrosis factor alpha.

also include the development of a validated histological score for ICI colitis and exploration of the value of therapy tailored to specific histological patterns of colitis.

CONCLUSION

The spectrum of DIMI is broad, and GIT involvement is common. An increasing list of drugs, particularly ICIs, can closely mimic IBD. Histopathologists have a central role in supporting the diagnosis of DIMI of the GIT and in excluding other causes, and may soon have a role in predicting the outcome of ICI enterocolitis. DIMI can be distinguished from IBD more easily when patterns such as microscopic colitis, ischaemic colitis and apoptotic enteropathy are present. Even if there is an IBD-like histological pattern, clues such as prominent intraepithelial lymphocytosis and apoptotic microabscesses may alert the histopathologist to the possibility of drugs. Perhaps most importantly, accurate interpretation depends on good clinicopathological correlation because a confident diagnosis of DIMI is rarely possible based on histology alone.

CONFLICT OF INTEREST

The authors declared that they have no conflicts of interest to this work.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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