Mimics of inflammatory bowel disease: commonly encountered differentials of an uncommon condition

Positioning of inflammatory bowel disease in Australia in 2024

Australia has one of the highest rates of inflammatory bowel disease (IBD) in the world; its prevalence has increased significantly over the past 20 years and is projected to increase by >250% from 2010 to 2030, to then affect 1% of the population.[1] Although advances in clinical practice have led to increased identification, this increase is thought to be due to urbanisation of communities, with changes in sanitation and dietary practices. Such changes seen in Asia over the past 20 years have mirrored the rapidly increasing rates of IBD in the Western society, lending support to the "hygiene hypothesis", and explaining, in part, the increasing burden of IBD on Australian health care due to our high rates of immigration.[1,2]

Paediatric-onset IBD has seen the incidence of Crohn's disease rise from 0.128 per 100 000 to 2.0 per 100 000, and an 11-fold increase of ulcerative colitis in Victoria since the 1990s.[3,4] Earlier onset of disease has been recognised to portend a more aggressive phenotype and is associated with disease extension, stricturing and penetrating complications, and higher rates of both surgery and colorectal cancer.[5] Given the changing epidemiology, it is imperative to diagnose IBD early, as a treat-to-target approach may prevent long term complications, improve quality of life, and lessen the burden on health care resources.

Red flags: differentiating IBD from functional gut disorders

Although presenting with bloody diarrhoea does not equate to IBD, the diagnostic approach in this patient cohort is intuitive and usually involves colonoscopy. What can be challenging, particularly in primary care, is the approach to patients with non-specific abdominal and extra-intestinal symptoms and hence differentiating between organic disease and functional gastrointestinal disorders (FGID). Patients with ulcerative colitis commonly present with rectal bleeding, urgency and increased stool frequency; whereas fatigue, abdominal pain, loose bowel motions, and bloating may predominate in Crohn's disease, particularly ileal disease.[6] Complicating matters further is the significant overlap of FGID in patients with concomitant IBD.[7] The presence of rectal bleeding, nocturnal bowel motions, perianal disease, weight loss or previous bowel obstructions are red flags for IBD (and organic disease in general); however, objective evidence is required for diagnosis.

Faecal calprotectin (FCP) is a direct marker of intestinal inflammation and, when elevated, is a sensitive, objective measure suggesting organic pathology. Testing with faecal calprotectin is a practical non-invasive preliminary investigation; a negative result (≤ 40 μg/g) portends a ≤ 1% chance of underlying IBD.[8] FCP testing uptake in Australia has previously been limited by cost; however, a recent change to the Medicare Benefits Schedule has seen this test bulk-billable in primary care.[9] Mildly elevated calprotectin concentrations of 50–150 μg/g are non-specific and may be difficult to interpret. Calprotectin levels may be elevated due to any cause of diarrhoea (ie, infection) and falsely elevated in the presence of rectal bleeding, and therefore are not specific for IBD. Evidence of iron deficiency, hypoalbuminaemia, elevated C-reactive protein and thrombocytosis are associated with systemic inflammation and may indicate IBD.[10] Testing for FCP levels is less reliable in patients with isolated ileal Crohn's disease;[10] however, a micronutrient assessment may be useful as higher rates of vitamin B12, iron and vitamin D deficiencies and lower folate levels are seen in Crohn's disease compared with healthy controls.[11-13]

Unfortunately, biomarkers such as FCP and C-reactive protein are imperfect screening tests; for example, 28–42% of patients with active IBD will have normal C-reactive protein levels.[14] Cross-sectional imaging, such as magnetic resonance imaging (MRI) scans of the small bowel, is helpful and qualifies for a Medicare rebate in known small bowel Crohn's disease, but carries a high cost in the undifferentiated patient. Trans-abdominal gastrointestinal ultrasound is an emerging technology available in many tertiary hospitals. It has been shown to correlate accurately with inflammatory burden seen at colonoscopy and is being used by gastroenterologists as part of their diagnostic armamentarium, and to monitor established IBD. Gastrointestinal ultrasound is fast, non-invasive, does not require bowel preparation and is reproducible.

Mimics of IBD: how to differentiate

The Box outlines a range of disease processes that may result in intestinal inflammation and hence mimic IBD; the most common and interesting differentials are presented in the text below. Ultimately, many of the patients with these diagnoses should be referred to a gastroenterologist for appropriate investigation and treatment; however, these mimics should be kept in mind in primary care.

Non-steroidal anti-inflammatory drug enteropathy

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective first-line analgesic drugs. Although selective COX-2 inhibitors offer some gastrointestinal protection, they are frequently implicated in small bowel injury. Both short and long term use is associated with NSAID-enteropathy in up to 50–70% of

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Pathologies that mimic IBD organised by disease process and typical intestinal distribution

	Ileal predominance	Colonic predominance	Rectal predominance	Any location
Infective	• Tuberculosis • Histoplasmosis • Yersinia • Salmonella	• *Clostridioides difficile* • *Escherichia coli* • *Shigella* spp • *Campylobacter* spp • *Salmonella* spp • *Aeromonas* spp • *Entamoeba histolytica* • CMV	• Lymphogranuloma venereum • Herpes simplex	• Rotavirus • Norovirus
Drug/therapy	• NSAID enteropathy	• Checkpoint inhibitor colitis		• Radiation
Immune-mediated	• Behcet's syndrome	• CVID • Microscopic colitis		• Vasculitides • Sarcoidosis • Amyloidosis • GVHD
Non-immune, non-infective		• Diverticulitis • Diversion colitis • Segmental colitis associated with diverticulosis	• Solitary rectal ulcer • Chemical colitis	• Ischaemic colitis • FGID • Malignancy

CMV = cytomegalovirus; CVID = common variable immunodeficiency; FGID = functional gastrointestinal disorders; GVHD = graft versus host disease; IBD = inflammatory bowel disease; NSAID = non-steroidal anti-inflammatory drugs. ◆

users.[15] Complications include iron deficiency anaemia, ulceration resulting in protein-losing enteropathy, and small bowel strictures, presenting as recurrent abdominal pain or bowel obstruction. Biochemistry may reveal hypoalbuminaemia and micronutrient deficiencies. At endoscopy, strictures typically have a diaphragm-like appearance and may result in obstruction and, rarely, perforation.[15] Endoscopic and histologic features may mimic Crohn's disease and, as such, a detailed drug history is imperative in distinguishing the two.

Infectious colitis

Differentiating between acute infectious colitis and IBD begins with clinical assessment. Stool culture is positive in up to 50% of cases.[16] Infectious colitis typically presents with sudden-onset loose stools, often with bleeding. Vomiting and fever are common. Experience from a single-centre retrospective cohort study of over 800 patients, presented in abstract form, suggests thrombocytosis may indicate underlying IBD rather than infection.[17] A detailed travel history, along with information on the occurrence of sick contacts, is helpful. Common pathogens are listed in the Box.[16] Infectious colitis typically resolves spontaneously and requires no further investigation. In those with persisting abdominal pain, *Yersinia* spp should be considered as this often affects the ileum, may mimic appendicitis and may cause a reactive arthritis.[18]

Microscopic colitis

Microscopic colitis includes collagenous and lymphocytic colitis, and is a common cause of chronic, watery diarrhoea, particularly among the older population and in females. Implicated medications associated with onset include NSAIDs, anti-depressants, proton pump inhibitors, and anti-Parkinsonian drugs. Smoking is also a risk factor. Coeliac disease is associated with microscopic colitis, albeit infrequently.[19] As the name suggests, colonoscopy results appear normal visually, whereas subtle changes may sometimes be observed. Histology reveals inflammatory infiltrate of subepithelial collagen or intra-epithelial lymphocytes, in collagenous and lymphocytic colitis respectively.[19]

Ischaemic colitis

Ischaemic colitis occurs when the blood supply to the colon is insufficient to meet its metabolic demands and results in mucosal injury that may progress to transmural necrosis. It affects the left colon in 75% of cases and may mimic left-sided IBD, presenting with rectal bleeding and abdominal pain.[20] Clinicians should be suspicious in patients presenting with acute symptoms and typical vascular risk factors. Using a computerised tomography (CT) scan, segmental colitis has been found in up to 40% of patients, with watershed areas most affected, whereas the presence of a target sign (ie, a circle of submucosal oedema between mucosal and serosal hyperenhancement) is highly suggestive. Right-sided involvement is a marker of severity.[20] Characteristic features on endoscopy results include a single, longitudinal ulcer (single-stripe sign) and dusky mucosa indicating gangrenous transformation.[20]

Segmental colitis associated with diverticulosis

Segmental colitis associated with diverticulosis is an uncommon cause of chronic diarrhoea, crampy abdominal pain (particularly in the left lower quadrant) and episodic rectal bleeding. The aetiopathogenesis and disease course are poorly understood; however, it typically affects the sigmoid, and colonic inflammation of surrounding areas of diverticula is observed. Endoscopic and histologic appearances may mimic IBD, although there is rectal sparing. Treatment is typically with ciprofloxacin or metronidazole, whereas those with persistent symptoms may respond to mesalazine or glucocorticoids.[21]

Vasculitides

Vascular assessment via CT or MRI scans assists in distinguishing systemic vasculitis from IBD.[22] Behcet's syndrome may mimic Crohn's disease with ileocaecal ulceration in up to 50% of cases and is associated with human leukocyte antigen B51. These ulcerations are typically large, deep lesions with a punched-out appearance.[23] It typically affects patients from the ancient silk road (Eastern Asia to the Mediterranean) and co-existing ocular disease, genital ulceration and pathergy are clues to the diagnosis.

Polyarteritis nodosa may have gastrointestinal involvement and is distinguished by characteristic microaneurysms on dedicated imaging. Conversely, gastrointestinal manifestations of anti-neutrophil cytoplasmic antibody-associated vasculitis are uncommon but often serious, including bowel infarction or perforation.[22]

Tuberculosis

Although *Mycobacterium tuberculosis* is not endemic to Australia, it remains an important differential due to our large migrant population, of which India is the most common country of origin.[24] Differentiating gastrointestinal tuberculosis (GITB) from Crohn's disease is challenging. Both commonly affect the ileum and, accordingly, present similarly; however, a shorter duration of disease, fever and an abdominal mass favour GITB. The presence of haematochezia and perianal disease are more common in Crohn's disease. Pulmonary involvement occurs in 25% of GITB cases. Necrotic lymph nodes on cross-sectional imaging are highly specific for GITB, whereas other indicators include ascites, asymmetric mural thickening, and involvement of other solid organs.[25]

Endoscopic assessment is essential. The presence of a patulous ileocaecal valve and transverse ulcers is seen more frequently in GITB, in contrast to aphthous or longitudinal ulcers in Crohn's disease. Both diseases may cause granulomatous inflammation; however, caseating, confluent granulomas, along with macrophage-lined ulcers, are specific to GITB. A negative QuantiFERON-TB Gold Plus test (QIAGEN) may help exclude past or latent tuberculosis infection but a sensitivity of 75% limits its application. Microbiological assessment with mycobacterial culture and polymerase chain reaction-based testing of affected tissue, captured at endoscopy, is considered the gold standard. Of note, acid-fast bacillus staining has a limited role in diagnosing GITB compared with pulmonary disease.[25]

Distinguishing between GITB and Crohn's disease is important as misdiagnosis may result in significant consequences. Immunosuppressive treatment for misdiagnosed Crohn's disease, in particular with anti-tumour necrosis factor therapies, may result in disseminated tuberculosis, which may be life threatening. Conversely, anti-tuberculosis treatment may expose patients to drug toxicity, and a delay in Crohn's disease diagnosis may result in disease progression to a more complicated phenotype and an increased risk of surgery. Such patients are frequently discussed in multidisciplinary meetings and when a definitive diagnosis cannot be reached, a trial of anti-tuberculosis treatment is commonly initiated with mucosal healing at two months considered confirmatory of GITB.[25]

Lymphogranuloma venereum

Chlamydia trachomatis infection is the most common sexually transmitted infection in Australia, seeing a 60% rise in incidence over the past ten years.[26] Genital ulcerating disease caused by the biovars L1, L2 and L3 of *C. trachomatis* is referred to as lymphogranuloma venereum (LGV). When transmitted via anoreceptive intercourse, LGV results in a lymphoproliferative reaction presenting as proctitis with proctalgia, mucopurulent rectal discharge, tenesmus and altered bowel habits, and patients may be systemically unwell with locoregional lymphadenopathy. Colorectal fistulae and strictures may complicate untreated disease.[27] Men who have sex with men, and those with human immunodeficiency virus (HIV) are most affected. A detailed sexual history is important. At endoscopy, LGV may be indistinguishable from IBD and the diagnosis is made by rectal swabs;[27] treatment is with antibiotics.

Chemical colitis

Rectal administration of a range of chemicals may cause colonic toxicity, which may present with haematochezia, pain and diarrhoea. Commonly implicated agents include alcohol, herbal medicines and household detergents. Intentional administration for the purpose of intoxication, bowel cleansing, suicide attempts, or sexual practices is not uncommon. Most cases result in superficial mucosal injury that resolves with conservative management; however, severe cases may cause necrosis and perforation, requiring surgical resection.[28]

Conclusion

IBD is increasing in prevalence in Australia and should be considered in the primary care setting. A wide range of conditions may mimic IBD. Testing FCP levels is an effective first investigation in differentiating IBD from FGID and is now subsidised by the Medicare Benefits Schedule. Patients with abnormal investigations or concerning features should be referred to a gastroenterologist for further investigation and management.

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