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Review

Differential Diagnosis of Inflammatory Bowel Disease

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Abstract

Differentiating inflammatory bowel disease (IBD) from other gastrointestinal inflammatory conditions is essential for accurate diagnosis and effective management. This review examines various infectious, ischemic, drug-induced, and rare pathologies that can mimic IBD both clinically and histologically. Intestinal tuberculosis (ITB) presents a significant diagnostic challenge due to its resemblance to Crohn's disease, particularly in the ileocecal region. Infectious agents, such as *Yersinia* and cytomegalovirus (CMV), as well as drug-induced enteropathies, especially those caused by nonsteroidal anti-inflammatory drugs (NSAIDs), can produce symptoms and morphologies similar to IBD.

Advanced diagnostic tools, including tissue polymerase chain reaction (PCR), specialized histological staining, and imaging techniques, are recommended to identify distinctive features, such as granulomas in ITB or vasculitic involvement in systemic vasculitis. Monogenic disorders, Behçet's disease, and gastrointestinal vasculitis must also be considered, particularly in cases unresponsive to standard treatments. Differentiating factors such as symptom duration, endoscopic findings, and associated systemic signs play a critical role in guiding a precise diagnosis.

An accurate assessment, supported by a multidisciplinary approach, improves clinical outcomes by ensuring the appropriate treatment for conditions that resemble IBD but have distinct therapeutic requirements.

Keywords: Crohn's disease, differential diagnosis, inflammatory bowel disease, ulcerative colitis

INTRODUCTION

Inflammatory involvement of the gastrointestinal (GI) tract often resembles inflammatory bowel disease (IBD) macroscopically, and in chronic cases, histological features may also mimic those seen in IBD. Accurately identifying the underlying cause is essential for timely and effective management. While clinical and endoscopic findings are critical for diagnosing IBD, additional methods such as histology, polymerase chain reaction (PCR) for microbiological analysis, imaging, and, in rarer cases, genetic testing, may be necessary for a differential diagnosis.

The endoscopic appearance and the pattern of involvement play a particularly important role. For example, the classic cobblestone appearance in the ileocecal region is characteristic of Crohn's disease (CD), whereas long (>5 cm), linear, often solitary or paired antimesenteric ulcers in the left colon are more indicative of ischemia. In contrast, aphthous ulcers or widespread colitis are less specific findings.

Chronic inflammatory conditions of the GI tract, including those considered in the differential diagnosis of IBD, often present along a spectrum. These may include CD-like involvement of the ileocecal region with CD-like ulcers or ulcerative colitis (UC)-like involvement predominantly affecting the left colon, which typically manifests as diffuse, mucosal-dominant superficial inflammation. It is important to note that these two forms can overlap in certain pathologies within the differential diagnosis spectrum, as well as in cases exhibiting "indeterminate" morphology (Table 1).

In this section, we will examine the key pathologies more commonly encountered in clinical practice that should be considered in the differential diagnosis of IBD and its exacerbations.

INFECTIOUS PATHOLOGIES

Various acute inflammatory processes-including viral, bacterial, fungal, protozoan, and helminthic infections-are significant considerations both during IBD flare-ups and in the differential diagnosis.[1] Among these, intestinal tuberculosis (ITB) presents a notable clinical challenge due to its chronic symptoms, such as diarrhea, weight loss, and abdominal pain, which closely mimic CD in clinical presentation, intestinal involvement, and endoscopic morphology.

Pathogens such as cytomegalovirus (CMV) and *Clostridioides difficile* may occasionally cause diagnostic confusion with IBD, particularly in severely immunosuppressed patients. However, their role is more frequently discussed in the context of triggering IBD exacerbations.[2]

Table 1. Differential diagnosis of endoscopic morphology

UC like morphology	Indeterminate / overlapping morphology	CD like morphology
Acute infectious colitis	Lymphoma	GI-Behçet Disease
Antibiotic related hemorrhagic colitis	Pseudomembranous enterocolitis	ITB
Lymphoma	Vasculitis	Ischemic colitis
Peri-diverticular colitis	Ischemic colitis	Vasculitis
Diversion colitis	GVHD enteritis / colitis	NSAIDs related enteritis / colitis
Radiation colitis	Drug related enteritis / colitis	CVID related enteritis / colitis
Vasculitis	Radiation enteritis / colitis	Lymphoma
	Eosinophilic enteritis / colitis	Amebic colitis / Yersinia infection
		Drug related (5-FU, Colchicum, MMF)

UC: Ulcerative Colitis; CD: Crohn's Disease; GI: Gastrointestinal; ITB: Intestinal Tuberculosis; GVHD: Graft versus host disease; NSAID: Non-steroid anti-inflammatory drugs; CVID: Common variable immune deficiency; 5-FU: 5-fluorourasil; MMF: Mycophenolate mofetil

CMV, typically latent in the neural cord, generally does not require antiviral treatment in IBD patients unless there are accompanying bone marrow findings, such as cytopenia, that necessitate intervention.

INTESTINAL TUBERCULOSIS

ITB, like CD, most commonly affects the ileocecal region. In CD, typical mucosal involvement manifests as ulcers running parallel to the lumen, with a tendency to merge and sometimes form star-shaped lesions at varying stages of ulceration. A less common but distinctive feature of CD is the cobblestone appearance.

In contrast, ITB ulcers typically begin as circumferential ring ulcers at various stages and are often accompanied by a polypoid appearance. These ulcers can progress to a proliferative ulcerative form, potentially leading to lumen obstruction. Additionally, severe deformation of the cecum may result in fibrotic narrowing of the lumen, and in some cases, a pseudotumor appearance can be observed.[3]

The definitive diagnosis of ITB relies on detecting acid-fast bacilli in tissue samples or identifying *Mycobacterium tuberculosis* through culture or PCR. Histological findings, such as necrotizing granulomas or necrotic lymph nodes observed on imaging, provide strong support for diagnosis.[4] However, gold-standard tests for *M. tuberculosis* have limited sensitivity, particularly in the gastrointestinal system.

More than 50% of ITB cases are associated with pulmonary involvement or miliary dissemination, which, during the diagnostic stage, often presents as a consuming and debilitating disease profile. Notably, the onset of IBD-like symptoms in ITB typically occurs within 6–12 months, whereas similar symptoms in a patient with CD often date back 1–2 years or more. This distinction in symptom duration is frequently overlooked in clinical practice.

MAIN POINTS

- Differentiating IBD from other gastrointestinal inflammatory conditions is crucial and depends on a combination of clinical evaluation, endoscopic findings, and advanced diagnostic techniques, such as PCR and histology.
- Infectious causes, drug-induced enteropathies, and vascular diseases can closely mimic IBD. Identifying specific histological features, such as granulomas in ITB or ischemic changes in vasculitis, aids in accurate diagnosis.
- A multidisciplinary approach, including comprehensive clinical assessment and tailored diagnostics, is vital for identifying non-IBD inflammatory conditions that require distinct management strategies.

In the presence of any ulcer that does not exhibit the typical linear morphology or cobblestone appearance of CD, ITB should also be considered. When an endoscopist encounters an atypical ulcer morphology, testing for acid-fast bacilli, TB-PCR, TB culture, and histopathological examination should be conducted. ITB can be definitively diagnosed through histology if granulomas are widespread, large, and tend to merge.

In such cases, it is the gastroenterologist›s responsibility to retrospectively evaluate the patient for symptoms such as fever, review pulmonary imaging findings, and assess interferon-gamma release assay (IGRA) test results.[5]
A history of tuberculosis (TB) exposure among family members or close contacts, prior exposure to the bacillus (evidenced by positive purified protein derivative [PPD] or interferon-gamma release assay [IGRA] tests), combined with laboratory and histological investigations, plays a significant role in diagnosing ITB.

Histologically, ITB is characterized by granulomatous inflammation, similar to CD. However, granulomas are observed in only about 15% of CD punch biopsies, a much lower frequency compared to the 90–100% seen in ITB. In CD, granulomas are typically small, focal microgranulomas, whereas in ITB, they are larger, tend to merge, and are covered by epithelioid histiocytes, making them prominent and easily detectable by a pathologist. Caseous necrosis or the presence of acid-fast bacilli is diagnostic for ITB, although these features are rarely identified.[2,6]

OTHER RARE BACTERIAL INFECTIONS

Certain rare bacterial infections, such as *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*, are often overlooked, as many cases resolve spontaneously without a confirmed diagnosis. These pathogens primarily target the ileocecal region and appendix, leading to mesenteric lymphadenitis.[7] Aphthous or irregular ulcers and thickened, nodular mucosa may also be observed.[8] In *Y. pseudotuberculosis*, fissure-like ulcers and skip lesions can mimic CD. Histologically, findings may include transmural lymphoid aggregates, granulomas with central necrosis, and micro-abscesses.[9] Diagnosis can be confirmed using PCR when clinical suspicion arises.

Actinomyces israelii may cause colitis, predominantly involving the appendix and, less commonly, the right colon.[10] Lymphoid hyperplasia,

fissures, or ulcers may be present, and widespread inflammation often results in significant fibrosis. This inflammation may be associated with non-necrotizing epithelioid granulomas resembling those seen in CD. Diagnosis is established by identifying filamentous bacterial colonies through Gram or silver staining.

LYMPHOGRANULOMA VENEREUM AND SYPHILIS

Lymphogranuloma venereum, caused by *Chlamydia trachomatis*, and syphilis, caused by *Treponema pallidum*, can present as proctitis or proctocolitis, particularly in individuals with a history of anal intercourse. Endoscopic findings may include ulcers and, in rare cases, mass-like lesions. Diagnosis is confirmed by identifying the pathogen through molecular or immunohistochemical analysis. These infections should be considered in high-risk groups, especially in association with conditions involving immunosuppression.

PROTOZOAN INFECTIONS - AMEBIASIS

Amebiasis is primarily found in tropical regions, such as Central America. In Türkiye, however, it has become quite rare due to improvements in water hygiene and the widespread use of bottled water. Despite this, over-diagnosis based solely on light microscopy and stool antigen tests remains common.

Risk factors for amebiasis include travel to endemic areas and the use of contaminated water sources in rural regions. In the absence of these risk factors, we do not recommend testing for amoebas in patients presenting with IBD-like symptoms and clinical signs in Türkiye.

Although patients may be asymptomatic carriers, amebic colitis can occur and is characterized by bloody or mucus-laden diarrhea accompanied by colicky pain and tenesmus.[11] Endoscopically, amebiasis in the left colon-though rarely involving the cecum-may present as a mass-like morphology with chronic proliferation, termed "ameboma." More commonly, it manifests as diffuse colonic involvement with aphthous ulcers or large, irregular, serpiginous ulcers.

Histologically, periodic acid-Schiff (PAS)-positive trophozoites can be identified on the surface of ulcers. However, false positives from light microscopy and stool antigen tests, as well as cross-reactivity with non-pathogenic microorganisms, present significant clinical challenges. Inexperienced laboratory evaluations often misidentify tissue macrophages as amoebas and leukocytes as cysts, especially when motile amoebas are not observed in fresh stool samples.

Stool antigen tests frequently yield false-positive results because they often fail to distinguish between the non-pathogenic *Entamoeba dispar* and the pathogenic *Entamoeba histolytica*. In cases with a high suspicion of amoebiasis-due to exposure to contaminated water or travel to endemic areas-the preferred diagnostic method is specific PCR testing for *E. histolytica*. Amoebic cysts observed under light microscopy, which are often misinterpreted as trophozoites, are generally of little significance except as indicators of endemic exposure in individuals from endemic regions.[12]

OPPORTUNISTIC INFECTIONS

Certain infections in immunocompromised patients may present with clinical findings that resemble IBD and should be considered in the differential diagnosis. One such infection is *Mycobacterium avium-intracellulare* complex (MAC), which primarily affects the small intestine. Endoscopic findings may include either normal mucosa or multiple yellow-white nodules. Histologically, MAC causes layers of pale macrophages in the lamina propria, which contain numerous PAS-diastase or acid-fast resistant microorganisms.[13]

CMV, Epstein-Barr virus (EBV), and herpes simplex virus (HSV) are latent infections that reside in the neural cord. By adulthood, more than 80% of the population has already been exposed to these pathogens.

The significance of primary CMV infection in patients with severe bone marrow suppression, such as those in transplant units, differs substantially from its importance in patients undergoing long-term immunosuppression for IBD. In IBD patients, particularly those on steroid therapy, CMV tends to proliferate primarily in inflamed colonic tissue. This is characterized by its lytic effects and the presence of intranuclear "owl's eye" inclusions in tissue biopsies.[14] While immunohistochemistry can enhance the detection of these inclusions, their clinical significance and density are generally minimal unless the patient shows signs of bone marrow suppression.

In cases where CMV infection complicates the clinical course of an IBD patient receiving steroid treatment, determining whether CMV is a bystander or a true pathogen can be challenging. When considering antiviral treatment, which may have toxic side effects, it is essential to evaluate systemic or bone marrow involvement by CMV. Since the level of immunosuppression in IBD treatment is typically far less severe than in bone marrow transplantation, CMV reactivation can usually be monitored without intervention, provided there are no signs of bone marrow suppression.[15]

VASCULAR DISEASES

Vasculitis

Approximately one-third of patients with systemic vasculitis present with GI involvement. The most common causes of GI vasculitis include immunoglobulin A (IgA) vasculitis, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, polyarteritis nodosa, Takayasu arteritis, and Behçet's disease. Notably, Takayasu arteritis can coexist with IBD.

The clinicopathological features of GI involvement in vasculitis are often nonspecific, with symptoms varying based on the affected intestinal region and the size of the involved vessels.[16] In cases with atypical IBD symptoms-such as perforation, overt bleeding, or systemic involvement-vasculitis should be considered. Evaluation should include an assessment for systemic manifestations of vasculitis, including involvement of the kidneys, lungs, and skin.

In vasculitis involving large vessels, ischemia is the predominant feature, while smaller-vessel vasculitis can cause mucosal lesions that resemble those seen in IBD. It is essential to consider vasculitis in the differential diagnosis of IBD, especially since GI involvement in vasculitic cases can be highly morbid and life-threatening. Endoscopic findings in GI vasculitis are nonspecific and may include erosions, ulceration, petechiae, nodularity, edema, submucosal hemorrhage, strictures, and, in severe cases, ischemic signs.

Because the diagnostic vasculitic changes are often located in the submucosa or deeper layers, routine punch biopsies frequently fail to detect them due to the inability to sample these deeper tissues.[17] In the early stages of vasculitis, endoscopic findings may reveal submucosal hemorrhages consistent with ischemic morphology. Histopathologically, deep submucosal biopsies, if obtained, may show early changes such as neutrophilic infiltration, which suggests ischemic morphology, whether vasculitic or non-vasculitic.

As the disease progresses and becomes chronic, the characteristic neutrophilic vasculitic features diminish, often evolving into what is referred to as vasculopathy. This term describes nonspecific findings that lack definitive histopathological evidence of vasculitis. Even in resection specimens, hallmark vasculitic findings, such as thrombosed or partially recanalized vessels and necrosis, may be obscured. As a result, histopathological confirmation of GI vasculitis in clinical practice is rarer than anticipated.

To mitigate the high mortality and morbidity associated with severe GI vasculitis-regardless of other systemic involvement-early and high-dose pulse steroid therapy, combined with cyclophosphamide and/or anti-TNF agents, is crucial. Prompt intervention is essential for effectively managing severe GI involvement in vasculitis.

GI-Behçet

Behçet's disease is characterized by recurrent oral and genital ulcerations.[18] Diagnosis is based on fulfilling specific criteria, which may take time to establish. Due to the frequent involvement of the ileocecal region, distinguishing GI-Behçet from CD and ITB can be challenging. However, the shape and type of ulcers in GI-Behçet may provide clues for differentiation. Ulcers in GI-Behçet are typically oval or round with a focal distribution, in contrast to the linear and diffuse patterns seen in CD (Table 2).[19,20]

In practice, treatment for GI-Behçet often parallels that for IBD, as the therapeutic strategies are largely similar. GI-Behçet is sometimes regarded as a component of IBD, and much of its management is extrapolated from IBD treatment protocols.

GI-Behçet carries a high risk of complications, such as perforation and overt GI bleeding, occurring in up to one-third of cases or more. This risk is especially elevated in patients with deep, volcano-shaped ulcers, compared to only about 1% of CD cases. Close monitoring of ulcerative lesions is essential, even in patients who have not yet been definitively diagnosed with Behçet's disease or GI-Behçet, as these complications can result in significant morbidity and potential mortality.

Acute Ischemic Colitis

As the name suggests, acute ischemic colitis typically resolves within 3–4 weeks, with a low recurrence rate and rare progression to chronicity. Due to these characteristics, it should be considered in the differential diagnosis of acute-onset IBD-like clinical presentations rather than chronic conditions. Acute ischemic colitis is most commonly caused by non-obstructive ischemia, with sudden-onset symptoms such as abdominal pain, rectal bleeding, and bloody diarrhea.

Endoscopic findings vary widely, ranging from submucosal hemorrhages and edematous, fragile mucosa resembling UC to well-demarcated, sharply limited areas of involvement. A characteristic feature is the presence of solitary antimesenteric linear ulcers longer than 5 cm (the "single strip sign"), which resemble CD.[21,22] The rectosigmoid junction and splenic flexure are the most frequently affected areas in acute ischemic colitis.

In its acute phase, ischemic colitis can be mistaken for UC. Although rectal involvement typically suggests UC, the rectum-owing to its robust blood supply-is rarely affected by ischemia, except in cases following surgeries involving the inferior mesenteric artery.

Histological findings in ischemic colitis range from vascular congestion and edema to coagulative necrosis. Hemosiderin deposition in the lamina propria may also occur, sometimes accompanied by microthrombi.[23]

Diagnostic factors for acute ischemic colitis include older age, a history of atherosclerotic risk factors, acute clinical onset, the characteristic distribution of involvement, and sparing of the rectum, which is reported in only about 3% of cases inlarger studies. Key diagnostic indicators also include histological features of acute inflammation, such as a neutrophilic burst, and spontaneous resolution within 3–4 weeks, with rare recurrence.

Prolonged chronic ischemia, however, can result in significant complications, including diffuse fibrosis that may lead to strictures and scar formation.

Drug Effects

Medications can induce intestinal findings that may need differentiation from IBD through various mechanisms.[15,24,25] The endoscopic findings of drug-induced enterocolitis are generally nonspecific, including erythema, edema, erosions, and, in some cases, ulcers.

Histologically, drug-induced colitis may exhibit features resembling lymphocytic colitis, collagenous colitis, ischemia, pseudomembranous colitis, eosinophilic colitis, or even mimic characteristics of IBD.

NSAIDs

Nonsteroidal anti-inflammatory drug (NSAID)-induced damage can closely resemble IBD. NSAIDs may also exacerbate IBD symptoms and worsen conditions such as diverticulosis, increasing the risk of complications like perforation or bleeding.[26]

An isolated ulcer surrounded by normal mucosa should raise suspicion of NSAID or other drug-related causes.[27] A specific finding indicative of prolonged NSAID use is NSAID-induced diaphragm disease, which typically affects the jejunum and ileum but can occasionally involve the proximal colon. Endoscopic findings associated with NSAID-induced damage include erythema, erosions, bleeding, aphthous or well-demarcated ulcers, and strictures.[15] These findings are often widespread and frequently involve the ileocecal region.

Aphthous ulcers, particularly in the ileum, can indicate either mild endoscopic activity in CD or drug-induced lesions in patients with extensive NSAID or aspirin use. Although there is no definitive method to distinguish NSAID-related lesions from IBD, ulcers persisting for more than three months after discontinuation of the drug suggest IBD, preferably CD, and warrant treatment. Another practical but unproven approach is to consider CD when aphthous ileal ulcerations are accompanied by intestinal wall thickening observed on imaging.

In patients with ankylosing spondylitis or sacroiliitis who frequently use NSAIDs, incidental aphthous ulcerations observed during colonoscopy-whether or not accompanied by GI symptoms-may paradoxically indicate underlying IBD, particularly CD. These lesions might result from the combined effect of NSAID use superimposed on an existing histological inflammatory burden. Notably, even if the lesions resolve after discontinuing NSAIDs, this does not necessarily exclude the presence of concurrent IBD.

In NSAID enteropathy, histological findings are often non-diagnostic and may include mild crypt distortion, erosions, ulcers, fibrosis, villous atrophy, and increased mitosis (the latter more commonly associated

Table 2. Differential diagnosis of Inflammatory bowel disease

	Gastrointestinal TBC	Behçet's Diesease	Ischemic Colitis*	Crohn's Disease	Ulcerative Colitis	NSAID rel.
Clinical Findings	-Short disease duration (<6m) -Fever -Night sweats -Ascites -Pulmonary symptoms	-Recurrent oral – genital ulcers -Uveitis -CNS involvement -Papule-pustular lesion -Pseudo-folliculitis	-Acute presentation and resolution -Abdominal pain -Hematochezia -Bloody diarrhea -Cardiovascular disease history	-Long disease duration -Diarrhea is prominent -Hematochezia -Perianal disease	-Tenesmus -Bloody diarrhea -Hematochezia	-Asymptomatic -IBD like -Bleeding -Perforation -Obstruction
Site	-Ileo-cecal -Recto-sigmoid involvement rare	- Ileo-cecal	-Splenic flexure -Recto-sigmoid angulation	- Ileo-cecal	- Rectum to the proxima	-Frequently ileocecal -Entire GI tract can be involved
Endoscopy	-Transvers ulcers -Nodulation and hypertrophy -Deformed open ileo-cecal valve	-Round ulcer -Focal ulcers -Inflammation adjacent to the ulcer is rare	-Submucosal hemorrhage -Unilateral (anti-mesenteric) longitudinal ulcer (>5cm) - Rectal involvement is not expected	-Longitudinal ulcer -Aphthous ulcers -Cobblestone appearance -Stricture -Skip lesions	-Well-demarcated inflammation -Diffuse erythema -Loss of vascularization	-Erythema -Erosion -Aphthous ulcer - Well-demarcated ulcers -Stricture
Pathology	-Confluent granuloma -Caseating granuloma -Giant granuloma -Multiple granuloma -Serous tubercule	- Vasculitis findings are rare but diagnostic -Granuloma rare	-Vascular congestion -Microthrombus -Coagulative necrosis	- Few small granulomas that do not tend to coalesce -Skip inflammation -Transmural involvement	-Inflammation limited to the submucosa -Rare granulomas in severe cases	-Non-specific and non-sensitive changes
Imaging	-Short segment involvement -Necrotic lymph nodes -Pulmonary findings	-Wall thickening is not expected -Perforation may be observed	- CT angiography findings are not expected -Rare findings on conventional angiography	-Wall and layer thickening -Mesenteric stranding -Mesenteric fat hypertrophy -Stenosis, fistula, abscess	-Wall thickening rectum to proximal -Stenosis, fistula, abscess not expected	Diaphragm disease is pathognomonic
Serology / Laboratory	-Interferon-γ release test + -Tissue PCR+ -Tissue AFB + -Tissue culture +	-Pathergy + -HLAB51 + (Less common compared to systemic Behçet›s)	-	-ASCA + (low sensitivity and specificity)	-ANCA + (low sensitivity and specificity)	

* Ischemic colitis mostly reflects acute ischemic processes, rarely recurs, and is not associated with chronic findings

with colchicine use). Granulomas are extremely rare.[28,29] Severe crypt distortion, transmural involvement, significant inflammation, or the presence of granulomas strongly supports a diagnosis of IBD.

OTHER DRUGS

Colitis induced by immune checkpoint inhibitors (ICIs) can mimic UC or CD. There are no specific routine biomarkers for ICI-related enterocolitis, and the gold standard for differential diagnosis relies on the patient's history-particularly the absence of prior IBD-like findings-combined with endoscopic evaluation and biopsy.[15]

Mycophenolate mofetil (MMF)-induced colitis can also resemble IBD. Common findings include diffuse or segmental erythema, erosions, and ulcers, typically sparing the rectum. Although diarrhea is a frequent symptom in these patients, endoscopic findings may occasionally appear normal.[30]

Histologically, MMF-related colitis may exhibit structural changes similar to those seen in IBD, although significant inflammation is uncommon. Increased crypt cell apoptosis has been described as a hallmark of MMF colitis. However, similar histological findings have been reported in other conditions, raising questions about its specificity and diagnostic utility.[31]

Other drugs to consider in the differential diagnosis of IBD-related GI symptoms include secukinumab, colchicine, and anakinra. Cases of de novo IBD have been reported following the use of secukinumab (an IL-17A monoclonal antibody) and anakinra (an IL-1 receptor antagonist).[15] These drugs are believed to unmask underlying subclinical or histological inflammation and/or induce an IBD-like clinical presentation by altering dominant inflammatory pathways. Typically, they cause severe entero-colitis that does not resemble the linear CD morphology on endoscopy.

Colchicine, a microtubule inhibitor, impairs mucosal regeneration by causing mitotic arrest. Diarrhea is a significant dose-dependent side effect of colchicine. In cases of colchicine toxicity, aphthous ileal ulcers may be detected, and their severity can be exacerbated by concomitant NSAID use. The small intestine is the most affected area in colchicine toxicity. Histologically, findings include irregular nuclear alignment, increased mitotic figures (mitotic arrest), and nuclear hyperchromasia, which may mimic dysplasia.[32]

MONOGENIC DISEASES

In individuals with early-onset IBD-like symptoms, certain diseases are associated with monogenic IBD-like disorders.[33] These include primary immunodeficiencies and intestinal epithelial cell defects. Some primary immunodeficiencies may manifest in late childhood, and in approximately 10% of cases, they can appear in adulthood.

Monogenic diseases that manifest in early adulthood often present with more resistant clinical courses. Fever, widespread oral ulcers, and GI and perianal involvement are commonly observed. Interleukin-10 (IL-10) deficiency is an example of a primary immunodeficiency that presents at a young age with severe enterocolitis and widespread perianal disease.[34]

Chronic granulomatous disease (CGD), characterized by impaired phagocytosis, can lead to a spectrum of symptoms ranging from mild manifestations to severe infections and monogenic IBD-like disorders.[35] Diarrhea is a common symptom, and there is often a notable discrepancy between the lack of overt symptoms and extensive segmental involvement seen on endoscopy.

There is significant overlap between the histological findings of monogenic IBD-like diseases and classical IBD. Gastrointestinal involvement occurs in approximately one-third of monogenic diseases, which are characterized by monogenic antibacterial defects with Mendelian inheritance and minimal association with environmental factors. Compared to adult-onset multigenic IBD, the clinical course of monogenic diseases is often much more severe and difficult to control.

An onset before the age of six and a history of frequent infections should raise suspicion of a monogenic disorder. In cases where monogenic formations are identified based on phenotypic similarities, genetic research should be performed to detect potential new mutations, and treatment should be adjusted accordingly. These patients should be followed up at an academic center for optimal management.

RADIATION INJURY

Abdominal and pelvic radiotherapy can lead to acute or chronic intestinal injury, with involvement varying depending on the irradiated area. Rectal and sigmoid involvement are the most commonly affected regions.[36]

Acute radiation injury is characterized by findings such as edema, erythema, fragility, and ulcers.[37] In chronic radiation proctocolitis, atrophy and telangiectasias are typically observed, while strictures, perforation, and fistulas are less common.[38]

Enteric radiation injury can mimic CD with long-segment, fibrosis-dominant small bowel involvement. In contrast, distal colorectal distribution and vascular changes may resemble UC. However, radiation-associated colitis is notably more resistant to treatment compared to IBD.

DIVERSION COLITIS

Diversion proctocolitis (DPC) occurs in the residual segment of the colon within the first year after the cessation of fecal flow. It can develop following surgery for any reason and typically resolves once bowel continuity is restored.[39]

Nonspecific inflammatory changes, mucosal exudation, nodularity, and aphthoid ulcers are common findings. In patients without a prior diagnosis of IBD, a new diagnosis of IBD should not be made solely based on the presence of diversion-related changes.

DIVERTICULITIS-ASSOCIATED COLITIS

Segmental colitis associated with diverticulosis refers to inflammation occurring between or near diverticula. On endoscopy, findings may range from mild to severe inflammation, including reddish round lesions, loss of vascular pattern, edema, erosions, and ulcerations.[40] Notably, the diverticula themselves are not affected.

The inflammation typically involves the interdiverticular mucosa, with the rectum being spared.[41] If clinical, endoscopic, and radiologic findings fail to resolve with antibiotic treatment, distinguishing this condition from IBD can be challenging.

CONCLUSION

Conditions resembling IBD include Behçet's disease, ITB, NSAID-related enterocolitis, drug-induced intestinal pathologies, diverticular

colitis, diversion proctocolitis, and, rarely, monogenic immune disorders.

Monogenic IBD**,** although most commonly diagnosed in early childhood and infancy, may account for up to 10% of patients in adult IBD clinics. Early-onset symptoms (before six years of age), frequent and complicated infections, and severe disease resistant to treatment should raise suspicion of a monogenic disorder.

Classification of differential diagnoses based on potential involvement sites and endoscopic ulcer morphologies (UC-like or CD-like) can guide diagnosis and narrow down potential causes.

Infectious, ischemic, and antibiotic-associated colitis, which present acutely and resolve spontaneously within 3–4 weeks, may mimic IBD due to insufficient clinical evaluation and an overemphasis on acute-phase inflammation in histopathology. Rare infectious conditions such as Yersinia and Actinomyces, which cause ileocolitis and have recovery periods of 3–6 months, can closely mimic CD. Specific PCR testing is the most effective diagnostic tool in suspected cases.The high rate of false positives in light microscopy (trophozoite, cyst) and/or stool antigen tests for *Entamoeba histolytica* must be considered. Amoebic colitis has become rare in Türkiye due to the widespread use of bottled water. In suspected cases, specific PCR testing is preferred over light microscopy or stool antigen tests.Ileocecal involvement with ulcer morphology resembling CD is most commonly confused with ITB or GI Behçet's disease. However, less than 0.5% of ileocecal involvement cases in high-volume tertiary centers in Türkiye are due to TB or Behçet's disease.In cases of aphthous ulcers in the ileum or colon, it is necessary to inquire about medication use, particularly NSAIDs. If there is no increased wall thickness, an NSAID or drug-related condition may be suspected if endoscopic normalization occurs after discontinuing the drug for at least three months.Colchicine, alone or in combination with NSAIDs, can induce aphthous GI lesions.While NSAIDs are primarily responsible for widespread aphthous ulcers, especially in the ileum, these may also indicate mild IBD (symptomatic or incidental) exacerbated by NSAIDs, particularly in patients with ankylosing spondylitis.The only specific finding associated with NSAIDs is the diaphragm-like lesion**,** which frequently develops with heavy and prolonged NSAID use. The potential role of CMV and *Clostridium difficile* infections in clinical exacerbations should not be overlooked in IBD patients receiving immunosuppressive therapy (commonly steroids). However, the clinical benefit of treating these latent infections is debatable unless there are signs of bone marrow suppression.The treatment of primary CMV colitis with antiviral agents is essential in patients with profound immunosuppression, such as those who are HIV-positive or in bone marrow transplant units. This approach differs from the management of CMV replication in IBD patients. In cases of atypical endoscopic morphology**,** differential diagnoses should prioritize Behçet's disease (vasculitis), ITB, and drug effects. Thorough evaluation should include tissue TB-PCR, TB culture, AFB staining, lung screening, Quantiferon testing, anamnesis findings, and family history to distinguish between GI Behçet and ITB. For rare infectious conditions like amoebiasis**,** a broader PCR panel can effectively identify potential pathogens. Ischemic pathologies are suggested by advanced patient age, atherosclerotic risk factors, acute and atypical colonic involvement, and submucosal bleeding. In UC-like presentations without rectal inflammation, local treatment effectiveness should be reassessed, and ischemic processes should be considered, particularly in older patients. Crohn's colitis-like linear ulcers longer than 5 cm (the "single strip sign") in the left colon are highly specific for ischemic colitis but have low sensitivity. In suspected **ischemic pathologies**, vasculitis should be investigated, especially in cases with systemic involvement (e.g., kidney, lung, or skin) and/or involvement of the stomach, duodenum, or small intestine. In cases of severe inflammation presenting as limited proctitis or proctocolitis**,** understanding the patient's sexual history may help clarify potential infections contributing to diagnostic uncertainty.

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