

Diagnostic Approach in Inflammatory Bowel Diseases

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Abstract

There is no single diagnostic test for inflammatory bowel diseases. Diagnosis is established through a combined evaluation of medical history, physical examination, laboratory tests, imaging, and pathology. This comprehensive assessment not only enhances diagnostic accuracy but also facilitates the identification of other conditions that may coexist with inflammatory bowel disease and require consideration in the differential diagnosis.

In most cases, a diagnosis can be made based on medical history, physical examination, laboratory tests, endoscopic biopsies, and pathological evaluation. However, in complex cases, advanced techniques such as double-balloon enteroscopy and capsule endoscopy may be necessary to achieve an accurate diagnosis.

Keywords: Bowel diseases, diagnosis, endoscopy, inflammatory, pathology

INTRODUCTION

No single symptom, sign, or diagnostic test can definitively diagnose inflammatory bowel disease (IBD). Diagnosis is established through a comprehensive assessment that includes clinical presentation, as well as radiological, endoscopic, biochemical, and often pathological findings (Figures 1 and 2). The initial evaluation involves taking a detailed medical history (anamnesis), performing a physical examination, and conducting basic laboratory tests.¹

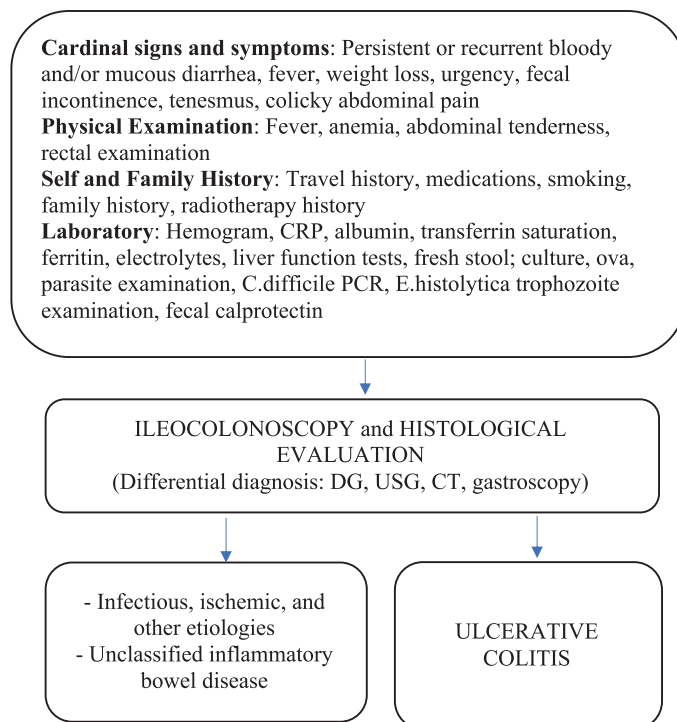


Figure 1. Ulcerative Colitis diagnostic algorithm¹²

DG: Direct radiography, USG: Ultrasonography, CT: Computed tomography

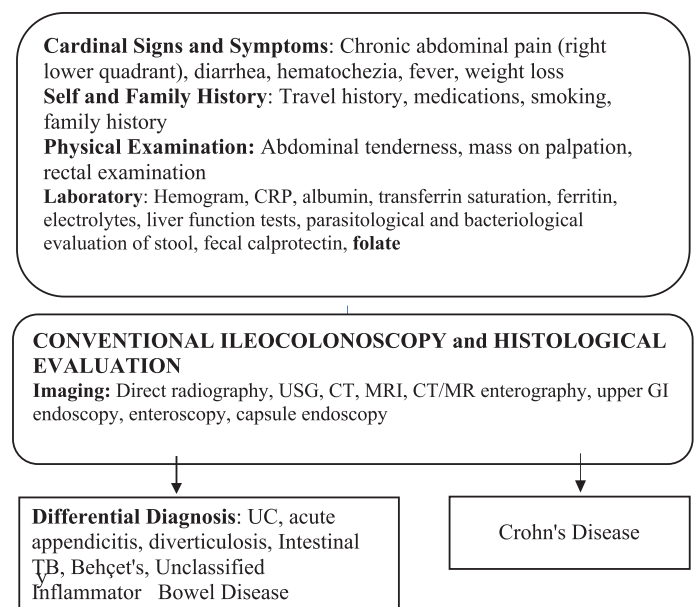


Figure 2. Crohn's Disease diagnostic algorithm¹²

UC: Ulcerative colitis, DG: Direct radiography, USG: Ultrasonography, CT: Computed tomography, MRI: Magnetic Resonance

CLINICAL AND BIOCHEMICAL DIAGNOSIS

Anamnesis and Physical Examination

When taking the patient’s history, it is essential to inquire in detail about recent travel, previous episodes of gastroenteritis, current or past medications (particularly antibiotics and NSAIDs), history of appendectomy, dietary habits, smoking status, sexual preference, and family history of IBD or gastrointestinal malignancies. Additionally, the duration of symptoms-particularly diarrhea lasting more than four weeks-and elevated acute phase reactants should be carefully assessed, as these factors can help differentiate IBD from most cases of infectious diarrhea (Table 1).^{2,3}

Laboratory

Although completely normal laboratory test results are not typically expected in IBD, they can occasionally occur. A hemogram may reveal findings such as anemia due to iron, folate, or B12 deficiency, anemia of chronic disease, reactive thrombocytosis, or normal to elevated band forms.

In patients presenting with nonspecific symptoms, elevated levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) may also be observed. While these biomarkers are not pathognomonic for IBD, they may indicate the need for further diagnostic testing. CRP has a significant negative predictive value for active IBD; however, up to 30% of individuals with Crohn’s disease may have normal CRP levels.⁴⁻⁶

Fecal calprotectin (FC), a protein secreted from neutrophil granules, is the most sensitive laboratory biomarker of inflammation in IBD. It demonstrates a strong correlation with endoscopic markers of disease activity and plays a critical role in various clinical stages, including diagnosis, relapse, and evaluation of therapeutic response.⁷

Although a definitive threshold for distinguishing IBD from functional bowel disorders has not been established, a threshold value of 150 µg/g has been shown to provide reliable diagnostic accuracy.⁸

In a recent study, a cut-off value of 60 µg/g for FC in ulcerative colitis demonstrated 97% specificity in differentiating 1–3 from 0 on the Mayo Endoscopic Score (MES).⁹ Since FC levels are typically elevated in cases of bloody diarrhea, it should not be ordered in such scenarios.¹⁰

MAIN POINTS

- The diagnosis of inflammatory bowel diseases is typically achieved through conventional methods, including medical history, physical examination, endoscopic and pathological evaluations, computed tomography, magnetic resonance imaging, and, increasingly, sonographic imaging, which has become a routine part of diagnostic practice.
- Since there is no single definitive diagnostic method for these diseases, the appropriate use of diagnostic techniques can help shorten the diagnostic process and improve cost-effectiveness.
- Specialized techniques, such as double-balloon enteroscopy, which require significant expertise, should be reserved for cases where initial diagnostic methods are inconclusive but clinical suspicion of the disease remains high.

Additionally, fecal calprotectin levels can be elevated in various other conditions associated with inflammation (Table 2).^{11,12}

ENDOSCOPIC DIAGNOSIS

Conventional Ileocolonoscopy

No endoscopic findings are specific to Crohn’s disease (CD) or ulcerative colitis (UC). Ileocolonoscopy should be the first-line procedure in the diagnostic algorithm for all patients being evaluated with a preliminary diagnosis of inflammatory bowel disease.

Endoscopic Findings in Ulcerative Colitis

The hallmark feature of ulcerative colitis is symmetrical and continuous inflammation that begins at the anorectal junction and extends throughout the colon. Early manifestations include mucosal erythema, edema, and attenuation or loss of the normal vascular architecture. As inflammation progresses, the mucosa becomes granular and fragile, covered with yellow-brown mucopurulent exudate and associated with ulcerations that may bleed spontaneously (Figure 3).

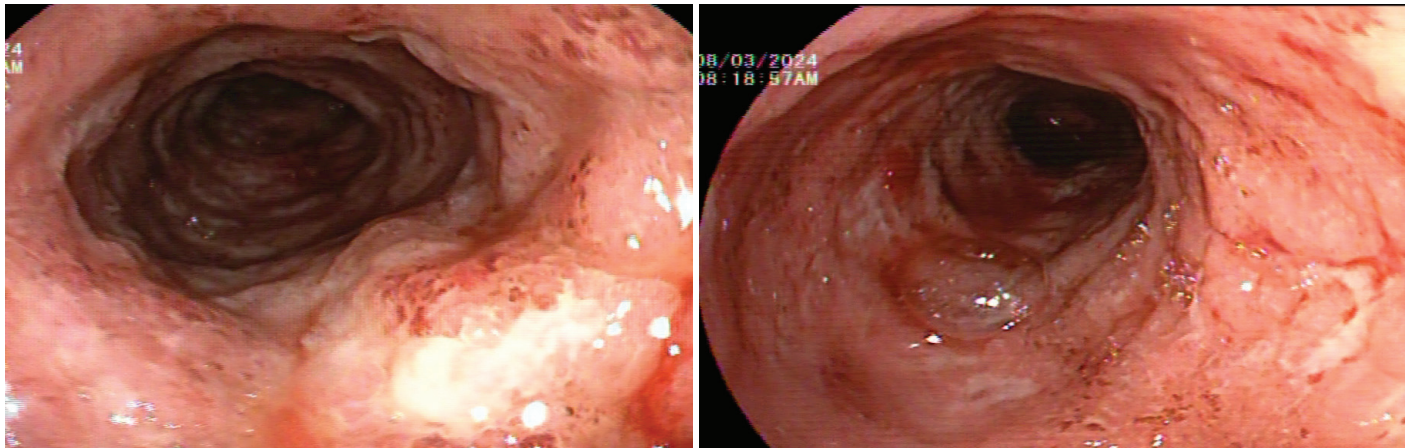
Sigmoidoscopy is valuable for assessing disease activity and excluding cytomegalovirus (CMV) infection, in addition to facilitating histologic evaluation, particularly when the treatment response is uncertain. In patients diagnosed via sigmoidoscopy (e.g., in cases of acute severe colitis), a full colonoscopy should be performed after active inflammation is controlled to evaluate disease extent and exclude CD.^{13,14}

Table 1. Symptomatology and Physical Examination in Inflammatory Bowel Diseases

| Symptomatology and Physical Examination in IBD | |
|--|---|
| Anamnesis | Travel history Medicines (antibiotics and NSAIDs) History of appendectomy Diet Sexual preference Smoking status Recent gastroenteritis Family history of IBD Gastrointestinal cancer Duration of symptoms (diarrhea lasting longer than four weeks and elevated acute phase reactants usually distinguish IBD-associated colitis from most cases of infectious diarrhea). |
| System Query | Nocturnal symptoms, weight loss, urgency to defecate, fecal incontinence Joint, eye, mouth, skin involvement |
| Physical Examination | Extraintestinal manifestations such as unexplained perianal abscess, complicated fistula Fever→ (may be associated with underlying disease or suppurative complication) Abdominal examination (obstruction, tenderness, distension, and mass) Perineal inspection and rectal examination→ (findings that are highly diagnostic for Crohn’s disease can be obtained) |

Table 2. Laboratory Tests in the Diagnosis of Inflammatory Bowel Disease

| Laboratory Tests in the Diagnosis of Inflammatory Bowel Diseases | |
|--|--|
| Hemogram | Anemia→ Iron, folate, B12 deficiency, anemia of chronic disease Thrombocytosis→ Reactive Leukocyte count→ Normal/Increased band forms indicate a pyogenic complication or active disease. |
| CRP and erythrocyte sedimentation rate (ESR): | In patients with nonspecific symptoms, although not specific to IBD, increased CRP and ESR may indicate the need for further investigation. |
| Biochemistry | Liver function tests, electrolytes, creatinine, albumin, ferritin, transferrin saturation, immunoglobulin levels (especially in young patients), anti-tissue transglutaminase IgA |
| Stool examination | In fresh stool samples ; culture, examination for ova and parasites, PCR for <i>C.difficile</i> infection, examination for <i>Entamoeba histolytica</i> trophozoite should be performed before endoscopy. |
| Serologic tests (ASCA and ANCA) | They are not useful for routine diagnosis and cannot distinguish ulcerative colitis from Crohn's disease with colonic involvement ⁸ |
| FC | There is no definitive cut-off value that distinguishes IBD from functional bowel disease, but potentially good diagnostic accuracy can be achieved at a cut-off value of 150 µg/g . ⁸ |
| New Biomarkers | Antiglycan and antimicrobial antibodies such as Anti-OmpC and Antiflagellin (CBir1) have low additional diagnostic value. Although more than 250 IBD-associated single nucleotide polymorphisms [SNPs] have been identified, genetic testing is not recommended for the diagnosis of IBD. |
| Fecal volatile organic metabolites [VOMs] | It may play a role in the future by helping to understand metabolic changes in the intestine in IBD. Analyzing fecal VOMs by gas chromatography may help differentiate CD from UC. ^{11,12} |

**Figures 3.** Fragile, spontaneously hemorrhagic mucosa in severe ulcerative colitis. Edema, loss of vascularity, subepithelial hemorrhage (From Istanbul Medical Faculty Gastroenterohepatology Endoscopy Unit Archive)**Table 3.** Endoscopic findings in ulcerative colitis and Crohn's disease

| Endoscopic Findings | Ulcerative Colitis | Crohn's Disease |
|----------------------------|--|---|
| Descriptive Feature | Persistent, symmetrical inflammation | Non-continuous aphthous erosions, stellate ulcers, cobblestone appearance, narrowing of the lumen |
| Early Period | Mucosal erythema, edema, loss of vascular pattern | Scattered, well-circumscribed, small aphthous ulcers on a normal mucosal background |
| Severe Inflammation | Mucosal fragility, ulceration, spontaneous bleeding | Scattered, large ulcers, widely distributed small ulcers, multiple, passable stenoses, fistulas |
| Chronic Period | Inflammatory pseudopolyps, muscle hypertrophy, loss of haustra and colonic architectures | Large ulcers, strictures, fistulas |

Evaluation of the ileocecal valve and terminal ileum is necessary for a comprehensive assessment, but biopsy of an endoscopically normal terminal ileum is not recommended. Inflammatory pseudopolyps, commonly associated with long-standing ulcerative colitis, are primarily located in the sigmoid colon. During active disease, these pseudopolyps arise from inflamed, regenerating epithelium between ulcerations and do not regress with treatment (Table 3).

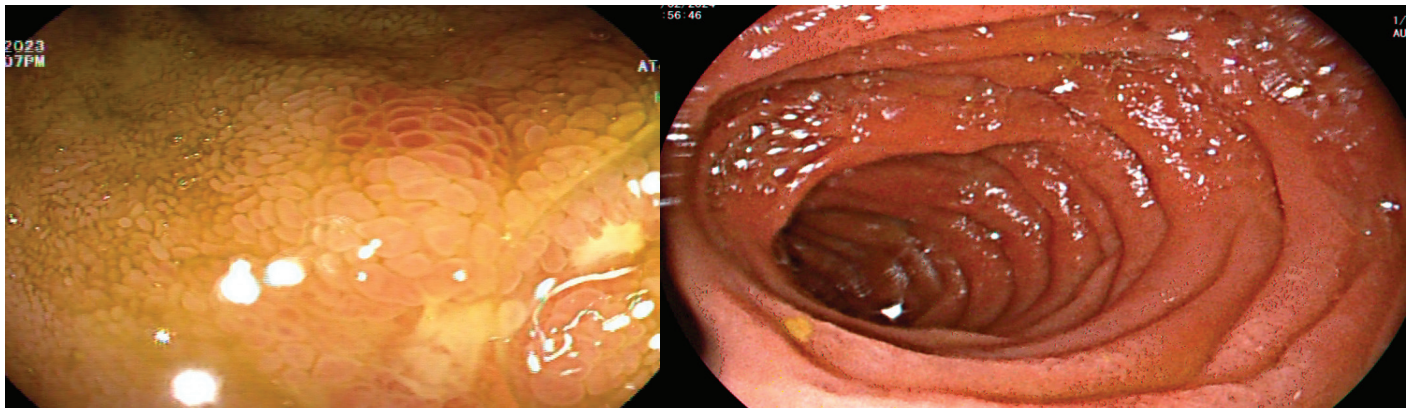
Endoscopic Findings in Crohn's Disease

Endoscopic features of Crohn's disease include non-continuous seg-

mental involvement, aphthous erosions, stellate or discrete ulcers, mucosal edema, a cobblestone appearance, and luminal narrowing (Table 3). Gastroscopy is recommended for patients presenting with upper gastrointestinal symptoms or suspected coexisting celiac disease.⁸

Enteroscopy

Evaluation of the small intestine-using intestinal ultrasonography, MR enterography, capsule endoscopy, or enteroscopy-is recommended for all patients at the time of diagnosis when Crohn's disease is suspected.⁸ Patients with negative endoscopy findings but suspected Crohn's dis-



Figures 4. Erythema, inflammatory changes, and aphthous ulcer in the ileum, aphthous ulcer in the jejunum (from the archive of Istanbul Medical Faculty Gastroenterohepatology Endoscopy Unit).

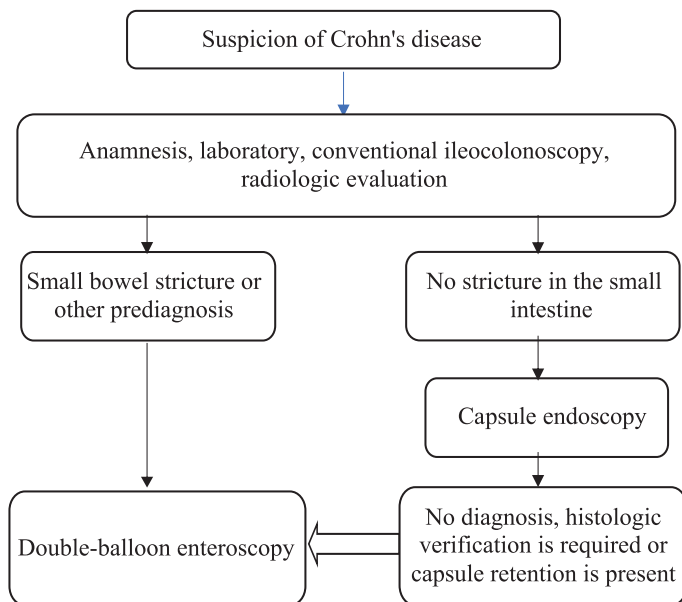


Figure 5. Endoscopic diagnostic algorithm for suspected Crohn's disease.

case based on MRI or small bowel capsule endoscopy should undergo enteroscopy for endoscopic and histologic confirmation of the diagnosis.¹⁵

Double-balloon enteroscopy enables direct visualization of the small intestinal mucosa, biopsy collection, and therapeutic procedures (Figure 4). Its diagnostic accuracy reaches up to 80% in experienced centers, with a complication rate of 1.2–1.6%.

In a retrospective cohort study by Schulz et al.,¹⁶ patients with normal gastroscopic and colonoscopic findings, subileus, a history of perianal fistula, and exclusion of infectious etiologies were evaluated using double-balloon enteroscopy. The diagnosis of Crohn's disease was confirmed in 11 patients (69%) based on a combination of enteroscopic findings, imaging, and clinical presentation.¹⁶

Video Capsule Endoscopy

UC involves only the colon and can therefore be effectively examined using colonoscopy. However, the role of capsule endoscopy remains controversial. Studies have shown that capsule endoscopy is signifi-

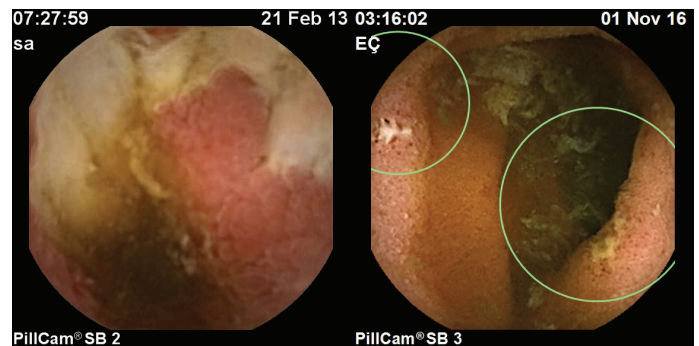


Figure 6. Ileal ulcers with capsule endoscopy. Akyüz F., Atlas of Capsule Endoscopy 2018.

cantly more effective than other techniques in identifying mucosal damage in patients with Crohn's disease.¹⁷

In cases of suspected Crohn's disease, endoscopic examinations should be performed first (including ileal intubation). If symptoms of obstruction are present, CT or MR enterography should be conducted. If endoscopic examinations are normal, there is no clinical evidence of obstruction, and Crohn's disease is still suspected, Video Capsule Endoscopy (VCE) should be the next preferred diagnostic method. NSAIDs should be discontinued for at least one month prior to performing VCE.

Patients with normal endoscopic findings but suspected Crohn's disease on MRI or capsule endoscopy (CE) should undergo double-balloon enteroscopy for biopsy confirmation of the diagnosis (Figure 5). The detection of at least three intestinal ulcers on VCE is strongly indicative of Crohn's disease, provided the patient has not taken NSAIDs in the month preceding the examination (Figure 6).

Contraindications for VCE include gastrointestinal obstruction, strictures, and swallowing disorders.⁸

RADIOLOGICAL DIAGNOSTIC METHODS

Plain Films of the Abdomen

Patients with severe ulcerative colitis should be closely monitored for the risk of toxic megacolon using serial abdominal radiographs. Plain radiography is especially valuable in patients receiving corticosteroid therapy, as the clinical signs of toxic megacolon may be masked (Figure 7).

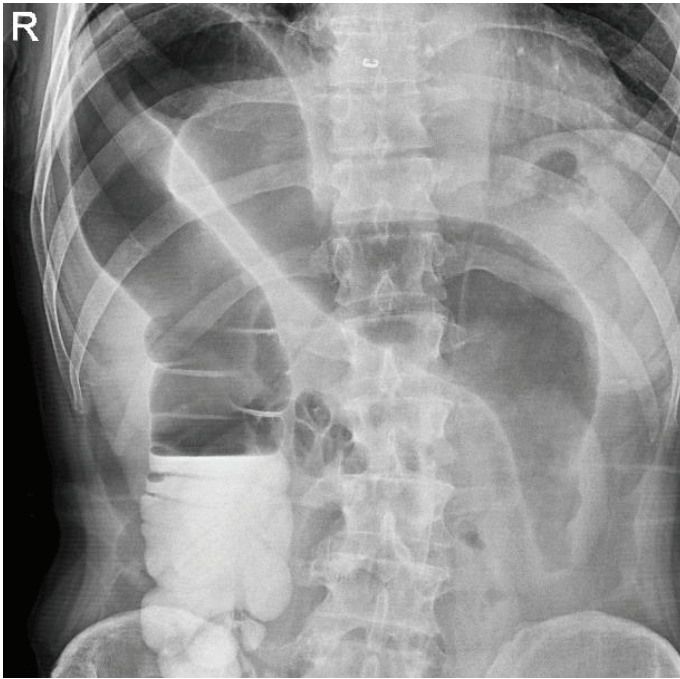


Figure 7. Dilated transverse colon, thickening of the colon wall, mucosal islets, and dilated small intestine segment are seen in a patient with severe ulcerative colitis. (From the Archives of Gastroenterohepatology Department of Istanbul Medical Faculty).

Computed Tomography and Magnetic Resonance Imaging

In CD, magnetic resonance imaging (MRI) and computed tomography (CT) enterography, along with transabdominal ultrasound, complement endoscopy by allowing evaluation of the degree and extent of inflammation, obstruction, and fistulizing disease. These imaging modalities also assess disease severity and activity by evaluating mural thickness and contrast enhancement patterns.

CT is more widely available and less time-consuming than MRI, but both techniques are operator-dependent. Standard CT does not provide detailed visualization of the mucosa and may appear normal in the early stages of the disease. However, oral contrast-enhanced CT enterography allows assessment of mucosal changes and extraluminal features.

Radiologic findings of Crohn's disease activity that strongly correlate with endoscopic results include mural enhancement (segmental enhancement of all or part of the small intestinal wall) and increased peri-enteric fat density. The "comb sign," characterized by segmental dilation of the vasa recta accompanied by mural enhancement, is one of the most significant diagnostic features (Figure 8).

CT enterography has a sensitivity of 82% and a specificity of 89% for diagnosing Crohn's disease.¹⁸

As an alternative to CT, MRI provides equal image quality for evaluating the intestines.¹⁹ MR enterography offers several advantages, including high soft tissue contrast, the ability to produce both static and dynamic images, and the elimination of ionizing radiation.²⁰

Signs of active disease identifiable on MR enterography include intestinal wall thickening, submucosal edema, vasa recta engorgement, and lymphadenopathy. Pelvic or anal MRI is the imaging modality of choice for evaluating suspected pelvic, perirectal, or perianal abscesses, as well as detecting fistulas in Crohn's disease.

Ultrasonography

Transabdominal ultrasonography is primarily used to exclude other causes of abdominal pain, such as biliary or gynecologic pathologies, but it can also help assess the activity of luminal Crohn's disease. Contrast-enhanced Doppler ultrasonography (USG) offers increased sensitivity and specificity in detecting disease activity by identifying increased bowel wall thickness, which has a sensitivity ranging from 75% to 94%.

The ileocecal region, ascending colon, and descending colon can be adequately visualized in most patients. Intestinal ultrasonography is also a valuable tool for monitoring Crohn's disease over time. However, the primary utility of endoscopic ultrasonography in differentiating Crohn's disease from transmural ulcerative colitis is limited to the evaluation of perianal disease (Table 4).

Pathological Diagnosis

In distinguishing IBD from infectious or acute conditions, preserved crypt architecture accompanied by acute inflammation is typically observed. However, in early-stage IBD, the crypt structure may also remain intact. It is essential to recognize that the diagnosis of IBD relies

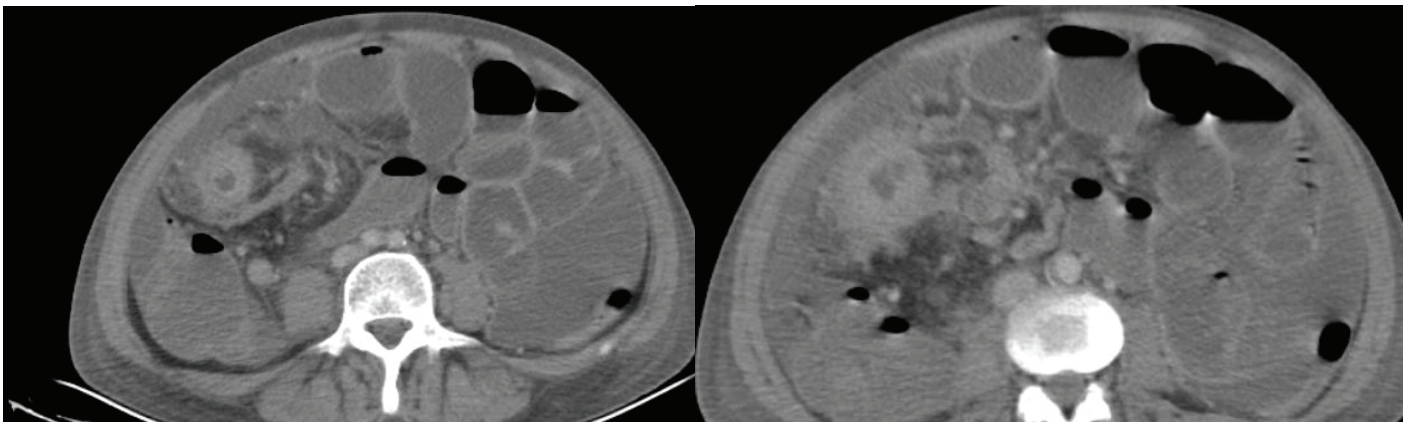


Figure 8. CT enterography showing intestinal stricture, abscess, vasa recta engorgement, and prestenotic dilatation in a patient with Crohn's disease. The stricture is considered inflammatory because it shows mural thickening, perienteric inflammation, and increased contrast enhancement. (From ITF Gastroenterohepatology Archive).

Table 4. Comparison of imaging modalities in the diagnosis of inflammatory bowel diseases

| | MR | BT | USG |
|---------------------------|---|--|---|
| Crohn's | Intestinal wall thickening, submucosal edema, vasa recta engorgement, and lymphadenopathy | Mural prominence, increased perienteric adipose tissue, comb sign | Thickening of the terminal ileum wall, stricture, abscess, fistula |
| Ulcerative Colitis | Colonic mural thickening (>3 mm), edema, loss of haustra, vasa recta engorgement, pericolic lymph nodes | Thickening of the intestinal wall, increased contrast enhancement, mural stratification, pericolic lymph nodes | High sensitivity in the sigmoid and descending colon, low sensitivity in the rectum Increased Doppler flow, wall thickening, loss of bowel compressibility |
| Advantage | No radiation exposure | Easily accessible | Easy to apply, inexpensive, no preparation required |
| Disadvantage | Expensive, time-consuming, requires preparation, difficult access | Radiation exposure | Low sensitivity in the rectum and in assessing disease prevalence |

MRI: Magnetic Resonance, CT: Computed tomography, USG: Ultrasonography

Table 5. Pathologic findings in ulcerative colitis and Crohn's disease

| Material | Ulcerative Colitis | Crohn's Disease |
|---|--|---|
| Resection specimen | Extensive, superficial, persistent inflammation Erythematous, granular, fragile mucosa | Deep, transmural inflammation, serosal abscess, patchy-skip involvement [At least three histologic features suggestive of CH in the absence of granuloma (segmental crypt structure abnormalities and mucin depletion, presence of mucin in active zones, and focal chronic inflammation without crypt atrophy)], + 1 more diagnostic feature if granuloma is present |
| Biopsy specimen | Focal or diffuse basal plasmacytosis, diffuse mucosal or crypt architectural distortion, mucosal atrophy, and irregular or villous mucosal surface | Compact, well-circumscribed granulomas, mucin in active areas, thickened fibrous stroma |
| COMMON FINDINGS Chronicity Findings: Crypt distortion, loss, basal lymphoid hyperplasia, metaplastic epithelial changes | | |

on the integration of clinical and endoscopic findings, with pathology serving as an adjunctive tool, as no single pathological feature is pathognomonic for the disease.

In the diagnosis of Crohn's disease, histopathological features include granulomas, focal crypt architectural distortion, and focal or patchy chronic inflammation characterized by the presence of lymphocytes and plasma cells. Additionally, mucin deposition within areas of active disease is commonly observed in association with Crohn's disease.²¹⁻²³ However, no single feature is considered diagnostic.^{24,25}

In diagnosing UC, focal or diffuse basal plasmacytosis is recognized as one of the earliest and most predictive histopathological features, detectable within two weeks of symptom onset in approximately 38% of patients.²⁵ Diffuse distortion of the mucosal or crypt architecture, mucosal atrophy, and irregular or villous mucosal surfaces typically appear at least four weeks after symptom onset.

Not all microscopic features of UC manifest early in the disease course. However, in approximately 75% of cases, the presence of two or three of these features is sufficient to make an accurate diagnosis. The exact number of criteria required for a definitive diagnosis has not yet been firmly established.⁸

CONCLUSION

The diagnosis of IBD is strongly suggested by the presence of chronic symptoms, elevated acute phase reactants, and evidence of intestinal wall inflammation on radiologic imaging. Endoscopic examination findings specific to ulcerative colitis or Crohn's disease, combined with pathological features that indicate chronicity, are instrumental in estab-

lishing the diagnosis. Advanced methods such as capsule endoscopy and enteroscopy should be reserved for rare cases when necessary.

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