IBD REVIEWS REVIEW ARTICLE

Diagnostic approach to inflammatory bowel disease

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Abstract

Inflammatory bowel disease has seen a rise in incidence and prevalence in recent years, entailing the need for early and precise diagnostic approach as the clinical management and outcome of the patient are dependent on the accuracy of the diagnosis. It is equally important to establish extent and the severity of the disease, as these also influence treatment options and possibly the progression of the disease. A bibliographic search was performed, citing 60 articles in the final analysis, to establish an approach to the diagnosis of ulcerative colitis and Crohn's disease based on current accepted procedures and criteria.

(IBD Rev. 2018;4:30-8)

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Key words: *Inflammatory bowel disease. Ulcerative colitis. Crohn's disease. Diagnosis. Ileocolonoscopy.*

Introduction

Inflammatory bowel disease (IBD) is an idiopathic disorder characterized by chronic relapsing and remitting inflammation of the gastrointestinal (GI) tract. It has two main subtypes, ulcerative colitis (UC) and Crohn's disease (CD). UC is confined to colonic mucosa and extends proximally, in an uninterrupted pattern, from the anal verge to involve the entirety or a portion of the colon. In contrast, in CD, the inflammation process is transmural and may involve any part of the GI tract from mouth to anus presenting as patches of inflammation intertwined with areas of normal mucosa. In a small proportion of patients, indeterminate colitis may occur, diagnosed as such because of inability to differentiate between UC and CD with current established criteria. All three, UC, CD, and indeterminate colitis, can be associated with extraintestinal manifestations. IBD etiology remains unknown, although it has been postulated as a multifactorial disease with genetic, immunologic, and environmental factors as contributors to its development.

An early and precise diagnosis is important for the course of the disease, guiding management of the patient, and therapeutic decisions. The diagnosis of IBD should be based on the

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correlation of clinical, laboratory, endoscopic, and histologic aspects, ruling out differential diagnostics[1-3].

Clinical aspects

Helpful to the diagnosis is the completion of a richly detailed medical history that includes evaluation of the family history of IBD, recent travel, infections, and the use of anti-inflammatory drugs. Smoking habit, sexual behavior, and previous appendectomy should also be recorded. Interrogating onset of symptoms and previous crises as well as the presence of rectal bleeding, diarrhea, abdominal pain, urgency, tenesmus, incontinence, weight loss, perianal lesions, and the presence of extraintestinal manifestations is essential (Table 1)[1,3].

Ulcerative colitis

The onset of symptoms may be gradual or sudden but is usually progressive over several weeks. These may include an increase in bowel movements and bloody diarrhea, fecal urgency, tenesmus, incontinence, and cramping pain. Symptoms may be preceded by an isolated self-limited episode of rectal bleeding weeks or months earlier. The course of the disease is variable with periods of exacerbation, improvement, and remission that may occur with or without medical therapy.

The left side of the colon can be involved to different extents: proctitis, proctosigmoiditis, and disease extending from the splenic flexure distally. Constipation, tenesmus, and rectal bleeding are the presenting symptoms in patients with disease limited to the rectum[4-6]. Diarrhea can vary from 1 to 20 or more loose or liquid stools daily, which are usually worse in the morning and immediately after meals. Abdominal pain is usually worse after meals or bowel movements. Patients with moderate and severe symptoms often have nocturnal stools. Furthermore, anorexia, weight loss, and nausea are common in severe and extensive disease in the absence of bowel obstruction and uncommon in mild-to-moderate disease or that is limited to the left colon. Urgency, incontinence, and upper GI tract symptoms are more frequent in children, and growth failure is common. Extraintestinal symptoms occur in up to 20% of patients and may precede intestinal symptoms in up to 10% of cases[6-8].

Patients may also present with systemic symptoms that include fever, fatigue, and weight loss. Dyspnea and palpitations can occur due to anemia secondary to iron deficiency due to blood loss. The presence of systemic symptoms is dependent on the clinical severity of the disease, and about 15% of cases present with a severe attack with systemic symptoms[6].

Crohn's Disease

Clinical manifestations in CD are more variable than those in UC; patients can have symptoms for many years before diagnosis and depend on the anatomical location of the disease[2,9]. Abdominal pain, diarrhea, and fever are typical in ileocecal disease. In colonic disease, bloody bowel movements with diarrhea, weight loss, and low-grade fever are common symptoms. Symptoms in gastroduodenal CD are usually burning epigastric pain and early satiety, frequently overshadowing those of coexisting ileal or colonic disease. In oral or esophageal CD, dysphagia, odynophagia, and chest pain are the presenting symptoms even without eating. Findings in perianal disease include perirectal abscesses and anal and perianal fistulas. Rectovaginal fistulas can occur in women with rectal CD and cause gas or stool to be passed from the vagina[2]. In children, the onset of CD is insidious, and weight loss and growth failure occur before any intestinal symptoms[9,10]. Systemic symptoms include fatigue, common in CD, and weight loss related to either decreased oral intake or related to malabsorption. Fever is less common but may be a manifestation of perforation with a peritoneal infection. Abnormalities of the musculoskeletal system are the most common extraintestinal manifestations in IBD patients and can present before any GI symptoms[7,11].

Table 1. Clinical characteristics of UC and CD[3]

Symptom	UC	CD
Abdominal pain	Cramps, mainly left lower quadrant	Prominent, frequent complain, right lower quadrant
Diarrhea	Frequent in adults can alternate with constipation	Frequent in adults may be absent in children
Hematochezia	Always in active patients, intensity related to disease activity	20-30% of patients, mainly in distal disease
Abdominal mass	Left lower quadrant if sigmoid is inflamed in slim individuals	Right lower quadrant (inflamed ileum)
Hyposomnia	Rare	Occasional
Malnutrition	Occasional	Frequent
Abdominal distension	Only in severe disease	Occurs
Obstructive symptoms	No	Frequent
Perianal disease/fistula	No	In up to 30% of patients

CD: Crohn's disease; UC: ulcerative colitis.

Physical examination

Examination should include general well-being, pulse rate, blood pressure, temperature, abdominal examination for tenderness and distension, palpable masses, as well as perineal and oral inspection, digital rectum examination, and measurement of body mass index.

In mildly active UC, physical examination is usually normal, abdominal tenderness, especially with palpation over the sigmoid colon, may be present. Patients with moderate-to-severe disease may have pallor due to anemia, tachycardia, fever, diminished bowel sounds, and diffuse abdominal tenderness with rebound. Abdominal tenderness with rebound can be a sign of perforation. Rectal examination may reveal evidence of blood. Patients with prolonged diarrhea may have evidence of muscle wasting, loss of subcutaneous fat, and peripheral edema[6].

In CD, findings can be normal or may include any one or more of the following: fever, weight loss, muscle wasting, abdominal tenderness (usually in the lower abdomen), and a palpable mass, usually in the ileocecal region of the right lower abdomen. A rectal examination can expose large, edematous, external hemorrhoid tags, fistulas, anal canal fissures, and anal stenosis[2]. Perianal fistulas are present in 4-10% of patients at the time of diagnosis and may be the presenting complaint[12]. Ulcers can be found on the lips, gingiva, and buccal mucosa.

Investigations to establish diagnosis of ulcerative colitis

The diagnosis of UC is based on the presence of chronic diarrhea for more than 4 weeks and evidence of active inflammation on endoscopy with chronic changes on biopsy, but since these findings are not specific for UC, the exclusion of other causes of colitis by history, laboratory studies, and biopsies of the colon is required to establish the diagnosis (Table 2)[1,6,13].

Every patient should have a full blood count, inflammatory markers, electrolytes, liver function tests, and stool samples taken[6]. Full blood count may reveal thrombocytosis as a result of chronic inflammatory response and anemia that may indicate severe or active disease. The presence of leukocytosis may

suggest a possible infectious complication. Inflammatory markers can be normal in mild-to-moderate UC. With the exception of patients with proctitis, C-reactive protein (CRP) is associated with clinical severity, and in patients with severe clinical activity, CRP correlates with an elevated erythrocyte sedimentation rate[14-16]. None are specific enough to differentiate UC from infectious or other causes of colitis.

Stool studies should be obtained and should include stool *Clostridium difficile* toxin, routine stool cultures for *Salmonella, Shigella, Campylobacter,* and *Yersinia*, and specific testing for *Escherichia coli*. Additional tests may be performed according to the medical history, such as recent travel to endemic areas. In addition, testing for sexually transmitted infections may be warranted in patients with severe rectal symptoms, particularly men who practice sex with other men. In addition, microbial stool tests should be performed in cases of treatment refractory or severe relapse[6,17,18].

Biomarkers

Perinuclear antineutrophil cytoplasmic antibodies (pANCAs) and anti-*Saccharomyces cerevisiae* antibodies (ASCAs) are most widely studied serological markers. pANCAs are detected in up to 65% of patients with UC and in <10% of patients with CD[6-20]. Given the limited sensitivity of these markers, they are not part of the diagnostic evaluation of patients with suspected IBD.

Of several neutrophil-derived proteins that have been evaluated as markers of intestinal inflammation in IBD, fecal calprotectin appears to be the most sensitive, but as with all fecal tests, it lacks the specificity to discriminate between different types of inflammation[21]. Still, it represents a useful non-invasive marker in the follow-up of UC patients[22,23].

Endoscopy

Endoscopic changes in UC characteristically start at the anal verge and extend proximally in a continuous and concentric fashion with the demarcation between inflamed and normal areas usually being very clear with an abrupt start. The granularity, vascular pattern, ulceration, and bleeding and friability have been reported to predict the assessment of endoscopic severity[24].

Endoscopic features of mild inflammation include erythema, vascular congestion, and partial loss of visible vascular pattern. In moderate disease, there is a complete loss of vascular pattern, blood adherent to the surface of the mucosa, and erosions, often with a coarse granular appearance and mucosal friability. Severe colitis is characterized by spontaneous bleeding and ulceration[25,26]. However, colonoscopy should be avoided in hospitalized patients with severe colitis because of the risk of precipitating toxic megacolon or perforation. In these cases, a rectal sigmoidoscopy should be performed and be limited to the rectum and distal sigmoid colon.

In comparison to CD, ulcers in severe UC are always embedded in the inflamed mucosa with the presence of deep ulceration being a poor prognostic sign[25]. In long-standing disease, loss of haustral folds, luminal narrowing, and post-inflammatory polyps can be found as a result of mucosal atrophy[6].

If colonoscopy is incomplete due to a colonic stricture, a computed tomography (CT) colonography should be performed to assess mucosal pattern proximal to the stricture and exclude any extra-intestinal pathology[6,27].

Colon capsule endoscopy is not yet widely used in practice but can differentiate active from inactive UC, with a sensitivity of 89% and specificity of 75% for the identification of active colonic inflammation[6].

Assessment of extent

Rectal sparing has been described in untreated children with UC, but in adults, normal or patchy inflammation in the rectum is usually due to topical therapy[28,29]. In patients with left-sided colitis, a cecal patch or patchy in-

flammation in the cecum can be observed. Involvement of the appendix as a skip lesion is reported in up to 75% of patients with UC[30]. Continuous extension of inflammation from the cecum into terminal ileum or "backwash ileitis" is observed in up to 20% of patients with extensive colitis, and they seem to be prone to a more refractory course of disease[6,31]. If rectal sparing or a cecal patch is observed in newly diagnosed colitis, and in cases of backwash ileitis, additional imaging of the small bowel should be considered to exclude CD[32].

Histopathology

For a reliable diagnosis, a minimum of two biopsies from at least five sites around the colon including the rectum and the ileum should be obtained and be accompanied by clinical information, such as endoscopic findings, duration of disease, and current treatment[6].

The microscopic features that have been evaluated in UC can be broadly classified into four main categories: mucosal architecture, lamina propria cellularity, neutrophil granulocyte infiltration, and epithelial abnormality. Not all microscopic features are observed in early-stage disease with only about 20% of patients showing crypt distortion within 2 weeks of the first symptoms of colitis, making the distinction from infectious colitis, characterized by preserved crypt architecture and acute inflammation, a great concern[6,33].

The exact number of features needed for diagnosis has not been established, with correct diagnosis being reached in approximately 75% of cases where two or three of the four following features are found: severe crypt architectural distortion, severe decreased crypt density, an irregular surface, and heavy diffuse transmucosal inflammation, in the absence of genuine granulomas[6,34].

Focal or diffuse basal plasmacytosis has been recognized as the earliest diagnostic feature of UC with the highest predictive value, being identified in 38% of patients within the first 2 weeks after the presentation of symptoms. Preserved crypt architecture and absence of transmucosal inflammatory cell infiltrates do not rule out UC at an early stage, and with repeat biopsies after an interval, definitive diagnosis can be established by showing additional features[3,35].

Inactive disease can still show features related to chronic mucosal injury such as crypt distortion, atrophy, and Paneth cell metaplasia, even though active inflammation is usually not observed. the Although resolution of crypt architectural distortion and inflammatory infiltrate is characteristic of histological mucosal healing, the mucosa can still show some features of sustained damage, such as decreased crypt density with branching and atrophy of crypts[6,33,36]. Still, no standardized definition for "histological mucosal healing" exists, making definitions of pathological remission ranging from residual inflammation with persistent architectural distortion to normalization of the colonic mucosa[36].

Investigations to establish diagnosis of Crohn's disease

Diagnosis of CD is established with endoscopic findings or imaging studies in a patient with a compatible clinical history. The order of testing will be determined by the presenting symptoms with colonoscopy being most appropriate for patients presenting predominantly with diarrhea, while imaging studies are more suiting for those with abdominal pain (Table 2).

Initial laboratory investigations should include a complete blood count, blood chemistry, inflammatory markers, and serum iron and Vitamin B12 levels. Additional testing for infectious diarrhea including ova and parasites as well as *C. difficile* toxin is recommended, especially for those with a history of recent travel.

In the full blood count, anemia and thrombocytosis are the most common abnormalities[37]. CRP is associated with disease activity of CD and indicates serial changes in inflammatory activity because of its short half-life of 19 h[15,38]. Fecal calprotectin and lactoferrin have also

proved useful in the diagnosis of active inflammation[22,39]. Still, none of these inflammatory markers are specific enough to permit differentiation from UC or enteric infection.

Serological testing for ASCA and ANCA may be used as an adjunct to diagnosis, but they are unlikely to be useful in routine diagnosis, being ineffective at differentiating colonic CD from UC[40]. There are still no genetic tests recommended routinely for diagnostics.

Endoscopy

Ileocolonoscopy with multiple biopsy specimens is the first-line procedure for diagnosing CD[3,41]. Ileoscopy with biopsy can be achieved with practice in at least 85% of colonoscopies and increases the diagnostic yield[42]. The endoscopic hallmark of CD is the patchy distribution of inflammation, with skip lesions. CD ulcers tend to be longitudinal and can be associated with a cobblestone appearance of the ileum or colon, fistulous orifices, and strictures[1,3,42].

Rectal sparing is often found, and circumferential continuous inflammation patterns are infrequent. Anatomical criteria of severity are defined as deep ulcerations eroding the muscle layer or mucosal detachments or ulcerations limited to the submucosa but that extends to more than one-third of a defined colonic segment[43]. When there is severe, active disease, full colonoscopy carries a higher risk of bowel perforation. In these cases, flexible sigmoidoscopy is safer to perform and ileocolonoscopy should be postponed until the clinical condition improves[1,44].

Ileoscopy is superior for the diagnosis of CD of the terminal ileum when compared with radiologic examinations, such as magnetic resonance imaging (MRI) and CT, especially for evaluation of mild lesions[27,45,46]. In selected patients with suggestive symptoms of CD and after failure of radiologic examinations, capsule endoscopy and enteroscopy with biopsy have proven useful procedures for the diagnosis of the disease and are also well tolerated by the patient[47].

Assessment of extent

In 10% of patients, CD can affect the ileum out of reach of an endoscope or involve more proximal small bowel; in addition, 15% of patients suffer penetrating lesions such as fistulas, phlegmons, or abscesses at the time of diagnosis[42]. Complementary to endoscopy, MRI, CT, and trans-abdominal US offer the opportunity to detect and stage inflammatory, obstructive, and fistulising CD[27,48,49].

After endoscopy, cross-sectional imaging techniques possess the unique advantage of a complete and sensitive staging of the small bowel and perineum to assess mural and extramural disease[42]. CT and MRI are the current standards for assessing the small intestine. Based on wall thickness and increased intravenous contrast enhancement, both of these techniques can establish disease extension and activity[49]. The extent of these changes, paired with the presence of edema and ulcerations, enables categorization of disease severity[50].

Trans-abdominal US is another non-invasive and non-ionizing imaging technique that is well tolerated and accepted by patients. The ileocecal region, sigmoid, and most times ascending and descending colon can be adequately visualized in most cases. Proximal ileum and jejunum are sometimes difficult to assess, and the study of the transverse colon can prove challenging because of its inconstant anatomy. US diagnosis of CD relies primarily on the detection of increased bowel wall thickness, considered the most common and constant finding in CD with sensitivities of 75-94% and specificities of 67-100% being reported for the accuracy of diagnosis[42,51,52].

Even though leukocyte scintigraphy is well tolerated and non-invasive and could potentially permit assessment of the extent and activity of inflammation, it has seen reduced the use due to radiation exposure and limited sensitivity, especially in patients under steroid treatment[53].

Direct and indirect comparisons of the relative accuracy of the different imaging modalities (US, CT, MRI, and white blood cell scintigraphy) for the diagnosis of disease activity and severity in CD show that the techniques provide similar sensitivities and specificities overall[45].

Ileocolonoscopy is the recommended procedure for the detection of stenosis in the colon and distal ileum allowing at the same time tissue sampling for pathological diagnosis, as dysplasia or cancer complicates 3.5% of colonic strictures[54]. The most reliable measure for defining a stricture is a localized, persistent narrowing whose functional effects can be judged from pre-stenotic dilatation[42,55]. When the stricture is impassable with the endoscope, complementary radiological techniques are necessary to rule out additional lesions. US, MRI, or CT are necessary as plain film radiography may distinguish small bowel obstruction but cannot determine the cause.

CD patients with dyspepsia, abdominal pain, and vomiting benefit from an upper GI endoscopy[56].

Small bowel capsule endoscopy is a sensitive tool to detect mucosal abnormalities in the small bowel with a superior diagnostic yield compared to those of other modalities for diagnosing small bowel CD and a very high negative predictive value on normal examination essentially ruling out small bowel disease. However, it is limited by a lack of specificity with over 10% of healthy subjects demonstrating mucosal breaks and erosions in their small bowel making SBCE findings of mucosal lesions alone insufficient to establish a diagnosis of CD[42,57].

Histopathology

For the initial diagnosis, analysis of a full colonoscopic biopsy series produces the most reliable diagnosis of CD. A minimum of two biopsies from five sites around the colon, preferably from both involved and uninvolved areas, including the rectum as well as the ileum, should be obtained[1,42].

Focal chronic inflammation and patchy chronic inflammation, focal crypt irregularity, and granulomas are the generally accepted microscopic features that allow the diagnosis of CD to be made. With the addition of an irregular villous architecture, the same features can be used for analysis of endoscopic biopsy samples from the ileum.

Only granulomas in the lamina propria not associated with active crypt injury may be regarded as a corroborating feature of CD, and those associated with crypt injury are less reliable[58].

Features that can be identified in the mucosa include granulomas and focal crypt architectural abnormalities, in concurrence with focal or patchy chronic inflammation, or mucin preservation at active sites. Patchy inflammation is only diagnostic in adult patients not undergoing treatment as inflammation can become patchy in UC after treatment, and young children with UC may also present with discontinuous inflammation[59].

The presence of a single feature is not sufficient for a firm diagnosis. Although there is no data available as to how many features must be present for a solid diagnosis of CD, it has been suggested that a diagnosis should be made when three features are present in the absence of granulomas, or when an epithelioid granuloma is present with one other feature, provided that specific infections are excluded[42,60].

The absence of diagnostic features or those that are highly suggestive of UC can also help toward a diagnosis of CD. In contrast to UC, disease activity is not generally assessed by pathologists, mainly due to the discontinuous character of the disease, with possible sampling error and the probability that the ileum may be the only area involved[60].

Conclusions

The diagnosis of IBD is complex and requires clinical suspicion and biomarkers as the first step in many cases, Differential diagnosis in IBD colitis still relies on a multidisciplinary ap-

Table 2. Laboratory, endoscopic, and radiologic characteristics of UC and CD3

	UC	CD
Laboratory abnormality		
Acute reactant proteins (CRP)	In extensive or severe disease	Frequent
Anemia	In severe disease	Frequent
Macrocytosis	Rare	Occurs (chronic ileal involvement)
Hypoalbuminemia	In severe disease	Frequent
pANCA	++ (in UC with PSC)	+ (in Crohn's Colitis)
ASCA	+	++
Endoscopic appearance		
Distribution	Continuous spread from the rectum	Any segment of the GI tract
Small bowel involvement	Rare (back-wash ileitis)	Frequent
Rectal involvement	Almost always	30-50%
Uniform, continuous disease	Always	Infrequent (Crohn's colitis)
Longitudinal, polycyclic ulcers	No	Frequent
Cobblestone appearance of ileum	No	Frequent
Normal mucosa with inflamed areas	No	Frequent "skip lesions"
Strictures	Rare, always suspicious for carcinoma	Occasional
Mucosal edema	Frequent	Occasional
Ulceration	Often flat and extensive	Deep
Circumferential inflammation	Frequent	Rare
Imaging		
Increased bowel wall thickness	Moderate	Extensive

ASCA: anti-*Saccharomyces cerevisiae* antibodies; CD: Crohn's disease; CRP: C-reactive protein; GI: gastrointestinal; pANCA: perinuclear antineutrophil cytoplasmic antibodies; PSC: primary sclerosing cholangitis; UC: ulcerative colitis; (+) association variably seen. +: associated; ++: frequently associated; +++: strongly associated.

proach based on clinical evaluation, standard biomarkers, lower and upper endoscopy, histopathology, and radiology. Additional investigations such as enteroscopy, special serologic tests, and advanced endoscopic imaging techniques can help in specific situations but should not routinely be advocated (Table 1).

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