Diagnosing Inflammatory Bowel Disease

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INTRODUCTION

Inflammatory bowel disease (IBD) are characterized by chronic recurrent inflammation, which result from an inappropriate immune response in genetically susceptible individuals. Essentially IBD comprises two forms of presentation: ulcerative colitis (UC) and Crohn's disease (CD). The UC affects the mucosa of colon and rectum and, classically, has symmetrical distribution, ascending and continuous. The DC is characterized by a chronic transmural inflammation of the digestive tract, which can affect the mouth to the anus segmentally or sauteed, with frequent involvement of the ileal or ileocecal region [1-3].

The disease pathogenesis is not fully understood, it appear to be triggered by the interaction of genetic, environmental, intestinal microbiota and immunoregulation of intestinal mucosa [2,3]. UC and DC are diagnosed by its clinical, pathological, radiological, endoscopic and laboratory aspects. Other causes of intestinal inflammation and infections (e.g., bacterial, viral, mycobacteria and amoebic), ischemia, iatrogenic damage (e.g., radiation, drugs), cancer (e.g., lymphoma) should be excluded [4].

IBD can affect individuals of both sexes at any age, however, focuses predominantly between 20 and 40 years of age, with a strong impact on quality of life, labor, social activity and economic. Ethnic factors related to IBD are very controversial, but there seems to be a higher incidence in Caucasian individuals. The genetic basis of IBD has been much explored in genome-wide association studies, which gave rise to the identification of over 50 susceptibility genes [2,3]. The environmental hypothesis most widely accepted terms of greater consumption of processed foods, high in xenobiotic (e.g., preservatives, colorings and additives) with powerful antigenic effect. Indeed, IBD occurs most commonly in industrialized countries, a fact that points to urbanization as a potential risk factor, with the Westernization of lifestyle, change of eating habits and smoking. The incidence of IBD may be rising significantly in developing countries, which has modified the epidemiological profile of the disease [5-7].

The inflammation of UC is limited to the mucosa and sub mucosa, often begins in the rectum and extends in a symmetrical and continuous pattern, involving all or part of the colon. The UC is classified according to the segment involved: proctitis, left colitis (rectum, sigmoid and descending colon) and pancolitis (beyond the splenic flexure and the entire colon). Patients with pancolitis can sometimes provide “backwash ileitis”, which describes an abnormal appearance of the terminal ileum observed in patients with ulcerative pancolitis. This should not be confused with CD ileocolitis. Recognition of the anatomic extent of mucosal inflammation is essential for the selection of treatment and has prognostic implications in the short and long-term follow-up [2].

In contrast CD can affect any part of the gastrointestinal tract, the inflammatory process affects all layers of the intestine (transmural inflammation), ulcers show segment involvement, they are discontinuous, tend to be deep, serpiginous, with areas of normal mucosa around and cobblestone aspects. A histological marker is the no-caseating granuloma epithelioid. Complications can arise in evolution as stenosis, abscesses and fistulas [3].

CLINICAL PICTURE AND DIAGNOSIS

Classically patients with UC show diarrhea, mucus and blood. Other symptoms such as tenesmus, rectal and abdominal pain may be present and in severe cases, there may be systemic inflammatory response signs as fever, tachycardia and hypotension [2]. In CD, the ileal and ileocecal are the most region affected. The disease manifests as diarrhea, weight loss, abdominal pain, fever, nausea and vomiting. Others areas of the digestive tract could be compromised and symptoms occur according to area (s) affected (s). If the CD compromises the colon, the patient

may exhibit the same symptoms of UC patients. Some patients with CD may have complications such as stricture of the intestinal segments, causing symptoms of sub occlusion or obstruction. Fistulas usually in the anal and perianal region and less frequently to skin in the abdominal area, bladder, vagina and between bowel. Thus, it is recommended a thorough clinical examination of the anal and perineal region in all cases where it is suspected of CD, including those where the clinical history does not suggest any abnormality in these regions [3].

Intestinal manifestations may occur in about 30% of individuals with IBD and include extra intestinal symptoms like arthralgia / arthritis, oral ulcers, erythema nodosum, pyoderma gangrenosum, episcleritis, uveitis, sacroiliitis, ankylosing spondylitis and primary sclerosing cholangitis (PSC), among others. These extra intestinal complications possibly may precede digestive symptoms, which delays the diagnosis. Furthermore, they may be related or unrelated to the activity of IBD (Table 1) [8,9]. IBD patients are also at increased risk of thromboembolic events [10].

Table 1: Extra intestinal manifestations in inflammatory bowel disease and its relationship with inflammatory disease activity.

MANIFESTATIONS	RCU	Crohn Disease	RELATIONSHIP WITH DISEASE ACTIVITY
Rheumatological	6 – 30%	15 - 35%	+ ou -
Arthralgia / arthritis *	5 – 15%		-
• Sacroiliitis • Ankylosing spondylitis	1 – 6%		-
Dermatological	4 – 25%	10 – 30%	+
• Oral thrush	2 – 5%	até 15%	+
• Erythema nodosum • Pyoderma gangrenosum	1 – 5%	1 – 2%	+ or -
Ophthalmic			
• Episcleritis	2 – 4%		+
• Uveitis	0,5 – 3,5%		+ or -
Hepatobiliary			
• Primary sclerosing cholangitis	2 – 8%	1 – 2%	-
• Cholelithiasis	-	15 – 30%	-
Other systems			
• Nephrolithiasis	2 – 5%	5 – 20%	-
• Venous thromboembolism	1.5-3 fold increase in risk the general population		+

* Peripheral arthropathy (asymmetric, large joints [knees, ankles, elbows, shoulders, etc.], non-erosive) is related to activity of IBD; arthropathy small joints (e.g., hands), generally symmetrical, non-deforming, seronegative, not necessarily related to IBD activity.

The clinical manifestations of UC depend on the seriousness of the disease and this is usually classified according to the Truelove and Witts index activity in mild, moderate and severe (Table 2) [11-13].

Table 2: Disease activity in ulcerative colitis [11].

Characteristics	Mild	Moderate	Severe
Number of bowel movements / day	<4	4 - 5	≥6
Blood in the stool	Little or intermittent	Intermittent	Frequent
Temperature (ºC)	Normal (<37.5)	Intermediate (≤37,8)	> 37.5 ≥37,8 and at least 2 days for a total of 4 days
Pulse (bpm)	Normal (<90)	≤90	> 90
Hemoglobin (g / dL)	Normal> 11.5	≥10,5	<10.5

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

The clinical manifestations of activity disease are also variable and dependent on the location, extent and severity of the disease. For the DC activity level exist activity indices available (e.g., Crohn's Disease Activity Index - CDAI [14], Harvey & Bradshaw index [15]), but in practice, clinical data obtained by anamnesis, physical examination and laboratory tests to assess the intensity of the outbreak of DC, as well as provide guidance for treatment, as we shall see [16].

The diagnosis of IBD is based on the analysis of suggestive clinical manifestations, described above, laboratory tests, radiologic, endoscopic and pathologic compatible (Table 1). Complementary tests assist in the diagnosis, staging, prognosis, monitoring response to treatment and possible complications of IBD [16-17]:

- Laboratory: complete blood count, inflammatory activity tests, electrolytes, vitamins and minerals (e.g., iron profile, zinc, magnesium, (e.g., C-reactive protein - PCR, alpha1 - acid glycoprotein, erythrocyte sedimentation rate ESR) folic acid, vitamin B12 and vitamin D).
- The serological markers, p-ANCA (Perinuclear anti-neutrophil cytoplasmic antibody) in the UC and the ASCA (anti-Saccharomyces cerevesiae) in CD, have low accuracy for the diagnosis of IBD and should not be asked routine. They can help in cases where it is difficult to differentiate the two diseases (16).
- Infection by *Clostridium difficile* occurs in up to 20-30% of patients with IBD. Most of the cases, about 40% there is no previous history of antibiotic use. Thus, we depart from this infection (positive search for toxins A and / or B in the stools or PCR) and differential diagnosis causes false or reactivation of disease [18].
- More recently, fecal calprotectin and lactoferrin dosage has been used and correlates well with endoscopic and histological activity. It is an important exam in the diagnosis, and in the monitoring of patients [19].
- Radiological: enterography computed tomography (CT) or magnetic resonance imaging (MRI), intestinal transit and barium enema (the latter two less and less used) (Figure 1).

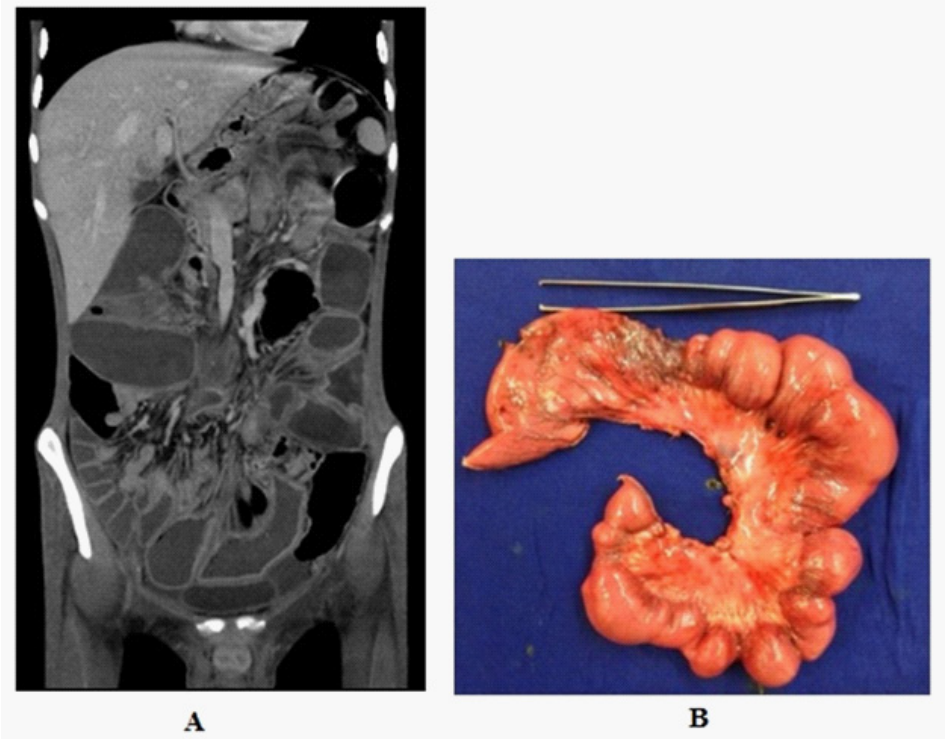

Figure 1: A 21 year-old male with abdominal pain, diarrhea, and hypoalbuminemia. Small intestinal Crohn disease. (A) (CT enterography - coronal image): hyper enhancement mucous (double arrow) + signs of inflammation in the mesentery / engorged vessels (single arrow - "sign comb"). Expansion some slender handles (suggesting stenosis); (B) (Specimen): Multiple stenoses in small intestine.

- Endoscopic: Upper endoscopy, colonoscopy, enteroscopy, and capsule endoscopy (Figures 2, 3 and 4).
- Clinical pathology: in most cases observed a nonspecific inflammation in the intestinal mucosa. Pathology assists mainly on ruling out other causes inflammation of the intestine. In a classic CD and extremely suggestive entity is the finding of non caseating granuloma (present in up to 20% - 30% of cases, particularly in surgical specimens), however, often encountered in deeper layers of the bowel that, in most often they are not achieved by conventional endoscopic biopsies.

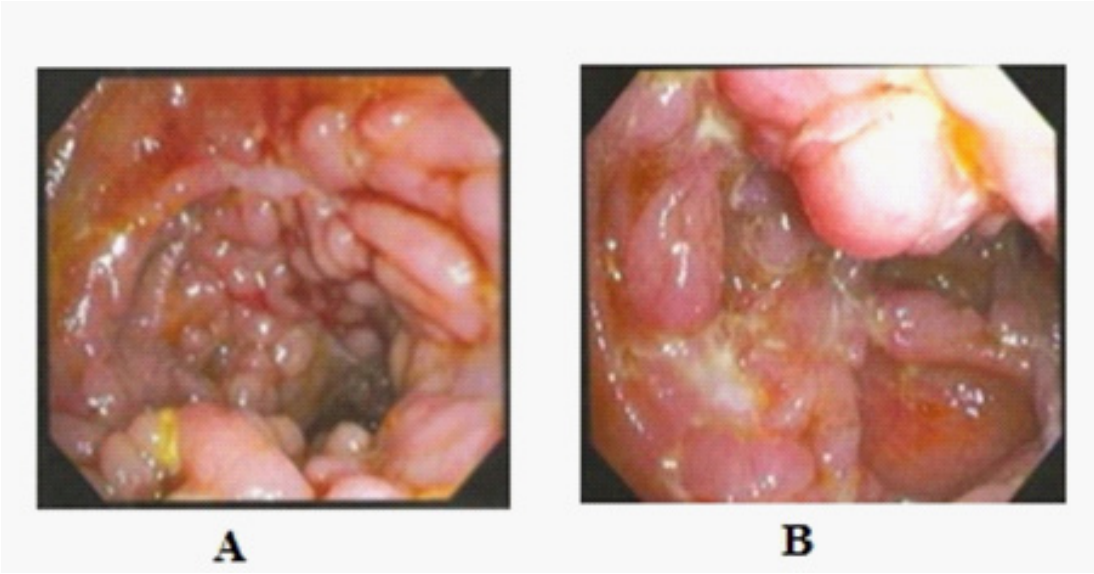

Figure 2: Images anterograde enteroscopy in Crohn's disease affects the small intestine. (A) "cobblestone" image; (B) Deep ulcers in jejunum.

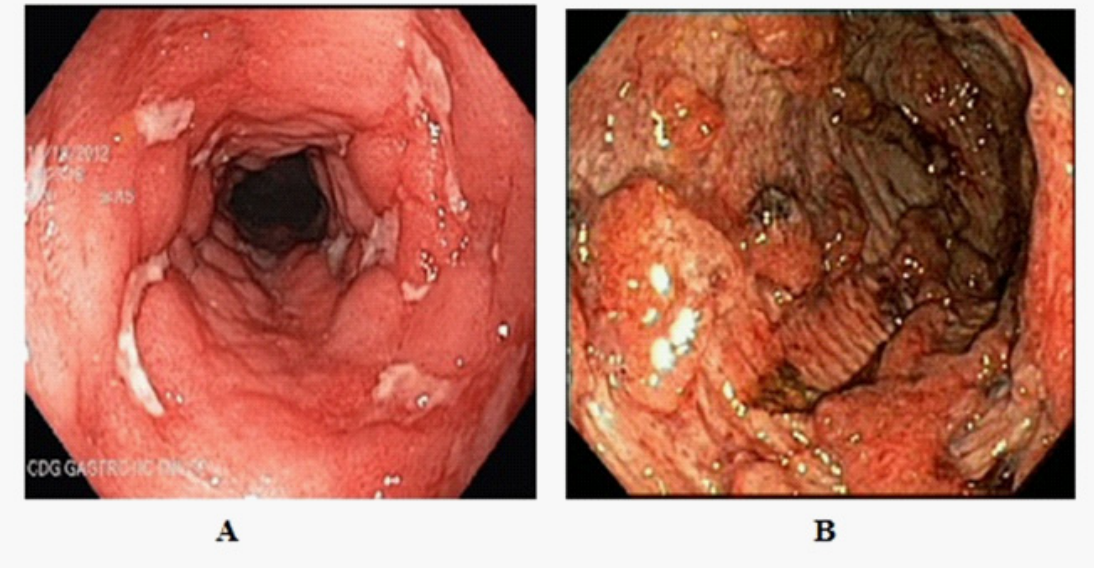

Figure 3: Endoscopic Images of Crohn's disease colonic involvement. (A) longitudinal, deep ulcers of the colon; (B) deep ulcers in the rectum exposing the muscle layer.

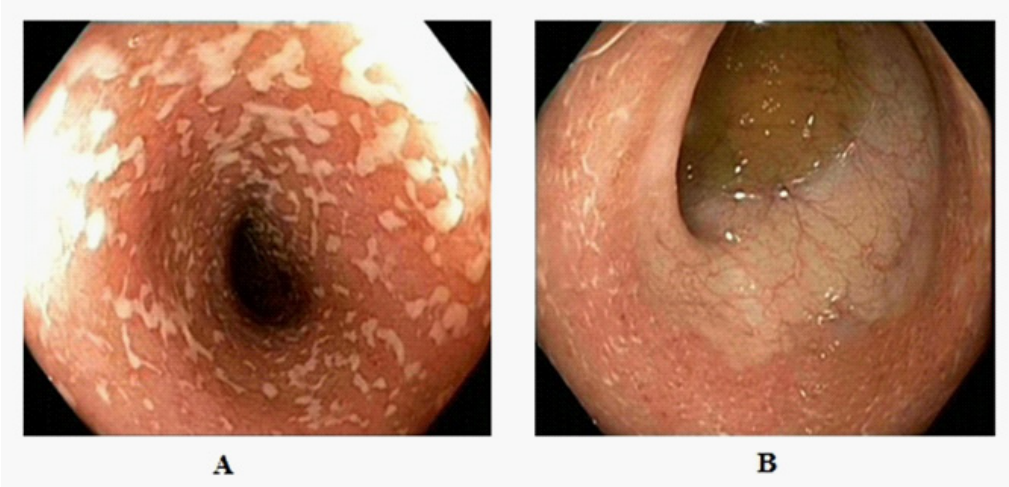

Figure 4: Endoscopic Images of ulcerative colitis. (A) superficial ulcers, continuous pattern and homogeneous; (B) clear differentiation between the inflamed mucosa and normal mucosa (proctitis).

The main differences between UC and CD are listed in Table 3.

Table 3: Main differences between ulcerative colitis (UC) and Crohn's disease (CD).

	UC	CD
Clinical characteristics		
Fever	less common	Common
Abdominal pain	Common	Common
Diarrhea	Very common	Common
rectal bleeding	Very common	less common
Weight loss	less common	Common
Disease anal / perianal	Rare	Common
abdominal mass	Rare (think of cancer)	Common
Deficit growth	less common	Common
Intestinal complications		
Stenosis	Unusual (think of cancer)	Common
fistulas	Missing / rare	common
toxic megacolon	occasional	Very rare
Drilling	rare	uncommon
Cancer	Common	less common
Endoscopic findings ***Endoscópicos Endoscópicos***		
Friability mucosa	Very common	Common less
Aphthous ulcers and linear	Missing / rare	common
Aspect "cobblestone" papapapapapap "" cobblestone "	Absent	Common

pseudopolyps	common	Less common
rectal involvement	virtually universal	less common
Picture findings		
Distribution	To be continued	segmental
ulcerations	superficial	deep
Localization	Colon / Straight	Ileum (+ common)
Stenosis / fistula	unusual	common
ileal involvement	Ileitis as "backwash"	Frequent
Laboratory findings		
pANCA *	40 - 70%	0 - 20%
ASCA **	0 - 30%	40 – 70%

*pANCA: Perinuclear antibody against cytoplasmic neutrophil

** ASCA: antibody *Saccharomyces cerevisiae*

Laboratory - The Main Findings

CU and CD - iron deficiency anemia, elevated inflammatory activity as ESR, CRP, alpha1-acid glycoprotein, leukocytosis and thrombocytosis; and increased calprotectin in the faeces of lactoferrin, vitamin B12 deficiency (most commonly in ileal CD).

Endoscopy

UC - continuous aspect, homogeneous, erosion, erasing the vascular network, friability, straight almost always compromised.

CD - discontinuous aspect (segmental), adjacent areas of normal, aphthous ulcers, serpiginous ulcers, deep, longitudinal aspect “cobblestone” or “cobblestone”.

Histopathological

UC - mucosa with polymorphonuclear and lymphocytic infiltration (mainly in the quiescent phase), crypt abscesses; Goblet cell depletion;

CD - transmural inflammation with lymphocytic infiltration, noncaseating granulomas.

Diagnostic Imaging

It is recommended that all patient with IBD undergo an upper GI with small bowel follow through at the time of initial diagnosis. Newer imaging modalities are currently replacing the barium radiography in many centers. Non-barium imaging modalities like ultrasound, nuclear medicine, computed tomography and magnetic resonance image are greatly used in centers in the differentiation of UC from CD. They also reveal the extent and severity of the inflammatory process and assess complications of disease such as an obstruction, fistula, or abscess. This information allow to recommend the best course of therapy.

Computed tomography (CT) and Magnetic Resonance Image (MRI)

CT can also be used to aid therapeutic procedures (e.g. drainage of abdominal abscesses). A disadvantage of CT is ionizing radiation; this must be taken into consideration, since the majority of patients with IBD is young and may require repeated tests throughout life, which can lead to a high cumulative doses of radiation.

Currently, the radiological exam of choice for evaluating the small intestine and the possible complications of IBD is enterography, either by computed tomography (CTE) or Magnetic Resonance Enterography (MRE).

CT enterography (CTE) for small bowel evaluation

Consists of the administration of oral neutral contrast associated with the contrast intravenously. Polyethylene glycol (PEG), and mannitol are the neutral contrasts most widely used in our environment and permit adequate distension of the intestinal segments, for reviews of constricted loops that could be confused with stenosis or thickening, moreover, the neutral contrast increase the definition of the layer mucosa which would be lost with the use of contrast as barium. This allows greater sensitivity in detection than 95% of CD, for example. The CTE can identify segmental thickening of the handles (thickness greater than 5 mm), extrinsic injuries and complications such as fistulas and abscesses. One of the signs associated with the disease activity is the increased density of the mesenteric fat and engorgement of mesenteric vessels ("vasa recta"), known as "comb" sign. The luminal narrowing associated with dilation upstream indicates stenosis lesion [20-22].

MR Enterography (MRE)

Is non-invasive method for quantifying wall thickness, grade inflammation and determine the extent of disease. It is also able to offer static and dynamic images, does not involve ionizing radiation, it has excellent resolution in soft tissues and is safe in pregnancy. Can provide superior performance to CTE in differentiating between fibrotic scar component or current inflammatory activity in the assessment of stenoses of CD, which can guide different therapeutic approaches [20,21]. MRE of the pelvis can be used in documenting the extent of disease and presence of abscess or infection in patients with perianal Crohn's disease.

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