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Endoscopic Approach in Ulcerative Colitis

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1. Introduction

The term inflammatory bowel disease (IBD) is frequently used in the medical literature to define a set of diseases involving the digestive tract, particularly the small and the large intestine. The major IBDs are Crohn's Disease (CD) and ulcerative colitis (UC).

Ulcerative colitis is a chronic inflammatory disease characterized by diffuse mucosal inflammation limited to the colon. UC affects 500,000 individuals in the United States with an incidence of 12 per 100,000 per year. The lifetime risk of a severe exacerbation of UC requiring hospitalization is 15%. Patients with extensive disease (macroscopic disease proximal to the splenic flexure) are more likely to develop acute severe colitis. Approximately 4% to 9% of UC patients will require colectomy within the first year of diagnosis; the risk of colectomy following that is 1% per year. The vast majority of UC patients will require medical therapy throughout their lifetime.

Ulcerative colitis, usually, involves the rectum at presentation and may extend proximally in a symmetrical, circumferential, and continuous pattern to involve parts or all of the large intestine. The disease course of UC is characterized by exacerbations and remissions, which may occur spontaneously or in response to treatment changes, superimposed infection. The diagnosis of inflammatory bowel disease is based on clinical history in combination with the results of various tests, once a single pathognomonic test allowing for a diagnostic definition is not available. Hence, the following can be cited: radiology, laboratory and hematological tests, and endoscopy combined with histology in particular.[1-3]

With this respect, endoscopy has revolutionized the management of patients with IBD by increasingly enabling the identification and study of lesions. Some more recent advances in endoscopic techniques can be cited, such as double-balloon enteroscopy and the capsule endoscopy, which allow for evaluating areas of the small intestine that have not been thoroughly studied to this date, in addition to digital chromoendoscopy.

Improvement in IBD diagnostic capacity has direct implications in the diagnosis and follow-up of patients that have or are suspected to have IBD as well as in better understanding their pathogenesis, which consequently influences treatment.

Great changes have occurred in IBD treatment and management in the last few decades due to the introduction of biological agents in its therapeutic arsenal. Biological therapy, represented by its major drugs – anti-TNF antibodies – has rapidly become the top of a mountain whose base is represented by other drugs that have been used in the treatment of inflammatory bowel disease for several decades.

These new drugs directly interfere with the individual's immune response by decreasing the activation of T cells and inducing apoptosis of defense cells, thus controlling this complex mechanism which is still not fully known and triggers diseases such as ulcerative colitis and Crohn's Disease.

Some time ago, it was believed that the most important objective in treatment would be the patient's clinical remission, normally based on symptom and sign scores, in CD (CDAI – Crohn's disease activity index < 150 points), and in UC (Mayo Score < 5 points). However, after the advent of biological therapy, which induces healing of the inflamed intestinal mucosa, such objectives have changed, that is, in addition to seeking sustained clinical remission, mucosal healing should also be sought.

Due to these characteristics and to the fact that such healing can be maintained for long periods, it is believed that the development and prognosis of IBD will also change.

As previously pointed out, mucosal healing is one of the objectives of clinical trials and of daily clinical practice. For this reason, endoscopy, and colonoscopy in particular, assumes a major role in these patients' follow-up by enabling the direct visualization of the mucosa as well as the removal of fragments for histological analysis.

2. Indications

The diagnosis of UC can be suggested initially by sigmoidoscopy in great number of cases during first attack of UC, fewest biopsies usually are sufficient to confirm the diagnosis and indicate the initial therapy. In patients with diarrhea, mucus, active and flares, this exam can be performed in unprepared bowel so the earliest signs of UC can be detected; other reason to do the sigmoidoscopy without bowel prep is to decrease the hyperemia that is often present after enemas.

In this active fase, colonoscopy is not recommended for fear of perforation and the risk of cause great distention in colon. Only after this acute and active fase the colonoscopy can be performed to establish the extent of the disease and to exclude other disease and Crohn's disease.

The initial aim points in colonoscopy are to evaluate both the extension and intensity of UC. In a second moment, to evaluate the response to the treatment. Thus, the colonoscopy is useful to make the diagnosis, to follow the evolution and response and finally prevent colorectal cancer (displasia).

The most recent studies confirm that the mucosal healing is the end point of treatment, so the indications of colonoscopy do not resume in diagnostic only. In TABLE 1, are the most important indications of colonoscopy in UC.

Acute	Sub acute	chronic
Diagnosis	Extension	Treatment response
Biopsy	Intensity	Displasia surveillance
Differential diagnosis	Biopsy	Cancer surveillance
	Treatment response	

Table 1. Indications of colonoscopy in ulcerative colitis

3. Bowel preparation

Correct diagnostic of colonoscopy depends on the quality of the colonic preparation or cleansing. The ideal preparation should reliably empty the colon of fecal material in a rapid fashion and do not cause histological alteration or gross of the rectal and colonic mucosa.
For patients, the preparation should not cause discomfort and shifts in electrolytes and fluids; those are the ideal bowel preparation, unfortunately none of the preparations available meet them.
Recently, the American Society of Colon and Rectal Surgeons (ASCRS), the American Society for Gastrointestinal Endoscopy (ASGE), and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) made a document: "A Consensus Document on Bowel Preparation Before Colonoscopy". [4] Based on this document the recommendations are (grade of recommendation supported by evidence-based medicine):

1. Diet- Dietary modifications, such as a clear liquid diet, alone are inadequate for colonoscopy. However, they have proven to be a beneficial adjunct to other mechanical cleansing methods (Grade IIB).
2. Enemas - Use enemas in patients who present to endoscopy with a poor distal colon preparation and in patients with a defunctionalized distal colon.
3. High-Volume Gut Lavage - Neither high-volume nor unbalanced solutions, such as mannitol, should be used for colonic preparation (Grade IA). In addition, caution should be exercised when using nasogastric tubes for the administration of any bowel preparation infusion (Grade VD).
4. Rectal Pulsed Irrigation - administered immediately before the procedure combined with magnesium citrate given the evening before the procedure is a reasonable alternative to full-volume (4-liters) PEG in those individuals who cannot tolerate per oral administration of PEG (Grade IIB).
5. PEG - Faster, more effective, and better-tolerated method for cleansing the colon than a restricted diet combined with cathartics, high-volume gut lavage, or mannitol/NaP (Grade IA). PEG is safer than osmotic laxatives/NaP for patients with electrolyte or fluid imbalances, such as renal or liver insufficiency, congestive heart failure, or liver failure and is, therefore, preferable in these patient groups (Grade IA). Divided-dose PEG regimens (2–3 liters given the night before the colonoscopy and 1–2 liters on the morning of procedure) are acceptable alternative regimens that enhance patient tolerance (Grade IIB). Cleansing preparations for colonoscopies performed in the afternoon should instruct that at least part of the PEG solution be given the morning before the procedure (Grade IIB). Enemas, bisacodyl, and metaclopramide as adjuncts to the full volume of PEG have not been demonstrated to improve colonic cleansing or patient tolerance and are, therefore, unnecessary (Grade IIB).
6. NaP - Aqueous NaP colonic preparation is an equal alternative to PEG solutions except for pediatric and elderly patients, patients with bowel obstruction, and other structural intestinal disorders, gut dysmotility, renal or failure, congestive heart failure, or liver failure (Grade IA). Dosing of aqueous NaP should be 45 ml in divided doses, 10 to 12 hours apart with one of the doses taken on the morning of the procedure (Grade IIB). Aqueous NaP is the preferable form of NaP at this time (Grade IIB). Apart from anecdotal reports, the addition of adjuncts to the standard NaP regimen has not demonstrated any dramatic effect on colonic cleansing preparation. Carbohydrate-electrolyte solutions such as E-Lyte\ may improve safety and tolerability.

In those patients with possible underlying IBD, NaP preparations may cause mucosal abnormalities that mimic Crohn's disease [5-7]. However, the frequency of this problem is rare and may not mitigate against using NaP. This caveat is most important in the initial colonoscopic evaluation of patients with symptoms suspect for colitis.
We may conclued that bowel preparation is safe for patients with UC and must be avoid in acute phases.

4. Macroscopic characteristics of ulcerative colitis

The macroscopic characteristic of UC is symmetrical and continuous inflammation, which begins in the rectum and extends proximally without interruption during the whole extension of the disease. When present, this aspect is easily made visible by colonoscopy.
The figure 1 shows the initial endoscopic signs of UC:

1. Reduction or loss of normal vascular patterns.
2. Loss or distortion of vascular markings and relief, and, many times, this aspect may be the only endoscopic alteration in patients with UC in its quiescent phase
3. Mucosal erythema and edema

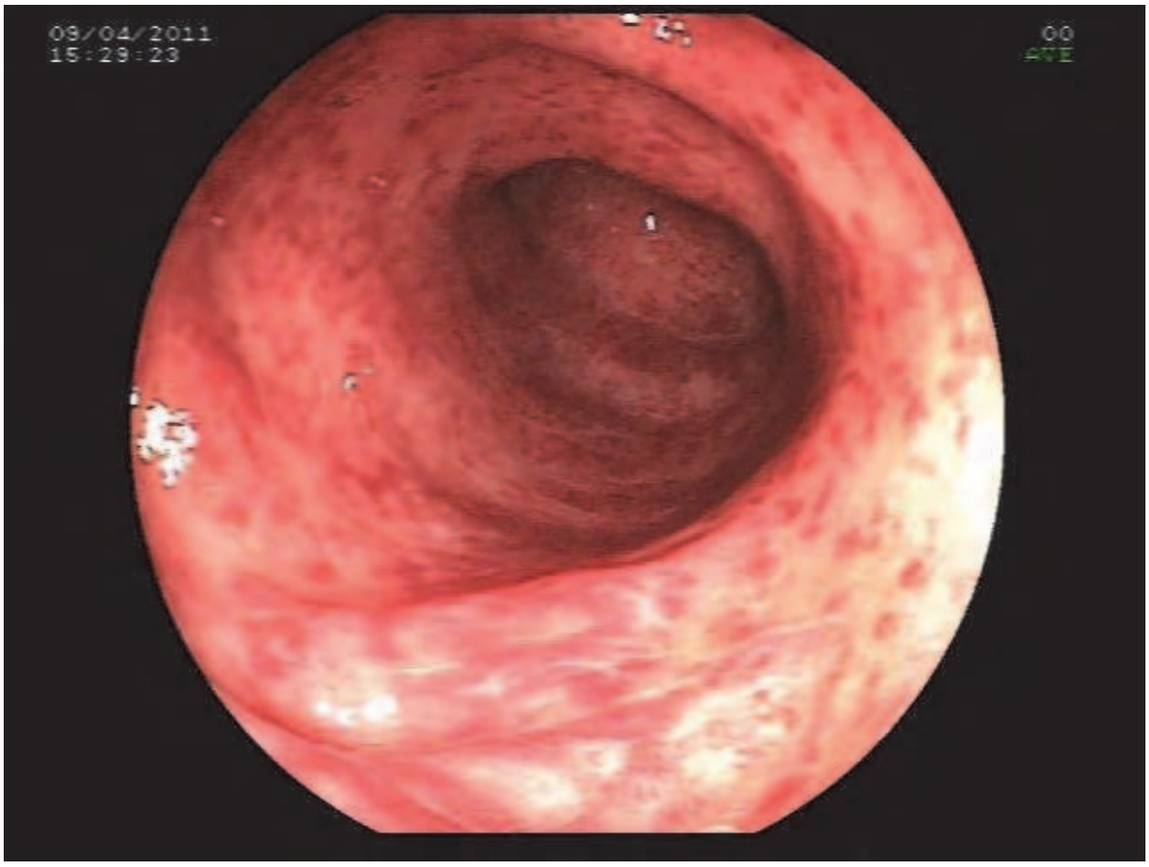

Fig. 1. Mucosal friability, loss of vascular pattern, eythema and edema

As the disease progresses, the mucosal pattern changes, becomes extremely friable, and shows a granular aspect. The disease, then, enters the most severe phase, when the mucosa

is covered with yellowish and sometimes mucopurulent exudate, with intense ulceration of the adjacent mucosa. (FIGURE 2) Such exulceration and ulceration pattern is mainly characterized by a serpiginous, linear, dotted or annular aspect, or even an association of such aspects. As to size, they may vary from millimeters to centimeters, and may, at times, be deep, depending on the phase and inflammation intensity.

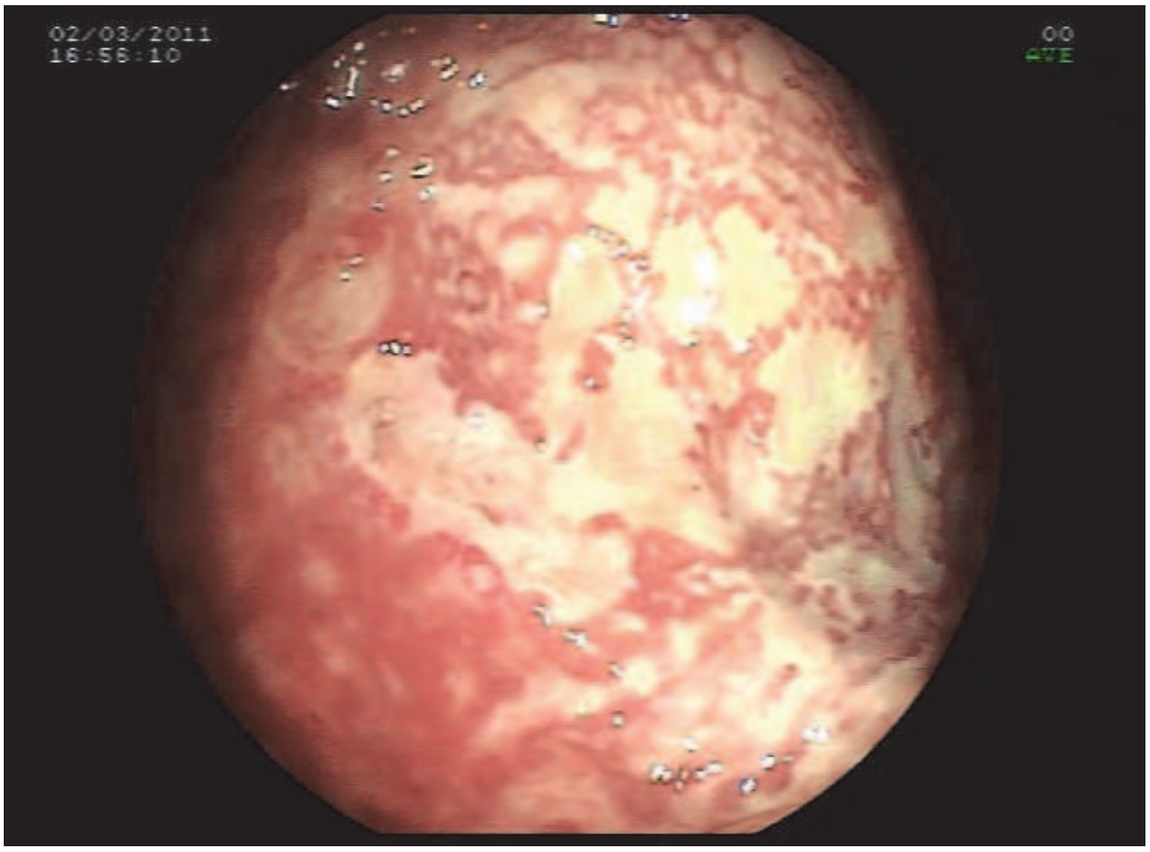

Fig. 2. Colonic mucosa with intense ulceration covered with yellowish and mucopurulent exudates

In the active and acute phase of the disease, a simple touch to these lesions by the instrument may cause bleeding due to mucosal friability. Another important aspect is that when such edema is intense and diffuse, it may lead to lumen narrowing. The differential diagnosis is made by adenomatous polyps, which can only be differentiated under microscopy. Another important differential diagnosis is made by CD. Crohn´s colitis endoscopic features includes: skip lesions(pathchy inflammation adjacent to normal mucosa), rectal sparing, aphtous ulcerations and cobblestone appearance of the mucosa due to the presence of deep linear ulcers.

The inflammation/cicatrization process may lead to the onset of pseudopolyp images, which, in reality, are healthy mucosal areas amidst areas of an intense inflammatory process. (FIGURE 3) They can be characterized by endoscopy with small, bright and soft lesions that may develop to large pedunculated or sessile lesions. Also, they may be detected both in the acute and chronic phases of the disease and are largely suggestive of UC, showing the appearance of cobble-like shapes both by colonoscopy and opaque enema.

Other endoscopic aspects that can be made visible in patients with a chronic form of the disease are:

1. Loss of normal haustration patterns
2. Loss of normal colon architecture, with muscle hypertrophy
3. Colon shortening
4. Luminal diameter reduction
5. Stenosis. In this case, the differential diagnosis is made from cancer.

With this regard, some UC endoscopic activity scales have been developed with the purpose to classify and quantify such inflammatory activity in the colonic mucosa. The scale proposed and used by the Mayo Clinic is noteworthy.

Stool frequency
0 = Normal
1 = 1-2 stools/day more than normal
2 = 3-4 stools/day more than normal
3 = >4 stools/day more than normal
Rectal bleeding*
0 = None
1 = Visible blood with stool less than half the time
2 = Visible blood with stool half of the time or more
3 = Passing blood alone
Mucosal appearance at endoscopy†
0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern, mild friability
2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)
Physician rating of disease activity
0 = Normal
1 = Mild
2 = Moderate
3 = Severe

*A score of 3 for bleeding required patients to have at least 50% of bowel motions accompanied by visible blood and at least one bowel motion with blood alone.
†The mucosal appearance at endoscopy is not included in the Partial Mayo Score.

Table 2. Mayo score for ulcerative colitis *

* from: Cima RR, Pemberton JH. Medical and surgical management of chronic ulcerative colitis. Arch Surg. 2005;140(3):300-10

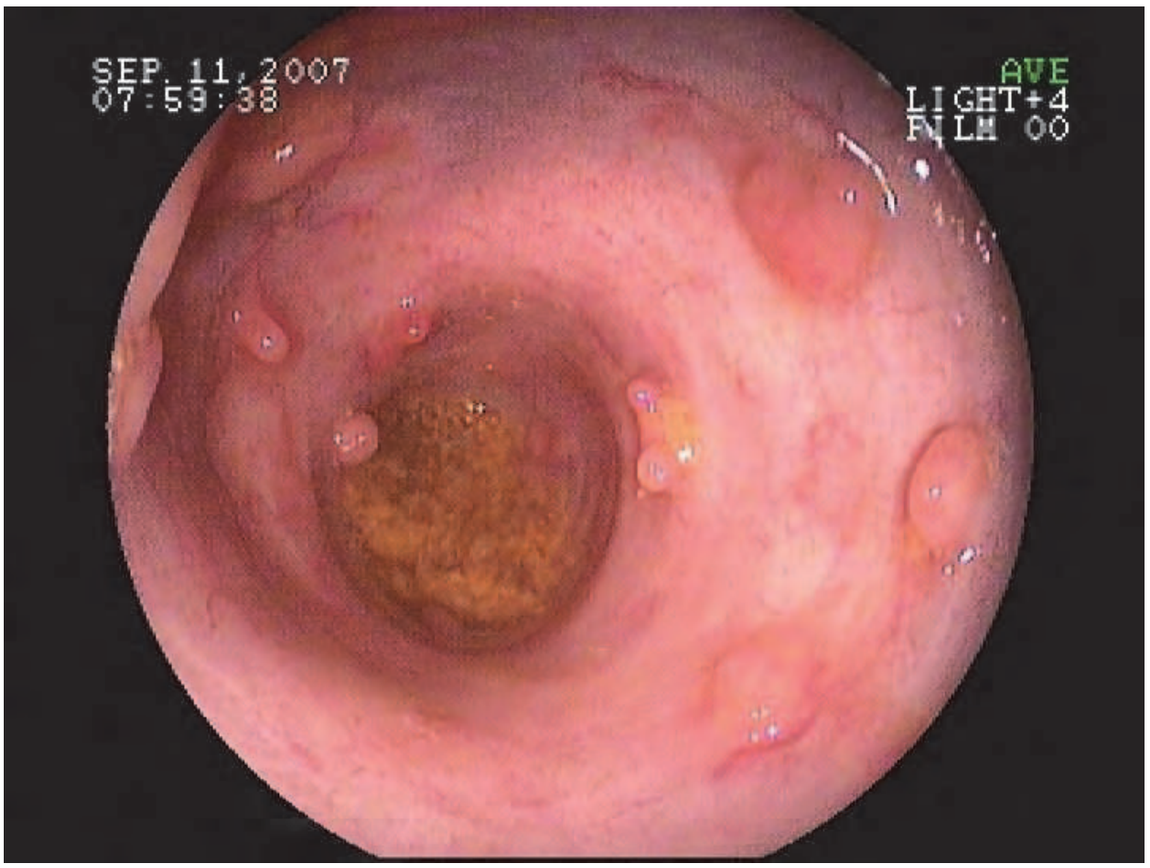

Fig. 3. Pseudopolyps and colonic mucosal healing after infliximab treatment

5. Histology

The histological analysis of biopsy has the following aims: confirm the UC diagnosis, graduate the inflammatory response and third, confirm the presence of displasia or cancer.
An early and accurate diagnosis is necessary. It is important to distinguish between IBD and acute self-limited colitis and a differential diagnosis between UC and CD. The histopathological diagnosis of UC should, therefore, be based on discriminating histological features which are sufficiently reproducible and suitable in routinely processed biopsy specimens.
In cases where the clinical picture is unclear, the histomorphologic analysis often plays a pivotal role in determining the diagnosis and thus the management. By contrast, a biopsy analysis may be indeterminate, and thus the clinical progression of the disease must inform its treatment.
Great changes have occurred in IBD treatment and management in the last few decades due to the introduction of biological agents in its therapeutic arsenal. Thus, mucosal healing is one of the objectives of clinical trials and of daily clinical practice. FIGURE 3 For this reason, colonoscopy assumes a major role in these patients' follow-up by enabling the direct visualization of the mucosa as well as the removal of fragments for histological analysis.[11-19]

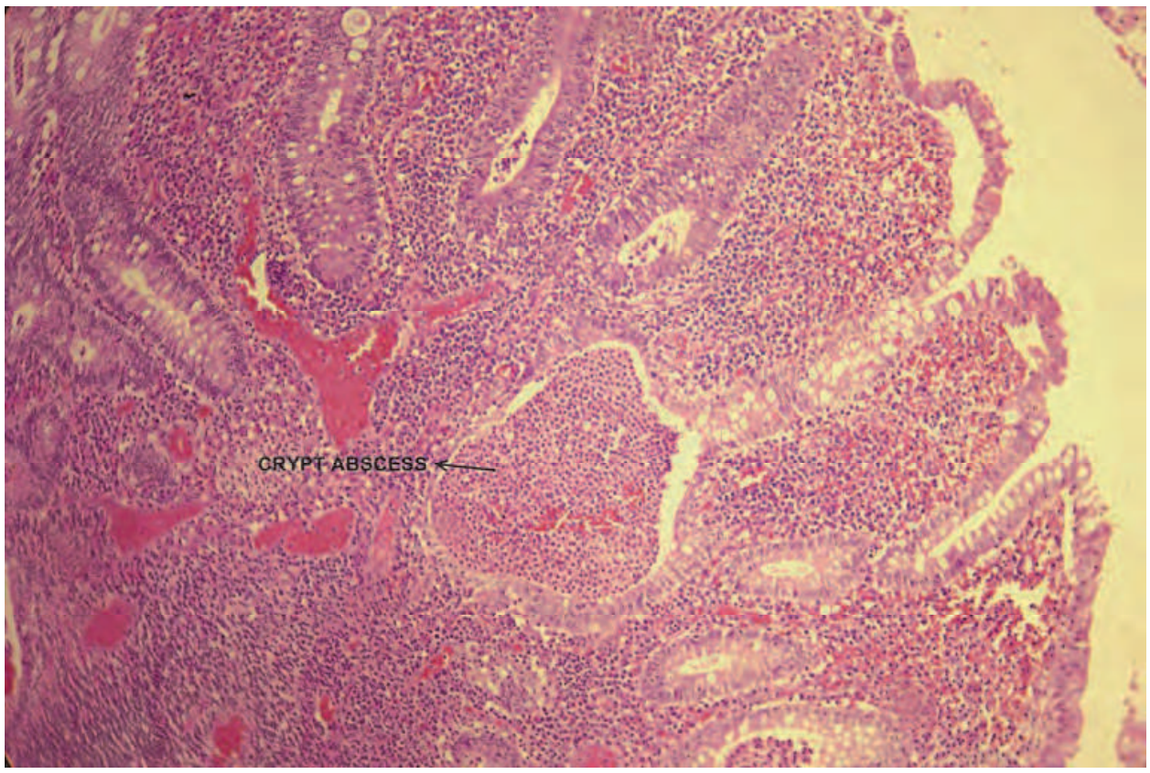

Fig. 4. Photomicrography of a colectomy specimen (pancolitis): we observe distortion of crypt architecture, inflammation of crypts (cryptitis) and crypt abcess (arrow) Courtesy of Prof. Dr. Marcus M. Matsushita, professor of the Pathology Department of the Hospital Universitário - ABHU, Medical School of the University of Marilia, São Paulo, Brazil. www.unimar.br

6. Dysplasia and Colorectal Cancer (CRC) surveillance

Dysplasia is considered the best marker of cancer risk in UC. The clinical management depends on the endoscopic and histological identification of dysplasia in mucosal biopsy specimens of the colon by pathologists with particular expertise in gastrointestinal disorders. The dysplasia can be divided in two groups: low-grade dysplasia (LGD) and high-grade dysplasia (HGD), not all patients with LGD will progress through detectable HGD. Patients with HGD have higher risk of progression to colorectal cancer.[19]

Rubin and colleagues in Seattle showed that among a group of colectomy specimens obtained from UC patients, 33 biopsies per examination was the number of nontargeted biopsies required to exclude dysplasia with 90% confidence. [19] It has being reported that 80% to 90% of UC patients with cancer have dysplasia when analyzed the colectomy specimen. However, colorectal cancer can develop in patients without a prior history of dysplasia. [14-15,19]

In a meta-analysis with 116 published studies, Eaden and colleagues found that the overall prevalence of CRC in any patient with UC is 3.7% which increases to 5.4% for those with pancolitis. [18] The cumulative risk for CRC of any patient with UC is 2% at 10

years, 8% at 20 years, and 18% at 30 years. Increasing duration of disease is as one of the most important risk factors for the development of cancer in UC, which is significant after 9 years of disease and increases in subsequent years.[13-19] The extension of the disease is also a risk factor for cancer. Most cancers arise in patients when the whole colon is affected (pancolitis). Patients with UC beyond the distal sigmoid and rectum are at increase risk of CRC and risk is intermediate in patients with left-sided disease and lower in patients with proctitis.[14-19]

Recently, we have published the Brazilian consensus for management of IBD. Supported by evidence-based medicine, we recommend that the screening should be performed using colonoscopy every 3 years in the 2nd decade, every 2 years in the 3rd decade and yearly in the 4th decade of illness together with 4-quadrant biopsies of non-inflamed mucosal at every 10 cm of colon, in the whole colon in association with biopsies of suspected areas. [14]

7. Chromoendoscopy

Because of the limitations of what could be seen with traditional colonoscopies emitting white light, adjunct techniques have been investigated in colitis and sporadic polyp surveillance practices that have the potential to enable endoscopists to better visualize the colorectal mucosa. It has being demonstrated a higher diagnostic accuracy for dysplasia diagnosis in biopsies targeted by chromoendoscopy when compared to biopsies obtained with standard colonoscopy.[17] Chromo colonoscopy with biopsy of suspected area is a valid alternative to multiple biopsies.[14] There are a stronger correlation between the endoscopic assessment of colonic inflammation and histopathologic findings. In this scenario, chromoendoscopy allow for the differentiation between nonneoplastic and neoplastic lesions with a sensitivity and specificity of 93%.

It became apparent that adding an adjunct technique would enable us to identify more patients with dysplasia. Unfortunately, however, there are no longitudinal data showing that chromoendoscopy actually lessens either the incidence of dysplasia on follow-up colonoscopy or cancer-related morbidity or mortality. On the other hand, once this technique are inexpensive, safe, and relatively easy to perform, it should be have an important role in surveillance of dysplasia and cancer in UC patients.

8. Narrow Band Imaging (NBI)

Narrow band imaging (NBI) and Multi-Band Imaging (MBI)* are real-time, on-demand endoscopic imaging techniques designed to enhance visualization of the vascular network and surface texture of the mucosa in an effort to improve tissue characterization, differentiation, and diagnosis. [17] NBI and MBI were developed to be an alternative to chromoendoscopy. The techniques may allow contrast enhancement of tissue surface structures helping in the endoscopic diagnosis. In contrast, neither NBI nor MBI have being studied extensively as chromoendoscopy.[17]

It has being reported in the literature that, in ulcerative colitis, the role of NBI is not as promising as observed in other scenarios. [8-10] On the other hand, in an uncontrolled study consisting of 46 patients with ulcerative colitis, the relative frequency of dysplasia was higher in areas of tortuous pattern (8%) than in those of honeycomb-like or villous pattern (0.4%), as seen under NBI with magnification. The tortuous pattern determined by NBI may be a clue for the identification of dysplasia during surveillance of UC. [9,16]

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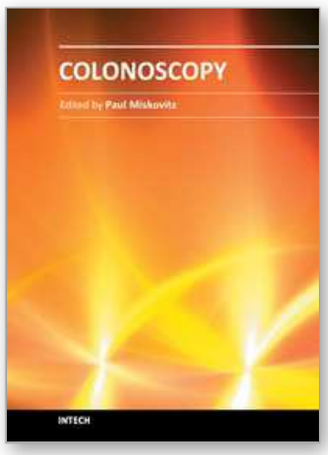

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To publish a book on colonoscopy suitable for an international medical audience, drawing upon the expertise and talents of many outstanding world-wide clinicians, is a daunting task. New developments in videocolonoscope instruments, procedural technique, patient selection and preparation, and moderate sedation and monitoring are being made and reported daily in both the medical and the lay press. Just as over the last several decades colonoscopy has largely supplanted the use of barium enema x-ray study of the colon, new developments in gastrointestinal imaging such as computerized tomographic colonography and video transmitted capsule study of the colonic lumen and new discoveries in cellular and molecular biology that may facilitate the early detection of colon cancer, colon polyps and other gastrointestinal pathology threaten to relegate the role of screening colonoscopy to the side lines of medical practice. This book draws on the talents of renowned physicians who convey a sense of the history, the present state-of-the art and ongoing confronting issues, and the predicted future of this discipline.

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