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VILLOUS HYPERMUCINOUS APPEARENCE IN LONGSTANDING INFLAMMATORY BOWEL DISEASE: A CASE REPORT AND REVIEW OF LITERATURE

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ABSTRACT
THE CORRECT EXAMINATION, BY AN ANATOMOPATHOLOGIST WITH EXPERTISE IN INFLAMMATORY BOWEL DISEASES, OF BIOPSIES OR RESECTION PIECES IS OF OVERWHELMING IMPORTANCE FOR ESTABLISHING THE DEFINITE DIAGNOSIS, BUT ALSO CONSIDERING MANAGEMENT STRATEGIES AND SUBSEQUENT SURVEILLANCE OF THE PATIENT, GIVEN THE FACT THAT THERE IS A POSSIBILITY OF PROGRESSION OF DYSPASTIC LESIONS TO ADENOCARCINOMA, IN THE LONGSTANDING DISEASE. THE RISK OF COLORECTAL CANCER IS CUMULATIVE, ESPECIALLY IN ULCERATIVE COLITIS, AS THE YEARS PASS, SO BIOPSIES FROM SUSPICIOUS AREA SHOULD BE TAKEN, WHENEVER NEEDED. REGULAR ENDOSCOPIC FOLLOW-UP IS RECCOMENDED BY THE NTERNATIONAL GUIDELINES AND SHOULD BE TAILORED TO EACH INDIVIDUAL, TAKING INTO ACCOUNT THE RISK FACTORS, THE DETECTION OF DYSPALSIA BEING THE MOST IMPORTANT GOAL OF SURVEILLANCE COLONOSCOPY. EARLY IDENTIFICATION OF DYSPLASIA (MACROSCOPICALLY VISIBLE OR NOT) IS THE CORNERSTONE OF REDUCING THE RISK OF COLORECTAL CANCER. IN RECENT YEARS, SEVERAL NEW TYPES OF UNCONVENTIONAL DYSPLASIA HAVE BEEN RECOGNIZED, BUT EXACT MORPHOLOGIC CRITERIA ARE REQUIRED. OF ALL PATTERNS ENCOUNTERED, THE HYPERMUCINOUS DYSPLASIA HAS BEEN THE MOST COMMONLY DETECTED AND DESCRIBED. THE ASSOCIATION WITH CLASSIC DYSPLASIA OR EVEN COLORECTAL CANCER IS STILL NOT ENOUGH STUDIED SO FAR.

KEYWORDS: INFLAMMATORY BOWEL DISEASE, HISTOPATHOLOGY, UNCONVENTIONAL DYSPLASIA, VILLOUS DYSPLASIA

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INTRODUCTION

Conceptually, patients with longstanding inflammatory bowel disease have an increased risk to develop colorectal cancer compared to the general population; most cases derive from dysplastic lesions, so considerable efforts should be made to detect the lesions early in order to minize the risk of progression to cancer and the endoscopic or surgical sanction must be applied as soon as possible. The risk of colorectal cancer seems to be quite similar for both pathologies (ulcerative colitis and Crohn's disease), but studies have shown that it occurs later in Crohn's disease, as opposed to ulcerative colitis[5].

Many of the diagnostic recommendations for dysplasia came from old observations in the literature, so in 2015 the Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients International Consensus (SCENIC) was developed and published, which aims to establish which is the optimal endoscopic method for detecting dysplastic lesions and which is their favorable management.

The optimal method for detecting this kind of lesions in inflammatory bowel disease has long been debated. Taken into consideration that most of the lesions are macroscopically visible, it is recommended to use high-definition equipment to increase the chance of finding the lesions and if the medical institution does not have such a device, it would be advisable to use chromoendoscopy; this means spraying methylene blue or indigo carmin through a cateter, to accentuate the changes on the colonic surface[6]. This maneuver, unlike colonoscopy with white light, increases the duration of the investigation with 9-12 minutes. Although this method increases the rate of dysplasia detection, it is not clear whether the additionally detected lesions have the same risk of developing colorectal cancer.

One communication at United European Gastroenterology Week in 2015 showed the results of a randomized three arm comparison of high definition alone with high definition dye spraying and electronic virtual chromoendoscopy using ISCAN for detection of colonic dysplastic lesions during IBD surveillance colonoscopy; they included 155 patients with inactive disease randomized 1:1:1 ratio into the tree arms and used a high-resolution colonoscope (Pentax, Japan) and detected lesions of dysplasia , sessile serrated-adenomas, adenoma-like popyps, hyperplastic polyps and inflammatory polyps and the final results of the study were that high-definition colonoscopy had the best detection rate for adenomas, but they could not demonstrate the advantage of chromoendoscopy in revealing dysplastic lesions compared to the other two methods used[7].

Once potential dysplastic lesions are found, their most complete endoscopic description is required. It is not known for sure whether polypoid or nonpolypoid lesions have the same risk of malignancy, although molecular biology studies show that nonpolypoid cancers differ from polypoid ones, showing less KRAS and APC mutations and more BRAF mutations[8].

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[5] Gillen CD et al. Ulcerative colitis and Crohn's disease: a comparison of the colorectal cancer risk in extensive colitis. Gut. 1994

[6] Soetikno R et al. The detection of nonpolypoid (flat and depressed) colorectal neoplasm in patients with inflammatory bowel disease. Gastroenterology 2013

[7] Marrietta Iacucci et al. A randomized three arm comparison of high definition alone with high definition dye spraying and electronic virtual chromoendoscopy using ISCAN for detection of colonic dysplastic lesions during IBD surveillance colonoscopy; UEG 2015

[8] Voorham QJ et al. Tracking the molecular features of nonpolypoid colorectal neoplasms: a systematic review and meta-analysis. Am J Gastroenterol 2013

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Among the risk factors incriminated in the occurrence of colorectal cancers we mention: onset at a very early or advanced age, hereditary history of colorectal cancer, pseudopolpyposis, primary sclerosing cholangitis, male sex[9].

One of the most important questions is ‘‘what is the role of histology in patient management, including searching for dysplasia’’?

The first biopsies taken, when you suspect an inflammatory bowel disease are very important because histological features and pattern of disease will be influenced as the time passes, by the drug therapy, so accurate histopathological assesment might help for the management of the inflammatory bowel disease. A study by Dejaco showed that the accuracy of diagnosing colitis increases from 66% to 92% when segmental biopsies are taken rather than two biopsies throughout the colon[10].

Regarding surveillance, on the other hand, the American Gastroenterological Association guidelines published in 2010 recommend obtaining at least 32 random biopsy specimens from all segments of the colon[11].

Dysplasia is a marker of malignancy and 4 morphological categories have been described: negative, indefinite and positive for low-grade and high-grade. Dysplasia related to IBD develops only in areas with chronic inflammation, may occur in any part of the colon and it may be multifocal[12]. The histopathologic features are similar to those characterising neoplastic lesions in general.

Colitis-associated dysplasia consists of flat (the macrosocpic appearance may be unremarkable and carry a higher risk of colorectal cancer) and elevated lesions and we should always take biopsies from the lesion and also from the surrounding mucosa for accurate diagnosis and treatment decision. There are studies that show that distal low-grade dysplasia progresses more rapidly to cancer than proximal low-grade dysplasia[13].

Reffering to Crohn’s disease, colonoscopy with biopsy may similarly be used in such patients depending on the extent of colon involvement, knowing that this is a risk factor for colorectal development and if the small bowel is incriminated, the most common location of the neoplastic lesions is the distal jejunum/ ileon[14].

In some cases, dysplasia associated with inflammatoy bowel disease may reveal low-grade cytologic features or atypical features limited to the crypt bases, without surface involvement. So, neoplasia may show villi composed of elongated, predominately mucinous (‘‘hypermucinous’’) epithelium with many goblet cells, either with or without cytologic atypia. In cases with atypia, it is typically limited to the bases of the crypts. This neoplastic proliferation was named villous dysplasia or villous hypermucinous mucosa and has been described in both ulcerative colitis and Crohn‘s disease[15]. The villous neoplastic precursor

[9] Velayos FS et al. Predictive and protective factors associated with colorectal cancer in ulcerative colitis: a case-control study. Gastroenterology. 2006
[10] Dejaco C et al. Diagnosing colitis: a prospective study on essential parameters for reaching a diagnosis. Endoscopy 2003
[11] Farraye FA et al. AGA technical review on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. Gastroenterology 2010
[12] Ullman T et al. Diagnosis and management of dysplasia in patientswith ulcerative colitis and Crohn’s disease of the colon. Inflamm Bowel Dis 2009
[13] Goldstone R et al. Progression of low-grade dysplasia in ulcerative colitis: effect of colonic location Gastrointest Endosc 2011
[14] Palascak-Juif V et al. Small bowel adenocarcinoma in patients with Crohn’s disease compared with small bowel adenocarcinoma de novo Inflamm Bowel Dis 2005
[15] Kilgore SP et al. Hyperplastic-like mucosal change in Crohn’s disease: an unusual form of dysplasia? Mod Pathol. 2000

lesions were usually covered by cytologically normal epithelium, but the bases of the crypts, had conventional high-grade dysplasia. In one study, by Andersen et al, villous hypermucinous neoplastic precursor lesions without cytologic atypia were identified from 6 of 13 patients with UC; 61% of the lesions showed KRAS mutations, a frequency that was significantly higher than in areas of conventional low-grade dysplasia. As a consequence, the authors demonstrated the potential for a distinct pathway of carcinogenesis that progresses from a non–cytologically atypical form of precursor neoplasia to cancer. Similar changes were detected in patients with Crohn‘s disease[16].

The subtypes of nonconventional dysplasia include : hypermucinous; goblet cell deficient; terminal epithelial differentiation also known as crypt cell dysplasia; traditional serrated adenoma-like; sessile serrated lesion-like; and serrated lesion, not otherwise specified[17].

MAIN TEXT

Below is the case of a non-smoking, non-consuming ethanol woman, with no significant hereditary history, aged 50-years old, who was diagnosed at the age of 25, in another clinical unit with inflammatory bowel disease (endoscopic evidence supported by histopathological examination) elements of ulcerative colitis (pancolitis). The patient denies allergies and does not present associated pathologies until that time.

The first outbreak was moderate-severe, requiring intravenous corticosteroids and 5 aminosalicilic acids (oral and topical, in the form of enemas). Over the following years, the patient presented three more episodes of moderate exacerbation (1991, 1993, 2002), according to the Mayo classification; all three episodes required hospitalization and administration of corticosteroids, concomitantly with 5 aminosalicilic acids. At the last presentation in the clinic where the initial diagnosis of ulcerative colitis was established, a colonoscopy was performed, which this time describes macroscopic lesions suggestive of colonic Crohn's disease, a diagnosis currently also supported by histopathological examination.

The patient continues the therapy with 5 ASA (4 grams) orally and remains in clinico-biological and endoscopic remission until 2011, when she begins to have inflammatory joint pain in the hip and patellofemoral joints, which is why she addresses to a rheumatologist.

Clinically and radiologically, the diagnosis of axial spondylitis type I HLA B27 negative is established and short courses of nonsteroidal anti-inflammatory drugs and sulfasalazine (2 grams / day) are administered, with a good efficacy. The patient remained in the records of the rheumatologist, given the debilitating potential of such disease.

In September 2014, she presented for the first time in our clinic, without pathological products in the stool, but with diffuse abdominal pain syndrom, flatulence and occasional bloating; denies fever / chills or extra-articular manifestations and her weight remains constant. Biologically, except for a discrete nonspecific inflammatory syndrome, there are no other changes in the parameters.

Upper gastrointestinal endosocopy is performed and it describes aphthous erosions in the duodenum, from which biopsies are taken: a fragment of the duodenal mucosa shows epithelial erosion, slightly modified villous architecture, with focal foveolar metaplasia of the

[16] Kilgore SP et al. Hyperplastic-like mucosal change in Crohn’s disease: an unusual form of dysplasia? Mod Pathol. 2000; Andersen SN et al. Villous, hypermucinous mucosa in long standing ulcerative colitis shows high frequency of K-ras mutations. Gut 1999

[17] Won-Tak choi et al. Nonconventional dysplasia in patients with inflammatory bowel disease and colorectal carcinoma: a multicenter clinicopathologic study. Mod Pathol 2019

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surface epithelium, moderate lymphoid infiltrate of the lamina propria, rich in plasma cells and polymorphonuclears, with hyperplasia of Brunner glands; no granulomas are found. Conclusion - histological aspect compatible with erosive duodenitis. (figure 2)

Also, a colonoscopy is performed which detects a normal appearance of the rectum and at the colonic level (starting from approximately 20 cm from the anal verge) the surface has ulcerations, edema and is bleeding when touched with the endoscope (friability); the lesions are asymmetrical, gentle, on the whole colonic route, alternating with scar areas, being more severe on the right colon, cecum and ileocecal valve; the terminal ileum is intubated and has ulcers and ulcerations suggestive of Crohn's disease. (figure 1)

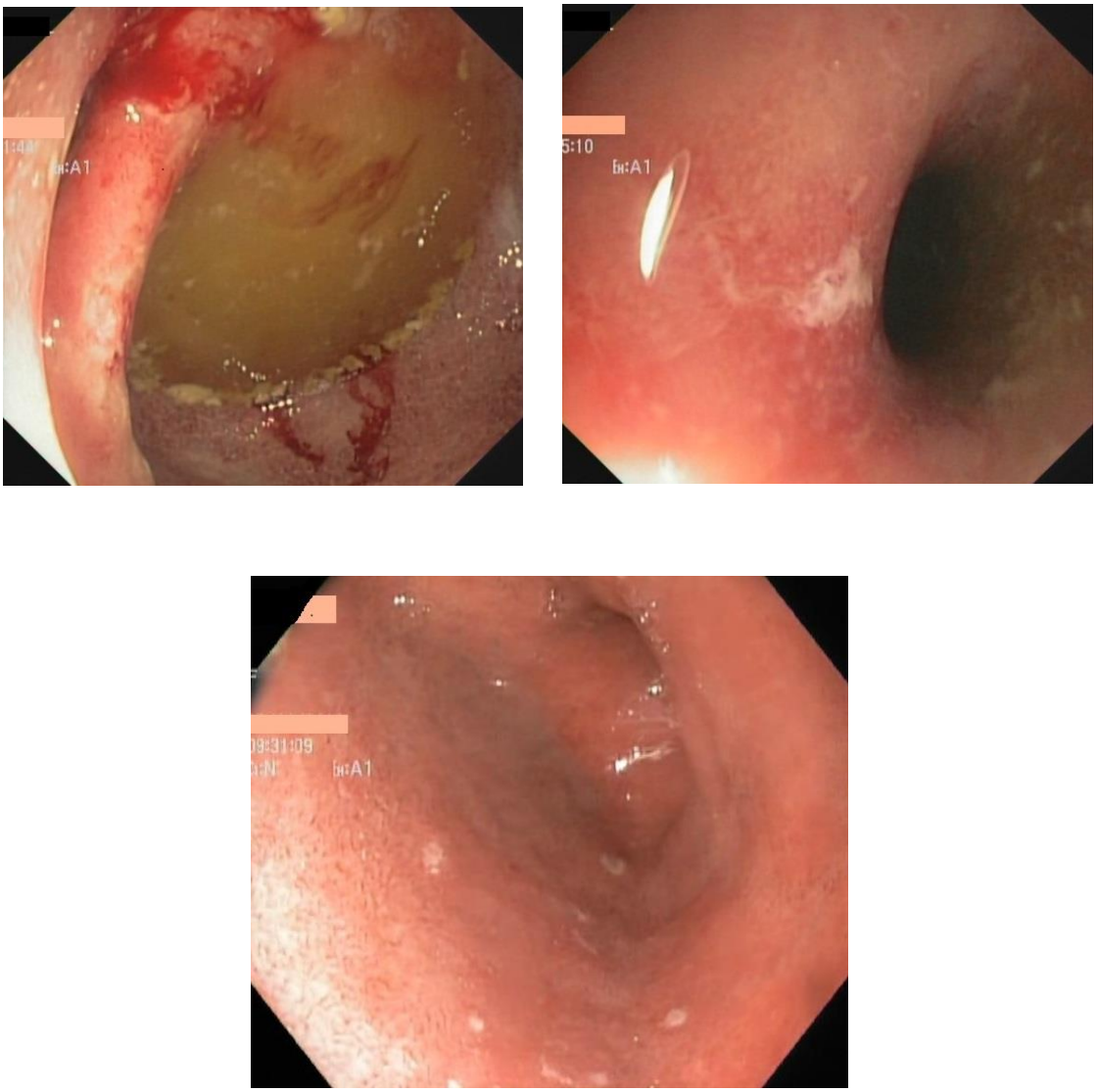

Figure 1

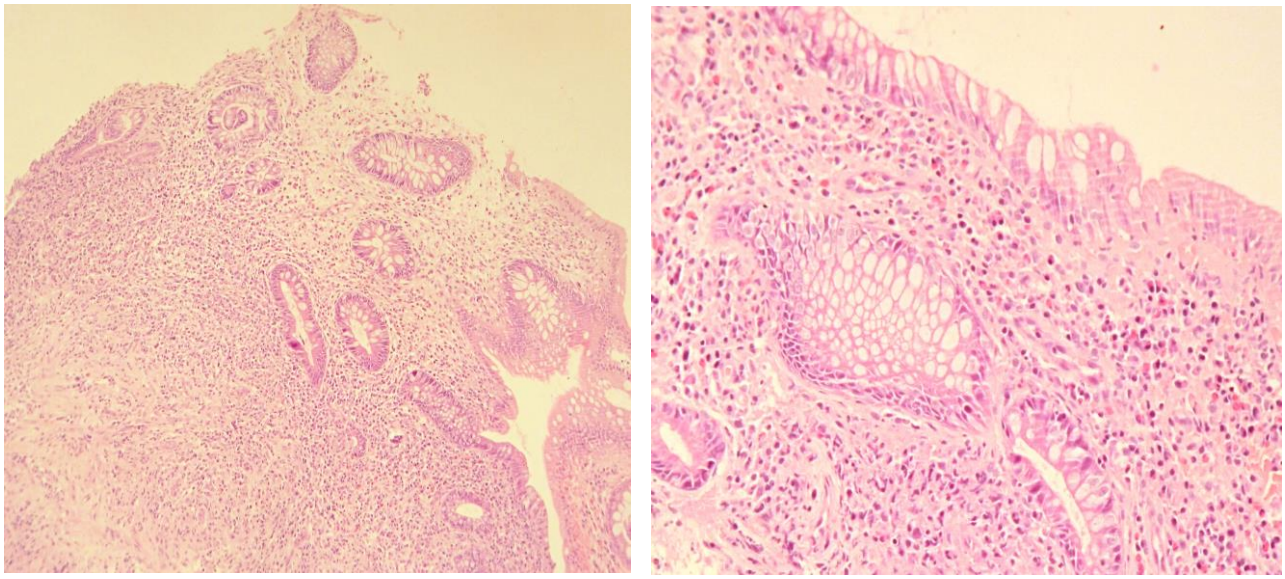

Figure 2

The final conclusion of the anatomopathologist for the lesions in the colon was that there was colonic mucosa with lesions of chronic active colitis, erosive, non-granulomatous, with glandular atrophy and architectural reshaping of the remaining glands.

An MR enterography was performed and it showed asymmetric segmental mural hyperenhancement, with mild wall thickening and intramural edema and focal narrowing of the lumen with upstream bowel dilatation. (figure 3)

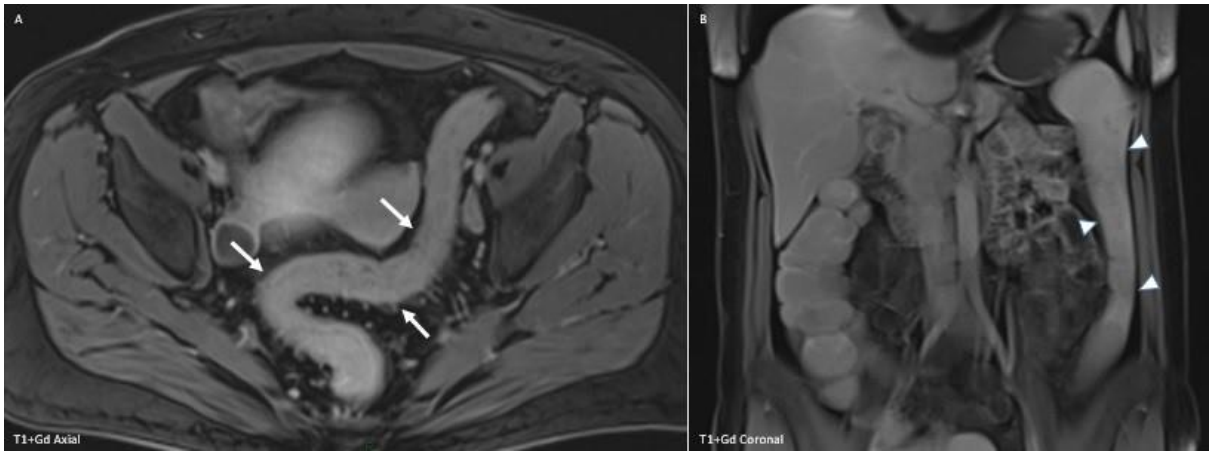

Figure 3

Treatment with Budenofalk 9mg / day is initiated for 10 weeks, followed by a gradual dose decrease over the next period; it is also associated 5 aminosalicilic acid given orally (4 grams / day), an oral proton pump inhibitor and a prebiotic, with favorable evolution.

Azathioprine therapy has also been recommended at the appropriate dose for her body weight, but after the risks of this therapy have been communicated, the patient decides to delay the medication for the time being.

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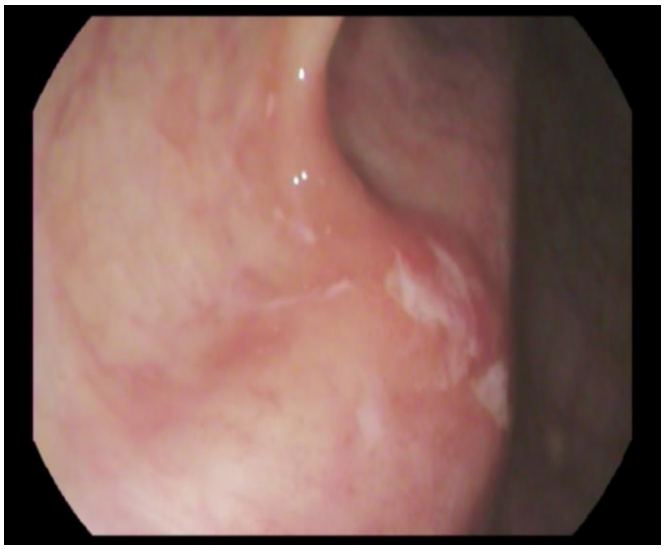
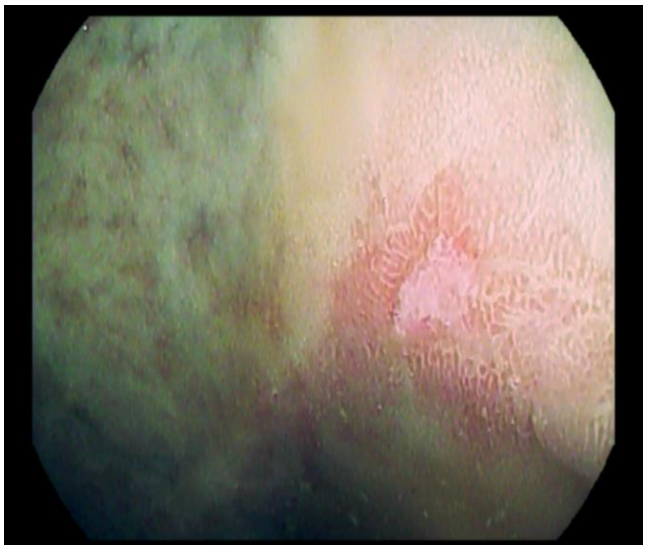
Until August 2018, she remains in the records of the gastroenterologist in the territory, lowering the dose of 5 aminosalicilic acid to 2 grams / day (six months after discharge from our clinic) and continuing to have 2-4 stools / day exclusively daily, without pathological products, but of low consistency; however, this mild coprological syndrome is accompanied by weight loss of approximately 3 kg / 6 weeks and the recurrence of joint manifestations. Laboratory tests reveal only mild inflammatory syndrome and minimal thrombocytosis; hemoglobin is kept within normal limits.

Upper gastrointestinal endoscopy does not describe pathological changes.

It is decided to repeat the colonoscopy that detects the rectum of normal macroscopic appearance, pseudopolyps along the entire colonic trajectory, and from the level of the transverse colon to the cecum ulcers and ulcerations appear on a scarred mucosa, from which biopsies are taken; the terminal ileum has the same appearance of active Crohn's disease. (figure 4)

The result of the colonic biopsies describes 5 medium-sized biopsy fragments showing diffuse architectural changes (shortened, branched glands, some areas with pseudo-villous appearance) and lesions of chronic active colitis, with ulceration areas covered by non-specific granulation tissue; hypercrynia is also described and there is no conventional epithelial dysplasia spotted; Paneth cell hyperplasia is focally present and no granulomas are observed. Conclusions: there is a histological aspect of chronic active colitis, focally with ulcerations covered by nonspecific granulation tissue and a mucous area with villous, hypermucinous appearance. (figure 5)





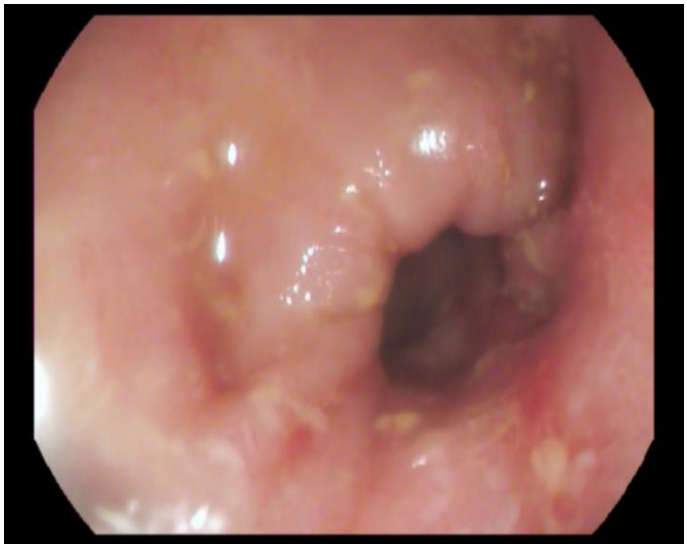
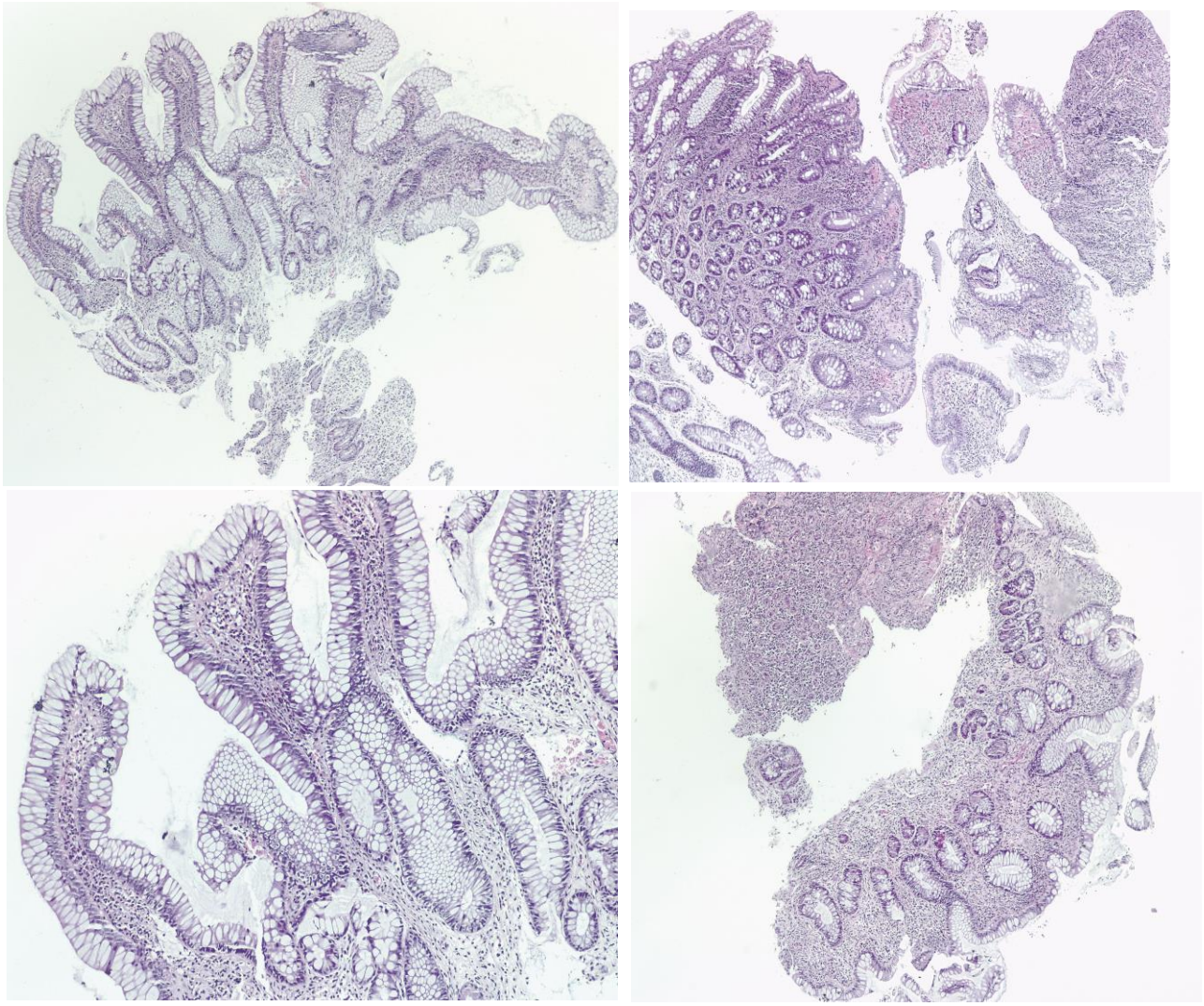


Figure 4



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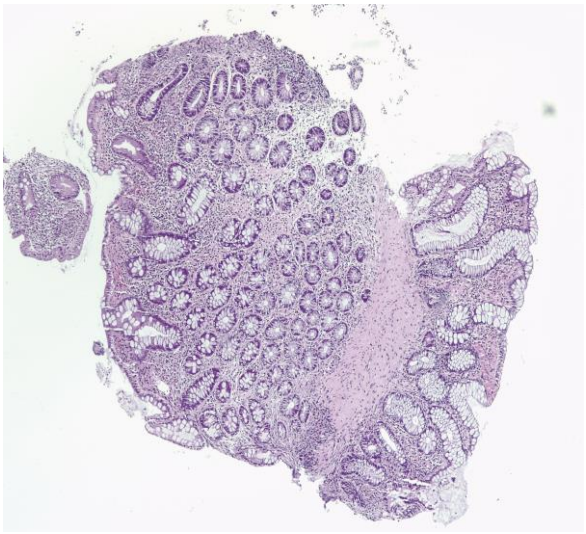

Figure 5

The rectal biopsies describe five medium biopsy fragments, showing preserved glands and mucosecretory epithelium, without associated pathological inflammation and without the presence of granulomas. The conclusions are that the rectal mucosa does not show particular histological changes.

Given these facts and considering the multiple episodes of exacerbation of the disease, the need for corticosteroids, the longstanding disease and the existence of extra-intestinal manifestations, biological therapy option is proposed. We've also talked with the patient the need of careful and accurate endoscopic surveillance, on a regular basis versus the possibility of surgery. For the time being, the patient refuses the surgery and decides to delay the initiation of biological therapy and she wants to be re-evaluated endoscopically and histologically in a clinical unit, nine months after discharge from our clinic.

The results of chromomoendoscopy and biopsies taken and communicated by our colleagues describe changes similar to those described in our clinic, which is why the therapeutic opportunities with the patient are being re-discussed and she chooses for the initiation of biological therapy with Adalimumab, in the classic 40mg dose, subcutaneously every two weeks and endoscopic periodic re-evaluation.

Until now, the patient is in clinico-biological remission, and will be re-evaluated colonoscopically in a short period of time.

CONCLUSION

Conventional dysplasia is one of the most well-known and described forms of dysplasia and includes lesions such as tubular-adenomas, tubulo-villous adenomas and villous-adenomas. In recent years, the term "unconventional dysplasia" has appeared and it comprises lesions with certain morphologic pattern. Among them, hypermucinous dysplasia was the most frequently detected lesion in a multicenter study performed on patients with colorectal neoplasms associated with a long history of inflammatory bowel disease (approximate 17 years) and whose results were published at the end of 2019. These kind of unconventional dysplasia may be associated with intestinal dysplasia as well.

The villous dysplastic lesions characterized by mucin overproduction are most commonly detected in the vicinity of the neoplastic area associated with colitis and due to the fact that they may be associated with carcinoma, there is an indication for proctocolectomy.

Diagnostic precision is increased if multiple features are assessed together and if the clinical details are taken into consideration . Modification of an already established diagnosis of inflammatory bowel disease, should be made if there is strong data for a change, after reviewing anterior histology and clinical features in a multidisciplinary team. Histologically, dysplasia may be laborious to discriminate from epithelial regeneration in the setting of mucosal inflammation or ulceration. The aspects of unconventional dysplasia are not quite familiar to all pathologists and untill now there is limited research on this field . Some of the pathologists, who are not very familiar with these lesions, can consider that they are benign or reactive lesions, so, for complicated cases from a histopathological point of view, the opinion of a second pathologist experienced in inflammatory bowel diseases is imperative. It is very well known the fact that interobserver variability is significant.

Multiple societies support the role of colonoscopy as the standard of care for surveillance and all patients with inflammatory bowel disease that involves at least one-third of the colon should perform a colonoscopy eight years after disease onset.

Even if chromoendoscopy has a clearly established role in the detection of dysplastic lesions, there are some experts who advice against using it, before trials show a clear advantage in daily practice, it’s longstanding profit and before further evidence on chromoendoscopy in contrast to high-definition white light endoscopy is accessible.

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