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Colorectal Cancer and Inflammatory Bowel Disease

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Abstract

Inflammatory bowel disease (IBD) with its two entities, ulcerative colitis and Crohn's disease, is at increased risk of developing colorectal cancer (CRC). Risk factors for CRC are represented by the duration of the disease, extent of disease, the association of primary sclerosing cholangitis, family history, and early age at onset. In inflammatory bowel disease, colonic carcinogenesis appears on an inflamed colon, being determined by different genetic alterations. The main element of the process of carcinogenesis is the dysplasia, which is a neoplastic intraepithelial transformation, limited to the basal membrane surrounding the glands around which it appears. The stages of carcinogenesis process start with dysplasia of varying degrees as follows: indefinite dysplasia, low-grade dysplasia, high-grade dysplasia, and finally invasive adenocarcinoma.

Endoscopic surveillance in IBD is absolutely necessary for early detection of dysplastic lesions. The endoscopic surveillance process begins after 7–10 years of disease progression, performed every 1 or 2 years, depending on the severity of the disease.

General principles of endoscopic surveillance involve the use of modern diagnostic methods (high definition, chromoendoscopy, indigo carmine with high definition, high-definition narrow band imaging).

The current standard-of-care (colonoscopy plus randomized biopsies) to detect dysplasia in IBD patients is inadequate. Guidelines now support to use of chromoendoscopy with targeted biopsy in the detection of dysplasia and/or colorectal cancer in patients with IBD.

Chemopreventive drugs involve the administration of therapeutic agents such as 5-ASA derivatives, ursodeoxycholic acid and folic acid, and possibly statins.

As for future goals, understanding the mechanisms of colonic carcinogenesis in IBD can identify patients at high risk for developing CRC and thus chemoprevention can be

initiated. The discovery of new therapeutic agents plays an important role in chemo-prevention and represents a significant desideratum among researchers.

Keywords: colorectal cancer, inflammatory bowel disease, carcinogenesis, colono-scopic surveillance, chromoendoscopy, high-definition narrow band imaging

1. Introduction

Inflammatory bowel diseases with its two separate entities (ulcerative colitis and Crohn's disease) are conditions considered at high risk for developing colorectal cancer. Because inflammatory bowel diseases are relatively rare in the general population, only about 1% of colorectal cancers are attributed to them. Meta-analyzes showed that the risk is 2% at 10 years, 8% at 20 years, and 18% at 30 years after onset [1]. Absolute cumulative frequencies of colorectal cancer to Crohn's disease and ulcerative colitis are almost identical 7% for the first to 8% for the second, after 20 years of evolution [2]. Most knowledge about the pathogenesis of colorectal cancer come from studies on sporadic cancers or those associated with in-creased risk of hereditary disease (familial adenomatous polyposis or non-polyposis colorec-tal cancer), this data being then extrapolated for inflammatory bowel diseases.

Eaden et al. [3] reviewed 116 studies involving 55,000 patients with ulcerative colitis. One thousand seven hundred of these patients developed colorectal cancer, having an incidence of 2% after 10 years of evolution, and of 8% after 20 years finally increasing to 18% after 30 years.

2. Risk factors for colorectal cancer in inflammatory bowel disease

In ulcerative colitis, onset of colorectal cancer is correlated with many factors. Thus, the duration of the disease is recognized as one of the leading risk factors for developing colorectal cancer in ulcerative colitis. Neoplastic risk occurs after 8 years of evolution and increases exponentially after 20 years [1].

A systematic colonoscopy surveillance can detect early dysplastic lesions, and the systematic use of 5-ASA therapy can lower the risk of developing colorectal cancer in patients with IBD. The reduced incidence of prophylactic colectomy for dysplastic lesions determines a high risk for colorectal cancer. This information is an argument for preventive colonoscopy surveillance of patients with IBD and surgical prophylaxis in case of dysplasia [4, 5].

Younger age at onset is in the opinion of some authors, an independent risk factor for colorectal cancer. Younger patients have a potentially greater lifespan and therefore higher risks, which may reflect the longer duration of the disease [1, 4–6]. The association of PSC increases the risk of colorectal cancer. Its incidence in patients with ulcerative colitis is 2–5% [1]. In 1992, Broome et al. reported an increased risk of colorectal cancer in patients with ulcerative colitis associ-

ating PSC. Subsequent studies have shown that the cumulative risk of colorectal cancer is higher in patients with combination of cholangitis and ulcerative colitis compared with the ones only known for ulcerative colitis, that is, 9% after 10 years compared to 2, 31% after 20 years compared to 5, and 50% after 25 years to 10% [7].

The extent of the disease is also an important risk factor for the risk of developing colorectal cancer. Pancolitis presents the highest risk of malignancy [1]. The extension of inflammatory areas is an independent risk factor involved in the carcinogenesis and Crohn's disease.

A family history of colon cancer cancer is associated with an increased risk of colorectal −2 or 3 times higher, in the general population, which remains increased in patients with ulcerative colitis. A case–control study conducted on 297 patients at the Mayo Clinic found that a family history of sporadic colorectal cancer represents an independent risk factor for malignancy in patients with ulcerative colitis [7].
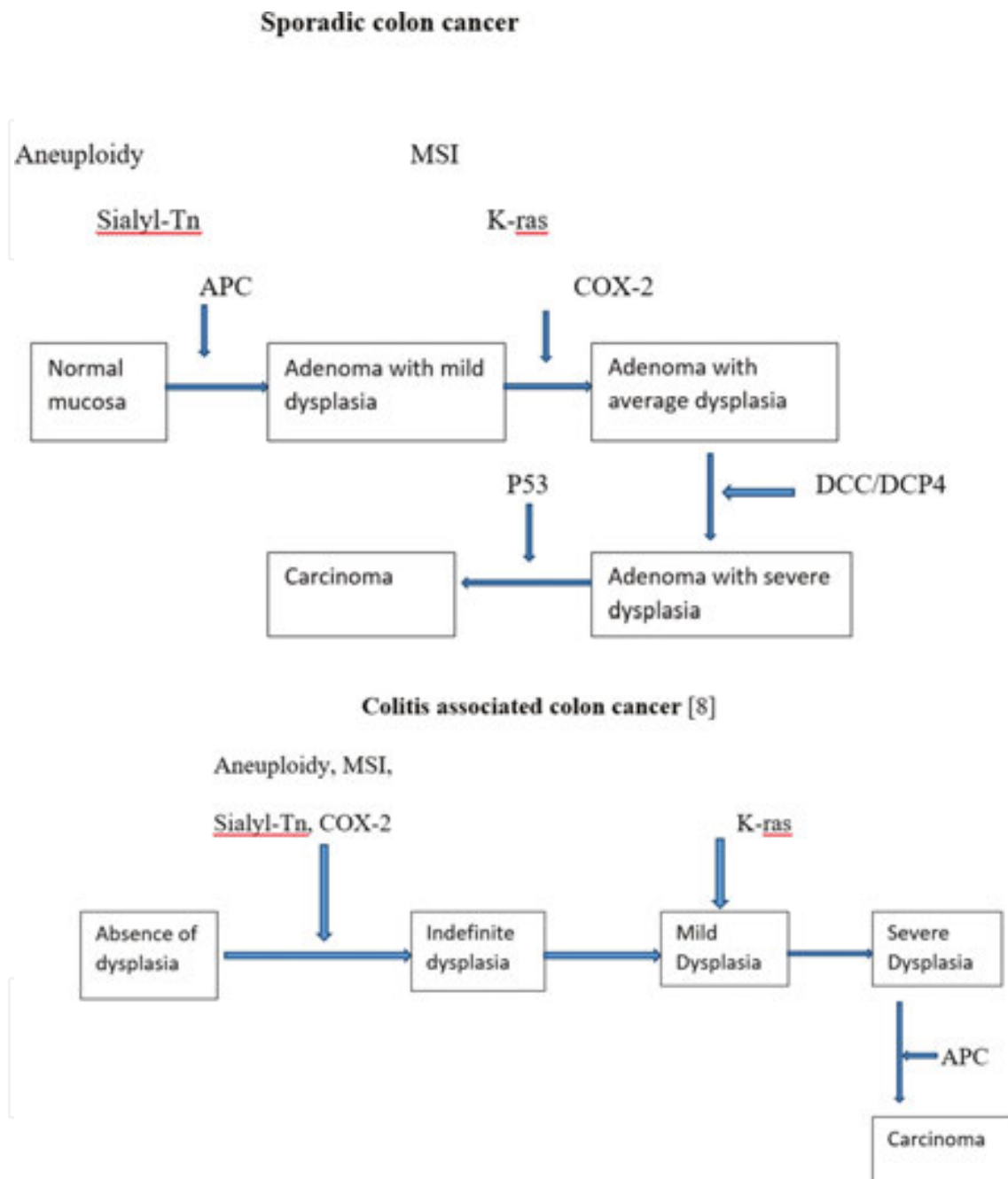
An interesting finding is that patients with asymptomatic disease (therapeutically controlled) have higher risks of malignancy compared with fulminant forms of ulcerative colitis that often require colectomy before the onset of dysplasia. In centers where a large number of colectomies are performed, the incidence of colorectal cancer (CRC) is significantly lower because the procedure eliminates the risk [1].

In Crohn's disease, the risk factors involved in carcinogenesis are areas of stenosis, inflammatory extension areas, younger age at onset and age >45 years at diagnosis. Risk factors specific to patients with inflammatory bowel disease [8]:

- Coexisting primary sclerosing cholangitis

- Increasing cumulative extent of colonic inflammatory lesions

- Increasing duration of inflammatory bowel disease

- Active chronic inflammation endoscopically assessed

- Active chronic inflammation histologically assessed

- Anatomical abnormalities such as:

  - Foreshortened colon

  - Strictures

  - Pseudo polyps

- Personal history of flat dysplasia.

The severity of inflammatory colonic lesion correlates with the risk of colorectal cancer in patients with IBD. There is a correlation between the degree of inflammation and the risk of dysplastic lesions and indirectly with the colorectal cancer incidence. Various studies have shown the relationship between the risk of colorectal cancer in patients with IBD and the degree of inflammation, extent of lesions and coexistence of other sites of inflammation [9]. Involved in the colonic carcinogenesis in patients with IBD are, besides inflammation areas of various degrees, also genetic and immunological factors.

3. Molecular and genetic markers

Sporadic colon cancer

Aneuploidy   MSI

Sialyl-Tn   K-ras

APC   COX-2

| Normal mucosa | → | Adenoma with mild dysplasia | → | Adenoma with average dysplasia |

P53   DCC/DCP4

| Carcinoma | ← | Adenoma with severe dysplasia |

Colitis associated colon cancer [8]

Aneuploidy, MSI,

Sialyl-Tn, COX-2   K-ras

| Absence of dysplasia | → | Indefinite dysplasia | → | Mild Dysplasia | → | Severe Dysplasia |

APC

| Carcinoma |

Pathogenesis of sporadic colon cancer and colitis-associated colon cancer [8].

Involved in the appearance of colorectal cancer associated with inflammatory bowel disease, are, on the one hand the chromosomal instability caused by abnormal chromosome separation (CRS) aneuploidy and loss of genetic material, and on the other hand, the microsatellite instability (MSI) mechanisms found in sporadic carcinogenesis. The trigger element for chromosomal instability is represented by impairing the function of APC associated with the

induction of K-ras oncogene and inactivation of tumor suppressor gene on CRS 18q in DCC and DPC4 region. Adenoma–carcinoma transformation is a direct result of the loss of p53 gene function [1, 6, 8].

Microsatellite instability, which is absent on normal mucosa, is described as an early event in non-dysplastic mucosa in patients with ulcerative colitis.

It is important to understand what mechanisms and factors can contribute to dysplastic lesions and colorectal cancer in IBD. Inflammation and genetic mutations play a major role. The supervision and therapeutic intervention in these disorders depends on understanding of these pathological processes. Thus, some genes associated with inflammation such as cyclo-oxygenase-2, nitric oxide synthase-2, and 1–8 interferon inducible genes are increased in inflamed colonic mucosa and remain elevated in colonic neoplasms [10, 11].

Genetic changes, responsible for colorectal cancer in inflammatory bowel disease, are similar to those involved in sporadic colon cancer [8].

Oxidative stress and its role in cell destruction in inflamed tissue may also play an important role in the pathogenesis of colorectal cancer in IBD [12].

Figures 1 and **2** depict some pathology aspects of colon mucosa with inflammatory changes. The inflammatory context is suggested by an abundant lymphoplasmocitary infiltrate and polimorphonucleated within the mucosal corion.
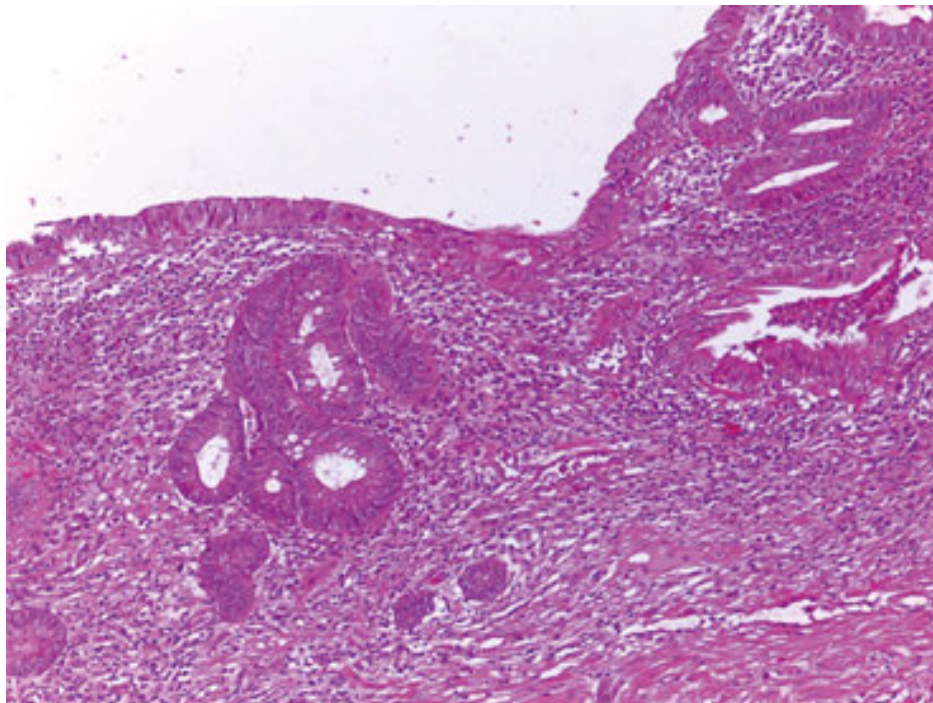
Figure 1. Inflammatory aspect of colonic mucosa. Modified cytoarchitectonics. Epithelial pseudostratification of the glandular tissue.
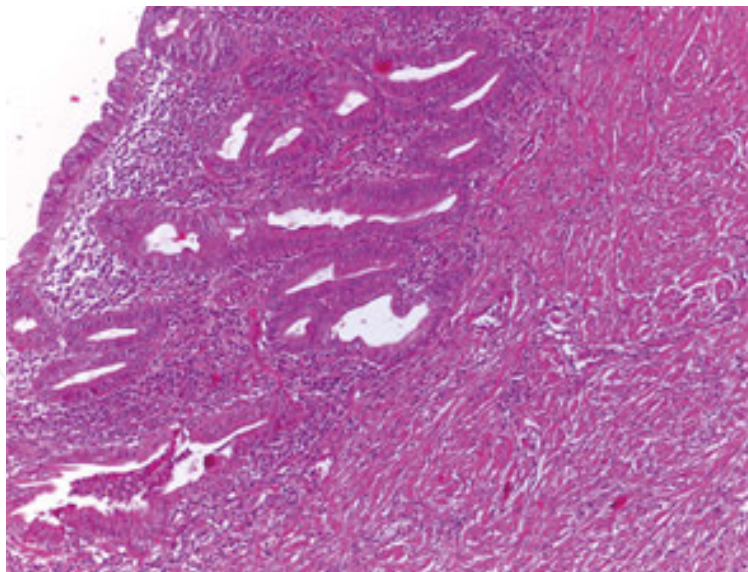
Figure 2. Inflammatory aspect of colonic mucosa. Nuclear pleomorphism. Mucus depletion, with a decreased number of secretory cells within normal glands.

4. Prevention of colorectal cancer in inflammatory bowel disease

4.1. Endoscopic surveillance in IBD

Endoscopic surveillance in IBD is designed to detect dysplastic lesions that can be treated surgically. As dysplastic lesions are difficult to recognize via endoscopic examination, their detection requires colectomy that prevents colorectal cancer (CRC). This fact is also determined by the risk of developing synchronous or metachronous cancer in IBD [13].

Colonoscopy surveillance reduces the risk of death from CRC in patients with long-term evolution of inflammatory disease. Given the cost–benefit ratio, this surveillance is especially recommended in patients with evolving active disease of over 7–10 years. The first colonoscopy screening program will be carried out in a remission period of the disease to avoid difficulties in identifying dysplasia in areas of increased inflammatory activity (**Figures 3** and **4**). The entire colonic mucosa will be examined and four biopsies will be taken from 10 to 10 cm. Any suspicious lesions will be biopsied. If the initial biopsy does not describe dysplastic foci, the colonoscopy is recommended to be repeated after 2 years or annually if the disease has more than 20 years of evolution when the risk of cancer increases exponentially. This interval is reduced to 6 months, 1-year maximum if the pathology result of the lesions comes back as indefinite dysplasia. The most controversial attitude is regarding mild dysplasia. In the case of dysplastic lesions associated with IBD, there are opinions saying that endoscopic resection can be done if the pathological examination of the fragments collected from the base of the polyp and also from the colon are negative for dysplasia [14]. The marking of the polypectomy site is recommended, and the colonoscopy should be repeated after 3–6 months. The confir-

mation of unifocal or multifocal dysplasia by a second expert requires that a colectomy should be performed. High-grade dysplasia is an absolute indication for colectomy.

Figure 3. Ulcerative colitis with areas of low grade dysplasia.

Figure 4. Ulcerative colitis with high grade dysplasia.

There is an evolution of the inflammatory lesions that either do not have dysplastic lesions or evolve from indefinite dysplasia to low-grade dysplasia, high-grade dysplasia, and finally carcinoma.

Dysplasia, detected at colonoscopic examination, represents an indication for colectomy. When low-grade dysplasia is detected, it is considered that the risk of developing colorectal cancer is nine times higher than in normal individuals and there is a 12 times higher risk of developing other advanced dysplastic lesions.

In patients with low-grade dysplasia, when colectomy is performed immediately, it was noted that 19% of the cases had high-grade dysplasia and 29–54% were at risk of developing advanced neoplasia in the following 5 years. High-grade dysplasia has a risk of 43% of combination with synchronous malignancy [14].

Dysplastic lesions are lesions that precede colorectal cancer development. Flat dysplasia can be discovered through microscopic examination of biopsy fragments, collected through random biopsies, sometimes from apparently normal mucosa. Often, flat dysplasia can be discovered with superior detection techniques such as chromoendoscopy, high-definition, and high magnification endoscopy [15–18].

Treatment for patients with dysplastic lesions and IBD depends on the degree of dysplasia. Patients presenting with multifocal flat low-grade dysplasia lesions or repetitive flat low-grade dysplasia should be advised to undertake prophylactic proctocolectomy.

Dysplasia-associated lesion or mass (DALM) is a specific endoscopic feature found in patients with ulcerative colitis. DALM is associated in a proportion of 40% with colorectal cancer; this
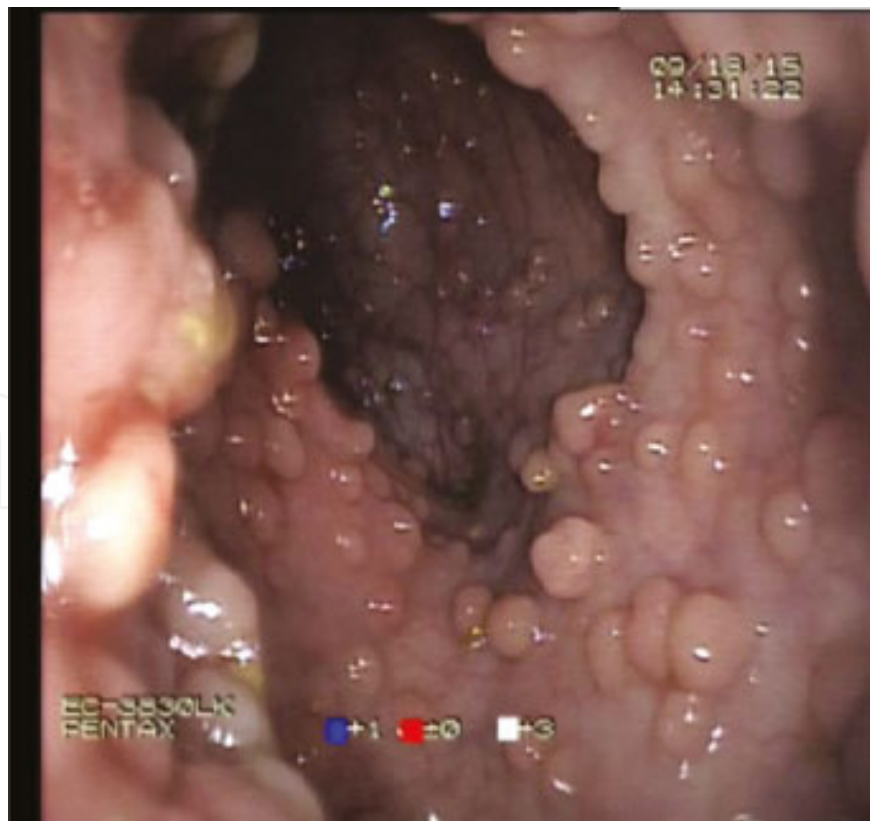

Figure 5. Polipoid lesions in a patient suffering from Crohn's disease.

association is enhanced by the presence of high-grade dysplasia lesions. DALM is an indication of proctocolectomy regardless of the degree of dysplasia.

Polypoid lesions identified in patients with IBD are not always malignant and can be treated with endoscopic polypectomy, especially if the polyps are adenomatous [19] (**Figure 5**).

Dysplastic lesions detected in biopsy samples from patients with IBD usually occur in areas of inflammation and can be polypoid, ulcerated lesions, or plague-like lesions (DALM). (**Figure 6** describes various instances of lesions in a patient with IBD).
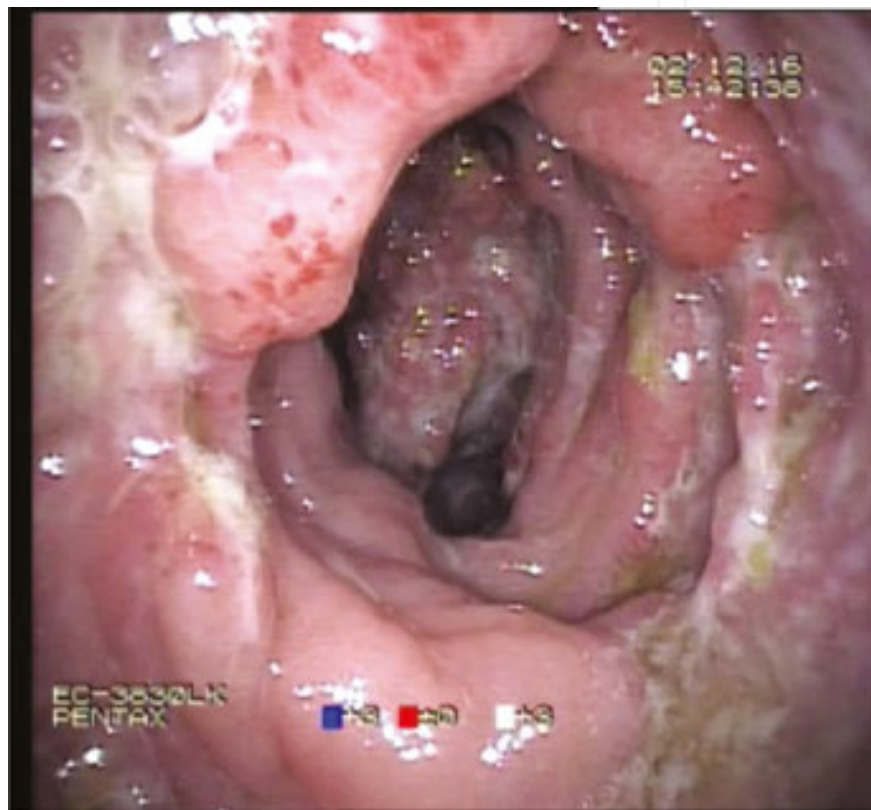
Figure 6. High grade dysplasia in a patient with Crohn's disease.

Although prophylactic proctocolectomy ensures the elimination of the risk of colon cancer (42% of cases in patients with high-grade dysplasia and 19% of cases in patients with low-grade dysplasia), there are practitioners who opt for a lifelong schedule of surveillance. They choose periodic examination at 6 months to 1 year by endoscopically investigating the entire colon, harvesting biopsy fragments and using preventive treatment with anti-inflammatory drugs and potentially chemopreventive agents. There are some major limitations to this attitude, namely the possibility of omission of malignant or dysplastic lesions during colonoscopy, especially if the number of biopsies is insufficient. Also, the lack of compliance of patients to colonoscopy surveillance programs is also an important risk factor for malignant lesions.

Guidelines from the Crohn's and Colitis Foundation of America (CCFA) and from European Crohn's and Colitis Organization (ECCO) mention the same methods for Crohn's colitis surveillance and ulcerative colitis as well due to the similar risk of developing colorectal. Colonoscopic screening is performed during remission of the disease, every 1 or 2 years, after 8–10 years of evolution. Screening interval may decrease with increasing duration of disease progression. Patients with proctosigmoiditis, who have a lower risk of malignancy compared to the general population, will be monitored using standard colorectal cancer prevention measures.

Patients with PSC, who have an increased risk of malignancy, should be monitored annually. Biopsy samples are collected from 10 to 10 cm (2–4 random biopsy specimens) and from suspect areas. In addition, in ulcerative colitis, biopsies are harvested from every 5 cm from the rectum and sigmoid, because the risk of developing colorectal cancer is higher in these regions. The degree of detection of dysplastic lesions is higher if a greater number of randomized biopsies are taken (90% if 33 and 95% if 56 random biopsies were taken) [20, 21].

4.2. New methods for early detection of dysplasia

To increase the rate of detection of dysplastic lesions, targeted biopsy represents an alternative. Guidelines now support the use of chromoendoscopy with targeted biopsy in the detection of dysplasia and/or colorectal cancer in patients with inflammatory bowel disease (IBD). Chromoendoscopy can see injuries that are not visible in the white light of standard endoscopy. Two substances are used, namely methylene blue and indigo carmine. High-magnification chromoendoscopy increases the detection of dysplastic lesions 3–4.5 times over [22–26].

Because of these arguments chromoendoscopy is used for routine surveillance of patients with IBD. With this method, the majority of dysplastic lesions can be discovered in patients with IBD during surveillance colonoscopy. Using only conventional colonoscopy is obviously insufficient in detecting dysplastic lesions [27–30].

Confocal laser endomicroscopy (CLE) is a modern technique for visualization of the histology of colonic mucosa in real time, being extremely useful for diagnosing intraepithelial neoplasia. With concomitant use of chromoendoscopic and CLE evaluation, the detection rate of dysplastic lesions was increased by 4.75 times compared to classical colonoscopy [21, 28–30].

Confocal chromoscopic endomicroscopy is superior to chromoscopy alone for the detection of intraepithelial neoplasia. Difficulties are caused by the high cost of exploration and biopsy interpretation difficulty that often requires an experienced pathologist.

The use of narrow band imaging (NBI) is not superior to conventional colonoscopy in detecting dysplastic lesions [31, 32].

Although many lesions can be identified by NBI, unfortunately equal numbers of dysplastic lesions can be missed by both conventional colonoscopy and this method. More studies are needed to clarify these issues.

We again underline that chromoendoscopy with targeted biopsy is indicated by all current guidelines for detecting dysplastic lesions in IBD.

4.3. Chemoprevention

Surveillance colonoscopy does not prevent colorectal cancer but allows early detection of dysplastic lesions and surgical therapeutic intervention.

Treatment of inflammatory lesions of IBD with specific anti-inflammatory therapy represents an important method of primary chemoprevention of colorectal cancer [33–36].

4.3.1. Aminosalicylates and other anti-inflammatory agents

IBD anti-inflammatory treatment in addition to relieving symptoms and improving lesions can prevent dysplastic lesions and colorectal cancer. Although studies are contradictory, most authors recommend administration of anti-inflammatory therapy for colorectal cancer prevention [37].

5-aminosalicylic acid preparations (5-ASA) are the main anti-inflammatory drugs used for the treatment of digestive tract inflammation in patients with IBD. Aminosalicylates inhibit cyclooxygenase and 5-lipoxygenase, thus inhibiting the synthesis of leukotriene B4, thromboxane A2 and prostaglandins and thus intervene in the immune response, reducing the production of antibodies and phagocytic activity. The administration of 5-ASA preparations reduces the risk of colorectal cancer, especially at higher doses of 2 g per day.

Mesalazine is effective in preventing colorectal cancer in IBD, proven experimentally on colon cancer cell lines [38].

4.3.2. Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA) used for treating PSC has a preventive effect in colorectal cancer by decreasing the concentration of biliary acids in the colon and through its antioxidant properties. On the other hand, it is unclear whether ursodeoxycholic acid is effective in preventing colorectal cancer in patients with IBD without the association of primary sclerosing cholangitis. In IBD forms associated with PSC, UDCA can reduce mortality and prevent the evolution of dysplastic lesions [39].

Further studies are necessary to establish the dose of UDCA to be used for secondary chemoprevention.

4.3.3. Folic acid

There are numerous studies showing that as in sporadic CRC, folic acid supplementation would decrease the risk of CRC in patients with IBD. Although there is no consensus in this regard, given that it is a cheap drug, that offers long-term safety, folic acid is recommended in patients with IBD as chemopreventive purposes. The mechanism of action is possibly related to the process of maintenance of DNA methylation and maintenance of DNA precursors level.

4.3.4. Statins

There is little data on the protective effect of statins on the development of CRC. It seems that the protective effect is lower in sporadic colorectal cancer and more expressed in colorectal cancer associated with inflammatory bowel disease. Experimental studies on mice show the protective effect of statins in reducing colorectal Dysplasia by inhibiting DNA destruction. Also in experimental models simvastatin significantly reduced tumor development by inducing apoptosis and inhibiting angiogenesis [40, 41].

These experiments provide important arguments that statins could be a potential chemopreventive and therapeutic agent effective in CRC associated with IBD. Extensive studies over long periods of time are needed to bring new arguments and insights on these aspects.

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