RESEARCH ARTICLE

COLORECTAL CANCER IN INFLAMMATORY BOWEL DISEASE: MYTH OR REALITY IN OUR CONTEXT?

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Introduction: Colorectal cancer (CRC) is a major and recognized complication marking the prognosis of inflammatory bowel disease (IBD). The risk factors for its occurrence are the extent of the lesions (pancolitis), the age of the disease and the association with primary sclerosing cholangitis. The aim of this study was to identify the epidemiological, clinical, therapeutic and progressive profile of these patients and to emphasize the importance of surveillance.

Methods: This is a retrospective descriptive study which collected all cases of colonic degeneration on IBD followed up within our department.

Results: Among the 1388 cases of IBD followed, 6 cases (0.4%) of CRC were collected. The average age of our patients was 52.3 years [38-61 years] with an sex ratio (F / M) of 2. It was an ileocolic Crohn's disease (CD) in one case and ulcerative colitis (UC) in 5 cases (66%) with pancolitis in 4 patients and left colitis in one patient. CRC was discovered during control colonoscopy in 5 known IBD carriers while it was found simultaneously with UC in 1 case. There has been an evolution of more than 10 years in the majority of our patients under anarchic surveillance. No case of associated sclerosing cholangitis was noted. Perendoscopic biopsies confirmed the diagnosis of adenocarcinoma in all cases. After a multidisciplinary consultation meeting, treatment was based on surgery (coloprotectomy) in 5 patients, combined with chemotherapy in one case. One patient was placed on isolated palliative chemotherapy for distant metastases.

Conclusion: Colon degeneration during IBD is a reality, although its incidence in our context is low (0.4%).

Introduction:-
Cancers during inflammatory bowel disease (IBD) are frequent problems and difficult to manage. Indeed, the meta-analysis by Eaden et al is frequently cited when approaching the subject of colorectal cancer associated with IBD because it strongly highlights the risk of neoplasia. This review of the literature compiling the data from 116 studies, i.e. nearly 54,000 patients with ulcerative colitis (UC) observed in 2001 high rates of cancer during UC of 2%, 8% and 18% at 10, respectively 20 and 30 years of evolution, i.e. an additional risk of cancer of 0.5 to 1% / year of illness. These rates ultimately reflect the natural history of the disease at a time (1950-2000) when screening...
strategies remained to be determined and treatments for colonic inflammation less effective. These CCR rates have been gradually revised downwards over the past 20 years between 3.1 and 7.8% at 30 years. Concerning Crohn's disease, it remains more difficult at the scale of population studies to determine the risk of colorectal cancer in colic forms because these studies do not allow taking into account the spread of the disease, the disease being classified ileocolic or colic in the registers. This classification does not allow to specify the percentage of surface reached at the level of the colon. In the French CESAME cohort (prospective observational cohort aiming to evaluate Cancers and Surrrisque Associated with Inflammatory Bowel Diseases), this subtlety was well observed. In fact, the risk of colon cancer was at the limit of significance for all patients with colonic Crohn's disease. In detail, there was no increased risk in patients with old extensive colitis. On the other hand, in patients with extensive colitis (more than 50% of the colon surface) and old, the risk was 9 times greater than the general population. In detail, there was no increased risk in patients without old extensive colitis. On the other hand, in patients with extensive colitis (more than 50% of the colon surface) and old, the risk was 9 times greater than the general population. In detail, there was no increased risk in patients without old extensive colitis. On the other hand, in patients with extensive colitis (more than 50% of the colon surface) and old, the risk was 9 times greater than the general population [1, 16].

In summary, patients with colic IBD, Crohn's and UC, have almost twice the risk of developing colon cancer, a risk that gradually increases with the duration of the disease and the spread of colitis. the observation in certain studies of an increase in excess mortality during IBD is partly linked to cancers, emphasizing the need to properly identify patients at risk and to develop specific and personalized screening programs for these cancers in parallel with management of the disease [1, 16]. The aim of our study was to identify the epidemiological, clinical, therapeutic and evolutionary profile of these patients and to emphasize the importance of surveillance.

Methods:-
We carried out a retrospective descriptive study collecting all the files of patients with IBD and having had colonic degeneration, supported by the hepato-gastroenterology service of the university hospital center HASSAN II of Fez during a period nine years from January 2010 to January 2019. Data entry epidemiological, clinical, therapeutic and progressive and their analysis were done with the SPSS 21.0 software. The inclusion criteria were all patients followed for IBD having a colonic degeneration. The exclusion criteria were any patient followed for an IBD without colonic degeneration or having a degeneration other than colic.

Results:-
Among the 1388 cases of IBD followed in our gastroenterology department, 6 cases (0.4%) of colorectal cancer were collected. The average age of our patients was 52.3 years [38-61 years] with an F / M sex ratio of 2. We had one case of ileocolic CD and 5 cases of UC with 4 cases of pancolitis and one left colitis. Four patients were treated with salazoyrine, the fifth was evaluated to start treatment and whose discovery of the tumor was made simultaneously with the diagnosis of UC.

All of our patients were in clinical remission. CRC was discovered during control colonoscopy in 5 known IBD carriers while it was found simultaneously with UC in 1 case. There has been an evolution of more than 10 years in the majority of our patients under anarchic surveillance.

Two of our patients were smokers; no cases of associated sclerosing cholangitis or a family history of CRC were noted.

Colonoscopy was performed in 5 patients for screening, the preparation was average (Boston score between 5 and 7). The tumor was located preferentially on the left colon (5 cases) and transverse colon (1 case) with the presence of inflammatory signs in all patients and pseudo-polyps in two patients. The process biopsy was performed as well as colon biopsies in stages. Perendoscopic biopsies confirmed the diagnosis of adenocarcinoma in all cases, the other biopsies revealed lesions of low grade dysplasia in two patients and high grade in one patient and inflammatory IBD lesions without dysplasia in the rest of case.

The thoracoabdominal computed tomography was carried out in all our patients, it showed an irregular thickening of the tumors preferentially on the left colon associated with an infiltration of mesenteric fat in one case, a perirectal lymphadenopathy in one case and distant metastases in another, imagery also showed inflammatory thickening linked to IBD.
In our series, the cancer most often exceeded the muscularis and the serosa with a significant predominance of tumors classified as T3. In addition, it has been demonstrated in the majority of cases a lymph node extension. The different stages identified have been summarized in the following table:

**Table 1:** TNM stages of colonic cancers in our series.

| Staging       | Number |
|---------------|--------|
| T2N1M0        | 1      |
| T3N0M0        | 4      |
| T3N2M1        | 1      |

After a multidisciplinary consultation meeting, the treatment was based on surgery (coloprotectomy) in 5 patients, combined with chemotherapy in one case for the presence of peri-rectal lymphadenopathy tumors. One patient was placed on isolated palliative chemotherapy for distant metastases.

The evolution of our patients was marked by a good response with close monitoring in three patients. One patient presented a complication-type stenosis of the ileo-anal anastomosis having benefited from two sessions of dilation with good progress. The patient who was on palliative chemotherapy died after two sessions. While a patient was lost to follow-up after surgery.

**Discussion:**

Inflammatory bowel disease is a lifelong disease resulting from an interaction between genetic and environmental factors, observed mainly in developed countries. Its precise etiology is unknown, and therefore curative medical therapy is not yet available. Patients with long-standing IBD are at increased risk of developing CRC compared to the general population [1,2]. CRC complicating UC was first recognized in 1925 by Crohn and Rosenberg [3], but it was not until 1948 that Warren and Sommers reported CRC in a patient with CD [4]. Justice Eaden and colleagues reported that <1% of all CRC cases were due to IBD [5], which is consistent with our results (0.4%).

Risk factors for the development of CRC in ulcerative colitis (UC) or CD include onset of disease, longer duration of disease, greater colonic involvement, coexisting primary sclerosing cholangitis (PSC), inflammation endoscopic or histologically active, family history of CRC in a first-degree relative diagnosed before age 50, history of dysplasia, narrowing of the disease in UC, inflammatory polyps, shortened tubular colon, and possibly male [6–7].

Regarding the duration of the illness; older studies found an increasing cumulative risk of developing colorectal cancer as the disease progressed. However, this risk was cumulative and the relative value of seniority does not seem to constitute an independent risk factor justifying increased surveillance over time [15].

Extension is a major risk factor associated with colorectal cancer. It is important to specify that the maximum microscopic (histological) and non-macroscopic extension is to be taken into account, requiring the performance of systematic step sampling to assess this colonic involvement. This risk is easily quantifiable during ulcerative colitis, proctitis not exposing to an increased risk, left colitis increasing by 2 to 3 times and pancolites by almost 5 to 15 times the risk of colorectal cancer. The extent of colonic involvement in Crohn's disease is more difficult to measure. It has been more or less arbitrarily defined as extensive colitis as reaching more than 50% of the area of the colon. In this case, an almost 9-fold increase in the risk of colorectal cancer was observed in the CESAME cohort. The risk is probably not binary and increases with the increase in the spread of colitis during CD [15].

Regarding primary sclerosing cholangitis (CSP): Regardless of the inherent risk of cholangiocarcinoma, the presence of CSP greatly increases the risk of colorectal cancer by almost 4 times compared to the general population. In a Swedish case-control cohort, the incidence of colorectal cancer was 10%, 33% and 40% respectively after 10, 20 and 30 years of evolution of UC associated with PSC. The mechanism is not clearly understood, the over-risk of colorectal cancer persisting after liver transplantation. The presence of sclerosing cholangitis frequently decreases the intensity of colitis and associated symptoms, patients do not always adhere easily to screening programs and require education [15].

Regarding chronic intestinal inflammation which remains one of the key points of colorectal carcinogenesis. It is therefore not surprising that witnesses to this severity of inflammation or its chronicity were found as risk factors for
colorectal cancer: pseudopolyposes, tubular colon, stenosis, inflammation visible to the naked eye or under the microscope. Microscopic inflammation has been consistently found to be associated with an increased risk of colorectal cancer in recent years regardless of the histological score used, increasing the risk of developing colorectal cancer by up to 4.6 times. Colonic strictures pose a double problem in cancer monitoring during IBD: the risk that the stenosis is cancer on the one hand and on the other hand the impossibility of monitoring the colon upstream when they are low and cannot be crossed. In a recent GETAID series, dysplasia or cancer was found in 3.5% of colonic strictures during IBD [15].

In our series, the main risk factor was the long duration of the disease, with poor therapeutic adherence and uncontrolled monitoring.

The objective of endoscopic surveillance is to reduce mortality and morbidity due to CRC by detecting and resecting dysplasia or by detecting CRC at early and potentially curable stages [8]. Endoscopic surveillance has been shown to reduce the risk of death from CRC in the population with IBD and is also cost-effective in various case series, case-control studies, and population-based cohort studies [9-10].

Since an increased risk of CRC is associated with a dysplastic change in the colonic mucosa, surveillance colonoscopies have been developed to reduce the morbidity and mortality associated with CRC. This monitoring involves not only a systematic evaluation of the colonoscopy, but also a review of the patient's symptoms, medication and laboratory test results, as well as an update of the personal and family medical history. At the start of these programs, a first screening colonoscopy is performed to reassess the extent of the disease and confirm the absence of dysplastic lesions [11]. Colonoscopic monitoring is best done when the disease is in remission, as it is also difficult to distinguish between dysplasia and inflammation on mucosal biopsies. Proper bowel preparation is essential for an effective surveillance colonoscopy [11].

Chromoendoscopy with targeted biopsies has been shown to increase the rate of detection of dysplasia. Alternatively, random biopsies (quadrant biopsies every 10 cm) and targeted biopsies of any visible lesion should be performed if white light endoscopy is used. High definition endoscopy should be used if available [11].

Unfortunately, chromoendoscopy could not be used in our context due to lack of equipment.

Table 2:- The recommendations of the European Crohn's and Colitis Organization (ECCO) (adapted from Maaser C, et al) [16].

| Risk level | Risk factors | Surveillance |
|------------|--------------|--------------|
| Low        | Low endoscopic and / or histological activity inflammation Extension of colitis <50% | Every 5 years |
| Intermediate | Pancolite with low endoscopic and / or histological activity History of first degree colorectal cancer (over 50 years) | Every 2-3 years |
| Student    | Pancolith with moderate to severe activity (endoscopic and / or histological) History of first degree colorectal cancer (less than 50 years old) Primary sclerosing cholangitis Stenosis in the last 5 years Dysplasia in the last 5 years without surgical management | Annual |

Chemoprevention with mesalamine compounds can reduce the incidence of colorectal cancer in UC. Thiopurines, MTX and biologics [anti-TNF] could theoretically either increase the risk of CRC via immunosuppression, or be chemopreventive via a reduction of chronic mucosal inflammation. There are no data for MTX or anti-TNF, and the data for thiopurines are contradictory. There is currently insufficient evidence to recommend for or against
chemoprevention with thiopurines; however, thiopurines may increase the risk of urinary tract cancers, acute myeloid leukemia, myelodysplastic syndrome, lymphoproliferative disorders, and non-melanoma skin cancer [11].

Conclusion:
IBD patients should be encouraged to go to the hospital at least once a year, even if they are asymptomatic. This opportunity should be taken to inform and remind patients of their risk of cancer, to reinforce the importance of surveillance and to ensure that they continue to receive maintenance treatment. Patients should be aware that surveillance can in no way guarantee a reduced risk of cancer, but rather offers a reasonable chance of detecting cancer in a precancerous or asymptomatic state. This should be clearly explained to patients with an estimate of their individual risk, so that those who are not enthusiastic about monitoring can make an informed decision.

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