UNIVERSITY OF MEDICINE AND PHARMACY "CAROL DAVILA", BUCURESTI

DOCTORAL SCHOOL

FIELD OF GASTROENTEROLOGY

ENDOSCOPIC AND HISTOPATHOLOGICAL CRITERIA FOR THE DIFFERENTIATION OF CROHN'S COLITIS FROM ULCERATIVE HAEMORRHAGIC PANCOLITIS IN PATIENTS EVALUATED IN FUNDENI CLINICAL INSTITUTE

ABSTRACT OF THE DOCTORAL THESIS

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2022

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Under the umbrella of inflammatory bowel disease (IBD) are the two major pathologies Crohn's disease (CD) and ulcerative colitis (UC), which are chronic conditions characterized by intestinal inflammation of varying extent and location throughout the digestive tract, occurring in genetically predisposed individuals.

Current studies show an upward trend in the incidence and prevalence of these diseases, both globally and in our country, due to industrialisation and the consumption of a modern Western-style diet, which includes refined sweets and fast food. The results on the epidemiology and phenotypic characteristics of IBD from the national IBD registry in Romania showed that in 2004 we had an incidence of 0.5 per 100,000 inhabitants for BC and 0.97 per 100,000 inhabitants for HUSR and prevalences of 2.25 per 100,000 inhabitants for BC and 1.51 per 100,000 inhabitants for HUSR. The mean age at diagnosis for BC was 43.9 ± 15.6 years (similar to the literature) and 44.2 ± 14.6 years for HUSCR, and in terms of gender distribution, a slight male bias of 1.29:1 for BC and 1.23:1 for HUSCR was identified (this phenomenon was described in areas of low incidence). The diagnosis was also established 2.3 times and 5.6 times more frequently in urban areas respectively. [1]

Numerous factors have been implicated in the etiopathogenesis, such as genetics, with the risk of developing IBD being higher in first-degree relatives of patients with BC than in those with HUSCR, and the highest prevalence of IBD in first-degree relatives has been reported in studies of the Ashkenazi Jewish population (4-4.5% and 2.6-2.7% for BC and HUSCR, respectively) [2-5] Immunological and environmental factors also play an extremely important role, these being perhaps the most difficult to understand. There are several theories that have been incriminated to explain the pathogenesis of IBD, and the most commonly cited is the hygiene theory, which proposes that the increased incidence of immunological imbalances may be attributed to lack of exposure of children to enteric pathogens since childhood. [6]

Another direct causal factor is smoking; a meta-analysis suggests that active smokers are more likely to develop UC than non-smokers or passive smokers; on the other hand, active smokers appear to have a higher risk of developing BC, in contrast to others. [7] The exact mechanism by which smoking predisposes to IBD is not fully elucidated, but it is thought that nicotinic acetylcholine receptors (nAChRs) are found on the surface of intestinal epithelial cells, but also on the surface of T lymphocytes, modulating their function.

Other frequently incriminated factors are: appendectomy, oral contraceptive/antibiotic administration, or impairment of the gut microbiota, as alterations in the microbiome act as a trigger for aberrant mucosal immune response in individuals who are predisposed to develop the disease. [8]

Clinical manifestations in HUSCR are variable from person to person and depend on the extent of lesions on the colonic frame and their severity; most of the time there is a directly proportional relationship between clinical symptoms and endoscopic lesions, but cases with blunted symptoms and severe endoscopic lesions have also been described. [9] Most cases start with progressively worsening symptoms. In severe cases with fulminant forms, the general manifestations are fever, chills, coprological syndrome amounting to more than ten stools/24 hours, dehydration, weight decline or colicky pain, and the patient requires admission to a clinic experienced in treating HUS. The most commonly reported symptoms are: rhetorrhoea (especially in the pustules of the disease, and the colour and amount vary according to the extension of the lesions), coprological syndrome (the mechanism of action being explained by the fact that proinflammatory cytokines and eicosanoids released by mononuclear cells from inflamed colonocytes lead to changes in the transport of certain electrolytes, altering Na-H exchange, Cl-HCO3, Na/K ATP-ase, induced by TNF-α, IF gamma and IL1b) [10] or abdominal pain, which is an important symptom that refers the person to the doctor if the disease is severe.

Clinical manifestations in Crohn's disease vary from patient to patient, related to the extent of lesions and pattern, and the existence of complications or extra-intestinal manifestations may contribute to the variability of the clinical picture. The cardinal symptoms are abdominal pain and diarrhoea, and if components of transmural inflammation are present, then we will detect fistulas, abscesses or phlegmons.

Manifestations of systemic involvement usually occur in both pathologies, predominantly in moderate-severe forms of the disease, and are represented by non-selective anorexia, nausea, febrile syndrome (as a result of the catabolic state), involuntary weight decline (protein loss through the inflamed mucosa or malabsorption, in a smaller percentage), asthenia and fatigability (explained by anaemia), but also gambiense oedema (explained by hypoalbuminemia secondary to malnutrition and inflammatory status).

Extraintestinal manifestations are prevalent in both HUSCR and BC, and the most commonly detected are musculoskeletal and dermatological. Up to half of patients with IBD experience an extradigestive manifestation, which may be present even before the diagnosis of IBD is made. [11] These include: spondyloarthropathies, metabolic bone damage (osteoporosis and osteopenia), ocular manifestations (blepharitis, episcleritis and anterior uveitis), dermatological manifestations (pyoderma gangrenosum, erythema nodosum), hepato-bilio-pancreatic manifestations (sclerosing cholangitis), coagulopathies or reno-urinary manifestations (those with BC being prone to develop renal lithiasis containing uric acid or calcium oxalate).

The definitive diagnosis of IBD requires the corroboration of paraclinical data (blood count, markers of inflammation and nutritional status, autoantibodies or coprological examination),

endoscopic data (this plays an important role both in the positive diagnosis of the disease, in monitoring the evolution under treatment - being useful to exclude other causes that may explain the coprological syndrome, but also to monitor complications such as colorectal neoplasms), imaging (transabdominal ultrasound which is non-invasive, enteroCT or enteroRM). Imaging methods have the benefit of assessing extraluminal complications such as abscesses, adenopathies, strictures or fistulas. The ultrasound evidence of disease activity is the detection of bowel wall thickening >3 mm[12].When referring to enteroCT, the criteria for a positive diagnosis of these diseases are: detection of wall thickening, hyperemic appearance of the wall, presence of lymphadenopathy and submucosal fat deposits. [13,14] At the top of the pyramid is perhaps the best imaging method, namely nuclear magnetic resonance (NMR) with a dedicated small bowel protocol, whose major benefit is the lack of irradiation.

Endoscopy (upper and lower) plays an important role both in the positive diagnosis of the disease and in monitoring the evolution under treatment, being useful to exclude other causes that may explain the coprological syndrome, can differentiate the two pathologies and can certify the severity or extension of the disease. The particular endoscopic features that plead for HUSCR are: erythema, oedema, obliteration of the vasculature, granularity of the mucosa, friability or spontaneous bleeding, erosions, ulcers or pseudopolyps (chronic mucosal hyperplasia), they are not specific for ulcerative colitis and may mimic the neoplastic appearance, so biopsy is necessary to confirm or rule out malignancy.

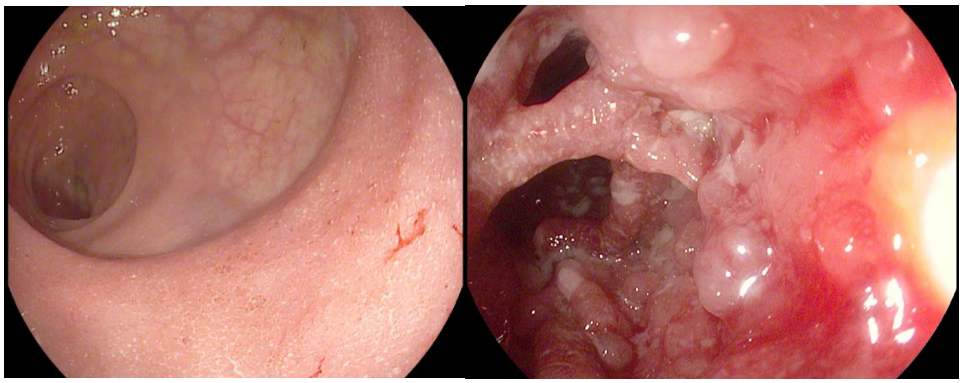
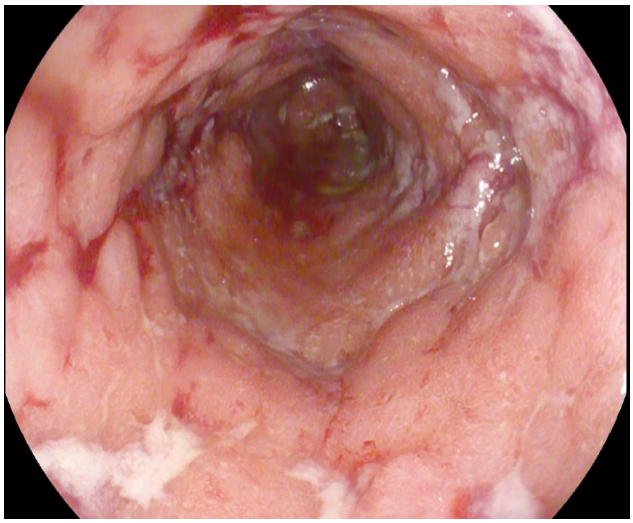


Figure 1 and 2 - moderate and severe form of HUSCR respectively (images from the archive of the Endoscopy Department of Fundeni Institute).

The macroscopic features suggestive of BC are the segmental distribution of lesions alternating with areas of normal mucosa, the presence of apthoid ulcerations (in the early stages of the disease), followed by the identification of ulcers developing in the longitudinal axis (in more advanced stages),

the "paving stone" appearance, the detection of the presence of fistulous orifices or stenosis, and the rectum is usually spared by lesions.



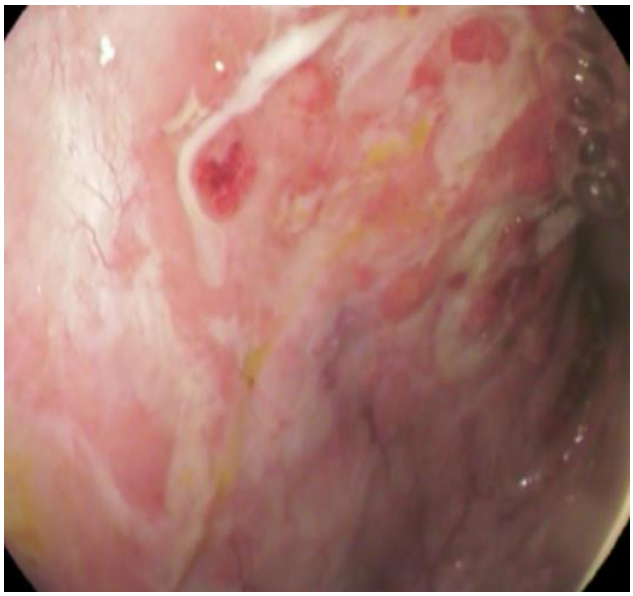


Figure 3 and 4- Severe BC with longitudinal ulcers and "paving stone" appearance: images from the archive of the Endoscopy Department of Fundeni Clinical Institute

There is no diagnostic certainty without a quality histopathological interpretation of the biopsy or resected specimen. Concerning the microscopic appearance of HUSCR, the particular aspects are: architectural distortion of the crypts, presence of a diffuse transmucosal inflammatory infiltrate and basal plasmacytosis, and if there is also an active component, then cryptitis and cryptic microabscesses will also be associated. Cryptic abscesses are more common in HUSCR (41%) than in BC (19%).15] Inflammation can also cause mucin depletion in the epithelium, a feature that can be detected in both infectious diseases and BC.

Other criteria that argue for chronicity are Paneth cell metaplasia (especially on the left colon), inflammatory pseudopolyps, mucosal muscle hypertrophy and, less commonly, identification of submucosal fibrosis. [16]

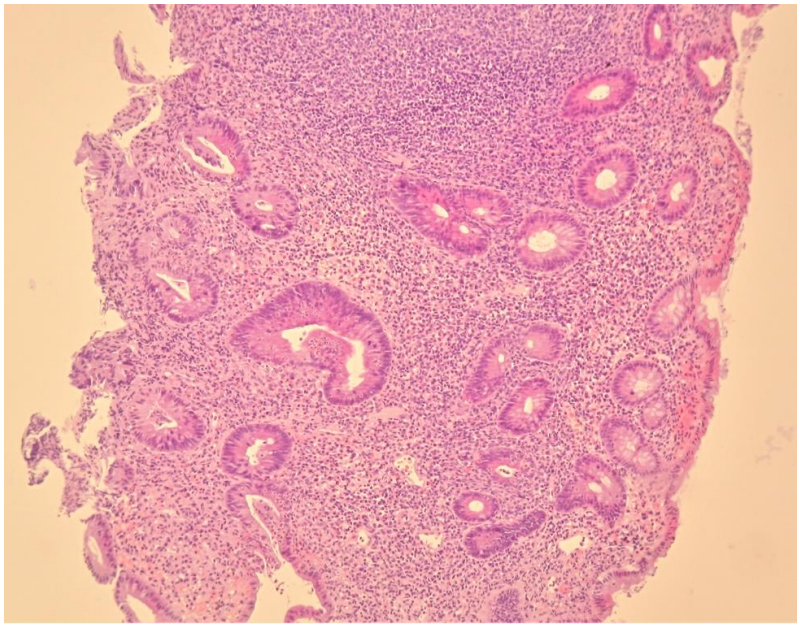


Figure 5- RCUH (mucosa with markedly disorganized glandular architecture and diffuse, active, chronic inflammation with cryptids and cryptic microabscesses): image from the archive of the Department of Pathology, Fundeni Clinical Institute.

If the macroscopic appearance of the lesions is suggestive of HUSCR, but the biopsy does not depict the presence of cryptids or cryptic microabscesses, the recommendations of the European guidelines for the diagnosis and treatment of IBD are to repeat colonoscopy in six weeks, as an onset of disease cannot be ruled out.

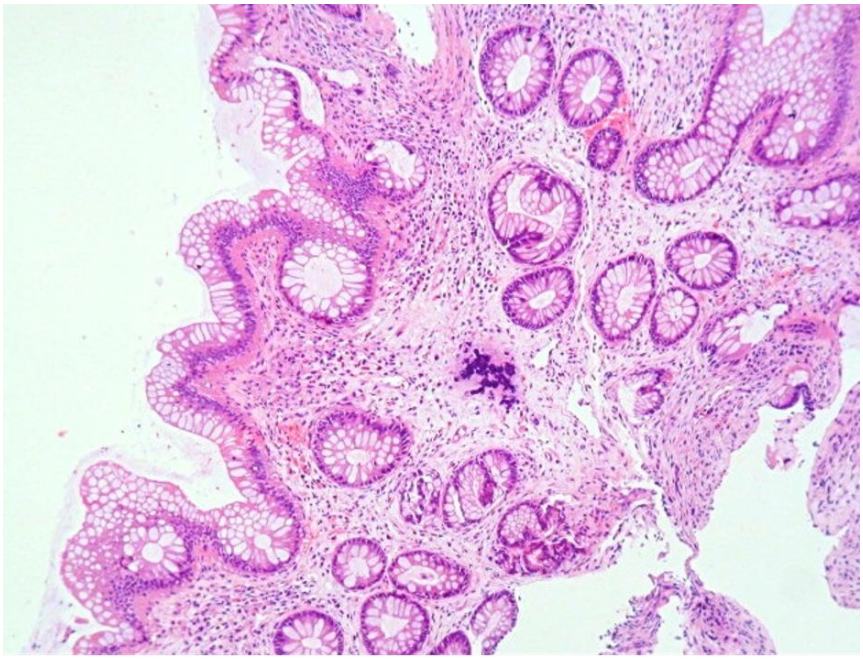


Figure 6- quiescent colitis (edema, architectural disorganization, chronic mild superficial inflammation, inactive)- image from the archive of the Pathology Department of Fundeni Clinical Institute

Microscopic features that may point to a diagnosis of Crohn's disease are chronic focal discontinuous inflammation, focal crypt irregularities and detection of granulomas. These features together with an irregular villous architecture (if biopsies are taken from the ileum) are suggestive of Crohn's disease. Granulomas in Crohn's disease are defined as a collection of epithelioid histiocytes (monocytes and macrophages) with poorly demarcated margins, necrosis usually not present; only granulomas in the lamina propria, unrelated to crypt injury, can be considered a histological feature of Crohn's disease.

Chronic focal discontinuous inflammation involves a variable increase in lymphoplasmacytic cellularity in the lamina propria, and crypt irregularity involves the presence of abnormalities in >10% of crypts (distortions, branching or shortening of crypts); these may or may not be accompanied by inflammation. [15,18] Pyloric gland metaplasia is a good indicator of chronic inflammation, and this change is frequently seen in those with operated disease.

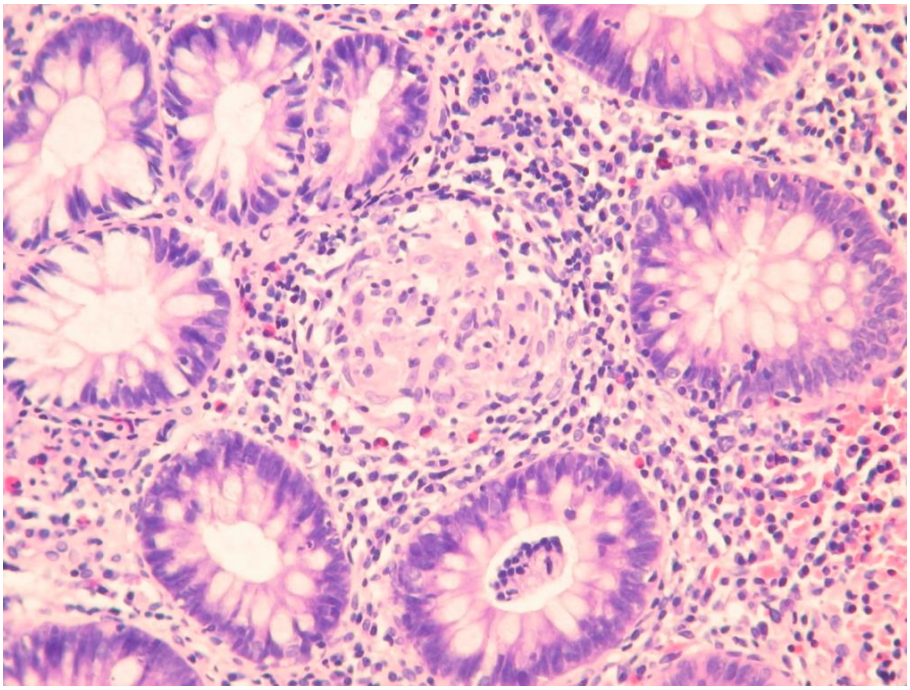


Figure 7- Crohn's disease with detection of an epithelioid granuloma - image from the archive of the Pathology Department of the Fundeni Clinical Institute.

One of the most commonly used scores for BC, particularly in clinical trials, is the GHAS (Global Histological Activity Score) developed by D'Haens in 1998 [19] which assesses epithelial damage, architectural changes, presence of neutrophils and monocytes in the lamina propria, existence of neutrophils in the epithelium, erosions/ulcerations, granulomas and number of biopsy specimens affected. Results showed that a score <4 points indicates remission of disease, and a score >10 points suggests severe disease.

The present PhD work is a single-center study with retrospective recruitment of patients with first diagnosis of inflammatory bowel disease and its primary objective is to analyzewhether or not there is a relationship between the macroscopic diagnosis raised by the endoscopist and the histopathological diagnosis made by the pathologist. The included patients underwent endoscopies with biopsies taken at the Digestive Endoscopy and Pathological Anatomy Departments of the Fundeni Clinical Institute of Digestive Diseases and Liver Transplantation.

As secondary objectives we aimed to analyse epidemiological data, clinical symptoms of these patients, macroscopic description (including the existence of particular forms) and to detect the existence of microscopic lesions corresponding to each disease, the presence of certain extraintestinal manifestations, histopathological scores (GHAS for BC and Geboes for RCUH) and classes of medication administered throughout the evolution of the disease.

In order to carry out this study in good conditions, the consent of the Ethics Committee of the Fundeni Clinical Institute was obtained.

The statistical plan was developed using R, version 4.0.2 Copyright (C) 2020 The R Foundation for Statistical Computing, R Core Team (2020) R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, to ensure scientifically meaningful results.

Thus, according to the inclusion and exclusion criteria, 174 patients were eligible and were distributed into two groups, as follows: 80 patients with macroscopic presumptive diagnosis of BC (group A) and 94 patients with macroscopic presumptive diagnosis of HCCR (group B).

In this way, the gender disposition was as follows: 92 males (52.9%) and 82 females (47.1%), most of them from urban areas-130 patients (74.7%), with a mean age of disease onset of 38.0 years (16.0, 79.0). The data quantify the male preponderance among both those with BC- 41 persons (51.3%) and those with HUSCR- 51 persons (54.3%). The pattern of BC is represented by the inflammatory form for 55 of the patients (68.7%), respectively stenosing in 25 persons (31.3%).

Regarding tobacco use, the results (for the whole group) are as follows: 48 patients (27.6%) are smokers, 41 patients (23.6%) are non-smokers, 37 patients (21.3%) are former smokers and for 48 patients (27.6%) we have no data on this status. If we refer to the BC- group 24 (30.0%) of the patients are active smokers, it being known that smokers have a higher risk of developing this disease, so our data agree with the literature. Unfortunately, however, we have no data mentioned for 19 people (23.8%). In group B (those with HCCR), only 17 patients (18.1%) are found to be current smokers. The percentage of non-smokers, however, is much different - 19 patients (23.8%) for BC and 29 patients (30.9%) for those with GVHD.

Regarding surgery, we found that appendectomy was described in the personal pathological history in 45 patients (25.9%), with approximately equal percentages in both groups: 23 patients (28.8%) with BC and 22 (23.4%) with RCUH.

We also looked for data on the detection of opportunistic infections (particularly with Mycoplasma tuberculosis) prior to initiation of biological therapy, with all patients tested for exclusion of pulmonary tuberculosis, and found 12 patients (6.9%) who were diagnosed with latent tuberculosis (8 with BC and 4 with RCUH), for which the start of therapy was delayed by at least 30 days.

Extra-intestinal manifestations had a mean value of 1.94 (2.34), the most frequently reported being: iridocyclitis (2 cases), ankylosing spondylitis (4 cases), erythema nodosum (1 patient) and sclerosing cholangitis (2 patients with HUSCR, one of whom required liver transplantation during the course of the disease); we find these conditions mainly in the group with BC.

The predominant symptomatology reported was diarrheal syndrome - 142 patients (81.6%), more frequent in the group with HCAI - 81 patients (86.2%), accompanied by pathological products 72 (76.6%), compared to those with BC where diarrheal syndrome was reported in 61 patients (76.3%), and 46 patients (57.5%) also reported the emission of pathological products. Another very frequently described manifestation is the abdominal algic syndrome. We obtained higher percentages in group A: 56 (70.0%) for BC and 57 (60.6%) for group B.

In order to estimate activity pustules, we calculated the CDAI score for those with BC, respectively the Mayo score for RCUH. In this way, we obtained mean CDAI scores of 173 points for those with mild BC - 23 patients (28.8%), 301 points for 34 patients (42.5%) with moderate disease and 486 points for 23 subjects (28.8%) with severe disease pustules.

Mild and severe HUSCR were recorded in 18 and 19 individuals respectively (with a mean score of 3 and 8 points), but the majority of patients had moderate disease (57 patients).

Regarding the most commonly reported macroscopic appearance, we found that erythema and oedema scored high percentages in both groups: 133 (76.4%) persons and 152 (87.4%) persons, respectively. Mucosal friability was also reported in 63 (36.2%) patients, but predominantly in those of group B (RCUH), and granular appearance in 77 (44.3%) patients, also more common in the same group. Justification of severe disease in the background was justified by the description of pseudopolyps in 44 (25.3%) of those recruited, and by the existence of scarring - 26 (14.9%) patients.

Mucosal erosions were reported in an overwhelming 132 (75.9%) patients, but with equal percentages between the two groups.

The appearance of BC was reasoned by the presence of the "cobblestone" type lesions described in 28 (16.1%) patients and the lack of clear demarcation between lesions and normal mucosa in 117 (67.2%) patients. In parallel, normal-appearing mucosa interposed between the lesion areas also contributed to the diagnostic orientation towards BC in 119 (68.4%) patients, considering that all were naive to any form of medication. For one person initially diagnosed with HUSCR, the macroscopic appearance of "cobblestone" was described, and this person subsequently changed her disease pattern during the course (the disease started with a fulminate puss and the lesions were considered to be the consequence of very severe rectocolitis).

In terms of histological severity, severe forms (translated by Geboes score >3.1, i.e. GHAS >10) are overwhelmingly found for both groups, and mild and moderate clinical forms are found with a higher frequency in BC compared to RCUH.

If we refer to the medication used according to the severity of the case, we obtained the following results: corticosteroids were administered for 96 patients (55.2%) with an average of 1.22 (1.07) treatments needed during the course of the disease, 144 people (82.8%) received 5 ASA, regardless of

the form of presentation, azathioprine was appropriate for 72 people (41. 4%), and antiTNF medication was administered as follows: 28 patients (16.1%) with Remicade, 8 patients (4.6%) with Inflectra, 20 patients (11.5%) with Remsima, 1 person (0.6%) with Zessly and another with Humira, 2 persons (1.1%) with Imraldi and 10 patients (5.7%) with Vedolizumab. Anti-TNF medication was administered from disease onset for about half of the patients.

All the data presented above (both overall and for each individual group) are extensively presented in Table V of the PhD thesis.

Next, an algorithm was composed in order to classify the two IBD, using univariate simple/multiple logistic binomial regression models, the dependent variable being the type of IBD (BC or RCUH), and the independent variables were represented by the endoscopic and histological parameters followed in the study. Randomly, we chose to report probabilities to RCUH.

The first model was the simple one (only one variable in the model), and all endoscopically described histological aspects are recorded in Table VI (displayed in the extended paper).

Based on the data illustrated in this table, several inferences were made:

1. Absence of fistulae is associated with an almost 20-fold increased likelihood that the evaluated IBD is RCUH, the effect being statistically significant ($p = 0.004$). This aspect is very clearly stated in the literature and occurs as a result of transmural (BC) versus superficial mucosal (RCUH) inflammation.

2. Declining presence of abscesses is associated with an approximately 7.5-fold lower likelihood of HURR, with the effect being statistically significant ($p= 0.011$).

Data provided in the literature show that abscesses occur as a consequence of obstruction of a fistulous tract, a corresponding complication of BC.

3. The detection of the presence of mucosal erythema is associated with an almost 5-fold higher probability of HUS, yielding a p-value <0.001.

4. Similarly, endoscopic description of mucosal oedema is associated with an approximately 3-fold higher probability of HCAI, yielding a p-value $= 0.030$.

5. Mucosal granularity is associated with a more than 10-fold increased likelihood of GVHD (also with statistical significance - $p < 0.001$). However, granularity is more commonly described in mild disease.

6. Mucosal friability, another frequently endoscopically detected feature, is associated with a 4-fold increased likelihood of GVHD, the effect being statistically significant ($p<0.001$). The

description of friability plays a very important role in distinguishing between moderate and severe GVHD.

7. Detection of the presence of pseudopolyps, which is a chronic mucosal hyperplasia occurring as a result of severe iterative episodes of inflammation, was reported in our group of patients 2 times more frequently in those with a presumptive diagnosis of HUSCR, resulting in a p-value = 0.045. And literature studies also report a higher frequency of these inflammatory lesions among patients with HUSCR.

8. Another important feature was that the absence of erosions was found to be 2.66 times more frequent in HICUR, the result being statistically significant (p= 0.011). These data are consistent with the literature.

9. Absence of ulcer deceleration is associated with more than 2 times lower probability of HCAI, a result that is also statistically significant (p= 0.010).

10. Absence of continuous colonic lesions with circumferential involvement is associated with an almost 100-fold lower probability of HCAI, which is well known. We obtained a p-value = 0.001. This description is perhaps the most commonly encountered in endoscopic reports.

11. The presence of ulcerated stenosis correlated with an almost 12-fold lower probability of HUSCR, the effect being statistically significant (p=0.021). Whenever the appearance of stenosis is documented, biopsies should be taken to exclude associated malignant pathology.

12. Absence of non-ulcerated stenosis is associated with a nearly 4-fold increased likelihood of HUSCR, the resulting data are also statistically significant (p=0.002).

13. Lack of endoscopic description of the presence of aphthoid ulcers leads to a 22-fold lower probability of HCAI; the results are similar to those already known , the results being statistically significant (p<0.001).

14. Detection of a clear demarcation between normal-appearing mucosa and lesions is associated with a more than 10-fold higher probability of HCAI (p<0.001); results are consistent with what is already established.

15. The absence of areas of normal mucosa interspersed with lesions raises a 22.5-fold diagnostic probability in favour of HUSCR (p<0.001), and the results are similar to those in the literature.

16. Linear, serpinous ulcers leading to the classic "cobblestone" appearance are associated with a 47.5-fold lower probability of HUSCR, guiding the presumptive diagnosis to BC. Statistical value obtained <0.001.

16. Absence of rectal lesions is associated with an almost 40-fold higher probability of Crohn's disease, and the effect is statistically significant ($p<0.001$).

We further investigated possible associations between the Mayo score and the Geboes score obtained by lower GI biopsy in those with HCCR. As histopathological lesions (and thus the scores quantifying them) can have a significant variability in the same patient, the analysis was done only for patients in whom a sufficient number of biopsies were taken (example 4). In conclusion, 204 biopsy samples were statistically evaluated.

The statistical data are represented in detail in Table VIII of the PhD thesis. Following the analysis we have developed the following ideas:

1. In patients with normal-appearing mucosa, the mean Mayo score is slightly less than 1, with a CI (confidence interval) of -1.9 to -0.30 and a p-value of 0.008. The Mayo score is expected to record lower values when the disease burden is mild or the disease is in remission.
2. An increase of 1 in the architectural change score is associated with a mean increase of 0.65 in the Mayo score (CI 0.34-1.0); in this case, p-value < 0.001.
3. A 1-fold increase in chronic inflammatory infiltrate score is associated with a mean increase in Mayo score of 0.59 points (CI 0.30-0.89). There is not much data in the current literature assessing a relationship between endoscopic score (e.g. Mayo) and various histological scores, but it is expected that this is justified, as more severe microscopic inflammation also demonstrates more severe endoscopic lesions.
4. A 1-fold increase in the degree of neutrophil presence in the lamina propria is associated with a mean 0.65 increase in Mayo score; CI 0.35- 0.94 and $p<0.001$. It is well known that neutrophils also betray a chronic inflammatory process, which may also explain the more severe endoscopic appearance.
5. A 1-fold increase in eosinophil presence in lamina propria is associated with a mean 0.31 increase in Mayo score (CI 0.08 - 0.54). However, it should be taken into account that they can be increased in both active and quiescent disease, so this result should be viewed with caution.
6. A 1-fold increase in neutrophil presence at the epithelial level is associated with a mean increase of 0.65 in the Mayo score (CI 0.37 - 0.93) and a p-value <0.001.
7. A 1-fold increase in the degree of crypt destruction is associated with a 0.5-fold increase in the mean Mayo score (CI 0.24- 0.75); p-value <0.001. If the pathologist only describes crypt injury but does not specify whether or not cryptic abscesses are present, it should also be kept in mind that this change (crypt destruction) may also occur secondary to colonoscopy preparation.

8. An increase of 1 in the degree of erosions or ulcerations is associated with a mean increase in Mayo score of 0.35 (CI 0.2 - 0.49). These findings were described particularly in those with severe endoscopic damage; p-value < 0.001.
9. A 1-fold increase in microabscesses is associated with a mean 0.62 increase in Mayo score (CI 0.30 - 0.94). In our study, in mild and moderate cases, cryptic abscesses affected <50% of crypts, and in severe cases >50% of crypts had changes. These data agree with those in the literature. The data obtained are also statistically significant p<0.001.

The next part of the analysis was performed on histopathological variables that could not be quantified correctly for all observations, which is why the results should be interpreted with circumspection .

1. Decreased mucosecretion is associated with a mean increase in Mayo score of 0.71 (CI 0.23 - 1.2), giving a statistical value of p = 0.004. These results were shown in 189 biopsies out of 204 examined in total. There is agreement among histopathology experts that a decrease in mucosecretion is representative of the pattern of HUSCR.

2. When basal plasmacytosis is detected, it is associated with a mean increase of 0.84 in the Mayo score (CI 0.09 - 1.6); this change was seen in 152 biopsies out of 204 examined. The presence of basal plasmacytosis is described in the literature as an important predictor of IBD, particularly for HUS. This is also true for clinical relapse.

3. Although the p-value is marginally insignificant (p = 0.058), we consider that there is evidence that allows us to consider plausible an association between the presence of polyps on the mucosa with lesions and a mean increase in Mayo score of 1.5 (CI 0.04 - 3.1). Since pseudopolyps are known to betray more severe inflammation, it is predictable that their presence correlates with a higher endoscopic score.

To investigate a possible association between BC severity and histopathological changes, a simple univariate linear regression was used, with dependent variable "severity degree" of disease and independent variables-histopathological parameters followed in the study.

A very important observation is that no statistically significant association between predictors and the degree of severity of BC was evident. Also, observing the value of the coefficients (β) for the predictors, as well as the 95% CI associated with them, we can hypothesize that a possible influence of HP lesions on disease severity is small. All the data obtained are represented unfolded in Table XI of the PhD thesis.

Architectural changes in BC (shortened, dilated, irregular crypts) register a mean value of 0.738 (0.769), with a median of 1.00 [0, 2.00]. However, these changes are found both in acute inflammatory and regenerative processes.

Cryptolytic and epithelioid granulomas and fibrosis in lamina propria were described in only one person with HUSCR (0.5%) of all biopsies examined. Our data to date indicate that these giant cells and epithelioid granulomas distant from the crypts are indicative of a diagnosis of BC. On the other hand, they are rare findings even in BC; in our group of patients, only 5 (4.7%) biopsies showed granulomas and only 3 (2.8%) biopsies showed epithelioid cells.

Erosions and ulcerations are found in 24 (22.4%) of the biospheres studied in BC, data that are similar to those already known.

The mean number of affected specimens (in group A- those with BC) has a mean value of 1.20 (1.00) and a median of 1.00 [0, 4.00], and the mean GHAS score is 4.10 (3.38), with a median of 4.00 [0, 12.0], which translates into mild inflammatory damage. We note, however, that clinically, most patients had moderate or severe disease flares.

Compared to group A (BC), those in group B (RCUH) have slightly higher values of the degree of architectural changes, with a mean value of 1.45 (0.889) and a median of 1.00 [0, 3.00], which subsequently translates into higher histopathological scores .

Similar inferences are valid for the mucosecretory grade, for which a mean value of 0.635 (0.573) and a median of 1.00 [0, 2.00] was calculated. Unfortunately, however, in 15 (7.4%) biopsies, the degree of mucosecretion could not be assessed.

Of the 204 biopsies examined in those with HUSCR, there was an increased value for chronic inflammatory infiltrate - 1.64 (0.929) being the mean value, with a median of 2.00 [0, 3.00], betraying at least moderate impairment.

If we consider the presence of neutrophils in the lamina propria and epithelium, we observe similar mean values of 1.03 (0.964) and 1.60 (0.923), respectively, with a median of 1 and 2, respectively. These results translate slight, respectively moderate increases in neutrophil counts.

Eosinophils, whose presence also betrays a chronic inflammatory process (although the total number has high inter-individual variability) register a mean value of 1.07 (1.24), with a median of 0.500 [0, 3.00], which means a minor increase in the number of eosinophils.

Basal plasmacytosis, the earliest histological marker of HCCR, was present in 110 (53.9%) of the biopsies examined, but could not be assessed in 52 (25.5%) of them. All patients in whom this was described also had endoscopically active disease.

The degree of crypt destruction was reported with a mean value of 1.31 (1.07) and a median value of 2.00 [0, 3.00], which also indicates moderate inflammatory damage, and erosions had a median value of 3.00 [0, 4.00], indicating that they were frequently found on biopsy specimens in high numbers. On the other hand, cryptids had a median value of 1.00 [0, 3.00], so they were found in moderate numbers when examining the slides.

Epithelial abnormalities, which among other things sum up Paneth cell metaplasia, were reported to be absent in 184 (90.2%) of the 204 biopsies examined, and pseudopolypses certifying the existence of severe disease were biopsied in only 7 (3.4%) patients. Of these, only 3 biopsies (1.50%) attested low-grade dysplasia. None of the colonic biopsies taken raised suspicion of indeterminate colitis.

Integrating all necessary variables, we obtained a mean Geboes score of 4.03 (1.87), but with a median of 5.30 [0, 5.40]. These results reflect severe inflammatory damage, a result that correlates with macroscopic and clinical aspects. Recall that most patients with pancolitis had moderate disease flares.

In the last part of the work, we calculated the probability that the patient's diagnosis was HCCR or BC and thus randomly divided our group into two subsamples: on one subsample comprising 2/3 of the initial group (116 patients) the model was trained, and the other subsample comprising 1/3 of the initial group (58 patients) was used for testing, and we obtained a sensitivity of 100. 00% for RCUH, respectively specificity of 90.00%, and for BC a sensitivity of 90.32%, respectively specificity of 100.00%.

In conclusion, we had a sufficient number of patients with IBD and the epidemiological data are similar to those reported in other European countries. Concerning the concordance between the macroscopic appearance reported by the endoscopist and the microscopic appearance concluded by the pathologist, it correlated positively with the degree of chronic inflammation for patients with HCC, but we did not obtain similar results for those with BC, partly reflecting the discontinuous nature of the lesions. The results of the correlation between Mayo score and Geboes score demonstrated that any increase in the degree of chronic inflammation, architectural changes, presence of eosinophils or neutrophils in the lamina propria, or erosions/ulcerations were associated with an increase in Mayo score.

Concerning a possible correlation between the severity of BC and histopathological appearance, we deduced a striking observation, namely that no statistically significant association between predictors and the degree of severity of BC was evident. In conclusion, we hypothesized that a possible influence of HP lesions on disease severity is small.

As a concluding remark, we consider that there are still various unresolved research questions in all subsets concerning the mechanisms responsible for the pathogenesis, diagnosis, differentiation or management and monitoring decisions of these heterogeneous diseases, and these uncertainties need to be clarified by thorough studies to which all personnel with an interest in this sphere should contribute.

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List of published scientific papers

1. **Monica Cojocaru**, Cristian Gheorghe, Gabriel Becheanu, Adrian Dijmarescu. Villous Hypermucinousappearence in longstanding inflammatory bowel disease: a case report and review of literature. Research and science today, 2020; S1.10:85-95, DOI:10.38173/RST.2020.S1.10:85-95
2. **Monica Cojocaru**, Cristian Gheorghe, Gabriel Becheanu. The peri-appendiceal red patch: a trademark skip lesion in ulcerative colitis. Research and science today, 2(22)/2021; DOI: 10.38173/RST.2021.22.2.13:131-137

Posters at scientific events organised by national professional associations

1. Prevalence of chronic inflammatory bowel disease in the Bucharest-Ilfov area: an interim analysis of the EPIROM population based registry data; RăzvanIacob , Simona Nicula , Anca Dimitriu , Monica Cojocaru, Eva Csiki Irma , Gabriel Constantinescu , Madalina Ilie , Corina Pop , Lucian Negreanu , Bogdan Mateescu , Mircea Diculescu ,Ion Dina, Cristian Gheorghe, Liana Gheorghe (Grup de Studiu EPIROM)- Al XXXVI-lea CongresNațional de Gastroenterologie, HepatologieșiEndoscopieDigestivă, Cluj-Napoca 2016
2. Tuberculosis in patients with inflammatory bowel disease under treatment with anti-TNF alpha antibodies: a frequent complication in our geographical area. Roxana Vadan, Monica Cojocaru, Cristian Gheorghe, Mircea Diculescu, Ioana Stanel, Narcisa Zamfirescu, Liliana Gheorghe. Al XXXVI-lea CongresNațional de Gastroenterologie, HepatologieșiEndoscopieDigestivă, Cluj-Napoca 2016
3. Early clinical experience regarding the safety and efficacy of Hemospray for hemostasis in patients with upper digestive bleeding within 72 hours. Monica Cojocaru, Bogdan Cristian Gheorghe, Cotruta, Mihai Ciocarlan, Ion Bancila. Al XXXVI-lea CongresNațional de Gastroenterologie, HepatologieșiEndoscopieDigestivă, Cluj-Napoca 2016
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