Medical and Research Publications
International Open Access

Research Article **Journal of MAR Gastroenterology (Volume 2 Issue 4)**

The association between the severity of histologic lesions with the disease location and presence of colonic lesions in patients with UC

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Received Date: January 18, 2023

Published Date: February 01, 2023

Abstract

Background and Study Aims: *With the introduction of biologic treatment for IBD, the current objective is to achieve mucosal healing; however the ultimate goal would be to achieve histologic remission. Multiple histological scores evaluate the disease activity in ulcerative colitis including GEBOES, GUPTA, Gramlich, amongst others. The first objective of this study was to assess the severity of histologic lesions in patients with UC using these three scores and to check if there is an association with disease location, presence of pseudopolyps, dysplasia and cancer. The second objective was to determine whether there was an interscore agreement between the validated GEBOES score and the two simplified but non-validated scores (Gralimish and Gupta).*

Patients and Methods: *This is a retrospective study whereby all UC pathology reports collected between 2006 and 2015, were reviewed and subjected to a second reading in a tertiary referral center. Geboes, Gupta and Gramlich scores were used to evaluate the severity of the histologic lesions.*

Result: *1096 patients with UC were included in this study; 35.6% of them had their first disease flare, 27.2% had a relapse and 10.2% had quiescent disease. Based on Monreal classification, 53 % of patients were E3; 20.2% of patients were E2 and 26.8% E1. Hyperplastic polyps were found in 1% of the patients, adenomas in 2.5% of the patients and inflammatory pseudopolyps in 6.1% of the patients. There was no difference in locations of the hyperplastic polyps and adenomas. In patients with adenomas, low grade dysplasia was noted in 82.8%, high grade dysplasia in 10.3% and cancer in 6.9%, whereas 1.6% of patients with inflammatory pseudopolyps had dysplasia. The presence of flat dysplasia and cancer on colonic biopsies was 0.8% and 0.9% respectively, with a mean age of 63 years for patients with dysplasia and 56 years for patients with cancer. There was no difference in the presence of hyperplastic polyps and adenomas in regards to the different disease locations.*

Regarding histological severity, high correlation coefficient was found between the different ulcerative colitis severity scores. Histological severity scores (Geboes, Gupta, or Gramlich) were not associated with an increased occurrence of adenomas or dysplasia.

Conclusion*: We found no correlation between pathological severities and the age, phenotype, also no correlation between the presence of adenoma and hyperplastic polyps compared to the location and histological severity. We also demonstrate a high correlation between the 3 scores used (GEBOES, Gralmish and Gupta), this data should be confirmed by further prospective studies.*

Keywords*: Ulcerative colitis, histological scores severity, gebeos, gupta, gramblich*

Introduction

With the introduction of biologic treatment for IBD, the current objective is to achieve mucosal healing. Despite the appearance of endoscopic healing colonic mucosa, microscopic inflammation can persist representing a harbinger of residual active disease [1,2]. Extensive evidence has been published in the past decade, advocating the importance of histological healing as it demonstrated excellent correlation with reduced risk of relapse and hospitalization [2–5].

Histology is the most sensitive measure of disease activity and may correlate better with clinical remission.[3]. Persistent histologic inflammation in the presence of normal appearing mucosa was associated with poorer clinical outcome6 and the development of dysplasia and colorectal cancer [7].

About 30 scoring indices were identified in order to classify the severity of histologic lesions in patients with ulcerative colitis (UC) [8]. Such indices determine the presence of chronic inflammation: polymorphonuclear infiltration of the crypts and surface epithelium, architectural distortion and alteration of the integrity of the superficial epithelium. Inflammation persists in 16-100% of biopsies in patients with quiescent disease on endoscopy and predicts relapse in a healed mucosa on endoscopy [9,10]. The Geboes score was first reported in 2000 [10] ; it is a commonly used histologic index for UC, using a multivariate regression model which results in an index composed of seven categories. It shows good reproducibility and modest agreement with the endoscopic grading system. This Index includes seven items: architectural change, chronic inflammatory infiltrate, lamina propria neutrophils and eosinophils, neutrophils in epithelium, crypt destruction and erosion or ulcers [10]. The Gramlich and Gupta system scoring assess only histological disease activity defined by neutrophil granulocyte infiltration and epithelial damage11. Two new, validated indices have been developed for use in patients with ulcerative colitis: the Nancy Index 12 and the Robarts Histopathology Index (RHI) [13]. The Nancy Index and the RHI are validated, reproducible and respond to therapy [12, 13]. The Nancy Index has three histological descriptors (ulceration, acute and chronic inflammatory infiltrates) [12]. The RHI incorporates four histological descriptors (chronic inflammatory infiltrate, the number of neutrophils in the lamina propria and the epithelium and erosions or ulceration) [13].

No clear association between histological severity and disease phenotype as well as colonic lesions has been found. The first objective of this study was to assess the severity of histologic lesions in patients with UC using these three scores and to check if there is an association with disease location, presence of polyps, dysplasia and cancer. The second objective was correlate the validated GEBOES to the Gralimish and Gupta, simple scores.

Patients and Methods

We performed a retrospective study during a period of 10 years (2006 to 2015), in which all patients with confirmed UC were included. We reviewed pathology reports and subjected all colonic biopsies to a second reading by two specialized gastrointestinal pathologists. We used GEBEOS, GUPTA and Gramlich scores to evaluate the severity of the histologic lesions. We compared and correlated the GEBOES score to two simplified non-validated scores (Gralmish and Gupta). In parallel, several variables were analyzed: age, sex, phenotype, presence of polyps, dysplasia and cancer.

Statistical analysis: Categorical variables were represented as frequency and proportions. Continuous variables were shown as mean ± standard deviation. Categorical data were compared using a chi-square test. Correlation between different ulcerative colitis scoring systems was analyzed by a non-parametric ordinal Spearman test that measures the strength of dependence between two categorical variables. Inter-score agreement for different qualitative items ulcerative colitis scores was calculated using the kappa coefficient. The kappa score is interpreted as an excellent agreement when it ranges from 0.81–0.99, and a good agreement between 0.61–0.80. Statistical analysis was performed using the statistical package SPSS 20 for Windows **[**SPSS Inc., Chicago, IL**]**.

Results

The studied population consisted of 1096 patients. Twelve patients were excluded because of missing data. The characteristics of the population are summarized in table 1.

The localization of the disease did not differ across different age groups. Proctitis ranged from 15% to 27 % of the cases among different age groups, and colitis ranging from 52 to 66%. (P=0.587). Geboes, Gramlich and Gupta scores are shown in Table 2.

There was no difference in the presence of hyperplastic polyps and adenomas in regards to the different disease locations. In patients with adenomas, low grade dysplasia was noted in 82.8%, high grade dysplasia in 10.3% and cancer in 6.9%, whereas 1.6% of patients with inflammatory pseudopolyps had dysplasia.

The mean age of patients without neoplastic lesions or dysplasia was 42 +/-18, whereas the mean age for patients with colorectal adenocarcinoma was 56 +/- 16 ($P<0.05$), and the mean age for the occurrence of dysplasia was 63 +/-16 ($P<0.05$).

We noted an increased prevalence in the occurrence of adenoma with age. This increase was especially present in male gender population and was not significant in the female population. The differences are represented in table 3. Histological severity scores (Geboes, Gupta, or Gramlich) were not associated with an increased occurrence of adenomas or dysplasia in both male and female genders.

A high correlation coefficient was found between the different UC severity scores. Pairwise correlations of different scores, namely Geboes versus Gramlich scores, Geboes versus Gupta scores, and Gramlich versus Gupta scores, had respectively correlation indices R= 0.991, 0.991, and 1 (P values <0.001 for the three comparisons). The Kappa values for inter-score agreement for Gramlich versus Gupta score was 0.99 (P<0.001), Geboes vs Gramblich index was 0.67 (p <0.001) and Gebeos vs Gupta 0.66 (p=<0.001).

Characteristics		**N (%)**
Gender	**(Male)**	559 (51.9%)
Age groups	1-14	41(4.2%)
	15-45	530 (54.9%)
	46-65	277 (28.7%)
	>65	118 (12.2%)
Clinical Characteristics	First episode	380 (35.6%)
	Recurrence	291 (27.2%)
	Control after treatment	109 (10.2%)
	Unknown	288 (27.0%)
Phenotype	Pancolitis	**53%**
	Left sided colitis	**20.2%**
	Proctitis	**26.8%**
Relevant pathology findings	Adenoma	**27 (2.5%)**
	Cancer	10 (0.9%)
	Dysplasia	9 (0.8%)
	Hyperplastic polyps	1%
	Inflammatory pseudopolyp	6.1%

Table 1: Baseline demographic characteristics.

	Age Group	1-14	15-45	46-65	>65	P Value
Clinic	Control After treatment	2 (5%)	57 (10.8%)	36 (13%)	8 (6.8%)	0.029
	Initial diagnosis	17 (42.5%)	200 (37.8%)	77 (27.8%)	48 (40.7%)	
	Recurrence	10 (25%)	130 (24.6%)	96 (34.7%)	34 (28.8%)	
Polyp	No Polyp	40 (10%)	492 (93%)	246 (88.8%)	100 (84.7%)	0.003
	Polyps	0 (%)	37 (7%)	31 (11.2%)	18 (15.3%)	
Localization of disease	Colon	27 (67.5%)	272 (51.4%)	152 (54.9%)	63 (53.4%)	NS
	Rectum	7 (17.5%)	143 (27%)	67 (24.2%)	28 (23.7%)	
	Recto-sigmoid	6 (15%)	114 (21%)	58 (20.9%)	27 (20.9%)	
Geboes	0	0 (%)	5 (1%)	5 (1.8%)	2 (1.7%)	NS
	1	0 (%)	5 (1%)	2 (0.7%)	2 (1.7%)	
	2	0 (%)	1 (0.2%)	2 (0.7%)	0 (%)	
	3	9 (23.7%)	100 (19.3%)	70 (25.5%)	25 (21.6%)	
	4	29 (76.3%)	406 (78.5%)	193 (70.4%)	87 (75%)	
	5	0 (%)	0 (%)	2 (0.7%)	0 (%)	
Gramlich index	0	0 (%)	11 (2.1%)	9 (3.3%)	3 (2.6%)	0.024
	1	3 (7.9%)	51 (9.8%)	50 (18.2%)	12 (10.3%)	
	2	6 (15.8%)	49 (9.5%)	20 (7.3%)	15 (12.8%)	
	3	29 (76.3%)	407 (78.6%)	195 (71.2%)	87 (74.4%)	
Gupta index	0	0 (%)	11 (2.1%)	9 (3.3%)	3 (2.6%)	0.032
	1	3 (7.9%)	53 (10.2%)	50 (18.2%)	12 (10.3%)	
	2	6 (15.8%)	47 (9.1%)	20 (7.3%)	15 (12.8%)	
	3	29 (76.3%)	407 (78.6%)	195 (71.2%)	87 (74.4%)	

Table 2: Phenotypic distribution and histological score severity in relation to age. Chi square was used for statistical analysis. P<0.005 is considered statistically significant. (NS: non-significant)

		1-14	15-45	46-65	>65	P-Value
Overall population	Adenoma	0 (0.0%)	7 (1.3%)	9 (3.2%)	8 (6.8%)	0.004
	Dysplasia	0 (0.0%)	3 (0.6%)	3 (1.1%)	4 (3.4%)	0.011
	Adenocarcinoma	0 (0.0%)	1 (0.2%)	4 (1.4%)	3 (2.5%)	0.011
male patients	Adenoma	0 (0.0%)	3 (1.1%)	5 (3.6%)	7 (11.5%)	< 0.001
	Dysplasia	0 (0.0%)	2 (0.7%)	1 (0.7%)	4 (6.6%)	0.136
	Adenocarcinoma	0 (0.0%)	1 (0.4%)	2 (1.5%)	1 (1.6%)	0.017
Female patients	Adenoma	0 (0.0%)	4 (1.6%)	4 (2.9%)	1 (1.8%)	0.756
	Dysplasia	0 (0.0%)	0 (0.0%)	2 (1.4%)	2 (3.5%)	0.136
	Adenocarcinoma	0 (0.0%)	1 (0.4%)	2 (1.4%)	0 (0.0%)	0.017

Table 3: Prevalence of dysplasia and adenocarcinoma in different age groups according to gender. Chi square was used for statistical analysis. P<0.005 is considered statistically significant.

Discussion

Polyps, dysplasia and cancer:

The mean age was significantly different between patient with adenomatous polyps compared to hyperplastic polyps or pseudopolyps. But there is no difference concerning the sexe. The presence of adenomatous polyps, hyperplastic polyps and pseudopolyps was respectively 2.6%, 1% and 6.1% less than reported in other studies25–28. It is well known that the incidence of pseudopolyps increases with extensive colitis as a reasonable consequence of a more severe disease course 29–31. Similarly, in our study, pseudopolyps were more common in patient with pancolitis. But there is no difference in the presence of adenoma and hyperplastic polyps between the 3 phenotypes. Vieth et al found the same phenotype distribution in patient with adenoma and hyperplastic polyps32 where Lik Hang Lee et al showed that adenoma and hyperplasic polyps were more common in patient with proctitis28,33,34. Low grade dysplasia, high grade dysplasia and carcinoma in situ were found in 82.8%, 10.3% and 6.9% respectively in patient with adenoma. Also we noted in non polypoid mucosa the presence of dysplasia and cancer in 0.8% and 0.9% respectively with a mean age of 63years for dysplasia patients

and 56years for cancer patients. It is established that the severity of colonic inflammation in patients with long-standing, extensive ulcerative colitis, is an important risk factor for colorectal neoplasia35. In our study Histological severity was not linked to the disease location and there is no correlation between the histological severity and the presence of adenoma or dysplasia.

Also we noted a significant reduction of the severity GEBOES score in patient under treatment compared to those with initial manifestations and recurrence.

Histology

Based on ECCO guidelines, microscopic diagnosis of ulcerative colitis is based on widespread crypt architectural distortion, a diffuse transmucosal inflammatory infiltrate with basal plasmacytosis, eventually associated with an active component, causing cryptitis and crypt abscesses. Mucin depletion is less specific, but a helpful diagnostic feature **[**36**]**. About 30 scoring indices were identified in order to classify the severity of histologic lesions in patients with IBD **[**8**]**. Such indices determine the presence of chronic inflammation, polymorphonuclear infiltration of the crypts and surface epithelium, architectural distorsion and alteration of the integrity of the superficial epithelium, hence predict relapse in normal looking mucosa on endoscopy, since inflammation persists in 16-100% of biopsies in patients with quiescent disease on endoscopy **[**9,10**]**. Those scoring systems help also as a treatment target in patients with IBD. However, none of these systems was fully validated due to the lack of reproducibility **[**8**]**.

Bressenot et Al, showed that the best interobserver agreement concerning Geboes, Gramlich and Gupta indices were : “erosions/ulcerations” and “acute inflammatory infiltrate/neutrophils in lamina propria **[**37**]**. In our study a percentage of 75%, 74.4% and 74.4% for erosions/ulcerations in the Geboes, Gramlich and Gupta indices were noted respectively. This result is practically the same for the three systems and is however a reproducible tool in scoring patients in active disease and in relapse. Since most of the patients presented with severe lesions, the histologic grading systems can be substituted by one scoring index that can include as well the neutrophils in the lamina propria. Gramlich showed a moderate interobserver agreement for crypt abcesses **[**37**]**. In our study it was 83.8%. The neutrophilic infiltration of <50 or >50% of the crypts in Gupta index was not a reproducible tool. Comparing to the study done by Bressenot et Al that has previously correlated intra-rater and inter-rater agreement between different histological scores and that showed good to very good intra-rater and inter-rater agreement for Geboes score and almost perfect intra and inter observer agreement for Gramlich and Gupta scores, our study compare the agreement between the histological scores and

showed the best match was for Gramlich and Gupta due to the near resemblance of the parameters. As done by Christian Arkteg et al in 2021 who evaluates the performance of the three most validated histological scores for UC (Geboes, Nancy and Robarts) in a remission setting with the main findings are a poor to excellent inter-rater agreement between the three histological scores, as well as a fair to moderate inter-rater agreement for determining remission.**[**38**]**

This study has several limitations. First it is a retrospective study. We don't have any data concerning the endoscopic lesions, severities and the location of the specimen. Also there is a lack concerning the treatment (medication, duration and response) and the correlate.

In conclusion, in our study we demonstrated that there is no correlation between pathological severity and the age, phenotype, also there is no correlation between the presence of adenoma and hyperplastic polyps compared to the location and histological severity. In our study we demonstrate that there is a high correlation between the 3 scores used (GEBOES, Gralmish and Gupta), this data should be confirmed by further prospective studies.

Finally future studies are needed to determine the clinical, endoscopic and histological correlation Also it's important to determine the number of tissues sampling required for the optimized examination, anatomical location of the tissue sampling and timing of tissue collection after treatment.

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