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ORIGINAL ARTICLE

Histological Features and Predictors of Early Relapse in Patients of Ulcerative Colitis

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ABSTRACT

Objective: To determine the proportion of histological features and histological feature predicting frequency of elapse in known patients of ulcerative colitis.

Methodology: One hundred and ninety cases each had endoscopic colonic biopsies from the rectum, distal colon, and proximal colon.

Study Design: Retrospective Case series

Setting: Sheikh Zayed Hospital Lahore, Department of Histopathology, from February 25, 2016, to February 25, 2017.

Results: The majority of patients complained of generalized abdominal pain (55.3%). The commonest histological feature is cryptitis 189(99.5%). Majority patients with basal plasmacytosis 38(42.2%) and crypt abscess 36(29.8%) relapsed at 4th month.

Conclusion: Histological features basal plasmacytosis and crypt abscess are of prognostic importance. A greater chance of relapse can be predicted in patients with increased number of basal plasma cells and cryptitis. These findings will help in further management of ulcerative colitis patients.

Keywords: Inflammatory bowel disease, Ulcerative colitis, Remission, Relapse

INTRODUCTION

Idiopathic inflammatory bowel disease (IBD) includes two illnesses with distinct clinical phenotypes: ulcerative colitis (UC) and Crohn's disease (CD). UC is a persistent relapsing and remitting intestinal inflammation that places an increasing strain on health-care systems. In affluent countries, the prevalence of UC is steadily rising[1]. However, as compared to affluent countries, the incidence and prevalence of UC in Asia is still lower[2,3]. With an equal sex inclination, UC is more common in Asia than CD. The incidence of UC in Minnesota Omlsted county is 214/100,000[4].

The cause of UC is unknown, however it is thought to be a combination of genetic, environmental, microbial, and immunological factors. Mutations in the autophagy receptors ATG16L1, IRGM, IL23R, and NOD2 receptors have recently been found. , which interact with altered microbiota and dysregulated innate intestinal immunity, have recently been identified as the cause. The hygiene theory, together with additional lifestyle risk factors such as smoking, dietary habits, social stressors, and Nsaid abuse, catalyzes an individual's genetic predisposition, resulting in abnormal innate immune responses [5,6].

Patients with UC typically exhibit symptoms such as fever, weight loss, exhaustion, bloating abdominal pain, alternating episodes of diarrhoea and constipation, high mucus production, tenesmus, and rectal bleeding. Multiple sclerosis and Primary Sclerosing Cholangitis are two examples of autoimmune diseases that can occur together with UC. Extra intestinal symptoms in UC patients are infrequent in Pakistan and India [1, 2].

The initial tests for UC include a stool analysis, CBC, ESR, CRP, and p-ANCA. The following definitions on the management of UC were provided by the European Society of Pathology (ESP) and the European Crohn's and Colitis Organization (ECCO). Instead of performing a rectoscopy alone, an ileocolonoscopic examination should be performed to identify the extent and severity of the disease using samples from two mucosal biopsies collected from five distinct places, the terminal ileum, and the rectum [7,8]. Modern medicine causes significant diversity in the colonic mucosa, making histological intestinal mucosal assessment necessary [9].

The ongoing therapy of UC patients who experience remissions and relapses includes additional surveillance endoscopies. They are crucial in identifying disease activity, visible endoscopic lesions, the efficacy of treatment, and most importantly, any colorectal neoplasia. The efficacy of magnifying endoscopy with vital staining in predicting indelible outcomes, identifying dysplasia and carcinoma. Any endoscopic technique is prohibited in the presence of fulminant colitis. [10,11] .

ESP-ECCO explains the terms used in microscopic diagnostics. Chronic active colitis that is segmentally distributed is a hallmark of UC. Shortening, deformation, bifurcation, and branching of crypts are signs of chronicity, which is an architectural distortion of the crypts. The muscularis mucosa base and intense lymphoplasmacytic inflammation are separated by basal plasmacytosis. Chronicity is indicated by the pronounced presence of inflammatory pseudopolyps, left sided colonic paneth cell metaplasia, and hypertrophied muscularis mucosae. A crypt abscess is characterised by an accumulation of neutrophils in the crypt lumen, while cryptitis is characterised by neutrophil invasion of the crypt wall. Different scoring systems are used to evaluate each of these factors, but the Geboes Score is the most well-known. When treating UC histologically, the rectum can be spared, but the mucosa heals unevenly and the inflammation is patchy both endoscopically and histologically [8].

Clinically silent, quiescent UC presents on endoscopy with ordinary intestinal mucosa. Remission is defined by the ESP-ECCO as the full disappearance of clinical symptoms and endoscopic mucosal healing. Endoscopic mucosal healing is described as the absence of friability, blood erosions, and ulcers in all segments of the colonic mucosa that can be seen under a microscope. The mucosa is fully normal and exhibits clearance of the inflammatory infiltration and crypt architectural deformation in mucosal healing (MH) and histological healing (HH). In UC patients, MH/HH is a poor predictor of relapse and malignancy. As a result, patients can get maintenance therapy for a longer period of time, improving the likelihood of a successful outcome[9].

The mayo endoscopic score is one of the endoscopic ratings that clinicians most frequently use to assess the degree and severity of disease in quiescent UC. Histological healing and endoscopic mucosal healing are connected. The measurement of activity is crucial for assessing level of activity, therapeutic response, relapse risk, and early colorectal neoplasia identification. Patients with quiescent illness are predicted to relapse by two distinct microscopic markers, basal plasmacytosis and cryptitis[7].

Depending on the severity of the illness, 20 to 30 percent of UC patients must undergo emergent, urgent, and elective surgical operations. Rectal inflammation is ongoing, although there are no skip lesions, fissures, or ulcers. The mucosa of the colon is friable and has breeches on the surface. Inflammatory pseudo polyps are visible in the ascending and sigmoid colonic segments[9].

Due to similar clinical symptoms, it is crucial to distinguish UC from diverticular associated colitis (DAC), chronic ischemia, infectious colitis, medication-induced colitis (MIC), and CD. The multiple clinical manifestations of UC12 must be identified through clinicopathological correlation.

The colonic mucosa and rectal sparing on endoscopy are unremarkable in children and young adults with UC. In youngsters, basal plasmacytosis, a sign of chronicity, is less common[13].

METHODS

Study Design: Case series study
Settings: Department of Histopathology, Sheikh Zayed Hospital, Lahore Pakistan.
Duration: One year from February 25, 2016 to February 24, 2017.
Sample Size: One hundred and ninety cases.
Sampling Technique: Non-Probability Purposive Sampling
Data collection procedure: All the cases underwent endoscopic colonic biopsies from three sites, proximal colon, distal colon and rectum, received in separate container. Mucosal samples underwent a 16-hour overnight processing procedure in the automatic tissue processor that included ethyl alcohol dehydration, xylene clearing, paraffin wax impregnation, and tissue block formation. Stains with hematoxylin and eosin were applied
Inclusion criteria: Outdoor diagnosed relapsed UC patients of both gender. Patients with all sets of colonic mucosal sampling
Exclusion criteria: Pediatric patients, biopsy proven cases of colorectal carcinoma, patients on endoscopic & clinical remission, patients who refused to give informed consent.
Data Analysis: The data for age, gender, clinical features, histological features and time since last remission were analyzed by using SPSS version 23.0 and described by using mean, median and interquartile range respectively. Qualitative variables like clinical features and histological features were described as frequencies and percentages (Table I).

The relative risk of earlier relapse was measured on the basis of basal plasma cells present at baseline and was presented with 95% confidence interval, adjusted odd ratio of basal plasma cell with other confounding feature like crypt abscess was calculated by using binary logistic regression and was presented by using 95% confidence interval.

RESULTS

One hundred ninety patients of ulcerative colitis, relapsed during one year included. Among these patients majority patients are in 31-45 age group 64(33.7%). Mean age of all patients is 39.98±16.34. Minimum, maximum and inter quartile age range is15, 82 and 27 years.

Table-1: Main clinicopathological features of Ulcerative colitis patients

Mean age	39.68 year	
Gender	Frequency	Percentages (%)
Males	117	61.6
Females	73	33.7
Clinical features		
Vague abdominal pain	105	55.3
Per rectal bleeding	74	38.9
Diarrhea	68	35.8
Mucus discharge in stool	56	29.47
Altered bowel habits	42	22.1
Anemia	28	14.74
Histological features		
Cryptitis	189	99.5
Chronic inflammation	188	98.5
Neutrophils in lamina propria	151	79.5
Crypt distortion	129	67.9
Crypt abcess	121	63.7
Basal plasma cells	90	47.4
Basal lymphoid aggregates	64	33.7
Eosinophils	24	12.6

There is slight predominance of males 117 (61.6%) in our study. Clinically most patients reported vague generalized abdominal pain 105(55.3%) and least presented with anemia 28(14.74%). Commonest histological feature is cryptitis 189(99.5%) and least seen microscopic feature is eosinophils in lamina propria 24(12.6%). Rest of the clinicopathological features are described in Table-I.

Out of one hundred ninety patients 38(20%) patients had last remission at 4th month and 25(13.16%) patients had last remission at 6th month. Mean last remission was 6.6±2.36 with 1, 12 and 5 as minimum, maximum values and inter quartile age range. Peak time for relapse in most patients is after 4 to 6 months as shown in figure-I.

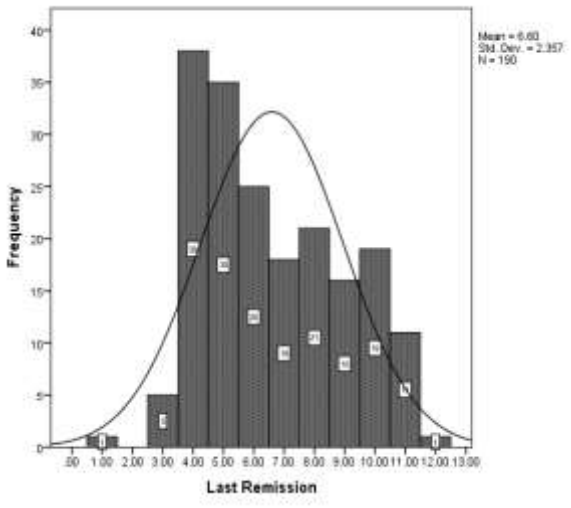

Figure 1: Graphical Presentation of Last Remission

Table-2: Comparison between Last Remission and Basal plasma cells

Last remission	Basal plasma cells		
	Present	Absent	Total
1	1	0	1
	0.90%	0.0%	100.0%
3	5	0	5
	5.56%	0.0%	100.0%
4	38	0	38
	42.2%	0.0%	100.0%
5	28	7	35
	31.1%	20.0%	100.0%
6	14	11	25
	15.5%	44.0%	100.0%
7	3	15	18
	2.70%	83.3%	100.0%
8	1	20	21
	0.90%	95.2%	100.0%
9	0	16	16
	0.0%	100.0%	100.0%
10	0	19	19
	0.0%	100.0%	100.0%
11	0	11	11
	0.0%	100.0%	100.0%
12	0	1	1
	0.0%	100.0%	100.0%
Total	90	100	190
	47.4%	52.6%	100.0%

p-value 0.000001

Patients whose colonic mucosa showed basal plasma cells had an early relapse even 1(0.90%) patient had relapse at 1st month while 38(42.2%) relapsed at 4th month rest is shown in Table- II.

Table-3: Comparison between Last Remission and Crypt Abscess

Last remission	Crypt Abscess		
	Present	Absent	Total
1	1	0	1
	0.82%	0.0%	100.0%
3	5	0	5
	4.13%	0.0%	100.0%
4	36	2	38
	29.6%	5.2%	100.0%
5	33	2	35
	27.3%	5.7%	100.0%
6	22	3	25
	18.2%	12.0%	100.0%
7	9	9	18
	7.44%	50.0%	100.0%
8	6	15	21
	4.96%	71.4%	100.0%
9	6	10	16
	4.96%	62.5%	100.0%
10	3	16	19
	2.48%	84.2%	100.0%
11	0	11	11
	0.0%	100.0%	100.0%
12	0	1	1
	0.0%	100.0%	100.0%
Total	121	69	190
	63.7%	36.3%	100.0%

p-value 0.000001

Similarly, patients with crypt abscess had an early relapse even 1(0.82%) patient relapsed in 1st month while rest of the patients with crypt abscess relapsed at 36(29.8%) at 4th month rest is shown in Table-III.

Both these histological features showed an early relapse between 1st to 6th month after treatment. These microscopic features are helpful for gastroenterologist to continue maintenance therapy of UC patients for a longer time tenure so they could not go in early relapse for the next time as shown in figure III.

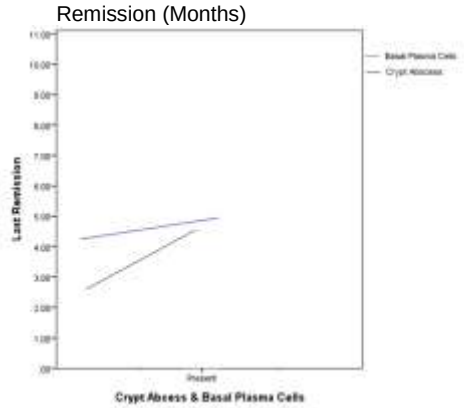

Figure 2: Graphical Presentation of Crypt Abscess and Basal Plasma Cells in Last

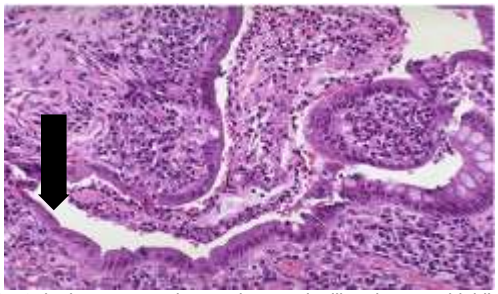

Figure 3: Colonic mucosa shows elongated, dilated crypts highlighted by arrow, Crypt Distortion (400x; H/E)

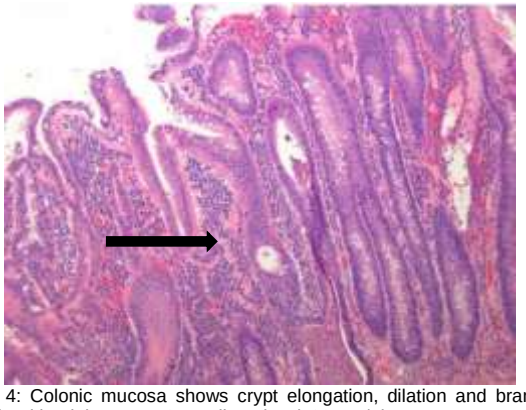

Figure 4: Colonic mucosa shows crypt elongation, dilation and branching highlighted by right arrow, Crypt distortion (400x; H/E)

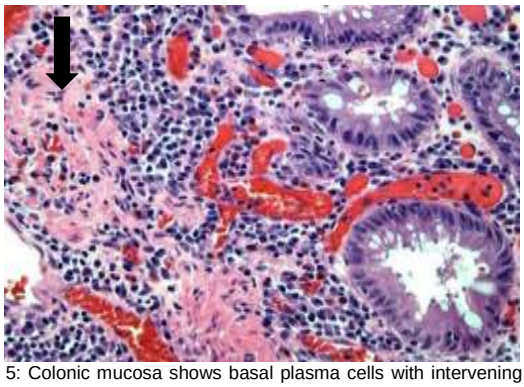

Figure 5: Colonic mucosa shows basal plasma cells with intervening crypts in the lower one third of mucosa highlighted by down arrow, Basal plasmacytosis (400x;H/E)

DISCUSSION

UC is a chronic, lifelong illness that is both remitting and relapsing. Finding the histological characteristics of UC is crucial, but it must also be interpreted in light of clinical, endoscopic, and radiographic data. The biological UC treatment has significantly altered patient outcomes and improved quality of life[9].

In our investigation, the average computed age was 39.98 years (Table 1), and the majority of patients were between the ages of 31 and 45. In contrast to Robert V. Bryant et al, who reported 50 years of age at six years of follow-up, Alain Bitton et al. observed a mean age of 40 years over the course of one year. The average age was noted to be 38 years by Aranzazu Jauregi Amezaga[16] and 37.8 years by Petrille Andre Cavalcante De Barros et al [17] for the Brazilian population.

In terms of sex, we had 117 patients who were mostly male (61.6%) (Table 1), which matched two prior works conducted by S.A. Riley et al. [18, 19]. Our study, however, only included 73 (38.4%) females, whereas Angela Rochi et al. found a modest increase in female prevalence of 1.3 [20]. In contrast, more females were recorded by Aranzazu Jauregi Amezaga et al. [16], Petrille Andre Cavalcante de Barros et al. [17], and Alain Bitton et al. [14]. There is no correlation between gender and UC patients.

In contrast to Yasmin Ozmin et al, 105 (55.3%) of the clinically relapsing UC patients in our study (Table 1) reported having vague stomach pain [22]. Rectal bleeding was the second-most frequent presenting complaint in our sample (70.53%), compared to studies by Sang Hyoung Park et al. (90.8%) and Yasmin Ozmin et al (91.2 %). [21,22] As opposed to research conducted by Joshua E. Melson et al. 22 (46%) [23], Sheenam Azad et al. 8 (53.33%) [24], and Alain bitton et al.[14]

Our investigation's primary histology finding was cryptitis 189 (99.5%) (Table 1). Our study showed crypt distortion 129 (67.9%), compared to Joshua E. Melson et al 44 (92%) and Sheenam Azad

et al [15] (100%). Alain Bitton et al. [14], SA Riley et al. [19], Aman et al. [25] In contrast to SA Riley's 82(100 %) [19] and Aranzazu et al 222 (65%)[16], our investigation revealed Basal plasma cells 90 (47.4 %).

One twenty one patients out of 190 individuals relapsed in the fourth month 36(94.7%). Our investigation revealed that the majority of patients experienced relapses at the fourth, fifth, and sixth months at rates of 28%, 38%, and 14%, respectively, with a significant p value of 0.000001. Thus, supporting previous research by Alain Bitton et al.[14], Rish K.Pai[26], Sheenam Azad et al.[24], Klaudia Frakas et al. [27], and SA Riley et al.[19] showing the presence of basal plasma cells and crypt abscess is a stronger predictor of relapse. According to research by Laurent Peyrin Biroulet et al, histological remission is a main end point since it is directly connected with patients' improved outcomes.

CONCLUSION

Patients with relapsed UC typically presented with nebulous abdominal pains. In our investigation, the histological feature most frequently observed in relapsing ulcerative colitis patients is cryptitis. Patients should be treated with prolonged maintenance medication since the presence of cryptitis and basal plasma cells suggested an early relapse. The monitoring of UC patients needs to use a multimodality approach, and the function of histological/mucosal healing needs to be clarified.

Limitations: It was beyond the scope of this study to correlate with endoscopic findings. Other limitation were smaller sample size, limited time duration, limited finances, poor compliance of patients and lack of careful histological evaluation.

Recommendations: It is advised that all gastroenterologists offer endoscopic information for all UC patients. .

Conflicts of Interest: There were no conflicts of interest.

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