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Evaluation of causes of Flare up and Correspondence of Clinical symptoms with Colonoscopic and Histopathologic Findings

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KEYWORDS

Ulcerative Colitis, Flare Up, Rectosigmoidoscopy

A B S T R A C T

Ulcerative colitis has a relapsing nature, which these recurrent attacks can be debilitating. The social factors involved in flare up and also the comparison between colonoscopic and histopathologic findings and severity of clinical symptom will be reviewed in this study. 51 patients with previously proved ulcerative colitis and flare up symptoms were studied during a year. In addition, paraclinical tests to check for possible causes, all patients underwent rectosigmoidoscopy and biopsy, within first 24 hours of admission. To assess the severity of clinical symptoms and also colonoscopic-pathologic findings, the criteria's of True love-witts and modified UCDAI were used respectively. No positive stool culture or clostridium difficile toxin was found. In 12 patients the cyst or Trophozoites of Entamoeba histolytica was seen and one patient had CMV colitis. 19 patients were with moderate symptoms, and 32 patients had severed symptoms, which of these 32 patients, in 30 patients, in the colonoscopic view, Friability and ulceration with drastic changes were seen. Also in 27 patients of which, sever inflammatory histopathological changes (Grade 3) were observed. Most cases of ulcerative colitis, flares up, are due to relapsing nature of disease and sever clinical symptoms are matched with colonoscopy and pathology findings.

Introduction

UC (ulcerative colitis) is a chronic inflammatory disease of the colon mucosa with unknown etiology which occurs with symptoms such as chronic diarrhea, rectorrhagia, abdominal pain and fever. The diagnosis is based on a set of symptoms, colonoscopy and histopathology (1-2). The remission and exacerbation periods are experienced in about 80% of the patients and this nature of the disease is also seen even up to 20 years after

diagnosis. The few patients have sustained disease with no remission and exacerbation periods (1). In exacerbation period, anemia, leukocytosis, thrombocytosis, hypoalbuminemia, and increased CRP and ESR might be seen in the laboratory tests (1).

Despite UC doesn't have a high mortality and its mortality rate could decline from 30% to less than 2% during attack disease by use of corticosteroids, the quality of the patients life could be influenced by UC flare-up resulted in hospitalization and reducing the individual's ability (1-2).

There is no doubt that UC is associated with remission and exacerbation periods but it should be noted that the flare up period does not necessarily indicate a recurrence of the disease.

Various factors such as bacterial intestinal infections (Salmonella, Shigella, E.coli etc), protozoa (amebiasis), viruses (CMV), drugs (antibiotics, NSAIDs), psychological stress and special seasons might also be involved in the UC flare-up. On the other hands, the recurrence could be caused by poor patient compliance in taking any medications or rebellious nature of the disease (1).

The aim of this study was to identify possible factors involved in the flare up and also to evaluate the correlation of the colonoscopic and histopathologic findings with the clinical symptoms.

Materials and methods

In 2013, we evaluated the possible factors involved in UC flare-up as well as the correlation of the colonoscopic and histopathologic findings with the clinical symptoms which was conducted at Internal Medicine department of Tabriz Medical Sciences University on patients with UC in a descriptive-analytical and predictive research.

All the patients who have our inclusion criteria were counted and then they were enrolled in the study.

Ethical considerations

According to the type of the research and the same specific treatment administered for all the patients and considering that there were no additional laboratory and therapeutic interventions, this study have no specific ethical considerations.

The UC patients who were previously diagnosed with colonoscopy and pathology and hospitalized with the flare up symptoms, considered as the target population and they were selected based on the inclusion and exclusion criteria and enrolled in this study.

Inclusion criteria include

1- The presence of the ulcerative colitis (UC) approved by colonoscopy and pathology
2- Flare up Symptoms such as fever, abdominal pain, diarrhea and rectorrhagia, leading to patient hospitalization.

Exclusion criteria include

1- No access to previous medical records of the patients
2- New case of UC

Besides the history and clinical examination, the necessary tests such as CBC-diff, ESR, CRP, LFT, Na, K, Alb, S / E, S / C, Clostridium difficile toxins A and B in the stool, and CMV_Ab (IgM, IgG) were requested. at the first 24 hours of the hospitalization, rectosigmoidectomy and biopsy (at least 4 samples)were performed for the patients. It should be mentioned that the therapeutic measures administered for the total patients were based on the latest medical resources. 51 patients were evaluated during one year.

Trulove and Witts table (Table-1) and Modified UCDA model (Table-2) was respectively used to estimate the UC symptoms and classifying the colonoscopic and histopathologic findings. The rectosigmoidectomy was conducted by the (Gastroenterology Fellowship) researcher with the help of Pentax colonoscopy device and the pathological samples were reported by the gastroentropathologist.

Results and Discussion

51 eligible patients were enrolled. 25 patients (49%) were men and 26 cases (51%) were female. The mean age of the patients was 32.27 ± 12.07 (from 13 to 76 years old). Half of the patients (50%) were younger than 32 years. 43 cases (84.3%) were non-smokers, and 8 patients (15.7%) were smokers. The most common symptoms were abdominal pain (45(88.2%)) and rectorrhagia (39(76.5%)). According to the patients' previous records, the extent of colonic involvement in the cases were Rectosigmoid (13.7%), left side (19.6%), Extensive (31.4%) and pancolites (35.3%). Demographic and laboratory characteristics of patients are presented in Table 3. Stool culture was negative after 48 hours for all patients and no clostridium difficile was found in any cases.

A positive CMV-IgM by positive PCR was reported which considering the extensive ulceration at colonoscopy so the examination of the colon was no possible. The Amoeba was reported in 12 patients (5 cases with Trophozoites and 7 cases with Entamoeba histolytica). The various drugs such as Azathioprine, 5ASA and biological medications were

being consumed by all the cases before the recent flare up. Furthermore the types and combinations of mentioned drugs are shown in Table 4. The patients were placed in two separate groups by use of Trulove and Witts classification. Due to the above criteria, the moderate and severe symptoms were found in 19 cases (37.3%) and 32 cases (62.7%) respectively.

In colonoscopy, Granular mucosa (grade 2) was observed in 9 cases, the friability condition and ulceration (Grade 3 and 4) were found in 10 cases among the 19 patients but among the 32 patients who had presented with severe symptoms, the granular condition (grade 2) was just observed in 2 cases and the colonoscopy reports of 30 other patients presents the Friability and ulceration (grade 3 and 4) indeed. In addition there was a significant correlation between the colonoscopic view and the symptoms severity of the patients (P= 0.002) (Table 5).

Among the 10 patients with moderate symptoms, friability and ulceration, the severe inflammation (grade 3) was observed in the histopathologic changes of the 5 cases. In addition, among the 30 patients with the severe symptoms and friability and ulceration, the sever inflammation (grade 3) was presented in the histopathologic changes of 27 cases (90%) thus the severity of inflammatory in pathology reports and the colonoscopic view were significantly corresponded (P=0.001). In addition there was a significant correlation between the colonoscopic view and the pathology reports of the patients (P= 0.001) (Table 6).

The nature of UC is based on the remission and exacerbation periods. The exacerbation periods leading to hospitalization of the patient could be associated with high costs, reduce in efficiency and quality of life. Despite the turbulent nature of the ulcerative colitis (UC), other factors such as infection and drugs are involved in the UC flare up too. Concerning this fact that no discussion is found about the impact of these factors on UC flare up but the relationship among colonoscopic-pathologic findings, symptoms and the factors predicted relapse has been studied.

In research conducted by Bart Lemmens and colleagues on the 131 UC patients, there was a significant correlation between colonoscopic findings and pathologic features in severe cases but this relationship has been weekly observed in mild cases(3). Although this study is approximately consistent with our research but it should be noted that our examination included only moderate and sever cases, but the mild cases were also investigated in the mentioned study.

Table.1 Truelove and Witts Classification of the Severity of Ulcerative Colitis

Mild	
	<4 stools/day without or with only small amounts of blood
	No fever
	No tachycardia
	Mild anemia
	ESR < 30 mm/hr
Moderate	
	Intermediate between mild and severe
Severe	
	>6 stools/day, with blood
	Fever > 37.5$^{\circ C}$
	Heart rate > 90 beats/min
	Anemia with hemoglobin level < 75% of normal
	ESR > 30 mm/hr

Table.2 Endoscopic and Histologic Assessment of Disease Activity in Ulcerative Colitis

Score	Criteria
Endoscopic Assessment	
0	Normal mucosa
1	Loss of vascular pattern
2	Granular, nonfriable mucosa
3	Friability on rubbing
4	Spontaneous bleeding, ulceration
Histological Assessment	
0	Normal
1	No significant inflammation: Possibly architectural changes of chronic disease and small foci of lymphocytes but no acute inflammation, crypt abscesses, or epithelial destruction
2	Mild to moderate inflammation: Edema, vascularity, increased acute and chronic inflammatory cells but intact epithelium
3	Severe inflammation: Heavy infiltrate of acute and chronic inflammatory cells, crypt abscesses, ulceration of surface epithelium, purulent exudate

Table.3 Laboratory of patients between two Genders

	Sex				
	Male		Female		P
	Mean ± Std Deviation	Range	Mean ± Std Deviation	Range	
Hb	11.7 ± 2.9	6.1-17	9.9 ± 2.2	6.5-15.8	0.018
WBC	7907.4 ± 3965.5	105-15000	10650 ± 4494.8	3900-20000	0.025
PLT	289.4 ± 95.7	119-504	356.1 ± 178.8	52-790	0.103
ESR	30.6 ± 23.1	4-88	35.9 ± 19.8	3-75	0.381
Cr	1 ± 0.12	0.8-1.3	0.88 ± 0.2	0.5-1.3	0.015
AST	21.3 ± 18.7	6-100	12.92 ± 6.24	3-28	0.036
ALT	23.12 ± 14.01	9-69	15.88 ± 10.93	4-58	0.045
Alb	3.64 ± 0.68	1.8-4.4	3.62 ± 0.63	2-4.5	0.893
$Na^{\pm}$	139.6 ± 2.8	135-147	137.5 ± 3.5	130-144	0.023
$K^{\pm}$	3.9± 0.4	2.8-4.7	3.88 ± 0.43	3-5	0.951

Table.4 The types and combinations of mentioned drugs of patients

Medication	Frequency	Percent
5ASA	10	19.6%
Biologic	1	2.0%
5ASA & Corticosteroid	9	17.6%
5ASA & Corticosteroid& Azathiopurin	15	29.4%
5ASA & Corticosteroid& Biologic	2	3.9%
5ASA & Azathiopurin	5	9.8%
5ASA & Corticosteroid & Azathiopurin& Biologic	7	13.7%
5ASA & Azathiopurin & Biologic	2	3.9%

Table.5 Correlation between the colonoscopic view and the symptoms severity of the patients

		Severity of UC		Total
		Moderate	Sever	
Colonoscopic View	Granular	9(17.6%)	2(3.9%)	11(21.6%)
	Friability	8(15.7%)	18(35.3%)	26(51%)
	S.B. ulceration	2(3.9%)	12(23.5%)	14(27.5%)
Total		19(37.3%)	32(62.7%)	51(100%)

Table.6 Correlation between the colonoscopic view and the Pathology Reports of the patients

		Pathology Reports			
		No Inflammation	Mild to Moderate Inflammation	Sever Inflammation	Total
Colonoscopic View	Granular	4(7.8%)	7(13.7%)	-	11(21.6%)
	Friability	-	8(15.7%)	18(35.3%)	26(51%)
	S.B. ulceration	-	-	14(27.5%)	14(27.5%)
Total		4(7.8%)	15(29.4%)	32(62.7%)	51(100%)

Taro Osada et al' study indicated that the clinical findings during colonoscopy have a significant relationship with involvement value of the distal colon and ESR and CRP increase display the severity of proximal colon. Furthermore it has been suggested that the total colonoscopy should be performed for the patients with and increased ESR and CRP during the UC flare up(4).
Although this study is valuable but there are some restrictions which make it inapplicable. In severe cases, the total colonoscopy has not been confirmed as a practical and scientific method because it might increase the risk of toxic megacolon. In Y Nishio et al study, it was emphasized on the importance of the pit pattern scheme as a predictor of the recurrence in UC by use of chromoscopy (5).

This study was conducted on the patients with inactive UC and it is not generalized to cases who suffered from an active ulcerative colitis. In numerous studies such as Ventsislav et al research, it was emphasized on the measurement of fecal Calprotectin as a non-invasive test to assess the mucosal inflammation, treatment process evaluation and the recurrence prediction(6). This is an appropriate study that could be used in the future researches which is similar to our study. In Asuka Nakarai et al's study the FIT is recommended to predict mucosal healing rather than the colonoscopy and FOBT (7). Talat Bessissow and colleagues study noted that the pathologic findings, especially Basal Plasmacytosis, could better predict the relapse and the observation of mucosal healing during the colonoscopy could not be a guarantee of non-recurrence in the patients, therefore the histological improvement in these cases should be considered (8). In Anne E. Gifford et al research, the random measurement of the urinary salicylate has been suggested to identify the UC patients with poor compliance to take the 5ASA components (9). This was a remarkable study, we were able to simultaneously measure the urinary and mucosal salicylate to determine their relationship but it was impossible because of the hardware problems.

All reviews of Clostridium difficile in the stool cultures were negative in a recent study. The CMV colitis and active amebiasis were respectively observed in one and five cases. In 45 cases (88%) there was no specific agent as a secondary factor for flare up and the possible flare up was only due to the relapse in patients. The most of these patients have been treated by the preservatives therapy and not taking the medication could not be considered as a flare up factor. Perhaps if we were able to measure the amount of mucousal 5ASA in the patients, we could better evaluate the inadequate acceptance or insufficient dose of the drugs but it is certain that

the most flare ups are related to the nature of the ulcerative colitis disease. Among 32 patients with severe symptoms, the mucosal friability and the ulceration were evaluated in the colonoscopic findings of 30 cases (93.75%) and the histopathologic changes as the severe inflammation (grade 3) were found in the 27 of them.

The more severity of the clinical symptoms would associate with the higher mucosal involvement in the colonoscopy. The more severe mucosal involvement in colonoscopy may increase the likelihood of severe inflammation of the mucous. There was a significant consistent between the Colonic mucosa involvement and the symptoms in colonoscopic view. Furthermore the correlation between the Colonic mucosa involvement and the mucosal inflammation was remarkable too in histopathology ($P<0.001$).

Among 10 patients of the 19 patients with moderate symptoms, the intense mucosal involvements have been observed as the friability and ulceration. The severe inflammation symptoms (grade 3) were found in 5 cases (50%). Among the 40 patients (30 patients with the severe symptoms and 10 patients with moderate symptoms) who present the mucosal involvements as the friability and ulceration during the colonoscopy; the severe inflammation symptoms (grade 3) was observed in the 32 cases (80%).

It should be mentioned that the severe mucosal involvements (as the friability and ulceration) has a remarkable consistent with the intense mucosal inflammation which refers to the inability to control the disease ($P<0.001$).

Conclusion

In most cases, ulcerative colitis flare up is due to the relapse of the disease and the infectious factors have a weak effect in the meantime.

Severe clinical symptoms are consistent with severe mucosal involvement in colonoscopy; severe mucosal involvement in colonoscopy (Along with moderate or severe symptoms) has a significant correlation with the intensity of the mucosal inflammation which indicates the lack of proper control on the disease.

Suggestions

This study has some limitations:

1. Patients were studied in a period of one year. The sample size was relatively small. Maybe the results would be generalizable in a longer timeframe of the study.
2. In this study, the hospitalized patients with the moderate and severe symptoms were evaluated and the outpatients were not included, so the study was less generalizable.

3. If it was possible to evaluate the mucosal 5ASA, we were able to comment on the causes of relapse and insufficient patient compliance more precisely so it could be the basis of other studies.
4. The sufficient follow up was not performed for these patients. it was probably better to allocate a specific budget to perform total colonoscopy following the clinical remission and then the pathological changes would be investigate by the further biopsy.

References

1- Sleisenger, Ffordtran, gastrointestinal and liver disease, pathophysiology diagnosis management, vol.2,2010, pp. 1991-2.

2- C. Bello, J. Belaiche, E. Louis, C. Reenaers, Evolution and predictive factors of relapse in ulcerative colitis patients treated with mesalazine after a first course of corticosteroids, Journal of Crohn's and Colitis (2011) 5, 196–202.

3- Bart Lemmens, Gert Van Assche, Xavier Sagaert, Karel Geboes, Marc Ferrante, Paul Rutgeerts, Séverine Vermeire and Gert De Hertogh, Correlation Between the Endoscopic and Histologic Score in Assessing the Activity of Ulcerative Colitis, Crohn's & Colitis Foundation of America, Inc, Volume 19, Number 6, May 2013.

4- Taro Osada, Toshifumi Ohkusa, Isao Okayasu, Tsutomu Yoshida, Shu Hirai, Kazuko Beppu, Tomoyoshi Shibuya, Naoto Sakamoto, Osamu Kobayashi, Akihito Nagahara, Takeshi Terai and Sumio Watanabe, Correlations among total colonoscopic findings, clinical symptoms, and laboratory markers in ulcerative colitis, Journal of Gastroenterology and Hepatology 23 (2008) Suppl. 2; S262–S267 © 2008 The Authors Journal compilation © 2008 Journal of Gastroenterology and Hepatology Foundation and Blackwell ublishing Asia Pty Ltd.

5- Y Nishio, T Ando, O Maeda, K Ishiguro, O Watanabe, N Ohmiya, Y Niwa, K Kusugami, H Goto, Pit patterns in rectal mucosa assessed by magnifying colonoscope are predictive of relapse in patients with quiescent ulcerative colitis, Pit patterns in rectal mucosa, Gut 2006;55:1768–1773. doi: 10.1136/gut.2005.

6- Ventsislav N Nakov, Plamen I Penchev, Milko T Shishenkov, Radislav V Nakov, Todor G Kundurzhiev, Fecal Calprotectin for Assessment of Inflammatory Activity, Monitoring of Therapy and Prediction of Relapse in Ulcerative Colitis, Gastroenterology and Hepatology Research, Journal of GHR 2012 December 21 1(11): 297-302.

7- Asuka Nakarai , Jun Kato, Sakiko Hiraoka, Motoaki Kuriyama ,Mitsuhiro Akita ,Tomoko Hirakawa ,Hiroyuki Okada and Kazuhide Yamamoto , Evaluation of Mucosal Healing of Ulcerative Colitis by a Quantitative Fecal Immunochemical Test, Am J Gastroenterol 2013; 108:83–89; doi: 10.1038/ajg.2012.315; published online 25 September 2012

8- Talat Bessissow , Bart Lemmens , Marc Ferrante , Raf Bisschops, Kristel Van Steen , Karel Gert, Prognostic Value of Serologic and Histologic Markers on Clinical Relapse in Ulcerative Colitis Patients With Mucosal Healing, The American Journal of GASTROENTEROLOGY VOLUME 107 | NOVEMBER 2012.

9- Anne E. Gifford , Anders H Berg , Conor Lahiff , Adam S. Cheifetz , Gary Horowitz and Alan C.Moss , A Random Urine Test Can Identify Patients at Risk of Mesalamine Non-Adherence: A Prospective Study, Am J Gastroenterol 2013; 108:249–255; doi: 10.1038/ajg.2012.419; published online 8 January 2013.