Descriptive study of Extragastrointestinal Manifestations of Ulcerative Colitis and their relation to disease activity in 100 Iraqi patients

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Fac Med Baghdad 2011; Vol. 53, No. 1
Received Sept. 2010
Accepted Jan. 2011

Summary:

Background: Ulcerative colitis is a chronic inflammatory bowel disease (IBD); its extragastrointestinal manifestations vary from one country to another. This study identifies the prevalence of the extragastrointestinal manifestations in a sample of Iraqi patients with ulcerative colitis and their relation to disease activity.

Patients and Methods: A descriptive study was conducted on 100 patients with established diagnosis of ulcerative colitis, who attended Baghdad Teaching hospital and Gastroenterology center in Baghdad during the period from May 2009 to January 2010. A direct interview and thorough clinical examination were done to determine the history of the disease, its severity and the presence or absence of the extraintestinal manifestations.

Result: The Extragastrointestinal manifestations were observed in 17 patients (17%). The most common EGlMs were the peripheral arthritis and mouth ulcer. The EGlMs were more common in patients with severe disease.

Conclusion: The EGlMs of ulcerative are less common in Iraqi patients than in patients from western countries, but their relation with disease activity was relatively similar.

Keywords: ulcerative colitis. extragastrointestinal manifestatio

Introduction

Ulcerative colitis (UC) is a chronic inflammatory condition of unknown aetiology, mainly involving the large bowel, characterized by diffuse mucosal and submucosal inflammation limited to the colon and rectum. It extends proximally in a symmetrical, circumferential pattern to involve parts or all of the large intestine. The dominant symptom in ulcerative colitis is diarrhea, which is usually, but not always, associated with blood in the stool. The diarrhea is often associated with rectal urgency and tenesmus. The clinical course is characterized by exacerbations and remissions that may occur spontaneously or in response to medical management. (1), the incidence and prevalence of ulcerative colitis vary with geographic location; the highest rates occur in white populations in northern Europe & North America, where the incidence is about 5 per 100,000 and the prevalence is approximately 50 per 100,000. (2)

Extraintestinal Manifestation : Some of these manifestations are related to the activity of the colitis other are not (3) The reported frequency of EGlMs in patients with IBD varies from 6%-47%, but generally up to one-third of IBD patients have at least one extragastrointestinal-manifestation (4,7) , **Related to activity of colitis**: Peripheral arthropathy , Erythema nodosum , Episcleritis, anterior uveitis conjunctivitis , Aphthous ulceration of the mouth , Fatty liver , Pyoderma gangrenosum , **Unrelated to activity of colitis**: Sacroiliitis , Ankylosing spondylitis , Primary sclerosing cholangitis , Metabolic bone disorders , Thromboembolic disorders , Pericarditis , Acute febrile neutrophilic dermatosis Sweets syndrome , Amyloidosis.

Patients and Methods:

This descriptive study was conducted on 100 patients who attended Baghdad Teaching Hospital and Gastroenterology center in Baghdad, during the periods from May 2009 to January 2010. All eligible patients had an established diagnosis of ulcerative colitis based on clinical, endoscopic and histopathological findings.

Any patient who had in addition a diagnosis of other autoimmune disease (e.g. rheumatoid arthritis, SLE) was excluded from the study because they may have clinical features that simulate extraintestinal manifestations of ulcerative colitis.

A questionnaire was designed to evaluate the patients by direct interview including patient name, age, gendre, date of diagnosis, and history of smoking.

The other parts of the questionnaire included assessment of disease activity and reporting any extragastrointestinal manifestations may the patient had.

Table -1- Mayo Scoring system for assessment of ulcerative colitis severity. [6]

1.Stool frequency
= Normal no. of stool
= 1 to 2 stools more than the normal
= 3 to 4 stools more than the normal
= 5 or more stools more than the normal
2.Rectal bleeding
= No bleeding seen
= streaks of blood in the stool less than half the time
= Obvious blood with the stool most of the time
= Blood alone pass
3.Finding on endoscopy
= Normal
= mild disease (erythema, decrease vascular pattern , mild friability)
= moderate disease.(marked erythema, lack of vascular pattern,
friability, erosions)
= Severe disease (spontaneous bleeding, ulcerations)
4.Physician's global assessment£
= Normal
= Mild disease
= Moderate disease
= severe disease

- £ Physician's global assessment acknowledges the three other criteria, the patient daily recollection of abdominal discomfort and general sense of well being, and other observations, such as physical findings and patient performance state.

Results:

One hundreds (100) patients were included in the study, 57 (57%) were males and 43 (43%) were females, the youngest patient was 17 years old and the oldest was 83 years, the mean age of the patients was (46.2).the duration of the disease was ranging from less 1 years to 20 years. Table (2) shows the

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distribution of Ulcerative colitis in the studied patients according to age , gender , and the duration of the disease**.**

Table 2: Distribution of ulcerative colitis according to gender, age, and disease duration.

1- Gender	**Number**	**%**
Male	57	57%
Female	43	43%
2- Age group (years)		
<20	3	3%
20-40	34	34%
40-60	45	45%
>60	18	18%
3- Disease duration(years)		
<1	14	14%
1-5	48	48%
>5	38	38%
Total	**100**	**100%**

Extragastrointestinal manifestations were verified in 17 patients (17%), 9 (52.9%) of them were males and 8 (47.1%) were females, table (3) shows distribution of EGlMs among the studied patients .

Table -3- Distribution of ElMs among patients.

Extraintestinal manifestation	**Male n(%)**	**Female n(%)**	**Total n(%)**
Oral ulcer	1(5.88%)	1(5.88%)	2 (11.76%)
Peripheral arthritis	1(5.88%)	1(5.88%)	2 (11.76%)
Ankylosing spondylitis	1(5.88%)	0 (0%)	1(5.88%)
Sacroiliitis	0 (0%)	1(5.88%)	1(5.88%)
Deep venous thrombosis	1(5.88%)	0 (0%)	1(5.88%)
Oral ulcer + Periph. arthritis	1(5.88%)	1(5.88%)	2 (11.76%)
Oral ulcer + conjunctivitis	1(5.88%)	0 (0%)	1(5.88%)
Oral ulcer + Anterior uveitis	0 (0%)	1(5.88%)	1(5.88%)
Periph.arthrits + Ankylosing spondylitis	1(5.88%)	1(5.88%)	2 (11.76%)
A.spondylitis + Sacroiliitis	0 (0%)	1(5.88%)	1(5.88%)
Oral ulcer + Periph.arthritis + Erythema nodosum	1(5.88%)	0 (0%)	1(5.88%)
Oral ulcer+Periph.arthritis + Erythema nodosum +Conjunctivitis	0 (0%)	1(5.88%)	1(5.88%)
Oral ulcer + Periph.arthritis + Ankylosing spondylitis	1(5.88%)	0 (0%)	1(5.88%)
Total	9 (52.9) %	8 (47.1)	17 (100%)

Extragastrointestinal manifestations were more common in patients with age less than 40 years than in those with age more than 40 years and this difference stated as significant **(p-value** =0.04). The mean age of males with EGIM was (40.1) years and of females was (40.3) years and the difference was statistically insignificant (**p-value=0.9).** Which means that there was no age predominance of ElMs in neither gender compared to the other, Table (4) shows the distribution of extraintestinal manifestations according to age groups and gender.

Table- 4 - Distribution of patients with and without EGIMs according to age groups and gender

All Patients				**Males**			**Females**		
Age groups	EIM	No EIM	Total	EIM	No EIM	Total	EIM	No EIM	Total
<20	1	2	3	1	1	2	0	1	1
20-40	9	25	34	4	14	18	5	11	16
40-60	5	40	45	3	24	27	2	16	18
>60	2	16	18	1	9	10	1	7	8
Total	**17**	**83**	**100**	**9**	**48**	**57**	**8**	**35**	**43**
Mean ageing	**40.2**	**47.1**	**46.2**	**40.1**	**46.8**	**46.3**	**40.3**	**47.3**	**46.4**
-+SD	**13.2**	**12.6**	**12.4**	**13.5**	**12.3**	**12.7**	**13.4**	**12.4**	**12.5**

The presence of Extragastrointestinal manifestations were more common among females (8 of 43=18.6%) than in males (9 Of 57= 15.7%) but the difference was statistically insignificant (p-value=0.45). table (5).
The extraintestinal manifestations were more common in patients with disease duration more than 5 years than in those with less than 5 years duration and the association of extragastrointestinal manifestations with disease duration was statistically significant (p-value= 0.047). table (6).

Table- 5 - Distribution of patients with EIM according to disease.

Disease duration	**With EIM**	**Without EIM**	**Total**	**P-value**
< 1 year	1(7.1%)	13(92.9%)	14(100%)	0.047
1-5 years	6(12.5%)	42(87.5%)	48(100%)	
> 5 years	10(26.3)	28(73.7%)	38(100%)	

Table (6) shows the prevalence of Extragastrointestinal manifestations among the studied patients , where the peripheral arthritis and oral ulcer were the most common Extragastrointestinal manifestations ,while episcleritis and pyoderma gangrenosum were not verified in any patient.

Table -6- The prevalence of extraintestinal manifestations among all patients

Extraintestinal manifestation	**patient with EIM**	**% of total pt.**
Mouth ulcer	9	9%
conjunctivitis	2	2%
episcleritis	0	0%
Anterior uveitis	1	1%
Peripheral arthritis	9	9%
Ankylosing spondylitis	4	4%
Sacroiliitis	3	3%
Erythema nodosum	2	2% •
Pyoderma Gangrenosum	0	0%
Deep venous thrombosis	1	1%

Table (7) shows the prevalence of each Extragastrointestinal manifestation according to gender , despite the difference in the prevalence of EIM among genders, no one of these differences was statistically significant .(all the estimated P-value was > 0.05, although the number of some EIM was very low for valuable statistical analysis)

Table 7 : Distribution of ElMs according to gender

	Total	Male(% among male)	Female(%among female)	P-value
Oral Ulcer	9	5(8.7%)	4(9.3%)	0.59
Conjunctivitis	2	2(3.5%)	0(0%)	0.32
Episcleritis	0	0(0%)	0(0%)	
Anterior Uveitis	1	0(0%)	1(2.3%)	0.43
Peripheral arthritis	9	5(8.7%)	4(9.3%)	0.59
Ankylosing Spondylitis	4	2(3.5%)	2(4.6%)	0.57
Sacroiliitis	3	2(3.5%)	1(2.3%)	0.61
Erythema Nodosum	2	1(1.7%)	1(2.3%)	0.67
Pyoderma Gangrenosum	0	0(0%)	0(0%)	
DVT	1	1(1.7%)	0(0)	0.57

Table (8) Represent the patients with extraintestinal manifestation according to the severity of ulcerative colitis ,and show that the risk of having extraintestinal manifestations was significantly higher in patients with moderate to severe disease than in patients with mild and in a remission disease (p-value=0.002).

Table – 8 – Distribution of the patients with EIM according to the severity of DIA (Mayo) score

Disease severity	Total	Patients with EIM%
Remission (score <2)	**22**	**1(4.5%)**
Mild (score 3-5)	**46**	**5(10.6%)**
Moderate (score 6-10)	**19**	**5(31.2)**
Severe (score > 10)	**13**	**6(46.1%)**
Total	**100**	**17**

Table (9) shows the prevalence of each extraintestinal manifestation according to the severity of ulcerative colitis as following:

Oral Ulcer: the risk of having oral ulcer is significantly higher in patients with moderate to severe disease than in patients with mild and in a remission disease (p-value =<0.001) which indicate that oral ulcer is highly related to disease activity

Peripheral arthritis: the risk of having Peripheral arthritis is significantly higher in patients with moderate to severe disease than in patients with mild and in a remission disease (p-value =0.003) which indicate that: Peripheral arthritis is highly related to disease activity Erythema Nodosum: present only in patients with severe disease, and its relation to disease activity stated as significant (P-value: 0.01) which indicate its relation to disease activity.

Sacroiliitis: was verified in 1 patient with mild disease and 2 patients with moderate disease but its relation to disease activity was statistically not significant.(P-value=0.24) i.e not related to disease activity.

Ankylosing spondylitis: was only verified in patients with mild & in a remission disease and it was not related to disease activity.(P-value=0.19)

Eye manifestations: conjunctivitis found in one patient with mild disease and one with severe disease, uveitis in one patient with moderate activity. The number was low to show the relation with disease activity.

DVT: was present in one patient with mild disease.

Table-9- Distribution of ElMs according to the severity of DAI (Mayo) score

The Extraintestinal Manifestation	Remission Score <2	Mild Score 2-5	Moderate score 6-10	Severe score>10	Total	P-value
Oral ulcer	-	1(11.1%)	3(33.3%)	5(55.6%)	9(100%)	< 0.001
Conjunctivitis	-	1(50%)	-	1(50%)	2(100%)	0.41
episcleritis	-	-	-	-	-	
Ant.Uveitis	-	-	1(100%)	-	1(100%)	0.34
Periph.arthritis	-	2(22.2%)	2(22.2%)	5(55.6%)	9(100%)	0.003
Ank.spondylitis	1(25%)	3(75%)	-	-	4(100%)	0.19
Sacroiliitis	1(33.3%)	-	2(66.7%)	-	3(100%)	0.24
Erythem.Nodosum	-	-	-	2(100%)	2(100%)	0.01
Pyo.Gangrenosum	-	-	-	-	-	
DVT	-	1(100%)	-	-	1(100%)	0.34

Two patients (11.7%), one with ankylosing spondylitis and the other with sacroiliitis had developed these ElMs before the intestinal manifestations of Ulcerative colitis became clinically evident.

Two of the studied patients were having a skin disease which diagnosed as lichen planus.

Discussion:

Ulcerative colitis is a chronic, relapsing and progressive inflammatory bowel disease of uncertain etiology thought to be triggered by genetic, environmental, and immunological factors [7].

Far from its bowel manifestation, ulcerative colitis has many extraintestinal manifestations (ElMs), and it has been reported that these ElMs affect almost any organ system in the body [8] . Due to the fact that one EIM increase the risk for developing the other ElMs [9], this study tries to focus on the most commonly and easily described ElMs. Many systems were discussed for the evaluation of the disease activity, we selected the Mayo score system due to its simplicity and its collection to a numerical score, indeed that the Food and Drug Administration (FDA) currently favors the Mayo score, or Disease Activity Index (DAI) [4], for trial design in ulcerative colitis, although it is not yet completely wedded to this.

From 100 patients who were enrolled in this study the Extragastrointestinal manifestations were verified in 17 patients (17%) although we didn't include the all ElMs of UC, this rate was lower than the prevalence of the same ElMs in many western countries (10, 11,) , but it was relatively consistent with many studies from the middle east (12, 13,) , also it has been reported that EIMs is less commonly observed in Arab population (14). and other studies reported that the EIMs is significantly lower in Asia and Africa (15,16).

In agreement with many studies, this study showed that the EIMs of ulcerative colitis tend to occur in younger patients (17, 18).

In this study we found that the occurrence of EIMs was significantly associated with longer disease duration which was consistent with many studies [69~71]

No much data are available that compare the rate of EIM between males and females , how ever our study was in consistence with three Other studies done in the western countries (18,19) which reported a slight female predominance . In agreement with most of references (2), and studies (15, 16, 20), our study showed that the patient with greater severity of colitis carry a higher risk for the development of EIMs. As with most other studies our study showed that the most frequent EIM is peripheral arthritis (15, 21, and 22). The rate of peripheral arthritis in this study was 9%. and despite the different ranges of the rate of peripheral arthritis mentioned in the references (2, 3), the rate in our patients was lower than what reported in western studies in which the rate was >22% [23, 24, 25], and consistent with one Omani study (12) in which the rate was also 9%.in accordance to many references and studies (2, 26), this study showed that

peripheral arthritis ran a course parallel to the disease activity.

Also different ranges for Ankylosing spondylitis is reported from 1% to 20% [3,28].in our study Ankylosing spondylitis was verified in 4% of the patients and as with those studies it ran a coarse independent to disease activity. The reported range of sacroiliitis is (10-20%) [3,28,29], while only 4 patients (4%) in our study have sacroiliitis , and in consistent with these reports ,the coarse of sacroiliitis in our patient was not related to disease activity.

In argument with many reports [30,31]; which mentioned that oral ulcer is more commonly related to Crohn's disease ,in our study the oral ulcer was found in 9 patient (9%) but in accordance to these reports it was highly related to disease activity.

The reported rates of Erythema nodosum in western area was (5-15%) [27] ,while the rate in this study was 2%,which was also lower than what was reported in the study of Aftab A. et al in Omani population. In consistent with most of references (8,27) Erythema nodosum was related to disease activity in our study.

Pyoderma gangrenosum reported in 2-5% of patient with IBD and it was suggested that it is more common in U.C than Crohn's disease (27) , While no single case is reported in this study

The reported rate of ocular manifestations is 1-6% [32]/ in our study it was 3% .studies relate them to disease activity (38), in our study it was verified in mild moderate and severe disease .It had been reported that episcleritis is the most common ocular manifestation of UC (32), while no single case is found in our study.

The rate of DVT is estimated to be l-2% (34,35). in our study it was verified in one patient (1%) ,and as with those report it was unrelated to disease activity.

Two of patients(11.7%) who were enrolled in our study developed EIMs (one with Ankylosing spondylitis and the other with sacroiliitis) before the intestinal symptoms of ulcerative colitis became clinically evident, this was in consistent with many reports (19,36)

Two patients in our study had been diagnosed with Lichen planus, despite the wide spectrum of skin manifestations mentioned in many references (37,38, 39, 40) no one reported that lichen planus is a manifestation of inflammatory bowel disease, whether this manifestation is related to Ulcerative Colitis or not it need to be followed more.The pathogenesis of EIMs associated with IBD is poorly understood. Many ElMs are hypothesized to be due to immune reactions, supported by the observations that primarily immunological derangements progress to the development of IBD and that patients with EIM have an increased risk of autoimmune diseases (41)

Genetic factors also have been implicated in the pathogenesis of ElMs in IBD. Ethnic and racial differences in IBD phenotype have potential implications for diagnosis and management of IBD and its complications (42). Studies reveal associations of ElMs in IBD with major histocompatibility complex loci. For examples, patients with CD who have ElMs are more likely to have HLA-A2, HLA-DR1, and HLA-DQw5, whereas patients with UC and ElMs are more likely to have HLA-DR103, B27, and B58 phenotypes (43).

Some of above facts may explain the lower incidence of ElMs in our population, in addition it has been reported that ulcerative colitis in the Middle Eastern population is generally a less extensive disease of mild to moderate severity (44, 45).

Conclusion

Although this study didn't enroll all the extragastrointestinal manifestations of Ulcerative colitis, the studied ElMs were less common in our locality compared to western countries. And relatively were in accordance with reports from Middle East countries

The ElMs were more common in patients with active disease.

ElMs of Ulcerative tend to occur in younger patients with longer duration of the ulcerative colitis.

There was no significant difference in the rate of ElMs between males and females.

ElMs may precede the intestinal symptoms of Ulcerative Colitis.

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