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Extension of ulcerative colitis

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Background/aims: *It is known that ulcerative proctitis might show extension, but in practice, patients with proctitis are not considered as important with regard to regular follow-up and treatment. The aim of this study was to evaluate the extension of ulcerative colitis cases limited to the rectum and compare them with the patients with rectosigmoid and left colonic ulcerative colitis for their features, risk factors influencing the extension and natural course of the disease.* ***Methods:*** *The study involved 193 (62 rectal, 49 rectosigmoid and 82 left-sided) ulcerative colitis patients.* ***Results:*** *Fourteen percent of the patients showed extension to at least one proximal segment in 3.9±2.9 (range: 0.8-12) years. The extension was found as 16.1% in proctitis, 12.2% in rectosigmoiditis and 13.4% in left-sided colitis groups. Extension was found 2.79-fold (95% confidence interval: 1.1-7.1) higher in patients with chronic active disease. Further, the patients with amoebic attacks, those under steroid treatment and those without treatment showed higher risk for extension.* ***Conclusions:*** *Patients with proctitis, like the patients presenting with more extensive colitis, should be offered regular treatment and follow-up.*

Key words: Amoeba, chronic active state, extension, proctitis, ulcerative colitis

Ülseratif kolitin ekstansiyonu

Amaç: *Ülseratif proktitin ekstansiyone olabileceği bilinmektedir, ama pratikte proktitli hastalar ciddi hasta olarak kabul edilmezler. Bu çalışmanın amacı rektuma sınırlı ülseratif kolit olgularının proksimale ekstansiyonunu araştırmak ve bunları rektosigmoid ve sol kolona sınırlı olgularla özellikleri, ekstansiyonu etkileyen faktörler ile hastalığın seyri yönünden karşılaştırmaktır.* ***Yöntem:*** *Çalışmaya toplam 193 (62 rektum, 49 rektosigmoid ve 82 sol kolon) ülseratif kolitli hasta alındı.* ***Bulgular:*** *Hastaların %14'ü ortalama 3.9±2.9 (range: 0.8-12) yılda en az bir segment daha proksimale ekstansiyon gösterdi. Ekstansiyon oranı proktitli hastalarda %16.1, rektosigmoid tutulumlu hastalarda %12.2 sol kolon hastalarında %13.4 olarak bulundu. Kronik aktif hastalığı olan hastalarda ekstansiyon oranı 2.79 kat (%95 güven aralığı: 1.1-7.1) daha fazla bulundu. Ayrıca amibik atak geçiren hastalar, steroid tedavisi alan hastalar ile tedavisiz kalan hastaların ekstansiyon riski daha yüksekti.* ***Sonuç:*** *Proktit ile başvuran hastalara da daha ekstansif hastalıkla başvuranlara olduğu gibi düzenli tedavi ve izlem uygulanmalıdır.*

Anahtar kelimeler: Amip, kronik aktif hastalık, ekstansiyon, proktit, ülseratif kolit

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease that affects the mucosa of the colon, with unknown etiology. The degree and extent of involvement vary and generally determine the clinical severity of the disease. At the time of diagnosis, about 46% of patients had distal colitis, 37% had pancolitis and 17% had left-sided colitis (1). There is a pattern for the course of the disease based mostly on the original anatomic location. Patients with an initial diagnosis of pancolitis have more frequent complications, extraintestinal manifestations and systemic symptoms, need more immunosuppressive and surgical therapy and have greater cancer risk. Ulcerative proctitis or rectosigmoiditis is a recurring, limited form of UC. The majority of such patients have a benign course with a

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restricted involvement. Distal UC is usually a chronic nuisance with a low incidence of complications, extraintestinal manifestations or cancer (2). It is known that proctitis might show extension, but in practice, patients with proctitis are not regularly followed or treated. As extension is an important event in the natural course of UC, if a patient progresses to more proximal colitis, all of the therapy and the management strategies must be changed. We aimed to evaluate patients with UC limited to the rectum regarding extension and to compare them with the patients with rectosigmoid and left colonic UC for their features, risk factors for the extension of the disease and natural course of the disease in an inflammatory bowel disease (IBD) group from Turkey. This study also aimed to reveal epidemiologic data from Turkish IBD patients from the aspect of extension.

MATERIALS AND METHODS

The study patients were selected from an IBD group from Turkey High Specialty Hospital with certain criteria. The inclusion criteria were as follows: 1) the UC diagnosis was based on the standard clinical, radiologic, endoscopic, and histological methods, 2) the assessment of the extent of the disease was done at the initial admission, with at least one new assessment of localization during the follow-up, 3) the assessment of the extension during all colonoscopies was based on biopsies taken from the cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum, 4) the follow-up period was at least one year, and 5) the UC patients had rectal, rectosigmoid or left colonic involvement at the initial evaluation. The age, sex, duration of the disease, the duration of follow-up, presence or not of chronic active state and its duration in months, number of relapses and amoebic attacks, initial localization, extension, time of extension, type of treatment, and colectomy were determined retrospectively. The extension of disease was determined by observing the macroscopic inflammation that progressed to a proximal colon segment during any follow-up colonoscopy. For example: progression from proctitis to rectosigmoiditis, rectosigmoiditis to left-sided colitis and left-sided colitis to extensive or pancolitis. The state of the disease was determined as 'chronic active' when the activation of the disease continued at least six months or more under adequate treatment.

Statistical Method

All statistical tests were done using SPSS 13 software. For non-parametric values, Kruskal-Wallis test and for parametric values one-way ANOVA and t-test were used. Logistic regression analysis was done for the parameters affecting extension. Statistical significance was set as p values lower than 0.05.

RESULTS

The clinical features of the patients included in this study are shown in Table 1. The study involved 193 UC patients (91 female; mean age 43.8±13.2 years). The mean duration of the disease was 7.1±5.2 years and the mean follow-up was 3.5±2.3 years. Thirty-nine patients (20.2%) were in the chronic active state. Only 12 (12/193, 6.2%) patients had no relapse during the follow-up period. One hundred and fifty-one patients (151/193, 78.3%) were using topical and/or oral 5 acetylsalicylic acid (5-ASA) preparations, 37 patients (37/193, 19.1%) were using oral and/or intravenous prednisolone together with oral and/or topical 5-ASA, and 5 patients (2.6%) were not using any treatment during the evaluation.

In the initial study evaluation, 62 patients had rectal, 49 had rectosigmoid and 82 had left colonic involvement. When these three groups were compared (Table 2), only the ratio of the patients who were in chronic active state showed a statistically significant difference. Patients with rectal involvement had lower chronic active state than rectosig-

Table 1. General clinical parameters of the entire study group

	UC patients (n=193)
Age	43.8±13.2 (18-80)
Gender Female	91 (47.2%)
Male	102 (52.8%)
Duration of the disease (year)	7.1±5.2 (1-29)
Duration of the follow-up (year)	3.5±2.3
Localization: Rectum	62
Rectosigmoid	49
Left-sided colon	82
Extension	27 (14%)
Extension time (year)	3.9±2.9 (0.8-12)
Chronic activation	39 (20.2%)
Duration of chronic activation (month)	2.8±6.6 (0-43)
Relapse (at least 1 attack)	181/193 (93.8%)
Number of relapses	2.4±1.7 (0-8)
Amoebic attack	41/193 (21.2%)
Number of amoebic attacks	0.3±0.6 (0-4)
Colectomy	9 (4.7%)

Values are given as mean ± standard deviation.

Table 2. Features of the patients according to localization of ulcerative colitis at the initial diagnosis

	Proctitis (n=62)	Proctosigmoiditis (n=49)	Left-sided colitis (n=82)
Age	42.4±12.7	45.2±11.9	43.9±14.3
Gender Female	35 (56.5%)	15 (30.6%)	41 (50%)
Male	27 (43.5%)	34 (69.4%)	41 (50%)
Duration of disease (year)	6.3±4.6	7.9±5.3	7.3±5.5
Duration of follow-up (year)	3.2±1.9	4.1±2.8	3.5±2.1
Extension	10 (16.1%)	6 (12.2%)	11 (13.4%)
Extension time (year)	3.2±2.7	3.8±2.4	4.9±3.2
*Chronic activation (CA)	6 (9.7%)	12 (24.5%)	21 (25.6%)
Duration of CA (month)	1.5±5.7	3.7±8.6	3.1±5.9
Number of relapses	2.0±1.6	2.6±1.8	2.5±1.6
Amoebic attack	8 (12.9%)	13 (26.5%)	20 (24.4%)
Number of amoebic attacks	0.2±0.5	0.3±0.5	0.4±0.7
Colectomy	1	2	6

* $p < 0.05$.

CA: Chronic activation. Values are given as mean ± standard deviation.

moid and left colonic patients (9.7%, 24.5% and 25.6%, respectively, p=0.04). Mean chronic active time was lower in the rectal group but without any statistical difference. The percent of the patients showing extension was highest in the ulcerative proctitis group but no statistical significance was found.

In 27 of the patients (27/193, 13.9%), extension to at least one proximal segment was determined (Tables 2 and 3). The mean extension time was 3.9±2.9 years (range: 0.8-12). These patients' initial localizations were the rectum in 10 patients (10/62, 16.1%), rectosigmoid region in 6 patients (6/49, 12.2%) and left colon in 11 patients (11/82, 13.4%). Although the patients with proctitis showed more extension, no statistical difference was found. Five patients with proctitis progressed to left colon, 3 patients to extensive colitis and 2 patients to pancolitis. Four patients with rectosigmoiditis progressed to left-sided colitis and 2 patients to extensive colitis. Ten patients with left- sided colitis extended to extensive colitis and 1 patient to pancolitis. Fourteen patients (14/27, 51.8%) extended only to one proximal segment of the colon. The chronic active state was present in 11 patients with extension (11/27, 40.7%) and in 28 patients without extension (28/166, 16.9%), and the difference was statistically significant (p=0.004). The mean chronic active time was longer in the extension group than the group without extension

Table 3. Clinical factors associated with the extension of ulcerative colitis

	Patients with extension (n=27)	Patients without extension (n=166)	p values
Age	42.2±12.0	44.0±13.4	ns
Gender Female	14 (51.9%)	77 (46.4%)	ns
Male	13 (48.1%)	89 (53.6%)	
Duration of the disease (year)	6.9±3.1	7.2±5.5	ns
Duration of the follow-up (year)	4.2±2.3	3.4±2.2	ns
Extension time (year)	3.9±2.9 (0.8-12)	na	na
Chronic activation (CA)	11/27 (40.7%)	28/166 (16.9%)	0.004
Duration of CA (month)	7.9±11.8	1.9±4.9	0.000
Number of relapses	3.3±1.7	2.2±1.6	0.001
Amoebic attack	10/27 (37%)	31/166 (18.7%)	0.031
Number of amoebic attacks	0.6±0.9	0.2±0.6	0.005
Colectomy	4/27 (14.8%)	5/166 (3%)	0.024

na: Not applicable. ns: Not significant. CA: Chronic activation.

Values are given as mean ± standard deviation.

(7.9±11.8, 1.9±4.9, p<0.0001). The number of relapses (3.3±1.7, 2.2±1.6, p=0.001) and the number of amoebic attacks (0.6±0.9, 0.2±0.6, p=0.005) were both significantly higher in the extension group than in the non-extension group. There was no difference regarding age, sex, duration of the disease, and follow-up period between the extension and non-extension groups. The modalities of treatment were evaluated for intake of prednisolone and 5-ASA preparations (mesalazine or sulfasalazine), and it was found that patients with extension had used prednisolone more frequently (Table 4). Forty percent (2/5) of the patients without any treatment, 9.9% (15/151) of the patients under 5-ASA treatment and 27% (10/37) of the patients under 5-ASA together with prednisolone treatment showed extension, and the difference was statistically significant (p=0.03).

Nine of the patients in the whole study group had total colectomy in the follow-up period. These patients' initial localization was rectum in 1 patient, rectosigmoid in 2 patients and left colon in 6 patients. The indication of surgery was chronic active state in 6 patients. The only patient who progressed to colectomy who had rectal involvement as the initial localization underwent colectomy after extending to uncontrollable pancolitis. One patient in the rectosigmoid group had colectomy after extension to the left colon with intractable disease. Two of the left colonic UC patients had colectomy after progressing to chronic active extension colitis. One patient from the rectosigmoid group and 4 patients from the left colonic group had colectomy without extension.

According to the logistic regression analysis, the most important factor was the presence of chronic active state. Patients with chronic active state showed 2.79-fold (95% confidence interval [CI] 1.1-7.1, p=0.031) more risk for extension compared to the patients without chronic activation. The risk of extension was increased 2.45-fold (95% CI 0.99-6.15, p=0.05) with amoebic attack and 2.48-fold (95% CI 1.0-6.18, p=0.049) with prednisolone treatment or no treatment.

Table 4. Medications used by the study patients

Modalities of treatment	Entire study group (n=193)	Extension group (n=27)
No treatment	5 (2.6%)	2 (40%)
Topical 5-ASA therapy	47 (24.4%)	2 (4.3%)
5-ASA oral	62 (32.1%)	10 (16.1%)
5-ASA oral + topical	42 (21.8%)	3 (7.1%)
5-ASA + prednisolone topical	23 (11.9%)	6 (28.1%)
5-ASA+prednisolone oral ± topical	14 (7.3%)	4 (28.6%)

5-ASA: 5 acetylsalicylic acid.

DISCUSSION

Ulcerative colitis (UC) is a chronic disease with a heterogeneous clinical picture. Understanding the prognosis and clinical course of the disease is important for determining medical and surgical treatment and follow-up strategies for different subgroups of patients (3). In the past, ulcerative proctitis and UC were discussed as two independent diseases. However, long-term epidemiological studies have revealed that proctitis often extends to more proximal and even total colitis (4). In the reported studies, different numbers of patients with extension were observed, but their design and the duration of follow-up varied. Farmer et al. (1) reported that 53% of patients with UC showed extension. Langholz et al. (5) reported that 41% of initial proctitis cases showed extension in 10 years. More recently, the risk of proximal extension after 5 and 10 years was found as 44.7% and 60.0%, respectively, for patients with proctitis among Korean UC patients (6). However, in the IBSEN study (3), the extension rate of proctitis patients was 28%. Recently reported studies from different Mediterranean countries found the extension rate as 10-28% in patients with proctitis (7-10). In our study group, 16.1% of the patients with proctitis showed extension. The extension rate of our patients was close to the rates reported recently.

It is important to emphasize that patients with proctitis showed more extension than patients with rectosigmoiditis and left-sided colitis in our study, but we did not find statistically significant differences. Recently published articles of the IBSEN study (3), Park et al. (6) and Chatzicostas et al. (7) demonstrated a more significant extension rate in patients with proctitis than in patients with left-sided colitis, but Farmer et al. (1) reported that patients with left-sided colitis had a higher extension risk.

Karoui et al. (9) reported from Tunisia that the extension was observed during the initial years of the UC. In our study, the mean extension time was 3.9±2.9 years; one of the patients of our study group progressed after 12 years.

In the past, multiple demographic and clinical factors that may affect proximal extension of UC we-

re evaluated. Ayres et al. (11) could find no factor affecting the extension of UC. Different parameters related with disease activity (relapse, severe bleeding, refractoriness, joint symptoms, and toxic colitis) were found to significantly affect extension of UC in some of the studies (1,5,8,9). In our study, in univariate analysis, chronic active state, time in chronic active state, number of relapses, and number of amoebic attacks were found to affect the extension of UC. In logistic regression analysis, the presence of the chronic active state was found as the most important and probably the only factor affecting extension. Of the patients with UC, 50-80% had a relapsing course with repeated flares, and in 15-30% of patients, the disease was chronically active (12). It seems that the patients having more relapse, longer chronic active state or refractoriness to treatment show more extension to proximal colon segments.

In our study, the presence of amoebic attack showed borderline significance in the logistic regression analysis. We could not find any information in the literature about the relation between the extension of UC and amoebic attacks. Amoebic attack is important as an activating factor and it is more common in developing countries, similar to Turkey.

A few studies reported that maintenance remission therapy had no significant effect on colonic extension (9,13,14). However, in our study, although the number of patients with no treatment was small, 40% of them had extension. Further, the extension rate of the patients needing prednisolone treatment was 2.48-fold higher than in the patients maintaining remission with 5-ASA. Appendiceal orifice inflammation, appendectomy, smoking, family history of UC, and parity are other suspected factors (10,11,15). The colectomy rate was higher in extension patients in our study. Four of our patients first progressed proximally and then to colectomy.

At the present time, it is not possible to know whether or not the disease will progress proximally. Fdez-Morera et al. (16) studied major histocompatibility complex (MHC) class I chain-related-transmembrane (MICA-TM) polymorphism in relation with behavior and extension of UC. MICA-A5.1 allele seems to be protective against extension and MICA-A5 may condition a worse progression of the disease. Perhaps real extension of the disease can be determined genetically. The onset of the disease may be proctitis, but some factors like disease activation might trigger extension in the patients with a genetic base.

It is also important to emphasize that, while the most important factor affecting extension was found as chronic active state in this study, the proctitis group with the least chronic active patients showed a higher extension rate than the rectosigmoiditis and left-sided colitis groups. Thus, proctitis patients may be more prone to extension than the other groups.

As shown in the last IBSEN study, an important portion (at least one-fifth) of patients with proctitis or left-sided colitis show extension to the proximal colon (17). Thus, if patients with distal or left-sided colitis have a chronic active state or refractoriness to therapy, colonoscopic follow-up should be done. Patients with proctitis, like the patients presenting with more extensive colitis, should be offered regular treatment and follow-up.

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