

Types and frequencies of extraintestinal involvement in our cases with inflammatory bowel disease

İnflamatuvar barsak hastalığı tanılı olgularımızda ekstraintestinal tutulum tipleri ve sıklığı

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Background and Aims: Inflammatory bowel disease includes two important diseases - ulcerative colitis and Crohn's disease. Although they are described as bowel diseases, they also have systemic involvement. In this study, we aimed to determine the types and frequencies of extraintestinal involvement in inflammatory bowel disease cases followed after admission in our clinic and to investigate the relationship of extraintestinal involvement with the disease activity. **Materials and Methods:** The study was performed on 85 patients with an inflammatory bowel disease diagnosis who were followed in our Gastroenterology Clinic. The study group included 39 patients with Crohn's disease and 46 patients with ulcerative colitis. **Results:** There was no statistically significant difference between the Crohn's disease group and ulcerative colitis group regarding age, gender, height, body weight, body mass index, erythrocyte sedimentation rate, C-reactive protein, hemoglobin, disease duration, and the frequency of extraintestinal involvement ($p>0.05$). Average white blood cell count was found to be significantly lower in the Crohn's disease group compared to the ulcerative colitis group ($p: 0.003$). When the patients were divided into two groups as to the presence or not of extraintestinal involvement, there was no significant difference between the groups regarding age, gender, height, body weight, body mass index, C-reactive protein, erythrocyte sedimentation rate, hemoglobin, white blood cell count, and disease duration ($p>0.05$). Types of extraintestinal involvement, in order of frequency, were as follows: sacroiliitis (40.7%), arthralgia (11.1%), psoriasis (11.1%) arthritis (7.4%), ankylosing spondylitis (7.4%), iridocyclitis (7.4%), primary sclerosing cholangitis (3.7%), and uveitis (3.7%). No significant correlation was determined between the presence of extraintestinal involvement and disease activity, type of extraintestinal involvement, or areas of involvement on endoscopy in these patients. **Conclusion:** In conclusion, the extraintestinal involvement rate in our inflammatory bowel disease patients was 38.46% in the Crohn's disease group and 26.08% in the ulcerative colitis group, and these rates are in accordance with the literature. It is important that these patients are regularly examined and followed from the time of the diagnosis regarding extraintestinal symptoms.

Keywords: Ulcerative colitis, Crohn's disease, extraintestinal involvement

INTRODUCTION

Inflammatory bowel disease (IBD) is a group of chronic inflammatory diseases in genetically predisposed individuals characterized by an unknown etiology and mechanism and chronic periods of remission and exacerbation. It includes two important diseases - ulcerative colitis (UC) and Crohn's disease (CD) (1-3).

Amaç: İnflamatuvar barsak hastalıkları; ülseratif kolit ve Crohn hastalığı olarak iki önemli hastalığı içerir. Barsak hastalıkları olarak nitelendirilmelerine rağmen sistemik tutulumları da mevcuttur. Bu çalışmadaki amacımız kliniğimizde yatırarak takip ettiğimiz inflamatuvar barsak hastalarında ekstraintestinal tutulum tiplerini ve sıklığını belirlemek, hastalık aktivitesiyle ilişkisini araştırmaktır. **Gereç ve Yöntem:** Çalışma gastroenteroloji kliniğimizde takip ettiğimiz inflamatuvar barsak hastalıkları tanısı olan 85 hasta üzerinde yapıldı. Hastalar 39 Chron hastası ve 46 ülseratif kolit hastasından oluşmaktaydı. **Bulgular:** Crohn hastalığı grubu ve ülseratif kolit grubu arasında yaş, cinsiyet, boy, vücut ağırlığı, beden kitle indeksi, eritrosit sedimentasyon hızı, C-reaktif protein, hemoglobin, hastalık süresi, ekstraintestinal tutulum sıklığı açısından istatistiksel anlamlı farklılık bulunmadı ($p>0.05$). Lökosit sayısı ortalaması Crohn hastalığı grubunda ülseratif kolit grubuna göre anlamlı düşük bulundu ($p:0.003$). Hastalar ekstraintestinal tutulum olup olmamasına göre ikiye ayrıldığında gruplar arasında yaş, cinsiyet, vücut ağırlığı, beden kitle indeksi, C-reaktif protein, eritrosit sedimentasyon hızı, hemoglobin, lökosit sayısı, hastalık süresi açısından anlamlı farklılık bulunmadı ($p>0.05$). Ekstraintestinal tutulum tipleri sıklık sırasına göre: sakroileit (%40.7), artıralji (%11.1), psöriazis (%11.1) artrit (%7.4), ankilozan spondilit (%7.4), iridosiklit (%7.4), primer sklerozan kolanjit (%3.7) ve üveit (%3.7) şeklindeydi. Hastalarda ekstraintestinal tutulum varlığı ile hastalık aktivitesi, tipi ve endoskopik tutulum bölgeleri arasında anlamlı ilişki saptanmadı. **Sonuç:** Sonuç olarak inflamatuvar barsak hastalarımızda ekstraintestinal tutulum oranı Crohn hastalığı grubunda %38.46, ülseratif kolit grubunda %26.08 olmak üzere, literatürle uyumlu olarak siktir. Hastaların tanı aldıkları andan itibaren ekstraintestinal bulgular açısından düzenli muayene ve takiplerinin yapılması önemlidir.

Anahtar kelimeler: Ülseratif kolit, Crohn hastalığı, ekstraintestinal tutulum

according to the type of involvement. Joint (excluding axial), mouth, eye and skin involvement is associated with disease activity and they are referred to as inflammatory diseases (4). Areas of involvement other than these are generally not associated with disease activity; the underlying mechanism is attributed to autoimmune, nutritional and metabolic causes (4).

While the most important variables related to extraintestinal involvement in UC are extent of colonic involvement and disease activity, the variables in CD are multifactorial (5).

Our aim in this study was to determine the types and frequencies of extraintestinal involvement in IBD cases followed after admission to our clinic and to investigate the relationship between extraintestinal involvement and disease activity.

MATERIALS AND METHODS

A total of 85 patients (42 females, 43 males) with IBD diagnosis who were followed after admission to our Gastroenterology Clinic (mean age: 36.64 ± 12.54 ; min: 16, max: 74 years) were included in the study. The patients, matched for age and gender, were divided into two groups according to the type of IBD. Group 1 included 39 patients (22 females, 17 males) with CD, and Group 2 included 46 patients (20 females, 26 males) with UC. All cases were informed about the study protocol, and written informed consent was obtained from all cases included in the study. A form for each patient was filled, inquiring about their age, gender, type and duration of the disease, area and extent of disease involvement in the bowel, any medicines used to treat IBD, and any history or not of a surgical operation. A general physical examination and locomotor system examinations were performed. Venous blood samples were drawn into EDTA tubes, sodium citrate tubes and gel-containing tubes (Becton Dickinson, USA) between 08:00-08:30 a.m. after a 10-12-hour overnight fasting period. Gel-containing tubes were centrifuged at 3500 rpm (1300 g x 10 minutes) after a 30-minute waiting period. Complete blood count, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) tests were studied without delay. Complete blood count tests were performed from the EDTA blood samples of all patients, and ESR rates were measured from sodium citrate blood samples using the Westergren method and Sed Rate Screener 100 device (SRS 100, Greiner Bio-one GmbH, Austria). CRP measurements were performed from the serum sample using the nephelometric method (Immage, Beckman Coulter, USA).

Statistical Analysis

During the assessment of the study data, SPSS (Statistical Package for the Social Sciences) for Windows 16.0 program was used for statistical analysis. Student t test was used regarding the comparisons of descriptive statistical methods (mean \pm standard deviation, median (range)) as well as the intergroup comparisons of parameters with normal distribution, and Mann-Whitney U test was used for the intergroup comparisons of parameters without normal distribution. Chi-

square test or Fisher's exact probability test was used for the intergroup comparisons of qualitative data. Pearson correlation analysis or Spearman's rho correlation test was used in the correlation analyses according to the distribution of the parameters. The results were evaluated in 95% confidence interval and at a significance level of $p < 0.05$.

RESULTS

The mean age of the patients with CD (Group 1) was 36.67 ± 12.07 (min: 19, max: 63) years, and the mean age of the patients with UC (Group 2) was 36.61 ± 13.06 (min: 16, max: 74) years. There was no statistically significant difference between the groups regarding age and gender (p : 0.983, 0.235, respectively).

There was no statistically significant difference between Group 1 and Group 2 regarding height, body weight, body mass index (BMI), ESR, CRP, hemoglobin (Hb), disease duration, and the frequency of extraintestinal involvement ($p > 0.05$). Average white blood cell (WBC) count was $7.28 \pm 2.07/\text{mm}^3$ in Group 1 and $8.78 \pm 2.33/\text{mm}^3$ in Group 2, and the difference between them was found to be statistically significant ($p = 0.003$).

Demographic and clinical characteristics and laboratory data of Group 1 and Group 2 are seen in Table 1.

Patients were divided into two groups regarding the presence or not of extraintestinal involvement. Group A (with extraintestinal involvement) comprised 27 patients (16 females, 11 males), and Group B (without extraintestinal involvement) comprised 58 patients (26 females, 32 males). The mean age of Group A was 37.41 ± 13.52 (min: 19, max: 70) years, and the mean age of Group B was 36.28 ± 13.16 (min: 16, max: 74) years. There was no statistically significant difference between groups regarding age and gender (p : 0.701, 0.215, respectively).

There was no statistically significant difference between Group A and Group B regarding body weight, BMI, ESR, CRP, Hb, WBC, or disease duration ($p > 0.05$). Mean height was 164.81 ± 7.05 cm in Group A and 168.34 ± 6.70 cm in Group B, and the difference between them was found to be statistically significant ($p = 0.029$).

Demographic and clinical characteristics and laboratory data of the groups with and without extraintestinal involvement are seen in Table 2.

The types of extraintestinal involvement were investigated, and were determined as follows, in decreasing order of frequency: sacroiliitis 40.7% (11 patients: 7 CD, 4 UC), arthralgia 11.1% and psoriasis (11.1%). The other types of extraintestinal involvement included arthritis (7.4%), ankylosing spondylitis (7.4%), iridocyclitis (7.4%), primary sclerosing cholangitis (3.7%), and uveitis (3,7%).

Types and frequencies of extraintestinal involvement seen in our study group are shown in Table 3.

When the disease activity of the patients with UC was evalu-

Table 1. Demographic and clinical characteristics and laboratory data of CD and UC groups

	Group 1, n: 39 (CD) Mean±SD	Group 2, n: 46 (UC) Mean±SD	P
Age (year)	36.67±12.07	36.61±13.06	0.983*
Male gender, n (%)	17 (43.6)	26 (56.5)	0.235***
Height (cm)	165.92±6.28	168.33±7.39	0.114*
Body weight (kg)	62.31±11.78	65.80±11.19	0.165*
BMI (kg/m ²)	22.66±4.37	23.20±3.90	0.547*
ESR (mm/h)	34.97±21.39	32.95±18.93	0.647*
CRP (mg/dL); median (range)	1.56 (13.9)	1.20 (107.90)	0.265**
WBC (K/mm ³)	7.28±2.07	8.78±2.33	0.003*
Hb (g/dL)	11.55±2.05	11.23±2.86	0.564*
Disease duration (year); median (range)	5 (14)	5 (16)	0.613**
Extraintestinal involvement, n (%)	15 (38.46)	12 (26.08)	0.222***

p: Significance level (significant at the p<0.05 level)

BMI: Body mass index, ESR: Erythrocyte sedimentation rate

(1st hour), CRP: C-reactive protein, WBC: White blood cell count, Hb: Hemoglobin

* Student t test ** Mann-Whitney U test *** Chi-square test

Table 2. Demographic and clinical characteristics and laboratory data of the groups with and without extraintestinal involvement

	Group A (with involvement) (n=27) Mean±SD	Group B (without involvement) (n=58) Mean±SD	P
Height (cm)	164.81±7.05	168.34±6.70	0.029*
Body weight (kg)	64.78±13.26	63.93±10.75	0.755*
BMI (kg/m ²)	23.86±5.06	22.53±3.56	0.167*
ESR (mm/h)	32.92±22.06	34.31±19.11	0.767*
CRP (mg/dL); median (range)	1.14 (9.90)	1.46 (13.90)	0.552**
WBC (/mm ³)	7.73±2.39	8.25±2.29	0.354*
Hb (g/dL)	11.52±2.40	11.31±2.57	0.721*
Disease duration (year); median (range)	5 (16)	4 (16)	0.207**
Male gender, n (%)	11 (40.74)	32 (55.17)	0.215***
Age (year)	37.41±13.52	36.28±13.16	0.701*

p: Significance level (significant at the p<0.05 level)

BMI: Body mass index, ESR: Erythrocyte sedimentation rate

(1st hour), CRP: C-reactive protein, WBC: White blood cell count, Hb: Hemoglobin

* Student t test was used ** Mann-Whitney U test *** Chi-square test

ated according to Truelove and Witts' criteria, mild, moderate and severe disease activity was determined in 12 (26.1%), 23 (27.1%) and 11 (12.9%) patients, respectively. When the disease activity of the patients was evaluated according to the Mayo scoring system, the numbers of patients with a score of 0, 1, 2, and 3 were 5 (10.9%), 4 (8.7%), 24 (52.2%), and 13 (28.3%), respectively. Areas of involvement on endoscopy were as follows: rectum in 4 patients, distal colon in 10 patients, left colon in 15 patients, and entire large intestine in 17 patients.

There was no significant difference between the UC patients with and without extraintestinal involvement regarding disease activity, Mayo index and areas of involvement on endoscopy (p: 0.902, 0.632, and 0.645, respectively).

When the disease activity of the patients with CD was investigated, inactive, mild and moderate disease activity was determined in 22 (56.4%), 9 (23.1%) and 8 (20.5%) patients, respectively. The types of CD were as follows: inflammatory in

Table 3. Types of extraintestinal involvement

Type of extraintestinal involvement	n	(%)
Sacroiliitis	11	40.7
Arthralgia	3	11.1
Arthritis	2	7.4
Ankylosing spondylitis	2	7.4
Iridocyclitis	2	7.4
Uveitis	1	3.7
Psoriasis	3	11.1
Primary sclerosing cholangitis	1	3.7
Erythema nodosum	2	7.4
Total	27	100.0

18 patients (47.4%), obstructive in 10 patients (26.3%), fistulizing in 9 patients (23.7%), fibrotic in 1 patient (2.6%), and unknown 1 patient (2.6%). Areas of involvement on endoscopy were as follows: normal in 4 patients, colonic in 6 patients, ileal in 13 patients, and ileocolonic in 14 patients.

There was no significant difference between the CD patients with and without extraintestinal involvement regarding disease activity, type of disease, Crohn's Disease Activity Index (CDAI), Crohn's Disease Endoscopic Index of Severity (CDEIS) and areas of involvement on endoscopy ($p=0.352, 0.427, 0.522, 0.959, \text{ and } 0.988$, respectively).

DISCUSSION

In the studies investigating the frequency of extraintestinal involvement in IBD patients, it was reported that systemic involvement was present in approximately one-third of the patients (6,7). Depending upon the areas of reporting, this rate ranges between 20% and 40% (6). We determined this rate as 32% in this study conducted on the patients followed up after admission in our clinic. Although the extraintestinal involvement rate in the patients with CD (38.46%) was higher than in the UC group (26.08%), the difference between them was not statistically significant.

In the studies performed, joint involvement was reported to be the most frequent involvement encountered in IBD, with a rate of 10-30% (8). Joint involvement in IBD can be axial, peripheral or combined. Peripheral arthritis is generally nonerosive, oligoarticular and shows a parallelism with disease activity. Axial arthritis can be grouped as inflammatory back pain, sacroiliitis and ankylosing spondylitis (9). In our patient group, extraintestinal involvement was seen in 27 of 85 patients, and in 11 of those 27 (40%), the involvement was sacroiliitis. The frequency of sacroiliitis in different published studies ranges from 10-32% (8-12). The reason for this wide range may be due to some of the studies being population-based and others hospital-based, variability of activ-

ity status of the patients and geographical differences. In this study, we determined the prevalence of sacroiliitis as 11/85, namely 12%. However, no prominent extraintestinal involvement other than sacroiliitis was observed. The prevalences of arthralgia and psoriasis were determined to be approximately 3.5%. We determined the frequency of erythema nodosum as 2.3%, and the frequencies of uveitis and primary sclerosing cholangitis as 1.2%, similar to each other. These rates showed similarity with many studies in the literature (8-15).

In this study, there was no significant difference between the CD patients with and without extraintestinal involvement regarding disease activity, type of disease, CDAI, CDES index and areas of involvement on endoscopy. There was no significant difference between the UC patients with and without extraintestinal involvement regarding disease activity (according to Truelove and Witts' criteria), Mayo index, and areas of involvement on endoscopy. These findings show us that there is no correlation between the presence of extraintestinal involvement and the disease activity, type of the disease and mucosal healing in the IBD cases followed up in our clinic.

The major limitation in our study is the small sample size and the nonhomogeneity of the patient population due to their selection from the patients admitted to our clinic. Despite the present limitations, this study shows that frequencies of extraintestinal involvement are high in IBD patients independent of the parameters of disease activity, type of the disease and areas of involvement on endoscopy. Our results call attention to the importance of regular examination and follow-up of the patients, from the time of diagnosis, regarding extraintestinal symptoms.

KAYNAKLAR

- Scalaferrri F, Fiocchi C. Inflammatory bowel disease: progress and current concepts of etiopathogenesis. *J Dig Dis* 2007;8:171-8.
- Hanauer SB. Inflammatory bowel disease: epidemiology, pathogenesis, and therapeutic opportunities. *Inflamm Bowel Dis* 2006;12(Suppl 1):S3-9.
- Xia B, Crusius J, Meuwissen S, Pena A. Inflammatory bowel disease definition, epidemiology, etiologic aspects, and immunogenetic studies. *World J Gastroenterol* 1998;4:446-58.
- Veloso FT. Extraintestinal manifestations of inflammatory bowel disease: do they influence treatment and outcome? *World J Gastroenterol* 2011;17:2702-7.
- Vilela EG, Torres HO, Martins FP, Ferrari Mde L, Andrade MM, Cunha AS. Evaluation of inflammatory activity in Crohn's disease and ulcerative colitis. *World J Gastroenterol* 2012;18:872-81.
- Larsen S, Bendtzen K, Nielsen OH. Extraintestinal manifestations of inflammatory bowel disease: epidemiology, diagnosis, and management. *Ann Med* 2010;42:97-114.
- Beslek A, Onen F, Birlik M, et al. Prevalence of spondyloarthritis in Turkish patients with inflammatory bowel disease. *Rheumatol Int* 2009;29:955-7.
- Brakenhoff LK, van der Heijde DM, Hommes DW, Huizinga TW, Fidler HH. The joint-gut axis in inflammatory bowel diseases. *J Crohns Colitis* 2010;4:257-68.
- Hwangbo Y, Kim HJ, Park JS, et al. Sacroiliitis is common in Crohn's disease patients with perianal or upper gastrointestinal involvement. *Gut Liver* 2010;4:338-44.
- Marques MR, Oliveira S, Gorrão Clara JP. [Ulcerative colitis initial presentation with multiple extra-intestinal manifestations]. *Acta Med Port* 2010;23:705-8.
- Queiro R, Maiz O, Intxausti J, et al. Subclinical sacroiliitis in inflammatory bowel disease: a clinical and follow-up study. *Clin Rheumatol* 2000;19:445-9.
- Orchard TR, Holt H, Bradbury L, et al. The prevalence, clinical features and association of HLA-B27 in sacroiliitis associated with established Crohn's disease. *Aliment Pharmacol Ther* 2009;29:193-7.
- Denadai R, Teixeira FV, Saad-Hossne R. The onset of psoriasis during the treatment of inflammatory bowel diseases with infliximab: should biological therapy be suspended? *Arq Gastroenterol* 2012;49:172-6.
- Tozun N, Atug O, Imeryuz N, et al. Clinical characteristics of inflammatory bowel disease in Turkey: a multicenter epidemiologic survey. *J Clin Gastroenterol* 2009;43:51-7.
- Schwartz RA, Nervi SJ. Erythema nodosum: a sign of systemic disease. *Am Fam Physician* 2007;75:695-700.