

## Extraintestinal manifestations of inflammatory bowel disease

İnflamatuvar barsak hastalığının ekstraintestinal tutulumu

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**Background and Aims:** The reported frequency of extraintestinal manifestations in inflammatory bowel disease varies from 6% to 47%. We evaluated extraintestinal manifestations of inflammatory bowel disease patients who were followed up in our clinic. **Materials and Methods:** The epidemiological findings, disease duration, extraintestinal manifestations, and complications were evaluated between April 1998 and April 2008, retrospectively. **Results:** Four hundred and ninety-four patients (254 males; mean age, 38,63±13,32 years; range, 16-78) were evaluated: 283 (57,3%) with ulcerative colitis, 194 (39,3%) with Crohn's disease and 17 (3,4%) with indeterminate colitis. The mean disease duration was 70,66±75,93 months (1-1008 months), and the mean follow-up was 36,40±45,09 months (1-288 months). The extraintestinal manifestation rate was 19,2% (95/494) in the whole group, and included arthritis in 32 (6,5%), hepatobiliary in 13 (2,6%), skin in 13 (2,6%), multiple extraintestinal manifestations in 16 (3,2%), renal calculus in 12 (2,4%), thromboembolic events in 5 (1%), and eye involvement in 4 (0,8%). Complications were observed in a total of 78 patients (15,8%). Complication rates were as follows: 29 (5,9%) abscess, 15 (3%) perforation, 5 (1%) malignancy, 1 (0,2%) toxic megacolon, and 15 (2,6%) others. The complication rate was higher in Crohn's disease than ulcerative colitis (29,3% vs 3,6%). There was a positive correlation between extraintestinal manifestations and the complication rate in ulcerative colitis ( $p=0,007$ ,  $r=0,173$ ), and a positive correlation was observed between colonic involvement and extraintestinal manifestations in Crohn's disease ( $p=0,04$ ,  $r=0,144$ ). **Conclusions:** The most common extraintestinal manifestation was arthritis, and the most frequently seen complications were abscess and perforation. The complication rate was higher in Crohn's disease than ulcerative colitis. Extraintestinal manifestations may enhance the complication rate in UC. In Crohn's disease, the extraintestinal manifestations rate is higher in colonic involvement than in ileocolonic and ileal involvement. Colonic involvement in Crohn's disease is a predictive factor for extraintestinal manifestations.

**Key words:** Inflammatory bowel disease, extraintestinal manifestation.

### INTRODUCTION

The etiology of inflammatory bowel disease (IBD) is still unknown. Crohn's disease (CD) and ulcerative colitis (UC) are immune-mediated disorders of unknown etiology that primarily affect the gastrointestinal tract. In addition,

**Giriş ve Amaç:** İnflamatuvar barsak hastalığında ekstraintestinal bulguların sıklığı %6-47 olarak bildirilmiştir. Kliniğimizde takip edilen inflamatuvar barsak hastalarında görülen ekstraintestinal bulguları değerlendirdik. **Gereç ve Yöntem:** Nisan 1998 ve Ocak 2008 arasında takip edilen hastalar ekstraintestinal bulgular, epidemiyolojik veriler, hastalık süreleri, komplikasyonları açısından retrospektif olarak değerlendirildi. **Bulgular:** 494 hasta (254 erkek, yaş ortalaması 38,63±13,32 yıl, yaş dağılımı 16-78) değerlendirilmeye alındı. Bu hastalardan 283'ü (%57,3) ülseratif kolit, 194'ü (%39,3) Crohn hastalığı ve 17'si (%3,4) indeterminate kolit idi. Hastalık yaşı ortalama 70,66±75,93 (1-1008) ay idi. Ortalama takip süresi 36,40±45,09 ay (1-288 ay) idi. Tüm inflamatuvar barsak hastalarında ekstraintestinal bulguların sıklığı %19,2 (95/494) olup dağılımı: seronegatif artrit 32 (%6,5), hepatik tutulum 13 (%2,6), deri tutulumu 13 (%2,6), kombine 16 (%3,2), renal kalkül 12 (%2,4), tromboemboli 5 (%1), göz tutulumu 4 (%0,8) idi. 78 hastada (%15,8) komplikasyon görüldü: [29 abse (%5,9), 15 perforasyon (%3), 5 malignite (%1), 1 toksik megakolon (%0,2) ve 15 diğer komplikasyonlar (%2,6)]. Crohn hastalığında komplikasyon oranı ülseratif kolitten fazla idi (%29,3'e %3,6). Ülseratif kolitli hastalarda ekstraintestinal bulgular ile komplikasyon sıklığı arasında ( $p=0,007$ ,  $R=0,173$ ), Crohn hastalarında kolonik tutulum ile ekstraintestinal bulgular arasında ( $p=0,04$ ,  $R=0,144$ ) pozitif korelasyon tesbit edildi. **Sonuç:** İnflamatuvar barsak hastalarında en sık ekstraintestinal bulgu seronegatif artritir. En sık komplikasyon ise abse ve perforasyondur. Ekstraintestinal bulguların varlığı ülseratif kolit seyirinde komplikasyon riskini artırır. Crohn hastalığında kolonik tutulum, ekstraintestinal bulguların varlığını gösteren prediktif bir faktördür.

**Anahtar kelimeler:** İnflamatuvar barsak hastalığı, ekstraintestinal bulgular

tion, other organ systems can be involved, such as joint/bones, skin, eyes, hepatobiliary tract, lungs, and kidney. Overall, they represent extraintestinal manifestations (EIMs) of IBD, and may present before, in conjunction

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**Geliş Tarihi:** 23.12.2013 • **Kabul Tarihi:** 01.03.2014

with, or after the onset of bowel disease. Considering the epidemiological, genetic and immunological data, UC and CD are heterogeneous disorders of multifactorial etiology in which hereditary (genetic) and environmental (microbial, behavior) factors interact to produce the disease (1-4). Patients with any of these manifestations have a higher risk of developing another one. EIMs of IBD are prevalent in both UC and CD (5,6).

Inflammatory bowel disease (IBD) is associated with EIMs in approximately 20-40% of patients (4,7-10). Due to the relative refractoriness of the disease and a possible increase in morbidity and mortality, prompt recognition of extracolonic organ involvement in IBD is important (11,12). IBD is associated with a variety of EIMs that may produce greater morbidity than the underlying intestinal disease and may even be the initial presenting symptoms of the IBD. Some are more commonly related to active colitis (joint, skin, ocular, and oral manifestations). Others are seen especially with small bowel dysfunction (cholelithiasis, nephrolithiasis, and obstructive uropathy), and some are nonspecific disorders (osteoporosis, hepatobiliary disease and amyloidosis) (9).

The most common EIMs affect the joints, skin, eyes, and biliary tract. The successful treatment of EIMs is essential for improving the quality of life of IBD patients (8). EIMs do not change the remission rate, but prolong the time to achieve remission. Perhaps even more important, these extraintestinal symptoms can be the primary manifestation of CD and UC (13,14).

The aim of this study was to evaluate EIMs in IBD patients and the effect of these manifestations on the clinical course.

## MATERIALS AND METHODS

The epidemiological findings, disease duration, EIMs, and complications were evaluated between April 1998 and April 2008 retrospectively. This administrative definition has previously been validated in CD, UC and indeterminate colitis (ID).

In order to investigate EIMs, abdominal ultrasonogra-

phy, sacroiliac radiography and eye examination were performed. Intestinal and extraintestinal symptoms and laboratory tests were followed up regularly. Any alteration suggesting an EIM was investigated by a specialist.

The Statistical Package for the Social Sciences (SPSS) 15,0 (Chicago, IL) was used for statistical evaluation. Univariate analyses, correlation matrices and multivariate regression were performed. Further subgroup analyses were performed.

## RESULTS

Totally, 494 IBD patients (254 male, 240 female; mean age, 38,63±13,32 years; range, 16-78) were evaluated retrospectively. Distribution of IBD was as follows: 283 (57,3%) UC, 194 (39,3%) CD and 17 (3,4%) ID.

The mean disease duration was 70,66±75,93 months (1-1008 months), and the mean follow-up period was 36,40±45,09 months (1-288 months).

The rate of EIMs was 19,2% (n=95) in the whole group. Distribution of EIMs was as follows: seronegative arthritis 32 (6,5%), hepatobiliary involvement 13 (2,6%), skin involvement 13 (2,6%), multiple EIMs 16 (3,2%), renal calculus 12 (2,4%), thromboemboli 5 (1%), and eye involvement 4 (0,8%) (Figure 1).

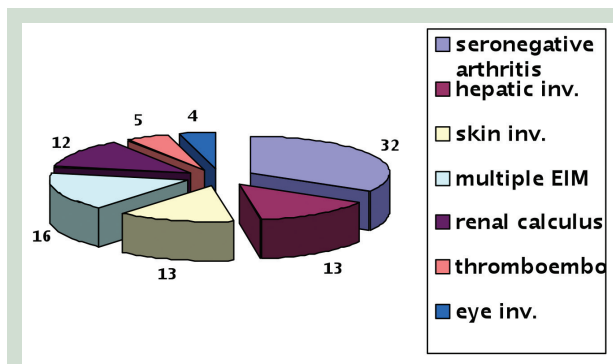
The rates of EIMs of CD, UC and ID were 18%, 19,1% and 17,6%, respectively. There was no statistically significant difference between the groups ( $p>0,05$ ). Thromboembolic events (4/283 vs 1/194), arthritis (19/283 vs 12/194), hepatobiliary involvement (8/283 vs 5/194), and renal calculus (8/283 vs 2/194) were higher in UC; however, this difference was not statistically significant. There was also no significant difference between UC and CD patients according to the incidence of ocular (2/283 vs 2/194) and skin involvement (7/283 vs 6/194). The rate of multiple EIMs (9/194 vs 7/283) was higher in CD than UC, but the difference was not statistically significant ( $p>0,05$ ).

Rates of EIMs of CD were as follows: seronegative arthritis in 12 (6,2%), hepatobiliary involvement in 5 (2,6%),

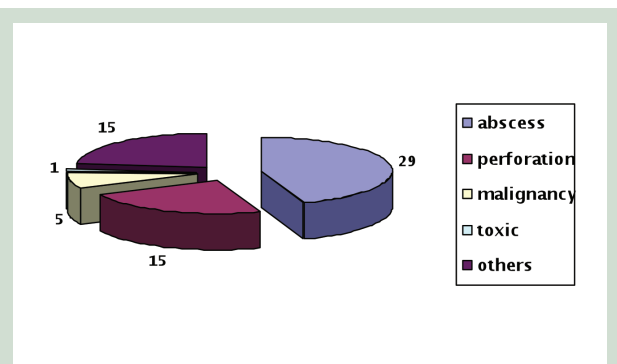
**Table 1.** Distribution of EIMs

	Arthritis	Multiple EIMs	Hepatobiliary	Skin inv.	Renal calculus	Thromboemboli	Eye inv.
UC	19 (6,7%)	7 (2,5%)	8 (2,8%)	7 (2,5%)	8 (2,8%)	4 (1,4%)	2 (0,7%)
CD	12 (6,2%)	9 (4,6%)	5 (2,6%)	6 (3,1%)	2 (1%)	1 (0,5%)	2 (1%)
ID	1 (5,9%)				2 (11,8%)		
Total	32 (6,5%)	16 (3,2%)	13 (2,6%)	13 (2,6%)	12 (2,4%)	5 (1%)	4 (0,8%)

EIMs: Extraintestinal manifestations. UC: Ulcerative colitis. CD: Crohn's disease. ID: Indeterminate colitis. inv: Involvement.



**Figure 1.** Distribution of EIMs of inflammatory bowel disease (EIM: Extraintestinal manifestation, inv.: Involvement).



**Figure 2.** Distribution of complications in inflammatory bowel disease.

skin in 6 (3,1%), multiple EIMs in 9 (4,6%), renal calculus in 2 (1%), thromboembolic events in 1 (0,5%), and eye involvement in 2 (1%). Rates of EIMs of UC were as follows: seronegative arthritis in 19 (6,7%), hepatobiliary involvement in 8 (2,8%), skin in 7 (2,5%), multiple EIMs in 7 (2,5%), renal calculus in 8 (2,8%), thromboembolic events in 4 (1,4%), and eye involvement in 2 (0,7%). EIMs of ID were recorded as seronegative arthritis in 1 (5,9%) and renal calculus in 2 (11,8%) (Table 1).

Complications were observed in a total of 78 patients (15,8%). Complication rates were as follows: 29 (5,9%) abscess, 15 (3%) perforation, 5 (1%) malignancy, 1 (0,2%) toxic megacolon, and 15 (2,6%) others (amyloidosis, growth retardation, bowel resection, colectomy, septicemia, demyelinating disease, etc.) (Figure 2).

The complication rates in CD, UC and ID were 29,3%, 3,6% and 5,9%, respectively. The complication rate in CD was found to be higher than that of UC and ID ( $p < 0.005$ ). Abscess (27/194 vs 1/283) and perforation (14/194 vs 1/283) rates were significantly higher in CD than UC. There was no significant difference between CD and UC according to the incidence of malignancy (2/194 vs 3/283). One patient with toxic megacolon had ileocolonic CD.

There was a positive correlation between EIMs and the complication rate in UC ( $p = 0,007$ ,  $r = 0,173$ ), and a positive correlation was also observed between colonic involvement and EIMs in CD ( $p = 0,04$ ,  $r = 0,144$ ). EIMs were seen at rates of 10,6% in ileal, 19,5% in ileocolonic and 28,6% in colonic CD.

## DISCUSSION

Inflammatory bowel disease (IBD) is a systemic disease associated with a number of EIMs involving almost every organ in the body. The reported frequencies of EIMs in patients with IBD have varied between 6% and 47% (15-

20). Globally, about one-third of patients develop systemic manifestations (10). The true prevalence of the EIMs associated with IBD may vary depending on the geographic area, IBD population, location and duration of the disease, medication, and diagnostic accuracy (1). In our series, the EIM rate was 19,2% ( $n = 95/494$ ) in the whole group.

In the literature, the rates of EIMs of UC and CD were 5,7% and 19%, respectively, and of complications in UC and CD were 6,4% and 50,8%, respectively (21). In our series, EIM rates were similar (CD 18%, UC 19,1%, ID 17,6%), but the complication rate was higher in CD than UC (29,3% vs 3,6%).

Mendoza et al. (16) evaluated 566 patients in a prospective study and showed that joint manifestations were the most common EIM. Hepatobiliary manifestations, venous thromboembolism and arthralgias were more frequent in UC than CD. Erythema nodosum and peripheral arthritis were more frequent in CD. The prevalence rates of ocular manifestations and the remaining joint manifestations were not different between UC and CD. Thromboembolic events and hepatobiliary and renal involvement were higher in UC in our study; however, this difference was not statistically significant. There was also no significant difference between CD and UC according to incidence of arthritis and ocular and skin involvement. Multiple EIMs were not statistically significantly higher in CD.

The most common EIMs affect the joints, skin, eyes, and biliary tract (8,22). Seronegative arthritis (6,5%), hepatic involvement (2,6%) and skin involvement (2,6%) were the most common extraintestinal diseases of all groups in our patients. Eye involvement (0,8%) was seen less frequently than the others.

The presence of one EIM appears to confer a higher likelihood of developing other manifestations than would be expected by chance alone (9). Multiple EIMs were seen in 16 of our patients.

In the literature, only 3% of UC patients required surgery, whereas 27% of CD patients underwent surgical procedures ( $p < 0,001$ ) (21). Both extraintestinal and local complications were more frequent in CD patients, whereas arthritis was the most common EIM in both diseases (23). We observed complications in a total of 78 patients (15,8%).

Familial IBD was associated with the presence of EIMs, while ileal involvement and noninflammatory behavior independently increase the risk of surgery (24). Female gender, steroid dependency and colonic involvement are associated with the risk of developing EIMs of CD (19). In another study, perianal complications alone were found significantly more common in patients with colitis and ileocolitis than in those with disease of small bowel

involvement only. There was a significantly positive association between perianal disease and the presence of extraintestinal features (25). We observed a positive correlation between colonic involvement and EIMs in CD ( $p = 0,04$ ,  $r = 0,144$ ). Data regarding the complication rates in IBD and the relation of EIMs are rare in the literature. In our study, there was a positive correlation between EIMs and the complication rate in UC ( $p = 0,007$ ,  $r = 0,173$ ). In conclusion, the most common EIM of IBD was seronegative arthritis, and the most common complications were abscess and perforation. The complication rate was higher in CD than UC. EIMs may enhance the complication rate in UC. The EIM rate in CD was higher in colonic involvement than in ileocolonic and ileal involvement. Colonic involvement in CD is a predictive factor for EIMs.

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