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CASE STUDY

Prevalence of Extraintestinal Manifestations of Ulcerative Colitis Patients in Turkey: Community-Based Monocentric Observational Study.

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Abstract

INTRODUCTION AND OBJECTIVE:
Extraintestinal findings are encountered in about 50% of Ulcerative Colitis (UC) patients. The objective of this study is to find out the prevalence and clinical features of extraintestinal manifestations (EIM) in ulcerative colitis (UC) patients in Turkish society and its relationship with diagnosis of disease, age and gender.

METHODS:
The prevalence of all extraintestinal findings associated with the disease was investigated in patients diagnosed with ulcerative colitis who were followed up in the gastroenterology clinic between January 2014 and March 2019. We retrospectively investigated the prevalence of elevated liver enzyme, primary sclerosing cholangitis, peripheral arthritis, anky-losing spondylitis, iritis/uveitis, pyoderma gangrenosum, erythema no-dosum, venous thromboembolic events, lung findings, cardiac diseases and psychiatric disorders as extraintestinal findings in UC patients.

FINDINGS:
Of the 199 patients included in the study, 114 (57.3%) were male and 85 (42.7%) were female (mean age 45 ± 5). The mean disease age of the UC patients studied was 68 months (8-276 months).

Whereas the disease was in remission in 89% of the UC patients, it was active in 11%.

The extra intestinal findings detected include rheumatological diseases in 18 patients (9.2%), cardiac diseases in 9 patients (4.5%), skin diseases in 4 patients (2% [erythema nodosum in 3 patients (1.5%) and pyoderma gangrenosum in 1 patient (0.5%)]), venous thromboembolic events in 7 patients (%4), elevated liver enzyme in 26 patients (13%), primary sclerosing cholangitis in 2 patients (1%), erythema nodosum in 3 patients (1.5%), pyoderma gangrenosum in 1 patient (0.5%), osteopenia in 17 patients (26%), osteoporosis in 4 patients (6%), depression in 3 patients (1.5%), and ocular involvement in 6 patients (3%). At least one extra intestinal involvement was detected in 100 (50.2%) out of 199 patients included in the study.

CONCLUSION: Rheumatological diseases and elevated liver enzyme were found to be the most prevalent extraintestinal findings in ulcerative colitis patients. Relationships of immune-mediated diseases in extraintestinal regions are closely related to activation of IBD. Furthermore, EIMs may help us better understand the pathogenesis of UC.sta

Keywords: Ulcerative colitis, extraintestinal findings, prevalence nd the pathogenesis of UC.

1 | INTRODUCTION

Ulcerative colitis (UC) is a chronic idiopathic disease that is limited to colon mucosa, characterized by recurrent inflammation attacks, often involves the rectum, and can spread to the proximal colon by 30-50%. It is a disease of the young population, usually diagnosed when the person is in their 30s. The disease is most common at the ages of 15-25 and secondly at the ages of 55-65. The prevalence of the disease does not change by gender, but is equal in men and women. It tends to be prevalent in regions and in patients with a higher socioeconomic level (1) (2) .

The disease is more prevalent in Northern Europe and North America in terms of geography, and in Jews as ethnic origin, and in white people as a race (3) (4) .

Although the etiology of the disease is not yet known, environmental, genetic and immunological factors are blamed.

At least one extraintestinal finding is encountered in around 50% of UC patients (1) .

The disease is primarily an immune-mediated disorder involving the gastrointestinal tract. In addition, immune-mediated inflammatory diseases may involve extraintestinal organs (joints, bones, skin, eyes, lungs, hepatobiliary system, endocrine system). Factors such as genetic factors, intestinal flora changes and environmental factors play a role in their common etiopathogenesis. While extraintestinal involvement exists before the diagnosis of disease in 25% of patients, extraintestinal involvement is detected in 75% of patients after the diagnosis of UC (5) (6) (7) .

It is possible that an extraintestinal manifestation develops as the duration of the disease increases in patients. Whereas primary sclerosing cholangitis and ankylosing spondylitis are more common in men, it is detected that uveitis and iridocyclitis are more common in women. Most extraintestinal involvements other than ankylosing spondylitis and uveitis go parallel with disease activity, whereas disease activity is uncertain in the case of pyoderma gangrenosum and primary sclerosing cholangitis (1) .

The genetic inheritance of inflammatory bowel diseases could not have been explained with a simple Mendelian inheritance. Thanks to the "Genome-wide association scans" (GWAS) conducted to investigate the relationship between major diseases and single nucleotide polymorphisms, it has been determined that there are total of 163 risk loci for IBD, 110 of which are common for UC and CH. These loci have also been found to be common in a number of autoimmune diseases, such as ankylosing spondylitis, primary immune deficiencies, mycobacterial infections, and psoriasis (8) .

Intestinal inflammation caused by an excessive immune response to the trigger antigen in this disease leads to epithelial damage. The leukocytes of myeloid series, especially neutrophils and monocytes, which intensely infiltrate the intestinal mucosa, cause widespread inflammation with proinflammatory cytokines secreted into the environment (9) .

UC patients with any extraintestinal involvement have a higher risk of developing one of the other additional diseases. About 40% of patients with UC and Crohn's disease have extraintestinal involvement (10) (11) . Involvement of the extraintestinal organs poses a risk of increasing morbidity and mortality of the disease (11) .

It is reported that joint, eye and skin involvements are more common in active colitis (12) . Joint, eye, skin and hepatobiliary system involvements are the most common in UC; and the patients' quality of life increases with their treatment. Extraintestinal involvements do not affect the remission rate of the disease, but prolong the disease's remission (5) .

The purpose of this study is to evaluate the prevalence of Extraintestinal organ involvement (EIM) in UC patients and to analyze the relationships between age, gender and disease activity of patients with EIM.

Supplementary information The online version of this article (https://doi.org/xx.xxx/xxx.xx) contains supplementary material, which is available to authorized users.

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2 | MATERIALS AND METHODS

The study was conducted by retrospectively reviewing the information of the UC patients, who were followed up and treated in Manisa Celal Bayar University, Faculty of Medicine, Gastroenterology Department and who came to our hospital between January 2014 and December 2019, recorded in the hospital information system during the routine diagnosis and treatment process. It is a monocentric observational study.

The ethics committee approval (no. 18/04/2018-E. 10-008CC) of the study was obtained from Celal Bayar University, Faculty of Medicine, Ethics Committee.

For evaluation of the disease activity, the "Truelove-Witts" classification that is calculated according to clinical and laboratory findings and "Mayo scoring" including endoscopic findings were used, as well as "Rachmilewitz Endoscopic Activity Index" and "Montreal Classification" to determine the prevalence of Ulcerative Colitis. Presence of normal mucosa in endoscopy was considered as remission in addition to less than 3 and blood-free stools per day.

Patients were divided into two groups as a patient group in remission and a patient group in progression according to clinical conditions and endoscopic findings.

Clinical findings (body temperature, pulse, number of defecations, blood in stool) of the patients were recorded and their general physical examination and skin examination were performed. Chest x-rays, ECGs, eye examinations, abdominal ultrasonography, routine laboratory examinations, joint x-rays and examination of endoscopic findings were performed. 4 patients who underwent surgery (colectomy due to colon cancer) were identified. The results of 65 patients whose bone densitometry (DEXA) was measured were obtained from the hospital record system and evaluated.

3 | FINDINGS

Of the 199 patients included in the study, 114 (57.3%) were male and 85 (42.7%) were female (mean age 45 ± 5). The mean disease age of the UC patients studied was 68 months (8-276 months) Whereas the disease was in remission in 89% of the UC patients, it was active in 11%..

Table 1 shows the demographic characteristics of the patients.

TABLE 1: Demographiccharacteristics of the patients

Ulcerative Colitis Patients		%
Gender	85	42.7
Female	114	57.3
Male		
Age	26	13.1
18-28	58	29.1
29-39	40	20.1
40-50	41	20.6
51-61	22	11.1
62-72	12	6
73+	199	100
Total		

The extraintestinal findings detected include rheumatological diseases in 18 patients (9.2% [sero(-) arthritis in 13 patients (6.7%), ankylosing spondylitis in 2 patients (1%), sacroiliitis in 3 patients (1.5%)]), cardiac diseases in 9 patients (4.5% [coronary artery diseases in 6 patients (3%) and heart valve diseases in 3 patients (1.5%)]), skin diseases in 4 patients (2% [erythema nodosum in 3 patients (1.5%) and pyoderma gangrenosum in 1 patient (0.5%)], lung diseases in 4 patients (2% [asthma in 2 patients (1.5% and lung tuberculosis in 1 patient (0.5%)], thromboembolic events in 7 patients (%4 [portal vein thrombosis in 1 patient (0.5%), cerebral venous sinus thrombosis in 1 patient (0.5%), deep vein thrombosis in 1 patient (0.5%), and pulmonary thromboembolism in 3 patients 1.5%)], elevated liver enzyme in13 patients 26% primary sclerosing cholangitis in 2 patients (1%), erythema nodosum in 3 patients (1.5%), pyoderma gangrenosum in 1 patient (0.5%), depression in 3 patients (1.5%), as well as osteopenia in 17 patients (26%) and osteoporosis in 4 patients (6%) out of 65 patients whose DEXA results could be obtained.

Furthermore, ocular diseases were detected in 6 patients (3% [episcleritis/scleritis in 4 patients (2%) and uveitis in 2 patients (1%)]. Whereas there was extraintestinal involvement in 135 of 199 patients (67.8%), there was no extraintestinal involvement in 100 patients (50.2%). Table 2 shows the prevalence of extraintestinal involvement in UC patients. Figure 1 shows the percentage of extraintestinal manifestation.

TABLE 2: Prevalenceof extraintestinal involvement in UC patients

Extraintestinal diseases	Prevalence (n)	%
Rheumatological diseases	18	9.2
Ankylosing spondylitis	2	1
Sacroiliitis	3	1.5
Arthritis (sero negative)	13	6.7
Osteopenia	17	26
Osteoporosis	4	6
Elevated liver enzyme	26	13
Primary sclerosing cholangitis	2	1
Cardiac diseases	9	4.5
Coronary artery disease	6	3
Heart valve diseases	3	1.5
Skin diseases	4	2
Erythema nodosum	3	1.5
Pyoderma gangrenosum	1	0.5
Thromboembolic events	7	4
Portal vein thrombosis	1	0.5
Cerebral sinus vein thrombosis	1	0.5
Deep vein thrombosis	3	1.5
Pulmonary thromboembolism	2	1
Eye diseases	6	3
Episcleritis/Scleritis	4	2
Uveitis	2	1
Lung diseases	4	2
Asthma	3	1.5
Lung tuberculosis	1	0.5
Psychiatric Disorder (Depression)	3	1.5
Total	100	50.2

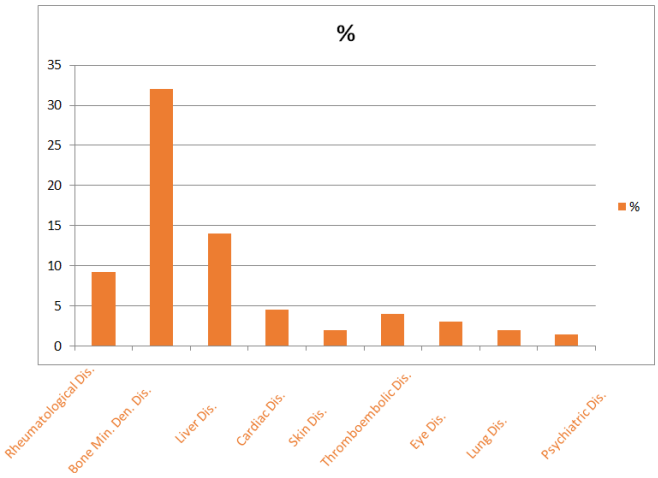

FIGURE 1: Distribution ofextraintestinal involvement in EC patients (%)

4 | DISCUSSION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by ulcers, which is induced by widespread inflammation of the colon mucosa and then has a course with activations and remissions. Activations can either be spontaneous or take place during treatment changes and/or other intervening infections.

Ulcerative colitis is diagnosed by evaluating clinical features, laboratory tests, endoscopic, radiographic and histological findings together (13) .

The goal in treatment of ulcerative colitis is to induce remission of the disease, prevent exacerbations and extraintestinal involvement, reduce hospitalization requirements, and provide both clinical and mucosal long-term improvements without corticosteroid where minimal surgery is required (14) .

Ulcerative colitis is a lifelong disease that is generally diagnosed in young adults at the age of 30-40. Although we come across different results in terms of prevalence in women and men in different studies, the general belief is that there is equal prevalence in women and men. Colectomy rates and proximal extension rates vary between 10-30% during the course of ulcerative colitis (15) , (16) .

Consistently with the literature, our study found the prevalence to be highest in the age group 29-39, and 57.3% of our patients were male and 42.7% were female, and the mean disease age was found to be

66 months (24-276 months).

The disease is primarily an immune-mediated disorder that involves the gastrointestinal tract. In addition, immune-mediated inflammatory diseases are named according to the organ which they involve. Skin, eyes, musculoskeletal system, kidneys, endocrine system, lungs, liver may be involved. Factors such as genetic factors, intestinal flora changes and environmental factors play a role in their common etiopathogenesis (1) .

About 50% of ulcerative colitis cases are associated with various extraintestinal involvements. For example, sclerosing cholangitis accompanies UC by 1-4% (1) and, in our study, sclerosing cholangitis was detected in 2 patients (1%), which is consistent with the literature.

It has been reported that prevalence of ankylosing spondylitis and isolated sacroileitis in patients with UC is 1-11% and 7-15%, respectively (1) . In our study, we detected ankylosing spondylitis disease in only 2 (1%) and sacroileitis in 3 (1.5%) out of 199 patients. Peripheral arthritis decreases when active disease is treated in UC; and the low rate of ankylosing spondylitis and sacroileitis in our patients may be attributable to the fact that our patients are mostly in remission (89%).

Thrombosis prevalence in IBD varies between 1 and 7%. The most prevalent are deep vein thrombosis and pulmonary thromboembolism. In a study conducted, pulmonary embolism or deep vein thrombosis was detected in 3.3% of UC patients (1) . The risk of venous thromboembolism is associated with disease activity. The risk of venous thromboembolism increased 4 times in all IBD patients and 15 times in active disease. As the duration of the disease increases, the risk of venous thromboembolism also increases. Studies performed show that the risk of recurrence of thromboembolism within 33 years is 33.4% in IBD patients, while this rate is 21.7% in patients with no IBD (1) . Consistently with the literature, we detected thromboembolic events in 7 patients (4%) in our study, which are 2 pulmonary embolism cases, 3 deep vein thrombosis cases, 1 portal vein thrombosis case and 1 cerebral sinus vein thrombosis case.

In addition, it is possible to detect depressive disorder and anxiety disorder 5 times more frequently in UC patients compared to the general population. This type of psychiatric illness is more common in the active period of the disease. It occurs especially after the diagnosis of IBD (17) . Depression was observed in 3 (1.5%) of our UC patients.

In studies conducted, the prevalence of osteopenia and osteoporosis in UC patients was found to be 34% (12/35) and approximately 14% (5/35) espectively in DEXA scans (18) .

In a study by Süleymanlar et al., it was reported that the prevalence of osteopenia and osteoporosis was found between 17-42% for ulcerative colitis in patients with IBD (19) .

In our study, DEXA results of 65 patients were obtained, and osteopenia and osteoporosis were detected in 17 (26%) and 4 (6%) patients, respectively.

Skin involvement in IBD is 15%, and the most common skin symptoms are erythema nodosum and pyoderma gangrenosum (20) . Prevalence of erythema nodosum in IBD is 4.2-7.5%. Its pathogenesis is not fully known. Some data suggest that there may be a Type-4 hypersensitivity reaction (1). It is associated with disease activity, and active UC regresses after treatment. Pyoderma gangrenosum develops in 0.6-2.1% of UC patients. The cause is unknown, but impaired neutrophil function and impaired cellular immunity have been blamed (1). In our study, skin involvement was detected in 4 patients (2%). 3 (1.5%) of these patients had erythema nodosum and 1 (0.5%) had pyoderma gangrenosum.

Literature shows that joint involvement in IBD is between 4-23% (13) . In our study, joint involvement was detected in 13 (6.7%) patients, which is consistent with the literature.

When the literature is examined in terms of hepatobiliary involvement in IBD, it is seen that prevalence of elevated liver enzyme and primary sclerosing cholangitis are around 30% and 4-5%, respectively [1,23]. In our study, elevated liver enzyme was observed in 26 patients (13%). Primary sclerosing cholangitis was detected in 2 (1%) patients.

Ophthalmological complications occur in approximately 12% of those with IBD in the literature [11]. The most prevalent eye manifestations in IBD are anterior uveitis and episcleritis. Scleritis and pos-

terior uveitis are less than 1%. Episcleritis reflects IBD disease activity whereas uveitis is independent of disease activity (1) .

In our study, at least one eye finding (scleritis/episcleritis, uveitis) was detected in 6 patients (3%). This was lower than then the rate of patients in the literature. This may be due to the fact that the vast majority of our patients were in remission.

The risk of colorectal cancer is increased in UC. The rate is 5-10% in cases followed for 20 years and 12-20% in cases followed for 30 years (21) .

Long disease duration is the most significant risk factor. Other risk factors may be listed as family history, age of patient when diagnosed, backwash ileitis, presence of primary sclerosing cholangitis, presence of pseudopolyps, and severity of inflammation (22) . Colectomy rates range from 10 to 30% during the course of ulcerative colitis (17) (18) .

Detection of colorectal cancer development is a definitive indication for colectomy. Colorectal cancer developed in 4 patients (2%) that we followed up and colectomy was performed.

In our study, colectomy rate (2%) was found lower than the rates seen in the literature.

Neurological findings are reported to be 3-39% in IBD [1]. Peripheral neuropathy incidence of 772 UC patients performed in the Mayo clinic was detected to be 0.7% after 20 years and 2.4% after 30 years [1]. No neurological findings were detected in any of our patients.

The meta-analyses conducted report increased ischemic heart disease, cerebrovascular disease and mesenteric ischemia in IBD. Peripheral vascular disease is present in 5% of patients with IBD. Studies in Denmark and Finland reported increased cardiac vascular mortality in active UC [1]. Hyper homocysteinemia, which is a risk factor for arterial and venous thrombosis, is 4 times more prevalent in people with IBD than the general population. It also contributes in hypercoagulability induced by systemic inflammation, early atherosclerosis, and thus increased arterial thromboembolic events. In our study, coronary heart disease and heart valve disease were detected in 6 (3%) and 3 of our UC patients, respectively.

Bronchopulmonary diseases are rare in IBD, and the true prevalence is unknown. Pulmonary function tests are often abnormal even when patients do not have respiratory symptoms [1].There is a relationship between chronic obstructive pulmonary disease (COPD) and IBD. In studies conducted, interstitial pulmonary involvement was reported to be 5-20% while infection or drugs have been shown as the most common cause. It is reported that particularly salicylates, methotrexate, thiopurines and anti-TNF may cause parenchymal lung disease [1]. 3 (1.5%) of our patients had asthma and 1 (0.5%) had previous pulmonary tuberculosis.

5 | CONCLUSION

UC is a lifelong disease. Patients included in the study were mostly in the age group 29-39, and unlike the literature, the number of male patients was higher. Other immune-mediated diseases are mostly co-existing in our UC patients. The quality of life that is impaired due to possible delays in diagnosis and primary disease may be further impaired due to accompanying extraintestinal manifestations. Therefore, when evaluating UC patients, extra intestinal manifestations should always be investigated by looking into joint, eye, skin, liver, biliary tract and other organ involvements, performing thorough examinations and measuring bone density, and these patients should be followed up and treated using multidisciplinary approaches.

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