

## CLINICAL EXTRAINTESTINAL MANIFESTATIONS OF ULCERATIVE COLITIS

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**Summary.** *Ulcerative colitis is a chronic, inflammatory bowel disease which can clinically be manifested either only with bowel symptomatology or with extraintestinal symptoms. A prospective study analysed 107 patients with ulcerative colitis (57 male and 50 female, mean age 41.25, range 21-70). The presence of the most common extraintestinal manifestations (EM) (myoskeletal, skin, ocular and hepatobiliary) has been analyzed. Out of the whole number of the examined, these manifestations were verified in 23 (21.49%) patients (10 male and 13 female, mean age 43.25, range 27-70). Patients with EM suffered longer from UC on the average, that is 6.06 years, while the others suffered for 4.44 years. Peripheral arthritis was the most common EM, verified in 13 (56.52%) patients. In 9 (39.14%) patients two or more EM were verified. In 77.27% patients, EM were clinically detectable after the intestinal symptomatology. No statistically significant difference was established in the duration of disease between patients with one EM and those with several EM. Patients with EM had more extensive and more active UC on average, in relation to others. No statistically significant difference was established, in extension and activity of disease, between patients with and without EM. The fact that EM can affect the clinical course of UC, therapy response and the quality of patient's life, oblige the doctors to be very cautious during the evaluation of patients with UC in order to recognize EM on time. In case of the above-mentioned illnesses without clinically manifested or undeveloped UC, large bowel screening should be performed to diagnose possible UC in the subclinical stage.*

**Key words:** *Ulcerative colitis, extraintestinal manifestations, index activity*

### Introduction

Ulcerative colitis (UC) is an idiopathic, chronic-relapsing, progressive, inflammatory bowel disease. The inflammatory process is limited to mucosa. Ulcerative colitis affects the distal rectum and extends for varying distances proximally. Clinically, it manifests most often through diarrhea, blood and/or mucus in stools, tenesmus, abdominal pain and weight loss. The explicitness of intestinal symptomatology depends on the level of inflammatory process, that is the activity of the disease. By complementary analysis of clinical symptoms and signs, as well as laboratory parameters, it is possible to clinically grade UC activity as mild, moderate and severe. Activity assessment has therapeutic and prognostic significance (1,2).

In patients with UC, it is possible to develop extraintestinal manifestations (EM) which are the consequence of a pathological process in different extraintestinal structures. These structures are far from the bowel, and they differ from it in shape and function. According to their origin, extraintestinal manifestations can be classified into two groups. The first group consists of those manifestation which are the consequence of the basic bowel disease (iron-deficiency anemia, amyloidosis, hepatic steatosis and al.) or they are complications from the drugs used to treat UC (urticaria, osteoporosis

and al.). They follow the clinical course of the basic bowel disease and react well to the therapy against UC. The second group most often consists of musculoskeletal, skin, ocular and hepatobiliary illnesses. The mechanism, which provokes the manifestations of the second group, is still not clear enough, as well as their relation to the existent bowel disease (2,3). The intriguing question is: is it the very same disease that attacks other organic structures besides the bowel, or is it different, coincidental or perhaps "metastatic" form of UC (4). Das et al. think that these EM are the consequence of an autoimmune response to the same antigen (bacterial protein the so-called 40-kDa), localized in various structures (the chondrocyte of a joint, the ciliary body of the eye, the bile duct epithelial cell and al.) whose substance is similar to tropomyosin or its isoforms on the surface of the colonic epithelial cell (5). One can find in the relevant literature much emphasis put on genetic factors for both UC and EM development. It is considered that the closest relatives of UC patients are at greater risk of getting the same bowel disease and developing the same EM type (5,6).

In 80% cases EM appear after the development of UC clinical symptoms and signs, in 10% they begin synchronically whereas in the remaining 10% they precede clinical manifestations of the basic bowel disease. With their symptomatology, they can conceal the exist-

tent bowel disease and, at one point, become dominant disorder (2,7,8).

The most common groups are respectively: myoskeletal (peripheral arthritis, ankylosing spondylitis, sacroiliitis), skin (erythema nodosum, pyoderma gangrenosum), ocular (iritis, uveitis and conjunctivitis) and hepatobiliary (primary sclerosing cholangitis). The greatest risk for the development of these EM is found in patients with long term and extensive colitis. Except ankylosing spondylitis, sacroiliitis, pyoderma gangrenosum and primary sclerosing cholangitis (PSC) all the other EM are in positive correlation with UC activity, so that with the optimal therapy of the basic bowel disease we also accomplish their remission (9,10).

In the last 50 years, extensive literature has shown that the existence of one EM increases the risk of the development of other EM (5). The risk of pouchitis development is greater in patients with EM. That is particularly characteristic of primary sclerosing cholangitis and the risk remains even after the liver transplantation (11,12,13).

The fact that further enhances the significance of EM is that patients with PSC and UC suffer from greater risk of developing colorectal cancer even after liver transplantation. Colectomy does not have any effect on the clinical progression or the mortality of patients with ankylosing spondylitis, pyoderma gangrenosum and primary sclerosing cholangitis, so that these manifestations can develop years after total colectomia (14,15,16).

Several EM can develop in one UC patient. The most commonly engaged organs in case of overlap EM are joints, skin and eyes. It is considered that HLA system has some part in EM overlap (17).

The fact that EM can affect the clinical course of UC, therapy response and the quality of life obliges the doctors to be very cautious during the evaluation of patients with UC in order to recognize EM on time. In case of the above-mentioned illnesses without clinically manifested or developed UC, large bowel surveillance should be performed to diagnose possible UC in the subclinical phase.

## Patients and methods

There were 107 examined patients, out of which 57 (53.3%) male and 50 (46.7%) female. The average age of the patients was 41.2 years. The youngest patient was 21 and the oldest 70 years old.

A prospective study included patients with ulcerative colitis, examined and treated in the Clinic of gastroenterology and hepatology, Clinical center of Nis, from April 1996 to March 2000. All basic and some necessary additional laboratory analyses were performed in all patients, as well as ultrasonography of the abdomen and colonoscopic examination of large bowel. Based on the criteria given by Truel and Witts (1955) all patients received a clinical evaluation of the disease activity (clinical index activity). During colonoscopic examina-

tion we gave the endoscopic evaluation of the extension and activity of the disease. After the histology analysis of biopsies, we were able to confirm UC diagnosis as well as give histology evaluation of the disease activity. EM diagnoses were established by means of consultative examinations. Rheumatologic EM have been diagnosed by a rheumatologist after the clinical, radiologic and biochemical examination.

For statistical analysis Student's t test and  $\chi^2$  test were applied.

## Results

The patients were grouped according to the existence or absence of EM. We analysed those EM which are most often verified in practice: peripheral arthritis, ankylosing spondylitis, sacroiliitis, erythema nodosum, pyoderma gangrenosum, ocular manifestations and primary sclerosing cholangitis. Out of the whole number of patients, analysed EM were verified in 23 (21.49%) (Table 1).

Table 1. EM representations according to sex of the patients

Extraintestinal manifestations	Patients	
	male	female No(%)
PA	3 (13.04)	/ 4 (17.39)
AS	2 (8.69)	/ 0
PA--SI	1 (4.35)	/ 0
PA--SI--AS--PG	0	/ 1 (4.35)
PA--SI--PG	1 (4.35)	/ 0
PA--PG	0	/ 1 (4.35)
EN	0	/ 1 (4.35)
EN--O	0	/ 1 (4.35)
EN--SI--O	0	/ 1 (4.35)
O	1 (4.35)	/ 2 (8.69)
PA--O	2 (8.69)	/ 1 (4.35)
PSC	0	/ 1 (4.35)
TOTAL	10 (43.48)	/ 13 (56.52)

PA-peripheral arthritis; SI-sacroiliitis; AS-ankylosing spondilitis; EN-erythema nodosum; GP-pyoderma gangrenosum; O-ocular manifestations; PSC-primary sclerosing cholangitis

Extraintestinal manifestations were found in 13 (56.52%) women, average age (at the time of examination) was 48.55 years and in 10 (43.48%) men whose average age was 43.25 years. The youngest patient was 27 and the oldest 70 years of age old. The peripheral arthritis was evident in 13 (56.52%), ocular manifestations in 8 (34.78%), sacroiliitis as well as erythema nodosum, pyoderma gangrenosum and ankylosing spondylitis in 3 (13.04%) and primary sclerosing cholangitis in 1 (4.35%) patient (Fig. 1).

One EM was verified in 14 (60.86%) patients, while two or more EM were diagnosed in the remaining 9 (39.14%). Patients with EM have been diagnosed with UC over a longer period of time (average 6.06 years), compared to the group of patients without EM (average 4.44 years). The correlation of the duration of UC between patients with one EM and patients with several

EM showed no statistical significance. Fig. 2. gives a representation of time manifestation of clinical EM in relation to UC. With the greatest number of patients (77.27%) EM are clinically detectable after intestinal symptomatology (Fig. 2).

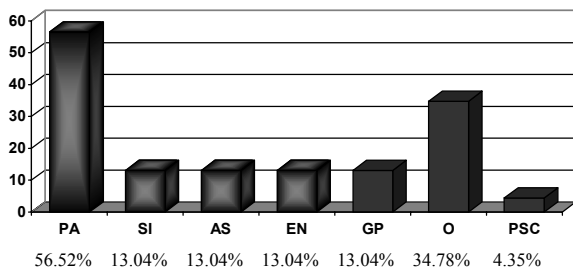


Fig. 1. The incidence of extraintestinal manifestations

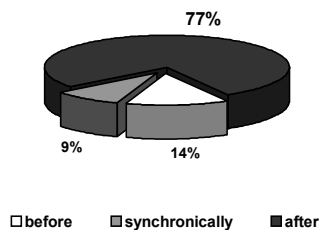


Fig. 2. Percentage representation of time manifestation of EM in relation to UC

In one patient with ankylosing spondylitis, colonoscopic examination was performed without previous intestinal symptomatology, and UC (minimal activity) was diagnosed.

The correlation of the clinical, endoscopical and histological indices of UC activity verified a statistically significant difference ( $p < 0.001$ ) in the activity of the basic bowel disease between patients with and without EM (Table 2). No statistically significant difference in the UC activity in patients with one or with more EM was established. UC activity was not in a positive correlation with the extension of the disease.

Patients with EM most often had pancolitis as opposed to the group where proctosigmoiditis was dominant (Fig. 3). The correlation of UC extension between patients with one or more EM showed no statistical significance ( $p > 0.001$ ).

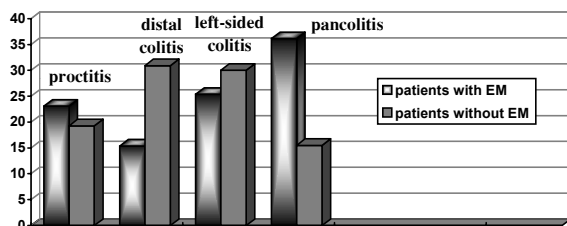


Fig. 3. Representation of UC extension in groups with and without EM

### Discussion

In this study, the analysed extraintestinal manifestations were present in 23 (21.49%) UC patients. The result was compared with the results of those studies which analysed identical EM in their UC patients. The prevalence of these manifestations in the study of Das et al. is 21% (5). Gumaste and al. analysed a group of 1274 UC patients and diagnosed EM in 21 % (18). Similar results were obtained in other studies in Western Europe (19,20,21,22). It has been noted that EM prevalence is significantly lower in Asia and Africa (23,24, 25,26,27). Jiang and al. analysed 10.218 UC patients and verified EM only in 6.1% (28). How the geographical area affects the development of EM remains still unknown.

In our study, EM were more often verified in women, which is in accordance with the results of other studies (8,15,24). Patients with developed EM were, at the point of examination, somewhat older and suffered from UC longer than the others. No significant relation was found between the age of the patients and the number of developed EM. Goudet et al. point out that EM manifest themselves more often in younger patients with long term colitis (15).

As with most other authors, our EM analysis has shown the most frequent evidence of peripheral arthritis (56.52%) (23,29,30,31,32,33). It is still not very clear why is arthritis manifested more often than all the other EM. Peripheral arthritis was associated with other EM in 7 (30.43%) patients. In the study Tromm et al. arthritis was the most frequent (28.8%) associated (overlap) EM (25). In our study, the clinical course of peripheral arthritis follows the UC activity. UC applied therapy accomplishes the remission of both UC and peripheral arthritis.

Ankylosing spondylitis was diagnosed in 3 (13.04%) patients. In two patients ankylosing spondylitis developed before UC intestinal symptomatology. In one patient colonoscopy was performed without intestinal symptomatology and UC was diagnosed accordingly. By means of colonoscopy surveillance of patients with ankylosing spondylitis and without intestinal symptoms or previous UC diagnosis. Biddle et al. verified signs of intestinal microscopic inflammation in 60% patients with ankylosing spondylitis at that time these patients did not develop clinical characteristics of UC (34). Not only does this suggest that EM can be joined with microscopic bowel inflammation but also points to the fact that there is a certain number of nondiagnosed patients with UC in the population of rheumatic patients. Ankylosing spondylitis does not follow UC activity (14). With one of our patients it persisted and evolved even after colectomy.

Our study shows that sacroiliitis manifested exclusively associated with other EM. This joints are visibly changed in almost 80% of UC patients if more sensitive diagnostic methods are used (23,31,35). In our study, sacroiliitis manifested in two patients before clinically

Table 2. Comparative representation of significant characteristics of the two groups UC

Characteristics	Patients with EM	Patients without EM	Total
Sex m/f	10 (9.35%) / 13 (12.15%)	47 (43.92%) / 37 (34.58%)	57 (53.27%) / 50 (46.73%)
Mean age m/f	43.25 / 48.55	46.67 / 39.25	44.96 / 43.90
Duration of UC	6.06 years	4.44 years	5.25 years
Extension of UC	pancolitis	left-sided colitis	left-sided colitis
Clinical activity	moderate *	mild*	mild
Endoscopic activity	moderate*	mild *	mild
Histological activity	moderate*	moderate*	moderate

(\*statistically significant -  $p < 0.001$ )

manifested UC which is a diagnostic problem for the basic bowel disease.

In this study, the analysed skin changes (erythema nodosum, pyoderma gangrenosum) were verified in the same percentage (13.04%). In literature, erythema nodosum mainly carries the prevalence (25,29,36). In accordance with the data from literature, in our patients erythema nodosum correlated with the UC activity as opposed to pyoderma gangrenosum, which persisted in one patient even after performed colectomy (37).

Out of the whole number of patients, ocular manifestations were verified in 8 (34.78%) and mainly in women, which corresponds with the results of other studies (29,38). Ocular manifestations followed UC activity and withdrew during remission. With regard to the significant prevalence of changes on eyes, this and all the other studies suggest ophthalmic examinations of all UC patients (38,39).

Our research shows the smallest prevalence (4.35%) of primary sclerosing cholangitis which is in accordance with the data in literature (9,10,40). In the study of Olsson et al. 55 (3.7%) of 1500 UC patients had primary sclerosing cholangitis (41). The outcome of primary sclerosing cholangitis does not relate at all to the activity, weight and clinical course of colitis in either our study or the others (29).

The exact prevalence of hepatobiliary abnormalities is difficult to determine because it involves insight into histology of liver of non-selective group of UC patients. Minimal abnormalities in the liver tissue are common in UC patients without a biochemically evident liver disease. Morphological changes cannot help much in the prediction of future risk, with UC patients, of the development of significant hepatobiliary complications (7,9,10). PSC is more prevalent in patients with pancolitis than in those with distal colitis (5.5 versus 0.5%) (42). The fact that 25 to 90% of patients with primary sclerosing cholangitis have subclinically or clinically

manifested UC is of great importance (13,40,43). That is why it is necessary for all patients with primary sclerosing cholangitis to have surveillance colonoscopy in order to diagnose possible UC on time. With the greatest number of patients with primary sclerosing cholangitis has a symptomatic course and is detected by routine laboratory (19,40).

In this study we have verified an occurrence of "overlapped" EM in 9 (39.13%) patients, which is more in relation to the results of other studies (8,44). The most often engaged organs in case of "overlapped" EM are skin, joints and eyes which is in accordance with the study of Das et al (5).

Quite a number of studies emphasize the significance of UC extension for the development of EM. The analysis of UC extension in this study has verified pancolitis with the greatest number of patients (36.15%) which is in accordance with the data from literature (24,45). Skrede et al. verified an equal presence of EM in patients with pancolitis and left-sided colitis (46).

The analysis of UC activity in patients with and without EM led to the conclusion that patients with a greater degree of activity are at greater risk of EM development. In their study, Mosebach et al. also came to the conclusion that UC activity was significantly greater in patients with EM (47). Mohammed et al. also concluded that UC activity was greater in patients with EM (23).

The basic prerequisite for a timely diagnosis of EM is their knowledge, and accordingly their timely recognition. For that purpose, patients with UC should be monitored by dermatovenerologists, ophthalmologists and other specialists. This applies particularly to those UC patients who have run a greater risk of EM development. With regard to the fact that EM may develop before the intestinal symptomatology of UC, it is necessary for these patients to perform an exploration of the large bowel for the purpose of a timely UC diagnosis.

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## KLINIČKE EKSTRAINTESTINALNE MANIFESTACIJE ULCEROZNOG KOLITISA

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Kratak sadržaj: *Ulcerozni kolitis je hronična, zapaljenska bolest debelog creva koja se može manifestovati kako intestinalnom tako i ekstraintestinalnom simptomatologijom. Prospektivnom studijom je analizirano 107 obolelih od ulceroznog kolitisa (57 muškaraca i 50 žena, prosečne starosti 41,25, koja se kretala od 21 do 70). Analizirano je prisustvo najčešćih ekstraintestinalnih manifestacija (EM). Od ukupnog broja ispitanika ove manifestacije su verifikovane u 23 (21,49%) (10 muškaraca i 13 žena, prosečne starosti 43,25, koja se kretala od 27-70). Ispitanici sa EM su u proseku duže bolovali od UC, 6,06 godina, za razliku od preostalih koji su bolovali 4,44 godina. Periferni artritis je bila najčešća EM, verifikovana u 13 (56,52%) ispitanika. U 9 (39,14%) ispitanika su verifikovane po dve i više EM. U 77,27% ispitanika EM su se klinički ispoljile nakon intestinalne simptomatologije. Nije uočena statistički značajna razlika u dužini trajanja bolesti između pacijenata sa jednom i pacijenata sa više EM. Ispitanici sa EM su u proseku imali ekstenzivniji i aktivniji UC u odnosu na ostale ispitanike. Nije uočena statistički značajna razlika u ekstenzivnosti i aktivnosti bolesti između ispitanika sa i bez EM.*

*Činjenica da EM mogu da utiču na klinički tok UC, terapijski odgovor i kvalitet pacijentovog života, obavezuje kliničara da tokom evaluacije obolelih od UC bude na oprezu kako bi pravovremeno prepoznao EM. U slučaju postojanja navedenih bolesti bez klinički manifestnog ili još ne razvijenog UC treba uraditi skrining debelog creva u cilju eventualne dijagnoze UC u subkliničkoj fazi.*

**Ključne reči:** *Ulcerozni kolitis, ekstraintestinalne manifestacije, indeks aktivnosti*