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Correlation between extraintestinal manifestations and clinical parameters with the histologic activity index in patients with inflammatory bowel diseases

Povezanost vancrevnih manifestacija i kliničkih parametara sa indeksom histološke aktivnosti kod bolesnika sa inflamatornim bolestima creva

Miloš Štulić*, Djordje Ćulafić*†, Dragana Mijač*†, Goran Janković*†, Ivana Jovičić*, Miodrag Krstić*†, Tomica Milosavljević*†

***Clinic of Gastroenterology, Clinical Center of Serbia, Belgrade, Serbia; †Faculty of Medicine, University of Belgrade, Serbia**

Abstract

Bacground/Aim. Crohn's disease (CD) and ulcerative colitis (UC) are chronic, idiopathic, inflammatory diseases of the digestive tract. The aim of this study was to determine a possible correlation between the clinical parameters of the disease activity degree and the presence of extraintestinal manifestations with disease activity histopathological degree, in patients presented with CD and UC. **Methods.** This cross-sectional study included 134 patients (67 with CD and UC, respectively) treated at the Clinic of Gastroenterology, Clinical Center of Serbia, Belgrade. After clinical, laboratory, endoscopic, histopathologic and radiologic diagnostics, the patients were divided into two groups according to their histopathological activity. The group I comprised 79 patients whose values of five-grade histopathological activity were less than 5 (45 with CD and 34 with UC), while the group II consisted of 55 patients with the values higher than 5 (22 with CD and 33 with UC). The CD activity index (CDAI) and Truelove and Witts' scale of UC were used for clinical evaluation of the disease activity. **Results.** CD extraintestinal manifestations were present in 28.9% and 63.6% of the patients in the groups I and II, respectively ($p < 0.05$). Comparison of the mean CDAI values found a significant difference between these two patients groups (the group I: 190.0 ± 83.0, the group II: 263.4 ± 97.6; $p < 0.05$). No correlation of extraintestinal manifestations of the disease, Truelove and Witts' scale and histological activity was found in UC patients ($p > 0.05$). **Conclusion.** In the patients presented with CD, the extraintestinal manifestations with higher CDAI suggested a higher degree of histopathological activity. On the contrary, in the UC patients, Truelove and Witts' scale and extraintestinal manifestations were not valid predictors of the disease histopathological activity.

Key words:
crohn disease; colitis, ulcerative; severity of illness index; signs and symptoms; histological techniques.

Apstrakt

Uvod/Cilj. Kronova bolest (*Crohn's disease* – CD) i ulcerozni kolitis (*ulcerative colitis* – UC) su hronične, idiopatske, zapaljenske bolesti digestivnog trakta. Cilj rada bio je da se utvrdi da li kod bolesnika sa CD i UC postoji uzajamni odnos između kliničkih pokazatelja stepena aktivnosti bolesti i prisustva vancrevnih manifestacija sa patohistološkim stepenom aktivnosti bolesti. **Metode.** Studija preseka obuhvatila je 134 bolesnika (67 sa CD i 67 sa UC) lečena u Klinici za gastroenterologiju Kliničkog centra Srbije u Beogradu. Nakon kliničke, laboratorijske, endoskopske, patohistološke i radiološke dijagnostike, bolesnici su na osnovu patohistološke aktivnosti bolesti podeljeni u dve grupe. U grupu I svrstano je 79 bolesnika čije su vrednosti petostepenog gradusa patohistološke aktivnosti bile manje od 5 (45 sa CD i 34 sa UC), dok je u grupi II bilo 55 bolesnika sa vrednostima većim od 5 (22 sa CD i 33 sa UC). Za kliničku procenu aktivnosti bolesti korišćen je indeks aktivnosti CD bolesti (CDAI) i Truelove i Wittsova skala za UC. **Rezultati.** Vancrevne manifestacije CD bile su prisutne kod 28,9% bolesnika grupe I i 63,6% bolesnika grupe II ($p < 0,05$). Upoređivanjem srednjih vrednosti CDAI uočena je statistički značajna razlika između dve grupe bolesnika (grupa I: 190,0 ± 83,0, grupa II: 263,4 ± 97,6; $p < 0,05$). Kod bolesnika sa UC nije utvrđena veza između prisustva vancrevnih manifestacija bolesti, Truelove i Wittsove skale i patohistološke aktivnosti bolesti ($p > 0,05$). **Zaključak.** Kod bolesnika sa CD prisustvo vancrevnih manifestacija, zajedno sa višim CDAI, ukazuje na veći stepen patohistološke aktivnosti bolesti. Nasuprot tome, kod bolesnika sa UC, Truelove i Wittsova skala i prisustvo vancrevnih manifestacija nisu bili pouzdani prediktori histološkog stepena aktivnosti bolesti.

Ključne reči:
kronova bolest; kolitis, ulcerativni; bolest, indeks težine; znaci i simptomi; histološke tehnike.

Correspondence to: Miloš Štulić, Clinic of Gastroenterology, Clinical Center of Serbia, Nikšićka 2, 11 000 Belgrade, Serbia. Phone: 064/246-55-15. E-mail: milosstulic@yahoo.com

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are idiopathic, chronic, inflammatory diseases of the digestive tract. Due to similar clinical manifestation, histopathological findings, diagnostics, complications and treatment, these diseases are both described as inflammatory bowel diseases (IBD).

In CD patients, changes are most usually localized in the terminal ileum and ascending colon, then in the colon or terminal ileum only, and the rarest location is only in the ileum and/or jejunum. The most characteristic histopathological finding is chronic inflammation which involves all intestinal wall layers, followed by deep ulcerations, frequently seen as linear fissures with "cobblestone" appearing mucosa between them [1].

On the contrary to CD, in UC patients changes always affect the rectum and may be continuously spread to the proximal colon all the way to the caecum. Mucosa is primarily involved, being uniformly hyperemic, edematous, ulcerated and fragile. In a long-term course of the disease, fibrosis and longitudinal retraction result in the loss of haustra, and X-ray finding demonstrates typical "lead-pipe" appearance of the colon [2].

There is no possibility to distinguish UC from CD, up to 10–20% of cases, what is a special clinical entity called indeterminate colitis. The majority of these patients is differentiated as UC patients over time. Indeterminate colitis is a histopathological term, meaning the condition where biopsy specimens of the colon have overlapping characteristics [3].

The commonest intestinal IBD symptoms are following: diarrhea, abdominal pain, hemorrhage, body weight loss and fever. Extraintestinal manifestations (EIM) are also significant, manifesting as: skin changes (erythema nodosum, vasculitis, pyoderma gangrenosum), arthralgia and arthritis, ankylosing spondylitis, uveitis, episcleritis, biliary lithiasis and urolithiasis. Additionally, IBDs are frequently associated with primary sclerosing cholangitis, thrombosis and embolies [4].

The aim of the study was to find out if there was a correlation between clinical parameters of the disease activity and the EIM presence with the histopathological activity index of the disease.

Methods

This cross-sectional study was conducted at the Clinic for Gastroenterology, Clinical Center of Serbia, Belgrade, including a period from December 2006 to January 2011. The study involved 134 patients (67 with CD and UC, respectively).

All the patients were analyzed for the following parameters: age, sex, localization of changes in the digestive tract, histopathological degree of the disease activity (five-grade activity), present EIM, Crohn's Disease Activity Index (CDAI) [5] and Truelove and Witts' scale for the assessment of the activity [6].

The investigation was based on the medical history data, physical examination and laboratory analyses used for CDAI (Table 1) and Truelove and Witts' scale (Table 2) calculations. All the patients underwent colonoscopy with histopathological verification. The patients with non-determined colitis were excluded.

Table 1

Crohn's Disease Activity Index – (CDAI)[5]

Parameter	Index
Number of liquid or soft stools in 7 days	× 2
Abdominal pain – pain score per day (0 = none, 1 = mild, 2 = moderate, 3 = severe)	× 5
General well-being – general well-being score per day (0 = generally well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible)	× 7
Number of complications (presence or absence): arthritis or arthralgia iritis or uveitis anal fissure, fistula or abscess erythema nodosum, pyoderma gangrenosum, aphthous stomatitis other fistula fever over 37.8°C	× 20
Loperamide or diphenoxylate for diarrhea	× 30
Abdominal mass (none = 0, questionable = 2, definite = 5)	× 10
Hematocrit [males 47 (%), females 42 (%)]	× 6
Body weight: (1- Body weight/standard weight) × 100	× 1

Table 2

Truelove and Witts' index [6]

Parameter	Mild	Moderate	Severe
Bloody stools	< 4	≥ 4	≥ 6
Pulse rate	< 90/min	≤ 90/min	> 90/min
Temperature	< 37.5 °C	≤ 37.8 °C	> 37.8 °C
Hemoglobin	> 11.5 g/dL	≥ 10.5 g/dL	≥ 10.5g/dL
ESR/CRP	normal	≤ 30	> 30

ESR – erythrocyte sedimentation rate; CRP – C reactive protein.

The patients were divided into two groups according to the values of five-grade inflammation activity (FGA) by Geboes et al. [7], which is a numerical scale for evaluating the histological disease activity (Table 3).

Table 3

The histologic grading system according to Geboes et al. [7]

GRADE 0 – structural (architectural change)
0.0. No abnormality
0.1 Mild abnormality
0.2 Mild or moderate diffuse or multifocal abnormalities
0.3 Severe diffuse or multifocal abnormalities
GRADE 1 – Chronic inflammatory infiltrate
1.0 No increase
1.1 Mild but unequivocal increase
1.2 Moderate increase
1.3 Marked increase
GRADE 2 – Lamina propria neutrophils and eosinophils
2A Eosinophils
2A.0 No increase
2A.1 Mild but unequivocal increase
2A.2 Moderate increase
2A.3 Marked increase
2B Neutrophils
2B.0 None
2B.1 Mild but unequivocal increase
2B.2 Moderate increase
2B.3 Marked increase
GRADE 3 – Neutrophils in epithelium
3.0 None
3.1 < 5% crypts involved
3.2 < 50% crypts involved
3.3 > 50% crypts involved
GRADE 4 – Crypt destruction
4.0 None
4.1 Probable – local excess of the neutrophils in part of the crypt
4.2 Probable – marked attenuation
4.3 Unequivocal crypt destruction
GRADE 5 – Erosion or ulceration
5.0 No erosion, ulceration, or granulation tissue
5.1 Recovering epithelium + adjacent inflammation
5.2 Probable erosion focally stripped
5.3 Unequivocal erosion
5.4 Ulcer or granulation tissue

Descriptive and analytical statistical methods were used for data analysis: Mann-Whitney test for numerical characteristics and χ^2 test for categorical characteristics. The values of $p < 0.05$ were considered significant. SPSS for Windows v.17.0 (SPSS Inc. Chicago, IL) was used for statistical data processing.

Results

There were 45 CD patients in the group I, with the values of FGA < 5.0, while the group II included 22 patients with the values of FGA > 5.0. Among the UC patients, 34 patients with FGA < 5.0 were in the group I and 33 patients with FGA > 5.0 were in the group II.

The average age of the patients with CD was 37.1 ± 14.2 years, of which 28 (41.8%) were males and 39 (58.2%) females. Upon group analysis, no significant difference in age (Mann Whitney U Z= -1.094; $p = 0.274$) and sex ($\chi^2 = 0.010$; $p = 0.918$) was found in the CD patients (Table 4).

There was no statistical significance in relation to CD localization ($\chi^2 = 2.919$; $p = 0.232$). Ileocolitis was manifested in 24 (53.3%) patients with the lower histopathological activity index and 13 patients with FGA > 5 (59.1%), what is the most frequent localization of CD. Second by frequency was Crohn colitis presented in 12 (26.7%) patients with FGA < 5 and 8 (36.4%) patients with FGA > 5, while the localized disease of the terminal ileum was found in 9 (20%) patients with FGA < 5 and only in one (4.5%) with high histopathological activity index.

Comparison of the mean values of CDAI (in patients with FGA < 5 190.0 ± 83.0, and in the group with high histopathological activity 263.4 ± 97.6), showed a direct correlation and highly significant difference between (Mann Whitney UZ = -3.385; $p = 0.001$).

Out of a total number of patients, at least one EIM was reported in 39 (29.1%) patients (CD 40.3%; UC 17.9%). In the CD patients, EIMs were manifested in the forms of: arthralgia in 19 (28.4%), aphthous stomatitis in 5 (7.5%), ery-

Table 4

Distribution of patients with Crohn's disease (CD) and ulcerative colitis (UC) according to age, sex and five-grade inflammation activity (FGA)

Disease	FGA	Patients			
		age (years), $\bar{x} \pm SD$	*p*	sex (M/F), n	*p*
CD	< 5	38.8 ± 2.4 (n = 34)	0.274	19/26	0.918
	> 5	33.8 ± 2.4 (n = 30)		9/13	
UC	< 5	40.5 ± 3.7 (n = 35)	0.994	16/18	0.895
	> 5	40.4 ± 3.0 (n = 34)		15/18	

thema nodosum in 5 (7.5%), uveitis anterior in 2 (3%) and primary sclerosing cholangitis in 2 (3.0%) of the patients. In relation to histopathologic activity index of CD, EIM were present in 13 (28.9%) of the patients with a low histologic grade of the disease activity and 14 (63.6%) patients with FGA > 5 ($\chi^2 = 7.415$; $p = 0.009$) (Figure 1).

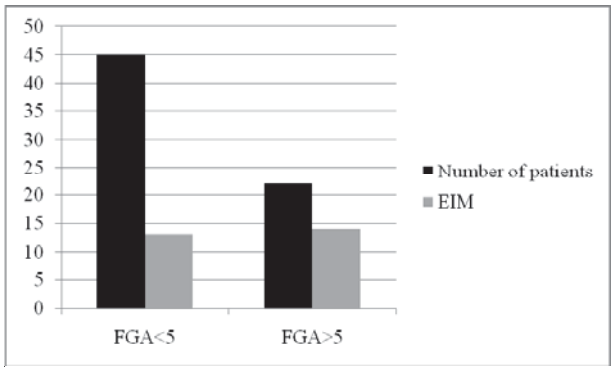

Fig. 1 – Distribution of patients with extraintestinal manifestations (EIMs) of Crohn's disease in relation to five grade inflammation activity (FGA) ($p = 0.009$).

In 67 patients with UC, the mean age was 40.5 ± 15.5 years, out of which 31 (46.3%) were males and 36 (53.7%) females. Group analysis failed to show any difference in age (Mann Whitney U Z = -0.007; $p = 0.994$) and sex ($\chi^2 = 0.017$; $p = 1.000$) of the patients with different velues of FGA (Table 4).

Comparison of the diseases distribution in patients with UC to the histopathological disease activity found a statistically significant difference ($\chi^2 = 9.439$; $p = 0.003$). A total of 12 (35.3%) patients with a moderate histological form of the disease were diagnosed with pancolitis, while the rest of 22 (64.7%) patients had "left side' distribution of the disease. In the patient group with FGA > 5, 24 (72.7%) patients had pancolitis, while others had "left side" colitis.

Testing the correlation of Truelove and Witts' scale and histopathological activity index failed to show any significant difference in the diseese distribution ($\chi^2 = 1.679$; $p = 0.432$) (Figure 2). The moderate form of disease was presented in 15 (44.1%) patients with low histopathological activity index and in 15 (45.5%) patients with FGA > 5. A severe form of the disease had 11 (32.4%) patients with FGA < 5 and 14 (42.4%) patients with FGA > 5, while a mild form of it was lightly represented in only 8 (23.5%) patients, whose FGA was lower than 5 and in 4 (12.1%) patients with FGA > 5.

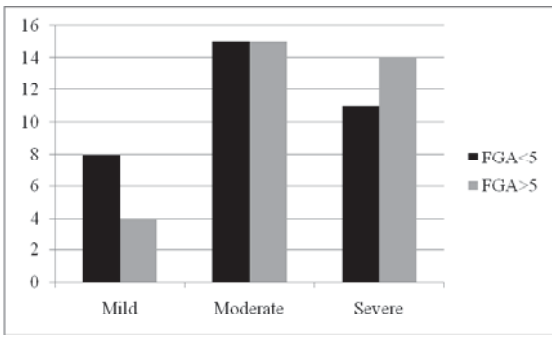

Fig. 2 – Distribution of patients with ulcerative colitis according to values of the Truelove and Witts' scale and five grade inflammation activity (FGA) of the disease ($p = 0.432$).

EIMs were verified in 7 (20.6%) of the patients with lower histopathological activity index of UC and in 5 (15.2%) patients with FGA > 5. Arthralgia and primary sclerosing cholangitis (PSC) were manifested in 5 (7.5%) patients, respectively, and pyoderma gangrenosum in 3 (4.5%) patients. In distinction from CD, UC patients were not verified with a significant difference between the EIM and the histopathological activity index ($\chi^2 = 0.337$; $p = 0.752$) (Figure 3).

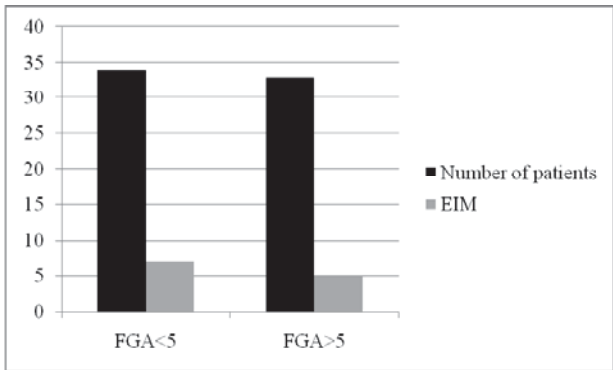

Fig. 3 – Distribution of patients with extraintestinal manifestations (EIMs) of ulcerative colitis in relation to five-grade activity (FGA) of the disease and ($p = 0.752$).

Discussion

The maximum age of the onset for both diseases is between 15 and 25 years. In some series, the second, lower peak of incidence occurs between 55 and 65 years. Most series show approximately equal incidence of both diseases in males and females. Some studies show CD incidence higher in females by 30%, while it may be somewhat higher among males [8, 9].

In our study, the majority of patients were between 35 and 45 years of age, what is compatible with literature data.

Most studies report that females are more affected with CD than males, contrary to UC where the incidence is higher in males. Also, a large study of Herrinton et al. [9] reported a higher incidence rate of CD in women than in men (1.2 times as frequent), and higher incidence rate of UC in men than in women (1.3 times as frequent).

Our study also confirmed higher incidence of CD in women. However, contrary to earlier articles, the incidence of UC was also higher in women than in men.

Younger age at diagnosis (< 20 years), compared with the older age (≥ 40), was associated with higher incidence of CD family history (29.9% *vs* 13.6%, respectively), greater small bowel involvement (88.7% *vs* 57.5%, respectively), more stricturing disease (45.8% *vs* 28.8%, respectively), and higher frequency of surgery (70.6% *vs* 55.3%, respectively). Older age *vs* yunger one at diagnosis was associated with higher incidence of colonic disease (84.8% *vs* 71.2%, respectively) and the inflammatory subtype (54.5% *vs* 34.4%, respectively) [10].

Epidemiological and family studies demonstrate that genetic factors play a role in the susceptibility to IBD. UC and CD may be heterogeneous polygenic disorders sharing some but not all susceptibility loci. Most likely, the disease phenotype is determined by several factors, including the interaction between allelic variants at a number of loci, as well as genetic and environmental influences [11]. Genome-wide scanning with microsatellite DNA markers has identified several genetic sites as being potentially associated with UC or CD [11]. Significant linkages have been reported on chromosomes 1, 3, 6, 7, 12, 14, 16, and 19 [12]. Detailed analysis has resulted in the identification of the nucleotide-binding oligomerization domain 2 (NOD2) gene and protein. NOD2 is also known as caspase activation and recruitment domain 15 (CARD15). This is a polymorphic gene, the product of which is involved in the innate immune system. It is estimated that defects in NOD2 account for 17% to 27% of CD cases [13].

In addition, pathogenic microbes such as: *Mycobacterium paratuberculosis, Listeria monocytogenes, Chlamydia trachomatis, Escherichia coli, Cytomegalovirus, Saccharomyces cerevisiae*, have been proposed as having a potential etiologic role [14]. Bacterial superinfection (most commonly *Clostridium difficile*, but also *Entamoeba histolytica, Campylobacter spp.*) is also able to elicit relapse of IBD. This hypothesis was confirmed in the study of Mylonaki et al. [15] 2004, where 10.5% of all relapses were associated with the enteric infections. In another study, 20% of all relapses were associated with *Clostridium difficile* [16].

In genetically susceptible host with IBD, other local factors in the colon with the antigen presenting cells may trigger an immune reaction to a shared antigen in the involved organs. This pathogenetic mechanism may explain the development of EIMs, which are observed in up to 20–40% of patients with IBD. Moreover, patients with CD are more susceptible to EIM than patients with UC [17].

EIMs may involve nearly any organ system including musculoskeletal, dermatologic, hepatopancreatobiliary, ocular, renal and pulmonary systems that can cause a significant challenge to physicians managing IBD patients [18]. Some of them are very rare: tracheobronchitis, acute respiratory distress syndrome, membranous glomerulonephritis, acute pancreatitis, lower extremity arterial occlusive disease, pericarditis or acute CNS white matter lesions.

Few studies have specifically examined how frequently EIM is a patient's presenting symptom or is present at the time of diagnosis *vs* occurring later in the disease course. In a retrospective study of 448 IBD patients Aghazadeh et al. [19] showed that 31.4% of UC patients and 40.4% of CD patients had 1 of the 5 major manifestations. A smaller percentage of patients had more than 1 EIM.

The study of Yüksel I et al. [20], included 352 patients. Among them, 34 (9.3%) patients presented with at least 1 cutaneous manifestation. The prevalence of erythema nodosum and pyoderma gangrenosum in IBD was 7.4% and 2.3%, respectively. Erythema nodosum was more common in CD (16/118) than UC (10/234) and was found to be related to disease activity of the bowel. In addition, they reported that the prevalence of arthritis was significantly higher in the IBD patients with erythema nodosum and pyoderma gangrenosum [20].

In a study of Vavricka et al. [21] 950 IBD patients were prospectively included from an adult clinical cohort in Switzerland. There were 580 (61%) cases with CD and 370 (39%) with UC. Out of these, 249 (43%) of CD and 113 (31%) of UC patients had one to five EIMs. The following EIMs were found: arthritis (CD 33%; UC 21%), aphthous stomatitis (CD 10%; UC 4%), uveitis (CD 6%; UC 4%), erythema nodosum (CD 6%; UC 3%), ankylosing spondylitis (CD 6%; UC 2%), psoriasis (CD 2%; UC 1%), pyoderma gangrenosum (CD and UC each 2%), and primary sclerosing cholangitis (CD 1%; UC 4%) [21].

In our study, the EIM incidence in CD patients was 40.3%, what is compatible with earlier reports. The frequency of arthralgia, aphthous stomatitis, erythema nodosum, uveitis anterior and primary sclerosing cholangitis did not deviate from other study data. However, in distinction from the aforementioned studies, the EIM incidence in the UC patients was 17.9%. A low EIM incidence in UC could be accounted for correlation between the EIM and histopathological disease activity found no in our study.

Mendoza et al. [22] described that EIM related to IBD occurred at least once in 46.6% of patients. Joint manifestations were the most common EIM (UC 51.5%; CD 42.2%). Hepatobiliary manifestations, venous thromboembolism and arthralgias were more frequent in UC than CD. Erythema nodosum and peripheral arthritis were more frequent in CD. The incidence of the ocular and the rest of joint manifestations were not different in relation to UC or CD.

Asymptomatic sacroiliitis may be actually seen in up to three-quarters of IBD patients. Careful survey may also reveal many patients with a history of swollen joints and other musculoskeletal symptoms, often preceding the diagnosis of IBD in several years. The prevalence of axial arthritis varies from 3% to 25% of patients with IBD and may or may not be associated with peripheral arthropathy [23]. Moreover, several

case studies have described acute idiopathic pancreatitis manifested many years before diagnosis of CD was made [24].

EIM sometimes impair the overall life quality much more than the bowel-related symptoms. Extraintestinal manifestations need to be distinguished from secondary diseases or complications of inflammatory bowel diseases, as they require different and specific treatment [25].

Conclusion

In patients with CD, EIMs together with higher CDAI indicate higher histopathological activity grade. On the contrary, in UC patients, Truelove and Witts' scale and EIMs were not valid predictors of histopathological activity of the disease.

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