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Does the location of inflammatory lesions in the gastrointestinal tract determine the clinical course of Crohn's disease?

Czy lokalizacja zmian zapalnych w obrębie przewodu pokarmowego determinuje przebieg kliniczny choroby Leśniowskiego-Crohna?

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Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Introduction: Crohn's disease (CD) is a chronic, inflammatory bowel disease that can affect any part of the digestive system. The ileocecal region is most commonly involved. Recently, there have been reports about Crohn's disease isolated to the colon, which may be associated with different clinical behaviour and the need for various treatment options.

Materials/Methods: The study included 305 patients with CD, 171 women (56%) and 134 men (44%), hospitalized at the Department of Gastroenterology, University Hospital in Lodz. Among them, a group of 101 patients was identified with a lesion location only in the colon (L2) and 204 in the small intestine and colon (L1 and L3). An attempt was made to analyze patients with CD in terms of demographic data, clinical behavior of the disease and location of inflammatory lesions.

Results: Among the features distinguishing the location of inflammatory lesions isolated to the colon (L2), statistically significantly less frequent occurrence of stenoses (21% at L2 location to 79% at L3, $p < 0.01$) was observed compared to other locations. Moreover, patients with location of L2 lesions required surgery less frequently (27% with L2 vs. 73% L1 with L3, $p < 0.05$). It was also demonstrated that among all the subjects, 42 patients underwent appendectomy before the diagnosis of CD, which constituted 19% of the L2 group patients to 81% of the L1 and L3 group ($p < 0.05$).

Conclusions: In CD there is a great diversity in the clinical behavior of the disease, which is undoubtedly related to its location. The obtained results indicate that in the group of patients with the location isolated to the colon, stenoses are less common and patients require surgery less frequently.

Keywords: **Crohn's disease, inflammatory bowel disease**

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INTRODUCTION

Crohn's disease (CD) is a chronic, non-specific inflammatory disease of the gastrointestinal tract with periods of exacerbation and remission. Inflammation involves the entire wall and can affect any part of the digestive tract from the mouth to the anus. Segmental inflammation is the characteristic feature of the disease, which means that diseased segments are separated by fragments of normal mucosa. Terminal ileum and cecum are most commonly affected sites in about 40–50% of patients. In 30–40% of patients both the small intestine and the colon are involved and in 20% of patients inflammation is located solely in the colon [14, 24]. Only in less than 5% of patients the location of lesions may affect the upper gastrointestinal tract. Assessment of the location of the disease in the gastrointestinal tract, age at diagnosis and assessment of the behavior of the disease are part of the Montreal classification of CD [18]. The etiology of the disease is multifactorial. The role of an abnormal immune response, genetic predisposition and the contribution of environmental, infectious or nutritional factors are taken into account in its etiopathogenesis [9].

Ulcerative colitis (UC) was the first from among nonspecific inflammatory bowel diseases to be characterized as a distinct entity. The first physician who used the term ulcerative colitis to describe the condition was Samuel Wilks in 1859, but it is suspected that the case described at the time may have been Crohn's disease located in the colon [15]. First cases of Crohn's disease called ileitis terminalis were described by Professor Antoni Leśniowski in 1903 in the weekly Medicine – Journal for General Practitioners. Then in 1932, the Americans Burrill Bernard Crohn, Leon Ginzburg and Gordon Oppenheimer again drew the attention of the medical world to inflammatory bowel diseases. On 13 May 1932, at the session of Gastroenterological and Proctological Section of American Medical Association in New Orleans, the team delivered a lecture in which they presented descriptions of 14 patients with granulomatous inflammation of the terminal segment of the small intestine, after which the new disease entity was called regional ileitis – 'segmental enteritis' [6]. First reports, written by surgeon Ralph Colp, that CD can only involve the colon come from 1934. Then in 1936, Burrill Bernard Crohn and Bernard Rosenak made the same observation as well. Since then, these speculations had caused much confusion over the relationship between Crohn's disease and ulcerative colitis. Confirmation of CD location in the colon was first described by a British surgeon, Charles Wells, in 1952 as 'granulomatous segmental colitis' and later by Bryan Brook in 1959. These considerations were definitively confirmed in 1960 by Lyn Lockhart-Mummery, who presented 25 patients with Crohn's disease with the involvement of the colon, in whom the disease was manifested by the occurrence of bloodless diarrhea, anal fistulas, strictures and segmental lesions with rectal sparing [13, 22]. Polish physicians have also contributed to the development of knowledge about Crohn's disease. The first Polish description of the disease located in the colon, by Professor Witold Bartnik, was published in 1971 in the Polish Archives of Internal Medicine [2, 3].

The results of the studies published in the last few years indicate differences in the clinical course of Crohn's disease with isolated colonic involvement compared to the form of the disease located in the small intestine. Some authors suggest recognition of CD located in the colon as a separate disease entity in the group of nonspecific inflammatory bowel diseases. One of the differences in the course of Crohn's disease that has been reported so far in the literature is the lower number of relapses after proctocolectomy in the case of colonic involvement compared to the location in the small intestine. Furthermore, Crohn's disease in the large intestine, similarly to ulcerative colitis, is associated with pANCA and ASCA antibodies are detected in the form of Crohn's disease with the involvement of the small intestine [11]. The division of Crohn's disease with the involvement of the small intestine and the colon as two separate entities is also supported by molecular studies, which show that the NOD/CARD15 gene mutation is associated with the location in the small intestine and the presence of the HLA-DRB1 allele with colonic disease [4, 5].

Inflammation of various parts of the small and/or large intestine may be associated with a different clinical course and behavior of the disease, which is why the development of various types of complications determines the choice of different treatment options. Therefore, we described the clinical features and disease course of colonic CD and compared it with ileal and ileocolonic CD.

MATERIAL AND METHODS

A retrospective analysis was made of clinical data of patients with Crohn's disease hospitalized at the Department of Gastroenterology, University Teaching Hospital in Lodz and those under the care of the Gastroenterological Outpatient Clinic in the years 2012–2018. Diagnosis of CD was established on the basis of the criteria of the European Crohn's and Colitis Organization (ECCO) and the Guidelines of the Working Group of the Polish National Consultant in Gastroenterology and the Polish Society of Gastroenterology taking into account the results of laboratory, endoscopic, histopathological and radiological tests [14].

The following demographic data were analyzed: gender, patient's current age, age at diagnosis. The average duration of follow up was 24 months.

On the basis of the Montreal classification, the following disease locations were distinguished: L1 – small intes-

Table 1. Location, behaviour and disease activity in the investigated group

Parameter	n (%)
Gender (M/F)	134 (44%)/171 (56%)
Age at diagnosis	
A1	22 (7%)
A2	194 (63%)
A3	89 (29%)
Lesion location:	
L1 – ileal	46 (15%)
L2 – colonic	101 (33%)
L3 – ileocolonic	158 (52%)
Disease behaviour	
B1	134 (44%)
B2	81 (27%)
B3	90 (29%)
Extraintestinal symptoms	68 (22%)
Cigarette smoking	91 (30%)
Appendectomy in the history	42 (14%)

tine, L2 – colon, L3 – terminal ileum and colon, L4 – upper gastrointestinal tract. Location of disease was defined by the maximal extent of lesions recognized by colonoscopy/gastroscopy and/or computed tomography and/or magnetic resonance imaging.

Patients with disease location in the colon (L2) and patients with involvement of the small intestine and colon (L1 and L3) were analyzed for the presence of extraintestinal manifestations, complications, such as abscesses, fistulas and strictures, and undergone surgeries related to the underlying disease. Furthermore, both groups were compared for previous appendectomies, biological and immunosuppressive therapies and current and former cigarette smoking. The incidence of depressive disorders requiring antidepressants was also analyzed.

After obtaining clinical data, CD patients were classified according to the Montreal classification as A1 if the age at diagnosis was less than or equal to 16 years, A2 if between 17 and 40 years, and A3 if it was more than 40 years. Behavior of disease (B) at diagnosis was categorized into B1 – inflammatory, B2 – stricturing, B3 – penetrating. Perianal disease (p), if present, was also recorded [18].

Patient data were not taken into account for the above analysis if complete data on the onset of disease symptoms, location, clinical course were not obtained, and when the disease was detected less than 6 months before the analysis.

STATISTICAL ANALYSIS

Due to the nature of the data – data on a nominal and ordinal scale – nonparametric tests were used to compare two independent groups: the $\chi 2$ (chi square) and the Mann-Whitney test.

Table 2. Comparison of demographic and clinical features depending on the location of inflammatory lesions

Parameter	Location L2 N = 101	Location L1 and L3 N = 204	p
Gender: Female Male	56 45	115 89	p>0.05
Mean age	46 ±16.28	40 ±13.79	p>0.05
Age at diagnosis:			
A1 (less than 17 years)	4 (4%)	18 (9%)	p>0.05
A2 (17–40 years)	60 (59%)	134 (65%)	
A3 (more than 40 years)	37 (37%)	52 (26%)	
Strictures	21%	79%	p<0.01
Abscesses	24%	76%	p>0.05
Fistulas	33%	67%	p>0.05
Surgical procedures	27%	73%	p<0.05
Extraintestinal manifestations	41%	59%	p>0.05
Appendectomy	19%	81%	p<0.05
Biological therapy	33%	67%	p>0.05
Azathioprine	32%	68%	p>0.05
Depressive disorder	33%	67%	p>0.05
Cigarette smoking	27%	73%	p>0.05

RESULTS

Between January 2012 and December 2018, 340 patients with CD were registered at the Department of Gastroenterology and Gastroenterological Outpatient Clinic. Thirty patients out of these groups were followed up for less than 6 months and were excluded. In addition, in 10 patients (3% of all patients), during the observation, the diagnosis was changed from UC to Crohn's disease and the final diagnosis of Crohn's disease was taken for analysis. Patients (5 persons, 1.5%) with the initial diagnosis of Crohn's disease, whose diagnosis was changed to UC during the year of follow-up, were not included in the analysis. The average duration of follow-up was 24 months.

Finally, the study included 305 patients with Crohn's disease, 171 women (56%) and 134 men (44%). Twenty-two (7%) patients belonged to A1 category, 194 (64%) belonged to A2 and 89 (29%) to A3 category.

The following groups of patients were distinguished according to the location of inflammatory lesions according to the Montreal classification: 46 (15%) L1 – small intestine, 101 (33%) L2 – colon and 158 (52%) L3 – small intestine and colon. No L4 location (upper gastrointestinal tract) was found in the study group. Behavior was categorized into B1 (non-stricuring, non-penetrating) in 134

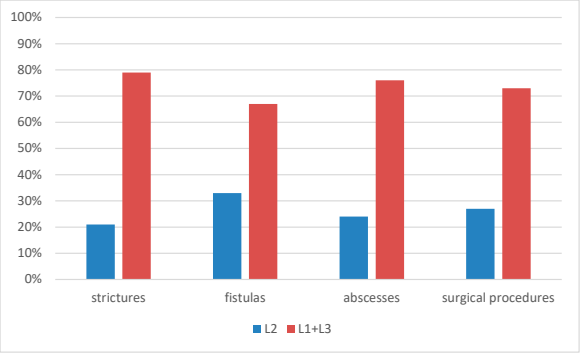

Fig. 1. The incidence of complications depending on the location

patients (44%), B2 – stricturing in 81 (27%) and B3 (penetrating/fistulizing) in 90 patients (29%).

In the entire study group, the presence of abscesses and fistulas was found in 158 people (52%), of which the perianal lesions constituted the vast majority – 126 patients.

There were 91 (30%) tobacco smokers in the investigated group. Patients with appendectomy prior to the diagnosis of CD were a group of 42 patients (14%). Of all the patients – 68 (22%) reported extra-intestinal manifestations such as: peripheral arthropathy, skin lesions – *pyoderma gangrenosum*, erythema nodosum and ocular symptoms in the form of uveitis.

The analyzed data for the entire study group are demonstrated in Table 1.

Then, clinical data and the behavior of the disease were compared in patients with CD of the lesion location in the small intestine and in the colon with patients in whom the disease was located solely in the colon (Table 2).

In the group of patients with isolated colonic involvement, the mean age at diagnosis was 37.25 ±15.98 years and it was higher than in the group of patients with L1 and L3 – 31.14 ±13.2 years ($p < 0.001$). Moreover, an analysis was made in individual age ranges <17 years of age, 17–40 years of age and > 40 years of age. There were no statistically significant differences regarding age at diagnosis (< 17 years – 4% with L2 vs. 9 % with L1 and L3, 17–40 years – 59% with L2 vs. 65% with L1 and L3, ˃ 40 years – 37% with L2 vs. 26% with L1 and L3) and the largest number of diagnoses was for the age range 17–40 years – 63% of patients (Table 2). Patients with isolated colonic CD (L2) were not different from those with ileal disease (L1 and L3) in the proportion of women (55,4% vs. 56,4%).

Among the features distinguishing the location of inflammatory lesions isolated to the colon (L2), statistically significantly less frequent occurrence of strictures was found (L2 – 21%; L1 and L3 – 79%, $p < 0.01$). However, this correlation was not confirmed for abscesses that occurred in 23% of patients with L2 and fistulas – in 33% of patients with L2. Moreover, patients with L2 lesions less frequently required surgery (27% with L2 vs. 73% with L1 and L3, $p < 0.05$) (Fig. 1).

In patients with the disease located in the colon and small intestine, an appendectomy was significantly more often performed prior to the diagnosis of Crohn's disease compared to patients with lesion location only in the colon (81% vs. 19%; $p<0.05$). The next analysis included the incidence of extraintestinal manifestations, which was similar in both analyzed patient groups, in 41% with L2 and in 59% with L1 and L3.

Then, the effect of cigarette smoking on the location of inflammatory lesions in the intestine was analyzed: 27% of smokers with L2 to 73% with L1 and L3, without statistically significant differences. Depressive disorders occurred in 33% of patients with L2 and 67% of patients with L1 and L3, which was not statistically significant, either. Patients were also analyzed as regards the frequency of the use of immunosuppressive treatment with azathioprine: 32% in L2, 68% in L1 and L3, and biological treatment with adalimumab and infliximab: 33% in L2 and 67% in L1 and L3, which was not statistically significant.

DISCUSSION

Significant variations were observed in the clinical course of Crohn's disease, which may be associated with the location of inflammatory lesions. On the basis of the collected data, the behavior of the disease was compared depending on the distribution of inflammatory lesions in CD patients. Analysis of the age of patients at diagnosis showed that patients with colonic involvement were older compared to those with lesion location in the small intestine and the colon. These results are consistent with the results of other authors who showed that late age at diagnosis (>55 years of age) was associated with more frequent location of inflammatory lesions in the colon as well as less penetrating clinical behavior and less frequent need for surgery [12]. In the analyzed group of patients, there were no differences in the location of Crohn's disease in women and men, although some authors noted a higher incidence of colonic involvement in women [21].

Obtained results of own research indicated that patients with colonic location of the disease were significantly less likely to present complications in the form of strictures. Furthermore, it was found that patients with colonic lesions less often require surgery compared to patients whose disease affected both the small intestine and the colon. One of the studies reviewed publications on the course of the disease isolated to the colon. It pointed out the lower likelihood of having to undergo surgery within 10 years of the disease if only the colon was involved as compared to patients with the involvement of the small intestine and the colon [21]. The same study also indicated the problem of diagnostic distinction between Crohn's disease with colonic involvement and UC solely on the basis of histopathological examination. That is why it is so important to consider other forms of inflammation in the differential

diagnosis, such as segmental colitis associated with diverticulosis (SCAD), ischemic colitis and inflammation induced by infectious agents [21].

In turn, another publication from Asia, which is a retrospective analysis of the clinical behavior of Crohn's disease, clearly confirmed the less aggressive disease behavior and significantly lower requirement of surgery in colonic CD. Extraintestinal manifestations, such as peripheral arthropathy, skin lesions, pyoderma gangrenosum, erythema nodosum, ocular symptoms or primary sclerosing cholangitis, were also more common in patients with only colonic involvement, which has not been demonstrated in our analysis. The lack of statistical significance in our analysis could result from the much lower incidence of extraintestinal manifestations in our study group [1]. In another publication, where a higher incidence of extraintestinal symptoms was also observed in patients with colonic involvement, it was noted that these symptoms were more common in smokers and females [8].

In the next stage of our research, the incidence of appendectomy before the diagnosis of the underlying disease was analyzed, depending on the location of the inflammatory lesions. In the group with colonic involvement lower incidence of the history of appendectomy was noted. No such conclusion was found in the analyzed publications. Another aspect of the analysis concerned the attempt to find a correlation between disease location and immunosuppressive therapy using azathioprine and biological treatment. No significant relationship was found. However, several studies noted a different response to anti-TNF treatment depending on the location of the disease. In patients with isolated small intestinal involvement weaker response to treatment and achievement of remission were observed with biological treatment [8]. When discussing treatment options, it is worth paying attention to the effectiveness of enteral nutrition (EN) therapy. Studies have shown that enteral nutrition is a safe and effective therapy in inducing remission and improving nutritional status in active enteritis in Crohn's disease not only in children but also in adults. However, one study indicated that the effectiveness of this therapy depended on the location of inflammatory lesions. This method was shown to be more effective in patients with small intestinal involvement. Patients with isolated colonic involvement required more time to achieve clinical remission and benefit from EN therapy [23]. The mean time to achieve remission in colonic involvement was 31.5 ±8.9 and in patients with small intestinal involvement 25.6 ±8.6 days. Moreover, worse response to the therapy occurred in patients with pancolitis. [23].

The next step was the analysis of cigarette smoking and its impact on the location of inflammatory lesions. Higher prevalence of smoking was observed in patients with ileal involvement and thus a higher risk of complications, such as bowel stenosis and the need for surgical interventions. This problem and its negative effects were more frequently observed in women [8, 16]. Similar correlations were not found in this study.

Lower frequency of surgical procedures and less prevalent strictures are common observations in all analyzed studies and are undoubtedly associated with less aggressive course of colonic Crohn's disease [1, 20, 21].

In recent years, numerous studies analyzing have been published about various aspects of the clinical behavior of Crohn's disease [10, 19]. The authors of some publications attempt to create prognostic models of the clinical course of Crohn's disease. In one of the analyzed papers, prognostic models were proposed to assess the likelihood of developing advanced disease after 5 and 10 years of disease duration [19]. Data on 5-year results were limited to a subgroup of patients with non-penetrating and non-stricturing disease at the time of diagnosis, and at least one of the following criteria was considered as disease progression: intestinal resection, progression in disease behavior or need for thiopurines. However, after 10 years, all patients were analyzed regardless of the clinical course, and the severity of the disease in this group was defined as the need for resection of the small intestine or the need for surgery due to a fistula. The results showed that the presence of ASCA antibodies, younger age at the time of diagnosis, location of lesions in the small intestine and the need for chronic systemic use of steroids are undoubtedly associated with the risk of a more severe course of the disease [19]. In both the above and previously cited publications, the location of inflammatory lesions is of fundamental importance for the course of the disease, which was also shown in our analysis. Referring the created prognostic models to our analysis, an additional analysis of the examined group of patients was conducted. Among the patients in the course of follow-up care followed by surgery, it was found that the majority was in the age group below 40, on chronic steroid therapy, in whom the affected segment was not isolated L2 location.

Most of the papers on the clinical course of Crohn's disease do not include specific disease location data based on the Montreal classification, which means that little is still known about the clinical, epidemiological and pathological aspects associated with isolated colonic Crohn's disease. The current state of knowledge takes into account the heterogeneous nature of Crohn's disease and does not allow us to distinguish the location of the disease in the colon as a separate disease entity. However, it is worth emphasizing that a recently published study by Dulai et al. suggests a new classification of CD as an ileum-dominant disease and colon-dominant disease. The results of our retrospective analysis and recently published studies of other authors have shown differences in the clinical behavior of Crohn's disease depending on the location of lesions in the gastrointestinal tract. To our state of knowledge, very little data in the literature have been published on the colonic Crohn's disease. Further research and observation of a larger group of patients are needed to determine whether Crohn's disease isolated to the colon is a separate disease entity among nonspecific inflammatory bowel diseases and requires new rules regarding treatment and monitoring.

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