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Articular involvement in inflammatory bowel disease – the most frequent extraintestinal manifestation

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ABSTRACT

Objectives. Inflammatory bowel disease (IBD) are part of a pathology that has an ascending incidence both in Romania and around the world. It is well known that intestinal inflammation in IBD is not limited to the intestinal epithelium. Sometimes, extraintestinal manifestations (EIM) may have a more severe clinical expression than the intestinal disorder or may even encourage an increased morbidity. The research motivation focused on the development of specific clinical and epidemiological data for patients diagnosed with IBD who associate EIM.
Material and methods. We performed a retrospective study including 517 patients with intestinal inflammation (Crohn disease - CD, ulcerative colitis - UC or undifferentiated colitis - NC) diagnosed during 1975-2016 in the N-E region of Romania. All the cases were extracted from the national database (IBD Prospect).
Results. In our study the prevalence of UC versus CD cases prevailed. There were 368 cases (71.2%) of UC, 135 cases (26.1%) of CD and 10 cases of NC (1.9%). The prevalence of EIM in IBD patients in N-E Romania was 9,9% which was quite low. In the study group, EIMs occurred with a higher frequency in patients diagnosed with CD compared to UC. Thus, of the 51 cases of IBD and EIM, 27 (52.9%) belonged to the CD's phenotype and 24 cases (47.1%) of the UC's phenotype.
Discussions. Both patients with CD and UC experienced a greater risk than the rest of patients for developing EIM. The most frequent EIMs were highlighted at the level of musculoskeletal system. Among EIM, there were 38 cases (74,5%) with articular manifestations (of which 26 had peripheral manifestations - arthritis, 12 cases developed axial manifestations – sacroiliitis/ankylosing spondylitis - SI/AS). Also, cases with multiple EIM had at least one articular manifestation.
Conclusions. Our results sustain, once again, the fact that inflammation in IBD is not limited at the level of gastrointestinal tract. The presence of EIM, especially joint involvement, is a certainty validated by the results of many clinical trials.

Keywords: Crohn disease, ulcerative colitis, extraintestinal manifestations, peripheral arthritis, ankylosing spondylitis

INTRODUCTION

Inflammatory bowel diseases (IBD), with the two representative diseases – Crohn disease (CD) and ulcerative colitis (UC), are systemic inflammatory disorders which can affect both the gastrointestinal tract and other organs and systems. Many clinical trials have analized the presence of extraintestinal manifestations (EIM) in patients diagnosed with BII in terms of frequency, incidence and prevalence, onset of the disease, association with a particular disease phenotype or with a particular distribution of the intestinal inflammation. Epidemiological trials have also been carried out to discuss the incidence of these EIM regarding a particular geographical region or a certain population (ethnicity, race).

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IBD are part of a pathology that has an ascending incidence both in Romania and around the world. It is well known that intestinal inflammation in IBD is not limited to the intestinal epithelium. Sometimes, these EIM may have a more severe clinical expression than the intestinal disorder or may even encourage an increased morbidity.

Systemic prevalence of EIM in IBD vary widely, ranging between 6 and 47% (1,2). Recent studies have highlighted that the presence of an EIM increases the risk of other manifestations (3). The most common are manifestations at the level of musculoskeletal system – axial or peripheral arthritis, followed by skin involvement – aphthous stomatitis, erythema nodosum, pyoderma gangrenosum or ocular damage – uveitis, iridocyclitis (3,4).

Inflammatory bowel activity plays an important role in both the emergence and the evolution of these EIM. The most important risk factors involved in the occurrence of EIM are: the age and sex of the patient, family history of IBD, smoking, concomitant medication (especially the use of anti-inflammatory nonsteroidal drugs – NSAIDs), IBD location, extension and activity (5). The occurrence of EIM may precede the diagnosis of IBD in approximately 25% of cases, may be concomitant with or may follow the diagnosis of intestinal disease (in almost 75% of cases) (6). Hepatobiliary manifestations, venous thromboembolism and arthralgia are more common in patients with UC. In CD, erythema nodosum and peripheral arthritis have a higher prevalence. Ocular manifestations have the same incidence in both IBD (7).

MATERIAL AND METHODS

We performed a case-control retrospective study including 517 patients with intestinal inflammation (CD, UC or undifferentiated colitis – NC) diagnosed during 1975-2016 in the N-E region of Romania. All the cases were extracted from the national database (IBD Prospect).

The inclusion criteria were: age over 18; patient consent and signing an informed consent; certain diagnosis of CD, UC or NC based on the current diagnosis criteria and on histopathological examination. The exclusion criteria consisted of: uncertain diagnosis of CD, UC or NC; the patient‘s refusal to be included in the national database.

Data was centralized into SPSS 22.0 databases. In the statistical analysis, both descriptive and analytical methods were used at 95% significance (CI 95%).

All patients included in the study were clinically and paraclinically analyzed. Of the EIM, the following manifestations were considered: articular signs (arthritis, sacroiliitis/ankylosing spondylitis), cutaneous manifestations such as pyoderma gangrenosum and erythema nodosum, ocular manifestations: uveitis/episcleritis, primary sclerosing cholangitis (PSC), renal manifestations: oxalate kidney lithiasis, renal amyloidosis, multiple urinary tract infections.

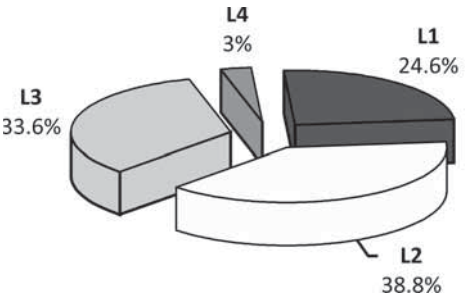
RESULTS

Depending on the phenotype of the disease, there were 368 cases (71.2%) of UC, 135 cases (26.1%) of CD and 10 cases of NC (1.9%). Gender distribution was slightly higher in males, the odds ratio M/F = 1.3/1 revealing significant differences depending on phenotype: in patients with CD (51.1% vs. 48.9%) and NC (70% vs. 30%) predominates female gender, while in UC patients the male gender predominates (60.3% vs. 39.7%) (p=0,016). Age ranged between 18 and 81 years, with a mean of 48.24 ± 15,11 years, significantly increased in patients with UC (p=0.003).

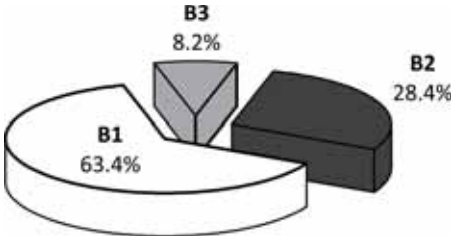
The number of patients with IBD was higher from urban areas (341 vs. 172, 66.7% vs 34.9%), with no significant differences depending on the disease phenotype (p=0.536). Of the patients included in the study, 276 (53.2%) were non-smokers, ex-smokers 164 cases (31.8%), while the active smokers have a percentage of 15% (77 cases). Active smokers were found to be much more in groups of patients with NC (60%) and with CD (25.2%). In patients with UC (54.3%) and CD (51.9%) predominate non-smoker cases (p=0.001).

In the group of patients diagnosed with CD (n=135) predominated the colonic location of inflammation (L2) (52 cases, 38.8%), followed by ileo-colonic inflammation (L3) (45 cases, 33.6%) and ileal damage (L1) (34 cases, 24.6%); only 3% of patients with CD had upper digestive tract involvement (L4) (4 cases) (Fig. 1). Regarding the CD's phenotype, the predominant was the inflammatory form (B1) (84 cases, 63.4%), followed by the stricturing form (B2) (40 cases, 28.4%); 8.2% of patients with CD presented a penetrating disease (B3) (Fig. 1).

In the group of patients with UC (n=368), procto-sigmoiditis (left colitis) (E2) predominated (203 cases, 55.2%); pancolitis (E3) was identified in 94 (25.5%) of cases and proctitis (E1) only in 71 (19.3%) of patients with UC (Fig. 2, A).



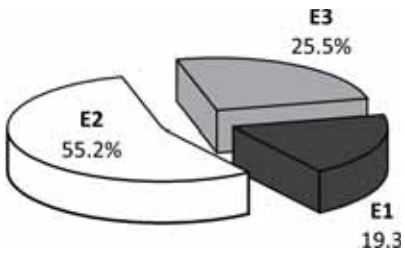
A



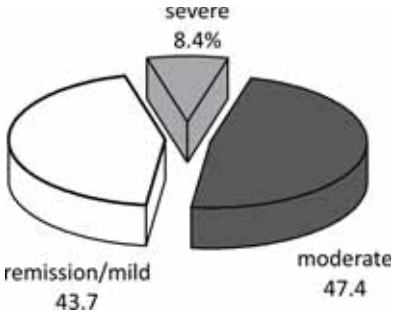
B

FIGURE 1. *The distribution of cases according to CD's location (A) and phenotype (B)*

Most of the included patients had a moderate form of intestinal inflammation (242 cases, 47.4%), 226 cases (43.7%) a mild/remission activity; only 43 of the patients (8.4%) had a severe form of gut inflammation (Fig. 2, B).



A



B

FIGURE 2. *Distribution of UC cases depending on the location of the inflammatory process (A) and distribution of IBD patients depending on severity of gut inflammation (B)*

In the study group, 51 (9.9%) cases with IBD had EIM. There were 38 cases with articular manifestations (of which 26 had peripheral manifestations – arthritis, 12 cases developed axial manifestations – sacroiliitis/ankylosing spondylitis – SI/AS); 6 cases presented cutaneous involvement (2 cases – erythema nodosum, 4 cases – pyoderma gangrenosum) 1 case of primary sclerosing cholangitis (PSC), 3 cases of oxalic kidney lithiasis, 8 cases with multiple urinary infections. Six patients presented associations of several EIM (Table 1).

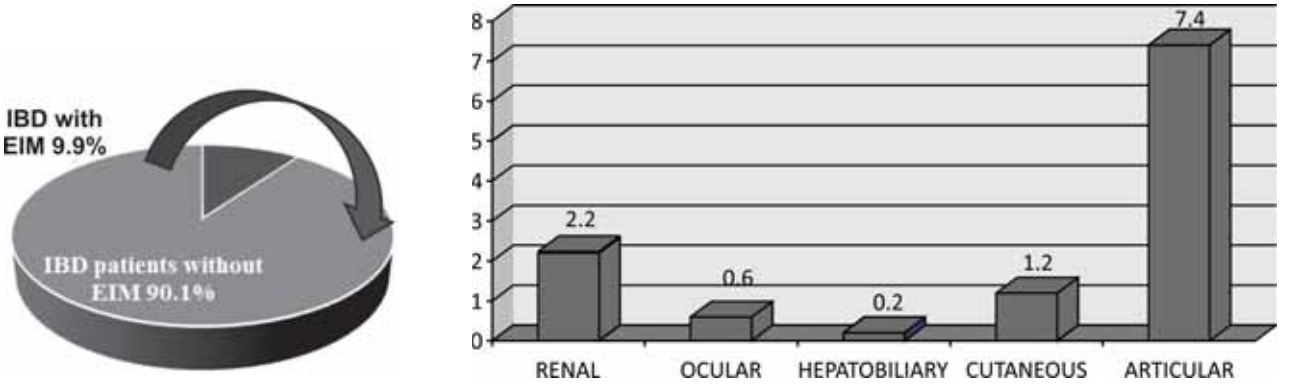
TABLE 1. *Extraintestinal manifestations in the study group*

Extraintestinal manifestation	Association of several EIM
• Arthritis – 26 cases	• Arthritis + pyoderma gangrenosum – 2 cases
• SI/AS – 12 cases	• SI/AS + pyoderma gangrenosum – 1 case
• Erythema nodosum – 2 cases	• Uveitis + arthritis – 2 cases
• Pyoderma gangrenosum – 4 cases	• Uveitis + oxalic renal lithiasis + multiple urinary infections + arthritis – 1 case
• Uveitis – 3 cases	
• PSC – 1 case	
• Oxalic renal lithiasis – 3 cases	
• Multiple urinary infections – 8 cases	

EIM occurred more frequently in patients with CD. Thus, of the 51 cases of IBD having EIM, 27 (52.9%) belonged to the CD phenotype and 24 cases (47.1%) had an UC phenotype, statistically significant data ($p<0.001$) (Fig. 3, A). Most commonly, musculoskeletal manifestations were identified: 5.1% of patients with arthritis and 2.3% with SI/AS, followed by renal manifestations: 2.6% multiple urinary tract infections and 0.6% oxalic renal lithiasis (Fig. 3, B).

Of the 51 patients having EIM, 27 (52.9%) were female, slightly higher in the CD group (55.6% vs. 50%, $p=0.692$). Mean age was higher in patients who presented EIM (49.31 vs 48.13 years, $p=0.595$). The analysis of smoker status in the group with EIM highlighted the following: among the 51 cases, 10 (19.6%) were active smokers, over half – 28 (54.9%) non-smokers and former smokers –13 cases (25.5%). It was confirmed that active smokers had a 1.3 times higher risk than non-smokers to manifest EIM. Former smokers had a risk of 0.758 times higher, so smoking status can be considered a protective factor for the emergence of EIM in patients with IBD.

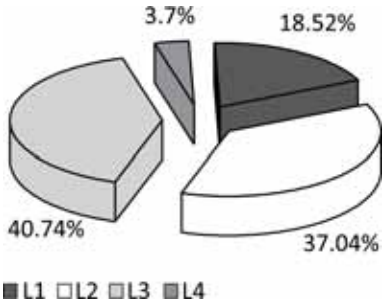
Of the patients presenting EIM, 52.9% belonged to the CD phenotype. In the CD and EIM group, the ileo-colonic localization of intestinal inflammation (L3) predominated (11 cases – 40.7%), followed by colonic (L2) (10 cases – 37%), ileal (L1) (5 cases – 18.5%) and upper digestive tract (L4) (1 case – 3.7%) involvement. Correlations between CD's phe-



A B

FIGURE 3. *Frequency (%) of EIM in the study group (A) and of EIM groups in patients with IBD (B)*

notype and EIM revealed 17 patients (63%) with an inflammatory form (B1), 9 cases (33.3%) having a stenotic phenotype (B2) and only one patient (3.7%) with a penetrating form of CD (B3). The obtained data had no statistical significance (Fig. 4). Overall, patients diagnosed with CD had a 3,687-fold greater risk than other patients to develop EIM (p <0.001).



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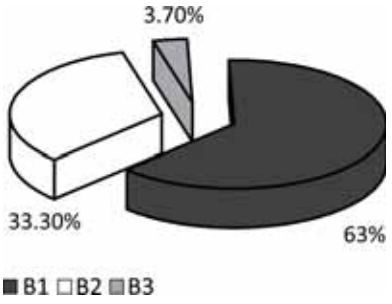

B

FIGURE 4. *Distribution of cases with EIM depending on location (A) and CD's phenotype (B)*

Patients having UC and EIM were divided as follows: 5 cases (20.8%) with proctitis (E1), 11 cases (45.8%) having left colitis (E2) and 8 patients (33.3 %) with an extensive form of UC (E3). Although a large number of patients had the inflammation in the left colon, the resulting data had no statistical significance (p=0.593) (Fig. 5). Overall, patients diagnosed with UC had a 1,337-fold greater risk than other patients to develop EIM (p <0.001).

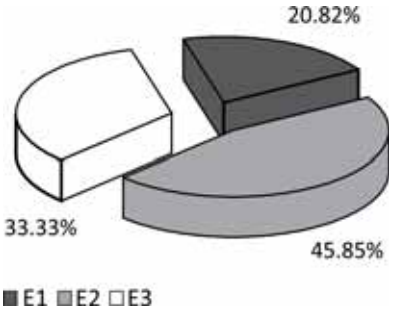

FIGURE 5. *Distribution of cases with EIM based on UC's location*

DISCUSSIONS

Our results sustain, once again, the fact that inflammation in IBD is not limited at the level of gastrointestinal tract. The presence of EIM is a certainty validated by the results of numerous clinical trials published in the literature (8,9).

In our study the prevalence of UC versus CD cases prevailed. In the group of patients with CD female cases prevailed (51.1% vs 48.9%) while, among those with UC, there was a higher percentage of male gender (60.3% vs 39.7%). Patients with UC had a more advanced age compared to the rest of the cases. Most of the included patients, both those with CD phenotype and those having UC, came from the urban environment (70.4% vs. 65.2%). The peak incidence of IBD cases was recorded in 2012, with an increasing trend of prevalence over the next period of time.

The prevalence of EIM in IBD patients in N-E Romania was 9,9% which was quite low, but consistent with published data. Studies support an incidence of EIM that varies greatly between 6% to 45%) (8-10).

In our study group, the most frequent EIMs were highlighted at the level of musculoskeletal system. This data is supported by other studies which confirm that the greatest incidence among EIM is owned by articular manifestations (11,12).

In the study group, EIMs occurred with a higher frequency in patients diagnosed with CD compared to UC. Thus, of the 51 cases of IBD and EIM, 27 (52.9%) belonged to the CD's phenotype and 24 cases (47.1%) of the UC's phenotype. Most studies in the literature suggest an increase in EIM prevalence in CD patients compared to UC cases (13,14).

Following the performed statistical analysis, both patients with CD and UC experienced a greater risk than the rest of patients for developing EIM.

In the study group having EIM, 38 cases had articular manifestations (of which 26 had peripheral manifestations – arthritis and 12 cases axial manifestations – SI/AS), 6 cases cutaneous involvement (2 cases – erythema nodosum, 4 cases – pyoderma gangrenosum), 3 cases uveitis, 1 case of PCS, 3 cases of oxalic renal lithiasis, 8 cases of multiple urinary tract infections. Six patients presented associations of multiple EIM. In patients with CD, articular manifestations, pyoderma gangrenosum, uveitis and oxalic renal lithiasis were more commonly reported, while in UC patients there was a higher ratio of PSC.

The link between smoker status and the presence of EIM in IBD patients was also analyzed. 10 patients (19.6%) were active smokers, over half – 28 (54.9%) non-smokers and former smokers 13 cases (25.5%). It was statistically confirmed that active smokers have a 1.3 times higher risk than non-smokers to develop EIM. Former smokers have a 0.78-fold risk of having EIM, so smoking status may be a protective factor for the occurrence of EIM. The association between smoking and the occurrence of EIM was sustained by other authors (15). One study confirms that active smoker patients with CD have a higher risk for developing EIM (16).

CONCLUSIONS

Correct and complete assessment of IBD patients should include mandatory EIMs analysis.

Sometimes, these EIMs may develop a worse clinical expression than intestinal disease and may raise diagnostic and treatment problems. A multidisciplinary approach to these cases is occasionally necessary for an optimal management.

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