ORIGINAL PAPER

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Looking beyond gut inflammation in inflammatory bowel disease

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Abstract

Patients diagnosed with inflammatory bowel disease (IBD) often develop one or more extraintestinal manifestations (EIM). We performed a prospective study that included 517 patients with IBD (Crohn's disease – CD, ulcerative colitis – UC or undifferentiated colitis – CN) diagnosed between 1975 and 2016 in the Northeastern region of Romania. The patients were extracted from the national database (IBD Prospect). UC cases predominated compared to CD cases (n=368 *vs.* n=135). Only 10 patients were diagnosed with CN. In the study group, 51 cases with IBD and EIM were identified, having a prevalence of 9.9%. Musculoskeletal manifestations were the most common EIM. Peripheral involvement – arthritis (n=26, 68.42%) predominated, followed by axial damage – sacroiliitis/ankylosing spondylitis (SI/AS) (n=12, 31.58%) (p=0.001). Patients with CD had a 3.48-fold greater risk of developing joint manifestations [p<0.001, odds ratio (OR)=3.478, 95% confidence interval (CI) 1.779–6.801]. In both CD and UC patients, arthritis cases were the most frequent observed (68.42% *vs.* 31.58%). Patients with CD had a 5-fold higher risk of developing arthritis (p<0.001, OR=5.009, 95% CI 2.21–11.34). Neither CD, nor UC patients, had a confirmed risk of developing SI/AS (p=0.468, OR=1.565, 95% CI 0.463–5.293 for CD) (p=0.586, OR=0.714, 95% CI 0.211–2.413 for UC). Cases of arthritis and CD (n=16) mainly correlated with the colonic localization of inflammation (n=7, p=0.723) followed by ileo-colonic form of CD (n=7, p=0.321). Patients with arthritis and UC (n=10) initially correlated with pancolitis (n=5, p=0.072, OR=3.023, 95% CI 0.855–10.69) then with proctitis (n=3, p=0.392) and left-sided colitis (n=2, p=0.024, OR=0.196, 95% CI 0.041–0.938).

Keywords: inflammatory bowel disease, arthritis, sacroiliitis/ankylosing spondylitis, Crohn's disease, ulcerative colitis.

Introduction

Inflammatory bowel diseases (IBD) are chronic autoimmune disorders characterized by an imbalance between proinflammatory cytokines and anti-inflammatory cytokines, as well as an increased recruitment of leukocytes [1]. Crohn's disease (CD) and ulcerative colitis (UC) are different diseases regarding pathogenic and clinical manifestations.

Patients with IBD often develop one or more extra-intestinal manifestations (EIM). The prevalence of EIM varies widely, ranging from 6% to 47% [2, 3]. The most common are manifestations at the level of musculoskeletal system – axial or peripheral arthritis, followed by skin involvement – aphthous stomatitis, nodular erythema, *pyoderma gangrenosum* and ocular damage – uveitis, iridocyclitis. Recent studies have highlighted that the presence of an EIM increases the risk of other EIM, patients frequently having an association of up to five EIM [4].

From a pathogenic point of view, the occurrence of EIM is due to the implication of an autoimmune reaction to tropomyosin-related peptide detected in the skin, joints, eyes, biliary and intestinal epithelium, and due to the presence of a common genetic background, human leukocyte antigen (HLA) being one of the major associated genetic markers [5–8]. EIM may precede the diagnosis of IBD in about 25% of cases, may be concomitant with or may follow the diagnosis of intestinal disease (most commonly – 75% of cases) [9].

IBD frequently presents intestinal complications that may vary regarding clinical presentation and severity. Some published studies included intestinal complications among EIM, but other authors considered them separate clinical entities. The most frequent intestinal complications were: intestinal stenosis and fistula, abscesses, inferior digestive hemorrhage (Hdi) or malignancies (especially colorectal cancer) [6, 10].

The aims of this study were to: (*i*) develop specific clinical and epidemiological data on patients diagnosed with IBD who associate EIM and intestinal complications in the Northeastern (NE) region of Romania, (*ii*) establish the risk factors associated with the occurrence of EIM and intestinal complications, (*iii*) establish correlations between EIM, intestinal complications and IBD characteristics (localization of intestinal inflammation, disease phenotype), (*iv*) assess the link between intestinal complications and EIM.

Patients, Materials and Methods

We performed a retrospective case-control study, which included 517 patients with IBD (CD, UC or undifferentiated colitis – CN) diagnosed between 1975 and 2016 in the Northeastern (NE) region of Romania. The patients were extracted from the national database (IBD Prospect). The inclusion criteria were: age over 18; patient consent and signing the informed consent;

certain diagnosis of CD, UC or CN [11, 12]. Exclusion criteria were: uncertain diagnosis of CD, UC or CN; the patient's refusal to be included in the national database. The Montreal classification [11–13] was used to classify IBD by phenotype and to localize intestinal inflammation. The demographic characteristics of patients (age, gender, ethnicity, environment, occupation, smoker status) and of IBD (year of diagnosis, phenotype and location of the disease, presence and number of EIM as well as the presence of intestinal complications, the following treatment), were extracted from the national database.

Among EIM, it has been taken into consideration articular manifestations (arthritis or sacroiliitis/ankylosing spondylitis – SI/AS), dermatological manifestations (*erythema nodosum*, *pyoderma gangrenosum*), ophthalmic signs (uveitis/episcleritis), hepatobiliary manifestations (primary sclerosing cholangitis – PSC) and urinary events (oxalic nephrolithiasis, kidney amyloidosis, urinary tract infections). The diagnosis of arthritis was based on clinical symptoms (pain, joint swelling) and on rheumatological examination made by a specialist doctor who excluded the presence of other associated autoimmune pathologies. SI was highlighted by pelvis radiography or magnetic resonance imaging (MRI). Patients diagnosed with AS have met the 1984 modified *New York Diagnostic Criteria* [14]. The skin manifestations have been diagnosed by a dermatologist (clinically or skin biopsy). Eye manifestations were evaluated by an ophthalmologist. The PSC diagnosis included abnormal liver tests and cholangio MRI ± liver biopsy. Reno-urinary manifestations were diagnosed by serum and urine tests (urine culture, urine analysis), ultrasonography or renal biopsy (in the case of suspicion of renal amyloidosis).

Among intestinal complications, there were considered: abscesses, intestinal or perianal fistula, intestinal stenosis, toxic megacolon, intestinal perforation, Hdi or the presence of malignancies. All patients included were periodically monitored clinically and paraclinically (blood tests, colonoscopy with biopsy and pathological examination).

The obtained data were centralized in the Statistical Package for the Social Sciences (SPSS) 18.0 database. Statistical analysis used both descriptive and analytical methods at 95% significance – 95% confidence interval (CI). Among statistical tests were used: analysis of variance (ANOVA) and χ^2 (*chi*-square) tests, linear regression, odds ratio (OR). A *p*-value less than 0.005 ($p<0.005$) was considered statistically significant.

Results

Characteristics of the study group

The study included 517 patients with IBD of which only 513 had all data required for the statistical analysis (Table 1). UC predominated against CD cases (n=368 *vs.* n=135). Only 10 patients were diagnosed with CN. Female gender (51.1% *vs.* 48.9%) predominated in the group of CD patients, while, in the UC group, male gender prevailed (60.3% *vs.* 39.7%) (p=0.016). UC patients had an older age than the rest of the cases (p=0.003) (Figure 1, Table 2).

Table 1 – ***Demographic and clinical characteristics of the study group with IBD (CD, UC)***

	IBD, *n* (%)	CD, *n* (%)	UC, *n* (%)	*p*
No. of patients	517 (100)	135 (26.1)	368 (71.2)	0.001
Males/females	294 (56.9)/223 (43.1)	66 (48.9)/69 (51.1)	221 (60.3)/147 (39.7)	0.016
Average age [years]	48.24	44.52	49.65	0.003
Area of origin: urban/rural	341 (66.7)/172 (34.9)	95 (70.4)/40 (29.6)	240 (65.2)/128 (34.8)	0.536
Smokers/ex-smokers/ non-smokers	77 (15)/164 (31.8)/276 (53.2)	34 (25.2)/31 (23)/70 (51.9)	37 (10.1)/131 (35.6)/200 (54.3)	0.001
Disease activity: mild/moderate/severe	226 (44.2)/242 (47.4)/43 (8.4)	56 (41.5)/73 (54.1)/6 (4.4)	165 (44.8)/166 (45.1)/37 (10.1)	0.062
Form of CD: L1/L2/L3/L4	NA	34 (25.2)/52 (38.5)/45 (33.3)/4 (3)	NA	0.818
Phenotype of CD: B1/B2/B3	NA	84 (62.2)/40 (29.6)/11 (8.1)	NA	0.026
Form of UC: E1/E2/E3	NA	NA	71 (19.3)/203 (55.2)/94 (25.5)	0.012

IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; *n*: No. of cases; L1: Ileitis; L2: Colitis; L3: Ileocolitis; L4: Upper gastrointestinal tract; B1: Inflammatory; B2: Stricturing; B3: Penetrating; E1: Proctitis; E2: Left-sided colitis; E3: Pancolitis; NA: Not applicable.

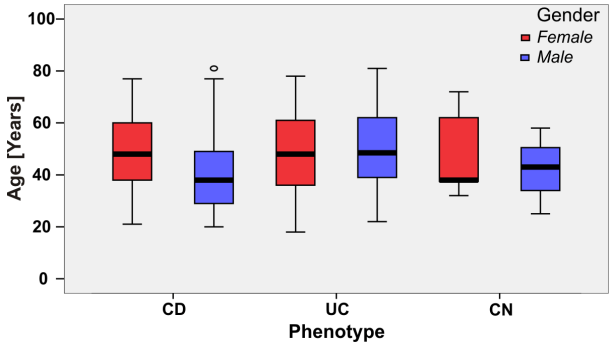

Figure 1 – ***Average age by gender according to the phenotype of the disease. CD: Crohn's disease; UC: Ulcerative colitis; CN: Undifferentiated colitis.***

Most of the included patients, both those with CD or UC phenotype, came from urban areas (70.4% *vs.* 65.2%) (p=0.536). The peak incidence of IBD cases was recorded in 2012, with an increasing trend over the next period of time ($y=0.5x-1.23$), which was maintained at a level of approximately 10% (Figure 2).

CD summarized 135 cases. Colonic involvement (L2) (n=52, 38.8%) predominated, followed by ileocolitis (L3) (n=45, 33.6%). Eighty-four (63.4%) of these patients had an inflammatory phenotype (B1) and 40 (28.4%) a stricturing form. The ileal inflammation was identified in 27.4% of patients with a non-stricturing form of CD and in 27.3% of those with a penetrating form of disease. Most commonly, the colonic location of intestinal inflammation was identified in patients with a stricturing disease (42.1%), and the most rare in those with a penetrating form of CD (27.3%). Ileocolitis was most commonly associated with the penetrating phenotype (45.5%). Involvement on the upper gastrointestinal tract was present in 3.6% of patients with non-stricturing disease and in 2.6% of those having a stricturing phenotype.

Table 2 – ***Descriptive indicators of age [years] in patients with IBD***

Phenotype	*n*	Median	Standard deviation	Standard error	95% Confidence interval (CI)		Min.	Max.	F_{ANOVA} test
					-95% CI	*+95% CI*			
UC	368	49.65	15.08	0.79	48.11	51.2	18	81	0.003
CD	135	44.52	14.58	1.25	42.04	47	20	81	
CN	10	46.7	16.27	5.14	35.06	58.34	25	72	
Total	513	48.24	15.11	0.67	46.93	49.55	18	81	

IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease; CN: Undifferentiated colitis; *n*: No. of cases; ANOVA: Analysis of variance.

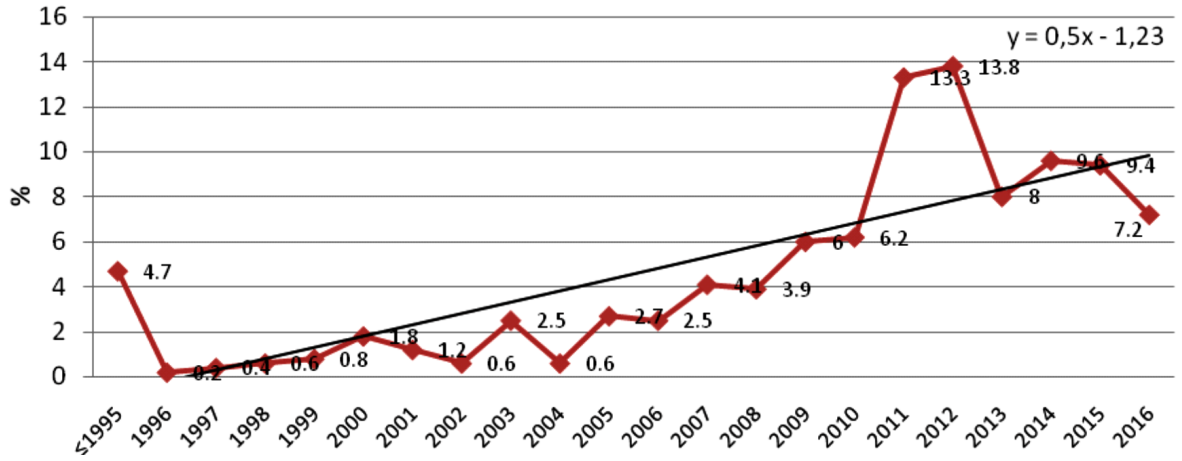

Figure 2 – ***Prevalence of IBD cases per study year. IBD: Inflammatory bowel disease.***

Patients diagnosed with UC have totalized 368 cases. Among these cases, left-sided disease (*n*=203, 55.16%), then pancolitis (*n*=94, 25.5%) predominated. Most patients with UC and those diagnosed with CD had a moderate form of intestinal inflammation (*n*=242, 47.4%).

All patients underwent colonoscopy with biopsy and pathological examination. Diagnosis of CD, UC or CN was based on biopsy examination, which revealed specific and multiple lesional aspects. Chronic follicular colitis presented as a diffuse and follicular lympho-plasmocytary inflammatory infiltration, edema and congestion in chorion (Figure 3). Active UC's pathological examination showed: abundant and polymorph inflammatory infiltration, rich in neutrophils, congestion in chorion; surface epithelium with erosions; deformed crypts, some with a tendency to ramification, elevated from the mucosal muscle, some with decreased mucus secretion, crypt inflammation and crypt abscesses (Figure 4). In CD's biopsies were highlighted: predominant transmural lympho-plasmocytary inflammation, edema and congestion, ulcerations, pyloric metaplasia, granulomatous inflammation without central caseification, lymphoid follicles "in rosary" in subserosa (Figures 5 and 6).

Over 90% of IBD cases (*n*=484, 93.6%) were on medication at the time of enrollment [Mesalazine – 5-Aminosalicylic Acid (5-ASA), Azathioprine (AZA), Methotrexate, tumor necrosis factor-alpha (TNF-α) blockers – Infliximab (IFX), corticosteroids (CS) and Budesonide, antibiotics – commonly Rifaximine, probiotics]. Of these, 223 (46.07%) patients were treated with 5-ASA and 216 (44.62%) had combined therapy, most cases (*n*=136, 62.96%) being treated with 5-ASA and CS.

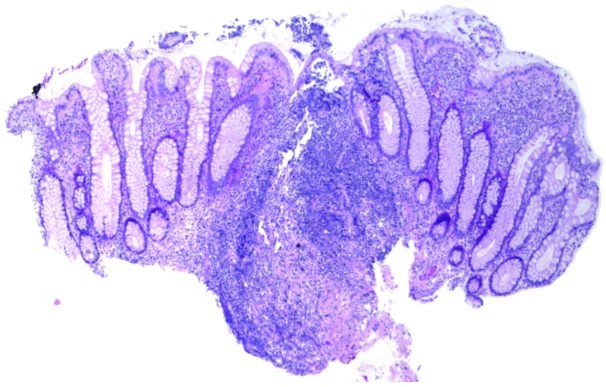

Figure 3 – ***Chronic follicular colitis: diffuse and follicular lympho-plasmocytary inflammatory infiltrate, edema and congestion in chorion [Hematoxylin–Eosin (HE) staining, ×40].***

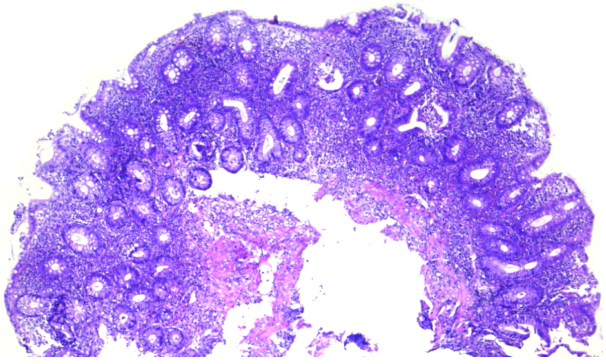

Figure 4 – ***Active ulcerative colitis: abundant and polymorph inflammatory infiltrate, rich in neutrophils, congestion in chorion; surface epithelium with erosions; deformed crypts, some with a tendency to ramification, elevated from the mucosal muscle, some with decreased mucus secretion, crypt inflammation and crypt abscesses (HE staining, ×40).***

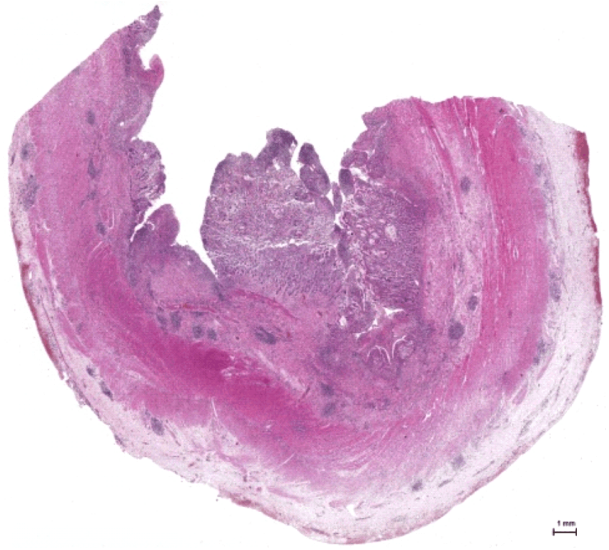

Figure 5 – ***Crohn's disease: predominant transmural lympho-plasmocytary inflammation, edema and congestion, ulcerations, pyloric metaplasia, granulomatous inflammation without central caseification, lymphoid follicles "in rosary" in subserosa (HE staining, ×40).***

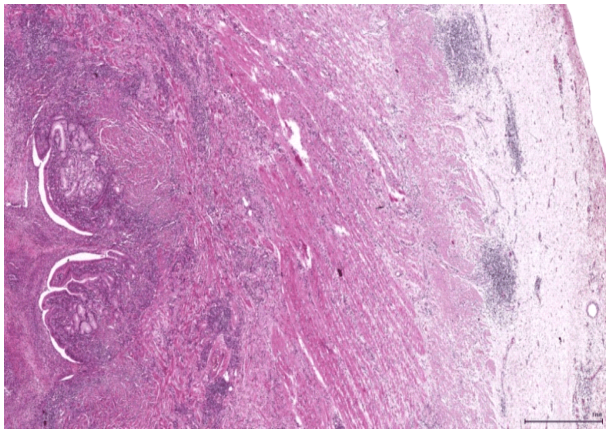

Figure 6 – ***Crohn's disease: detail from previous figure (HE staining, ×100).***

EIM in the study group

In the study group, 51 cases with IBD and EIM were identified, having a prevalence of 9.9% (Table 3). The most common EIMs were musculoskeletal manifestations (7.4%), followed by renal manifestations (2.2%), cutaneous manifestations (1.2%), ocular (0.6%) and hepatobiliary manifestations (0.2%). EIMs occurred with a higher frequency in patients diagnosed with CD than UC (52.9% *vs.* 47.1%) (p<0.001). No patients with CN presented EIM (p=0.289). Over 50% of cases of IBD and EIM belonged to female gender (52.9%, p=0.142), higher in the CD group (55.6% *vs.* 50%, p=0.692). Mean age was slightly higher in patients who had EIM (49.31 *vs.* 48.13 years, p=0.595). Most patients diagnosed with IBD and EIM came from urban areas (n=38, 74.5%, p=0.202). The peak years for the occurrence of EIM were in 2011, 2012 and 2015. Ten (19.6%) patients were active smokers, over half – 28 (54.9%) non-smokers and 13 (25.5%) former smokers (p=0.465). By logistic regression, it was confirmed that active smokers had a 1.3 times higher risk to develop EIM than non-smokers (OR=1.306, p=0.497). Former smokers presented a risk of 0.758 (OR=0.758, p=0.431), so smoking status may be a protective factor for the occurrence of EIM.

Patients with CD and EIM (n=27) exhibited a risk of 3.687 times higher than the rest of the cases for developing EIM (p<0.001, OR=3.687, 95% CI 2.04–6.65). In these patients, ileocolitis predominated (n=11, 40.7%, p=0.361). Based on the statistical analysis, UC may be considered a protective factor for the occurrence of EIM (p<0.001, OR=0.305, 95% CI 0.169–0.549). Among these patients, left-sided colitis (n=11, 45.8%, p=0.342) predominated.

Most patients with IBD and EIM (n=49, 96.1%) were on medical treatment. By comparison with the group without EIM, patients with EIM had frequently CS (7.8% *vs.* 1.1%, p=0.017) and IFX therapy (5% *vs.* 11.8%, p=0.145). Patients without EIM received more frequently 5-ASA and antibiotics (46.1% *vs.* 19.6%, p=0.569). CS therapy exhibited a 10.8-fold increased risk for EIM compared to the treatment-free group (p=0.017, OR=10.8, 95% CI 1.541–75.699).

Musculoskeletal manifestations were the most common EIM (n=38, 74.5%, p=0.001). Peripheral involvement – arthritis (n=26, 68.42%) predominated, followed by axial damage – SI/AS (n=12, 31.58%) (p=0.001). Patients with CD had a 3.48-fold greater risk of developing joint manifestations than the rest of the patients (p<0.001, OR=3.478, 95% CI 1.779–6.801). In both CD and UC patients, arthritis cases prevailed over SI/AS (68.42% *vs.* 31.58%). Patients with CD had a 5-fold higher risk of developing arthritis (p<0.001, OR=5.009, 95% CI 2.21–11.34). Neither CD, nor UC patients, had a confirmed risk of developing SI/AS (p=0.468, OR=1.565, 95% CI 0.463–5.293 for CD) (p=0.586, OR=0.714, 95% CI 0.211–2.413 for UC). The cases of arthritis and CD (n=16) mainly correlated with colitis (n=7, p=0.723) and ileocolitis (n=7, p=0.321). UC patients with arthritis (n=10) were linked to pancolitis (n=5, p=0.072, OR=3.023; 95% CI 0.855–10.69), proctitis (n=3, p=0.392) and left-sided colitis (n=2, p=0.024, OR=0.196, 95% CI 0.041–0.938). Left-sided colitis was considered to be a protective factor for the onset of arthritis, while pancolitis constituted a possible risk factor for the development of arthritis.

Uveitis was highlighted in two patients with CD and in an UC case. All cases with ocular signs also showed peripheral articular manifestations – arthritis. *Pyoderma gangrenosum* was more common in CD patients than in UC cases (n=3 *vs.* n=1) and was associated with articular manifestations. PSC was highlighted in one patient with UC and did not associate other EIM. Renal manifestations occurred with a higher frequency in CD and were associated with the presence of other EIM. Because the number of these cases was very small, the statistical analysis did not have statistical consistency (Table 3).

Intestinal complications in the study group

In the study group (n=513), there were 66 (12.9%) cases associated with intestinal complications as follows: abscesses – seven (10.6%) cases, fistula – 11 (16.16%) cases, stenosis – 22 (33.33%) cases, inferior digestive hemorrhage (Hdi) – eight (12.12%) cases, malignancies – six (9.09%) cases, and 12 (18.18%) patients had multiple intestinal complications. Most patients who developed

intestinal complications belonged to CD phenotype (*n*=49, 74.2%) ($p<0.001$). Patients with CD had a 12.5-fold greater risk ($p<0.001$, OR=12.5) to develop intestinal complications compared to UC patients ($p<0.001$, OR=0.08, 95% CI 0.043–0.147). Of the 66 patients who developed intestinal complications, the majority (*n*=64, 97%) were on treatment ($p<0.001$).

In patients with CD, intestinal stenoses were the most frequent (21 cases, 42.85%), followed by fistula (10 cases, 20.4%) and abscesses (five cases, 10.2%). Seventeen (34.7%) patients had ileocolitis ($p=0.604$). Stricturing phenotype (*n*=27, 55.1%, $p<0.001$, OR=10.385, 95% CI 4.325–24.932), respectively penetrating phenotype (*n*=8, 16.3%; OR=13.333, 95% CI 3.141–56.595) had an increased risk of developing intestinal complications.

Among patients with UC and intestinal complications (*n*=16), Hdi (*n*=7, 43.75%) predominated. The rate of malignancy was double that in patients diagnosed with CD (*n*=4, 25%). Intestinal complications mainly occurred in left-sided colitis (*n*=8, 50%) and pancolitis (*n*=6, 37.5%) ($p=0.492$).

Table 4 presents the risk for patients with CD, UC and CN to develop intestinal complications.

The association between intestinal complications and EIM was highlighted in 15 (22.7%) patients ($p=0.007$), being more common in CD cases than in UC (*n*=12 *vs.* *n*=3) (Table 5). The risk of developing intestinal complications was found to be 3.35 times higher in patients with EIM as compared to the rest of the cases ($p<0.001$, OR=3.358, 95% CI 1.72–6.55). Of the intestinal complications, intestinal stenosis and Hdi predominated, while the most common EIM were articular manifestations (with a predominance of peripheral manifestations – arthritis). The stricturing phenotype and ileocolitis in CD apparently favored the association between intestinal complications and EIM (without statistical significance – very few cases).

Table 3 – ***EIM classification in patients with IBD depending on disease phenotype***

EIM	CD (n=27)		UC (n=24)		*p*	OR	RR	95% CI
	n	%	*n*	%				
Articular manifestations								
Arthritis	16	59.3	10	41.7	0.209	2.04	1.4_{CD}	0.82–2.39
SI/AS	4	14.8	8	33.3	0.118	0.35	1.63_{UC}	0.94–2.81
Cutaneous manifestations								
Erythema nodosum	1	3.7	1	4.2	0.932	0.89	1.07_{UC}	0.26–4.4
Pyoderma gangrenosum	3	11.1	1	4.2	0.345	2.88	1.47_{CD}	0.78–2.76
Hepatobiliary manifestations								
PSC	0	0	1	4.2	0.216	–	2.17_{UC}	1.61–2.94
Ocular manifestations								
Uveitis	2	7.4	1	4.2	0.619	1.84	1.28_{CD}	0.55–2.98
Renal manifestations								
Oxalate nephrolithiasis	2	7.4	1	4.2	0.619	1.84	1.28_{CD}	0.55–2.98
Multiple urinary infections	5	18.5	3	12.5	0.553	1.59	1.22_{CD}	0.66–2.25

EIM: Extraintestinal manifestations; IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; OR: Odds ratio; RR: Relative risk; CI: Confidence interval; *n*: No. of cases; SI/AS: Sacroiliitis/ankylosing spondylitis; PSC: Primary sclerosing cholangitis.

Table 4 – ***The risk of developing intestinal complications depending on the phenotype of the disease***

Disease phenotype	Patients			*p*	OR	95% CI	
	Without intestinal complications, n (%)	*With intestinal complications, n (%)*	*Total, n (%)*			*Min.*	*Max.*
CD	86 (63.7)	49 (36.3)	135 (100)	<0.001	12.5	3.428	47.829
L1	19 (22.1)	15 (30.6)	34 (25.2)	0.604	–	–	–
L2	36 (41.9)	16 (32.7)	52 (38.5)				
L3	28 (32.6)	17 (34.7)	45 (33.3)				
L4	3 (3.5)	1 (2)	4 (3)				
B1	70 (81.4)	14 (28.6)	84 (62.2)	<0.001	–	–	–
B2	13 (15.1)	27 (55.1)	40 (29.6)	<0.001	10.385	4.325	24.932
B3	3 (3.5)	8 (16.3)	11 (8.1)	<0.001	13.333	3.141	56.595
UC	352 (95.7)	16 (4.3)	368 (100)	<0.001	0.08	0.043	0.147
E1	69 (19.6)	2 (12.5)	71 (19.3)	0.492	–	–	–
E2	195 (55.4)	8 (50)	203 (55.2)				
E3	88 (25)	6 (37.5)	94 (25.5)				
CN	9 (90)	1 (10)	10	0.126	0.195	0.024	1.585

n: No. of cases; OR: Odds ratio; CI: Confidence interval; CD: Crohn's disease; L1: Ileitis; L2: Colitis; L3: Ileocolitis; L4: Upper gastrointestinal tract; B1: Inflammatory; B2: Stricturing; B3: Penetrating; UC: Ulcerative colitis; E1: Proctitis; E2: Left-sided colitis; E3: Pancolitis; CN: Undifferentiated colitis.

Table 5 – ***The association between intestinal complications and EIM***

IBD				Intestinal complications	EIM
Disease phenotype	*Location of inflammation*	*Form of IBD*	*Severity of disease*		
CD	L1	B2	moderate	intestinal stenosis	arthritis
CD	L3	B2	moderate	intestinal stenosis	multiple urinary tract infections
UC	E2	–	mild	Hdi	multiple urinary tract infections
CD	L3	B2	moderate	intestinal stenosis	arthritis + uveitis
UC	E1	–	mild	Hdi	arthritis
CD	L2	B1	mild	abscesses + fistula	arthritis + uveitis + oxalic nephrolithiasis + multiple urinary tract infections
CD	L3	B1	moderate	Hdi	arthritis
CD	L3	B2	moderate	intestinal stenosis	arthritis
CD	L2	B2	moderate	intestinal stenosis	arthritis + *pyoderma gangrenosum*
CD	L2	B2	severe	intestinal stenosis	arthritis
CD	L3	B1	severe	fistula	multiple urinary tract infections
CD	L1	B2	moderate	abscesses	multiple urinary tract infections
CD	L2	B3	mild	fistula	oxalic nephrolithiasis
UC	E3	–	mild	malignancy	oxalic nephrolithiasis
CD	L3	B1	mild	fistula + Hdi	SI/AS

EIM: Extraintestinal manifestations; IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; L1: Ileitis; L2: Colitis; L3: Ileocolitis; E1: Proctitis; E2: Left-sided colitis; E3: Pancolitis; B1: Inflammatory; B2: Stricturing; B3: Penetrating; Hdi: Inferior digestive hemorrhage; SI/AS: Sacroiliitis/ankylosing spondylitis.

Discussions

This study brings important data on the epidemiological and clinical characteristics of patients with IBD in the NE region of Romania. It also highlights the association and correlations between IBD and EIM, as well as those regarding intestinal complications. Most of the obtained results are consistent with the data published in the literature.

In the NE region of Romania, the EIM prevalence in patients with IBD was 9.9%, being relatively low compared to other geographical areas. Numerous clinical studies have analyzed the incidence of EIM in patients with IBD. The prevalence of EIM varies greatly, ranging from 6% to 47% [4, 15–18]. The most common EIMs were musculoskeletal manifestations, followed by renal, cutaneous, ocular and hepatobiliary manifestations. Our results coincide with data from other published studies that support the fact that, in patients with IBD and EIM, the highest incidence is assigned to articular manifestations [6, 19]. On the second place are mucocutaneous manifestations, followed by ophthalmological symptoms [17, 18, 20].

Both EIM and intestinal complications showed a higher incidence among CD patients. Thus, of the 51 cases of IBD and EIM, 27 belonged to the CD phenotype and 24 to UC phenotype, statistically significant data. The obtained results are consistent with the study published by Vavricka *et al.* [4] or with Bernstein *et al.* results [15] that support the high prevalence of EIM among patients with CD. Also, over 50% of cases of IBD and EIM belonged to the female gender, with a higher percentage among CD patients. The increased prevalence of EIM in female is supported by the published results [4, 15, 18]. Most patients diagnosed with IBD and EIM came from urban environment, having a slightly higher average age. A recent study by Karmiris *et al.* [21] shows consistent results.

Following the smoking status of patients with IBD and EIM, it was argued that active smoking is considered to be a risk factor for the development of EIM, while former smokers developed some protection. Lakatos *et al.* [22] reported the association between smoking and the occurrence of EIM. The study published by Ott *et al.* supports the increased risk of smokers diagnosed with CD to develop EIM [23]. There are no studies to analyze the link between EIM and ex-smokers diagnosed with IBD.

Compared with UC cases, patients with CD had a risk of over three times greater to develop EIM. We cannot sustain that a particular phenotype of CD favors the appearance of EIM. However, there is a difference between the group of patients with CD and EIM *versus* CD without EIM regarding the location of intestinal inflammation. In patients with CD without EIM predominated the colonic form of the disease. Those having EIM had a more frequent ileo-colonic disease. The study published by Karmiris *et al.* [21] supports the association of EIM (especially articular manifestations) with an extensive CD.

Statistical analysis revealed that UC can be considered a protective factor for the occurrence of EIM. Among these patients, the left colonic form of the disease predominated. The obtained results are in contradiction to the literature. The presence of EIM in patients with UC has been mostly correlated with an extensive form of disease (pancolitis) [21].

Most patients with IBD and EIM were on medical treatment. It has been shown that CS therapy has been a risk factor for the onset of EIM. Patients without EIM were given more frequent 5-ASA and antibiotherapy (especially Rifaximin). Numerous clinical trials support the beneficial effect of Rifaximin in inducing remission

in CD and UC. Rifaximin has promising clinical results because: it decreases inflammation induced by 2,4,6-trinitrobenzenesulfonic acid and prevents bacterial translocation [24], modulates colon microflora in patients with CD (increases in *Faecalibacterium prausnitzii* and *Bifidobacterium*) [25] and antagonizes the effect of TNF-α on intestinal epithelial cells [26, 27]. In CD, Rifaximin induced clinical remission after only 16 weeks of treatment, in almost 70% of cases [28]; in UC, the percentage was even higher – 76.6% [29].

Of all EIM, musculoskeletal manifestations proved to be the most frequent, the results having statistical significance and being consistent with those from the literature. The cases of peripheral involvement (arthritis) predominated, followed by axial damage – SI/AS. Patients with CD had a significantly higher risk. Arthritis has been shown to be more common in patients diagnosed with CD. Patients with UC developed more frequently SI/AS. Numerous published studies support the high incidence of peripheral joint manifestations among patients diagnosed with CD as compared to UC phenotype [21, 30, 31]. Also, the obtained results in this study and those published by Karminis *et al.* [21] confirm the association between AS and ileo-colonic form of CD, between SI and CD with colonic involvement. An extensive form of UC is considered to be a risk factor for the occurrence of EIM.

In the study group, CD patients showed more frequently articular manifestations, *pyoderma gangrenosum*, uveitis and oxalic nephrolithiasis, while in patients with UC there was a higher ratio of PSC. The greater incidence of ophthalmic manifestations in CD cases is also supported in literature (especially uveitis and episcleritis) [17, 20, 32, 33]. The close association between UC and PSC has been punctuated in various trials, having an estimated incidence of 2% to 7.5% [6, 34, 35]. Specialty studies have shown a 10-fold higher risk for patients with CD to develop reno-urinary manifestations [36]. Some clinical trials support the higher prevalence of *pyoderma gangrenosum* among UC patients [23, 37], others an increased incidence in CD cases [17].

There were 66 cases of intestinal complications, having a prevalence of 12.9% (greater than the incidence of EIM – 9.9%). In a recent study published in 2017 by Hsu *et al.*, the incidence of intestinal complications in a group of 3153 patients was 22.2% [38]. Patients with CD had a much higher risk of developing intestinal complications. Data already published support the increased prevalence of complications in CD cases, especially in male patients [38, 39].

In patients with CD, stenoses were the most common intestinal complications, followed by fistulas and abscesses. Published data support the higher prevalence of stenoses, abscesses, fistulas and perforations in CD patients. Abscesses, often associated with fistulas, showed an incidence between 23 and 62%, and anal fissures of 21–35% [38–40]. A lower incidence of perianal complications in CD – 5.6% – was reported in a Chinese study [41]. Although the ileo-colonic form of the disease predominates, a certain location of the inflammatory process in patients with CD does not seem to favor the development of intestinal complications. However, literature results argue that an extensive CD is a favorable site for intestinal complications and EIM [21]. Data on the association between intestinal complications and phenotype of CD are similar to those found in patients with CD and EIM. Regarding the phenotype of CD, the results suggest that it may represent a risk factor for the occurrence of intestinal complications (B2 and B3, respectively).

In UC patients, intestinal complications mainly occurred in left-sided colitis and pancolitis. The rate of malignancy was double compared to patients diagnosed with CD. The study published by Manser *et al.* [42] sustains that an extensive disease is considered to be a risk factor for complications. Also, both UC and CD cases, present a 2–3 times higher risk of developing colorectal cancer than the general population [43]. A meta-analysis that comprised 116 studies revealed a prevalence of 3.7% for colorectal cancer in patients with UC [44].

Conclusions

This study also focused on highlighting the correlations between EIM and intestinal complications. The obtained results after statistical analysis are promising, even if the number of the analyzed subjects was small. The risk of developing intestinal complications was found to be 3.35 times higher in patients who also had EIM compared to the rest of the patients. The association between EIM–complications was much more common in CD cases. Specialty literature does not currently provide specific data on the association between EIM and intestinal complications. What we know for sure is that CD represents the phenotype of IBD, which has a higher incidence for EIM and intestinal complications.

Conflict of interests

The authors declare that they have no conflict of interests.

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Received: February 10, 2018

Accepted: January 3, 2019