EXTRAINTESTINAL MANIFESTATIONS IN INFLAMMATORY BOWEL DISEASE - RESULTS FROM NORTH-EASTERN ROMANIA

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EXTRAINTESTINAL MANIFESTATIONS IN INFLAMMATORY BOWEL DISEASE - RESULTS FROM NORTH-EASTERN ROMANIA (Abstract): The presence of extraintestinal manifestations (EIM) in inflammatory bowel disease (IBD) is a common and well-known finding. **Material and methods:** Using the national database IBD Prospect, we conducted a prospective case-control study that included 325 patients diagnosed with Crohn's disease (CD) or ulcerative colitis (UC). Between these cases, 81 (24.92%) were classified in the group CD, 242 (74.46%) having UC and 2 cases (0.62%) were classified as having undifferentiated colitis. Among them, 30 patients (9,23%) had EIM including 24 cases of articular manifestations. Regarding joint events, we found 5 cases of arthritis, 10 cases having axial manifestations like sacroiliitis or ankylosing spondylitis and 9 cases of multiple EIM including articular damage. **Results:** In both study arms, articular manifestations occupy the first place into EIM (14/17 CD *vs.* 10/13 UC, 82.35% *vs.* 76.92%, p=0.927). Into the CD group, joint manifestations first correlated with the ileo-colonic form of CD (8/14; 57,14%) followed by the colonic involvement (4/14; 28,57%). Into the UC arm, joint damage was associated with an extended colonic involvement (4/10; 40%) followed by proctitis and left side colitis. Both groups of patients with articular manifestations were associated with a moderate form of IBD activity - 10/14 CD *vs.* 5/10 UC (71.43% *vs.* 50%, p = 0.199). **Conclusions:** Most patients included in this study and having EIM belong to CD phenotype. Articular manifestations occurred at a higher frequency in patients with CD as compared to those diagnosed with UC. The most common articular manifestation is the axial involvement, followed by peripheral arthritis. **Keywords:** INFLAMMATORY BOWEL DISEASE, CROHN'S DISEASE, ULCERATIVE COLITIS, ARTICULAR MANIFESTATIONS, EXTRAINTESTINAL MANIFESTATIONS.

Inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory diseases different from both the pathogenic mechanisms, as well as from clinical manifestations. In addition to inflammatory intestinal damage, CD and UC may have lots of extraintestinal manifestations (EIM). The most common EIM are at the level of musculoskeletal system - axial and peripheral arthritis, followed by skin involvement - erythema nodosum, pyoderma gangrenosum or eye damage - uveitis, iridocyclitis.

EIM can be divided into three catego-

ries: extraintestinal immune- related manifestations of IBD, autoimmune disorders associated to IBD and extraintestinal complications. Extraintestinal immune- mediated manifestations have the same pathogenic mechanism and correlate with the activity of intestinal inflammation. Autoimmune diseases associated with IBD develop independently of IBD activity and are characterized by a high genetic susceptibility. Extraintestinal complications may occur due to: intestinal inflammatory activity, use of medication, anatomical and metabolic changes that accompany IBD, malabsorption etc. (1, 2).

MATERIAL AND METHODS

We performed a prospective case-control study using the national database IBD PROSPECT (Inflammatory Bowel Disease Prospect). All patients signed an informed consent form before being included in the database. In University Center Iasi were included 325 patients with IBD. Among these, 140 (43.08%) were female and 185 (56.92%) male. Most patients were coming from urban areas - 227 cases (69.85%), while in rural areas were recorded only 98 cases (30.15%). The average age was 43 years with a minimum of 17 years and a maximum of 76 years. Among the patients included, 81 (24.92%) were classified in the group of CDs 242 (74.46%) in the UC's group and 2 cases (0.62%) were categorized as undifferentiated colitis. The detailed patient history also included the smoking status. 40 cases (12.30%) of smokers, 122 cases (37.54%) of ex-smokers and 163 cases (50.16%) of never-smoking were recorded.

All patients were examined clinically and paraclinically. The history followed significant personal or family history, the clinical symptoms like: the number of stools / 24 hours, the presence of rectal tenesmus, lower gastrointestinal bleeding, weight loss within 3 months, abdominal pain and asthenia.

Evaluation of the disease phenotype was performed using colonoscopy with biopsy and histopathological examination. CD has been divided, according to the localization of the inflammation, in L1 - ileal, L2 - colonic, L3 - ileo-colonic and depending on the type of disease in B1 - inflammatory, B2 - stenosing and B3 - penetrating disease. Depending on the location of the inflammatory process, UC was divided into E1 - proctitis, E2 - left colitis and E3 - extensive colitis. In both groups of patients, the assessment of severity of the disease flare was quantified by remission, mild, moderate or severe.

The study also analyzed the treatment of these patients. There have been considered the following classes of drugs: 5 ASA (5-aminosalicylic acid), corticosteroids, budesonide, the use of antibiotics, probiotics and immunosuppressive agents such as azathioprine, methotrexate or biological therapy with anti-TNF-α agents such as infliximab or adalimumab.

Regarding the complications related to the disease, they were divided into two categories: intestinal and extra-intestinal manifestations. The intestinal complications included: abscesses, intestinal and perianal fistulas, stenosis, the presence of toxic megacolon, intestinal perforation, lower intestinal bleeding and the development of a malignancy. Extraintestinal manifestations included joint signs like arthritis or sacroiliitis/ankylosing spondylitis (SI/AS), skin manifestations: erythema nodosum, pyoderma gangrenosum, eye manifestations: uveitis / episcleritis, gastrointestinal symptoms: peri cholangitis, primary sclerosing cholangitis or renal manifestations such as

oxalate nephrolithiasis, renal amyloidosis or multiple urinary infections.

RESULTS

In the study group, 30 cases (9.23%) with EIM were highlighted. Of these, we noticed 5 cases (16.66%) of arthritis, 10 cases (33.33%) of SI/AS, erythema nodosum 2 cases (6.66%), pyoderma gangrenosum 1 case (3.33%), 1 case of primary sclerosis cholangitis (3.33%), multiple urinary infections 2 cases (6.66%) and associations between two or more EIM - 9 cases (30%). Because all the cases with multiple EIM also have articular involvement, they were considered as articular manifestations, being in total 24 cases (80%) (tab. I).

In the group of patients who had articular manifestations (n = 24; 80%), 14 cases (58.33%) of axial manifestations (sacroiliitis/ankylosing spondylitis), 9 cases of arthritis (37.5%) and one case (4.16%) of association between peripheral and axial involvement were recorded (fig. 1).

TABLE I.

Extraintestinal manifestations in study group

Extraintestinal manifestation	n (%)
Articular manifestations (n, %)	24 (80%)
Arthritis	5 (16,66%)
SI/AS	10 (33,33%)
Association of EIM	9 (30%)
SI/AS + pyoderma gangrenosum	2 (6,66%)
SI/AS + uveitis/episcleritis	1 (3,33%)
SI/AS + uveitis/episcleritis + oxalate urolithiasis + multiple urinary infections	1 (3,33%)
Arthritis + multiple urinary infections	1 (3,33%)
Arthritis + erythema nodosum	1 (3,33%)
Arthritis + uveitis/episcleritis	2 (6,66%)
Arthritis + SI/AS	1 (3,33%)
Erythema nodosum (n, %)	2 (6,66%)
Pyoderma gangrenosum (n, %)	1 (3,33%)
Primary sclerosing cholangitis (n, %)	1 (3,33%)
Multiple urinary infections (n, %)	2 (6,66%)

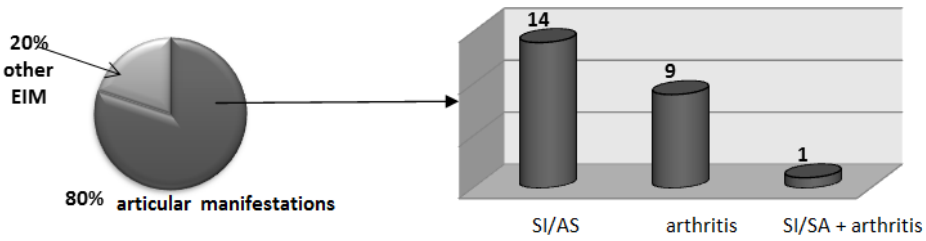

Fig.1. Articular manifestations in patients with IBD

CD and EIM

There were 17 patients diagnosed with CD who also had EIM as follows: 14 cases (82.35%) with articular manifestations, one case (5.88%) having erythema nodosum, 1 case (5.88%) with pyoderma gangrenosum,

1 case (5.88%) with multiple urinary infections. Most patients with CD and EIM were female - 11cases (64.70%) than male - 6 cases (35.30%). 16 patients (94.12%) were from urban areas, only one patient (5.88%) being from rural areas. The analysis of smoking status revealed the following data: 8 cases (47.06%) of active smokers, 3 cases of ex-smokers (17.65%) and non-smoking 6 cases (35.29%).

For patients with CD and EIM, the most frequent localization of the inflammatory process was L3 (ileo-colonic disease) - 9 cases (52.94%), followed by L2 (colonic disease) - 5 cases (29.41%), L1 (ileal disease) - 2 cases (11.76 %) and L4 (upper digestive tract disease) - 1 case (5.88%). Referring to the form of the disease, 13 patients (76.47%) had B1 (inflammatory form) and 4 patients (23.53%) had B2 (stricturing form). Most of cases - 11 (64.7%) - had a moderate intestinal inflammation, while 6 cases (35.30%) had remission or a mild form of BC (fig.2).

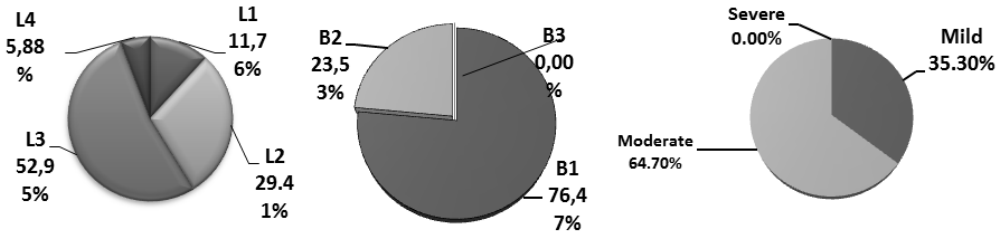

Fig. 2. Association between different forms of CD and EIM

The group of CD patients presented 14 cases (82.35%) of articular manifestations, which are the most common EIM. There were 3 cases (17.65%) of arthritis, 6 cases (35.30%) of SI/AS and 5 cases (29.41%) of association between different EIM including joint symptoms.

Articular manifestations occurred in a higher percentage in patients with L3 localization of CD - 8 cases (57.14%), followed by L2 - 4 cases (28.57%) and L1 - 2 cases (14.28%). The largest number of cases with an inflammatory phenotype (B1) - 11 (78.57%), followed by the stenosing form (B2) - 3 cases (21.43%), was recorded in subjects with associated articular manifestations. Also, moderate inflammation of the gut was associated with joint symptoms - 10 cases (71.43%), followed by the mild form - 4 cases (28.57%) (fig.3).

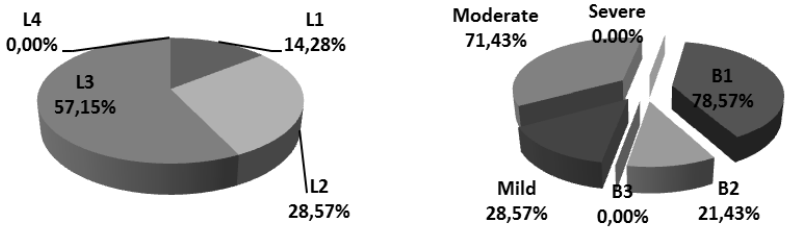

Fig. 3. Association between different forms of CD and articular manifestations

It should also be noted that patients with CD and EIM can develop intestinal complications. There were seven cases (41.17%) of such complications: 4 cases (57.14%) of stenoseses, 1 case (14.28%) of lower digestive hemorrhage, 1 case (14.28%) of fistulas + lower digestive hemorrhage, 1 case (14.28%) of abscesses + fistula. Of the 7 cases of intestinal complications, 6 (85.71%) have developed in patients who also associate articular manifestations.

UC and EIM

The group of patients with IBD include 13 cases of UC and EIM: 10 patients (76.92%) with joint manifestations, 1 patient (7.69%) with primary sclerosing cholangitis, 1 patient (7.69%) with erythema nodosum and 1 case (7.69%) of multiple urinary infections. Of these 13 cases of UC, 8 (61.54%) were women and five (38.46%) men. Most patients came from urban areas - 9 (69.23%), 4 (30.77%) being from the countryside. Analyzing the smoking status, we found 8 patients (61.54%) non-smoking, 5 patients (38.46%) ex-smokers, none active smoker.

The location of the intestinal inflammation in UC correlated differently with EIM. Therefore, left colitis (E2) was found in 6 cases (46.15%) of patients who associate EIM, extended colitis (E3) in 4 cases (30.77%) and proctitis (E1) in 3 cases (23,07%). Regarding the severity of the intestinal inflammation, 6 patients (46.15%) with EIM showed a mild form of the disease, 5 patients (38.46%) a moderate form, only 2 patients (15.38%) having a severe inflammation of the bowel (fig. 4).

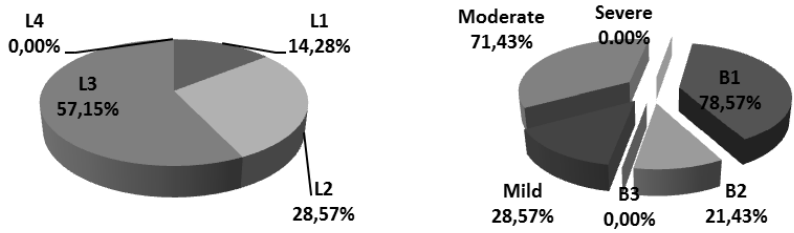

Fig. 4. Association between different forms of UC and EIM

Articular manifestations associated with UC were 10 (76.92%) distributed as follows: 2 cases (20%) of UC and arthritis, 4 cases (40%) of UC and SI/AS, 4 cases (40%) multiple EIM and UC.

According to the location of the inflammation of the bowel, articular manifestations associated with UC patients correlate as follows: 3 cases (30%) with form E1, 3 cases (30%) with form E2 and 4 cases (40%) with E3. The severity of the gut inflammation was divided into: 3 cases (30%) of mild symptoms associated with joint symptoms, 5 cases (50%) of moderate inflammation and 2 cases (20%) of severe bowel symptoms associated with axial or peripheral joint manifestations (fig. 5).

It must be pointed out that 2 patients (15.38%) with UC and EIM also associated intestinal complications such as lower digestive hemorrhage. Both patients had peripheral joint symptoms - arthritis.

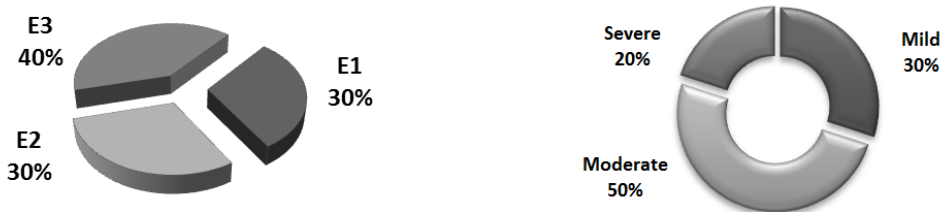

Fig. 5. Association between different forms of UC and articular manifestations

DISCUSSION

The aim of this study was to highlight the presence of EIM in patients with IBD. The overall prevalence of EIM found was 9,23% quite like that reported in the literature ranging from 6 and 47% (3-6). Both in the CD and UC group predominate female cases - 11/17 *vs.* 8/13 (64.70% *vs.* 61.54%, p = 0.838). Most patients come from urban areas - 16/17 CD *vs.* 9/13 UC (94.12% *vs.* 69.23%, p = 0.187). In the group of CD patients, 8/17 cases are active smokers, while in the case with UC patients 8/13 cases are non-smokers (p = 0.015) (statistically significant).

EIM occurred with a higher incidence among patients with CD and among females, this result being supported by other studies (7). In both study arms, articular manifestations have been shown to be the most frequent EIMs (14/17 CD *vs.* 10/13 UC; 82,35% *vs.* 76,92%, p=0,927). Numerous clinical trials have demonstrated that axial and peripheral articular manifestations occur frequently in patients with IBD, being classified as the most common EIMs (8-11).

In the group of patients with CD there is no difference between joint manifestations and other EIMs regarding the association with the location and the phenotype of the disease. Most cases of CD and EIM, including articular manifestations, correlated with form L3 (ileo-colonic) - 9/17 (52.94%), followed by form L2 (colonic) - 5/17 (29.41%). Regarding the phenotype, 11/17 (64,70%) had a moderate form of intestinal inflammation.

As opposed to patients with CD, in the group of cases with UC there is difference between joint manifestations and other EIMs regarding the association with the location and the phenotype of the disease. Most cases of UC and EIM correlated with left-colitis (E2) - 6/13 (46.14%), followed by pancolitis (E3) - 4/13 (30.77%). Regarding articular manifestations, they first correlated with pancolitis, then with left-colitis (4/10 *vs.* 3/10).

In both groups of patients with IBD and EIM, intestinal complications occurred with a higher rate in CD patients compared to those with UC - 7/17 *vs.* 2/13 (41.17% *vs.* 15.38%, p = 0.260). We raised the following hypothesis: a more severe disease characterized by the presence of intestinal complications can be considered as a risk factor for the emergence of EIM, including articular manifestations.

CONCLUSIONS

The results of our study confirmed that UC is more frequently found both in Northeastern Romania and in city of Iasi. Most of the patients enrolled in the study and who presented EIM belong to CD phe-

notype. Joint manifestations have been shown to be the most common EIM in both CD and UC patients. The most common articular manifestations are the axial forms (SI/AS), followed by peripheral arthritis. Joint manifestations occurred with a higher frequency among CD patients compared to those diagnosed with UC.

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