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Prevalence, risk factors and response to treatment of extra-intestinal manifestations in patients with inflammatory bowel disease

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ABSTRACT

Introduction: Patients with inflammatory bowel disease can experience extra-intestinal manifestations that may cause significant morbidity.

Aims: To describe the prevalence, characteristics, treatment and evolution of extra-intestinal manifestations in inflammatory bowel disease patients treated in our hospital and to identify associated risk factors.

Methods: This was a retrospective, observational, case-control study. All inflammatory bowel disease patients with extra-intestinal manifestations were considered as cases and inflammatory bowel disease patients without extra-intestinal manifestations were considered as controls.

Results: Six hundred and nineteen patients with inflammatory bowel disease (327 Crohn's disease, 265 ulcerative colitis, 27 indeterminate colitis) were included in the study; 16.5% experienced at least one extra-intestinal manifestation (CI 95% 13.5-19.5; n = 102). The most frequent extra-intestinal manifestations observed were musculoskeletal (n = 50; 40%) and cutaneous manifestations (n = 50; 40%). With regard to treatment, arthropathies were treated with non-steroidal anti-inflammatory drugs (31%) and corticosteroids (19%, oral or intra-articular), and the majority of the cutaneous manifestations were managed with corticosteroids. Overall, the efficacy of extra-intestinal manifestation treatment was 90% and only 13% of patients had a recurrence of extra-intestinal manifestations. The multivariate analysis showed that female gender (p = 0.012; OR = 1.61; 95% CI 1.11-2.34) and the severity of inflammatory bowel disease (p = 0.009; OR = 1.65; 95% CI 1.13-2.4 if immunosuppressant therapy alone, or p = 0.029; OR = 2.28; 95% CI 1.09-4.78 if in combination with adalimumab) were associated with an increased risk of developing extra-intestinal manifestations.

Conclusions: The most frequent extra-intestinal manifestations in our environment were musculoskeletal and cutaneous manifestations. Female gender and a more severe disease were associated with a higher risk of developing extra-intestinal manifestations. Individualized treatment of extra-intestinal manifestations is effective and the risk is low in our series.

Key words: Inflammatory bowel disease. Extra-intestinal manifestations. Risk factors.

INTRODUCTION

Patients with inflammatory bowel disease (IBD), Crohn's disease (CD), ulcerative colitis (UC) or unclassified colitis may suffer from extraluminal involvement related to their underlying disease. The extraintestinal involvement can occur in different organs and systems; the musculeskeletal system is mainly affected. These manifestations have a negative impact on the patients' quality of life and may also be life-threatening (for example, primary sclerosing cholangitis or venous thromboembolism) (1). Occasionally, extraintestinal manifestations (EIMs) may precede the occurrence of IBD

over several years (2) and a recent study (3) has shown that around 25% of patients have a combination of up to five different types of EIMs during the natural history of the disease. Repiso et al. showed (4) that 46% of CD patients presented at least one MEI and articular and mucocutaneous manifestations were the most frequent, especially in patients with colic disease.

Some of these EIMs are associated with inflammatory intestinal activity but others have an independent course (3). Depending on this association, EIMs can be classified into three groups. Firstly, EIMs that are specifically associated with IBD, either associated to intestinal activity (peripheral arthritis, erythema nodosum, oral thrush) or independent of disease course (pyoderma gangrenosum, uveitis, spondyloarthropathy, primary sclerosing cholangitis). The second category includes autoimmune diseases that are not specifically associated with IBD, such as thyroiditis, hemolytic anemia, vitiligo and insulin-dependent diabetes mellitus. The third group includes complications related to IBD secondary to metabolic alterations (such as phosphocalcic metabolism alterations and nephrolithiasis) (3) or exaggerated inflammatory mediator production (thromboembolic events).

The knowledge of the IBD pathophysiology has considerably improved during the last decade but the etiology of IBD remains an enigma (5). Several precipitating factors such as genetic, microbiological, environmental (smoking), immunological, vascular and psychological factors have been identified. The involvement of nonsteroidal anti-inflammatory drugs (NSAIDs) or oral contraceptives remains controversial (6). The frequency of IBD has significantly increased in recent years (7), with a noticeable difference in incidence and prevalence in different geographical areas. As IBD affects multiple organs and systems that are not related to the gastrointestinal tract, physicians should not only be suspicious of an intestinal flare but also be aware of the onset of EIMs. Moreover, a rapid diagnosis of EIMs allows them to be treated earlier, and this, consequently, reduces morbidity. In addition, some EIMs respond to intestinal flare treatment but those with an independent course require a specific treatment. Therefore, dealing with the EIMs can be very difficult and requires a multidisciplinary approach (8), as in our hospital. We aim to determine the epidemiological characteristics of both EC and CU (only EIMs were analyzed in CD

patients in previous studies in Spain) (4), evaluate therapeutic strategies and response to treatment of EIMs, and identify associated risk factors in a large cohort of patients with IBD in Spain.

MATERIALS AND METHODS

Patients

We performed a retrospective observational case-control study in the Department of Digestive Diseases of our hospital. The study was approved by the hospital ethical committee. Data from patients diagnosed with IBD in our center between 2004 and 2014 were analyzed according to the classic criteria (9). All patients were recruited in an IBD specialized clinic and their data were retrospectively collected from an electronic clinical history database. IBD patients with at least one EIM were considered as study cases and those without EIMs were considered as controls. Data related to epidemiology (gender, age, family history and smoking) and other data related to the disease, both at an intestinal and extraintestinal level (type and classification of IBD, onset date, type of EIMs) were collected. Data with regard to therapeutic strategies both before and after the EIM occurrence (need for surgery and/or use and type of immunomodulators used before the diagnosis of EIMs and specific treatment used for the extraintestinal symptoms) were also collected. Patients who required immunosuppressive and/or biological therapy were considered as severely affected. Finally, information about EIM evolution (response to treatment and relapse) was also collected. A symptom-free period of six months was defined as response to treatment and the recurrence of symptoms after an asymptomatic period of time was considered as a relapse.

Statistical analysis

Qualitative data were summarized as percentages with 95% confidence levels. Quantitative data are presented as mean ± standard deviation for Gaussian data or median and interquartile range for non-Gaussian data. The Kolmogorov-Smirnov test was used to assess the normal distribution of the continuous data.

Differences in categorical data distribution between groups were assessed using the Chi-squared test. Differences in quantitative and qualitative data of two categories between groups were assessed using the Student's t-test (for Gaussian data) or the U-Mann-Whitney test (for non-Gaussian data). Differences in quantitative and qualitative data with three or more categories were performed using the analysis of variance (ANOVA) test or the Kruskal-Wallis test. The relative risk was determined by calculating the odds ratio (OR). Finally, a multivariate analysis was performed using a logistic regression to identify possible risk factors associated with a higher risk of developing EIMs. A p value < 0.05 was considered as statistically significant.

RESULTS

Clinical characteristics of the study population

A sample of 619 patients with IBD (327 patients with CD, 265 with CU and 27 with unclassified colitis) with a 10-year follow-up period were included in the study. The mean age was 45 ± 14 years; 51% were women and 24% were smokers. The clinical and demographic data of the cohort of patients with IBD and EIM are listed in table 1 according to IBD type.

Frequencies, types and treatment of EIMs in the study population

Prevalence of EIMs in the study population was 16.5% (95% CI = 13.5-19.5, p < 0.05). One hundred and two patients suffered at least one EIM during the study period. One hundred and twenty-six EIMs were observed in 102 patients with IBD: 50 musculoskeletal, 50 cutaneous, 14 ocular, eight venous thromboembolic diseases and four hepatobiliary diseases. The different types of MEI observed are shown in table 2. Skin manifestations were more frequent in patients with CD (75%; 95% CI = 61.1-89.9%, p = 0.006) than in patients with CU (25%; 95% CI = 11, 1-39.0%, p = 0.006). However, there were no differences in joint or ocular manifestations depending on the type of IBD.

The drugs used to treat cases of arthropathies were NSAIDs (31%), corticosteroids (oral or intraarticular) (19%), methotrexate (10%), anti-tumor necrosis factor (anti-TNF) (10%) and sulfasalazine (10%). The majority of cutaneous manifestations were treated

with corticosteroids (83%) and occasionally with anti-TNF (2%). Ocular manifestations were treated with topical corticosteroids (69%) and anti-TNF (8%). Overall, the efficacy of the EIMs treatment was 90% and no significant differences were found depending on the type of disease (94.3% therapeutic efficacy in CD patients *vs* 87.3% in UC; p = 0.18). Thirteen per cent (95% CI: 5.8-19.7) of patients had an EIM recurrence and no differences were found with regard to IBD type (15.4% of recurrence of CD *vs* 7.3% for UC, p = 0.24).

Risk factors associated with the development of EIMs

A relationship between the presence of MEI and the type of IBD was observed in the univariate analysis: EIMs were more frequent in CD than in UC patients (29.3% *vs* 22%, p = 0.03). A relationship between gender and EIM was observed, being more frequent in women than in men (41.9% *vs* 20.7%, p = 0.012). In addition, patients that had undergone previous treatments with biological drugs, either infliximab or adalimumab (37.7% *vs* 23.1%, p = 0.03) or immunomodulators (31.0% *vs* 20.2%, p = 0.002) had a higher prevalence of EIMs than patients that had not undergone this type of therapy. Multivariate analysis showed that female gender was a risk factor for the development of EIMs (OR = 1.61, CI 95%: 1.11-2.34, p = 0.012). IBD severity was also associated with the development of MEI, therefore patients with more severe IBD who required immunosuppressive therapy (OR = 1.65, CI 95%: 1.13-2.4, p = 0.009) or combined therapy with immunosuppressant plus adalimumab (OR = 2.28, CI 95%: 1.09-4.78; p = 0.029) had a higher risk of MEI occurrence. On the other hand, IBD type and previous treatment with infliximab were not risk factors for the development of EIM (they did not reach the statistical significance in the univariate study). Similarly, no differences were found with regard to the location of the disease, smoking habits or previous perianal disease (data not shown).

DISCUSSION

The study showed that 16.5% of patients had at least one MEI. The prevalence of IBD-related EIMs varied according to geographic distribution, IBD type, location, duration of the disease, therapeutic management and early diagnosis (10). The prevalence

found in our study is lower than that found in other series. For instance, Vavricka et al. reported a prevalence of 29.3% of any EIM during the natural history of IBD in a Swiss cohort of 366 patients. However, other studies have reported an overall occurrence of at least one EIM between 6 and 47% (3). The large variability of EIM prevalence and incidence is likely due to the heterogeneous study populations, different case recruitment and the varying periods during which the studies were carried out. Some studies performed in our region also reported an overall prevalence higher than that observed in this study. Mendoza et al. reported at least one EIM in 46.6% of patients (10). However, these studies were performed around 10-15 years ago (all before 2004).

Thus, a plausible hypothesis that could explain these differences is the fact that our cohort is more recent. It should be highlighted that there were more diverse treatments available during this study which implied a better disease control and improved control of EIMs (for those manifestations associated with disease activity). Thus, other biological treatments including biosimilar infliximab have been accepted for the treatment of IBD between 2003 and 2013, with the exception of infliximab, which was approved in Europe in 1998. Another hypothesis that could explain the lower prevalence of EIMs in our study could be that fact that this study also included UC patients, unlike the study by Repiso et al., where only data from CD patients was collected. Finally, the number of patients included in our study was significantly higher than in the Repiso study (619 *vs* 157 patients) (4). Similarly, the lower prevalence found in our study may also be due to the fact that osteoporosis or non-alcoholic fatty liver diseases such as EIMs associated to IBD were not included.

We agree with other authors (3,7,11) that the most frequent EIMs are musculoskeletal and cutaneous. Prevalence depending on EIM type was: cutaneous-mucosa (40%), ocular (11.2%), venous thromboembolic disease (6.4%) and hepatobiliary disease (2.4%). This distribution was similar to previously published series (3,7,11), except that hepatobiliary manifestations were more frequent that thromboembolism in some studies. This is probably due to the fact that our study exclusively considered primary sclerosing cholangitis and autoimmune hepatitis as hepatobiliary manifestations (12), while other alterations of liver function were excluded as they were associated with

potentially hepatotoxic drugs (corticoids, methotrexate) or non-alcoholic fatty liver disease. Some studies define hepatobiliary disease as any alteration of liver function that persists longer than six months as well as a normal magnetic cholangioresonance imaging test (7). In this study, hepatobiliary manifestations were defined as those manifestations with consistent autoimmunity profile tests or radiologic findings. The recent European Crohn's and Colitis Organisation (ECCO) consensus for the EIM management (1) emphasizes that the prevalence of non-alcoholic fatty liver disease is between 1.5% and 55% for CU and between 1.5% and 39.5% for CD (the average prevalence is 23%). In addition to risk factors related to the metabolic syndrome, there are also IBD specific factors such as intra-abdominal abscesses, fistulizing disease, CU severity and malnutrition. Therefore, according to several studies (3,12-14), the occurrence of EIM is significantly higher in patients with CD than in patients with UC (43% *vs* 31%, respectively).

It is well-known that some EIMs are more frequently associated with one or another subtype of IBD. Along with these lines, Mendoza et al. (10) describe hepatobiliary manifestations, venous thromboembolic disease and arthralgias as more often associated with UC, whereas erythema nodosum and peripheral arthritis are usually linked to CD (7). The authors found differences when EIM was classified according to the affected organ or tissue but not when the overall frequency within CU was analyzed. In this study, no differences were observed between groups, except when sub-classified according to the type of EIM when a significantly higher occurrence of cutaneous EIMs *versus* the CU was observed.

EIMs varies according to the presence of inflammatory bowel activity. When associated with intestinal activity, the treatment is the same as that used for a flare-up. Whereas if intestinal activity is not involved, NSAIDs and corticoids treatment are often used and a wide range of therapeutic strategies are also available.

With regard to type I peripheral arthritis (linked to inflammatory bowel activity), experts report that symptoms disappear after eight to ten weeks of treatment. However, NSAIDs or selective cyclooxygenase 2 inhibitors can relieve symptoms earlier in 60% of patients. However, they must be used cautiously as intestinal activity could occur as previously described in up to 25% of cases, mainly during the first few days.

Brown et al. state that first-line treatment for type II peripheral arthritis (not associated with inflammatory bowel activity) should be sulfasalazine or, in the case of a non-response, methotrexate at a weekly dose of 7.5 mg with additional folic acid (8). When sulfazalazine and/or methotrexate are not effective, a biological therapy should be used. Kaufman et al. (15) demonstrated symptomatic relief in seven of eleven patients with refractory arthritis with a single infliximab dose of 5 mg per kg. Brown et al. (8) report that the management of axial arthropathy (independent of intestinal activity) is similar to axial arthropathy that is not associated with IBD, and recommend adequate physical activity and specific exercises that enhance backbone mobility. NSAIDs and/or local corticosteroids may cause immediate relief (with a risk of a flare-up) but systematic use is not recommended as symptomatic relief is transient and they do not modify the natural course of the disease. A 36 patients study with IBD and spondyloarthropathy (16) (24 patients treated with infliximab and 12 treated with steroids, azathioprine, antibiotics and/or salicylates) found that patients randomized to the infliximab arm had a quicker improvement and more sustained response in disease activity (quantified by the BASDAI index).

Another EIM frequently associated with IBD is erythema nodosum; the course of this disease is similar to intestinal activity. In mild cases, dermatologists recommend general measures (rest, lifting and compression of the affected limb) (17), and the use of systemic corticosteroids and immunosuppressant drugs (few series describe the need for infliximab or adalimumab to control this type of EIM) is only recommended in severe cases (18). A higher occurrence of cutaneous disorders associated with anti-TNF drugs has been observed with the increased use of biological drugs (used for luminal as well as for extraintestinal activity control) (19). In support of this observation, Guerra et al. observed a higher prevalence of anti-TNF-induced psoriasis in their case series (21 cases in 1,294 IBD patients under biological treatment), which was higher than the general population (20). NSAIDs and corticosteroids were used in our study for arthropathies and only steroids were used for cutaneous symptoms, with a very high overall efficacy and low rate of relapse.

There is limited data available on the potential risk factors associated with an increased likelihood of developing EIM throughout the natural history of IBD. Vavricka

et al. observed a higher occurrence of EIM in patients with an active CD and in those patients with a family history of IBD (14). There was no association between smoking and an increased risk of EIM occurrence. With regard to UC, there was an increased prevalence of EIM in patients previously treated with steroids and/or biological treatment which was lower in active smokers at the time of inclusion into the study. On the other hand, the appearance of one EIM is associated with an increased susceptibility of suffering another EIM (14,17).

In our cohort, we found that the female population (95% CI: 1.11-2.34; OR = 1.61, p = 0.012) and severe IBD (defined as the need for immunosuppressive or anti-TNF treatment) (p = 0.009, OR = 1.65, 95% CI 1.13-2.4 if immunosuppressant therapy alone, or p = 0.029, OR = 2.28, 95% CI 1.09-4.78 if in combination with adalimumab) were risk factors associated with a higher incidence of EIM. The Swiss group also observed increased therapeutic requirements; however, their regression model analysis did not include gender and, therefore, these data cannot be compared to our data.

Our study has some limitations, such as the fact that the data was collected retrospectively and the chronology of the EIM appearance has not been analyzed. On the other hand, the sample size is sufficiently representative to provide considerable consistency to our data. In addition, this is a unicentric study and patients have been evaluated by the same group of physicians. Thus, referral and management by other specialists has been performed in a homogeneous manner which provides strength to the results.

Thus, we can conclude that the most frequent EIM observed in Spain are the same as in other studies performed in different geographic areas. The most frequent are musculoskeletal and cutaneous manifestations. We can also conclude that females and patients with severe IBD (and a consequent greater therapeutic requirement) have a greater risk of developing EIM. In addition, we conclude that the individualized treatment of EIM is effective in most patients, with a low frequency of relapse.

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Table 1. Characteristics of the patients

	Crohn's disease	*Ulcerative colitis*	*Unclassified colitis*
n	327	265	27
Sex *- Female*	175	130	10
Age (years): mean ± SD	43 ± 13	48 ± 14	49 ± 15
Smoking *- Smoker*	120	27	3
IBD family history *- Yes*	54	41	2
*Extent of UC** *- Proctitis* *- Left-sided colitis* *- Pancolitis* *- Atypical*	---------	67 124 76 3	-------
*Age at EC diagnosis (years)** *- A1 (≤ 16)* *- A2 (17-40)* *- A3 (> 40)*	22 213 86	-------	-------
*Disease location of CD** *- L1 (terminal ileum)*	117	--------	--------

- L2 (colon) *- L3 (ileocolon)* *-L1 + L4 (upper GI location)* *- L2 + L4*	77 113 5 3		
*CD behavior** *-B1 (non-stricturing, non-penetrating)* *-B2 (stricturing)* *-B3 (penetrating)*	240 29 42	--------	--------

* Montreal phenotype classification.

Table 2. EIM type and frequency

EIM type	*Ulcerative colitis (n)*	*Crohn's disease (n)*	*Total (n)*
Musculoskeletal manifestations (40%)*	9 peripheral arthropathies 6 spondyloarthritis 2 axial arthropathies	17 peripheral arthropathies 9 spondyloarthritis 7 axial arthropathies	26 15 9
Skin disease (40%)*	7 erythema nodosum 3 aphtous stomatitis 2 pyoderma gangrenosum 1 Sweet syndrome 0 granulomatous dermatitis	21 erythema nodosum 11 aphtous stomatitis 4 pyoderma gangrenosum 0 Sweet syndrome 1 granulomatous dermatitis	28 14 6 1 1
Eye disease (11%)*	1 uveitis 2 episcleritis	6 uveitis 5 episcleritis	7 7
Thromboembolic disease (6%)*	3 venous thrombosis	1 venous thrombosis	4
Hepatobiliary disease (3%)*	2 primary sclerosing cholangitis 0 autoimmune hepatitis	1 sclerosing cholangitis 1 autoimmune hepatitis	3 1

*Percentages in relation to total EIM's number.