



Extraintestinal Manifestations in Patients with Inflammatory Bowel Disease: Study Based on the ENEIDA Registry

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Abstract

Background Patients with inflammatory bowel disease (IBD) may present extraintestinal manifestations (EIMs) that affect the joints, skin, eyes, and hepatobiliary area, among others.

Aims Our aim was to analyse the prevalence and characteristics of EIMs in patients with IBD and to identify the possible risk factors associated with the development of EIMs in the largest series published to date.

Methods Observational, cross-sectional study including patients from the Spanish ENEIDA registry promoted by GETECCU. We retrospectively identified all cases of EIMs in the ENEIDA registry until January 2018.

Results The study included 31,077 patients, 5779 of whom had at least one EIM (global prevalence 19%; 95% CI 18.2–19.0). Among the different types of EIMs, rheumatic manifestations had a prevalence of 13% (95% CI 12.9–13.7; 63% of EIMs), with a prevalence of 5% (95% CI 4.7–5.2) for mucocutaneous manifestations, 2.1% (95% CI 1.9–2.2) for ocular manifestations, and 0.7% (95% CI 0.6–0.8) for hepatobiliary manifestations. The multivariable analysis showed that the type of IBD (Crohn's disease, $p < 0.001$), gender (female, $p < 0.001$), the need for an immunomodulator ($p < 0.001$) or biologic drugs ($p < 0.001$), a previous family history of IBD ($p < 0.001$), and an extensive location of IBD ($p < 0.001$) were risk factors for the presence of EIMs.

Conclusions One-fifth of patients with IBD may have associated EIMs, with rheumatic manifestations as the most frequent (> 60% of EIMs). Female patients with severe Crohn's disease represent the group with the highest risk of developing EIMs. These patients should therefore be specially monitored and referred to the corresponding specialist when suggestive symptoms appear.

Keywords Inflammatory bowel disease · Rheumatic diseases · Skin manifestations · Eye manifestations · Sclerosing cholangitis

Introduction

Patients with inflammatory bowel disease (IBD)—which includes Crohn's disease (CD) and ulcerative colitis (UC)—may present extraintestinal manifestations (EIMs). EIMs have a negative impact on the patient's quality of life and can determine the treatment used to control IBD [1, 2]. EIMs most frequently involve the joints, skin, or eyes,

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although organs such as the liver, lungs, and pancreas can also be affected [3]. Certain EIMs are related to the activity of IBD, such as erythema nodosum or peripheral arthritis, while others—ankylosing spondylitis and uveitis, for example—have a course independent of IBD [3]. The reported prevalence of EIMs in patients with IBD is highly variable, ranging from 16 to 40% [4–6]. Additionally, a single patient may frequently have several EIMs (37%) [7]. Although its etiopathogenesis is not well known, the literature highlights that the presence of perianal CD, colon involvement, and smoking increase the risk of EIMs [8]. EIMs may also vary according to the geographical distribution, type, location, and time of progression of IBD [5, 9].

EIMs can be highly disabling for patients and may even penetrate further than the intestinal disease itself. A large series is therefore necessary to determine the true prevalence and characteristics of these manifestations in populations in our surroundings. To our knowledge, no data from large patient registries have been published to date.

The aims of the present study were: (1) to describe the prevalence and type of EIMs in patients with IBD and (2) to identify the risk factors associated with the development of EIMs.

Materials and Methods

Design

Retrospective, multicentre, cross-sectional study including patients from the Spanish ENEIDA registry (Estudio Nacional en Enfermedad Inflamatoria Intestinal sobre Determinantes Genéticos y Ambientales). The ENEIDA registry is a nationwide Spanish project that includes IBD patients promoted by GETECCU (Grupo Español de Trabajo de Enfermedad de Crohn y Colitis ulcerosa). The ENEIDA registry started including patients in October 2006. At the time the present study was conducted, the ENEIDA registry included 49,028 IBD cases from the 78 actively participating centres. The database is maintained prospectively and continuously monitored externally to ensure the completeness and the consistency of the data entered in the registry, but only local researchers can enter and modify the data.

Patients

The study included IBD patients registered in ENEIDA until January 2018. IBD was diagnosed according to the criteria of the “The European Crohn’s and Colitis Organisation” [10]. To ensure the robustness of the data, only the data from centres considered “good compilers”—defined as centres with $\geq 75\%$ of the patients with all variables completed—were analysed.

Definitions

The diagnosis of EIM was performed based on the standard diagnostic criteria of each of the entities and confirmed by the respective specialists.

Articular Manifestations

We included peripheral and axial arthropathies. Peripheral arthropathies were classified in type I and type II according to the number of joints involved. Type I (pauciarticular) was the one that affected fewer than five large joints, such as ankles, knees, hips, wrists, elbows, and shoulders (acute). Type II (polyarticular) symmetrical arthritis involved five or more small joints. Axial arthropathies encompassed ankylosing spondylitis and sacroiliitis. Ankylosing spondylitis required the presence of back pain and stiffness for > 3 months that did not improve with rest but did improve with exercise, or limitation of motion in both the sagittal and frontal planes, or limitation of chest wall expansion. Sacroiliitis was defined as inflammation of the sacroiliac joint, asymptomatic or painful.

The diagnosis/classification of articular arthropathies was clinical based on symptoms and/or radiologic (characterized by little or no joint destruction) and/or serologic tests with a negative rheumatoid factor. A rheumatologist confirmed the diagnoses in most cases.

Skin Manifestations

We considered reactive skin manifestations that do not share the same histopathologic findings as IBD, which included erythema nodosum, pyoderma gangrenosum, sweet syndrome, and stomatitis.

The diagnosis was most often clinical, and biopsy was required only in atypical cases. A dermatologist confirmed the diagnoses in most cases.

Ocular Manifestations

Ocular manifestations included uveitis and episcleritis. These entities were diagnosed based on symptoms, ocular examination, and complementary tests if they were necessary. As in the previous manifestations, an ophthalmologist confirmed the suspicious cases.

Hepatobiliary Manifestations

Primary sclerosing cholangitis diagnosis was determined following current international criteria with magnetic resonance cholangiography, endoscopic retrograde

cholangiopancreatography, and/or liver biopsy with characteristic findings of primary sclerosing cholangitis.

Variables of Interest

The main variable analysed was the presence of EIMs at any time during the progression of IBD. Additionally, epidemiologic characteristics including age at diagnosis, gender, smoking, characteristics of IBD such as location and behaviour in the case of CD, and extension in the case of UC, as well as required surgeries and treatments (immunomodulators and biologic drugs) at some point in the progression of IBD, were collected from each patient. The immunosuppressive therapies, which include the ENEIDA Registry, are thiopurines and methotrexate. Regarding biologic drugs, the database includes treatment with infliximab, adalimumab, certolizumab, golimumab, vedolizumab, and ustekinumab. In addition, in this database it is possible to obtain whether the main indication of an immunosuppressive or biologic treatment was the EIM. The ENEIDA registry specifies whether each patient has presented rheumatic, dermatologic, ophthalmologic, or hepatobiliary EIMs and the type of EIM: peripheral arthropathy, ankylosing spondylitis, sacroiliitis, erythema nodosum, pyoderma gangrenosum, other cutaneous manifestations, stomatitis, uveitis, episcleritis and primary sclerosing cholangitis, thrombosis and other manifestations. All these variables were also included in the analysis.

Statistical Analysis

Regarding the statistical analysis, the qualitative variables were presented using percentages and 95% confidence intervals. The Kolmogorov-Smirnov test was performed to evaluate the normality of the continuous variables. The quantitative variables were expressed using mean and standard deviation or median and interquartile range when the variable did not follow a normal distribution. We calculated the overall prevalence of EIMs and the independent prevalence of each different type of EIM (joint, cutaneous, ocular, and hepatobiliary) based on epidemiologic and clinical criteria.

In the bivariate study, categorical variables were compared using the chi-square test (χ^2), and the comparisons between quantitative and qualitative variables were performed using the Student's *t* test or the Mann–Whitney *U*-test if the variables did not follow a normal distribution. The multivariable analysis was performed to study which variables were associated with the presence of EIMs using a logistic regression model. The statistical tool that was used to conduct the analysis was the SPSS program.

Table 1 Demographic and clinical characteristics of the patients included in the study

	Patients with IBD and EIMs <i>N</i> = 5779	Patients with IBD and without EIMs <i>N</i> = 25,298	<i>p</i> value
Gender			
Female	3220 (55.8%)	11,646 (46.0%)	< 0.001
Age at IBD			
Age at IBD diagnosis (years)	34.2 ± 14.3	37.2 ± 16.3	< 0.001
IBD follow-up (years)	13.1 ± 9.6	9.7 ± 9.0	< 0.001
Type of IBD			
CD	3616 (64.0%)	11,770 (48.2%)	< 0.001
Location CD			
Ileal (L1)	989 (28.0%)	4375 (38.4%)	< 0.001
Colon (L2)	393 (11.1%)	1114 (9.8%)	
Ileocolon (L3)	1571 (44.6%)	4006 (35.2%)	
Upper GI (L4) + L1	248 (7.0%)	1134 (9.9%)	
L4 + L2	14 (0.4%)	34 (0.3%)	
L4 + L3	312 (8.9%)	726 (6.4%)	
Location UC			
Proctitis	212 (11.1%)	2612 (22.0%)	< 0.001
Left sided UC	686 (35.8%)	4668 (39.4%)	
Extensive UC	1020 (53.2%)	4563 (38.6%)	
Behaviour (CD)			
B1	2375 (60.1%)	7672 (60.8%)	> 0.05
B2	918 (23.2%)	2847 (22.6%)	
B3	661 (16.7%)	2096 (16.6%)	
Smoking			
Yes	1287 (30.1%)	4990 (26.2%)	< 0.001
Family history of IBD			
Yes	848 (16.0%)	2944 (12.7%)	< 0.001
IMM treatment ^a			
Yes	4026 (69.8%)	12,191 (48.3%)	< 0.001
Anti-TNF treatment ^a			
Yes	2671 (46.5%)	6220 (24.8%)	< 0.001
Surgery			
Yes	1885 (32.8%)	5621 (22.5%)	< 0.001

Bold values are statistically significant results with *p* value < 0.05

IBD inflammatory bowel disease, *CD* Crohn's disease, *UC* ulcerative colitis, *EIMs* extraintestinal manifestations, *CI* confidence interval, *IMM* immunomodulator, *anti-TNF* anti-tumour growth factor

^aAt some point in the progression of inflammatory bowel disease

Results

Prevalence of EIMs

Of the 49,028 patients registered in the database, 31,077 met the inclusion criteria and were ultimately included in the study (52% men, 49.5% CD). Of these patients, 5779 had at least one EIM, with a prevalence of 19% (95% CI

18.2–19.0). Table 1 shows the epidemiologic characteristics of the patients included based on the presence or absence of EIMs.

Overall, the presence of EIMs was more frequent in women than in men (21.7% vs. 15.7%, $p < 0.01$) and more frequent in patients with CD than in patients with UC (23.5% vs. 13.7%, $p < 0.01$). Ileocolic involvement in CD patients and extensive colitis in UC patients were more frequent in patients with EIMs than in patients without them (43.4% vs. 34.0% and 50.0% vs. 35.9%, respectively). The presence of EIMs was also more frequent in smokers at the time of the IBD diagnosis (20.5% vs. 17.1%, $p < 0.01$) and in patients with a family history of IBD (22.4% vs. 18.0%, $p < 0.01$). Moreover, patients who required immunosuppressive therapy (24.8% vs. 11.8%; $p < 0.01$), biologic treatment (30.4% vs. 14.0%; $p < 0.01$), or surgery (25.1% vs. 16.6%; $p < 0.01$) at some point in the progression of IBD had a higher risk of EIM.

These data were similar according to the different types of manifestations. Articular, cutaneous, and ocular manifestations were also more frequent in female (55.6% vs. 44.4%; 68.9% vs. 31.1%; 61.7% vs. 38.3%, respectively, $p < 0.01$ in the three analyses), CD patients (66.2% vs. 33.8%; 72.0% vs. 38.0%; 70.1% vs. 29.9%; respectively, $p < 0.01$ in the three analyses), CD patients with ileocolic involvement (43.7% vs. 38.3%; 50.3% vs. 39.5%; 49.7% vs. 40.8%; respectively, $p < 0.01$ in the three analyses), UC patients with extensive disease (49.9% vs. 43.2%; 60.5% vs. 47%; 46% vs. 38.8%, respectively, $p < 0.01$ in the three analyses), smokers (55.6% vs. 44.4%; 68.9% vs. 31.1%; 61.7% vs. 38.3%; respectively, $p < 0.01$ in the three analyses), and patients with a family history of IBD (15.8% vs. 12.7%; 17.8% vs. 12.5%, $p < 0.01$ only for articular and cutaneous manifestations).

On the contrary, hepatobiliary manifestations were more frequent in male (74% vs. 26%; $p < 0.001$) and UC patients (71% vs. 29%; $p < 0.001$). Most of the patients who developed sclerosing cholangitis had extensive colitis (82.9% vs. 46.9% in patients without this EIM; $p < 0.001$).

Regarding the number and type of EIMs, 6581 EIMs were diagnosed. Rheumatic manifestations were the most frequent (63.3% of the EIMs), followed by cutaneous manifestations (23.5%), ocular manifestations (9.7%), and hepatobiliary manifestations with (3.5%; Fig. 1).

The prevalence of each group of extraintestinal manifestations and the frequency of the different entities identified in each group are represented in Table 2.

Of the patients who developed EIMs, 889 (15.4%) presented two or more EIMs. The most frequent association was the presence of rheumatic and cutaneous manifestations (566 patients) and, in particular, the presence of peripheral arthropathy and erythema nodosum together (286 cases).

Risk Factors for EIM

In the multivariable analysis, we found that the type of IBD (CD, $p < 0.001$, OR 1.36, 95% CI 1.3–1.5), the gender (female, $p < 0.001$, OR 1.57, 95% CI 1.5–1.7), the need for an immunomodulator ($p < 0.001$ OR 1.48, 95% CI 1.4–1.6), biologic drugs ($p < 0.001$, OR 1.8, 95% CI 1.7–2.0), the presence of a family history of IBD ($p = 0.17$ OR 1.13, 95% CI 1.0–1.2), time of follow-up (> 5 years; $p < 0.001$, OR 1.74, 95% CI 1.6–1.9), ileocolic involvement in CD patients ($p < 0.001$, OR 1.40, 95% CI 1.3–1.5), and extensive location in UC patients ($p < 0.001$, OR 1.46, 95% CI 1.3–1.6) were significant.

Fig. 1 Type of extraintestinal manifestations observed in our series

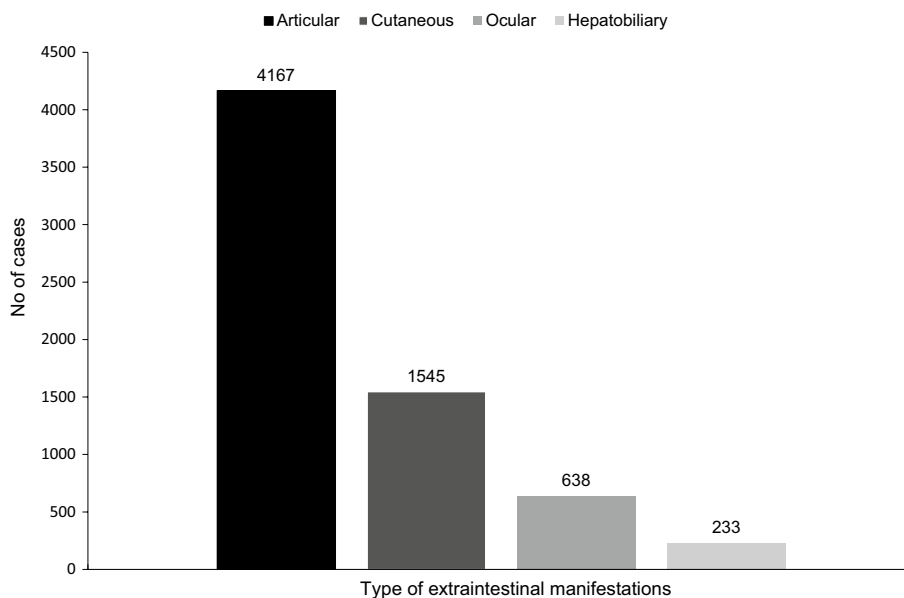


Table 2 Prevalence of each extraintestinal manifestation group and the frequency of the different entities in each group

Type of EIM (N) Prevalence (95% CI)	Entities (N) Prevalence (% from the total of EIM in each group)
Articular (4165) 13% (12.9–13.7)	Peripheral arthritis (2683)
	8.6% (64.4%)
	Type I (1647)
	Type II (598)
	Not specified (438)
Cutaneous (1545) 5% (4.7–5.2)	Ankylosing spondylitis (822)
	4.8% (19.7%)
	Sacroilitis (660)
	2.1% (15.8%)
	Erythaema nodosum (919)
Ocular (638) 2.1% (1.9–2.2)	2.9% (59.5%)
	Pyoderma gangrenosum (269)
	0.9% (17.4%)
	Others: stomatitis. Sweet syndrome (394)
	1.3% (25.5%)
Hepatobiliary (233) 0.75% (0.6–0.8)	Uveitis (252)
	0.8% (39.5%)
	Episcleritis (236)
	0.8% (37.0%)
	Others: unspecified (150)
	0.5% (23.5%)
	233 sclerosing cholangitis
	0.7% (100%)

EIM extraintestinal manifestation, CI confidence interval

The multivariable analysis with the specific type of EIM (articular, cutaneous, ocular, and hepatobiliary manifestations) is represented in Table 3.

Regarding the demographic characteristics of the patients included according to the number of extraintestinal manifestations diagnosed, we found that female ($p < 0.01$; OR 1.9, 95% CI 1.6–2.2), CD patients ($p < 0.01$; OR 14.4, 95% CI 11.8–17.6), and smokers ($p < 0.01$; OR 2.0, 95% CI 0.9–1.4) were more likely to develop multiple EIMs.

Treatment of EIMs

Of the 5779 patients who developed an EIM, 380 received immunosuppressive treatment exclusively for the treatment of the EIM (6.6%, 95% CI 5.9–7.2), 221 patients for joint manifestations (58.1%), 64 for cutaneous manifestations (16.8%), 38 for ocular manifestations (10%), and 13 for sclerosing cholangitis (3.4%). Of these patients, 447 received biologic treatment for the EIM (7.7%, 95% CI 7.0–8.4), 312 received treatment for joint manifestations (69.8%), 82 for cutaneous manifestations (18.3%), 50 for ocular manifestations (11.2%), and 3 for sclerosing cholangitis (0.7%).

Discussion

EIMs had an overall prevalence of 19% in our large series (31,077 patients with IBD). The data published to date in this regard vary widely according to the design, number of patients, and geographical location with values that range between 6 and 40% [4, 9, 11–22]. Therefore, in spite of the retrospective nature of the data collection (in a registry updated prospectively), the large amount of data ensures that

Table 3 Factors associated with the development of specific type of extraintestinal manifestations: multivariable analysis

Type of EIM OR (95% CI)	Articular	Cutaneous	Ocular	Hepatobiliary
Age of diagnosis	1.2 (1.1–1.4) (> 40 years)	1.3 (1.1–1.5) (< 40 years)	NS	1.6 (1.2–2.2) (< 40 years)
Gender (female) ^a	1.4 (1.2–1.5)	2.4 (2.1–2.8)	1.5 (1.3–1.8)	2.2 (1.6–3.0)
Type of IBD (CD) ^a	1.5 (1.4–1.7)	1.4 (1.3–1.6)	1.6 (1.3–1.9)	3.5 (2.6–4.7)
Need for IMM ^b	1.3 (1.2–1.5)	2.1 (1.8–2.5)	NS	NS
Need for anti-TNF ^b	2.2 (2.0–2.4)	1.4 (1.3–1.7)	1.5 (1.3–1.8)	NS
Surgery ^b	1.3 (1.2–1.4)	NS	NS	NS
Tobacco at diagnosis	1.2 (1.1–1.3)	NS	NS	NS
Family history of IBD	1.2 (1.0–1.3)	1.3 (1.1–1.5)	NS	NS
Ileocolic involvement (CD)	1.2 (1.1–1.3)	1.5 (1.2–1.7)	1.4 (1.1–1.7)	NS
Extensive UC	NS	1.4 (1.1–1.8)	NS	5.3 (3.2–8.6)

EIM extraintestinal manifestation, OR odds ratio, IBD inflammatory bowel disease, CI confidence interval, CD Crohn's disease, IMM immunomodulator, anti-TNF anti-tumour growth factor, NS not significant, UC ulcerative colitis

^aThe results for hepatobiliary manifestations refer to male gender and ulcerative colitis as type of inflammatory bowel disease

^bAt some point in the progression of inflammatory bowel disease

the results are sound. Our results are found in the intermediate range of the prevalence of EIMs included in the previously published data.

Rheumatic manifestations were the most frequent EIMs identified in this work, which coincides with previous series. Among them, peripheral arthritis was the major joint EIM (63.3% of joint manifestations), which also can be found in other publications [20, 23]. The overall prevalence of rheumatic manifestations was 13%. The data published in this aspect vary depending on the country in which the work was carried out and the methodology used, varying between 4.4 and 28% [24–30]. Some series have even published that the prevalence of peripheral arthritis may reach up to 40%, although these series controversially include arthralgias in this category of EIM [3]. In fact, in the work by Ditisheim et al. [31], in which 44% of the patients presented joint manifestations, only 29% of the patients had been evaluated by a rheumatologist. The ENEIDA registry only considers peripheral arthropathies confirmed by a rheumatologist (no arthralgias), and this fact explains the difference between the figures for the prevalence found in other works and ours.

Concerning axial arthropathies, the recently published meta-analysis by Karreman et al. included 71 studies and found a 3% prevalence of ankylosing spondylitis and a 10% prevalence of sacroiliitis, while the prospective study by Ibsen found a prevalence of 7.7% for axial spondyloarthritis and 4.5% for ankylosing spondylitis [32, 33]. The ankylosing spondylitis data are in line with our results and present higher prevalence than those previously described, probably because of better knowledge and diagnostic techniques at present. However, in our series the percentage of sacroiliitis was lower than had been previously described. This result may be because many cases of sacroiliitis are asymptomatic and it is difficult to assess this phenomenon unless a radiologic study (generally magnetic resonance imaging) is performed to confirm the diagnosis or unless the study is aimed at obtaining explicit knowledge of joint pathology. Due to the high number of patients included in our study, it was not possible to request additional information from the researchers. It is therefore possible that patients with asymptomatic sacroiliitis are underrepresented.

Furthermore, in concordance with our results, other studies have published that joint manifestations are more common in patients with CD than in patients with UC [34]. Regarding gender, our study showed that both peripheral and axial joint manifestations were more frequent in women. Other studies have shown that women more frequently developed manifestations with peripheral involvement while men tended to have more axial involvement [26].

Regarding cutaneous manifestations, it has been reported that these manifestations can be present in up to 15% of patients and the majority are diagnosed during the clinical progression of IBD [20, 35]. Our series only included

reactive manifestations (manifestations with different histopathologic findings than IBD), and we found that more than half of the cases were erythema nodosum (59.5% of cutaneous manifestations), followed by pyoderma gangrenosum. These manifestations, like the previous ones, were more frequent in women than in men and more frequent in patients with CD than in patients with UC. Other studies in line with ours have described that erythema nodosum (3–12.9%) is more frequent in patients with CD than in those with UC, while it is slightly more frequent in women and may appear associated with joint manifestations [4, 36, 37]. Coinciding with our data, it has been reported that pyoderma gangrenosum is less frequent than erythema nodosum (1–3%) [37]. However, there is no agreement about its prevalence in different inflammatory entities, although the most recent studies find that it is more frequent in patients with CD than in patients with UC [37, 38].

Ocular manifestations are also associated with IBD, such as episcleritis or uveitis, which are observed in varying percentages (0.3–13%). These manifestations are somewhat more common in CD [39–43]. In our study, as with the previous manifestations, its prevalence was higher in women and in patients with CD. Uveitis and episcleritis exhibited quite similar frequencies, although the frequency was slightly higher for the former, unlike what was previously described. This may be because episcleritis is a benign condition, one that usually progresses better than uveitis and sometimes does not require treatment. Patients suffering from episcleritis may not consult a specialist, and there would therefore be no definitive diagnosis of the manifestation.

Finally, primary sclerosing cholangitis is the most common type of hepatobiliary manifestation. The literature reports that it is observed more frequently in UC, and it can sometimes be diagnosed years apart from IBD [44–46]. Our group has recently published a study that describes that sclerosing cholangitis, although rare (with an incidence of 61.2 cases per 100,000 patients/year), should be suspected in the case of elevated alkaline phosphatase values and when properly diagnosed using colangio-resonance. This requires regular radiologic reviews and colonoscopies for the risk of cancer [47]. In the present study we found 233 cases of sclerosing cholangitis, which implied a prevalence of 0.75% (95% CI 0.6–0.8%). Contrary to what happens with other EIMs, this manifestation was more frequent in males and in patients with UC, which falls in line with what has been described previously.

The pathogenesis of EIMs remains unknown. It is not known if EIMs are a direct result of the inflammatory process that occurs in the gastrointestinal tract or are due more to a genetic alteration that leads to a dysfunction of the immune system against environmental stimulation [7]. In the present study, as we have previously mentioned, we found that different epidemiologic characteristics such as age at

diagnosis of intestinal disease, the type and location of IBD, and gender were risk factors for the development of EIMs. In this way, female patients with CD and ileocolic involvement were more predisposed to suffer from rheumatic, cutaneous, and ocular manifestations. On the other hand, male patients with extensive UC diagnosed before 40 years were more likely to develop hepatobiliary manifestations. Also, patients with a family history of IBD had a higher risk of suffering an EIM, highlighting the importance of genetic factors in how EIMs develop. Furthermore, patients who at some point required immunosuppressant or biologic drugs to control IBD, that is, patients with a more aggressive disease behaviour also had a higher risk for the presence of EIMs.

Our study had several limitations. First, it should be considered that the ENEIDA registry does not include the date that the EIMs appear or data concerning the treatment of the EIMs, except in the cases in which a biologic or immunomodulator drug was expressly prescribed for that indication. Therefore, we cannot know the efficacy of the different treatments, and this was not included as an objective of the study. Furthermore, we cannot describe the appearance of EIMs prior to the diagnosis of IBD or the chronology of the EIMs in patients with multiple manifestations. It is also likely that the prevalence of some manifestations may be underrepresented simply because of the lack of completion by the researchers. In addition, the multicentric nature of the study means that the diagnoses of the EIMs were made by different physicians who use a wide range of diagnostic criteria. Finally, we cannot specify the locations of the EIMs, which may be of interest in the case of peripheral arthritis and cutaneous manifestations. However, our series has a very large number of patients, greater than any series published to date, and it also provides new data about the real prevalence of EIMs as well as the characteristics of the patients that are most likely to suffer them in our facilities and at centres with different levels, not just reference centres.

In conclusion, more than one-fifth of patients with IBD may have associated EIMs, with joint manifestations being the most frequent, so a proactive clinical follow-up would be advisable. Female patients with CD and patients with a more severe and extensive IBD are at a greater risk for EIMs. These patients should be therefore specially monitored and referred to the corresponding specialist when suggestive symptoms appear.

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Compliance with Ethical Standards

Ethical approval This study was approved by the ENEIDA Committee and by the Ethics Committee of the Hospital Universitario de Fuenlabrada. The ENEIDA project was approved by the ethics committees of each participating hospital. Informed consent was obtained in writing from each patient.

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