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Prevalence of and Factors Associated With Extraintestinal Manifestations and Their Remission in Inflammatory Bowel Disease: The EXTRA-Intestinal Manifestation Prospective Study From the Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif

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INTRODUCTION: Extraintestinal manifestations (EIMs) of inflammatory bowel disease (IBD) are challenging clinical situation. No prospective study assessed remission risk factors of EIMs. The aim of this study was to prospectively investigate the epidemiology, risk factors of EIM occurrence, and EIM remission in a large IBD cohort.

METHODS: We conducted a cross-sectional study in 30 French referral centers. Between May 2021 and June 2021, all consecutive patients attending to hospital appointment were systematically invited to fill out a questionnaire.

RESULTS: A total of 1,971 consecutive patients with IBD were analyzed. There were 1,056 women (53.8%), and the median age of patients was 41 years (31–54). The median disease duration was 11 years (1–18). Overall, 544 (27.6%) had at least 1 EIM. In 20.2% of cases, patients had multiple EIMs. The most frequent EIMs were rheumatological (19%) and dermatological (10%) manifestations. Immunosuppressant treatment (odds ratio [OR] = 2.56; $P < 0.001$) was a risk factor of EIM, while the Montreal A3 classification (OR = 0.61, $P = 0.023$) and male gender (OR = 0.61, $P < 0.001$) were associated with a lower risk of EIM occurrence. IBD current clinical remission (OR = 2.42; $P < 0.001$) and smoking cessation (OR = 2.98; $P < 0.001$) were associated factors of EIM remission. Conversely, age at IBD diagnosis (OR = 0.98; $P < 0.018$) was associated with a lower risk of EIM remission.

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DISCUSSION: One quarter of patients had at least 1 EIM. Beyond factors associated with the presence of EIMs, patients with IBD current clinical remission and smoking cessation are more likely to achieve EIM remission, while increasing age at IBD diagnosis is associated with decreased chance of remission.

KEYWORDS: inflammatory bowel disease; extraintestinal manifestation; risk factor; epidemiology

SUPPLEMENTARY MATERIAL accompanies this paper at <http://links.lww.com/CTG/A985>, <http://links.lww.com/CTG/A986>, <http://links.lww.com/CTG/A987>

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INTRODUCTION

Inflammatory bowel disease (IBD), encompassing ulcerative colitis (UC) and Crohn's disease (CD), are chronic diseases with a relapsing and remitting course (1,2). Although the most frequent IBD symptoms involve the gut tract, a broad variety of extraintestinal manifestations (EIMs) can be observed: articular (axial and peripheral spondyloarthritis, arthralgia), ocular (uveitis, scleritis), cutaneous (pyoderma gangrenosum, erythema nodosum, Sweet syndrome), hepatopancreatobiliary (primary sclerosing cholangitis, hepatitis, pancreatitis), and other associated immune-mediated inflammatory diseases (psoriasis, psoriatic arthritis) (3,4). Depending on the definition, the prevalence of EIMs ranges from 19% to 40% in patients with IBD (5–8). These manifestations have relevant consequences on patients' quality of life (9).

EIMs are challenging clinical situation and require a complex and multidisciplinary management (3). Recently, the International Organization for the Study of Inflammatory Bowel Diseases and US specialist gastroenterologists conducted expert consensus to homogenize practice and provide clinical guidance (10,11). While the prevalence of EIM is well known in patients with IBD, data on predictive factors for their occurrence are scarce. Active disease, use of biologics or immunosuppressant, female gender, family history of IBD, ileocolonic CD, and extensive UC were found as risk factors in 2 studies (5,8). Only 1 study has prospectively assessed these factors in a cohort of 950 patients with IBD (5). In the literature, risk factors of EIM remission not yet been studied are lacking in the management of patients.

Hence, we assessed the prevalence and risk factors of both EIM occurrence and remission in a large nationwide cross-sectional study of patients with IBD followed up in Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID) centers.

METHODS

Study design and study population

We conducted a cross-sectional study in 30 French referral IBD centers affiliated to the GETAID during 3 weeks between May 2021 and June 2021. All consecutive patients attending a consultation or an outpatient hospital appointment (for intravenous biologic treatment), who are older than 18 years with a confirmed diagnosis of IBD for at least 3 months and able to receive information, were systematically invited to fill out the "EXTRA-intestinal manifestation" (EXTRA) questionnaire (see Supplementary Document, <http://links.lww.com/CTG/A985>) with their gastroenterologist. Included patients from outpatient hospital appointment for biologic infusion should not exceed

50% of all participants to reduce the risk of bias related to the inclusion of only severe patients.

The study was conducted in accordance with the ethical principles and French regulatory agency requirements. For such study, patients' information and ethical committee submission were not mandatory.

Data collection

The questionnaire first investigated information about patients' characteristics (age, sex, height, weight, and smoking status), disease characteristics (date of diagnosis, location, ongoing treatment(s), and history of surgery), and disease activity (Harvey-Bradshaw index for CD and partial Mayo score for UC). The second part of the questionnaire was about the presence of an EIM(s). In case of EIM(s), the questionnaire asked about the type of EIM, date of diagnosis, remission status, ongoing specific treatment(s), use of comotherapy or combination of targeted therapies), and the impact on IBD treatment management. Patients completed the questionnaire in the waiting room and then with their gastroenterologist during the consultation for misunderstood items. After their completion, questionnaires were returned to the head office of the GETAID.

Statistical analysis

Descriptive statistics were used to describe the demographics and clinical characteristics of patients at baseline. Continuous variables were displayed as mean and SD or median and interquartile range according to data distribution. Discrete variables were expressed as percentages. The proportion of patients who developed an EIM after an IBD diagnosis was calculated. Logistic regression was used to identify the factors associated with (i) the development of EIM in patients with IBD and (ii) EIM remission. Only subjects whose dates of EIM came after the date of their IBD diagnosis were included in the analysis to account for the temporal sequence of events and to avoid biasing the analyses. Potential variables were identified using a univariate analysis with a *P* value cutoff of less than 0.2. All covariates whose *P* values were less than 0.2 from the univariate analysis were selected to be included in a multivariate model. A *P* value below 0.05 was considered statistically significant. R version 4.1.2 was used to perform the statistical analysis.

RESULTS

Patients' characteristics and treatments

A total of 2005 consecutive patients with IBD were included in the EXTRA study. Among them, 1971 questionnaires were analyzed. The median number of included patients per center was 60.5 (59.25–66). Table 1 summarizes the main characteristics of the study population. There were 1,056 women (53.8%), and the

Table 1. Patient characteristics

	N	%/median	Q1	Q3
Total	1,971			
Gender	1,056	53.8		
Female				
Median age (yr)	1,971	41	31	54
Smoking				
Current	312	15.8		
Former	443	22.5		
Never	1,040	52.8		
Missing	176	8.9		
IBD type				
CD	1,113	56.5		
UC	854	43.3		
IBD-U	4	0.2		
Montreal A				
A1: ≤16 yr	198	10		
A2: 17–39 yr	1,240	62.9		
A3: ≥40 yr	492	25		
Montreal L				
L1 (ileitis)	333	29.9		
L2 (colitis)	243	21.8		
L3 (ileocolitis)	478	42.9		
L4 (upper disease)	96	8.6		
Montreal B				
B1 (nonstricturing and nonpenetrating)	473	42.5		
B2 (stricturing)	294	26.4		
B3 (penetrating)	218	19.6		
Anoperineal lesion	223	20		
Montreal E				
E1 (proctitis)	140	16.4		
E2 (left-sided colitis)	280	32.8		
E3 (pancolitis)	413	48.4		
Median disease duration (yr)	1,971	11	1	18
Disease activity				
Harvey-Bradshaw index	1,113	1	0	3
Partial Mayo score	854	0	0	2
History of surgery	441	22.4		

CD, Crohn's disease; IBD, inflammatory bowel disease; IBD-U, unclassified IBD; N, number; Q, quartile; UC, ulcerative colitis; 5-ASA, 5-aminosalicylic.

median age of patients was 41 years (31–54). The median disease duration was 11 years (1–18). There were 1,113 patients with CD (56.5%) and 854 with UC (43.3%). Regarding disease activity, 70.5% of patients were in clinical remission, and 22.4% have a history of surgery.

Table 2. Treatment exposure

	N	%
5-ASA		
Oral	254	12.9
Suppository	113	5.7
Steroids		
Budesonide	0	0
Suppository	0	0
Systematic	2	0.1
Advanced therapies		
Infliximab	735	37.3
Adalimumab	256	13
Golimumab	47	2.4
Certolizumab	2	0.1
Ustekinumab	169	8.6
Vedolizumab	334	16.9
Tofacitinib	44	2.2
Other JAK inhibitors	9	0.5
S1P1 modulators	2	0.1
Other	1	0.06
Immunosuppressants		
Methotrexate	84	4.3
Azathioprine/6-mercaptopurine	332	16.8

EIM, extraintestinal manifestation; IBD, inflammatory bowel disease; 5-ASA, 5-aminosalicylic acid.

The ongoing treatment at inclusion is summarized in Table 2. The 4 most used drugs during the study were infliximab (37.3%), vedolizumab (16.9%), adalimumab (13%), and oral 5-aminosalicylic acid (12.9%). Immunosuppressants (methotrexate or thiopurine) were used in 21.1% of patients.

Prevalence of extraintestinal manifestations

Overall, 544 patients (27.6%) had at least 1 EIM. EIMs were identified in 30.3% patients with CD (337/1,113) and 24.2% in UC (207/854). In 20.2% of cases (110/544), patients had multiple EIMs. The first EIM was diagnosed after IBD in 80.2%, before IBD in 17.8%, and at the same time in 2.0%. For 339 patients (62.3%), EIM was in clinical remission. The most frequent EIMs were rheumatological (19%, 374/1,971) and dermatological (10%, 196/1,971) manifestations (Figure 1). Hepatopancreatobiliary and ophthalmological EIMs represented 3.6% (71/1,971) and 3.4% (67/1,971) of the patients in the cohort, respectively. Finally, other EIMs were reported in 0.8% (15/1,971) of the cases. Table 3 summarizes the distribution of EIMs in the cohort.

A dedicated follow-up of EIM(s) by a referral specialist (e.g., rheumatologist, dermatologist, ophthalmologist) was recorded for 68% of patients. The use of at least 1 combination therapy with an immunosuppressant during the EIM course was reported in 85.1% of patients. The use of at least 1 combination therapy (combination of 2 advanced therapies) was reported in 9% of cases. For 277 patients (50.9%), a dedicated treatment for the EIM was

Table 3. Extraintestinal manifestation distribution

	N	%
Rheumatological manifestations		
Arthritis/arthralgia (peripheral disease)	192	9.7
Axial spondyloarthritis	171	8.7
Psoriatic arthritis	11	0.6
Dermatological manifestations		
Erythema nodosum	41	2.1
Pyoderma gangrenosum	15	0.8
Verneuil disease	29	1.5
Psoriasis	65	3.3
Aphthous stomatitis	38	1.9
Eczematous eruption	4	0.2
Orofacial granulomatosis	4	0.2
Ophthalmological manifestations		
Uveitis	46	2.3
Scleritis	16	0.8
Keratitis	4	0.2
Blepharitis	1	0.05
Hepatopancreatobiliary manifestations		
Primary sclerosing cholangitis	59	3
Autoimmune hepatitis	8	0.4
Autoimmune pancreatitis	4	0.2
Other manifestations		
BOOP	5	0.3
IgA nephropathy	4	0.2
Urinary lithiasis	2	0.1
Pericarditis	1	0.1
Deep vein thrombosis	1	0.1
Interstitial nephropathy	2	0.1

BOOP, bronchiolitis obliterans organizing pneumonia; IgA, immunoglobulin A.

introduced. These were mainly advanced therapies, immunosuppressants, topical or oral steroids, ursodeoxycholic acid, antibiotics, or dermatological topical therapies. In 31.3% of cases (170/544), the IBD treatment was influenced by the EIM, and for 14.5% of patients (79/544), the IBD treatment was stopped or modified because of the EIM.

Risk factors of extraintestinal manifestation and their remission

In the univariate analysis (see Supplementary Table 1, <http://links.lww.com/CTG/A986>), the covariates age at IBD diagnosis, gender, smoking status, IBD type, advanced therapies, antitumor necrosis factor, immunosuppressant treatment, and 5-aminosalicylic acid treatment were selected to be included in the multivariate model. In the multivariate analysis, immunosuppressant treatment (odds ratio [OR] = 2.56, 95% confidence interval [CI] 1.60–4.04; $P < 0.001$) was positively associated with EIM development, while the Montreal A3 classification (OR = 0.61, 95% CI 0.40–0.94; $P = 0.023$) and

male gender (OR = 0.61, 95% CI 0.48–0.78; $P < 0.001$) were associated with a lower risk of EIM occurrence (Table 4).

Regarding the factors associated with EIM remission, the univariate analysis identified the following covariates to be included in the multivariable model: age at IBD diagnosis, smoking cessation, advanced therapies, and IBD current clinical remission. In the multivariate analysis, 2 covariates were found to be positively associated with EIM remission: IBD current clinical remission (OR = 2.42, 95% CI 1.58–3.71; $P < 0.001$) and smoking cessation (OR = 2.98, 95% CI 1.61–5.63; $P < 0.001$) (Table 5). Conversely, age at IBD diagnosis (OR = 0.98, 95% CI 0.97–1.00; $P < 0.018$) was associated with a lower risk of EIM remission. Finally, a positive effect on EIM remission was identified for advanced therapies (OR = 1.49, 95% CI 0.91–2.41; $P < 0.11$).

DISCUSSION

Our work evaluated for the first-time risk factors of EIM occurrence and remission in a large cross-sectional study of 2005 consecutive patients with IBD. The EXTRA study showed that EIMs were more common in patients with CD (30.3%) than in those with UC (24.2%) and more frequent in female individuals. These data are in line with the previous epidemiological study on EIMs published in the literature (6,8,12,13). Vavricka et al (12) showed that 25% patients manifested the first EIM before IBD diagnosis, with a median time of 5 months before IBD diagnosis, and 75% of patients manifested the first EIM after IBD diagnosis. Our study reported similar findings about timing of EIM occurrence regarding IBD: 17.8% were reported before IBD diagnosis, 80.2% after, and 2.0% at the same time. Concerning the EIM epidemiology, the EXTRA study found that rheumatological EIMs, dermatological EIMs, ophthalmological EIMs, and primary sclerosing cholangitis were the more frequent manifestations encountered by patients. Previous epidemiological work on the topic has shown similar results about the distribution of the main EIMs in patients with IBD (3,4,6,8,14). Of note, regarding peripheral rheumatological diseases, no difference was made on the objective signs of inflammation between arthralgia and arthritis. For less common manifestations, such as autoimmune hepatitis or pancreatitis, nephropathy, or bronchiolitis obliterans organizing pneumonia, it is tough to make comparisons because exact prevalences are unknown. However, the order of magnitude is similar to few published data (3,4,14).

The EXTRA study found immunosuppressant therapy as a risk factor of developing EIMs, while the Montreal A3 classification and the male gender were at lower risk of EIM occurrence. In a retrospective study of 31,077 patients with IBD, Algaba et al (8) also found that female gender and immunosuppressant medication were risk factors of EIM presence. In addition, they reported that CD, biologic treatment, family history of IBD, ileocolonic CD, and extensive UC as risk factors for EIMs (8). Our work has not shown that type of IBD or advanced therapies were associated with EIM presence. Although our prospective cohort was large, it has certainly lack of power to demonstrate these associations. Similarly, we did not show association with EIM occurrence and history of resection, antitumor necrosis factor, and 5-aminosalicylic acid. Our study did not analyze association with disease location or extension and with family history of IBD. In a shortest prospective study of 950 patients with IBD, Vavricka et al (5) reported that active disease in CD and family history were associated with developing EIMs. Similarly, our study found that IBD current clinical remission was a strong risk factor of EIM remission (OR = 2.42; $P < 0.001$). The EXTRA study has also

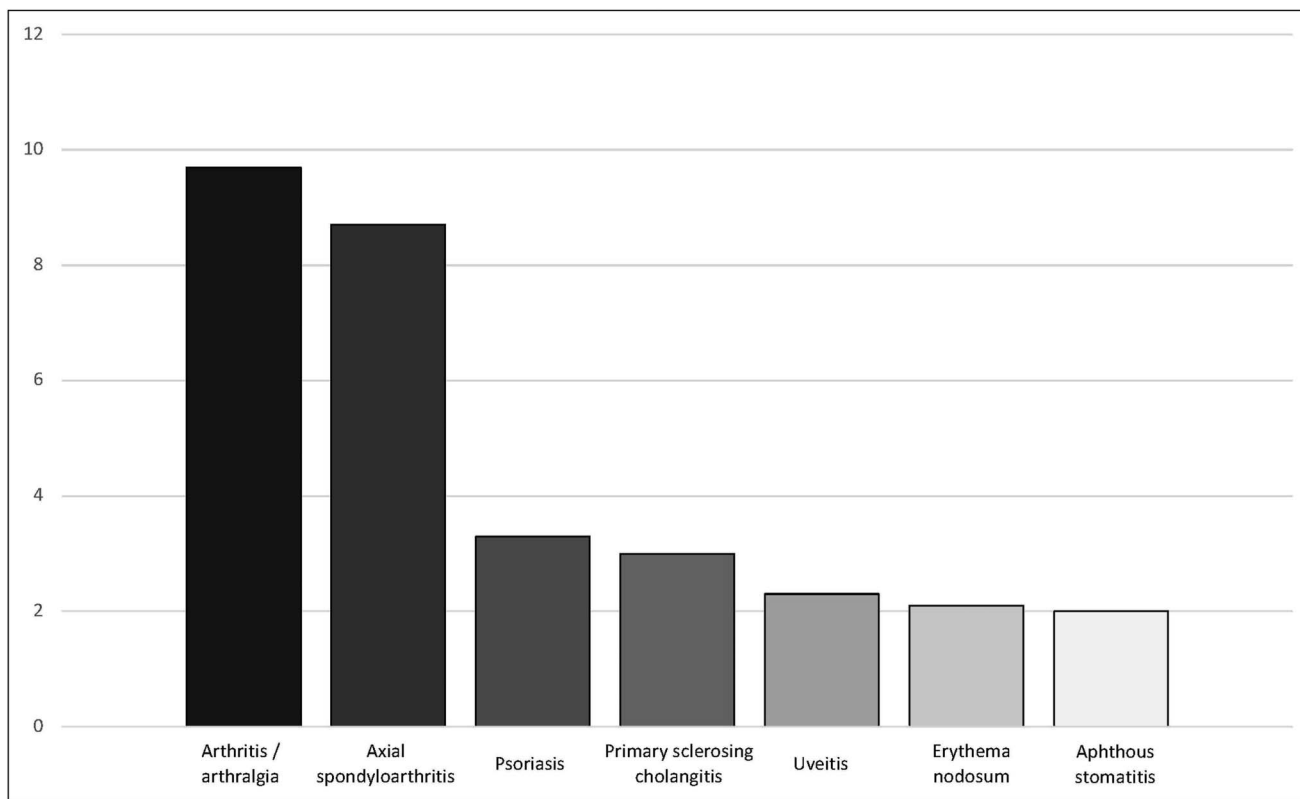


Figure 1. Main EIMs of the cohort. Percentage of the most common EIMs of the EXTRA cohort. EIMs, extraintestinal manifestations.

shown a strong association with smoking cessation and EIM remission (OR = 2.98; $P < 0.001$), while age at IBD diagnosis was associated with lower chance of remission (OR = 0.98; $P < 0.018$). Regarding risk factors of EIM remission, no comparative data are available in the literature. It seems that decrease of inflammation triggers, such as smoking and disease activity, are associated with the EIM remission. In the same way, we reported that advanced therapies seem also have a positive effect on EIM remission (OR = 1.49, 0.91–2.41; $P < 0.11$).

Our study assessed for the first time both risk factors of EIM occurrence and EIM remission. This cross-sectional study was conducted in a large IBD population (the sample represents approximately 1% of the general population of patients with IBD in France) and in a multicenter cohort. The EXTRA study reported detailed information regarding IBD medications, disease activity, and wide prevalence of a wide panel of EIMs. Last, the EXTRA study is the largest prospective cohort on the topic of EIM in the literature. The main limitation was the enrollment of patients

Table 4. Factors associated with extraintestinal manifestation occurrence (multivariate analysis)

Characteristic	OR	95% CI	P value
Age at IBD diagnosis			
≤16			
17–39	0.79	0.55–1.15	0.20
≥40	0.61	0.40–0.94	0.023
Gender			
Female			
Male	0.61	0.48–0.78	<0.001
Smoking			
Current			
Former	1.06	0.75–1.51	0.70
Never	0.79	0.58–1.08	0.14
IBD type			

Table 4. (continued)

Characteristic	OR	95% CI	P value
CD			
UC	1.03	0.79–1.33	0.80
Advanced therapies			
No			
Yes	1.11	0.82–1.52	0.50
Anti-TNF			
No			
Yes	1.18	0.90–1.54	0.20
Immunosuppressant treatment			
No			
Yes	2.56	1.60–4.04	<0.001
5-ASA treatment			
No			
Yes	0.80	0.54–1.17	0.30

CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; OR, odd ratio; Anti-TNF, Antitumor necrosis factor; UC, ulcerative colitis; 5-ASA, 5-aminosalicylic acid.

from tertiary referral centers, which could induce bias due to a higher proportion of severe patients. Proportions of EIMs that typically track with bowel inflammation and those that typically not were not explored in our study. In addition, there were some missing data because few questionnaires were not fully completed and had possible memory and reporting bias. Finally, data on objective inflammatory makers such as fecal calprotectin or endoscopy were lacking.

In conclusion, one quarter of patients had at least 1 EIM, and the diagnosis was made after IBD in 4 of 5 patients. Immunosuppressant treatment was a risk factor of EIM, while the Montreal A3 classification and male gender were associated with a lower risk of EIM occurrence. Patients with IBD in current clinical remission and smoking cessation are more likely to

achieve EIM remission, while increasing age at IBD diagnosis is associated with decreased chance of remission. Advanced therapies seem also have a positive effect on EIM remission. Physicians should be aware of these factors to properly manage patients with IBD with concurrent EIMs.

CONFLICTS OF INTEREST

Guarantor of the Article: Lucas Guillo, MD.

Specific author contributions: L.G.: wrote the article. L.G. and L.P.-B.: conceived and supervised the study. Y.E. and L.G.: performed the statistical analysis. All authors critically revised the manuscript. The manuscript was approved by all authors.

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Table 5. Factors associated with extraintestinal manifestation remission (multivariate analysis)

Characteristic	OR	95% CI	P value
Age at IBD diagnosis	0.98	0.97–1.00	0.018
Smoking			
Current			
Former	2.98	1.61–5.63	<0.001
Never	1.28	0.77–2.12	0.30
Advanced therapies			
No			
Yes	1.49	0.91–2.41	0.11
IBD current clinical remission			
No			
Yes	2.42	1.58–3.71	<0.001

CI, confidence interval; IBD, inflammatory bowel disease; OR, odd ratio.

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Data availability statement: Data underlying this article are available in the article and in its online supplementary material.

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Study Highlights

WHAT IS KNOWN

- ✓ Extraintestinal manifestations (EIMs) of inflammatory bowel disease (IBD) are challenging clinical situation and require a complex and multidisciplinary management.

WHAT IS NEW HERE

- ✓ IBD current clinical remission and smoking cessation are more likely to achieve EIM remission.
- ✓ Increasing age at IBD diagnosis is associated with decreased chance of EIM remission.
- ✓ Physicians should be aware of these factors to properly manage patients with IBD with concurrent EIMs.

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