Factors Associated with the Presence of Extraintestinal Manifestations in Patients with Ulcerative Colitis in a Latin American Country

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Keywords

Extraintestinal manifestations · Inflammatory bowel disease · Ulcerative colitis

Abstract

Background and Aim: Ulcerative colitis (UC) is a subtype of inflammatory bowel disease that can develop extraintestinal manifestations (EIMs) in a subgroup of patients. The aim of this work was to study the frequency and clinical factors associated with the development of EIMs. **Methods:** We evaluated a total of 260 Mexican patients with confirmed UC who were followed retrospectively in order to identify the factors associated with the presence of EIMs. **Results:** The frequency of EIM was 55.8%. The factors associated with the development of EIM were pancolitis ($p = 0.003$, OR = 2.44, 95% CI = 1.34–4.56) and previous colectomy ($p = 0.024$, OR = 7.54, 95% CI = 1.20–60.44). A clinical course of initial activity and then long remission for >5 years was found to be a protective factor ($p = 0.002$, OR = 0.31, 95% CI = 0.14–0.67). **Conclusion:** The frequency of EIM was 55.8% in our population, and the factors associated with their development were pancolitis and colectomy; meanwhile, a clinical course of initial activity and then long remission was a protector feature.

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Introduction

As many as 36–56% of patients with inflammatory bowel disease (IBD) have at least one extraintestinal manifestation (EIM) along the course of the disease, affecting mainly articular, ocular, hepatobiliary, hematologic and dermatologic levels. These EIMs might present before, after, or at the time of IBD diagnosis, even more, they could emerge several years after a proctocolectomy. Some of these EIMs have a negative impact in daily activities with a significant decrease in the life quality [1] setting the need for a multidisciplinary team in their diagnosis and treatment.

According to the relationship with ulcerative colitis (UC) activity, EIMs can be classified into 2 different groups: those who have a direct relationship with intestinal activity (i.e., pauciarticular arthritis and erythema nodosum) and those with an independent course from the underlying IBD activity that may suggest an autoimmune component (i.e., uveitis and ankylosing spondylitis); other manifestations like pyoderma gangrenosum might or might not be related with activity of IBD [2–4]. The pathophysiology process of EIMs is unknown; however, numerous mechanisms have been proposed, including genetic susceptibility, based on high concordance reported in siblings and first-degree relatives [5] aberrant self-

Fig. 1. Distribution of EIM in patients with ulcerative colitis. EIM, extraintestinal manifestation; PSC, primary sclerosing cholangitis; PG, pyoderma gangrenosum; AS, ankylosing spondylitis; EN, erythema nodosum.

recognition and autoantibodies against shared proteins between colon epithelium and different target organs like biliary track, skin, eyes, and joints [6, 7]. Some studies have shown the relationship between EIMs and some genes located in the major histocompatibility complex on chromosome 6, for instance, HLA B8/DR3, HLA BRB1*0103, HLA B*7, and HLA B*58 were associated with primary sclerosing cholangitis, arthropathies, cutaneous, and ocular manifestations, respectively. Albeit ankylosing spondylitis has been linked with HLAB*27, this association is not as strong as in the absence of IBD [8–11]. The presence of IBD family history, active smoking, and positive perinuclear anti-neutrophilic cytoplasmic antibody have been associated with the development of EIMs along UC course.

It is well known that the recurrence of the same EIMs is common, and patients with one EIM have an increased risk for developing another one [8]. A positive association of arthritis with dermatologic and ophthalmologic complications has been observed, suggesting a common pathogenic mechanism [12]. The aim of this study was to determine the frequency of EIMs in patients with UC and the factors associated with its development.

Methods

Patients

Two hundred sixty Mexican patients with a diagnosis of UC confirmed by histology were studied. These patients were recruited from the Inflammatory Bowel Diseases Clinic at the National Institute of Medical Sciences and Nutrition in Mexico City during the period between January 1, 2007, and December 31, 2014.

Demographic, clinical, endoscopic, and histologic data were gathered from medical records and direct interviews. The variables evaluated included sex, current age, age at diagnosis, family history of IBD, disease duration, extent of disease, medical and surgi-

cal treatment, clinical course, histologic activity, high-sensitive C-reactive protein (hs-CRP), perinuclear anti-neutrophilic cytoplasmic antibody, history of appendectomy, current or past smoke history, and concomitant autoimmune disease.

For the determination of hs-CRP, we used a cutoff level of 0.36 mg/dL since a previous study from Yamamoto-Furusho and colleagues [13] showed had good correlation with histological activity. The extent of disease was defined according to the Montreal classification: proctitis (E1), left-sided colitis (E2), and extensive colitis (E3). The clinical course of disease was defined as active then inactive (first episode followed by a long-term remission for >5 years), intermittent (fewer of 2 relapses per year), and chronic activity (persistent activity despite medical treatment). For the clinical, endoscopic, and histologic evaluation, we used the Truelove-Witts, Mayo, and Riley indexes, respectively. The grade of activity was divided into 3 categories: mild, moderate, and severe. Regarding the EIM, we considered the most frequent EIMs such as peripheral arthropathies, primary sclerosing cholangitis, erythema nodosum, pyoderma gangrenosum, uveitis, sacroiliitis, and ankylosing spondylitis.

Statistical Analysis

Descriptive statistics are expressed as mean and standard deviation. Data were analyzed by Student's *t* test for numerical variables and χ^2 and Fisher's exact tests for categorical variables. When data were non-normally distributed, Wilcoxon's nonparametric rank sum test was used. Those risk factors with *p* values <0.1 in the univariate analysis were included into the multivariate model. The results were expressed as odds ratio (OR) with corresponding 95% confidence interval (CI). Two-tailed tests for significance were used in all statistical analyses, and *p* < 0.05 was considered statistically significant. The data analysis was performed with SPSS version 20 for Windows.

Results

A total of 260 patients with UC were included in the study, 125 females (48.10%) and 135 males (51.90%) with a mean current age of 44.6 years (range 16–80 years old)

Table 1. Clinical and demographic characteristics of patients with ulcerative colitis

Characteristics	Sample size (<i>n</i> = 260)
Gender, <i>n</i> (%)	
Female	125 (48.10)
Male	135 (51.90)
Current age, mean (range), years	44.66 (16–80)
Diagnosis age, mean (range), years	31.62 (6–65)
Family history of IBD, <i>n</i> (%)	6 (2.30)
Years of evolution of disease, mean (range)	13.3 (3–68)
Extraintestinal manifestations, <i>n</i> (%)	145 (56.00)
Appendectomy, <i>n</i> (%)	12 (4.60)
Smoking, <i>n</i> (%)	100 (38.50)
Concomitant autoimmune disease, <i>n</i> (%)	24 (9.20)
Histologic activity, <i>n</i> (%)	
Remission	56 (21.5)
Mild	87 (33.4)
Moderate	71 (27.3)
Severe	46 (17.8)
Elevated hs-CRP (>0.36 mg/dL)	127 (48.84)
Positive p-ANCAs	86 (33.10)
Extension of the disease, <i>n</i> (%)	
Extensive colitis	204 (78.50)
Left-sided colitis	13 (5.00)
Proctitis	43 (16.50)
Clinical course, <i>n</i> (%)	
Active then inactive	35 (13.50)
Intermittent activity	202 (77.70)
Chronic activity	23 (8.80)
Treatment, <i>n</i> (%)	
5-ASA (oral or topical)	234 (91.90)
Steroids	62 (23.80)
Azathioprine	76 (29.20)
Anti-TNF	8 (3.10)
Colectomy	10 (3.80)

IBD, inflammatory bowel disease; hs-CRP, high-sensitive C-reactive protein; TNF, tumor necrosis factor; ASA, aminosalicylic acid.

and a mean diagnosis age of 31.6 years (range 6–65 years). EIM was present in 145 UC patients (55.8%) with the following distribution: peripheral arthropathies 30%, primary sclerosing cholangitis 9.20%, pyoderma gangrenosum 3.90%, uveitis 3.80%, sacroiliitis 1.90%, ankylosing spondylitis 1.90%, and erythema nodosum 0.40%, as shown in Figure 1.

The presence of peripheral arthropathies and erythema nodosum only had correlation with disease activity. The extent of disease was distributed as follows: extensive colitis (E3) in 78.5%, left colitis (E2) in 5%, and proctitis (E1) in 16.5%. Regarding the clinical course, 13.5% had

an active then inactive course, 77.7% had an intermittent activity, and 8.8% had chronic continual activity. Histological remission was present in 56 patients (21.5%). The hs-CRP was elevated in 127 persons (48.84%), and 86 patients (33.1%) were positive for p-ANCAs. Concerning the medical treatment, the distribution was as follows: 5-aminosalicylic acid 91.9%, steroids 23.8%, azathioprine 29.2%, anti-tumor necrosis factor 3.1%, and colectomy 3.80% as shown in Table 1.

Factors Associated with the Development of EIMs

The clinical factors associated with the development of EIMs in Mexican patients with UC were an active then inactive clinical course ($p = 0.002$, OR = 0.31, 95% CI = 0.14–0.67), pancolitis ($p = 0.003$, OR = 2.44, 95% CI = 1.34–4.56), and the presence of colectomy ($p = 0.024$, OR = 7.54, 95% CI = 1.20–60.44). It is important to mention that peripheral arthropathies predicted the presence of other concomitant EIMs such as pyoderma gangrenosum ($p = 0.01$, OR = 8.44, 95% CI = 1.6–66.9), uveitis ($p = 0.01$, OR = 8.44, 95% CI = 1.6–66.9), and primary sclerosing cholangitis ($p = 0.00003$, OR = 18.8, 95% CI = 2.48–142.7) in our population. Table 2 summarizes the factors associated from uni- and multivariate analysis. Other variables such as sex, current age, age at diagnosis, family history of IBD, disease duration, history of appendectomy, current or past smoke history, and concomitant autoimmune disease were not associated with the presence of EIMs.

Discussion

The finding of the present study was the frequency of 56% of EIMs in Mexican patients with UC, being the most common peripheral arthropathy (30%) followed by PSC (9.20%), uveitis (3.8%), pyoderma gangrenosum (3.8%), sacroiliitis (1.90%), ankylosing spondylitis (1.90%), and erythema nodosum (0.40%). The overall frequency is in accordance with other populations from Europe and North America [14], although it is increased compared with a previous evaluation of the period from 1986 to 2007 by Yamamoto-Furusho [15] where the frequency was 41.5%. Concerning peripheral arthropathies, the literature describes an occurrence of 30%, which is in agreement with our findings [16]. On the other hand, several studies have shown a PSC frequency between 2 and 7.5% [17] which is lower than our population. It is important to mention that there is a reference bias because our hospital is a tertiary care center.

Table 2. Univariate and multivariate analysis for characteristics associated with the presence of extraintestinal manifestations

Variable	Univariate <i>p</i> value	Multivariate <i>p</i> value	OR	95% CI
Peripheral arthropathies	0.00003	0.00003	132.7	18–976.2
PSC	0.0003	0.0003	18.8	2.48–142.7
Active-inactive clinical course	0.002	0.002	0.31	0.14–0.67
Pancolitis	0.003	0.003	2.44	1.34–4.56
Pyoderma gangrenosum	0.001	0.010	8.44	1.6–66.9
Uveitis	0.001	0.010	8.44	1.6–66.9
History of colectomy	0.022	0.024	7.54	1.20–60.44
Ankylosing spondylitis	0.058	0.060	4.96	0.58–41.52
Use of anti-TNF	0.066	0.067	5.78	0.78–44.6
Elevated hs-CRP	0.070	0.074	1.48	0.89–2.44
Positive p-ANCAs	0.070	0.111	1.53	0.90–2.61
Use of steroids	0.070	0.113	1.61	0.89–2.90
Intermittent clinical course	0.073	0.107	1.61	0.89–2.90
Female gender	0.096	0.191	1.42	0.87–2.33

PSC, primary sclerosing cholangitis; TNF, tumor necrosis factor; hs-CRP, high-sensitive C-reactive protein.

This work showed that the frequency of pyoderma gangrenosum was 3.8%, which is over the 0.6–2.2% reported in other studies [18], although some other reports exposed higher frequencies even of 10% [19]. In the case of erythema nodosum, the occurrence in our sample was 1% compared with 4–6% presented on other studies [18, 19]. We found that the frequency of uveitis was (3.8%) similar to reported in other populations between 2 and 6% [20]. Since sacroiliitis use to be an asymptomatic and non-progressive manifestation, there are different frequency reports in the literature; moreover, depending on the imaging method used to detect it, occurrence might vary widely. A distinct scenario is observed in ankylosing spondylitis, with a reported frequency of 5–10%, where the severe pain and progressive damage aid to the diagnosis [21]. In this study, the frequency of sacroiliitis and ankylosing spondylitis was 1.9% for each one.

In the present study, the strongest factor associated with the presence of EIMs was the existence of another EIM, especially arthropathies ($p = 0.000003$, OR = 132.7, 95% CI = 18.0–976.2) and followed in importance by primary sclerosing cholangitis ($p = 0.00003$, OR = 18.8, 95% CI = 2.48–142.7), pyoderma gangrenosum ($p = 0.01$, OR = 8.44, 95% CI = 1.6–66.9), and uveitis ($p = 0.01$, OR = 8.44, 95% CI = 1.6–66.9). These findings are comparable with those presented by Veloso et al. [12, 22] who described that arthritis had a significant association with concomitant dermatologic and ocular manifestations. All these data support the hypothesis of a common inflam-

matory pathway known as the joint-gut axis where gut epithelium lymphocytes are recruited into the synovial due to structural shared antigen proteins [23, 24].

Furthermore, features like active then inactive clinical course ($p = 0.002$, OR = 0.31, 95% CI = 0.14–0.67), pancolitis ($p = 0.003$, OR = 2.44, 95% CI = 1.34–4.56), and the presence of colectomy ($p = 0.024$, OR = 7.54, 95% CI = 1.20–60.44) were the most important factors associated with EIMs bracing the role of the degree and extension of inflammation in the pathogenesis of the EIMs [25]. An active then inactive clinical course protects against EIMs compared to pancolitis and presence of colectomy that were associated with the development of EIMs in our population. Nevertheless, inflammatory process does not explain every case of EIMs so that there should be other physiologic pathways in the genesis of these manifestations. In conclusion, the frequency of EIMs was 55.8%, and the factors associated were pancolitis, presence of colectomy, concomitant EIM, and the clinical course of disease characterized by initial activity and then long-remission.

Statement of Ethics

This work was performed according to the principles expressed in the Declaration of Helsinki, 1989. The study was approved by the ethical committee in our institution (Ref. 1037) and written informed consent was obtained from all patients recruited in this study.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

Funding Sources

The authors did not receive any funding.

Author Contributions

Jesus K. Yamamoto-Furusho provided the research idea, directed, performed data analysis, and prepared the manuscript. German E. Sanchez-Morales performed the review of the clinical medical records, performed the data base, and prepared the manuscript.

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