World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i46.17463

World J Gastroenterol 2014 December 14; 20(46): 17463-17467
ISSN 1007-9327 (print) ISSN 2219-2840 (online)
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RETROSPECTIVE STUDY

Extraintestinal manifestations in a large series of Italian inflammatory bowel disease patients

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Received: March 18, 2014 Revised: May 21, 2014
Accepted: July 15, 2014
Published online: December 14, 2014

Abstract

AIM: To investigate prevalence, type and time of onset of extraintestinal manifestations (EIMs) in a series of Italian inflammatory bowel disease (IBD) patients.

METHODS: Data of 811 IBD consecutive patients, first referred to our Centre from 2000 to 2011, were retrospectively evaluated.

RESULTS: Eight hundred and eleven IBD patients (437 M, 374 F) were studied: 595 ulcerative colitis (UC) (73.4%) and 216 Crohn's disease (CD) (26.6%). Among these, 329 (40.6%) showed EIMs: 210 UC (35.3%) and 119 CD (55.1%) ($P < 0.0001$). Considering the time of the diagnosis of IBD, 37 EIMs (11.2%) were developed before, 229 (69.6%) after and 63 (19.2%) were simultaneous. The type of EIM were as follows: 240 musculoskeletal (29.6%), in 72 CD patients and in 168 UC ($P < 0.0001$); 47 mucocutaneous (5.8%), in 26 CD and in 21 UC ($P = 0.0049$); 26 ocular (3.2%), in 16 CD and in 10 UC (CD 7.4% *vs* UC 1.7%, $P = 0.0093$); 6 hepatobiliary (0.8%); 10 endocrinological (1.2%). In particular, with regards to the involvement of the musculoskeletal system, arthritis Type 1 was found in 41 CD (19%) and in 61 UC (10.2%) ($P = 0.0012$) and Type 2 in 25 CD (11.6%) and in 100 UC (16.8%) ($P = 0.0012$).

CONCLUSION: Mucocutaneous manifestations, arthritis Type 1 and uveitis were significantly more frequent in CD than UC. The complications of the musculoskeletal system were the mostly observed ones, often with symptoms more severe than intestinal ones, confirming the need for close cooperation with rheumatologists.

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Key words: Crohn's disease; Extraintestinal manifestations; Inflammatory bowel diseases; Musculoskeletal manifestations; Ulcerative colitis

Core tip: Extraintestinal manifestations (EIMs) are commonly seen in association with inflammatory bowel disease (IBD), both in patients with ulcerative colitis and in those ones with Crohn's disease. The reported prevalence of EIMs in IBD is highly variable, ranging from 25% to 40%. EIMs can involve any organ or system, even if the musculoskeletal and the dermatologic are the most common ones. Hepatopancreatobiliary, ocular, renal and pulmonary systems may also be affected.

Zippi M, Corrado C, Pica R, Avallone EV, Cassieri C, De Nitto D, Paoluzi P, Vernia P. Extraintestinal manifestations in a large series of Italian inflammatory bowel disease patients. *World J Gastroenterol* 2014; 20(46): 17463-17467 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i46/17463.htm DOI:

http://dx.doi.org/10.3748/wjg.v20.i46.17463

INTRODUCTION

Extraintestinal manifestations (EIMs) are commonly seen in association with inflammatory bowel disease (IBD), both in patients with ulcerative colitis (UC) and Crohn's disease (CD). The incidence of EIMs reported in IBD is highly variable, ranging from 25% to 40%[1,2]. These manifestations are in most of the cases associated with colonic inflammation, but in a proportion of patients EIMs may be present prior to the onset of colonic symptoms[3]. EIMs can involve any organ or system, even if the musculoskeletal and the dermatologic are the most common ones. Hepatopancreatobiliary, ocular, renal and pulmonary systems may also be affected. In some cases, EIMs may be found in association with autoimmune diseases or result from nutritional and metabolic dysfunction[3].

The aim of the present retrospective study was to investigate, in a large series of Italian IBD patients, the prevalence, time of onset and type of EIMs.

MATERIALS AND METHODS

Patients

We retrospectively studied and recorded in a computer database 811 IBD out-patients consecutively in our Gastroenterology Unit, seen from 1 January 2000 to 31 December 2011, and followed-up (median follow-up 40.7 ± 31.5 mo).

In all patients, diagnosis was established on the basis of usual clinical, endoscopic and histological criteria.

Data regarding sex, age at diagnosis, clinical history, smoking habit, and presence of EIMs were analyzed in each patient.

EIMs were classified in 5 major groups: musculoskeletal (arthritis, ankylosing spondylitis); mucocutaneous (erythema nodosum, psoriasis, pyoderma gangrenosum, aphthous stomatitis); hepatobiliary (sclerosing cholangitis); ocular (uveitis) and metabolic (Hashimoto's thyroiditis).

Arthritis was further divided into: Type 1 (pauciarticular) arthropathy involving fewer than 5 joints, which is usually strongly correlated to exacerbations of bowel symptoms; Type 2 (polyarticular) arthropathy involving 5 or more joints with symptoms typically independent from the activity of IBD.

Statistical analysis

Fischer's Exact test (including Yates' correction) was used for categorical data. Probability values and confidence intervals (CI) were calculated at the 95% level. Differences were considered significant when $P \leqslant 0.05$ was reached.

RESULTS

Demographics characteristics

Eight hundred and eleven IBD patients were enrolled in the study, 437 males (53.9%) and 374 females (46.1%). The UC-Group consisted of 595 (73.4%) patients, with a mean age at diagnosis of 33.1 ± 13.7 SD years. The CD-Group consisted of 216 (26.6%) patients, with a mean age at diagnosis of 31.9 ± 13.1 SD years.

The localization of disease in patients with CD was as follows: ileal in 103 patients, colic in 39, ileal-colic in 64, upper gastrointestinal tract in 10. Patients with UC showed the following localization of disease: proctitis in 98 cases, left-sided colitis in 353, diffuse colitis in 144.

According to the Vienna Classification, 98 CD patients had inflammatory disease, 79 a stricturing course, 37 fistulizing disease and 3 only perianal involvement (Table 1).

Two hundred and thirty-eight patients (29.4%) were smokers upon diagnosis (98 CD, 140 UC), 148 (18.2%) ex-smokers (17 CD, 131 UC) and 425 (52.4%) not smokers (101 CD, 324 UC) ($P = 0.0565$, OR = 1.36, 95%CI: 0.99-1.26).

Extraintestinal manifestations

EIMs were found in 329 (40.6%) patients (210 UC, 119 CD), with a prevalence of 35.3% and 55.1%, respectively, ($P < 0.0001$, OR = 0.44, 95%CI: 0.32-0.61). One hundred and fifty-five (47.1%) were males (53 CD, 102 UC) and 174 (52.9%) females, ($P = 0.49$, OR = 0.85, 95%CI: 0.54-1.34).

Particularly, 37 (11.2%) EIMs (20 CD, 17 UC) were present at the onset of IBD (mean period 4.6 ± 3.1 SD, range: 1-24 years), 229 (69.6%) (72 CD, 157 UC) EIMs were observed after the diagnosis (mean period 10.4 ± 8.4 SD, range: 2-44 years) and 63 (19.2%) (27 CD, 36 UC) EIMs were present at the same time.

EIMs reported were: musculoskeletal in 240 cases (227 arthritis and 13 ankylosing spondylitis); mucocutaneous in 47 cases (22 erythema nodosum, 12 psoriasis, 7 pyoderma gangrenosum and 6 aphthous stomatitis); ocular in 26 cases (26 uveitis); hepatobiliary in 6 cases (sclerosing cholangitis) and endocrinological in 10 cases (Hashimoto's thyroiditis) (Table 2).

Seventy-two CD and 168 UC patients suffered from musculoskeletal diseases, ($P < 0.0001$, OR = 0.35, 95%CI: 0.22-0.59). In more detail, arthritis was present in 66 CD and in 161 UC (30.5% *vs* 27.1%) ($P = 0.53$, OR = 0.65, 95%CI: 0.21-2.08) and ankylosing spondylitis was observed in 5 CD and in 8 UC patients (2.3% *vs* 1.3%), ($P = 0.53$, OR = 1.52, 95%CI: 0.48-4.8).

Forty-one CD and 61 UC patients showed arthritis Type 1 (19% *vs* 10.2%) ($P = 0.0012$, OR = 2.69, 95%CI: 1.49-4.85), while Type 2 was present in 25 CD and in 100 UC ones (11.6% *vs* 16.8%) ($P = 0.0012$, OR = 0.37, 95%CI: 0.21-0.67).

Twenty-six CD and 21 UC patients came to our attention due to mucocutaneous manifestations ($P = 0.0049$, OR = 2.52, 95%CI: 1.34-4.71). Erythema nodosum was present in 13 CD and in 9 UC patients (6% *vs* 1.5%) ($P = 0.77$, OR = 1.33, 95%CI: 0.42-4.24); pyoderma gangrenosum in 5 CD and in 2 UC patients (2.3% *vs* 0.3%),

Table 1 Clinical and demographic characteristics of inflammatory bowel disease patients

	Crohn's disease *n* = 216	Ulcerative colitis *n* = 595
Males/Females	131/85	306/289
Mean ± SD (age years at diagnosis)	31.9 ± 13.1	33.1 ± 13.7
Location/extension, *n*		
Ileum	103	-
Ileum + colon	64	-
Colon	39	-
Upper gastrointestinal	10	-
Diffuse colitis	-	144
Left-sided colitis	-	353
Procto-sigmoiditis	-	98
Behaviour, *n*		
Inflammatory	98	-
Fistulizing	37	-
Stricturing	79	-
Perianal Involvement	3	
Smoke at diagnosis	98	140
Ex-smoke at diagnosis	17	131
No smoke at diagnosis	101	324

(P = 0.44, OR = 1.33, 95%CI: 0.39-13.1); psoriasis was observed in 13 CD and in 7 UC patients (2.3% *vs* 1.5%), (P = 0.37, OR = 1.33, 95%CI: 0.61-6.57); and aphthous stomatitis was present in 3 CD and in 3 UC patients (1.4% *vs* 0.5%, P = 1.0, OR = 0.78, 95%CI: 0.14-4.35).

Sixteen CD and 10 UC subjects (7.4% *vs* 1.7%) developed ocular manifestations (uveitis) (P = 0.0093, OR = 3.11, 95%CI: 1.36-7.09).

Hepatobiliary manifestations (sclerosing cholangitis) were found in 2 CD and in 4 UC patients (0.9% *vs* 0.7%), (P = 1.0, OR = 0.88, 95%CI: 0.16-4.88).

Endocrinological manifestations (Hashimoto's thyroiditis) were seen in 3 CD and in 7 UC patients (1.4% *vs* 1.2 %), (P = 1.0, OR = 7.5, 95%CI: 0.19-2.96).

The statistical significance in the differences of EIMs observed in CD-Group and UC-Group are summarized in Table 3.

DISCUSSION

IBD are heterogeneous disorders often associated with involvement of extraintestinal organs and EIMs are frequently observed. Their clinical spectrum may vary from transitory mild forms to severe disabling complications, that in some instances may impair quality of life more than the intestinal disease itself.

EIMs may occur in up to 40% of IBD patients. In some series, but not in all, these are more common in CD than in UC[4,5]. Vavricka *et al*[5] have found EIMs in 43% of 580 CD and 31% of 370 UC patients. In our series, EIMs were found in 329 cases (40.6%) (119 CD, 210 UC) with a prevalence of 35.3% and 55.1% respectively, confirming previously published data.

Musculoskeletal manifestations are considered to be the most common EIMs with a reported prevalence in

Table 2 Percentage of type of extraintestinal manifestations calculated in the inflammatory bowel disease population (811 pts) and in inflammatory bowel disease patients with extraintestinal manifestations (329 pts)

Type of EIMS	Percent in IBD pts (40.6%)	Percent in EiMS pts (100%)
Muscoloskeletal	29.6	72.9
Mucocutaneous	5.8	14.3
Ocular	3.2	7.9
Hepatobiliary	0.8	1.8
Endocrinological	1.2	3.1

EIMs: Extraintestinal manifestations; IBD: Inflammatory bowel disease.

Table 3 Total extraintestinal manifestations in ulcerative colitis (210) and Crohn's disease (119) patients

Type of EIMs	CD (119 pts)	UC (210 pts)	*P* value
Muscoloskeletal	71	169	< 0.0001
Mucocutaneous	26	21	0.0049
Ocular	16	10	0.0093
Hepatobiliary	2	4	1.0000
Endocrinological	3	7	1.0000

CD: Crohn's disease; UC: Ulcerative colitis; EIMs: Extraintestinal manifestations.

IBD patients ranging from 9% to 53%[6-8]. In our cohort of patients, musculoskeletal manifestations were recorded in 240 cases (29.6%), these being the main EIMs found (72.9%). The prevalence was significantly higher in UC than in CD.

In IBD, peripheral arthritis is usually divided into types 1 and 2[9-11]. Orchard *et al*[12] in a large retrospective study (976 UC, 483 CD) found type 1 and type 2 arthropathy, respectively, in 3.6% and in 2.5% of UC patients and in 6% and in 4% of CD cases.

In our series, arthritis was slightly more common in CD than in UC (CD 30.5% *vs* UC 27.1%). Arthritis Type 1 was significantly more frequent in CD (CD 19% *vs* UC 10.2%) while, on the contrary, the Type 2 form was significantly more present in UC (UC 16.8% *vs* CD 11.6%).

About 3%-12% of patients with IBD show ankylosing spondylitis and in those with human leukocyte antigen B27 (HLA-B27) positivity the development of this condition is almost the rule. Independent from gut disease is the axial involvement[3]. In our series, ankylosing spondylitis was observed in 5 CD and in 8 UC (CD 2.3% *vs* UC 1.3%).

Skin involvement was described in 10%-15% of patients with IBD[13]. Erythema nodosum (EN) and pyoderma gangrenosum are the two major skin manifestations associated with IBD, with a prevalence of 3%-12%[1,14-16]. Bernstein *et al*[1] investigated EIMs in 4 445 IBD cases, arguing the same rate of erythema nodosum (1.9%) in patients with CD and UC. Women with IBD and people with CD seem to be more affected by EN[9]. In our series, no statistical significance was observed regarding the

prevalence of erythema nodosum between CD-Group and UC-Group (CD 6% *vs* UC 1.5%).

After erythema nodosum, pyoderma gangrenosum represents the second most common cutaneous manifestation of IBD (1%-3%), but this is also the most severe and debilitating disease[17-19]. Pyoderma gangrenosum is more common in UC (5%-12%) than CD (1%-2%) and, like erythema nodosum, some studies showed a female predilection[1]. We found pyoderma gangrenosum in 5 CD and in 2 UC patients (CD 2.3% *vs* UC 0.3%) and, on the contrary, it seems apparently to be more common in CD patients, even if no statistical significance was observed.

Other skin lesions include psoriasis and oral aphthous stomatitis. These last ones are seen in 5%-10% patients with UC and in 20%-30% with CD[20]. The involvement of the oral cavity may come before the intestinal symptoms or even may show a synchronous course with this, in accordance with the degree of their activity. According to our data, aphthous stomatitis was present in 3 CD and in 3 UC patients (CD 1.4% *vs* UC 0.5%).

Psoriasis seems to be more frequent in CD[21], as observed by the study of Danese *et al*[17], in which this was found in 1%-2% of the general population and in 7%-11% of the IBD population. Yates *et al*[22] in their study observed that psoriasis was more prevalent in CD (11.2%) than in UC (5.7%). In our series, psoriasis was observed in 13 CD and in 7 UC (CD 2.3% *vs* UC 1.5%), confirming the prevalence in CD subjects. Both psoriatic lesions and those found in patients suffering from CD, show high levels of TNF-α, thereby assuming a common immunological pathway, in which genetic factors also may contribute[18]. Recently, Binus *et al*[23] compared 146 patients with psoriasis and IBD to 146 with only psoriasis, finding that the first showed much more and significantly higher rates of diabetes (26.7% *vs* 11.0%), autoimmune thyroiditis (6.8% *vs* 2.1%) and hepatitis (6.2% *vs* 0.7%).

In a large Italian IBD population, Cesarini *et al*[24] found 18 cases (1.98%) of Hashimoto's thyroiditis among 909 IBD patients. In particular, this kind of thyroiditis was found in 10 CD patients (2.15%) and in 8 UC patients (1.8%). In our study, autoimmune thyroiditis (Hashimoto's thyroiditis) was found in 3 CD and in 7 UC patients (CD 1.4% *vs* UC 1.2 %).

Ocular manifestations related to IBD are reported in 1.6%-4.6% of UC patients and in 3%-6.3% of CD patients[14,25]. The most common ocular lesions are episcleritis and uveitis. In our IBD series, uveitis was observed in 16 CD in 10 UC patients, being this statistically more prevalent in CD (CD 7.4% *vs* UC 1.7%).

The most important complication of IBD, in the hepatopancreatobiliary system, is sclerosing cholangitis[26], which is, in particular, strongly associated to UC. Patients with sclerosing cholangitis have a coexisting UC in at least 75% of cases and a CD in only a 5%-10%. However, on the contrary, patients who may develop primary sclerosing cholangitis are only 5% of UC and 2% of CD[3].

We found sclerosing cholangitis in 2 CD and in 4 UC patients (CD 0.9% *vs* UC 0.7%).

In conclusion, our data align with those emerging from the literature. Specifically, we found an increased association between EIMs (arthritis Type 1, uveitis and mucocutaneous ones) and CD. Undoubtedly, it is important to work closely with rheumatologists, since the musculoskeletal events are the most frequent. Often, these compromise the quality of life of patients much more than intestinal symptoms themselves.

ACKNOWLEDGMENTS

We thank Dr. Saveria De Vito (Area of Health Technology Assessment, OsMed Unit, Italian Medicines Agency) for English editing.

COMMENTS

Background

In inflammatory bowel disease (IBD), extraintestinal manifestations (EIMs) are important in order to improve treatment, but they are not necessarily concomitant with the intestinal symptoms, active phases or remissions. The reported prevalence of EIMs in IBD varies from 25% to 40%. EIMs can involve any organ or system, even if the musculoskeletal and the dermatologic are the most common ones.

Research frontiers

Various EIMs may be associated to the underlying disease, sometimes with serious complications, such as uveitis and cholangitis. In these cases, we warmly suggest a prompt multidisciplinary approach. The present paper provides data of the epidemiology and clinical characteristics of extraintestinal manifestations related to Italian IBD patients.

Innovations and breakthroughs

For the correct therapy, involving other specialists readily offers the possibility to better face any complications or emergency situations.

Applications

The study results suggest that a multidisciplinary approach of these patients can be helpful in optimizing their management.

Peer review

This topic is well known and researched but nonetheless this paper represents an interesting read.

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P- Reviewer: Seow-Choen F **S- Editor**: Qi Y
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ISSN 1007-9327

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