

Extraintestinal Manifestations in Inflammatory Bowel Disease: About an Epidemiological Survey

Jihane Rizkou^{1*}, Hala Aouroud¹, Fatimaezzahra Lairani¹, Adil Ait Errami¹, Sofia Oubaha², Zouhour Samlani¹, Khadija Krati¹

¹Department of Gastro-Enterology and Hepatology, Arrazi Hospital, Mohammed VI University Hospital Center, Marrakesh, Morocco

²Department of Physiology, Faculty of Medicine and Pharmacy, Cadi Ayyad University, Marrakesh, Morocco

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*Corresponding author: Jihane Rizkou

Department of Gastro-Enterology and Hepatology, Arrazi Hospital, Mohammed VI University Hospital Center, Marrakesh, Morocco

Abstract

Original Research Article

Introduction: Inflammatory bowel disease (IBD) is a systemic disorder primarily targeting the gastrointestinal tract but may affect other organs. Extraintestinal manifestations (EIMs) are common in IBD. We aimed to assess the prevalence of EIMs in IBD patients and to emphasize their epidemiological character. **Methods:** The study population consisted of IBD patients with EIMs who were followed up in consultation or been hospitalized. Demographic and clinical characteristics of patients were analyzed, and prevalence of different types of EIMs and their respective frequencies were carried out. **Results:** 190 IBD patients had EIMs, of which 111 were Crohn's disease (CD) and 79 were ulcerative colitis (UC). The mean age of the patients was 30 years. Sex ratio (M/F) was 0.9. Musculoskeletal manifestations were the most common in our study and 29 patients developed EIM before IBD diagnosis. **Conclusion:** in conclusion, we emphasize that the prevalence of EIMs in IBD patients suggests the need to show more attention, proper treatment and effort towards EIMs in clinical practice.

Keywords: Inflammatory bowel disease, extraintestinal manifestations, Crohn's disease, ulcerative colitis, epidemiology.

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INTRODUCTION

Inflammatory bowel disease (IBD) is a systemic disorder primarily targeting the gastrointestinal tract but may affect other organs [1, 2]. Extraintestinal manifestations (EIMs) are mainly represented by joint, mucocutaneous, hepatobiliary, ophthalmological, renal and hematological lesions, and are sometimes more alarming than the disease itself. The pathogenesis of systemic manifestations in IBD is not well understood and involves inflammatory, autoimmune and infectious mechanisms [1, 3]. The evolution of these disorders is most often parallel to the activity of the intestinal disease, but they can evolve independently and are sometimes precede IBD diagnosis, thereby posing a diagnostic problem.

The main aim of our study was to determine the frequency and the prevalence of EIM during IBD and to emphasize their epidemiological character,

MATERIALS AND METHODS

This is a retrospective and analytical study conducted in our gastroenterology department from

March 2011 to March 2021. We included 190 patients meeting the inclusion criteria: patients with a definite diagnosis of IBD with EIMs, followed up in consultation or been hospitalized during this period. The data collection was carried out through hospitalization or consultation registries. Demographic as well as disease characteristics were registered and collected, emphasizing the epidemiological parameters. Statistical analysis was made via SPSS 2.0 software.

RESULTS

EIMs represented 41.4% of the 458 IBD cases (190 patients); of which 111 were Crohn's disease (CD) and 79 were ulcerative colitis (UC). The mean age of patients was 30 years with extremes of [16- 63 years]. 32.7% of patients were between 31 and 40 years old and 3.7% of the cases were older than 61 years. There was a slight female predominance with a sex ratio (M/F) of 0.9 (90 males (47.4%), and 100 females (52.6%)). CD was found in 52 men and 59 women with a sex ratio (M/F) of 0.8. UC was found in 41 women and 38 men with a sex ratio (M/F) of 0.9 (Table 1).

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Table 1: Demographic characteristics of patients

	Crohn's disease	Ulcerative Colitis	IBD
	n (%)	n (%)	n (%)
No. of patients	111(58.4)	79(41.6)	190(100)
Female	59(31)	41(21.6)	100(52.6)
Male	52 (27.4)	38(20)	90(47.4)
Age (y):			
<20	8(4.2)	2(1)	10(5.2)
21-30	33(17.4)	21(11.1)	54(28.5)
31-40	37(19.5)	25(13.2)	62(32.7)
41-50	28(14.7)	17(8.9)	45(23.6)
51-60	4(2.1)	8(4.2)	12(6.3)
>61	1(0.5)	6(3.2)	7(3.7)

For the extent of luminal disease; 30% of the patients with CD had an ileo-caecal location. Ileocolic, colonic, ileal, and upper gastrointestinal locations were present in 40%, 20%, 8%, and 2% of the cases respectively. For UC; 18% of patients had Ulcerative proctitis, 57% of cases had Left sided UC and 25% of cases had pancolitis. The duration of the disease in our patients from the time of diagnosis varied from 1 month

to 18 years. 48% of the patients had severe disease activity at the time of EIMs diagnosis.

EIMs reported were: musculoskeletal in 125 cases (66%); mucocutaneous in 27 cases (14%); ocular in 32 cases (17%). Hepatobiliary, thromboembolic and respiratory disorders were rare in our study (3%, 2%, and 2% respectively). Only one patient had a neurological manifestation (0.5%) (Table 2).

Table 2: EIMs in patients with inflammatory bowel disease according to disease type

EIMs	CD	UC	Total
Musculoskeletal	66 (35%)	59 (31%)	125 (66%)
Ocular	18 (10%)	14 (7%)	32 (17%)
Mucocutaneous	16(8%)	11 (6%)	27 (14%)
Hepatobiliary	1 (0,5%)	5 (2,5%)	6 (3%)
Thromboembolic (vascular)	3 (1,5%)	1 (0,5%)	4 (2%)
Respiratory	1 (0,5%)	3 (1,5%)	4 (2%)
Neurological	1 (0,5%)	0 (0%)	1 (0,5%)
Total	106	93	199

Musculoskeletal manifestations were the most common in our study. 72 patients reported arthralgia. X-rays were performed in 29 patients and revealed no radiological abnormalities. 10 of our patients had arthritis. Axial arthropathy was dominated by sacroiliitis and ankylosing spondylitis. 12 patients had anterior uveitis. Mucocutaneous lesions were mainly presented by erythema nodosum in 10 patients, Aphthous ulcers in 9 patients, pyoderma gangrenosum in 3 patients and psoriasis in 5 patients. Two patients in our series had bronchiectasis and 6 patients had primary sclerosing cholangitis (PSC). Cavernous sinus thrombosis and superficial venous thrombosis were noted in 2 cases respectively.

In all, 29 patients developed an EIM before IBD diagnosis, 88 EIMs were present at the same and 73 EIMs were observed after the IBD diagnosis with a variable onset time. For therapeutic management, our patients received, in addition to the treatment of IBD, a specific treatment of the associated extra-intestinal pathology whenever it was necessary. The evolution of these manifestations was favourable in the majority of the cases. However, in some patients they evolved on their own, mainly the axial joint manifestations.

DISCUSSION

The pathogenesis of EIMs in IBD is not well understood. Immunological mechanisms are probably responsible for most of them. The likelihood of developing an autoimmune response increases with the presence of foreign proteins or bacterial products in the intestinal mucosa with an extension of this response outside the digestive tract [4, 5].

The European Crohn's and Colitis Organisation (ECCO) has defined EIMs in IBD as "an inflammatory pathology in a patient with IBD that is located outside the gut and for which the pathogenesis is either dependent on the extension/translocation of immune responses from the intestine, or is an independent inflammatory event perpetuated by IBD or that shares a common environmental or genetic predisposition with IBD" [6].

The prevalence of EIMs in IBD remains controversial. Overall, between 6-47% of IBD patients develop extra-digestive manifestations [5, 7, 8]. In our study, the frequency of EIMs was 44.1%, equivalent range of rates was reported in several retrospective

national studies; 40.6% in an Italian [9], 38.1% in a Swiss [10], 33.1% in a Greek [11], and 23.3% in a Colombian study [12]. Lower frequencies were observed mainly in Asian and Romanian studies [13-15], and a higher frequency was observed in the Middle East (52.3%) [16]. The variations between prevalence rates could be attributed to a longer patient follow-up, larger number of studied manifestations, differences in inclusion and exclusion criteria, and geographical diversity [15, 16].

Extraintestinal manifestations in patients with inflammatory bowel disease according to disease type are unequal. This study confirms the higher prevalence of EIMs in CD rather in UC. Karmiris *et al.*, [11] and

Singearp *et al.*, [15] showed the same results. The Middle Eastern study revealed no difference in EIMs prevalence between UC and CD patients [16]. However, EIMs were more associated in patients with UC in the rest of the studies reviewed [9, 12, 13].

EIMs had been reported in female more than male [1], and may be more common in early-onset IBD and in younger patients [17]. However, this was not found in all studies reviewed.

EIMs are dominated by osteoarticular, skin and ocular lesions. However, many other organs may also be affected, including the liver, the biliary tract, the pancreas, and the kidneys (Table 3) [4].

Table 3: Extraintestinal manifestations and their prevalence

EIMs	In literature	In our study
Musculoskeletal ➤ Arthritis ➤ Ankylosing spondylitis ➤ Isolated sacroiliitis ➤ Arthralgia	6 à 46% [5]	66%
Ocular ➤ Anterior uveitis ➤ Conjunctivitis ➤ Episcleritis	4 à 12% [2]	17 %
Mucocutaneous ➤ Erythema nodosum ➤ Pyoderma gangrenosum ➤ Oral aphthosis ➤ Psoriasis ➤ Sweet's syndrome ➤ Epidermolysis bullosa	5 à 15% [18]	14%
Hepatobiliary ➤ Primary sclerosing cholangitis ➤ Crohn's granulomatous hepatitis ➤ Chronic autoimmune hepatitis ➤ Biliary cirrhosis	10 à 30% [19]	3%
Thromboembolic (vascular)	1 à 8% [20]	2%
Pancreatic ➤ Acute pancreatitis ➤ Chronic pancreatitis	4 à 39% [21]	0%
Respiratory ➤ Chronic bronchitis, bronchiectasis ➤ Interstitial lung disease ➤ Acute laryngotracheitis ➤ Tracheal stenosis ➤ Serous Pleuresis	37 à 55% [26]	2%
Neurological ➤ Demyelinating disease ➤ Optic neuritis	0,2 à 35,7% [28]	0.5%
Renale ➤ Tubular proteinuria ➤ Glomerulonephritis ➤ Interstitial nephritis	4 à 23% [22]	0%
Cardiac ➤ Pericarditis ➤ Myocarditis	2 à 15% [23]	0%

Most EIMs; with the notable exception of uveitis and ankylosing spondylitis; run in parallel with underlying luminal disease activity such as peripheral arthropathy, erythema nodosum, aphthous stomatitis, episcleritis and Sweet syndrome [1].

The chronological occurrence of EIMs related to the time of IBD diagnosis remains variable. With three quarters of patients, EIMs appear after IBD diagnosis [24]. The main manifestations that appear before IBD is diagnosed are peripheral arthritis, ankylosing spondylitis, primary sclerosing cholangitis, uveitis, oral aphthosis, erythema nodosum, pyoderma gangrenosum, and psoriasis. This finding is important to know to reduce the diagnostic delay in patients with IBD [24]. In addition, developing one EIM increases the susceptibility of having other EIMs.

For most EIMs, the management is based on the treatment of the underlying active luminal disease. However, some EIMs follow a clinical course independent of IBD activity and require specific treatment [25, 27].

CONCLUSION

Extraintestinal manifestations of IBD are frequent, multiples, with variable epidemiological character. They are sometimes more alarming than the luminal disease itself. The most common are joint, eye and skin lesions. Their evolution is most often parallel to the IBD disease activity, but they may run independently. They are generally sensitive to IBD treatment; nevertheless, their occurrence may sometimes require a change in treatment strategy. Considering the impact of EIMs on the quality of life of the patients, the prevalence presented in this study suggests that more attention and appropriate effort should be paid to EIMs in IBD patients.

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