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ORIGINAL ARTICLES

Musculoskeletal manifestations in a Portuguese cohort of 235 inflammatory bowel disease patients

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ABSTRACT

Background: Musculoskeletal symptoms represent the most common extraintestinal manifestations of inflammatory bowel disease (IBD) and a major cause of impaired quality of life in these patients. Spondyloarthritis (SpA) is classically associated with IBD, but other rheumatic manifestations may occur.
Objective: To characterize musculoskeletal symptoms and rheumatic diseases in an IBD cohort.
Methods: Retrospective monocentric descriptive study including all the patients with IBD consecutively referred from Gastroenterology to the Reumatology Department (from January of 2013 to April of 2021) in a Portuguese tertiary university hospital. Demographic and clinical data were collected and musculoskeletal symptoms and rheumatic diseases diagnosed in the Rheumatology outpatient center were registered.
Results: A total of 235 patients were included: 177 (75.3%) with Crohn´s disease (CD) and 58 (24.7%) with ulcerative colitis. Musculoskeletal symptoms were observed in 142 (60.4%) patients and 105 (44.7%) had some rheumatic condition. Regarding spondyloarthritis, 46 (19.6%) patients fulfilled ASAS (Assessment of SpondyloArthritis international Society) criteria for axial SpA and 5 (2.1%) for peripheral SpA. Osteoarthritis (n=70, 29.8%) and osteoporosis (n=33, 14%) were the most frequent non-inflammatory rheumatic conditions observed, mostly previously undiagnosed. No significant differences were observed between CD and UC.
Conclusion: Rheumatic conditions are frequent in IBD patients and are not limited to SpA features. They remain mostly undiagnosed and the collaboration between gastroenterologists and rheumatologists is important for their best management.

Keywords: Inflammatory bowel disease; Rheumatic manifestations.

INTRODUCTION

Inflammatory bowel diseases (IBD) are inflammatory conditions affecting the gastrointestinal tract and comprise ulcerative colitis (UC) and Crohn´s disease (CD)[1]. They are characterized by episodes of intestinal inflammation and their prevalence is higher at younger ages[2]. The pathogenesis is not fully understood, but may be associated with genetic susceptibility, intestinal microbiota, immunological abnormalities and environmental factors[3].

Extraintestinal manifestations are common in both UC and CD and can involve nearly any organ system[4]. Musculoskeletal symptoms represent the most common extraintestinal manifestations of IBD and are a major cause of impaired quality of life in these patients[5]. Several cell-mediated and humoral immunopathophysiological mechanisms have been identified underlying gut and joint inflammation[6]. Spondyloarthritis (SpA) is the classical rheumatic inflammatory disease associated with IBD and clinical features may include inflammatory back pain with sacroiliitis (axial SpA) or arthralgia/arthritis of the peripheral joints, enthesitis and dactylitis (peripheral SpA)[7]. Other rheumatic conditions in IBD populations are less well characterized and may include articular, periarticular and muscular involvement[8].

Also, patients with IBD have an increased risk of low bone mineral density (BMD) and bone fractures due to several mechanisms[9]. Risk factors for low BMD include activity and severity of gut inflammation, perianal disease, systemic steroid usage, intestinal malabsorption, low body mass index, and advanced age[10]. Despite this knowledge, the best management of low BMD in this population is yet to determine[11].

MATERIALS AND METHODS

Patient Selection and Design

We designed a retrospective monocentric descriptive study including all patients with IBD consecutively referred from Gastroenterology to the Reumatology De-

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Table I. Demographic characteristics and IBD data from the population

	Total population (n=235)
Sex	
Male - n (%)	101 (43)
Female - n (%)	134 (57)
Age – mean ± SD	46.5 ± 13.6 years
Body mass index - median (min-max)	25.4 (16.4-43.5) kg/m2
Smoking Status	
Active smokers - n (%)	20 (8.5)
Former Smokers - n (%)	19 (8.1)
IBD duration – mean ± SD	11.5 ± 9.8 years
CD - n (%)	177 (75.3)
Non-stricturing Non-penetrating - n (%)	109 (61.6)
Penetrating - n (%)	40 (22.6)
Stricturing - n (%)	28 (15.8)
UC - n (%)	58 (24.7)
Distal UC - n (%)	27 (46.6)
Pancolitis - n (%)	23 (39.7)
Ulcerative proctitis - n (%)	8 (13.7)
Perianal disease - n (%)	58 (24.7)
Bowel resection - n (%)	19 (8.1)

CD: Crohn´s disease; IBD: Inflammatory bowel diseases; SD: standard deviation; UC: ulcerative colitis.

partment between January of 2013 and April of 2021 in a tertiary university hospital (Centro Hospitalar Universitário São João, Porto, Portugal). The diagnosis of IBD was made by colonoscopy and/or histopathology.

Demographic and clinical data and musculoskeletal symptoms were collected at the time of the first visit in the Rheumatology outpatient center and the rheumatic diseases diagnosed during the entire follow-up were registered. All the diagnostic work-out was decided by the Rheumatologist based on his clinical judgement.

Data

Data collected included demographic features (gender, age, smoking status, body mass index) and IBD data (Montreal classification, perianal disease, age at diagnosis, past and current medication).

Data from the Rheumatology consultation were collected at baseline (musculoskeletal symptoms, other extraintestinal manifestations, previous rheumatic diagnosis) and at the follow-up (blood tests, radiologic findings, new rheumatic diagnosis).

Assessment of SpondyloArthritis international Society (ASAS) criteria for axial and peripheral SpA[12,13] were used to classify the patient with axial or peripheral SpA.

Statistical Analysis

The Statistical analyses were made using IBM SPSS Statistics (version 25). In the descriptive analysis, categorical variables were presented as absolute number and percentage and continuous variables were presented as mean/median and standard deviation.

Mann-Whitney U and chi-squared tests were used in the comparison analysis between groups. Differences were considered statistically significant at $p<0.05$.

Ethics

The protocol was approved by the Ethics Committee of Centro Hospitalar Universitário São João. The study was run in accordance with the principles of the Declaration of Helsinki as amended in Fortaleza (2013).

RESULTS

Patient Characteristics

A total of 235 patients with the diagnosis of IBD were included: 134 (57%) were females and the mean age at the first Rheumatology consultation was 46.5 (±13.6) years.

Concerning IBD: 177 (75.3%) had CD and 58 (24.7%) had UC. The mean duration of IBD was 11. 5 (±9.8) years. Regarding CD, most patients ((n=109 patients; 61.6%) had non-stricturing non-penetrating disease. With respect to UC patients, 27 (46.6%) had distal UC, 23 (39.7%) had pancolitis and 8 (13.7%) had ulcerative proctitis. Fifty-eight (24.7%) patients had perianal disease and 19 (8.1%) patients had previous history of bowel resection. There were no statistically significant differences regarding body mass index

Table II. Description of IBD medication

	Total population (n=235)
Azathioprine - n (%)	95 (40.4)
Infliximab - n (%)	68 (28.9)
Mesalazine - n (%)	65 (27.7)
Sulfasalazine - n (%)	32 (13.6)
Adalimumab - n (%)	16 (6.8)
Vedolizumab - n (%)	5 (2.1)
Ustekinumab - n (%)	4 (1.7)
Golimumab - n (%)	1 (0.4)
Current GC - n (%)	11 (4.7)
Previous GC - n (%)	181 (77)
Previous high dose of GC - n (%)	124 (52.8)

GC: glucocorticoids; IBD: Inflammatory bowel diseases.

and disease duration between the two types of IBD but UC patients were older than CD patients (47.6±13.3 vs 42.2±14.4, p=0.01). Demographic data and IBD characteristics are presented in Table I.

Azathioprine (n= 95, 40.4%) was the most currently used drug for IBD. Eleven patients (4.7%) were currently taking glucocorticoids, 181 (77%) patients had already been treated with glucocorticoids and 124 (52.8%) had already been exposed to an equivalent glucocorticoid dose equal or greater than prednisolone 7.5mg/day for at least three months. Table II describes the drugs used for IBD.

Musculoskeletal Symptoms

Musculoskeletal complaints in the first assessment at the Rheumatology outpatient center were accessed in the medical history and classified into two groups, axial and peripheral symptoms, which in turn were subdivided according to the characteristics of pain in terms of "rhythm": "inflammatory" (worst in the morning, no improvement with rest, morning stiffness longer than 30 minutes), "mechanical" (worst at the end of the day, relieved by rest, morning stiffness during less than 30 minutes) or "mixed" (features of "inflammatory" and "mechanical") peripheral joint pain; "inflammatory" (at least 4 of the 5 ASAS inflammatory back pain parameters[14]), "mechanical" (worst at the end of the day, relieved by rest, morning stiffness during less than 30 minutes) and "mixed" (features of "inflammatory" and "mechanical") back pain. Axial symptoms were more frequent (99 patients, 42.1%) than peripheral symptoms (82 patients, 36.2%). Mechanical back pain (n=35, 14.9%) and mechanical joint pain (n= 32, 13.6%) were the most frequent complaints among axial and peripheral symptoms, respectively. Table III describes the musculoskeletal symptoms in the IBD cohort.

Regarding the type of IBD, axial symptoms were numerically more prevalent in CD (43.5% vs 37.9%, p=0.394); similarly, peripheral symptoms were more frequent in UC patients (33.9% vs 38.0%, p=0.536). However, peripheral arthritis was more commonly observed in CD patients (10.7% vs 8.6%, p=0.742), although without statistical significance.

Spondyloarthritis and other extraintestinal manifestations

Imagiologic study was requested, if necessary, by the rheumatologist. Fifty-one (21.7%) patients exhibited imagiologic sacroiliitis: 28 (11.9%) radiographic sacroiliitis, 14 (6%) sacroiliitis on computed tomography and 9 (3.8%) on magnetic resonance. Radiographic sacroiliitis was defined according to the radiologic criteria (grade 2 bilaterally or grade 3-4 unilaterally) of the Modified New York criteria for ankylosing spondylitis[15] as observed by the rheumatologist. Sacroiliitis on computed tomography was defined by the radiologist report and sacroiliitis on magnetic resonance was caracterized by the radiologist respecting ASAS/OMERACT definitions[16]. Although a total of 51 (21.7%) patients presented with imagiologic findings of sacroiliitis, only 46 (19.6%) patients fulfilled ASAS criteria for axial SpA. In addition, 5 (2.1%) patients satisfied ASAS criteria for peripheral SpA.

More patients with CD fulfilled ASAS criteria for axial (22.6% vs 10.3%, p=0.05) and peripheral SpA (2.3% vs 1.7%, p=0.827) in comparison with UC patients.

Regarding other extraintestinal manifestations related to IBD, 17 (7.2%) patients had psoriasis and 5 (2.1%) a previous history of uveitis.

Other Rheumatic Diagnosis

During follow-up at the Rheumatology outpatient center, the rheumatic diseases diagnosed in the meantime

Table III. Characterization of peripheral and axial musculoskeletal symptoms in patients with IBD

	Musculoskeletal manifestations	N (%)
Peripheral Symptoms (n=82)	No	153 (65.1)
	Arthritis / "inflammatory" joint pain	25 (10.6)
	"Mixed" rhythm joint pain	18 (7.7)
	"Mechanical" joint pain	32 (13.6)
	Enthesopathy	7 (3)
Axial symptoms (n=99)	No	136 (58.9)
	"Inflammatory" back pain	46 (19.6)
	"Mixed" rhythm back pain	18 (7.7)
	"Mechanical" back pain	35 (14.9)

IBD: Inflammatory bowel diseases

were successively registered. Osteoarthritis was the most frequent rheumatic disease in the IBD cohort (n=70, 29.8%), followed by osteoporosis (n=33, 14%).

A myriad of rheumatic conditions was diagnosed in this population, as observed in Table IV. Six cases of drug-induced lupus were noticed, all with infliximab. No statistically significant differences were observed in terms of these conditions regarding the type of IBD.

DISCUSSION

Our study aimed to characterize the prevalence of musculoskeletal symptoms and rheumatic diagnoses in a IBD population followed in a Portuguese tertiary university hospital. Overall, 60.4% of the patiens had some sort of musculoskletal symptom (axial or peripheral) and 44.7% suffered from some type of rheumatic condition. Most studies focus on the inflammatory rheumatic manifestations associated with IBD, classically associated with SpA. However, the latter are quite heterogeneous and, consequently, the prevalence of these manifestations varies widely between different studies. One study with 350 IBD patients showed a prevalence of at least one self-reported musculoskeletal SpA feature in 36.9% of the patients[17]. A systematic review with meta-analysis that included 71 studies revealed a pooled prevalende of up to 13% for SpA, 13% for peripheral arthritis, 10% for sacroiliitis and 3% for ankylosing spondylitis[18]. Other studies reported prevalences of rheumatic manifestations between 34.6%[19] and 57.5%[20]. Our higher prevalence of rheumatic symptoms and diagnoses may be related with the detailed observation and follow-up carried out by the rheumatologist, unlike the methods applied in other studies[17]. We made an innovative approach as we subdivided the axial and peripheral symptoms in other specific detailed complaints that guided the rheumatologist to a more accurate diagnosis. Mechanical complaints were more frequent (both in axial and peripheral symptoms) than inflammatory ones. Objectivated arthritis was more common in CD patients, in line with the literature[21]. However, in our study sample, axial complaints were more common than peripheral complaints, wich is different from other studies[19,20]. Also, differently from most studies, our data showed a higher prevalence of patients fulfilling ASAS criteria for axial SpA (19.6%) than peripheral SpA (2.1%). These findings may be explained by the fact that, although the referral of the patients from Gastroenterology to Rheumatology was consecutive, gastroenterologists may have been more prone to this when the patients revealed axial complaints. Moreover, a significant number of patients were referred after verifying the presence of sacroiliitis as an incidental finding in an imagiological exam required for assessment of bowel disease activity (namely, in a computed tomography enterography or a magnetic resonance enterography).

The previous stated thorought observation by the rheumatologist also allowed the diagnosis of other more common (osteoarthritis and osteoporosis) and less common rheumatic conditions. Despite the lack of comparative data and given the mean age of our population, our significant number of patients with features of osteoarthritis may be explained by the accurate assessment of the initial radiographic degenerative findings by the rheumatologist. Regarding osteoporosis, several factors are responsible for a higher incidence

Table IV. Characterization of other rheumatic conditions in patients with IBD

Diagnosis	N (%)
Osteoarthritis	70 (29.8)
Osteoporosis	33 (14)
DISH	6 (2.6)
Drug-induced lupus	6 (2.6)
Rotator cuff tendinopathy	4 (1.7)
Vitamin D deficiency and secondary hyperparathyroidism	3 (1.3)
Spinal disc herniation	3 (1.3)
Calcium	1 (0.4)
pyrophosphate deposition disease	2 (0.9)
Fibromyalgia	2 (0.9)
Osteitis condensans ilii	2 (0.9)
Avascular necrosis of the femoral head	2 (0.9)
Lower limbs dysmetria	2 (0.9)
Rheumatoid arthritis	1 (0.4)
Gout	1 (0.4)
Dupuytren's contracture	1 (0.4)
Mandibular dislocation	1 (0.4)
Sjogren's syndrome	1 (0.4)

DISH: diffuse idiopathic skeletal hyperostosis; IBD: Inflammatory bowel diseases; SLE: systemic lupus erythematosus.

of this condition in IBD patients. Our data showed a prevalence of 14%, mainly previously undiagnosed osteoporosis, not unlike other studies that reported prevalences between 15.38%[22] and 19.8%[9].

The major limitations of our study should be stressed: the fact that it is a retrospective study with no control group, precluding the direct comparison of the prevalence of the musculoskeletal symptoms and rheumatic diagnoses between our IBD population and the general population.

In conclusion, musculoskeletal complaints are frequent in IBD patients and rheumatic conditions are not limited to SpA features. The collaboration between gastroenterologists and rheumatologists is important to the diagnosis and management of not only SpA but also other frequently undiagnosed conditions as osteoarthritis and osteoporosis. The rheumatologist can also be a valuable help in the early diagnosis and treatment of drug-induced lupus in the context of IBD.

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