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TOPIC HIGHLIGHT

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Clinical features and epidemiology of spondyloarthritides associated with inflammatory bowel disease

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Abstract

Inflammation of axial and/or peripheral joints is one of the most frequent extra-intestinal manifestations complicating the clinical course and therapeutic approach in inflammatory bowel diseases (IBD). The frequency of these complications seems to be similar for both diseases, Crohn's disease and ulcerative colitis. Arthritis associated with IBD belongs to the category of spondyloarthropathies. Axial involvement ranges from isolated inflammatory back pain to ankylosing spondylitis, whereas peripheral arthritis is noted in pauciarticular and in polyarticular disease. Asymptomatic radiological involvement of the sacroiliac joints is reported to occur in up to 50% of patients. Other musculoskeletal manifestations such as buttock pain, dactylitis, calcaneal enthesitis, and thoracic pain are frequently underdiagnosed and, consequently, are not treated appropriately. Several diagnostic approaches and criteria have been proposed over the past 40 years in an attempt to correctly classify and diagnose such manifestations. The correct recognition of spondylarthropathies needs an integrated multidisciplinary approach in order to identify common therapeutic strategies, especially in the era of the new biologic therapies.

Key words: Crohn disease; Ankylosing spondylitis; Ulcerative colitis; Spondylarthropathies; Arthritis; Enthesopathy

INTRODUCTION

Arthritis, belonging to the category of spondylarthropathy, is the most frequent extra-intestinal complication of inflammatory bowel diseases (IBD). The clinical spectrum of spondylarthropathies includes axial symptoms, peripheral arthritis, dactylitis and enthesopathy. Musculoskeletal manifestations occur in 20%-50% of patients with IBD[1-3].

Spondyloarthropathies (SpA), or spondyloarthritides as recently proposed[4], represent a group of distinct diseases with similar clinical features and a common genetic predisposition. The 5 major subtypes are ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis, IBD-associated SpA (IBD-SpA), and undifferentiated SpA. The main recognized genetic association is with HLA-B27, but it is clear that there are other genes involved.

According to the European Spondyloarthropathy Study Group (ESSG) criteria[5], IBD is a criterion of spondylarthropathy; psoriasis or enteric infections are 2 other manifestations included in the ESSG criteria for identifying patients with psoriatic arthritis and reactive arthritis. Thus, patients with IBD presenting with inflammatory back pain and/or synovitis (predominantly of the lower limbs) are diagnosed as having spondyloarthropathy (Table 1). The ESSG criteria, designed to be applicable without radiological examination and laboratory testing, have good sensitivity (75%) and specificity (87%), at least in established disease. An alternative classification scheme was put

forward by Amor *et al*[6] (Table 2), which is more complicated but gives improved sensitivity (85%) and specificity (90%) due to the incorporation of common extra-articular manifestations of disease, including enthesopathy, dactylitis, eye disease and HLA-B27 positivity. The basic concepts underlying each classification set are nevertheless similar.

CLINICAL FEATURES

The clinical picture of IBD-SpA is characterized by axial and/or peripheral joint involvement in the absence of rheumatoid factors and of typical extra-articular findings of rheumatoid arthritis (e.g. subcutaneous nodules)[7].

Axial joint disease

The spectrum of axial involvement ranges from inflammatory lower back pain with or without radiological evidence of sacroiliitis (SI), asymptomatic SI, and overt AS characterized by the "classical" clinical (spine stiffness, pain) and radiologic features (squaring, syndesmophytes, bamboo spine).

Inflammatory back pain (IBP)

IBP is usually difficult to localize, insidious in onset, frequently monolateral and intermittent at onset, more intense at rest, associated with stiffness but relieved by movement, exacerbated by cough or sneezing, and accompanied by fatigue. The diagnosis is clinical and defined according to Calin's criteria[8] (Table 3), based on morning stiffness, age and modality of onset, and duration. The diagnosis of IBP is based on the positivity of at least 4 out of 5 parameters. A modification of these criteria with a higher sensitivity has been recently proposed and, apart from the duration of pain and morning stiffness, also considers improvement with exercise, awakening because of pain, and the presence of alternating buttock pain[9].

According to this modification a 70% sensitivity and an 81% specificity are achieved if at least 2 parameters are fulfilled with a positive likelihood ratio 3.7; if at least 3 are fulfilled, the positive likelihood ratio raises to 12.4.

In the presence of IBP, the radiologic evaluation of the sacroiliac joints allows to make diagnosis of SI. SI is graded according to the radiologic criteria established since 1966[10] (Table 4). In the absence of findings with conventional X-ray examination, magnetic resonance imaging (MRI) evaluation may allow diagnosis and, thus, effective early treatment for axial spondyloarthritis[11]. The evidence of an increased signal in the bone and bone marrow (bone edema) with T1 post-gadolinium and STIR (short tau inversion recovery) techniques is a sign of active inflammation in the SI joints and/or spine (Figure 1).

The importance of an early diagnosis has been underlined in a study carried out on 25 HLA-B27 positive patients with IBP and a grade 2 (or lower) unilateral SI on conventional radiography. In these patients, when studied by MRI, 36/50 joints were diagnosed as having grade 2 or higher SI, and bone edema was found in 20/50. The same patients were studied 3 years later by conventional radiography and demonstrated grade 2 or more SI in 21/44 sacroiliac joints, with the conclusion that MRI is more sensitive than conventional radiography for the detection of SI in the early stages[12].

The diagnostic criteria for classic AS have been subjected to several changes over the past decades from the Rome Criteria[13] to the New York Criteria[7] and then to the Modified New York Criteria[14] in 1984 (for more detail concerning evolution of diagnostic criteria)[15]. This

Table 1 Diagnostic criteria according to the ESSG[2]

Inflammatory spinal pain or/and synovitis asymmetric or predominantly of the lower limbs
One or more of the following
Positive family history
Inflammatory bowel disease
Urethritis, cervicitis, or acute diarrhea within 1 mo before arthritis
Buttock pain alternating between right left gluteal areas
Enthesopathy
Sacroiliitis

Table 2 Amor diagnostic criteria for spondylarthropathy[3]

Clinical symptoms or past history of
Lumbar or dorsal pain at night, or lumbar or dorsal morningstiffness = 1
Asymmetric oligoarthritis = 2
Buttock pain (buttock pain = 1, alternating buttock pain = 2)
Sausage-like finger or toe = 2
Heel pain = 2
Iritis = 2
Non-gonococcal urethritis or cervicitis accompanying, or within 1 mo before, the onset of arthritis = 1
Acute diarrhea accompanying, or within 1 mo before, the onset of arthritis = 1
Presence or history of psoriasis and/or balanitis and/or of inflammatory bowel disease (ulcerative colitis, Crohn's disease) = 2
Radiological findings
Sacroiliitis (grade > 2 if bilateral, grade > 3 if unilateral) = 3
Genetic background
Presence of HLA-B27 and/or family history of ankylosing spondylitis reactive arthritis, uveitis, psoriasis or chronic inflammatory bowel disease = 2
Response to therapy
Definite improvement of musculoskeletal complaints with NSAIDs in less than 48 h or relapse of the pain if NSAIDs are discontinued = 2
A patient is considered as having spondylarthropathy if the sum of the scores is 6 or more

Table 3 Calin's criteria for the clinical diagnosis of inflammatory back pain[5]

Onset before age 45 yr
Insidious onset
Improvement with exercise
Morning stiffness
Persistence (at least 3 mo)
Coexistence of 4 out of 5 criteria allows the definition of inflammatory back pain

Table 4 Radiologic criteria for staging of inflammatory changes related to sacroiliitis[7]

Sacro-iliac joints	
Grade 0	Normal
Grade 1	Suspicious changes
Grade 2	Minimal abnormality-small localized areas with erosions or sclerosis without alterations in joint width
Grade 3	Unequivocal abnormality-moderate or advanced sacro-iliitis with one or more of the following: erosions, sclerosis, widening
Grade 4	Severe abnormality-total ankylosis

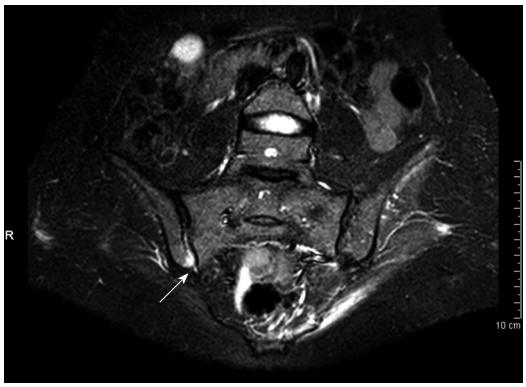

Figure 1 MRI of the sacroiliac joints of a 39-year-old patient with inflammatory back pain and ulcerative colitis (pelvis radiograph was negative for sacroiliitis): STIR MRI of the sacroiliac joints shows bone marrow edema (arrow) of the right sacroiliac joint.

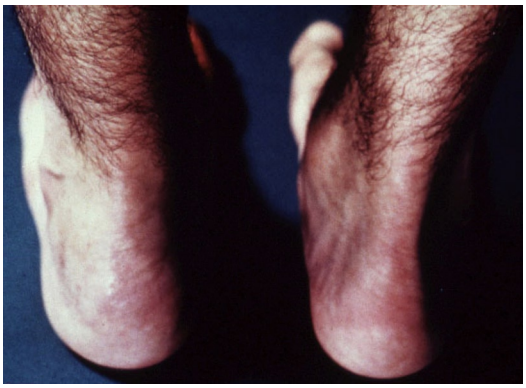

Figure 2 Achilles tendonitis due to enthesitis of the tendon insertions.

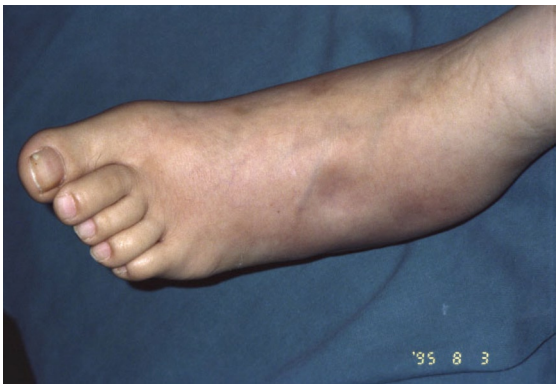

Figure 3 Dactylitis with sausage-like appearance of the Ⅱ toe.

latter classification is based on: (1) lower back pain of at least 3 mo duration that improved with exercise and was not relieved by rest; (2) limited lumbar spinal motion in sagittal (sideways) and frontal (forward and backward) planes; (3) decrease of chest expansion, assessed at the Ⅳ intercostal space, relative to normal values for sex and age; and (4) bilateral SI grade 2-4 or unilateral SI grade 3 or 4. A definite diagnosis of AS is made if criterion 4 (radiology) and any one of the other criteria are fulfilled.

Apart from radiologic alterations, one of the key features of AS is the presence of IBP and/or alternate buttock pain. Other clinical signs to search for in order to assess reduced spine mobility include the Schober test, finger to floor distance, maneuvers for cervical spine assessment (occiput to wall, tragus to wall, cervical rotation), and investigation in order to establish a reduced chest expansion (for review see the INSPIRE study)[16].

Peripheral arthritis

The recognition of this entity is based on clinical diagnosis, e.g. joint swelling and tenderness but may be confirmed by ultrasound examination[17] or MRI[18], whereas conventional radiographs usually are not helpful.

Two subtypes of peripheral arthritis are recognized[1]. Type 1 involves less than 5 joints and is clinically characterized by acute self-limiting attacks of less than 10 wk duration often paralleling intestinal inflammatory activity. Moreover, it is strongly associated with other extra-intestinal manifestations of IBD such as erythema nodosum. Type 2 peripheral arthritis is polyarticular, involving 5 or more joints with symptoms that persist for months and years running independently from IBD flares. This type is associated with uveitis but not with other extra-intestinal manifestations. Both types are seronegative, usually non-erosive and non-deforming, but may become chronic and erosive in 10% of patients[19]. In addition, no significant association has been shown between peripheral arthropathies and HLA-B27 in IBD[1,19-21].

A type 3 peripheral arthritis has been proposed, which includes patients with both axial involvement and peripheral arthritis[22].

Other manifestations

Enthesitis is inflammation at the site of the tendon, ligament and joint capsule insertion to bone. The most frequent clinical expressions are Achilles tendonitis (Figure 2), plantar fasciitis and/or pain and swelling of the tibial tubercle[23]. Diagnosis is clinical but may be confirmed by ultrasound[24] or MRI[25].

Dactylitis (Figure 3) is characterized by the inflammatory swelling of one or more fingers (sausage fingers) or toes caused by tenosynovitis of the flexor tendons. Metacarpophalangeal or proximal interphalangeal arthritis may be associated.

Thoracic pain results from enthesitis of costovertebral,

Table 5 Early epidemiologic studies on IBD-associated arthropathies

Author	Yr	Population	Patients	AS (%)	SI (%)	Peripheral arthritis (%)	HLA-B27 (%)
Acheson[27]	1960	USA	CD 742	2.3	NA	NA	NA
			UC 1175	2.0	NA	NA	NA
Ansell[28]	1964	Canada	CD 91	6.5	19.7	15.3	NA
Haslock[29]	1973	Great Britain	CD 116	16	NA	20.4	NA
Wright[30]	1965	Great Britain	UC 234	6.4	17.9	NA	NA
Wright[31]	1965	Great Britain	UC 269	5.5	NA	11.5	NA
Dekker-Saeys[20]	1978	Netherlands	CD 51	3.9	15.6	11.7	3.9
			UC 58	3.4	12.0	14.0	18.9
Rankin[32]	1979	USA	CD 569	NA	NA	19.0	NA
Műnch[33]	1986	Germany	CD 167	9.0	20.0	14.0	5.3

NA: Not available; IBD: Inflammatory bowel diseases; CD: Crohn's disease; UC: Ulcerative colitis; SI: Sacroiliitis.

Table 6 Epidemiologic studies on mixed IBD populations unless otherwise indicated

Author	Yr	Country	Patients	AS[1] (%)	SI (%)	Peripheral arthritis (%)	IBD-SpA[2] (%)	IBP[3] (%)	Enthesopathy (%)	Overall (%)
Scarpa[34]	1992	Italy	79 (UC)	25.3	43	18.9	-	-	-	62
Protzer[35]	1996	Germany	521	45.1	-	28.1	11.5	-	-	-
Veloso[36]	1996	Portugal	792	3.0	-	16.2	-	-	-	-
Orchard[1]	1998	Great Britain	1459	1.0	-	7.4	-	5.2	-	21.4
Suh[4][37]	1998	Korea	129	1.6	6.2	15.5	-	-	-	17.1
De Vlam[38]	2000	Netherlands	103 (CD)	3.8	21.8[4]		34.9	30	7	39
Queiro[39]	2000	Spain	62 (UC)	3.2	24.2	30.6	-	-	-	-
Salvarani[2]	2001	Italy Netherlands	160	2.6	3.6	10.6	18.1	8.8	10	33.1
Christodoulou[5][40]	2002	Greece	252	-	5.9	2.8	-	-	-	17.0
Palm[6][41]	2002	Norway	406	2.4	2.0	17	22	18.0	26	32.5
Mendoza[42]	2005	Spain	566	1.8	1.9	6.7	-	-	-	-
Turkcapar[3]	2006	Turkey	162	9.9	45.7	14.8	45.7	-	50.0	-
Peeters[43]	2008	Belgium	251 (CD)	6	27	29	-	-	-	-
Rodriguez[44]	2008	Puerto Rico	100	2.6	13	5	42	42	-	-
Lanna[45]	2008	Brazil	130	6.2	9.2	25.4	-	10	5.4	31.5

[1]Modified New York criteria; [2]IBD-SpA according to ESSG criteria; [3]Calin's criteria; [4]Classification according to Gravallese[62]; [5]Only symptomatic SI, X-ray assessment; Undefined arthralgia group; no definitions are given for spondylitis or arthritis; [6]IBP and SI were considered excluding patients with AS; asymptomatic patients included in SI.

costosternal, manubriocostal articulations, exacerbates with cough and deep inspirations, limits respiratory expansion, and episodes are of variable duration.

Buttock pain is part of the IBP, irradiates to the sacrum and may be alternating; it is related to inflammation of sacroiliac joints.

Extra-articular features are represented by uveitis (25%), aortic insufficiency (4%-10%), and cardiac conduction disturbances 3%-9%[26]. These latter cardiologic complications seem to be related to disease duration and are associated with HLA-B27.

EPIDEMIOLOGY

With respect to the evolution of diagnostic criteria, studies on IBD populations from the 1960s, 70s and 80s include patients with axial joint involvement with application of restricted criteria substantially mirroring classic AS or SI together with peripheral arthritis. Table 5 summarizes the principal data from those early studies[20,27-33]. From these studies AS was found to be present in 2% to 16% of patients with higher numbers for Crohn's disease (CD) compared to ulcerative colitis (UC). Asymptomatic and symptomatic SI was found in 12% to 20% of patients and peripheral arthritis in 11% to 20%. Association with HLA-B27 ranged from 3.9% to 18.9%.

Studies on IBD populations after the introduction of the ESSG criteria or Amor criteria are summarized in Table 6[1,34-45]. A discrete number of papers reporting on IBD-associated joint disease were not included. Most of the excluded studies aimed to detect the frequency of every kind of extra-intestinal manifestation of IBD and were not specifically directed to identify IBD-SpA lacking exact definitions of diagnostic criteria. So, Maeda *et al*[46] found that out of 203 Japanese CD patients, 21 had arthritis (10.3%) and 3 had spondylitis (1.5%). Triantafillidis *et al*[47] reported a frequency of 30% of arthritis/arthralgias in a cohort of 155 Greek CD patients. The study by Bernstein *et al*[48] from Canada was based on the ICD code from hospitalized patients with IBD reporting a 4% prevalence of AS with male CD patients being more frequently affected than male UC patients. Souza *et al*[49], in a mixed Brazilian IBD population found a prevalence of 14.4%, with no difference between CD and UC. Al-Shamali *et al*[50] reported

an 8.9% prevalence of arthritis in UC patients from Kuwait with an overall prevalence of rheumatologic complaints of 31%.

Other studies aimed to identify the frequency of symptomatic or asymptomatic SI. Steer *et al*[51] found on CT examination 31/134 of CD patients, symptomatic for back pain, signs of SI (16 of these patients were missed by conventional X-ray). In another study carried out in 50 CD patients symptomatic for back pain, 28% fulfilled the modified NY criteria for AS on X-ray examination[52]. On the other hand, asymptomatic SI may be present in 10% to 50% of patients with IBD[19]. In a comparative study employing conventional X-ray and CT, changes compatible with SI were found in 29% of CD patients being symptomatic only 3%[53].

In the studies included in Table 6, overall prevalence of any manifestation ranged from 17% to 62%. AS ranged from 1% to 25.3%, SI from 1% to 45.7%, peripheral arthritis from 2.8% to 30.6%, IBD-SpA according to the ESSG criteria from 5% to 45.7%, and IBP in 5.2% to 42%. Other manifestations such as inflammatory enthesopathies, when present, were found in 7% to 50% of patients.

With regard to differences between CD and UC, most studies reported similar figures for peripheral and axial involvement in both pathologies. Concerning disease localization, most studies agreed that ulcerative proctitis is rarely complicated by joint inflammation and, concerning CD, that inflammatory joint disease occurs with increased frequency in Crohn's colitis compared to ileal involvement. A discrete percentage of patients will develop one or more spondylarthropathy-related manifestations (such as isolated calcaneal enthesitis and/or dactylitis)[39] without fulfilling any of the classification criteria.

Whereas type I peripheral arthritis is associated with intestinal disease activity[1], SI, especially in its asymptomatic form, is equally present in CD and UC[38,54], and seems more related to duration of IBD. Taken together, SI is one of the most frequent joint inflammations found in IBD patients[39]. The onset of axial symptoms may precede the diagnosis of intestinal disease by decades.

HLA-B27

The importance of HLA-B27 in conferring susceptibility to AS is well known, although the molecular basis is not completely understood. The HLA-B27 gene is located on the short arm of chromosome 6 and comprises 31 proteins with HLA-B*2705, 02, 04, and HLA-B*2707 as the major subtypes associated with disease. Several hypotheses are discussed on how HLA-B27 works on a molecular level in mediating joint inflammation. The arthritogenic peptide hypothesis postulates that HLA-B27 specific receptors on $CD8^+$ T-cells recognize antigenic peptides and subsequently elicit a cytotoxic T-cell mediated autoimmune response. The misfolding hypothesis states that an aberrant folding of HLA-B27 heavy chains occurs in the endoplasmic reticulum leading to a misfolded B-pocket of the peptide-binding groove and hyperaccumulation leading finally to cytokine and chemokine transcription. A third hypothesis suggests sharing of homing receptors on gut epithelium and synovium together with an impaired elimination of intracellular bacteria by HLA-B27 to represent the base for joint inflammation[55].

The prevalence of HLA-B27 varies greatly in the different ethnicities ranging from 0% in African Bantu and Australian Aborigines to 50% in Native Americans[56]. The prevalence in Western European countries varies from 3% to 18%. In Western European populations, HLA-B27 is found in 90% of patients with AS, in 30%-70% of patients with reactive arthritis, in approx 70% of undifferentiated SpA, in 50% of acute anterior uveitis and in 88% of patients with heart block associated with aortic insufficiency.

The association between axial involvement and HLAB27 in IBD patients is much less conclusive: only 25%-75% of patients with CD and AS present positivity for HLA-B27[34,57,58]. Pure asymptomatic SI in CD is not strongly associated with HLA-B27 and a very recent study indicates a prevalence of 7% (comparable to prevalence in the healthy population)[43], and it seems that evolution to AS is more likely to occur in HLAB27-positive patients[59]. This suggests that SI and AS in IBD patients are different entities. A similar distinction has been proposed for peripheral arthritis. Recently, Orchard *et al*[60] have observed an association with HLA-DRB1*0103, B*35 and B*27 in type 1 peripheral arthritis. Similar associations were observed in a control group consisting of patients with postenteric reactive arthritis. Neither HLA-B27 nor DR-4 associations were observed in type 2 arthropathy. These data indicate that type 1 and 2 arthropathies are immuno-genetically distinct entities and that type 1 is more similar to axial spondyloarthropathies

HLA-B27 testing as a tool for achieving diagnosis is useful only in patients with high pre-test probability and thus its use as a screening test is not recommended. In patients with clinically assessed presence of IBP (14% probability of axial SpA), HLA testing may follow and a positive test result would mandate a subsequent referral to a rheumatologist for further evaluation because the probability of axial SpA in such a patient would increase to 59%[61].

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