Clinical features and epidemiology of spondyloarthritides associated with inflammatory bowel disease

Carlo Salvarani, Walter Fries

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 spondylarthropathies. 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.

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
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 study was conducted to evaluate the accuracy of MRI in diagnosing axial spondyloarthritis (SpA) and to compare it with conventional radiography. The study included 25 patients with SpA and 25 healthy controls. MRI was performed using a 3.0-Tesla scanner with a dedicated spine coil. The MRI protocol included T1-weighted, T2-weighted, and STIR images, as well as T1-weighted images with and without contrast. The results showed that MRI was more accurate than conventional radiography in the diagnosis of SpA, with a sensitivity of 90% and a specificity of 95%. The study also demonstrated that MRI is an effective tool for the early detection of SpA, especially in the presence of clinical signs and symptoms such as persistent morning stiffness, asymmetric oligoarthritis, and peripheral arthritis. 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. The diagnostic criteria for classic AS have been subjected to several changes over the past decades from the Rome Criteria to the New York Criteria and then to the Modified New York Criteria in 1984 (for more detail concerning evolution of diagnostic criteria). This
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 [19]. 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 [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,
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%. 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. 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. 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 found that out of 203 Japanese CD patients, 21 had arthritis (10.3%) and 3 had spondylitis (1.5%). Triantafillidis et al reported a frequency of 30% of arthritis/arthralgias in a cohort of 155 Greek CD patients. The study by Bernstein et al 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, in a mixed Brazilian IBD population found a prevalence of 14.4%, with no difference between CD and UC. Al-Shamali et al reported

| Author     | Yr   | Population | Patients | AS (%) | SI (%)  | Peripheral arthritis (%) | IBD-SpA (%) | IBD (%) | Enthesopathy (%) | Overall (%) |
|------------|------|------------|----------|--------|---------|---------------------------|-------------|---------|-----------------|-------------|
| Scarpa     | 1992 | Italy      | 79 (UC)  | 25.3   | 43      | -                         | -           | -       | -               | 62          |
| Protzer    | 1996 | Germany    | 521      | 45.1   | -       | 28.1                      | 11.5        | -       | -               | -           |
| Veloso     | 1996 | Portugal   | 792      | 3.0    | -       | 16.2                      | -           | -       | -               | -           |
| Orchard    | 1998 | Great Britain | 1459 | 1.0    | -       | 7.4                       | -           | 5.2     | -               | 6.4         |
| Suh        | 1998 | Korea      | 129      | 1.6    | 6.2     | 15.5                      | -           | -       | -               | 17.1        |
| De Vlam    | 2000 | Netherlands | 103 (CD) | 3.8    | 21.8    | 34.9                      | 30          | 7       | 39              | -           |
| Querco     | 2000 | Spain      | 62 (UC)  | 3.2    | 24.2    | 30.6                      | -           | -       | -               | -           |
| Salvianzi   | 2001 | Italy      | 160      | 2.6    | 3.6     | 10.6                      | 18.1        | 8.8     | 10              | 33.1        |
| Christodoulou | 2002 | Greece | 252      | -      | 5.9     | 2.8                       | -           | -       | -               | 17.0        |
| Palm       | 2002 | Norway     | 406      | 2.4    | 2.0     | 2.7                       | 22          | 18.0    | 26              | 32.5        |
| Mendoza    | 2005 | Spain      | 566      | 1.8    | 1.9     | 6.7                       | -           | -       | -               | -           |
| Turkcapar  | 2006 | Turkey     | 162      | 9.9    | 45.7    | 14.8                      | 45.7        | -       | -               | 50.0        |
| Peeters     | 2008 | Belgium   | 251 (CD) | 6      | 27      | 29                        | -           | -       | -               | -           |
| Rodriguez  | 2008 | Puerto Rico | 103     | 2.6    | 13      | 5                         | 42          | 42      | -               | -           |
| Lanna      | 2008 | Brazil     | 130      | 6.2    | 9.2     | 25.4                      | -           | 10      | 5.4             | 31.5        |
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.[31] 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[32]. On the other hand, asymptomatic SI may be present in 10% to 50% of patients with IBD[33]. 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%[34].

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)[35] without fulfilling any of the classification criteria.

Whereas type 1 peripheral arthritis is associated with intestinal disease activity[48], SI, especially in its asymptomatic form, is equally present in CD and UC[38,39], 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[48].

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[46]. 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[45,58]. 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)[48], and it seems that evolution to AS is more likely to occur in HLAB27-positive patients[39]. 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.[40] 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 spondyloarthopathies.

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 prevalence of axial SpA in such a patient would increase to 59%[40].

**REFERENCES**

1. Orchard TR, Wordsworth BP, Jewell DP. Peripheral arthropathies in inflammatory bowel disease: their articular distribution and natural history. Gut 1998; 42: 387-391
2. Salvarani C, Vlachonikolis IG, van der Heijde D, Iannone R, Giancotti G, Macchioni G, Beltrami M, Olivieri I, Di Gennaro F, Politi P, Stockbrügger RW, Russel MG. Musculoskeletal manifestations in a population-based cohort of inflammatory bowel disease patients. Scand J Gastroenterol 2001; 36: 1307-1313
3. Turkcapar N, Toruner M, Soykan I, Aydintug OT, Cetinkaya H, Duzgun N, Ozden A, Duman M. The prevalence of extraintestinal manifestations and HLA association in patients with inflammatory bowel disease. Rheumatol Int 2006; 26: 663-668
4. Braun J, Sieper J. Building consensus on nomenclature and disease classification for ankylosing spondylitis: results and
discussion of a questionnaire prepared for the International Workshop on New Treatment Strategies in Ankylosing Spondylitis, Berlin, Germany, 18-19 January 2002. *Ann Rheum Dis* 2002; 61 Suppl 3: iii6-ii67.

5 Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, Cats A, Dijkmans B, Olivieri I, Pasero G. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991; 34: 1218-1227

6 Amor B, Dougados M, Mijiyawa M. [Criteria of the classification of spondylarthropathies] *Rev Rhum Mal Osteoartic* 1985; 52: 85-89.

7 Zochling J, Brandt J, Braun J. The current concept of spondyloarthritis with special emphasis on undifferentiated spondyloarthritis. *Rheumatology (Oxford)* 2005; 44: 1483-1491

8 Celin A, Porta J, Fries JF, Schurman DJ. Clinical history as a screening test for ankylosing spondylitis. *JAMA* 1977; 237: 2613-2614

9 Rudwaleit M, Metter A, Listing J, Sieper J, Braun J. Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. *Arthritis Rheum* 2006; 54: 569-578

10 Bennett PH, Wood PHN. Population studies of the rheumatic diseases. Amsterdam: Excerpta Medical Foundation, 1968: 456-457

11 Braun J, Sieper J. Early diagnosis of spondyloarthritis. *Nat Clin Pract Rheumatol* 2006; 2: 536-545

12 Oostveen J, Prevo R, den Boer J, van de Laar M. Early detection of sacroiliitis on magnetic resonance imaging and subsequent development of sacroiliitis on plain radiography. A prospective, longitudinal study. *J Rheumatol* 1999; 26: 1953-1958

13 Kellgren JH, Jeffrey MR, Ball J. The epidemiology of chronic rheumatism. Oxford: Blackwell, 1963: 326-327

14 van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984; 27: 361-368

15 Goie The HS, Steven MM, van der Linden SM, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis: a comparison of the Rome, New York and modified New York criteria in patients with a positive clinical history screening test for ankylosing spondylitis. *Br J Rheumatol* 1985; 24: 242-249

16 Gladman DD, Inman RD, Cook RJ, van der Heijde D, Landewé RB, Braun J, Davis JC, Mease P, Brandt J, Vargas RB, Chandran V, Hellwell P, Kavaunagh A, O'Shea FD, Khan MA, Pipitone N, Rahman P, Reveille JD, Stone MA, Taylor W, Veale DJ, Maksymowycz WP. International spondyloarthropathies interobserver reliability exercise--the INSPIRE study: I. Assessment of spinal measures. *J Rheumatol* 2007; 34: 1733-1739

17 Kane D, Grassi W, Sturrock R, Balint PV. Musculoskeletal ultrasound--a study of the art review in rheumatology. Part 2: Clinical indications for musculoskeletal ultrasound in rheumatology. *Rheumatology (Oxford)* 2004; 43: 829-838

18 Østergaard M, Duer A, Moller U, Ejbjerg B. Magnetic resonance imaging of peripheral joints in rheumatic diseases. *Best Pract Res Clin Rheumatol* 2004; 18: 861-879

19 Mielants H, Veys EM, Goethals K, Van Der Straeten C, Ackermann C. Destructive lesions of small joints in seronegative spondylarthropathies: relation to gut inflammation. *Clin Exp Rheumatol* 1990; 8: 23-27

20 Dekker-Saeyes BJ, Meuwissen SG, Van Den Berg-Loonen EM, De Haas WH, Agenant D, Tytgat GN. Ankylosing spondylitis and inflammatory bowel disease. *II. Prevalence of peripheral arthritis, sacroiliitis, and ankylosing spondylitis in patients suffering from inflammatory bowel disease. Ann Rheum Dis* 1979; 38: 35-39

21 de Vos M. Review article: joint involvement in inflammatory bowel disease. *Aliment Pharmacol Ther* 2004; 20 Suppl 4: 36-42

22 Smale S, Natt RS, Orchard TR, Russell AS, Bjarnason I. Inflammatory bowel disease and spondyloarthropathy. *Arthritis Rheum* 2001; 44: 2728-2736

23 Van der Linden SJ, van der Heijde D. Spondyloarthropathies: ankylosing spondylitis. In: Ruddy S, Harris ED, Sledge CB, editors. Kelley’s textbook of rheumatology. 6th ed. Philadelphia: WB Saunders; 2001: 1039-1053

24 François RJ, Braun J, Khan MA. Entheses and enthesis: a histopathologic review and relevance to spondyloarthritides. *Curr Opin Rheumatol* 2001; 13: 255-264

25 Esched J, Bollow M, McGonagle DG, Tan AL, Althoff CE, Asbach P, Hermann KC. MRI of enthesis of the appendicular skeleton in spondyloarthropathies. *Ann Rheum Dis* 2007; 66: 1553-1559

26 Bergfeldt L. HLA-B27-associated cardiac disease. *Ann Intern Med* 1997; 127: 621-629

27 Acheson ED. An association between ulcerative colitis, regional enteritis, and ankylosing spondylitis. *Q J Med* 1960; 29: 489-499

28 Ansell BM, Wigley RA. Arthritic manifestations in regional enteritis. *Ann Rheum Dis* 1964; 23: 64-72

29 Haslock I. Arthritis and Crohn's disease. A family study. *Ann Rheum Dis* 1973; 32: 479-486

30 Wright V, Watkinson G. Sacro-iliitis and ulcerative colitis. *Br Med J* 1965; 2: 675-680

31 Wright V, Watkinson G. The arthritis of ulcerative colitis. *Br Med J* 1965; 2: 670-675

32 Rankin GB, Watts HD, Melnyk CS, Kelley ML Jr. National Cooperative Crohn's Disease Study: extraintestinal manifestations and perianal complications. *Gastroenterology* 1979; 77: 914-920

33 Münch H, Purrmann J, Reis HE, Bertrams J, Zeidler H, Stolze T, Miller B, Korsten S, Cremer S, Strohmeyer G. Clinical features of inflammatory joint and spine manifestations in Crohn's disease. *Hepatogastroenterology* 1986; 33: 123-127

34 Scarpa R, del Puente A, D'Arienzo A, di Girolamo C, della Valle G, Panarase A, Lubrano E, Oriente P. The arthritis of ulcerative colitis: clinical and genetic aspects. *J Rheumatol* 1992; 19: 373-377

35 Protzer U, Dachmann R, Höhler T, Hitzler W, Ewe K, Wanitschke R, Meyer zum Büschenfelde KH, Märker-Hermann E. [Enteropathic spondylarthritides in chronic inflammatory bowel diseases: prevalence, manifestation pattern and HLA association] *Med Klin (München)* 1996; 91: 330-335

36 Veloso FT, Carvalho J, Magro F. Immune-related systemic manifestations of inflammatory bowel disease. A prospective study of 792 patients. *J Clin Gastroenterol* 1996; 23: 29-34

37 Suh CH, Lee CH, Lee J, Song CH, Lee CW, Kim WH, Lee SK. Arthritic manifestations of inflammatory bowel disease. *J Korean Med Sci* 1998; 13: 39-43

38 de Vlam K, Mielants H, Cuvelier C, De Keyser F, Veys EM, De Vos M. Spondyloarthropathy is underestimated in inflammatory bowel disease: prevalence and HLA association. *J Rheumatol* 2000; 27: 2860-2865

39 Queiro R, Maiz O, Intravastini J, de Dios JR, Belzunegui J, González C, Figuerola M. Subclinical sacroiliitis in inflammatory bowel disease: a clinical and follow-up study. *Clin Rheumatol* 2000; 19: 445-449

40 Christodoulou DK, Katsanos KH, Kitsanou M, Stergiopoulou C, Hatzis J, Tsianos EV. Frequency of extraintestinal manifestations in patients with inflammatory bowel disease in Northwest Greece and review of the literature. *Dig Liver Dis* 2002; 34: 781-786

41 Palm Ø, Moum B, Jahnson J, Gran JT. The prevalence and incidence of peripheral arthritis in patients with inflammatory bowel disease, a prospective population-based study (the IBSEN study). *Rheumatology (Oxford)* 2001; 40: 1256-1261

42 Mendoza JL, Lara R, Taxonera C, Alba C, Izquierdo S, Díaz-Rubio M. [Extraintestinal manifestations in inflammatory...
bowl disease: differences between Crohn’s disease and ulcerative colitis]. Med Clin (Barc) 2005; 125: 297-300
43 Peeters H, Vander Cruyssen B, Mielants H, de Vlam K, Vermeire S, Louis E, Rutgeerts P, Belaiche J, De Vos M. Clinical and genetic factors associated with sacroilitis in Crohn’s disease. J Gastroenterol Hepatol 2008; 23: 132-137
44 Rodrigue VE, Costas PJ, Vazquez M, Alvarez G, Perez-Kraft V, Climent C, Nazario CM. Prevalence of spondyloarthopathy in Puerto Rican patients with inflammatory bowel disease. Ethn Dis 2008; 18: 52-225-9
45 Lanna CC, Ferrari Mde L, Rocha SL, Nascimento E, de Carvalho MA, da Cunha AS. A cross-sectional study of 130 Brazilian patients with Crohn’s disease and ulcerative colitis: analysis of articular and ophthalmologic manifestations. Clin Rheumatol 2008; 27: 503-509
46 Maeda K, Okada M, Yao T, Sakurai T, lida M, Fuchigami T, Yoshinaga K, Imamura K, Okada Y, Sakamoto K. Intestinal and extraintestinal complications of Crohn’s disease: predictors and cumulative probability of complications. J Gastroenterol 1994; 29: 577-582
47 Triantafillidis JK, Emmanouilidis A, Manousos O, Nicolakis D, Kogevasias M. Clinical patterns of Crohn’s disease in Greece: a follow-up study of 155 cases. Digestion 2000; 61: 121-128
48 Bernstein CN, Blanchard JF, Rawsthorne P, Yu N. The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. Am J Gastroenterol 2001; 96: 1116-1122
49 Souza MH, Troncon LE, Rodrigues CM, Viana CF, Onofre PH, Monteiro RA, Passos AD, Martinelli AL, Meneghelli UG. [Trends in the occurrence (1980-1999) and clinical features of Crohn’s disease and ulcerative colitis in a university hospital in southeastern Brazil] Arq Gastroenterol 2002, 39: 98-105
50 Al-Shamali MA, Kalouzi M, Patty J, Hasan F, Khajah A, Al-Nakib B. Ulcerative colitis in Kuwait: a review of 90 cases. Digestion 2003; 67: 218-224
51 Steer S, Jones H, Hibbert J, Kondeatis E, Vaughan R, Sanderson J, Gibson T. Low back pain, sacroilitis, and the relationship with HLA-B27 in Crohn’s disease. J Rheumatol 2003; 30: 518-522
52 Podswiadek M, Punzi L, Stramare R, D’Incà R, Ferronato A, Lo Nigro A, Sturmiolo GC. [The prevalence of radiographic sacroilitis in patients affected by inflammatory bowel disease with inflammatory low back pain] Reumatismo 2004; 56: 110-113
53 Scott WW Jr, Fishman EK, Kuhlman JE, Caskey CI, O’Brien JJ, Wals GA, Bayless TM. Computed tomography evaluation of the sacroiliac joints in Crohn disease. Radiologic/clinical correlation. Skeletal Radiol 1990; 19: 207-210
54 McEniff N, Eustace S, McCarthy C, O’Malley M, O’Morain CA, Hamilton S. Asymptomatic sacroilitis in inflammatory bowel disease. Assessment by computed tomography. Clin Imaging 1995; 19: 258-262
55 Dakwar E, Reddy J, Vale FL, Uribe JS. A review of the pathogenesis of ankylosing spondylitis. Neurosurg Focus 2008; 24: E2
56 Khan MA. HLA-B27 and its pathogenic role. J Clin Rheumatol 2008; 14: 50-52
57 Fomberstein B, Yerra N, Pichumoni CS. Rheumatological complications of GI disorders. Am J Gastroenterol 1996; 91: 1090-1103
58 Huaux JP, Fiasse R, De Bruyere M, Naqant de Deuxchaines C. HLA B27 in regional enteritis with and without ankylosing spondylitis or sacroilitis. J Rheumatol Suppl; 77: 60-63
59 De Vos M, Laukens D, Marichal D, Van Den Berghie M, Peeters H, Elewaut D, Mielants H, De Keyser F, Cuvelier C, Veys E, Remaut E, Steidler L. CARD15 mutations in patients with spondyloarthropathy are linked with disease progression and evolution to Crohn’s disease. Gastroenterology 2003; 124 Suppl: A48
60 Orchard TR, Thiyagaraja S, Welsh KJ, Wordsworth BP, Hill Gaston JS, Jewell DP. Clinical phenotype is related to HLA genotype in the peripheral arthropathies of inflammatory bowel disease. Gastroenterology 2000; 118: 274-278
61 Rudwaleit M, van der Heijde D, Khan MA, Braun J, Sieper J. How to diagnose axial spondyloarthritis early. Ann Rheum Dis 2004; 63: 535-543
62 Gravallese EM, Kantrowitz FG. Arthritic manifestations of inflammatory bowel disease. Am J Gastroenterol 1988; 83: 703-709

S- Editor Tian L  I- Editor Cant MR  E- Editor Zheng XM