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Rheumatic manifestations in inflammatory bowel disease.

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Abstract

Rheumatic manifestations are the most frequent extra-intestinal manifestations (EIMs) in Inflammatory Bowel Disease (IBD) patients, and they are responsible for a relevant reduction of quality of life. IBD is associated with a variety of musculoskeletal manifestations such as arthritis and non-inflammatory pain as well as with metabolic diseases, such as osteoporosis. Different imaging techniques (primarily ultrasound, magnetic resonance imaging and X-rays) can help the clinician to correctly identify the nature of manifestations and to treat the patient accordingly. Nowadays, in the setting of IBD-related arthritides, different drugs are available and can be effective on both articular and intestinal involvement. Therefore, a multi-disciplinary approach provides an early diagnosis and a better clinical outcome that can only be given from the recognition and consideration of the different EIMs. As for rheumatic manifestations, namely IBD-related arthritis, an early intervention allows to control disease activity and to prevent structural damage.

Keywords: inflammatory bowel diseases, extra-intestinal manifestations, Spondyloarthritis

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Introduction

Inflammatory bowel disease (IBD), including Crohn's Disease (CD) and Ulcerative Colitis (UC), is a group of chronic systemic inflammatory disorders, primarily involving the gut, which are characterized by a relapsing-remitting course.[1-2] Extra-intestinal manifestations (EIMs) are estimated to affect up to 10-46% of patients, involving different sites, such as the skin, the eye, the liver and the joints.[3-4]Among EIMs, rheumatic manifestations are the most frequent, being detected in up 30-40% of patients.[3-5]A wide spectrum of musculoskeletal manifestations can be observed in IBD patients: inflammatory arthritides (axial and peripheral), peri-articular inflammatory alterations (dactylitis and enthesitis), non-inflammatory manifestations, such as arthralgias, fibromyalgia, osteoporosis.[3-6] IBD-related arthritis is included in the group of spondyloarthropathies since it shares some of the pathogenetic, genetic and clinical backgrounds.[3] In several studies, it has been observed that axial and peripheral arthritides are more frequently diagnosed in patients with colonic involvement in both CD and UC.[3-7] In the last years, the common etiopathogenic basis of IBD and spondyloarthritis (SpA) has become more and more evident; the gut-joint axis, characterized by a cytokinic interplay and reciprocal influences between the two micro-environments, has a leading role in both IBD-related SpA pathogenesis and intestinal manifestations of SpA.[8]

Rheumatic manifestations in IBD are not merely inflammatory: arthralgias, myalgias, osteoporosis, fibromyalgia and skin manifestations, such as erythema nodosum and pyoderma gangrenosum, are detected in a large number of patients. [3-6] A multidisciplinary approach is fundamental in the management of IBD patients, as it is helpful to recognize and promptly treat the disease and to prevent or minimize the numerous manifestations that could affect patients' morbidity and quality of life. [3- 5,9]

A summary of the most frequent rheumatic manifestations is reported in table 1.

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Table 1 – Rheumatic manifestations in IBD.

	Definition	Prevalence
Peripheral arthritis[7,13,17]		
Type 1 peripheral arthritis	<5 joints Mainly large weight bearing joints of the lower limbs. Acute, self-limiting attacks (<10 weeks) Association with bowel activity	4–8%
Type 2 peripheral arthritis	≥5 joints Mainly small joints of the upper limbs Symmetrical distribution Duration usually months to years No association with bowel Activity	1–3%
Enthesitis	Pain and swelling at the site where a tendon inserts the bone	5–10%
Dactylitis	"Sausage-like digit": Entire digit is painful and swollen	2–4%
Axial arthropathies [7,14,17]		
Isolated Sacroiliitis	Diagnosis based on imaging techniques showing sclerosis, erosions and/or ankylosis of the sacroiliac joint	2-32%
Inflammatory back pain	Calin criteria: box 1[23]	5–30%
Ankylosing Spondylitis	Diagnosis based on a combination of inflammatory back pain symptoms, limitation in spinal mobility and imaging techniques showing bilateral sacroiliitis grade ≥2 or unilateral sacroiliitis grade 3–4 [55]	1-10%
Non-inflammatory pain [80,81,82]		
Arthralgia	Joint pain (without swelling)	8–30%
Fibromyalgia	Widespred pain	3-49%
Metabolic pathologies [57,83,84]		
Osteopenia	T score <1,5 at DEXA examination	17-41%
Osteoporosis	T score <2,5 at DEXA examination	20-50%

IBD-RELATED SpA

CLASSIFICATION AND CLINICAL FINDINGS

IBD-related arthritides are a group of inflammatory arthritides which are included within the larger category of spondyloarthropathies, since they share some clinical, radiological and genetic features with the other diseases of these groups (Figure 1). [2,3,7,10]

Figure 1. Spectrum of Spondyloarthritides (Adapted by Parisi S et al.[76])

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IBD-related SpA can be characterized by a peripheral or axial involvement (Figure 1). Different studies have investigated IBD in order to establish possible risk factors for the development of SpA: active intestinal disease, a family history of IBD, smoking, dysbiosis, history of appendectomy and other EIMs (such as erythema nodosum and pyoderma gangrenosum) have been associated with an increased risk for SpA manifestations. [11,12]

IBD-related arthritis, appears to be the EIM with the strongest impact on quality of life, assessed using different scoring methods, such as SF-36 questionnaire .[13]

In retrospective and prospective studies, arthritis prevalence is reported to be between 16% to 33% in Caucasian population. [11-13]

Peripheral arthritis – According to Orchard's classification (1998), IBD-related peripheral arthritides can be distinguished into type 1, oligoarthritis of large joints, and type 2, bilateral symmetrical polyarthritis. [14] This classification has been mainly used by gastroenterologists and less frequently by rheumatologists. [3,7] Oligoarthritis of large joints is the peripheral involvement with the highest prevalence in IBD patients (up to 7-16%). [7,14-16] Oligoarthritis is characterized by the involvement of less than 5 joints, with a sudden onset and a self-limiting, non-erosive disease course (<10 weeks). Arthritis usually appears during IBD flares. Type 1 arthritis can be associated with other EIMs, such as uveitis and erythema nodosum.[14-16] Type 2 arthritis is usually a polyarthritis (≥ 5 joints), affecting symmetrically small joints, especially in the upper limbs, with a persistent course of articular disease and a structural damage if no treatment is administered. The onset and the progression are frequently independent from intestinal disease flares. [14-16]

Peripheral arthritides usually occur after intestinal disease onset as they are more frequently associated to CD and colonic involvement.[17,18]

Enthesitis – it is characterized by inflammation of tendons, ligaments or capsule insertion on the bone and it is a common element of SpA group. This manifestation has not been specifically assessed in clinical studies involving patients with IBD, with a few exceptions made for studies with small sample size, in which the prevalence of enthesitis in IBD is reported to be up to 5-10%. [18-20] Achilles tendon, plantar fascia, elbow tendons insertions are frequently involved, as in other types of SpA.[7,18]

Dactylitis – it is described as a "sausage-like finger", characterized by flexor tendon tenosynovitis, arthritis and subcutaneous oedema; it is a typical feature of SpA and it is reported in up to 2-4% of IBD patients. [7,18,21]

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Axial arthritis – According to Orchard's classification, type 3 arthritis is defined by the association of axial and peripheral arthritis; however, this association is not frequent whilst axial involvement alone is more frequently reported.[14,18,19] Spondyloarthritis onset usually precedes intestinal disease manifestations. Axial involvement can be distinguished in inflammatory low-back pain, isolated sacroiliitis and ankylosing spondylitis. [7,18,22,23] Inflammatory low-back pain, affecting up to 5-30% of IBD patients, can be defined by the fulfilment of at least four out of five criteria (Table 2)[24]

Table 2. Calin criteria for inflammatory back pain.[24]
At least four out of five criteria:
- Age of onset <40 years
- Insidious in onset
- Duration ≥3 months
- Association with morning stiffness
- Improvement after exercise

Ankylosing spondylitis (AS) (1-10% of IBD patients) usually affects young patients (onset between 15 and 40 years of age) and it is characterized by inflammatory back pain and sacroiliitis. Modified New York criteria are the most widely used for the classification of AS in IBD patients.[25] However, classification criteria for axial SpA are largely used in research and clinical practice and these also include the patients with non-radiographic sacroiliitis.[26] In a study by Palm et al. in IBD patients, the diagnosis of AS was not associated with the localization nor with the extent of intestinal inflammation.[27] Isolated sacroiliitis (2-32%) usually occurs in patients with long-standing intestinal disease and is frequently clinically silent. [7,18,23]

PATHOGENESIS

IBD-related SpA pathogenesis is not completely clarified; genetic and environmental factors seem to be involved in immune system dysregulation.

Genetic background emerged as an important predisposing factor associated with development of EIMs. It has been noticed that more than one third of the patients presents with at least two EIMs, postulating a role for common genetic polymorphisms.[28] Different HLA haplotype loci have been associated to different types of EIMs, HLA-B27 being the most studied. [28] In IBD-related SpA, it has been demonstrated that HLA-B27 expression is higher in patients with IBD and AS than in general population (50-80%); nevertheless, it does not reach the prevalence of HLA-B27 expression

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that is seen in AS patients from North-European cohorts (approximately 94%).[20,23,26] On the other hand, HLA-B27 positivity in patients with SpA does not increase the risk of IBD. [18,28] Furthermore, HLA-B27 is also associated with uveitis, skin manifestations and type 1 arthritis. [28] Other HLA loci are associated with specific joint manifestations: i.e. HLA-B35 with type 1 arthritis, HLA-B44 with type 2, HLA-B58 and HLA-DRB1*0103 with skin, joint and ophthalmologic manifestations.[28,29,30]

Different hypotheses regarding the mechanisms by which HLA-B27 may cause intestinal inflammation have been proposed, including the persistence of bacteria due to the misfolding of HLA-B27 β-pockets and to a defective intracellular killing by cells expressing HLA-B27. [30] It has been proposed that HLA-B27 restricted T-lymphocytes can present either bacterial peptides or arthritogenic self-peptides, thus cross-reacting with bacterial antigens.[31,32] Endoplasmic reticulum (ER) stress has been acquiring an important role in IBD pathogenesis: in murine models, it has been demonstrated that HLA-B27 heavy chain has the tendency to misfold during the formation of class I complex in the ER and to form dimers and activate the unfolded protein response (UPR) which alters cellular metabolism, ultimately resulting in inflammation.[32,33]

In the last years, polymorphisms in NOD2/CARD15 gene, which codifies for an intracellular receptor that is present on different kinds of cells (monocytes, macrophages and dendritic cells) recognizing bacterial lipopolysaccharides, have been implied in alterations of the clearance of bacterial components in lymph nodes, leading to an intracellular persistence of pathogens and to an ensuing subclinical gut inflammation in patients with SpA. [34]

Recent genome-wide association studies shed the light on the pathway leading to T helper 17 (Th17) cell development and its relationship with gut and joint inflammation in IBD.[35] Variants in interleukin (IL)23R gene, which is implied in the perpetuation of Th17 population, have been associated with both an increase and a decrease of the risk for CD and AS.[33,36] Different polymorphisms in genes involved in IL23R signalling and Th17 differentiation have been shown in both IBD and SpA.[36,37]

Various hypotheses have been analysed to explain the link between gut inflammation, typical of IBD, and synovial inflammation, characteristic of IBD related arthritides.

Increased gut permeability has been demonstrated both in IBD patients and AS patients, being compared to healthy subjects, and this finding has been proved to be independent from the use of drugs capable of damaging bowel mucosa, such as non-steroidal anti-inflammatory drugs (NSAIDs). [38,39,40]

Microbiota alterations are widely studied in IBD patients[41-44] and recent works have demonstrated the central role of these abnormalities in SpA pathogenesis. A condition of dysbiosis is largely

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present in SpA patients and the increase of Dialister species and Ruminococcus gnavus has been associated with a higher disease activity in AS patients. [49-51]

In CD, bacterial persistence in mesenteric lymph-nodes has been demonstrated to be different from healthy subjects; this element shows there are some undeniable alterations in microbial clearance. On the other hand, intestinal bacterial genome is found to be expressed in synovial tissue of IBD patients; the two microenvironments, gut and synovium are therefore interconnected and the gut-synovium axis hypothesis originated from these evidences.[52] Supporting this hypothesis, T cells that react to bacterial antigens have been found in joint microenvironment; a possible T cells priming could be present in the gut, followed by a recirculation, homing to the synovium and development of arthritis.[53] Furthermore, identical T cells clones have been demonstrated both in gut mucosa and in the synovium of SpA patients.[54]

In addition, in germ-free murine models expressing HLA-B27 allele, it has been shown that mice do not develop arthritis, even under conditions of genetic predisposition, whilst they develop it after their recolonization.[55]

Pathogenetic mechanisms implied in the development of IBD-related arthritis are summarized in figure 2.

Figure 2- Pathogenetic mechanisms involved in gut and articular inflammation.

In presence of genetic predisposing factors (e.g. HLA-B27, IL-23R, CARD15), dysbiosis could promote the activation of inflammatory responses, inducing an imbalance in T-helper (Th) populations that leads to an increase in Th1 and Th17 cells; this element can increase the production of pro-inflammatory cytokines, including IL-17, IL-23, IFN, TNF, IL-6 and IL-1. Intestinal mucosal barrier dysfunction promotes a translocation of damaged bacteria products (such as LPS) which get internalized and processed by antigen-presenting cells (APC), which present the antigen by using HLA class II molecules to CD-4+ T cells. In the gut, B cells promote the production of autoantibodies directed against the shared epitopes of the gut and the joints; this process is caused by the cross-reactivity between bacterial and host epitopes.

Abbreviations: IL interleukin, *ILC* innate lymphoid cell, *IFN* interferon, *TNF* tumor necrosis factor, *LPS* lipopolysaccharide, *MNP* mono-nuclear phagocytes, *GM-CSF* granulocyte-monocyte colony stimulating factor.

DIAGNOSIS

Diagnosis of IBD-related SpA is based on clinical evaluation: patient's clinical history and pain characteristics have a fundamental role in the diagnostic process. History of inflammatory pain,

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both peripheral and axial, and findings of tender and swollen joints or axial impairment are highly suggestive of SpA. Laboratory tests and imaging may support the clinical examination.

Laboratory findings

Nowadays, specific laboratory tests to confirm the diagnosis of IBD-related arthritides are still lacking. Inflammatory markers, erythrocytes sedimentation rate (ESR) or C-reactive protein (CRP) can be elevated either in IBD or in arthritis, so that they are not useful in differentiating the involvement of the bowel from the articular one. In some cases of arthritis, acute phase reactants can also be in the normal range. Anti-citrullinated proteins antibodies (ACPA) and rheumatoid factor (RF) are not markers of SpA as they are usually absent, and their assessment is not useful in clinical practice.[56] Axial arthritis is associated with HLA-B27 haplotype; in IBD, spondylitis is connected with the presence of HLA-B27, but its association is less frequent than the one found in AS (50-70% vs 94%, respectively). Therefore, HLA class I typing is useful in the study of the axial forms.[28,30]

Imaging

Different imaging techniques can be used in the assessment of joint inflammation in IBD-related arthropathies. In the suspect of peripheral arthritides, enthesitis and dactylitis, ultrasound (US) and magnetic resonance imaging (MRI) are valid tools to evaluate inflammatory signs, the former being more easily accessible and rapid.[3,7,18] In axial SpA, MRI is the gold standard for the evaluation of inflammation at the level of sacroiliac (SI) joints and spine.[57] Conventional radiography provides useful information regarding structural damage, both in peripheral and in axial SpA.[58]

Ultrasound– Power-doppler (PD) US is a non-invasive, rapid and inexpensive technique that is capable of assessing inflammatory lesions of peripheral joints and periarticular structures, such as synovitis, tenosynovitis, enthesitis and bursitis.[59] It is useful in the diagnosis as well as in the evaluation of disease activity, in treatment response and as a guide for steroid injections, when needed.[59,60] Whereas PD is the major index of inflammation, grey scale can also evaluate structural lesions, such as bone erosions.[59,61] An important role is emerging for US in the assessment of enthesitis: a study by Bandinelli et al. has shown that the signs of subclinical inflammation in the enthesis were present in many IBD patients, probably indicating the possibility of development of SpA.[62] Furthermore, US can be particularly useful in patients with both SpA and a central sensitivity pain syndrome, such as fibromyalgia, since it allows the physician to clarify if the pain is sustained by inflammation, with consequent implications on therapy.[63]

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MRI - Magnetic resonance imaging (MRI) provides a valuable assessment of inflammation both in peripheral and axial SpA.[57,58] In the first stages of axial disease, in which plain X-rays are still normal (non-radiographic axial SpA), MRI has the ability to detect sacroiliitis by using T1 Weighted Image (T1WI), *Short Tau* Inversion Recovery (STIR) sequences and *T2* weighted *fat saturated* (Fat Sat) sequences. The inflammation is identifiable as a subchondral bone marrow oedema, represented by low T1 and increased T2 and STIR signal intensity. Bone marrow oedema (one area present in almost two consecutive slices or more areas in the same slice) in SI MRI is fundamental, according to ASAS criteria to fulfil the definition of sacroiliitis in axial SpA (Table 3).[64,65]

Table 3. Definition of sacroiliitis on MRI (adapted by Rudwaleit et al. [64])
Types of findings required for definition of sacroiliitis by MRI
- Active inflammatory lesions of the sacroiliac joints (reflecting active sacroiliitis) are required for the fulfilment of the imaging criterion ‘‘sacroiliitis on MRI’’ as applied in the ASAS classification criteria for axial SpondyloArthritis (SpA). - Bone marrow oedema (BMO) (on STIR) or osteitis (on T1 post-Gd) highly suggestive of SpA must be clearly present and located in the typical anatomical areas (subchondral or periarticular bone marrow). - The sole presence of other active inflammatory lesions such as synovitis, enthesitis or capsulitis without concomitant BMO/osteitis is not sufficient for the definition of sacroiliitis on MRI. - Structural lesions such as fat deposition, sclerosis, erosions or bony ankylosis are likely to reflect previous inflammation. At this moment, however, the consensus group felt that the sole presence of structural lesions without concomitant BMO/osteitis does not suffice for the definition of a positive MRI.
Amount of signal required
If there is only one signal (BMO lesion) for each MRI slice suggesting active inflammation, the BMO lesion should be present on at least two consecutive slices. If there is more than one signal (BMO lesion) on a single slice, one slice may be sufficient.

The first European Evidence-based Consensus (ECCO) on EIMs in IBD, published in 2016, confirmed that MRI may identify early sacroiliitis in symptomatic patients with a normal radiography (non-radiographic SpA).[66] Identifying early non-radiological axial SpA allows the prevention of the progression to radiographic axial SpA that occurs in 10–20 % of patients within 2 years if elevated CRP or active inflammation on MRI are present.[67] Moreover, MRI can assess spine inflammatory lesions and it can be used to evaluate disease activity during the follow-up.[58] In

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the spine, MRI can show the "Romanus sign", characterized by a T1-hypointense, and T2- and STIR-hyperintense signal in the vertebral body corner, revealing focal osteitis. In the later stages of disease, fatty bone marrow degeneration can be seen in vertebral endplate; it is characterized by T1 and T2 hyperintensity. [64] Therefore, the use of MRI in SpA can detect inflammatory lesions, as bone marrow oedema, enthesitis, synovitis, dactylitis and capsulitis as well as structural lesions, including bone erosions, bone sclerosis, syndesmophytes, fatty degeneration and ankylosis. [58,68]

Conventional X-rays - Plain radiography of the spine and pelvis show the typical signs of AS and sacroiliitis; however, such elements only appear in the later stages of the disease. In the SIjoints, typical lesions consist of bone sclerosis, erosions, widening of the joint space and ankyloses. [58] According to ECCO guidelines, radiological evidence of sacroiliitis is identifiable in 20-50% of IBD patients, but progressive ankylosing spondylitis only occurs in 1–10% of them.[66,69] In the spine, enthesitis of the annulus fibrosus, followed by sclerosis of the borders of vertebral bodies, leads to the squaring of vertebral bodies as well as to the formation of syndesmophytes, bony bridges which connect the margins of vertebral bodies. In the later stages of uncontrolled disease, the typical "bamboo spine" is also visible.[70] X-rays can also show structural damage in peripheral joints, such as erosions and calcifications, enthesophytes, erosions and bone cortex irregularities.[58] Conventional X-rays are still useful for the diagnosis and follow-up of SpA; according to EULAR recommendations for the use of imaging in the diagnosis and management of Spondyloarthritis in clinical practice,[71] conventional radiography of the SI joints is still recommended as the first imaging method to diagnose sacroiliitis as part of axial SpA.[25] MRI of the SI is an alternative method in young patients and for those with a short-lasting pain, or in those in whom the suspicion of axial SpA is strong but diagnosis cannot be established by using clinical elements and X-rays. Furthermore, plain radiography of the SI joints and/or spine may be used for monitoring of structural damage both in axial and peripheral arthritides. In axial SpA, it can provide information on new bone formation that is predictive of future damage. X-rays should be performed every two years. In peripheral settings, it is the clinical scenario that guides the monitoring of structural damage. [71]

Computed tomography and scintigraphy - Computed tomography (CT) is highly specific in the identification of early bone alterations such as erosions and sclerosis, but it is unable to detect active inflammation; as of today, it is reserved for specific cases in which it is not possible to perform MRI.[72] Likewise, scintigraphy (in selected cases) can detect inflammation even if the sensitivity and

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specificity are lower than MRI. In fact, in a 2008 systematic literature review, a sensitivity of 52% and a specificity of 78% were reported in case of a positive exam.[73]

CLINIMETRY

Disease activity indices allow the physician to choose the proper treatment and to evaluate the efficacy during the follow-up.

Clinimetric scales and function indices are not specific for IBD-related SpA, but they have been validated in AS. In clinical practice, the most used indices are:

- Visual Analogue Scale (VAS) Pain or Numeric Rating Scale (NRS) for pain intensity;
- Health Assessment Questionnaire - Score adapted for SpA(HAQ-S) for functional ability and quality of life;
- articular assessment on 66/68 joints for swollen and tender joints for the peripheral involvement;
- Bath Ankylosing Spondylitis Disease Activity (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) for axial involvement;
- Leeds Enthesitis Index (LEI) for enthesis evaluation.[18,74]

TREATMENT

IBD-related SpA treatment requires the collaboration of gastroenterologists, rheumatologists and other specialists. Type I peripheric arthritis is often related to bowel disease activity; therefore, the treatment of IBD can usually be enough to control this kind of joint inflammation. In UC patients, colectomy can especially be effective on both intestinal and articular involvements.[75] However, some cases of new development of arthritis, after colectomy with ileo-pouch anal anastomosis and consequent pouchitis, have been described.[66] Glucocorticoids injections or a short cycle of oral glucocorticoids can be useful to induce arthritis remission.[57,67] NSAIDs should only be used for short periods, because of their gastrointestinal side effects and for the risk of IBD flares.[68] The use of COX2-inhibitors could be safer for their lower risk of flare.[66,77-79] Type 2 arthritis is often persistent and independent from IBD course; first-line treatment with sulfasalazine or methotrexate (MTX) can be effective in many cases, controlling the inflammation and preventing structural damage.[66] In resistant cases, biological DMARDs can be useful in reducing disease activity. Monoclonal antibodies TNF-inhibitors (TNF-i), especially infliximab and adalimumab, are effective in controlling both articular and intestinal disease, as it has been demonstrated in small case-series.[80-82] On the contrary, etanercept, TNF receptor and IgG1 Fc fusion protein, is not effective on intestinal disease.[83]

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In patients with axial SpA, conventional synthetic DMARDs have not proved to be of any value in controlling disease activity; consequently, TNF-i are recommended in early phases of disease, especially considering the contraindications of using NSAIDs for a long time. [80,84]

In patients with TNF-i failure (either primary or secondary), ustekinumab, a monoclonal antibody against IL-12 and IL-23 p40 subunit that is used for psoriatic arthritis (PsA) and psoriasis, has been approved for CD and UC with moderate-severe disease activity, but not for IBD-related SpA.[85] Tofacitinib, a pan-JAK inhibitor with a major affinity for JAK1 and JAK3, has recently been approved for rheumatoid arthritis (RA), PsA and UC and a phase 3 trial is ongoing to demonstrate its efficacy in axial disease.[86] According to ASAS-EULAR management recommendations in axial SpA, the use of IL-17i therapy should be avoided in patients with active IBD; studies on secukinumab versus placebo showed that it was not effective in CD and resulted in more adverse events;[84] CD and UC onset or exacerbations occurred more frequently in the ixekizumab (IL-17i) group (CD 0.1%, UC 0.2%) than in the placebo group (0%) during the 12-week placebo-controlled period in patients with plaque psoriasis.[87,88] However, in a pooled analysis of three clinical trials, an increase of disease activity during treatment with ixekizumab was not confirmed.[89]

Physiotherapy is the cornerstone of non-pharmacological treatment, especially in patients with axial disease. Its main purpose is to maintain spine flexibility and to prevent deformities who may compromise respiratory function.[90]

NON-INFLAMMATORY PAIN

Arthralgias are the most frequent EIM in patients with IBD and they should be promptly investigated to exclude inflammatory joint involvement. Joint pain prevalence was estimated to be present in up to 22%-30% of these patients in different studies.[6,7,91] However, such a percentage may be higher since this symptom is frequently not reported in clinical studies.[7,18] Central sensitivity pain syndromes are frequently associated with IBD. The prevalence of fibromyalgia is debated: different studies showed different results, demonstrating in some cases a much higher prevalence (22-49%) than general population, in contrast with other studies (approximately 3%).[92,93]

OSTEOPOROSIS

Osteopenia and osteoporosis are common in both male and female patients (20-50%) with IBD due to malabsorption.[66] Diagnosis of osteoporosis is based on evaluation of bone mineral density (BMD) in dual-energy X-ray absorptiometry (DEXA). A BMD of at least 2.5 standard deviations

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(T-score ≤ −2.5) lower than the level of the general population indicates osteoporosis.[94] In IBD patients, whose age is usually 20 to 40 years old, osteopenia and osteoporosis are linked to intestinal disease activity. In several studies, TNF-i treatment induced an improvement of BMD, acting on disease activity.[95] A 2003 study showed that a large population of IBD patients normalized BMD status after 3 years of disease remission.[96] IBD patients have a higher risk of vertebral fractures in comparison to general population, regardless of a normal or reduced BMD. The strongest predictor for future fractures is a previous vertebral fracture.[66,97]

In ECCO guidelines, IBD patients are suggested to be given the same screening of the general population.[66] Chronic inflammation, corticosteroid treatments, extensive small-bowel disease or resection with consequent malabsorption and nutritional deficiencies, smoking, low physical activity and sarcopenia are the most frequent risk factors for osteoporosis in IBD patients. Weight-bearing exercise, stopping smoking and an adequate calcium intake are recommended in preventing bone loss. Patients receiving a systemic steroid therapy and those with a T score less than -1.5 should receive appropriately calcium and vitamin D supplementations as prophylaxis.[66,98] Treatments with bisphosphonates and other agents should be considered for patients receiving steroid therapies for 3 months or more, as reported by the Italian intersocietal guidelines for osteoporosis.[99,100] This therapy should also be considered in patients with low BMD and additional risk factors, such as previous vertebral fractures.[66] The evidence for treatment and prevention of osteoporosis in young patients is limited; treatments should be adjusted considering the clinical history as well as other risk factors for bone loss.[66] Treatment of IBD is fundamental for BMD improvement, especially in young patients; in postmenopausal women and in patients with spontaneous fractures, bisphosphonates and other specific treatments should be considered to reduce the risk of further bone loss and fractures. [66,101,102]

Conclusions

Rheumatic manifestations in IBD are the most frequent EIMs and have a strong impact on the quality of life. The correct assessment of IBD patients often requires a multi-disciplinary approach to diagnose and eventually treat EIMs, such as SpA, that can conduct, if misrecognized, to articular damage and loss of functionality. The availability of different imaging techniques may help the clinician to identify subclinical inflammation or early stage of the disease, which allows a prompt treatment and good clinical outcome.

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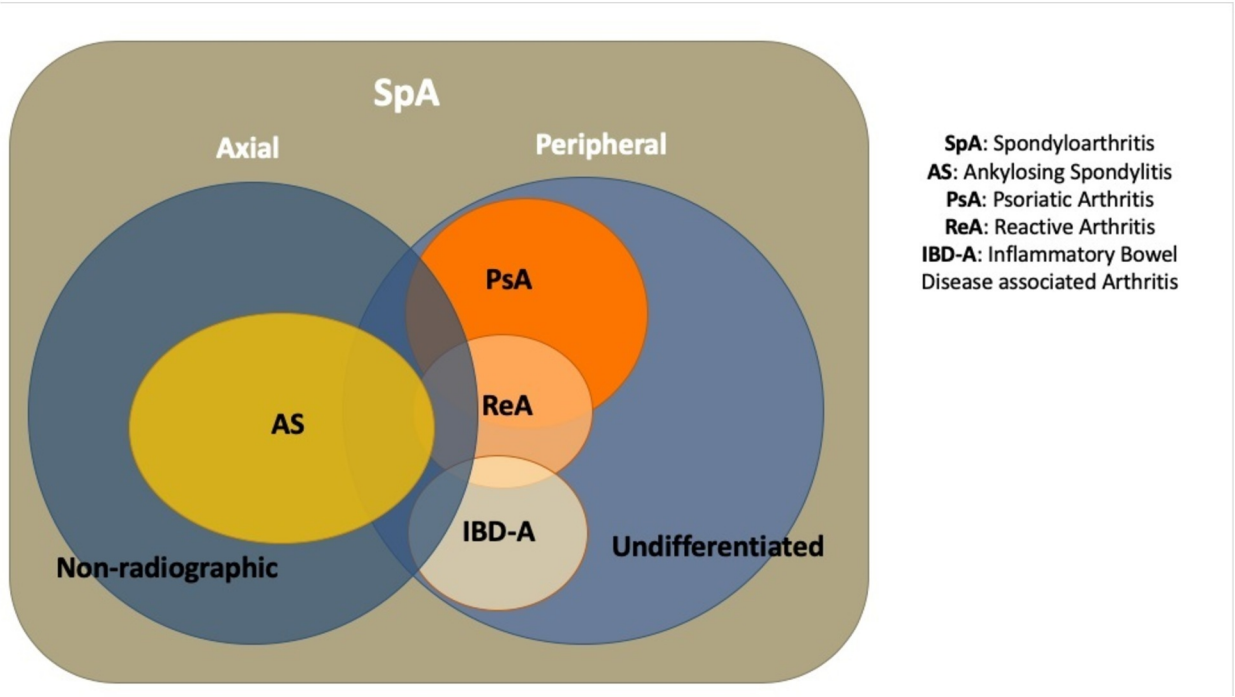

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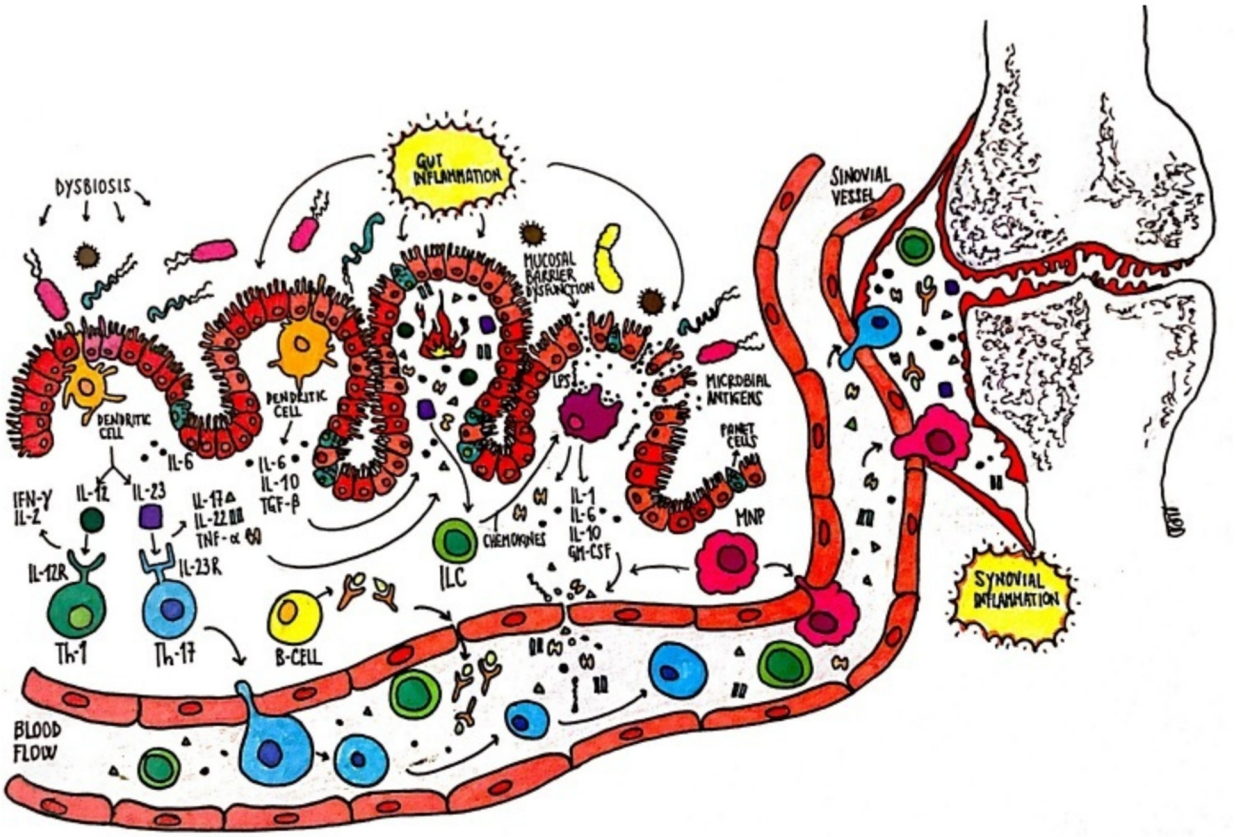

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