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REVIEW ARTICLE

Occult spondyloarthritis in inflammatory bowel disease

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Abstract Spondyloarthritis (SpA) is a frequent extra-intestinal manifestation in patients with inflammatory bowel disease (IBD), although its real diffusion is commonly considered underestimated. Abnormalities in the microbioma and genetic predisposition have been implicated in the link between bowel and joint inflammation. Otherwise, up to date, pathogenetic mechanisms are still largely unknown and the exact influence of the bowel activity on rheumatic manifestations is not clearly explained. Due to evidence-based results of clinical studies, the interest on clinically asymptomatic SpA in IBD patients increased in the last few years. Actually, occult enthesitis and sacroiliitis are discovered in high percentages of IBD patients by different imaging techniques, mainly enthesis ultrasound (US) and sacroiliac joint X-ray examinations. Several diagnostic approaches and biomarkers have been proposed in an attempt to correctly classify and diagnose clinically occult joint manifestations and to define clusters of risk for patient screening, although definitive results are still lacking. The correct recognition of occult SpA in IBD requires an integrated multidisciplinary approach in order to identify common diagnostic and therapeutic strategies. The use of inexpensive and rapid imaging techniques, such as US and X-ray, should be routinely included in daily clinical practice and trials to correctly evaluate occult SpA, thus preventing future disability and worsening of quality of life in IBD patients.

Keywords Inflammatory bowel disease · Occult enthesitis · Occult sacroiliitis · Spondyloarthritis

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Introduction

The inflammatory involvement of sacroiliac joints (SIJ), entheses, and peripheral joints is one of the most frequent extra-intestinal manifestations complicating the clinical course and therapeutic approach in inflammatory bowel disease (IBD) [1]. The frequency of musculoskeletal manifestations is about 20–50 % in both Crohn's disease (CD) and ulcerative colitis (UC) [2–4], although their real diffusion is commonly considered underestimated [5]. Unfortunately, until now, the exact link between IBD and spondyloarthritis (SpA) is not clearly explained and the influence of the bowel activity on rheumatic manifestations is still uncertain.

The interest on clinically occult SpA in patients with IBD has increased in the last few years for the acknowledgment of the evidence-based results of clinical studies employing new imaging techniques such as ultrasound (US) [6], as well as basic research findings highlighting possible shared pathogenetic mechanisms between the two diseases [7]. In particular, the increasing use of imaging techniques in SpA diagnosis and the advent of anti-tumor necrosis factor-α (TNF-α) therapies effective in both diseases have deeply fostered collaboration between rheumatologists and gastroenterologists [8].

The SIJ and the enthesis, this latter defined as the site of attachment of tendons, ligaments, joint capsules, and fascia to bone, seem to be the most important targets in the early phase of SpA [6, 9, 10]. The enthesis was even interpreted as a unique organ including functionally linked structures considered as the *primum movens* of the inflammatory process in SpA [11]. Although biological agents seem effective in preventing enthesitis in animal models [12], currently, there is no sufficient knowledge of the natural history of subclinical joint damage progression to support the use of anti-TNF-α therapies in IBD patients with occult SpA.

The aim of this review article is to discuss the possible correlation between SpA and IBD, as well as the utility of new imaging techniques in the diagnosis of occult SpA in patients with IBD.

Pathogenetic bases of the joint–gut axis in IBD

The close relationship between joint and gut inflammation has been confirmed by several studies. As aforementioned, the prevalence of articular involvement in IBD patients is underestimated and ranges from 20 to 50 % [2–4]. On the other hand, gastrointestinal tract inflammation that resembles IBD has been reported in about 70 % of patients with SpA and, in the long term, 7 to 12 % of patients with SpA will develop overt IBD, suggesting a shared etiology [13–16]. Moreover, although initial studies proposed that some articular complications in IBD may be associated with gut relapse, the association of SpA clinical manifestation and gut inflammation is still controversial. In fact, some biopsy studies demonstrated that the clinical course of articular disease was independent of IBD activity [13–15, 17]. In another study, when SpA patients with initial gut inflammation were followed up clinically and at gut endoscopy, clinical articular remission was associated with endoscopic and histological gut remission. Moreover, the evolution to ankylosing spondylitis (AS) correlated to initial chronic gut inflammation [17].

It is now increasingly recognized that the gut microbiome, which is defined as the collective genomes of the microbes living inside the human intestine, plays a crucial role in the pathogenesis of both CD and UC, and may take center stage in the link between IBD and SpA [18]. The evidence that the microbiome is critical in IBD primarily derives from animal models. As an example, the absence of NLRP6 gene, which is expressed by intestinal epithelial cells and contributes to innate immunity, results in colitis and alteration of the intestinal microbiota in mice [19]. Moreover, several studies reported that murine models of bowel inflammation are markedly improved in a germ-free setting. In this context, in the SKG mouse model, which has features of IBD and SpA, and like human AS shows marked involvement of interleukin-23 (IL-23)-dependent immunological pathways [20], mice raised in germ-free conditions are unaffected [21].

Some of the evidence that AS may be a microbiome-driven disease is based on genetic analogy between IBD and AS. Indeed, a large number of genes associated with IBD are also associated with AS, and in the majority of cases, the genetic variant shows the same risk direction in both diseases [22]. Interestingly, a high proportion of those genes are involved in mucosal immunity [23]. In fact, several studies reported that AS is associated with genetic variants in genes encoding for the transcription factors RUNX3, EOMES, and TBX21, as well as the cytokine receptors IL7R and IL23R [18, 23], all of which are key regulators of the differentiation and activation of innate lymphoid cells, which are in turn critical components of mucosal immune defenses. CARD15 is another gene that may play a peculiar role in the genetic link between intestinal and joint inflammation. This gene encodes for the intracellular protein NOD2 which is expressed in monocytes, granulocytes, and dendritic, epithelial, and Paneth cells, and has binding affinity for bacterial cell wall components [16, 24]. NOD2 participates in the innate immune response by activating nuclear factor-kB, a key transcriptional regulator controlling the expression of a large number and variety of genes encoding for proinflammatory cytokines, adhesion molecules, chemokines, growth factors, and inducible enzymes [16, 24]. Mutations in CARD15 gene result in a disturbed cellular response to bacterial components, leading to intracellular persistence of pathogens [25, 26]. A significantly higher frequency of CARD15 mutation carriers has been reported in the subgroup of SpA patients with chronic inflammatory gut lesions than in the control population or the other SpA patients [27]. Moreover, CARD15 variants have been identified as possible genetic predictors of CD-related radiological sacroiliitis [28].

The evidence that the microbiome may be important in the pathogenesis of AS and IBD-related joint disease relies mainly to studies on the human leukocyte antigen (HLA) gene and, in particular, the HLA-B27 allele [18]. No gene locus within the genome is as polymorphic as the HLA. The main theory is that the HLA type would affect the response to bacterial antigens such that different HLA types would determine the differential survival of specific microorganisms, thus shaping the microbiome. Some experimental evidence to support this hypothesis has been reported in mice which are transgenic for the expression of the human HLA type DR4 [29]. As far as HLA-B27 is concerned, it has been proposed that this allele leads to a state of mucosal immunodeficiency [30] and that genes associated with AS may either contribute to that immunodeficiency or lead to enhanced immunological reactions driven by bacterial invasion permitted by HLA-B27 [18]. This might either be a direct effect due to reduced ability to drive immunological responses against particular luminal bacteria, an indirect effect due to changes in intestinal permeability, or caused by alterations in the gut microbiome such as a loss of protective bacterial species [18]. A strong association has been reported between HLA-B27 and AS, with more than 90 % of patients being HLA-B27 positive [31]. Moreover, 25–78 % of IBD patients with AS are HLA-B27 positive [32–35]. In contrast, isolated sacroiliitis in CD patients seems to be unrelated to HLA-B27 [33, 35, 36].

The importance of HLA-B27 and possible related microbiome alterations in the link between AS and IBD is mainly supported by experimental models. In particular, rats transgenic for HLA-B27 and human β2-microglobulin develop a disease that strikingly resembles human SpA, including

colitis and arthritis [10, 37, 38]. Of note, the development of gut and joint inflammation does not occur in HLA-B27 transgenic rats bred in germ-free conditions, but strikingly manifests after reintroduction of the normal intestinal bacteria [39]. These findings provide the most convincing evidence for the important role of intestinal microbiome in the pathogenesis of B27-associated gut and joint inflammation. In HLA-B27 transgenic rats, colitis with diarrhea is the earliest clinical manifestation, while after several weeks of the onset of intestinal inflammation, most affected rats develop peripheral arthritis [10, 37, 38]. In these rats, arthritis is characterized by swelling and tenderness of the tarsal joints of one or both hind limbs. Histologically, earlier studies by Taurog and colleagues reported that in HLA-B27 transgenic rats, the involved joints show lesions resembling peripheral arthritis in humans, with synovial hyperplasia, pannus formation, inflammatory cell infiltration, and destruction of articular cartilage and bone, ultimately leading to fibrous ankylosis [10, 37, 39]. Subsequently, other authors described diffuse subcutaneous edema and inflammatory infiltrate in the plantar fascia, around tendons, and extending into the entheseal region, while no inflammatory infiltrate was detected in the synovium of HLA-B27 transgenic rats [12]. Interestingly, it is known that entheseal involvement is a pivotal event in the development of SpA in humans [11, 40–42], although the functional relationship between the enthesis and the adjacent synovium is not yet fully understood [11].

An explanation for the pathogenesis of joint inflammation in IBD patients may be the specific trafficking of intestinal lymphocytes to the joints. Indeed, experimental evidence suggests that activated intestinal lymphocytes in IBD patients may adhere to inflamed synovial vessels via multiple adhesion molecules and their counter receptors [16]. In vitro studies demonstrated that activated human intestinal immune cells adhere selectively both to intestinal mucosa and synovial high endothelial venules, but do not bind to peripheral lymph node vasculature, thus supporting the notion that intestinal lymphocytes may have the capacity to enter the joints, also known as the "gut iteropathy concept" [16, 43–45]. Most importantly, if intestinal T cells in SpA patients migrate to the joints, then identical clonally expanded T cells must be found in both intestine and joints. T cell clones, specific for enterobacterial antigens, have been derived from the synovial fluid or membrane of patients with infection-triggered reactive arthritis, a condition in which a full-blown SpA can develop following a bacterial gut infection [45]. The existence of identical expanded T cell clones could be demonstrated in a patient with enterogenic SpA, even if the evidence that only a few clones were shared by both gut and joint compartments suggests that this phenomenon cannot be simply explained by intestinal lymphocyte activation [46]. Furthermore, the aberrant migration of lymphocytes into the joints does not explain the presence of bacterial components in synovial fluid or tissue from SpA patients. Considering that macrophages are primary cellular targets for the intracellular pathogens associated with SpA, it is conceivable that trafficking of monocytes/macrophages from gut to joint could be a critical factor in the relation between gut and joint inflammation. In fact, macrophages could contribute to disease pathogenesis by the uptake of bacterial components in the intestine, with subsequent presentation to T cells and migration to the target joints. In support of this hypothesis, it has been shown that not only lymphocytes but also macrophages isolated from intestinal mucosa can bind in vitro to vessels from inflamed human synovial tissue [43]. In particular, a subset of macrophages expressing the scavenger receptor CD163 was found to be enriched in the gut mucosa of patients with SpA and CD [47]. This specific macrophage subset appears also selectively increased in SpA synovium and correlated with disease activity [48, 49].

Occult enthesitis in IBD

The pathology of entheses in IBD and SpA patients is often underdiagnosed or mistaken for overuse tendon pathology [50]. Actually, it is discovered by clinical examination only in a low percentage of patients [8, 51]. Several studies reported the usefulness of US in the evaluation of abnormalities of fibrocartilaginous entheses in the course of SpA [8].

In 2005, Outcome Measures in Rheumatology (OMERACT) defined enthesopathy as "the abnormally hypoechoic (loss of normal fibrillar architecture) and/or thickened tendon or ligament at its bony attachment (that may occasionally contain hyperechoic foci consistent with calcification), seen in two perpendicular planes that may exhibit Doppler signal and/or bony changes including enthesophytes, erosions or irregularity" [52]. This definition has the advantage of focalizing the main characteristic of entheseal abnormalities, but has the great limitation of not clearly defining the difference between enthesopathy and enthesitis [8]. While enthesopathy is commonly assessed by grey scale US and is defined as the presence of erosions, enthesophytes, bursitis, and thickness [53], enthesitis is studied by power Doppler (PD) US that allows the evaluation of entheseal vascularity and is considered a specific sign of active disease [54]. Furthermore, the degree of entheseal perfusion at PD US might also be relevant to guide the choice of drugs and to monitor the efficacy of treatments [55–57].

Numerous US scoring systems have been developed with great heterogeneity of the examined sites [8]. The most commonly investigated entheses are those located in the lower limbs (i.e., patellar, quadriceps and achilleon tendons, and plantar fascia), but elbows (i.e., common extensor and triceps tendons) are also included in some scores [58].

Increasing evidence indicates that US assessment of entheses is a powerful tool to discover either subclinical or occult SpA [8]. While subclinical enthesitis in the early phase of SpA is underestimated by routine objective clinical examination in comparison with US findings, occult enthesitis can be discovered only by US in IBD and psoriasis patients without any signs and symptoms of SpA [51]. Otherwise, the definition of this hidden disease is often unclear as the terms "subclinical" and "occult" may be confused.

In recent years, different groups demonstrated that objective clinical examination has a lower sensitivity (14.4–22.6 %) than US (57–62 %) for discovering enthesopathy in SpA [53, 54]. In a cohort of 113 early SpA patients, De Miguel et al. confirmed the high sensitivity (53.1 %) and specificity (83.3 %) of entheseal US compared with non-inflammatory controls and other rheumatic diseases [59]. Enthesitis might be often underdiagnosed overall in early disease phase as also shown in early psoriatic arthritis (PsA) patients, in which tenderness of entheses was detected only in 29.3 % at objective clinical examination, while US revealed enthesopathy in 100 % and enthesitis in 40.2 % of cases [60]. The most relevant findings shown by US in the early phase of entheseal pathology were thickness and PD signal at entheses [60, 61], probably due to edema, neovascularization, and cell infiltration, as reported also at histological examination in both human SpA and the HLA-B27 transgenic rat model [12, 62]. To date, numerous studies showed the presence of occult enthesopathy and enthesitis in patients with psoriasis and without rheumatic clinical signs [63–65]. In IBD patients without signs and symptoms of SpA, Bandinelli et al. recently demonstrated by US the presence of enthesopathy and enthesitis in 92 and 16 % of cases, respectively, without any correlation with the IBD activity indices [6].

Tinazzi et al. reported that occult entheseal thickness of quadriceps in patients with psoriasis has prognostic value for the development of PsA in a follow-up of 3.5 years [66]. Furthermore, in a prospective study on patients with early SpA, D'Agostino et al. established that PD US had a good predictive value (76.5 % sensitivity and 81.3 % specificity) for the diagnosis of definitive SpA [61]. Otherwise, the predictive value of occult entheseal US abnormalities in IBD patients for the development of definitive SpA has not yet been studied in prospective studies.

Occult sacroiliitis in IBD

The involvement of SIJ is the major expression of axial disease in SpA, and it is well known that the early detection of SIJ inflammation is essential to identify and treat the disease on time [6, 67]. Nevertheless, the SIJ abnormalities in SpA and IBD may be frequently underdiagnosed and the onset of inflammatory processes may precede even of many years the emergence of clinical symptoms [68]. Even if magnetic resonance imaging (MRI) is now widely accepted as the gold standard to detect SIJ involvement in SpA [69, 70], other imaging techniques are also used to study SIJ involvement in SpA and IBD, such as traditional X-ray and computerized tomography (CT) [71–74]. X-ray is still the less expensive and the most diffuse imaging technique that uses a limited quantity of ionizing radiation to evaluate the pelvis, and is a specific diagnostic tool to diagnose low-grade sacroiliitis in early SpA, although it is considered less sensitive than MRI and CT [75]. Since 1965, radiographic surveys suggested a prevalence of 18–27 % of isolated sacroiliitis in IBD [28, 36, 71, 72], but in the majority of patients, it was commonly considered a non-progressive condition to severe spinal involvement [13]. Subsequently, McEnnif et al. demonstrated the high prevalence of asymptomatic occult SIJ abnormalities on X-ray (18 %) and CT (32 %) in IBD patients without inflammatory back pain [74]. In particular, this study described signs of sclerosis and erosions of SIJ until complete ankylosis but did not report the frequency of the different radiological grades observed [74]. Later on, Bandinelli et al. showed occult SIJ abnormalities at X-ray in 27 % of IBD patients, with isolated sclerosis in 77.2 % and localized erosions with sclerosis in 22.7 % of patients [73]. Moreover, none of the patients had partial or complete ankylosis [73], according to previous results of Queiro et al. reporting a subclinical low-grade sacroiliitis in 60 % of the IBD patients examined [36]. A higher prevalence of sacroiliitis in IBD was also previously estimated by scintigraphy, with radioisotope uptake found in up to 52 % of patients with CD and 42 % of patients with UC [76]. However, given the large degree of inter- and intra-observer variability, the significance of these findings is unclear. In fact, the specificity of scintigraphy for sacroiliitis is actually considered very low [77].

Recently, Leclerc-Jacob et al. found bone marrow edema in the subchondral or peri-articular compartment at MRI with diagnosis of sacroiliitis according to Assessment of SpondyloArthritis international Society (ASAS) criteria in 31/186 (16.7 %) of IBD patients (with a very low interreader variability) [78]. The authors evaluated retrospectively the prevalence of SIJ abnormalities in IBD patients from MRI colonography or enterography (T1 with fat suppression and contrast agent injection) images performed during the follow-up of IBD activity. However, the authors included also 32 IBD patients with rheumatic symptoms (7 with complete SpA diagnosis) followed up by rheumatologists (12/32 with SIJ involvement at MRI). Thus, we might deduce that 19/154 (12.3 %) patients with bone edema at MRI had an occult SIJ disease, even if the authors did not specifically report the absence of rheumatic symptoms [78].

Furthermore, only few studies prospectively investigated the progression of occult SIJ abnormalities to axial SpA and AS, as well as the role of factors predisposing to such

progression [36, 73, 77]. Queiro et al. investigated the evolution of subclinical sacroiliitis in IBD patients, showing that the former classification criteria for SpA were not useful to diagnose the onset of SpA in a follow-up of 4 years [36]. Subsequently, the new ASAS criteria for axial SpA were introduced to better allow the early recognition of SpA [77].

According with previous results on low-grade sacroiliitis as a prognostic factor for progression of undifferentiated SpA to AS [75], Bandinelli et al. showed that in IBD patients minimal occult SIJ abnormalities on X-ray might precede the onset of axial SpA, suggesting the usefulness of early screening with pelvis X-ray [73]. In addition, at 3 years follow-up, the development of full-blown axial SpA was confirmed also by MRI findings of bone edema at SIJ [73].

To date, in IBD patients, no study detected possible genetic and clinical risk factors for SIJ involvement at baseline. Patients with isolated sacroiliitis are commonly considered likely to carry the HLA-B27 aplotype that is also considered a marker of progressive axial disease in AS [10, 13]. However, the prevalence of the HLA-B27 aplotype in IBD patients is lower than in AS with wide variation across populations and ethnic groups [79]. Accordingly, Bandinelli et al. found that among IBD patients with occult SpA, none was HLA-B27 positive [73], which is consistent with other studies that failed to detect a correlation between the HLA-B27 aplotype and radiological sacroiliitis in IBD [28, 35, 36, 80]. Similarly, in psoriasis patients, the occult X-ray sacroiliitis occurring in 64.3 % of cases did not correlate with HLA-B27 positivity [81]. A controversial role for the CARD15 gene in the predisposition to occult sacroiliitis in IBD patients has also been reported [28, 72]. The possible association of occult SIJ abnormalities in IBD and the HLA-B35, HLA-B44, and HLA-DRB1 aplotypes which have been previously associated with peripheral arthritis in IBD [82] have not been studied until now.

Concerning possible clinical risk factors, although some authors demonstrated that sacroiliitis was more prevalent in patients with a long history of IBD [5, 32, 78], no significant differences in duration of bowel symptoms were found between patients with and those without radiological sacroiliitis in other studies [72–74]. Furthermore, a possible link between gut histology and peripheral manifestation of SpA has been proposed [83]. Instead, other authors demonstrated that SIJ involvement did not correlate to bowel activity and previous bowel surgery intervention in IBD patients [73, 74, 78]. These findings might suggest that enteric and rheumatic manifestations are probably due to the same pathogenetic mechanisms, but are likely two distinct diseases. However, the only study that specified the IBD activity scores investigated only remittent and low-activity patients [73]. Therefore, early and high-activity IBD patients should be further evaluated in future studies to confirm these data.

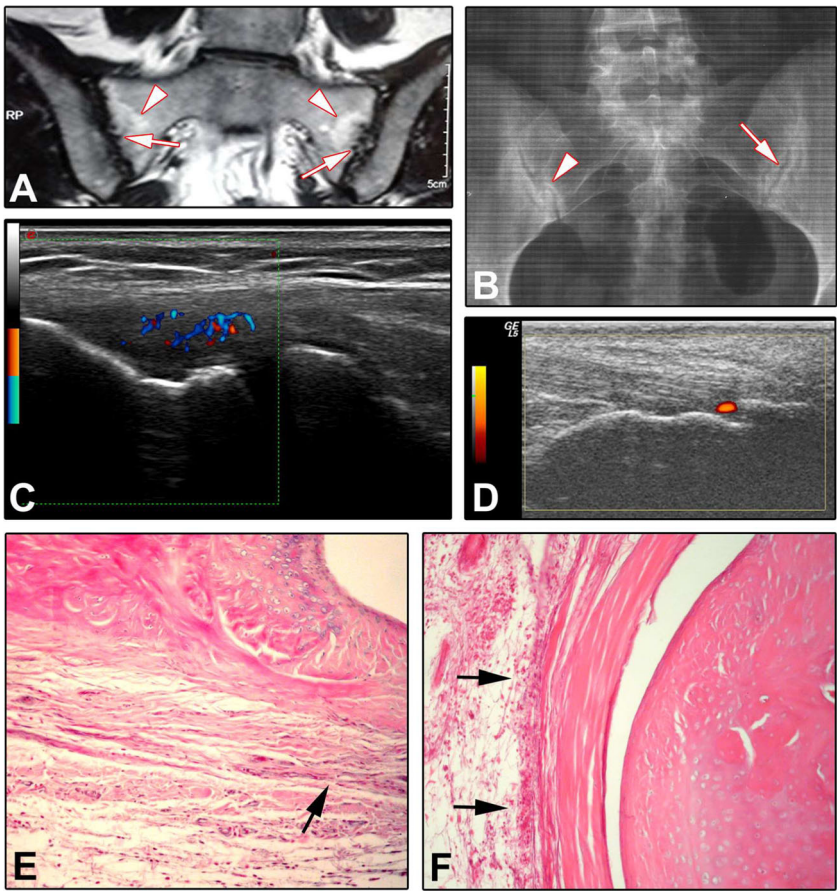

Fig. 1 **a** Occult sacroiliitis in a patient with inflammatory bowel disease (IBD) detected by magnetic resonance imaging (T1 with contrast). *Arrows* indicate bone erosions, while *arrowheads* indicate bone edema at sacroiliac joints (SIJ). **b** Occult sacroiliitis in a patient with IBD detected by X-ray. Bone erosions (*arrow*) and sclerosis (*arrowhead*) at SIJ are evident. **c** Occult enthesitis of the elbow common extensor tendon revealed by intense power Doppler (PD) signal at ultrasound (US) in a patient with IBD. The enthesis appears thickened. **d** Occult enthesitis of the achilleon tendon revealed by low PD signal at US in a patient with IBD. Note the presence of an enthesophyte near the PD signal. **e**, **f** Histological images of entheses in the HLA-B27 transgenic rat model of human IBD-associated spondyloarthritis. *Arrows* indicate the presence of inflammatory infiltrate at the entheseal tendon insertion (**e**) and around tendon and plantar fascia (**f**). Hematoxylin-eosin staining

Conclusion

The inflammatory involvement of entheses and SIJ is one of the most frequent and underestimated extra-intestinal manifestation in patients with IBD. Although complex microbiologic and genetic factors have been suggested, the exact pathogenetic link between articular and gut involvement is not clearly defined. Of note, the microbiome may take center stage in the pathogenesis of IBD-related joint disease as suggested by studies on the HLA-B27 gene and animal models, such as the HLA-B27 transgenic rat model which develops pathological features resembling human IBD-associated SpA (Fig. 1). From a clinical point of view, the examination of entheses by US and the assessment of SIJ by X-ray might be useful to detect subclinical and occult SpA abnormalities (Fig. 1) and even predict their possible progression to definite SpA. Several genetic and clinical features of IBD were investigated as possible predictors for the evolution of occult entheseal and sacroiliac SpA to overt axial SpA and AS; however, currently, there are no proven risk factors. The correct recognition of occult SpA needs an integrated multidisciplinary approach in order to identify common diagnostic and therapeutic strategies, especially in the era of the new biologic therapies. The use of inexpensive and rapid imaging techniques, such as US and X-ray, should be routinely included in daily clinical practice and trials to correctly evaluate occult SpA, thus preventing future disability and worsening of quality of life in IBD patients.

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