

# Seronegative Spondyloarthropathies: Evolving Concepts Regarding Diagnosis and Treatment

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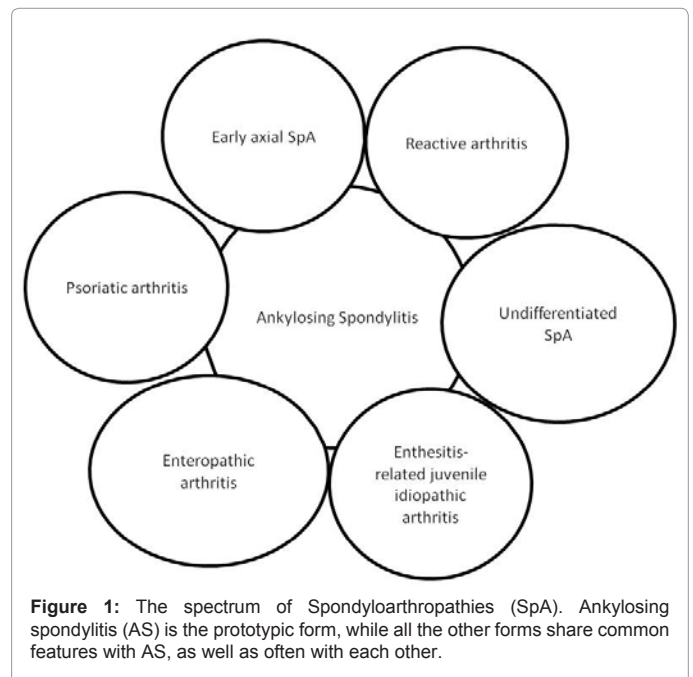
The story of the seronegative spondyloarthropathies (SpA) is one of splitting and lumping. Initially regarded as a form of rheumatoid arthritis (RA), it became evident that they have some distinct clinical, radiographic and immunogenetic features that compel them to be classified as disease entities different from RA [1,2]. The RA hallmarks, i.e. the symmetric involvement of the small diarthrodial joints of hands and feet with the occurrence of erosions and absent new bone apposition, the frequent auto-antibody [rheumatoid factor (RF) and anti-citrullinated peptide antibody (anti-CCP)] positivity and a recurring genetic polymorphism termed the “shared epitope” hosted on the B chain of certain HLA-DR alleles, are lacking in patients with SpA. In particular, the absence of RF was the basis the SpA group of diseases was labeled “seronegative”. However, this term is presently considered obsolete, since the significance of RF in SpA has been limited in differentiating psoriatic arthritis (PsA) from RA in the context of classification criteria [3,4] and bears no prognostic value for SpA patients.

In contrast, SpA patients are characterized by a particular type of involvement of the axial skeleton (sacroiliitis and/or spondylitis with a propensity for syndesmophyte formation and ankylosis) or the extremities (asymmetrical involvement of the peripheral joints, predominantly large joints of the lower limbs, dactylitis and enthesitis). Moreover, a variety of common genetic and extra-skeletal features, among them the frequent presence of the HLA-B27 allele and the susceptibility for acute anterior uveitis, further support the concept that these diseases are related. Multiple mechanisms have been described implicating HLA-B27 in SpA pathogenesis [5]. Additionally, an array of clinical manifestations has helped identify distinct SpA syndromes, which occasionally differ as regards treatment and prognosis. Thus, the classical types of SpA are ankylosing spondylitis (AS), the prototype of SpA, psoriatic arthritis (PsA), reactive arthritis (ReA) and enteropathic arthritis (EA), i.e. a chronic inflammatory axial and/or peripheral arthritis associated with inflammatory bowel disease, and enthesitis-related juvenile idiopathic arthritis (Figure 1) [6]. However, these syndromes are often inter-related since up to 20% of patients with ReA eventually develop features of classical AS, while up to 60% of AS patients have subclinical gut inflammation as observed endoscopically or histopathologically [7]. Besides, a proportion of patients with features of SpA do not fulfill criteria to be classified in one of the defined forms above and therefore they are referred to as having undifferentiated SpA [8]. The realization that diverse clinical presentations may be fundamentally related led to the development of different sets of criteria (Amor [9], ESSG [10], ASAS [11], Figure 2, 3) to facilitate the diagnosis and classification of patients for clinical trials.

Despite the advances in definitions, little progress in SpA treatment had been made up to early 2000's. The mainstay of medical therapy was non-steroidal anti-inflammatory drugs (NSAIDs), while persistent peripheral arthritis, especially in PsA patients, was (and still is) treated with modalities adopted from RA therapeutics [12]. Axial disease, however, remained a major cause of morbidity, functional loss and permanent disability, since failure of NSAIDs left no other option to relieve patients [13,14]. The advent of Tumor Necrosis Factor- $\alpha$  (TNF $\alpha$ ) blockers (infliximab, etanercept, adalimumab and recently golimumab) was a major step forward for the treatment of SpA filling the therapeutic gap for axial disease [15-18], as well as for disease-

modifying anti-rheumatic drug (DMARD)-resistant peripheral disease [12,19]. Therefore, the introduction of TNF $\alpha$  inhibitors caused a major shift in the approach of SpA patients: on clinical grounds, what truly matters is whether the patient has only peripheral SpA (and should thus be given a trial of DMARDs after NSAIDs have failed); or, alternatively, if the patient has signs of axial disease (and should thus be prescribed anti-TNF $\alpha$  treatment after a proper trial of NSAIDs has failed).

The clinical problem described above, although seemingly straightforward, raised the question of which patients have axial disease and the appropriate methods for proving it. Indeed, the 2003 and 2006 Assessment of SpondyloArthritis international Society (ASAS) recommendations for the use of TNF $\alpha$  blockers in SpA actually referred only to patients with AS classified according to the 1984 modified New York criteria [20-22]. However, these criteria require the presence of sacroiliitis advanced enough to be unequivocally identified on plain radiographs. Yet, it is now known that bone changes advance in a slow



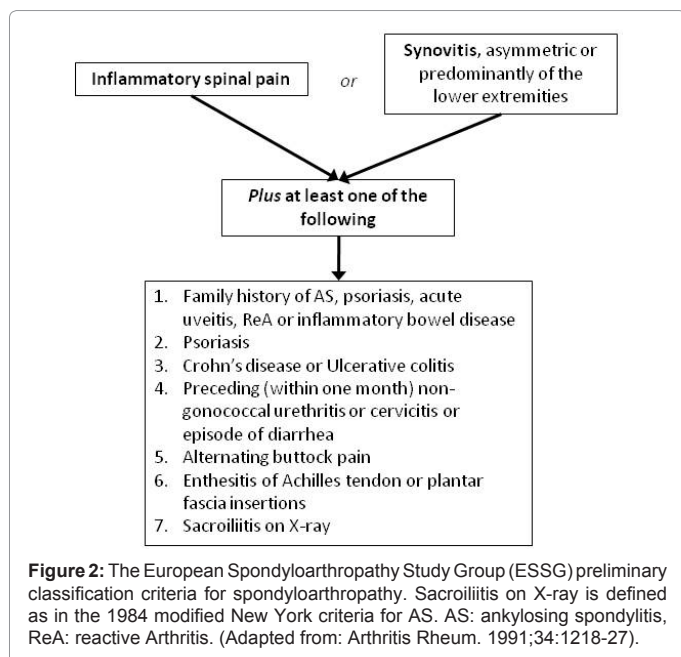
**Figure 1:** The spectrum of Spondyloarthropathies (SpA). Ankylosing spondylitis (AS) is the prototypic form, while all the other forms share common features with AS, as well as often with each other.

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pace and it takes years from the onset of symptoms, until bone damage is visible on X-rays [23]. AS patients have been reported to have had symptoms for almost a decade until the diagnosis of AS was made, one of the reasons obviously being the need of spondylitis to advance to ankylosis in order for the diagnosis to be established [24]. Thus, the term pre-radiographic axial SpA has been introduced to accommodate this group of patients [25].

Hence, various new issues emerged: How to identify patients with pre-radiographic axial SpA? What is the disease burden of patients with pre-radiographic axial SpA as compared to patients with overt AS? Could aggressive treatment with TNF $\alpha$  inhibitors at earlier stages provide a relief significant enough to justify the costs? What kind of pathologic processes take place at this stage of the disease? Finally, could early anti-TNF $\alpha$  treatment be more effective than late treatment in preventing axial ankylosis?

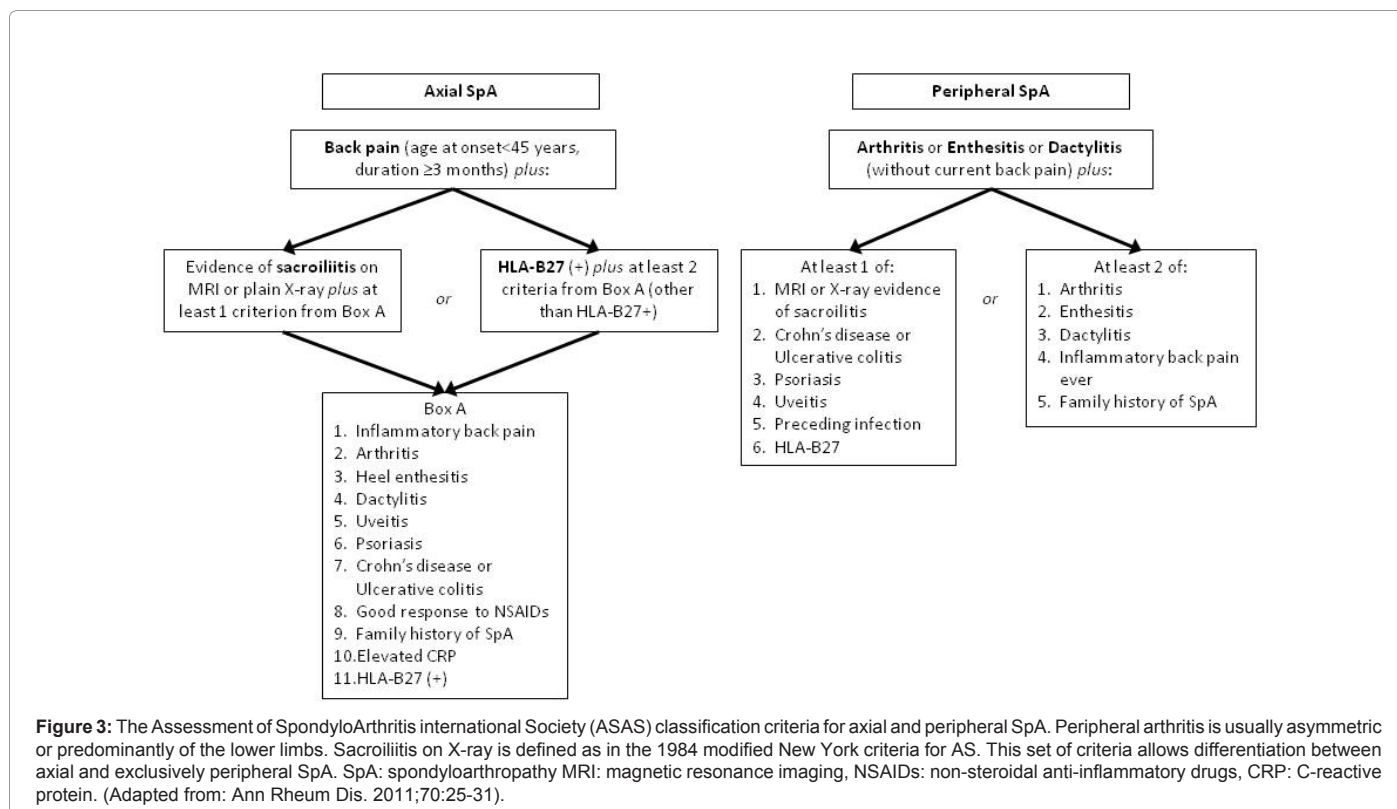
Since magnetic resonance imaging (MRI) was introduced in the diagnosis of SpA and with the development of sequences that suppress fat signal and highlight bone marrow edema and inflammation, MRI has been the gold standard for the diagnosis of axial SpA, particularly when inflammatory back pain is present and no lesions in X-ray are visible yet [26,27]. Indeed, the ASAS classification criteria for axial SpA, acknowledging that pre-radiographic and radiographic axial SpA are separate stages within a continuous disease process, require the presence of radiographic sacroiliitis either on plain X-rays or on MRI [28].

Moreover, it has been clear that patients with pre-radiographic axial SpA are comparable to their "post-radiographic" counterparts regarding clinical manifestations, pain, disease activity as assessed by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and fatigue. However, pre-radiographic axial SpA patients had lower levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) and were better concerning function and metrology [29]. Further, clinical trials have shown that early axial SpA patients derive significant clinical benefits from TNF $\alpha$  blockade, which are associated with regression of spinal inflammation on MRI [30-32]. These observations have been incorporated in the 2010 updated ASAS recommendations

for the use of anti-TNF $\alpha$  agents in SpA. In this update, the term axial SpA (according to ASAS classification criteria) in addition to AS (according to the modified New York criteria) is used to define the group of patients that should be considered eligible for anti-TNF $\alpha$  treatment, apparently including as well the patients with axial disease on MRI, but not on plain X-ray. Of note, the updated recommendations advocate that a patient has an adequate trial with NSAIDs for one month before anti-TNF $\alpha$  treatment is initiated, instead of 3 months that the previous version of recommendations required [33].

However, little is known about the inflammatory and reparatory processes in the axial skeleton along the disease course, partially due to the inaccessibility of the joints for histopathological examination. Since the first observations of increased TNF $\alpha$  mRNA expression in the cellular infiltrates of sacroiliitis and increased TGF $\beta$  mRNA expression in the vicinity of sites of new bone formation [34], the whole process is still poorly understood. The successful clinical and radiographic (on MRI) suppression of spinal inflammation with TNF $\alpha$  inhibition [35,36] has not been paired to an equivalent suspension of abnormal bony overgrowth [37-39]. A possible explanation may be that spinal inflammation continues to smolder despite anti-TNF $\alpha$  treatment, so that the ultimate event, bone apposition, is not prevented. Alternatively, perhaps bony overgrowth is a process distinct from (and possibly subsequent to) inflammation, dependent on different mediators, such as prostaglandins and the Wnt/Dkk/sclerostin system [40,41]. The key point, then, is what drives the switch from a TNF $\alpha$ -dependent inflammatory process to a TNF $\alpha$ -independent phase of neo-osteogenesis and when this switch takes place [42].

It has been shown in a 2-year study of AS patients that syndesmophytes are more likely to develop at sites of spinal inflammation and fatty infiltration as observed on MRI [43]. Furthermore, in a 48-week prospective study of patients with early axial SpA, spinal fatty lesions evident on MRI developed almost exclusively at sites of baseline MRI-detected spinal inflammation. However, in this study no significant progression of ankylosis could be observed over time [44]. This disparity might reflect differences in diagnosis (early axial SpA versus AS) or the treatment of the patients recruited in both studies or may be merely the result of a shorter follow-up in the latter study. On the other hand, a randomized prospective trial of continuous versus on-demand treatment of AS patients with NSAIDs proved that continuous treatment was associated with less radiographic progression compared to the on-demand group, highlighting the importance of the prostaglandin-mediated pathways of bone metabolism [45]. However, current recommendations for the treatment of AS do not explicitly advocate continuous use of NSAIDs, in order to prevent radiographic progression [46]. Moreover, as pharmacologic agents affecting abnormal bone metabolism in SpA are essentially lacking, the only sensible option to date is to effectively and continuously suppress spinal inflammation with the use of approved medications: NSAIDs and, in case of failure, TNF $\alpha$  blockers. This strategy, apart from apparently relieving the symptoms and improving patients' function and quality of life, offers the best opportunity to abort the potentially initiating event, spinal inflammation, before subsequent non-inflammatory mechanisms take over that produce ankylosis. In this regard, long-term prospective studies of the effect of TNF $\alpha$  inhibition on the progression from pre-radiographic axial SpA to overt AS, as well as on radiographic progression of AS would certainly be informative. Of note, although TNF $\alpha$  inhibition is recommended by ASAS for the treatment of patients with non-radiographic axial SpA who have active disease despite NSAIDs, the current state of anti-TNF $\alpha$  therapy reimbursement requires a diagnosis of AS, although not explicitly according to the modified New York criteria.



In conclusion, great advances have taken place in the past 4 decades concerning SpA. Departing from “rheumatoid spondylitis”, a whole spectrum of diseases has been described pertaining to the same, distinct and well-defined group of SpA. Advances in therapeutics have imposed a more clinically-oriented classification between peripheral and axial SpA, with the latter attracting significant interest due to its resistance to traditional treatment modalities. Moreover, the realization of the chronicity of the disease, as well as the use of MRI in the diagnostic approach of spinal inflammatory diseases have allowed the recognition of early/pre-radiographic axial SpA and the impact it has on patients. Diagnostic/classification criteria and treatment recommendations have recently been amended to take into account this group of patients as well. However, the impact of long-term treatment of patients with axial disease especially concerning long-term radiographic progression is still a matter that deserves further research.

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