SPONDYLOARTHRITIS: PATHOGENESIS, CLINICAL MANIFESTATIONS, DIAGNOSIS, AND MANAGEMENT

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ABSTRACT

The term spondyloarthritis (SpA) is used to describe a heterogeneous group of diseases sharing certain characteristics. Traditionally, patients with SpA have been classified in five subgroups: ankylosing spondylitis (AS), psoriatic arthritis, arthritis associated with inflammatory bowel disease (IBD), reactive arthritis, and undifferentiated SpA. The pathogenesis of SpA is still not entirely clear; it is considered to be multifactorial, the result of interaction between genetic risk factors and environmental triggers that lead to activation of autoinflammation and autoimmunity. This group of diseases is characterised by a chronic inflammation in entheses and other anatomical structures, leading to their main clinical features: sacroilitis, enthesitis, and peripheral arthritis. An association with extra-articular manifestations such as psoriasis, uveitis, and IBD is also a distinctive feature of SpA.

Several diagnostic and classification criteria have been proposed over time. However, all of these criteria have a main limitation, which is the difficulty to identify patients at an early stage of the disease. The Assessment of Spondyloarthritis International Society (ASAS) proposed the ASAS classification criteria that introduced two major changes: first, the classification of patients with SpA based on the predominant symptoms (axial or peripheral); second, the introduction of magnetic resonance imaging, which allows detection of sacroiliitis at the early stages of the disease. Nowadays, the ASAS criteria classify SpA in two groups: axial SpA, including classical AS and non-radiographic axial SpA, and peripheral SpA. The therapy for SpA has evolved dramatically over time. The introduction of biological therapy in recent years, which has continuously progressed, has improved the functional and clinical prognosis of SpA patients.

Keywords: Spondyloarthritis (SpA), clinics, review.

INTRODUCTION

The term spondyloarthritis (SpA) is used to describe a heterogeneous group of diseases that share certain characteristics that differentiate them from other rheumatic diseases: familial history, common pathogenesis, *HLA-B27* association, relation with gastrointestinal or genitourinary infections, and similar clinical features mainly characterised by the presence of enthesitis, sacroiliitis, and arthritis.[1]

The group includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), arthritis associated with inflammatory bowel disease (IBD), reactive arthritis, and undifferentiated SpA.[1] However, at an early stage of the disease it may be difficult to classify patients into a definitive category. The Assessment of Spondyloarthritis International Society (ASAS) criteria allows classification of SpA patients through the use of predominant symptoms in axial (Figure 1) and peripheral SpA (Figure 2).[2-4] This review analyses the clinical manifestations, pathogenesis, diagnosis, and treatment of SpA.

EPIDEMIOLOGY

The prevalence of SpA depends on the genetic background, especially *HLA-B27* frequency,

ethnicity, and geographical distribution of the population under study. Therefore, the prevalence varies, and it is estimated to be 0.1–2.5%. The prevalence reported in Europe of AS is 0.3–1.8%, considering the factors commented above.[5]

PATHOGENESIS

The pathogenesis of SpA is not entirely clear. It is the result of a complex interaction between genetic risk factors and environmental triggers that leads to the activation of autoimmunity and autoinflammation.

Genetic Risk Factors

The mode of inheritance is polygenic and related to several genetic factors. Estimated heritability in AS is >90%, and this condition increases with several clinical manifestations of AS such as radiographic damage, age of onset, and BASDAI.[6] First, second, and third-degree relatives of patients with AS have a relative risk of 94%, 25%, and 4%, respectively of developing the disease.[7]

The principal genetic factors associated with SpA are:

MHC genes

HLA-B27 is the most important genetic factor in AS. It is present in 85–95% of white patients with AS, although only 7–8% of *HLA-B27* carriers in general population develop AS.[8] *HLA-B27* is also associated with other forms of SpA to a lesser degree.[7,9] *HLA-B27* is encoded by an allele of the major histocompatibility complex (MHC) class I HLA-B region, and all the molecules of this group share a common canonical structure that allows presenting antigenic peptides to the T cell receptors of CD8+ lymphocyte. Several different hypotheses have been suggested to explain the role of *HLA-B27* in the pathogenesis of SpA:
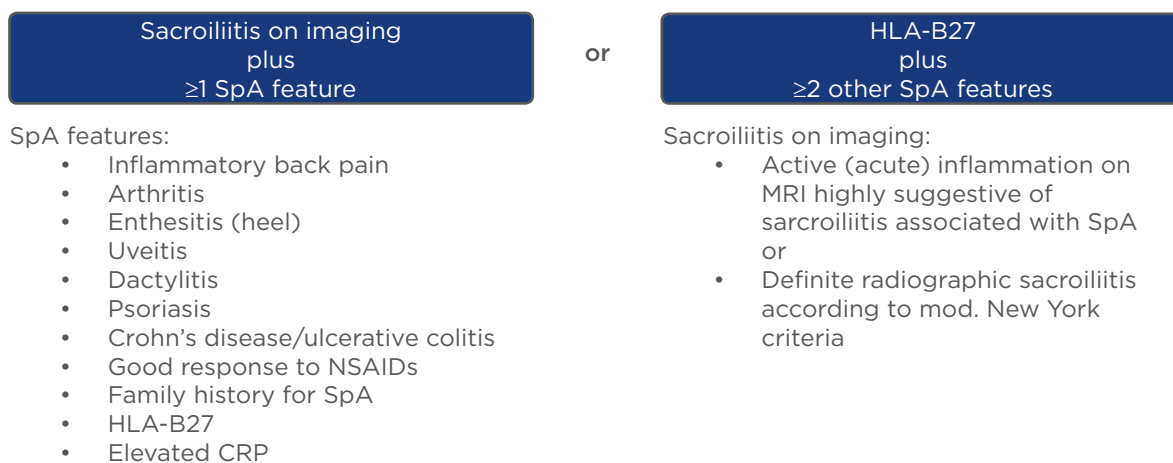
Arthritogenic peptide hypothesis

Certain microbial peptides very similar to self-peptides could mimic them and cause reactivity of T lymphocytes, leading to autorreactivity and autoimmune disease.[10-12] The validity of this hypothesis is questioned by the fact that *HLA-B27* rats can still develop arthritis in the absence of T CD8+ cells.[13]

Heavy chain homodimer hypothesis

HLA-B27 heavy chains can form stable dimers that can engage receptors of several types of cells in a way different from the canonical structure, so that they can be recognised by natural killer (NK) receptors, developing an inflammatory process. Leukocyte receptors that could recognise homodimers are: LILRA1, LILRB2, KIR3DL1, and KIR3DL2.[14]

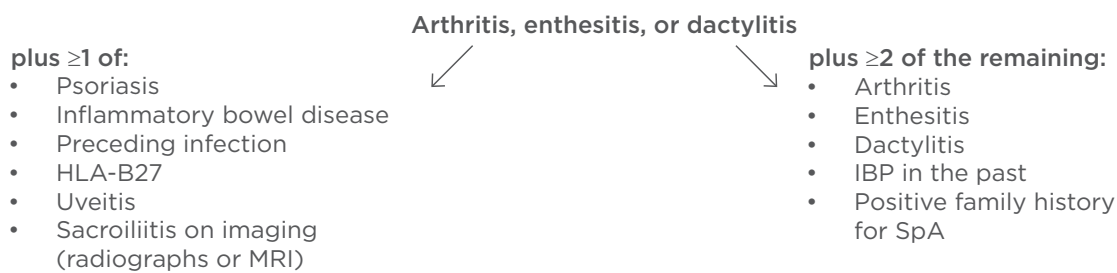### *HLA-B27* misfolding hypothesis

Due to several reasons, the folding process of *HLA-B27* is slower than other HLA alleles, and could generate misfolding proteins that accumulate in the endoplasmic reticulum, leading to activation of autophagy and IL23/17 pathway.[14]

Sacroiliitis on imaging plus ≥1 SpA feature	or	HLA-B27 plus ≥2 other SpA features

SpA features:
- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn's disease/ulcerative colitis
- Good response to NSAIDs
- Family history for SpA
- HLA-B27
- Elevated CRP

Sacroiliitis on imaging:
- Active (acute) inflammation on MRI highly suggestive of sarcroiliitis associated with SpA or
- Definite radiographic sacroiliitis according to mod. New York criteria

Figure 1: Assessment of Spondyloarthritis International Society classification criteria for axial spondyloarthritis.
For use in patients with back pain ≥3 months and an age of onset <45 years of age.
NSAIDs: non-steroidal anti-inflammatory drugs; MRI: magnetic resonance imaging; CRP: c-reactive protein.

Arthritis, enthesitis, or dactylitis

plus ≥1 of:
• Psoriasis
• Inflammatory bowel disease
• Preceding infection
• HLA-B27
• Uveitis
• Sacroiliitis on imaging (radiographs or MRI)

plus ≥2 of the remaining:
• Arthritis
• Enthesitis
• Dactylitis
• IBP in the past
• Positive family history for SpA

Figure 2: Assessment of Spondyloarthritis International Society classification criteria for peripheral spondyloarthritis.
MRI: magnetic resonance imaging; IBP: inflammatory back pain; SpA: spondyloarthritis.

More than 100 subtypes of *HLA-B27* have been characterised, however not all of them have the same degree of association with SpA/AS. *B27:02, 04*, and *05* are strongly associated with AS. Other HLA-B alleles such as *HLA-B60, B39, B38*, and *B40* have been associated with AS.[14]

Non-MHC genes

Genome-wide association studies (GWAS) have involved several genes in the pathogenesis of SpA grouped into several functional categories.

Polymorphisms in the endoplasmic reticulum aminopeptidase 1 and 2 (*ERAP1* and *ERAP2*) are strongly associated with SpA. The mechanism by which ERAP1 predisposes to SpA remains unknown. One hypothesis suggests that *ERAP1* alters *HLA-B27* peptide presentation. *ERAP1* variants found in patients with AS are present mostly in patients who are *HLA-B27* positive rather than in *HLA-B27* negative.[15] The mechanism by which *ERAP2* affects disease risk remains unclear.

IL17/23 pathway

GWAS have identified association with genes for the IL23 receptor (IL23R) as well as tyrosine kinase 2 (TYK2), and signal transducer and activator of transcription (STAT3), which are involved in the IL23R pathway. New therapeutic options against these targets have shown efficacy.[16]

Other non-MHC genes implicated have been the tumour necrosis factor (TNF) receptor gene family and the genes modulating activation and differentiation of CD4+ or CD8+ lymphocytes.

Environmental Triggers

The important role of abnormal intestinal microbiota and infections in the development of joint disease has been confirmed in several studies. Of the patients with IBD, 10–20% develop sacroiliitis, and many patients with AS show microscopic inflammatory lesions in the biopsy without intestinal symptoms, this may be due to the two diseases sharing a common pathogenetic cause. In other cases, such as reactive arthritis and Reiter's syndrome, arthritis develops a short-time after a gastrointestinal or genitourinary infection.[16]

The role of mechanical stress in inflammation and bone formation has been widely discussed in the literature regarding pathogenesis of SpA. The 'synovio-entheseal complex' represents the sophisticated integration between insertions and the adjacent synovium. The fibrocartilages at insertions are prone to microdamage and/or aberrant tissue repair that may manifest as adjacent tenosynovitis or synovitis, due to the synovium being rich in immune cells and its ability to undergo hyperplasia and vessel ingrowth.[17] This makes the 'enthesis organ' a place where molecules from bacteria may be preferentially deposited. Microdamage and bacterial deposition in the context of HLA-B27 could lead to the characteristic inflammatory changes of AS. The sequence of entheseal inflammation followed by new bone formation is not formally proven, although magnetic resonance imaging (MRI) studies suggest that new bone formation preferentially occurs in advanced inflammatory spinal lesions, characterised by reparative processes such as bone sclerosis.[18] Acute lesions resolve without sequelae, but in chronic inflammatory lesions, resolution of the process results in fat metaplasia and bone formation, therefore mechanical stress is involved in disease progression.[19]

Animal models have showed the multifactorial aetiology of SpA with genome (*HLA-B27*), microbial, and biomechanical stress models shaping the disease phenotypes. At a molecular

level, there is evidence with TNF and IL23/IL17. Additionally, at the cellular level, resident entheseal IL-23R+, CD3+/CD4-/CD8- T cells have been identified, although their role still remains unclear. However, selection of animal models must be careful due to high sensitivity to environmental changes and different genetic backgrounds.[20]

CLINICAL FEATURES

Patients with axial SpA characteristically have chronic lower back pain. Patients with either axial or peripheral SpA can present arthritis, enthesitis, and dactylitis.

Lower Back Pain

Chronic lower back pain affects approximately 20% of the general population, but a reduced percentage of these patients have axial SpA.[21] Therefore, the lower back pain in axial SpA is described as 'inflammatory low back pain'. It is present in 70–80% of patients with axial SpA, and characterised by:[22] age of onset <45 years, insidious onset, evolution >3 months, improving with movement and non-steroidal anti-inflammatory drugs (NSAIDs), but not with rest. It is associated with morning stiffness and pain at night. The early stage of the illness is quite intense and can irradiate to the dorsal spine or pelvis. Sacroiliitis can manifest as alternating left-right gluteal region pain and it is very specific for axial SpA and AS.

The cervical spine, and less frequently the thoracic spine, can also be affected, especially in AS, with loss of range of motion.

Peripheral Arthritis

This often involves the lower extremities, especially knees and ankles, and is associated with swelling. Its pattern is acute, non-erosive, asymmetrical, and oligoarticular.[23] Hip and shoulder arthritis are frequent in AS.[24]

Enthesitis

Enthesitis is characteristic of SpA. Enthesis is the site of insertion of ligaments, tendons, joint capsule, or fascia to bone. The most common site of enthesitis is the Achilles tendon. Iliac crests, costochondral junctions at the sternum, the greater trochanters, and the tibial plateaus can also be affected. Enthesitis produces swelling and tenderness on palpation.[24]

Dactylitis

Dactylitis is the global inflammation of fingers and toes, which can make them look like sausages. Dactylitis is particularly characteristic of PsA and reactive arthritis but is not a specific characteristic of SpA. It is observed in syphilis, tuberculosis, and sarcoidosis.[25] It can be acute (with inflammatory signs) or chronic (often not painful). Dactylitis can affect one or more fingers and/or toes asymmetrically.

Non-Articular Features

These are characteristic of SpA spectrum disease:

- Eye involvement: Acute unilateral anterior uveitis is a symptom of SpA, especially in HLA-B27 patients, and may be the presenting problem. It usually responds to local therapy. Non-purulent, transient conjunctivitis could also be associated[26,27]
- Inflammatory bowel disease: Articular disease related to SpA is the most common extra-intestinal feature in IBD, although the clinical course of both diseases is independent. IBD has been diagnosed in 10% patients with AS. On the other hand, AS is diagnosed in 3–10% patients with IBD, although 15–50% patients have sacroiliitis on imaging. Sixty percent of patients with AS show microscopic inflammation of bowel mucosa without IBD symptoms[28,29]

Other Clinical Features

These include aortic insufficiency, conduction abnormalities, neurological manifestations secondary to spinal fractures or atlantoaxial subluxation, amyloidosis, and osteoporosis.[20]

DIAGNOSIS

Laboratory Findings

There are no laboratory findings absolutely specific for SpA. HLA-B27, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) are the markers most commonly used in clinical practice.

In most ethnic groups, >90% of AS and 50–70% of patients with other forms of SpA are positive for HLA-B27, and it is included in the ASAS criteria. However, HLA-B27 positivity is not diagnostic by itself of either AS or SpA. HLA-B27 is particularly helpful in diagnosis of non-radiographic axial SpA in combination with MRI. The combination of severe sacroiliitis on MRI with

HLA-B27 positivity is an excellent predictor of future AS development.[30]

CRP and ESR have both low sensitivity and specificity and they do not represent the disease process or activity in AS and SpA. Elevated CRP is included in axial ASAS SpA classification; however, elevated CRP or ESR are only present in 40–50% of patients with AS.[31] This percentage may be greater in peripheral forms such as PsA. Thus, normal ESR or CRP levels do not rule out active disease or AS diagnosis.

Other markers such as cytokines, matrix metalloproteinases, osteoprotegerin, or calprotectin are under investigation.[32]

Radiographic Findings

Plain radiographs

There are several characteristic findings that may be observed in patients with SpA, although these are not present in early stages of the disease. In axial SpA, the most specific finding is sacroiliitis, and this has been included in many classification criteria. According to grading of radiographic sacroiliitis (Figure 3) there is positive evidence for sacroiliitis at Grade 2 or higher bilaterally, or Grade 3 unilaterally. Patients considered as non-radiographic axial SpA do not have definite plain radiographic findings of sacroiliitis. Syndesmophytes (ossification originating from the intervertebral ligaments that may bridge vertebral bodies) are also very specific for axial SpA, and can be observed in the absence of sacroiliitis.[31,33]

Radiographs of peripheral joints and entheses show variation in the degree and kind of radiographic changes seen in different types of SpA. In axial SpA, the most severe peripheral joint involvement observed is in the hip joints, where extensive destructive changes may occur.[31] Radiographic changes in peripheral joints are common in patients with PsA, even at early stages of the disease. These changes are very characteristic of PsA, showing the coexistence of erosive changes and new bone formation within the same joint or in different joints within the same digit. Fluffy erosions can be observed in areas of enthesitis in patients with SpA, such as the heels, although these findings are not specific for SpA.[34]

Magnetic resonance imaging

MRI has become an important tool in the diagnosis of patients in the early stage of disease, without abnormalities on plain radiographs, allowing an early diagnosis. MRI findings in sacroiliac joints are included in ASAS criteria. These findings include active inflammatory lesions of sacroiliac joints, observed as high-intensity bone marrow oedema on short-tau inversion recovery (STIR) or on T2 with fat absorption images. Bone marrow oedema is not exclusive for SpA and could appear in malignancies, infections, and osteitis condensans ilii. Findings on MRI of the spine show lesions that are triangular in shape at one or more corners of the vertebrae.[31]

Other imaging techniques

Computed tomography scanning and scintigraphy are less frequent used. Ultrasonography is useful for enthesitis, showing hypoechogenicity, increased thickness of the tendon insertion, calcifications, enthesophytes, and power Doppler activity.[35]

Classification Criteria

Classification criteria for SpA and AS were developed for use in epidemiological and clinical research. Currently ASAS criteria have replaced older classification criteria. Although there are specific criteria for different types of SpA, such as the ClASsification criteria for Psoriatic ARthritis (CASPAR) for PsA, it may be difficult to classify a patient into a definitive SpA disease group, especially at onset. ASAS criteria allow the classification of practically all patients with SpA according to predominant symptoms in axial or peripheral SpA. These classifications also include MRI findings allowing classification of early and non-radiographic forms. ASAS criteria for axial SpA have a sensitivity of 82.95% and a specificity of 84.4%. For peripheral SpA, ASAS criteria have an estimated sensitivity of 75% and specificity of 82.2%.[2-4]

- Grade 0: Normal
- Grade 1: Suspicious changes
- Grade 2: Minimal abnormality, small localised areas with erosions or sclerosis, without alteration in the joint width
- Grade 3: Unequivocal abnormality, moderate or advanced sacroiliitis with erosions, evidence of sclerosis, widening, narrowing, or partial ankylosis
- Grade 4: Severe abnormality, total ankylosis

Figure 3: Grades of sacroiliitis based upon the presence of the characteristic radiographic findings.

TREATMENT

The main goal of SpA management is to reduce disease activity and control joint damage, improving quality of life and preserving functional abilities, autonomy, and social participation of patients.

The management of axial SpA is different, in terms of pharmacological treatment, from peripheral SpA. NSAIDs and anti-TNF blockers are the cornerstone in treatment of axial SpA. Although these treatments have also demonstrated efficacy in peripheral SpA, non-biological disease-modifying anti-rheumatic drugs (nb-DMARDs) are an essential tool in peripheral SpA.

Non-Steroidal Anti-Inflammatory Drugs

According to ASAS and the European League against Rheumatism (EULAR), NSAIDs, including the selective cyclo-oxigenase-2 antagonists, are the first-line therapy of SpA, especially axial SpA.[36] There is often clinical improvement of lower back pain in patients with AS treated with NSAIDs, with a clinically significant response in >70% of the patients compared with patients with mechanical back pain.

Corticosteroids

Intra-articular injections of steroids can be used in monoarthritis, enthesitis, and dactylitis. Systemic steroids are not usually recommended in the treatment of axial involvement due to a lack of efficacy in axial symptoms. In the case of peripheral SpA, systemic steroids may be useful in short-term treatment in severe forms with the lowest possible dosage.[37]

Non-Biologic Disease-Modifying Anti-Rheumatic Drugs

Methotrexate, leflunomide, and sulfasalazine are generally ineffective for axial manifestations, but are useful in peripheral SpA. Although methotrexate is the most widely nb-DMARD used, the choice may be based on the patient's clinical profile, considering also the coexistence of extra-articular manifestations. Methotrexate can improve psoriasis and methotrexate and sulfasalazine are useful if uveitis and/or bowel disease are present.[37,38]

Biological Disease-Modifying Anti-Rheumatic Drugs

TNF-α blocking therapies are currently the only effective treatment available for patients with axial SpA who are unresponsive to the first-line therapy with NSAIDs. Each of the currently available TNF blocking agents (adalimumab, infliximab, etanercept, golimumab, and certolizumab pegol) has a strong and similar clinical efficacy in active AS.[28] The choice of a TNF blocker depends on the patient preference, experience of the medical professional with the drug, comorbidities, and extra-articular manifestations. Adalimumab and etanercept are useful when treating psoriasis. Infliximab and adalimumab have been demonstrated to improve uveitis. Infliximab and adalimumab are used in IBD (Crohn´s disease and ulcerative colitis). Golimumab has been shown to improve ulcerative colitis and certolizumab pegol to improve Crohn´s disease.[8,27,28]

All the TNF-α blockers are also effective in the control of peripheral disease unresponsive to nb-DMARDs. Ustekinumab, a fully human immunoglobulin monoclonal antibody direct against IL-12 to 23 is effective in the treatment of PsA and psoriasis.[29] The investigation of new targets for SpA treatment is in constant evolution, and many new drugs will be available in a short period of time, improving the therapeutic tools for SpA.

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