UNIT NO. 3

SERONEGATIVE SPONDYLOARTHROPATHIES

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ABSTRACT

The seronegative spondyloarthropathies are a heterogenous groups of inflammatory diseases which may present with sacroilitis, inflammatory arthritis, spondylitis and enthesitis, as well as extra-articular manifestations of inflammation most commonly involving the eye, skin and gastrointestinal tract. There is a familial preponderance to these conditions, and an association with the HLA-B27 gene. The new ASAS classification system for these conditions aims to classify patients into 2 broad categories based on the predominant site of their symptoms. The diagnosis of early spondyloarthropathy relies on a detailed history and physical examination as radiographic changes occur late, and blood work-up may be normal. Management of these chronic diseases requires a holistic multidisciplinary approach with both pharmacological and non-pharmacological interventions. In recent years, many newer therapies, especially biologic agents have become available for treatment of these conditions.

Keywords: Seronegative spondyloarthropathy; spondylitis; enthesitis; HLA-B27;

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1. What are the seronegative spondyloarthropathies?

The seronegative spondyloarthropathies (SpA) are a heterogenous group of inflammatory rheumatic diseases with overlapping common clinical features that occur with differing frequencies, such as inflammation of the sacroiliac joints (sacroilitis); inflammatory back pain (spondylitis); peripheral arthritis; enthesitis; dactylitis; extra-articular manifestations such as uveitis, psoriasis and inflammatory bowel disease;[1] and an association with the human leucocyte antigen (HLA)-B27 epitope.[2]

Traditionally, the spondyloarthropathies were thought of as distinct conditions under the same umbrella, e.g. ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA) — including Reiter's syndrome, inflammatory bowel disease-associated spondyloarthropathy, juvenile spondyloarthropathy and undifferentiated spondyloarthropathy.

The traditional classification was based on each member of the group having its own distinct clinical and epidemiological features (see Table 1).

Table 1: Clinical and Epidemiological features of Spondyloarthritides (adapted from Imboden et al[3])

		AS	PsA	ReA	IBD
Prevalence worldwide		0.1%	0.02-0.42%	0.03%-0.05%	<0.1%
HLA B27 positivity		85-90%	30%	50-80%	20-30%
Male: Female		3:1	1:1	1:1, unless urogenital source of infection (male predominant)	1:1
Typical age of onset		usually late teens – early 20s (rare after 45)	35-50yrs	20-40 yrs	
Frequency of axial arthritis		100% by definition	20%	20%	10-15%
sacroiliitis		Bilateral	Unilateral	Unilateral	Bilateral
Peripheral arthritis	frequency	50%	60-90%	90%	5-20%
	distribution	Oligo/mono articular large joint	Oligo/poly articular, hands inc DIPJ and large joints	Oligo/mono articular, lower limb esp knee and ankle	Oligo mono articular, lower limb esp knee and ankle
Dactylitis		Uncommon	20-30%	30-50%	Uncommon
Uveitis		25-40%	15%	15-20%	5%
Skin involvement		None	Skin and nail psoriasis	Oral ulcers, Circinate balanitis Keratoderma Blennorhagicum	Erythema nodosum, Pyoderma gangrenosum

However, the reality of clinical practice is that most patients seen in the clinic do not fit nicely into one single category above, and there exists a great deal of overlap features, or incomplete manifestations leading to the label of "undifferentiated spondyloarthropathy".

Previous classification criteria for the above conditions, such as the modified New York Criteria for Ankylosing Spondylitis were not sensitive enough to classify patients with early disease, because in addition to inflammatory back pain, it required radiographic changes of sacroilitis to be present as one of the criteria. Radiographic changes tend to occur late — up to 10 years after the onset of active disease. The other criteria of limitation in spinal mobility and reduction in chest expansion also both occur late due to irreversible damage. It also focused on solely the axial symptoms and disregarded peripheral and extra-articular symptoms.

In an attempt to encompass the breadth of the SpA spectrum of patients, experts from the Assessment of SpondyloArthritis International Society (ASAS) developed criteria to try and classify patients with SpA into two broad categories, namely:

1. those with predominantly axial symptoms (axSpA) (Figure 1);[4] and
2. those with predominantly peripheral symptoms (peripheral SpA) (Figure 2).[5]

There are patients who will fit into the axSpA group or the pSpA

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group and there are also those that overlap between the two groups. Nevertheless, these criteria have been shown to have good sensitivity and specificity when tested against the rheumatologists' diagnosis,[6] and may pave the way for further studies to test their applicability as part of diagnostic criteria for this group of conditions in future.

Figure 1: ASAS classification criteria for axial SpA [Rudwaleit, et al (2009)]

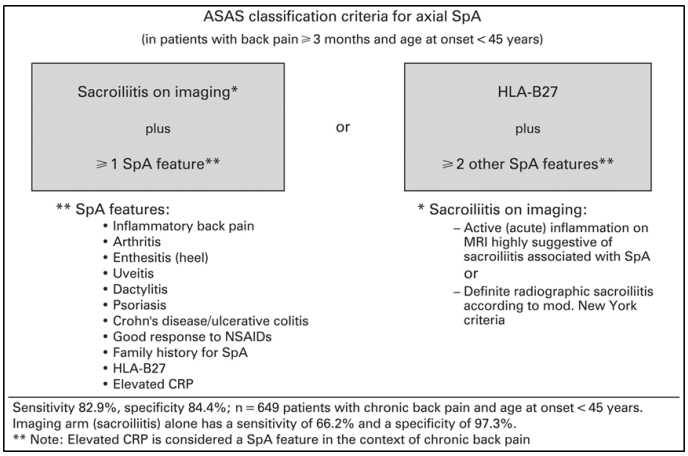
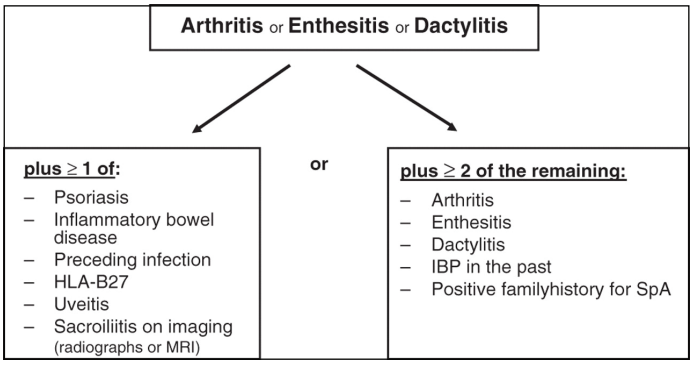


Figure 2: ASAS classification criteria for peripheral SpA [Rudwaleit, et al (2011)]



2. Recognising a patient with seronegative spondyloarthropathy.

The seronegative spondyloarthropathies as a group, has an overall estimated prevalence of around 1–2 percent, approaching that of rheumatoid arthritis.[7] Early recognition, referral for diagnosis and therapeutic intervention are important to modify disease progression, decrease the disease burden and avoid unnecessary diagnostic and therapeutic procedures.[8]

Case Study I — The Patient With Axial Spondyloarthropathy

A 22-year-old university student comes to see you with a 6-month history of low back pain.

His lower back feels stiff with discomfort that often radiates into the buttocks, making it difficult for him to turn over in bed in the middle of the night or to get up in the mornings. He has developed a habit of doing stretches while standing under a hot shower to ease the symptoms. It takes about an hour for the stiffness and discomfort to ease. His symptoms are worse with inactivity, e.g. when sitting still during lectures, he has difficulty getting up afterwards, and he has had to stretch and pace up and down in the MRT carriage on his hour-long journey to and from the university daily. There are no neurological symptoms and no problem with bowel or bladder control.

He had a similar attack about a year ago, which he attributed to "pulling a muscle" after a football game — that settled after a course of acupuncture over 6 weeks. This time, acupuncture hasn't really helped. Out of desperation he has tried some diclofenac tablets belonging to his mother and found that, with them, he does get 3–4 hours of significant reduction in the pain and stiffness.

He has otherwise been fit and well with no previous illnesses. Systems review revealed an episode of plantar fasciitis 2 years ago, which resolved after a change in footwear and after doing some stretching exercises. His father has skin psoriasis.

This case describes a patient that would have traditionally been classified as having a clinical diagnosis of early ankylosing spondylitis (AS), with symptoms of inflammatory low back pain.

Inflammatory low back pain is the most common presenting complaint in patients with axial spondyloarthropathy. It usually begins in the 3rd decade of life, and its onset may be very mild and non-specific in the early stages, such that patients often end up mistakenly attributing their symptoms to some physical event. In addition, the symptoms are also often more relapsing and remitting in nature than chronic, and it is not uncommon for patients to have long periods free of pain. Because of the fluctuation in symptoms, this can lead to a delay in the patient presenting to primary care and, therefore, a delay in diagnosis.

Table 2: Features that differentiate patients with inflammatory back pain from those with mechanical (non-inflammatory) back pain:[9]

FEATURE	INFLAMMATORY BACK PAIN	NON-INFLAMMATORY BACK PAIN
Age	Patients <40 yrs old	Patients of any age
Onset of pain	Insidious	Abrupt
Effect of exercise	Improves pain	Exacerbates pain
Effect of rest	No improvement	Improves pain
Pain at night	Yes	No
Early morning stiffness	>30mins	<30 mins

The patient in case study 1 also had a previous history of plantar fasciitis that predated his inflammatory back pain symptoms. Plantar fasciitis is an example of an enthesitis, which is the term used to describe inflammation at the site of insertion of ligaments, tendons, joint capsule, or fascia to bone. Inflammation at the entheses is now increasingly recognized to be the likely primary site of pathology in the spondyloarthropathies[10]. Besides plantar fasciitis, other common entheseal areas that can be affected in SpA include the Achilles tendon insertion, lateral and medial epicondyles of the elbow, the iliac crest and the tibial tuberosity.

Case Study 2 — The Predominantly Peripheral SpA Patient

A 28-year-old housewife comes to your clinic with a 3-month

history of musculoskeletal symptoms — beginning with triggering of both thumbs and ring fingers 3 months previously, with no precipitating trauma or unusual activity. In the past 6 weeks she has gone on to develop pain, swelling and stiffness in her right knee, a painful arc and stiffness on abduction of her right shoulder, as well as discomfort in her heels at the Achilles tendon insertion bilaterally, particularly first thing in the morning. In the past 2 weeks, the 2nd toe on both feet have become painful, swollen and sausage-like, such that she can't wear covered shoes. She has not had any axial symptoms of inflammatory back or neck pain. She has no skin rashes, nail abnormalities, urinary or gastrointestinal symptoms.

She has recurrent attacks of anterior uveitis that have been treated in the past with steroid eye drops, but otherwise has no other significant history.

This second case is an example of a patient with an undifferentiated SpA. In addition to an oligo arthritis affecting her right knee and right shoulder, this patient in case 2 also has other musculoskeletal symptoms of dactylitis and enthesitis (in this case Achilles tendonitis). The presence of these two features, together with the history of anterior uveitis, are suggestive of the diagnosis of a SpA rather than other types of arthritides (eg Rheumatoid arthritis). Peripheral manifestations of SpA tend to be commoner in female patients, whereas pure axial disease is commoner in men[11].

Extra articular manifestations such as the history of anterior uveitis in this patient, may predate the onset of musculoskeletal symptoms, and the common ones must always be asked for specifically, when suspecting a diagnosis of SpA.

Extra articular manifestations of SpA	
Common	Rare
Uveitis (30%)	Cardiac manifestations eg aortic regurgitation, conduction abnormalities
Psoriasis/Psoriasiform lesions	IgA nephropathy, secondary amyloidosis
Inflammatory bowel disease	Upper lobe lung fibrosis

3. An Overview of Workup and Management of Patients with SpA

The diagnosis of SpA can usually be made from a detailed history and thorough physical examination, with supportive imaging tests. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are elevated in about 75 percent of patients with axial spondyloarthropathy, and are markers for more aggressive disease. However, it is also worth noting that many patients with active SpA may have normal levels of ESR and CRP.

The typical radiographic changes of spondyloarthropathy are seen in the axial skeleton as well as entheseal sites. As mentioned previously, radiographic changes especially for sacroiliitis is a late occurrence in the disease course for most patients with axial SpA. Magnetic resonance imaging (MRI) is the imaging modality of choice for detection of early inflammation (before radiographical damage) in the axial skeleton and other less accessible sites, and musculoskeletal ultrasound is increasingly being used for evaluation of the entheseal sites in the periphery.

The management of these potentially serious diseases requires a carefully considered, holistic approach delivered by a multidisciplinary team.[12] The primary aim is to control the symptoms and inflammation, and by doing so, to minimise progressive structural damage and preserve function. A combination of non-pharmacological and pharmacological treatment modalities is needed for optimal management (see Table 3), and the treatment should be individualised to the patient's unique condition and life situation, and based on a shared decision between the patient and his /her physician.

Non-pharmacological strategies should be adopted by all patients; this should include a daily stretching and exercise programme to maintain good posture and minimize deformities, education about self management of the condition and smoking cessation.

NSAIDs (including the COX-2 inhibitors) are the first-line of pharmacological management in SpA, especially for axial disease. Analgesics such as paracetamol are useful for pain relief in addition to NSAIDS but should not replace its use. Sulfasalazine may be helpful for the patient with predominantly peripheral arthritis, but doesn't help those with axial disease. Biologic therapies such as the anti tumour necrosis factor (anti TNF) agents are effective in reducing both axial and peripheral inflammation as well as refractory extra-articular manifestations such as uveitis . Newer biologics targeting cytokines such as IL-17 (eg secukinumab) and IL12/23 have recently become available for treatment in axial and peripheral spondyloarthropathies. It is hoped that with reduction in the inflammatory process at an early stage, the sequelae of inflammatory damage and subsequent calcification that leads to reduction in mobility would be minimized, and thus minimizing the need for subsequent corrective surgical management.

Table 3: Management approaches to the SpA patient

Non pharmacological management	Pharmacological management	Surgical management
• Education about condition • Regular exercise • Physiotherapy • Stopping smoking	• Nonsteroidal anti-inflammatory drugs (NSAIDS) are first line up to maximum dose • Analgesia (e.g. paracetamol, tramadol) for residual pain • Local glucocorticoid injections to the site of musculoskeletal inflammation (avoid systemic glucocorticoids for axial SpA patients) • Sulfasalazine if patient has predominantly peripheral symptoms • Biologic agents, e.g. anti-TNFa agents, anti-IL17 inhibitor (taper when clinically better)	• Arthroplasty • Arthrodesis • Spinal corrective osteotomy e.g. if patient has a severe kyphosis which is disabling

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LEARNING POINTS

- **Seronegative spondyloarthropathies are a heterogeneous group with certain characteristic clinical features in common, especially inflammatory back pain, sacroiliitis, arthritis and extra-articular features, e.g. uveitis, psoriasis, with a strong association to the HLAB27 gene.**
- **It is crucial to recognise the features of inflammatory back pain as well as the features pointing to the pattern of different subtypes of seronegative spondyloarthropathies. Investigations may be normal in the early stages.**
- **A holistic multidisciplinary approach to patients with seronegative spondyloarthropathies is crucial to achieving the best possible outcome for them.**