Suspecting and Diagnosing the Patient with Spondyloarthritis and What to Expect from Therapy

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KEYWORDS

• Spondyloarthritis • Axial spondyloarthritis • Psoriatic arthritis • Reactive arthritis
• Inflammatory bowel disease arthritis • Ankylosing spondylitis

KEY POINTS

- Understanding of the clinical presentation, natural history, epidemiology, and pathogenesis of the spondyloarthritides is rapidly evolving. The disease is more common than previously recognized.
- Because of the array of clinical manifestations, it may be difficult to recognize the spondyloarthritides in their various clinical manifestations.
- Case finding and appropriate referral to a rheumatologist are important to treat spondylarthritis early for the best opportunity to achieve remission or low disease activity.
- Advances in treatment of the spondyloarthritides have been dramatic, allowing us to potentially achieve remission or low disease activity for most patients.

INTRODUCTION

Although the spondyloarthritides have been recognized in the medical literature for more than 100 years, the understanding of their distinct genetics, pathophysiology, and clinical presentation is still in evolution, as is a true understanding of their epidemiology. Although spondyloarthritis (SpA) (preferred term over "spondyloarthropathy") is optimally considered a singular overarching disease concept, clinicians who initially recognize and those who confirm diagnosis and manage these patients have historically balkanized SpA into several subsets: ankylosing spondylitis (AS), psoriatic arthritis (PsA), the arthritis associated with inflammatory bowel disease (IBD), reactive arthritis (ReA; associated with a triggering infection), and undifferentiated SpA, the last for placing those who clinically behave like SpA but do not fall into one of the other

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Med Clin N Am 105 (2021) 325–339
https://doi.org/10.1016/j.mcna.2020.10.001 **medical.theclinics.com**

subsets. The 7 blind men and the elephant metaphor can be applied here. For example, a spine orthopedist or physiatrist, when encountering a young male patient with persistent back pain and prominent morning stiffness, out of proportion to radiographic findings, may consider the diagnosis of AS. A dermatologist who is treating a patient with psoriasis, upon encountering a dactylitic finger (complete swelling of a digit), considers PsA. An internist whose patient has developed polyarticular tenderness and swelling as well as disabling pain at the Achilles tendon insertion (a manifestation of enthesitis) after having a bout of diarrhea while traveling in Central America considers the condition ReA (historically known as "Reiter syndrome"). An ophthalmologist, seeing a young patient with acute anterior uveitis, asks the patient if they have had back pain or arthritis, considering some form of SpA. A gastroenterologist reading an MRI enterography report on a patient with Crohn disease, in which the radiologist comments that the patient "lights up" not only in the intestine but also in the sacroiliac (SI) joints, considers the form of SpA that accompanies IBD. In all of these instances, it is hoped, these considerations will prompt referral of the patient to a rheumatologist to help sort out whether a SpA is present, distinguishing it from other musculoskeletal and inflammatory diseases, such as degenerative arthritis of the spine or peripheral joints, rheumatoid arthritis (RA), gout, fibromyalgia (FM), or other disorders. Part of the "sorting" is the recognition that the diagnosis may not be "either-or"; it is very common to have more than one of these conditions simultaneously, especially as degenerative joint disease occurs in virtually every human as we age. The key point of a rheumatologic consultation will be to sort whether an immunologic inflammatory disease is present, because we now have an evolving pharmacopeia of advanced therapies, including immunologically targeted biologic and synthetic disease-modifying drugs (DMARDs) with which we are potentially able to achieve disease remission or low disease activity.

SPONDYLOARTHRITIS BACKGROUND AND HISTORY

It may come as a surprise to the reader that the prevalence of all forms of SpA is up to 2% of the general population in most parts of the world, with some geographic differences based on population genetic differences. RA occurs in approximately 1% of the general population, yet tends to be more recognized by clinicians and the public. Part of the reason for lack of recognition of the spondyloarthritides is the historical subsetting of SpA into different disease entities that are not as well understood or recognized, leading to frequent misdiagnosis or lack of diagnosis. The SpA conditions have been noted in the archeologic record dating at least back to the fifth century AD, with skeletal osseous changes consistent with PsA recovered from ruins of Christian monasteries where people with psoriasis (considered to be leprosy) sheltered, and even before, in Egyptian mummies with spinal osseous changes consistent either with SpA or diffuse idiopathic skeletal hyperostosis. Nevertheless, the classification of SpA was not codified until the 1961 Rome criteria for AS. In the mid-1970s, Moll and colleagues[1] distinguished the SpA conditions from RA as typically seronegative for rheumatoid factor antibody and variably manifest with spinal involvement, asymmetric peripheral arthritis, enthesitis (inflammation of tendon and ligament attachments to bone), and association with IBD, psoriasis, and uveitis. It was during this same period that association with the gene marker HLA-B27 was noted,[2] and Calin and colleagues[3] developed the first criteria set for "inflammatory back pain" (IBP) to help clinicians distinguish it, through patient history, from degenerative or mechanical back pain. In 1984, the modified New York (mNY) criteria for the classification of AS was published, which anchored the disease in radiographically visible SI joint damage along with

several clinical features.[4] Since that time, especially with the introduction of advanced imaging technology such as MRI, wider application of genetic testing, and increased awareness of a broader spectrum of clinical presentation representing SpA, various updated classification criteria have been put forward.[5,6] In 2006, the CASPAR criteria for the classification of PsA was published, based on a study of nearly 1000 patients with either PsA or another inflammatory arthritis condition, yielding a specificity of 99% and sensitivity of 93%[7] (**Box 1**).

Axial Spondyloarthritis Classification Criteria

The reader is referred to a current review of the general topic of axial spondyloarthritis (AxSpA), which has been recently published as a textbook.[8] In 2009, the Assessment of SpondyloArthritis International Society (ASAS) group published classification criteria for AxSpA,[9] and in 2011, for peripheral spondyloarthritis (pSpA)[10] (**Figs. 1** and **2**). The ASAS criteria reflect a more clinically practical recognition that patients with SpA tend to present with either predominantly axial manifestations or predominantly peripheral features, including peripheral arthritis, enthesitis, and dactylitis, albeit acknowledging that overlap can occur. Patients with AxSpA may either have classic radiographic changes in the SI joints (eg, periarticular sclerosis, joint space narrowing, erosions, ankylosis) or MRI changes consistent with inflammation of the SI joints (periarticular bone edema) plus 1 other characteristic SpA feature, such as IBP (**Box 2**) or a positive HLA-B27 gene marker plus at least 2 characteristic SpA features. Those patients with characteristic radiographic changes of the SI joint are

Box 1
The CASPAR criteria

To meet the CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with $\geq$3 points from the following 5 categories:

1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis.
   Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.[a]
   A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider.
   A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report.
2. Typical psoriatic nail dystrophy, including onycholysis, pitting, and hyperkeratosis, observed on current physical examination.
3. A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range.
4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist.
5. Radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.

The CASPAR criteria have specificity of 98.7% and sensitivity of 91.4%.[a] Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.

From Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54(8):2671; with permission.

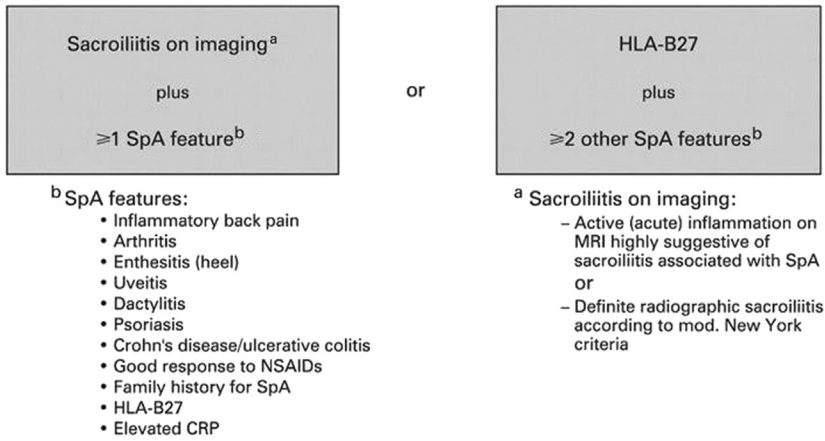

Fig. 1. ASAS classification criteria for AxSpA (in patients with back pain > 3 months and age at onset < 45 years). Sensitivity 82.9%, specificity 84.4%; n = 649 patients with chronic back pain and age at onset < 45 years. Imaging arm (sacroiliitis) alone has a sensitivity of 66.2% and a specificity of 97.3%. **Note: Elevated CRP is considered a SpA feature in the context of chronic back pain. (*From* Rudwaleit M, Landewé R, van der Heijde D, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68(6):777-83; with permission.)

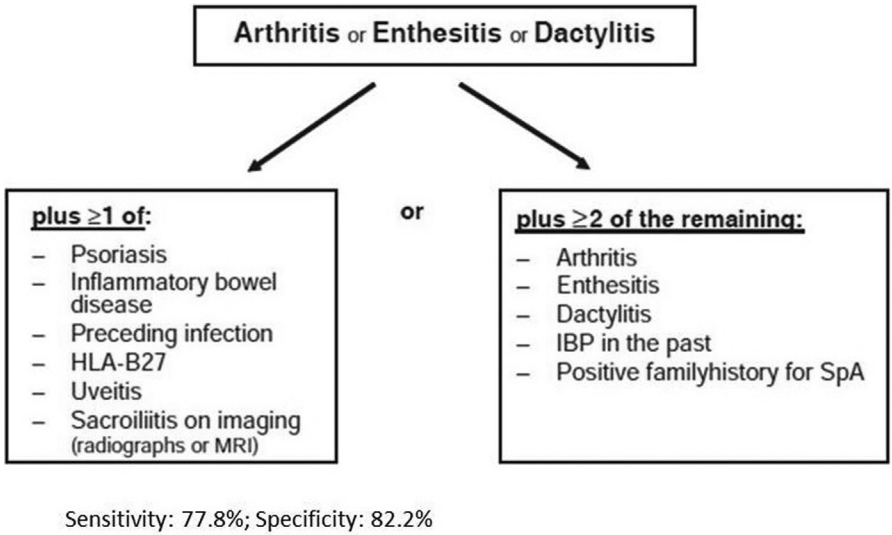

Fig. 2. ASAS classification criteria for peripheral SpA. (*Adapted from* Rudwaleit M, van der Heijde D, Landewé R, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis 2011;70(1):28; with permission.)

Box 2
Inflammatory back pain (Assessment of SpondyloArthritis International Society criteria)

1. Age at onset less than 40 years
2. Insidious onset
3. Improvement with exercise
4. No improvement with rest
5. Pain at night (with improvement upon getting up)

IBP if 4/5 are present.

Sensitivity 79.6%; specificity 72.4%.

From Sieper J, van der Heijde D, Landewé R, et al. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). Ann Rheum Dis 2009;68(6):784-8; with permission.

considered to be synonymous with those formerly classified by the mNY criteria with AS, and those without these radiographic features are, for the moment, being called "nonradiographic" axial spondyloarthritis. The term "axial spondyloarthritis" reflects the larger set of patients now included, many of whom do not have classic ankylosis of the spine or SI joints. Population studies in the United States suggest that AS, or radiographic AxSpA, is present in 0.5% of the population, whereas the broader set of patients may be present in up to 1.4% of the population. Whereas AS is considered to be present in a 2:1 male-to-female proportion, the full spectrum of AxSpA is considered to be equi-gender, an important point for the clinician to consider when evaluating a woman with back pain. Whereas some patients may present with radiographic and/or MRI changes in the spine consistent with AxSpA, there can be many "false positive" changes in the spine, thus the focus in these criteria on changes in the SI joints, which are less likely to show false positive changes than the spine. It is important to take in the "stem" of the criteria, that is, that in order to apply the criteria, the symptoms of the condition should be chronic, and onset should be before the age of 45.

Peripheral Spondyloarthritis Classification Criteria

The pSpA criteria include peripheral arthritis (typically asymmetric and predominantly lower limb), enthesitis, or dactylitis plus either one or 2 characteristic SpA features[10] (see **Fig. 2**). Although, classically, SpA subsets, such as PsA, the arthritis of IBD, ReA, and undifferentiated SpA, present more peripherally and thus tend to be categorized in this set, there can be considerable overlap with AxSpA features[11] (**Fig. 3**). For example, axial involvement may occur in up to 40% of PsA patients, such that such a patient may be simultaneously classifiable as having PsA and AxSpA (either radiographic or nonradiographic). Intriguingly, the axial manifestations seen in PsA may differ from classic AxSpA in that spine involvement may appear at an older age, sacroiliitis may be unilateral, spinal syndesmophytes may have a different morphologic appearance, there may be more cervical spine involvement, and there may be different genetic markers, for example, HLA-B8 positivity. Furthermore, it has been shown that the CASPAR criteria, developed specifically for PsA classification, are more reliable in positively identifying true positive cases and excluding negative ones compared with the ASAS pSpA criteria.[10] In ReA, the spinal involvement may be more transient than is classic for AxSpA. It is recognized that as the understanding

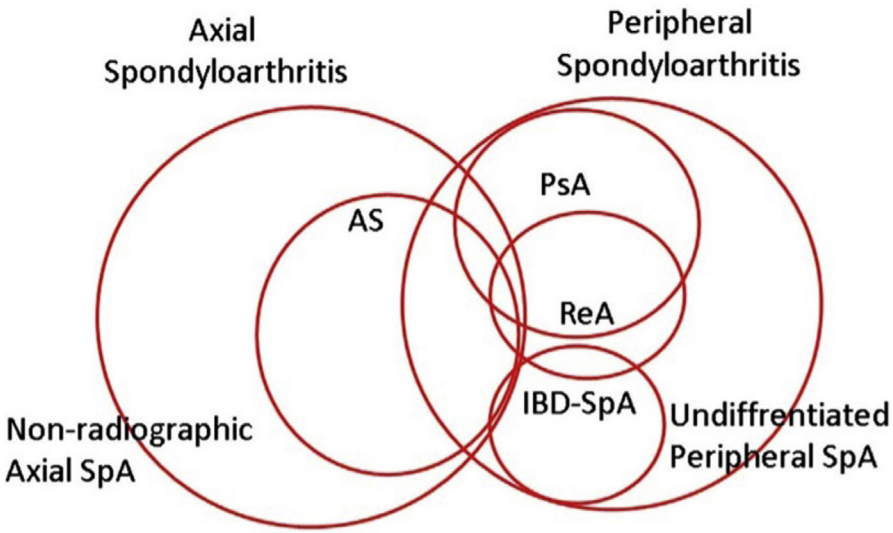

Fig. 3. Spectrum of SpA: current concept. (*From* Raychaudhuri SP, Deodhar A. The classification and diagnostic criteria of ankylosing spondylitis. J Autoimmun 2014;48-49:129; with permission.)

of SpA continues to mature, there will likely be further evolution of the classification criteria, which in the future will likely include genotype and other disease-specific serum biomarkers that will allow more precise categorization of patients for diagnostic and treatment stratification purposes.

In the previous historical survey of the SpA concept, note the emphasis on classification criteria. Such criteria are useful particularly for research purposes, when one is trying to identify a more homogeneous group to study disease characteristics, comorbidity frequency, and effects of treatment. Thus, such criteria ideally should have a high specificity, which may be at the expense of sensitivity, meaning that some true positive cases may not be included, for example, patients that have disease onset after the age of 45 in the case of AxSpA. In order for the classification criteria to be applied to a patient, one should first have clinical diagnostic judgment that the patient could possibly have an SpA condition.In particular, being aware of a possible SpA condition may be a challenge for nonrheumatologists as they try to distinguish if an immunologic, inflammatory condition could be accounting for at least a portion, if not all, of a patient's symptoms of back pain, peripheral arthritis, enthesitis, and other features. Although there are no formal diagnostic criteria for the spondyloarthritides, if enough characteristic features identified through history, family history, physical examination, laboratory testing, and imaging are present, then the patient is certainly appropriate for referral to a rheumatologist, and then, depending on the rheumatologist's judgment about diagnosis and disease severity, worthy of progressing up the treatment ladder. Sometimes even expert rheumatologists cannot be certain, and a diagnosis becomes more certain, positive or negative, after seeing the results of treatment trials. Just as much care needs to be taken to not overdiagnose to avoid treatment that may be expensive or harmful, as to underdiagnose and miss the opportunity to effectively treat disease. The following sections provide approaches to effective differential diagnosis of SpA, beginning with AxSpA and progressing to other forms of SpA.

Axial Spondyloarthritis Diagnosis

A key starting point in sorting out AxSpA is to ask 5 key IBP criteria questions[12] (see **Box 2**). Did the pain that is characteristic of the patient's back pain begin before the age of 40? Did the pain problem gradually grow on them (insidious) rather than being sudden in onset? Does pain get better as the patient moves about and is active? Is there no improvement in pain with rest? Does the pain awaken the patient at night, especially in the second half of the night, and improves if the patient gets up? If the answer is "yes" to at least 4 of these 5 questions, then the possibility of an inflammatory condition is increased. A corollary question is are they particularly stiff when first moving about, and how long does it take for stiffness to resolve; is it sometimes more than an hour? As can be seen in **Fig. 4**, the responses to these questions will likely be different if the main reason for the back pain is degenerative/mechanical or a problem such as an infection or malignancy. Rudwaleit and colleagues[13] have identified additional features in addition to IBP that cumulatively increase the likelihood that the 5% of chronic back pain patients who have IBP may ultimately have a diagnosis of AxSpA (**Table 1**). Additional features include accompanying peripheral arthritis, typically asymmetric and lower extremity, persistent pain around the heel (Achilles or plantar fascia enthesitis), dactylitis (sausage digit), family history of an SpA condition, a good response to nonsteroidal anti-inflammatory drugs (NSAIDs), a history of an associated condition, such as psoriasis, IBD, or uveitis, and objective laboratory testing and imaging, such as a positive HLA-B27 test, elevated C-reactive protein (CRP), or MRI findings characteristic of SpA. An algorithmic approach to diagnosis has been suggested by van den Berg and colleagues[14] (**Fig. 5**) in which a patient with the proper

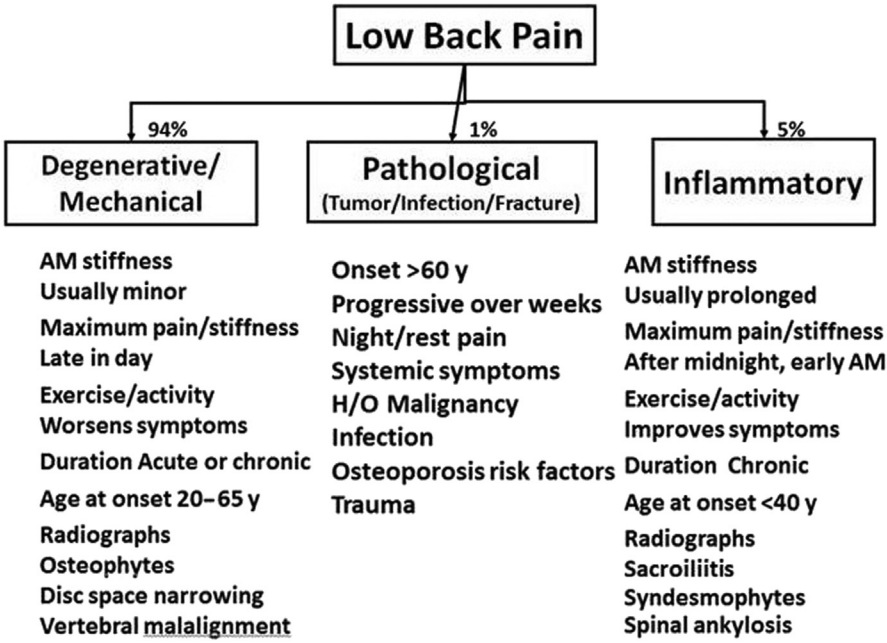

Fig. 4. Low back pain. (*From* Sieper J, van der Heijde D, Landewé R, et al. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). Ann Rheum Dis 2009;68(6):784-8; with permission.). H/O, History of.

Table 1
Clinical utility of the clinical parameters of SpA

	Sensitivity	Specificity	+LR
Inflammatory back pain (updated information)	80%	72%	2.9
Enthesitis (heel pain)	37%	89%	3.4
Peripheral arthritis	40	90	4.0
Dactylitis	18	96	4.5
Acute anterior uveitis	22	97	7.3
Positive family history for AS, AAU, IBD, ReA	32	95	6.4
Psoriasis	10	96	2.5
Inflammatory bowel disease	4	99	4.0
Good response to NSAIDs	77	85	5.1
↑ acute phase reactants	50	80	2.5
HLA-B27 (*updated information*)	*Variable*	*Variable*	11
MRI (STIR) sacroiliitis (*updated information*)	*Variable*	*Variable*	11

Abbreviation: LR, Likelihood ratio; SIJ, sacroiliac joints.
Adapted from Rudwaleit M, van der Heijde D, Khan MA, et al. How to diagnose axial spondyloarthritis early. Ann Rheum Dis 2004;63(5):535-43; with permission.

"stem," that is, has chronic back pain with onset less than 45 years of age, has either a pelvis radiograph consistent with sacroiliitis, leading to a diagnosis of AS, or has a normal SI radiograph, but does have other characteristic SpA features, prompting further evaluation. If enough of these features are present, triage to a rheumatologist is appropriate.

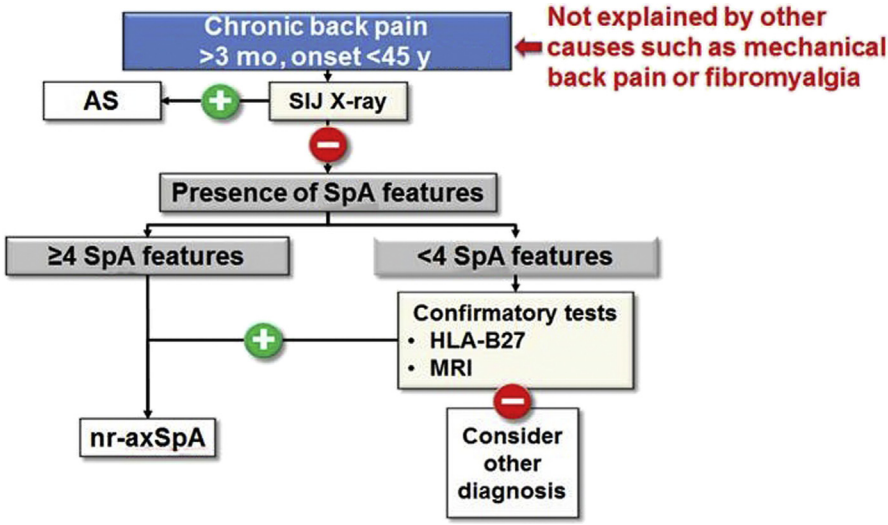

Fig. 5. How should we diagnose axial SpA in practice? (*From* van den Berg R, de Hooge M, Rudwaleit M, et al. ASAS modification of the Berlin algorithm for diagnosing axial spondyloarthritis: results from the SPondyloArthritis Caught Early (SPACE)-cohort and from the Assessment of SpondyloArthritis international Society (ASAS)-cohort. Ann Rheum Dis 2013;72(10):1646-53; with permission.)

Take note of the focus on radiographic evaluation of SI joints; a plain pelvis radiograph will do. It is all too common for a patient to have multiple sets of lumbar spine radiographs and MRI scans that show modest degenerative changes, yet no attention to the SI joints. There has been controversy about how to best radiographically image the SI joints, partly because the local radiologist may have been taught that angled views of the joints are best because the joint runs at an angle to the anteroposterior (AP) plane. However, there is risk of increased radiation exposure as the radiology technician makes several attempts to get the correct angled shot. The SpA research community's most common recommendation is that a single AP view will suffice. Regardless of radiographic technique, numerous studies have shown that there is significant variation in what is considered truly abnormal, and to what degree, especially with intermediate grades of abnormality. MRI is more sensitive and reliable to give information about the presence of inflammation as well as damage. Computed tomography (CT) scan can provide exquisite detail about damage, albeit at the expense of radiation exposure. For this reason, low-dose CT is now beginning to be used. Beyond radiograph, it is probably best to leave ordering of advanced imaging up to the rheumatologist, who may have a special understanding about technique with local musculoskeletal radiologists.

The only laboratory studies for AxSpA are the CRP—we rely on this more so than erythrocyte sedimentation rate (ESR)—and the HLA-B27 gene marker. Other autoimmune disease–related autoantibodies or disease activity markers may be assessed, for example, to rule out RA, lupus, and so forth, in the differential diagnosis, but are not used to rule in SpA. Note that the CRP is often not elevated in SpA, even with active disease, so if normal, it is not necessarily helpful, unless it has become normal with effective treatment. Similarly, HLA-B27 may be negative in up to 20% of classic AS and even more in other subtypes. Furthermore, HLA-B27 varies with race, for example, being present less frequently in African Americans but more frequently in certain Native American populations. Thus, one cannot rely on any laboratory testing for reliable diagnostic purposes. Discovery of biomarkers that can more reliably be used for diagnosis or evaluating disease severity remains an unmet need and is an active area of research.

Peripheral Spondyloarthritis Diagnosis

In a similar way, diagnosis and monitoring of patients with primarily peripheral, or mixed peripheral and axial SpA, are a matter of pattern recognition of symptoms, such as persistent pain arising from inflammation in joints, sites of tendon and ligament insertion into bone (classically around the heel, knee, pelvis, thorax, shoulder, and elbow), and swelling of a whole digit, known as dactylitis. The presence of a genetically associated condition, such as IBD, psoriasis, and uveitis, or a family history of the same or similar autoimmune disease is an important clue for diagnosis. The most common form of SpA presenting in this manner is PsA. Psoriasis occurs in 3.2% of the US population.[15] PsA occurs in up to 30% of patients with psoriasis in North America and Western Europe.[16] In most patients, psoriasis precedes the onset of PsA, by, on average, 10 years, but in some, the skin manifestations develop at the same time as musculoskeletal symptoms, whereas, in a few, the skin manifestations follow the appearance of arthritic and entheseal ones. Because of the first appearance of skin and nail disease, clinicians caring for these manifestations, for example, dermatologists and primary care physicians, are in the best position to be monitoring patients for musculoskeletal symptoms suggestive of PsA in order to triage the patient to rheumatologists for early treatment. Certain patient-reported questionnaires, such as the PEST[17] can help with case finding by questioning if there has been any history of

joint swelling, a diagnosis of arthritis, nail pitting, pain in the heel (enthesitis), or swelling of a whole digit (dactylitis). In the early stages of PsA, oligoarticular involvement (<5 inflamed joints) is common, but as the disease matures, polyarticular presentation is the norm. Distal interphalangeal (DIP) joints are frequently involved, unlike RA, and may make it difficult to discern from osteoarthritis changes of DIP joints. Enthesitis is present in 30% to 70%, dactylitis in 40% to 50%, and spine disease in up to 50% of PsA patients.[18] Spine disease includes sacroiliitis, often asymmetric, nonmarginal syndesmophytes, and frequent cervical spine involvement, features that distinguish axial PsA from classic AxSpA.[19,20] Radiographs and advanced imaging, such as ultrasound (US) and MRI, are diagnostically useful, and US and MRI can distinguish inflammatory arthritis and enthesitis from degenerative disease and FM. As in AxSpA, there is a paucity of laboratory biomarkers to diagnose PsA. CRP is elevated in less than half the patients, even with active disease. HLA-B27 may be present in patients with axial presentation. Although rheumatoid factor and cyclic citrullinated peptide are typically negative, in a small percentage of patients, they may be positive, so positivity of these tests cannot rule out PsA.

Inflammatory bowel disease

Musculoskeletal symptoms, including oligoarticular arthritis, polyarthritis, polyarthralgias, and spondylitis, occur in 10% to 20% of patients with IBD, more so with Crohn than with ulcerative colitis. Associated conditions include uveitis, episcleritis, erythema nodosum, pyoderma gangrenosum, and psoriasis. The obvious clue to the cause of these symptoms is the presence of IBD.[21] As in PsA, the gastroenterology clinical staff should be sensitive to this association to improve case findings and prompt referral to rheumatology for evaluation and collaborative decision making about therapeutic approach.

Reactive arthritis

ReA, which used to be called Reiter syndrome, occurs as a sequela of a triggering infection with microbes, such as Salmonella, Shigella, Yersinia, Campylobacter, and Chlamydia, among others.[22] Accurate figures on incidence and prevalence are hard to come by. It appears that between 0.5% and 2% of infected individuals may present with ReA, based partly on genetic factors, including HLA-B27. Clinical symptoms include typically asymmetric arthritis, predominantly lower extremity, spondylitis, enthesitis, and/or dactylitis and relatively recent, not necessarily active, history of infection. Associated conditions can include conjunctivitis, uveitis, urethritis, erythema nodosum, and keratoderma blennorrhagica, the presence of which can help with the differential diagnosis. The natural history of most cases of ReA is to remit over the course of 3 months to 6 months, but some may develop a chronic course.

There are several comorbidities that are present in a higher prevalence in the spondyloarthritides, depending on the spondyloarthritis subset, than in the general population. Some of these include metabolic syndrome (obesity, hyperlipidemia, and hypertension), cardiovascular disease, nonalcoholic steatotic hepatitis, depression, and FM, to name a few.[23,24] Some of these comorbidities are modifiable, and when addressed, can improve disease outcomes. For example, this has been shown with weight reduction programs. Comanagement of cardiovascular comorbidity is especially important for the patient's health care team. When FM, partially synonymous with central sensitization syndrome, is coexistent, as can be seen in 10% to 30% of patient cohorts, measures of disease activity that include subjective elements will typically be worse. When these measures are used as targets of treatment, patients with concomitant FM are less likely to achieve these targets. Concomitant FM needs to be

recognized in order to avoid potentially unnecessary switching between immunomodulatory medicines, and efforts to treat FM should be instituted.[24]

Why does early identification of an SpA condition matter? Over the last 2 and a half decades, parallel advancements have been witnessed in both the understanding of the pathophysiology of SpA diseases and the development of increasingly effective treatment options that now allow routine achievement of remission or low disease activity, particularly in patients who do not have long delays in their diagnosis and treatment. A detailed review of pathophysiology is beyond the scope of this article; the reader is referred to several excellent reviews.[18,25–28] Although the balance of immune cell proliferation and activation and proinflammatory cytokine constituency will vary from 1 disease subset and 1 tissue domain (synovium, enthesium, bone, skin, gut, eye, and so forth) to another, there are certain commonalities between SpA subsets and their associated conditions. There appears to be a greater involvement of innate immune system activation than in more classically adaptive immune system diseases, such as RA. In other words, more "front-line" defense mechanisms at play responding to external-internal incitement, such as infections, perturbation in the gut or skin microbiome, mechanical microtrauma, and HLA-B27 unfolded protein response.[29] Dendritic and other cells then overproduce cytokines, such as interleukin-23 (IL-23), which migrates to potential sites of inflammation where both resident immune cells of the innate immune system and cells of the adaptive immune system are activated, producing more proinflammatory cytokines, including IL-17 and tumor necrosis factor-α (TNF-α). These cytokines, in turn, interact with receptors on effector cells, such as macrophages, neutrophils, other lymphocytes, keratinocytes, and osteoblasts, leading to inflammation and tissue destruction in synovium, bone, skin, and so forth. By targeting these proinflammatory cytokines and cells with specific inhibitors, inflammation and tissue destruction can be controlled, and in many cases, if treatment is maintained, the disease can be in a state of remission or near-remission.

TREATMENT

The landscape of treatment of the spondyloarthritides has undergone a revolutionary change in the last 2 decades because of the discovery and increasingly widespread use of medications that inhibit or regulate specific immunologic targets. Achieving outcomes, such as remission or low disease activity, are now reachable for our patients. The following is a brief review of the treatment "ladder" for the spondyloarthritides. It is within the purview of nonrheumatologists to initiate treatment of SpA patients with NSAIDs and nonnarcotic analgesics, as well as nonpharmacologic therapies, such as physical therapy. Glucocorticoids are avoided except to briefly treat flares. Traditionally, initiation of immunomodulatory medications has been left to the rheumatologist because of potential safety concerns with these agents and also because of the more recent proliferation of medications to choose from.[30–33] **Box 3**[34–36] and **Box 4**[37,38] include listings of various immunomodulatory medications and their classes that have shown efficacy in the treatment of SpA conditions, most of which have gained regulatory approval, although for some, approval is still pending. Fortunately, for patients, there has been an exponential growth of treatment options that can be effective. Efficacy is determined by assessing, through subjective questioning about symptoms, for example, pain and fatigue, physical examination, joint palpation for tenderness and swelling, entheseal insertion tenderness, finger swelling consistent with dactylitis, spine motion, and skin involvement. It is also assessed by measuring change in CRP, in those in whom CRP is elevated. One can also assess change in inflammation using US and MRI, and damage by radiograph. It is very common for

Box 3
Psoriatic arthritis therapeutic groups

- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Conventional synthetic DMARDs (cs-DMARDs)
  - Methotrexate, sulfasalazine, leflunomide
- TNF inhibitors (TNFi)
  - Etanercept, infliximab, adalimumab, golimumab, certolizumab
- IL12/23i
  - Ustekinumab
- IL17i
  - Secukinumab, ixekizumab, brodalumab, bimekizumab
- IL23i
  - Guselkumab, risankizumab, tildrakizumab
- T-cell modulator
  - Abatacept
- Targeted synthetic DMARDs (ts-DMARDs)
  - PDE4i (apremilast)
  - JAKi (tofactinib, baricitinib, upanacitinib, filgotinib)

Data from Mease PJ. Biologic Therapy for Psoriatic Arthritis. Rheum Dis Clin North Am 2015;41(4):723-38; and Mease PJ, Armstrong AW. Managing patients with psoriatic disease: the diagnosis and pharmacologic treatment of psoriatic arthritis in patients with psoriasis. Drugs 2014;74(4):423-41.

a drug to work for a period of time and then lose adequate efficacy, so the optimal care of an SpA patient has to do with frequent quantification of disease severity (or absence thereof) and adjusting or switching medications to address changes.

Choice of therapy is individualized based on a shared decision-making process between patient and clinician. Does the patient have a preference for an oral option versus parenteral? For example, a frequent traveler may prefer an oral medicine because of ease of transport, or the person may be needle phobic. Are there cost implications of 1 choice over another? What clinical domains are most involved, and are there specific safety concerns? If skin disease is severe, should an IL-17 inhibitor be chosen that yields better skin clearance? What if skin disease improves significantly but not the joints or vice versa; both outcomes can be seen unpredictably, necessitating course correction. If the patient has active uveitis and IBD along with

Box 4
Axial spondyloarthritis therapeutic groups

- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- TNF inhibitors (TNFi)
  - Etanercept, infliximab, adalimumab, golimumab, certolizumab
- IL17i
  - Secukinumab, ixekizumab, bimekizumab
- Targeted synthetic DMARDs (ts-DMARDs)
  - JAKi (tofactinib, baricitinib, upanacitinib, filgotinib)

From Mease P. Emerging Immunomodulatory Therapies and New Treatment Paradigms for Axial Spondyloarthritis. Curr Rheumatol Rep 2019;21(7):35; with permission.

musculoskeletal involvement, should a monoclonal antibody construct of TNF inhibitor be used that can benefit these manifestations as well as skin and musculoskeletal domains? Conversely, if IBD is present, should NSAIDs and IL-17 inhibitors be avoided? There is also the need for close monitoring of safety and tolerability of each medication. A common denominator concern with any immunomodulatory agent is the potential for increased infection. For some, there are also risks for malignancy (rare), allergic reactions, and laboratory abnormalities about which the patient needs to be educated and placed on a monitoring regimen. If the patient has frequent sinus infections with a therapy, should medicines be switched, seeking less frequent infection? If the patient develops a paradoxic TNF inhibitor-induced psoriasis or lupuslike syndrome, should the patient be switched to a different mechanism of action? In general, the benefit-cost ratio of disease control versus side effects comes down significantly on the side of benefit from disease control. Although for many patients, need for treatment is ongoing, in some, it is warranted to taper or stop medications if prolonged remission has been achieved. Treatment course is best determined through shared decision making between the patient and their care team. Ideally, members of the care team, for example, rheumatologists, primary care clinicians, dermatologists, gastroenterologists, ophthalmologists, physiatrists, orthopedists, and physical therapists, are communicating readily with each other.

CLINICS CARE POINTS

- Spondyloarthritis should be considered in patients presenting with chronic inflammatory back pain, peripheral arthritis, tendon or ligament insertion pain (enthesitis), especially if there are associated conditions, such as uveitis, IBD, or psoriasis.
- There are few laboratory abnormalities that can aid in diagnosis, other than CRP/ESR, which may be variably elevated, and the HLA B27 gene; thus, history and physical examination are critical in initial screening.
- Imaging, especially advanced imaging such as MRI of the pelvis and spine, to assess for inflammatory changes in bones and joints, or US of peripheral joints and entheses, can be helpful in diagnosis.
- Differential diagnosis with conditions such as osteoarthritis, degenerative spine disease, mechanical back pain or tendonitis, gout, and FM can be difficult to sort out. Referral to a rheumatologist is often warranted for the establishment of an accurate diagnosis.
- Once a diagnosis is made and effective therapy is initiated, coordinated teamwork between the rheumatologist, primary care physician, dermatologist, gastroenterologist, ophthalmologist, physiatrist, orthopedic surgeon, physical therapist, and other caregivers is optimal for patient management.

DISCLOSURE

Research grant, consultation fees, and/or speaker honoraria: AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Galapagos, Gilead, GlaxoSmithKline, Janssen, Novartis, Pfizer, Sun, UCB.

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