REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Ankylosing Spondylitis and Axial Spondyloarthritis

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Chronic back pain is common worldwide and is cared for by a variety of providers, but specific, satisfactory treatment is often lacking. Ankylosing spondylitis, an inflammatory disorder that in its extreme form can lead to the bony fusion of vertebral joints, is an uncommon but well-established cause of chronic back pain. During the past decade, ankylosing spondylitis has come to be considered as a subset of the broader and more prevalent diagnostic entity referred to as axial spondyloarthritis. The estimated prevalence of axial spondyloarthritis in the United States is 0.9 to 1.4% of the adult population, similar to that of rheumatoid arthritis.[1] Axial spondyloarthritis is generally diagnosed and treated by rheumatologists, and there is specific treatment for it. However, prolonged delay in reaching the diagnosis is common and is usually the result of the failure of recognition by nonrheumatologists.[2] This review is intended to enhance awareness and understanding of axial spondyloarthritis and ankylosing spondylitis — and the relationship between the two — in order to facilitate prompt and accurate diagnosis and proper treatment. Recent advances in our understanding and treatment of these conditions are discussed.

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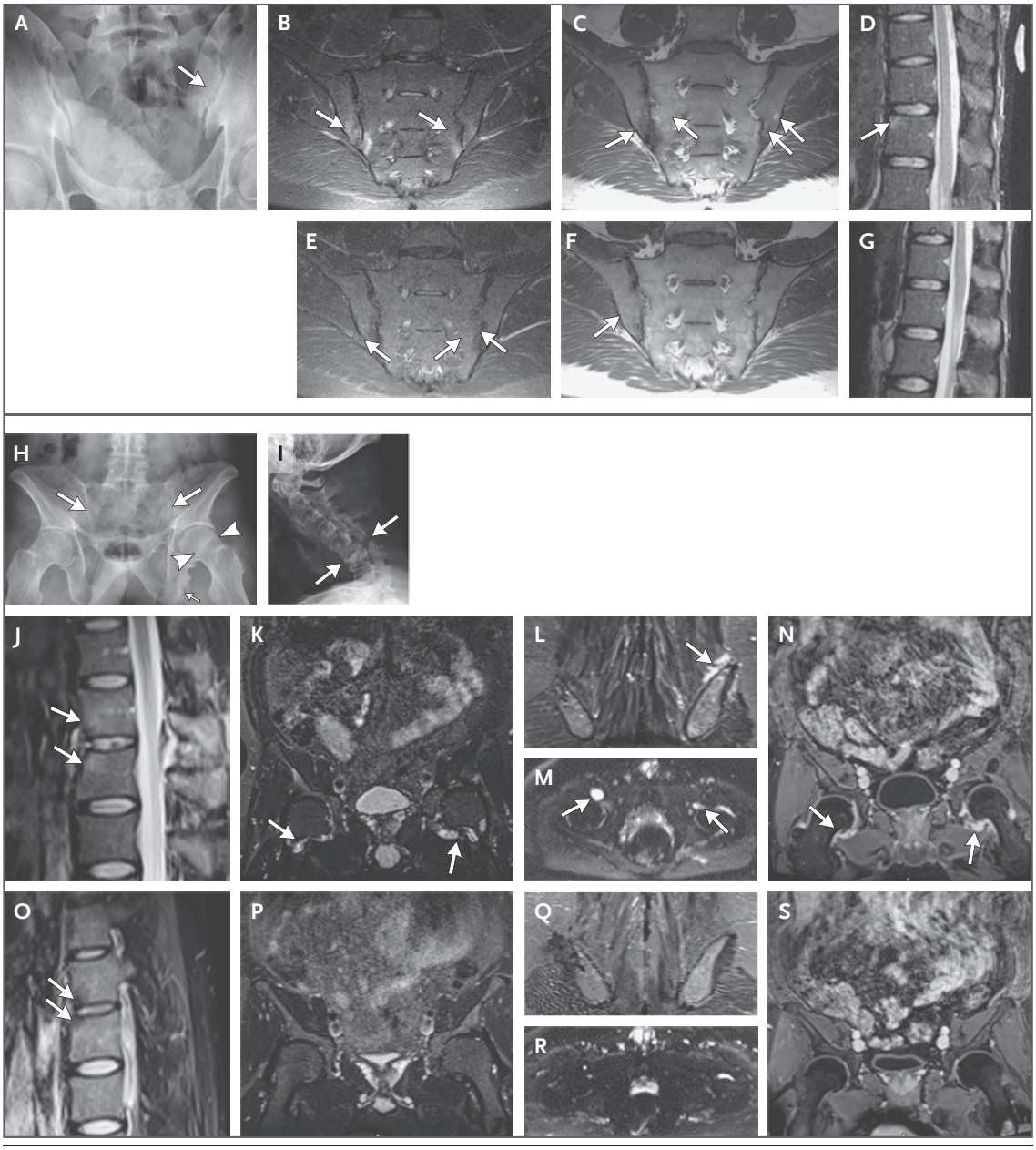
Conceptual History and Classification

The dramatic phenotype caused by fusion of the sacroiliac, vertebral, and apophyseal joints was recognized in postmortem specimens in the 17th and 18th centuries. The classic clinical description of ankylosing spondylitis was made in the late 1800s and was refined by the addition of radiographic descriptions during the 1930s.[3] After World War II, the hereditary nature of ankylosing spondylitis was established, and descriptions of large patient cohorts led to the formulation of diagnostic criteria in the 1960s. These criteria emphasized the detection of advanced sacroiliitis on radiography (Fig. 1H), together with pain, stiffness, and limited motion of the lumbar and thoracic spine.[4] The concept of spondyloarthritis was proposed in 1974 to emphasize the interrelatedness of ankylosing spondylitis and several other conditions that had previously been described separately.[5,6] (See Table 1 for current classifications of spondyloarthritis, adapted from the Assessment of SpondyloArthritis International Society [ASAS]). Spondyloarthritis is currently classified as predominantly axial, affecting the spine, pelvis, and thoracic cage, or predominantly peripheral, affecting the extremities.

The identification in 1973 of a very strong association with HLA-B27 led to heightened awareness of the disorder. The ratio of affected male patients to female patients, which was previously thought to be 10 to 1, was found to be much lower. It gradually became recognized that symptoms are often present for years before advanced sacroiliitis supervenes and a proper diagnosis is made.[7] The inadequacy of advanced radiographic sacroiliitis as a diagnostic criterion was accentuated by the observation in the mid-1990s of spinal and sacroiliac inflammation on magnetic resonance imaging (MRI) in patients with early disease. This new diagnostic sensitivity, together with the dramatic response to the inhibition of tumor necrosis



factor α (TNF-α), first reported in 2000, has led to efforts to characterize the predictive value of early symptoms and to reformulate the diagnostic and classification criteria applicable in early disease.

Spondyloarthritis accounts for a minority of the cases of chronic low back pain.[2] Increased specificity for spondyloarthritis is obtained when the nature and pattern of the pain and the age of the patient are considered. The most typical symptom is inflammatory back pain (Table 2).[8,9] The pain is usually dull and insidious in onset and is felt deep in the lower back or buttocks. Another prominent feature is morning back stiffness that lasts for 30 minutes or more, diminishes with activity, and returns after inactivity. Although initially the back pain is intermittent, over time it becomes more persistent. Nocturnal exacerbation of pain is common, particularly during the second half of the night, forcing the patient to rise and move around. Pain is often present in the thoracic spine as well. Cervical involvement typically occurs late but can predominate. Pain in the chest occurs in more than 40% of patients with spondyloarthritis.[10] If the source of this pain is not accurately diagnosed, patients may be subject to unnecessary diagnostic workups for cardiovascular disease or other intrathoracic diseases.

Inflammatory back pain occurs in 70 to 80% of

Figure 1 (facing page). Sensitivity of MRI in the Diagnosis of Axial Spondyloarthritis.

Panels A through G show images for a 26-year-old man with a 2-year history of inflammatory back pain that was unresponsive to nonsteroidal antiinflammatory drugs. A posteroanterior pelvic radiograph (Panel A) shows early erosive changes in the left iliac bone (arrow) that could be interpreted as grade 2 sacroiliitis. The right sacroiliac joint is normal. Since these changes do not meet the 1984 modified New York criteria for ankylosing spondylitis,[4] a diagnosis of nonradiographic axial spondyloarthritis was made. Coronal sections of the sacroiliac joints obtained with short tau inversion recovery (STIR) (Panel B) and T_1-weighted (Panel C) sequencing show subchondral bone marrow edema in both sacroiliac joints, with erosions and pseudo-widening of the joint spaces (arrows). A sagittal image of the spine obtained with STIR sequencing shows a Romanus lesion on the anterosuperior end plate of the T12 vertebra (Panel D, arrow). Corresponding images obtained after treatment with anti–TNF-α indicate the resolution of bone marrow edema (Panels E through G), with fatty metamorphosis (Panel F, arrows) consistent with healed lesions.

Panels H through S show images for a patient with ankylosing spondylitis. He presented at 36 years of age after a traumatic cervical fracture. He had had axial symptoms since 16 years of age. A posteroanterior pelvic radiograph obtained at that time (Panel H) shows sacroiliac joints that are almost completely fused (long arrows), a ring osteophyte of the left femoral neck (arrowheads), and left ischial periostitis, or "whiskering" (small arrow). A radiograph of the cervical spine shows a fracture through the C5–C6 intervertebral disk and the C6 superior end plate, extending through the posterior elements (Panel I, arrows). This fracture was corrected surgically and resulted in only minimal neurologic sequelae. At 38 years of age, pain in his back and left hip worsened, and levels of inflammatory markers became elevated. MRI was performed with and without intravenous contrast material before treatment and after 20 weeks of therapy with anti–TNF-α. Images obtained before treatment are shown in Panels J through N, including a sagittal image of the spine obtained with STIR sequencing (Panel J), three-dimensional coronal T_2-weighted images (Panels K and L), an axial diffusion-weighted image (Panel M), and a three-dimensional coronal T_1-weighted image obtained after administration of contrast material (Panel N). The images show Romanus lesions on two vertebral bodies (Panel J, arrows), synovitis of both hips (Panels K, M, and N, arrows), and enthesitis of the left posterior superior iliac spine (Panel L, arrow). Images obtained after treatment are shown in Panels O through S; bone marrow edema, diffusion signaling, and enhancement have resolved. Fatty metamorphosis indicates healed Romanus lesions (Panel O, arrows). Images for the first patient courtesy of Dr. Walter Maksymowych.

Table 1. Current and Classic Classifications of Spondyloarthritis.*

Current classifications
Axial spondyloarthritis
With radiographic sacroiliitis
Without radiographic sacroiliitis
Sacroiliitis on MRI
HLA-B27 positivity plus clinical criteria
Peripheral spondyloarthritis
With psoriasis
With inflammatory bowel disease (Crohn's disease or ulcerative colitis)
With preceding infection
Without psoriasis or inflammatory bowel disease or preceding infection
Classic classifications
Ankylosing spondylitis
Reactive arthritis (infection-associated arthritis)
Psoriatic spondyloarthritis
Predominantly peripheral
Predominantly axial
Enteropathic spondyloarthritis (associated with inflammatory bowel disease)
Predominantly peripheral
Predominantly axial
Juvenile-onset spondyloarthritis (enthesitis-related juvenile idiopathic arthritis)
Undifferentiated spondyloarthritis

* Current classifications are adapted from the Assessment of SpondyloArthritis International Society (ASAS) by Rudwaleit et al.[5,6] MRI denotes magnetic resonance imaging.

Table 2. Characteristics of Inflammatory Back Pain.*

Characteristic
Age at onset, <45 yr
Duration, >3 mo
Insidious onset
Morning stiffness >30 min
Improvement with exercise
No improvement with rest
Awaking from pain, especially during second half of night, with improvement on arising
Alternating buttock pain

* The presence of two or more of these features should arouse suspicion for inflammatory back pain, and the presence of four or more features can be considered diagnostic. The sensitivity of inflammatory back pain for the diagnosis of axial spondyloarthritis is 70 to 80%. The specificity varies, depending on the population being studied.[8,9]

patients with ankylosing spondylitis and is relatively uncommon in patients whose pain has another source.[9] Consequently, inflammatory back pain was included as one of the three clinical criteria for diagnosis listed in the 1984 modified New York criteria for ankylosing spondylitis.[4] These criteria required the detection of advanced sacroiliitis on plain radiographs together with any one of three clinical criteria: inflammatory back pain, limitation of the motion of the lumbar spine, and

restricted chest expansion. Although these criteria are quite specific, they proved to be impractically insensitive for the purpose of diagnosing early disease. In addition, large intraobserver and interobserver variation in interpretation further confounds the reliance on plain radiographs of the sacroiliac joints. Inflammation of the sacroiliac joints can be detected on MRI in patients with symptoms of ankylosing spondylitis even when these joints do not appear to be abnormal on conventional radiography. The same MRI techniques also reveal spinal inflammation in many patients. The detection of these conditions on MRI led to the development of the concept of axial spondyloarthritis, a diagnosis that includes patients with definite ankylosing spondylitis and patients with symptoms similar to those of ankylosing spondylitis and findings of sacroiliitis on MRI but without the detection of advanced sacroiliitis on conventional radiography, which is included in the New York criteria for the diagnosis of ankylosing spondylitis. The latter entity was termed preradiographic or nonradiographic axial spondyloarthritis.

Meanwhile, epidemiologic studies determined the sensitivity and specificity of a number of clinical and laboratory findings characteristic of spondyloarthritis. In 2009, the ASAS formulated classification criteria for axial spondyloarthritis that were based on these imaging, clinical, and laboratory criteria.[5] With these criteria, the diagnosis is established in persons who have had back pain for 3 or more consecutive months before reaching 45 years of age, who have had the presence of sacroiliitis confirmed on MRI or plain radiography, and who have at least one clinical or laboratory finding that is characteristic of spondyloarthritis. Alternatively, persons with this history who have a positive test result for HLA-B27 plus two features of spondyloarthritis as detected on clinical examination or laboratory analysis also fulfill the criteria for a diagnosis of axial spondyloarthritis. The various criteria have an additive effect on the certainty of diagnosis.[11]

Thus, according to the ASAS criteria, the diagnosis of axial spondyloarthritis encompasses two subsets — nonradiographic axial spondyloarthritis and classic ankylosing spondylitis (i.e., radiographic axial spondyloarthritis). Progression to ankylosing spondylitis occurs in only a minority of patients who have had nonradiographic axial spondyloarthritis for a decade or more.[12] It is unclear whether nonradiographic axial spondyloarthritis and ankylosing spondylitis reflect a single entity that varies along a continuum of duration and severity or whether nonradiographic axial spondyloarthritis includes one or more pathogenetically distinct subsets of disease that either have not been previously recognized or have been given other diagnoses, including undifferentiated spondyloarthritis.[13-15] Among patients with nonradiographic axial spondyloarthritis, there is a significantly higher proportion of female patients, a shorter median duration of disease, and lower levels of inflammatory markers than among those with ankylosing spondylitis. In some but not all studies, the prevalence of HLA-B27 detection was lower among patients with nonradiographic axial spondyloarthritis than it was among patients with ankylosing spondylitis. The ASAS criteria for axial spondyloarthritis have been criticized for introducing additional diagnostic heterogeneity, through both the inclusion of the imaging and nonimaging diagnostic groups together within the category of nonradiographic axial spondylitis and the inclusion of nonradiographic axial spondyloarthritis and ankylosing spondylitis together within the category of axial spondyloarthritis.[16] These criteria will probably undergo further revision in coming years.

These classification criteria have limited use outside the arena of clinical research. To facilitate the diagnosis or exclusion of axial spondyloarthritis in clinical practice, algorithms have been developed that are based on the likelihood ratios of clinical features. Figure 2 shows a modification of a recent ASAS-sanctioned algorithm for the approach to diagnosis in patients with chronic low back pain that began when they were younger than 45 years of age.[9] A diagnosis of axial spondyloarthritis should also be entertained in patients in this age group who have chronic neck, thoracic, shoulder, or hip pain. Up to 15% of patients with ankylosing spondylitis first have symptoms before the age of 16 years.[17] Children and early adolescents typically have predominantly peripheral arthritis and enthesitis (i.e., inflammation at the enthesis, the site at which ligaments or tendons attach to bone) and less axial involvement at onset but often have asymptomatic axial disease that can be detected on MRI.[18]

THE USE OF IMAGING IN DIAGNOSIS

In a patient who has had back pain for 3 months or more and for whom one or more of the clinical criteria listed in Figure 2 apply, the presence of

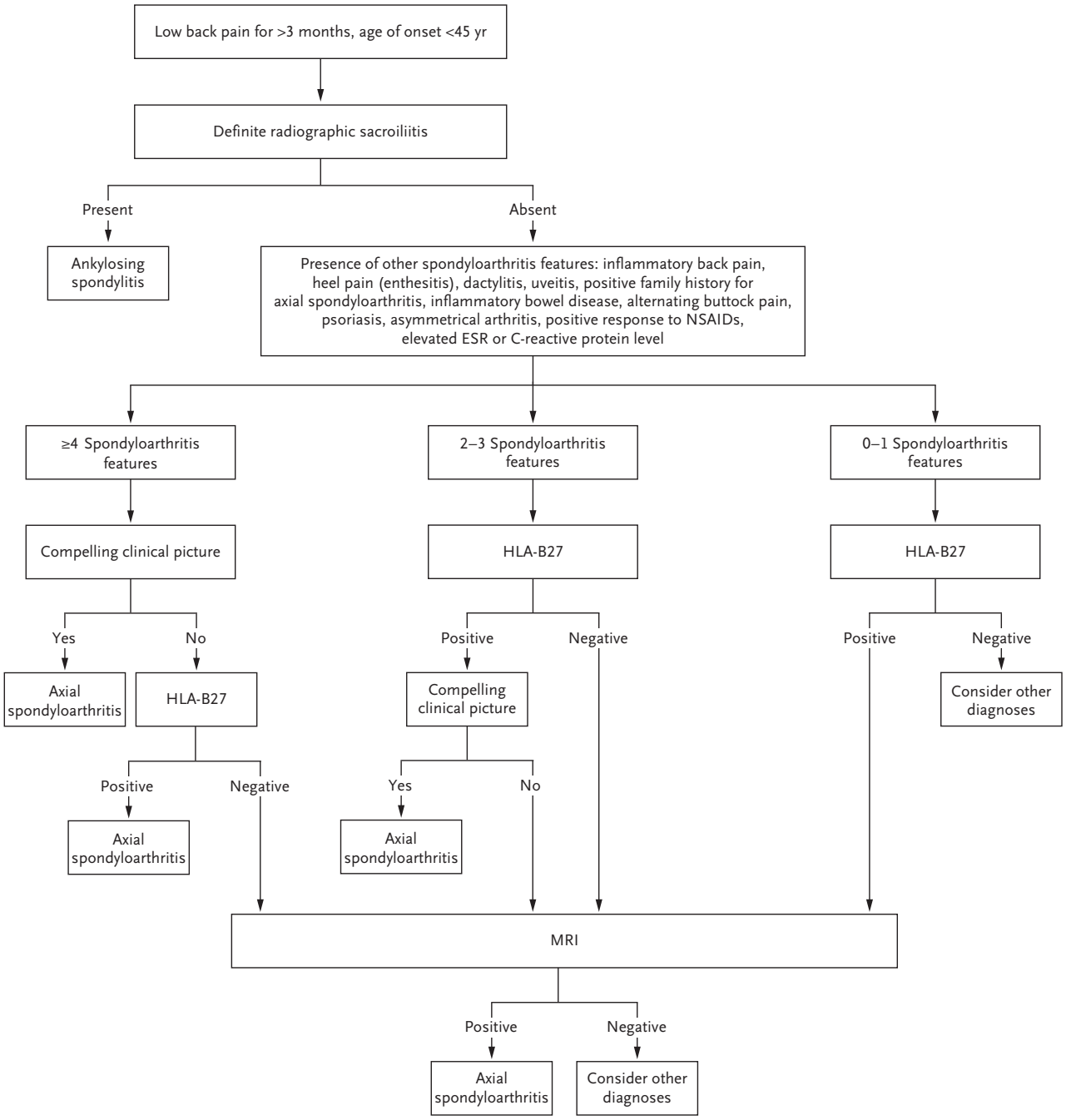


Figure 2. Algorithm for the Diagnosis or Exclusion of Axial Spondyloarthritis.

The algorithm is designed for use in patients with at least a 3-month history of unexplained chronic low back pain that started before the age of 45 years. Definite radiographic sacroiliitis is based on the modified New York criteria for ankylosing spondylitis.[4] The algorithm is based on the analysis of 157 patients, as reported by van den Berg et al.[9] The determination of whether or not a clinical picture is compelling is based on the relative weights of the spondyloarthritis features[11] and on clinical judgment. The list of clinical features includes features of axial and peripheral spondyloarthritis. ESR denotes erythrocyte sedimentation rate, MRI magnetic resonance imaging, and NSAID nonsteroidal antiinflammatory drug.

advanced sacroiliitis on plain radiography can be said to establish a diagnosis of ankylosing spondylitis. In a patient for whom these changes are not shown on radiography or a patient for whom conventional radiography is contraindicated and who does not already meet the criteria for axial spondyloarthritis on clinical grounds, MRI should be performed to identify active inflammatory lesions of the sacroiliac joints[19,20] (Fig. 1B and 1C).

The ASAS criteria for the diagnosis of axial

spondyloarthritis[19] require the presence of subchondral or periarticular bone marrow edema in sacroiliac joints (in plane resolution of 0.4 to 0.6 mm, with slice thickness of 3 to 4 mm) on fat-saturated, T_2-weighted or short-tau inversion-recovery (STIR) sequences, with two or more lesions visible on one slice or a single lesion visible on two or more consecutive slices. The appearance of erosion of the sacroiliac joint on T_1-weighted spin-echo sequencing adds sensitivity (Fig. 1C).[21] Bone marrow edema in the sacrum alone or in both the sacrum and the ilium is an independent predictor of spondyloarthritis.[22]

The areas of subchondral edema and erosion can undergo fatty metamorphosis with healing and secondary bone formation in both the sacroiliac joints and the spine[23,24] (Fig. 1D through 1G). A variety of other lesions, particularly enthesitis, can also be identified together with the use of the same setting on MRI[25] (Fig. 1L). If clinically indicated, large joints can be imaged at specific sites to detect coexistent lesions, including enthesitis, tendinitis, bursitis, and synovitis[26] (Fig. 1K, 1L, and 1N).

It is important to emphasize that the MRI protocols that are routinely used in the evaluation of low back pain have a low sensitivity for the detection of inflammation and, unfortunately, often yield false negative results in patients with axial spondyloarthritis. The absence of skill on the part of the reader and a low index of suspicion also play a role in this process, but even with experienced radiologists, the rates of false negative and false positive findings can be substantial.[22] This situation can be expected to improve as new three-dimensional imaging techniques acquired in an isotropic resolution of 1 to 1.5 mm and diffusion imaging come into common use, enhancing the sensitivity of detection of small areas of subchondral edema and enthesitis[27] (Fig. 1K through 1N). Close communication between radiologist and clinician is also required to obtain the best possible results.

MEASURES OF DISEASE ACTIVITY AND OUTCOME

Several tools for assessing disease activity and outcome in ankylosing spondylitis have become widely used, most notably the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI), which are self-administered patient questionnaires; the Bath Ankylosing Spondylitis Metrology Index (BASMI), which is used to assess spinal mobility; and the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), which is used to assess radiographic damage.[28,29] More recently, ASAS has developed the Ankylosing Spondylitis Disease Activity Score (ASDAS). The score is calculated on the basis of patient ratings with regard to spinal pain, the duration of morning stiffness, an overall global assessment, and peripheral arthritis plus laboratory assessments of either the C-reactive protein level or the erythrocyte sedimentation rate (www.asas-group.org/clinical-instruments/asdas_calculator/asdas.html). The ASDAS also performs well in patients with nonradiographic axial spondyloarthritis.[30]

Studies of the progression of radiographic changes have focused on development of erosions and syndesmophytes in the lumbar and cervical spine, as defined by means of the mSASSS. The strongest predictor of the development of new lesions is the presence of syndesmophytes at baseline. Other predictors include a history of smoking and elevated levels of inflammatory markers at baseline.[31] Impairment of spinal mobility is influenced primarily by inflammation in early disease and by structural damage in later disease.[32] Whether TNF inhibitors limit the development of new radiographic lesions is a matter of debate. Older studies suggested that TNF inhibitors do not have this effect, but more recent data have suggested that long-term therapy may reduce the rate of development of new lesions, especially with early initiation of treatment and longer duration of follow-up.[33]

Involvement of one or often both hips, in the coxofemoral joint, occurs in 24 to 36% of patients with ankylosing spondylitis and is associated with greater functional impairment than when there is no hip involvement. On occasion, symptoms related to the hip are the first seen on presentation.[34] The highest prevalence is in patients with juvenile-onset disease. Up to 8% of all patients with ankylosing spondylitis ultimately require total hip replacement. Shoulder involvement, particularly enthesitis, is at least as common as hip involvement but is less frequently disabling.[26]

ASSOCIATED CLINICAL MANIFESTATIONS

PERIPHERAL SPONDYLOARTHRITIS

Up to half of patients with ankylosing spondylitis have arthritis in peripheral joints or peripheral

entheses at some point in the disease course. Peripheral arthritis, enthesitis, or dactylitis can also be the predominant clinical manifestation of spondyloarthritis, with little or no axial involvement. The ASAS recently formulated criteria to distinguish peripheral spondyloarthritis from other forms of peripheral arthritis and from axial spondyloarthritis.[6] The topic of peripheral spondyloarthritis has recently been reviewed elsewhere.[35]

EXTRA-ARTICULAR MANIFESTATIONS

Acute anterior uveitis has a lifetime prevalence of 30 to 40% in patients with ankylosing spondylitis.[36] Typical attacks are abrupt and unilateral, with intense circumlimbal hyperemia, pain, photophobia, and visual impairment. Subsequent attacks may involve the contralateral eye. Psoriasis occurs in more than 10% of patients with ankylosing spondylitis, and inflammatory bowel disease in 5 to 10%, with Crohn's disease being more common than ulcerative colitis. The incidence of positivity for HLA-B27 and male predominance are more pronounced in patients who have ankylosing spondylitis with uveitis and less pronounced in those with psoriasis or inflammatory bowel disease. Microscopic inflammatory lesions are detected in biopsy specimens of the colon or distal ileum in approximately half of patients with axial spondyloarthritis.[37]

Osteoporosis of the spine and peripheral bones is common in ankylosing spondylitis.[38] The combination of spinal rigidity from the formation of syndesmophytes and osteoporosis within trabecular bone contributes to a spinal fracture rate that is as high as 10% among these patients and is associated with a high risk of devastating spinal cord injury[38] (Fig. 1I). The sudden occurrence of new neck or back pain in a patient with ankylosing spondylitis should prompt a search for fracture, even in the absence of trauma, by means of computed tomography (CT). Bone loss is thought to result from inflammation and has been documented in patients with nonradiographic axial spondyloarthritis.[39]

PATHOGENESIS AND GENETICS

ENTHESITIS AND IMMUNOPATHOGENESIS

Spondyloarthritis is marked by enthesitis and by synovitis and osteitis. Working from anatomical dissections and imaging studies, one group of investigators conceptualized the enthesis as an organ that comprises the ligamentous or tendinous insertion site itself along with adjacent tendon and the fibrocartilage, fat pad, bursa, and synovium, the primary purpose of which is to dissipate mechanical stress.[40] Although the basic trigger for the inflammation of spondyloarthritis remains unknown, several lines of evidence implicate the cells and molecules in the pathway involving interleukin-23 and interleukin-17.[41-43] In mice, entheseal-resident T cells that are negative for both CD4 and CD8 and that respond to interleukin-23 by producing interleukin-17 and other proinflammatory cytokines were shown to mediate peripheral and axial enthesitis, linking the interleukin-23–interleukin-17 pathway to the spondyloarthritis phenotype.[44]

ROLE OF HLA-B27

HLA-B27, a class I surface antigen encoded by the B locus in the major histocompatibility complex (MHC), is found in 74 to 89% of patients with either nonradiographic axial spondyloarthritis or ankylosing spondylitis,[45] (odds ratio for the allele, >50). The absolute risk of spondyloarthritis in persons with HLA-B27 positivity is estimated to be 2 to 10% but is higher if a first-degree relative is affected. More than 140 variant alleles (subtypes) of HLA-B27 have been described at the level of protein sequence (www.ebi.ac.uk/ipd/imgt/hla/). Associations with ankylosing spondylitis are firmly established for subtypes B*27:02 (Mediterranean populations), B*27:04 (Far Eastern populations), B*27:05 (white and worldwide populations), and B*27:07 (South Asian and Middle Eastern populations) and are anecdotal for approximately 12 other subtypes. The subtypes B*27:06 (Southeast Asian populations) and B*27:09 (southern Italian and Sardinian populations) are not associated with ankylosing spondylitis.[46] The latter two differ from B*27:04 and B*27:05 by two amino acids and one amino acid, respectively. These substitutions affect the repertoire of bound peptides, biochemical and intracellular behaviors, and the conformational flexibility of the HLA-B27 heavy chain, and these features correlate with susceptibility to disease.[47-49] A recent study of single-nucleotide polymorphisms (SNPs) in the HLA region identified a small number of other statistically significant but weakly associated HLA class I and class II alleles (odds ratio for the alleles, 1.06 to 2.35).[50]

The basis for the association between HLA-B27 and axial spondyloarthritis and ankylosing spondylitis remains unexplained. The major hy-

potheses for this association have recently been reviewed (Fig. 3).[41,51,52] A free cysteine at position 67, in the B pocket of the peptide-binding groove, is a characteristic feature of HLA-B27, and HLA-B27 heavy chains readily form disulfide-linked dimers and oligomers, unlike other HLA-B alleles. Within the endoplasmic reticulum, these oligomers can trigger an unfolded protein response that can promote the production of interleukin-23, and on cell surfaces the dimers can interact with innate immune receptors, particularly the killer-cell immunoglobulin-like receptor 3DL2 (KIR3DL2). In studies in humans and animals, these processes have triggered inflammatory responses.[53-55] Peptide presentation by HLA-B27 to CD8+ T cells may play a role, but no specific peptide has been implicated, and arthritis and spondylitis develop in HLA-B27 transgenic rats lacking CD8+ T cells. Whatever the molecular role of HLA-B27, it evidently involves abnormalities in antigen-presenting cells.[56,57] Dendritic cells from spondyloarthritis-prone HLA-B27 transgenic rats show numerous abnormalities, including impaired stimulation of T-cell responses, cytoskeletal alterations, reduced expression of class II MHC molecules, enhanced apoptotic death, preferential induction of type 17 helper T-cell expansion, and alteration of regulatory T-cell function.[58,59]

Alteration of the microbiome is hypothesized to contribute to the pathogenesis of spondyloarthritis.[52] Recent studies in children support this theory,[60] and studies in animals suggest that HLA-B27 may play a role in shaping the microbiome.[61]

GENOMEWIDE ASSOCIATION STUDIES

Association studies based on SNPs have revealed more than 30 non-MHC genes or genetic regions that influence susceptibility to ankylosing spondylitis (odds ratio, 1.1 to 1.9).[50,62] The majority of these loci also confer susceptibility to other immune-mediated diseases, particularly inflammatory bowel disease and, to a lesser degree, psoriasis.[63,64] Genes that affect the interleukin-23–interleukin-17 pathway are prominently represented in this group. *CARD9*, *IL12B*, and *PTGER4* can promote the production of interleukin-23, whereas *IL23R*, *TYK2*, and *STAT3* can affect the production of interleukin-17 and other cytokines in response to interleukin-23 stimulation.[65] Other associated genes encode other cytokines or cytokine receptors, transcription factors involved in the differentiation of immune cells, other molecules involved in the activation or regulation of immune or inflammatory responses, or aminopeptidases. The aminopeptidase ERAP1 is the primary enzyme that trims peptides within the endoplasmic reticulum to generate ligands that are the appropriate length for binding to MHC class I molecules, and intense interest has focused on the functional significance of the ERAP1 variants associated with ankylosing spondylitis and their interaction with HLA-B27.[66]

STRUCTURAL DAMAGE

In axial spondyloarthritis, skeletal damage is a consequence of bone destruction and aberrant bone formation, which may occur simultaneously or in virtual juxtaposition. Osteoproliferation results in the formation and growth of syndesmophytes and is a major contributor to the structural damage that is characteristic of this disease.[67] Syndesmophyte progression is highly variable in patients with axial spondyloarthritis, but in severe cases it can lead to the complete fusion of the axial skeleton and even of peripheral joints. Much remains to be learned about the factors underlying this process. Recent investigations have focused on rates of development with the use of three-dimensional CT, patient characteristics associated with syndesmophyte growth, local vertebral abnormalities identified on MRI, systemic biomarkers, and the correlation with the inhibition of TNF-α and the administration of nonsteroidal antiinflammatory drugs (NSAIDs).[68]

TREATMENT

Treatment goals for axial spondyloarthritis include reducing symptoms, improving and maintaining spinal flexibility and normal posture, reducing functional limitations, maintaining the ability to work, and decreasing the complications associated with the disease. Guidelines for management have been issued by expert panels in Europe,[69] the United States,[70] and Canada.[71] Each of these guidelines is based on a systematic review of the literature, and there is substantial agreement among the three. Whether spondyloarthritis is active or stable, patients are advised to follow an active exercise program designed to maintain posture and range of motion.

NSAIDs, including selective inhibitors of cyclooxygenase 2, are the first-line drug treatment for pain and stiffness. Continuous NSAID treatment is recommended for persistently active, symptomatic disease, with doses adjusted in accordance

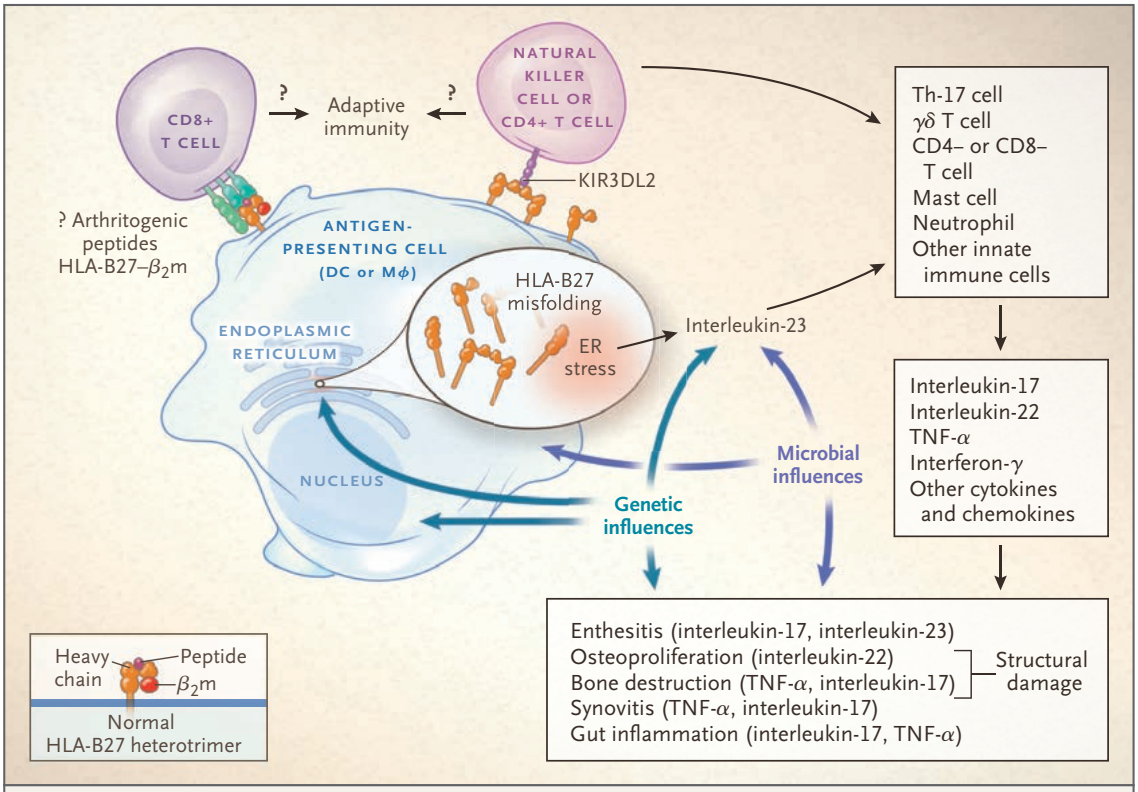


Figure 3. Pathogenic Mechanisms in Axial Spondyloarthritis.

The abnormal function of antigen-presenting cells (dendritic cells [DC] and macrophages [Mϕ]) has been implicated in pathogenesis. Aberrant features of HLA-B27 that are related to its tendency to misfold and dimerize may trigger the production of interleukin-17 through interaction with the killer immunoglobulin-like receptor 3DL2 (KIR3DL2) on CD4+ T cells or through excess production of interleukin-23 mediated by the response to stress in the endoplasmic reticulum. Autoreactive CD8+ T cells may also recognize the arthritogenic peptides displayed by HLA-B27. In addition, HLA-B27 may generate an immune response that promotes microbial influences (dysbiosis) in the gut, contributing to inflammation and further driving the production of interleukin-23 and other proinflammatory cytokines. These cytokines can act on Th17 and $\gamma\beta$ T cells, CD4- or CD8- T cells, mast cells, neutrophils, and other innate immune cells, promoting the production of interleukin-17, interleukin-22, tumor necrosis factor α (TNF-α), interferon-γ, and other cytokines and chemokines. The response to interleukin-23 may be further altered by the influence of risk alleles (i.e., by genetic influences). Interleukin-17 and interleukin-23 have been implicated in enthesitis, interleukin-22 in osteoproliferation, and TNF-α and interleukin-17 in synovitis, bone destruction, and gut inflammation. The inset (lower left) shows a schematic of normal HLA-B27–heavy-chain β_2-microglobulin (β_2m) complexed with a peptide.[41,42,51,52]

with the severity of symptoms. On-demand treatment with NSAIDs is acceptable when continuous treatment causes unacceptable side effects and is recommended for persons with stable spondyloarthritis. No particular NSAID is preferred in terms of efficacy. The risks of cardiovascular, gastrointestinal, and renal effects should be taken into account.

For patients whose symptoms are not controlled by NSAID therapy or for whom NSAIDs have unacceptable side effects, the use of TNF inhibitors is strongly recommended. In 13 randomized, controlled trials and many open-label studies, five TNF inhibitors — infliximab, etanercept, adalimumab, golimumab, and certolizumab — have produced rapid, profound, and sustained improvement in both objective and subjective indicators of disease activity and patient functioning (To see the effect of TNF inhibitors on inflammatory lesions that are visible on MRI, compare the pretreatment images in Fig. 1B, 1C, 1D, and 1J through 1N with the respective posttreatment images in Fig. 1E, Fig. 1F, Fig. 1G, and Fig. 1O through 1S). Approximately 60% of patients have an adequate and usually sustained response to these agents, often with partial or full remission of symptoms. The predictors of a good response to TNF inhibitors include a young age, a short disease duration, a high baseline level of inflammatory markers, and a low baseline level

of functional disability, but patients at any disease stage may benefit. No particular agent is preferred. However, etanercept, a soluble TNF receptor, is less effective than antibodies to TNF in treating anterior uveitis and inflammatory bowel disease and is therefore not preferred in patients with these associated conditions. In a meta-analysis, the response to TNF inhibitors in patients with nonradiographic axial spondyloarthritis was similar to that in patients with ankylosing spondylitis.[72] Regulatory approval of nonradiographic axial spondyloarthritis as an indication for treatment with TNF inhibitors has been more forthcoming in Europe than in the United States, although the weight of expert opinion favors this indication.[73] TNF inhibitors can be given to children and adolescents with axial spondyloarthritis.[74]

The presence of active infection or a high risk of infection, advanced heart failure, lupus, multiple sclerosis, and cancer are contraindications to treatment with TNF inhibitors. Patients should be tested for the presence of latent or active tuberculosis. If either form of tuberculosis is present, treatment must be started before the initiation of a TNF inhibitor. Carriers of the hepatitis B virus (HBV) surface antigen should be treated prophylactically, and patients with antibodies to the HBV core antigen should be monitored for reactivation. Recent data support the cautious use of TNF inhibitors during pregnancy.[75]

For patients with isolated local inflammation of sacroiliac joints, one or two peripheral joints, or entheses, local glucocorticoid injections can be used sparingly. Peritendon injections of the Achilles', patellar, or quadriceps tendons should be avoided because of the risk of tendon rupture.

The long-term use of systemic glucocorticoids is relatively contraindicated, partly because of the increased risk of vertebral osteoporosis, but may be unavoidable in some patients with severe uveitis or inflammatory bowel disease. Sulfasalazine is considered useful for patients with peripheral arthritis. There is little evidence to indicate that methotrexate is beneficial for patients with ankylosing spondylitis, even in conjunction with TNF inhibitors. In patients with ankylosing spondylitis, no efficacy has been shown for abatacept (which inhibits T-cell costimulation), anakinra (which blocks interleukin-1), and two anti–interleukin-6 agents. It is unclear at present whether there may be a role for the anti-CD20 monoclonal antibody rituximab.

In one recent phase 3 trial that included some patients in whom previous therapy with a TNF inhibitor had produced an inadequate response or unacceptable side effects, secukinumab, a monoclonal antibody to interleukin-17A, showed dramatic efficacy — similar to that seen in the original trials of TNF inhibitors.[76] This agent has recently been approved by the Food and Drug Administration for the treatment of ankylosing spondylitis. A small, phase 2, open-label study suggested that ustekinumab, an antibody to the subunit shared by interleukin-12 and interleukin-23, was efficacious. A variety of other agents targeting the interleukin-23–interleukin-17 pathway are currently in clinical trials.[42] Practices for screening for osteoporosis, as well as prevention and treatment of this disorder, should follow the guidelines for postmenopausal women.[38]

SUMMARY

A high index of suspicion and clinical acumen are often needed to diagnose axial spondyloarthritis and to prevent misdiagnosis. No single clinical feature, laboratory test, or imaging result is either necessary or sufficient for the diagnosis. Referral to a rheumatologist should be considered for adolescents and young adults with unexplained back pain with a duration of more than 3 months. MRI is important for early diagnosis but requires careful attention to the protocol used, communication between the clinician and radiologist, and experience on the part of the MRI reader in order to achieve appropriate levels of sensitivity and specificity. Axial spondyloarthritis should be considered in the differential diagnosis during the evaluation of chest pain. TNF inhibitors are a mainstay of therapy for patients in whom NSAID therapy is inadequate or contraindicated. Therapy targeting the interleukin-23–interleukin-17 pathway appears to be promising, but its role in treating spondyloarthritis remains to be determined.

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