III SERONEGATIVE SPONDYLOARTHRITIS

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Definition

The term spondyloarthritis encompasses a family of clinically, epidemiologically, and genetically related inflammatory diseases that primarily affect spinal and peripheral joints. Once considered a variant of rheumatoid arthritis, spondyloarthritis has been shown to differ in such fundamental clinical and pathogenetic ways from rheumatoid disease that the two are now considered distinctly separate entities [see Table 1]. The term seronegative refers to the uniform absence of serum IgM autoantibodies to IgG (rheumatoid factor) in patients with spondyloarthritis. Other distinguishing characteristics are the following:

1. The sacroiliac joints are affected (sacroiliitis); ascending spinal inflammation and bony fusion (spondylitis) often develop after sacroiliitis.
2. Peripheral joints are affected, typically in an oligoarticular and asymmetrical pattern.
3. There is inflammation of sites of ligamentous insertions into bone (entheses), referred to as enthesis or enthesopathy, as well as inflammation of joint synovium. Inflammation occurs both along the spine and near peripheral joints.
4. There may be inflammation of extra-articular sites, including the eye, the aortic valve, the gastrointestinal tract, the genitourinary system, and the skin.
5. Disease onset typically occurs in young adulthood.
6. There is a strong familial tendency and a striking genetic association with the histocompatibility antigen HLA-B27.
7. Certain bacteria play important pathogenic roles.

Classification

Spondyloarthritis includes the prototypical spinal arthritis, ankylosing spondylitis; reactive spondylitis (formerly known as Reiter syndrome); psoriatic arthritis; enteropathic arthritis (accompanying ulcerative colitis and Crohn disease); juvenile spondyloarthritis (or juvenile ankylosing spondylitis); and such rare disorders as acnec-associated arthritis, or SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome, and Whipple disease. The various forms of spondyloarthritis can usually be distinguished from one another by the pattern of joint involvement and associated extra-articular features [see Table 2]. However, some patients have overlapping clinical manifestations that defy categorization; these patients are usually designated as having undifferentiated spondyloarthritis. Because of such patients, the European Spondyloarthopathy Study Group (ESSG) proposed classification criteria for spondyloarthritis that may be useful in clinical diagnosis and epidemiologic studies.1

Epidemiology

Estimations of prevalence rates for spondyloarthritis using the ESSG criteria are few.1 Among Germans in Berlin, the prevalence of spondyloarthritis has been reported to be 1.9%; in Inuits in Alaska and Siberia, rates of 2% to 3.4% have been reported. Spondyloarthritis appears to be rare in African and Japanese populations. These differences among ethnic groups are explainable in large part by differences in the frequency of HLA-B27.1

Pathogenesis

The various forms of spondyloarthritis appear to be complex disorders resulting from the interplay of several genetic and environmental factors, only a few of which have been identified.

GENETIC FACTORS

Heredity plays a major role in predisposition.14 Family studies have shown that 15% to 20% of patients with ankylosing spondylitis have one or more first-degree relatives with the same disease. In the families of some patients with ankylosing spondylitis, there are relatives with other types of spondyloarthritis or other associated disorders, such as uveitis, psoriasis, and inflammatory bowel disease. Concordance for ankylosing spondylitis in monzygotic twins approaches 63% to 75%, compared with 13% to 23% in dizygotic twins. Genetic modeling in twins and families indicates that ankylosing spondylitis is associated with a multiplicative, polygenic pattern of inheritance, with 97% of the susceptibility to the disease attributed to genetics. These studies suggest that the environmental factors that contribute to development of the disease are probably ubiquitous.

The HLA-B27 allele encoded by the class I HLA-B locus within the major histocompatibility complex (MHC) is the one genetic factor identified thus far that is strongly associated with spondyloarthritis. This allele is present in 90% of patients with ankylosing spondylitis and confers a relative risk for the disease of over 100, but it is found less often in patients with other forms of spondyloarthritis [see Table 2].1 HLA-B27 shows linkage to ankylosing spondylitis in families and appears to contribute 30% to 50% of the genetic risk; in most cases, it appears essential for disease expression.1 Other HLA alleles, including HLA-B60, HLA-DR1, and HLA-DR8, also appear to increase the risk of ankylosing spondylitis. In addition, different HLA alleles predispose to psoriasis and psoriatic arthritis, including HLA-B13, HLA-B17, HLA-Cw6, HLA-B38, and HLA-B39.4 The HLA region shows genetic linkage to inflammatory bowel diseases, but specific HLA alleles show only weak associations.7 Ongoing human genome searches have revealed additional non-HLA loci linked to ankylosing spondylitis,8 some of which also may be common to Crohn disease and psoriasis.9,10

Laboratory evidence strongly suggests that the HLA-B27 gene itself, rather than a linked locus, directly participates in the pathogenesis of ankylosing spondylitis and reactive arthritis. Transgenic rats expressing the human HLA-B27 and β2-microglobulin genes spontaneously develop colitis, peripheral and spinal arthritis, enthesitis, skin and nail lesions resembling psoriasis, and genitourinary inflammation.9 Littermates raised in a germ-free environment do not develop most of these manifestations, however. That finding emphasizes the importance of both the HLA-B27 gene and gut bacteria, possibly Bacteroides species, in pathogenesis and suggests that antibiotics (e.g., sulfasalazine) may be useful in the treatment of reactive arthritis and ankylosing spondylitis in humans. The mechanism by which HLA-B27 promotes disease is unknown, but the following are the prevailing hypotheses:11 (1) in its function as an MHC class I molecule,
HLA-B27 presents a so-called arthritogenic self-peptide or bacterial peptide to cytotoxic CD8 T cells, which causes an autoimmune attack on various self-structures; (2) HLA-B27 contains stretches of amino acid sequences that also occur in bacterial proteins, and as a result of this molecular mimicry, a cytotoxic or humoral immune response to these bacterial sequences also involves HLA-B27; (3) HLA-B27, either intracellularly or extracellularly, promotes bacterial persistence or dissemination to joints and other structures; and (4) HLA-B27 is unique among HLA class I molecules in forming so-called homodimers, which may cause misfolding of the protein, resulting in an inflammatory response.5,13,14

ENVIRONMENTAL FACTORS

Reactive arthritis provides the strongest evidence of bacterial pathogenesis in spondyloarthritis. Enteric infections by Shigella flexneri, Salmonella (many species), Yersinia enterocolitica, Y. pseudotuberculosis, and Campylobacter jejuni have all been implicated as triggers of the disease in various epidemics and in sporadic cases, especially in HLA-B27–positive persons.2,3,9 Similarly, sexually acquired infections with Chlamydia trachomatis10,16 and perhaps Ureaplasma urealyticum may cause reactive arthritis.5 Pulmonary infection with Chlamyphila pneumoniae (formerly known as Chlamydia pneumoniae) has also been implicated.9 Patients with chronic reactive arthritis have been found to have IgA antibodies to the initiating microbe, suggesting a persistent mucosal infection.9 Moreover, synovial fluid T cells were found to proliferate when challenged with the bacterium that triggered the arthritis.10 There is no evidence, however, that these microorganisms cause ankylosing spondylitis. Normal gut flora seem more likely to be implicated in ankylosing spondylitis, as suggested by studies of the HLA-B27 transgenic rat11 and by a high frequency of asymptomatic foci of gut inflammation in patients with ankylosing spondylitis or reactive arthritis.30

Pathology

Chronic inflammation with infiltrating mononuclear cells (macrophages, T cells, and B cells) occurs in both peripheral and axial joint structures of patients with spondyloarthritis.12,21,22 CD4+ helper T cells and CD8+ suppressor-cytotoxic T cells appear to be equally represented. A high concentration of the inflammatory cytokine tumor necrosis factor–α (TNF-α) has been found in the dense cellular infiltrates in synovial portions of sacroiliac joints.23 When cytokines from the joints and blood of patients with spondyloarthritis were compared with those of patients with rheumatoid arthritis, the cytokines from patients with spondyloarthritis showed a higher ratio of immunosuppressive cytokines, such as interleukin-4 (IL-4) and IL-10, to inflammatory cytokines, such as TNF-α and interferon gamma. This leads to a blunted T helper type 1 (Th1) response in patients with spondyloarthritis.24 Inherent levels of cytokines, such as TNF-α and IL-10, are determined by genetic polymorphisms in their respective genes.2 In ankylosing spondylitis, the observed tendency for ligamentous ossification, enthesopathy, and widespread new bone formation is associated with the finding of transforming growth

Table 1 Comparison between Spondyloarthritis and Rheumatoid Arthritis

<table>
<thead>
<tr>
<th></th>
<th>Spondyloarthropathies</th>
<th>Rheumatoid Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>Racial (more prevalent in whites)</td>
<td>Worldwide</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0.2%–1.9%</td>
<td>1%–2%</td>
</tr>
<tr>
<td>Etiology</td>
<td>Genetic and bacterial</td>
<td>Genetic and unknown</td>
</tr>
<tr>
<td>Positive family history</td>
<td>Frequent</td>
<td>Rare</td>
</tr>
<tr>
<td>Sex distribution</td>
<td>More frequently diagnosed in males</td>
<td>More common in females</td>
</tr>
<tr>
<td>Age at onset</td>
<td>Peak incidence at 20–30 yr</td>
<td>All ages affected; peak incidence 30–50 yr</td>
</tr>
<tr>
<td>Joint involvement</td>
<td>Oligoarthritis; asymmetrical; large joints; lower limbs more than upper limbs</td>
<td>Polyrthritis; symmetrical; small and large joints; upper and lower limbs</td>
</tr>
<tr>
<td>Sacroiliac involvement</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Spinal involvement</td>
<td>Ascending; all segments with fusion</td>
<td>Cervical only; erosions and instability</td>
</tr>
<tr>
<td>Subcutaneous nodules</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ocular involvement</td>
<td>Uveitis, conjunctivitis</td>
<td>Sicca syndrome; scleritis; scleromalacia perforans</td>
</tr>
<tr>
<td>Lung involvement</td>
<td>Upper lobe pulmonary fibrosis</td>
<td>Pleural effusions; lower lobe pulmonary fibrosis; nodules; Caplan syndrome</td>
</tr>
<tr>
<td>Rheumatoid factor and/or anti-CCP</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>HLA-B27</td>
<td>Yes</td>
<td>No (normal frequency)</td>
</tr>
<tr>
<td>HLA-DR4</td>
<td>25% (normal frequency)</td>
<td>60%–70%</td>
</tr>
<tr>
<td>Pathology</td>
<td>Synovitis and enthesopathy</td>
<td>Synovitis</td>
</tr>
<tr>
<td>Radiographic findings</td>
<td>Asymmetrical erosive arthritis and periostitis; new bone formation and ankylosis; sacroiliitis, spondylitis</td>
<td>Symmetrical erosive arthritis with bony destruction</td>
</tr>
</tbody>
</table>

anti-CCP—antibodies to cyclic citrullinated peptides
factor–β (TGF-β) near these sites. TGF-β is a reparative cytokine that stimulates connective tissue matrix formation.

Reactive arthritis was once considered a sterile joint disease triggered in some unknown manner by a distant infection, but more recent studies of synovial fluids and tissues affected by reactive arthritis have consistently revealed the presence of intracellular bacterial antigens from each of the known offending microorganisms. Reactive arthritis was once considered to be almost exclusively a disease of males, but recent studies suggest a more uniform distribution by sex (the ratio of males to females is 3:1). In females, the disease may be diagnosed less frequently and later in the course of disease because physicians still consider it primarily a disorder of males. Some studies suggest that females have milder disease, with less progressive spinal involvement and more peripheral arthritis. Other studies suggest that the overall pattern of disease is similar in males and females.

Table 2  Features of Seronegative Spondyloarthritis

<table>
<thead>
<tr>
<th></th>
<th>Ankylosing Spondylitis</th>
<th>Reactive Arthritis (Reiter Syndrome)</th>
<th>Psoriatic Arthritis</th>
<th>Enteropathic Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex distribution</td>
<td>Male &gt; female</td>
<td>Male &gt; female</td>
<td>Female &gt; male</td>
<td>Female = male</td>
</tr>
<tr>
<td>Age at onset (years)</td>
<td>≥ 20</td>
<td>Any age</td>
<td>Any age</td>
<td>Peripheral sudden</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Spinal gradual</td>
</tr>
<tr>
<td>Mode of onset</td>
<td>Gradual</td>
<td>Sudden</td>
<td>Gradual</td>
<td>Periarticular sudden</td>
</tr>
<tr>
<td>Peripheral joints</td>
<td>Often lower limbs</td>
<td>Usually lower limbs</td>
<td>Upper &gt; lower limbs</td>
<td>Lower &gt; upper limbs</td>
</tr>
<tr>
<td></td>
<td>Asymmetrical</td>
<td>Asymmetrical</td>
<td>Asymmetrical</td>
<td>Symmetrical</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enthesopathy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>– Peripheral Spinal</td>
</tr>
<tr>
<td>Heel pain</td>
<td>Occasional</td>
<td>Frequent</td>
<td>Occasional</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Spinal involvement</td>
<td>+++ (always)</td>
<td>+ (20%)</td>
<td>+ (20%)</td>
<td>+ (10%)</td>
</tr>
<tr>
<td>Symmetry (sacroiliitis and syndesmophytes)</td>
<td>+</td>
<td>+/–</td>
<td>+/–</td>
<td>+</td>
</tr>
<tr>
<td>Familial aggregation</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>HLA-B27 positive</td>
<td>90%</td>
<td>63%–75%</td>
<td>20% (50% with sacroiliitis)</td>
<td>10% (50% with sacroiliitis)</td>
</tr>
<tr>
<td>Risk for B27-positive person</td>
<td>2% (20% when a relative)</td>
<td>20% (when infected)</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Urethritis</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Skin involvement</td>
<td>–</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Nail involvement</td>
<td>–</td>
<td>+</td>
<td>+++</td>
<td>–</td>
</tr>
<tr>
<td>Mucous membrane involvement</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Cardiac involvement</td>
<td>+</td>
<td>+</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Self-limiting</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>++ Peripheral Spinal</td>
</tr>
</tbody>
</table>

Ankylosing Spondylitis

Epidemiology

The prevalence of ankylosing spondylitis parallels the frequency of HLA-B27 in different ethnic populations. HLA-B27 occurs in 7% to 9% of the white population, and the disease has a prevalence of approximately 0.2% to 0.9%. One study from Norway, where the frequency of HLA-B27 is twice that seen in the white populations of the United States and the United Kingdom, found that ankylosing spondylitis occurred in 1.9% to 2.2% of men and 0.3% to 0.6% of women. The disease is distinctly rare in African and Japanese populations, in which HLA-B27 is found in low frequency; however, ankylosing spondylitis is common in certain Native-American groups, such as the Haida and Pima, in which the frequency of HLA-B27 is high.

In randomly chosen cohorts of whites possessing HLA-B27, ankylosing spondylitis developed in approximately 2% to 6%. In HLA-B27–positive relatives of patients with ankylosing spondylitis, however, the risk of disease is 20% to 30%. Similar estimates are not available for other ethnic groups, but rates may differ because multiple molecular subtypes of HLA-B27 have been discovered, each with different distributions among various ethnic groups. HLA-B*2705, followed in frequency by HLA-B*2702, is predominantly found in whites; HLA-B*2704 is found in Chinese; and HLA-B*2703 is found in Africans. Most HLA-B27 subtypes appear to predispose to ankylosing spondylitis, with the possible exceptions of HLA-B*2706, found in Indonesians and Thais, and HLA-B*2709, found in Sardinians.

Ankylosing spondylitis was once considered to be almost exclusively a disease of males, but recent studies suggest a more uniform distribution by sex (the ratio of males to females is 3:1). In females, the disease may be diagnosed less frequently and later in the course of disease because physicians still consider it primarily a disorder of males. Some studies suggest that females have milder disease, with less progressive spinal involvement and more peripheral arthritis. Other studies suggest that the overall pattern of disease is similar in males and females.

Onset typically occurs between 16 and 30 years of age, peaking at around 24 years; ankylosing spondylitis seldom begins in patients older than 40 years. Childhood onset before 16 years
of age occurs in approximately 10% to 20% of cases in the United States and Europe but is more common (54%) in developing countries, suggesting earlier exposure to the environmental triggers.28

DIAGNOSIS

The modified New York criteria1 are currently used to diagnose ankylosing spondylitis. A patient should have one or more of the following clinical criteria:

1. Low back pain of at least 3 months’ duration that is alleviated by exercise and is not relieved by rest.
2. Restricted lumbar spinal motion.
3. Decreased chest expansion relative to normal values for age and sex.

In addition, the patient must have definitive radiographic evidence of sacroiliitis (i.e., bilateral sacroiliitis of grade II to IV or unilateral sacroiliitis of grade III or IV) [see Figure 1].

A simpler approach in diagnosis is to accept symptomatic sacroiliitis as an adequate definition. Sacroiliitis, as defined radiographically, should be definitive (i.e., grade III or IV changes should be evident) and should be present bilaterally [see Figure 1]. In addition, the patient should have no other diseases that could cause sacroiliitis (i.e., reactive arthritis, psoriasis, or inflammatory bowel disease).

Clinical Presentation

Low back pain and stiffness are the usual presenting symptoms of ankylosing spondylitis. Because back pain is such a common complaint in the general population and its causes are myriad, certain characteristics that specifically suggest inflammatory back pain have been formulated:

1. Onset in a person younger than 40 years.
2. Insidious rather than abrupt onset.
3. Persistence of back symptoms for 3 months or longer.
4. Worsening of back pain or stiffness with inactivity.
5. Subsiding of back pain or stiffness with exercise.

Figure 1  (a) Radiograph of normal sacroiliac joints showing clearly defined joint margins and no sclerosis (grade 0). (b) Sclerosis on both margins of each sacroiliac joint but no joint erosions (grade II). (c) Sclerosis and erosions of both sacroiliac joints (grade III). (d) Complete bony fusion of both sacroiliac joints (grade IV).
Some patients describe buttck pain that often alternates from one side to the other and sometimes radiates down the posterior leg, which is indicative of sacroiliac joint disease. Other patients present with a peripheral arthritis, typically monoarticular or oligoarticular, that affects joints of the lower extremity, often the knee. Careful questioning about subtle musculoskeletal symptoms in such patients is often fruitful. Fatigue can be a major symptom in patients with ankylosing spondylitis and has been found to correlate with level of disease activity, functional ability, global well-being, and mental health status.\textsuperscript{29} Elicitation of a history of uveitis or the presence of spondyloarthritic features in family members also strongly suggests the disease. Radiologic evidence of sacroilitis in any of these clinical presentations, however, is essential in confirming a diagnosis of ankylosing spondylitis [see Radiographic Features, below]. In patients whose sacroiliac radiographs are normal, the presence of HLA-B27 is highly suggestive but not definitive evidence of the disease. Follow-up studies of patients in whom the diagnosis was strongly suspected on the basis of the clinical picture and HLA-B27 positivity showed that sacroiliac joint abnormalities eventually appear on plain x-rays, but the evolution may occur over as many as 10 years. MRI of the sacroiliac joints is a very sensitive method for detecting early sacroilitis, as well as inflammation elsewhere in the spine.

Patients with juvenile-onset ankylosing spondylitis typically present with peripheral oligoarthritis, often with enthesopathy and infrequently with spinal symptoms.\textsuperscript{30} Such patients may be misdiagnosed as having juvenile rheumatoid arthritis [see Juvenile Spondyloarthritis, below]. Spinal involvement usually appears later, in young adulthood.

**Physical Examination**

Examination of the back may be relatively normal early in the course of the disease. Sacroiliac joints are usually painful when palpated or stressed. When the disease advances into the lumbar spine, the normal lordotic curvature may be lost, and paravertebral muscle spasm is prominent. Forward bending, or flexion, may be restricted, as measured by the Schober test. In this measurement, two points are drawn with the patient standing erect, one at the L5–S1 region and the other 10 cm above this region. With normal flexion, the distance between these two points increases by 4 to 6 cm, but when the lumbar spine becomes fused, there may be little or no increase in distance between the two points. Lateral lumbar bending and extension are also typically restricted.

Thoracic spine involvement causes an exaggerated dorsal kyphosis; in patients with costovertebral joint fusion, chest expansion (as measured circumferentially at the fourth intercostal space from full expiration to inspiration) is reduced to 2.5 cm or less. When the disease ascends into the neck and causes fusion, cervical lordosis is lost and a fixed flexion deformity may occur. Spinal fusion often results in the patient’s being severely stooped forward with neck immobile and flexed; the patient has difficulty looking straight ahead.

Peripheral arthritis, especially of the hips, shoulders, and knees, occurs in approximately 30% of patients with ankylosing spondylitis and further increases disability. Peripheral enthesopathic features may include Achilles tendinitis, plantar fasciitis, or costochondritis.\textsuperscript{30}

**Laboratory Findings**

The HLA-B27 histocompatibility antigen is present in more than 90% of ankylosing spondylitis patients. HLA-B27 testing of individual patients, however, is indicated only in atypical cases, when the clinical suspicion is high but the most definitive finding—radiographic evidence of sacroilitis—is not present. In HLA-B27-positive patients and HLA-B27-negative patients, the patterns and severity of arthritis are similar. HLA-B27-negative patients differ from HLA-B27-positive patients in that in HLA-B27-negative patients, disease onset occurs at an older age, there is no family history of spondylitis, and uveitis or cardiac complications occur infrequently.\textsuperscript{31} HLA-B27 is found less commonly (50%) in patients with ankylosing spondylitis who are of African ancestry.

Elevation of the erythrocyte sedimentation rate (ESR) occurs in many patients, but it may be normal despite severe disease. C-reactive protein (CRP) levels may be elevated. Serum IgA levels are often elevated.\textsuperscript{32} Some patients have a mild normocytic normochromic anemia because of chronic inflammation; in these patients, the platelet count may be high.

**Radiographic Features**

Bilateral sacroilitis is the most specific finding that supports a diagnosis of ankylosing spondylitis, and meticulous interpretation of the radiographs is imperative. A grading system that assesses each sacroiliac joint for juxta-articular bony sclerosis, blurring or erosion of joint margins, and bony fusion has been formulated and tested [see Figure 1]. Grade 0 findings are normal. Grade I findings are suspicious but not definitive. Grade II findings show sclerosis on both sides of a joint; such findings are even more suspicious when they occur bilaterally, but they should be interpreted with great caution. Findings of grades III and IV are definitive. Another radiographically defined entity, osteitis condensans illii, may be misinterpreted as sacroilitis, and vice versa. Patients with osteitis condensans illii have sclerosis on the iliac side of both sacroiliac joints; the condition occurs in women who have borne children. Although quantitative radionuclide scans, computed tomography, and MRI have been suggested as superior diagnostic methods, well-performed plain radiographs of the sacroiliac joints (Ferguson view or oblique view) are usually adequate.

An early spinal change seen on radiographs is squaring of the normally concave anterior side of vertebral bodies [see Figure 2]. This phenomenon is caused by inflammation and bony erosion at the site of insertion (enthesis) of the outer fibers of the annulus fibrosus. Later changes are ossification of ligaments, which are seen on radiographs as syndesmophytes that bridge adjacent vertebral bodies [see Figure 3], producing the classic bamboo-spine appearance [see Figure 4]. Zygaphyseal joints become fused into solid bone. Finally, diffuse osteoporosis may occur, making the spine susceptible to fracture. Bony fusion across joint spaces of affected peripheral joints in ankylosing spondylitis may be the most distinctive change seen on radiographs.

Similar spinal changes are seen in primary ankylosing spondylitis and in the spondylitis associated with inflammatory bowel disease. In spondylitis associated with reactive arthritis and psoriatic arthritis, the sacroiliitis and syndesmophytes tend to be asymmetrical.\textsuperscript{33} Another disease that may mimic ankylosing spondylitis is diffuse idiopathic skeletal hyperostosis (DISH).\textsuperscript{34} DISH occurs in middle-aged and older persons, especially men; it is characterized by large, flowing syndesmophytes that restrict spinal motion; sacroilitis is not found, however, and there is no association with HLA-B27.
Extra-articular Manifestations

A number of extraskeletal features may complicate the course of ankylosing spondylitis and contribute to morbidity and mortality.

**Ocular involvement**  Acute anterior uveitis, usually occurring episodically and affecting one eye at a time, occurs in 25% of patients. Acute pain, redness, and photophobia are the usual symptoms. Prompt referral to an ophthalmologist for treatment is essential. Uveitis does not correlate with arthritis activity or severity and shows a strong association with HLA-B27, even in patients without spondyloarthritis.33

**Cardiovascular disease**  A fibrosing cardiovascular lesion occurs in 2% to 10% of patients with ankylosing spondylitis. The lesion causes the aortic valve and proximal root to thicken, and it often extends into the conducting system, causing aortic regurgitation, atrioventricular block, or both. The lesion probably occurs with a similar frequency in patients with reactive arthritis.34 In rare instances, mitral regurgitation may also occur. One study emphasized a high prevalence of underlying spondyloarthritis, often undiagnosed, in men requiring cardiac pacemakers for bradyarrhythmias.34 In addition, this study revealed the strong association of the clinical combination of lone aortic regurgitation and heart block with HLA-B27, with or without apparent arthritis. Fulminant cardiac disease typically appears only after the patient has had spondyloarthritis for many years, but such disease has been described even in very early spondyloarthritis. Echocardiography may detect cardiac abnormalities in some patients without clinical signs.35 No treatment is known to prevent progression of spondylitic heart disease; most patients require permanent cardiac pacemakers, aortic valve replacement, or both.

**Pulmonary disease**  Despite restriction of chest wall motion by joint fusion, respiratory function is preserved in most patients with ankylosing spondylitis, owing to good diaphragmatic function. Severe kyphotic deformity, however, may compromise breathing. Approximately 1% of patients with ankylosing spondylitis, usually those with severe disease, also have fibrosis in the upper lung fields that mimics tuberculosis. Cavitation may occur and may be complicated by Aspergillus infection. Cough, dyspnea, and even hemoptysis are typical symptoms. Currently available treatment is unsatisfactory.

**Renal disease**  Kidney function is usually normal. The appearance of proteinuria, with or without a nephrotic syndrome, usually indicates complicating amyloidosis or IgA nephropathy. Secondary amyloidosis occurs in approximately 4% of patients and can be diagnosed with abdominal fat-pad or rectal biopsy.37 IgA nephropathy is being increasingly recognized. It correlates with high serum IgA levels. Renal function may become impaired, but episodes are usually self-limited.39

**Neurologic disease**  Spinal fracture is a major cause of morbidity and mortality in patients with ankylosing spondylitis; cord compression occurs even with seemingly minor trauma.1 A rigid and osteoporotic cervical spine is most susceptible to fracture, usually at the C6 or C7 level. A high degree of suspicion for fracture is always warranted in patients with localized spinal pain, even when plain x-rays fail to reveal an acute abnormality;
Patients with severe ankylosing spondylitis may develop the classic bamboo spine, as shown in this radiograph.

Additional imaging with CT is often necessary.

A cauda equina syndrome occurs in rare instances, usually because of arachnoiditis around sacral nerves that leads to progressive leg weakness, paresthesias, and sphincter dysfunction.38

**Retroperitoneal fibrosis** Fibrosis in the retroperitoneum may be another extra-articular feature of ankylosing spondylitis.39

### Treatment and Prognosis

Early diagnosis and treatment of ankylosing spondylitis appear to improve functional outcome, but it is not clear whether any drug modifies the disease pathology. Objectives of treatment are pain relief, reduction of inflammation, and maintenance of good posture and spinal function.40 Patient education is very important. Excellent sources for patient education are available at www.spondylitis.org and www.arthritis.org.

Nonsteroidal anti-inflammatory drugs (NSAIDs) relieve inflammatory symptoms of pain and stiffness and allow patients to engage in an appropriate exercise program. In clinical practice, certain NSAIDs appear to be more often effective than others as treatment for spondyloarthritis [see Table 3]. However, the efficacy of individual agents varies greatly from patient to patient; for that reason, some patients may need to try several NSAIDs before finding one that provides relief. There is no strong evidence that any NSAIDs alter disease progression.

There are now incontrovertible data that selective cyclooxygenase-2 (COX-2) inhibitors, and possibly other NSAIDs, increase a person’s risk for cardiovascular disease. Therefore, careful assessment of other risk factors and of the potential benefit compared with risk is essential in all patients. Gastrointestinal intolerance of any of the NSAIDs may present as nausea, gastric discomfort, diarrhea, or, more seriously, gut hemorrhage or perforation. Concomitant use of a gastroprotective agent, such as misoprostol or a proton pump inhibitor, may significantly reduce GI toxicity in patients treated with NSAIDs. All of these drugs may decrease renal tubular capacity to secrete potassium and can cause an abrupt reduction in renal function when used in patients with renal disease or with renal hypoperfusion resulting from ineffective circulatory volume. Because patients with ankylosing spondylitis will probably take NSAIDs for many years, physicians must diligently monitor for renal and GI tract damage.

In a 6-month randomized, controlled clinical trial, the bisphosphonate pamidronate, given monthly by intravenous infusion, was shown to be effective in improving symptoms and function in patients with ankylosing spondylitis whose disease was refractory to treatment with NSAIDs.41

Low-dose corticosteroids (e.g., prednisone, 5 to 10 mg daily) may be necessary to quell inflammation in some patients with highly active disease, but these agents should be used sparingly because they promote osteoporosis and do not improve spinal disease. Injection of repository corticosteroids into affected peripheral joints also may be useful. Injection into the sacroiliac joint, guided by either CT or MRI, may offer relief.

Sulfasalazine, 2 to 3 g daily in two divided doses, has been shown in several placebo-controlled trials to be an effective long-term treatment of ankylosing spondylitis, as well as of other types of spondyloarthritis. Sulfasalazine is very effective for peripheral joint symptoms but not especially effective for axial joint symptoms.42 The drug moiety responsible for the efficacy of sulfasalazine has been proved to be sulfapyridine rather than salicylate; however, it is not clear whether the efficacy results from antimicrobial or other properties of the drug.43 Because sulfasalazine has been shown to lower acute-phase reactants, such as the ESR and the CRP level, it may modify disease progression; however, this desirable effect has yet to be proved.

Other long-acting agents used to treat rheumatoid arthritis, including gold salts, penicillamine, and hydroxychloroquine, are not effective in ankylosing spondylitis.44 Methotrexate therapy, which is highly effective for rheumatoid arthritis, is clearly effective in psoriatic arthritis but not in other forms of spondyloarthritis.45 Administration of radiation therapy to the spine was once used successfully but is no longer recommended because of the risk of subsequent malignancy.

The TNF antagonists etanercept and infliximab have been approved for the treatment of ankylosing spondylitis, as well as psoriatic arthritis. An increasing number of controlled and open-label studies of the use of these agents in each of the forms of spondyloarthritis have shown dramatic and rapid improvement in symptoms; significantly reduced inflammatory changes in the spine and peripheral joints, as evidenced on MRI; and lowered acute-phase reactants such as ESR and CRP. Long-term efficacy and modification of disease progression and outcome have yet to be determined.46-50 Treatment with TNF-α antagonists also has been shown to halt progression of secondary amyloidosis.46 Because of the high cost of these agents and still-unanswered questions about their long-term safety, guidelines have been developed by international consensus to facilitate the judicious use of TNF antagonists.51 Many patients with mild disease may never require TNF antagonists.

All patients with ankylosing spondylitis should be informed of potential spinal deformities and how to prevent them. Good posture should be emphasized. A firm mattress and minimal pillow support are recommended. An exercise program of spinal extension and peripheral joint range-of-motion exercises, along...
with hydrotherapy, should be prescribed. Swimming is a very effective means of achieving exercise goals.1,5

Some patients who experience hip involvement—a major cause of disability—greatly benefit from total hip replacement. Wedge osteotomy for severe spinal kyphosis is controversial. Pregnancy does not appear to be significantly affected by ankylosing spondylitis.

The prognosis for individual patients is often difficult to ascertain.6 Worse outcomes have been associated primarily with hip joint involvement and, to a lesser extent, early age at onset. The course of the disease in its first 10 years appears to predict its future course and the functional outcome. Despite long-standing and severe disease, ankylosing spondylitis often does not affect a patient’s ability to work. Mortality from the disease is infrequent but may result from cardiac or neurologic complications or amyloidosis.

**Reactive Arthritis**

Reactive arthritis was originally defined as the triad of nongonococcal urethritis, conjunctivitis, and arthritis. It is now recognized that most patients present with arthritis alone and have no clinical evidence of urethritis or conjunctivitis.1,13,16,24 The concept of reactive arthritis arose from observations that the disease followed certain enteric infections (such cases are termed epidemic or postenteric) and sexually acquired infections (such cases are termed endemic or postvenereal) [see Pathogenesis, Environmental Factors, above]. Despite this association with previous infection, affected sites were seemingly sterile when cultured for bacteria. It has been found that bacterial antigens, if not viable microorganisms, are present in the joints of affected patients15,16,26 [see Pathology, above]. Like ankylosing spondylitis, reactive arthritis may be complicated by sacroiliitis, spondylitis, uveitis, and cardiac lesions. It is also strongly associated with HLA-B27 [see Table 2].

**Epidemiology**

Reactive arthritis probably has a worldwide distribution, but most epidemiologic and clinical studies have come from Europe and the United States.15,16 The prevalence of the disease is difficult to ascertain because it changes over time, depending on sexual behavior and the prevalence of enteric pathogens in different populations.46 It was estimated that from 1950 to 1980 in Rochester, Minnesota, the incidence of reactive arthritis in men younger than 50 years was 0.035%; however, 10- to 20-fold higher rates were reported in homosexual men and in certain Native Americans in whom the frequency of HLA-B27 was high (30% to 40%) and who had endemic exposure to enteric or venereal pathogens.15 Reactive arthritis, probably the postvenereal form, is the most common cause of inflammatory arthritis in young men. The disease is recognized in women far less frequently; the reasons for this are unclear, because the ratio of affected men to affected women after epidemics of gastroenteritis is typically 1:1 and, overall, the incidence of reactive arthritis approaches 1% to 2% of persons infected with any of the triggering pathogens.15,16 The incidence appears to have fallen significantly since the HIV epidemic and the adoption of safer sexual practices.46

HLA-B27 is found in 63% to 75% of patients with both forms of reactive arthritis and confers a relative risk of approximately 37. Of persons with HLA-B27 who are infected with one of the causative bacteria, reactive arthritis develops in approximately 20%. **Diagnosis**

Clinical Presentation

Reactive arthritis typically develops 10 to 30 days after an

### Table 3 Treatment for Spondyloarthritis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Efficacy Rating</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indomethacin</td>
<td>50 mg t.i.d. or 75 mg SR, q. 12 hr</td>
<td>Effective for symptoms</td>
<td>Side effects: headaches, changes in mentation, peptic ulcers, GI toxicity, renal insufficiency</td>
</tr>
<tr>
<td>Tolmetin</td>
<td>600 mg t.i.d.</td>
<td>Effective for symptoms</td>
<td>Side effects: peptic ulcers, GI toxicity, renal insufficiency</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>20 mg q.d.</td>
<td>Effective for symptoms</td>
<td>Side effects: peptic ulcers, GI toxicity, renal insufficiency</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>75 mg b.i.d.</td>
<td>Effective for symptoms</td>
<td>Side effects: peptic ulcers, GI toxicity, renal insufficiency</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>1–3 g daily in two divided doses</td>
<td>Long-term efficacy; lowers acute-phase reactants</td>
<td>Side effects: headache, GI intolerance</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>7.5–20 mg weekly</td>
<td>Effective for skin and arthritis in psoriatic arthritis; effectiveness in other diseases improved</td>
<td>Side effects: GI intolerance, hepatotoxicity, marrow suppression, pulmonary disease</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg b.i.d.</td>
<td>Effective in preventing relapse and in long-term treatment of reactive arthritis only</td>
<td>Side effects: GI intolerance, photosensitivity</td>
</tr>
<tr>
<td>Infliximab</td>
<td>5 mg/kg I.V. every 6–8 wk after loading</td>
<td>Highly effective and immediate response: improved inflammation in joints by MRI; long-term effects unknown</td>
<td>Side effects: allergic reactions; increased susceptibility to infection, especially tuberculosis</td>
</tr>
<tr>
<td>Etanercept</td>
<td>25 mg subcutaneous injections twice a week</td>
<td>Same as infliximab</td>
<td>Injection-site reactions, increased risk of infections</td>
</tr>
</tbody>
</table>

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RHEUMATOLOGY:III Seronegative Spondyloarthritis–
episode of gastroenteritis or sexual exposure to a venereal pathogen; however, many patients deny any such antecedent events. Episodes of urethritis or conjunctivitis may have been mild and transient or not perceived at all. Thus, recognition of the pattern of musculoskeletal involvement, as well as several other mucocutaneous manifestations, is important in establishing the correct diagnosis.

The arthritis usually is oligoarticular and asymmetrical and predominantly affects lower-extremity joints, most often the knees, ankles, and feet. Diffuse, painful swelling of entire digits (sausageing or dactylitis) occurs frequently. Pain in the heels from Achilles tendinitis or plantar fasciitis, or both, reflects the most common sites of enthesitis; however, enthesopathic pain at other sites is also frequent. Low back pain is a complaint of 60% of patients, and 20% ultimately experience radiographically detectable sacroiliitis. An ascending spondylitis ensues in approximately 10% to 12% of patients.

One or more of the mucocutaneous features can be found on examination in more than 50% of patients, usually early in the disease. Keratoderma blennorrhagica is a papulosquamous skin rash that usually begins on the soles or palms as painless and nonpruritic excrescences resembling mollusk shells [see Figure 5]. With time, these lesions evolve into scaling plaques that may coalesce into a more generalized exfoliative dermatitis. Keratoderma blennorrhagica is clinically and histopathologically the same as the disorder pustular psoriasis [see 2:III Psoriasis]. A similar scaling rash on the glans penis in circumcised men is termed circinate balanitis. Moist, shallow ulcers characterize balanitis in uncircumcised men, who may be unaware of the lesions unless the foreskin is retracted [see Figure 6]. Similar painless oral ulcers may be found on the tongue or palate. Nails may become hyperkeratotic, thickened, and deformed, but the characteristic nail pitting of psoriasis is usually absent [see Figure 6]. It is important to search for all of these lesions; they are frequently asymptomatic but are definitive and can establish a diagnosis.

Some patients experience low-grade or high fever at disease onset; malaise—or even prostration—and significant weight loss may ensue. Acute anterior uveitis occurs in approximately 20% of patients with reactive arthritis. Cardiac bradyarrhythmia, aortic regurgitation, or both may also occur during the acute disease phase or may appear later in patients whose illness follows a chronic course. Patients with reactive arthritis who are HLA-B27 positive are more likely to experience sacroiliitis and spondylitis, as well as uveitis, cardiac lesions, or both, and to experience a prolonged disease course.

Reactive arthritis has been frequently described in patients with HIV infection; the joint and skin disease may be more severe than usual in such persons. This association is now believed to result from sexually acquired enteric and venereal pathogens common to both diseases.

**Laboratory Evaluation**

Tests of patients with reactive arthritis usually show a modest leukocytosis, thrombocytosis, and anemia, along with elevation of the ESR, reflecting systemic inflammation. Examination of the synovial fluid reveals inflammatory changes of poor mucin clot and leukocytosis; but in contrast to septic arthritis, the glucose level is not low, and bacterial cultures are negative. Polymerase chain reaction (PCR) analysis of synovial fluid or tissue biopsies has been used successfully to detect specific bacterial DNA or RNA in research laboratories; PCR kits should become clinically available soon. Cultures or molecular probes for *C. trachomatis* should be obtained in patients with venereal exposure, genitourinary symptoms, or both. At the same time, tests for concomitant gonorrhea, syphilis, and HIV infection should be performed. In patients with preceding GI symptoms, stool cultures for the triggering organisms are usually negative by the time joint symptoms appear. Serologic tests for *Salmonella* and other enteric pathogens are usually unreliable but may be useful in some cases.
Radiographic Features

X-rays are of no diagnostic value early in the disease; however, MRI may show inflammatory changes of enthesitis and arthritis. After several months of persistent joint symptoms, enthesopathic symptoms, or both, radiographs may show the distinctive changes of periostitis and bony ankylosis. Patients with chronic heel pain may show a fluffy periosteal reaction or spur formation at the Achilles or plantar tendon insertions. Similar radiographic changes may be seen along metatarsal or phalangeal bones of the feet; bony fusion across joints may be visible. Sacroilitis, when present, is more often unilateral than bilateral, and large asymmetrical syndesmophytes may be seen in the lumbar spine.

TREATMENT AND PROGNOSIS

Reactive arthritis runs a self-limited course in most patients, lasting 4 to 12 months, although annoying residual musculoskeletal symptoms may persist for years. From 15% to 30% of patients suffer permanent disability. Relapses are not uncommon; it is unclear whether they result from repeat infection or other endogenous mechanisms. The same NSAIDs used to treat ankylosing spondylitis [see Ankylosing Spondylitis, Treatment and Prognosis, above] are usually effective in quieting inflammatory joint symptoms. Some patients with highly active disease, however, may require short courses of low-dose systemic corticosteroids or repository corticosteroid injections into joints.

Early treatment of genitourinary infections with appropriate antibiotics (e.g., tetracycline or erythromycin) has been shown to reduce the likelihood of subsequent reactive arthritis; however, even early antibiotic use in patients with gastroenteritis does not appear to prevent reactive arthritis. A blinded, placebo-controlled trial of the use of tetracycline for the treatment of reactive arthritis demonstrated that the duration of disease was shortened only in patients who had Chlamydia-induced disease. Ciprofloxacin has not been shown to shorten the course of chronic reactive arthritis. Controlled studies have shown that sulfasalazine, in dosages similar to those used in the treatment of ankylosing spondylitis, is effective in all forms of spondylarthritides. Whether any of these antibiotic approaches change the natural history of the disease remains to be proved. Patients with spondyloarthritides that persist despite treatment with NSAIDs and antibiotics may benefit from the use of anti-TNF agents. An increasing number of studies are documenting immediate and dramatic benefit from the use of TNF-α antagonists (e.g., infliximab and etanercept) in such patients. Physical therapy is important in maintaining joint motion and preventing disability.

Psoriatic Arthritis

Epidemiology

The prevalence of cutaneous psoriasis is estimated to be 2% in most white populations; it appears to be lower in populations who are of African or Asian ancestry. An inflammatory arthropathy attributable to psoriasis appears in 5% to 7% of patients with the skin disease, especially in those whose nails are affected. Psoriasis is highly familial, and there is strong evidence that it is a complex genetic disease associated with several HLA alleles and other non–HLA-linked loci. Genomic studies now strongly suggest major but yet unidentified loci for psoriasis susceptibility near HLA-C in the MHC region and on chromosome 17. HLA-B27 is only weakly associated with psoriasis and peripheral psoriatic arthritis, but it occurs in 50% of persons who have psoriatic spondylitis. Potential environmental triggers are streptococcal infection and physical trauma. Psoriatic arthritis is slightly more common in females than in males. Psoriasis frequently first appears in childhood; psoriatic arthritis typically appears in early or middle adulthood, although there are many exceptions. The arthritis may appear before the psoriasis in as many as 40% of children and 15% of adults. Although the incidence of psoriasis and psoriatic arthritis in HIV-positive persons is similar to that in uninfected persons, severe exacerbations of both skin disease and joint disease have been observed in patients with HIV infection, especially as the number of CD4+ T cells declines.

Diagnosis

Clinical Presentation

In general, there is little relation between joint and skin severity. In fact, psoriatic skin lesions may be found only after careful scrutiny of the scalp, the umbilicus, or the gluteal region, and nail pitting or other changes may be the only clues supporting a diagnosis of psoriatic arthritis. Several clinical patterns of joint involvement, often overlapping, have been described:

1. Asymmetrical oligoarthritis of both small and large joints is the most common form of psoriatic arthritis. Involvement of distal interphalangeal joints and sausage-shaped toes or fingers are highly suggestive signs. A disparity is often noted between clinical appearance and subjective symptoms; overly involved joints may be largely asymptomatic, unlike the concordance usually found in rheumatoid arthritis.

2. Symmetrical polyarthritis may resemble rheumatoid arthritis, although tests for rheumatoid factor and antibodies to cyclic citrullinated peptides (anti-CCP) should be negative. Anti-CCP is a newly discovered autoantibody marker for rheumatoid arthritis that is 65% sensitive and 96% specific. Uncertainty about classification is reasonable because psoriasis and rheumatoid arthritis are both relatively common diseases and are expected to occur together by chance.

3. Arthritis mutilans is the most destructive form of psoriatic arthritis; it occurs in approximately 5% of patients with psoriatic arthritis. Striking bone resorption and telescoping of fingers (opera-glass hand) are characteristic. Affected patients often have concomitant spinal involvement.

4. Psoriatic spondylitis occurs in approximately 20% of patients with psoriatic arthritis, often with unilateral sacroilitis and large asymmetrical syndesmophytes, similar to the pattern seen in patients with reactive arthritis.

5. Dominant or exclusively distal interphalangeal joint involvement with psoriatic nail changes may occur.

Laboratory Findings

An elevated ESR or CRP level, anemia, and hyperuricemia may be found. Rheumatoid factor, anti-CCP, and antinuclear antibody tests are negative. Synovial fluid shows nonspecific inflammatory changes.

Radiographic Features

A characteristic change is whittling of the distal ends of phalanges, giving the joints a so-called pencil-in-cup appearance, which is radiographically distinctive for psoriatic arthritis. Periostitis—which results in whiskering around joints—bony erosions, and joint fusion in the absence of osteopenia also are common and diagnostically useful findings.
TREATMENT AND PROGNOSIS

NSAIDs similar to those used for ankylosing spondylitis [see Ankylosing Spondylitis, Treatment and Prognosis, above] [see Table 3] are the mainstay of arthritis therapy in most patients but have no effect on the skin disease, which may require separate dermatologic approaches [see 2:III Psoriasis]. Sulfasalazine, methotrexate, or cyclosporine may be beneficial for both skin and joint disease in NSAID-resistant or severe, progressive disease. Well-controlled studies have demonstrated that TNF-α antagonists (etanercept and infliximab) are highly effective for symptoms and probably modify outcomes for both the arthritis and the skin disease. Gold, penicillamine, and hydroxychloroquine are not useful agents.

Psoriatic arthritis usually runs a more benign course than rheumatoid arthritis does, although clearly there are many patients with severe disease. Many patients with psoriatic arthritis maintain reasonable function, often despite extensive deformities.

Enteropathic Arthritis

Two major clinical patterns of arthritis associated with inflammatory bowel diseases are peripheral arthritis and spondylitis.

Peripheral Arthritis

Approximately 20% of patients with Crohn disease or ulcerative colitis experience an acute peripheral arthritis. Symmetrical swelling of the knees, ankles, or wrists is the most common articulat pattern; large effusions may occur. The pathogenesis of the arthritis is unknown, but the disease occurs during periods of active inflammation of the gut and may be the first sign of a bowel flare-up. HLA-B27 is not increased in frequency among inflammatory bowel disease patients with peripheral arthritis, as compared with the normal population. Extraskeletal and extraintestinal manifestations may occur simultaneously and include fever, acute anterior uveitis, painful oral ulcers, erythema nodosum (in Crohn disease), and pyoderma gangrenosum (in ulcerative colitis). Treatment of the arthritis should be aimed at controlling the inflammatory bowel disease. The arthritis seldom results in deformities.

Spondylitis

Sacroiliitis develops in about 10% of patients with inflammatory bowel disease. Clinically, the spondylitis may progress to total spinal ankylosis; radiographically, it is indistinguishable from ankylosing spondylitis. There is no correlation of the spondylitis with activity of the bowel disease. HLA-B27 is found in approximately 50% of such patients. Therapy is largely the same as for ankylosing spondylitis [see Ankylosing Spondylitis, Treatment and Prognosis, above]. Despite the bowel disease, NSAIDs are usually well tolerated.

Undifferentiated Spondyloarthritides

Inevitably, the presentations of many patients do not conform to the typical presentations described above, and the symptoms and signs defy specific disease classification. Examples are a patient with unilateral sacroiliitis, a sausage digit, and uveitis; a patient with typical reactive arthritis who experiences psoriatic arthritis; and a patient with typical ankylosing spondylitis who years later experiences Crohn disease. Such patients are often designated as having undifferentiated spondyloarthritis. The ESSG criteria now make the classification of patients with spondyloarthritides more definitive. There remains, however, a large number of patients with formes frustes that do not fulfill the new criteria but probably fall within the spectrum of spondyloarthritides. Such entities, which are strongly associated with HLA-B27, are chronic inflammatory back and chest pain syndromes (in which radiographs are normal), chronic dactylitis, chronic plantar fasciitis or Achilles tendinitis, pustular psoriasis (keratoderma blennorrhagica), circinate balanitis, acute anterior uveitis, and spondylitic heart disease without evidence of arthritis. In patients suspected of having a limited form of spondyloarthritis, typing for HLA-B27 may prove clinically useful in supporting such a diagnosis.

Juvenile Spondyloarthritis

Until recently, the term juvenile rheumatoid arthritis was used, inappropriately, to describe all forms of chronic childhood arthritis. Careful clinical evaluation, autoantibody testing, and HLA typing have revealed a heterogeneous group of diseases in which only a small proportion of affected children truly have rheumatoid arthritis.

Juvenile spondyloarthritis occurs most often in boys; it typically begins in late childhood or adolescence with lower extremity oligoarthritis and enthesopathy. Spinal symptoms are rare initially but often appear years later. Bony ankylosis of the tarsal bones has been described in some of these patients. Acute anterior uveitis is not uncommon. Such patients are seronegative for rheumatoid factor, anti-CCP, and antinuclear antibodies but are positive for HLA-B27. Less often, a patient may present with chronic polyarthritis with prominent cervical spine fusion rather than lower spine involvement.

Subsets of juvenile arthritis include the following:

1. Oligoarthritis appearing in early childhood, more often in girls; it is associated with antinuclear antibodies, a high risk of chronic iridocyclitis and blindness, and HLA-DR5 (DR11), HLA-DR8, or HLA-DR6, as well as HLA-DP2, but not HLA-B27.

2. Polyarthritis appearing in early childhood, more often in girls who are seronegative for rheumatoid factor and antinuclear antibodies; it is associated with HLA-DR8 and HLA-DP3 but not HLA-B27.

3. Polyarthritis associated with rheumatoid factor, anti-CCP, and HLA-DR4 (but not HLA-B27), which probably represents true juvenile rheumatoid arthritis.

4. Still disease, characterized by high, spiking fever, evanescent rash, hepatosplenomegaly, lymphadenopathy, and polyarthritis in patients who are seronegative and HLA-B27 negative.

Miscellaneous Arthropathies

ACNE-ASSOCIATED ARTHRITIS

A rare inflammatory oligoarthritis may occur in patients with severe forms of acne, including acne conglobata, acne fulminans, hidradenitis suppurativa, and dissecting cellulitis of the scalp. Such patients experience fever and inflamed joints; symptoms resemble those of septic arthritis, but the joints are sterile by culture. Sacroiliitis has been described in some patients.

SAPHO is an acronym for a syndrome that consists of synovitis, severe acne, palmpoplantar pustulosis, hyperostosis, and osseous and joint disease. Several patients have been reported with HLA-B27 negative. Antibiotic therapy is usually of little or no benefit, but some patients respond to NSAIDs or low-
dose corticosteroids. Surgical excision of the affected skin, when possible, has been reported to resolve the arthritis.

**WHIPPLE DISEASE**

Whipple disease is a rare multisystem disorder that usually affects men (the ratio of affected men to women is 9:1). Patients may present with arthralgias or transient episodes of additive, symmetrical polyarthritis that is nondeforming. Sacroilitis has been reported in rare instances, and the frequency of HLA-B27 may be increased in patients with Whipple disease. Patients usually have GI symptoms, including diarrhea, steatorrhea, and profound weight loss. Other clues to diagnosis are skin hyperpigmentation, serositis (pleural effusions), lymphadenopathy, uveitis, nervous system disease (ocular palsies or encephalopathy), leukocytosis, and thrombocytosis. The diagnosis traditionally has been based on small-bowel biopsies showing deposits on periodic acid–Schiff staining or electron microscopic demonstration of rodlike bacillary organisms in intestinal macrophages. The causative organism has been identified by RNA sequence analysis and cultured as a gram-positive actinomycte named *Tropheryma whippelii.* Diagnosis can be made on the basis of results from PCR analysis of DNA from affected tissues or blood samples. Long-term treatment with tetracycline usually results in complete remission.

*The author has no commercial relationships with manufacturers of products or providers of services discussed in this chapter.*

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