emphasized that the characteristics of peripheral arthritis in AS and other forms of SpA are similar, and distinct from those of rheumatoid arthritis.

Inflammation in the fibrocartilaginous enthesis, the region where a tendon, ligament, or joint capsule attaches to bone, is a characteristic lesion in AS and other SpAs, both at axial and peripheral sites. Enthesitis is associated with prominent edema of the adjacent bone marrow and is often characterized by erosive lesions that eventually undergo ossification.

Subclinical intestinal inflammation has been found in the colon or distal ileum in a majority of patients with SpA. The histology is described below under "Enteropathic Arthritis."

PATHOGENESIS

The pathogenesis of AS is immune-mediated, but there is little direct evidence for antigen-specific autoimmunity, and there is evidence to suggest more of an autoinflammatory pathogenesis. Uncertainty remains regarding the primary site of disease initiation. The dramatic response of the disease to therapeutic blockade of tumor necrosis factor α (TNF-α) indicates that this cytokine plays a central role in the immunopathogenesis of AS. Other genes related to TNF pathways show association with AS, including *TNFRSF1A*, *LTBR*, and *TBKBP1*. More recent evidence strongly implicates the interleukin (IL) 23/IL-17 cytokine pathway in AS pathogenesis. At least five genes in this pathway show association with AS, including *IL23R*, *PTER4*, *IL12B*, *CARD9*, and *TYK2*. All of these genes are also associated with inflammatory bowel disease (IBD), and three of them are associated with psoriasis. Serum levels of IL-23 and IL-17 are elevated in AS patients. Mice expressing high levels of IL-23 show spontaneous infiltration in the entheses of CD3+CD4–CD8– cells bearing IL-23 receptors and producing IL-17 and IL-22. This finding suggests the possibility that site-specific innate immune cells may play a critical role in the anatomic specificity of the lesions. Mast cells and, to a lesser extent, neutrophils appear to be the major IL-17-producing cells in peripheral arthritis, whereas neutrophils producing IL-17 are prominent in apophyseal joints. High levels of circulating γδ T cells expressing IL-23 receptors and producing IL-17 have been found in AS patients.

Other associated genes encode other cytokines or cytokine receptors (*IL6R*, *IL1R1*, *IL1R2*, *IL7R*, *IL27*), transcription factors involved in the differentiation of immune cells (*RUNX3*, *EOMES*, *BACH2*, *NKX2-3*, *TBX21*), or other molecules involved in activation or regulation of immune or inflammatory responses (*FCGR2A*, *ZMIZ1*, *NOS2*, *ICOSLG*).

The inflamed sacroiliac joint is infiltrated with CD4+ and CD8+ T cells and macrophages and shows high levels of TNF-α, particularly early in the disease. Abundant transforming growth factor β (TGF-β) has been found in more advanced lesions. Peripheral synovitis in AS and the other spondyloarthritides is characterized by neutrophils, macrophages expressing CD68 and CD163, CD4+ and CD8+ T cells, and B cells. There is prominent staining for intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), matrix metalloproteinase 3 (MMP-3), and myeloid-related proteins 8 and 14 (MRP-8 and MRP-14). Unlike rheumatoid arthritis (RA) synovium, citrullinated proteins and cartilage gp39 peptide–major histocompatibility complexes (MHCs) are absent. However, citrullinated proteins can be seen in the circulation.

No specific event or exogenous agent that triggers the onset of disease has been identified, although overlapping features with reactive arthritis and IBD and the involvement of the IL-23/IL-17 pathway suggest that enteric bacteria may play a role, and microdamage from mechanical stress at enthesial sites has also been implicated.

It is firmly established that HLA-B27 plays a direct role in AS pathogenesis, but its precise role at the molecular level remains unresolved. Rats transgenic for HLA-B27 develop arthritis and spondylitis, and this is unaffected by the absence of CD8. It thus appears that classical peptide antigen presentation to CD8+ T cells may not be the primary disease mechanism. However, the association of AS with ERAP1, which strongly influences the MHC class I peptide repertoire, is only found in B27+ patients, and this suggests that peptide binding to B27 is nonetheless important. The pairs of ERAP1 alleles found in AS patients show diminished peptidase activity, compared with those found in healthy controls. The B27 heavy chain has an unusual tendency to misfold, a process that may be proinflammatory. Genetic and functional studies in humans have suggested a role for natural killer (NK) cells in AS, possibly through interaction with B27 heavy chain homodimers. SpA-prone B27 rats show defective dendritic cell function and share with AS patients a characteristic "reverse interferon" gene expression signature in antigen-presenting cells.

New bone formation in AS appears to be largely based on enchondral bone formation and occurs only in the periosteal compartment. It correlates with lack of regulation of the Wnt signaling pathway, which controls the differentiation of mesenchymal cells into osteophytes, by the inhibitors DKK-1 and sclerostin. Indirect evidence and data from animal models also implicate bone morphogenic proteins, hedgehog proteins, and prostaglandin E_2. There is sharp controversy as to whether vertebral new bone formation in AS is a sequela of inflammation or whether it arises independently of inflammation. The second hypothesis is based on the observation that syndesmophyte formation is not suppressed by anti-TNF-α therapy that potently suppresses inflammation. TNF-α is also a known inducer of DKK-1, which inhibits bone formation. Recent magnetic resonance imaging (MRI) studies suggest that it is vertebral inflammatory lesions that undergo metaplasia to fat (increased T1-weighted signal) that are the predominant site of subsequent syndesmophytes despite anti-TNF-α therapy, whereas early acute inflammatory lesions resolve. A recent study suggested that the rate of syndesmophyte formation decreases after >4 years of anti-TNF-α therapy.

CLINICAL MANIFESTATIONS

The symptoms of the disease are usually first noticed in late adolescence or early adulthood; the median age in Western countries is approximately 23 years. In 5% of patients, symptoms begin after age 40. The initial symptom is usually dull pain, insidious in onset, felt deep in the lower lumbar or gluteal region, accompanied by low-back morning stiffness of up to a few hours' duration that improves with activity and returns following inactivity. Within a few months, the pain has usually become persistent and bilateral. Nocturnal exacerbation of pain often forces the patient to rise and move around.

In some patients, bony tenderness (presumably reflecting enthesitis or osteitis) may accompany back pain or stiffness, whereas in others it may be the predominant complaint. Common sites include the costosternal junctions, spinous processes, iliac crests, greater trochanters, ischial tuberosities, tibial tubercles, and heels. Hip and shoulder ("root" joint) arthritis is considered part of the axial disease. Hip arthritis occurs in 25–35% of patients. Shoulder arthritis is much less common. Severe isolated hip arthritis or bony chest pain may be the presenting complaint, and symptomatic hip disease can dominate the clinical picture. Arthritis of peripheral joints other than the hips and shoulders, usually asymmetric, occurs in up to 30% of patients. Neck pain and stiffness from involvement of the cervical spine are usually relatively late manifestations but are occasionally dominant symptoms. Rare patients, particularly in the older age group, present with predominantly constitutional symptoms.

AS often has a juvenile onset in developing countries. Peripheral arthritis and enthesitis usually predominate, with axial symptoms supervening in late adolescence.

Initially, physical findings mirror the inflammatory process. The most specific findings involve loss of spinal mobility, with limitation of anterior and lateral flexion and extension of the lumbar spine and of chest expansion. Limitation of motion is usually out of proportion to the degree of bony ankylosis and is thought to possibly reflect muscle spasm secondary to pain and inflammation. Pain in the sacroiliac joints may be elicited either with direct pressure or with stress on the joints. In addition, there is commonly tenderness upon palpation of the posterior spinous processes and other sites of symptomatic bony tenderness.

The modified Schober test is a useful measure of lumbar spine flexion. The patient stands erect, with heels together, and marks are made on the spine at the lumbosacral junction (identified by a horizontal line between the posterosuperior iliac spines) and 10 cm above. The patient then bends forward maximally with knees fully extended, and the distance between