Spondyloarthropathies

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1. Introduction

The spondyloarthropathies are a group of inflammatory arthritic conditions whose main clinical feature is an inflammatory arthritis of the back. In the first half of the last century, these conditions were considered variants of rheumatoid arthritis (RA). However, the discovery of rheumatoid factor in 1948 allowed the recognition that certain forms of inflammatory arthritis were seropositive for rheumatoid factor while others were seronegative; this facilitated the classification of the rheumatologic conditions. It was noted that the conditions that included inflammatory back disease were seronegative.

The inflammatory arthritis that affects the back in the conditions classified among the spondyloarthropathies manifests with pain associated with stiffness in the buttocks and back. Radiological evidence of sacroiliitis and spondylitis may be documented on radiographs of the pelvis and spine. Peripheral arthritis may be associated with the spondylitis. Some of the features that distinguish the seronegative spondyloarthropathies from the seropositive forms of arthritis are documented in Table 1.

Table 1

A Comparison Between Seropositive and Seronegative Arthritis

Feature	Seronegative	Seropositive
Peripheral arthritis	Usually asymmetric Large joints Lower extremities	Usually symmetric Small and medium size joints Upper and lower extremities
Axial involvement	Sacroiliac joints Apophyseal joints of spine Syndesmophytes	Nil Rarely rheumatoid inflammation
Enthesitis	Common	Uncommon
Periostitis	Common	Uncommon
Tendinitis	Achilles, plantar fascia	Finger tendons
Rheumatoid nodules	Never	Often
Iritis	Common	Uncommon
Aortic root dilatation	Common	Uncommon
Scaly skin rash	Common	Unusual
Bowel inflammation	Common	Unusual
Urethritis	Common	Unusual

Peripheral arthritis tends to be asymmetric and most commonly involves the lower extremities. There is often enthesitis, inflammation at the insertion of tendons into bone. Certain extra-articular features are common to this group of conditions, including skin and mucous membrane lesions, bowel complaints, eye involvement, and aortic root dilatation. Another feature common to the spondyloarthropathies is the familial aggregation, which occurs not only within each condition, but also among the entities within the group. An association with HLA-B27 has been documented in the diseases included in this group that is now recognized as the "HLA-B27 seronegative spondyloarthropathies." The diseases included in this group include: the prototype, ankylosing spondylitis; reactive arthritis (previously known as Reiter's syndrome); psoriatic arthritis; the arthritis of inflammatory bowel disease; and an entity called undifferentiated spondyloarthropathy (USpA). Other forms of arthritis associated with bowel disease are also included.

2. Ankylosing Spondylitis (AS)

Clinical Features

Ankylosing spondylitis (AS) is primarily an inflammatory arthritis of the back.[1] It involves the sacroiliac joints and the apophyseal joints of the spine. It affects men in a higher frequency than women (at a ratio of 5:1), with an age of onset usually in the late teens. AS begins with an insidious onset of pain and stiffness in the low back. The most characteristic feature of the back pain is pain at night.[2] Patients often awaken in the early morning between 2 AM and 5 AM with back pain and stiffness, and usually take either a shower or exercise before resuming sleep. In time, AS progresses to involve the whole spine and results in spinal deformities, including flattening of the lumbar lordosis, kyphosis of the thoracic spine, and hyperextension of the cervical spine. These in turn result in flexion contractures of the hips and knees with significant morbidity and disability.

Peripheral Arthritis

Peripheral arthritis occurs uncommonly in AS, but when it occurs, it is usually late in the course of the arthritis.[3] Peripheral arthritis developing early in the course of the disease is a predictor of disease progression.[4] The arthritis usually presents in the lower extremities in an asymmetric distribution. Involvement of the "axial" joints, including shoulders and hips, is more common than involvement of more distal joints. In the shoulder, there may be a unique lesion of erosion at insertion of the rotator cuff.[5] There may be progressive flexion deformity in the hips and eventual destruction of the joint.

Enthesitis

Other sites of inflammation in AS include the tendons and their insertions. Common sites for tendinitis include the Achilles tendon and the plantar fascia. These present with pain which is inflammatory in nature, being worse with inactivity and improving with activity. Inflammation at tendon insertion, or enthesitis, is common at the site of the Achilles tendon or the insertion of the plantar fascia, into the calcaneous. Other sites include the ischial tuberosity, rotator cuff insertion, trochanteric area and the patellar tendon insertion. Enthesitis presents with pain that like the other articular manifestations is inflammatory in nature. It tends to be aggravated by rest and improve with activity. Several attempts to develop an instrument to assess enthesitis in AS have been pub-

lished. The Mander enthesitis index includes 66 sites, some of which may overlap with fibromyalgia tender points.[6] A recent modification of the Mander index, the "Maastricht Ankylosing Spondylitis Enthesitis Score" (MASES) reduced the number of sites to only thirteen, and is likely to be more manageable clinically.[7] Recent evidence suggests that enthesitis may be underestimated by clinical examination, and that ultrasound is better suited to document these features of AS.[8,9]

Extra-articular Manifestations of AS

Extra-articular features include: iritis, particularly anterior uveitis; cardiac manifestations, including dilatation of the root of the aorta and conduction defects; fibrosis of the upper lobes of the lungs; cauda equina syndrome which results from multiple thecal diverticulae or dilated lumbar sacs; and later in the course of the disease, amyloidosis.

Uveitis, particularly acute anterior uveitis (AAU) occurs in 20% to 30% of patients.[10] The eye involvement in AS is characterized by: 1) its acute presentation, usually in a unilateral distribution; 2) its frequent recurrence; and 3) the development of anterior synechiae, adhesions between the iris and the cornea. It has been suggested that uveitis in AS is associated with more severe spondyloarthropathy. A decrease in anterior uveitis was documented following treatment with anti-TNF agents.[11]

Aortic root dilatation was recognized in the 1960s as a complication of AS. It was initially described among patients who had had the disease for a prolonged period. The pathology is similar to that of AS in other areas. There is an initial inflammatory infiltrate at the base of the aorta that results in fibrosis, which in turn leads to aortic root dilatation and conduction defects. Thus, patients with longstanding AS may present with a tambour quality of their second heart sound, an aortic diastolic murmur, or with first, second and even complete heart block. Several patients have required surgical intervention.[12]

Radiological Changes in AS

The radiological changes reflect the clinical disease process. The sacroiliac joints are commonly the initial sites of inflammation. They demonstrate erosions with subsequent ankylosis of the joints. The New York criteria[13] describe the sacroiliac involvement according to four grades: grade 1 is suspicious; grade 2 shows erosions and sclerosis; grade 3 shows erosions, sclerosis, and early ankylosis; and grade 4 reflects total ankylosis. These radiographic changes reflect damage rather than inflammation. Magnetic Resonance Imaging (MRI) provides a better approach to identifying inflammation in the sacroiliac joints, and may help earlier diagnosis of AS.[14,15,16]

Radiologic Signs and Disease Progression

In the spine, the thoracolumbar junction tends to be an early site of involvement, with subsequent progression both caudally and distally to affect the whole spine. The early radiologic sign is the Romanus lesion,[17] which reflects erosion at the disc margin. Squaring of the vertebra then results, followed by the development of the syndesmophyte, as a consequence of ossification of the outer layer of the nucleus fibrosus of the intervertebral disc. In the late stages of the disease, total ankylosis of the spine occurs with ossification of the longitudinal ligaments.

The Bath Ankylosing Spondylitis Radiology Index (BASRI) provides a method for assessing the spine and the hip. It includes an assessment of erosions and syndesmophytes with values weighted by the number of vertebral sites involved.[18] The modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) provides a more detailed analysis of the changes in the spine in AS.[19] The use of these indices together with clinical assessment is recommended when assessing patients with AS.[20]

The enthesitis observed in AS patients may be detected radiologically by spurs at the insertion of tendon into bones at the calcaneous, both at the Achilles insertion and at the insertion of the plantar fascia, as well as around the pelvic bones. Indeed, recent observations by McGonagle et al[9] suggest that an entheseal-associated pathology may explain spinal and synovial joint inflammation of AS and related spondyloarthropathy.

Etiological Factors

The cause of AS is unknown. However, genetic, environmental and immunological factors are thought to play a role in its pathogenesis. An interplay among these factors likely leads to the disease.

HLA-B27

Genetic factors have long been known to play a role in the disease, as there is a strong familial aggregation in AS. In 1973 the genetic contribution to AS was further enhanced with the recognition that it was associated with the HLA antigen B27.[21,22] There have been multiple studies of HLA-B27 in AS, showing increased frequencies in patients with AS in most populations studied.[23] No specific association between AS and specific HLA-B27 alleles was demonstrated.[24] An unequivocal linkage of MHC region with AS was demonstrated in a study of 15 multiplex families with AS.[25] Recent twin studies revealed a concordance rate of 67% for monozygotic twins and 23% in dizygotic twins.[26] These studies suggest that while there is a significant genetic contribution to the development of AS, it is not entirely due to the HLA-B27.

In addition to HLA-B27, other B locus antigens, particularly HLA-B60 have been incriminated and class II alleles have also been identified.[28] A recent genome-wide search in 121 sib-pairs with AS confirmed the role of HLA as the major region for the susceptibility to AS but also suggested that there are other areas, including chromosome 4 and chromosome 22.[27]

Microbial Factors

Animal models for AS support the role of HLA-B27 but clearly indicate that an interaction with microbial factors is important.[28] Several theories attempt to explain the mechanism of the association between HLA-B27 and AS.[29] The molecular mimicry theory is based on a similarity between bacterial epitopes and B27 molecules. While some sequences of the HLA-B27 molecule are similar to some bacterial epitopes, it is unclear how this would actually lead to disease. It has been proposed that there is an arthritogenic peptide that is presented preferentially by HLA-B27. However, a specific peptide has not been eluted from all B27 molecules from patients with AS.

HLA-B27 may impair immunity of arthritogenic organisms by association with arthritogenic epitopes from other HLA molecules or by altering T-cell response to inhibitory cytokines. It has been suggested that AS results from a loss of tolerance resulting from altered antigenicity of B27 following oxidation of cysteine 67 at the mouth of the B amino acid recognition pocket. Indeed transgenic rats carrying serine at position 67 instead of cysteine develop gut manifestations but no arthritis. It has also been suggested that HLA-B27 derived peptides elicit immune response following presentation by HLA-class II antigens, or that free B27 heavy chain could bind as a homodimer that could mimic sufficiently a class II molecule to activate CD4+ cells. An interplay between genetic and environmental factors likely plays a role in the development of AS.[30]

It has further been suggested that the HLA-B27 allele serves as marker for an MHC-linked disease-determining gene. Evidence for involvement of IL-1 gene cluster and AS is emerging.[31] Genome-wide searches certainly suggest that there may be other genes involved, and some may actually be within the MHC.[23,32]

Diagnosis of AS

There are no validated diagnostic criteria for AS. The New York criteria of 1968 were meant to be diagnostic criteria; however, they are insensitive to identifying early disease (Table 2). These criteria were modified in 1984 in an attempt to address this issue,[33] but these criteria were not thought broad enough.

The recent criteria devised by the European Spondyloarthropathy Study Group are 94% sensitive for clinically definite AS but are only 66% sensitive in early disease.[34] The diagnosis of AS should be suspected in a young individual, particularly a young man, who presents with inflammatory back pain. The presence of the HLA-B27 is diagnostically helpful only in those cases where the a priori diagnosis is between 40% and 60%. In individuals who clearly have "bamboo spine" the HLA-B27 is irrelevant. Likewise in an individual whose back pain is clearly mechanical in nature and who has no other clinical features suggestive of AS, the presence of HLA-B27 is not helpful in making the diagnosis. In both these scenarios knowledge of the HLA-B27 status may change the a priori probability of less than 10% to a posteriori probability of 15% to 20%.[35]

Table 2

Classification Criteria for Ankylosing Spondylitis

New York Criteria	Modified New York Criteria	ESSG Criteria
Clinical 1. Limitation of motion lumbar spine all planes. 2. Pain in the thoracolumbar junction or the lumbar spine. 3. Limitation of chest expansion to 2.5 cm.	Clinical 1. Low back pain of at least 3 months duration improved by exercise and not relieved by rest. 2. Limitation of lumbar spine in sagittal and frontal planes. 3. Chest expansion decreased relative to normal for age and sex.	Inflammatory spinal pain **OR** Synovitis • Asymmetric • Predominantly in the lower limbs **AND** One or more of the following: • Positive family history • Psoriasis • Inflammatory bowel disease • Urethritis, cervicitis, or acute diarrhea within one month of arthritis • Buttock pain alternating between left and right gluteal areas • Enthesopathy • Sacroiliitis
Radiological grading 0 = normal 1 = suspicious 2 = minimal sacroiliitis 3 = moderate sacroiliitis 4 = ankylosis	Radiological • Bilateral sacroiliitis grades 2-4 • Unilateral sacroiliitis grades 3-4	
Definite AS • Grades 3-4 bilateral sacroiliitis with at least one clinical criterion • Grades 3-4 sacroiliitis unilateral, **OR** grade 2 bilateral with clinical criterion one **OR** with both 2 and 3	Definite AS Any clinical criterion with: • Unilateral sacroiliitis grades 3 or 4 **OR** • Bilateral sacroiliitis grades 2-4	

The diagnosis of AS is made in women much less often than it is in men. This is likely related to the gender difference in the development of the disease. However, this may also be due to the fact that the disease in women may not be as severe as it is in men. Moreover, in women ankylosing spondylitis may present with neck pain and, on occasion, breast pain, in the absence of the typical lower back pain of sacroiliitis.[36] The disease in women is often diagnosed later than in men.

Assessment of Disease Activity and Damage in AS

Over the past few years a concerted effort has been made to standardize measurement instruments for AS. This has been accomplished under the auspices of the ASsessment of Ankylosing Spondylitis (ASAS) working group. Based on nominal group processes and clinical trials the group has come up with an accepted measure to assess disease activity and function, and has recommended criteria for the clinical management of AS.[37] It should be noted that patients and physicians assess disease activity differently.[38] Using the BASRI to assess damage Brophy et al[39] demonstrated that spinal progression was a function of disease duration, while early hip involvement indicated more severe disease. At the same time the group has also identified preferred methods for radiological assessment of AS.[40]

Treatment

The treatment of AS begins with the administration of nonsteroidal anti-inflammatory medications, particularly indoleacetic acid derivatives. An exercise program is particularly important for these patients to maintain functional spinal outcomes. Although there are no controlled trials to demonstrate significant differences in outcome, it is clear that cases of AS seen in the last 20 years are not as severe as those described in the 1940s and 1950s. This is likely due to the addition of the nonsteroidal anti-inflammatory medications, as well as regular exercise programs. The latter has been shown to be of some benefit for patients with AS.[41] The addition of 3 weeks of spa therapy together with an exercise program to nonsteroidal anti-inflammatory medications has proven effective for as long as 40 weeks.[42] When the disease is resistant, disease-modifying medications have been tried. Sulfasalazine has been used with benefit in some trials,[35] but a meta-analysis revealed that while it had a modest effect on peripheral arthritis it failed to improve spinal mobility.[43] Intra-articular corticosteroid injections may be of benefit for individual peripheral joints. A novel approach has been the use of intravenous pamidronate, which appears to work for the spinal disease but not for peripheral arthritis.[44]

While DMARDs have not worked well for AS, the use of anti-TNF agents has been quite rewarding.[45] Infliximab, a chimeric anti-TNF antibody, has been proven effective in several uncontrolled trials and in randomized controlled trials. Etanercept, a TNF receptor p75 fusion protein has also been effective.[45] Several other anti-TNF agents are currently under investigation for AS.

Prognosis

Longitudinal studies in patients with AS revealed that the deformities and disability occur within the first 10 years of disease.[4] Most of the loss of function occurred during the first 10 years of disease, and correlated significantly with the occurrence of peripheral arthritis, radiographic changes of AS in the spine and development of bamboo spine.

In the United Kingdom, a recent cross-sectional study of 133 patients identified 31% of patients with AS who were unable to work because of their disease, and an additional 15% who had to modify their work.[46] Work disability was associated with older age, longer disease duration, comorbidity and more severe functional disability. In the United States, a study of 234 patients identified 13% of patients with AS as having permanent work disability.[47] Risk factors for functional limitation in patients with AS include a history of physically demanding jobs, more comorbid conditions, and smoking.[48]

Survival is reduced among patients with AS compared to the general population with a relative risk of 1.93. Radiation therapy has been demonstrated to be a risk factor for death.[49] Causes of death included heart disease, cerebrovascular disease, malignancy, renal failure, pneumonia, and other.

Table 3

A Comparison of Extra-articular Features in the Spondyloarthropathies

Feature	Psoriatic Arthritis	Ankylosing Spondylitis	Reiter's/ Reactive Arthritis	IBD Arthritis
Gender (M:F)	1:1	9:1	8:1	1:1
Age of onset	35-45 years	20s	20s	Any age
Peripheral arthritis	96%	25%	90%	Common
Distribution	Any joint	Axial, lower limbs	Lower limbs	Lower limbs
Dactylitis	35%	Uncommon	Common	Uncommon
Enthesitis	Common	Common	Common	Less common
Sacroiliitis	40%	100%	80%	20%
Skin lesions	Always	Rare	Common	Occasional
Type of skin lesion	Psoriasis vulgaris, psoriasis guttate, nail lesions	Nil specific	Keratodermia blenorrhagica, nail changes	Pyoderma gangrenosum, Erythema nodosum
Mucous membrane	Uncommon	Uncommon	Common	Uncommon
Conjunctivitis	Occasional	Rare	Common	Rare
Uveitis	Occasional	Occasional	Common	Occasional
Urethritis	Occasional	Rare	Common	Rare
Aortic regurgitation	Rare	Occasional	Occasional	Occasional
Familial aggregation	Common	Common	Common	Common
HLA-B27	40%	90%	80%	30%

3. Reactive Arthritis (ReA)

This form of arthritis usually begins after an infection of the genitourinary or gastrointestinal tract, and manifests at least one other extra-articular feature. The majority of patients are males who carry the HLA-B27 antigen. "Reiter's syndrome" refers to the clinical triad of nongonococcal urethritis, conjunctivitis, and arthritis first described by Reiter in 1916.[50] Cases of similarly reactive arthritis were documented following infections with *Shigella, Salmonella, Campylobacter,* and *Yersinia*. It was the outbreak with the latter that introduced the term reactive arthritis (ReA), which has been used to describe an acute, sterile synovitis associated with a localized infection elsewhere in the body.[51] The term ReA will be used in this chapter.

Clinical Features of ReA

Peripheral Arthritis
The arthritis of ReA tends to be asymmetric; there is involvement of the distal interphalangeal joints and the sacroiliitis is often asymmetric. Indeed, the skin lesions seen in Reiter's syndrome are sometimes difficult to distinguish from pustular psoriasis, both clinically and pathologically. Both lesions affect the palms and soles and have similar pathological features. Dactylitis is also a feature of ReA. Although not tested epidemiologically, patients with ReA likely demonstrate more pain than patients with psoriatic arthritis, because the former often presents with features suggestive of septic joints.[52] ReA affects men more commonly than women, whereas psoriatic arthritis affects women and men almost equally. ReA is more commonly associated with conjunctivitis, urethritis, and iritis than is psoriatic arthritis (Table 3).

Tendinitis and Enthesitis
Enthesitis is a common feature of ReA. The same sites described for ankylosing spondylitis may be affected, but the Achilles tendon and plantar fascia are most commonly affected.

Extra-articular Manifestations of ReA
Conjunctivitis is part of the clinical triad and is found in 30% to 60% of the patients. It may be noted early in the course of the disease, prior to or simultaneous with the development of arthritis. Conjunctivitis appears to be more common among patients with sexually acquired and post-*Shigella* reactive arthritis than in patients with other prior infections.[53] Uveitis is less common in patients with ReA than in patients with AS.[10]

Urethritis is also part of the clinical triad. It is classically a sterile urethritis, although in many cases *Chlamydia trachomatis* and *Ureoplasma urealyticum* have been isolated.[54] Circinate balanitis is a painless erythematous lesion of the glans penis which is seen in about a quarter of the patients with ReA patients.

Oral ulcers are common among patients with ReA. They tend to be superficial but may coalesce. Because they are painless, they may be not be noted by the patient. Other skin manifestations include keratodermia blenorrhagica, a hyperkeratotic lesion that often begins as a clear vesicle on an erythematous base, and progresses to macules, papules, and nodules. These lesions are found on the soles of the feet and the palms of the hands. These lesions are difficult to differentiate from pustular psoriasis.

Diarrhea is often a presenting manifestation in patients with ReA following *Shigella, Yersinia*, or *Salmonella* infections. There have been some case reports of patients with ReA who had the cardiac manifestations of the seronegative spondyloarthropathies.

Radiological Changes in ReA

The radiographic features of ReA syndrome include spinal changes as well as changes in the peripheral joints. In the spine, asymmetric sacroiliitis and paramarginal syndesmophytes are seen, in contrast to the symmetric sacroiliitis and marginal syndesmophytes that typify AS. In the peripheral joints there may be erosive changes in distal interphalangeal joints, which in extreme cases lead to pencil-in-cup changes. There may also be periosteal reaction. These changes are similar to those seen in psoriatic arthritis.[54] Like patients with ankylosing spondylitis, patients with ReA commonly manifest enthesitis, particularly around the ankle joints. In addition, in ReA erosions at the Achilles tendon insertion may be noted.

Etiology and Pathogenesis of ReA

Because of the association between the articular symptoms and preceding genitourinary or gut infection, ReA was originally considered an infectious arthritis. However, bacteria have seldom been isolated

from the joints, hence the term ReA. Various techniques to identify organisms within the joints have been attempted, and bacterial antigens have been recognized by a variety of methods, suggesting that bacterial antigens are present in the joints.[53] A study of 52 patients with ReA and 74 patients with possible ReA demonstrated that *Chlamydia trachomatis, Yersinia,* and *Salmonella* can be identified as the causative pathogen in about 50% of patients with probable or possible ReA if the appropriate tests are used.[55] Indeed, in experimental *Chlamydia*-induced arthritis, recent studies reported that synoviocytes could serve as a reservoir of the viable organism acutely and as a repository of microbial antigens chronically.[56] Many of these antigens have been shown to be arthritogenic.

HLA-B27 has been shown to confer susceptibility to ReA. HLA-B27, like other HLA class I molecules, codes for glycoprotein with a three-dimensional structure on the cell surface responsible for presentation of microbe-derived peptide to T lymphocytes within the joint. Based on its structure it has been found that certain peptides would fit in its antigen-presenting groove. It has therefore been suggested that certain bacteria share peptides that preferentially bind to the HLA-B27 groove resulting in a T lymphocyte, more specifically a CD8 positive cell response. HLA-B27 transgenic mice are more susceptible to systemic infection with *Yersinia* but without arthritis. HLA-B27 transgenic rats develop features of seronegative spondyloarthropathy which resemble ReA,[21] and transfer of HLA-B27+ bone marrow cells transmits the disease to nontransgenic mice.[57] Thus, in an individual with a genetically determined alteration in cytokine profile, infection with the type of organism associated with ReA may develop it. A recent study of 85 Finnish patients with ReA and 62 healthy Finnish HLA-B27 positive controls suggests that certain of the IL-10 cytokine promoter alleles (G10 and G12) are protective against the development of ReA.[58] ReA may persist due to impairment in protective host defenses which play a central role in the evolution of an autoimmune response.[59] As in AS, an interplay between genetic and environmental factors is thought to be responsible for the development of ReA.[30]

Diagnosis of ReA

Not only are there no uniformly accepted diagnostic or classification criteria for ReA, there is still a debate as to what constitutes the disease.[60] In a recent meeting there appeared to be some agreement as to the essentials of the diagnosis of ReA, but there are still outstanding issues requiring further study. In the literature, ReA and Reiter's syndrome are often used synonymously, but the term ReA is the currently used term. For the diagnosis of ReA one requires a typical arthritis, which often affects the lower limbs and is asymmetrical, along with evidence of a preceding infection with either diarrhea or urethritis. For the diagnosis of Reiter's syndrome, the presence of conjunctivitis and urethritis were crucial.

Pacheco-Tena et al[61] recently reviewed the literature on ReA and noted how seldom published criteria have been used. They propose that possible ReA be diagnosed either when arthritis and an extra-articular manifestation such as mucositis, urethritis, or cervicitis are present, or when the arthritis is preceded by clinical evidence for infectious disease but without bacterial identification. They further suggest that definite ReA be diagnosed when bacterial identification in the course of diarrhea or urethritis is followed by arthritis, or when bacteria are identified in a patient with a recent onset of arthritis. They also distinguish a group of bacteria-associated oligoarthritis or spondyloarthropathy. However, the newly proposed criteria remain nonspecific. It has further been suggested that the actual method of identifying the bacteria be considered in the proposed criteria.[62] Some of the issues related to the development of such criteria were recently reviewed.[63]

Treatment of ReA

Current treatment of the arthritis includes nonsteroidal anti-inflammatory medications, and in severe cases, sulfasalazine has been shown to be effective.[64] Many rheumatologists treat refractory cases of ReA with methotrexate or imuran. Intra-articular injections with corticosteroids are used to control disease in individual joints. Because of the role of bacteria in the development of ReA, antibiotics have been proposed both as a short-term and prolonged therapy for the condition. However, antibiotics for the treatment of ReA have been shown to be ineffective.[65]

As in the case of AS, the development of biologic agents has been welcomed in the treatment of ReA. There are no specific clinical trials in ReA, as the patients are included in RCTs for AS.[66]

Prognosis

ReA usually runs a self-limited course of 3 to 12 months. However, in one study,[67] 20% to 40% of the patients had evidence of chronic indolent arthritis at 12 months, while only 5% had persistent arthritis at 2 years. Follow-up studies after an outbreak of *Salmonella typhimurium* food poisoning in 423 police officers of whom 27 developed joint disease revealed that while 9 patients resolved within 4 months of onset, the remainder had persistent disease at 5 years. Of the 27 patients, 10 had intermittent flares of arthritis with interval remissions, 4 had flares without true remissions, and 4 had a persistent unremitting arthritis.[68,69]

At a follow-up of 48 patients with Reiter's disease, with an average disease duration of 6 years, 30% of the patients reported recurrent major symptoms but none was in functional class 3 or 4 (marked limitation of activities of daily living).[70] While initial studies suggested that patients with HLA-B27 tended to develop chronic arthritis, recent studies do not support this observation.

4. Psoriatic Arthritis (PsA)

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis, an inflammatory skin condition that may afflict 1% to 3% of the population.[71] Up to a third of the patients with psoriasis may develop an inflammatory form of arthritis thus the prevalence of PsA may be as high as 1%.[72] However, the actual prevalence of the disease is unknown. One difficulty in establishing the frequency of the disease is that while in 80% of the patients the skin manifestations precede the joint features, there is a group of 15% to 20% in each reported series in whom the joint manifestations preceded the skin disease. In these cases either the diagnosis was delayed, or it was suspected because of the clinical and radiological manifestations of the disease.

Clinical Features of PsA

Five patterns of PsA at presentation have been recognized.[73] These include: 1) a distal joint pattern in which only the distal interphalangeal joints are involved; 2) an oligoarticular pattern, affecting 4 or fewer joints; 3) polyarticular disease, which affects 5 or more joints often in an asymmetric distribution; 4) arthritis mutilans, which is a destructive form of arthritis with either joint lysis or ankylosis; and 5) a spondyloarthropathy where the sacroiliac joints and the joints of the spine are involved. However, it has been difficult to ascertain whether these patterns have prognostic implications since there have been few prospective longitudinal studies in this disease. Moreover, in the few studies that did follow patients, the patterns change over time.[74] Thus, although several studies of at least 100 patients have been performed[75-80] (Table 4), they describe patients at one point in time. While several studies have been able to document the 5 patterns described by Moll and Wright, recent studies suggest that the patterns should be reduced to peripheral arthritis and spondyloarthropathy.[80-81]

Peripheral Arthritis

The arthritis of PsA is similar to the peripheral arthritis of the other spondyloarthropathies in that it tends to be asymmetrical, and in many cases begins with an oligoarticular distribution. The arthritis of PsA can be distinguished from rheumatoid arthritis by the absence of rheumatoid factor, the asymmetric distribution, the presence of distal joint disease, and the occurrence of the spondyloarthropathy. Patients with

Table 4

Psoriatic Arthritis Studies: Large Series (>100 patients)

Author (Reference no.)	Roberts (69)	Kammer (70)	Gladman (71)	Torre-Alonso (72)	Veale (73)	Jones (74)
No. of patients	168	100	220	180	100	100
M/F	67/101	47/53	104/116	99/81	59/41	43/57
Age of onset	36-45	33-45	37	39	34	38
Oligoarthritis (%)	?	53	21	37	43	26
Polyarthritis (%)	78	28	45	35	33	63
Distal (%)	17	11	16	0	16	1
Back (%)	5	2	2	7	4	6
Mutilans (%)	5	7	16	4	2	4
Sacroiliitis (%)	?	11	27	20	15	6
Joints before skin (%)	16	30	17	15	?	18

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PsA are less tender both over affected joints and over tender points than patients with rheumatoid arthritis.[82] In addition there is often a purplish discoloration over the affected joints in PsA.

Spondyloarthritis

The spondyloarthropathy of PsA may be distinguished from that of AS by the pattern of the sacroiliitis. Whereas in AS the sacroiliitis tends to be symmetrical, affecting both sacroiliac joints to the same degree, it tends to be asymmetric in psoriatic arthritis. In AS the syndesmophytes occur in a symmetric distribution and are usually classical, arising from the disc margins. In PsA both marginal and non-marginal syndesmophytes occur, often skipping vertebrae along the spine. Indeed, patients with PsA do not have as severe a spondyloarthropathy as patients with AS.[29] Patients with psoriatic spondyloarthropathy have a higher frequency of peripheral arthritis than patients with AS.[36] The changes noted in the spine in patients with PsA are similar to those noted in patients with ReA. HLA-B27 occurs in a much higher frequency in AS than in PsA, whereas the PsA associated HLA antigens (HLA-B13, B17, B39, and Cw6) occur more frequently in that disease than in AS.

Extra-articular Features of PsA

The main extra-articular feature of PsA is the presence of skin and nail lesions. As noted earlier, the majority of patients present with their skin lesions prior to the joint manifestations. The skin lesions tend to be those of psoriasis vulgaris, although in a lower frequency guttate psoriasis may be present. As noted, the skin lesions may be hidden and need to be searched for if the correct diagnosis is to be made. The relationship between skin and joint man-

ifestations of PsA is not uniform. It was initially thought that patients with more severe psoriasis tended to develop arthritis. This notion was based on the fact that studies of PsA among patients hospitalized for psoriasis tended to show a higher frequency of arthritis among these patients than had previously been reported. However, on history, only 35% of the patients recognize that their skin and joint features flare together.[77] More formal attempts to correlate skin and joint manifestations in PsA suggest that there is no constant relationship between the two.[83] Moreover, the fact that there are patients who are diagnosed with PsA prior to the development of skin lesions is against the notion that the arthritis is more likely to occur in the face of severe psoriasis. Nail lesions, including pits and onycholysis, occur in over 80% of the patients with PsA, and have been found to be the only clinical feature distinguishing patients with PsA from patients with uncomplicated psoriasis.[84] In addition, patients with PsA demonstrate nail ridges. Nail changes are often present in the digits that demonstrate distal joint involvement.

Another articular feature of PsA includes the presence of dactylitis in 48% of the patients. Dactylitis involves inflammation of the whole digit. It is thought to result from both joint inflammation and tenosynovitis. It may affect the fingers and toes and may be the initial manifestation of the disease. Dactylitis is associated with more destructive changes.[85] Patients also develop ***tenosynovitis***, often digital in flexor and extensor tendons, and in the Achilles tendon. As in the other spondyloarthropathies ***enthesitis*** is also a feature of PsA. Patients commonly present with spurs at both the Achilles insertion and the insertion of the plantar fascia.

Iritis occurs in patients with PsA as it does in the other spondyloarthropathies. Iritis also occurs among patients with psoriasis without arthritis, albeit in a lower frequency.[84] Urethritis is also a recognized extra-articular feature in patients with PsA. The other manifestations seen in patients with AS such as the aortic root lesions have also been documented among patients with PsA.

Radiological Changes in PsA

Radiologically, patients with PsA demonstrate an erosive arthritis that can be distinguished from rheumatoid arthritis by the absence of juxta-articular osteopenia, the presence of pencil-in-cup changes, ankylosis, and periosteal reaction. The presence of erosive disease in the distal interphalangeal joints is typical for PsA. Like the clinical presentation, the erosive changes in PsA are more asymmetric than those seen in rheumatoid arthritis. While it has been suggested that radiographic changes in PsA are not as severe as those of rheumatoid arthritis,[86] a study in patients with rheumatoid arthritis and PsA who were matched by age, gender and disease duration demonstrated no differences in the severity of the radiological changes between the two groups.[87] Of interest is the observation that in the same individual, even within the same digit, both joint lysis (as in pencil-in-cup) and ankylosis may occur. The periosteal reaction may occur in the digits, but may also occur in the distal ends of the long bones, particularly the ankles, and may present as hypertrophic osteoarthropathy. An additional radiological feature of PsA is the presence of tuft resorption, particularly in the toes. The differences between the radiological features of the spine in AS and PsA have been noted above. Recent studies suggest that magnetic resonance imaging may be more sensitive in identifying joint manifestations in patients with psoriasis.[88] Current efforts are under way to standardize radiological assessment in patients with PsA.

Etiology and Pathogenesis of PsA

Etiology

The etiology of PsA is unknown. However, as for the other spondyloarthropathies, genetic, immunologic, and environmental factors are considered important. There is a clear familial aggregation of both psoriasis and PsA.[89] A genetic link with the short arm of chromosome 6 (6p) has been demonstrated showing associations with HLA-B13, HLA-B17, HLA-B27, HLA-B38, HLA-B39, HLA-Cw6, and HLA-DRB1*07.[79] Recent genome scans in a large number of multiplex families confirm the linkage of psoriasis to 6p.[90,91,92,93]

Pathogenesis

The pathology of skin and joint lesions in PsA is that of an inflammatory reaction, and there is evidence for autoimmunity as well, perhaps mediated by complement activation.[94] The inflammatory nature of the skin and joint lesions in PsA is demonstrated by synovial lining cell hyperplasia and mononuclear infiltration, resembling the histopathological changes in RA.[95,96] However, the presence of Th1 cytokines (TNF-alpha, IL-1B, and IL-10) in PsA was higher than in a group of RA patients, suggesting that these two disorders may result from a different underlying mechanism.[97] Fibroblasts from the skin and synovia of patients with psoriatic arthritis have an increased proliferative activity and the capability to secrete increased amounts of interleukin-1 (IL-1), IL-6, and platelet derived growth factors.[98,99] A recent study shows that erosive disease in PsA is associated with increased osteoclast precursors in the peripheral circulation.[96,100]

There is some evidence to suggest that trauma may be a trigger in PsA.[101,102] The role of infection in the pathogenesis of PsA has been suggested. Initially streptococcus was thought to be responsible for the development of both psoriasis and PsA,[103] although the reactivity to streptococcal antigens was similar in patients with PsA and those with rheumatoid arthritis.[104] Increased prevalence of PsA in patients with HIV infection has been documented.[105]

Winchester proposed a three-cell model which incorporates genetic, immunological, and environmental influences.[106] The model is based on dendritic cell presentation of peptides to CD8+ and CD4+ T-cells, since it has been recognized that CD4 response is required to activate CD8 cells. This would explain an interaction between class I and class II molecules in the susceptibility to disease progression in PsA.[107]

Diagnosis of PsA

There are no validated criteria for the diagnosis or classification of PsA. The currently used criteria for the classification of PsA, including Moll and Wright's criteria[73] and the European Spondyloarthropathy Study Group[34] are not sensitive enough to identify cases of PsA and thus affect epidemiological studies. Recently, several sets of criteria were compared using an international cohort of 588 patients with psoriatic arthritis and 536 controls with other inflammatory forms of arthritis, primarily rheumatoid arthritis.[108] The CASPAR study demonstrated that most of the criteria sets, except for those proposed by Bennett and the ESSG, had at least 90% sensitivity and sensitivity for PsA. A newly generated set of criteria provided a sensitivity of 92% and a specificity of 99%. This is the CASPAR criteria, which includes the presence of psoriasis (or a history of psoriasis; or family history of psoriasis if current psoriasis is absent); the presence of dactylitis (or history by a rheumatologist if not current); nail lesions; negative rheumatoid factor; and new bone formation (not osteophytes). These criteria now await use in clinical and research settings. The lack of diagnostic criteria has not prevented individual physicians from making the diagnosis, since the presence of an inflammatory arthritis in a patient with psoriasis certainly suggests that diagnosis, and the patterns of presentation and clinical features described above, can alert the physician to the correct diagnosis even in the absence of obvious psoriasis. An international effort is currently underway to develop valid and widely accepted criteria for PsA.

The diagnosis of PsA is easier if the rheumatoid factor is negative. If the rheumatoid factor is positive, one must try to rule out the possibility that the patient has a coexistence of both psoriasis and rheumatoid arthritis. A patient with psoriasis who presents only with distal interphalangeal joint disease may also pose a diagnostic dilemma, since psoriasis and osteoarthritis can coexist; the presence of inflammatory features and the radiologic appearance may help to identify the correct diagnosis. It is more difficult to make the diagnosis of PsA in a patient not known to have psoriasis. Indeed, one study demonstrated that even rheumatologists miss the diagnosis when they forget to ask the patient about the presence of psoriasis, or do not examine the patient appropriately.[109]

Clinical and radiographic features, including the pattern of the arthritis, the distribution, the type of joints involved, and the presence of a spondyloarthritis, may facilitate the diagnosis. It is therefore crucial to perform a careful history and physical examination, looking for hidden psoriatic lesions, particularly in the ears, the hairline, the umbilical area, the anal cleft, and the nails. It is also necessary to perform radiographs to determine the type and extent of joint involvement and, in particular, whether the spine is involved.

Assessment of Disease Activity and Damage in PsA

Both peripheral joints and axial joints, as well as the skin disease, require assessment in patients with PsA. Current efforts through the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) are directed at developing valid and widely acceptable instruments for PsA. The use of the American College of Rheumatology (ACR) joint count has been proven reliable in two studies. The assessment of clinical damage is also reliable.[110] Radiographic damage is an important outcome measure and in one study shown to be detectable before clinical damage.[111]

Treatment of PsA

Treatment of PsA is directed at controlling the inflammatory process. In patients with PsA, both skin and joint manifestations of the disease require attention.[112] Although there is no clear correlation between the skin and joint inflammation in every patient, the skin and joint aspects of the disease need to be treated simultaneously. Initial treatment is with nonsteroidal anti-inflammatory drugs (NSAIDs) for joint disease, and topical therapies for the skin.

Intra-articular injections with corticosteroids are used to control disease in individual joints. It has been suggested that the peripheral arthritis in PsA is more resistant to intra-articular injections, but this has not been proven with a controlled trial. In many patients, this approach is sufficient to control disease manifestations, although some patients have a worsening of psoriasis with NSAIDs. In these cases, a drug belonging to a different family of NSAIDs should be used. In individuals with resistant arthritis, disease-modifying drugs should be used. If the skin disease is well controlled with topical medication, the joint disease can be treated with a variety of second-line or cytotoxic drugs, including gold salts (intramuscularly), antimalarials, D-penicillamine, and azathioprine.

When both skin and joint disease are active, it is preferable to use medications effective for both skin and joints. These include methotrexate, retinoic acid derivatives, psoralen with ultraviolet A light (PUVA) treatment and cyclosporin.[112] Sulfasalazine has been proposed as a medication that works for both skin and joints,[113] but it has a very modest effect and has been somewhat disappointing in clinical practice.[114]

Recent controlled studies demonstrate the efficacy of the anti-TNF agents etanercept,[115,116] infliximab,[117,118] and adalimumab.[119] These agents have all been proven effective for both skin and joints manifestations of PsA. These anti-TNF agents have now been approved by the FDA and the Canadian HPB for use in PsA and psoriasis.

Several T-cell modifiers have been tested in PsA. Alefacept, a LFA3 receptor, has shown efficacy similar to that noted by the anti-TNF agents.[120] Other anti-TNF agents as well as several T-cell modifiers are currently in drug trials.

Prognosis in PsA

PsA may result in significant joint damage and disability.[74] Clinical predictors for disease progression include 5 or more swollen joints at presentation and a high level of medication; a low sedimentation rate appears protective.[121] Actively inflamed joints continue to be predictive of further clinical damage at any time in the course of the disease.[122] The clinical features, however, are not as strong as the HLA markers. HLA markers of disease progression include HLA-B27 in the presence of HLA-DRB1*07, HLA-B39, and HLA-DQB1*03 in the absence of HLA*DRB1*07; HLA-B22 appears protective.[107] In addition, it has been shown that patients with psoriatic arthritis are at an increased risk for death compared to the general population.[123] Severe disease at presentation as manifested by the number of actively inflamed and damaged joints and a high erythrocyte sedimentation rate is a mortality risk.[124]

On the other hand, male gender and a small number of involved joints at presentation identify individuals who may sustain a remission, defined as the absence of inflammatory activity for at least 12 months.[125] Thus it is recommended that patients with PsA be diagnosed and treated as early as possible in order to prevent untoward outcomes.

5. SAPHO Syndrome

SAPHO is a syndrome of Synovitis, Acne, Palmoplantar Pustulosis, Hyperostosis and Osteitis. The synovitis may affect any joints but usually lower extremity joints. Enthesitis has also been recognized as a feature of this syndrome. Skin lesions include acne and pustulosis, the latter occurring particularly on the palms and soles. These features occur in the presence of osteitis that commonly affects the clavicle, but may affect the mandible or other bones, and may present with a picture of osteomyelitis. There is evident hyperostosis in the affected areas. Unilateral sacroiliitis has been reported.[126,127,128]

It is not clear whether SAPHO represents a subset of PsA, or a separate disease entity. Helliwell et al[81] felt that it should be classified as PsA, but Kane et al recently suggested that it should not.[126] The pathogenesis of the syndrome is unknown. There is no association with HLA-B27. *Propionibacterium acnes (P acnes)* is suspected to be involved in the pathophysiology of SAPHO syndrome, since it has been isolated repeatedly through open surgical bone biopsy.[129] Long-term follow up of patients with the SAPHO syndrome indicates generally a good prognosis. Most patients respond to nonsteroidal anti-inflammatory medications or intra-articular steroid injections but some may require disease-modifying drugs.[130] The use of pamidronate in SAPHO syndrome has been suggested.[131]

6. Arthritis of Inflammatory Bowel Disease

While arthritic manifestations may occur in individuals with a variety of bowel conditions, this chapter deals only with the arthritis that complicates inflammatory bowel disease, including Crohn's disease and ulcerative colitis. Arthritis occurs in up to 20% of patients with Crohn's disease or ulcerative colitis. Some patients actually present with the inflammatory arthritis before the diagnosis of inflammatory bowel disease is recognized. It may begin at any age, but occurs most often in young adults. It affects males and females in an equal distribution. Recent evidence suggests that the occurrence of spondyloarthritis among patients with inflammatory bowel disease has been greatly underestimated. In a recent study, 39% of 122 patients with inflammatory bowel disease were found to have associated spondylitis.[133] Similarly, features of bowel inflammation have been recognized among patients with spondyloarthritis.[134]

Clinical Features of Inflammatory Bowel Disease Arthropathy

The pattern of arthritis is variable.[132] It may be migratory or additive. It is commonly asymmetric, affecting primarily the lower extremity joints. In some cases, however, particularly those with ulcerative colitis, it may be indistinguishable from rheumatoid arthritis. Deformities are rare. In ulcerative colitis the activity of the arthritis parallels the activity of the bowel inflammation. In addition, there are granulomas of bones and joints and periostitis.

The spondyloarthropathy of inflammatory bowel disease constitutes 10% to 20% of the arthropathy. Clinically it is very similar to that of idiopathic AS. It occurs more commonly in men than women. The spondyloarthropathy is not affected by the bowel inflammation. There is a much lower association with HLA-B27, but there is a clear familial aggregation of these conditions.[135]

Extra-articular Features of Inflammatory Bowel Disease Arthropathy

The extra-articular manifestations of the arthropathy of inflammatory bowel disease are similar to those of other spondyloarthropathies (Table 2). However, the skin lesions are more likely to be erythema nodosum in Crohn's disease and pyoderma gangrenosum in ulcerative colitis. Other extra-intestinal and extra-articular manifestations include clubbing, which may

occur in patients with either Crohn's disease or ulcerative colitis and may be associated with the presence of erythema nodosum, granulomatous vasculitis, amyloidosis, osteoporosis, and osteomalacia.[132]

Radiological Changes in Inflammatory Bowel Disease Arthropathy

The peripheral joint disease in inflammatory bowel disease may resemble that of the other spondyloarthropathies and tends to be nonerosive, although in the subset with polyarticular disease erosive disease may occur. The axial disease resembles that of idiopathic AS.

Etiology and Pathogenesis of Inflammatory Bowel Disease Arthropathy

Etiology

A link between gut inflammation and arthropathy has been noted in the HLA-B27 transgenic rat. In this animal model, rats transgenic for HLA-B27 and human b2 microglobulin develop a spontaneous multisystem inflammatory disorder resembling a spondyloarthritis, including prominent gut inflammation.[136] In the absence of bacterial flora the inflammation is totally suppressed.[31] The presence of gut pathogens in the joints also supports the link between gut and joint disease in the spondyloarthropathies. Indeed, many patients, including asymptomatic patients with spondyloarthritis, demonstrate gut inflammation on endoscopy.[137]

Pathogenesis

Thus, from a pathogenetic point of view, both genetic and environmental factors lead to inflammatory bowel disease and spondyloarthropathy. The genetic link includes, in addition to HLA-B27, a genetic region on chromosome 16 which has been documented in Crohn's disease as well as in ankylosing spondylitis and psoriasis.[30,138,139] The relationship between gut flora and the inflammatory changes is important.[140] As in the other spondyloarthropathies it is likely that an interplay between genetic, environmental, and immunological factors is responsible for the development of the various manifestations of the disease.

Treatment of Inflammatory Bowel Disease Arthropathy

The treatment of the inflammatory arthritis includes the treatment of the underlying bowel disease. Sulfasalazine has been used for the treatment of inflammatory bowel disease since the 1950s, and it also seems to control the arthritis. Other medications used to control inflammatory bowel disease such as azathioprine and methotrexate, have also been used to treat inflammatory arthritis and may be effective in the enteropathic arthropathy as well. Nonsteroidal anti-inflammatory medications are used with caution in patients with inflammatory bowel disease because of their potential effect on the bowel. The use of anti-TNF agents in the treatment of inflammatory bowel disease may have a beneficial effect on the associated arthritis.[140,141,142]

Prognosis of Inflammatory Bowel Disease Arthropathy

The peripheral arthropathy of inflammatory bowel disease usually does not lead to deformity or damage. The axial disease often follows the course of AS with fusion of the spine and sacroiliac joints with associated deformity and disability.

7. Arthropathies Associated with Other Bowel Disease

Whipple's Disease

Whipple's disease was originally described as a multisystem disease in a physician in 1907. Its cause was eventually identified in the 1990s as an infectious organism, *Tropheryma whippelii,* and eventually cultured from affected tissue.[143,144]

The disease is rare. It affects men more than women, at a mean age of 55 years. Whipple's disease presents with arthritis in 67% of the patients. The arthritis is most commonly peripheral, affecting the large and medium size joints, although the axial skeleton may be affected. While it may be chronic and indolent, it usually does not cause joint destruction. Gastrointestinal complaints including diarrhea or abdominal pain are common. Neurological disorder may be a presenting or dominant feature including confusion, dementia, encephalopathy, central motor deficit, and hypothalamopituitary involvement. Constitutional complaints such as fatigue, weight loss, fever and lymphadenopathy are also common in this disease. Cardiopulmonary manifestations include myocarditis, endocarditis, and pleuritis. Mucocutaneous involvement including hyperpigmentation and nonthrombocytopenic purpura have also been reported.[145]

The treatment of Whipple's disease is with antibiotics. If antibiotics are instituted the prognosis is good; however, untreated the disease may be fatal.

Celiac Disease

Celiac disease is a gluten sensitive enteropathy presenting primarily with diarrhea, malabsorprtion and weight loss. The disease likely results from accumulation of gliadin and other prolamine present in wheat, barley and rye. It is easily treated with a gluten-free diet. Now that there are diagnostic tests, particularly anti-endomesial antibodies directed against tissue transglutaminase (tTG), the prevalence of the disease seems much higher than previously thought and the presentation is somewhat different. Most patients with celiac disease have dermatitis herpetiformis. Arthritis may be associated with this condition.[146] Celiac disease is genetically mediated and there is an association with HLA-DR3/HLA-DQ2 haplotypes as well as with CD28/CTLA4 alleles on chromosome 2. Celiac disease has been found in higher frequency in patients with PsA, but not with SLE, despite the similar genetic association with chromosome 6 alleles. The extra-intestinal manifestations usually respond to a gluten-free diet.

Arthropathy with Intestinal Bypass

Intestinal bypass procedure was a method to induce weight reduction for morbid obesity. This procedure was often complicated by the development of arthritis as well as a dermatitis and is seldom performed today.[147,148] The arthritis may develop as long as 4 years after the procedure, is usually transitory, and does not leave permanent damage. The skin lesions are pustular in nature, reminiscent of gonoccocal infection. It is thought to result from immune complex disease related to bacterial debris which occurs following this procedure. Some patients required reversal of the procedure to improve the joint and skin manifestations.

8. Undifferentiated Spondyloarthropathy

There are patients who present with symptoms and signs of spondyloarthropathy but in whom a definite diagnosis of a specific condition cannot be made. For example, patients who present with an asymmetric oligoarthritis and inflammatory back disease who do not have enough evidence to support the diagnosis of AS, and who do not have extra-articular manifestations to support the diagnosis of ReA, PsA, or inflammatory bowel disease, are generally labeled as undifferentiated spondyloarthropathy. Many of these patients eventually evolve into one or the other members of the spondyloarthropathy group of diseases when they develop clear evidence of sacroiliitis or spondylitis, or an extra-articular feature. A search of antibodies to one of the bacteria implicated in ReA suggested that the majority of patients with undifferentiated spondyloarthropathy may have ReA.[149] The therapeutic management of patients with undifferentiated spondyloarthropathy depends on the presenting manifestations.

The presence of this entity underscores the difficulties with the classification of all spondyloarthropathies and makes genetic linkage studies more difficult to interpret. These patients require follow-up and reassessment to determine whether they evolve over time not only because of the need to accurately describe disease for genetic studies but also for management. One needs to evaluate the requirement for treatment of either bowel or skin manifestations should they occur.

9. Summary

The spondyloarthropathies are a group of inflammatory conditions affecting the peripheral joints and axial skeleton. There are associated features that permit their classification into distinct groups, each requiring special attention to other organ systems. While the conditions share common etiologic factors, there are likely differences that result in different forms of disease expression and prognosis.

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9. Questions

1. Which of the following is not an articular feature of psoriatic arthritis?

A. Dactylitis

B. Achilles tendinitis

C. Asymmetric oligoarthritis

D. Sacroiliitis

E. Para-articular osteopenia

2. Which is not a typical feature of inflammatory axial pain?

A. Pain at night

B. Improvement with rest

C. Reduced forward flexion

D. Morning stiffness

E. Elevated sedimentation rate

3. A 45-year-old man with ankylosing spondylitis has a 12-year-old son with a 3-month history of a painful swollen knee joint. Which of the following is true about the likelihood that the son has juvenile ankylosing spondylitis (JAS)?

A. If there is a history of preceding trauma, it is unlikely he has JAS

B. If he and his father are HLA-B27 positive, the chance of his having JAS is up to 20%

C. If he had a monozygotic twin with ankylosing spondylitis, the chance of him having JAS would be 20%

D. If he has no back pain, there is little likelihood of the diagnosis of JAS

E. If he does not have sacroiliitis on x-ray, it is unlikely that he has JAS

4. Which medication is the least likely to be effective in ankylosing spondylitis?

A. Oral indomethacin

B. Intravenous pamidronate

C. Oral sulfasalazine

D. Intramuscular gold

E. Intravenous infliximab

5. The following features help distinguish psoriatic arthritis from rheumatoid arthritis, except:

A. IgM rheumatoid factor

B. Atlanto-axial subluxation

C. Asymmetric oligoarthritis

D. DIP joint involvement

E. Sacroiliitis

6. Which statement regarding the arthritis of inflammatory bowel disease is true?

A. It is usually symmetric

B. It is often oligoarticular

C. It rarely mirrors the inflammatory bowel disease activity

D. It usually involves the upper extremities

E. Inflammatory back disease is always present

7. In the treatment of psoriatic arthritis, the best result of a randomized clinical trial has been reported with:

A. Methotrexate

B. Gold

C. Prednisone

D. Sulfasalazine

E. Etanercept

8. Patients with seronegative spondyloarthropathies share the following features except:

A. Skin lesions

B. Mucous membrane lesions

C. Scleromalacia

D. Aortic root dilatation

E. Urethritis

9. Which of the following is not a helpful prognostic marker for disease progression in psoriatic arthritis?

A. Disease activity at presentation

B. Elevated ESR at presentation

C. Disease activity at any visit

D. Damaged joints at any visit

E. Level of medication at presentation

10. Which of the following may predispose to reactive arthritis?

A. *C trachomatis*

B. *N gonorrheae*

C. *E coli*

D. *T whipplei*

E. *C difficile*

Answers

1. E.
Radiological para-articular osteopenia is a common feature of early inflammatory rheumatoid arthritis but is unusual in psoriatic arthritis. In fact, periosteal new bone formation may be seen in psoriatic arthritis.

2. B.
Inflammatory back disorders, unlike mechanical back pain, often worsen with rest, with increased pain and stiffness.

3. B.
In the families of patients with AS, 10% to 20% of first degree relatives with HLA-B27 develop AS. The concordance rate of AS in monozygotic twins is up to 60%. Traumatic arthritis is unlikely to last for 3 months but trauma may precipitate an inflammatory arthropathy in a predisposed individual. Patients with JAS may present with a peripheral arthritis without back pain. SI joint x-rays may be difficult to read in young patients prior to epiphyseal fusion and sacroiliitis may not be present at this early stage.

4. D.
There is no evidence that gold is effective for AS.

5. B.

Atlanto-axial inflammation and subluxation occur in both RA and psoriatic arthritis whereas the other features are characteristic of one or the other.

6. B.
The arthritis of IBD is usually an asymmetric, oligoarticular arthritis of the lower extremities which often mirrors the activity of the bowel disease. Inflammatory spine disease is present in 10% to 20%.

7. E.
Etanercept is now approved by the FDA for the treatment of psoriatic arthritis.

8. C.

9. D.

10. A.
Triggers of reactive arthritis include diarrheal infections due to *Shigella*, *Salmonella*, *Yersinia* and most likely urethritis secondary to *Chlamydia trachomatis*.