CHAPTER 10

Reactive and Enteropathic Arthritis

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- In reactive arthritis (ReA), exposure of the host to infectious agents leads to the development of an inflammatory arthritis and other manifestations of systemic disease in the absence of an ongoing infectious process.
- Approximately 50% of ReA and undifferentiated oligoarthritis cases can be attributed to a specific pathogen by a combination of culture and serology. The predominant organisms are *Chlamydia*, *Salmonella*, *Shigella*, *Yersinia*, and *Campylobacter* species.
- The annual incidence of ReA, found to be 28/100,000 individuals in one study, may exceed that of rheumatoid arthritis.
- In a study of 91 individuals exposed to food-borne *Salmonella enteritidis*, 17 (19%) individuals developed ReA. Other studies have estimated the frequency of ReA following exposure to potential etiologic agents to be on the order of 10%.
- Reactive arthritis characteristically involves the joints of the lower extremities in an asymmetric, oligoarticular pattern.
- A dactylitis ("sausage digit") pattern in the feet is typical of ReA.
- Enthesopathy (inflammation at the sites of insertion of tendons and ligaments into bone) and anterior uveitis are often found in ReA, as in other seronegative spondyloarthropathies.
- Cutaneous manifestations of ReA include: keratoderma blenorrhagicum, a papulosquamous rash affecting the palms and soles; nail dystrophy; circinate balanitis, characterized by shallow ulcers on the glans or the shaft of the penis; and oral ulcers, typically painless.
- Enteropathic spondyloarthritis is the inflammatory arthritis that often accompanies ulcerative colitis or Crohn's disease.
- The peripheral arthritis of enteropathic spondyloarthritis is typically pauciarticular, asymmetric, and migratory. It has a predilection for joints of the lower extremities.
- The axial disease of enteropathic spondyloarthritis is indistinguishable clinically from that of primary ankylosing spondylitis.

REACTIVE ARTHRITIS

The role of infection as a triggering factor in the pathogenesis of the various forms of spondyloarthritis (SpA) is implicated with varying degrees of certainty among the SpA subcategories. The very definition of reactive arthritis (ReA)—a sterile synovitis following an extra-articular infection—clearly implicates infection in its defining features, and ReA occupies the conceptual ground somewhere between septic arthritis and the classic autoimmune rheumatic diseases, such as rheumatoid arthritis (RA). An etiologic classification has fueled the search for definitive links between particular pathogens and ReA. Many of these studies are based on guilt by association, in that the demonstration of a particular immune response profile by serology or cellular responses leads to identification of the causative pathogen even when there is no direct demonstration of the organism or its antigens in synovial tissues or fluid. The predictive power of a diagnostic microbiology test, however, critically depends on the prevalence of positives in the healthy population at large (1), and this is an important consideration in the case for causality in ReA.

Epidemiology

Studies on the epidemiology of ReA have provided insight into the frequency of this complication of enteric infections. Data indicate that approximately 50% of ReA and undifferentiated oligoarthritis cases can be attributed to a specific pathogen by a combination of culture and serology. The predominant organisms are *Chlamydia, Salmonella*, *Shigella, Yersinia,* and *Campylobacter* species (2). Species-specific analysis of serological responses to pathogens might increase this detection rate further (3). A prospective study of the annual incidence of inflammatory joint disease in Sweden found that the annual incidence of ReA (28/100,000) exceeded that of RA (24/100,000), empha-

sizing the importance of ReA in the overall burden of rheumatic diseases (4). Studies on both sporadic (5) and outbreak-related (6) *Salmonella typhimurium* infections have provided further support for the role of *Salmonella* spp in triggering ReA. The frequency of ReA in this context has generally been in the range of 10% (6), but in a study of 91 individuals exposed to food-borne *Salmonella enteritidis,* 17 individuals developed ReA, indicating that this might be more frequent than previously thought (7). In a population-based study, it was determined that ReA is common after campylobacter infections, with an annual incidence of 4.3/100,000 (8). These incidence figures are no doubt strongly influenced by the unique aspects of a particular population under study: ReA appears to be more prevalent in Alaskan Eskimo populations (9), for example, and the incidence of ReA after a salmonella outbreak appears to be lower in children than adults (10).

Clinical Features of Reactive Arthritis

Reactive arthritis is characteristically a lower extremity, asymmetric oligoarthritis. The pattern may be additive. Hip disease is uncommon and exclusively upper extremity involvement is extremely rare. The joints are typically warm, swollen, and tender, and can mimic a septic arthritis, reminding that aspiration of synovial fluid and cultures are mandatory when assessing such patients. A dactylitis pattern in the feet is not uncommon.

Enthesitis (inflammation at sites of ligamentous attachment to bone) is a characteristic feature of ReA. Achilles tendonitis and plantar fasciitis are the most common sites, but pain in the iliac crests, ischial tuberosities, and back can be seen. This aspect of the disease can be disabling, with marked restriction in weight bearing and ambulation.

Low back pain and buttock pain, reflecting sacroiliac joint inflammation, occurs in up to 50% of cases, but progression to ankylosing spondylitis (AS) is uncommon. The latter event is strongly associated with human leukocyte antigen (HLA)-B27.

The extra-articular features of ReA can often be helpful in diagnosis, particularly in circumstances when it is difficult to identify a triggering infection. Keratoderma blenorrhagicum is a papulosquamous rash most commonly affecting palms and soles. The lesions can be indistinguishable clinically and histopathologically from pustular psoriasis. Nail dystrophy can occur with ReA, further highlighting the clinical overlap of some features with psoriatic arthritis. Circinate balanitis presents as shallow ulcers on the glans or the shaft of the penis, and is plaquelike and hyperkeratotic. Dysuria and pyuria present an interesting clinical feature because urethritis can be the clue to the inciting infection (as in chlamydial urethritis) or can be an extra-articular feature of postdysenteric ReA. The distinction is important because there may be great concern on the part of the patient about a possible sexually transmitted disease when genital symptoms occur, and a discussion with the patient (and often the spouse) becomes a key element in care. Oral ulcers on the hard palate or tongue are typically painless, so the patient may be unaware of their presence in the mouth. Acute anterior uveitis occurs in 20% of patients at some point during the course of ReA. As in the case of evolution into AS, whether the uveitis is triggered by the antecedent infection or is a feature of a common genetic predisposition has not been resolved.

Pathogenesis of Reactive Arthritis

With respect to ReA, the most common triggering urogenital agents are urogenital (*Chlamydia* spp) and enteric (*Shigella, Salmonella, Yersinia,* and C*ampylobacter* spp) pathogens (11). Substantial regional differences are evident, however, particularly with regard to the enteric pathogens (12). *Chlamydia* spp are regarded as the most common causative agents in ReA. *Chlamydia* DNA, mRNA, rRNA, and intact *Chlamydia*-like cells have been found in synovial tissues and peripheral blood of ReA patients (13,14). The mechanisms accounting for the persistence of *Chlamydia* and the thwarting of host immune defenses have been studied from several perspectives. In chronic disease, altered regulation of specific *Chlamydia* genes is apparent, with reduced expression of the major outer membrane protein and increased expression of heat shock protein (HSP) and lipopolysaccharide (LPS). *Chlamydia* spp can also downregulate the expression of major histocompatibility complex (MHC) antigens on the surface of infected cells. *Chlamydia* spp may induce T-cell apoptosis by stimulating the local production of tumor necrosis factor (TNF) (15). There is also evidence that *Chlamydia* spp can alter host response to the organisms by inhibition of host cell apoptosis, by reducing the release of cytochrome C, and by sequestering protein kinase C delta in the membrane of the organisms' vacuoles (16). Newer analytic techniques are being used to probe synovial fluids and tissues for evidence of prior or current microbes (17,18).

Serological studies have previously provided suggestive evidence that certain Gram-negative bacteria, notably *Klebsiella pneumoniae*, contribute to the pathophysiology of AS. The implication of such studies is that AS may be a form of ReA. One recent analysis, however, which addressed both humoral and cellular host immune responses, found no evidence to support the notion that *K. pneumoniae* has a pathogenic role in AS (19). LPS in synovial tissue is a potent macrophage stimulator and

this could set the stage for persistence of activated macrophages within the synovium and for ensuing chronic inflammation. One unresolved issue is the mechanism by which antecedent infection can induce inflammation and erosions in a joint in the absence of viable organisms. Synovial fibroblasts might have an intermediary role in this sequence of events. In laboratory models, synovial fibroblasts infected with *S. typhimurium* mediate osteoclast differentiation and activation (20).

Human Leukocyte Antigen-B27 and Direct Host–Pathogen Interactions

The conventional role ascribed to class I HLA molecules such as HLA-B27 is the presentation of processed peptides to CD8+, cytotoxic T lymphocytes (CTL). It has been difficult to demonstrate that such CTL mediate the chronic inflammation that is the hallmark of SpA, however. Two points related to HLA-B27 may be relevant. First, HLA-B27–positive cells kill *Salmonella* less efficiently than do control cells (21). Second, LPS stimulation results in a more pronounced increase in nuclear factor κB activation and TNF secretion in HLA-B27–positive cells (22).

This phenomenon of more permissive intracellular replication of *Salmonella* might depend on the unique characteristics of the HLA-B27 B pocket, in particular the glutamic acid residue at position 45 (23). In contrast, some investigators have found that HLA-B27 expression alters neither the rates of infection nor the rate of replication of *C. trachomatis* in cell lines (24). Using synoviocytes harvested from HLA-B27–positive patients, it was observed that HLA-B27 had no direct role in either the internalization of *S. typhimurium* or in the kinetics of intracellular killing (25). A biochemical approach has been used to examine endogenously labeled HLA-B27–bound peptides by mass spectrometry (26). This technique allows investigators to radiolabel peptides that are specifically bound to the HLA-B27 molecule, and thereafter to isolate these peptides for characterization. Using this approach, there was no evidence of significant changes in the range of peptides that were bound by the HLA-B27 molecule after infection of the target cells with *S. typhimurium*. Although this does not exclude a role for altered CTL recognition of infected HLA-B27–positive target cells, harvesting arthritogenic peptides using such a biochemical approach will be an extremely challenging undertaking using current methods.

Human Leukocyte Antigen-B27 and Host Immune Responses

The strong association between HLA-B27 and SpA has indirectly implicated microbial antigen-specific, MHC class I–restricted CD8+ CTLs as having a role in the pathogenesis of these diseases. CD8+ T cells in synovial fluid can express a heterogeneous array of natural killer (NK) cell receptors (27), which might modulate their cytotoxicity and contribute to disease pathogenesis. An analysis of the specificity of T-cell clones demonstrated that target cells pulsed with *Yersinia* HSP60, but not with other *Yersinia* proteins, were successfully lysed by CTLs, and that this killing was controlled by B27 (28). A single nonamer derived from *Yersinia* HSP60 was the dominant epitope in this recognition event. Using a computer-generated algorithm that incorporated HLA-B27 binding motifs and proteosome-generated motifs, an approach has been undertaken to identify immunodominant peptides from *C. trachomatis* (29). Nine peptides identified using this method proved to be stimulatory for CD8+ T cells, and many of these same peptides were recognized by CD8+ T cells derived from patients with ReA. A recent study successfully used HLA-B27 tetramers to identify low frequency antigen-specific T cells in *Chlamydia*-induced reactive arthritis (30). Such cells could be expanded ex vivo, suggesting a functional capability that might contribute to the arthritis.

Molecular Mimicry

Whether microbial peptides share functional homology with self-proteins such as HLA-B27 itself remains unknown. There is some supportive evidence for this notion of molecular mimicry in SpA (31). This theory postulates that an autoimmune process can ensue after an infection if there is some degree of cross-reactivity in host and microbial antigens. But several important questions need to be addressed. For example, the target organ specificity of seronegative spondyloarthropathies remains unexplained, as does the apparent frequency of homologous sequences, even among bacteria not commonly thought to be arthritogenic on clinical grounds.

An immunodominant epitope from the *S. typhimurium* GroEL chaperonin molecule (a member of the HSP60 protein family) was recognized by CTLs after natural infection in mice (32). These CTLs cross-reacted with peptides derived from mouse HSP60. A dodecamer derived from the intracytoplasmic tail of HLA-B27 was found to be a natural ligand for disease-associated HLA-B27 subtypes, but not for non–disease-associated subtypes. This peptide showed striking homology to a region of the DNA primase from *C. trachomatis*, indicating that some molecular mimicry exists between HLA-B27–derived and chlamydial peptides (33). In a study investigating CTL recognition in B27-transgenic animals (34), it was observed that these animals are tolerant to immunization with B27 DNA, but if splenocytes from these animals are exposed to *Chlamydia* spp in vitro, then autoreactive B27-specific CTLs are

generated. This indicates a dynamic interrelationship between the pathogen and host B27 that might have important implications for the pathogenesis of ReA. These interactions might result in a break in self-tolerance, or perhaps an impaired clearance of the organism on the basis of impaired recognition of the organism as non-self.

Therapy for Reactive Arthritis

First-line treatment of ReA includes nonsteroidal anti-inflammatory drugs (NSAIDs), which in most cases prove adequate for control of the acute synovitis and enthesitis. Intra-articular corticosteroid injections can be useful for a monoarthritis. Second-line agents for persistent synovitis have included sulfasalazine and methotrexate, but there are few controlled trials to objectively evaluate efficacy. Because the triggering event in ReA is infection, there has been particular interest in the role of antibiotics in the treatment of ReA. Some studies to date indicate that only *Chlamydia*-induced ReA is responsive to antibiotic treatment, raising the question of fundamental differences between ReA induced by this pathogen and disease triggered by enteric pathogens. The cellular basis for such differences, if genuine, are not clear.

A 3-month, double-blind, randomized, placebo-controlled study found no benefit of ciprofloxacin treatment in patients with ReA and undifferentiated oligoarthritis (35). In subgroup analysis, however, ciprofloxacin was better than placebo in *Chlamydia*-induced ReA, but not in *Salmonella*- or *Yersinia*-induced ReA. A subsequent report showed that lymecycline therapy decreased the duration of acute arthritis in *Chlamydia*-induced ReA, but not in patients with ReA induced by other pathogens (36). Of 17 patients followed for 10 years in this study, 1 patient had AS, 3 had radiographic sacroiliitis, and 3 had radiographic changes in peripheral joints, but long-term lymecycline treatment did not change the natural history of the disease.

A 3-month trial of doxycycline for chronic SpA showed this drug to be no better than placebo for reducing pain or improving functional status, but the causative organism was only identified in a few patients (37). In a group of patients with undifferentiated SpA, it was reported that a combination of doxycycline and rifampin was superior to doxycline alone, although no placebo was included in the design (38). In a 4- to 7-year follow-up of an earlier ReA trial, it was noted that chronic arthritis developed in 41% of patients initially treated with placebo, in contrast to 8% of patients initially treated with ciprofloxacin, suggesting that long-term prognosis might be favorably influenced by antibiotic treatment (39). Recently the results of a 3-month, placebo-controlled trial of azithromycin in ReA were reported (40). Azithromycin, given orally for 13 weeks, was ineffective in ReA, based on the data from 152 patients who were analyzed for a response.

ENTEROPATHIC SPONDYLOARTHRITIS

The arthritis accompanying the inflammatory bowel diseases (IBDs)—Crohn's disease (CD) and ulcerative colitis (UC)—is included in the family of spondyloarthritis because so many clinical features of this arthritis are shared with other members of this family of disorders. In contrast, the arthritis associated with Whipple's disease and celiac disease, albeit enteropathic by definition, are generally not considered part of the spondyloarthritis spectrum. Arthritis occurs in 10% to 22% of patients with IBD, with a higher prevalence in CD than in UC. Arthritis may precede the gastrointestinal (GI) symptoms by lengthy periods of time, and the patients may be regarded as undifferentiated SpA until the IBD declares itself. The studies of Mielants and Veys have provided evidence that patients with undifferentiated spondyloarthropathies (uSpA) and even AS may have subclinical bowel inflammation that plays an important role in triggering and perpetuating joint inflammation (41). One 20-year follow-up study of patients with IBD reported musculoskeletal features in 30% (42). Another study, employing computed tomography scans, detected sacroiliitis in 45% of patients with CD complaining of back pain (43). Magnetic resonance imaging (MRI) is the most sensitive means of detecting sacroiliitis in IBD patients. Asymptomatic sacroiliitis may occur in 14% of patients with IBD (44). HLA-B27–positive patients with CD have a high likelihood of progressing to frank AS. Enteropathic arthritis can occur in a peripheral, axial, or mixed pattern.

Peripheral Arthritis

The arthritis is typically pauciarticular and asymmetric, and may occur in a migratory pattern in some patients. In one study, 6% of uSpA patients developed CD 2 to 9 years after the onset of arthritis (45). The arthritis is typically nonerosive, occurring in intermittent attacks lasting up to 6 weeks (46). There is a predilection for lower extremity joints. Dactylitis and enthesitis reiterate the close relationship to the SpA family. The activity of the peripheral arthritis generally correlates well with the degree of active bowel inflammation, particularly in UC. Indeed, colectomy performed for control of UC can be associated with a complete arthritis remission. The same is not true of surgical interventions for CD.

Axial Arthritis

The axial pattern of enteropathic arthritis is indistinguishable clinically and radiographically from primary AS, although some studies have observed that severity, defined by spinal mobility impairment, is enhanced in IBD-related spondylitis in comparison with primary AS (47). Unlike the peripheral arthritis, axial disease in IBD does not parallel the activity of the bowel disease, and may precede it. Similarly, surgical therapy of UC or CD has no impact on the associated spondylitis. An association with HLA-B27 is seen in axial but not in the peripheral form of enteropathic arthritis.

Nonarticular Complications of Inflammatory Bowel Disease

Skin lesions can be seen in up to 25% of patients. Erythema nodosum tends to mirror the activity of the bowel disease and can often parallel the activity of the peripheral arthritis. Pyoderma gangrenosum, with painful deep skin ulcerations, is a more serious skin manifestation but is less common. Acute anterior uveitis can be seen in up to 11% of patients and is usually the unilateral, transient pattern of eye inflammation characteristic of SpA patients. CD may also be associated with a granulomatous uveitis that is more chronic. Recurrent oral ulcerations may reflect the activity of underlying CD.

Diagnostic Studies

Anemia is common in enteropathic SpA, reflecting both the anemia of chronic disease and GI blood loss. C-reactive protein and erythrocyte sedimentation rate are usually elevated when the disease is active. Rheumatoid factors and antinuclear antibodies are absent in most patients. Radiographic studies of peripheral joints generally do not reveal erosive changes, but a destructive process in the hip can occur. Imaging of the sacroiliac joints and spine are usually similar to primary AS, although a higher frequency of asymmetric sacroiliitis and zygapophyseal joint ankylosis has been reported (48).

Genetics

The peripheral arthritis of IBD is not associated with HLA-B27, whereas the axial form of arthritis is, although to a lesser extent than primary AS (33% B27-positive for the former vs. 85% for the latter). CD has been associated with mutation in the *NOD2* (*CARD15*) gene on chromosome 16. This is of interest in the pathogenesis of CD because *NOD2* plays an important role in innate immunity to pathogens and indirectly implicates microbial triggers in IBD. But studies to date have found no significant relationship between CARD15 and SpA and indicate no enhanced risk for primary AS associated with this gene. However, CARD15 mutations may be found more commonly among patients with CD complicated by sacroiliitis (49).

Treatment

Therapies for enteropathic arthritis follow the same principles as those guiding treatment of SpA in general. NSAIDs are first-line treatment for joint inflammation in both axial and peripheral disease. The cautionary note in these patients, however, is that NSAIDs may exacerbate underlying IBD, particularly UC. NSAID-related adverse events may also mimic a flare of IBD and complicate management. Decisions on NSAID use should be undertaken jointly by the rheumatologist and the gastroenterologist.

Sulfasalazine, which has a role in the treatment of colonic inflammation in IBD, has been effective in treating peripheral, but not axial, arthritis in these patients. Studies that address the efficacy of methotrexate in the peripheral form of enteropathic arthritis are lacking. Intra-articular glucocorticoid injections can be used for flares of the peripheral arthritis. Budesonide, a glucocorticoid with first-pass hepatic metabolism and fewer systemic side effects as a result, has been used increasingly for CD flares, but there are no studies to date addressing the effect of this steroid on enteropathic arthritis. In RA, budesonide has not found to be superior to prednisone therapy (50).

Anti-tumor necrosis factor therapies have had a major impact on the therapeutic approach to IBD and to the associated joint diseases. Striking differences in IBD are apparent between different modes of TNF inhibition, however, with infliximab (a monoclonal antibody) showing efficacy for many patients with IBD—particularly CD—but etanercept (a soluble fusion protein) being ineffective. Etanercept can control the arthritis associated with CD while having no effect on the bowel disease itself (51). Infliximab mediates the healing of fistulas in CD and also helps maintain disease control. Recent studies have demonstrated that infliximab is as effective for both axial and peripheral arthritis associated with CD as it is for primary AS (52).

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