Reactive Arthritis

GENERAL FEATURES

- 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.

REACTIVE ARTHRITIS

The role of infection as a triggering factor in the pathogenesis of the various forms of spondyloarthropathies (SpA) is implicated with varying degrees of certainty among the SpA subcategories. The very definition of reactive arthritis (ReA)—a sterile synovitis following an extraarticular 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, 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. Species-specific analysis of serological responses to pathogens might increase this detection rate further. 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), emphasizing the importance of ReA in the overall burden of rheumatic diseases. Studies on both sporadic and outbreak-related *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%, 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. In a population-based study, it was determined that ReA is common after campylobacter infections, with an annual incidence of 4.3/100,000. 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, for example, and the
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. Adactylitis 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 planter 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 blennorrhagicum 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 Campylobacterspp) pathogens. Substantial regional differences are evident, however, particularly with regard to the enteric pathogens. Chlamydia spp are regarded as the most common causative agents in ReA. Chlamydia DNA, mRNA, rRNA, and intact Chlamydia-like ells have been found in synovial tissues and peripheral blood of ReA patients. 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 pacific 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). 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. Newer analytic techniques are being used to probe synovial fluids and tissues for evidence of prior or current microbes.

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. 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...
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. Second, LPS stimulation results in a more pronounced increase in nuclear factor κB activation and TNF secretion in HLA-B27 positive cells.

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. 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. 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. A biochemical approach has been used to examine endogenously labeled HLA-B27-bound peptides by mass spectrometry. 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, 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. 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. 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. 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. 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. 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. In a study investigating CTL recognition in B27-transgenic animals, 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 antiinflammatory 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. 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. 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. In a group of patients with undifferentiated SpA, it was reported that a combination of doxycycline and rifampin was superior to doxycycline alone, although no placebo was included in the design. 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. Recently the results of a 3-month, placebo-controlled trial of azithromycin in ReA were reported. Azithromycin, given orally for 13 weeks, was ineffective in ReA, based on the data from 152 patients who were analyzed for a response.