Clinics in Dermatology (2015) **33**, 531–537

Clinics in Dermatology

Seronegative reactive spondyloarthritis and the skin

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Abstract Spondyloarthritidies represent a group of conditions affecting the axial and peripheral muscoloskeletal apparatus and are often associated with psoriasis, infections, and inflammatory bowel diseases. Other diseases included in this category are psoriatic arthritis, ankylosing spondylitis, and enteropathic arthritis. Reactive arthritis is an elusive spondyloarthritis, commonly occurring 1 to 3 weeks after a digestive or a genitourinary tract infection, in which microorganisms do not infect the joint directly. Reactive arthritis is classically characterized by large-joint arthritis, urethritis in men and cervicitis in women, and eye inflammation (usually conjunctivitis or uveitis) but encompasses numerous other symptoms and signs, including manifestations of dermatologic interest such as keratoderma blenorrhagicum and circinate balanitis. The diagnosis of reactive arthritis is clinical, and the infectious agent cannot always be identified due to disease latency after the infection. Most cases are self-limiting, but reactive arthritis may become chronic in 30% of cases. Treatment options include anti-inflammatory drugs, steroids, and sulfasalazine; biologic agents, such as tumor necrosis factor α (TNF-α) blockers, have been recently used, but there are only a few randomized clinical trials on the treatment of reactive arthritis. The effectiveness of antimicrobials needs further evaluation.

General terms

Reactive arthritis (ReA) (previously including Reiter syndrome, an eponym now abandoned due to its connections to the late Hnad Reiter and his involvement in the crimes of Nazi fascism) is a disease characterized by a classic clinical triad represented by inflammatory arthritis, urethritis in men and cervicitis in women, and eye involvement in the form of conjunctivitis or uveitis. ReA further represents a broader group defined as the onset of inflammatory arthritis—usually involving large peripheral joints—after a digestive or genitourinary tract infection, in which microorganisms do not infect the joint directly, although different studies have found that antigens can be detected in the synovial fluid of affected joints.[1] ReA is a subgroup of seronegative spondyloarthritis, which includes different forms of seronegative arthritis, affecting the spine and with a clear environmental trigger[2] leading to the clinical phenotype in a susceptible individual.[3] Different skin conditions are associated with

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http://dx.doi.org/10.1016/j.clindermatol.2015.05.004
0738-081X/

seronegative spondyloarthritis, especially psoriasis, which is associated with psoriatic arthritis and affects almost 30% of patients presenting with the skin condition. Other skin manifestations are represented by keratoderma blenorrhagicum, circinate balanitis, and oral ulcers.

History

ReA was described by Hans Julius Reiter (1881-1969) in 1916 with the classic triad of symptoms in a soldier after a digestive infection; Reiter attributed it to *Treponema pallidum* infection.[4] ReA is a disease with an ancient history; in fact, around 460 BCE Hippocrates was probably the first to postulate the association between arthritis and genitourinary infections, writing that "a youth does not suffer from gout until sexual intercourse."[5] Even in ancient Egypt, ReA was reported in a medical papyrus.[6]

Christopher Columbus may have developed ReA, probably after a *Shigella flexneri* infection in 1494. Later, he had different arthritis flares that were attributed to gout.[5] By the following decade, such arthritis was already mentioned in Mexican texts.

Benjamin Brodie (1783-1862) and Pierre Emile Launois (1856-1914) made the first two descriptions of the classic triad in the 1800s, and during the same period Astley Cooper (1768-1841) associated venereal disease with arthritis.[5] During both World Wars, many cases of ReA were observed, being referred to as Fiessinger-Leroy-Reiter syndrome.[7,8] Lately, the term *Reiter syndrome* has been abandoned due to Reiter's conducting medical experiments on concentration camp prisoners.[9] The disease is now referred to as ReA.

Epidemiology

The epidemiology of ReA is difficult to assess due to the lack of diagnostic and classification criteria and also due to the broad spectrum of clinical manifestations of the disease. ReA is more common in young adults, 20 to 40 years of age, and is rarely observed during childhood. Both sexes are equally affected when the cause is a digestive infection, but when it follows a *Chlamydia trachomatis* infection, it is more common in men. The prevalence of ReA is higher in white patients, probably due to the higher frequency of the human leukocyte antigen (HLA) B27 allele in this population.[10,11] ReA is generally seen in sporadic cases, but familial aggregation has been reported, especially in association with the HLA-B27 allele.[4] The annual incidence of ReA is estimated to be 30 in 100,000 cases, depending on the criteria applied for the diagnosis.[3,12,13]

ReA has also been associated with HIV and AIDS, and in particular the positivity of the HLA-B27[14] leads to higher risk of severe ReA.[15,16]

Genetics and infectious agents

Although twin data are lacking,[17] the HLA-B27 allele has been associated with ReA, but this genetic test is not routinely recommended as a diagnostic tool for two main reasons: First, nearly 90% of patients with ankylosing spondylitis, another disease included in the group of spondyloarthropathies, carry this allele; second, in the general population the association between ReA and HLA-B27 positivity has not been confirmed.[18] More likely, we can assume that patients carrying the HLA-B27 allele suffer from a more severe ReA disease and may develop a disease with a protracted course.[19–21]

The immune response is activated when bacteria enter the mucosal tissue, either digestive or genitourinary, similar to other scenarios.[22] It is not yet clear what favors this invasion, and some host factors determine the incomplete elimination of the microorganisms and the permanence of their DNA and RNA in the synovial fluid, as will be illustrated later. Arthritis requires adaptive immune response activation; $CD4^+$ T cells along with $CD8^+$ T cells trigger articular inflammation, leading to an unbalanced T helper 2 (Th2) cytokine production.[23–25] Based on these mechanisms, ReA follows an infection of the digestive or genitourinary tract caused by various microorganisms, including *Chlamydia trachomatis*, *Shigella flexneri*, *Salmonella enteritidis*, *Salmonella typhimurium*, *Salmonella muenchen*, *Yersinia enterocolitica*, *Yersinia pseudotuberculosis*, *Campylobacter jejuni*, *Campylobacter fetus*, *Ureaplasma urealyticum*, and *Clostridium difficile*.[4] Other less common microorganisms involved in ReA include *Neisseria gonorrhoeae*, *Borrelia burgdorferi*, *Chlamydia pneumoniae*, and *Escherichia coli*. These microorganisms are gram-negative bacteria, and all contain a lipopolysaccharide component in their cell walls.[5] The exact mechanism of how these bacteria trigger arthritis is not yet known. Cross-reactivity has been hypothesized due to the association with HLA-B27, and, in fact, antibodies directed against microorganism antigens may have an affinity for HLA-B27; however, more studies are needed to assess this hypothesis because molecular mimicry may play a minor role in the development of ReA. Contrary to the historical definition of ReA, chlamydia DNA and RNA have been found in the joints of patients affected by ReA; moreover, *U urealyticum* has been isolated in the synovial fluid.[26–28]*C trachomatis* and *C pneumoniae* represent the most common causes of ReA and can be found in the synovial fluid and tissue of the affected joints.[26,28,29]

Chlamydiae are the most common microorganisms causing ReA. *C trachomatis* is the most common microorganism involved in sexually transmitted diseases (STDs) worldwide. *C trachomatis* enters through the mucosa of the genitourinary tract, soon causing an infection that is often asymptomatic, especially in women. The incidence of *C trachomatis*–mediated ReA is about 13.6%. *C pneumonia* causes an acute upper respiratory tract infection that is often