Reactive Arthritis: Recent Advances and Clinical Manifestations

Key words: reactive arthritis, spondyloarthropathy, HLA-B27, *streptococcus*

Seronegative spondyloarthropathy and reactive arthritis

Joint pain (arthralgia/ arthritis) is associated with various physical conditions and various rheumatic or non-rheumatic diseases. Rheumatoid factor (RF) and antinuclear antibody (ANA) are good markers of screening for rheumatic diseases. However, there are many rheumatic diseases in which either RF or ANA is not demonstrated in patients' sera. Therefore, it is important to precisely inquire about the patients' past history and present illness precisely and perform a careful physical examination in order to achieve the proper diagnosis.

"Reactive arthritis" is classified as one type of seronegative spondyloarthropathy (SNSA), which consists of ankylosing spondylitis (AS), reactive arthritis (ReA; Reiter's syndrome), psoriatic arthritis and arthritis associated with chronic inflammatory bowel diseases. Typical clinical presentations are RF negative in their sera, axial joint arthritis (sacroiliitis, spondylitis), enthesitis and peripheral oligoarthritis. In many patients, the subtalar, metatarsophalangeal and toe interphalangeal joints tend to be affected. The number of affected peripheral joints is typically less than 5 (oligoarthritis) and are usually asymmetrically involved in the lower limbs. The musculoskeletal symptoms are generally acute in onset associated with constitutional symptoms such as fatigue, malaise, fever and weight loss. The arthritis is usually quite painful. Dactylitis, or "sausage digit", a diffuse swelling of a solitary finger or toe, is a distinctive feature of both ReA and psoriatic arthritis (1–3) (Figs. 1, 2).

Extra-articular manifestations

Tendinitis and fasciitis are characteristic lesions, producing pain at multiple insertion sites, especially the Achilles tendon (Fig. 3), the plantar fascia, and sites along the axial skeleton. Spinal and low-back pain are common features which are caused by insertional inflammation, muscle spasm, acute sacroiliitis or arthritis in intervertebral articulations.

Mucocutaneous manifestations are highly associated in ReA. Keratoderma blennorrhagium is a papulosquamous skin rash that appears most commonly on the sole or palms (Fig. 4). Circinate balanitis is the characteristic lesion involv-

A

B

Figure 1. Dactylitis in Chlamydia-induced reactive arthritis. A: Before treatment, B: After treatment.

ing the glans or shaft of the penis. Oral ulcers, which are shallow and usually painless, may appear on the tongue or hard palate. Acute anterior uveitis occurs in nearly 20% of patients.

Involvement of microorganism infection

Among SNSA, it is an important clinical manifestation that either urogenital or bowel infection is characteristically involved in the development of ReA. Therefore, we should ask patients whether they had an episode of urethritis or

A

B

Figure 2. Sausage digits in *Chlamydia*-induced reactive arthritis.

diarrhea within 4 weeks prior to the appearance of arthritis. *Chlamydia trachomatis* in urogenital infection, *Salmonella enteritidis*, *Yersinia enterocolitica*, *Shigella flexneri* and *Campylobacter jejuni* in bowel infection are microorganisms which are known to induce ReA (1–3). Episodes of *Chlamydia*-induced urethritis are sometimes subtle and often asymptomatic as a case report presented in this issue (4). Therefore, we inquire about any untypical sexual intercourse or ask whether the patient found stain in their underwear.

See also p 509.

Relation to HLA-B27

Typing for HLA-B27 is positive in approximately 70% of Caucasian patients with ReA. Around 7–14% of Caucasian population are positive for HLA-B27, however, less than 1% are positive in the Japanese population. Therefore, the incidence or prevalence of AS or ReA is quite low in Japan as compared to that in the USA or Europe. HLA-B27 is more

Figure 3. Enthesitis: inflammation of the left Achilles tendon insertion area. *Yersinia enterocolitica*-induced reactive arthritis.

likely to be found in patients with complicating sacroiliitis, and spondylitis. Therefore, Japanese patients with psoriatic arthritis and arthritis associated with chronic inflammatory bowel diseases, who have only peripheral joint arthritis, are seldom found to have HLA-B27. In addition to HLA-B27, HLA-B7 and B60 are HLA-B27-related antigens. It has been reported that the majority of HLA-B27 negative Japanese AS patients have HLA-B39 which is molecular homologous to HLA-B27 (5). Reactive arthritis after streptococcal infection of the pharynx or tonsils is reported as post-streptococcal reactive arthritis (PSRA) or tonsillitis-associated reactive arthritis (Fig. 5). This form of reactive arthritis is a different clinical entity from so-called HLA-B27-related “reactive arthritis”. The authors found that HLA-B39 was determined in the majority of patients with tonsillitis-associated reactive arthritis (6).

HLA molecules in general, and class I molecules in particular, evolved in response to specific environmental stresses, and polymorphisms of HLA class I molecules deal with infectious stresses, such as viruses and bacteria. HLA-B27-positive individuals are associated with less efficient intracellular elimination of *Chlamydia* and certain enteric bacteria than HLA-B27-negative individuals. Therefore, the HLA-B27 molecules may contribute to disease susceptibility due to its failure to eliminate intracellular organisms or by presentation of arthrogenic peptides.

Proposed classification criteria and laboratory tests determining *Chlamydia*

Proposed classification criteria and laboratory tests which are recommended for determining *Chlamydia* are listed in Tables 1, 2 (3, 7).

Figure 4. Keratoderma blennorrhagium in Chlamydia-induced reactive arthritis.

Figure 5. Arthritis at ankle joints in patients with post-streptococcal reactive arthritis.

Table 1. Preliminary Classification Criteria for Reactive Arthritis

Major Criteria
1. Arthritis (2 of 3)
Asymmetric
Mono or oligoarthritis
Lower limbs
2. Preceding symptomatic infection (1 of 2)
Enteritis (diarrhea for 1 day, 3 days to 6 weeks before infection)
Urethritis (dysuria/discharge for 1 day, 3 days to 6 weeks before infection)
Minor Criteria (1 of 2)
1. Evidence of triggering infection
Positive urine LCR or urethral/cervical swab for <i>Chlamydia trachomatis</i>
Positive stool culture for ReA related enterobacteria
2. Evidence of persistent synovial infection (A positive immunobistology is generally conceivable, but is not routinely used, as too laborious)
Positive PCR for Chlamydia
Additional Classification
Urogenic or enteric ReA
Acute (≤ 6 mo) and chronic (> 6 mo) ReA
Exclusion Criteria
Other defined rheumatic diseases should be excluded by clinical history and examination and by performing the following tests as a minimum:
Where synovial fluid is available, microscopy, culture, and crystal analysis
Serology for rheumatoid factor, antinuclear antibodies and, where appropriate, anti- <i>Borrelia burgdorferi</i> and antistreptococcal antibodies
Radiology for chondrocalcinosis, joint space narrowing
Definition of Reactive Arthritis
Definitive ReA: First and second major criteria and a relevant minor criterion
Probable ReA: First and second major criteria, but no relevant minor criteria
or
First major criterion and one or more minor criteria

The authors think that these are so-called “diagnostic criteria” but not “classification criteria” since the criteria have “exclusion criteria” and subclassification of “definite ReA” and “Probable ReA”. The style is similar to the ACR 1953 diagnostic criteria for RA.

Table 2. Laboratory Tests a Rheumatologist should Perform in Determining the Diagnosis of ReA

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1. In case of a preceding symptomatic infection in the urogenital tract
Obligatory
Urethral/cervical smear (for Chlamydia) or
Morning urine (for Chlamydia)
Facultative
Chlamydia serology?
HLA-B27?
Synovial fluid PCR (Chlamydia)?
No Yersinia or Salmonella serology is recommended.
2. In case of a preceding symptomatic infection in the enteral tract
Obligatory
Stool culture (enterobacteria)
Yersinia, Salmonella serology
Facultative*
HLA-B27?
No urethral smear, no morning urine, no Chlamydia serology, and no SF PCR are recommended.
3. In case of no preceding symptomatic infection
Morning urine (for Chlamydia)
Urethral smear (for Chlamydia)
Yersinia, Salmonella serology
Facultative*
HLA-B27?
Chlamydia serology?
SF PCR?
No stool cultures are recommended.
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*Recommended by only one-third of the experts. SF: synovial fluid.

Treatment

For Chlamydia-induced ReA, prompt, appropriate antibiotic treatment of acute urethritis is necessary and will prevent subsequent reactive arthritis. Non-steroidal anti-inflammatory drugs benefit most patients to some degree. Sulfasalazine is beneficial to patients with persistent ReA. Immunosuppressive agents such as azathioprine or methotrexate are also effective. Intra-lesional glucocorticoid injection is beneficial for tendonitis and for other enthesitic lesions.

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