Reactive Arthritis

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Overview of Reactive Arthritis

- In reactive arthritis (ReA), exposure to an infectious agent leads to the development of an inflammatory arthritis and other characteristic clinical findings. However, this syndrome occurs 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 frequency of ReA following exposure to potential etiologic agents is between 3% and 10%.
- ReA characteristically involves the joints of the lower extremities in an asymmetric, oligoarticular pattern.
- A dactylitis ("sausage digit") pattern of arthritis in the feet is typical of ReA, as it is of psoriatic arthritis. Enthesopathy and anterior uveitis often occur in ReA.
- Cutaneous manifestations of ReA include:
  - Oral ulcers, typically painless
  - Nail dystrophy
  - Keratoderma blenorrhagicum, a papulosquamous rash that affects the palms and soles
- Circinate balanitis, characterized by shallow ulcers on the glans or the shaft of the penis.
- The presence of HLAB27 increases disease susceptibility but is neither sufficient nor necessary for ReA to occur. Individuals who are HLA-B27 positive tend to have more severe and longer episodes of ReA.

Pearl *Always consider reactive arthritis (ReA) when confronted with monoarthritis in a young adult.*

Comment: ReA most often affects adults between 18 and 40 years of age. This disorder presents as an oligoarthritis, with pain and swelling in only a few joints (often only one). The knee, ankle, or one of the metatarsophalangeal joints is usually affected first (Fig. 9.1). When the patient is a child, ReA must be distinguished from juvenile idiopathic arthritis, particularly the oligoarticular form. Among adult patients, ReA must be differentiated from microcrystalline disorders. Septic arthritis must always be considered and excluded in any patient who presents with monoarthritis.

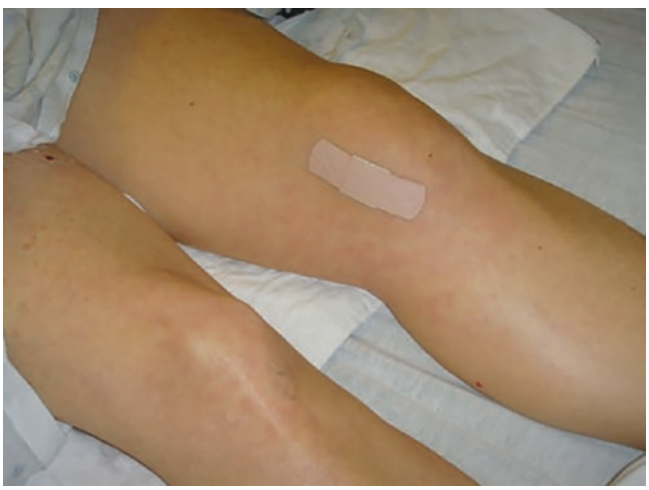

Fig. 9.1 Monoarthritis of the knee in a patient with post-streptococcal reactive arthritis

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Symptoms of ReA may develop before other features of the infection that triggered the inflammation become apparent. Thus, a clear history relating to other features of a spondyloarthropathy (past or present) and exposure to and symptoms of GU or enteric infection should be sought.

Pearl *Acute ReA may mimic septic arthritis.*

Comment: Most often ReA is associated with relatively mild systemic symptoms and characteristic multisite disease. In a few patients, however, monoarthritis is associated with high fever, marked malaise, and touch-me-not pain and swelling in an affected joint. Yersiniosis and salmonellosis are particularly likely to be associated with such systemic features. Septic arthritis may occur in *Campylobacter* and *Salmonella* infections. The culture of organisms from a joint indicates treatment for a septic arthritis, even if the patient's other clinical features are highly consistent with ReA.

Pearl *The only way to differentiate definitively between ReA and septic arthritis is through culture of the synovial fluid.*

Comment: Certain organisms, e.g., *Yersinia* and *Salmonella*, can cause both septic arthritis and ReA. Thus, sampling and culture of the synovial fluid is mandatory in the assessment of a patient with possible ReA. Differentiating gonococcal arthritis from post-genitourinary ReA is a common challenge in this regard. Recall that joint cultures for *Neisseria gonococcus* are frequently negative, even in the setting of disseminated gonococcal infection. This heightens the difficulty in discriminating between gonococcal infections and ReA.

Myth *ReA responds to antibiotic therapy.*

Reality: Despite the role of infections in triggering ReA, cultures of synovial fluid are sterile. There is no evidence that antibiotics alter the long-term course of ReA that follows a gastrointestinal infection and no indication that long-term treatment with antibiotics is effective for shortening episodes of ReA. There remains some uncertainty about the impact of antibiotics on the course of ReA after an infection of the genitourinary tract caused by *Chlamydia*. However, no compelling data support the prolonged use of antibiotics beyond the course required to eradicate the inciting infection (Hamdulay et al. 2006).

Pearl *Dysuria and a genital rash can follow gastrointestinal infections as well as genitourinary infections.*

Comment: A sexually transmitted disease need not be invoked to explain genitourinary features. When genitourinary complaints occur concurrently with an inflammatory arthritis, clinicians may assume that a sexually transmitted disease has been the inciting event. However, urethritis is perfectly compatible with the syndrome of ReA that follows a gastrointestinal infection (Ahvonen et al. 1969). Moreover, circinate balanitis may occur without an antecedent infection of the urogenital tract.

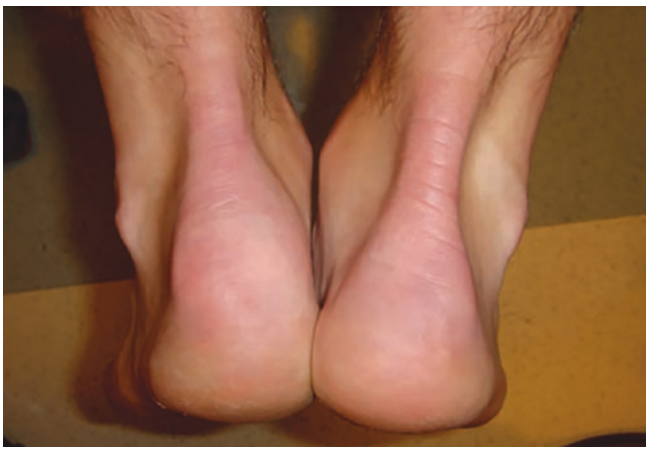

Fig. 9.2 Achilles' tendon swelling at the enthesis of the left tendon

Pearl *The enthesitis of ReA can be the dominant feature of the disease.*

Comment: Enthesitis, particularly Achilles tendonitis and plantar fasciitis, can be profoundly disabling in the acute phase of ReA. Enthesitis overshadows inflammatory joint symptoms in some patients. The patient should always be examined while he or she is standing, to facilitate the detection of Achilles' tendonitis (Fig. 9.2).

Myth *Post-streptococcal ReA is really acute rheumatic fever.*

Reality: In adult patients, post-streptococcal ReA is not accompanied by carditis, chorea, erythema marginatum, or subcutaneous nodules (Barash et al. 2008). Post-streptococcal ReA and acute rheumatic fever are two different entities. The implications of this are significant: long-term antibiotic prophylaxis is not indicated in adults with post-streptococcal ReA.

Pearl *No inflammation, no ReA!*

Comment: ReA is an inflammatory condition associated with genuine signs of joint or enthesial swelling. Tenderness or aching in the joints or periarticular tissues without hard signs of inflammation is not sufficient for the diagnosis. Similarly, nonspecific urethral symptoms in men must not be attributed to ReA if they are not associated with musculoskeletal symptoms that are compatible with ReA. No inflammation, no ReA.

Myth *HLA-B27 typing is a helpful diagnostic test for ReA.*

Reality: Approximately 50% of people with ReA carry the HLA-B27 gene, with the figure being somewhat higher in certain populations. Thus, negative HLA-B27 genotyping does not exclude the diagnosis of ReA. The diagnosis must be founded upon compatible clinical features and compelling evidence of an infection.

Pearl *The presence or absence of HLA-B27 affects clinical disease phenotype.*

Comment: HLA-B27 positivity is typical of patients who have persistent disease and is nearly universal among patients with ReA and uveitis. In addition, 90% of patients with radiographic evidence of sacroiliitis are HLA-B27 positive.

In patients with ReA in sub-Saharan Africa, an aggressive form of disease is observed. These patients are generally HLA-B27 negative but often are infected with the human immunodeficiency virus (Leirisalo-Repo 1998).

Myth *When ReA is suspected, examination of the joint fluid by PCR may reveal the infectious cause.*

Reality: Inflamed joints contain a wide range of bacterial proteins and some bacterial DNA. Some studies have revealed specific *bacterial* DNA (Hannu et al. 2006) and even RNA, indicating probable viability of the bacteria presumed to have caused the arthritis (Hannu et al. 2006). However, bacterial DNA from many different genera have been identified within joint material (Kempsell et al. 2000), and it remains unclear how (or if) to ascribe causality to any of these findings.

Pearl *The uveitis of ReA is anterior, unilateral, and highly symptomatic.*

Comment: ReA is associated with an anterior uveitis that tends to afflict one eye at a time. The contralateral eye may be involved in a subsequent disease flare. The finding of concurrent bilateral disease or disease in the posterior pole of the eye strongly invokes other diagnoses, e.g., sarcoidosis or Behcet's disease.

Patients with the anterior uveitis of ReA have pronounced photophobia, eye pain, ocular erythema, and tearing. Shining a flashlight in the contralateral (uninvolved) eye leads to pain in the involved eye because of the consensual light response, which leads to pupillary narrowing in the inflamed eye and an increase in ocular discomfort. In addition to topical glucocorticoid eyedrops, a mydriatic agent is essential to dilate the involved eye and prevent the formation of synechiae between the pupil and the lens.

Pearl *An episode of ReA may be followed by a prolonged period of non-inflammatory arthralgia.*

Comment: Most episodes of ReA resolve within 12 months (Keat 1983), but the persistence of symptoms following an episode of inflammatory disease is not uncommon in ReA. The explanation for this phenomenon is not clear though it may be a source of great anxiety for patients. Indeed, a psychological element may complicate the clinical picture, requiring great reassurance from the clinician. If all evidence of inflammation has resolved, there is no role for antibiotic treatment or disease-modifying anti-rheumatic drugs (DMARDs).

Pearl *Recurrence of ReA is common.*

Comment: Recurrence of sexually acquired ReA is common (Colmegna et al. 2004). Approximately 50% of such patients suffer subsequent episodes. In contrast, recurrence after enteric infection is uncommon. Patients should be advised about the risk of reinfection leading to recurrence of arthritis and about specific precautions for avoiding reinfection.

The precise role of repeated infections in precipitating recurrences of ReA is not clear. Additional genital tract infections *may be* associated with recurrent ReA, but reinfection with enteric bacteria—even when of the same species as that which caused the initial episode—does not always lead to a recurrence of ReA.

Myth *ReA is precipitated only by gastrointestinal and genitourinary infections.*

Reality: The commonly recognized arthritogenic pathogens are *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, and *Chlamydia*. However, ReA may occur after infection by any portal of entry and may be caused by a large number of other organisms, as well. As an example, cases of ReA following *Clostridium difficile* infections are well described.

In some patients whose clinical features are consistent with ReA, there is no antecedent history of infection. This suggests that this syndrome can result either from subclinical infections or from other environmental (non-infectious) triggers.

Myth *The interval between antecedent infection and ReA is 1 week or less.*

Reality: Although an interval of 1–2 weeks after the inciting infection is typical for the appearance of ReA, this time period can extend to up to 4 weeks. Patients with joint symptoms and other clinical features compatible with ReA must therefore be queried closely about more "remote" occurrences of infections.

Myth *ReA is a chronic disease similar to rheumatoid arthritis.*

Reality: ReA usually consists of either a single attack that runs its course within a matter of months or recurrent episodes of arthritis that last weeks to months between longer periods of remission. A chronic, destructive, disabling arthritis evolves in only a minority of patients.

Pearl *Not all inflammatory back pain symptoms in ReA are caused by spondylitis, sacroiliitis, or both.*

Comment: Some symptoms of low back pain in ReA are caused by enthesitis that involves the pelvic girdle. The pelvis, in addition to the Achilles tendon and the plantar fascia,

is another common site of involvement by enthesopathy. Unrelated, non-inflammatory causes of back pain should not be overlooked even during an episode of reactive arthritis.

Myth *DMARDs should be avoided in ReA.*

Reality: The typical course of ReA is a period of greatest joint activity over 8–12 weeks. Most patients respond satisfactorily to sustained doses of NSAIDs. If the symptoms are not controlled adequately or if the course is more protracted, methotrexate or a biologic agent such as a TNF inhibitor can be added to the NSAID regimen. Intra-articular glucocorticoid injections can be of symptomatic benefit.

Pearl *The appearance of circinate balanitis differs according to whether or not the patient is circumcised.*

Comment: If the male is ***un***circumcised, the lesions of circinate balanitis can appear as multiple, serpiginous, shallow ulcers on the glans or shaft of the penis. These lesions often have raised borders. In ***circumcised*** males, circinate balanitis can appear as dry, hyperkeratotic plaques that are reminiscent of psoriasis.

Pearl *If the arthritis of ReA persists beyond the time usually associated with this condition, consider whether the patient might have psoriatic arthritis instead.*

Comment: The clinical features of ReA overlap significantly with those of many patients with psoriatic arthritis. As examples:

- Asymmetric, oligoarticular patterns of joint disease are present in both ReA and psoriatic arthritis.
- Keratoderma blenorrhagicum, a finding associated with ReA, cannot be distinguished histologically from pustular psoriasis.
- The fingernails and toenails in ReA can become thickened and develop subungual debris and onychodystrophy. However, nail pitting in a patient with inflammatory joint disease clearly favors psoriatic arthritis as the underlying diagnosis.

Pearl *Preventing a recurrence of ReA is influenced more by advice than antibiotics.*

Reality: Safe sex practices are sound advice for all sexually active individuals. Among patients with a history of ReA following a genitourinary infection, such advice should be reinforced with particular vigor. Similarly, for patients who have had episodes of ReA following enteric infections, extra precaution with regard to local food and hygiene should be exercised when traveling to locales where enteric pathogens are common.

Pearl *Post-diarrheal arthritis should always occasion a search for gastrointestinal pathogens before the diagnosis of inflammatory bowel disease (IBD) is rendered.*

Comment: The new onset of joint pain in the setting of diarrhea may indeed herald a case of IBD with accompanying arthritis. However, infectious diarrhea from bacteria, parasites, or toxins must be excluded definitively as the first priority. Sending stool specimens for fecal leukocytes, ova and parasites, and *C. diff* toxin assays are critical in this evaluation.

Pearl *Gonococcal arthritis and ReA are different.*

Comment: The term "gonococcal arthritis" refers to a septic arthritis, often part of a syndrome of persistent gonococcemia in which primary infection with *Neisseria gonorrhoeae* disseminates widely, leading to low-grade fevers, sparse skin lesions, and septic arthritis. The primary infection is usually but not always in the genital tract. The disease responds to appropriate antimicrobial therapy.

The problem arises when aseptic arthritis arises in an individual who also has gonococcal infection. It is unclear whether *Neisseria gonorrhoeae* is a true initiator of ReA, but the prevailing view is that in this circumstance the gonococcal infection is accompanied by an additional simultaneous non-gonococcal infection (e.g., *Chlamydia*) and it is this co-infection that provokes the arthritis.

Pearl *Attempting to identify the presumed causal infection may be very helpful.*

Comment: Frequently the diagnosis of ReA is made (accurately) on evidence of infection—e.g., diarrhea or urethritis—without identification of a specific bacterial pathogen. Because the precise causal link between the bacterium and the arthritis is unknown, this is not a great problem. However, if there is an infection, knowing its cause or excluding some potential etiologies is valuable. A patient who develops severe ReA after bacterial diarrhea associated with ingestion of particular food may be an "index case" that explains a pattern of foodborne illness within a community. Moreover, the diagnosis of chlamydial urethritis offers the opportunity to treat this infection in the patient's sexual partners, who may or may not be symptomatic.

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