Chlamydia-Associated Reactive Arthritis

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Chlamydial infection has been identified as one of the triggers for the syndrome of reactive arthritis since the first concepts of this entity were developed. In various series and especially in the USA, *Chlamydia* has been identified as the preceding infection in 42 to 69% of reactive arthritis patients. The great majority of the literature and experience in this area relates to the genital pathogen, *Chlamydia trachomatis*, although recent reports on *C. pneumoniae* should also be considered [1].

As techniques have improved for the identification of *Chlamydia*, patients who do not meet the criteria for reactive arthritis are also being found with chlamydial antigens or nucleic acids in joints. Zeidler and Wollenhaupt [2] refer to some of these simply as *Chlamydia*-associated arthritis. Many of these patients do have oligoarthritis and probably have similar disease mechanisms. In addition, chlamydial nucleic acids in synovial specimens are also being reported in some patients with rheumatoid arthritis [3], osteoarthritis and even in asymptomatic individuals studied as controls [4]. We must also consider how such cases should be viewed in clinical evaluations, as well as the implications for therapy. Simple identification of bacterial nucleic acid in a joint does not define a disease.

Clinical features

In most cases reactive arthritis is an asymmetric oligoarthritis that involves predominantly the lower extremities. In the patients with *Chlamydia*-associated disease studied by Zeidler and Wollenhaupt [2], the knees were involved in 70%, ankles in 57%, and toes in 35%, but in up to 45% of cases also the wrists or fingers were affected. Sacro-iliac involvement is also common and is especially prominent in HLA B27 positive individuals. Sacro-iliitis was found in 33% of patients with *Chlamydia*-associated arthritis, with an increase to 54% in patients with HLA B27 [2].

The course of *Chlamydia*-associated arthritis requires a more thorough examination. The prognosis has generally been felt to be not as good as that after enteric infection-associated disease. One possibility is that reinfection is more common with *Chlamydia*-related disease, at least in the western world. For example, when Csonka [5] followed reactive arthritis patients from a venereal disease clinic, he found that among those whose disease resolved there were few exacerbations at 1 year but many at longer follow-up. Lerisalo-Repo et al. [6] have been following patients with *Salmonella*-induced reactive arthritis and surprisingly noted that only 20% had returned to complete health at a mean of 11 years. Additional long-term radiological studies are also required. Glennas and coworkers [7] found no erosions in peripheral joints in 25 patients in a 2 year study. Resnick and Niwayama [8] described bony proliferative changes and periostitis, noting the presence of joint space narrowing and erosions. However, it appears that this is less common than in rheumatoid arthritis.

Few studies have reported findings on routine synovial fluid analysis. Our own research of patients with classical reactive arthritis [9] showed a variety of patterns of inflammatory effusions, but a predominance of neutrophils was the most frequent. The so-called Reiter's cells, first noted by Pekin and Zvaifler, consist of mononuclear cells that have phagocytized apoptotic neutrophils. Whether these cells are more or less common with *Chlamydia* compared to other triggers, or if they are ever seen in patients with clinical rheumatoid arthritis who have chlamydial nucleic acids is not known.

Synovial biopsies in reactive arthritis have been reported to show surface fibrin, prominent vascular congestion, and infiltration with neutrophils [9,10]. Such findings might raise the suspicion of reactive arthritis, but biopsies have not been studied systematically nor were they from patients with and without chlamydial association. Special techniques for the identification of *Chlamydia* can add value to the biopsy. Electron microscopic studies have also noted vascular disease with Schwartzman-like reactions and fibrin infiltration of vessel walls that may merit more attention [9,11].

Keeping in mind that *Chlamydia* can also be found in some patients with clinical diagnoses of classic rheumatoid arthritis, clinicians and investigators must allow some

flexibility of concepts until we know more about the role of *Chlamydia* in these less classical situations.

Extra-articular features

Many patients with reactive arthritis have features outside of joints. Do these differ in patients with different infectious agent triggers? Chlamydial antigens have been found in the classical skin lesions termed keratoderma blennorrhagica [12], but little is known, for example, about whether *Chlamydia* is also present in conjunctivitis, in aortic valves of people who develop aortic insufficiency, and in enthesitis. Interestingly, the lesions in keratoderma were described as vasculitis, which draws further attention to a neglected vascular injury component to the pathogenesis of some aspects of the disease. Additional details on extra-articular features could make an important difference in concepts of the disease and approaches to treatment. Urethritis, although obviously common in arthritis following genitourinary infection, can also be seen after enteric infection. The mechanisms of this and the other extra-articular features offer an interesting area for research.

Diagnosis

The standard approach to the diagnosis of *Chlamydia*-associated reactive arthritis would be the identification of a chlamydial genitourinary infection, followed a few weeks later by an inflammatory oligoarthritis typical of reactive arthritis. Most cases meeting these criteria will probably have *Chlamydia* reactive arthritis as expected, although in a few this manifestation may also be due to gonococcal, *Ureaplasma* or other causes. Chlamydial infections do not always occur alone. Even more important, the above criteria will almost certainly miss many patients who have chlamydial infection as a factor in their arthritis. *Chlamydia* and other triggering infections are often totally asymptomatic or ignored. Weyand and Goronzy [13] found evidence for missed chlamydial infections in 36% of 83 patients with oligoarthritis of unclear origin versus none of their controls.

What methods are available to identify chlamydial infection (and its dissemination), and what is needed to increase the likelihood that this infection is in fact involved with the pathogenesis of the arthritis? Genitourinary infection has traditionally been established by culture, fluorescent staining of inclusions on urethral or cervical swabs, or by ligase chain reaction or polymerase chain reaction. Recent studies suggest that the latter two are useful and reliable.

There is a variety of available techniques to demonstrate disseminated *Chlamydia* or an immune response to *Chlamydia*, but it is necessary to evaluate their roles. Anti-chlamydial antibodies (immunoglubulin M, G and A) can be demonstrated in most patients with previous infections with or without arthritis. High titers of IgG antibodies or the presence of IgM antibodies have been used to suggest active infection, however the lack of correlation with DNA presence in the joint has been noted [14].

Lymphocyte transformation of peripheral blood or synovial fluid cells following exposure to chlamydial antigens has also been used in some of the seminal studies by Ford and coworkers [15] and Herman et al. [16]. Studies by Braun's team [1] suggest that responses of synovial cells are more likely to be specific and pathogenetically important than antibody tests, although these also do not correlate exactly with studies on bacterial nucleic acids.

PCR, reverse transcriptase PCR and hybridization techniques have provided recent evidence for chlamydial dissemination to joints, which has focused much attention on the concept of *Chlamydia*-associated arthritis [3,17–20]. Due to the considerable variations in the genes tested for, the primers used, and the sources of specimens, it is difficult to make comparisons [20]. *Chlamydia* plasmid is easier to detect as there are abundant copies of the plasmid, but whether this has the same clinical significance as identification of 16srRNA has not been studied. Synovial tissue appears more likely to be positive than synovial fluid [19], but the latter is worth testing if it is all that is available. PCR can and has also identified other organisms in joints. Our own studies on *C. pneumoniae* show that nucleic acids can be present in joints, but there is less correlation with disease pattern than seen with *C. trachomatis* [21].

Electron microscopy was actually one of the first techniques to suggest that chlamydial organisms may be present in joints [9,11] and it is still valuable for research. The addition of immunohistochemistry can confirm the presence of *Chlamydia* and provide some evidence as to its state and location [9,22]. Surprisingly, immunohistochemistry of synovium has hardly been investigated, but this as well as molecular studies should be pursued to further evaluate both the biologic status of the organism and the critical host response. *In situ* hybridization has successfully identified chlamydial RNA [23,24], suggesting that much of the RNA appears to be in deeper synovial macrophages. Are the sites where *Chlamydia* is identified of any importance? Recent studies that found *Chlamydia* in blood mononuclear cells of some patients [25] raise possibilities of less invasive ways to search for chlamydial DNA and RNA.

Host response may well be critical in determining whether *Chlamydia* causes symptoms (i.e., disease). Synovial fluids or biopsies can help in this evaluation. Cytokines produced by the host may well determine if organisms are eradicated or persist, and whether they produce disease [26]. Does HLA B27 or other genetic factors have any role? The typical reactive pattern of oligoarthritis is clearly not limited to patients with HLA B27. The fact that some patients who harbor *C. trachomatis* in synovium have a clinical diagnosis of rheumatoid arthritis fits with the possibility that infectious agents might cause different clinical syndromes, depending on genes.

PCR = polymerase chain reaction

Management

Should we use antibiotics to treat *Chlamydia*-associated reactive arthritis or other forms of arthritis in patients in whom *Chlamydia* has been identified in the joints? The answer is far from clear [27,28]. It does appear that early treatment of symptomatic genitourinary infections does prevent much of the resulting reactive arthritis [29]. Once articular disease has manifested, treatment is less likely to be effective. The widely quoted study by Lauhio et al. [30] from Finland showed that time to resolution of *Chlamydia*-associated reactive arthritis was shortened by a 3 month course of lymecycline (a tetracycline). However, patients with enteric infection-associated reactive arthritis did not show any benefit.

The many cases of reactive arthritis that resolve spontaneously have confounded attempts at evaluating treatment. Some argue that *Chlamydia*-associated reactive arthritis is more likely to become chronic, but this has not been well studied. In the earlier mentioned study of Glennas and colleagues [7], initial episodes of the disease resolved more slowly than did most enteric cases. Several studies on chronic *Chlamydia* and enteric-associated reactive arthritis did not show a significant benefit following the use of antibiotics [31,32], although a recent study with a small number of patients with *Chlamydia*-related reactive arthritis [31 exhibited a trend suggesting improvement after 3 months of therapy with ciprofloxacin.

Chlamydial nucleic acids have persisted in joints after 3 months of antibiotic therapy [24]. Might a longer course or repeat courses of antibiotic be useful, or might other antibiotics be better? *Chlamydia* was cultured from the urethras and conjunctivae of some patients after 12 months of 750 mg ciprofloxacin per day [32], and there has even been speculation that ciprofloxacin might induce a persistent form of infection [33]. Since reinfection could contribute to some failures, sexual partners should be examined and treated.

Symptomatic therapy remains the mainstay in the absence of curative measures. Non-steroidal anti-inflammatory drugs are often effective in providing relief of pain and swelling. Intraarticular injections of depot corticosteroids are also widely used [7] and often provide dramatic relief especially with knee synovitis. Few studies have addressed longer term effects. If active but indolent infection is present in the joint, one might expect that the disease would return, and it certainly does in some cases. The effects of intra-articular steroid injections on the biologic state of chlamydial organisms would be a useful area for investigation.

Sulfasalazine, a potentially disease-modifying agent, has had some impact on reactive arthritis [34]. Whether this is more or less effective in patients with *Chlamydia* has not been evaluated. Methotrexate has been reported to positively affect patients with reactive arthritis, but it has not been studied specifically in *Chlamydia*-associated disease. Combinations of therapies are being used in the treatment of rheumatoid arthritis and may well be appropriate for reactive arthritis. If organisms are persistent, a case could be made to encourage their growth by immunosuppressive therapy so that antibiotics might be more effective. Alternatively, the development of measures to improve macrophage function in eliminating organisms might be considered. Treatment of enthesitis in patients with *Chlamydia* has not been examined separately but could be another fruitful area for investigation.

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