EDITORIALS
SEXUALLY ACQUIRED REACTIVE ARTHRITIS: INFLAMMATION OR SEPSIS?

This journal has recently published two studies based on the use of the polymerase chain reaction (PCR) to detect DNA related to Chlamydia trachomatis in patients with sexually acquired reactive arthritis (SAReA) [1, 2]. Both reported negative results. However, it has subsequently been reported that chlamydial RNA can be detected within the joints of patients with SAReA [3]. Where does this leave us with respect to C. trachomatis and ReA?

The idea that chlamydial antigens are present within the joints of patients with SAReA was advanced by their detection using monoclonal antibodies [4-6]. If this data is taken together with the two negative PCR studies it would suggest that chlamydial antigens but not live organisms are disseminated via the blood stream to affected joints. This would parallel the accumulating data for ReA following infection with enteric organisms (EREa). Several reports have confirmed the presence of antigenic material from Yersinia [7, 8] and Salmonella [9] or the presence of bacterial lipo-polysaccharide [10] within the joints of patients with EREa but studies using PCR to detect bacterial DNA have yielded negative results in SF [11] and synovial tissues [12] from patients with Yersinia-related ReA.

Unfortunately the recent data concerning detection of chlamydial RNA [3] and results from earlier electronmicroscopic studies do not support such a neatly parallel concept for EREa and ReA related to C. trachomatis. The report of Ishikawa et al. in 1986 concerning a single case of SAReA clearly showed the presence within synovial macrophages of large numbers of both elementary (EB) and reticulate bodies (RB) [13]. Subsequently Schumacher et al. combined electronmicroscopy and identification using specific antibodies to demonstrate the presence of C. trachomatis in 8/13 patients with SAReA. Particles consistent with both EB and RB were found within deep phagocytic cells and free within joint tissues [14].

The first step in infection with C. trachomatis is adherence of an EB to a cell, a process dependent upon postulated adhesins within the EB cell membrane [15]. The EB is then taken up by the host cell in a process dependent upon the energy systems of that cell. The ingested EB within its phagosome transforms to a RB, the replicative form of C. trachomatis. Replication leads to the presence within the cell of a large inclusion which may contain up to several hundred EB, RB and intermediate forms. At the end of the replicative cycle all of these forms are released from the cell but only EB are capable of spreading infection. The presence within joint cells of EB and RB as described by Ishikawa and others is thus most compatible with local replication and active infection within the affected joint. If this is the case then one would expect to be able to detect chlamydial DNA using a sensitive method such as PCR. Failure to detect chlamydial DNA using PCR raises the question of just how sensitive the PCR method is for the detection of chlamydial DNA. In our own system seeding of samples with C. trachomatis DNA indicated that we could detect 10^-15 g under experimental conditions [2]. This would correspond roughly to 10 chlamydiae. Other reports describe detection of as little as 10^-16 g suggesting the ability to detect single organisms [16]. However, under 'field' conditions the sensitivity of PCR may not be so impressive and may be no more sensitive than the best antibody detection systems [17]. Since antibody-based methods of detection have been adequate to demonstrate the presence of C. trachomatis in some joint tissues lack of sensitivity is still an unlikely explanation for failure to detect chlamydial DNA.

In clinically-based studies the characteristics of the patients are of paramount importance. Schumacher has emphasized that patients in whom C. trachomatis was demonstrated within joint tissues using electronmicroscopy had early disease of less than 1 month's duration. Four of our patients had disease of comparable duration. A further important factor is preceding treatment with tetracycline which was a factor in 5 of the patients in our study, although others had active urogenital infection demonstrated at the time of study. In addition we studied SF cells rather than synovial tissue. Such variables rather than technical factors may provide the most likely explanation of these apparently discrepant results.

Given the direct electronmicroscopic evidence and recent evidence for the presence of C. trachomatis RNA it is hard to escape the conclusion that in the early phase of SAReA active chlamydial infection is present within affected joints despite the negative results from two PCR studies. This raises a number of further interesting questions. Is C. trachomatis infection present at other affected sites such as entheses and even within aortic lesions (chlamydial aortitis?). By implication, an infective phase may precede enteric ReA. Early elimination of infection assumes more significance in patient management in light of this data, particularly since information became available suggesting that this does limit occurrence of ReA [18] as well as hastening recovery from established ReA [19]. The recent data also focusses attention on fundamental aspects of the relationship between infection on intracellular organisms such as C. trachomatis and the ability of the host to control the spread of such infections. Spread of what is normally an infection confined to the epithelial cells of the genital tract to distant sites suggests defective ability to control dissemination of this and other intracellular infections.

Early control of infection by intracellular organisms depends upon the intrinsic characteristics of the host's...
macrophages, and subsequently upon effective arming of macrophages and a protective delayed type of hypersensitivity response (DTH). The possible increase in susceptibility of patients with HIV infection to ReA [20] could be compatible with failure of an effective DTH response to limit dissemination of infection within the host. Differences between chlamydial organisms also influences behaviour within the host. Different strains of chlamydiae differ in their ability to survive within monocytes/macrophages and this correlates with their tendency to cause systemic infection. Chlamydia psittaci readily replicates in mononuclear phagocytes and causes systemic infection. C. trachomatis biologics which cause lymphogranuloma venereum and disseminate to lymph nodes are killed by monocytes but survive within monocytes matured to macrophages [21]. By contrast, C. trachomatis biologics associated with urogenital infection are killed by both monocytes and matured macrophages [22]. Thus, the electron-microscopic demonstration of multiple EB and RB of C. trachomatis within the macrophages of inflamed joints suggests defective killing by host macrophages in patients with ReA.

In conclusion it seems likely that differences in the characteristics of patients studied as well as technical factors are most likely to be responsible for the variable reports upon detectability of C. trachomatis DNA and RNA in patients with SARtA. The accumulating evidence suggests that productive infection with C. trachomatis is present at least in the early phase of SARtA. This has implications for treatment and prevention, as well as further investigation. In particular, postulated mechanisms for development of ReA should include consideration of a relative deficiency of affected individuals to limit dissemination of intracellular infections such as C. trachomatis.

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REFERENCES


