Clinical and Experimental Rheumatology 2003; 21: 283-285.

What is this disease we call spondyloarthropathy?

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Received on January 20, 2003; accepted in revised form on April 30, 2003

Key words: Spondyloarthropathy, subchondral erosions, joint fusion, rheumatoid arthritis, collagen-induced arthritis, trophism.

Tropism is a term traditionally applied to biological responses to such stimuli as sun (helio) and gravity (geo) (1). Analogous application of the term tropism (as osseotropism) seems reasonable to describe skeletal distribution of disease. What determines which bones or joints are affected by a given disease? Osseotropism seems an appropriate neologism to describe disease-delineated patterns of osseous involvement. Arthrotropism might similarly be utilized to describe or categorize articular pathologies, especially those involving erosive disease.

The two major erosive forms of arthritis are rheumatoid arthritis and spondyloarthropathy. The former is a disease of diarthrodial joints; the latter is less perspicuity (2-7). The former predominantly causes marginal erosions; the latter, subchondral (3, 5-7). Marginal erosions affect (at least initially) that portion of intra-articular bone (the 'bare area') that is not covered by cartilage (3, 4). Subchondral erosions, as the name attests, affect the area originally covered by cartilage. Damage to the bare area is attributed to the direct action on bone by overgrown synovial membrane (pannus) (2-4).

The pathophysiology of spondyloarthropathy must be more complex, as cartilage is interposed. Subchondral damage of this type infers damage to/ removal of intervening cartilage, as the first step in the erosive process. This differs from rheumatoid arthritis in which synovial proliferation appears to directly and principally attack bone, with secondary/subsequent cartilage destruction (3-7).

Categorizing spondyloarthropathy as primarily a disease of cartilage (and secondarily of bone) explains the associated pattern(s) of disease. Absence of axial joint involvement is logical in rheumatoid arthritis, a disease that predominantly or at least initially affects bone (3-5). Sacroiliac joint involvement in spondyloarthropathy is recognized on the basis of subchondral bone damage (8). So too are zygapophyseal joint erosions (9). Examination of zygapophyseal joints reveals bone surface (subchondral) erosions in spondyloarthropathy, while sparing external (to the joint surface) bone (9).

These findings are parsimonious with the concept of a disease that initially attacks cartilage. While it is unclear what is attacking the cartilage, the osseotropism is clear. Whether it is synovial membrane overgrowth, with osseotropism determined by the underlying disease (rheumatoid arthritis or spondyloarthropathy), or a primary disease of cartilage are potential mechanisms to explore.

Two further phenomenon (2-4) in spondyloarthropathy require consideration: enthesitis and dactylitis. While the latter had been considered to be derived from the former (2), a recent MRI study suggests tendon sheath fluid accumulation, in the absence of enthesial reaction (10). This is perhaps analogous to pigmented villonodular synovitis, in which both tendon sheath and subchondral (as well as marginal) erosions are noted (11). It is unclear if tendon sheath and joint involvement in pigmented villonodular synovitis represent different ends of a spectrum, with the infrequent presence of both in a given patient. The issue of the relationship of dactylitis to erosive arthritis in spondyloarthropathy must similarly be considered (12). Do tendon sheaths and cartilage share a common target or receptor? As dactylitis is not present in all individuals with spondyloarthropathy, could dactylitis represent an epitope or receptor similar to, but not identical to the target in cartilage?

The remaining component of spondyloarthropathy to be addressed is enthesitis (2-4). The question of an epitope or target molecule that shares partial identity with cartilage could be considered. As some individuals with spondyloarthropathy have predominantly erosive disease (e.g., peripheral skeleton, zygapophyseal and sacroiliac), while others have predominantly enthesial disease (e.g., syndesmophytes) (3-5), the two phenomenon do not necessarily share a common pathophysiology.

It would be of interest to identify components common to cartilage and entheses. Lack of commonality would not be fatal to this hypothesis, nor would commonality confirm it. However, such commonality might represent a starting

point for investigation.

Cartilage is a complex tissue (2). Glycosaminoglycan, proteoglycan and collagen components are perhaps worthy of consideration as target tissues in spondyloarthropathy. As collagen fibrils are the mesh that contains the other components and a prominent surface-accessible target, could cartilage be the actual target? Perhaps, but not the Type II collagen so prominent in and specific to cartilage.

Type II collagen can specifically be eliminated from consideration as the target molecule. While the collagen (Type II)-induced model and spondyloarthropathy share the propensity to subchondral erosions, peripheral joint fusion and reactive new bone formation (2-5,13), extensive use of Type II collagen to produce inflammatory arthritis in animals (14-17, 19, 20) provides unequivocal refutation of its role in the human disease (13, 18). The arthritis induced by type II collagen does not model human disease (13). In contrast to spondyloarthropathy, Type II collagen-induced arthritis spares the zygapophyseal and sacroiliac joints in rhesus macaques (Fisher exact test, $p = 0.035$) (13, 14, 20). It should be noted that the naturally occurring erosive arthritis in rhesus macaques is indistinguishable both in character (e.g., subchondral erosion localization and joint fusion) and in the pattern of joint involvement (e.g., frequency of metacarpal phalangeal, elbow involvement) from that observed in human spondyloarthropathy (4, 5, 13).

Examination of patterns of peripheral joint involvement also easily distinguishes spondyloarthropathy from Type II collagen-induced arthritis (13, 14, 20). Metacarpal phalangeal and proximal interphalangeal (hand) joint involvement is present in 45-65% of rhesus macaques with Type II collagen-induced arthritis (14, 20), but present in only 5-13% of the naturally occurring spondyloarthropathy in that species (Chi square = 5.994, $p < 0.02$) (13). Ankles are involved in 64% of Type II collagen-induced arthritis, but in only one-third of the naturally occurring spondyloarthropathy (13,14,20). Pedal proximal and distal interphalangeal joint involvement is present in 36-45% of Type II collagen-induced arthritis (14,20), but is rare (13) in naturally occurring spondyloarthropathy (Fisher's exact test, $p = 9.023$). Thus, Type II collagen-induced arthritis does not model spondyloarthropathy and the presence of subchondral erosions and peripheral joint fusion preclude the diagnosis of rheumatoid arthritis (2-5, 7, 13).

There is further proof that Type II collagen-induced arthritis and spondyloarthropathy are different entities. While examples of spondyloarthropathy can be found in all Old World monkeys and apes, that is not true for New World monkeys (21). The dichotomy is especially pertinent for *Cebus* (Capuchin monkeys) and *Saimiri* (squirrel monkeys) (14,20,21). While spondyloarthropathy naturally occurs in *Cebus*, *Saimiri* are spared (21), exactly the opposite of species specificity to Type II collagen-induced arthritis. The latter affects *Saimiri*, but spares *Cebus* (14, 20).

The developers of the Type II collagen-induced arthritis model may have been on the right track (16, 17), but just focused on the wrong cartilage component. Perhaps examination of arthritis produced by other cartilage components and other collagen types would be insightful. Of course, species selection will be critical.

Twenty percent of rhesus macaques (at least in the Cayo Santiago and Sebana Seca colonies) develop spondyloarthropathy (13). It will be important to carefully select adequately sized placebo groups to control for this and to reduce obfuscation by concomitant natural disease.

If the desire is to develop a predictably reproducible study animal for spondyloarthropathy, it would seem reasonable to require that these studies be performed in species with documented naturally occurring disease. Spondyloarthropathy is widely represented among mammals (4,13,21-33). While reports have suggested a diagnosis of naturally occurring rheumatoid arthritis in animals (34-36), the presence of joint fusion and subchondral erosions (as well as axial disease) clearly identifies spondyloarthropathy as the appropriate diagnosis (2-7).

If it is felt unacceptable to limit research to animals which actually develop spondyloarthropathy naturally, what experimental animals could be considered? In addition to Old World primates (17-28% of apes are affected, 30% of baboons, 20% of rhesus macaques and 1-4% of other monkeys), New World Cebus and Alouatta (1%), pigs (6%), sheep (2%), cattle (24%), goats (18%), deer (1%), horses (5%), red kangaroos (4%) and wallabies (8%) (in consideration of Australian colleagues) and porcupines (2%) spontaneously develop spondyloarthropathy, at rates as identified in the parentheses (4, 13, 21-32). The occurrence of naturally occurring spondyloarthropathy in small rodents has yet to be clarified, although the common rat appears spared, as are rabbits (4).

Given the limited identification of appropriate small animal models, perhaps it would be appropriate to more closely examine rhesus macaques or perhaps even the large numbers of chimpanzees (spondyloarthropathy frequency 28%) in "retirement facilities" for animals previously used for research (13, 33).

Factors determining arthritis-susceptibility would be amenable to analysis in populations (13, 33) with such high (20-28%) disease penetrance. While my personal bias is to the evaluation (and treatment) of afflicted animals, a concerted study of the effect of the various cartilage components may provide insights critical to the advancement of our understanding of spondyloarthropathy and new approaches to treatment, or even prevention.

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