Hypothesis

Acetabular Osteitis in Ankylosing Spondylitis: Does Fibrillin Figure in Its Pathogenesis?

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ABSTRACT. In the hip and sacroiliac joints, ankylosing spondylitis attacks the acetabulum over the femoral head and the ilium in preference to the sacrum. Both sites involve inflammation in bone subjacent to fibrocartilage with relative sparing of opposing, hyaline cartilage-surfaced mates. This disease appears to target connective tissues rich in fibrillin-1. A cell-mediated autoimmune response may be involved. (J Rheumatol 2001;28:2663–6)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS OSTEITIS FIBRILLIN-1
ENTHESIS FIBROCARTILAGE

In a scholarly and compelling analysis, Maksymowych has recently argued that the most fundamental lesion in ankylosing spondylitis (AS) reflects "autoimmunity to cartilage, especially fibrocartilage" and its "primary pathologic consequence...is the development of underlying subchondral osteitis."[1] As Maksymowych makes clear, this is not a new idea. Eric Bywaters, in particular, stressed this concept on the basis of the limited pathological material available to him[2]. More recently, Rothschild has repeatedly emphasized the osseous origin of articular lesions in skeletal remains from individuals with spondyloarthropathies[3]. It has taken the ever-mounting evidence from magnetic resonance imaging (MRI), however, to firmly establish the central role of intraosseous inflammation in most active spondylitic lesions[4,5]. It should be clear, however, that the concept of a primary role for subchondral inflammation in spondylitis is in no sense a denial of the fact that concurrent synovitis is often seen. This is no more of an inconsistency than it is to recognize that secondary osteitis may occur together with the primary synovitis of rheumatoid disease.

Parenthetically, it seems likely that the major resistance to this paradigm arises from the idea that this major form of arthritis is not primarily a synovitis. Clinicians are conditioned by their training and experience to think of "arthritis" and "synovitis" as essentially synonymous terms. In most forms of arthritis, patient after patient presents with clinical findings that confirm the central role of synovitis in their disease. It is a short step to infer that inflammation in deeper and less accessible joints must reflect the same basic processes that are seen so regularly in the hands, knees, and feet of patients in the clinic. But this need not be so. The overt manifestations of inflammation (especially swelling, redness, and heat) reflect vascular responses that might flourish best with a generous vascular supply. Subchondral bone meets this criterion and should be considered the other highly vascular tissue of joints with resting blood flows that may exceed those of the adjacent synovial lining[6]. Thus, unlike articular cartilage, bone is fully capable of supporting an inflammatory attack on the joint.

Sacroiliitis serves as an excellent case in point. Many of the observations Maksymowych cites are taken from pathologic studies and MRI-based observations of the sacroiliac joint[1]. There, the fibrocartilagenous iliac member is involved earlier and more extensively than its relatively hyaline, sacral mate, and the lesions are more consistent with an attack from underlying bone than they are with marginal invasion from synovial or entheseal tissue.

A comparable selectivity may be seen in the hip, another major target of this disease. Disproportionate involvement of the acetabulum over the femoral head was recently seen in a spondylitic patient at the University of Washington (Figure 1), was illustrated by Maksymowych, and was classically described by Passion and Goodfellow in a 16-year-old girl who lost both hips to this disease[7]. At surgery, she had a normal appearing femoral head within an acetabulum of "raw and bleeding bone." Further reports of specific acetabular pathology are lacking, presumably because surgical intervention is usually deferred until the joint reaches "end stage" with substantial changes in both articular surfaces. What is described repeatedly, however, is concentric radiographic progression in which the normal contour of the femoral head is preserved, the joint space is uniformly narrowed and the acetabulum appears "moulded" around the head[8,9]. In some cases, this

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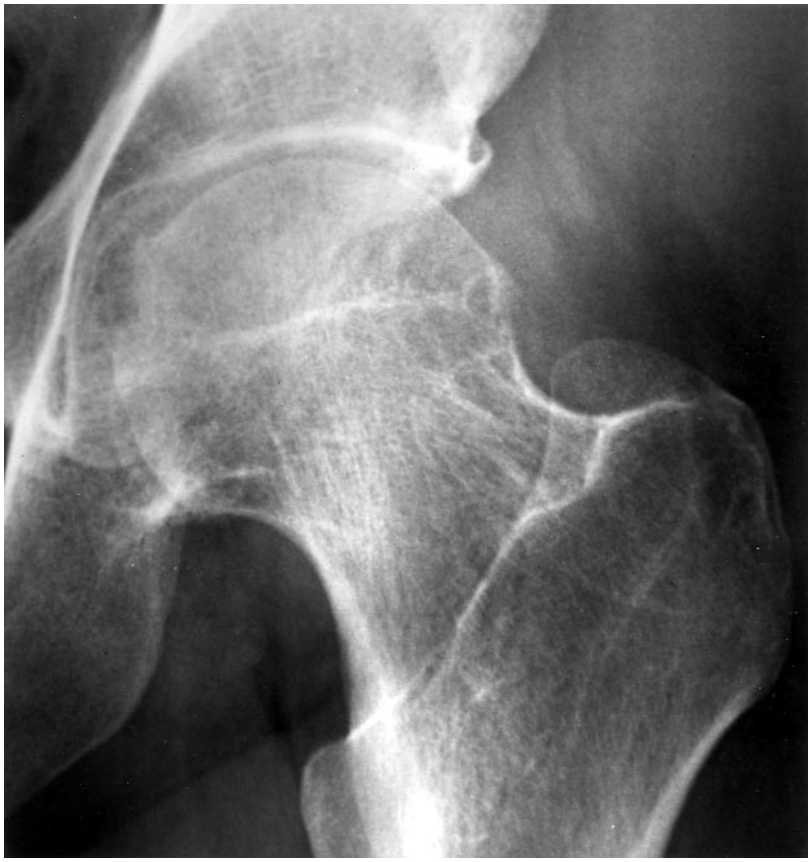

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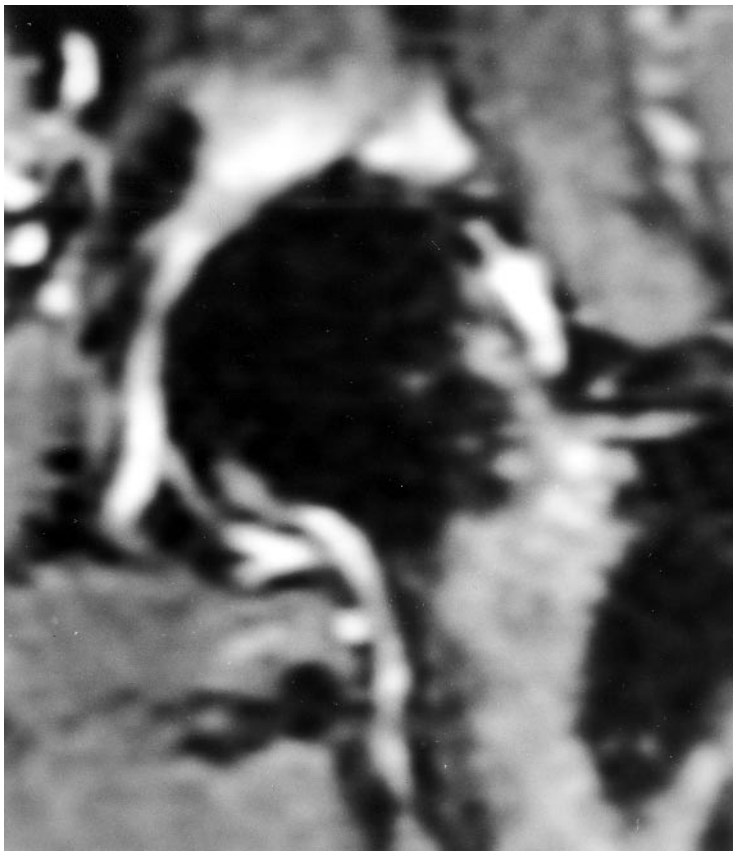

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Figure 1. A. Plain radiograph of a 31-year-old patient with longstanding AS and incapacitating left hip pain of recent onset. This view is chiefly remarkable for small osteophytes at the base of the femoral head with a "joint space" that remains within normal limits. B. STIR sequence MRI of the left hip reveals subchondral edema in the acetabulum with a small area of synovitis and/or effusion inferiorly.

moulding progresses to overt protrusio[10]. It seems reasonable to suspect that this characteristic finding of a "femoral head burrowing into the pelvis" reflects subchondral acetabular osteitis with secondary, incremental, trabecular failure[11]. Thus undermined by inflammation, the acetabulum of spondylitis represents a special subset among subchondral insufficiency fractures[12].

In its predilection for the iliac side of the SI joint and for the acetabulum in the hip, AS is not only arthrotropic but also osteotropic. Fibrocartilage overlies each of the preferred bony targets. The more vulnerable iliac surface has long been known to be not only thinner but also more fibrocartilagenous than its sacral mate[13,14]. The same finding holds for the hip, where the acetabular "zenith" is usually thin and fibrocartilagenous in contrast to the hyaline cartilage in the adjacent acetabular labrum and the opposing femoral head[15,16].

The vulnerability of fibrocartilage has always been apparent in the intervertebral discs, the manubrio-sternal joint and the pubic symphysis[17,18]. Less obvious, but now abundantly clear, is the consistent presence of fibrocartilage at another classic point of attack: the periarticular entheses where tendons and ligaments bond to bone[19-21]. Thus, fibrocartilage is virtually always present at the preferred sites of spondylitic musculoskeletal involvement.

In 1968, Bywaters suggested that AS might reflect "some change in cartilage, or in the body's reactions to cartilage whereby the latter becomes an active autoimmune target."[2] Hyaline cartilage is largely spared, however, and it now seems appropriate to focus on potential antigens that are more abundant in fibrocartilage. The microfibrillar protein fibrillin-1 provides one reasonable candidate[22,23]. This material is abundant in entheses[24]. It is present as "loose bundles" in immature articular cartilage, especially at the interface with bone, but is found less readily as broad banded fibers in adults (of interest because of the tendency of juvenile spondylitis to present in peripheral joints, especially the knee, and to remain axial in adults)[2,25]. Its altered structure in Marfan's syndrome leads to major morbidity in the eye, and in the base of the aorta — the 2 sites of greatest nonarticular morbidity in spondylitic patients[26-28]. A further parallel is the significant risk of protrusio in the acetabula of fibrillin-defective Marfan's patients[29]. Edwards, *et al*[30] have recently pointed out the parallel patterns of AS and Marfan's syndrome and suggested that fibrillin-1 may be involved in the pathogenesis of spondylitic inflammation (although they dismissed the likelihood of an immune mechanism). The essence of their essay, however, lies in the possibility that the defective fibrillin of Marfan microfibrils and the inflammation-targeted fibrillin of AS may each lead to comparable structural phenotypes of failure.

Finally, fibrillin and closely related proteins bind latent transforming growth factor-ß (TGF-ß) and bone morphogenic proteins within its family, which may be both released and activated by local inflammation[31,32]. This intriguing property fits well with the finding of TGF-ß in sacroiliac biopsies and with Poole's suggestion that TGF-ß may play a central role in spondylitic inflammation[33,34]. He stressed the histologic concurrence of inflammatory infiltration, bone resorption, and extensive formation of new bone and postulated that these findings suggest "excessive local production of bone morphogenic proteins with the properties of TGF-ß." Thus, a number of indirect associations suggest that fibrillin-1 could be a significant participant and perhaps even the missing antigen in the spondylitic inflammatory response. The hypothesis is presented schematically in Figure 2.

Fibrillin-1 is not a new candidate antigen to students of autoimmune disease. Fibrillin-directed antibodies have been found in the tight skinned mouse and in human patients with sclerodermatous diseases, but not in control diseases such as rheumatoid arthritis and systemic lupus[35,36]. Sera from spondylitic patients do not seem to have been studied, however, and the possibility of cellular autoimmunity has not been evaluated. Ziff has pointed out that spondylitis is unlike most prototypic autoimmune diseases in its lack of multiple autoantibodies, its failure to consume complement, its absence of cir-

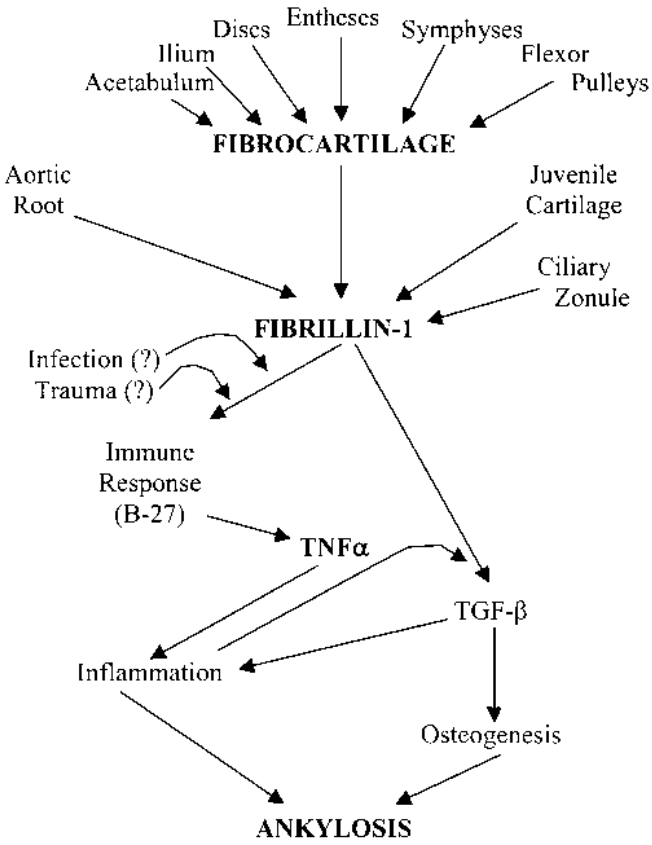

Figure 2. Most sites of inflammation in patients with AS involve fibrocartilage. Fibrillin-1, a major component of the microfibrils in fibrocartilage, may be the target of this response in the aorta and the eye as well as in bones and joints. Spondylitic inflammation may be triggered by infection or trauma, is mediated largely by tumor necrosis factor-α, and may include release and activation of latent transforming growth factor-ß from binding sites on fibrillin-1.

culating immune complexes, and its lack of vasculitic manifestations. He suggested that these features implied an exogenous rather than an endogenous antigen[37]. An alternative explanation might be that this disease centers in a cellular rather than a humoral attack on endogenous fibrocartilagenous tissues.

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