Hypothesis

Classification of inflammatory arthritis by enthesitis

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Imaging studies of early synovitis suggest that the first abnormality to appear in swollen joints associated with spondyloarthropathy is an enthesitis (inflammation at sites where ligaments, tendons, or joint capsules are attached to bone). We propose that the synovitis of spondyloarthropathy is secondary to liberation of proinflammatory mediators from the enthesis, whereas the synovitis of rheumatoid arthritis is primary. This suggestion allows a classification of arthritis as either primary synovial (rheumatoid-like) or entheseal (spondyloarthropathy-like) and allows differentiation of presentation of a polyarthritis with a good prognosis (spondyloarthropathy-like), from that with a bad prognosis (rheumatoid arthritis). Pathogenesis of spondyloarthropathy, in particular the part played by HLA-B27 and micro-organisms, should be assessed at the enthesis rather than in the synovium.

The primary abnormality in rheumatoid arthritis is synovitis, which accounts for all signs of the disease in the joint. The spondyloarthropathies are a group of inflammatory rheumatic diseases including reactive arthritis, psoriatic arthritis, ankylosing spondylitis, entheropathic arthritis, and undifferentiated spondyloarthropathy.[1] These arthropathies are associated not only with synovitis, but also with spinal inflammation (spondylitis), dactylitis (sausage digits), and enthesitis (inflammation at the point of ligament, tendon, or capsule insertion into the bone).[2] The synovitis of spondyloarthropathy is regarded as a distinct entity independent of enthesitis[3] and is histologically similar to that of rheumatoid arthritis.[4] Although enthesitis may explain spinal disease, there is no unifying concept explaining other features of spondyloarthropathies (panel).

Most nonrheumatoid inflammatory arthropathies have features more in keeping with spondyloarthropathy (table) than with rheumatoid arthritis: they are often asymmetrical in distribution and when symmetrical are characterised by a more acute onset with a better prognosis than rheumatoid arthritis.[5] Identification of a common underlying abnormality in spondyloarthropathy, would allow a unifying classification and also provide a framework to assess other inflammatory arthropathies.

Joint inflammation in spondyloarthropathy may be due to subclinical synovial infection[6,7] but evidence is lacking as to how infection, where detectable,[8] could sustain synovitis. Enthesitis is a major feature of spondyloarthropathic spinal disease and peripheral tendonitis but the extent of enthesitis in spondyloarthropathy-associated synovitis has not been established. Synovitis is a common response to many stimuli including infection, trauma, crystals, and cartilage degradation. An alternative explanation for subclinical synovial infection in spondyloarthropathy is that synovitis is an epiphenomenon due to local release of pro-inflammatory cytokines and growth factors from the enthesis (figure 1) and that synovitis is secondary.

Clinical features of spondyloarthropathy

Sacroilitis*
Spondylitis†
Peripheral enthesitis†
Synovitis—oligoarthritis
—polyarthritis (RA like with small joint involvement)*
—distal interphalangeal joint arthritis*
Dactylitis (sausage digits)
Hand/limb oedema†
SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteolysis)†
CMRO syndrome (chronic multifocal recurrent osteomyelitis)†
Lytic bone lesions—spondylodiscitis, arthritis mutilans†

*Is commonly associated with entheseal erosion and new bone formation radiographically. †Denotes inflammatory lesions outside joint cavities and tendon sheaths

Experimentally, the synovium is particularly susceptible to proinflammatory cytokines. Transgenic tumour necrosis factor (TNF)-α mice have an inflammatory arthropathy[9] indicating that in-vivo alteration of a key proinflammatory cytokine has effects on the synovium. Intra-articular injection of cytokines including interleukin (IL)-1 alone,[10,11] transforming growth factor (TGF)-β alone,[12] or TNF α with IL-1 acting synergistically,[13] provokes florid synovitis. Bacterial-cell constituents[14] and activated lymphocytes[15] isolated from the synovial cavity may similarly originate at the enthesitis and could be bystanders rather than initiating or sustaining synovitis.

The most characteristic features of spondyloarthropathy is sacroilitis, which is generally regarded as a synovitis, but bone erosion in the sacroiliac joint may occur in the upper third of the joint adjacent to the interosseous ligament, a region devoid of synovium.[16] Recognition of enthesitis in synovial joints is difficult as entheseal structures may be intra-articular, such as cruciate ligaments, situated deep to connective tissues, or closely related to the joint capsule or bursae[17] making clinical detection impossible.

Imaging techniques including radiography,[18] scintigraphy,[19,20] and magnetic resonance imaging (MRI)[21,22] have shown abnormalities in some patients with spondyloarthropathy-associated synovitis, although enthesitis was not found sufficiently frequently to suggest

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	Rheumatoid arthritis	Spondyloarthropathy	Oligoarthritis	Benign polyarthritis
Onset	Usually gradual	Often acute	Often acute/gradual	Acute
Rheumatoid factor	+	–	–	–
Peripheral enthesitis	–	+++	–	+/–
Associated spinal enthesitis	–	+++	–	+/–
Extrasynovial disease (dactylitis)	+/–	+++	–	+
Extrasynovial disease (hand/limb oedema)	+	+	–	+++
Prognosis	Poor; good if sudden onset	Usually good	Often good	Good/excellent

Spondyloarthropathy—includes reactive arthritis, psoriatic arthritis, ankylosing spondylitis, enteropathic arthritis.
Oligoarthritis—includes subsets of juvenile chronic arthritis, inflammatory monoarthritis, Lyme arthropathy, post streptococcal arthritis.
Benign polyarthritis—includes remitting seronegative arthritis (RS3PE), polymyalgia rheumatic association arthritis, viral arthritis.

Comparison of clincal features of RA spondyloarthropathy, oligoarthritis, and benign polyarthritis

a direct association with synovitis. We have shown with fat-suppressed MRI that early knee spondyloarthropathy synovitis, but not knee rheumatoid arthritis, is associated with entheseal abnormalities.[23] Fat-suppressed MRI eliminates the high signal from fat in the bone-marrow cavity and soft tissues, thus allowing the high signal from excess water at sites of inflammation to be seen. The ubiquitous nature of enthesitis of the synovial cavity suggests that enthesitis is the primary lesion in synovial joints, but whether chronic synovitis associated with spondyloarthropathy is dependent on enthesitis or is an autonomous process is unknown.

Other features

If primary enthesitis explains synovitis, could it also explain all musculoskeletal signs of spondyloarthropathy (figure 2)? Dactylitis is a characteristic feature of spondyloarthropathy and is considered to be predominantly a tenosynovitis,[24] but if this were the case, dactylitis would be common in rheumatoid arthritis. The circumferential digital thickening of dactylitis could be related to inflammatory epicentres located at several digital entheseal insertions not only resulting in synovitis and tenosynovitis but extensive soft-tissue swelling outside the joint capsule. Furthermore, a primary entheseal abnormality explains the radiographic features of new bone formation and erosion associated with the joint capsule in spondyloarthropathy-associated hand disease.[25] This is most readily appreciated at the distal interphalangeal joint where the characteristic pencil-in-cup deformity is seen.[25] The cup component of this lesion equates with distal capsular calcification with a central flexor or extensor tendon insertion erosion. Other features of hand radiographs suggestive of enthesitis include periostitis and erosion adjacent to the joint capsule.[25] The close anatomical proximity of the distal interphalangeal joint capsule insertion and the nail bed also explains the typical occurrence of nail dystrophy and arthritis associated with psoriasis.

Further support for a primary enthesitis in spondyloarthropathies comes from radiological studies in the syndrome of synovitis, acne, pustulosis, hyperostosis,

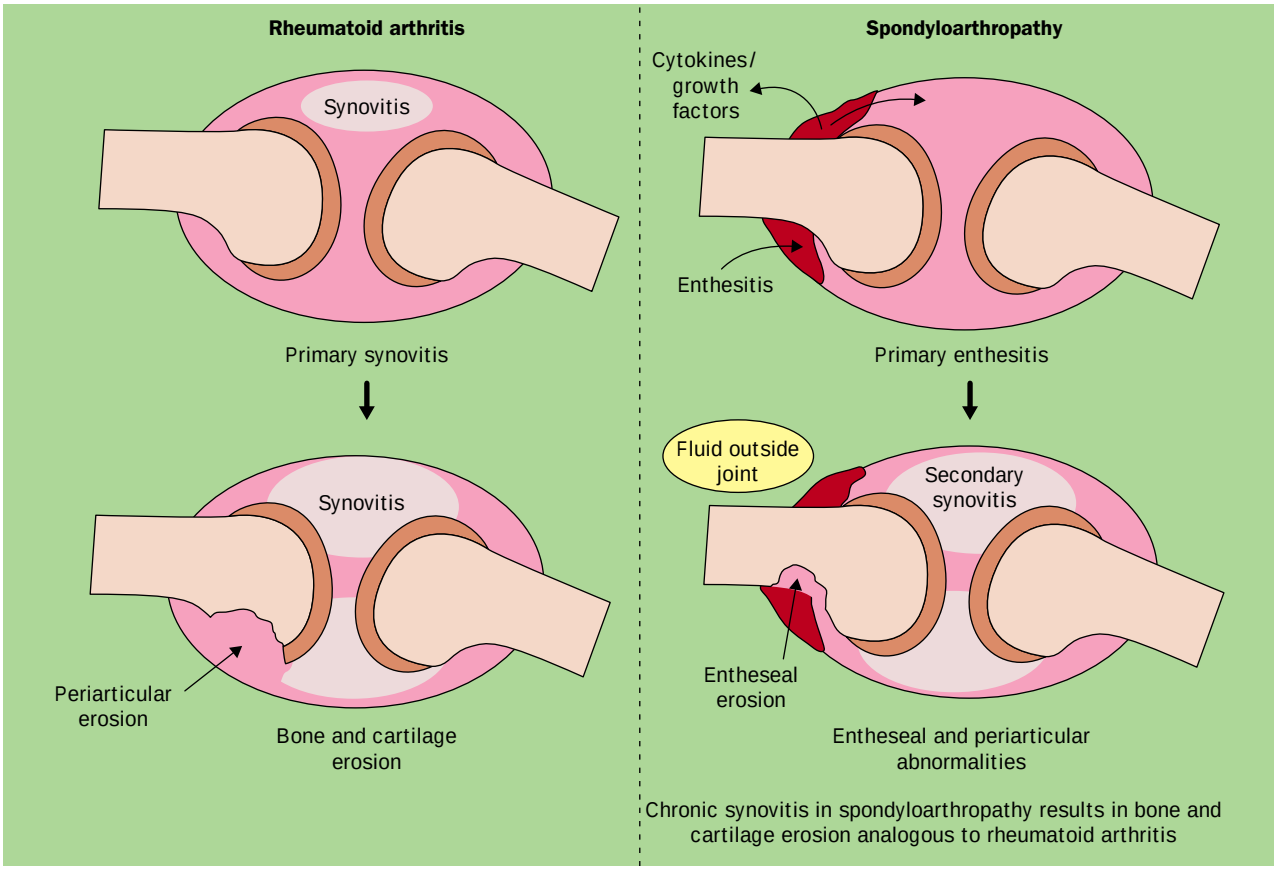

Figure 1: **Primary synovitis of rheumatoid arthritis and the proposed mechanism of synovitis and joint damage in spondyloarthropathy**

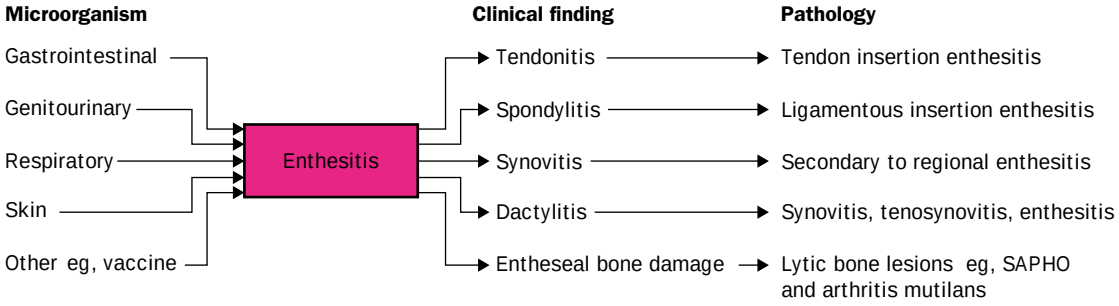

Figure 2: **Proposed link between micro-organisms, clinical features, and pathology of spondyloarthropathy**

and osteolysis (SAPHO), a diverse clinical entity associated with spondyloarthropathy, in which it has been shown that enthesitis predates other osseous abnormalities.[26] This is based on the observation that osteolysis adjacent to entheseal insertions predates new bone formation.[26] Extra-articular signs of spondyloarthropathies (eg, aortic regurgitation) may have similar pathogenic mechanisms to enthesitis. The root of the aorta is tethered to the heart, a mobile structure, in a similar manner in which a tendon, ligament, or capsule is inserted to bone at the enthesitis. The association of aortic regurgitation with HLA-B27[27] and the antigenic similarity between aorta tethering and bone entheses[28] provides further support for similar mechanisms of disease.

Pathogenic implications

The pathophysiology of inflammatory enthesitis is poorly understood. One study of synoval joints after inoculation of bacteria and particulate matter intravenously showed that the bone-enthesis interface was a common site of accumulation of bacteria, which may be due to a distinctive vascularity at this site.[29] There are some suggestions that bacteria also localise in the enthesis in human beings. Viable micro-organisms have been cultured from SAPHO-associated bone lesions, although this finding may have resulted from secondary contamination[30] and another study showed histological changes reminiscent of acute infection.[31] Some reports indicate that viable bacteria are not necessary to precipitate spondyloarthropathy-associated synovitis.[32] What is the association of infectious triggers to persistence of enthesitis? Based on the observation that reactive arthritis is usually self-limiting and infection temporary, whereas ankylosing spondylitis is chronic and probably a reaction to a persistent gut antigen, it is possible to postulate that ongoing colonisation or infection at the enthesis or a remote site is essential for continued enthesitis. Detailed evaluation of entheseal tissue from human beings and of HLA B27-transgenic animals with spondyloarthropathy-like disease[33] will not only provide insights into the role of infection but also of HLA B27 and cross-reactivity with native antigens[34] in the pathogenesis of spondyloarthropathy.

Diagnostic and prognostic implications

Rheumatoid arthritis is a symmetrical polyarthropathy that generally has a poor prognosis compared with other types of arthritis. Most other polyarthropathies clinically distinct from rheumatoid arthritis, such as remitting seronegative arthritis with pitting oedema (RS3PE),[35] polymyalgia rheumatica-associated polyarthritis,[36] and viral polyarthritis generally have a better prognosis and share other features with spondyloarthropathies including acute onset of symptoms, prominent extracapsular features including spinal symptoms, and seronegativity for rheumatoid factor (panel). Enthesitis is a well-recognised feature of viral polyarthritis[37] and the similarities of spondyloarthropathies and RS3PE are well described.[38] Could misdiagnosis of entheseal or capsular-associated disease explain so-called self limiting rheumatoid arthritis that has an acute onset, is seronegative, in which there is a raised acute-phase response, and for which prognosis may be good.[39] The prognosis of polyarthropathies may be a consequence of the primary site of inflammation with a primary synovitis generally being associated with a bad prognosis and primary entheseal-associated inflammation with a good prognosis.

Hypothesis

A primary inflammatory enthesitis could explain all of the rheumatic signs of spondyloarthropathies. An understanding of spondyloarthropathy pathogenesis will come from assessing the role of micro-organisms and HLA B27 at the enthesis.

This hypothesis could be tested with specialised MRI techniques and high-resolution ultrasonography to show that enthesitis is ubiquitous in all skeletal lesions of early spondyloarthropathies and by similarly assessing other hitherto unclassified arthropathies. Proof that synovitis is secondary to entheseal inflammation is testable in transgenic animals by showing that enthesitis precedes synovitis.

New classification of arthritis

On the basis of these concepts, joint inflammation may be classified as primarily synovial based like rheumatoid arthritis or entheseal based like spondyloarthropathy. This would not only provide a unifying classification for spondyloarthropathies, but also a framework for the classification of other arthropathies. The demonstration of primary synovial or entheseal abnormalities in various arthropathies including isolated inflammatory monoarthritis,[40] Beçhet's syndrome, psoriatic arthritis, Lyme arthropathy,[41] and juvenile chronic arthritis[42] will enable classification of these conditions to be based on the primary site of disease. This classification may even be relevant to osteoarthritis in which some patients have prominent synovitis, which is thought to be induced by fragments of cartilage liberated into the synovial cavity. However, osteoarthritis is also associated with joint

instability and secondary entheseal abnormalities.[43] This could result in abnormal tensile forces, entheseal damage, and an inflammatory response which could trigger secondary synovial inflammation, particularly where entheseal insertions are intra-articular, such as at the cruciate ligaments.

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