Anatomy and biochemistry of entheses
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There are two different types of entheses. Fibrocartilage entheses are characterised by pure dense fibrous connective tissue that links the tendon or ligament to the bone, but fibrocartilaginous entheses have a transitional zone of fibrocartilage at the bony interface. Most entheses are fibrocartilaginous—for example, those of the annulus fibrosus, Achilles tendon, and most insertions on long bone epiphyses or apophyses. Typically, four zones of tissue are present—dense fibrous connective tissue, uncalcified fibrocartilage, calcified fibrocartilage, and bone. The two fibrocartilage zones are separated by a calcification front known as the tidemark.

Uncalcified fibrocartilage probably reduces stress at enthesis insertion on long bone by gradually dissipating any fibre bending and stretch-induced narrowing of the tendon/ligament away from the functional region where wear and tear are most likely to occur. It is prominent at sites at which a marked bending of the tendon/ligament accompanies joint movement. It also creates a vascular and cellular barrier between bone and tendon/ligament cells.

The calcified fibrocartilage serves to link the tendon/ligament to the bone via an irregular interface—probably in the manner of a ligament, with little direct continuity of collagen fibres. The stress dissipation role of enthesial fibrocartilage hinges on its compression tolerance properties—any bending or narrowing of a tendon/ligament increases compressive loading. As in articular cartilage, its ability to resist compression is linked to the presence of aggregan and type II collagen in the extracellular matrix. These molecules have been demonstrated at several entheses by reverse transcriptase-polymerase chain reaction, western blotting, and/or immunohistochemistry. At most sites, they are synthesised by fibroblast metaplasia. In the inner annulus, however, the fibrocartilage is derived from hyaline cartilage that is present during early development.

Enthesophytes develop by endochondral ossification in enthesial fibrocartilage and their formation can be an extension of normal enthesis development.

detailed MRI assessments of the axial skeleton in spondyloarthropathy
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The sacroiliac joints (SIJ) are initially affected in most patients with ankylosing spondylitis (AS). In later stages affection of vertebral structures occurs in many patients. Conventional x rays and computed tomography are mainly able to show chronic changes at a time when bony changes—for example, ankylosis, have already developed. Magnetic resonance imaging (MRI) allows detection of early inflammatory changes at different anatomical sites. To learn about the pathogenesis of spondyloarthropathy (SpA), it is of interest which anatomical structures are initially affected. To determine the exact localisations of sacroiliitis in early disease, dynamic MRIs of 56 patients with SpA (112 SIJ) were retrospectively analysed. Of those, 43 were classified as undifferentiated SpA (including patients with early AS who progressed to AS in the further course of disease) and 13 as differentiated SpA (5 reactive arthritis, 4 psoriatic arthritis, 4 arthritis associated with inflammatory bowel disease). The mean (SD) age was 32 (12) years (range 16–57) and the mean (SD) disease duration 1.2 (1.3) years (0–37). Only patients with x ray stages <2 bilaterally were included: 50% of the patients were normal, 33% were graded as grade I, and 17% showed grade II changes unilaterally. In contrast, MRI detected 36 SIJ as normal, 35 had grade I, and 41 grade II changes according to the MRI criteria proposed; 60% showed strong gadolinium enhancement (grade b), 17% moderate enhancement (grade a), and 23% were normal (opposite sites).

The following anatomical structures were distinguished: joint space, joint capsule, entheses, ligaments, subchondral bone, and the bone marrow; ventral and dorsal involvement was differentially assessed. The differentiation between enthesal and ligamentous structures proved difficult. The joint capsule was commonly affected: the ventral capsule showed enhancement in 40% and the dorsal capsule in 75%; isolated enhancement was found most often in both, the ventral and the dorsal part. Enhancement in the joint space was detected in similar frequency: in 75% in the ventral and in 63% in the dorsal part. Involvement of enthesial structures was seen in 53% of the cases; in 32% extended enhancement of the dorsal interosseus ligaments was seen. The iliac juxta-articular subchondral bone was affected in 75% of the cases, similarly often in the ventral (53%) and dorsal (68%) part. Diffuse enhancement in the bone marrow was seen in 47% and circumscribed in 24% of the cases.

These data show that all structures examined are more or less involved in SpA associated sacroiliitis, with involvement of the joint capsule and subchondral bone being most common. MRI can also detect spinal inflammation at early stages. Examples of patients with AS with early spondylitis anterior and posterior and spondylolocicists were presented.

Successful anti-TNF treatment in ankylosing spondylitis (AS)
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The sacroiliac joint is centrally involved in SpA. Furthermore, peripheral and spinal entheses are characteristic and special features of SpA, and this is similar for anterior uveitis.

Dynamic magnetic resonance imaging (MRI) has proved helpful in the early diagnosis of sacroiliitis. Similarly, MRI of the spinal column can also identify active inflammatory lesions such as spondylitis and spondylolocicists—at a time when conventional x rays are still normal. Thus our ability to screen and quantify early active disease has significantly improved. This will be of major relevance for clinical studies. From MRIs of two patients with very early SpA who were

Figure 1 Ankylosing spondylitis disease activity assessments. CRP and BASDAI before, during, and after treatment with 5 mg/kg anti-TNFα (arrows indicate the dates of infusion).
consecutively followed up we suggest that the event may take place in the joint capsule entheses.

By computed tomography guided biopsies of the sacroiliac joints the inflammatory lesions were characterized: CD4+ and CD8+ T cells and macrophages predominate; cytokines such as tumour necrosis factor α (TNFα), interleukin 6, and transforming growth factor β (TGFβ) have been detected at mRNA and protein levels. In earlier disease there is more TNFα than TGFβ, also in the proximal bone marrow. The degree of cellularity correlates with the enhancement of gadolinium in sacroiliac MRIs.

By enzyme linked immunosorbent assay (ELISA) and FACS techniques we have shown that low TNFα secretion is associated with more chronic disease in reactive arthritis. By detection of intracellular cytokines at the single cell level an enhanced immune reactivity (interferon γ secretion) to the aggrecan G1 domain—which can induce spondylodiscitis in animal models—has been seen in patients with AS. When the same technique was used a decreased TNFα secretion after non-specific stimulation was found in patients with AS and also in healthy HLAA-B27 positive controls. Of interest, after successful anti-TNFα treatment both immune reactions proved to be increased, suggesting that immune suppression occurs in AS and arguing against a deleterious role of a high TNFα secretory capacity and against a pathogenetic role of an autoimmune Th1 response to the aggrecan G1 molecule.

Role of enthesitis in juvenile SpA

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Enthesopathy is one of the most prominent signs of disease in children with juvenile onset spondyloarthopathies (Jo-SpA). As part of the original description of seronegative enthesopathy and arthropathy syndrome and as part of the enthesitis related arthritis subgroup of childhood arthropitides, enthesopathy is the disabling feature of Jo-SpA.

The single entheses most commonly affected are those of the lower extremities, particularly the plantar fascia and Achilles tendon attachments to the calcaneus. In contrast, the foot tenosynovitis and bursitis, enthesitis has become part of a peculiar form of disease called ankylosing tarsitis. Imaging studies of ankylosing tarsitis, including x-rays and magnetic resonance, show striking similarities with spinal disease in patients with ankylosing spondylitis. Very rarely, the upper limb entheses become involved in Jo-SpA. In contrast, the search for enthesitis at spinal sites may show an increased representation of lumbar and thoracic segments in the active phase of the disease.

The specificity and diagnostic value of enthesitis is much more significant than that of arthritis and even that of HLA-B27. The clinical and imaging features of Jo-SpA from other forms of juvenile arthritis early on in the course of the disease, years before the occurrence of axial symptoms.

The evolution of enthesitis is variable. Some episodes are of short duration and involve one or few areas and others consist of recurrent episodes affecting many sites and lasting longer. A mean (SD) of 8.5 (5.4) peripheral entheses are involved in the active inflammatory phase of the disease in Jo-SpA.

The duration of such a phase extends for a mean of 1.9 (1.3) months, but the range is wide in certain areas. The therapeutic approach of enthesopathy is limited and no method seems to halt the disease process. Both the active inflammatory stage of enthesitis and the long term structural changes (bridging syndesmophytes) are functional capacity of patients with Jo-SpA. Persistent enthesitis is associated with cortical bone erosions, marked proliferation, and joint ankylosis. Many patients become severely disabled from adolescence to early adulthood.

Pathology of enthesitis in the spondyloarthopathies (SpA)

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Enthesitis is a cardinal feature of the SpA. Its pathological process seems to occur in the subchondral bone area, with an erosive inflammatory infiltrate composed of lymphoplasmocytes and sometimes polymorphonuclear cells, followed by tissue proliferation leading to cartilage and then bone formation. However, there is limited information about the quantitative distribution of the different cell types and lymphocyte subsets.

This is why we have conducted a quantitative-immunohistological study of the main inflammatory cell types in enthesis specimens obtained from patients with SpA at the time of orthopaedic hip surgery, and compared this with two other rheumatic diseases with different pathogenesis—namely, rheumatoid arthritis (RA) and osteoarthritis (OA). The predominant cells in the SpA group were CD8 lymphocytes. These results suggest that ankylosis of the ZA joint occurs preferably before the appearance of bridging syndesmophytes at the same level. Evaluation of the ZA joint by CT scan confirms this relation. The different types of lesions (except ankylosis) are independent of the formation of syndesmophytes and occur earlier than the radiographic appearance of syndesmophytes. The ZA joint may be first affected in AS and not secondary to the involvement of the vertebral body. The ZA joint can also influence the growth of syndesmophytes. Besides the age of onset of AS, ZA joint involvement determines the morphology of the enthesopathies: coarse (DISH-like) enthesopathies are seen at the level of AS without ZA ankylosis, whereas at the level of syndesmophytes the ZA joints are ankylosed.


Histopathology of ankylosing enthesopathy (ANKENT)

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ANKENT is a naturally occurring, progressive stiffening of the ankle and/or tarsal joints in mice. It occurs in up to 30% of adult mice of C57 black background strains, all in female mice. ANKENT usually starts at the age of 4–8 months, develops during a period of 2–4 weeks, and then remains stable. Ankylosing enthesopathy was found to begin with a short phase of proliferative inflammation of the joints and adjacent tissues, with some fibrous exudation, some leucocytic infiltration, and slight bone erosion during the first 2–3 weeks. This inflammation is soon accompanied and followed by proliferation of cartilaginous cells at the bone insertions of joint capsule ligaments (entheses). Their articular cartilage itself shows only slight proliferation. Ossification of the cartilage proliferations and some desmal ossifications lead to large bone spurs (syndesmophytes) that inhibit mobility. Fusion of cartilage proliferations or of bone spurs from adjacent bones occasionally leads to synchronous or marginal ankylosis.

ANKENT in mice strongly resembles the condition seen in the spinal joints in ankylosing spondylitis (AS) in man: a short lasting, scarcely destructive inflammation at the entheses followed by proliferation of cartilage and bone, leading to ankylosis mainly the margins of the joint and leaves the central articular cartilage intact for a long time. In nearly 60% of Mexican mestizos with AS tarsitis occurs. In AS affection of the spine is prominent, and involvement of an ever
increasing number of joints is usual, even though the disease often shows remissions and exacerbations. ANKENT seems to be limited to the tarsal/ankle region, and although several joints are affected, they are more or less at the same stage of pathology. The only place at which a second inflammation commonly occurs is the contralateral tarsal/ankle area. The spine is not affected in ANKENT. The histopathology of ANKENT has been published.1

The presence of a B2702 transgene causes increased frequency but does not markedly affect the severity or type of lesions. ANKENT differs considerably from the spontaneous inflammatory arthritis in rats transgenic for HLA-B27. From the spontaneous inflammatory arthritis reported by Khare et al in B27 transgenic mice lacking β2 microglobulin, and with progressive ankylosis that occurs in mice homozygous for the ank gene.


Is inflammation the trigger for new bone formation in ankylosing spondylitis?

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Objective—To test the hypothesis that new bone formation in ankylosing spondylitis (AS), a member of the “family” of HLA-B27 associated diseases, is triggered by inflammation.

Method—The study was based on light microscopic studies of tissue samples taken either at operations or as biopsy specimens from patients with AS and psoriatic arthritis (PsA). (Patients with AS—45 bone samples, 308 synovial tissue; patients with PsA—95 bone, 863 synovial tissue.)

Results—The typical formation of new bone in AS and PsA takes the form of desmal ossification: in the cambium layer, fibroblasts transform using irradiating type I collagen fibres, into pre-osteoblasts and osteoblasts. These subsequently form new, fibrous bone with no interference of any elements of inflammation.

Conclusion—Our study indicates that new bone formation in AS is a desmal ossification at the enthesis border of bone and that there is no evidence for inflammatory triggers. Analogueous processes have been seen in transgenic (BMP-6) mice.

Pathology of peripheral joints in spondyloarthropathy

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Peripheral joint involvement occurs in approximately 30% of patients with ankylosing spondylitis (AS) and is often a presenting feature. Immunohistological studies of synovial membrane (SM) show an intense inflammatory infiltrate characterised by a thin lining layer, prominent aggregates of CD4+ > CD8+ T cells, and a large number of factor VIII+ blood vessels. In addition, in a disease not associated with autoantibody production, prominent aggregates of B cells and plasma cells are seen.

Features of AS SM are similar to those described in another spondyloarthropathy, psoriatic arthritis (PsA). Further studies in PsA have focused on vascular staining and on T cells. The SM in PsA is highly vascular, suggesting prominent angiogenesis. Of interest, PsA SM endothelial cells express both NURR-1, an early activation gene which may have a role in cell proliferation, and MMP-1, which may help breakdown surrounding collagen.

Whereas CD4+ T cells predominate in PsA SM obtained during active disease, CD8+ T cells outnumber CD4+ T cells by 2:1 in synovial fluid. Given the association of PsA with HLA class I antigen, we proposed a CD8+ mediated immune recognition event. Studies of T cell receptor (TCR) phenotype confirmed that the CD8+ T cells are clonally expanded as compared with peripheral blood, with smaller, but none the less significant, clonal expansions also occurring in the CD4+ T cell population. Of interest, although TCR phenotype studies of PsA SM obtained during active disease do indeed confirm a predominant non-specific influx of T cells, with metathexe induced disease remission, the clonal nature of the remaining, probably disease-pathogenic populations of CD8+ and CD4+ T cells is still unexplained.

Thus these studies strongly support the concept of a specific T cell mediated immune event occurring in PsA SM, probably involving CD8+ and CD4+ T cells as well as dendritic cells which express both class I and class II HLA molecules.

Axial pathology in ankylosing spondylitis (AS)

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This presentation is based on a systematic screening of the histopathology of early involvement (5 biopsies, 2 bone and 7 necropsies) of patients with AS at different stages of the disease and of 22 control necropsy cases. Furthermore, spinal material from 9 necropsies of AS cases was studied.

In AS SI joints there is more frequent synovitis, pannus formation and superficial cartilage destruction, myocard narrowing, enthesis, intra-arterial fibrous strands, new bone formation and early ankylosis than in control cases (p<0.05). Cartilaginous fusion is seen in both groups, but occurred much earlier in AS. When a joint is ankylosed, no synovium remains.

Mild but destructive synovitis and myoid subchondral bone marrow are the earliest changes identified. Destruction of adjacent articular tissues is followed by scarring by fibrous tissue, woven bone, and new cartilage. The original cartilages fuse and this is the predominant mode of early ankylosis. All cartilaginous tissues are replaced by bone. Active enthesis and scars of presumed previous enthesis are seen at all stages except the early one. PsA SM is bone at first dense, but later becomes porotic.

In the spine the interdiscal joints exhibit either synovitis or enthesis with capsular ossification, myoid bone marrow, chondroid metaplasia, synchondrosis, and ossification. Inflammatory changes are seen all along the annulus fibrosus, particularly at its chondroid enthesis, in the deeper perivertebral liga- ments, and at their insertion by Sharpey’s fibres. Chondroid metaplasia is seen, as well as fibrosis and ossification whether endochondral or woven. Replacement of inflammatory changes by bone leads to syndesmophytes. Inflammation sometimes occurs within the vertebral body (spondylitis) or disc (discitis).

In conclusion, in AS associated sacroilitis, synovitis and subchondral bone marrow changes explain the widespread joint destruction better than enthesis. Enthesitis probably has a larger role in the spine, but otherwise spinal and SI changes are similar.

Possible role of TGFβ and BMPs in bone and entheses pathology

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Bone morphogenetic proteins (BMPs), members of the transforming growth factor β (TGFβ) family, play a critical part in bone, cartilage and tendon repair and may influence homeostasis of animals. Common effects of this growing number of morphogens have been described for the process of bone healing, distinctive and unique characteristics may belong to individual BMPs in human.

Currently, few data are available on the role of these molecules in the physiology and pathology of adult tissues. The most common expected effect is ossification. However, in adults, bone and cartilage contain several of these morphogens physiologically without induction of pathological calcification.

Our data have shown that several BMPs and TGFβs are differentially expressed in synovial tissue of normal, acute and destructively inflamed joints. BMP-4, BMP-5, and, to some extent, GDF-5 were found suppressed, correlating with the severity and chronicity of the inflammatory process. In contrast, TGFβ2 seems to be upregulated early after trauma to counterbalance destruction. These data suggest an important role for BMPs and TGFβs in homeostasis and repair in adult skeletal tissues. This role of morphogens and growth factors obviously depends on the type and differentiation of cells, the expression level of specific receptors, the quality of inflammation, and the mechanical stress on bone, tendons, and joints.

Appropriate signals are given by BMP-2 and BMP-4 during callus formation in bone healing. BMP-2 also enhanced tendon to bone healing, whereas GDF-5 and GDF-6 enhanced healing of tendoachilles tendon. In contrast, BMP-7 is inappropriate for Achilles tendon repair and may induce an ossicle. Overexpression of certain BMPs may promote degenerative processes of the intervertebrate disc or may induce fibrocartilaginous ossifications progressiva.

TGFβ may induce synovitis by chemo- taxis, synovial cell proliferation and hyperplasia, and mediate angiogenesis by induction of vascular endothelial growth factor. TGFβ supports non-specific wound healing and fibrosis. Over time TGFβ may enhance osteoarthritis.

In summary, TGFβ may provide protective signals early during the inflammatory process but induces non-specific fibrosis upon chronic disease progression. BMPs and TGFβ seem to have an important role in tissue homeostasis with an individual expression pattern depending on the type of tissue. Dysregulation of this process in two different pathological conditions: overexpression may induce pathological ossification; suppression, on the other hand, may give way to the dedifferentiating and destructive signals of decompensation.
Articular cartilage is a composite tissue with mechanical function. The composition and architecture of the matrix constituents differ between different sites in the joint. The tissue has to respond to changing functional requirements with age by adapting its structure via remodelling. The cells, chondrocytes, govern these processes. It is of key importance that they have the ability to monitor tissue function and structural integrity.

The tissue is composed of molecules assembled to provide structural features to give the essential tensile properties. Major contributions come from the network of collagen fibres that provide essential tensile properties and the aggrecan assemblies providing an extreme density of negatively charged proteoglycans and ensuring osmotic pressure essential for retaining water and restricting water movement. Minor components have key roles in regulating the molecular constituents, in remodelling matrix assembly, and in signalling matrix conditions back to the cells. Because functional requirements vary with age and the macromolecular assembly is variable, albeit the overall structure is rather constant. Thus in the superficial layer the structure is quite distinct from that at deeper layers. In each layer the organisation of the matrix close to the cells in the pericellular and territorial areas is quite distinct from that in the interterritorial area. Thus collagen fibre dimensions are essential for the tensile properties of the tissue, and abundance of collagen binding proteins differ between the various compartments. Also other constituents change with site in the tissue. Thus cartilage oligomeric matrix protein (COMP), a member of the thrombospondin superfamily, is particularly enriched in the superficial part of the adult articular cartilage, where it is found predominantly in an interterritorial location. Interestingly, the protein is in earlier stages of the joint development found primarily in a more pericellular location, where it is also particularly enriched in the growth cartilage. Another protein, cartilage link protein (CLIP), of M.9 kDa, is predominantly localised in the middle to bottom third of the articular cartilage, also enriched interterritorially. A family of leucine-rich proteins, including the collagen binding proteoglycans decorin, biglycan, fibromodulin, and lumican, seem to have major roles in the assembly of the collagen network and in maintaining its properties by interlinking collagen fibres. This family includes members not containing glycosaminoglycan chains, some of which promote cell attachment such as chondroadherin and osteoadherin, which are likely to have a key role in mechanical signals from matrix to cells important for tissue homeostasis.

Enthesitis: a broader definition

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Enthesitis is the characteristic primary lesion of ankylosing spondylitis (AS) and related spondyloarthropathies (SpA), starting with soft tissue inflammation, followed by the underlying bone marrow oedema with only occasional inflammatory cells. These changes predate the bone cortex erosion and new bone formation. Recent studies suggest that, unlike RA, where synovitis is the initial or primary lesion, the synovitis of SpA may be a secondary event, at least in some joints. A suggestion is made that we should broaden the definition of "enthesis" so that it includes not only the bony attachment sites of tendons and ligaments but also the attachment sites of the cartilage at the end of the bone. Thus the chondral-subchondral junction of a bone is an enthesis where cartilage (rather than a ligament, capsule, or a tendon) attaches to the bone. The additional reasons for this concept will be discussed.

A plea is made that the investigators interested in enthesitis of AS and related SpA should also study the enthesitis and its evolution in African patients who have HIV associated SpA. Prevalence of HIV in South Africa, where SpA is a rarity today, must be compared with the much higher prevalence of SpA in Western Europe. Thus the differences in the enthesitis of AS in Africa and Europe may reflect an evolutionary adaptation of this disease to different environmental conditions.

Enthesitis and reactive arthritis

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Enthesitis is a key feature of the spondyloarthropathies, and it has been suggested that it is associated with the pathogenesis of both peripheral arthritis and spondylarthropathy. Enthesitis is also common in patients with acute reactive arthritis, with reports of its incidence varying between 10 and 30%, usually associated with arthritis. However, recently, the term reactive enthesitis has been introduced. Enthesitis can be the only reactive musculoskeletal symptom in about 5–10% of patients with reactive musculoskeletal complications. According to previous studies with ultrasonography, enthesitis seems to be a frequent sign in patients with spondyloarthropathies, and seems to run a more chronic course than distinct arthritis. Patients with spondyloarthropathies have a high frequency of the HLA-B27 antigen. The importance of isolated reactive enthesitis has not been studied in detail, but the previous study and our own results favour a less significant association between HLA-B27 and reactive enthesitis.

Enthesitis in spondyloarthropathy

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Enthesal insertions are ubiquitous throughout the skeleton, and the importance of enthesitis in the pathology of spondyloarthropathy (SpA) has long been recognised. Enthesitis is a prominent feature of spine, foot, and pelvis pathology in SpA and to a lesser extent in small joints of reactive arthritis. The recent use of fat suppression magnetic resonance imaging (MRI) techniques, which are optimised for visualising sites of bone inflammation, has expanded our understanding of the enthesitis lesion.

The clinical concept of enthesitis is of a focal pathology at the insertion of a tendon, ligament, or joint capsule to bone. This is seen in MRI of the plantar fascia, but in many cases severe bone marrow inflammation (ostitis) affects much of the calcaneum. However, similar MRI findings are evident in patients with mechanical plantar fasciitis. This similarity between mechanical and inflammatory plantar fasciitis may suggest that biomechanical factors are also important in the pathology of SpA associated enthesitis. The structures which make up the enthesis (tendon, ligament, capsule) have a low water content and therefore are not well visualised by MRI and it is the adjacent soft tissue changes and bone changes that are best appreciated. Interpretation of MRI scans for the presence of enthesitis in spondyloarthropathy may therefore be difficult because of soft tissue changes related to synovitis. Nevertheless, many cases have diffuse bone oedema in knee joint synovitis in SpA. As assessed by MRI combined with...
sonography most of these changes are associated with focal enthesitis. The frequency and extent of enthesitis in synovial joints has implications for the mechanisms of synovitis in SpA and, possibly, synovitis may be secondary. The SpA are associated with an array of bone pathology, including SAPHO syndrome, arthritis mutilans, spondylodiscitis, CMRO, and others. Some authors have suggested that enthesitis is the primary lesion in SAPHO. The diffuse MRI changes in these conditions are highly reminiscent of enthesitis at other sites and an enthesitis associated pathology unifies these changes.

Classical pathological studies from the spine, and more recently the sacroiliac joints, have shown prominent inflammatory changes in the bone. Some have assessed the bone lesions from SAPHO and microbes have been recovered, but these are not universal. We have also noted that a lymphocyte infiltrate is not evident at the actual enthesis soft tissue insertion in early enthesitis, but changes are more likely in the underlying bone. Combined with pathological studies suggest that SpA associated periostitis may be secondary to the diffuse enthesitis associated bone changes.

Imaging of enthesitis

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Enthesitis, the inflammation at sites of a tendon, fascia, ligament, or joint capsule attachment to bone, is a distinctive pathological feature of spondyloarthropathy. Peripheral extra-articular enthesitis is a clinical hallmark of spondyloarthritis and may be seen in all conditions, including the undifferentiated ones.

The imaging methods useful in studying peripheral enthesitis include plain film radiography, low kilovolt radiography, bone scintigraphy, diagnostic ultrasonography (US) and magnetic resonance imaging (MRI).

Plain film radiography shows a combination of erosion and bone proliferation but only in the more advanced phases. In general, the bone proliferative changes of enthesitis are ill defined and finely speculated and differ from the coarse and well marginated non-inflammatory bony outgrowths such as those of diffuse idiopathic skeletal hyperostosis (DISH).

Low kilovolt radiography allows the visualization of more specific soft tissue diagnosis than conventional radiography. The drawback is the relatively high level of radiation exposure.

Technetium-99m ethylene diphosphonate scintigraphy has been shown to be a sensitive indicator of heel enthesitis, but its specificity has not been determined.

Real time, high frequency US shows the swelling of the entheses, alterations of the normal ultrasound texture consisting of decreased echogenicity owing to inflammation, the dissection of adjacent bursae by fluid collection, and peritendinous soft tissue swelling.

MRI shows swelling of the entheses and the peritendinous soft tissue, the deviations from the normally uniform low signal intensity of tendons and ligaments, the dissection of adjacent bursae by fluid collection, and oedema of the bone near the insertion.

Is there a unifying concept for the spondyloarthropathies?

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Clinical, epidemiological, genetic, and animal data suggest that exposure to bacteria is crucial to the pathogenesis of the spondyloarthropathies (SpA). In reactive arthritis (ReA) this means in vivo persistence of ReA associated bacteria, in inflammatory bowel disease (IBD) breakage of tolerance to gut bacteria because of a damaged gut mucosa and, possibly, in psoriatic arthritis a chronic stimulation of the immune system by bacteria such as streptococci, which might be responsible for both the skin and the joint manifestations. Primary ankylosing spondylitis (AS) and undifferentiated SpA are, by definition, not associated with any of these diseases, though they are the most common SpA subsets. However, in more or less in the patients asymptomatic manifestation of IBD or an asymptomatic infection with one of the ReA associated bacteria might be present.

Some of the SpA manifestations, such as peripheral arthritis, are only moderately associated with HLA-B27. However, others, such as sacroilitis/spondylitis, enthesitis, and uveitis, are strongly associated with HLA-B27. There is now growing evidence that the main target is the enthesis, which might be primarily affected also in peripheral joints and the spine. Thus in B27+ patients the primary target might be the synovium while in B27+ patients it might be the enthesis. This hypothesis has to be proved in future studies. Evidence from studies in ReA and IBD associated arthritis suggests that only a limited number of bacterial antigens are seen by CD8 T cells, possibly presented by HLA-B27. Although some of the immunodominant antigens have been identified, no common bacterial antigen shared by different bacteria has been identified.

It is clear that at least in ReA and IBD the peripheral arthritis is caused by the presence of bacteria. This is less clear for other manifestations, such as sacroilitis/spondylitis, enthesitis, and uveitis. No bacterial antigens have been detected in these structures and it seems unlikely that bacteria persist in such different structures. For these manifestations it is more likely that exposure to bacteria induces an autoimmune response to a crossreacting autoantigen. No such antigen has been identified to date. One interesting candidate antigen is proteoglycan, which is present in all structures, possibly affected in the course of disease such as entheses, uvea, and aorta. The G1 domain is immunodominant in animal models of AS.

Based on current evidence it is suggested that bacterial antigens shared by different bacterial species induce an autoimmune response in HLA-B27+ patients and that the autoantigen is located in enthesis, cartilage, and/or bone. In HLA-B27− patients the constant presence of bacterial antigens might be sufficient to explain the inflammation.

Proteoglycan aggrecan in enthesitis: facts and concept

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The inflammation of entheses attached to the axial and sacroiliac joints is a distinctive feature in spondyloarthropathies (SpA), typically seen in ankylosing spondylitis (AS). In SpA, the infiltration of proinflammatory lymphocytes and monocytes/macrophages in entheses and disc end plate indicates the involvement of immune and cytokine insults. Mice with H-2d genotype are susceptible to development of arthritis and spondylitis in response to repeated immunisation with proteoglycan aggrecan (PG). In contrast, the spondylitis is not seen in susceptible animal strains challenged with either type II collagen or link protein. The proteoglycan induced spondylitis is characterised by initial early mononuclear cell infiltration into the outer margins of the annulus in the enthesal insertions on the vertebral bodies, followed by angiogenesis and a progressive discitis, which lead to destruction of the nucleus and end plates as seen in human advanced AS. Injection of the aggrecan G1 domain (G1) alone also can induce the same spondyloarthropathy, indicating that the pathogenic epitope(s) that cause spondylitis may located in the G1 domain. In humans an increase of immunity to proteoglycan aggrecan and the G1 domain is seen in the patients with AS. This supports the concept that the aggrecan G1 domain may serve as an autoantigen, which may play a part in initiating and sustaining the inflammation in spinal entheses leading to syndesmophyte formation.

Although little is known about the biochemical nature of the entheses, recent evidence shows that it contains molecules typically seen in cartilage, such as collagen type II and large proteoglycan aggrecan including the G1 domain. Because SpA is strongly associated with HLA-B27 and gut or uninogenous pathology, immunity to an insult agent in gut or uninogenous tract may break the immune tolerance to PG or G1 in an SpA susceptible (HLA-B27) population by molecular mimicry mechanisms. We can isolate G1-specific autoreactive T cell lines from patients with rheumatoid arthritis as well as from healthy subjects. These T cells can produce arthritis when they home in to knee joints in immunodeficient SCID mice. These PG or G1-specific auto-aggressive T cells may therefore expand and home in to PG-rich tissues (entheses, articular cartilage, spinal disc, etc), initiating inflammatory reactions, including mononuclear cell (monocytes and lymphocytes) infiltration and cytokine ( interleukin 1α, interferon γ, transforming growth factor β, etc) secretion. G1-specific T cells may also attack extra-articular tissues, such as anterior uveal tract, heart, aorta, and brain, where aggrecan G1 and G1-related epitopes (versican G1 domain and linked heparans) are expressed.

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