The enthesis in psoriatic arthritis

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ABSTRACT

In recent years the argument that enthesitis is the primary lesion in many or most patients with psoriatic arthritis and spondyloarthritis has gained further credence from animal models including IL23/IL17 axis and TNF dependent models. The role of joint biomechanics at entheses and other sites of high physical stressing as a unifying underlying basis has also been strongly supported by animal models. Mirroring the animal model data, it has been empirically shown that therapies that work for entheseal-related inflammation in man including IL23/17 axis or TNF cytokine antagonism are effective for entheseal pathology. The biological basis for the effectiveness of other therapies including PDE4 inhibitors on enthesitis is poorly understood due to the relative difficultly in procurement of entheseal tissue. This absence of a histological gold standard renders it difficult to decipher how effective various therapies are in treatment of enthesitis. Despite advances in understanding enthesitis in animal models, there is a dearth of data thus far on the immunology of human entheses that likely will be key to further refinements in therapy development.

History of enthesitis in PsA

When Wright defined psoriatic arthritis (PsA) as a distinct entity from rheumatoid arthritis (RA), one of the defining features was axial disease which was present in up to 40% of cases (1, 2). Radiographic assessment of axial disease showed the presence of spinal fusion at different entheses around the spine thus pointing to an important role for the enthesis in axial changes. Moll and Wright were able to lump the spondyloarthropathies (SpA) including PsA, ankylosing spondylitis, reactive arthritis and inflammatory bowel disease associated arthritis together based on the axial disease proclivity, but also the tendency for peripheral enthesitis (3). Given that physicians tend to only recognise superficial easily accessible entheses, but there many hundreds of insertions around the skeleton when all the capsules, ligaments, tendon and fascial attachments are counted, the idea arose that maybe enthesitis was the primary lesion, or pointed towards a primary mechanism for disease (4, 5). Wright further described 5 groups of PsA, namely distal interphalangeal joint involvement, arthritis mutilans, symmetrical polyarthritis, oligoarthritis and spondylitis (2). The polyarthritis group had been suggested to be 'indistinguishable' from RA; it would be reasonable to question if the primary pathology for this group of patients is indeed entheseal. However, one could argue that this group could very well be seronegative RA with skin psoriasis; even then, it is likely that enthesitis is a feature, as will be described later in this review, where enthesitis is evident even in patients with skin psoriasis alone.

Clinical enthesitis in PsA

Following the enthesitis theory of disease being put forward, it is of note that the clinical prevalence of enthesitis as assessed by clinical means appears to be higher in clinical trials now than it was historically. The clinical assessment of enthesitis in PsA is rendered difficult because enthesitis may not be associated with significant swelling, and consequently may be difficult to distinguish between fibromyalgia, mechanically related or degenerative related enthesopathy, but which are more common in subjects with high BMIs, which is often the case in PsA (6). Nevertheless clinical enthesitis has been documented in a third of a PsA population (7). There are a number of enthesitis indices, all of which rely on subject assessment of response to pressure over insertion sites, so a "gold standard" assessment is not available (8-13).

Imaging enthesitis in PsA as a diagnostic test

The original studies from the 1990s by Jevtic and colleagues looking at the

hands, and the Leeds group studying the knees, suggested that MRI could differentiate between PsA and RA based on enthesitis and extracapsular inflammation (14, 15). However, for subjects with oligoarthritis the diagnosis remains largely clinical, and for subjects with polyarthritis the main diagnostic tests used are rheumatoid factor and anti-citrullinated protein antibodies to exclude RA. Numerous studies have shown that enthesitis and osteitis were more common in PsA compared to RA (Fig. 1), and that diffuse peri entheseal osteitis was a useful differentiating factor, but some studies have failed to show that osteitis was statistically more common in PsA (16), perhaps reflecting Wright's original observation that a small proportion of 'PsA' is in fact coincidental RA with psoriasis (17).

The differences between PsA and osteoarthritis (OA) are similarly not completely well defined. Although imaging studies show some differences between PsA and OA (18, 19), the changes may not be sufficient in certain patients to consider imaging as a diagnostic tool in distinguishing these common arthropathies (20). The basis that enthesitis as a primary site of pathology suggests that there may be a PsA-OA overlap phenotype (21), making clinical differentiation difficult in some patients.

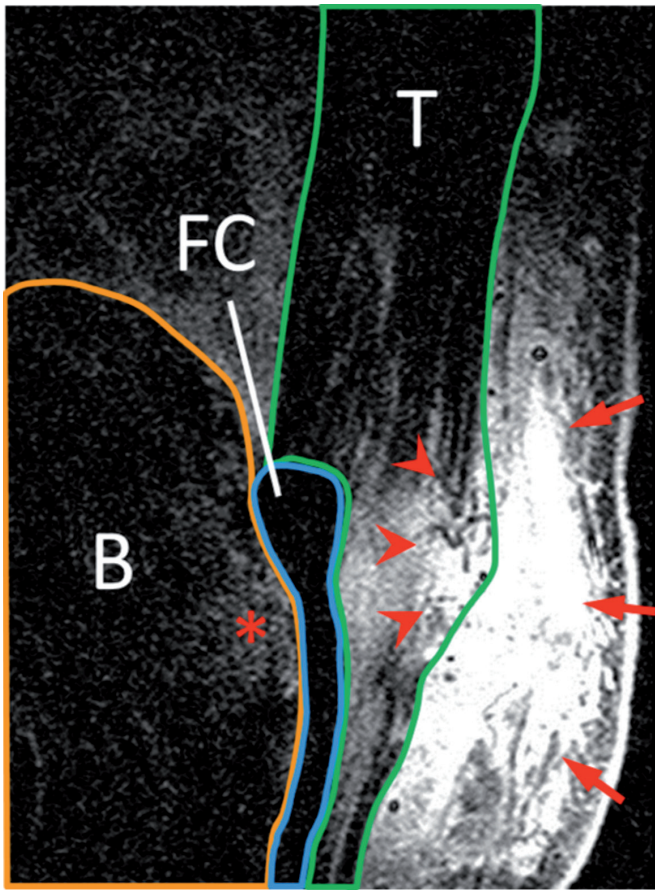

Fig. 1. High resolution MRI of the Achilles tendon (T) of a 32-year-old male with psoriatic arthritis associated with swelling around the heel. There is diffuse soft tissue inflammation (arrows) around the entheseal attachment with swelling and disruption of the tendon near the insertion (arrowheads). A layer of fibrocartilage (FC) forms part of the enthesis organ between the tendon and the calcaneal bone, which is the avascular region of maximal mechanical stressing. There is bone oedema (histologically an osteitis) (asterisk) in the calcaneum adjacent to the enthesis. The avascular nature of the FC leads to its sparing in the very earliest stages of disease.

Classification of controversial enthesitis associations

For a long time, it was unclear why nail disease predicted both PsA development and more common distal interphalangeal (DIP) joint involvement in PsA. The enthesitis theory of disease provided an anatomical explanation, since it was shown that the DIP joint entheses, including the extensor tendons, collateral ligaments and dermal ligaments, provide an elaborate anchorage mechanism to the nail (22). Moreover nail involvement is associated with diffuse remote systemic enthesopathy in the lower limbs (23).

Recently high resolution MRI has been used to explore flexor tenosynovitis which is the most striking abnormality in dactylitis (24). It was observed that microscopic enthesitis was seen in the minipulleys around the flexor tendon, including the A1-3 pulleys which could explain the tenosynovitis. Previous studies have reported enthesitis in other sites in dactylitis, including the collateral ligaments and dorsal tendons (25, 26). These findings in the nails and dactylitis are faithfully recapitulated in several animal models of inflammatory arthritis, that begins at the enthesis (27).

Animal models with PsA features: primary enthesitis

In recent years, animal models have been developed which demonstrate the primacy of enthesitis in SpA like disease. The arthritis in the DBA-1 male mice and that in TNF-transgenic (tg) mice was shown to start at the enthesis (27-30). The most exciting translational model is that of arthritis following systemic over expression of the IL-23 cytokine in the liver which resulted in 3 cardinal manifestations including a primary enthesitis, skin rash and aortic root inflammation (31). Of note the same model, analogous to the TNF tg model, had previously been reported as a surrogate for RA, with extensive synovitis and bone erosions. However the early histological assessment of enthesitis permitted the demonstration of a primary enthesitis that subsequently spread to the adjacent tissues. In this particular model a population of innate lymphoid like cells (ILC) were documented at the entheses and these were likely key to driving the disease process (31).

ILC type cells are pivotal to gut and skin barrier tissue repair via the elaboration of key pro inflammatory cytokines including IL-22 (32). Since the human enthesis exhibits extensive microdamage in the cadaveric setting, it is tempting to suggest that IL-23-related signalling at the enthesis is key to tissue repair but that the signalling might be altered in disease.

The SKG mouse model was also previously reported as RA like and is due to aberrant T cell gain of function (33). A recent modification of this model showed a primary enthesitis and also dactylitis and nail disease, both of which link to enthesitis in humans (34-

36). Two further models, the B10Q (37) and the K5.Stat3C:F759 mice have shown similar psoriatic presentations with a key role for enthesitis (38).

Enthesitis points towards a unified biomechancial concept

The presence of fibrocartilage at the enthesis points to complex compressive, tension and shearing forces (Fig. 1) (39). Fibrocartilage also is present where tendons wrap around bony pulleys especially in the ankle and foot, and it also is present in other PsA target sites (4). These most notably include the sacro-iliac joints and the sternoclavicular joints, both of which can be affected in PsA, and are synovial joints that have a perpendicular orientation to the ground, and consequently experience the same types of stress to the underlying bone. This strongly suggests that the enthesis and enthesis organ concepts point towards a unifying biomechanical basis for PsA. Clearly biomechanics may be important since subjects with higher BMIs who have psoriasis have a higher risk of PsA (40). Injury is also associated with a risk of PsA (41, 42). In the animal model setting, it has recently been shown that biomechanics alone are key to the development of SpA (43).

Imaging enthesitis in psoriasis to predict PsA

Given the continually emerging data that strengthens the enthesitis concept, more research is taking place on the importance of enthesitis in early PsA. Enthesopathy in subjects with psoriasis is very common and indeed much more common than synovial changes. Of note, sonography shows that about 40% of psoriasis cases have enthesopathy, but clinical studies indicate that fewer than 2% of psoriasis cases get PsA each year (44, 45). The need to define which groups develop PsA is of particular relevance for early therapy and prevention.

We and others have shown that about 10% of psoriasis cases have power Doppler changes on ultrasound at large entheses reflecting inflammation, but that this is not seen in normals (23). This may be the best imaging biomarker for predicting PsA development but further work is needed.

An emerging question is whether the treatment of skin psoriasis with agents that are known to be effective for PsA also may prevent arthritis development, or at least lead to the regression of subclincal arthropathy. A recent ultrasound study provided the first evidence for this and showed that anti TNF and methotrexate were associated with the regression of clinically occult enthesopathy (44). This places Dermatologists at the forefront of therapy for the possible prevention of enthesopathy that may evolve to PsA, but further studies are needed.

Lessons from therapies

Over the last few years, several studies have indicated that clinically determined enthesitis may respond to therapies that target both IL23 and IL17 (30, 46). Small molecules and PDE4 inhibitors also effectively target enthesitis and nail and dactylitic disease (47). It is not well understood why some patients with PsA who are well-treated with diminution of joint swelling and normalisation of CRP, complain of persistent entheseal symptoms (21).

Conclusions

In recent years a wealth of experimental data has emerged showing the primacy of enthesitis in animal models of PsA. Experimental and clinical data has also emerged showing the close functional link between enthesitis and nail disease and dactylitis. The assessment of human enthesitis is largely confined to imaging, and there is a need to evaluate the pathophysiological basis for disease localisation to this site in man.

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