Clues to the Pathogenesis of Psoriasis and Psoriatic Arthritis from Imaging: A Literature Review

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ABSTRACT. This article summarizes a presentation on imaging of skin and joints in patients with psoriasis and psoriatic arthritis (PsA) from the 2007 Annual Meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). Plain radiography provides valuable insights into the pathogenesis of PsA but is limited because only calcified tissue can be imaged. Newer techniques such as magnetic resonance imaging (MRI) and ultrasound (US) provide additional clues to the pathogenesis of this peripheral, axial, and dermatologic disease. MRI and to a lesser extent US allow visualization of articular and periarticular structures, showing widespread juxtaarticular inflammation in PsA. Bone edema, a surrogate marker of inflammation, can occur throughout the digit in psoriatic dactylitis. Localization of inflammatory change at the juxtaarticular entheses suggests this as the primary site of inflammation. Recent imaging studies provide insights into the relationship between nail and articular disease, demonstrating extension of inflammation from entheseal structures at the distal interphalangeal joint to the nail bed, but the temporal or anatomical progression of these changes remains elusive. Imaging of the skin lags behind that of the articular structures, partly because the skin is readily available for biopsy; however, newer techniques such as laser Doppler imaging provide insights into angiogenesis at the advancing edge of psoriatic plaques. Future work will explore the relationship between immunohistology and imaging of skin and joints. Improvements in imaging articular soft tissues with ultra-short echo time MRI and skin with multiphoton fluorescence microscopy promise insights into anatomical and functional changes. (J Rheumatol 2008;35:1438–42)

Key Indexing Terms:
PSORIATIC ARTHRITIS PSORIASIS DACTYLITIS ENTHESITIS NAIL PSORIASIS

At the 2007 Annual Meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), the imaging committee presented a discussion of the imaging of skin and joints in patients with psoriasis and psoriatic arthritis (PsA), including future trends. This article, which summarizes that presentation and reviews the literature, is structured as follows: articular disease, with literature review by imaging modality and inferences as to anatomical location, pathology, and pathogenesis; skin and nail disease, and future trends.

Articular Disease — Review by Imaging Modality

Plain radiography. The key radiographic features of PsA have been defined as joint erosions, joint space narrowing,

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bony proliferation, osteolysis (including pencil-in-cup deformity), ankylosis, and new bone formation at entheses, both central and peripheral[1]. Erosive changes are marginal [similar to rheumatoid arthritis (RA)] but become irregular with disease progression because of new bone formation adjacent to the erosions[2]. Spondylitis is seen in about 25% of patients with PsA and radiographically looks similar to ankylosing spondylitis (AS) with some important differences.

Radioisotope. Scintigraphic studies of patients with lesions of psoriasis but no clinical arthritis have been particularly interesting in raising the prospect of subclinical disease in those with psoriasis. Namey and Rosenthall scanned 12 psoriatic patients and 12 controls, showing that all psoriasis patients had markedly abnormal scans with symmetrically increased periarticular uptake. In contrast, none of the controls (with other inflammatory dermatological disorders) had similar findings[3]. Scintigraphic studies in PsA also have shown extrasynovial abnormalities[4].

Magnetic resonance imaging (MRI). Although synovitis in PsA and RA is indistinguishable on static or dynamic MRI scanning, features of enthesitis, dactylitis, extracapsular inflammation, and spondylitis can be used to differentiate the 2 conditions[5]. Bone edema is commonly described as an MRI feature of PsA. In RA, evidence is emerging that bone edema reflects inflammation and future damage[6]. Bone edema at entheses on MRI has been correlated with hot spots on radionuclide scanning[5] and has been shown to respond to anti-tumor necrosis factor therapy[5]. In addition, MRI has improved our ability to detect axial disease in PsA.

Ultrasound. Musculoskeletal US has been used in PsA to investigate synovial disease, enthesitis, and sacroiliitis. When imaging enthesitis, edema and increased vascularity at the tendon are characteristic findings, but more recently, power Doppler also has been used to help distinguish between inflammatory and mechanical enthesitis[7]. Dactylitic digits also have been imaged using US, with inflammation shown in all tissues of the affected digit.

Inferences as to Anatomical Location, Pathology, and Pathogenesis

Spine. Spinal disease in PsA is known to be asymmetrical, with unilateral changes seen in 21% of those with PsA-related sacroiliitis[8]. Syndesmophytes are seen less commonly in PsA and are also usually asymmetrical. It is unclear whether this may represent an important difference in the underlying pathology. Asymmetry may be a function of the paucity of syndesmophytes in the spine, rather than a true difference in pathology[9].

Syndesmophytes in PsA also show a different morphology. They are more frequently paramarginal and may not appear in consecutive vertebrae. Syndesmophytes in PsA are bulkier, described by Bunim as "tear-drop" or "comma-shaped," and show significant thickening of one portion (upper or lower) of the syndesmophyte[10]. The pattern of cytokine profile and the activity of osteoblasts, both of which may result in these morphological changes, are unknown to date in PsA, although in a murine model of ankylosing enthesitis, Lories, *et al* provide evidence for an important contribution from bone morphogenetic molecules that trigger activation of the syndesmophyte signaling pathway[11]. An alternative explanation is that PsA patients do not have the same degree of reduced spinal mobility caused by involvement of the apophyseal joints in AS, resulting in greater mechanical stresses on the anterior aspect of the vertebra[12].

Cervical spine involvement is estimated to occur in up to 70%–75% of patients with PsA[13], making it much more common than sacroiliitis. Two distinct pathological types have been described: a primary ankylosing and a rheumatoid-like form. In multivariate analysis, rheumatoid-like disease was associated with B39 and DR4 antigens and with evidence of radiocarpal erosions[13]. This may be explained in a similar way to the peripheral pattern of disease in PsA (see below). Thus, synovitis in zygoapophyseal joints and within the atlantoaxial joint could be associated with extensive extraarticular inflammation causing erosion and instability in this region.

Distal interphalangeal (DIP) joint disease. DIP joint involvement, although not exclusive to PsA, is one of its characteristic features. Nail involvement is more common in PsA than in uncomplicated psoriasis, and DIP joint involvement is almost never seen in the absence of nail disease[14]. MRI studies have confirmed the intimate relationship between the nail bed, the distal phalanx, the DIP joint, and the insertion of the extensor tendon[15,16]. Subclinical disease is common[15]. It has been suggested that the primary site of inflammation on imaging studies is the entheseal insertion of joint capsule and extensor tendon, but longitudinal studies are lacking[16]. Given that cutaneous abnormalities usually precede articular lesions, it seems more likely that the nail bed disease is primary. On the other hand, the same disease process may be responsible for both manifestations. Longitudinal studies with high resolution MRI may help in this respect.

Enthesitis as the primary pathology. Power Doppler US techniques have shown that entheseal involvement affects 98% of patients with spondyloarthropathy (SpA) but is less common in controls with mechanical back pain (44%) or RA (60%). The commonest sites of involvement in PsA are Achilles tendon, patellar tendon, plantar fascia, and greater trochanter[7].

McGonagle, *et al* have hypothesized the primary role of enthesitis in PsA with secondary spread of inflammation to the synovium[17]. Jevtic and co-workers first described the extensive extracapsular inflammation seen on MRI scans in PsA[18]. Half their patients showed extrasynovial inflammation including thickened collateral ligaments and periarticular soft tissue, particularly in dactylitic joints. In one joint, predominant extracapsular inflammation was seen without significant associated synovitis, thus raising the possibility of nonsynovial inflammation in PsA[18]. However, not all

patients showed evidence of extracapsular inflammation. Thus, in PsA some patients may have a predominantly synovial disease (as in RA), and some may show a predominantly entheseal disease (as in SpA; although it may be that the somewhat ambiguous criteria suggested by Moll and Wright[19] enabled the authors to include cases of seronegative RA within their series).

However, as yet, the primary entheseal hypothesis awaits further confirmation. Enthesitis in PsA is not found universally in imaging studies, but this does not detract from the hypothesis; other possible explanations include stage and activity of disease and heterogeneity of disease phenotype.

Dactylitis. Dactylitis, a hallmark clinical feature of PsA, occurs in 16%–48% of reported cases. It is often painful, but a chronic, nontender dactylitic swelling can occur. Further, diffuse swelling of the upper limb has been described and may be a similar manifestation. The pathogenesis of dactylitis is still not fully understood, and although flexor tenosynovitis is a key feature on imaging, other abnormalities are also seen.

Following the work of Jevtic and co-workers described above[18], Olivieri, *et al* imaged 12 dactylitic fingers using MRI and ultrasound and found contrasting results[20]. All the dactylitic fingers had moderate to severe flexor tenosynovitis but no peritendinous edema. These authors initially concluded that dactylitis was due to flexor tenosynovitis and that the peritendinous soft tissue was not involved[20]. However, they subsequently showed that peritendinous inflammation and edema was present in some dactylitic digits[21]. Following this, they suggested that the peritendinous edema was probably caused by increased capillary permeability secondary to flexor tenosynovitis.

Healy, *et al* imaged 19 dactylitic digits and found soft-tissue edema and synovitis to be the most frequent abnormalities in 69% of digits[22]. A wide range of other abnormalities were frequently found including flexor tenosynovitis and bone edema, the latter in several patterns from discrete areas in a periarticular distribution to abnormalities in the metaphysis of the phalanx[22].

US of dactylitic digits has shown subcutaneous soft tissue enlargement, flexor tenosynovitis, and some related synovitis. However, studies have differed significantly in the involvement of peritendinous soft tissues (also called pseudotenosynovitis) and synovitis[20,23,24].

Despite the earlier controversy about the site of tissue inflammation in dactylitis, it now seems clear that virtually all the tissues are involved in an affected digit. If dactylitis is considered a paradigm for PsA, what does it tell us about the pathology of the disease? In contrast to RA, there is inflammation outside the synovial cavity but seemingly localized to certain affected digits. Dactylitis has been suggested as a form of the Koebner phenomenon, occurring deep within the tissue of the digit. Given that dactylitis most commonly affects the second digit in the hand and the fourth digit in the foot, some evidence supports this[25]. It is also clear that repeated minor physical insults to our digital joints and entheses are commonplace; thus, occurrence of dactylitis depends on other factors such as the individual immunogenetic profile.

Skin and Nail Disease

Imaging of the skin has improved our understanding of skin psoriasis. US studies have found that the average skin thickness is increased within the psoriatic plaque. These changes, which are due to a dense layer of scaling, a subepidermal low-echogenic band, and diffuse enlargement of dermis itself, may correlate with the sum of acanthosis and the upper dermis with inflammatory infiltrate[26], as this correlates with histometric thickness of this layer of the skin[27].

Laser Doppler imaging uses the same principle as Doppler US but uses low-level laser light. Two methods of imaging can be used: laser Doppler flowmetry (LDF), which measures flow at a single point; or a newer technique of laser Doppler imaging (LDI, or scanning laser Doppler), which measures blood flow over an area of skin[28].

LDF and LDI have confirmed the increased blood flow in psoriatic plaques[29], and quantified the flow as around 4 times normal[30]. This technique can differentiate the advancing edge of the plaque[29,30], and show increased blood flow in adjacent clinically noninvolved skin, extending for around 4 mm beyond the clinically obvious plaque[29,30].

LDF and LDI have been used to identify leading edges of plaques to allow directed biopsies to further investigate pathology[29,30], Hull, *et al* biopsied this hypervascular area just beyond the advancing edge of the plaque, but found no epidermal changes of T lymphocyte infiltration when compared with the non-advancing edge[29]. It was therefore concluded that the laser Doppler had been able to identify the earliest identifier of evolving plaques in the form of increased blood flow[29]. This fits with the observation that vascular abnormalities appear before clinical relapse.

LDF also has been used with dual wavelength light to differentiate between superficial and deeper microvascular blood flow. Using this dual wavelength LDI in psoriasis has shown that although blood flow in both layers of the skin is increased, the increase is far more prominent in deeper larger vessels than superficial capillaries[31].

As well as recognizing angiogenesis, Braverman and Yen showed on US that lymphatic capillaries extended high into the papillary dermis[32]. However, investigations with microlymphography found fewer lymphatics in psoriatic skin and a poorer spread of fluorescein tracer[33]. The authors believed there was most likely a structural or functional lymphatic abnormality, which would agree with Ryan's hypothesis that the edema seen in the dermis of psoriatic plaques results in part from a failure of adequate lymphatic drainage[34].

Using US, Wortsman, *et al* found no significant differences between normal and psoriatic nail thickness overall, but showed an enlarged nail–bone distance in those with

psoriatic onychopathy, suggesting the pathology is deeper than the nail plate itself[35]. This was not seen in patients with skin psoriasis but no onychopathy, and contrasts with MRI work by Scarpa, *et al*, which found a significantly increased nail thickness in 95.7% of all PsA patients (100% of those with clinical onychopathy)[15]. However, all Scarpa's patients had PsA, not just skin psoriasis, and the vast majority had MRI abnormalities in the distal phalanx.

Future Trends

Vascularity and angiogenesis. The angiogenesis seen in skin psoriasis shares morphological features similar to abnormal vessels found within the synovium. Vascularity of the synovium demonstrated on US power Doppler correlates well with histological findings of new vessel formation[36]. The reduction in power Doppler signal can be seen clearly in patients with inflammatory arthritis when treated with immunosuppressant therapy. Further work is also under way in Dublin exploring the use of MRI in assessing synovitis and the vascularity seen in PsA (FitzGerald O, personal communication). As noted above, there is the need to correlate synovial immunohistochemical changes with MRI appearances to validate this approach. The use of software to accurately quantify synovitis and vascularity in the form of dynamic contrast enhancement has been explored[37] and is being further developed by Prof. FitzGerald and his team.

Low-field MRI. The use of low-field or extremity MRI machines in rheumatology is now expanding because of their practicality in the outpatient department and increased comfort for patients. In RA, they are equivalent to high-field MRI in sensitivity and specificity of detecting bone erosions and synovitis[38]. However, they are significantly less sensitive when identifying bone marrow edema[38], which is of concern when considering their use in the imaging of seronegative conditions.

The only study of low-field MRI scans in PsA was done by Scarpa, *et al*. They scanned 26 PsA patients to look at nail and DIP joint disease[39] and found similar results to their previous study using high-field MRI[15]. However, no studies have directly compared high-field and low-field MR images to formally validate these machines.

New MRI sequences. New techniques using high-field MRI scanners also are being developed. Ultrashort echo time (UTE) imaging is a novel MR technique that allows the detection of signal from tendons, fibrocartilage, and cortical bone. These tissues can be imaged directly, allowing differentiation from each other. Changes that lead to the high signal on conventional images should be seen at an earlier stage using this technique. Further, the use of intravenous contrast will permit imaging of vascularity. Thus, UTE has the potential to show early changes at the enthesis, localization of changes to the fibrocartilage or tendon, and visualization of vascular, edematous and structural changes.

Skin. Novel methods of imaging skin also are currently in development. Optical coherence tomography (OCT) was initially developed for imaging the human eye, but is now being evaluated in skin disease. OCT uses infrared light instead of US to produce 2-dimensional images[40]. In psoriasis, this has shown a pronounced entrance signal corresponding to the scaling in psoriatic plaques and has visualized the thickening of the epidermis and the ill-defined border between the enlarged papillary dermis and the epidermis[40]. OCT is a promising technique that should become of greater interest in dermatology as the resolution of these scans improves.

Multiphoton fluorescence microscopy allows visualization of individual cells in the skin. With this technique, reflection of light photons and autofluorescence due to naturally occurring fluorescent biomolecules is used to perform optical imaging of the tissues[41], allowing clear visualization of individual cells with much better resolution than OCT; further work may allow functional imaging.

Finally, photoacoustic microscopy uses short pulses of laser and detects acoustic waves created by rapid thermoelastic expansion. As blood has a significantly larger absorption coefficient, blood vessels can be clearly imaged. This technique has been used in an animal model, allows visualization to a larger depth than optical microscopy, and will enable the assessment of microvascular oxygenation and angiogenesis[42]. At present, there are no reports of its use in psoriasis, but its ability to visualize microvascular function and pathology promises a meaningful future.

Identifying pre-disease. The work of Namey and Rosenthall[3] could now be extended using the newer, more sophisticated, imaging techniques. In this respect, a recent study from Italy found entheseal abnormalities in the lower limb in patients with psoriasis only, a finding that deserves further study and longitudinal data[43]. In the majority of patients with PsA, the skin disease precedes the articular disease; thus, a longitudinal study is needed of a cohort of psoriasis patients both with and without abnormalities on imaging. It is possible that the newer imaging techniques such as UTE may reveal widespread abnormalities in these patients, indicating that the link between joints and skin is much stronger than previously believed.

Conclusions

Imaging techniques have helped us to more accurately phenotype PsA and continue to provide insights into the pathogenesis of this disease, from both a dermatologic and a rheumatic perspective. New developments promise to continue this tradition.

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