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The relationship between the extensor tendon enthesis and the nail in distal interphalangeal joint disease in psoriatic arthritis—a high-resolution MRI and histological study

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Objectives. **Diffuse swelling of the distal interphalangeal (DIP) joint beyond the joint margin is a common feature of arthritis in psoriatic arthritis (PsA). The purpose of this study was to explore the microanatomical basis for the inflammation and nail disease in PsA using a combined high-resolution magnetic resonance imaging (MRI) and histological studies.**
Methods. **High-resolution MRIs of the DIP joint were obtained in 30 subjects [10 PsA, 10 osteoarthritis (OA) and 10 normal volunteers]. The relationship between the DIP joint capsule and associated tendon enthesis and the nail bed and root were evaluated. Histological studies to define the relationship between the normal cadaveric DIP joint capsule and the nail root were performed on the middle and ring fingers of 10 dissecting room cadavers.**
Results. **On MRI, the dorsal capsular enthesis was the epicentre of an inflammatory reaction. This extended to involve the soft tissues adjacent to the nail in 8 of 10 cases in PsA, but only 4 of 10 cases in OA where the inflammation is less intense and in none of the normal fingers. The DIP joint capsule was intimately linked with the nail complex on histology, with the dorsal, volar and lateral aspects of the nail bed being ensheathed in fibres extending from the entheses.**
Conclusion. **The study suggests that the extended nature of the enthesis organ associated with the DIP joint may explain the diffuse nature of the inflammatory response around the nail in PsA. Therefore the nail is as much an integral part of the enthesis organ as it is of the skin, which has implications for a better understanding of the disease.**

KEY WORDS: Psoriatic arthritis, Distal interphalangeal joint, Magnetic resonance imaging, Histology, Enthesis, Nail, Extensor tendon.

Introduction

The relationship between nail disease and psoriatic arthritis (PsA) of the distal interphalangeal (DIP) joint is well-recognized [1–4], although the basis for this association is poorly understood. Our recent high-resolution magnetic resonance imaging (MRI) study has shown that DIP joint disease in PsA is intimately associated with polyenthesitis [5]. We also noted that entheseal and capsular changes occurred in the DIP joints of subjects with osteoarthritis (OA), but that these changes were less marked than in subjects with PsA. A plausible explanation for the nail changes associated with PsA, but not OA, is that the inflammatory changes are much greater in PsA than OA, and thus the disease process extends to the nail bed in PsA.

We have previously hypothesized that the relationship between the nail and arthritis in PsA was due to inflammation at enthesis insertions [6]. However, the inflammatory changes around the nail bed in PsA are extensive and difficult to explain solely in terms of inflammation at the dorsal capsule entheses. We hypothesize that there is an anatomical link for the enthesis in explaining the relationship between the nail and DIP joint disease in PsA. In this study, we used histological studies to determine the anatomical relationships of the nail root, and performed a detailed analysis of high-resolution MRI changes, specifically of the nail bed and root region in active PsA and OA and in normal volunteers as controls. We aimed to relate the histology findings to the MRI changes in the DIP joints.

Methods

MRI subjects

Thirty subjects {10 with PsA [mean age 40 yrs (18–76 yrs)], 10 with OA [mean age 56 yrs (49–68 yrs)] and 10 normal volunteers as control subjects [mean age 43 yrs (27–72 yrs)]} were recruited for this study, with written informed consent, following approval from the local ethics committee. Subjects were invited to participate either directly from the rheumatology out-patient clinics or via leaflets and posters about the study distributed in the clinics.

The clinical details of this cohort have been reported previously [5]. The PsA subjects had skin psoriasis and active involvement of at least one DIP joint as defined by the presence of two of the following features: swelling, tenderness and decreased range of movements. PsA patients with clinical evidence of OA or those in whom there was clinical diagnostic uncertainty about the DIP joint disease were excluded from the study. The patients with OA were recognized on clinical grounds with soft tissue swelling around the DIP joint or bony thickening and the absence of other

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arthropathies including rheumatoid arthritis, PsA and gout, and any traumatic injury to the joint selected for imaging. The control group of healthy volunteers had asymptomatic finger joints and had no known PsA, skin psoriasis or OA.

Nail changes were assessed clinically in all three groups of the 10 patients in the PsA group, eight had onycholysis and the remaining two were normal. All 10 PsA subjects had diffuse swelling around the DIP joint. None of the OA group or the normal group had nail involvement

Magnetic resonance imaging

High-resolution MRI of one affected DIP joint of the patients or a randomly selected DIP joint of the normal control subjects was performed on a 1.5T Gyroscan ACS-NT scanner (Philips Medical Systems, Best, The Netherlands) using a 23 mm diameter microscopy MRI surface coil as previously described [7]. The protocol sequences included T1-weighted (T1W) axial and coronal spin-echo (SE), T2-weighted (T2W) fat-suppressed (FS) SE, proton density-weighted two dimensional SE, three dimensional gradient-echo sagittal, axial and coronal T1W FS SE after intravenous injection of 10 ml of the contrast agent gadolinium diethylene triaminepentaacetic acid (Gd-DTPA) were also obtained. The imaging sequences employed a field of view (FOV) of either 40 or 45 mm. The total examination time was approximately 50 min.

In general, the high-resolution images allowed for coverage of the entire DIP joint but only the proximal half of the nail.

MRI analysis

The analysis of MRI results focused on the relationship between the nail bed and the DIP joint capsule. MRI scans were scored with emphasis on the nail-bed changes by one reader blinded to the clinical status of the subjects, with inflammation extending to the nail bed (extracapsular) being reported as present or absent. To assess the nail changes, the thickness of the nail plate was measured on axial images by an observer blinded to the clinical diagnosis.

Histology from cadaveric specimens

Twenty specimens of the DIP joint from the ring and middle fingers were taken from 10 dissecting room cadavers donated to Cardiff University for anatomical investigation under the provision of the 1984 Anatomy Act and the 1961 Human Tissues Act. The medical histories of these individuals, other than the cause of death, were unknown. The cadavers were randomly selected, were of both sexes (three females; seven males) and had a mean age of 82 years (age range 70–89 yrs). The cadavers had been embalmed in formalin, but all tissues were post-fixed for 1 week in 10% neutral buffered formal saline, decalcified in 5% nitric acid, dehydrated with graded alcohols, cleared in chloroform and embedded in 58°C paraffin wax. Sagittal longitudinal sections were cut on a Leitz rotary microtome at a thickness of 8 µm and sections systematically collected at 1 mm intervals throughout the block. Sections were stained with Masson's trichrome and photographed on a Leica DMRB microscope.

Statistics

Fisher's exact test was used to compare the proportion of abnormalities between the groups. A simple *t*-test was used to compare the nail thickness between the PsA group with the OA and normal subjects. All analyses were performed with the Statistical Package for the Social Sciences version 12.0.

Results

Magnetic resonance imaging

We noted that the inflammatory reaction around the DIP joint was so extensive in PsA as to completely involve the nail bed (Fig. 1A) thus providing a close anatomical link between nail inflammation and joint disease. The extracapsular soft tissue around the DIP joint of PsA demonstrated Gd-DTPA enhancement in 8 out of 10 cases (Fig. 1B), compared with only 4 out of 10 DIP joints of OA subjects ($P = 0.17$). Six of 10 PsA patients had high signal at the extensor tendon enthesis, which was only seen in 4 of 10 OA patients. Only one of these six PsA patients had a normal non-onycholytic nail. Occasionally linear regions of low signal similar to that of extensor tendon fibres could be seen extending to the nail bed of PsA on MRI (Fig. 1C). Although the enthesis was commonly abnormal in OA, the associated inflammatory reaction was slight and confined directly to this site (Fig. 2A and B), whereas in PsA it was much more extensive (Fig. 1A–C). Normal control subjects and the OA group also displayed some subungal enhancement that was indicative of the highly vascular nature of the healthy nail root (Fig. 2C), but the enhancement was not as prominent as in the PsA cohort.

The nail on MRI

Because of the small field of view of the high-resolution images, measurements were made on the most distal axial slice just before the cuticle disappears, corresponding to the proximal regions of the nail plate. The mean thickness of the proximal nail

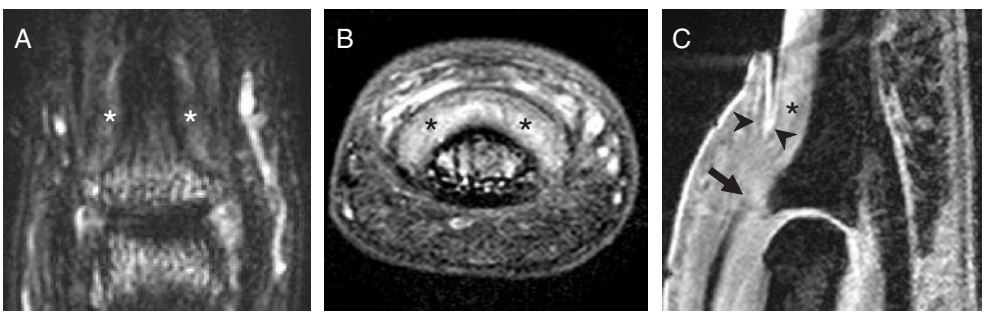

FIG. 1. MRI of a DIP joint of a 29-yr-old female with a 3-yr history of PsA affecting the joint: (A) shows a T2-weighted fat-suppressed coronal image of the dorsal DIP joint demonstrating high signal around the joint and adjacent to the distal phalanx near the nail bed (denoted by asterisk); (B) is a T1-weighted fat-suppressed post-gadolinium axial image of the same joint showing enhancement and thickening of the tissues under the nail bed (denoted by asterisk); and (C) is a water-selective excitation sagittal sequence of the joint demonstrating the thickened tissues under the nail bed (denoted by asterisk) and an abnormal extensor tendon enthesis, which was thickened and shows a loss of the low signal (arrow). Linear regions with low signal similar to the extensor tendon could be seen enveloping the nail (arrowheads), which could be fibres from the extensor tendon extending towards the nail bed.

plate in PsA [0.51 mm (0.31–0.70 mm)] was greater than in OA [0.43 mm (0.31–0.63 mm), $P = 0.13$] and in the normal controls [0.39 mm (0.31–0.55 mm), $P = 0.12$]. The nails were generally thicker in the PsA DIP joints with extracapsular inflammation and, as expected, in nails that were onycholytic.

Histology

The histological studies provided the basis for understanding the diffuse nature of the MRI changes. The extensor tendon attached to the dorsal aspect of the base of the terminal phalanx, also extended more distally in all cadavers to connect with the nail root. It formed a superficial lamina of dense fibrous connective tissue, which enclosed the proximal part of the nail root and its associated matrix (Fig. 3A and B). It also extended into the proximal skin fold, thus supporting the nail bed on both sides (Fig. 3C). A further *deep lamina* contributed to forming a thick periosteum on the terminal phalanx, distal to the site of attachment of the tendon, with this extending distally over the rest of the phalanx (Fig. 3A and B). Between the two laminae, there was a layer of adipose tissue with a rich neurovascular network (Fig. 3B). The blood vessels and nerves entered the region by piercing the superficial lamina on either side of the midline of the digit (Fig. 3D). At the sides of the phalanx, the superficial and deep laminae united with each other and with an extension of fibrous tissue derived from the deep flexor tendon, to form a sheet-like lateral lamina that attached to and supported the sides of the nail root and matrix, thus anchoring the nail laterally (Fig. 4A and B). Adjacent to the lateral lamina was a rich neurovascular network (Fig. 4C and D).

Discussion

This study explored the basis for diffuse inflammation around the DIP joint in PsA and its relationship to the nail. Histologically, we noted that the extensor tendon crossing the DIP joint was intimately linked with the nail root and its associated matrix. Indeed it fused directly with it, showing that the supporting fascia of the nail root was in effect a continuation of the enthesis. Although inflammatory changes were noted in some OA patients in their nail bed, these were more marked in PsA patients, in whom the enthesis appeared to be at the epicentre of the inflammatory response. Thus, the inflammation noted over the whole nail bed region on MRI is associated anatomically with an extensive enthesis organ apparatus.

Although the nail is an integral part of the integumentary system, it is less commonly involved clinically in patients with psoriasis alone, and is most commonly associated with PsA of the DIP joint, where a strong relationship has been described previously [4, 8]. However, a recent study in patients with PsA and psoriasis has challenged this paradigm, as nail changes were also common in subjects without arthritis [9]. We noted one PsA patient who had DIP joint involvement with extensor tendon enthesitis without nail onycholysis, which is a well-known clinical observation. We cannot explain this adequately but would speculate that inflammation at the nail root more commonly

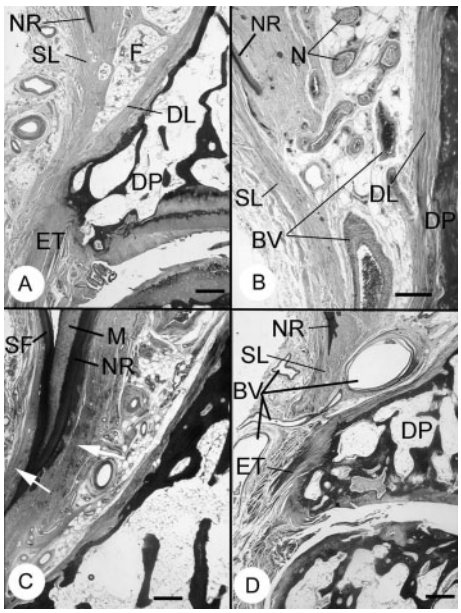

FIG. 3. Histology sections showing the superficial (SL) and deep (DL) laminae derived from the extensor tendon (ET), and their association with the nail root (NR) and its surrounding matrix (M). (A) The extensor tendon is seen attaching to the base of the distal phalanx (DP), but continuing beyond that point to form the superficial and deep laminae. Note the layer of fat (F) that fills the space between the two laminae. Scale bar = 500 μm. (B) A higher power view of the fatty layer between the two laminae, showing the conspicuous presence of blood vessels (BV) and nerves (N). Scale bar = 200 μm. (C) The superficial lamina (arrows) not only surrounds the nail root, but also extends into the proximal skin fold (SF), the free edge of which forms the cuticle or eponychium (data not shown). Scale bar = 500 μm. (D) Either side of the midline, blood vessels pierce the superficial lamina to enter or leave the underlying region of adipose tissue. Scale bar = 500 μm.

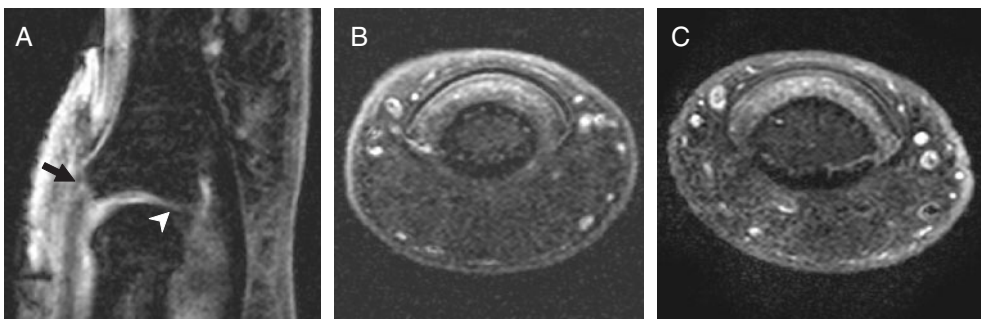

FIG. 2. (A) A water-selective, excitation sagittal sequence of an OA joint in the sagittal plane with an abnormal extensor tendon that is thickened (arrow) and joint space loss on the volar aspect (arrowhead), demonstrating less soft tissue swelling in the dorsum of the joint compared with a typical PsA joint (Fig. 1C). (B) and (C) T1-weighted fat-suppressed post contrast axial images of an OA DIP joint and a normal DIP joint respectively. As observed, the nail bed in the OA joint is not typically as inflamed and thickened like in the PsA joint (Fig. 1B). However there is some enhancement in the OA nail bed, which is also observed in normal joints, which reflects the vascularity of the nail bed.

leads to defects in proliferation or division of nail plate stem cells in most but not all cases. We have not observed any specific pattern of nail lesions and the DIP joint disease in this small study. This current study specifically evaluated the nail in PsA, and in the setting of arthritis, links peri-ungal inflammation in PsA with the enthesis organ concept.

It is worth noting that, as this is a small cross-sectional observation, it would be impossible to comment on the sequence of events or pathology with regards to the extensor tendon enthesitis and the nail changes. However, enthesitis at other sites is independent of the nail bed, so it is possible that the whole pathological process in the nail and DIP region occurs almost contemporaneously. Although the subject numbers are small, the power of high-resolution MRI and the combined histology findings clearly shows an anatomical link for the extensor tendon enthesis and the nail changes in PsA.

In the present study, we noted that on MRI the DIP joint extensor tendon was also involved in OA, but nail disease is not usually recognized. However in OA, longitudinal ridges have been reported, but nail pitting and onycholysis have not [10]. The basis for this phenotypic difference likely relates to the fact that PsA is an enthesis organ-based disease [11, 12] in which the diffuse nature of the inflammatory changes may extend to nail damage, whereas the more focal insertional disease with relative lack of inflammation in OA does not. It remains to be determined whether isolated nail disease in psoriasis is associated with subclinical enthesis disease. In conclusion, this combined high-resolution MRI and histological study provides a novel explanation for arthropathy and nail involvement in PsA.

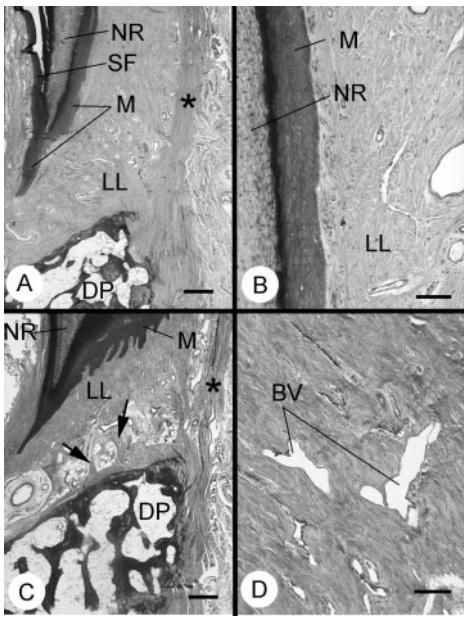

FIG. 4. Histology sections showing the lateral lamina (LL) of dense fibrous connective that is attached to the sides of the nail root (NR) and surrounding matrix (M). (A) A section to the side of the midline of the distal phalanx (DP), which has passed through much of the lateral lamina. The asterisk (*) denotes the extension of fibrous tissue derived from the deep flexor tendon which contributes to the formation of the lamina. SF, skin fold. Scale bar = 500 μm. (B) A higher power view of the lateral lamina to show its connection with the nail matrix. Scale bar = 100 μm. (C) A parasagittal section through the nail root and matrix. Note that the appearance of a greater width of the matrix is simply a consequence of the curvature of the lateral edge of the nail root, i.e. the microtome knife has grazed it obliquely. This section is immediately adjacent to the region where a complete lateral lamina is present and it shows how the deep lamina and the continuation of the deep flexor tendon (*) contribute to its formation. Fibrous strands (arrows) are evident, linking the deep and lateral laminae. Scale bar = 500 μm. (D) Numerous blood vessels (BV) associated with the lateral lamina. Scale bar = 200 μm.

Rheumatology	Key messages
	• Diffuse inflammation of the extensor tendon enthesis at the PsA DIP joint often extends to affect the nail beds. • The extensor tendon enthesis forms an integral supporting structure for the nail.

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The authors have declared no conflicts of interest.

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