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Pathophysiology, assessment and treatment of psoriatic dactylitis

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Abstract | Dactylitis is diffuse swelling of the digits that is usually related to an underlying inflammatory or infiltrative disorder. Psoriatic arthritis (PsA) is the most common severe disease thought to cause dactylitis. Our understanding of the pathogenesis of PsA-related dactylitis comes from experimental animal models of PsA-like disease, as well as advances in imaging and other clinical studies. Clinical trials in PsA have increasingly included dactylitis as an important secondary outcome measure. These studies indicate that cytokines drive multi-locus microanatomical pan-digital pathology. Given the importance of pro-inflammatory cytokines, the pathogenesis of dactylitis is best understood as an initial aberrant innate immune response to biomechanical stress or injury, with subsequent adaptive immune mechanisms amplifying the dactylitis inflammatory response. Regarding the treatment of dactylitis, no studies have been conducted using dactylitis as the primary outcome measure, and the current knowledge comes from analysis of dactylitis as a secondary outcome measure.

[H1] Introduction

Dactylitis, derived from the Greek word ‘daktylos’ meaning fingers, is diffuse finger or toe swelling that is usually related to an underlying inflammatory or infiltrative disorder[1]. Approximately half of patients with psoriatic arthritis (PsA) have dactylitis at some point during the course of disease (usually in the early stages of PsA), but dactylitis can also occur in patients with other types of spondyloarthritis (SpA) (BOX 1), including reactive arthritis and undifferentiated SpA[2].

The term ‘sausage digit’ is commonly used to describe the diffuse digital pathology typical of dactylitis[3]. Dactylitis can also be defined as uniform swelling such that the soft tissues between the metacarpophalangeal (MCP) and the proximal interphalangeal (PIP) and the distal interphalangeal (DIP) joints and the digital tuft (FIG. 1) are diffusely swollen to the extent that the actual joint swelling can no longer be independently recognized[4]. Digital swelling that does not include an MCP or the DIP region is also termed dactylitis and probably has the same underlying pathophysiology.

The importance of dactylitis in SpA (including PsA) is further supported by its inclusion in the classification criteria developed by international groups, including the Classification Criteria for Psoriatic Arthritis (CASPAR)[5] and the Assessment of SpondyloArthritis International Society (ASAS)[6]. Dactylitis seems to have a prognostic value not only regarding the affected digit but also as a measure of PsA progression in general[7]. The clinical importance of dactylitis in patients with PsA should not be underestimated, as dactylitis substantially impairs the basic motor functions required for daily living[8].

Since the original theory that enthesitis is a lesion associated with the pathogenesis of dactylitis[9,10], progress has been made in our understanding of the microanatomy, mechanisms of disease and therapeutic options for treating dactylitis. Several experimental animal models develop dactylitis or dactylitis-like lesions and together with information on response to therapy in humans indicate that pro-inflammatory cytokines and various immune cells are central to the pathogenesis.

[H1] Dactylitis in psoriatic arthritis

Dactylitis is a characteristic musculoskeletal lesion of PsA (FIG. 2). A seminal article outlining the importance of dactylitis in PsA showed that 260 out of 537 patients with PsA had dactylitis at some point, and almost 70% of these patients had dactylitis at the initial assessment[7]. In this study, more radiological damage was detected in digits with dactylitis than in those without[7]. However, the point prevalence of dactylitis in PsA is >50% in some contemporary studies that include TNF inhibitors and IL-17–IL-23 axis cytokine inhibitors (TABLE 1). Moreover, the efficacy of such therapies probably aborts the natural history of dactylitis with its association with joint damage[7].

[H1] Dactylitis types and triggers

Dactylitis is more common in the feet than in the hands and is often asymmetrical[7]. When the hands are involved, dactylitis typically involves the index finger of the dominant hand[7]. In the feet, the most commonly affected joint is the fourth toe, which is surprising given its relatively small size and anatomically protected location compared with the external facing first and fifth toes[7]. The greater involvement of the feet over the hands together with the pattern of hand disease has been interpreted as indicating that some kind of injury or trauma might trigger the disease. This interpretation led to the introduction of the idea of the deep Koebner phenomenon[11], a skeletal variant of the cutaneous Koebner phenomenon that describes the onset of psoriasis and other dermatological disorders resulting from cutaneous injury or trauma. The deep Koebner phenomenon has been reported to contribute to the pathogenesis of PsA[12], and injury is known to cause dactylitis in patients who are already genetically susceptible to PsA, with one study showing that identical twins developed disease in traumatized joints[13].

Biomechanical stress is well established as an initiating factor in SpA beyond the dactylitic lesion, especially from proof-of-concept studies, such as those that show that skeletal mechanical strain can cause both entheseal inflammation

and new bone formation in mouse models of SpA[14,15]. A link between physical injury and PsA in general (not specifically dactylitis) is also well established in humans[16]. Furthermore, in animal models of SpA-like disease, increased physical stress triggers experimental arthropathy with features similar to PsA[14]. However, differences in pressure under the toes (as measured by accurate electronic systems such as pedography measurement platforms) do not account for differences between patients with PsA who have a history of dactylitis and those without[17]; shear forces and footwear might account for these results.

[H1] Dactylitis scoring methods

In addition to dactylitis forming one of the classification criteria components of CASPAR for PsA[5], the number of PsA clinical outcome measures has increased rapidly over the past few years[18]. Dactylitis scores are important inclusions in most of these measures, including the Composite Psoriatic Disease Activity Index (CPDAI) and the Psoriatic Arthritis Disease Activity Score (PASDAS)[19,20]. In clinical trials, several methods for measuring dactylitis have been used[21] (TABLE 1). Perhaps the most straightforward method is to count affected digits (score range 0–20)[19,22]. Although this method has the advantage of simplicity, the reliability of the method has not been studied in borderline or debatable cases of dactylitis, in which it might have low inter-rater reliability. There is also the consideration of cold dactylitis (BOX 2), in which dactylitic swelling occurs in the absence of pain or tenderness, which some clinicians and researchers discount as a manifestation of active disease. To circumvent this problem, some researchers have modified the simple count by grading each digit for the degree of tenderness, usually from 0–3, so that the combined score range is 0–60 (REFS[23,24]). One study combined a measure of digital circumference with a four point rating of tenderness by utilizing both the Leeds Dactylitis Index (LDI) (which is a function of finger circumference and tenderness, assessed and added across all dactylitic digits)[25] and the original version (in which tenderness is recorded as present or absent)[26]. Subsequent studies of PsA with both skin and joint assessments show that the LDI is reliable[27] and responsive to change in an observational longitudinal study[26] and in an interventional study of certolizumab pegol treatment for PsA[28].

The application of all these dactylitis scoring methods requires some important considerations for patients with PsA, such as whether these patients are obese. Deposition of fatty tissue on the digits can make dactylitis difficult to detect, and this difficulty is of particular importance given the high prevalence of obesity among patients with PsA. Given current knowledge regarding the pathogenesis of dactylitis, the typically diffuse digital pathology and the robust performance of existing outcome measures in trials, we believe the formulation of new outcome measures will not make a substantial difference to existing assessment methods.

[H1] Anatomy of dactylitis

Despite the diffuse clinical nature of dactylitis, the most characteristic lesion detected by imaging is flexor tenosynovitis. Unlike with rheumatoid arthritis (RA), the tenosynovitis lesion in dactylitis is often associated with diffuse extra-tendinous inflammation, termed pseudotenosynovitis[29]. The flexor tendons are constrained by accessory pulleys that are sites of complex patterns of combined compressive and tensile biophysical stress and have thus been likened to ‘functional entheses’[30]. The accessory pulleys (FIG. 1) are at the interface between the tendon sheath and extracapsular soft tissues and are probably important structures in dactylitis pathogenesis but were historically difficult to visualize given their small size (FIG. 1). However, recent high-resolution MRI of early dactylitis has shown inflammatory changes in the accessory pulleys (FIG. 2c,d). These pulleys are strong restraints that prevent the flexor tendons from bowstringing during joint flexion and are elaborate mini-entheses that maintain proximity of tendons to the bone during movement. The anatomy of the human digit makes it unlikely that the nail is always integral to the dactylitic lesion; patients with PsA can have a dactylitic lesion of the proximal middle phalanx without lesions of the distal digit.

[H1] Imaging

Although psoriatic dactylitis is often evident on clinical examination and readily diagnosed, imaging is useful for the evaluation of less extensive disease or disease that is not clearly dactylitis, especially in patients with a high BMI. Ultrasonography and MRI are the main imaging techniques used for dactylitis assessment and are also useful for research purposes.

[H2] Ultrasonography.

In general, ultrasonography can detect lesions including tenosynovitis, extracapsular inflammatory changes and abnormalities of the accessory pulleys[11,29,31,32]. One ultrasonography study showed almost universal flexor tenosynovitis in a small group of patients with PsA and dactylitis, in addition to subcutaneous oedema and joint synovitis in 52% of the dactylitic digits[31]. In a power Doppler ultrasonography study of patients with PsA, pseudotenosynovitis was present in a quarter of patients with dactylitis, which provides further evidence of the diffuse nature of the inflammation[29].

Pseudotenosynovitis occurs in the non-synovial soft tissue and seems to correspond to accessory pulleys that are sites of stress (linked to restraining flexor tendons) caused by bowstringing (FIG. 3). The importance of the extra-tendon soft tissue inflammation and small joint enthesophytes at flexor tendon insertions seen by ultrasonography has been shown in patients with PsA-related tenosynovitis but not with RA-related tenosynovitis[32]. This pattern of dactylitis-related extra-tendon inflammatory change in the flexor compartment can be conceptualized as a ‘rope on fire’ (FIG. 3a), with inflammation present in the vascular soft tissues adjacent to the relatively avascular tendon fascicles and accessory pulleys

(FIG. 3).

High-resolution ultrasonography was used in one study to image the accessory pulleys in patients with PsA and a history of dactylitis, patients with PsA and no history of dactylitis, patients with psoriasis, patients with RA or healthy individuals[11]. The authors of this study tested if high physical stress occurring between the accessory pulleys and the flexor tendons during finger movement might cause thickening of accessory pulleys as part of a deep Koebner phenomenon[11]. Indeed, pulleys were thicker in patients with PsA, especially in those with a prior history of dactylitis. Collectively, these imaging data support the importance of accessory mini-pulleys as initiators of tenosynovitis in dactylitis pathogenesis and not the flexor tendon insertion as originally thought[10,33]. However, the diffuse nature of the dactylitis lesion, including diffuse osteitis, indicates that pathology in other tissues or heterogeneous mechanisms can lead to the same clinical outcome.

[H2] MRI. MRI is a good imaging option for dactylitis and is superior to ultrasonography for imaging bone in individuals in which a diagnosis is not clear or in patients with underlying primary osteomyelitis or nonspecific soft tissue swelling of finger digits of unclear aetiology.

Early MRI and ultrasonography studies of PsA-related dactylitis showed predominant flexor tenosynovitis with occasional synovitis and soft tissue oedema in the hands, with similar changes evident in the feet[34,35]. A follow-up study using the same imaging methods did not detect enthesitis in PsA-related dactylitis (despite a specific search for enthesitis), possibly reflecting the lower resolution of these imaging techniques at the time[36].

In a comprehensive MRI study of 17 patients with established PsA-related dactylitis, the severity of involvement and presence of nine features at each of the three joints of the digit (metacarpophalangeal joint, proximal inter-phalangeal joint and distal interphalangeal joint)[37] were assessed. The nine features included synovitis, bone oedema, subcutaneous oedema, flexor tenosynovitis, extensor tenosynovitis, inflammatory changes of the plantar and/or volar plates and/or the collateral ligaments, erosions and sesamoiditis at the thumb and great toe[37]. Multiple structures in both dactylitic and non-dactylitic digits were abnormal on MRI; synovitis and soft tissue oedema were the most common abnormalities (in 69% of tender dactylitic digits), but bone oedema and flexor tenosynovitis were also detected. Soft tissue oedema (as shown in FIG. 1) tended to be circumferential around the digits and not limited to association with the flexor or extensor tendons.

High-resolution MRI has been used to show a close link between dactylitis and enthesitis within single digits[38]. In addition to abnormalities at the enthesis and extensor tendon functional entheses, prominent features include changes at the flexor tendon pulleys. The close juxtaposition of such lesions to the tendon sheaths offers an enthesis-related explanation for the pathology and explains inflammatory changes outside the flexor tendon sheaths and pseudotenosynovitis (as shown in FIG. 3b,d). Iodine mapping with dual energy CT has been used to come to similar conclusions, showing enhancements at the site of accessory pulleys in patients with PsA[39].

[H1] Dactylitis in animal models

The development of animal models for psoriasis and PsA is complicated for several reasons, including the dissimilarity between human and murine skin, with no model accurately recapitulating the PsA phenotype of psoriasis, axial and peripheral arthritis, nail disease, enthesitis and dactylitis[40]. Furthermore, the small size of murine digits with the close juxtaposition of the MCP, PIP and DIP joints has hampered an understanding of the immunopathogenesis of dactylitis. Indeed, several published studies on SpA-like disease seem to show images of dactylitis but do not mention the lesion[41]. The animal models of PsA-like disease indicate the importance of diffuse inflammation, a central function for T cells and innate immunity and a dependence on cytokines that have been successfully targeted to treat PsA-related dactylitis. The insight gained from animal models is summarized in BOX 3.

[H2] DBA/1 model. Ageing male DBA/1 mice have been used as a model of PsA[42]. These mice developed dactylitis spontaneously in 6 of 50 paws from 33 male DBA/1 mice. Moreover, among the involved digits, subcutaneous oedema and neutrophilic infiltration were prominent (TABLE 2). Using the same model, another study showed that spontaneous dactylitis mainly affected the fourth and fifth digits, and changing the housing conditions (larger cages and filter tops) affected the disease incidence[43]. Intriguingly, the fourth digit of the toes is commonly involved in the DBA/1 model[43], a finding replicated in a Canadian cohort of patients with PsA[7].

[H2] PSTPIP2 model. Another animal model that results in dactylitis is dependent on mutations in Pstpip2 (which encodes mouse proline-serine-threonine phosphatase-interacting protein 2). These mice have an autosomal recessive macrophage-mediated autoinflammatory or innate immune disorder that develops spontaneously from the age of 6 weeks, with diffuse toe swelling and associated nail disease and eventual osteolysis[44]. Although the initial description of this model[44] did not use the term ‘dactylitis’, prominent diffuse swelling of the digits was evident, and the data indicate that innate immune dysregulation in monocyte lineage cells with osteoclast activation was sufficient to drive an exclusively innate immune-mediated form of disease. In this model, extensive macrophage infiltration of the interphalangeal regions of the paws occurs[44].

[H2] IL-23 transgenic model. Another model of dactylitis is reliant on systemic overexpression of IL-23 in B10.RIII mice using minicircle technology[41]. This method results in severe paw swelling and disease severity correlated with the dose

of IL-23 minicircle applied[41], supporting a function for the IL-17–IL-23 axis in the pathogenesis of dactylitis.

[H2] SKG model. The SKG model is a result of a gain-of-function mutation in T cell receptor protein ZAP70, and was originally reported as an RA-like model, even though these mice have prominent tail vertebral disease[45]. These mice spontaneously develop autoimmune inflammatory arthritis characterized by the presence of high titres of autoantibodies, namely, rheumatoid factor and anti-type II collagen[46]. The model is dependent on the IL-17–IL-23 axis.

In one study, SKG mice housed in specific pathogen-free conditions and immunized with intraperitoneal injection of curdlan developed SpA-like arthropathy with dactylitis, deformities of the tail and colitis[47]. In these mice, dactylitis typically occurred 10 weeks after curdlan injection in ~40–50% of mice along with soft tissue inflammation and macrophage infiltration[47]. A subsequent study reported that arthritis and enthesitis in this model are dependent on IL-23, IL-22 and IL-17A without specifically referencing a dactylitis lesion[48].

[H2] B10Q.Ncf1$^{m1j/m1j}$ model. The B10Q.Ncf1$^{m1j/m1j}$ mouse model is characterized by impaired expression of the Ncf1 gene (which encodes a subunit of NADPH oxidase), resulting in the function of the NADPH oxidase 2 (NOX2) complexes being blocked. This model involves the intraperitoneal injection of mannan, resulting in enthesitis and dactylitis onset after 3 days, with dactylitis often present in the hind paws[49]. In this model, mice deficient in reactive oxygen species (ROS) production have exacerbated PsA-like disease, and restoration of ROS production limits skin and joint disease[49]. The authors propose that mannan-induced TNF production from macrophages drives IL-17A-dependent enthesitis and dactylitis, with γδ T cells being the predominant source of IL-17A; however, the precise mechanisms regarding aberrant ROS expression in this model are not entirely understood.

Disease in this model has been shown to be independent of conventional T cells but dependent on TNF-producing myeloid cells and on IL-17A production, mainly from γδ T cells[49] (FIG. 4). Koebner phenomenon following injury in ear tissue has also been reported to occur in the B10Q.Ncf1$^{m1j/m1j}$ model, similar to the 'koebnerized' psoriatic skin characteristic of patients with psoriasis[11]. These experimental models are not without human comparisons, as the flexor tendon mini-enthesis accessory pulleys are thickened in patients with PsA in comparison with pulleys in patients with RA or psoriasis, possibly supporting the deep Koebner phenomenon as a causative factor[11].

[H2] STAT3 transgenic model. Another interesting model of PsA-like disease with dactylitis comes from crossing gp130$^{F759/F759}$ (F759) mice with transgenic mice that overexpress the transcription factor STAT3 specifically in epidermal tissue (K5.Stat3C mice)[50]. F759 mice have dysregulated IL-6–gp130–STAT3 signalling, resulting in aberrant IL-17 expression and a rheumatoid-like polyarthritis, whereas the K5.Stat3C transgenic model involves keratinocyte induction of the IL-17–IL-23 axis and psoriasiform dermatitis without arthritis[50]. A composite model (F759 mice crossed with K5.Stat3C transgenic mice) involves sausage digits or 'drumstick-like lesions'[50]. In this model, the severity of skin and nail lesions and arthritis has been linked directly to prominent neutrophil inflammation in the digits and mini-entheses adjacent to the nails[50].

[H2] K14-ARGE transgenic model. In the keratin 14 promoter amphiregulin gene (K14-ARGE) mouse model, overexpression of amphiregulin (an EGFR ligand) in the basal layers of the epidermis drives not only dermal inflammation but also underlying synovitis[51]. This PsA-like disease model involves skin pathology that has spread into deeper tissues, similar to dactylitis.

[H2] JunB/cJun knockout model. In a study of another PsA-like disease model, the inducible epidermal deletion of the transcription factor JUNB and its functional companion c-JUN resulted in psoriasis and underlying arthritic lesions[52]. This study did not specifically address the possibility of subcutaneous inflammation linking the skin involvement to the underlying joints. The idea that the epidermis and skin barrier are crucial in the pathogenesis of dactylitis in humans might be relevant in patients with nail involvement or digital psoriasis given these insights from animal models of PsA-like disease[9]. A synthesis of the various animal model studies can be used to propose a model of dactylitis pathogenesis (FIG. 4).

[H1] Human immunogenetic studies

Anterior uveitis, axial SpA and psoriasis with their respective HLA-B27 associations for ocular and joint disease and HLA-Cw0602 with psoriasis are collectively linked with severe, early-onset disease, which points towards the importance of adaptive immunity in driving these diseases[53]. Dactylitis is also associated with HLAB*2705 (REF.[54]), whereas HLAC*0602 is associated with patients with PsA being protected from developing dactylitis[55]. The initial studies (reviewed elsewhere[56]) have shown a link between dactylitis and HLAB*0801[56]. Collectively, these MHC class I associations indicate a potential function for CD8$^+$ T cells in driving disease in the dactylitis lesion, but this needs confirmation, as MHC class I disease associations might involve other mechanisms beyond classical antigen presentation to CD8$^+$ T cells[57]. Interestingly, the alleles associated with dactylitis, HLAB*2705 and HLAB*0801, are also linked with enthesitis and synovitis, respectively, which might reflect the diffuse and multi-site inflammatory changes that typify dactylitis[56]. A simplistic immunological model for dactylitis would involve an extensive immune reaction to common antigens present at multiple sites in the different inflamed digital tissues (FIG. 4). However, human data to firmly support this concept are

currently lacking.

[H1] Dactylitis therapy

[H2] NSAIDs. NSAIDs can be prescribed for dactylitis; however, dactylitis can progress even if treated with NSAIDs[58]. Controlled trials have not yet provided evidence to support the use of NSAIDs in PsA-related dactylitis.

[H2] Glucocorticoids. As many patients with dactylitis are not responsive to NSAIDs, many clinicians recommend injection of corticosteroids into the tenosynovial sheath, joint or soft tissues. However, controlled studies to assess the efficacy of such a strategy have not been conducted.

[H2] Conventional DMARDs. In patients who are resistant to NSAIDs and injected corticosteroids, DMARDs are often used; however, this almost always occurs in the context of coexisting active disease other than digital inflammation, so guidance for the use of DMARDs in cases of isolated dactylitis are lacking. Nevertheless, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) advocates the use of DMARDs including methotrexate, and EULAR PsA recommendations do not advocate the use of methotrexate but do suggest direct initiation of a biologic therapeutic[59,60]. One open-label study analysing data from the TICOPA study (which aimed to assess the effect of tight control on early PsA using a treat-to-target approach) indicates that methotrexate (15 mg weekly for 4 weeks and then 20 mg weekly for 2 weeks and 25 mg weekly thereafter, if tolerated) is an effective treatment for dactylitis, with complete resolution at 12 weeks in 37 of 59 patients with dactylitis at study inception[61].

The EULAR recommendations endorse methotrexate therapy for synovitis but not for dactylitis[60]. Obviously, synovitis (including that which occurs in the MCP, PIP, DIP joints and flexor tendon) is an integral part of the dactylitis lesion. However, it is difficult to understand the endorsement of methotrexate for synovitis in small joints but not for dactylitis; tenosynovitis and synovitis are integral features of dactylitis (FIG. 5). This confusion probably reflects the paucity of data on dactylitis therapy.

[H2] Biologic therapeutics. No clinical trial for biologic therapeutics in PsA has been conducted using dactylitis as the primary outcome measure, and most of the knowledge of the efficacy of various biologic agents comes from analysis of dactylitis as a secondary outcome measure (TABLE 1). Most studies have used unvalidated measures of dactylitis, and the most recent recommendations from GRAPPA suggest that biologic therapy should be initiated only after DMARD failure in patients with dactylitis[62]. Also, the point prevalence of dactylitis is remarkably high in some phase III PsA trials[63,64] of biologic therapeutics or small molecules (TABLE 1) compared with large real world studies in which the calculated prevalence of dactylitis was <40%[2]. Whether this high prevalence calculation of dactylitis in some phase III trials (TABLE 1) is accurate or affected by other factors (such as obesity) needs further study; application of ultrasonography or MRI in clinical trials might bring clarity to this point.

Substantial improvements in dactylitis have been noted in a variety of clinical trials. These trials include certolizumab pegol (TNF inhibitor) treatment in the RAPID-PsA trial[28] and ustekinumab (IL-12 and IL-23 inhibitor) treatment in the PSUMMIT-1 and PSUMMIT-2 trials[63]. Also, phase II studies of golimumab (TNF inhibitor) in the GO-REVEAL trials[65,66], infliximab (TNF inhibitor) in the IMPACT1 (REF.[67]) and IMPACT2 (REF.[68]) trials and a combination of infliximab plus methotrexate compared with methotrexate alone in an open-label study[69] showed improvements in dactylitis, as did adalimumab (TNF inhibitor) in prior treatment failures in other open-label studies. Molecular imaging with radiolabelled certolizumab pegol showed substantial TNF expression along the dactylitic digit in humans[70], providing compelling evidence for the function of this cytokine in the dactylitis lesion.

Other studies have shown efficacy for the IL-17A blockers secukinumab (FUTURE 3 (REF.[71]) and FUTURE 5 (REF.[72])) and ixekizumab (SPIRIT-P1 (REF.[73])) and for the PDE4 blocker apremilast (PALACE 4 (REF.[74])) (TABLE 1). Collectively, these studies confirm the importance of both the TNF and IL-23–IL-17 signalling pathways in dactylitis pathogenesis.

Tofacitinib (an oral Janus kinase inhibitor)[64,75] and abatacept (a selective T cell co-stimulation inhibitor)[76] have also been shown to be effective in treatment of dactylitis. Of critical importance is that drugs targeting the IL-17–IL-23 axis or PDE4 pathway blockers are ineffective for the treatment of synovitis in patients with RA[77,78] but seem to be effective in treating the swelling in dactylitis, which is often linked to tenosynovitis and synovitis[79]. These anatomical considerations around the extra-synovial structures that seem to have a pivotal function in the pathogenesis of dactylitis might be relevant for understanding why anti-IL-17A therapy seems to be a better therapy for synovitis and tenosynovitis in patients with PsA than for patients with RA[80]. Thus, the therapeutic importance of these pathways seems to be confined to PsA-related tenosynovial or synovial disease and helps us to conceptualize a model of joint inflammation in dactylitis (FIG. 4).

Collectively, these available therapeutic studies show that, unlike for enthesitis, therapy results in complete resolution of dactylitis in the majority of patients (TABLE 1). This difference might reflect the fact that dactylitis has fewer differential diagnoses than entheseal pain, with the resolution of diffuse digital swelling in dactylitis being an objective measure of inflammation resolution for this lesion in PsA. However, the more subjective nature of isolated enthesitis assessment, and the absence of swelling in most cases of enthesitis, makes it more difficult to assess inflammation as a cause of pain for that lesion.

[H1] Conclusions

The microanatomical and immunopathogenic basis for understanding experimental dactylitis is helpful and informs our understanding of human dactylitis, but translation of results from animal models to humans requires further study. Experimental models and human studies indicate that dactylitis involves inflammation in multiple tissues including bone, periosteum, entheses, peri-entheseal and peri-tendinous soft tissue, tenosynovium and articular synovium. The inflammation is most conspicuous in the vascular tissues adjacent to the relatively avascular tendons, pulleys and entheses (FIG. 3). This pattern distinguishes the inflammation of dactylitis from RA in which inflammation is generally maximal within synovial cavities. Further studies are needed to explore exactly how the innate and adaptive immune responses are triggered in dactylitis. Advances in imaging might also be required to identify how quickly and how well dactylitis lesions resolve in order to define optimal therapeutic strategies for PsA. The dactylitis phenotype in PsA is an intriguing (but treatable) lesion, but more evidence is required for a complete understanding of its pathogenesis.

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Box 1 | **Non-PsA dactylitis**

The non-psoriatic arthritis (PsA)-related causes of dactylitis, including infiltrative granulomatosis disorders such as sarcoidosis and tuberculous infections, and crystal arthropathies such as gout[9] probably all involve an inflammatory process that co-occurs in several tissues that might include bone marrow, periosteum, soft tissues and the skin[1,4]. In children, dactylitis can be caused by sickle cell anaemia, in which the primary abnormality is osseous microvessel thrombosis with avascular necrosis[81]. This condition is particularly noteworthy, as the pathology is linked exclusively to inflammatory events taking place in the bone, with this osseous pathology probably triggering periosteal and diffuse adjacent soft tissue inflammatory responses. Severe periosteal and adjacent soft tissue inflammatory responses are also a feature of fractures and can manifest as diffuse soft tissue oedema. Notably, diffuse osseous inflammation or osteitis is also a major feature of PsA at multiple sites, including affected phalanges[82,83]. Indeed, bone marrow oedema that probably represents osteitis has been detected by MRI in patients with dactylitis[37,84]. Therefore, the osseous and associated periosteal inflammation might be a neglected and major contributory factor to soft tissue oedema in PsA (FIG. 2). A strong link also exists between diffuse psoriatic osteitis and associated enthesitis[83]. These observations from other diseases in which dactylitis might occur as a result of bone pathology, for example, attest to the multifaceted pathogenesis of dactylitis.

Box 2 | **Other forms of dactylitis**

Somewhat surprisingly, the issue of tenderness and pain in dactylitis has been somewhat overlooked by physicians. One of the problems with the definition of dactylitis is that a chronic non-tender form exists in some patients with psoriatic arthritis[7]. The lack of tenderness might suggest inactive disease, but imaging might also reveal unrecognized synovitis and soft tissue oedema, demonstrating that the difference between tender and non-tender dactylitis is quantitative, not qualitative[37]. Whether this so-called cold dactylitis is predominantly a chronic reactive process related to tissue remodelling or an inflammatory reaction is not completely understood. Histopathology studies have not yet compared different types of dactylitis (such as cold dactylitis) to resolve this issue. In one case study, soft tissue lymphocyte infiltration was shown in a symptomatic patient with dactylitis[84].

Box 3 | **Insights from animal models with dactylitis or dactylitis-like features**

- Both adaptive and innate immune cells and pro-inflammatory cytokines (including IL-17A, IL-23 and TNF) are important in dactylitis pathogenesis
- Inflammation occurs in extra-synovial tissues
- Dactylitis is often associated with enthesitis (detected by histology) and nail involvement

Fig. 1 | **Anatomy of dactylitis.** The anatomical relationship between the accessory pulleys A1–A5 and the flexor tendons (flexor digitorum profundus and flexor digitorum superficialis) seems to be important for flexor tenosynovitis, which is a common feature of dactylitis. As the finger joints move in the flexion and extension planes, the flexor tendons (enveloped within flexor tendon sheaths; not shown) move within the pulleys, thus creating a 'functional enthesitis' with subsequent inflammation that can be diffuse along most parts or the whole of the finger, resulting in the characteristic 'sausage' swelling of dactylitis. There are multiple other entheses including collateral ligaments and nail-related entheseal anchorage networks around the digit. Sites of extensor tendon compression over the phalanges during flexion represent functional entheses that might be associated with dorsal extracapsular soft tissue inflammation.

Fig. 2 | **Enthesitis and osteitis in dactylitis. a** | 42-year-old female with 4-year history of psoriatic arthritis with associated dactylitis of the right second toe. **b** | T1-weighted fat-suppressed post-contrast coronal high-resolution MRI of the same digit showing widespread inflammatory changes in the digital soft tissues and also bone oedema (asterisks). **c** | Dynamic contrast-enhanced hand MRI from a patient with dactylitis of the middle digit showing that the initial contrast enhancement corresponds to the A1 pulley at the metacarpophalangeal joint (arrow). **d** | An axial image showing accumulation of contrast agent adjacent to the flexor tendon (arrow heads). Holding place to credit parts 2C and 2D which were kindly provided by Dr Hideharu Sugimoto, Department of Radiology, Jichi Medical University, Japan.

Fig. 3 | **Peri-tendinous tissue vascular changes in dactylitis.** Prominent extracapsular inflammation in the soft tissues is characteristic of psoriatic arthritis and dactylitis but not rheumatoid arthritis. **a** | A 'rope on fire' burns the oxygen in the atmosphere. **b** | The power Doppler ultrasonography image shows changes that correspond to inflammation in the adjacent vascular tissue. **c** | This pattern of dactylitis-related inflammation seems to be linked to the microanatomy of the tendon and adjacent accessory pulleys that are relatively avascular. **d** | The lesion detected by ultrasonography showing non-tenosynovial sheath enhancement is termed 'pseudotenosynovitis'. The response to stress in these structures manifests in the adjacent vascular tissues. Holding place to credit Mr Abed El Rahman Wattad for providing FIG. 3a and for help in preparation of FIG. 3c.

Fig. 4 | **Potential immune pathways in the pathogenesis of dactylitis.** A composite view of the pathogenesis of dactylitis from human and experimental models is shown. After triggering (for example, by deep Koebner responses) innate immune cell (neutrophils, macrophages and γδ T cells), over-activation can occur, and pro-inflammatory cytokines are released. The function of adaptive immune cells in this context is not completely understood, but some MHC class I molecules are associated with dactylitis, and soft tissue T cell infiltration in humans and conventional T cell dysregulation in animal models have been reported. The diffuse tissue involvement is associated with a number of different potential outcomes including new bone formation or bone loss. Animal models have confirmed a central function for TNF and the IL-17–IL-23 axis of cytokines in the pathogenesis of experimental dactylitis.

Fig. 5 | **Grouping of joints.** Some recommendations eschew the use of methotrexate for dactylitis, which typically involves the tendons and joints in the same digit (group A joints), and suggest going straight to treatment with a biologic therapeutic. However, if synovitis or tenosynovitis is present in a non-dactylitic pattern in a patient with PsA (for example, adjacent metacarpophalangeal joints as in group B joints), then methotrexate and other DMARDs such as sulfasalazine are generally recommended.

Table 1 | Dactylitis as an outcome measure in clinical trials

Therapy	Dactylitis assessment method	Dactylitis at baseline (at the inclusion in trial)	Therapy duration	Response	Refs
Ciclosporin A or sulfasalazine or NSAID, corticosteroids and/or	Number of tender and swollen digits	36 of 99 (36%) patients had dactylitis	6 months	Not reported, but it was mentioned that 4 of 99 (4%) pa-	[22]

analgesics alone				tients developed new dactylitis	
Infliximab or placebo (± stable dose of methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, gold, penicillamine and azathioprine)	0–3 scale for each digit	50% of the placebo-treated group and 48% of the 5 mg/kg infliximab-treated group	98 weeks (placebo crossed over to infliximab at week 16)	• At week 16: 85% improvement (infliximab) compared with 29% improvement (placebo); P < 0.001 • Number of dactylitic digits at week 50: 0.32 ± 0.95 • Number of dactylitic digits at week 98: 0.19 ± 0.72	[23,67]
Sulfasalazine or placebo	0-3 scale for each digit	Not reported	36 weeks	Dactylitis score (number) change: –0.5 ± 4.2 (sulfasalazine) and –0.9 ± 4.1 (placebo); P = 0.43	[24]
Certolizumab pegol or placebo (± stable dose of methotrexate, sulfasalazine and leflunomide)	Leeds Dactylitis Index[25]	25.7% of the placebo group, 25.4% of the 200 mg certolizumab pegol-treated group and 28.1% of subjects in the 400 mg treated group	24 weeks	Mean change: certolizumab pegol 200 mg Q2W (−40.7 (P = 0.002)) and certolizumab pegol 400 mg Q4W (−53.5 (P < 0.001)) versus placebo (−22.0)	[28]
Golimumab or placebo (± stable dose of methotrexate)	0–3 scale for each digit	34% of the placebo-treated group, 34% of the 50 mg golimumab-treated group and 34% of the 100 mg golimumab-treated group had dactylitis at presentation	52 weeks (placebo crossed over to golimumab at week 24)	Mean change: –4.37 (77%) (golimumab) and –1.68 (57%) (placebo); P = 0.002	[65,66]
Methotrexate ± infliximab	Number of dactylitic digits	The number of digits with dactylitis was 3.3 ± 4.2 and 3.1 ± 4.2 in the infliximab plus methotrexate and methotrexate groups, respectively	16 weeks	Median reduction: 2 digits (infliximab plus methotrexate) and 0 digits (methotrexate alone); P = 0.0006	[69]
Ustekinumab or placebo	0–3 scale for each digit	50% of the placebo-treated group and 52.2% of ustekinumab-treated group had dactylitis at presentation	24 weeks (Placebo switched to ustekinumab at week 24)	Mean improvement at week 24: 57.5% (ustekinumab) and 11.0% (placebo); P < 0.001	[63]
Tofacitinib, adalimumab or placebo	Dactylitis severity score (0–60)	55% of the placebo-treated group, 57% of 5 mg tofacitinib-treated group, 58% of the 10 mg tofacitinib-treated group and 55% of the adalimumab-treated group	12 months (placebo switched to tofacitinib at month 3)	• Mean change at 3 months: –2.0 (placebo), –3.5 (tofacitinib 5 mg), –5.5 (tofacitinib 10 mg) and –4.0 (adalimumab) • Mean change at 12 months: –6.7 (placebo to tofacitinib 5 mg), –7.7 (placebo to tofacitinib 10 mg), –7.4 (tofacitinib 5 mg), –7.5 (tofacitinib 10 mg) and –6.1 (adalimumab)	[64]

Tofacitinib or placebo	Dactylitis severity score (0–60)	48% of the placebo-treated group, 50% of subjects in the 5 mg tofacitinib group and 49% of subjects in the 10 mg tofacitinib group had dactylitis at presentation	6 months (placebo switched to tofacitinib at month 3)	Mean change at 3 months: –1.9 ± 0.8 (placebo), −5.2 ± 0.7 (tofacitinib 5 mg) and −5.4 ± 0.8 (tofacitinib 10 mg)	75
Abatacept or placebo	Leeds Dactylitis Index-Basic	23.7% of the placebo-treated group and 28.6% of the abatacept-treated group had dactylitis at presentation	52 weeks (inadequate responders switched to abatacept at week 16)	• Resolution at week 24: 44.3% (abatacept) and 34.0% (placebo) • Resolution at week 44: 68.9% (abatacept) and 60.0% (placebo to abatacept)	76
Apremilast or placebo	Change in dactylitis count and proportion of patients with dactylitis at baseline	51.1% of the placebo-treated group, 50.9% of the 20 mg apremilast-treated group and 47.7% of the 30 mg apremilast-treated group had dactylitis at presentation	52 weeks (placebo inadequate responders crossed over to apremilast at week 16; all placebo crossed over to apremilast at week 24)	• Dactylitis count = 0 at week 16: 31.1% (placebo), 40.1% (apremilast 20 mg) and 40.5% (apremilast 30 mg) • Dactylitis count = 0 at week 52: 75.0% (placebo to apremilast 20 mg), 78.9% (placebo to apremilast 30 mg), 68.6% (apremilast 20 mg) and 68.8% (apremilast 30 mg)	74
Secukinumab or placebo (± stable dose of methotrexate)	Patients with dactylitis	26.3% of the placebo-treated group, 26.1% of the 150 mg secukinumab-treated group and 33.1% of the 300 mg secukinumab-treated group had dactylitis at presentation	52 weeks (placebo non-responders crossed over to secukinumab at week 16 or 24)	• Dactylitis resolution at week 24: 47.8% (secukinumab 300 mg), 38.9% (secukinumab 150 mg) and 13.9% (placebo) • Dactylitis resolution at week 52: 60.9% (secukinumab 300 mg) and 52.8% (secukinumab 150 mg)	71
Secukinumab or placebo (± stable dose of methotrexate)	Patients with dactylitis	39.1% of patients had dactylitis at trial entry	16 weeks	Dactylitis resolution: 65.9% (secukinumab 300 mg with loading dose), 57.5% (secukinumab 150 mg with loading dose), 56.3% (secukinumab 150 mg without loading dose) and 32.3% (placebo)	72
Ixekizumab, adalimumab or placebo	Leeds Dactylitis Index-Basic	37.6% of patients had dactylitis at trial entry	24 weeks	Mean change: –75.4 (IXEQ4W), –66.1 (IXEQ2W), –76.0 (adalimumab) and –33.7 (placebo)	73
Ixekizumab	Leeds Dactylitis Index-Basic	12% of the placebo-treated group, 23% of the every 4 weeks ixekizumab-treated group and 16% of the every 2 weeks ixekizumab-	24 weeks	75% of subjects treated with ixekizumab (every 4 weeks) had improvement of dactylitis versus 21% of placebo group	85

		treated group had dactylitis				

IXEQ2W, ixekizumab 80 mg every 2 weeks; IXEQ4W, ixekizumab 80 mg every 4 weeks; Q2W, every 2 weeks; Q4W, every 4 weeks.

Table 2 | Animal models that result in dactylitis

Model	Model characteristics	Intervention and trigger	Prevalence	Description	Main immune cells involved	Refs
DBA/1 mice	Originally used as an RA model; immunization with type II collagen results in severe autoimmune polyarthritis	Environmental trigger (4–6 male mice were caged together)	6/50 paws (12%)	• Extensive subcutaneous oedema • Acute neutrophilic inflammatory reaction • No inflammatory infiltrates within the synovium • Tenosynovitis • Tendon sheet oedema • Cell infiltration	Neutrophils	[42]
Curdlan-induced and/or mannan-induced SKG mice	Gain of function in ZAP70 and originally reported as an RA-like model	Intraperitoneal injection of fungal β-glucan	40–50% of the curdlan-treated mice	• Periarticular erosions and deformity • Soft tissue of the foot in these mice revealed abundant macrophages	Macrophages	[47]
Zymosan-induced SKG mice	Gain of function in ZAP70 and originally reported as an RA-like model	Intraperitoneal injection of zymosan	Not reported	• Extensive subcutaneous oedema • Tenosynovitis • Inflammatory cell infiltration • Disruption of muscle and tendon	Not reported	[86]
F759 mice	STAT3 activation owing to impairment in SOCS3-dependent negative regulation	Crossed with K5.Stat3C transgenic mice	Up to 75% of mice	• Bone erosions • Epidermal hyperplasia • Mononuclear cell infiltrates	Mononuclear cell infiltrates	[50]
B10Q.Ncf1$^{m1j/m1j}$ mice	Impaired expression of Ncf1, completely blocking the function of NOX2 complexes	Intraperitoneal injection of mannan	Predominantly hind paws	• Enthesitis • Synovial hyperplasia with inflammatory cell infiltrates • Mild cartilage damage • Periostitis	Not reported	[49]
PSTPIP2 mice	Low expression of PSTPIP2 by macrophages, leading to an altered cytokine	Genetic mutation in Pstpip2	Not reported	• The term dactylitis was not used • An extensive infiltration of the interphalangeal regions	Macrophages	[44]

	production			of the paws was revealed		
B10.RIII mice	F1 GFP reporter	Bred with IL-23R–eGFP mice and RORγt–eGFP C57Bl/6 mice; administration of IL-23 minicircle	Not reported	The term dactylitis was not used	Macrophages and neutrophils	[41]

eGFP, enhanced green fluorescent protein; GFP, green fluorescent protein; PSTPIP2, proline-serine-threonine phosphatase-interacting protein 2; RA, rheumatoid arthritis.

Glossary terms

Bowstringing
The natural tendency of the tendon to pull away from bone surface on the flexor aspect, which is being restrained by the accessory pulleys.

Cold dactylitis
Dactylitis swelling without pain or tenderness.

Deep Koebner phenomenon
The skeletal counterpart of skin injury in the Koebner phenomenon, whereby enthesis and joint injury can be associated with psoriatic arthritis development.

Digital tuft
The terminal bony prominence at the end of the distal interphalangeal digits.

Koebner phenomenon
The appearance of skin lesions in areas of cutaneous trauma, mainly (but not only) in patients with psoriasis.

Minicircle technology
A method for introduction of DNA into somatic cells with resultant protein expression.

Sesamoiditis
Inflammation of the sesamoid bones and/or their supporting structures.