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Ultrasonographic evidence of predominance of acute extracapsular and chronic intrasynovial patterns in 100 psoriatic hand dactylitis.

Nicolò Girolimetto[1], Pierluigi Macchioni[2], Ilaria Tinazzi[3], Luisa Costa[1], Dennis McGonagle[4], Rosario Peluso[1], Antonio Del Puente[1], Olga Addimanda[2], Antonio Marchetta[3], Niccolò Possemato[2], Marco Tasso[1], Carlo Salvarani[2, 5], Raffaele Scarpa[1], Francesco Caso[1].

1. Department of Clinical Medicine and Surgery, Rheumatology Research Unit, University Federico II, Naples, Italy

2. Department of Rheumatology, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy

3. Unit of Rheumatology, Ospedale Sacro Cuore, Negrar, Verona, Italy

4. NIHR Leeds Musculoskeletal Biomedical Research Centre, Leeds Teaching Hospitals Trust and the University of Leeds, United Kingdom

5. Rheumatology Unit, University of Modena and Reggio Emilia, Italy.

Corresponding Author:

Raffaele Scarpa, MD, Full Professor

Rheumatology Unit, Department of Clinical Medicine and Surgery, University Federico II, via S. Pansini 5, 80131 Naples, Italy

Telephone: +39 0817463773;

Fax: +39 0815463445;

mail: rscarpa@unina.it

Running head: Psoriatic dactylitis ultrasonographic characteristics.

Abstract

Objective. To use ultrasonography to explore whether the duration of psoriatic dactylitis was associated with different patterns of extracapsular and synovial based involvement.

Methods. One hundred cases of hand dactylitis from 85 psoriatic arthritis (PsA) patients were consecutively enrolled in a multicentre cross-sectional study and divided into two groups according to dactylitis duration (shorter or longer than the median: 20 weeks). All dactylitis fingers were investigated using high frequency ultrasound (US) both in grey scale (GS) and Power Doppler (PD), evaluating the presence of flexor tenosynovitis, soft tissue oedema, subcutaneous PD signal (PDS), extensor tendon involvement and joints synovitis.

Results. Cases with a shorter dactylitis duration (<20 weeks) had a significantly higher prevalence of GS flexor tenosynovitis of grade ≥ 2, PD flexor tenosynovitis, soft tissue oedema and subcutaneous PDS ($p = 0.001$, $p < 0.001$, $p < 0.05$ and $p = 0.001$, respectively). However, the presence of synovitis in GS and PD mode (in both cases at proximal interphalangeal level) was more frequent in patients with the longer dactylitis duration ($p < 0.001$). When detected in the chronic form flexor tenosynovitis was grade 2 or less.

Conclusions. In a large cohort of PsA hand dactylitis, we found a predominant extracapsular inflammation (flexor tenosynovitis and soft tissue oedema) in early cases and a high prevalence of joint synovitis at PIP level in the chronic form. However, longitudinal imaging studies are need for clarifying these aspects.

Key words: dactylitis, ultrasound, psoriatic arthritis, tenosynovitis, oedema, flexor tendon.

INTRODUCTION

Dactylitis is a common feature of psoriatic arthritis (PsA), occurring in 16 to 49% of PsA patients, mostly in early disease [1-3]. As the most specific PsA manifestation it has been included in the ClASsification for Psoriatic ARthritis (CASPAR) criteria [4, 5], although it has been observed in all forms of spondyloarthritis [6], including the enteropathic form [7]. Dactylitis is defined as diffuse and uniform swelling of the entire digit and it is considered a clinical marker of disease severity [8, 9]. Clinically, it can present as a tender, painful, warm and erythematous digit (acute form). It can also present as swollen pauci-symptomatic digit, not associated with inflammatory modifications (chronic form) [10] that remains poorly understood [11, 12].

Dactylitis was considered to be the result of the metacarpophalangeal (MCP), proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints involvement associated with a flexor tenosynovitis for a long time [13, 14]. In the 90's, early US studies reported a predominant flexor tenosynovitis while the frequency of coexisting joint synovitis varied from 16% to 62% [15-17] and these data were confirmed by subsequent magnetic resonance imaging (MRI) studies [18-20]. These results led the authors to conclude that flexor tenosynovitis was a major contributor to the clinical appearance of dactylitis and joint synovitis was a variable coexisting feature. Subsequently, Fournië et al. [21] used US to show diffuse digital soft tissue inflammation in dactylitic patients (reported as subcutaneous and extra-tendinous) and termed this lesion as “pseudo-tenosynovitis.” A recent study independently reported that this lesion was useful in the differentiation of PsA from rheumatoid arthritis (RA) [22].

Only a recent US study of 48 cases of PsA dactylitis evaluated the correlation between sonographic features and duration of dactylitis. This study highlighted that a significantly higher prevalence of flexor tenosynovitis and peritendinous soft tissue oedema in acute form (< 24 weeks) and joint synovitis in the chronic one (> 24 weeks) [23]. We tested the hypothesis that earlier disease may be associated with a greater degree of extracapsular pathology in line with prominent accessory pulley involvement in early disease. This multi-centre observational cross-sectional study was designed to

confirm in a greater number of patients the association between US patterns of disease compartmentalization in dactylitis and its duration.

PATIENTS AND METHODS

Patients

We performed a cross-sectional multicenter study on consecutively enrolled PsA patients with finger dactylitis who were in 3 Italian rheumatology centers (Naples, Reggio Emilia and Negrar) with a recognized expertise in PsA and US imaging, between August 2017 and September 2018. The study was approved by the local ethical committees of the participating centers and was conducted in conformity with The Declaration of Helsinki (Ethical committee approval number: 5/12). A written informed consent was obtained from all participants.

The inclusion criteria were the fulfillment of CASPAR criteria in patients older than 18 years (1) having an acute or chronic dactylitis (2) with a duration of more than a month. The exclusion criteria were the following: (1) current engagement in heavy manual work, (2) recent history of hand trauma, (3) biologic synthetic disease modifying antirheumatic drugs (DMARDs) and (4) previous corticosteroid injection in the involved finger.

Before US examination, a clinical assessment was performed by clinicians (AM, CS, RS) with longstanding expertise in the field of PsA, who diagnosed the dactylitis using the dactylometer and the Leeds Dactylitis Index (LDI) [24]. The LDI measures the ratio of the circumference of the involved digit to the circumference of the contralateral digit; a minimum difference of 10% is necessary to define a dactylitic digit. The ratio of circumference is multiplied by a tenderness score (0 = no tenderness, 1 = tender, 2 = tender and winces, 3 = tender and withdraws).

The rheumatologic evaluation included tenderness of the involved finger, tender joint count (TJC) and swollen joint count (SJC). Erythrocyte sedimentation rate (ESR), C-reactive protein (C-RP) and rheumatoid factor (RF) were collected. The duration of dactylitis was defined from the onset of reported diffuse digital swelling and pain.

For the purposes of analysis, we divided all cases of dactylitis into two groups according to its duration (shorter or longer than the median: 20 weeks). Moreover, all the cases were split into quartiles based on dactylitis duration.

Ultrasound protocol

US examination of the dactylitis finger was performed by three rheumatologists (NG, PM, IT), expert in musculoskeletal US examination, blinded to clinical and laboratory data. All US scans were performed using a MyLab 70XVG machine equipped with a 6–18 MHz linear transducer (Esaote S.p.A., Genoa, Italy). The US grey-scale (GS) imaging parameters were optimised for maximal image resolution. Power Doppler (PD) settings were standardized at the following values: 500 Hz for pulse repetition frequency, 3 for wall filter, 4 for persistence, and color gain between 45–55%. The window of the color box was restricted to the areas studied.

Flexor and extensor tendons, MCP, PIP and DIP joints of the affected fingers were assessed by GS and PD US evaluation in longitudinal and transverse scanning views, in accordance with current guidelines and publications [25, 26]. Joints were examined from both dorsal and volar sides. The following dactylitis related sonographic lesions were investigated: flexor tenosynovitis (both in GS and in PD mode), soft tissue oedema, subcutaneous PD signal (PDS), extensor tendon involvement (including paratenonitis and enthesitis of extensor tendon at proximal-interphalangeal joint), synovitis (both in GS and in PD mode).

Tenosynovitis was defined in GS according to the Outcome Measures in Rheumatology (OMERACT) definitions [27]. Soft tissue oedema was defined as a diffuse hypo/isoechoic thickening of the extratendinous soft tissues around flexor tendon (pseudotenosynovitis) with positive PDS in the subcutaneous tissue, in long axis view [21]. We defined paratenonitis as a hypoechoic area surrounding a tendon without synovial sheath, with or without peri-tendinous PDS [28, 29]. Enthesitis of extensor tendon at PIP joint was defined by the presence of hypoechoic and increased thickness of

the tendon insertion into the bone, as compared to the body of tendon and to the controlateral [30, 31].

Synovitis was defined according to the recent EULAR-OMERACT definition as hypoechoic synovial hypertrophy (SH) regardless of the presence of effusion and any grade of PD signal [32]. Tenosynovitis was assessed using the four-grade semi-quantitative scoring scale in GS and Doppler mode, as proposed by the OMERACT US group [27]. Synovitis was scored using a semi-quantitatively score (0–3) both for GS and Doppler mode, according to recent studies [32, 33].

Statistical analysis

The statistical analysis was performed using SPSS, version 23. All quantitative variables were expressed in terms of mean ± SD or median and range in case of strong violation of normality, while qualitative variables were expressed as percentages.

Intra-observer and inter-observer reliabilities were obtained in two measurements (at basal and at 3 months from the first US evaluation) using 20 static images of 20 patients. We utilized the Cohen's kappa coefficient (k) for each sonographic lesion and values > 0.8 were considered as excellent. Continuous variables were compared using t-test or non-parametric tests when appropriate. Non-continuous variables were compared using Chi-square test. Statistical tests were performed at a significance level of $\alpha = 0.05$.

RESULTS

Clinical Features of the two dactylitis groups

The main demographic, clinic and laboratory characteristics of the two groups (shorter or longer than 20 weeks) are reported in Table 1. Both groups were not significantly different for BMI, PsA duration, TJC, SJC, ESR, CRP and therapies. However, patients with longer dactylitis duration were predominantly male ($p < 0.05$) and older ($p=0.01$). The patients of two groups were significantly different for the frequency of tenderness ($p<0.001$). Moreover, the mean values of LDI score and

patient pain visual analogue scale (VAS) score were significantly higher in cases with shorter dactylitis duration ($p<0.001$).

Sonographic Intra-observer reliability

For the 3 sonographers (NG, PM, IT), the intra-observer reliability was excellent for all parameters ($k>0.8$). The inter-observer reliability depicted by k coefficient was 0.87 (95%CI: 0.81-0.93) for GS flexor tenosynovitis, 0.83 (95% CI: 0.75-0.90) for PD flexor tenosynovitis, 0.89 (95%CI: 0.85-0.93) for soft tissue oedema, 0.86 (95% CI: 0.74-0.97) for subcutaneous PDS, 0.88 (95%CI: 0.84-0.92) for extensor tendon involvement, 0.84 (95%CI: 0.76-0.93) for GS synovitis and 0.91 (95% CI: 0.85–0.96) for PD synovitis.

Sonographic findings

At least one ultrasound abnormality was found in all patients. Flexor tenosynovitis was seen in 88% of dactylitis (grade ≥ 2 in 46% of cases), while related PD flexor tenosynovitis was observed in 72% of cases (grade ≥ 2 in 57% of cases). Soft tissue oedema was present in 91% of dactylitis and subcutaneous PDS was present in 85% of cases. Extensor tendon involvement was evident in 12% of dactylitic fingers (with associated PDS in 10% of cases). GS synovitis involving at least 1 joint was observed in 40% of cases; it was present more frequently at PIP level (28% of cases) while it was present at MCP and DIP level in 15% and 9% of cases, respectively. PD synovitis involving at least 1 joint was evident in 21% of cases; it was more frequently detected at PIP level (17% of cases) and it was seen at MCP and DIP level in 7% and 4% of cases, respectively. Simultaneous synovitis of MCP, PIP and DIP joints was not found in any patient.

Flexor tenosynovitis plus soft tissue oedema were present in 79% of cases, while flexor tenosynovitis plus joint synovitis involving at least 1 joint were observed in 31% of cases. Soft tissue oedema plus joint synovitis involving at least 1 joint were evident in 12% of dactylitic fingers.

Table 2 shows the frequency of US abnormalities in the two groups of patients. Cases with shorter dactylitis duration (<20 weeks) had a significantly higher prevalence of GS flexor tenosynovitis of grade ≥ 2 and PD flexor tenosynovitis (any grade) ($p = 0.001$ and $p < 0.001$, respectively).

Extracapsular soft tissue oedema was commoner in the shorter disease duration group ($p < 0.05$) (Figures 1 and 2). Likewise subcutaneous PDS was commoner in the shorter disease duration group ($p = 0.001$). On the other hand, the presence of synovitis in GS and PD mode (in both cases at PIP level) was more frequent in patients with a dactylitis duration longer/equal than 20 weeks ($p < 0.001$). Figure 3 reports the prevalence of selected US abnormalities after splitting cases into quartiles based on dactylitis duration.

We found no differences in the prevalence of the US abnormalities (in particular flexor tenosynovitis, soft tissue oedema and joint synovitis) comparing subjects treated vs not treated with csDMARDs either in general population or in the subgroups with dactylitis duration < and > 20 weeks (Table 3).

DISCUSSION

This is the first multicenter study to evaluate the relationship between US lesions and dactylitis duration in a large PsA hand dactylitis cohort using high-frequency US. Our findings revealed that the prevalence of GS flexor tenosynovitis of grade ≥ 2, PD flexor tenosynovitis, soft tissue oedema and subcutaneous PDS are higher in patients with shorter dactylitis duration. Moreover, the mean values of LDI score were significantly higher in cases with shorter dactylitis duration.

On the other hand, the presence of GS synovitis and intra-articular PDS at PIP level is more frequently observed in patients with longer dactylitis duration. However, flexor tenosynovitis was also present in the chronic form but was of a lesser magnitude. These results confirm the association between US patterns of disease compartmentalization in dactylitis and its duration, as already showed in a previous study with a smaller sample of patients [23].

At present the natural clinical course of dactylitis remains largely unknown and longitudinal studies on soft tissue changes in dactylitis have never been done. Previous US [15-17] and MRI [18- 20, 34] studies have demonstrated that dactylitis is characterized by the variable association of inflammatory involvement of flexor tendons (tenosynovitis), adjacent soft tissue thickening/oedema and synovitis of MCP, PIP and DIP joints. The main limits of previous US studies are the very small samples of

patients (usually less than 30 dactylitic digits), the low frequency of the probe used (7,5 or 10 MHz) and the absence of PD examination [15-17]. In accord with our data, a MRI study by Olivieri of dactylitic toes with a dactylitis duration shorter than 7 weeks showed flexor tenosynovitis and peritendinous soft tissue oedema in all patients and a low prevalence of joint synovitis [19].

In our study, patients were enrolled in a consecutive manner and they were not selected according to treatment. Although we can not exclude an influence of treatment on presence and severity of US abnormalities, the comparison of the prevalence of any US alterations did not differ between the treated and the untreated patient group.

The present study has several limitations, and the main of those is represented by its cross-sectional nature. The duration of symptoms is therefore obtained only by medical history. Another limitation of the our study is the artificial definition of acute or chronic dactylitis based on median of the duration of symptoms in the patient of our group. In addition, we cannot exclude that patients with dactylitis duration > 20 weeks could have had a less severe form of dactylitis but only longitudinal studies can clarify these aspects. Moreover, we have used a very general definition of oedema because there is currently no agreement on a definition of soft tissue thickening/oedema. However, the high intra- and inter-observer reliability of US abnormalities supported the validity of this definition. For a more correct evaluation of soft tissue changes in relation to dactylitis duration it would be useful to use a semi-quantitative score. Similarly, there is no precise definition and grading for the subcutaneous PDS. Another possible limitation is the fact that we have enrolled patients with different drug treatments. Currently there are no data about modification induced by treatment on US characteristics of dactylitis. Moreover, no significant differences were present comparing treatment in the two groups of patients. Furthermore, we didn't evaluate lesions of volar plate, pulley and extensor tendons at distal phalanx insertion because of limitation of the US machine we used. The study of these structures should be performed with a higher frequency probe (22-24 MHz).

In conclusion, this is the first multicenter study that evaluated the relationship between US lesions and dactylitis duration in a large PsA hand dactylitis cohort. Despite limitations of this study, we

found a predominance of flexor tenosynovitis, soft tissue oedema and subcutaneous PDS in early cases and a high prevalence of joint synovitis at PIP level in the chronic form. Our findings could suggest a possible change from a predominant extracapsular pattern in the early phase to an intrasynovial pattern in the chronic evolution. However, longitudinal imaging studies are need for clarifying these aspects.

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Table 1. Clinical and laboratory features according to dactylitis duration (shorter or longer than the median: 20 weeks).

Variable	**< 20 weeks**	**≥ 20 weeks**	**p value**
Total cases	54	46	
Sex distribuition (Male/Female)	26/28	32/14	0.031
Age in years (mean ± SD)	43.7 ± 15.6	51.4 ± 13.9	0.01
BMI, kg/m2 (mean ± SD)	25.3 ± 2.7	26.1 ± 3.6	ns
PSA duration disease, months (mean ± SD)	45.4 ± 47.1	52.5 ± 44.5	ns
Tenderness (%)	91%	42%	<0.001
LDI (mean ± SD)	35.4 ± 16.2	19.5 ± 19.5	< 0.001
Patient pain VAS score (mean ± SD)	6.8 ± 2.7	4.9 ± 2.2	<0.001
TJC, 68 joints (mean ± SD)	6.6 ± 5.1	5.7 ± 4.1	ns
SJC, 66 joints (mean ± SD)	3.2 ± 2.1	2.4 ± 1.9	ns
ESR, mm/hr (mean ± SD)	19.1 ± 14.4	17.2 ± 12.4	ns
C-RP, mg/dl (mean ± SD)	1.1 ± 1.9	0.8 ± 1.3	ns
No therapy, *n (%)*	18 (33.3%)	18 (39.1%)	ns
Actual therapy with only NSAIDs, *n (%)*	4 (7.4%)	3 (6.5%)	ns
Actual therapy with prednisolone, *n (%)*	3 (5.6%)	6 (13.1%)	ns
Actual therapy with csDMARDs, *n (%)*	29 (53.7%)	19 (41.3%)	ns
Methotrexate , *n (%)*	16 (29.6%)	9 (19.5%)	ns
Sulphasalazine, *n (%)*	9 (16.7%)	7 (15.2%)	ns
Leflunomide, *n (%)*	4 (7.4%)	3 (6.5%)	ns

Legend: BMI: body mass index; **CRP:** C-reactive protein; **csDMARDs:** conventional synthetic disease-modifying anti-rheumatic drugs; **ESR:** erythrocyte sedimentation rate; **LDI**: LEEDs dactylitis index; **NSAIDs:** non-steroidal anti-inflammatory drugs; **PsA:** Psoriatic Arthritis; **SD:** standard deviation; **SJC:** swollen joint count; **TJC:** tender joint count; **VAS:** visual analogue scale.

Table 2. Prevalence of ultrasonographic abnormalities according to dactylitis duration (shorter or longer than the median: 20 weeks).

Variable	< 20 weeks	> 20 weeks	p
Total cases	54	46	
GS flexor tenosynovitis (all cases)	93%	83%	ns
GS flexor tenosynovitis grade ≥2	65%	24%	0.001
PD flexor tenosynovitis (all cases)	87%	54%	<0.001
PD flexor tenosynovitis grade ≥2	74%	37%	0.001
Soft tissue oedema	97%	82%	0.018
Subcutaneous PDS	96%	71%	0.001
GS extensor tendon involvement	9%	15%	ns
PD extensor tendon involvement	9%	11%	ns
GS synovitis involving at least 1 joint	18%	65%	<0.001
PD synovitis involving at least 1 joint	9%	35%	0.02
MCP GS synovitis (all cases)	11%	20%	ns
MCP GS synovitis grade ≥2	0	4%	ns
MCP PD synovitis (all cases)	6%	9%	ns
MCP PD synovitis grade ≥2	2%	6%	ns
PIP GS synovitis (all cases)	6%	54%	<0.001
PIP GS synovitis grade ≥2	6%	45%	<0.001
PIP PD synovitis (all cases)	6%	30%	0.001
PIP PD synovitis grade ≥2	4%	4%	ns
DIP GS synovitis (all cases)	9%	8%	ns
DIP GS synovitis grade ≥2	3%	6%	ns
DIP PD synovitis (all cases)	3%	4%	ns
DIP PD synovitis grade ≥2	0	0	ns
GS flexor tenosynovitis plus soft tissue oedema	91%	65%	0.002
GS flexor tenosynovitis plus GS synovitis involving at least 1 joint	18%	48%	0.001
Soft tissue oedema plus GS synovitis involving at least 1 joint	19%	50%	0.001

Legend: DIP: distal interphalangeal; **GS:** grey-scale; **MCP:** metacarpophalangeal; **PD:** Power Doppler; **PDS:** Power Doppler signal; **PIP:** proximal interphalangeal; **US:** Ultrasonography.

Table 3. Prevalence of ultrasonographic abnormalities according to therapy.

Variable	**CsDMARDs Treated Patients**	**CsDMARDs** naïve patients **Patients**	**p**
Total cases	48	52	
GS flexor tenosynovitis	87%	88%	ns
PD flexor tenosynovitis	75%	69%	ns
Soft tissue oedema	96%	85%	ns
Subcutaneous PDS	85%	85%	ns
GS synovitis involving at least 1 joint	33%	46%	ns
PD synovitis involving at least 1 joint	23%	19%	ns
Cases with dactylitis duration < 20 weeks	29	25	
GS flexor tenosynovitis	97%	88%	ns
PD flexor tenosynovitis	86%	88%	ns
Soft tissue oedema	97%	96%	ns
Subcutaneous PDS	93%	100%	ns
GS synovitis involving at least 1 joint	14%	24%	ns
PD synovitis involving at least 1 joint	10%	8%	ns
Cases with dactylitis duration > 20 weeks	19	27	
GS flexor tenosynovitis	74%	89%	ns
PD flexor tenosynovitis	58%	52%	ns
Soft tissue oedema	95%	74%	ns
Subcutaneous PDS	74%	70%	ns
GS synovitis involving at least 1 joint	63%	67%	ns
PD synovitis involving at least 1 joint	42%	30%	ns

Legend: csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs**; GS:** grey-scale; **PD:** Power Doppler; **PDS:** Power Doppler signal; **US:** Ultrasonography.

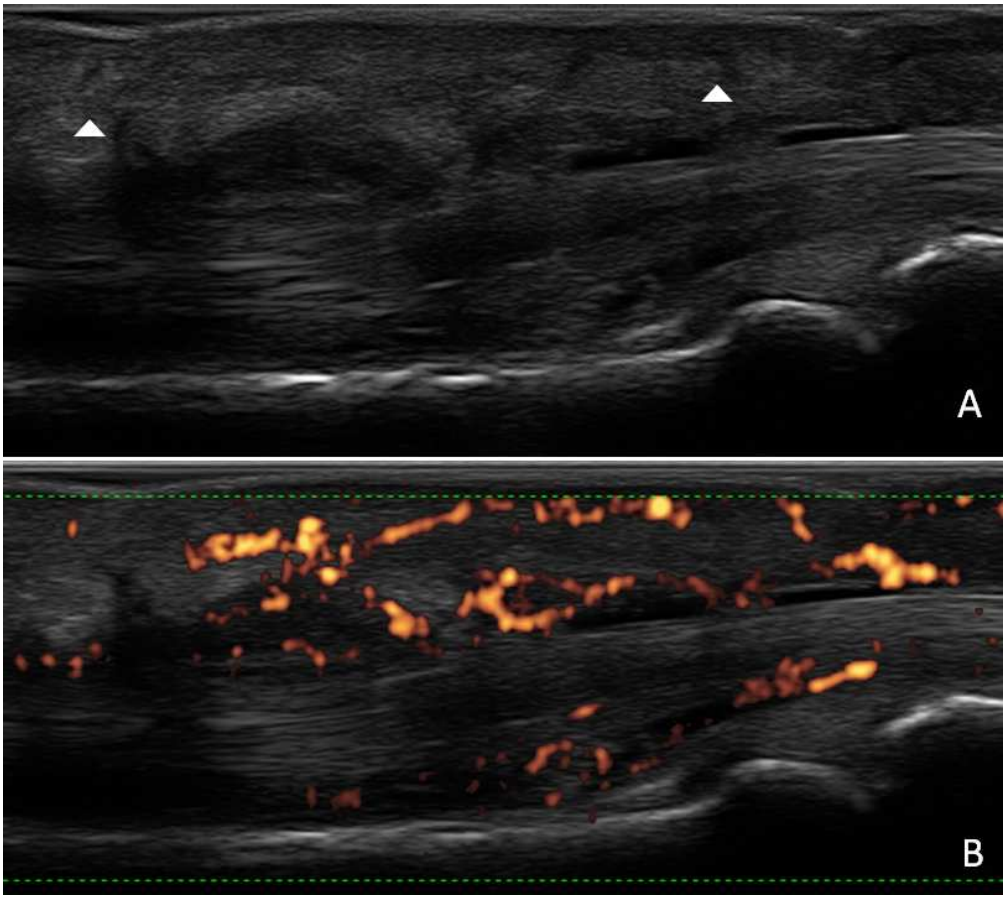

Figure 1. Longitudinal views of dactylitis belonging to the first group (dactylitis duration shorter than 20 weeks). (A) Ultrasound shows flexor tenosynovitis of grade 2 with soft tissue oedema (white arrowheads) whereas joint synovitis is absent. (B) Power Doppler signal (PDS) is present around the tendon fibers and in subdermal tissue; intra-articular PDS is absent.

213x190mm (96 x 96 DPI)

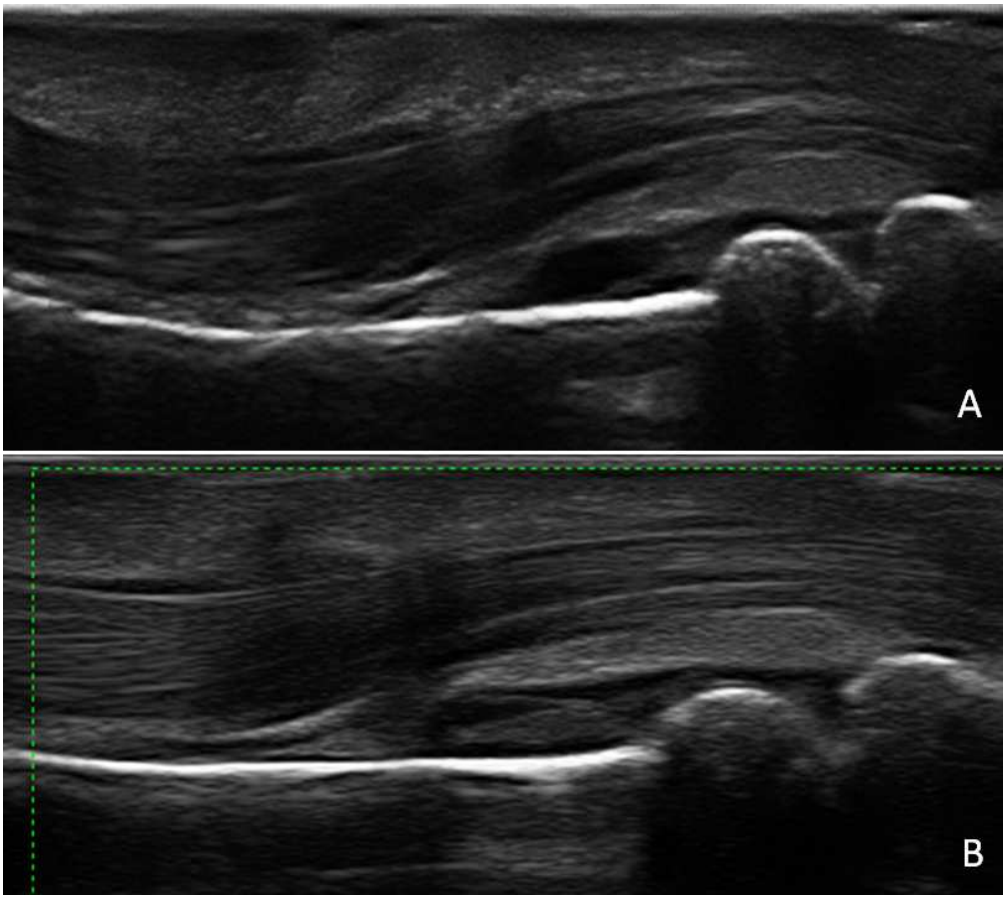

Figure 2. Longitudinal views of dactylitis belonging to the second group (dactylitis duration longer than 20 weeks). (A) Ultrasound shows no peritendinous oedema, distension of the flexor tendon sheath (grade 1) and of the capsule (grade 3) at proximal interphalangeal joint level. (B) PDS is absent in the articular, peritendinous and subcutaneous areas.

213x190mm (96 x 96 DPI)

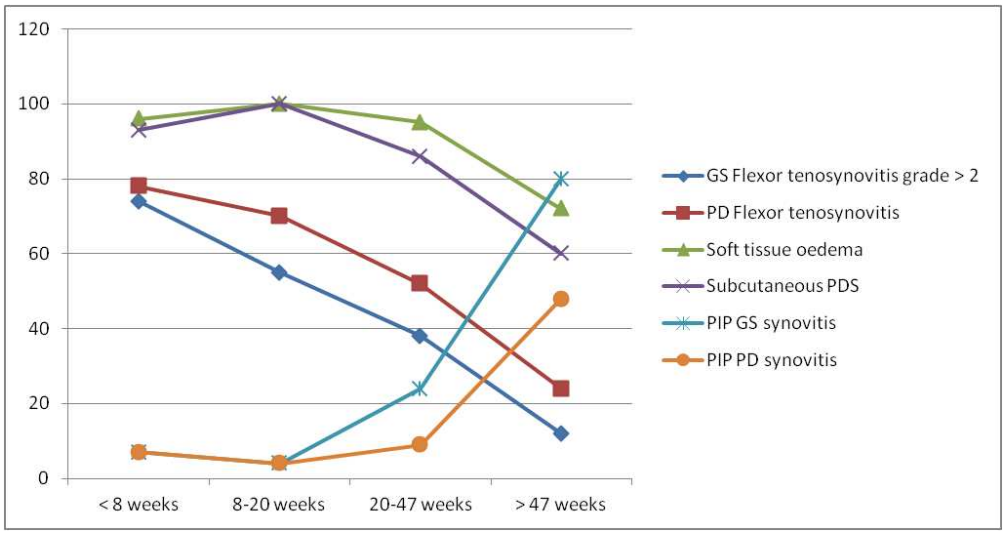

Figure 3. Prevalence of selected ultrasonographic abnormalities. Cases were split into the following quartiles: < 8 weeks (n= 27), > 8 to < 20 weeks (n= 27), > 20 to < 47 weeks (n=21) and > 47 weeks (n=25). The prevalence of grey scale (GS) flexor tenosynovitis of grade > 2, Power Doppler flexor tenosynovitis, soft tissue oedema and subcutaneous PDS decreased in patients with longer dactylitis duration. On the other hand, the prevalence of GS synovitis and intra-articular Power Doppler signal at PIP level increased over time.

271x142mm (96 x 96 DPI)