Ultrasonographic wrist and hand abnormalities in early psoriatic arthritis patients: correlation with clinical, dermatological, serological and genetic indices

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Abstract

Objective

The aims of our study are to describe the wrist and hand ultrasound (US) abnormalities compared to clinical examination in early psoriatic arthritis (ePsA) and to analyse their correlation with clinical, dermatological, serological and genetic indices.

Methods

We analysed 1120 fingers and 224 wrists of 112 early PsA, with MyLab70 Xview (Esaote, linear probe) ultrasound (US). Power Doppler active synovitis (AS), erosions, finger tendons tenosynovitis or peritendinitis (TP) and pseudotenosynovitis (PT), were compared to clinical (BASDAI, SHAQ), dermatological (PASI and psoriasis aspects), serological (ESR, CRP, ACPA) and genetic (HLA haplotypes) indices.

Results

All US abnormalities were present: AS was more frequent at wrists (50/224 [22.3%]), followed by hand PT (68/1120 [6,1%]) and TS (29/1120 [2.6%]), while erosions were rare (10/1120 [0.8%]). US abnormalities were independent of ePsA clinical indices (except erosions – even if represented only in a low percentage – that correlated to BASDAI [$p<0.05$]), while they were associated to several dermatological (except PASI), serological and genetic parameters: psoriasis (all $p<0.0001$), palmoplantar psoriasis (wrist and hand AS $p<0.0005$ and $p<0.005$, respectively), hand psoriasis (all $p<0.0001$), nail dystrophy (hand AS $p<0.05$, PT $p<0.0001$, erosions $p<0.0001$); positive CRP (all $p<0.0001$), ESR (wrist and hand AS $p<0.005$ and <0.0005, respectively, TS, PT and erosions $p<0.0001$) and ACPA – even if represented only in 1.78% of patients – (wrist and hand AS and TS $p<0.0001$, PT $p<0.5$); HLA-B27 (wrist and hand AS $p<0.0001$, TS $p<0.01$, PT $p<0.05$), -B35 (wrist and hand AS $p<0.01$ and $p<0.05$, respectively), -B38 (wrist and hand AS $p<0.0001$, TS $p<0.0001$, PT $p<0.005$), -CW6 (wrist AS $p<0.05$), -DR4 (wrist and hand AS $p<0.0001$, TS $p<0.0001$, PT $p<0.005$).

Conclusion

US abnormalities of hand and wrist were independent of clinical ePsA indices (except erosions), while they correlated to dermatological (except PASI), serological and genetic parameters of disease.

Key words

ultrasound, early psoriatic arthritis

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Received on September 15, 2014; accepted in revised form on December 1, 2015.

Competing interests: none declared.

Introduction

Early psoriatic arthritis (ePsA) usually appears as an enthesoarthritis with a consistent risk of evolving towards an erosive and deforming arthritis already in the first year of disease (1-2). It can be burdened by permanent invalidity (1) that can be avoided with a rapid therapeutic intervention before the onset of established structural damage (3). The clinical and serological measures, widely used in established disease, often fail to identify the early phases of PsA and to quantify the inflammatory activity of the affected joints and tendons (4).

In the last few years, ultrasonography (US) with power Doppler (PD) has demonstrated to be more sensitive than clinical examination in the diagnosis of synovitis and enthesitis and in the assessment of inflammatory activity in PsA (5-6).

Furthermore, although the genetic predisposition of human leukocyte antigen (HLA) in PsA is well known, it is not known whether HLA has a discriminating power on different US involvements of the hands and wrists

Finally, the relationship of PsA with psoriasis is, to date, controversial. Although they have been considered as two distinct diseases, a strict relationship with arthritis has recently been hypothesised for nail dystrophy (7) and the single term of "psoriatic disease" has been proposed to include the simultaneous involvement of different tissues (including joints, entheses, skin and nails) (8).

The aim of our study is to describe hand and wrist US abnormalities in a cohort of ePsA patients and to analyse their correlation with clinical, dermatological, serological and genetic indices.

Methods

Patients

One hundred and twelve consecutive patients with early PsA (with onset of first joint inflammatory joint symptoms lower than 1 year (4)) attending the early PsA clinic of University of Florence were studied (63 female and 49 male, 52.93±16.44 years old and with 8.0±4.01 months of duration of disease, expressed in mean and standard deviation, respectively). All the patients satisfied CASPAR classification criteria (9) and none assumed steroids before clinical and US assessments, belong flow chart guidelines defined to send patients to our clinic.

Inclusion criteria were patient's age >18 years and disease duration ≤12 months. The exclusion criteria were the coexistence of other inflammatory rheumatic diseases, recent infections, cancer, hyperuricaemia, severe previous hands and wrists trauma, surgery and joint infiltration.

To exclude severe osteoarthritis and crystal-mediated arthritis, all patient were also examined with traditional x-ray evaluation.

Clinical assessment was carried out by an expert rheumatologist (DV), who recorded tenderness and swelling of wrist and hand joints and the presence of dactylitis. Patients filled the following questionnaires: SHAQ (Health Assessment Questionnaire modified for Spondyloarthritis) and BASDAI (Bath Ankylosing Spondylitis Disease Activity Index). Psoriasis skin and nails involvement was assessed and scored with PASI by an expert dermatologist (PF). Laboratory assessment included: eritrosedimentation rate (ESR), C reactive protein (CRP), anticitrullinated protein antibodies (ACPA) and HLA haplotypes B27, B35, B38, CW6, CW7, DR1, DR4 (PCR analysis).

Ultrasound assessment

A systematic longitudinal and transverse multiplanar US examination of both wrists (radiocarpal joint, among the distal radius and the proximal carpal row, and intercarpal joints) and hands (metacarpo-phalangeal [MCP] joints; proximal [PIP] and distal [DIP] interphalangeal joints; flexor and extensor finger tendons) was performed by an experienced sonographer (BF) who was unaware of the patients clinical and laboratory data. A MyLab70 XVG machine (Esaote SpA, Genoa, Italy) equipped with a multifrequency linear probe (LA435 6–18 Mhz) was used. The images of all patients were saved in a digital archiving computer system.

US signs of active synovitis (echogenic non-compressible intra-articular syno-

vial hypertrophy with altered vascularisation, showed by Power Doppler signal) (AS) (10-11) and bone erosions (interruption of the bone profile documented on at least two perpendicular scanning planes) were reported (11). Vascularisation of the examined joints was evaluated with power Doppler US standardised with a pulse repetition frequency of 750 Hz and gain 53–55% dB and scored either with a binary item (negative if absent and positive if any signal) either with a semiquantitative scale from 0 to 3 (0 = absence of flow; 1 = mild, single vessel signal; 2 = moderate, confluent vessels; 3 = marked, vessel signals in over half the examined area) (10).

Erosions were semi-quantitatively scored (0 = normal; 1 = cortical break <2 mm; 2 = 2–4 mm; 3 = >4 mm) (12). Furthermore, in hand fingers, tenosynovitis or peritendinitis of tendons (hypoechoic or anechoic thickened tissue with or without fluid within the flexor tendons sheath or around extensor tendons, respectively, seen in 2 perpendicular planes) (11, 13) (TS) and pseudotenosynovitis (hypoechoic soft tissue surrounding the flexor tendon showing an intense power Doppler signal) (13, 14) (PT) were evaluated with binary method (presence/absence).

To estimate US inter-and intra-observer agreement, the saved images of 10 patients were read two months after the initial scanning by the same rheumatologist who performed US examination (BF), unaware of previous results, and by another experienced trader (CL) expert in musculoskeletal US.

Statistical methods

The inter- and intraobserver agreement for US examination were calculated using an unweighted κ test. A κ-value <0.40 was considered low; 0.41–0.60: moderate; 0.61–0.80 good; 0.81–1 excellent.

Descriptive statistics were expressed as mean ± standard error mean (SEM), 95% lower and upper confidence interval of mean (CI) and as number and percentage for categorical variables. A *p*-value less than 0.05 was considered statistically significant.

Normal distribution of parameters was verified by Kolmogorov-Smirnoff and D'Agostino and Pearson test.

The correlation among the number (in each patient) of AS, TS, PT and erosions with clinical indices (BASDAI, SHAQ and PASI) was evaluated with parametric Pearson and non-parametric Spearman *r*-test, respectively, when indicated.

The presence/absence of US parameters was compared with Yates χ^2 test to the presence/absence of serological positive parameters (ESR, CRP, ACPA), HLA haplotypes and dermatological aspects (psoriasis, hand psoriasis, palmoplantar psoriasis, nail dystrophy).

Results

There was an excellent level of intraobserver (κ=0.90) and a good level of interobserver (κ=0.80) agreement for all US parameters examined.

Description of US abnormalities of ePsA patients

At US, ePsA patients presented in different percentage: 32/112 (28.6%) (at wrists) and 29/112 (25.9%) (at hands) AS, 20/112 (17.8%) and 16/112 (14.3%) hand TS and hand PT, respectively, and 9/112 (8%) erosions.

We described the presence of US abnormalities in each joint (224 wrists and 1120 MCP- PIP-DIP, respectively) compared to clinical examination as shown in Table I.

Wrists and finger active synovitis (AS)

By US examination, AS at the wrist and small joints of the hands was more frequent in wrists 50/224 (22.3%) than other joints (MCP 28/1120 [2.5%], PIP 24/1120 [2.1%], DIP 3/1120 [0.3%]).

The semi-quantitative score (low, moderate, severe) of power Doppler was: 13/50 severe (26%), 16/50 moderate (32%), 21/50 low (42%), in the wrists; 6/28 severe (21.4%), 7/28 moderate (25%), 15/28 low (53.5%) in MCP; 1/24 severe (4.1%), 6/24 moderate (25%), 17/24 low (70.8%) in PIP; 3/3 low (100%) in DIP.

As shown in Table IA, US findings were in agreement with clinical examination (swelling and tenderness respectively) in different numbers and percentages: in wrists, only in 20/50 (40%) and 17/50 (34%); in MCP 0/28 (0%) and 8/28 (28.6%); in PIP 5/24 (20.8%) and 12/24 (50%); DIP 1/3 (33.3%) and 0/3 (0%).

The percentage of false negative (negative clinical examination for swelling and tenderness and positive AS) patients was high: in wrists in 30/50 (60%) and 33/50 (66%); in MCP 28/28 (100%) and 20/28 (71.4%); in PIP 19/24 (79.2%) and 12/24 (50%); DIP 2/3 (66.7%) and 3/3 (100%).

The percentage of false positive (positive joints at clinical examination out of total negative US synovitis) patients was lower: in wrists in 22/174 (12.6%) and 24/174 (13.8%); in MCP 11/1092 (1%) and 44/1092 (4%); in PIP 10/1096 (0.9%) and 36/1096 (3.3%); DIP 0/1117 and 3/1117 (0.3%).

US tenosynovitis/peritendinitis (TS) and pseudotenosynovitis (PT)

At US, PT was more frequent than TS (Fig. 1) (68/1120 [6,1%]), mostly localised at the II (22/68 [32.3%]), III (20/68 [29.4%]) and V fingers (10/68 [14.7%]).

The TS of flexors and extensors were present respectively in 29/1120 (2,6%) (mostly at second flexor 10/29 [34.5%] and third flexor 14/29 [48.3%] and 12/1120 (1%) (at first finger 3/12 [25%] and third finger 4/12 [33.3%].

As shown in Table IB, in 28/1120 fingers presenting dactylitis, US confirmed PT in 16/28 (57.1%), flexors tenosynovitis in 11/28 (39.2%), extensors peritendinitis in 1/28 (3.6%), and fingers AS in 9/28 (32.1%) (5/9 [55.5%] in MCP and 4/9 [44.4%] in IPP).

The percentage of false negative patients (absence of dactylitis at clinical examination with positive US features) was high: PT in 52/68 (76.5%), tenosynovitis in 18/29 (62%), peritendinitis in 11/12 (91.6%). No false positive patients were found (dactylitis at clinical examination with negative US).

Erosions

Ten out of 1120 (0.8%) erosions were found in different numbers and percentages: 5/10 grade 2 (2–4 mm) and 5/10 grade 1 (<2 mm) of Wakefield score; 8/10 (80%) localised on II MCP and 2/10 (20%) on III MCP. Only one

Table IA. Active synovitis examined by ultrasound compared to swelling/tenderness presence at clinical examination at wrists, metacarphophangeal (MCP), proximal (PIP) and distal (DIP) interphalangeal joints.

WRIST		Swelling		Total	Tenderness		Total
		present	*Absent*		*present*	*absent*	
Active synovitis	*present*	20	30	50	17	33	50
	absent	22	152	174	24	150	174
Total		42	182	224	41	183	224
MCP		Swelling		Total	Tenderness		Total
		present	*Absent*		*present*	*absent*	
Active synovitis	*present*	0	28	28	8	20	28
	absent	11	1081	1092	44	1048	1092
Total		11	1109	1120	52	1068	1120
PIP		Swelling		Total	Tenderness		Total
		present	*Absent*		*present*	*absent*	
Active synovitis	*present*	5	19	24	12	12	24
	absent	10	1086	1096	36	1060	1096
Total		15	1105	1120	48	1072	1120
DIP		Swelling		Total	Tenderness		Total
		present	*Absent*		*present*	*absent*	
Active synovitis	*present*	1	2	3	0	3	3
	absent	0	1117	1117	3	1114	1117
Total		1	1119	1120	3	1117	1120

IB. Tenosynovitis (flexors), peritendinitis (extensors) and pseudotenosynovitis examined by ultrasound compared to the presence of dactylitis at clinical examination of hands.

	Dactylitis		
	Present	*Absent*	Tot.
Tenosynovitis	11	18	29
Peritendinitis	1	11	12
Pseudotenosynovitis	16	52	68
Total	28	81	109

patient presented two erosions symmetrical at II MCP. Wrists, PIP and DIP were unaffected.

Three out of 10 (30%) erosions with score 2 at US (with measures, at US: 3.3 mm, 2.5 mm and 2.9 mm, respectively) were also visible at traditional x-ray. No other erosions were observed at traditional x-ray examination, performed in all other patients.

US abnormalities correlation with clinical, dermatological, serological, and genetic indices

The clinical, dermatological, serological and genetic indices analysed in the observed 112 ePsA patients are reported in Table II.

Only erosions correlated to BASDAI ($p<0.05$ and $r=0.189$ using Spearman r-test). All other US abnormalities were independent of PASI, BASDAI and SHAQ.

Furthermore, the presence of US abnormalities correlated to several dermatological, serological and genetic indices positivity (Yates χ^2 test): psoriasis (all $p<0.0001$), palmoplantar psoriasis (wrist and hand AS $p<0.0005$ and $p<0.005$, respectively), hand psoriasis (all $p<0.0001$), nail dystrophy (hand AS $p<0.05$, PT $p<0.0001$, erosions $p<0.0001$); positive CRP (all $p<0.0001$), ESR (wrist and hand AS $p<0.005$ and <0.0005, respectively, TS, PT and erosions $p<0.0001$) and ACPA (wrist and hand AS and TS $p<0.0001$, PT $p<0.005$); HLA -B27 (wrist and hand AS $p<0.0001$, TS $p<0.01$, PT $p<0.05$), -B35 (wrist and hand AS $p<0.01$ and $p<0.05$, respectively), -B38 (wrist and hand AS $p<0.0001$, TS $p<0.0001$, PT $p<0.005$), -CW6 (wrist AS $p<0.05$), -DR4 (wrist and hand AS $p<0.0001$, TS $p<0.0001$, PT $p<0.005$).

No patient was HLA DR1 positive.

Discussion

In agreement with the literature data (5, 6, 14, 15), in our study US proved to be more sensitive than clinical examination in detecting subclinical involvement of all examined osteo-articular structures, and therefore able to identify the "true disease" in early disease. Synovitis, tenosynovitis, pseudotenosynovitis and erosions of wrists and hands are commonly found on US examination in ePsA patients.

Unlike late PsA, in which a prevalent involvement of IPD and MCP has been demonstrated on US (16-17), in our cohort of ePsA we have shown a predominant involvement of the wrists, mainly asymmetric. Moreover, these data seem to be in disagreement with those of Scarpa *et al*. (1), who indicated IPP and the IPD as the most clinically affected joints in ePsA.

Interestingly, in the study conducted by Naredo *et al*. (5) on patients with psoriasis without inflammatory joint symptoms, the most frequent US subclinical synovitis was evidenced at wrists. If confirmed by other studies on a larger number of patients, these data could suggest that the pattern of osteoarticular involvement in ePsA is different than in late PsA and that wrists are the joints firstly involved in early disease.

Power Doppler signal in the synovium was also absent in patients with clinical signs of inflammation, above all in wrists (around 13%), with a percentage lower than in other similar studies on US sensitivity in PsA patients (false positivity of 70%) and in rheumatoid arthritis (false positivity of 36%). This datum is difficult to interpret; we might hypothesise a misinterpretation of clinical examination due to an incorrect perception of patients of pain localisation or to other causes of soft tissue inflammation such as subcutaneous oedema.

In our ePsA patients, we demonstrated also that pseudotenosynovitis was more frequent than tenosynovitis and peritendinitis in fingers. These findings are in agreement with previous histological, US and MRI evidences in dactylitis (20-21) as well as with the hypothesis that pseudotenosynovitis in the early phases of the disease precedes tenosynovitis and synovitis (14).

Table II. Clinical, dermatological, serological and genetic indices examined in ePsA patients, expressed in mean ± SEM, 95% CI, number and percentage.

Clinical indices:		
SHAQ (mean±SEM, 95% CI)	0.63±0.059	(0.51-0.749 CI)
BASDAI (mean±SEM, 95% CI)	3.78±0.259	(3.27-4.29 CI)
Dermatological indices:		
PASI (mean+SEM; 95% CI)	3.85±0.64	(CI 2.58-5.12)
Psoriasis (percentage)	87/112	(77.6%)
Palmoplantar psoriasis (number and percentage)	10/112	(9%)
Hand psoriasis (number and percentage)	67/112	(60.3%)
Hand nail dystrophy (number and percentage)	44/112	(39.6%)
Serological indices:		
ESR positive (>20mm/h (number and percentage)	56/112	(50.45%)
ESR mm/h (mean±SEM; 95% CI)	23.71±1.56	(CI 20.62-26.8)
CRP positive (>0,5 mg/dl) (number and percentage)	32/112	(28.57%)
CRP mg/dl (mean±SEM; 95% CI)	1.03±0.31	(CI 0.41-1.66)
ACPA positive (number and percentage)	2/112	(1.8%)
Genetic indices positive (number and percentage):		
HLA B27	6/112	(5.3%)
HLA B35	15/112	(13.4%)
HLA B38	2/112	(1.8%)
HLA CW6	17/112	(15.1%)
HLA CW7	23/112	(20.5%)
HLA DR4	2/112	(1.8%)

ACPA: Anti-citrullinated protein antibody; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CI: confidence interval; CRP: C-reactive protein; ESR: Erythrosedimentation rate; PASI: psoriasis area severity index; SEM: standard error mean; SHAQ: Health Assessment Questionnaire modified for Spondyloarthritis.

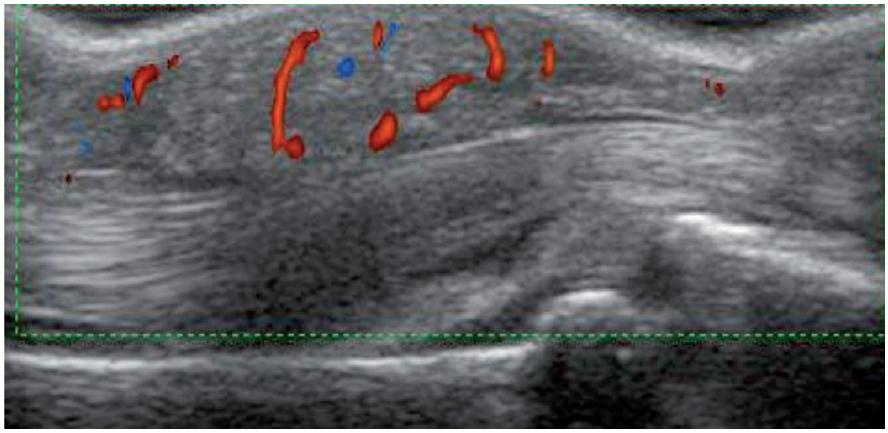

Fig. 1. Intense bidirectional Power Doppler signal inside the soft tissue surrounding the flexor tendon (pseudotenosynovitis) in a ePsA patient.

Although in a low percentage, US also showed the presence of bone erosions not visible in 70% of cases at traditional radiography. This finding might indicate a possible pre-radiographic cortical bone involvement in the early phases of the disease (1).

Furthermore, unlike the other US findings, which were found independent from clinical examination, the presence of erosions correlates with BASDAI.

Otherwise, this result might considered only exploratory, for the limited number of erosions examined, and needs further future studies to confirm the possible correlation between early detection of erosions at US and the severity of PsA activity.

In the early stage of the disease, serological measures are commonly considered not very useful to assess disease activity. However, a significant correlation between the positivity of CRP (28.5% of patients) and ESR (50.4%) with US parameters was found in our ePsA patients, which seems to emphasise their importance in the early phases. ACPA, which have been described as more frequently associated to an erosive pattern in established arthritis (22), in our ePsA patients correlated to all US parameters except with erosions. Otherwise in our cohort, differenly to Bogliolo *et al*. (22) that observed ACPA in 15% of PsA, we found only a very small number of patients ACPA positive (1.78%). Thus, this result might be confirmed by larger cohort of patients and the diagnostic value of ACPA in ePsA might be still a matter of debate for the future.

It is worthy of note that, in our ePsA patients the genetic loci known to be associated with psoriatic arthritis were linked to all US abnormalities (unless erosions), with the exception of HLA-B35 (wrist and hand active synovitis [AS], only) and HLA-Cw6 (wrist AS, only), which was associated only with wrist synovitis. This last observation is intriguing because the association of HLA-Cw6 with psoriasis type-1 has been well demonstrated, while its role in PsA is debated and not confirmed. The controversial relationship between HLA-Cw6, skin and joints has recently been pointed out (2), this haplotype being negatively linked to nail disease (23) which is instead considered a predictor of arthritis (24). A protective role at least on some ePsA aspects of this locus could therefore be hypothesised and researched in the future.

Although the subclinical osteoarticular involvement in psoriasis has been demonstrated by a growing number of imaging studies (5, 25, 26, 27), there are still some controversies about a common base of the two autoimmune diseases, especially in the early stages (2). In our study, the link between ePsA and skin psoriasis has been confirmed by the strong correlation emerged between osteoarticular US parameters and the presence of hand psoriasis, palmoplantar psoriasis and nail dystrophy correlated with US abnormalities.

In particular, our results are in according to the hypothesis on the strict link between arthritis and nail disease in early phase of disease (22, 28).

Otherwise, in agreement with previous literature data (3-26-27), this correlation was independent of the extension and severity of psoriasis (PASI) in ePsA.

Conclusions and take home messages:

- In hands and wrists of ePsA patients, active synovitis, erosions, tenosynovitis/peritendinitis, pseudotenosynovitis were demonstrated on US examination
- In these subjects, US proved to be more sensitive than clinical examination in detecting subclinical involvement of the osteo-articular structures
- US abnormalities resulted independent from clinical indices (BASDAI, SHAQ). The correlation of erosions and BASDAI might be considered only an exploratory result for the small number of erosions observed.
- US abnormalities correlated to dermatological (except PASI), serological and genetic parameters

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