Ultrasound imaging for the rheumatologist XXXIII. Sonographic assessment of the foot in early arthritis patients

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ABSTRACT

Objectives. *To investigate the ability of ultrasonography (US) to detect synovitis in metatarsophalangeal joints (MTP) in patients with suspicion of early arthritis, and to discriminate between diagnoses.*

Methods. *Patients referred to early arthritis clinics for differential diagnosis were enrolled, and clinical and laboratory measures were recorded. Ultrasonography of MTPs was performed searching for synovial hypertrophy (SH), joint effusion (JE) and power Doppler (PD), graded from 0 to 3 on a semi-quantitative scale.*

Patients were classified according to definite classification criteria, or as undifferentiated arthritis or non-inflammatory pathology. US findings were compared across different diagnoses and diagnostic accuracy was calculated taking clinical diagnosis as reference.

Results. *Out of 427 patients (71% rheumatoid arthritis (RA), 20% undifferentiated arthritis (UA), 15% spondyloarthritides (SpA), 13% non-inflammatory), 307 (71.9%) showed SH, 120 (25.5%) JE, 77 (18.0%) PD. RA patients had median JE, SH and PD scores significantly higher than non-inflammatory and other diseases. Patient with UA and SpA had higher scores of SH and JE compared to non-inflammatory, no significant differences were present among different diagnosis. In RA, SH and JE were more frequently detected in the second MTP, and PD in the fifth. Crystal-related arthritis showed a tendency towards a more frequent involvement of the first MTP. The diagnostic accuracy of single US measures was moderate, but the detection of a PD of 2 or more provided a high specificity for the diagnosis of RA.*

Conclusions. *US can be used as additional information in patients evaluated in an early arthritis setting. High scores of JE, SH and PD, together with the pattern of involvement are suggestive of RA.*

Introduction

Despite the introduction in the last decades of many innovative therapeutic agents and strategies in the management of rheumatoid arthritis (RA), early diagnosis and intervention are still crucial (1, 2). In this context, it is important to define features that are present at the onset in early arthritis and that could be helpful in order to define diagnosis and improve therapeutic management (3. 4).

Many clinical, demographical and laboratory parameters have been investigated for this purpose (3-6). In particular, the extent and sites of joint involvement are regarded as additional diagnostic and prognostic factors (7-10). For instance, the early involvement of metatarsophalangeal joints (MTPs) has been believed to be useful in detecting persistent and erosive arthritis at the onset (11).

The clinical involvement of MTPs occurs frequently in polyarticular onset inflammatory arthritis (up to 50.3% of patients) (12), and the fifth MTP has been shown in imaging studies to be an early site of bone erosions (13). Nevertheless, the reliability of clinical evaluation of these joints has been largely discussed. In fact, imaging studies comparing clinical evaluation to MRI as reference standard for the detection of synovitis, have shown poor sensitiv-

ity; conversely, ultrasonography (US) has proven to be more accurate (14).
A few studies have specifically addressed the potential role of US in the evaluation of MTPs. In particular, US has been demonstrated to be more sensitive than conventional radiography in detecting bone erosions in the fifth MTP (15, 16). A very recent study has investigated the potential role of an extensive US joint count, including MTPs, to predict the subsequent development of RA in a cohort of very early inflammatory arthritides (symptom duration <3 months). MTP synovitis, documented by US, was frequently clinically undetected and US involvement of MTPs was significantly more frequent in patients that developed RA subsequently. The same trend, even if less pronounced, was evident also for patients with longer symptom duration (more than 3 months but less than 1 year) (17).
In this work we systematically applied US to identify joint inflammation at the MTP joints in patients with early arthritis in order to investigate its diagnostic properties on the discrimination between different diseases. For this purpose we included a sample of patients with early arthritis and we cross-sectionally analysed the baseline association between US MTP involvement and clinical diagnosis.

Methods

Setting and participants

Patients with clinical suspicion of inflammatory polyarthritis were referred to the early arthritis clinics for differential diagnosis. The data collected during the baseline evaluation were used for cross-sectional analyses. All subjects gave written consent.

Patient assessment

The clinical assessment included: tender and swollen joint count (TJC, SJC) on 28 joints, tender and joint count at MTPs, visual analogue scale (VAS) for pain, examinator's global assessment (EGA) and global health assessment (GH). Laboratory tests included rheumatoid factor (RF), anti-citrullinated peptide antibodies (ACPA), antinuclear antibodies (ANA), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Functional disability was assessed by the Italian version of the HAQ (18).
At baseline patients were classified with a clinical diagnosis based on established classification criteria (19-22). Patient with clinical evidence of inflammatory arthritis of at least one joint who did not fulfil any classification criteria were defined as undifferentiated arthritis. Patients without any clinical sing of joint inflammation were labelled as "non-inflammatory".

Musculoskeletal ultrasonography

US assessment was performed in each centre by experienced operators, using a Logiq 9 (General Electrics Medical Systems, Milwaukee, WI) with multifrequency linear probes (8-14 MHz) according to the European League Against Rheumatism (EULAR) guidelines (23). Inter-reader reliability has been evaluated in a previous study (24). To avoid "review biases" the ultrasonographer was unaware of the clinical data at the exam session.
The scanning protocol of MTP joints was performed as already detailed elsewhere (25).
The presence of joint effusion (JE) and synovial hypertrophy (SH) was identified in each joint as abnormal anechoic/hypoechoic intra-articular material according to the OMERACT definitions (26). JE and SH were subjectively graded from 0 to 3 (0 = normal; 1 = mild; 2 = moderate; 3 = marked) (25, 27). Synovial power Doppler (PD) was assessed by selecting a region of interest that included the bony margins, joint space and a variable view of surrounding tissues (depending on the joint size). PD calibrations were adjusted at the lowest permissible pulse repetition frequency to maximise sensitivity and were taken as constant in different patients. Doppler frequency was set for the study of small joints and superficial tissues. Colour gain was set just below the level that causes the appearance of noise artefacts. Flow was demonstrated in two perpendicular planes and confirmed by pulsed wave Doppler spectrum to exclude artefacts. The PD signal was subjectively graded on a semi-quantitative scale from 0 to 3 (0 = absence or minimal flow; 1 = mild: single vessel signal; 2 = moderate: confluent vessels; 3 = marked: vessel signals in >50% of the joint area) on the image with the maximal enhancement on PD (23, 28, 29). A joint was considered involved when at least score 1 JE, SH and/or PD signal were detected by US.

Statistical methods

Summary statistics of mean and standard deviation (SD) or median and interquartile range (IQR) were presented for continuous variables when appropriate. Categorical variables were summarised using both absolute and relative frequencies.
Only patients with complete clinical and US data at baseline were included in analysis.
To test equality of population medians among groups, Kruskal-Wallis one-way analysis of variance by ranks was applied. Differences between specific diagnoses were analysed using the Mann-Whitney test. Due to multiple comparisons, statistical significance was set at 0.01 level.
Comparison between frequencies across different joints were tested using the two-sample test of proportion (z-test).
Diagnostic accuracy measures (sensitivity, specificity, likelihood ratios, area under the ROC curve) were calculated using clinical diagnosis as reference and US measures as index tests.
All analyses were done using Stata version 11 (StataCorp, College Station, TX).

Results

Participants

We cross-sectionally analysed a total of 427 subjects. Their main clinical characteristics are summarised in Table I.
Overall, the study sample included patients with median (IQR) age of 57 (46-69) years, higher prevalence of female gender (75.8%), median (IQR) symptoms duration of 3.86 (2.41–6.98) months, and average moderate functional disability (median [IQR] HAQ 1.0 [0.625–1.625]).
In the examined study sample, the subjects were clinically diagnosed as follows: 178 (41.7%) RA, 86 (20.1%)

Table I. Study sample clinical characteristics.

Characteristic	All subjects
Number	427
Age (years), median (IQR)	57 (46-69)
Female, n. (%)	323 (75.8)
Disease duration (months), median (IQR)	3.86 (2.41–6.98)
RF (+ve), n. (%)	97/423 (22.9)
ACPA (+ve), n. (%)	66/416 (15.8)
ANA, n. (%)	151/420 (35.9)
VAS pain (mm), median (IQR)	51 (40–75)
VAS physician (mm), median (IQR)	36 (20–50)
VAS GH (mm), median (IQR)	55 (50–75)
SJC28, median (IQR)	6 (3–10)
TJC28, median (IQR)	6 (2–12)
Swollen MTF, median (IQR)	2 (0–4)
Tender MTF, median (IQR)	1 (0–4)
ESR (mm/h), median (IQR)	20 (12–6)
CRP (mg/dl), median (IQR)	0.47 (0.30–1.51)
HAQ, median (IQR)	1 (0.625–1.625)

Table II. Mean ultrasonographic scores according to clinical diagnosis.

Diagnosis	n. (%)	JE score mean (SD)	SH score mean (SD)	PD score mean (SD)
RA	178 (41.7)	6.5 (5.5)	2.1 (3.6)	1.4 (2.9)
UA	86 (20.1)	2.7 (3.2)	0.5 (1.7)	0.1 (0.4)
SpA	63 (15.8)	2.8 (3.2)	0.7 (1.9)	0.3 (1.4)
CTD	21 (4.9)	3.0 (3.8)	0.8 (2.3)	0.2 (0.5)
CrA	20 (4.7)	2.0 (2.1)	0. (0.3)	0.05 (0.2)
N-I	59 (13.8)	1.1 (1.6)	0.3 (1.1)	0.03 (0.3)
Total	427 (100)	4.1 (4.7)	1.2 (2.7)	0.7 (2.1)

JE: joint effusion; SH: synovial hypertrophy; PD: power Doppler; RA: rheumatoid arthritis; UA: undifferentiated arthritis; SpA: spondyloarthropaties; CTD: connective tissue diseases; CrA: crystal-associated arthritis; N-I: non-inflammatory arthropathy.

UA, 63 (15.8%) SpA, 21 (4.9%) CTD, 20 (4.7%) CrA and 59 (13.8%) without clinically detectable inflammatory arthropathy.

US involvement of feet

Overall, 307 (71.9%) subjects showed at least JE score 1, while only 120 (25.5%) and 77 (18.0%) showed at least score 1 in SH and PD scores, respectively.

Descriptive measures of different US scores stratified by clinical diagnosis are reported in Table II.

All the US scores (JE, SH and PD) significantly differed across different diagnostic categories (Kruskal-Wallis $p<0.001$).

Analysing differences among different diagnoses, patients with RA showed median JE, SH and PD scores significantly higher than patients with both other inflammatory and non-inflammatory arthropathies. (Mann-Whitney all $p<0.01$)

Within inflammatory arthritides other than RA, no significant differences were observed in JE, SH and PD scores (Kruskal-Wallis $p=0.91$, 0.41 and 0.47, respectively).

Comparing single diagnoses to non-inflammatory arthropathy, only UA and SpA showed a significant difference in median JE score ($p<0.001$ and $p=0.001$, respectively), while in CTD and CrA median JE scores was only weakly increased ($p=0.02$ and $p=0.05$). Median SH score was significantly higher only for UA and SpA ($p<0.001$ and $p=0.001$), while median PD score was weakly increased in SpA and CTD ($p=0.03$ and $p=0.02$).

Pattern of joint involvement

Pattern and frequency of involvement at single joint level are depicted in Figure 1.

In RA, JE, SH or grey scale synovitis (GS) at single joint level were more frequent in 2nd to 4th MTP than in 1st MTP and 5th MTP (z-test $p=0.0001$ 1st *vs*. 2nd and $p=0.01$ 4th *vs*. 5th).

In subjects with other diagnoses, a prevalence of GS involvement showed a similar pattern, though with less significant differences in UA and SpA.

Crystal-related arthropathies showed a tendency toward more frequent involvement of the 1st MTP. Non-inflammatory arthropathy showed a decreasing medio-lateral trend of GS involvement.

In RA, the PD pattern showed a slightly more prevalent involvement of the 5th MTP joint bilaterally ($p=0.01$ and $p=0.005$ for 1st *vs*. 5th left and right MTP, respectively).

The presence of PD synovitis was minimally prevalent in conditions other than RA and did not show any particular pattern.

Diagnostic accuracy

Due to the association of both GS and PD US variable to the clinical diagnosis of RA we explored the diagnostic properties of US in discriminating between RA and other diagnoses in early arthritis setting.

Overall diagnostic accuracy of single US measures was moderate. The AUC was 0.75 (0.71, 0.80) for the JE score, 0.64 (0.60, 0.68) for the SH score, and 0.63 (95%CI 0.60, 0.67) for the PD score.

Analysing the different cut-offs, at least 1 point of JE score associated with a negative LR of 0.31, while more than 2 points of PD score associated with a positive LR of 46.16.

Discussion

With early referral and treatment becoming a central issue in the management of inflammatory arthritis, the focus is now on features that might distinguish between different types of arthritis at the onset, in order to optimise management and prevent long-term detrimental outcomes.

In this context, the discriminative ability of extensive US joint counts to detect RA has been evaluated (17), and in some cases added to diagnostic algorithms including clinical and laboratory parameters (31, 32). Site-specific US evaluations have not been specially considered yet.

To evaluate the usefulness for diagnostic purposes of targeted US of the MTPs in early arthritis, we studied a large sample of patients referred for suspicion of new onset arthritis.

The distribution of different diagnosis in our population demonstrated a higher frequency of RA and lower frequency of CrA, compared to similar cohorts, while the distribution of other diseases was similar (33).

So far, only a few studies have specifically dealt with US findings in MTPs. The main interest was focused on the detection of bone erosions in specific sites, such as the fifth MTP (15). Szkludarek and colleagues investigated the ability of US to detect synovitis, defined as synovial thickening, in the MTPs. In this population of treated RA patients, the US involvement of MTPs occurred in about half of patients, with the second and the fifth MTP being more frequently involved, which is consistent with our findings (14). A very recent study describing US features of feet in patients with RA, detected up to 62% of synovitis (JE with SH) in the MTPs (34). Overall, the frequency of US MTP involvement seems to be comparable to our population.

Despite these few studies, which were mainly based on patients with definite diagnosis of RA, there is still a lack of information on the diagnostic properties of US involvement of MTPs at early stages.

In our study, US in MTPs showed a possible role in discriminating between inflammatory and non-inflammatory arthropathies, and this might give additional information together with clinical and laboratory parameters. This potential diagnostic role was more evident for RA, UA and SpA, while not significant for other diseases, and this might be due to the small sample size in some categories of patients.

In particular, RA was associated with the highest scores of JE, SH and PD, with a significant difference compared to non-inflammatory conditions and other diseases. This is in line with previous findings, showing a significantly higher MTP involvement in patients who would later develop RA (17).

Conversely, in our analysis we did not find significant differences in median US scores among UA, SpA, CTA and CrA. As groups were unbalanced, due to the different prevalence of the disease in the study sample, the analysis is underpowered. True differences between these diagnoses could have been missed in this context. Similar considerations should be taken into account when interpreting post-hoc analyses comparing single diagnoses with non-inflammatory patients. Studies considering larger samples are needed for this purpose.

As previously reported, in RA the MTP joints that seem more frequently affected by SH are the second and the fifth MTP (14). This was partially confirmed in our population, in which the second MTP showed more JE and SH, while the fifth MTPs had more frequently positive PD, and this is coherent with the high rate of bone erosions reported at this site (15), as also confirmed by findings on our population (data not shown).

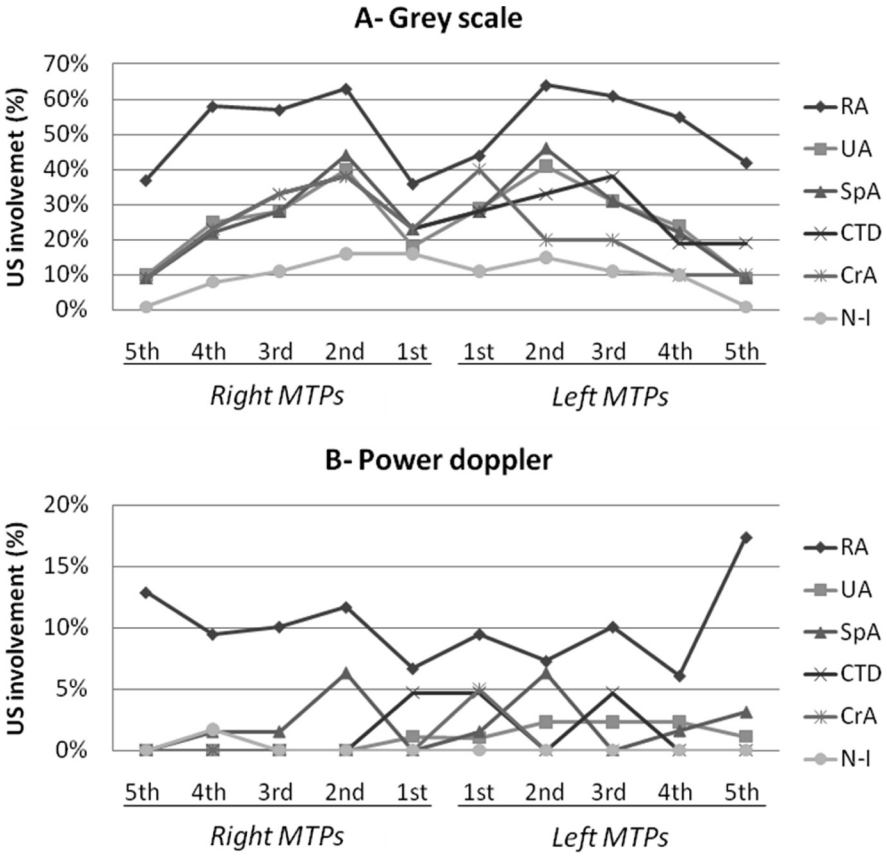

Fig. 1. Pattern of metatarsophalangeal (MTP) involvement identified by ultrasonography. Single joint involvements are presented according to different clinical diagnoses. In panel A, US involvement is defined as presence of at least grade 1 JE or SH (grey scale); in panel B US involvement is defined as presence of at least grade 1 PD signal. Single joints are reported in the x axis according to their "radiological" order from the fifth right MTP to the fifth left MTP.

In crystal-related arthritis, the first MTP is considered a frequently involved area (35). This is confirmed in our cohort, in which both GS and PD abnormalities showed a tendency towards a more frequent localisation at this site.

As expected the diagnostic accuracy of a single measure (US examination of foot) in discriminating RA patients from other diagnoses was only moderate. Previous studies have already used a more extensive US examination (31, 32) together with clinical and serological findings in predictive models in UA.

Nevertheless, the detection of 1 point JE score at foot level indicates a negative LR of 0.31, that indicates a moderate sensitivity in detecting RA patients. On the other hand, the detection of a PD score of 2 or more in MTPs provided a high positive LR of 46.16, indicating the ability to identify RA with high specificity.

The study carries some limitations as well. The cross sectional design does

not allow the evaluation of the predictive validity of US features against long term diagnosis. Furthermore, the application of a univariate analysis might not take into account possible confounders.

There might be a misclassification of the involvement in certain joints. For instance, the detection of PD in the fifth MTPs might have been overestimated, based on finding in the other MTPs, due to the known early involvement of this area. Conversely, considering that small effusions are detectable also in healthy individuals, findings in the first MTP might have been underestimated.

Overall, the use of MTP US provides additional useful information to integrate clinical history, physical examination and laboratory findings, in particular to discriminate between inflammatory and non-inflammatory pathology. US can individuate the subgroup of patients with more severe prognosis: in fact, the detection of high scores of GS and PD is highly suggestive for the diagnosis of RA, and further information can be obtained evaluating frequently involved sites, such as the fifth MTP. For these reasons, the application of foot US can be considered in patients presenting with suspicion of new onset arthritis.

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