Psoriatic Arthritis and Onycholysis — Results from the Cross-sectional Reykjavik Psoriatic Arthritis Study

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ABSTRACT. ***Objective.*** To measure the associations between subtypes of nail changes and psoriatic arthritis (PsA) among patients with psoriasis.

Methods. Patients age 18 years and older with active psoriasis were examined for skin and nail changes and asked if they had been diagnosed with PsA. Patients with arthritis were invited for a separate study 1–6 years after their initial visit. Univariate and multivariate analyses were used to test the strength of associations between subtypes of nail changes and arthritis.

Results. Of 1116 patients with psoriasis, 37% (95% CI 34%–40%) had nail changes. Age, any nail change, onycholysis, and pitting were each associated with PsA on univariate analysis. Multivariate analysis showed that onycholysis was the only type of nail change independently associated with PsA (OR 2.05, $p < 0.001$). Nail changes persisted and had increased in prevalence at the followup examination at a mean of 3.8 (median 4 yrs, interquartile range 3–4) years later. Previously reported associations between psoriasis location and arthritis were not seen in this dataset.

Conclusion. PsA is associated with onycholysis. Associations with pitting and subungual hyperkeratosis were not statistically significant. Subtypes of nail changes should be analyzed separately in future studies of PsA. (First Release May 15 2012; J Rheumatol 2012;39:1441–4; doi:10.3899/jrheum.111298)

Key Indexing Terms:
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Psoriatic arthritis (PsA) is an inflammatory joint disease associated with psoriasis[1]. While PsA affects 0.1%–0.2% of the general population, it is 100 times more common among patients with psoriasis, affecting 8%–16% in population-based studies[2,3,4]. This high prevalence results in a large absolute risk for PsA even if a risk factor is associated with a modest effect size. Confirming the risk of PsA associated with a clinical or laboratory finding among patients with psoriasis requires carefully designed prospective studies, but cross-sectional association studies can help identify candidate risk factors. Such associations also have the potential to shed light on the pathophysiology of PsA.

Previous studies show that PsA is associated with nail changes[5]. While 15%–50% of patients with psoriasis have nail changes the same is true of up to 85% of patients with PsA[2,5,6,7]. Recent magnetic resonance imaging studies suggest that nail changes represent a continuation of inflammation originating in entheseal structures and may be a manifestation of arthritis[8,9]. These studies did not investigate subtypes of nail changes, while an association between distal interphalangeal (DIP) joint involvement in PsA and onycholysis has been reported[10]. We previously reported an association between onycholysis and small-joint arthritis not limited to DIP joints[11]. These associations were not seen for either pitting or subungual hyperkeratosis. Thus, there is a need for better understanding of the relationship between subtypes of nail changes among patients with psoriasis and the presence of PsA.

We performed a cross-sectional study of the association between subtypes of nail changes in psoriasis and the presence of arthritis in a large population of patients with psoriasis. Further, we report the findings of a followup evaluation of nail changes among the patients with PsA up to 6 years after the initial visit.

MATERIALS AND METHODS

We performed a cross-sectional study of patients with psoriasis and PsA. Psoriasis cases were located from community sources, primarily a local psoriasis patient group. These patients were invited for a physical examination over a period of 5 years. Patients without active skin disease and children under 18 years of age were excluded. Pattern of skin involvement was recorded, as was nail involvement and family history of psoriasis. The details of the recruitment and data collection methods have been described[12].

Diagnosis of arthritis. All patients were asked if they had been diagnosed with PsA by a rheumatologist. As commonly used criteria for the diagnosis of PsA were not available until after the initial part of this study had concluded, the "gold standard" of rheumatologist diagnosis reported by the patient was accepted. However, the majority of patients who reported arthritis (76%) have been examined in a separate study, where 83% met the Swedish psoriatic

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arthritis register SweSpa criteria[13] and a minimum of 80% met the ClASsification for Psoriatic ARthritis (CASPAR) criteria, confirming that this group of patients is homogenous and has PsA by current definitions[2,11].

Followup procedure. One year after the psoriasis recruitment ended we invited those patients who had reported PsA to participate in a separate study, where they were evaluated for skin, nail, and joint disease as described[2]. The Psoriasis Area and Severity Index (PASI) score was used to evaluate severity of skin disease and tender and swollen joint counts were used to measure the severity of peripheral arthritis. The patients who participated in this second evaluation represent the followup group in this report.

Ascertainment of skin and nail disease. The initial examination was performed by a board-certified dermatologist (JEG), in training at the time. The followup examination was performed by a rheumatologist in training at the time (TJL), with specific training for this task provided by an experienced rheumatologist (BG). Only fingernails were evaluated because of the high frequency (17%) of fungal toenail infections in Iceland[14]. In addition to nail changes, the location and type of skin lesions was recorded.

Statistical analysis. The chi-square test was used to test for associations between dichotomous characteristics and the t test for comparison of the mean of continuous variables. All variables found to be associated with PsA at a p value ≤ 0.05 were included in a multivariate logistic regression model. Age and sex were included in all multivariate models. Because of concerns for potential collinearity between subtypes of nail changes, a correlation matrix was constructed to identify any strong correlations between nail change subtypes. The stability of the model was tested further by calculating the mean variance inflation factor (VIF) as well as the VIF for each independent variable. This was in addition to the collinearity testing built into the statistical analysis package used. Goodness of fit was calculated using the Hosmer-Lemeshow method. We further performed post hoc sensitivity analysis where we categorized nail changes into 3 scenarios: onycholysis without pitting, pitting without onycholysis, and pitting occurring with onycholysis, and tested each for association using the chi-square test. Finally, we tested for univariate associations between subclasses of nail changes and skin activity (measured by the PASI score) and joint activity (measured using tender and swollen joint counts). The results of this analysis were further analyzed in 3 post hoc linear regression models to estimate the strength of associations of the 3 subgroups of nail changes with the aforementioned skin and joint measures, adjusting for age and sex. Statistical analysis was performed using Stata version 11 (Stata Corp., College Station, TX, USA).

RESULTS

We included 1116 patients age 18 years or older with psoriatic lesions after examining 2547 patients with self-reported psoriasis or family history of psoriasis from the community. The mean age at onset of psoriasis was 21 years (95% CI 20–21) and 56% were women. The most common type of skin disease was chronic plaque psoriasis in 94%, and the most commonly involved sites were the arms, scalp, and legs, with 84%, 70%, and 70% of patients having involvement of these sites, respectively. Nails were involved in 37% (95% CI 34%–40%) of patients, and the most common nail change was onycholysis, found in 29% (95% CI 26%–32%). Table 1 presents these and other characteristics of the study group.

Nail changes and arthritis. When asked about arthritis, 187 patients (17%; 95% CI 15%–19%) reported having been diagnosed with PsA by a rheumatologist. Age, sex, onycholysis, and pitting were each associated with PsA on univariate analysis at a p value < 0.05. These 5 variables were included in a multiple logistic regression model to evaluate the independent contribution of each variable. We tested the model for collinearity and found a mean VIF of 1.10 (range 1.02 to 1.19), confirming variance inflation was not an issue in the model. Goodness-of-fit testing revealed a Hosmer-Lemeshow chi-square value of 5.25 with p = 0.73, indicating there was not a lack of fit in the model. Onycholysis was the only type of nail change that remained associated with PsA in the multivariate analysis (OR 2.06, p < 0.001). Table 2 summarizes the results of the multivariate model.

Based on findings from the multivariate model we performed a post hoc sensitivity analysis as described above. The OR for PsA in this analysis was 1.95 in patients with onycholysis alone (p < 0.001), 1.76 when both onycholysis and

Table 1. Baseline characteristics of the study group and the results of a univariate comparison between patients with psoriasis only and psoriasis with arthritis.

Characteristic	All	Skin Only	Skin and Arthritis	p
Age at examination, mean (95% CI) yrs	47 (46–48)	46 (45–47)	51 (49–53)	< 0.001*
Age at psoriasis onset, mean (95% CI) yrs	21 (20–21)	21 (20–21)	21 (19–23)	0.51
Male, n (%)	492 (44)	427 (46)	65 (35)	0.005*
Skin involvement, n (%)	1116 (100)	933 (84)	183 (16)	NA
Scalp	774 (70)	648 (70)	126 (68)	0.545
Ear	261 (23)	212 (23)	49 (26)	0.311
Trunk	473 (43)	389 (42)	84 (45)	0.427
Axillae	61 (5)	52 (6)	9 (5)	0.671
Arms	935 (84)	780 (84)	155 (83)	0.759
Groin	81 (7)	70 (8)	11 (6)	0.431
Legs	780 (70)	646 (70)	134 (72)	0.535
Perianal	74 (7)	59 (6)	15 (8)	0.398
Nail involvement, n (%)	415 (37)	316 (34)	99 (54)	< 0.001*
Pitting	204 (18)	155 (17)	49 (26)	0.002*
Onycholysis	322 (29)	241 (26)	81 (43)	< 0.001*
Subungual hyperkeratosis	137 (12)	106 (11)	31 (17)	0.052

P values represent results of chi-square test for dichotomous variables and the t test for age. * Significance at p = 0.05 level. NA: not applicable.

Table 2. Results of the multivariate logistic regression model.

	OR (95% CI)	p
Age at examination	1.02 (1.01–1.03)	< 0.001
Male	0.50 (0.36–0.71)	< 0.001
Onycholysis	2.05 (1.43–2.93)	< 0.001
Pitting	1.46 (0.97–2.21)	0.07

pitting were present (p = 0.009), and 1.52 when only pitting was present (p = 0.16).

Followup of nail changes. At a mean of 3.8 years after the initial physical examination (median 4, interquartile range 3–4), 139 of the 183 patients with PsA (76%) returned to participate in a study of PsA and were evaluated for skin, joint, and nail involvement. Most (97%) were seen 3 or more years after their first visit. All types of nail changes had increased in prevalence from the first to the second examination, with the overall prevalence of nail changes rising from about 53% to around 80%. Less than 4% of patients who had nail changes at the initial visit were free from nail changes at their followup visit.

Further post hoc analysis of this group suggested by reviewers showed univariate relationships between all subtypes of nail changes and skin disease activity measured with the PASI score, and a weaker relationship between onycholysis and tender joint count, as presented in Table 3. Linear regression models incorporating all types of nail changes showed a trend toward an association between pitting and the PASI score and a negative association with the tender joint count (p = 0.09 for both), as well as an association between onycholysis and the tender joint count (p = 0.02), as shown in Table 4.

DISCUSSION

We performed an analysis of associations between subtypes of nail changes and PsA in a large population-based sample of patients with psoriasis. Our findings show that onycholysis has a stronger association with arthritis than other types of nail changes, including pitting. Nail changes among patients with PsA tended to persist, and increased in frequency over time. We did not observe previously reported associations between psoriasis site and arthritis.

It has been suggested that pitting and onycholysis are a part of the joint disease in PsA rather than the skin disease based on anatomical observations[15]. We previously reported that onycholysis, but not other nail changes, is associated with small-joint arthritis in patients with PsA[11]. The data presented here lend further support to the idea that onycholysis is the subtype of nail changes that is most closely associated with arthritis. We present findings from 2 points in time. Using multivariate analysis we have shown that at the first timepoint the presence of arthritis was associated with onycholysis, and that at the second timepoint the tender joint count, but not the PASI score, was associated with onycholysis. It is important to note that the evaluation at the first timepoint was done by a different physician than that at the second timepoint, and that data from the first visit were not available to the physician

Table 3. Univariate analysis of disease and treatment characteristics of 139 psoriatic arthritis patients at followup. Results of the chi-square test for DMARD use and t test for all other variables, presented as mean (95% CI).

Variable	No Nail Changes	Onycholysis	p	Pitting	p	Subungual Hyperkeratosis	p
No. patients	27	97	NA	87	NA	73	NA
PASI score	2.55 (1.65–3.45)	4.66 (3.75–5.57)	0.02*	4.84 (3.87–5.80)	0.01*	5.07 (3.93–6.21)	0.01*
Tender joint count	2.22 (0.99–3.46)	4.30 (3.28–5.32)	0.05*	3.46 (2.59–4.33)	0.17	4.01 (2.89–5.14)	0.09
Swollen joint count	1.89 (0.97–2.81)	3.45 (2.66–4.25)	0.06	3.28 (2.40–4.15)	0.11	3.37 (2.50–4.24)	0.07
Current DMARD use	5 (19%)	30 (31%)	0.21	23 (26%)	0.40	24 (33%)	0.16

P values represent a comparison between a nail group subtype and the group with no nail changes. * Significance at p = 0.05 level. PASI: Psoriasis Area and Severity Index; DMARD: disease-modifying antirheumatic drug; NA: not applicable.

Table 4. Results of 3 multivariate linear regression analyses showing the association of age, sex, and subtypes of nail changes with each of 3 disease activity measures. Regression results are presented as ß-coefficient (95% CI).

Condition	1. Association with PASI Score	p	2. Association with Tender Joint Count	p	3. Association with Swollen Joint Count	p
Age at time of examination	0.00 (–0.06 to 0.05)	0.89	–0.02 (–0.09 to 0.04)	0.48	0.01 (–0.05 to 0.06)	0.82
Sex	0.22 (–1.36 to 1.80)	0.78	–0.89 (–2.67 to 0.90)	0.33	–0.30 (–1.89 to 1.30)	0.71
Pitting	1.40 (–0.20 to 3.00)	0.09	–1.58 (–3.39 to 0.23)	0.09	–0.13 (–1.75 to 1.48)	0.87
Onycholysis	0.72 (–1.18 to 2.62)	0.45	2.53 (0.38 to 4.68)	0.02*	0.94 (–0.98 to 2.86)	0.34
Subungual hyperkeratosis	1.26 (–0.56 to 3.09)	0.17	0.20 (–1.87 to 2.27)	0.85	–0.05 (–1.90 to 1.80)	0.96

* Significance at p = 0.05 level. PASI: Psoriasis Area and Severity Index.

determining fingernail status at the second visit. The presence of arthritis, arthritis activity, and skin activity were not associated with the other 2 types of nail changes evaluated. This finding is timely given the recent report from a prospective study that nail changes in patients with psoriasis predict the onset of arthritis[4].

Although limited by its cross-sectional design, this is a population-based study of a large number of patients with psoriasis. While nearly 1 in 5 patients with PsA did not meet the CASPAR criteria, this classification effort was incomplete due to lack of data. Thus, the data presented here are based on rheumatologist diagnosis and should be interpreted accordingly. Prospective studies of the risk of PsA will be needed to confirm our results and calculate the risk for PsA associated with onycholysis, but considering the literature on this subject[10,11,16], future studies of the risk of arthritis associated with nail changes should collect and analyze data on the subtypes of nail changes.

Both the nail matrix and the nail bed are in direct contact with entheseal structures[9,15], yet we found an association only between onycholysis and arthritis. Although pitting may also be entheseal-related, it is a very common type of nail change in the general population, affecting as much as 58% of healthy individuals in one study, whereas < 2% had onycholysis[17]. Further, the presence of nail pitting alone is a poor discriminator between psoriatic and other causes, while onycholysis favors a psoriatic origin[16]. Thus, pitting is less specific to psoriatic disease than onycholysis, perhaps explaining the complete lack of association seen in our sensitivity analysis of patients with pitting but no onycholysis.

We found an association between onycholysis and PsA in patients with psoriasis independent of other subtypes of nail changes. Future studies should pursue the subtypes of nail changes.

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