Original Article

Imaging features and diagnosis of early psoriatic arthritis with lower limb entheseal abnormalities in psoriasis patients under high frequency ultrasonography

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Abstract: Psoriatic arthritis (PsA) is a musculoskeletal inflammatory disease, which is always derived from psoriasis. Among psoriasis patients, about 3-8% display several similar articular symptoms with early psoriatic arthritis (ePsA). Studies have shown that ultrasound performs remarkably well in checking the effusion, soft tissue inflammation, tendon injury, etc. It is also reported that high-frequency ultrasound can be used to differentially diagnose PsA and rheumatoid arthritis (RA) by examining finger-joint soft tissue lesions. Thus, ultrasound is thought to be effective for the early diagnosis of PsA and the differential diagnosis of ePsA and psoriasis. However, this hypothesis remains unclear and unexplored. In our experiments, to investigate lower limb entheseal abnormalities in patients with early psoriatic arthritis (ePsA) and psoriasis, sixty patients with ePsA, one hundred patients with psoriasis and twenty healthy controls were divided into groups. High-frequency ultrasound was performed to examine the entheses (quadriceps, patellar, Achilles tendons and plantar fascia) of the lower limbs and the Glasgow Ultrasound Enthesitis Scoring System (GUESS) scores and a clinical assessment were conducted. The results showed that the mean GUESS scores were significantly higher in patients with ePsA (7.8±1.7) and psoriasis (7.4±0.9) compared to the controls (2.4±0.4) (P<0.01). The enthesophytes and bursitis of the Achilles tendon and the bony erosions and the PD signal of the ePsA group were higher than the psoriasis group (P<0.05). The GUESS scores did not correlate with the psoriasis course, morning stiffness, the Psoriasis Area and Severity Index (PSAI), the Maastricht Ankylosing Spondylitis Enthesitis Index (MASES) or the Health Assessment Questionnaire modified for SpA (SHAQ). In conclusion, entheseal abnormalities are common in patients with psoriasis and ePsA. Regular screening of patients with psoriasis via high-frequency ultrasound can help to detect ePsA.

Keywords: Early psoriatic arthritis, psoriasis, enthesitis, high-frequency ultrasound

Introduction

Psoriasis is a chronic inflammatory skin disease and is always caused by various factors [1-3]: genetics, infection, immunity, the endocrine system, etc. Clinically, approximately 30% of psoriasis patients gradually progress to the psoriatic arthritis (PsA) stage, which is also classified as a type of seronegative spondyloarthritis (SpA) [4]. Recent studies suggest that PsA is a musculoskeletal inflammatory disease closely associated with psoriasis [5, 6]. PsA can be divided into five distinct types according to the site of disease: peripheral arthritis, axial disease, enthesitis, dactylitis, and skin and nail disease [7]. Furthermore, before the differential diagnosis of PsA, which was based on its

typical inflammatory symptoms, about 3-8% of psoriasis patients also displayed articular symptoms, including arthralgia, morning stiffness, and paresthesia [8, 9]. As a result, the early diagnosis of PsA, especially for the differential diagnosis of early PsA (ePsA) and psoriasis with articular symptoms, is particularly important for the treatment and prognosis of PsA. However, there is currently no effective test that can serve as the "gold standard" for ePsA diagnosis.

Enthesitis is considered to be the inflammation derived from the tendon and ligament insertion of the bone, and about 48% of patients with psoriatic arthritis suffer from it [10, 11]. Studies have shown that ultrasound screening may be

helpful in detecting ePsA patients with entheseal abnormalities [12, 13]. Ultrasound is an inexpensive and non-invasive examination method, and it has wide applications in clinical practice. With the technological advances, more and more high-frequency adjustable probes and highly sensitive Doppler ultrasound are used in clinical practice to check the effusion, soft tissue inflammation, tendon injury, bone surface lesions, etc. It has been reported that high-frequency ultrasound can be used for the differential diagnosis of PsA and rheumatoid arthritis (RA) by examining finger-joint soft tissue lesions [14]. Although there have been cases of high-frequency ultrasound diagnosis of PsA in clinical practice, very few relevant studies has been published about the differential diagnosis of ePsA and psoriasis.

Therefore, the purpose of this study is to explore the value and possibility of high frequency ultrasound in the differential diagnosis of ePsA and psoriasis, by comparing the scan findings between ePsA, psoriasis, and healthy controls in multiple sites of the lower limbs (quadriceps tendon, patellar ligament, Achilles tendon, and plantar fascia). As a result, we demonstrated that entheseal abnormalities in the lower limbs of psoriasis and ePsA patients were significantly higher than normal controls. Furthermore, the enthesophytes and bursitis of the Achilles tendon, bony erosions, and PD signal of ePsA group were more common than in the psoriasis group. Therefore, we suggest that ultrasound examinations should be performed promptly for psoriasis patients with joint symptoms, which is very crucial for the early detection and timely treatment of PSA.

Methods

Patients and methods

Sixty ePsA patients were diagnosed according to the CASPAR criteria [5], and the patients had inflammatory musculoskeletal symptoms that had occurred for less than 1 year. One hundred psoriasis patients were diagnosed by experienced dermatologists and rheumatologists of Peace Hospital of Changzhi Medical College. We also recruited twenty healthy controls without present or past psoriasis, or a family history of psoriasis/SpA/inflammatory bowel disease.

The exclusion criteria were as follows: age below 18 or above 60, BMI higher than 30, isolated suspect entheseal symptoms occurred before the onset of disease (>1 year), engaged in competitive sports, a history of severe trauma or surgery or corticosteroid injection at the part of entheses scanned, metabolic disorders (hypercholesterolemia, diabetes, hyperuricemia), other rheumatologic disorders, cancer, previous treatment with retinoid. The whole protocol was approved by the Ethics Committee of the hospital, and written informed consent was provided by all the patients before enrollment.

Clinical assessment

The entheses of the patients' lower limbs (quadriceps tendon, patellar ligament, Achilles tendon, and plantar fascia) and the other entheses in the Maastricht Ankylosing Spondylitis Enthesitis Index (MASES) [15] were assessed with palpation to elicit tenderness by an expert rheumatologist.

All patients (psoriasis and ePsA) were investigated for a psoriasis course and morning stiffness, and a Health Assessment Questionnaire modified for SpA (SHAQ) was administered [16]. The area and severity of psoriasis were measured according to the Psoriasis Area and Severity Index (PASI) [17] by an expert dermatologist with a score from 0 (no psoriasis) to 72 (very severe psoriasis).

The healthy controls did not refer to any inflammatory pain at the entheses, joints, or spine presently or in the past, they answered negatively to SHAQ, and they showed no pain at the clinical examination.

High-frequency ultrasound assessment

The high-frequency ultrasound examination was performed by 2 experienced rheumatologists who were blinded to the diagnoses of the patients. A commercially available color-Doppler ultrasound machine (MyLab 30 CV; ESAOTE SpA, Genoa, Italy) equipped with a multi-frequency linear transducer (18 MHz) was used for scanning. The clinical examination and ultrasound examination were performed separately by different investigators who did not know each other's results. The sonographer did not know the clinical details of the patients. The supine position with the knee flexed at 30° was

Table 1. ePsA patients (eP) psoriasis patients (P) and healthy controls (C) demographic characteristics

	Niversia		ender	A = ()	Height	Weight	BMI (kg/	
	Number	Male	Female	Age (year)	(cm)	(kg)	m²)	
eР	60	33	27	43.4±15.2	165.2±5.6	61.6±8.8	22.6±2.6	
Р	100	55	45	43.5±18.1	164.6±6.1	60.8±8.4	23.1±2.3	
С	20	11	9	42.4±16.7	165.5±6.4	61.1±8.3	22.5±3.4	

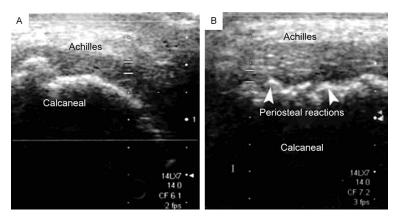


Figure 1. A, B. Ultrasonography appearances of Achilles tendon enthesitis in an ePsA patient: thickness, periosteal reactions (arrows), enthesophyte and bone erosion of calcaneal.

used for checking the quadriceps tendon, the proximal patellar ligament, and the distal patellar ligament, while the prone position with the feet hanging over the edge of the examination table at 90° of flexion was used for checking the Achilles tendon and plantar fascia. The exact position was confirmed by a goniometer [18].

Abnormalities (thickness, enthesophytes, bursitis and bony erosions) were scored by the 0-36 Glasgow Ultrasound Enthesitis Scoring System (GUESS) [18]. Thickness was measured at the point of the maximal thickness proximal to the bone insertion. The following criteria were used for abnormal structure thickness: quadriceps tendon thickness >6.1 mm, proximal and distal patellar ligament >4 mm, Achilles tendon >5.29 mm, plantar aponeurosis >4.4 mm. Enthesophytes and bony erosions were defined as an ossification of entheses with an irregularity of cortical bone insertion and as a cortical break with a step-down defect of the bone contour (visible in the longitudinal and transversal axis), respectively. Bursitis was considered as a well circumscribed, localized anechoic or hypoechoic area at the site of an anatomic bursa, compressible by the transducer, with a short axis >2 mm. Enthesitis thickness

was also scored as pathologic: quadriceps \geq 6.1 mm, proximal and distal patellar \geq 4 mm, Achilles \geq 5.29 mm and plantar fascia \geq 4.4 mm.

PD was standardized with a pulse repetition frequency of 750 Hz and a gain of 53 dB. The temperature of the room was set to 20°C [19]. Vascularity, studied at the insertion of enthesis at the cortical bone, was scored as a binary item (positive if any signal was present and negative if absent) and was also semi-quantitatively graded (no flow (grade 0); only one spot detected (mild or grade 1); 2 spots (moderate or grade 2); >3 spots (severe or grade 3)) [20]. Finally, a total PD was calculated by summing semi-quantitative PD sc-ores of each tendon [21, 22].

Statistical analysis

The statistical analysis was carried out using SPSS 19.0 software (SPSS Inc. Chicago, IL). Quantitative variables were presented as the mean (standard deviation (SD)). Categorical variables were presented as absolute frequencies and percentages. Comparisons between independent means (demographic, GUESS scores, psoriasis course, morning stiffness (min), PASI, MASES, SHAO) were analyzed using Student's t-test or the Mann-Whitney test. Relationships between categorical variables (e.g., the ultrasound assessment results) were evaluated by the χ^2 test or Fisher test. The correlations between ultrasonography and all clinical parameters were assessed with the Rho correlation coefficient of Spearman. A p-value < 0.05 was considered statistically significant.

Results

Demographic characteristics

The demographic characteristics of three groups are shown in **Table 1**. **Figure 1** lists the ultrasonography appearances of Achilles tendon enthesitis in an ePsA patient. 60 ePsA patients (33 male, 27 female), 100 psoriasis

Table 2. Percentage of tenderness, components of GUESS and PD in ePsA, psoriasis, and healthy controls

	Tende	Tenderness		Thickness		Enthesophytes		Bursitis		Erosions		PD	
	n	%	n	%	n	%	n	%	n	%	n	%	
	QUADRICEPS												
eР	8.00	6.67	51.00	42.50	52.00	43.33	0.00	0.00	4.00	3.33	14.00	11.67	
Р	9.00	4.50	79.00	39.50	84.00	42.00	0.00	0.00	5.00	2.50	6.00	3.00	
С	0.00	0.00	3.00	7.50	1.00	2.50	0.00	0.00	0.00	0.00	0.00	0.00	
	PROXIMAL PATELLAR												
eР	3.00	2.50	98.00	81.67	3.00	2.50	0.00	0.00	0.00	0.00	5.00	4.17	
Р	4.00	2.00	158.00	79.00	4.00	2.00	0.00	0.00	0.00	0.00	5.00	2.50	
С	0.00	0.00	6.00	15.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
	DISTAL PATELLAR												
eР	4.00	3.33	67.00	55.83	5.00	4.17	13.00	10.83	0.00	0.00	9.00	7.50	
Р	6.00	3.00	101.00	50.50	8.00	4.00	15.00	7.50	0.00	0.00	6.00	3.00	
С	0.00	0.00	3.00	7.50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
					,	ACHILLES							
eР	17.00	14.17	38.00	31.67	68.00	56.67	9.00	7.50	9.00	7.50	18.00	15.00	
Р	24.00	12.00	52.00	26.00	89.00	44.50*	5.00	2.50*	3.00	1.50*	11.00	5.50*	
С	0.00	0.00	2.00	5.00	1.00	2.50	0.00	0.00	0.00	0.00	0.00	0.00	
	PLANTAR FASCIA												
eР	4.00	3.33	16.00	13.33	7.00	5.83	0.00	0.00	3.00	2.50	0.00	0.00	
Р	6.00	3.00	24.00	12.00	12.00	6.00	0.00	0.00	4.00	2.00	0.00	0.00	
С	0.00	0.00	1.00	2.50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	

^{*:} The difference between the ePsA and the psoriasis groups was statistically significant (P<0.05).

patients (55 male, 45 female), and 20 healthy controls (11 male, 9 female) were enrolled. The median ages of these three groups were 43.4±15.2, 43.5±18.1, and 42.4±16.7, respectively, and no significant difference was found among the three groups (P>0.05). The BMI of the three groups were 22.6±2.6, 23.1±2.3, and 22.5±3.4 respectively, and no significant difference was found among the three groups (P>0.05).

High-frequency ultrasound assessment

Thickness: The mean GUESS scores were significantly higher in patients with ePsA (7.8±1.7) and psoriasis (7.4±0.9) compared with the controls (2.4±0.4, P<0.01). A total of 270 (45%) sites of enthesis thickness were found in the ePsA group, and there were 414 (41.1%) in the psoriasis group, and the two groups were significantly higher than the normal group (7.5%). The differences were statistically significant (P<0.01). However, there were no significant differences between the ePsA group and the psoriasis group (P>0.05). In addition, the dif-

ferences between the ePsA group and the psoriasis group were not statistically significant (P>0.05) in the examination of the enthesis of the quadriceps, proximal patellar, distal patellar, Achilles tendon, and sacral fascia. Moreover, the enthesis thicknesses in the ePsA and psoriatic groups were more likely to occur at the proximal patellar (81.7%, 79%, respectively).

Regarding the patients with ePsA and psoriasis, 56 (93.3%) patients with ePsA and 89 (89%) patients with psoriasis were found to have entheseal thickness, which was significantly higher than the 4 (20%) in the normal controls group (P<0.01), respectively. But, the difference between the ePsA group and the psoriasis group was not statistically significant (P>0.05). The results are shown in **Tables 2-4**.

Enthesophytes

Enthesophytes was higher in the ePsA (135 sites/22.5%) and psoriasis (197 sites/19.7%) groups than it was in the normal controls group (P<0.01). Furthermore, the enthesophytes

Table 3. Percentage of tenderness, components of GUESS and PD in the ePsA patients, the psoriasis patients, and the healthy controls

	Tenderness		Thickness		Enthesophytes		Bursitis		Erosions		PD	
	n	%	n	%	n	%	n	%	n	%	n	%
PeP	21.00	35.00	56.00	93.33	45.00	75.00	14.00	23.33	7.00	11.67	23.00	38.33
PP	32.00	32.00	89.00	89.00	71.00	71.00	20.00	20.00	6.00	6.00	11.00	11.00
PC	0.00	0.00	4.00	20.00	2.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00
Р	P>0.05		P>0.05		P>0.05		P>0.05		P>0.05		P<0.01	
SeP	36.00	6.00	270.00	45.00	135.00	22.50	22.00	3.67	16.00	2.67	46.00	7.67
SP	49.00	4.90	414.00	41.40	197.00	19.70	20.00	2.00	12.00	1.20	28.00	2.80
SC	0.00	0.00	15.00	7.50	2.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00
Р	P>C	0.05	P>0	.05	P>0	.05	P>0	.05	P <c< td=""><td>.05</td><td>P<0</td><td>.05</td></c<>	.05	P<0	.05

PeP: patients of ePsA, PP: patients of psoriasis, PC: patients of healthy controls. SeP: sites of ePsA, SP: sites of psoriasis, SC: sites of healthy controls. *P*: comparison between the ePsA and psoriasis.

Table 4. Clinical parameters of the ePsA and psoriasis patients (expressed in percentage, mean ± SD)

		ePSA		 - Р	
	M ± SD	Score >0 (percentage)	M ± SD	Score >0 (percentage)	P
Psoriasis course	13.8±4.2	-	5.6±2.7	-	<0.01
Morning stiffness (min)	38.4±30.2	78.9	35.2±26.7	75.1	>0.05
PASI (0-72)	2.6±3.3	>0% 78.2	4.4±4.3	>0% 84.1	<0.01
		>10% 11.1		>10% 13.5	
MASES (0-13)	3±2.1	63.7	3±1.8	59.3	>0.05
SHAQ (0-3)	0.4 ± 0.4	82.1	0.3±0.5	77.3	>0.05
GUESS (0-36)	7.8±1.7	1	7.4±0.9	1	>0.05

of the Achilles tendon was found at 68 (56.7%) sites in the ePsA group and higher than 89 (44.5%) sites in the ePsA group (P<0.05). There were no statistical differences between the ePsA group and the psoriasis group in the examination of the enthesis of quadriceps, proximal patellar, distal patellar tendon, or sacral fascia (P>0.05).

Otherwise, there were 45 (75%) patients with ePsA and 71 (71%) patients with psoriasis suffering from enthesophytes, which were significantly higher than the normal controls (2 (10%), P<0.01). But no statistical difference was found between the ePsA and the psoriasis groups (P>0.05). The results are also shown in **Tables 2** and **3**.

Bursitis

It was found that bursitis occurred more frequently at the distal patellar ligament (10.8% in ePsA, 7.5% in psoriasis), followed by the Achilles tendon (7.5% in ePsA, 2.5% in psoriasis), but no bursitis were found in other areas. A total of

20 (3.3%) sites of bursitis were found in the ePsA group, and 20 (2.4%) sites in the psoriasis group. Both groups were higher than the normal group (P<0.01). However, the differences between the ePsA group and the psoriasis group were not statistically significant (P>0.05).

Furthermore, in the ePsA and psoriasis patients, 14 (23.3%) ePsA patients and 20 (20%) psoriasis patients were found to have bursitis, but the normal controls were not. No statistical differences were found between the ePsA and the psoriasis group (P>0.05). The results are also listed in **Tables 2** and **3**.

Erosions

In the examination of bony erosions, the ePsA group (16 sites/2.7%) was higher than the psoriasis group (12 sites/1.2%, P<0.05), and no bone erosions were found in the normal control group. Moreover, at the Achilles tendon, the percentage of bony erosions in the ePsA group was significantly higher than in the psoriasis group (P<0.05).

In addition, 7 (11.7%) patients with ePsA and 6 (6%) patients with psoriasis were detected with bony erosions, and the condition was not detected in the normal controls group, and no significant differences were found between the ePsA group and the psoriasis group (P>0.05). The results are shown in **Tables 2** and **3**.

PD signal

PD was positive in 46 (7.7%) of the sites the ePsA group, and 52 (5.2%) of sites in the psoriasis group. No PD positive signal was found in the normal control group. There were no significant differences between the ePsA group and the psoriasis group (P>0.05). However, 18 (15%) of the PD signal sites were positive in the ePsA group and 11 (5.5%) sites were positive in the psoriasis group when the Achilles tendon was examined. The differences between the two groups were statistically significant. (P<0.05). There was no significant difference in the remaining examination sites. Moreover, the percentage of positive PD signals in the ePsA patients (38.3%) was significantly higher than in the psoriasis patients (11%, P<0.01). No positive PD signal was detected in the normal controls. The results are listed also in Tables 2 and 3.

Clinical assessment

There were no significant differences between the percentages of positive tenderness in the ePsA group (6%) and the psoriasis group (4.9%, P>0.05); nevertheless, the proportions were significantly lower than the results of the ultrasound examination. The course of psoriasis in the ePsA group was 13.8±4.2 years, significantly longer than the psoriasis group (5.6±2.7 years, P<0.01). The morning stiffness of the ePsA group lasted longer than the psoriasis group, but the differences between the two groups were not statistically significant (P> 0.05). At the same time, there were differences between the two groups in the MASES and SHAQ indices, but the differences were not statistically significant. The PASI indices of the ePsA and psoriasis groups were 2.6±3.3 and 4.4±4.3, respectively, and the differences were statistically significant (P<0.01). The GUE-SS scores did not correlate with the psoriasis course, morning stiffness, PSAI, MASES, or SHAO. The results are listed in Table 4.

Discussion

As a musculoskeletal inflammatory disease, PsA always occurs in parallel with or after psoriasis. Early diagnosis and treatment can alleviate the damage from the disease. However, due to the diversity of clinical manifestations of PsA, the diagnosis of early-stage PsA has always been a difficult problem. As an auxiliary examination method widely used in the clinic, ultrasound has an irreplaceable accuracy and effectiveness in the diagnosis of rheumatoid arthritis [14, 23, 24]. Besides, in recent years, ultrasound was considered a highly effective examination tool for the diagnosis of PsA [5, 6, 18, 25]. However, there is still a lack of detailed studies and established practices on the diagnosis of early-stage PsA and the relationship between psoriasis and PsA. Enthesitis is a very common disease of PsA, and studies have suggested that enthesitis is the first manifestation of joint disease in patients with PsA [26]. Previous studies have found that enthesitis in patients with psoriasis can be examined by ultrasound and can be used as a method for screening ePsA from patients with psoriasis [12].

This study aimed to compare the detection of enthesitis in the lower limbs of ePsA and psoriasis patients using high-frequency ultrasound probes. An examination of the enthesis thickness, enthesophytes, bursitis, and bony erosions of the lower limbs and the detection of PD signals was performed, and the positive sites of the lesions and the positive number of patients were counted separately. Our results showed that the enthesitis in the lower limbs of psoriasis and ePsA patients was significantly higher than it was normal controls, which is consistent with previous studies. Moreover, enthesis thickness accounted for the highest proportion of all examination sites, namely ePsA (45%), psoriasis (41.4%), and normal controls (7.5%). However, there was no statistical difference between the ePsA group and the psoriasis group. Furthermore, the enthesophytes and bursitis of the Achilles tendon, bone erosion, and the PD signal of ePsA group was higher than it was in the psoriasis group (P< 0.05). This may be a specific ultrasound manifestation that distinguishes between psoriasis and ePsA and may be used for the early detection of PsA. Previous studies have focused on the comparison between psoriasis and healthy

controls, or between PsA and healthy controls, confirming that enthesitis are common lesions in patients with psoriasis and PsA. However, there are fewer studies on psoriasis compared with PsA. It has been demonstrated that patients with psoriasis may progress to PsA when enthesopathy changes [7]; however, these patients may need a closer follow-up for the early detection of PsA when enthesophytes and bursitis of the Achilles tendon or bony erosions appears.

Additionally, in the clinical evaluation of tenderness, psoriasis course, morning stiffness, PASI, Mases, and SHAQ, the scores of the psoriasis and ePsA groups were significantly higher than the scores of the normal control group (P<0.01). Furthermore, the psoriasis course of the ePsA group was higher than the psoriasis group (P<0.05), suggesting that the long course of psoriasis may be more likely to cause PsA. However, there was no correlation between the GUESS score and the psoriasis course, morning stiffness, PSAI, MASES and SHAQ. Furthermore, the positive rate of the tenderness examination is significantly lower than the ultrasound examination, while there is a correlation between PD signal and tenderness in the study of PsA reported by Delle Sedie [27]. Otherwise, Bandinelli [22] and Spadaro [28] believe that this may be due to the high false positive rate of the tenderness examination and the vulnerability to other soft tissue diseases. In the clinical examination, symptoms such as tenderness and morning stiffness are often unable to clearly diagnose specific diseases, so imaging findings are generally required to support the diagnosis. In the past, MRI and X-ray examinations were more common in the examination of musculoskeletal diseases. In recent years, due to its popularity, ultrasound has played an increasingly important role in the diagnosis of musculoskeletal diseases [10, 29]. Additionally, it has been reported that the combined diagnosis of ultrasound and MRI or X-ray can improve the diagnosis rate of the disease [30, 31], and can be used to guide clinical treatment, judge its efficacy, and help determine the prognosis.

Conclusion

In conclusion, we confirmed that entheseal abnormalities are common in patients with psoriasis and ePsA. Regular screening of pa-

tients with psoriasis using high-frequency ultrasound can help to detect ePsA. Rheumatologists and dermatologists should be more alert to the possibility of psoriasis progressing to PsA, especially when enthesophytes and bursitis of the Achilles tendon or bony erosions occur.

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Disclosure of conflict of interest

None.

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