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ORIGINAL ARTICLE

Pain and inflammation in hidradenitis suppurativa correspond to morphological changes identified by high-frequency ultrasound

K. Zarchi,[1,*] N. Yazdanyar,[2] S. Yazdanyar,[1] X. Wortsman,[3] G.B.E. Jemec[1]

[1]Department of Dermatology, Roskilde Hospital, Health Sciences Faculty, University of Copenhagen, Roskilde, Denmark
[2]Department of Diagnostic Radiology, Herlev Hospital, Health Sciences Faculty, University of Copenhagen, Copenhagen, Denmark
[3]Department of Radiology and Department of Dermatology, Institute for Diagnostic Imaging and Research of the Skin and Soft Tissues (IDIEP), Clinica Servet, Faculty of Medicine, University of Chile, Santiago, Chile
*Correspondence: K. Zarchi. E-mail: kian_zarchi@yahoo.com

Abstract

Background Hidradenitis suppurativa (HS) is an inflammatory skin disease with a chronic intermittent course. The current classification systems used to categorize disease severity provide limited insight into the degree of inflammation and pain, which are key symptoms of the disease.

Objective We sought to investigate the correlation and validity of simple patient- and investigator-assessed items related to inflammation with morphological changes identified by high-frequency ultrasound in HS.

Methods Twenty patients with the clinical diagnosis of HS were enrolled in this study. All patients underwent clinical examinations during which one representative inflammatory nodule was selected in each patient based on the anamnestic information, patient experience and clinical presentation. Tenderness and flare activity of the representative nodule were graded by the patients and erythema by the investigator. Subsequently, all patients underwent high-resolution ultrasound scanning of their representative nodule.

Results We found significant associations between the size of the representative nodule (the diameter in the transverse plane) and patient assessments of flare activity and tenderness. Moreover, we found a marked association between the size of the nodules and investigator assessment of erythema.

Conclusion Patient assessments of flare activity and pain, and investigator assessment of erythema are strongly associated with morphological changes identified using ultrasound, suggesting that these patient- and investigator-assessed items might be strong indicators of the degree of present inflammation in HS.

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Conflicts of interest

None declared.

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Introduction

Hidradenitis suppurativa (HS) is a chronic, inflammatory, recurrent, skin disease primarily involving the apocrine gland-bearing areas of the body, most commonly the axillae, inguinal and anogenital regions.[1] HS is not an uncommon disease with an estimated point prevalence of 1–4%.[2,3] It causes tenderness, pain, suppuration and malodor, and has a substantial negative impact on quality of life.[4,5] The diagnosis is clinically based on the presence of typical lesions, including inflammatory nodules, abscesses and sinus tracts, typical topography and chronically recurring course.[1] Laboratory tests are generally not useful to determine the diagnosis and histopathologic investigations are rarely indicated.[6]

Disease classification is important in the identification of not only aetiology, pathogenesis and risk factors, but also when establishing treatment. Different approaches for disease classification have been proposed in HS. Among those, the Hurley classification system is commonly used.[7] It is a simple and rapid classification system, which is suitable for staging patients in daily clinical work. It is, however, based on structural characteristics of the lesions and therefore a static system, less suited for assessment of any dynamic changes in disease severity. Other

systems have been proposed for more dynamic disease assessment; the most widely documented is the Sartorius score, which is based on lesion counts in affected areas.[8] Nonetheless, Sartorius scores are also dominated by assessments of structural changes and both classification systems provide limited insight into the degree of present inflammation, suppuration or pain, which are key symptoms of HS.[9–11]

An ideal scoring system should include both patient-assessed items and objective measurements. Pain and inflammation are important indicators of disease severity, but unfortunately neither the Hurley nor Sartorius scoring system addresses these inflammatory features.

High and variable frequency ultrasound, a worldwide available imaging modality, has been proven useful for studying localized lesions of the skin,[12,13] detecting subclinical changes in HS and allowing disease classification based on detailed anatomical data.[14–16] The purpose of this study was to examine the correlation and validity of simple investigator- and patient-assessed items with objective measurement of nodules performed by high-frequency ultrasound.

Material and methods

Participants

Between January 2013 and August 2013, 20 patients with the clinical diagnosis of HS were enrolled in this study after informed consent was obtained. Patients were eligible if the diagnosis of HS was made by a dermatologist, their skin lesions included inflammatory nodules and they were able to differentiate symptoms caused by individual lesions. All patients underwent clinical examinations, including assessment of disease severity according to the Hurley classification system. During the examination, one representative inflammatory nodule was selected based on the anamnestic information, clinical presentation and patient experience. The intensity of erythema of the representative nodule was graded by the investigator on a 1–3 scale, 1 representing mild (faint but noticeable pink coloration), 2 moderate (moderate red coloration) and 3 severe (marked red coloration). Subsequently, the patients were asked to grade tenderness and flare activity of the representative nodule on a 0–3 scale, 0 representing no tenderness or flare, 1 mild, 2 moderate and 3 severe. Flare activity was defined as patient's assessment of disease activity in the representative nodule based on present symptoms such as pain, irritation, burning sensation, etc.

Ultrasound examination

All patients underwent high-resolution ultrasound scanning of the representative using a Mylab Twice unit (Esaote, Genova, Italy) with broadband linear probes working on variable frequencies 6–18 and 10–22 MHz. A thick layer of ultrasound gel (Bluescan, Lina Medical, Glostrup, Denmark) was applied on the imaging area, and the transducer was gently placed perpendicular to the skin surface, avoiding any compression of the nodule. During the scanning, the nodule was visualized and its largest diameter (mm) in the transverse plane was measured (Fig. 1). All ultrasound examinations were performed by the same investigator (KZ).

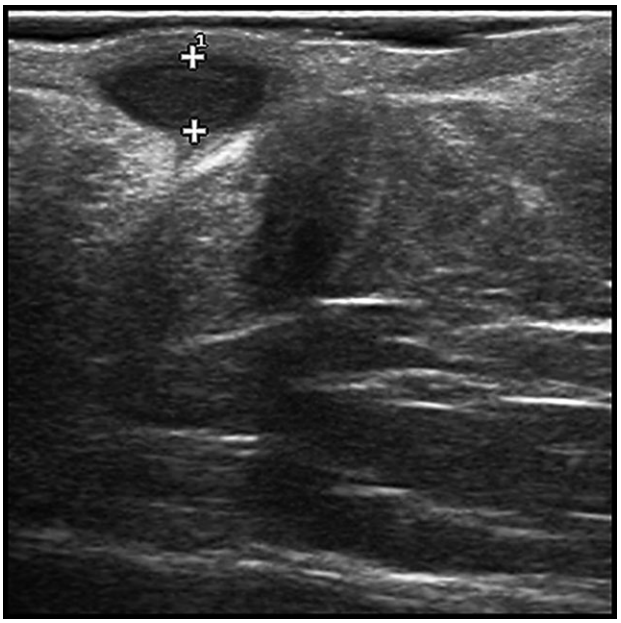

Figure 1 Measurement (4 mm) of the diameter of a clinical axillary inflammatory nodule by grey scale ultrasound. The nodule represents a fluid collection in the dermis and upper subcutaneous tissue.

Statistical analysis

Continuous variables are presented by mean and range and categorical variables by frequency and percentage. We used a univariate linear regression model to investigate the association between the transverse diameter, and patient and investigator evaluations of the representative nodules. Patient assessment of flare activity, tenderness and investigator assessment of erythema were selected as independent variables. Testing the assumptions of the linear regression model using residuals revealed non-normality; therefore, we log transformed the transverse diameter of representative nodules (the dependent variable). We considered associations significant if the *P*-values were less than 0.05. All analyses were performed in the statistical program R, version 2.15.2 (R Development Core Team, 2013, Vienna, Austria).

Results

A total of 20 HS patients were included in this study. Patient characteristics are summarized in Table 1. The mean age of the participants was 37 years (range: 19–61). Women were

Table 1 Patient characteristics

Patient no.	Sex	Age	Age of onset	Worst Hurley	Smoker	Treatment
1	Female	19	14	2	yes	adalimumab (s.c.)1
2	Female	36	16	2	yes	adalimumab (s.c.)
3	Female	25	18	2	yes	adalimumab (s.c.)
4	Male	61	32	3	yes	adalimumab (s.c.)
5	Female	54	16	1	yes	none
6	Male	52	21	1	yes	recorcinol (t)2 and clindamycin(t)
7	Female	36	22	2	yes	none
8	Female	50	20	2	yes	clindamycin (s)3 and rifampicin (s)
9	Female	32	<10	2	yes	none
10	Female	24	<10	1	no	none
11	Female	43	18	2	yes	none
12	Female	26	14	2	yes	none
13	Male	31	15	2	no	erythromycin (s)
14	Female	21	16	2	yes	tetracycline (s)
15	Female	40	26	1	yes	clindamycin (t)
16	Male	37	25	1	yes	none
17	Female	28	18	2	yes	clindamycin (t) and adapalen (t)
18	Male	68	<10	3	no	clindamycin (s), rifampicin (s) and resorcinol (t)
19	Female	31	23	1	yes	resorcinol (t)
20	Female	26	12	1	yes	resorcinol (t) and clindamycin(t)

1(s.c.) subcutaneous; 2(t) topical; 3(s) systemic therapy.

overrepresented with a female:male ratio of 3:1. Three patients reported pre-pubertal onset, whereas 17 patients had onset at second or third decade of life. The majority (17 patients) were smokers. The highest Hurley stage, scored in the most severely affected area, was I in 7 patients, II in 11 patients and III in 2 patients. Systemic treatment was given to eight patients at the time of the ultrasound examination; these patients were classified as Hurley stage II or III. Five patients received only topical treatment and seven patients were untreated at the time of the investigation.

Table 2 shows how the participants evaluated flare activity and tenderness of their representative nodule. About 50% of all patients scored themselves as having none or mild flare activity and tenderness. The investigator assessed the intensity of erythema of the representative nodule as mild in eight patients, as moderate in eight patients, and as severe in four patients. The nodules were identified on ultrasound in all cases as hypoechoic or anechoic fluid collections located in the dermis and subcutaneous tissue. The mean diameter of the ultrasonographic examined nodules was 5.2 mm (range: 1.4–13.2 mm). The two patients who had the highest scores in patient and investigator assessments (patient no. 2 and 17 in Table 2) had also the largest nodules measured by ultrasound.

By performing linear regression analysis (Table 3), we found significant associations between the diameter of the representative nodule and patient assessment of flare activity (none–mild: $P = 0.021$, none–moderate: $P = 0.0007$ and none–severe: $P < 0.0001$) and tenderness (none–mild: $P = 0.0016$, none–moderate: $P < 0.0001$ and none–severe: $P < 0.0001$). Moreover, we found a marked association between the diameter of the nodule and investigator assessment of erythema (mild–moderate $P = 0.002$ and mild–severe $P = 0.002$). In comparison to reporting no flare activity, having mild activity was associated with a 24% increase in the diameter of the representative nodule, moderate flare activity with a 44% increase in the diameter of the representative nodule and severe flare activity with a 97% increase (Table 3). The corresponding values were 25%, 61% and 107% increase in the diameter of the representative nodule for reporting mild, moderate and severe tenderness, respectively, as compared with no tenderness (Table 3). Having a moderate degree of erythema (investigator assessment) was associated with a 37% increase in the diameter, as compared with having mild erythema, whereas having severe erythema was associated with a 50% increase in the diameter, as compared with mild erythema (Table 3).

Discussion

Precise evaluation of disease severity is an important but challenging task in many dermatological diseases, and HS is no exception to this. Many medical specialties rely on paraclinical data for the assessment of disease severity and treatment effect. Because of the immediate accessibility of skin, this approach is not commonly used in dermatology as in, e.g. hepatology. For lesions that involve deep dermal or subcutaneous structures, it

Table 2 Patient and investigator assessments of the representative nodule and ultrasonic diameter

Patient no.	Region	Patient assessment of flare activity (0–3)	Tenderness (0–3)	Investigator assessment of erythema (1–3)	Transverse diameter (mm)
1	Axillary	1	1	2	3.9
2	Gluteal	3	3	3	10.7
3	Axillary	2	2	2	6.6
4	Axillary	1	1	3	4.0
5	Axillary	1	2	2	5.2
6	Pubic	0	0	1	1.4
7	Pubic	2	1	2	3.7
8	Inguinal	1	1	1	3.2
9	Axillary	2	1	1	4.1
10	Pubic	1	1	1	3.1
11	Axillary	1	0	1	2.8
12	Inguinal	1	0	1	3.1
13	Inguinal	2	1	3	4.3
14	Inguinal	2	2	2	5.1
15	Inguinal	0	0	1	2.0
16	Axillary	3	2	2	7.1
17	Pubic	3	3	3	13.2
18	Axillary	2	2	2	6.8
19	Pubic	0	1	1	3.6
20	Pubic	3	2	2	9.8

Table 3 Linear regression analyses investigating the association between the diameter of representative nodules and patient and investigator assessments of pain and inflammation

Independent variable	Regression coefficient (log-transformed-dependent variable)	95% confidence interval	Percentage increase in diameter*	*P* value
Patient assessment of flare activity				
None (0)	Reference			
Mild (1)	0.21	(0.037,0.39)	24%	$P = 0.021$
Moderate (2)	0.36	(0.18 ,0.54)	44%	$P = 0.0007$
Severe (3)	0.66	(0.47,0.86)	94%	$P < 0.0001$
Tenderness				
None (0)	Reference			
Mild (1)	0.22	(0.098 , 0.35)	25%	$P = 0.0016$
Moderate (2)	0.47	(0.34 ,0.61)	61%	$P < 0.0001$
Severe (3)	0.73	(0.55 ,0.91)	107%	$P < 0.0001$
Investigator assessment of erythema				
Mild (1)	Reference			
Moderate (2)	0.32	(0.13,0.50)	37%	$P = 0.002$
Severe (3)	0.40	(0.18,0.63)	50%	$P = 0.002$

*Percentage increase in transverse diameter was calculated using the regression coefficients: Percentage increase = $(e^{\beta}-1) \times 100\%$.

is, however, suggested that additional imaging may be beneficial to the management of patients. Ultrasound scanning is capable of providing imaging of structures > 0.1 mm in the skin, and appears particularly useful for changes that involve deep dermal or subcutaneous pathology, which cannot currently be imaged by other modalities such as optical coherence tomography or

confocal microscopy.[12] In previous studies, high-frequency ultrasound has been used for description of HS.[14–20] Indeed, it has been reported that imaging reveals significant, hidden structural components of lesions, indicating that many cases are more severe than clinically assessed.[14] In addition, the following ultrasound features have been reported in HS: (i) widening of hair follicles and pseudocystic dermal structures;[14,15,18] (ii) decreased echogenicity of the dermis and increased echogenicity of the subcutaneous tissue;[14,15] (iii) increased thickness of the dermis and subcutaneous tissue in lesions[14–18] and (iv) presence of hypoechoic or anechoic fluid collections and fistulas in the dermis and subcutaneous tissue.[14,15] Because of the dynamic qualities of ultrasound and the ease of use, the method may be used to gather not only structural data but also more dynamic data that can provide the needed record. We hypothesized that the diameter of nodules is a reliable measure of the degree of inflammation. The largest diameter in the transverse plane was selected as the objective measure, because it is most probably influenced to a lesser degree by the presence of scar in the surrounding tissue, as compared with diameter in other planes. Measurement of the diameter in the transverse plane is a simple, safe, accurate and quick examination method of lesions that are easily identified both clinically and on ultrasound. In studies of infection of the dermis and subcutaneous tissue, the ultrasound-measured diameter of abscesses has been used to suggest the treatment. If a classical abscess is small (<1 cm diameter), conservative treatment is preferred over incision and drainage.[21] It is therefore implied that diameter of an inflamed lesion can be used as an indicator of the disease severity. However, although measuring the diameter of nodules by ultrasound may allow objective quantification of the underlying inflammation, the approach cannot replace the clinical evaluation nor can it replace the complete ultrasound examination of affected areas. It should also be noted that a single nodule cannot reflect the entire disease state and that the representative nodules were selected merely to identify disease-specific lesions in which the association between patient- and investigator-assessed items and morphological changes could be studied.

The results in this study indicate that the transverse diameter of inflammatory nodules (collection on ultrasound) correlates well with the intensity of erythema and patient reports of pain and flare activity. Assessment of erythema and pain is included only in modified HS-LASI staging;[22] otherwise, none of the patient- and investigator-assessed characteristics, used in this study, is incorporated in available classification systems. This is despite erythema and pain being widely accepted as indicators of inflammation.[23] Patient assessment of flare activity, nonetheless, was not a validated item, and was introduced in this study to represent all inflammatory features, including those other than pain, such as itching, irritation and burning sensation that patients may experience. However, because the inflammatory features and cutaneous lesions are diverse in HS and these simple patient and investigator assessments do not reflect the entire disease picture, these items should only be used as incorporated segments of classification systems together with clinical data to strengthen their representativeness of the underlying inflammation.

The limitations of this study include the limited number of cases investigated, and the lack of blinding of the ultrasound investigator. Moreover, the approach taken in this study requires the presence of clinically palpable nodules. There are subclinical changes in HS, which can be identified only by ultrasound examination.[14] Evaluation of these subclinical changes, however, was not considered in the present analysis nor was ultrasound examination of other HS lesions, such as fistulas. Further studies are needed to confirm the usefulness of ultrasound measurement of the diameter of nodules in everyday practice. Moreover, evaluating the intensity of erythema might be a matter of perception; nevertheless, because all patients were evaluated by the same investigator, interobserver variability was not a source of bias in this study. Finally, the use of numeric rating scales for chronic diseases like HS can be discussed. Numeric rating scales are unidimensional, single-item scales that provide an estimate of patients' pain intensity. They are easy to administer and complete. However, they do not provide a comprehensive evaluation of pain in patients with chronic diseases such as HS. In this study, the aim of pain assessment, however, was merely to serve as a patient-reported outcome anchor and was therefore thought permissible.

In conclusion, we found strong and significant associations between morphological changes identified using ultrasound and patient assessments of flare activity and pain, and investigator assessment of erythema, suggesting that these parameters might be strong indicators of the degree of present inflammation in HS. This study suggests that such simple items should be incorporated in future classification systems of HS.

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