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Clinical, histological and high-frequency ultrasonographic evaluation (50 MHz) of morphoea treated with ultraviolet A1 phototherapy

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Summary

Background. There are few studies in the literature correlating the ultrasonographic findings, clinical scoring systems or histological findings in morphoea after ultraviolet (UV)A1 phototherapy.

Aims. To evaluate the quantitative and morphological aspects of high-frequency ultrasonography in the treatment of plaque morphoea in response to UVA1 phototherapy, and to correlate these with clinical and histological scores.

Methods. In total, 17 patients with morphoea were studied. Initially and at study end, high-frequency ultrasonography (50 MHz) was performed on the edge of a morphoea lesion treated with UVA1 phototherapy. A quantitative and qualitative analysis of dermal features was performed and compared with the features of healthy skin. Skin biopsy specimens were obtained from lesions analysed at the beginning and end of the study, assessing dermal sclerosis and dermal inflammatory infiltrate and their distribution.

Results. All affected skin showed a statistically significant increase in dermal thickness and hypoechogenicity, corresponding to a reduction in dermal density by ultrasonography compared with healthy skin. Morphological evaluation identified undulations of the dermis in 11 of 17 lesions (64.7%) and in 5 healthy skin areas (29.4%) ($P = 0.08$), while 'yoyo' figures were identified in 8 lesions (47%) but only 1 healthy skin area (5.9%) ($P = 0.02$). Ultrasonographic morphological analysis highlighted an improvement in dermal hyperechogenic bands and disappearance of yoyo figures after UVA1 treatment. Histology revealed a reduction in dermal sclerosis and inflammation, although this was not statistically significant.

Conclusions. Ultrasonographic pattern analysis of morphoea is a suitable technique for monitoring UVA1 phototherapy response.

Introduction

Several noninvasive investigations have been used in studies of morphoea,[1–5] and among these, high-frequency ultrasonography at 13–20 MHz has shown good inter- and intra-reproducibility of measurements.[6] Quantitative analyses are important to clarify how increased thickness and low echogenicity occurs during the initial inflammatory stage of morphoea, and how clinical improvement is associated with an increase in dermal echogenicity and dermal thinning.[7] A morphological pattern analysis of ultrasonographic dermal changes has also been proposed and correlated with clinical findings, in comparison with normal

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skin.[8] According to that study, morphoea produces characteristic 'yoyo' images (dense images whose shape resembles a flattened 'yoyo' or a snap fastener; their lateral limit is usually well demarcated with an acute V-shaped angle) at 13 MHz ultrasonography, with homogenization and undulations and thickened hyperechogenic bands in the dermis.[8]

UVA1 phototherapy is an effective therapy for the cutaneous form of scleroderma,[9–11] and many studies have used high-frequency ultrasonography to analyse its effects in morphoea.[9,12–14] However, there have been few studies that have correlated ultrasonographic findings, clinical scoring systems and histological findings by the use of a 50 MHz probe, and defined qualitative tissue pattern changes.

The aim of the current study was to evaluate quantitative and morphological high-frequency ultrasonography aspects of plaque morphoea in response to UVA1 phototherapy, and to correlate these with clinical and histological scores.

Methods

The study followed the principles outlined in the Declaration of Helsinki and was approved by the local ethics committee. All patients gave informed consent.

Patients

We enrolled 17 patients with active morphoea who were followed up at the Dermatologic Clinic of Brescia (Italy). Exclusion criteria included age > 18 years, pregnancy or breastfeeding, presence of systemic sclerosis, a history of photosensitizing dermatoses and use of potentially photosensitizing drugs.

All patients were examined by the same physicians (MA, MR) at the time of enrolment, including assessment of complete disease history and morphoea clinical subtype. Clinical outcome measures of disease severity and damage, Localized Scleroderma Skin Severity Index (LoSSI) and Localized Scleroderma Skin Damage Index (LoSDI) were assessed for each patient before and after phototherapy.[15] These scores were also combined with the Physician's Global Assessment (PGA) for activity and damage, which was completed the physician after clinical evaluation.[15]

Given that LoSSi and LoSDI are calculated on the totality of skin lesions, we decided to modify the standard method of their evaluation by calculating the same measures for a single lesion for which a biopsy and ultrasonography examination had been performed.

Phototherapy treatment

All patients underwent medium-dose UVA1 phototherapy (50–60 J/cm^2; MediSun Xenia UVA-1, Schulze & Böhm GmbH, Brühl, Germany) three times per week until complete resolution or no further amelioration of the dermatosis after four consecutive weeks in accordance with current guidelines.[16,17] Irradiance was measured with a SR 9910 spectroradiometer (Macam Photometrics Ltd, Livingston, UK) and found to be 13.60 mW/cm^2 at skin level.

Ultrasonographic evaluation

Initially and at study end, high-frequency ultrasonography was performed on the edge of a representative affected skin area with a digital 50-MHz ultrasonography scanner (DUB Skin Scanner, Taberna Pro Medicum, Im Dorf, Lüneburg). The usable depth of signal penetration was 4 mm and the gain 40 dB. Ultrasonography images were collected under standard conditions (environmental temperature was 20–23 °C and the patient remained in a lying position for at least 10 min before examination). Acquired images were exported into a dedicated database, and were evaluated using specific image-analysis software to assess epidermal and dermal thickness (μm) and lesional echogenicity (expressed as percentage dermal density). We determined percentage density quantitative cut-offs: hypoechogenic 0–15%, isoechogenic 15–20% and hyperechogenic > percentage 20%. The following morphological criteria were determined as being present or absent: (i) undulation in the dermis, (ii) 'yoyo' image with a lateral limit in the dermis and (iii) dermal bundles with overall increase of echogenicity. The same ultrasonography parameters were analysed for healthy skin areas contiguous to the affected lesion. Image analysis was performed by two investigators (MV, AZ) who were blinded to any clinical features, demographic data and treatment details.

Skin biopsies

Skin biopsy specimens (4 mm) were obtained from the edge of the lesion analysed with echography at the beginning of the study. Post-treatment specimens were obtained from previously affected areas adjacent to the first procedure. Each biopsy specimen was stained with haematoxylin and eosin, and analysed by two pathologists (PI, LL) blinded to patient details. The following histopathological aspects were assessed: (i) grading of dermal sclerosis on a 0–3-point scale (0 = absent/fair,

1 = mild, 2 = moderate, 3 = marked with possible interest of the subcutis); (ii) dermal inflammatory infiltrate on a 0–2-point scale (0 = absent/fair, 2 = mild to moderate, 3 = marked); (iii) dermal inflammatory infiltrate distribution (0 = superficial vs. 1 = profound). A seven-point scale (0–6) was used to score histological findings.[18]

Statistical analysis

Collected data were analysed using the SPSS® (v23.0; IBM SPSS, Armonk, NY, USA) and GraphPad Prism® (v6; GraphPad Software Inc. La Jolla, CA, USA) software programs. Based on previous data on qualitative ultrasonography features,[15] expecting dermal alterations in 94% of patients with morphoea and 12% of healthy subjects, and assuming a minimal clinically difference of 30%, a power of 80% and an α value of 0.05, the sample size required to show a statistical difference was 14 patients. Categorical variables were summarized using percentages, and continuous variables by calculating medians and range (minimum and maximum value). Normal distribution of collected data was analysed by the Kolmogorov–Smirnov test. Minimal clinically important difference (MCID) was determined using the half standard deviation (half-SD) benchmark of outcome measures at the second visit: patients improving by more than half of the outcome score SD of total LoSSi and/or LoSDI achieved MCID, and were considered good responders to treatment.[19] Correlation between echographical, clinical and histological data at baseline was assessed by Spearman rank correlation coefficient. The association between categorical variables before and after treatment was tested by the Fisher exact test and χ^2 test, while the medians of continuous variables were compared using the Wilcoxon test and Mann–Whitney *U*-test. All results were considered statistically significant at $P \leq 0.05$.

Results

In total, 17 patients (1 man, 16 women; mean age 64.05 years, range: 20–90 years) with active morphoea at baseline were enrolled in this study. Of these, 14 patients (82.3%) had generalized plaque morphoea (GM) and 3 (17.7%) had deep morphoea (DM). No patient had symptoms of systemic autoimmune diseases.

Medium-dose UVA-1 phototherapy was performed in all patients three times weekly. Mean therapy duration was 6.1 months (range 3–10 months), mean number of sessions was 35.2 (range 12–67) and mean cumulative dose was 1920 J/cm^2 (range: 600–4900 J/cm^2). Based on the achievement of MCID in two LoSSI/LoSDi scores, all 17 patients (100%) were globally classified as responders to phototherapy. Kolmogorov–Smirnov test showed that the data were not normally distributed ($P < 0.05$).

Ultrasonography features at baseline

At baseline, all affected skin samples showed a statistically significant increase in dermal thickness and hypoechogenicity, corresponding to a reduction in dermal density by ultrasonography analysis compared with healthy skin contiguous to the morphoea lesion ($P < 0.05$). We did not find any statistically significant difference in epidermal thickness (Table 1).

Morphological evaluation revealed undulations of the dermis in 11 of 17 lesions (64.7%) and in 5 healthy skin areas (29.4%), which was not significantly different ($P = 0.08$); there was a sensitivity of 64% and a specificity of 70%. Yoyo images were identified in 8 lesions (47%) and in only 1 healthy skin area (5.9%) ($P = 0.02$); sensitivity and specificity were 47% and 94%, respectively.

Ultrasonography at baseline confirmed a significant increase in dermal thickness but complete absence of dermal undulations in all patients with deep morphoea compared with patients with generalized plaque clinical variant (Fig. 1); both findings were significantly different between the two groups ($P < 0.05$).

Correlation between clinical, histological and ultrasonography features at baseline in morphoea lesions

When we assessed the modified single-lesion clinical scores LoSSi and LoSDI, we did not find any significant correlation between either of these and the total histological score or the ultrasonography-measured dermal thickness or echogenicity at baseline ($P > 0.05$) (Table 2).

Clinical, ultrasonography and histological analysis after phototherapy in morphoea lesions

All of the four clinical scores considered showed a statistical reduction after treatment ($P < 0.05$) (Table 1). Clinical subtype (generalized or deep) did not influence response to therapy.

Ultrasonography quantitative analysis did not show any significant improvement in dermal thickness or

Table 1 Clinical and 50-MHz ultrasonographic findings in lesional and unaffected skin before and after UVA-1 phototherapy.

		Affected skin		
	Healthy skin (baseline)	Baseline	Post-treatment	*P*
Clinical skin scores*				
LoSSI	–	24 (6–48)	6 (1–16)	< 0.001
LoSDI	–	9 (0–72)	3 (0–24)	< 0.001
PGA-A	–	70 (40–90)	60 (20–70)	< 0.001
PGA-D	–	70 (0–90)	50 (0–80)	< 0.001
Quantitative ultrasonography features*				
Epidermal thickness	121.9 (74–184)	123.6 (94–168)	109 (72–148)	
Dermal thickness	447.8 (180–922)	668.2 (227–1617)	629 (352–891)	< 0.01‡
Dermal density, %†	20.39 (2.55–70.63)	12 (1.95–34.96)	14.5 (3.66–37.62)	< 0.001‡
Morphological ultrasonography features, % (*n*/total *N*)§				
Dermal yoyo images	5.9% (1/17)	47% (8/17)	5.9% (1/17)	0.02¶
Dermal undulations	29.4% (5/17)	64.7% (11/17)	29.4% (5/17)	
Hyperechogenicity	52.9% (9/17)	41.2% (7/17)	82.3% (14/17)	0.03¶

LoSDI, Localized Scleroderma Skin Damage Index; mLoSSI, Localized Scleroderma Skin Severity Index; PGA-A, Physician's Global Assessment - activity; PGA-D, Physician's Global Assessment – damage. *Median (range); †echogenicity; ‡versus healthy skin; §% (n/total N); ¶versus affected skin at baseline.

density of treated lesions ($P < 0.05$) (Table 1), whereas morphological analysis highlighted an improvement in dermal hyperechogenic bundles and disappearance of yoyo figures ($P < 0.05$), but found no variation in dermal undulations (Fig. 1, Table 1). None of the patients with deep morphoea had any statistically significant improvement in dermal thickness, and all showed persistence of absence of dermal undulations. Post-treatment biopsy specimens revealed a reduction in dermal sclerosis and inflammation, although this was not statistically significant ($P < 0.05$). Distribution of dermal inflammatory infiltrate and alterations of adnexal structures were unchanged after therapy (Table 3).

Discussion

High-frequency ultrasonography is a useful device for studying sclerotic skin lesions and their evolution after phototherapy, although conflicting data are reported in the literature, owing to the use of different devices supporting different frequencies and probes.[8,12,14,20–24] Moreover, some studies have focused on systemic sclerosis,[21,23,24] and only a few have analysed the pattern of echographical features, studying their changes after UVA1 phototherapy[12,14] and their correlation with histology and clinical scores.[12]

We performed both quantitative and morphological analysis of ultrasonography features of morphoea treated with UVA1. Quantitative analysis of untreated affected skin compared with healthy skin highlighted the dermal nature of the pathological process in morphoea. Pattern analysis showed the prevalence of yoyo figures and dermal undulations in lesional skin, associated with a lower incidence of dermal hyperechogenic bundles, compared with unaffected skin areas. We hypothesize that the increase in dermal thickness reflects the deposition of more collagen in the dermis, whereas hypoechogenicity could be explained by the oedema and inflammation typical of the early stage of morphoea. Thus, morphologically, the dermal undulations could be generated by the presence of inflammatory fluid between collagen fibres, while yoyo images could indicate disarrayed collagen bundles. However, we did not find a significant correlation between clinical scores and the histological and ultrasonography features to corroborate our interpretation. This may be due to the lack of perfect matching of the involved skin site samples analysed.

The increased dermal thickness and the absence of undulations seen by ultrasonography in deep compared with plaque morphoea samples could be attributed to the depth of the pathological process. We suggest that collagen bundles deep in the hypodermis might exert a stretching effect on the upper dermis, and that inflammatory cells might have a deeper localization that cannot be visualized correctly and fully with a 50-MHz probe.

Despite the clinical data, only qualitative echographical analysis showed a statistically significant improvement in echogenicity and reduction of yoyo images in the dermis in UVA1-treated lesions. Based on these results, pattern analysis seems to be more useful for monitoring spatial reorganization of collagen in

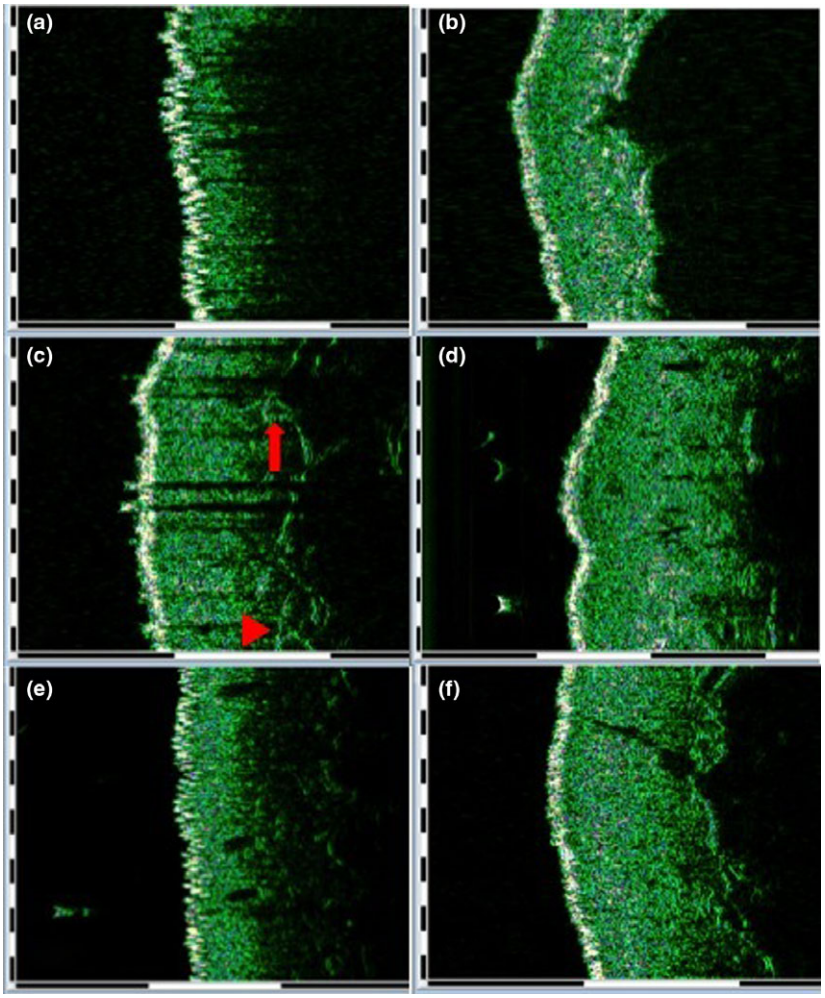

Figure 1 (a–f) Ultrasonography (50 MHz) images of generalized plaque morphoea (GPM) and deep morphoea (DM) compared with healthy skin. (a) Unaffected skin at baseline in a patient affected by GPM; (b) unaffected skin in a patient with DM; (c) a representative sclerotic area of GPM before therapy, showing dermal undulation (sharp arrow) and yoyo figures (thick arrow); (d) ultrasonographic assessment of DM before therapy, showing absence of dermal undulation and increase in dermal thickness; (e) generalized plaque morphoea lesion after therapy, showing an increase in echogenicity and homogenization of the dermis; and (f) DM after therapy, showing a partial (although not statistically significant) reduction in dermal thickness.

morphoea lesions before and after UVA1 phototherapy, and this could explain the discrepancies between reports in the literature. Quantitative analysis has not proved to be useful or reliable in the evaluation of therapeutic response, and this could be related to the presence of artefacts that could influence the measurement process.

The absence of statistical significance in our histopathological analyses may be the result of the relatively short follow-up and the small study size.

Table 2 Correlation between histological and ultrasonography features in morphoea lesions at baseline.

	Echogenicity			Dermal undulations		Dermal yoyo images		
	Hyper-	Iso-	Hypo-	Present	Absent	Present	Absent	*P*
Dermal sclerosis score: cases, %								
Grade 0	–	–	1 (5.9)	1 (5.9	–	1 (5.9)	–	< 0.05
Grade 1	1 (5.9)	2 (11.8)	–	3 (17.6)	–	1 (5.9)	2 (11.8)	< 0.05
Grade 2	1 (5.9)	–	3 (17.6)	3 (17.6)	1 (5.9)	1 (5.9)	3 (17.6)	< 0.05
Grade 3	5 (29.4)	1 (5.9)	3 (17.6)	4 (23.5)	5 (29.4)	5 (29.4)	4 (23.5)	< 0.05
Dermal inflammatory infiltrate score: cases, %								
Grade 0	1 (5.9)	1 (5.9)	1 (5.9)	2 (11.8)	1 (5.9)	2 (11.8)	1 (5.9)	< 0.05
Grade 1	6 (35.3)	2 (11.8)	4 (23.5)	8 (47.1)	4 (23.5)	5 (29.4)	7 (41.2)	< 0.05
Grade 2	–	–	2 (11.8)	1 (5.9)	1 (5.9)	1 (5.9)	1 (5.9)	< 0.05

Table 3 Histological aspects of skin lesions before (T0) and after treatment (T1).

	Affected skin, *n* (%)	
	Baseline	Post-treatment
Dermal sclerosis		
Grade 0	1 (5.9)	3 (17.6)
Grade 1	3 (17.6)	4 (23.5)
Grade 2	4 (23.5)	5 (29.4)
Grade 3	9 (53)	5 (29.4)
Dermal inflammatory infiltrate		
Grade 0	3 (17.6)	6 (35.3)
Grade 1	12 (70.6)	10 (58.8)
Grade 2	2 (11.8)	1 (5.9)
Dermal location if inflammatory infiltrate		
Superficial	6 (35.3)	7 (41.2)
Deep	11 (64.7)	10 (58.8)
Adnexal alterations		
Loss	1 (5.9)	3 (17.6)
Entrapment	15 (88.2)	10 (58.8)
Normal	1 (5.9)	4 (23.6)

Transformation of collagen bundles from a parallel to a basket-weave arrangement after UV irradiation takes time. We suggest that UVA1 phototherapy may induce a spatial redistribution of collagen fibres in morphoea in the early phase, without a reduction in their overall number. This could be an additional explanation for the absence of correlation between our clinical and histological findings, and the incomplete disappearance of skin lesions. Further studies with longer follow-up and more patients might allow us to clarify the ultrasonographic and histological aspects of morphoea evolution after UVA1 phototherapy. It would also be interesting to compare ultrasonographic and histological findings in treated and untreated plaques to effectively define dermal changes due to UVA1 phototherapy.

Conclusion

We performed quantitative and morphological analysis of ultrasonography features of morphoea treated with UVA1, and found that dermal undulations and yoyo figures were characteristic of deep morphoea. We could not correlate the clinical features with the ultrasonographic or histological features. The results indicate that ultrasonography can be used to evaluate the response of morphoea lesions to UVA1 phototherapy. Further studies are warranted to define the dermal changes in morphoea and the response to UVA1 therapy.

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What's already known about this topic?

- High-frequency ultrasonography at 13–20 MHz showed good inter- and intra-reproducibility of measurements in morphoea studies.
- Quantitative analyses are important to learn how skin involvement occurs during the initial inflammatory stage, with increased thickness and low echogenicity, and how clinical improvement is associated with an increase in dermal echogenicity along with dermal thinning.
- Morphological pattern analysis of ultrasonographic dermal changes has also been proposed and correlated with clinical findings, in comparison to normal skin.
- However, few studies correlating ultrasonographic findings, clinical scoring systems or histological findings after UVA1 phototherapy have been conducted.

What does this study add?

- This study highlights the applicability of morphological high-frequency 50-MHz ultrasonographic evaluation of plaque morphoea features in response to UVA1 phototherapy.
- Dermal undulations and yoyo figures were characteristic of deep morphoea.
- Thinning of the dermis and reduction in yoyo figures indicated response.

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