Rarities in rare: illuminating the microvascular and dermal status in juvenile localised scleroderma. A case series

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ABSTRACT

Objective. *To assess the (structural and functional) characteristics of the microvascular and dermal status in juvenile localised scleroderma (jLoS), using novel non-invasive standardised research tools commonly used in adult systemic sclerosis (SSc).*

Methods. *Ten consecutive patients with a confirmed jLoS diagnosis were studied cross-sectionally in this two-centre case series. For each patient, the most prominent lesion (i.e. "target lesion") was chosen for further examination of the centre, edge and contralateral unaffected site. High-frequency ultrasonography was used to determine dermal thickness, durometer for skin hardness, and laser speckle contrast analysis (LASCA) for a dynamical evaluation of the microcirculation. The structure of the microcirculation was evaluated at the nailfolds of the 2nd–5th finger bilaterally, using nailfold videocapillaroscopy (NVC).*

Results. *6 linear and 4 plaque subtype jLoS lesions were included. Dermal thickness was thinner at the centre of the "target lesions" vs. the edges ($p<0.001$) and control sites ($p<0.001$). Skin hardness was harder at the centre of the "target lesions" vs. the edges ($p=0.012$) and control sites ($p=0.003$). A higher perfusion was found in the centre of the "target lesion" (124.87±66.40 PU) vs. the edges (87.27±46.40 PU; $p<0.001$) and control sites (67.85±37.49; $p<0.001$). Of note, all patients had a "non-scleroderma" pattern on NVC.*

Conclusion. *This case series suggests the supportive value of both microcirculatory and dermal assessments of skin lesions using novel non-invasive research tools, adopted from adult SSc, for (j)LoS.*

Introduction

Scleroderma comprises a group of rare (incidence of ±1 per 100,000/year) fibrosing disorders with similar histopathological findings (1-8). Scleroderma can be broadly divided into systemic sclerosis (SSc, prevalence ranging between 7 and 44 per 100,000 individuals) and localised scleroderma (LoS, also called morphoea, estimated prevalence ± 50 per 100,000 individuals). SSc is a multisystem connective tissue disease hallmarked by a triad of vasculopathy, autoimmunity and fibrosis of the skin and/or internal organs, LoS is pathological process of local and chronic inflammation mainly affecting part(s) of the skin and underlying tissues, which eventually leads to fibrosis and atrophic changes (1, 6-12). In contrast to SSc, LoS is a very rare condition that usually presents in childhood (juvenile LoS [jLoS]) with a mean age of onset at 6-8 years (9, 12). The estimated incidence of jLoS is estimated at 3.4 cases per million children per year (13, 14).

It is believed that SSc and (j)LoS share common pathophysiological pathways with an initial inflammatory phase accompanied by endothelial activation, followed by a fibrotic phase characterised by tissue collagenisation and appreciable skin thickness sometimes accompanied by atrophic changes (3, 7-9, 15-17). The hypothesis of a common pathophysiological pathway is further supported by recent observations from our research group, as we found both in literature and in a pilot study that the coexistence of SSc and (j)LoS (2.4 to 7.4%) is higher than their individual prevalence in the healthy population (16).

Although it is not a lethal disease like SSc, (j)LoS can lead to severe physi-

cal damage with growth deformities, functional disabilities and cosmetic impairment, which may eventually lead to chronic psychological besides physical problems (18-20). As there are no antifibrotic therapies yet that can cure the disease, early anti-inflammatory aggressive systemic treatment regimens are often required to halt disease progression and prevent poor outcomes (21-25).

In daily clinical practice the validated Localised Scleroderma Cutaneous Assessment Tool (LoSCAT) is being used combining assessment of disease activity using the modified Skin Severity Index (mLoSSI) and assessment of disease damage using the modified Skin Damage Index (mLoSDI) (26, 27). Because the LoSCAT only provides a global impression of all affected (j)LoS localisations, there is a need for more validated (imaging) tools to objectively identify and monitor inflammation and tissue damage per (j)LoS lesion. Those tools are an unmet need in making treatment decisions, for instance when to increase, switch, taper or to stop treatment in young aged patients and should consequently predict and monitor treatment response. The lack of these tools not only hampers clinical daily treatment decisions, but also complicates the conduct of clinical trials. Several non-invasive imaging modalities, such as thermography, laser doppler flowmetry and (doppler) ultrasound have been proposed, but are hampered by user dependency and lack of standardisation (28). Magnetic resonance imaging (MRI) and cone beam computed tomography (CBCT) are other imaging possibilities with the disadvantages of high costs and invasiveness for young children, not only during examination (MRI) but also because of negative radiation risks (CBCT) (29-37).

Unlike in SSc, where the evaluation of the microcirculation (using non-invasive standardised tools such as nailfold videocapillaroscopy [NVC] and laser speckle contrast analysis [LASCA]) has earned a pivotal role and the evaluation of skin fibrosis using high-frequency ultrasonography (HFUS) and durometry is currently an area of significant research and standardisation efforts, exhaustive reports using these tools in jLoS are non-existent (1, 6-9, 38-54). Against this background, we felt it was time to descriptively assess the (structural and functional) characteristics of the microvascular and dermal status in a case series of jLoS patients, using non-invasive standardised research tools (*i.e.* NVC, LASCA, HFUS and durometer) that are commonly used in adult SSc.

Materials and methods

Ethical vote

This study was approved by the local institutional review boards and local ethics committees (Amsterdam University Medical Centre [2017-172], Ghent University Hospital [EC/2019/1639]), and conducted in accordance with the Declaration of Helsinki and Helsinki and its amendments. All parents or legal guardians (for patients <16 years old) and competent patients (over >12 years old) signed written informed consent before inclusion.

Study population

This two-centre, observational study was conducted in 2019 at the tertiary Amsterdam University Medical Centre (The Netherlands) and in 2021 at the tertiary Ghent University Hospital (Belgium). Consecutive juvenile patients (≤18 years) with a confirmed diagnosis of jLoS, regardless of disease duration, who visited the paediatric rheumatology/immunology and dermatology department for an outpatient visit were recruited (6, 17). The diagnosis of jLoS was made clinically and, if necessary in doubtful cases, confirmed by histopathological examination (6, 17). In addition, jLoS was classified according to Kreuter's guideline as limited, generalised, linear, deep or mixed type (6). Patients without demonstrable skin involvement at the time of recruitment, or with the presence of other systemic diseases (*e.g.* juvenile systemic sclerosis, juvenile idiopathic arthritis, lupus erythematosus) were deemed ineligible for the study.

Data collection

Demographic, anamnestic, clinical and serological data were collected cross-sectionally from electronic medical records. For the purpose of this study, all patients were subjected to a detailed skin and microvascular examination by a team of experienced (paediatric) dermatologists and rheumatologists on the same day.

- Skin examination

First, a clinical skin evaluation was performed, including a detailed description of the jLoS lesions in terms of their number, anatomical locations and dimensions and an assessment of clinical signs of disease activity and damage by completing the mLoSSI and the mLoSDI (which are combined in the LoSCAT) (26, 27). More specifically, disease activity was measured by assessing 3 separate items (new lesion/lesion extension, erythema and skin thickness) at 18 cutaneous anatomical sites (head, neck, chest, abdomen, upper back, lower back, upper arms, forearms, hands/fingers, buttocks/thighs, legs and feet), with a predefined score of 0–3. The scores for each anatomical site were based on the most severe (*i.e.* highest) score for each item (27). Disease damage was measured by the comparable mLoSDI, scoring 0–3 on three items (*i.e.*, dermal atrophy, subcutaneous atrophy and dyspigmentation) in the same 18 cutaneous anatomical areas as the mLoSSI (4). Identically to the mLoSSI, the most severe score obtained from each item was used to calculate the mLoSDI (26).

When multiple lesions were present, the most prominent lesion (*i.e.* "target lesion") was chosen for further examination, and in case of large lesions, the most affected site was designated by an expert dermatologist (M.M.-H.). Following the clinical skin evaluation, a bi-instrumental examination of the centre, edge and contralateral unaffected site of the "target lesion" was performed by an experienced investigator (A.V.) using HFUS to assess skin thickness, and a durometer to determine skin hardness. In case of presence of jLoS lesions on the contralateral site, the perilesional unaffected skin was examined.

HFUS images were taken by using a commercially available ultrasound

system with a linear probe operating at 18 MHz in B-mode (Logiq S8, GE Healthcare, Chalfont St. Giles, Buckinghamshire, UK). Briefly, the probe was placed perpendicular to the skin by hand, without applying pressure, using a layer of ultrasound gel acting as a coupling agent between the skin surface and the probe. Images were obtained of the centre, edge and contralateral/perilesional unaffected site of the "target lesion". The dermal thickness (DT), expressed in mm, was subsequently determined by measuring the distance between the epidermis-dermis interface and the dermis-subcutis interface three times and calculating an average DT value for each area (55, 56).
Durometer measurements were performed using a hand-held electronic durometer (RX-DD Digital Durometer, type OO), which has a calibrated continuous scale from 0 to 100 standard durometer units (DU). The durometer was placed perpendicular to the skin and left at rest by gravity of the durometer's weight. As during the HFUS examination, durometer readings were taken in the centre, edge and contralateral/perilesional unaffected site of the "target lesion" to obtain a durometer value for each of these areas (57, 58).

- Microcirculation
The microcirculation was evaluated both structurally and dynamically, respectively by using nailfold videocapillaroscopy (NVC) and laser speckle contrast analysis (LASCA).
First, the structure of the microcirculation was evaluated by examining the nailfolds of the 2nd–5th finger bilaterally with an NVC probe equipped with a 200x magnification lens. Two adjacent fields in the middle of the nailfold, extending over 1mm and corresponding to the distal row of capillaries, were captured per finger, resulting in 16 images per patient. The NVC images, with a 1 mm grid, were coded and read centrally at the Ghent University Hospital. Quantitative and qualitative assessments of these images were performed according to the consented capillaroscopic definitions of the EULAR Study Group on Microcirculation in Rheumatic Diseases (38, 47, 59, 60).
For the dynamic evaluation of the microcirculation, LASCA was performed under standardised conditions as previously described, using a commercially available LASCA instrument (Pericam PSI, Perimed, Jarfalla, Sweden). During the measurements, the areas of interest, being the centre, edge and contralateral/perilesional unaffected site of the "target lesion", were illuminated perpendicularly with a laser beam for 30 seconds, at a fixed distance (20±0.5 cm). Then, the blood perfusion (BP) was evaluated by drawing a standardised circular region of interest (ROI) with a fixed diameter of 1cm in the middle of the area of interest, using LASCA software (PIMSoft 15.1, Perimed AB, Jarfalla, Sweden). Hence, a BP value, expressed in arbitrary perfusion units (PU), was recorded for each of these areas (49-53, 61).

Statistical analysis
Descriptive statistics were used to summarise the data. For nominal categorical variables, absolute numbers with percentages are shown, for ordinal categorical and skewed continuous variables, medians with interquartile ranges (IQR) are shown, and for symmetric continuous variables, means with standard deviation (SD) are shown. To compare the means between the "target lesions" and control sites, paired sample t-tests were used. Pearson's correlations examined the relationship between the mLoSSI/mLoSDI and LASCA, HFUS and durometer measurements of the "target lesions". Significance was defined as $p<0.05$. Statistical analysis is performed with SPSS, version 27 (IBM SPSS Inc., USA).

Results

Study population
Ten patients with a confirmed jLoS diagnosis were included at the tertiary Amsterdam University Medical Centre (n=9) and the tertiary Ghent University Hospital (n=1). Their demographic, clinical and laboratory characteristics are summarised in Table I. The mean age was 14.6 years, and 60% were female patients. When categorised according to the jLoS subtype, there were 6 patients with linear (5 extremities, 1 ECDS) and 4 with plaque subtype. A total of 22 lesions were found, which were located on the trunk (n=12; with 4 on the chest, 4 on the abdomen and 4 on the back), lower extremities (n=9; with 6 on the upper legs, 2 on the lower legs, and 1 on the feet), and face (n=1).

NVC evaluation
By quantitative analysis, the mean capillary density was 7.4 (±0.8) capillaries/linear mm. No giant capillaries were observed. The mean number of abnormal capillary shapes was 0.3 (± 0.3) capillaries/linear mm and 5 (50%) patients showed microhaemorrhages. By qualitative analysis, all patients had a "non-scleroderma pattern". Of them, 5/10 (50%) were classified as having a "normal" NVC pattern, and 5/10 (50%) as having "non-specific abnormalities" (Table I).

Clinical and instrumental measurements
Table II lists per patient the mLoSSI and mLoSDI measurements, as well as all instrumental measurements of the centre, edge and contralateral/perilesional unaffected sites of each "target lesion".
When examining skin thickness and hardness, significant differences were observed in the centre of the "target lesions" compared to both the edge of the "target lesions" and control sites (Tables III and IV). More specifically, the dermal thickness was thinner in the centre of the "target lesions" than at the edge of the "target lesions" ($p<0.001$, Table III) and the control sites ($p<0.001$, Table IV). The centre of the "target lesions" was harder than the edge of the "target lesions" ($p=0.012$, Table III) and the control sites ($p=0.003$, Table IV). Furthermore, a significant higher BP was observed in the centre of the "target lesions" (124.87±66.40 PU) than at the edge of the "target lesions" (87.27±46.40 PU, $p=0.001$, Table III) and the control sites (67.85±37.49 PU, $p<0.001$, Table IV).

Discussion

This is the first case series in a jLoS population describing the use of non-invasive research tools to evaluate both microcirculatory and dermal proper-

Table I. Demographic, clinical and serological characteristics of jLoS patients.

n.	Age	Gender	Race	jLoS subtype	jLoS location	ANA	Age at diagnosis (years)	Disease duration (years)	Systemic treatment (ever)	NVC pattern	mLoSSI*	mLoSDI*
1	16	Male	African	Linear	**Upper leg left**	-	8	8	MTX, GCs	Normal	2	6
2	17	Female	Asian	Plaque	Thorax left, abdomen left (x2), **abdomen right**, back, lower leg left	+	10	7	MTX, GCs	Normal	2	3
3	14	Female	Caucasian	Plaque	**Thorax left**	-	5	9	MTX, tocilizumab	Non-specific	2	7
4	16	Male	Caucasian	Linear	**Foot left**	+	12	4	MTX, GCs	Non-specific	2	3
5	15	Male	Caucasian	Linear ECDS	**Face left**	+	12	3	MTX, GCs	Non-specific	3	5
6	18	Female	Mediterranean	Linear	**Upper leg left**	-	4	14	MTX	Normal	3	5
7	12	Female	African	Plaque	**Upper leg right**, abdomen right, back central	-	11	1	MTX, GCs	Non-specific	4	5
8	10	Female	Caucasian	Linear	**Upper leg left**	+	9	1	MTX, GCs	Non-specific	4	6
9	14	Male	Caucasian	Plaque	**Back right**	-	7	7	MTX, GCs	Normal	1	2
10	14	Female	Caucasian	Linear	**Thorax left**, upper leg left, upper leg right, thorax left, back middle	-	14	0	MTX, GCs	Normal	3	3

*Target lesion.
ANA: antinuclear antibodies; ECDS: en coup de sabre; jLoS: juvenile localised scleroderma; mLoSSI: modified localised scleroderma severity index; mLoSDI: modified localised scleroderma damage index; MTX: methotrexate; NVC: nailfold videocapillaroscopy; GCs: glucocorticosteroids.

Table II. Detailed overview of measurements of the "target lesion" and the corresponding control site.

Patient n°	jLoS location	mLoSSI (0-9)	LASCA			mLoSDI (0-12)	HFUS			Durometer		
			Centre	Edge	Control site		Centre	Edge	Control site	Centre	Edge	Control site
1	**Upper leg left**	2	144.03	96.64	75.75	6	0.10	0.12	0.14	37.5	20.5	13.2
2	**Abdomen right**	2	159.56	91.45	74.41	3	0.08	0.10	0.14	12.0	8.0	7.4
3	**Thorax left**	2	144.17	122.14	98.40	7	0.08	0.09	0.12	25.6	16.6	7.7
4	**Foot left**	2	34.83	24.42	22.16	3	0.08	0.10	0.15	33.4	29.9	19.1
5	**Face left**	3	261.73	184.99	142.68	5	0.09	0.13	0.15	16.6	8.2	4.8
6	**Upper leg left**	3	77.23	44.52	28.61	5	0.10	0.12	0.13	44.4	39.8	5.7
7	**Upper leg right**	4	49.85	42.11	30.43	5	0.08	0.09	0.12	44.0	36.1	36.2
8	**Upper leg left**	4	97.82	65.59	43.14	6	0.08	0.09	0.11	53.8	28.8	21.9
9	**Back right**	1	109.47	96.06	81.35	2	0.07	0.08	0.12	16.2	19.6	15.4
10	**Thorax left**	3	170.01	104.82	81.56	3	0.10	0.12	0.15	28.8	25.8	22.8

jLoS: juvenile localised scleroderma; LASCA: laser speckle contrast analysis; mLoSSI: modified localised scleroderma severity index; mLoSDI: modified localised scleroderma damage index.

ties, as commonly used in adult SSc. Our study provides evidence for future investigation of these tools in (j)LoS lesions.

Our results demonstrate that both skin thickness (*i.e.* "atrophy") and skin hardness (*i.e.* "fibrosis") of a (j)LoS lesion can be quantitatively measured separately by HFUS and durometer, respectively. Another striking finding is that the centre of a (j)LoS lesion has a higher perfusion than the edge of the same affected skin lesion (scored by LASCA). This higher perfusion within (j)LoS plaques has also been demonstrated by other study groups that used thermography, although their control site was healthy skin instead of the edge of the "target lesions" (62). Finally, our results show a higher perfusion value in the centre of the skin lesion, combined with a thinner but harder skin. This can be explained by fact that the lesions were already in the atrophy phase (*i.e.* thinner skin as demonstrated by HFUS, and harder skin as demonstrated by durometer), since atrophic changes in the skin make the underlying (prominent) blood vessels more easily visible.

Quantitative outcome measures are important for monitoring disease activity in (j)LoS, and the combined measurements of LoSCAT add up several dif-

Table III. Comparison of measurements of centre of "target lesions" *versus* edge of "target lesions".

Variable	Centre of "target lesions"	Edge of "target lesions"	*p*-value
HFUS, mean ± SD (mm)	0.086 ± 0.01	0.104 ± 0.02	**< 0.001**
Durometer, mean ± SD (DU)	31.23 ± 13.89	23.33 ± 10.77	**0.012**
LASCA, mean ± SD (PU)	124.87 ± 66.40	87.27 ± 46.60	**0.001**

Bold text: statistically significant finding ($p<0.05$).
DU: durometer units; HFUS: high-frequency ultrasonography; LASCA: laser speckle contrast analysis; mm: millimetre; PU: perfusion units; SD: standard deviation.

Table IV. Comparison of measurements of jLoS "target lesions" versus control sites.

Variable	Centre of "target lesions"	Control site	*p*-value
HFUS, mean ± SD (mm)	0.086 ± 0.01	0.133 ± 0.01	**< 0.001**
Durometer, mean ± SD (DU)	31.23 ± 13.89	15.42 ± 9.88	**0.003**
LASCA, mean ± SD (PU)	124.87 ± 66.40	67.85 ± 37.49	**< 0.001**

Bold text: statistically significant finding ($p<0.05$).
DU: durometer units; HFUS: high-frequency ultrasonography; LASCA: laser speckle contrast analysis; mm: millimetre; PU: perfusion units; SD: standard deviation.

ferent type of scoring items. To date, infrared thermography, MRI and ultrasonography have also been used to detect disease activity in (j)LoS but those tools may be limited in case of severe skin atrophy (28). More biomarkers are needed for the treating physician in the chronic treatment of (j)LoS because it is still difficult to know when to increase, modify, taper or stop systemic treatment. Methotrexate, steroids and mycophenolate mofetil are known to be effective in systemic treatment of (j)LoS but not all patients respond to these drugs and they are frequently not tolerated due to adverse side effects in their chronic use. Recently, biologic disease-modifying anti-rheumatic drugs like tocilizumab and abatacept, based on different molecular mechanisms, have been described as promising new treatment regimens for (j)LoS (63, 64). This current pilot study explores and suggests the potential of novel, and non-invasive, research tools that appear to be easily applicable by using them in systemic treatment decisions in the daily clinical practice of (j)LoS. The separate quantitative outcome measurements obtained by HFUS (for dermal thickness), by durometer (for skin hardness) and by LASCA (for microcirculatory dynamics) make these tools particularly interesting as potential new disease biomarkers.

A limitation of this study is the relatively low number of patients, which can be explained by the high rarity of jLoS. Another limitation is the cross-sectional design since this was a first pilot study. Of note, LASCA is not very accessible to most hospitals, although HFUS and durometer are easier to acquire tools, making these interesting modalities for future longitudinal studies.

Conclusion

This case series suggests the supportive value of both microcirculatory and dermal assessment using novel non-invasive research tools, adopted from adult SSc, for (j)LoS lesions. Longitudinal studies should elaborate further the value of those non-invasive tools in this, potential severely invalidating, chronic skin disease.

Take home messages

1. (j)LoS is a chronic very rare skin disease needing (systemic) anti-inflammatory treatment but there is need for more accurate disease biomarkers.
2. HFUS, durometer and LASCA measurements differed significantly between the centre of the jLoS lesions versus the edges and contralateral unaffected sites.
3. In jLoS, skin thickness (atrophy) and skin hardness (fibrosis) can be separately quantified by respectively HFUS and durometer.
4. Skin perfusion, measured by LASCA, is higher in centre of the jLoS lesions versus the edges and contralateral unaffected sites.

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Competing interests

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