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ORIGINAL ARTICLE

Nailfold capillary changes in adult new-onset dermatomyositis: a prospective cross-sectional study

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Abstract

Objectives It is to prospectively analyze nailfold capillaroscopy (NC) findings in new-onset dermatomyositis (DM) and to correlate NC findings with serum angiogenic cytokines and DM clinical and laboratory features.

Materials and methods Twenty-three patients with DM who experienced < 12 months of symptoms were included in the study. To assess serum cytokine levels, 23 age-, sex-, and ethnicity-matched healthy volunteers were used. NC characteristics and DM activity parameters were analyzed.

Results Significantly higher serum angiogenin (ANG) and vascular endothelial growth factor-1 (VEGF1) levels were observed in DM patients than in controls. Capillary density and avascular areas correlated positively and negatively, respectively, with serum levels of ANG. Moreover, the capillary density correlated inversely with the number of enlarged and giant capillaries and avascular areas. The number of enlarged capillaries correlated positively with patient and physician visual analogue scales (VAS), the presence of a facial rash, giant capillaries, and microhemorrhages. Giant capillaries had a positive correlation with physician and cutaneous VAS, enlarged capillaries, avascular areas, microhemorrhages and bushy capillaries, and a negative correlation with capillary density. Microhemorrhages correlated positively with the "V-neck" sign and physician VAS. VEGF1 showed no relationship with the NC parameters with DM-related clinical and laboratory features. Additionally, 15 out of 23 patients were assessed prospectively after 3.21 years. All patients had a major clinical response with significant improvement in all NC parameters, except for enlarged and bushy capillaries.

Conclusions The NC may be a useful tool to assess disease activity in recent-onset DM, and it can also reinforce the role of ANG in the angiogenesis of this myopathy.

Keywords Blood vessels · Cytokines · Dermato · Myositis · Myositis · Nailfold capillaroscopy

Introduction

Dermatomyositis (DM) is a rare systemic autoimmune myopathy characterized predominantly by proximal symmetric skeletal muscle weakness associated with cutaneous lesions [1–3]. The classical skin features are a heliotrope rash and Gottron's papules, but other lesions may occur, such as periungual telangiectasia with associated dystrophic cuticles, calcinosis, vasculitis, "shawl" sign, "V-neck" sign, and ulcers, among others [4].

Blood vessels have an important role in the pathogenesis of DM. It is suggested that the primary involvement of microcirculation is mediated by humoral processes with secondary vascular depletion, hypoxia, and myofiber necrosis [5–7]. This pathogenesis can induce upregulated angiogenic gene expression and their serum cytokine levels [8]. Consequently, local neovascularization compensates for the vascular depletion and ischemic condition [9]. In this context, some angiogenic cytokines, such as angiogenin (ANG) and vascular endothelial growth factor-1 (VEGF1), may have a role in the pathogenesis of DM [8, 10].

This vascular pathophysiological mechanism may also be present in other areas beyond the muscles, such as the skin (i.e., the nailfold). In this aspect, nailfold capillaroscopy (NC) is a relatively simple method to evaluate vascular abnormalities and, unlike muscle and cutaneous biopsies, is a non-invasive procedure.

In contrast to juvenile DM, there are currently few studies that analyze NC in adult DM [11–24]. Moreover, there is no study designed to longitudinally assess NC in adult new-onset DM and correlate possible nailfold vascular abnormalities with serum angiogenic cytokine levels (ANG and VEGF1)

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and DM-related clinical, laboratory, and treatment features. Therefore, the aim of this study was to assess these DM-related aspects.

Patients and methods

Study design This prospective cross-sectional, single-center study was conducted from 2013 to 2017 and included 23 consecutive adult patients with new-onset DM who met at least four of the five criteria of the Bohan and Peter criteria, including classical cutaneous lesions (heliotrope rash and/or Gottron's papules) [1] and the new European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for DM [25].

Patient data All patients were initially admitted to our service for investigation of progressive muscle weakness of the limbs, cutaneous lesions (heliotrope rash and/or Gottron's papules), and elevated muscle enzymes with no apparent cause and with less than 12 months of symptoms (defined in this study as new-onset DM). Moreover, patients underwent muscle biopsy (m. vastus lateralis) and/or electromyography, which were compatible with inflammatory myopathies or pure myopathic standards, respectively.

As part of the internal service protocol, these patients were submitted for computed tomography of the lungs, collection of peripheral blood samples, and NC in the same period of disease investigation.

The patients were followed up in the outpatient unit, and a new NC was repeated after approximately 3 years of follow-up. All the patients were submitted to the same treatment protocol according to disease severity.

Patients with clinically amyopathic DM, overlapped myositis, neoplasia-associated myositis, systemic infections, diabetes mellitus, uncontrolled chronic systemic arterial hypertension, tobacco use, and alcohol consumption were excluded.

Control groups To assess serum cytokine levels, 23 age-, sex-, and ethnicity-matched healthy volunteers were recruited as a control group during the same period of study.

The study was approved by the local ethics committee.

Clinical parameters All patients underwent a clinical evaluation that included a standardized interview. The following parameters were analyzed: current age, sex, ethnicity, time between diagnosis and symptom onset, constitutional symptoms, cutaneous involvement, pulmonary involvement (moderate dyspnea associated with computed tomography of the lungs that disclosed evidence of interstitial pneumopathy and/or "ground-glass" pneumopathy), and previous and current drug treatment (glucocorticoid, immunosuppressive agents, immunomodulators and/or biological agents).

Disease activity was evaluated by the same observer, based on the International Myositis Assessment and Clinical Studies Group (IMACS) core set measures as follows: Manual Muscle Testing-8 (MMT-8) [26], physician and patient global visual analogue scales (VAS) [27], Health Assessment Questionnaire (HAQ) [28], Myositis Disease Activity Assessment VAS (MYOACT) [29], and serum levels of muscle enzymes. The clinical response (minimal, moderate, or major) for DM activity (follow-up vs. at baseline) was based on the criteria established by the IMACS [30].

Laboratory parameters A peripheral blood sample (20 mL of blood) was collected from each participant after a 12-h overnight fast, and the following serum levels were analyzed: creatine phosphokinase (CPK: normal range 24–173 U/L), aldolase (1.0–7.5 U/L), lactic dehydrogenase (LDH 240–480 U/L), alanine aminotransferase (ALT < 31 U/L), and aspartate aminotransferase (AST < 31 U/L), which was measured using the automated kinetic method. Antinuclear antibodies were detected by indirect immunofluorescence using HEp-2 cells as the substrate. Anti-Mi-2 and anti-Jo-1 autoantibodies were assessed with a commercially available test kit (myositis profile Euroline blot test kit, EUROIMMUN, Lübeck, Germany), which was used according to the manufacturer's protocol. Reaction positivity was defined according to a previously published study [31].

Cytokines Part of the peripheral blood sample (5 mL of blood) from each patient was collected and immediately (< 30 min) centrifuged at 3000 rpm for 10 min at 4 °C. The serum was stored at − 80 °C until the cytokine (ANG and VEGF1) analysis was performed using the Luminex 200—xMAP Instrument (Millipore, USA), as described elsewhere [32]. The serum was collected before methylprednisolone and/or intravenous human immunoglobulin pulse therapies.

Nailfold capillaroscopy The NC panoramic studies were performed by the same observer (R.M.). Individuals were acclimatized for 20 min at room temperature (20 to 22 °C) prior to the examination. The NC examination was performed using a bifocal stereomicroscope (Olympus®) with 10 to × 20 magnification and lighting with a tungsten lamp shaded by green lens to have better visualization on the ten fingers of both hands. Immersion oil was applied to increase the transparency of the skin, and the whole nailfold region was examined, including the edges. The NC findings [33] were registered as follows: capillary density (average number of capillaries per mm of the ten fingers), total number of microhemorrhages, total number of enlarged capillaries (greater than three times the normal capillary loop diameter for the patient), total number of giant capillaries (greater than ten times the normal capillary loop diameter for the patient), total number of bushy capillaries, and avascular areas (loss of two consecutive loops

of the nail bed). The avascular areas were graduated in each finger (0, without loss of loops; 1, one or two avascular areas; 2, more than two avascular areas; 3, extensive areas greater than 0.5 mm without capillaries) and presented as a sum of all ten fingers. The scleroderma pattern (SD pattern) was defined as the presence of avascular areas or enlarged loops associated with at least one additional SD parameter (nailfold hemorrhages, reduced capillary density, enlarged loops and avascular areas) [33].

Statistical analysis The Kolmogorov–Smirnov test was used to evaluate the distribution of each parameter. The demographic, clinical, and laboratory features are expressed as the means ± standard deviation (SD) or medians [25th–75th interquartile] for continuous variables, or as frequencies (%) for categorical variables. The median (25th–75th percentile) was calculated for continuous variables not normally distributed. Comparisons of the parameters between patients and the control group were analyzed using Student's *t* test or the Mann–Whitney test. Spearman's chi-square test or Fisher's exact test was used to evaluate the categorical variables. Comparisons between the patients' data (follow-up vs. at baseline) were analyzed using the Wilcoxon test. Values of $P < 0.050$ were considered statistically significant. All of the analyses were performed using the SPSS 15.0 software (Chicago, IL, USA).

Results

Twenty-three patients with DM and 23 controls were evaluated. As expected, the mean age, sex frequency, and ethnicity were comparable between the groups (Table 1). The mean age at disease onset was 46.3 years, with a median of 3.0 months of symptoms prior to diagnosis. Constitutional symptoms and cutaneous and pulmonary involvement were present in 100%, 100%, and 47.8% of the cases, respectively. Approximately half of the patients tested positive for antinuclear antibodies, whereas 17.4% and 0% of the patients tested positive for anti-Mi-2 and anti-Jo-1 autoantibodies, respectively.

Regarding drug treatment, 22 (95.7%) patients used prednisone with a median dose of 60.0 mg/day. The median cumulative dose of glucocorticoid was 1.9 g until NC. Fifteen (65.2%) patients received methylprednisolone pulse therapy (1 g/day for 3–5 consecutive days) at diagnosis. Moreover, 8 (34.8%) out of these 15 patients also received intravenous human immunoglobulin (2 g/kg, split between 2 consecutive days). Approximately half of the patients started using one immunosuppressive agent after the diagnosis: nine (39.1%) patients received azathioprine, and five (21.7%) patients received methotrexate (Table 1).

The disease status parameters (HAQ, MMT-8, the physician's and patient's VAS, MYOACT and its components, and muscle enzymes) are shown in Table 2.

Regarding the cytokines, higher serum levels of ANG ($P = 0.017$) and VEGF1 ($P < 0.001$) were identified in DM patients than in the control group (Table 2).

Further analysis showed that the NC features were correlated to all DM patients' parameters shown previously in Tables 1 and 2. Only the relevant and significant correlations are shown in Table 3. Of note, the degree of capillary density and the loss of capillaries correlated positively and negatively, respectively, with serum levels of ANG. Moreover, capillary density correlated inversely with the number of enlarged and giant capillaries and avascular areas. The number of enlarged capillaries correlated positively with patient and physician VAS, the presence of a facial rash, and giant capillaries and microhemorrhages. Additionally, the number of enlarged capillaries correlated negatively with HAQ. Giant capillaries had a positive correlation with physician and cutaneous VAS, enlarged capillaries, avascular areas, and microhemorrhages and bushy capillaries and a negative correlation with capillary density. Microhemorrhages correlated positively with the V-neck sign and physician VAS.

VEGF1 showed no relationship with NC parameters with either DM-related clinical features or laboratory features.

During the follow-up period, three patients died, and five were lost to follow-up. Therefore, for further analysis, the NC parameters were assessed in 15 out of 23 DM patients after a median duration of 3.21 [2.64–3.43] years.

The general comparison of the disease status and treatment at baseline and follow-up is shown in Table 4. The patients showed a major clinical response and a significant tapering of the prednisone dose.

Regarding the NC features, there was a significant improvement in the degree of capillary density and reduction in avascular areas in addition to a reduction in the number of giant capillaries and capillary hemorrhages during the follow-up period (Table 5). However, the presence of the SD pattern and the number of enlarged and bushy capillaries were comparable between baseline and follow-up.

Discussion

This is the first study to cross-sectionally and longitudinally assess NC in an adult new-onset DM and to correlate nailfold vascular abnormalities with serum angiogenic cytokine levels and with DM-related clinical, laboratory, and treatment features.

Although DM is a rare disease and strict exclusion criteria were employed, the present study included a sample of 23 consecutive patients with well-defined activity and newly diagnosed DM. This study could evaluate the initial disease features with little influence of the treatment and its natural progression. Additionally, we excluded confounding factors that could interfere with the evaluation and interpretation of

Table 1 General features of patients with dermatomyositis and the control group

	DM ($N = 23$)	Control ($N = 23$)	P value
Current age (years)	46.3 ± 15.5	45.9 ± 13.4	0.935
Sex (female)	16 (69.6)	16 (69.6)	1.000
Ethnicity (Caucasian)	20 (87.0)	20 (87.0)	1.000
Diagnosis—symptom onset (months)	3.0 [2.0–6.0]	–	–
Clinical features			
Constitutional symptoms	23 (100.0)	–	–
Cutaneous involvement			
Gottron's papules	23 (100.0)	–	–
Heliotrope rash	22 (95.7)	–	–
Facial rash	17 (73.9)	–	–
"V-neck" sign	15 (65.2)	–	–
"Shawl' sign	14 (60.9)	–	–
Vasculitis	4 (17.4)	–	–
Ulcers	3 (13.0)	–	–
Pulmonary involvement	11 (47.8)	–	–
Laboratory features			
Antinuclear antibody	13 (56.5)	–	–
Anti-Mi-2 antibody	4 (17.4)	–	–
Anti-Jo-1 antibody	0		
Treatment			
Methylprednisolone pulse*	15 (65.2)	–	–
Prednisone			
Current use	22 (95.7)	–	–
Current dose (mg/day)	60 [40–60]	–	–
GC cumulative dose (g)**	1.9 [0.4–5.3]	–	–
Intravenous human immunoglobulin	8 (34.8)		
Immunosuppressive drugs***			
Azathioprine	9 (39.1)	–	–
Methotrexate	5 (21.7)	–	–

The data are expressed as the means ± standard deviation, medians [25th–75th interquartile] or percentages (%)

DM dermatomyositis, *GC* glucocorticoid

*At disease diagnosis; **until nailfold capillaroscopy; ***immunosuppressive drugs: azathioprine (2–3 mg/kg/day), methotrexate (15–25 mg/week)

the angiogenic cytokines. Finally, the study adopted similar standardization of analysis and interventions, thereby reducing interexaminer variability.

Despite several studies regarding the NC findings in systemic sclerosis and juvenile DM, there are currently few studies that include adult DM [11–24]. Moreover, to the best of our knowledge, there are no studies that exclusively involve patients with adult new-onset DM. In this group of patients, which included those who were still untreated or in the beginning of treatment, it was expected that we would find more changes that could help in diagnosis, the quantification of disease severity, or prognosis.

In the present study, all patients showed disease activity and had a median duration from symptoms to diagnosis of only 3 months. Despite this short time frame, abnormalities in NC studies were observed, and angiogenic cytokines (ANG and VEGF1) were significantly increased in serum measures compared to control group.

The cornerstone of DM pathogenesis involves vascular disturbances that lead to hypoxia, capillary necrosis, and muscle perifascicular atrophy [3]. Consequently, this pathogenesis can stimulate the expression of ANG and VEGF1, which are linked to the mechanism of angiogenesis, by activating endothelial cell proliferation and migration, chemotaxis, and capillary hyperpermeability [8, 34, 35].

Kikuchi et al. [36] identified a high serum level of VEGF in DM patients compared to controls. However, in contrast to our study, Kikuchi et al. [36] did not give detailed information about the treatment regimen or the status and duration of DM disease, which may influence the serum levels of VEGF.

Table 2 Disease status, cytokines, and nailfold capillaroscopy parameters of the patients with dermatomyositis and laboratory parameters of the control group

	DM ($N = 23$)	Control ($N = 23$)	P value
Disease status			
HAQ (0.00–3.00)	2.10 [1.50–2.63]	–	–
MMT-8 (0–80)	64 [58–74]	–	–
VAS (0–10 cm)			
Physician	6.0 [5.0–8.0]	–	–
Patient	6.0 [5.0–8.0]	–	–
MYOACT (0–60)	21.0 [14.0–27.0]	–	–
Constitutional symptoms	6.0 [4.0–9.0]	–	–
Cutaneous	6.0 [4.0–7.0]	–	–
Skeletal	6.0 [3.0–8.0]	–	–
Gastrointestinal	0.0 [0.0–5.0]	–	–
Pulmonary	0.0 [0.0–0.0]	–	–
Cardiac	0.0 [0.0–0.0]	–	–
Laboratory features			
CPK (U/L)	433 [138–1494]	127 [88–183]	0.002
Aldolase (U/L)	9.4 [4.7–19.0]	3.8 [3.2–4.7]	< 0.001
LDH (U/L)	353 [324–518]	370 [319–406]	0.955
AST (U/L)	49 [32–142]	22 [19–24]	< 0.001
ALT (U/L)	32 [27–125]	20 [15–25]	< 0.001
Cytokines			
ANG (μg/mL)	14.47 [14.10–15.00]	14.00 [13.35–14.44]	0.017
VEGF (ng/mL)	436 [198–1150]	57 [26–140]	< 0.001
Nailfold capillaroscopy			
SD pattern	22 (95.7)		
Capillary density (capillaries/mm)	5.0 [4.0–6.9]	–	–
Total number of			
Enlarged capillaries	31 [16–56]	–	–
Giant capillaries	5 [2–19]	–	–
Avascular areas	22 [13–30]	–	–
Capillary hemorrhages	30 [12–88]	–	–
Bushy capillaries	2 [1–6]	–	–

The data are expressed as the means ± standard deviation, medians [25th–75th interquartile] or percentages (%)

ANG angiogenin, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CPK* creatine phosphokinase, *DM* dermatomyositis, *HAQ* Health Assessment Questionnaire, *LDH* lactic dehydrogenase, *MMT* Muscle Manual Testing, *MYOACT* Myositis Disease Activity Assessment Analog Scale, *VEGF* vascular endothelial growth factor

Similar to our study, Grundtman et al. [8] demonstrated an increase in serum VEGF levels in newly diagnosed DM patients. Moreover, they observed a large number of muscle fibers expressing VEGF with a reduced number of capillaries compared to those in the muscle biopsies of healthy individuals.

In contrast to our data, Kuwahara et al. [10] found comparable serum levels of ANG between the control group and different types of rheumatic patients (including 21 DM, 5 polymyositis, and 11 patients with clinical amyopathic DM). However, the authors did not give any information about the

Table 3 Spearman's correlation between nailfold vascular abnormalities and different disease parameters and angiogenin

	Capillary density		Enlarged capillaries		Giant capillaries		Loss of capillaries		Capillary hemorrhages		Bushy capillaries	
	rho	P	rho	P	rho	P	rho	P	rho	P	rho	P
Facial rash	NS	NS	0.441	0.035	NS	NS	NS	NS	NS	NS	NS	NS
"V-neck" sign	NS	NS	NS	NS	NS	NS	NS	NS	0.448	0.032	NS	NS
Patient global VAS	NS	NS	0.497	0.016	NS	NS	NS	NS	NS	NS	NS	NS
Physician global VAS	NS	NS	0.569	0.005	0.506	0.014	NS	NS	0.481	0.020	NS	NS
HAQ	NS	NS	− 0.417	0.048	NS	NS	NS	NS	NS	NS	NS	NS
Cutaneous VAS	NS	NS	NS	NS	0.420	0.046	NS	NS	NS	NS	NS	NS
ANG	0.607	0.016	NS	NS	NS	NS	− 0.598	0.019	NS	NS	NS	NS
VEGF	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Capillary density	1.000		− 0.547	0.007	− 0.531	0.009	− 0.848	< 0.001	0.591	0.003		
Enlarged capillaries	− 0.547	0.007	1.000		0.764	< 0.001	NS	NS	0.558	0.006	0.424	0.044
Giant capillaries	− 0.531	0.009	0.764	< 0.001	1.000	NS	0.549	0.007	NS	NS	NS	NS
Loss of capillaries	− 0.848	< 0.001	NS	NS	0.549	0.007	1.000	NS	NS	NS	NS	NS
Capillary hemorrhages	NS	NS	0.591	0.003	0.558	0.006	NS	NS	1.000	NS	NS	NS
Bushy capillaries	NS	NS	NS	NS	0.424	0.044	NS	NS	NS	NS	1.000	NS

Only the parameters that correlated with the nailfold vascular findings were tabulated

ANG angiogenin, *HAQ* Health Assessment Quality, *VAS* visual analog score, *VEGF* vascular endothelial growth factor, *P P* value, *rho* Spearman's correlation, *NS* not significant

Table 4 Disease status, laboratory parameters, and treatment of patients with dermatomyositis at baseline and during follow-up

	At baseline ($N = 15$)	Follow-up* ($N = 15$)	P value
Disease status			
HAQ (0.00–3.00)	2.10 [1.60–2.50]	0.00 [0.00–1.00]	0.001
MMT-8 (0–80)	65 [58–76]	80 [80–80]	0.001
VAS (0–10 cm)			
Physician	6.0 [5.0–9.0]	1.0 [0.0–3.0]	0.001
Patient	6.0 [5.0–9.0]	0.0 [0.0–1.0]	0.001
MYOACT (0–60)	23 [14–28]	0.0 [0.0–0.0]	0.001
Constitutional symptoms	7.0 [3.0–9.0]	0.0 [0.0–0.0]	0.001
Cutaneous	7.0 [5.0–8.0]	0.0 [0.0–0.0]	0.001
Skeletal	7.0 [3.0–8.0]	0.0 [0.0–0.0]	0.001
Gastrointestinal	2.0 [0.0–7.0]	0.0 [0.0–0.0]	0.011
Pulmonary	0.0 [0.0–0.0]	0.0 [0.0–0.0]	1.000
Cardiac	0.0 [0.0–0.0]	0.0 [0.0–0.0]	1.000
Laboratory features			
CPK (U/L)	575 [138–2550]	330 [167–326]	0.041
LDH (U/L)	421 [325–974]	248 [229–259]	0.003
AST (U/L)	26 [32–205]	28 [21–35]	0.010
ALT (U/L)	32 [26–204]	27 [18–40]	0.272
Treatment			
Methylprednisolone pulse	11 (73.3)	5 (33.3)	–
Prednisone			
Current use	14 (93.3)	1 (6.7)	< 0.001
Current dose (mg/day)	50 [40–60]	0 [0–0]	0.004
Intravenous human immunoglobulin	6 (40.0)	7 (46.7)	–
Rituximab	–	3 (20.0)	–
Immunosuppressive drugs**			
Azathioprine	6 (40.0)	6 (40.0)	1.000
Methotrexate	4 (26.7)	8 (53.3)	0.450
Others***	–	3 (20.0)	–

The data are expressed as the medians [25th–75th interquartile] or percentages (%)

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *CPK* creatine phosphokinase, *DM* dermatomyositis, *GC* glucocorticoid, *HAQ* Health Assessment Questionnaire, *LDH* lactic dehydrogenase, *MMT* Muscle Manual Testing, *MYOACT* Myositis Disease Activity Assessment Analog Scale

*Follow-up: median duration from baseline 3.21 [2.64–3.43] years; **immunosuppressive drugs: azathioprine (2–3 mg/kg/day), methotrexate (15–25 mg/week); ***leflunomide 20 mg/day, mycophenolate mofetil 2–3 g/day

treatment regimen or disease status, both of which could influence the serum levels of ANG.

In additional analyses, although not observed with serum VEGF1, serum ANG levels were positively and negatively correlated with capillary density and avascular areas, respectively. Therefore, these data reinforce the hypothesis that vascular abnormalities that lead to hypoxia and capillary necrosis could primarily stimulate the production of ANG cytokines. VEGF1 expression in situ (skin or muscle) and not serum VEGF1 could possibly be partially responsible for vascular involvement. Unfortunately, in the present study, it was not possible to study cytokine expression in these tissues.

Indeed, the patients in our study were in an active disease state and in the early stages of treatment. Thus, several NC abnormalities were found and, in some way, correlated with the number of enlarged capillaries, capillary density, avascular areas, and microhemorrhages. Enlarged capillaries, giant capillaries, and microhemorrhages correlated respectively with facial rash, cutaneous VAS, and the V-neck sign, suggesting that NC studies may be part of the evaluation of cutaneous involvement. In this aspect, these features correlated with patient and physician VAS and cutaneous VAS.

Moreover, the SD pattern is characterized initially by enlarged capillaries that may progress to giant capillaries. Nailfold microhemorrhages are linked to the altered integrity of the microvessel wall and altered endothelial cell array. They emerge with vessel collapse and, subsequently, the loss of capillaries with avascular areas occurs. Capillary loss creates tissue

Table 5 Nailfold capillaroscopy features of patients with dermatomyositis at baseline and follow-up

	At baseline ($N = 15$)	Follow-up* ($N = 15$)	P value
SD pattern	14 (93.3)	13 (86.7)	1.000
Capillary density (capillaries/mm)	5.0 [4.0–5.8]	7.3 [6.6–8.0]	0.010
Number of			
Enlarged capillaries	31 [14–60]	18 [6–48]	0.118
Giant capillaries	12 [2–19]	0 [0–4]	0.012
Avascular areas	22 [19–30]	5 [1–17]	0.023
Capillary hemorrhages	43 [13–92]	6 [0–15]	0.005
Bushy capillaries	2 [1–6]	3 [0–10]	0.305

The data are expressed as the medians [25th–75th interquartile]

*Follow-up: median duration from baseline 3.21 [2.64–3.43] years

hypoxia and the local production of vessel growth factors (such as VEGF), which may stimulate the formation of new capillaries (neoangiogenesis) such as bushy capillaries [37]. Thus, NC abnormalities are interrelated, as we showed in our study.

In the literature, conflicting results regarding the correlation of NC findings in DM with global disease activity, organ involvement, clinical features, and prognosis are reported. For instance, Mugii et al. demonstrated that NC changes were significantly associated with disease activity [19]. Patients with an SD pattern more frequently had elevated serum CPK levels and higher VAS scores related to muscle disease activity than patients without this pattern. The same was not demonstrated for the cutaneous involvement [19]. In another study, disease activity and severity were both significantly associated with a larger number of capillaroscopy findings, and interstitial lung disease was associated with the findings [18]. Mercer et al. did not find an association between capillary density and disease activity and severity scores in their cross-sectional and longitudinal cohort of DM patients [17]. Finally, Shenavandeh and Nezhad [23] did not demonstrate a significant association between disease activity in each organ system and global disease activity, SD pattern, and other NC findings.

Further analysis showed that 15 patients included in the initial group of new-onset DM were followed up and experienced disease remission and a significant tapering of prednisone therapy in a period of time that averaged 3.21 years. For our internal protocol, the patients received the same intensive treatment that included methylprednisolone pulse therapy, intravenous human immunoglobulin, immunosupressive agents, and even rituximab, according to disease severity.

As well as disease activity, all NC parameters improved during the follow-up period, except for enlarged and bushy capillaries. Our findings are in agreement with Mugii et al. [19] who demonstrated longitudinally (in a period of time that averaged 9.2 months) that NC changes (hemorrhages, loss of capillaries, and irregularly enlarged capillaries) were significantly improved by disease stabilization. A decrease in the number of microhemorrhages and giant capillaries and improvement in capillary density and avascular areas may be important changes to show improvement in disease activity.

One of the limitations of the present study was that the serum levels of the angiogenic cytokines were only measured at the onset of disease; the serum profiles could have changed during the evolution of the disease and the establishment of treatment. Moreover, the cytokine expressions in muscle biopsies were not assessed.

Our findings reinforce the usefulness of NC as a possible biomarker of disease activity in new-onset DM and as a tool for the assessment of the role of ANG in the angiogenesis process in this myopathy.

Compliance with ethical standards

The study was approved by the local ethics committee.

Disclosures None.

References

1. Bohan A, Peter JB (1975) Polymyositis and dermatomyositis (first of two parts). N Engl J Med 292:344–347
2. Dalakas MC (2011) Review: an update on inflammatory and autoimmune myopathies. Neuropathol Appl Neurobiol 37:226–242
3. Dalakas MC (2015) Inflammatory muscle diseases. N Engl J Med 373:1734–1747
4. Mainetti C, Terziroli Beretta-Piccoli B, Selmi C (2017) Cutaneous manifestations of dermatomyositis: a comprehensive review. Clin Rev Allergy Immunol 53:337–356
5. De Visser M, Emslie-Smith AM, Engel AG (1989) Early ultrastructural alterations in adult dermatomyositis. Capillary abnormalities precede other structural changes in muscle. J Neurol Sci 94:181–192
6. Emslie-Smith AM, Engel AG (1990) Microvascular changes in early and advanced dermatomyositis: a quantitative study. Ann Neurol 27:343–356
7. Lundberg IE, Grundtman C (2008) Developments in the scientific and clinical understanding of inflammatory myopathies. Arthritis Res Ther 10:220

8. Grundtman C, Tham E, Ulfgren AK, Lundberg IE (2008) Vascular endothelial growth factor is highly expressed in muscle tissue of patients with polymyositis and patients with dermatomyositis. Arthritis Rheum 58:3224–3238
9. Nagaraju K, Lundberg IE (2011) Polymyositis and dermatomyositis: pathophysiology. Rheum Dis Clin N Am 37:159–171
10. Kuwahara A, Jinnin M, Makino T, Kajihara I, Makino K, Honda N, Nakayama W, Inoue K, Fukushima S, Ihn H (2012) Angiogenin expression in the sera and skin of patients with rheumatic diseases. Biosci Trends 6:229–233
11. Ganczarczyk ML, Lee P, Armstrong SK (1988) Nailfold capillary microscopy in polymyositis and dermatomyositis. Arthritis Rheum 31:116–119
12. Blockmans D, Beyens G, Verhaeghe R (1996) Predictive value of nailfold capillaroscopy in the diagnosis of connective tissue diseases. Clin Rheumatol 15:148–153
13. Ohtsuka T (1998) The relation between nailfold bleeding and capillary microscopic abnormality in patients with connective tissue diseases. Int J Dermatol 37:23–26
14. Bergman R, Sharony L, Schapira D, Nahir MA, Balbir-Gurman A (2003) The handheld dermatoscope as a nail-fold capillaroscopic instrument. Arch Dermatol 139:1027–2030
15. Nagy Z, Czirják L (2004) Nailfold digital capillaroscopy in 447 patients with connective tissue disease and Raynaud's disease. J Eur Acad Dermatol Venereol 18:62–68
16. Szabo N, Csiki Z, Szanto A, Danko K, SzodoraY P, Zeher M (2008) Functional and morphological evaluation of hand microcirculation with nailfold capillaroscopy and laser Doppler imaging in Raynaud's and Sjögren's syndrome and poly/dermatomyositis. Scand J Rheumatol 37:23–29
17. Mercer LK, Moore TL, Chinoy H, MurraY AK, Vail A, Cooper RG, Herrick AL (2010) Quantitative nailfold video capillaroscopy in patients with idiopathic inflammatory myopathy. Rheumatology 49:1699–1705
18. Selva-O'Callaghan A, Fonollosa-Pla V, Trallero-Araguas E, Martinez-Gomez X, Simeon-Aznar CP, Labrador-Horrilo M, Vilardell-Tarrés M (2010) Nailfold capillary microscopy in adults with inflammatory myopathy. Semin Arthritis Rheum 39:398–404
19. Mugii N, Hasegawa M, Matsushita T, Hamaguchi Y, Horie S, Yahata T, Inoue K, Someya F, Fujimoto M, Takehara K (2011) Association between nail-fold capillary findings and disease activity in dermatomyositis. Rheumatology (Oxford) 50:1091–1098
20. Pavlov-Dolijanovic S, Damjanov N, Stojanovic R, Vujasinovic Stupar N, Stanisavljevic D (2012) Scleroderma pattern of nailfold capillary changes as predictive value for the development of a connective tissue disease: a follow-up study of 3,029 patients with primary Raynaud's phenomenon. Rheumatol Int 32:3039–3045
21. De Angelis R, Cutolo M, Gutierrez M, Bertolazzi C, Salaffi F, Grassi W (2012) Different microvascular involvement in dermatomyositis and systemic sclerosis. A preliminary study by a tight videocapillaroscopic assessment. Clin Exp Rheumatol 30:S67–S70
22. Manfredi A, Sebastiani M, Cassone G, Pipitone N, Giuggioli D, Colaci M, Salvarani C, Ferri C (2015) Nailfold capillaroscopic changes in dermatomyositis and polymyositis. Clin Rheumatol 34:279–284
23. Shenavandeh S, Zarei Nezhad M (2015) Association of nailfold capillary changes with disease activity, clinical and laboratory findings in patients with dermatomyositis. Med J Islam Repub Iran 29:233
24. Bertolazzi C, Cutolo M, Smith V, Gutierrez M (2017) State of the art on nailfold capillaroscopy in dermatomyositis and polymyositis. Semin Arthritis Rheum 47:432–444
25. Lundberg IE, Tjärnlund A, Bottai M, Werth VP, Pilkington C, De Visser M et al (2017) International Myositis Classification Criteria Project Consortium, the Euromyositis Register, and the Juvenile Dermatomyositis Cohort Biomarker Study and Repository (UK and Ireland) 2017 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies and Their Major Subgroups. Arthritis Rheum 69:2271–2282
26. Rider LG, Koziol D, Giannini EH, Jain MS, Smith MR, Whitney-Mahoney K, Feldman BM, Wright SJ, Lindsley CB, Pachman LM, Villalba ML, Lovell DJ, Bowyer SL, Plotz PH, Miller FH, Hicks JE (2010) Validation of manual muscle testing and a subset of eight muscles for adult and juvenile idiopathic inflammatory myopathies. Arthritis Care Res 62:465–472
27. Rider LG, Feldman BM, Perez MD, Rennebohm RM, Lindsley CB, Zemel LS, Wallace CA, Ballinger SH, Bowyer SL, Reed AM, Passo MH, Katona IM, Miller FW, Lachenbruch PA (1997) Development of validated disease activity and damage indices for the juvenile idiopathic inflammatory myopathies: I. Physician, parent, and patient global assessments. Juvenile Dermatomyositis Disease Activity Collaborative Study Group Arthritis Rheum 40:1976–1983
28. Alexanderson H, Lundberg IE, Stenstrom CH (2002) Development of the myositis activities profile—validity and reliability of a self-administered questionnaire to assess activity limitations in patients with polymyositis/dermatomyositis. J Rheumatol 29:2386–2392
29. Isenberg DA, Allen E, Farewell V, Ehrenstein MR, Hanna MG, Lundberg IE et al International Myositis and Clinical Studies Group (IMACS) (2004) international consensus outcome measures for patients with idiopathic inflammatory myopathies. Development and initial validation of myositis activity and damage indices in patients with adult onset disease. Rheumatology (Oxford) 43:49–54
30. Aggarwal R, Rider LG, Ruperto N, Bayat N, Erman B, Feldman BM et al International Myositis Assessment and Clinical Studies Group and the Paediatric Rheumatology International Trials Organisation (2017) 2016 American College of Rheumatology/European League Against Rheumatism criteria for minimal, moderate, and major clinical response in adult dermatomyositis and polymyositis: an International Myositis Assessment and Clinical Studies Group/Paediatric Rheumatology International Trials Organization Collaborative Initiative. Ann Rheum Dis 76:792–801
31. Cruellas MG, Viana V, Dos S, Levy-Neto M, Souza FH, Shinjo SK (2013) Myositis-specific and myositis-associated autoantibody profiles and their clinical associations in a large series of patients with polymyositis and dermatomyositis. Clinics 68:909–914
32. Silva MG, Borba EF, Mello SB, Shinjo SK (2016) Serum adipocytokine profile and metabolic syndrome in young adult female dermatomyositis. Clinics 71:709–714
33. Maricq HR (1981) Wide field capillary microscopy. Arthritis Rheum 24:1159–1165
34. Ferrara N (1999) Molecular and biological properties of vascular endothelial growth factor. J Mol Med 77:527–543
35. Gao X, Xu Z (2008) Mechanisms of action of angiogenin. Acta Biochim Biophys Sin Shanghai 40:619–624
36. Kikuchi K, Kubo M, Kadono T, Yazawa N, Ihn H, Tamaki K (1998) Serum concentrations of vascular endothelial growth factor in collagen diseases. Br J Dermatol 139:1049–1051
37. Cutolo M, Sulli A, Smith V (2013) How to perform and interpret capillaroscopy. Best Pract Res Clin Rheumatol 27:237–248