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ORIGINAL ARTICLE

Long-term follow-up of nailfold videocapillaroscopic changes in dermatomyositis versus systemic sclerosis patients

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Abstract

To identify nailfold videocapillaroscopy (NVC) changes in patients with dermatomyositis (DM) during a 3-year follow-up and to compare the NVC findings between DM and systemic sclerosis (SSc) patients at their first visit. Retrospective study of 24 DM and 24 SSc patients, matched for age and disease duration at first NVC. Capillaroscopic patterns/scores and clinical parameters had been yearly assessed. Nineteen out of 24 DM patients (79%) showed a NVC "scleroderma-like pattern." No statistically significant variation of all the capillaroscopic scores was observed during the 3-year follow-up. By comparing DM patients with or without anti-Jo-1 positivity, no statistically significant difference of the scores of the main capillary parameters was observed at baseline between the groups. Comparing at baseline DM with SSc patients, the giant capillary and microhemorrhage scores were significantly higher in SSc than those in DM patients ($p = 0.04$ and $p = 0.05$, respectively), while capillary density, ramification (abnormally shaped capillaries, expression of angiogenesis), and disorganization scores were higher in DM patients ($p = 0.05$, $p = 0.002$, $p = 0.004$, respectively). The absolute number of ramified capillaries was significantly higher in DM patients ($p = 0.002$), while the absolute capillary number was significantly higher in SSc patients ($p = 0.05$) at baseline. This pilot study demonstrates, for the first time, over long-term, that the capillaroscopic manifestations of DM persist in contrast to the progressive changes described in SSc patients, and the anti-Jo-1 positivity does not seem to modify the NVC pattern.

Keywords Anti-Jo1 antibodies · Dermatomyositis · Microcirculation · Nailfold capillaroscopy · Systemic sclerosis

Introduction

Idiopathic inflammatory myopathies (IIM), collectively known as myositis, are heterogeneous disorders characterized by muscle inflammation and weakness [1]. The most common subgroups in adults are dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM) [2].

Recently, the International Myositis Classification Criteria Project (IMCCP), with the support of the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR), has developed new classification criteria for adult and juvenile IIM and its subtypes, including DM and PM [3]. The EULAR/ACR classification criteria model consists of 16 criteria which have been assigned distinct scores; this model has a sensitivity of 87–88% and a specificity of 88–89% [3].

Anti-histidyl-tRNA synthetase (anti-Jo-1) antibodies characterize a specific clinical IIM phenotype, known as the antisynthetase syndrome (ASS), occurring sometimes as an overlap syndrome with other autoimmune diseases. Histological studies also suggested that the ASS might be a separate disease entity within the spectrum of IIM [4]. Anti-Jo-1 autoantibodies, predominantly found in 20–30% of patients with PM and in 60–70% of those with interstitial lung disease (ILD), are the hallmarks of the ASS, which is characterized by multiple organ involvement and specific clinical feature symptoms [4, 5].

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Nailfold videocapillaroscopy (NVC), a noninvasive method for assessing the skin microvasculature, has become a useful test for evaluating patients with connective tissue diseases, particularly systemic sclerosis (SSc) [6, 7].

A characteristic disarranged microvascular pattern, named the "scleroderma-pattern" that consists in a cluster of alterations of the capillary distribution, shape, number, and dimension, has been described in SSc and may be observed also in other connective tissue disorders (scleroderma-like pattern), including DM [8–13]. DM offers an ideal scenario for the use of NVC due to the active involvement of the endothelium that may induce an intensive microvascular remodeling [14–16].

Several studies described the association between abnormalities in nailfold microvascular array and IIM, often considering together DM and PM [10, 11, 17]. Nevertheless, the literature investigations on the follow-up of the main NVC changes in patients with either DM or ASS have been poorly described or are totally absent [18].

The aim of the present retrospective study is to describe the main NVC changes in patients with DM, differentiating among patients with or without anti-Jo-1 positivity, during a 3-year follow-up, and to investigate possible differences in NVC findings at first visit in comparison with patients affected by SSc matched for sex, age, and disease duration.

Materials and methods

Patients

Twenty-four patients (4 males and 20 females; mean age 54 ± 15 SD years; mean disease duration 4 ± 5 years) affected by DM, all satisfying the EULAR/ACR 2017 criteria (3), have been retrospectively enrolled when they had undergone the first clinical assessment by NVC.

Among the enrolled patients, all capillaroscopic, clinical, and therapeutic data, including autoantibodies (13 patients anti-Jo-1 negative and 11 patients anti-Jo-1 positive), were available at 3 years for 12 patients with a disease duration at baseline of 3.7 ± 5 years. Globally, patients were taking different immunosuppressive drugs including cyclosporine A (38%), methotrexate (13%), mycophenolate (17%), cyclosporine+methotrexate (13%), and all glucocorticoids.

Also, 24 patients (4 males and 20 females; mean age 55 ± 13 SD years; mean disease duration 4 ± 5 years) affected by SSc (diagnosis based on EULAR/ACR 2013 criteria) matched for sex, age, and disease duration at first NVC were retrospectively enrolled [19].

All the patients gave written informed consent to enter the study.

Microangiopathy and nailfold capillaroscopy

NVC was performed using an optical probe, equipped with a 200× contact lens connected to image analysis software (Videocap, DS Medica, Milan, Italy). The same operator (CP) performed the NVC examinations in all patients, after permanence in a comfortable room temperature of 22–25 °C for 20 min. Two millimeters in the middle of the nailfold was studied in each finger. The following qualitative parameters were assessed: dilated (enlarged) loops (irregular or homogeneous increase of capillary diameter ≥ 20 and < 50 μm), giant capillaries (homogeneously dilated loops with a diameter of ≥ 50 μm), microhemorrhages (dark masses attributable to hemosiderin deposit), ramified capillaries (abnormally shaped capillaries, branching, bushy, interconnected, originating from a single capillary, expression of angiogenesis), disorganization of the microvascular array, and capillary loss (reduction of the number of capillaries) [8, 9, 20, 21].

All these parameters were also used to define the three validated NVC patterns of microangiopathy in SSc ("early," "active," "late") [7, 22].

The total number of capillaries, dilated and giant capillaries, microhemorrhages, ramified capillaries, and disorganization of the vascular array were scored by a semiquantitative rating scale (0, no changes; 1, less than 33% of capillary alterations/reduction; 2, 33–66% of capillary alterations/reduction; 3, more than 66% of capillary alterations/reduction, per linear millimeter), obtaining a mean score value for each capillaroscopic parameter, as already validated in SSc [22, 23].

Nailfold capillary parameter scores, as well as the absolute number of normal capillaries, the absolute number of ramified capillaries, and the absolute capillary number per linear millimeter were yearly evaluated by NVC (T0, T1, T2, and T3) in patients with DM and, at baseline, in SSc patients.

Autoantibodies detection

Antinuclear antibodies were tested by indirect immunofluorescence on HEp-2 cell substrates at a starting dilution of 1:80, and considered positive for a dilution ≥ 1:160. Anti-Jo-1 and other antibodies' anti-cellular-specific antigen (ENA: RNP, Sm, SSA, SSB, Scl70) were detected by immunoenzymatic assay (commercial ELISA test Euroimmun AG, Luebeck, Germany).

Statistical analysis

Statistical analysis was performed by non-parametric tests. In particular, the Wilcoxon signed-rank test was used to compare paired groups of variables and Mann-Whitney *U* test to compare unpaired groups of variables. Friedman test was employed to detect differences across multiple related

comparisons. The p values ≤ 0.05 were considered statistically significant.

Results

Out of 24 patients (79%) with DM, 19 showed a NVC "scleroderma-like pattern," a scleroderma-spectrum pattern including aspects of the validated NVC patterns "early," "active," or "late" described in SSc [13] (Fig. 1).

The other five DM patients showed normal capillaries (hairpin shaped), non-specific capillary alterations (tortuous, crossing), and capillaries with non-specific dilations. Among them, only two DM patients showed a mild reduced capillary density and minimal capillary abnormal shapes/ramifications not characteristic of the scleroderma-pattern. No patients showed giant capillaries.

No statistically significant variation of the capillaroscopic score of all capillary parameters was observed during the 3 years of follow-up in DM patients (Table 1). However, the percentage of DM patients showing ramified capillaries was 84% at T0, 88% at T1, 92% at T2, and 100% at T3.

By comparing DM patients with or without anti-Jo-1 positivity, no statistically significant difference for the score of the main capillary parameters was observed at baseline between the groups (Table 2). However, anti-Jo-1-positive patients showed a statistically significant decrease of capillary ramifications at T2 (1.4 ± 1.1 vs 2.6 ± 0.7, $p = 0.05$) and T3 (1.0 ± 0.0 vs 2.6 ± 0.5, $p = 0.03$), when compared with the anti-Jo-1-negative group.

Due to the small cohort of patients enrolled, no statistically significant correlation was observed between capillary parameters at baseline and during follow-up for the following clinical aspects: Raynaud phenomenon (100% of patients), myositis (100%), heliotrope rash (12%), dysphagia (8%), dyspnea (28%), sclerodactyly (32%), calcinosis (4%), skin rash (64%), telangiectasias (12%), arthritis (24%), mechanic's hands (17%), and pericarditis (4%), as well as no statistically significant difference was observed between capillary parameter scores and single treatments.

Comparing at baseline DM with SSc patients (matched for disease duration and age at first visit), the giant capillary and the microhemorrhage scores were significantly higher in SSc than those in DM patients ($p = 0.04$ and $p = 0.05$,

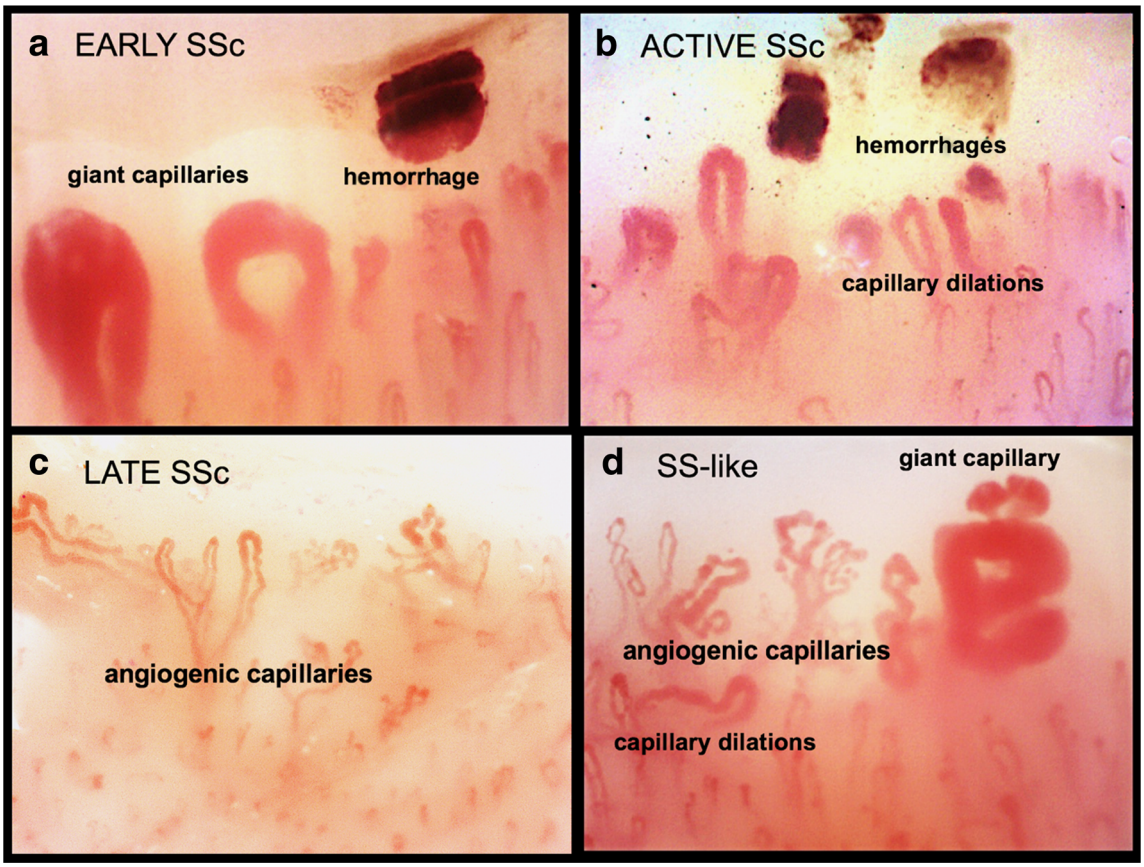

Fig. 1 Nailfold videocapillaroscopic patterns (**a** early, **b** active, **c** late patterns) in systemic sclerosis patients with prevalence of giant capillaries and hemorrhages in active stage (**b**) and of abnormally shaped and angiogenic capillaries in the late fibrotic stage (**c**). Nailfold videocapillaroscopic scleroderma-like pattern (**d**) in dermatomyositis patient with prevalence of capillary dilations (enlargements) and abnormally shaped/angiogenic capillaries

Table 1 Trends of nailfold videocapillaroscopic (NVC) parameters in DM/PM patients during a 3-year follow-up. Means ± standard deviations are reported. (T0, basal; T1, 1 year; T2, 2 years; T3, 3 years)

NVC parameters	T0	T1	T2	T3	*p*
Giant capillaries (score)	0.92 ± 0.67	0.92 ± 0.67	0.83 ± 0.58	0.78 ± 0.67	0.72
Microhemorrhages (score)	0.67 ± 0.49	0.67 ± 0.49	0.50 ± 0.52	0.44 ± 0.53	0.95
Dilated capillaries (score)	2.50 ± 0.52	2.50 ± 0.52	2.67 ± 0.49	2.56 ± 0.53	0.68
Capillary number (score)	1.58 ± 0.67	1.67 ± 0.65	1.58 ± 0.67	1.89 ± 0.60	0.53
Capillary abnormal shapes/ramifications (score)	2.17 ± 1.03	2.25 ± 0.97	2.08 ± 1.08	2.22 ± 0.83	0.89
Capillary disorganization (score)	1.75 ± 0.75	1.67 ± 0.89	1.83 ± 1.03	1.89 ± 0.93	0.75
Absolute number of capillaries	5.25 ± 1.60	5.42 ± 1.56	5.58 ± 1.44	4.56 ± 1.67	0.55
Number of abnormal shapes/ramifications	2.25 ± 1.06	2.58 ± 1.38	2.25 ± 1.29	2.33 ± 1.00	0.46
Number of normal capillaries	1.00 ± 1.13	0.67 ± 0.89	0.83 ± 1.19	0.89 ± 1.17	0.84

respectively), while the capillary density, the ramification, and the disorganization scores were higher in DM patients ($p = 0.05$, $p = 0.002$, $p = 0.004$, respectively) (Table 3). No statistically significant difference of the score of dilated loops, as well as of the number of normal capillaries, was observed between the two groups of patients. Furthermore, the absolute number of ramified capillaries was significantly higher in patients with DM ($p = 0.002$), while the absolute capillary number was significantly higher in SSc patients ($p = 0.05$) (Table 3).

By dividing all patients (DM and SSc) into two groups (disease duration lower or higher than 1 year), the following differences were observed: in patients with a disease duration shorter than 1 year, the capillaroscopic scores for dilated loops, capillary density, ramifications (angiogenesis), and disorganization were higher in DM than those in SSc patients ($p = 0.03$, $p = 0.009$, $p = 0.001$, and $p = 0.0005$, respectively). Furthermore, the absolute number of ramified capillaries was significantly higher in DM patients ($p = 0.004$), while the total capillary number was significantly higher in SSc patients ($p = 0.006$) (Table 4).

On the other hand, in patients with a disease duration longer than 1 year, the giant capillary and microhemorrhage scores were significantly higher in SSc than those in DM patients ($p = 0.03$ and $p = 0.06$, respectively) (Table 4). No further statistically significant difference was observed between SSc patients and patients with or without anti-Jo-1 positivity.

Our cohort of DM patients (anti-Jo-1 positive and negative) did not show any other ENA autoantibody positivity. During follow-up, malignancies were not observed in DM and SSc patients.

Discussion

This study analyzed NVC changes in patients with DM during a 3-year follow-up, also looking for differences in NVC findings between DM and SSc patients matched for age and disease duration.

By considering the small cohort of patients enrolled, no statistically significant variation of the score of main capillary parameters was observed during the follow-up in the whole patient population with DM. However, it is interesting to note that the percentage of patients showing ramified capillaries (abnormally shaped capillaries due to angiogenesis) increased during the 3-year follow-up.

Of note, this is the first report evaluating the morphological changes of the capillaries in anti-Jo-1-positive patients over time. Looking for differences between DM patients with or

Table 2 Means ± standard deviations of nailfold videocapillaroscopic (NVC) parameters at baseline in DM/PM patients split by anti-Jo-1 positivity

NVC parameters	Jo-1 pos	Jo-1 neg	*p*
Giant capillaries (score)	0.92 ± 0.79	1.00 ± 0.71	0.77
Microhemorrhages (score)	0.92 ± 0.67	0.54 ± 0.52	0.15
Dilated capillaries (score)	2.42 ± 0.67	2.23 ± 0.73	0.51
Capillary number (score)	1.33 ± 0.89	1.62 ± 0.65	0.44
Capillary abnormal shapes/ramifications (score)	1.58 ± 0.90	1.92 ± 1.12	0.31
Capillary disorganization (score)	1.50 ± 0.80	1.77 ± 0.83	0.46
Absolute number of capillaries	6.25 ± 2.05	5.31 ± 1.97	0.16
Number of abnormal shapes/ramifications	1.83 ± 1.03	2.00 ± 1.08	0.60
Number of normal capillaries	1.50 ± 2.32	1.77 ± 2.17	0.67

Table 3 Comparison of nailfold videocapillaroscopic (NVC) parameters at baseline in whole DM/PM and SSc patients. Means ± standard deviations are reported

NVC parameters	DM/PM	SSc	*p*
Giant capillaries (score)	1.00 ± 0.72	1.42 ± 0.58	0.04
Microhemorrhages (score)	0.67 ± 0.56	1.00 ± 0.66	0.05
Dilated capillaries (score)	2.33 ± 0.70	2.08 ± 0.58	0.15
Capillary number (score)	1.54 ± 0.72	1.12 ± 0.85	0.05
Capillary abnormal shapes/ramifications (score)	1.79 ± 1.02	0.79 ± 1.02	0.002
Capillary disorganization (score)	1.67 ± 0.82	0.83 ± 1.01	0.004
Absolute number of capillaries	5.62 ± 1.95	6.83 ± 2.18	0.05
Number of abnormal shapes/ramifications	1.92 ± 1.06	0.88 ± 1.08	0.002
Number of normal capillaries	1.58 ± 2.22	2.08 ± 1.79	0.16

without anti-Jo-1 antibodies, no statistically significant difference of the score of the main capillary parameters was observed at baseline, while a statistically significant decrease of capillary ramifications was detected during follow-up when compared with the anti-Jo-1-negative patients. To date, in the literature, there are no data concerning the morphological changes of the capillaries in anti-Jo-1 antibody-positive patients (ASS). Anti-Jo-1 antibodies were found to be positive in a higher proportion of patients (46%) than previous studies (up to 39% of DM patients) [24]. However, our cohort of DM patients was enrolled when they performed the first NVC: this might have contributed to select a specific cohort of patients, hence the mild discrepancy with the literature.

Out of 24 patients with DM (79%), 19 showed a "scleroderma-like pattern." From an accurate review in the field of NVC and DM in the last 30 years, the "scleroderma-like pattern" was reported between 27 and 57% of patients [25–27].

In our study, the comparison between DM and SSc at baseline demonstrated a particularly higher prevalence of giant capillaries and microhemorrhages in the latter and higher frequency of ramified capillaries (angiogenesis) and loss of capillaries in the former. Similarly, Manfredi et al. observed a higher prevalence of giant capillaries in early SSc, along with a more pronounced severity of capillary loss in advanced SSc, as well as a higher frequency of ramified capillaries in DM patients [18].

Interestingly, a relevant angiogenesis is a distinctive NVC feature in patients with DM and it seems to represent a vascular recovery reaction from microvascular damage [10–12].

At baseline, an early severe microangiopathy often characterizes DM, with appearance of some major capillaroscopic alterations (capillary loss, ramified capillaries); these abnormalities are conversely found only in the advanced stage ("late" pattern) of SSc microangiopathy [7].

In our work, we have not analyzed the progression of microvascular damage in SSc, because it is an already known process. Nailfold microvascular impairment is an early feature of SSc and its progression through different patterns of capillary damage ("early," "active," "late") is evaluable and quantifiable by NVC [7]. The SSc microangiopathy is a dynamic and sequential process, evolving from early dilation of capillaries (giant capillaries) to capillary loss, and finally, to reactive angiogenesis (which leads to abnormally shaped/ramified capillaries), with the disappearance of the giant capillaries [22,

Table 4 Comparison of nailfold videocapillaroscopic (NVC) parameters at baseline in patients split by disease duration. Means ± standard deviations are reported

NVC parameters	Disease duration					
	DM/PM < 1 year	SSc < 1 year	*p*	DM/PM > 1 year	SSc > 1 year	*p*
Giant capillaries (score)	1.08 ± 0.76	1.33 ± 0.49	0.39	0.83 ± 0.72	1.50 ± 0.67	0.03
Microhemorrhages (score)	0.85 ± 0.69	0.92 ± 0.67	0.78	0.58 ± 0.51	1.08 ± 0.67	0.06
Dilated capillaries (score)	2.38 ± 0.65	1.83 ± 0.58	0.03	2.25 ± 0.75	2.33 ± 0.49	0.90
Capillary number (score)	1.54 ± 0.78	0.75 ± 0.62	0.009	1.42 ± 0.79	1.50 ± 0.90	0.82
Capillary abnormal shapes/ramifications (score)	2.00 ± 1.00	0.50 ± 0.80	0.001	1.50 ± 1.00	1.08 ± 1.16	0.37
Capillary disorganization (score)	1.69 ± 0.75	0.33 ± 0.65	0.0005	1.58 ± 0.90	1.33 ± 1.07	0.59
Absolute number of capillaries	5.54 ± 2.07	7.83 ± 1.40	0.006	6.00 ± 2.04	5.83 ± 2.41	0.55
Number of abnormal shapes/ramifications	2.15 ± 0.99	0.67 ± 1.15	0.004	1.67 ± 1.07	1.08 ± 1.00	0.15
Number of normal capillaries	1.62 ± 2.26	2.92 ± 1.78	0.04	1.67 ± 2.23	1.25 ± 1.42	0.83

23, 25–28]. To date, several studies demonstrated also the diagnostic and prognostic roles of NVC in SSc [29–31].

On the contrary, the data from our cohort of patients, with a mean disease duration at first NVC of 4 years, seem to demonstrate that DM-related microangiopathy may be characterized by more stable microvascular changes over time. However, over time, De Angelis et al. observed a rapid change in capillary morphology and architecture in DM patients under treatment when compared with patients with SSc [32]. Different disease duration, treatments, and subsets of enrolled patients might explain the discrepancy between the two studies.

By considering the variety of symptoms and treatment background, this study did not evidence any association between nailfold capillary findings and either clinical involvement or effects of immunosuppressive treatments. However, a previous study reported a progressive improvement of nailfold microangiopathy following intravenous cyclophosphamide therapy during a 6-month follow-up but in a single DM patient with a half-year disease duration at baseline [33]. Our retrospective evaluation of DM patients with longer disease duration from baseline (> 4 years) did not offer the possibility to explore more successfully this issue. On the other hand, in SSc patients, several treatments induce over the years significant changes in capillaroscopic scores, as well as in absolute capillary number [34–37].

We are aware that our study presents some limitations. This is a retrospective study including a small number of patients; a second limitation is represented by the long and variable disease duration at the first visit and different treatment backgrounds that might interfere with the microvascular damage and the results of the study. Another limitation of the study is that DM activity was not assessed due to the retrospective nature of the study. Furthermore, for the same reason, the detection of other anti-synthetase antibodies besides anti-Jo1 was not performed.

Therefore, longitudinal studies by NVC are needed to better evaluate the progression of microangiopathy and effects of treatments in DM, and the rheumatologists should include NVC investigation in DM patient's routine check-up [38].

In conclusion, with the limit of a small cohort of patient, this pilot study demonstrates, for the first time, over long-term, that the capillaroscopic manifestations of the DM persist in contrast to the progressive changes described in SSc patients, as well as a higher number of abnormally shaped capillaries (ramifications) are observed in DM versus SSc patients with a disease duration < 1 year. The anti-Jo-1 positivity does not seem to modify the DM NVC pattern.

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Compliance with ethical standards

Disclosures None.

Ethical standards This retrospective study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, and was evaluated from the local IRB.

References

1. Plotz PH, Rider LG, Targoff IN, Raben N, O'Hanlon TP, Miller FW (1995) Myositis: immunologic contributions to understanding cause, pathogenesis, and therapy. Ann Intern Med 122:715–724
2. Dalakas MC (2015) Inflammatory muscle diseases. N Engl J Med 372:1734–1747
3. Lundberg IE, Tjärnlund A, Bottai M, Werth VP, Pilkington C, Visser M, Alfredsson L, Amato AA, Barohn RJ, Liang MH, Singh JA, Aggarwal R, Arnardottir S, Chinoy H, Cooper RG, Dankó K, Dimachkie MM, Feldman BM, Torre IG, Gordon P, Hayashi T, Katz JD, Kohsaka H, Lachenbruch PA, Lang BA, Li Y, Oddis CV, Olesinska M, Reed AM, Rutkowska-Sak L, Sanner H, Selva-O'Callaghan A, Song YW, Vencovsky J, Ytterberg SR, Miller FW, Rider LG, International Myositis Classification Criteria Project consortium, The Euromyositis register and The Juvenile Dermatomyositis Cohort Biomarker Study and Repository (JDRG) (UK and Ireland) (2017) 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. Ann Rheum Dis 76:1955–1964
4. Ghirardello A, Bassi N, Palma L, Borella E, Domeneghetti M, Punzi L, Doria A (2013) Autoantibodies in polymyositis and dermatomyositis. Curr Rheumatol Rep 15:335
5. Mahler M, Fritzler MJ (2010) Epitope specificity and significance in systemic autoimmune diseases. Ann N Y Acad Sci 1183:267–287
6. Cutolo M, Sulli A, Secchi ME, Olivieri M, Pizzorni C (2007) The contribution of capillaroscopy to the differential diagnosis of connective autoimmune diseases. Best Pract Res Clin Rheumatol 21:1093–1108
7. Cutolo M, Sulli A, Pizzorni C, Accardo S (2000) Nailfold videocapillaroscopy assessment of microvascular damage in systemic sclerosis. J Rheumatol 27:155–160
8. Cutolo M, Melsens K, Herrick AL, Foeldvari I, Deschepper E, De Keyser F, EULAR Study Group on Microcirculation in Rheumatic Diseases et al (2018) Reliability of simple capillaroscopic definitions in describing capillary morphology in rheumatic diseases. Rheumatology (Oxford) 57:757–759
9. Smith V, Beeckman S, Herrick AL, Decuman S, Deschepper E, De Keyser F, EULAR study group on microcirculation et al (2016) An EULAR study group pilot study on reliability of simple capillaroscopic definitions to describe capillary morphology in rheumatic diseases. Rheumatology (Oxford) 55:883–890
10. Selva-O'Callaghan A, Fonollosa-Pla V, Trallero-Araguás E, Martínez-Gómez X, Simeon-Aznar CP, Labrador-Horrillo M, Vilardell-Tarrés M (2010) Nailfold capillary microscopy in adults with inflammatory myopathy. Semin Arthritis Rheum 39:398–404
11. Mugii N, Hasegawa M, Matsushita T, Hamaguchi Y, Horie S, Yahata T et al (2011) Association between nail-fold capillary findings and disease activity in dermatomyositis. Rheumatology (Oxford) 250:1091–1098
12. 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
13. Smith V, Pizzorni C, de Keyser F, Decuman S, Van Praet JT, Deschepper E, Sulli A et al (2010) Reliability of the qualitative and semiquantitative nailfold videocapillaroscopy assessment in a systemic sclerosis cohort: a two-centre study. Ann Rheum Dis 69: 1092–1096
14. Dalakas MC, Hohlfeld R (2003) Polymyositis and dermatomyositis. Lancet 362:971–982
15. Huber A, Feldman BM (2013) An update on inflammatory myositis in children. Curr Opin Rheumatol 25:630–635
16. Feldman BM, Rider LG, Reed AM, Pachman LM (2008) Juvenile dermatomyositis and other idiopathic inflammatory myopathies of childhood. Lancet 371:2201–2212
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 (Oxford) 49:1699–1705
18. Manfredi A, Sebastiani M, Campomori F, Pipitone N, Giuggioli D, Colaci M, Praino E, Ferri C (2016) Nailfold videocapillaroscopy alterations in dermatomyositis and systemic sclerosis: toward identification of a specific pattern. J Rheumatol 43:1575–1580
19. Van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A et al (2013) 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 72: 1747–1755
20. Cutolo M, Sulli A, Smith V (2013) How to perform and interpret capillaroscopy. Best Pract Res Clin Rheumatol 27:237–248
21. De Angelis R (2010) The most important capillaroscopic parameters in normal and pathological conditions. In: Cutolo M (ed) Atlas of capillaroscopy in rheumatic diseases, vol I. Elsevier, Milan, pp 61–69
22. Cutolo M, Sulli A, Smith V (2010) Assessing microvascular changes in systemic sclerosis diagnosis and management. Nat Rev Rheumatol 6:578–587
23. Sulli A, Secchi ME, Pizzorni C, Cutolo M (2008) Scoring the nailfold microvascular changes during the capillaroscopic analysis in systemic sclerosis patients. Ann Rheum Dis 67:885–887
24. Dobloug C, Garen T, Bitter H, Stjärne J, Stenseth G, Grøvle L, Sem M, Gran JT, Molberg Ø (2015) Prevalence and clinical characteristics of adult polymyositis and dermatomyositis; data from a large and unselected Norwegian cohort. Ann Rheum Dis 74:1551–1556
25. Bergman R, Sharony L, Schapira D, Nahir MA, Balbir-Gurman A (2003) The handheld dermatoscope as a nail-fold capillaroscopic instrument. Arch Dermatol 139:1027–1030
26. Mugii N, Hasegawa M, Hamaguchi Y, Tanaka C, Kaji K, Komura K, Ueda-Hayakawa I, Horie S, Ikuta M, Tachino K, Ogawa F, Sato S, Fujimoto M, Takehara K (2009) Reduced red blood cell velocity in nail-fold capillaries as a sensitive and specific indicator of microcirculation injury in systemic sclerosis. Rheumatology (Oxford) 48: 696–703
27. 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
28. Trombetta AC, Smith V, Pizzorni C, Meroni M, Paolino S, Cariti C, Ruaro B, Sulli A, Cutolo M (2016) Quantitative alterations of capillary diameter have a predictive value for development of the capillaroscopic systemic sclerosis pattern. J Rheumatol 43:599–606
29. Ingegnoli F, Ardoino I, Boracchi P, Cutolo M, EUSTAR co-authors (2013) Nailfold capillaroscopy in systemic sclerosis: data from the EULAR scleroderma trials and research (EUSTAR) database. Microvasc Res 89:122–128
30. Cutolo M, Herrick AL, Distler O, Becker MO, Beltran E, Carpentier P, CAP Study Investigators et al (2016) Nailfold videocapillaroscopic features and other clinical risk factors for digital ulcers in systemic sclerosis: a multicenter, prospective cohort study. Arthritis Rheumatol 68:2527–2539
31. Cutolo M, Sulli A, Secchi ME, Paolino S, Pizzorni C (2006) Nailfold capillaroscopy is useful for the diagnosis and follow-up of autoimmune rheumatic diseases. A future tool for the analysis of microvascular heart involvement? Rheumatology (Oxford) 45: iv43–iv46
32. 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
33. Riccieri V, Vasile M, Macri V, Sciarra I, Stefanantoni K, De Luca N et al (2010) Successful immunosuppressive treatment of dermatomyositis: a nailfold capillaroscopy survey. J Rheumatol 37:443–445
34. Cutolo M, Ruaro B, Pizzorni C, Ravera F, Smith V, Zampogna G, Paolino S, Seriolo B, Cimmino M, Sulli A (2014) Longterm treatment with endothelin receptor antagonist bosentan and iloprost improves fingertip blood perfusion in systemic sclerosis. J Rheumatol 41:881–886
35. Trombetta AC, Pizzorni C, Ruaro B, Paolino S, Sulli A, Smith V, Cutolo M (2016) Effects of longterm treatment with bosentan and iloprost on nailfold absolute capillary number, fingertip blood perfusion, and clinical status in systemic sclerosis. J Rheumatol 43: 2033–2041
36. Filaci G, Cutolo M, Scudeletti M, Castagneto C, Derchi L, Gianrossi R et al (1999) Cyclosporin A and iloprost treatment of systemic sclerosis: clinical results and interleukin-6 serum changes after 12 months of therapy. Rheumatology (Oxford) 38:992–996
37. Aschwanden M, Daikeler T, Jaeger KA, Thalhammer C, Gratwohl A, Matucci-Cerinic M, Tyndall A (2008) Rapid improvement of nailfold capillaroscopy after intense immunosuppression for systemic sclerosis and mixed connective tissue disease. Ann Rheum Dis 67:1057–1059
38. Burmester GR, Bijlsma JWJ, Cutolo M, McInnes IB (2017) Managing rheumatic and musculoskeletal diseases—past, present and future. Nat Rev Rheumatol 13:443–448