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ORIGINAL ARTICLE

Nailfold videocapillaroscopy alterations in dermatomyositis, antisynthetase syndrome, overlap myositis, and immune-mediated necrotizing myopathy

Caroline Soubrier[1] · Julie Seguier[1,2] · Marie-Pierre Di Costanzo[1] · Mikael Ebbo[1,2] · Emmanuelle Bernit[1] · Estelle Jean[1] · Véronique Veit[1] · Laure Swiader[1] · Emmanuelle Salort-Campana[3] · Shahram Attarian[2,3] · André Maues De Paula[3] · Gilles Kaplanski[2,4] · Jean-Marc Durand[1,2] · Jean-Robert Harlé[1,2] · Nicolas Schleinitz[1,2]

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Abstract

Introduction/objectives The aim of our study was to investigate possible differences in nailfold videocapillaroscopy (NVC) features between patients with dermatomyositis (DM), overlap myositis (OM), antisynthetase syndrome (ASS), and immune-mediated necrotizing myopathy (IMNM).

Methods We performed a cross-sectional monocentric study. All patients with inflammatory myopathies (IMs) over a 6-month period were analyzed by NVC for giant and ramified capillaries, tortuosities, capillary density, disorganization, and scleroderma pattern. Clinical, biological, and pathological characteristics were retrospectively recorded. Patients were classified as having DM, OM, ASS, or IMNM for comparison. Patients were also compared with a group of patients with systemic sclerosis (SSc).

Results NVC was analyzed in DM ($n = 17$), OM ($n = 8$), ASS ($n = 12$), and IMNM ($n = 6$). Vascular disorganization and avascular zones were observed only in DM (11.8%) and OM (62.5%). The percentage of patients with giant capillaries was higher in OM ($n = 4/8$) than in DM ($n = 3/17$) and absent in ASS and IMNM. Frequency of ramified capillaries, tortuosities, hemorrhages, or thrombosis was not different between subgroups. A scleroderma pattern was only observed in OM patients.

Conclusion In this limited series of patients, we observed that DM and OM NVC abnormalities are different from ASS and IMNM. We could not determine NVC specific patterns associated with myositis-specific antibody subtypes of DM because of the small number of patients.

Key Points

- *Nailfold videocapillaroscopy abnormalities are different in subgroups of inflammatory myopathies.*
- *Giant capillaries, disorganization, and major capillary loss are observed in overlap myositis and dermatomyositis but not in antisynthetase syndrome (ASS) or immune-mediated necrotizing myopathy.*
- *Nailfold videocapillaroscopy abnormalities in overlap myositis (with the exclusion of ASS) are close to systemic sclerosis.*

Keywords Antisynthetase syndrome · Dermatomyositis · Immune-mediated necrotizing myopathy · Inflammatory myopathies · Nailfold capillaroscopy · Overlap myositis

✉ Caroline Soubrier
caroline.soubrier@ap-hm.fr

[1] Department of Internal Medicine AP-HM, Hopital Timone, 264 Rue Saint Pierre, 13385 Marseille cedex, France

[2] Aix-Marseille University, Marseille, France

[3] Referral Center for Neuromuscular Diseases and ALS AP-HM, Marseille, France

[4] Department of Internal Medicine AP-HM, Hopital Conception, Marseille, France

Introduction

Nailfold videocapillaroscopy (NVC) is a non-invasive and inexpensive imaging technique to study the capillary network. To date, capillary changes in NVC have been shown to correlate well with disease activity in systemic sclerosis (SSc) [1–6] and to be useful to evaluate the prognosis in Raynaud phenomenon in several studies [7–9]. NVC allows the direct observation of the capillary network and its alterations, and has been also studied in patients with inflammatory myopathies

(IMs), systemic lupus erythematosus, and Sjogren syndrome [10–12]. Dermatomyositis (DM) is typically associated with muscle microangiopathy and previous studies have reported NVC changes similar to SSc, defined as the scleroderma pattern. In a recent literature review in inflammatory myositis, it was concluded that NVC could help for both diagnosis between DM and polymyositis, and monitoring disease activity [13]. Studies have used variable criteria to define NVC changes and most of these studies are based on the Bohan and Peter IMs classification. This classification does not distinguish between more recent individualization of IMs subgroups.

The aim of our study was to investigate possible differences in NVC features between IMs patients from four different subgroups: DM, overlap myositis (OM), antisynthetase syndrome (ASS), and immune-mediated necrotizing myopathy (IMNM).

Materials and methods

Patients

We performed a monocentric cross-sectional study. From November 2016 to May 2017, we included all patients presenting in our universitary internal medicine or neurology departments with a diagnosis of IMs defined by (1) typical histological findings on muscle biopsy and/or (2) presence of myositis specific autoantibodies (MSAs) and/or (3) symmetrical proximal muscle weakness with increased serum muscle enzymes and magnetic resonance imaging (MRI) suggestive of inflammatory myopathy (at least two of these three criteria). Patients with IBM, congenital myopathy, cancer-associated myositis, and amyopathic DM were excluded. Clinical (muscle weakness, myalgia, dysphagia, Raynaud's syndrome, skin changes evocative of DM, or sclerodactyly/skin sclerosis and arthritis), biological (CPK, ANA titer, myositis-specific or myositis-associated antibodies (MSA or MAA)), pathological (muscle biopsy), and imaging (muscle MRI and chest CT for interstitial lung disease (ILD)) findings were recorded at the time of NVC evaluation. All patients were tested for antinuclear antibodies (ANA) by immunofluorescence, considered positive if > 1/160, and for nuclear soluble antigens. All patients were tested for MSAs by immunoblot (Euroimmun, Germany). Muscle biopsy was analyzed systematically by HES staining and immunohistochemistry for HLA class I, C5b9 and CD31 expression. Muscle vasculopathy was defined on pathological examination as evident capillaritis or vasculitis, and/or presence of C5b9 deposits on vascular wall or CD31 staining showing capillary density loss. Patients were classified into four groups according to recent IMs classification as having DM, OM, ASS, or IMNM [14–16]. Active disease was defined by increased CPK or clinical worsening or increased treatment. A group of patients with systemic sclerosis, without myositis, defined by the ACR/EULAR criteria was analyzed for comparison of NVC findings [1].

The study was performed in accordance with the ethical standards of the Helsinki Declaration. According to the French law (no. 2004–806, August 9, 2004), and because the data were collected retrospectively and patient management was not modified, this study did not require a specific research ethics committee approval.

Nailfold videocapillaroscopy

NVC was performed on a videocapillaroscope (CapXview-HD) with × 100 magnification. All fingers except the thumbs were examined. NVC was considered interpretable if capillaries were visible on at least 2 fingers. Data were validated by two investigators. In case of disagreement, results were discussed by the two investigators to reach a consensus. For each finger, a reference point was placed in the center of the nailfold. Capillary abnormalities were counted on 2 measures by finger at either side at 1 mm of the reference point. In accordance with the definitions of Maricq and Cutolo, we defined a giant capillaries as a capillary with a homogeneously enlarged loop and a diameter ≥ 50 μm, a ramified capillary as a branching or bushy interconnected capillary originating from a single capillary, and a tortuosity as a capillary with a single or multiple crossovers [2, 8–10, 12, 17]. Capillary density was determined by counting capillary sum score of all fingers. Capillary loss was scored as 0 = normal density (≥ 7 capillaries/mm), 1 = low density (4–6 capillaries/mm), and 2 = capillary rarefaction (≤ 3 capillaries/mm). An avascular area was defined by intercapillary distance > 500 μm. We defined the percentage of ramified capillaries, tortuosities, and giant capillaries by counting the number of each on either side at 1 mm of the reference point on all fingers, divided by the capillaries sum score. The percentage was defined similarly. Presence of thrombosis, hemorrhage (presence of one or more dark red mass characterized by hemosiderin deposits), and disorganization (loss of capillaries parallelism) was studied on the whole of each finger and evaluated by a semi-quantitative score: 0 = absence of abnormality, 1 = one anomaly in all fingers, 2 ≥ two anomalies of all fingers. Presence of a scleroderma pattern was defined according to Cutolo as early, active, or late [2].

Statistical analysis

Data were expressed as median or mean ± SD. Categorical variables were analyzed by chi-square test or Fisher's exact test as appropriate. Differences between mean were determined by the Kruskal-Wallis or Mann-Whitney *U* test as appropriate. Statistical analysis was performed on GraphPad Prism software. p values ≤ 0.05 were considered as statistically significant.

Results

Forty eight patients with IMs were included in the study and 43 had interpretable NVC; they were 14 males and 29 females, with mean age of 54.9 ± 17.4 years. Patients were classified as having either DM ($n = 17$), OM ($n = 8$), ASS ($n = 12$), or IMNM ($n = 6$) (Fig. 1). Patient's characteristics are shown in Table 1. Frequency of Raynaud's phenomenon ($p = 0.04$), skin involvement ($p = 0.005$), arthritis ($p = 0.007$), and ANA positivity ($p = 0.01$) was different between the four subgroups. Skin involvement considered here was typical signs of dermatomyositis. Of note, six patients from the OM group also presented with sclerodactyly. Thirty-three percent of patients had active disease at the time of NVC. Among 34 patients with SSc, 32 had interpretable NVC; they were 29 females and 3 males, with mean age of 64 ± 17 years. Median capillary density was 6.08 ± 1.5/mm in IMs versus 4.6 ± 0.9/mm in SSc.

NVC abnormalities observed in IMs are shown in Table 2. The percentage of patients with giant capillaries was different between subgroups ($p = 0.05$), more frequent in OM ($n = 4/8$, 50%) than in DM patients ($n = 3/17$, 17%), and absent in ASS ($n = 1/12$, 0.09%) or IMNM patients (0%). The frequency of giant-ramified capillaries was low and not different between DM (3.28 ± 6.75) and OM (3.19 ± 3.38) patients. In the few DM patients with giant capillaries, we observed no relation with MSA subtypes. The highest rate of giant capillaries was observed in one MDA5+ patient (84%) whereas two other MDA5+ patients did not present giant capillaries. MDA5+ patients presented all with muscle involvement. The other patients with giant capillaries were either SAE+ or TIF1γ+. None of the NXP2+ ($n = 2$), Mi2+ ($n = 2$), or MSA-negative DM patients presented with giant capillaries. Vascular disorganization was observed in OM (62.5%) and DM (11.8%), but not in ASS or IMNM patients ($p = 0.001$). Frequency of other abnormalities as ramified capillaries, tortuosities, hemorrhages, or thrombosis were not different between subgroups. Avascular zones were observed in DM (11.7%) and OM (62.5%) and never in ASS and IMNM patients. A scleroderma pattern was only observed in OM patients. In DM and OM, there was no difference for the frequency of giant capillaries ($p = 0.4$) or disorganization ($p = 0.7$) between patients in remission ($n = 4$) or with disease activity ($n = 14$).

Muscle biopsy was available for 78% of IMs patients. Only patients with informative biopsies were analyzed ($n = 27$). Muscle vasculopathy was absent in IMNM ($n = 6$), but observed in ASS (1/3), DM (9/12), and OM (3/6) patients. We compared DM and OM patients with or without vasculopathy on muscle biopsies and found no differences for the frequency of tortuosities ($p = 0.06$) and giant capillaries ($p = 0.3$).

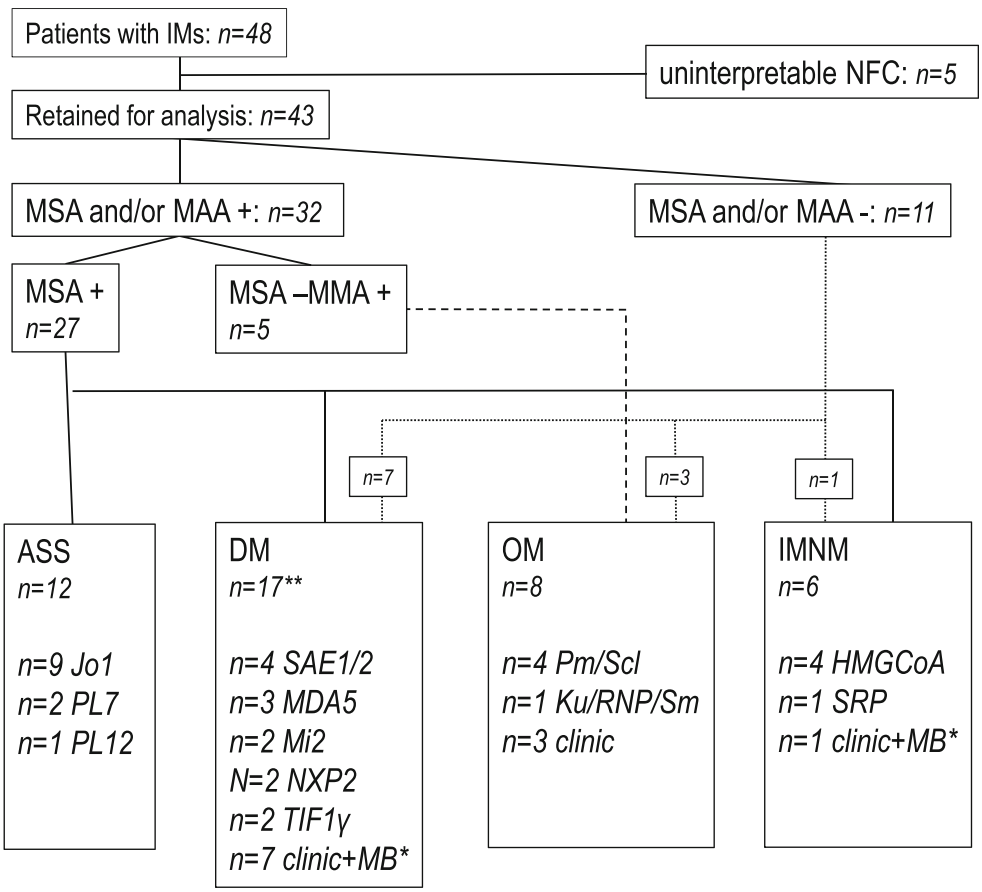

Fig. 1 Flowchart. MSA, myositis-specific autoantibodies; MMA, myositis-associated antibodies. *MB, muscle biopsy; **The sum of all autoantibodies is higher than the number of DM patients because some presented with two MSA positivity

Table 1 Patient characteristics

	All n=43	ASS n=12	DM n=17	OM n=8	IMNM n=6	pvalue
Age (mean±SD)	54.9 ±17.4	62.2 ±11.8	51.7 ±17.7	57.6±15.9	45.5±24.4	0.2
Female/Male	2.1	2	3.3	1.7	1	0.6
Disease duration months (mean±SD)	68±74.5	102±79	41.4 ±42.6	78.7±109.2	61±71	0.1
Muscle weakness n (%)	38 (88)	10 (83)	15 (88)	8 (100)	5 (83)	0.6
Myalgia n (%)	39 (91)	11 (92)	16 (94)	7 (88)	5 (83)	0.8
Dysphagia n (%)	21 (49)	5 (42)	7 (41)	6 (75)	3 (50)	0.4
Raynaud's n (%)	17 (40)	6 (50)	3 (18)	6 (75)	2 (33)	0.04
Skin * n (%)	26 (60)	6 (50)	15 (88)	5 (63)	0	0.005
Sclerodactyly n (%)	6 (14)	0	0	6 (75)	0	
Arthritis n (%)	21 (49)	10 (83)	8 (47)	3 (38)	0	0.007
ILD** n (%)	19 (44)	9 (75)	6 (35)	3 (38)	1 (17)	0.06
MSAs n (%)	27 (63)	12 (100)	10 (59)	0	5 (83)	
Type of MSA (n)		Jo1n=9 PL7=2 PL12=1	MDA5=3 SAE=4 NXP2=2 Mi2=2 TIF1γ=2		HMGCoA=4 SRP=1	
Type of MMA (n)		SSa=7	SSa=1	Pm/scl=4 Ku/RNP =1	SSa=3	
ANA>1/160 n (%)	31 (72)	5 (41)	14 (82)	8 (100)	4 (66)	0.001
CPK***(U/L) (mean±SD)	4170 ±6746	2428 ±3320	3113 ±3213	2607 ±3199	10608 ±13675	0.3
Muscle biopsy n (%)	32 (78)	7 (58)	13 (81)	6 (86)	6 (100)	

Typical signs of dermatomyositis. * ILD: Inflammatory lung disease. *** CPK levels at diagnosis.

SSc patients were classified into three groups given Cutolo's early, active or late states [2]. Avascular zones were observed in 43.7% of all SSc patients, and 92.8% of the patients with late state. Disorganization (score of 2) was similar in OM (62.5%) and SSc (75%) patients but lower in DM (11.8%). Avascular zones were higher in SSc (92.8% of late state SSc) and OM (62.5%) compared with DM (11.8%) patients. Frequency of patients with giant capillaries, but not ramified capillaries, and the percentage of giant capillaries per patient were higher in active SSc than in DM and OM patients (Fig. 2). Capillary density appeared to be higher in DM than in OM and active or late SSc patients without reaching significant statistical difference. Disorganization and avascular zones were higher in SSc late state than in DM and OM patients (Fig. 3).

Discussion

We report here in a cross-sectional study of 43 patients that NVC abnormalities vary between the DM, OM, ASS, and IMNM subtypes of IMs [14–16]. Giant capillaries, disorganization, and major capillary loss are observed in OM and DM but not in ASS and IMNM patients. OM can be distinguished from DM by the presence of a scleroderma pattern, as defined by Cutolo's criteria [2]. OM NVC abnormalities are close to those observed in active SSc.

Our study results are limited by the small sample of IMs subgroups and the unblinded NVC analysis. Conclusions are also limited by the absence of NVC changes analysis during time.

Previous studies have analyzed and compared IMs based on the Bohan and Peter classification [18] with variable methodologies to evaluate NVC abnormalities [13]. Using the Bohan and Peter classification, these studies could have overestimated PM frequency and missed new classification subgroups of IMs, for which different pathophysiological mechanism have been suggested. For example the comparison of muscle pathological features between DM and ASS suggest a different microvascular involvement [16, 19–24].

Here we found no correlation between NVC abnormalities in IMs and clinical manifestations, except for a higher frequency of giant capillaries in patients with Raynaud's phenomenon ($p = 0.01$). None of the NVC changes correlated with disease duration before videocapillaroscopy analysis (data not shown).

Table 2 : NVC abnormalities in IMs patients

NVC	DM n=17	OM n=8	ASS n=12	IMNM n=6	pvalue
Ramified capillaries (mean%±SD)	21,22% ±14.4	18,67% ±19.3	20,22% ±18.1	13,13% ±6.3	0.8
Tortuosities (mean%±SD)	36% ±22.32	36.9%±19.75	41%±17.6	33.3%±14.2	0.8
Giant capillaries	17%	50%	0.09%	0%	0.05
%* for each patient and type of AutoAb	n=3 15% SAE1 64% TIF1γ 82% MDA5	n=4 40% Pm/Scl 84% Pm/Scl 12% ANA 29% ANA	n=1 1% Jo1/SSa	n=0	-
Disorganisation (score of 2)	11.8%	62.5%	0%	0%	0.001
Capillary loss (score of 2)	11.8%	25%	0%	0%	0.02
Capillary density (mean±SD)	6.10±1.87	4.66±1.29	6.68±0.92	6.7±0.54	0.2
Avascular zones	11.8%	62.5 %	0%	0%	0.001
Thrombosis	35.2%	37.5%	41.6%	0%	0.3
score 1 (n)	4	1	4	0	-
score 2 (n)	2	2	1	0	
Hemorrhage	29.4%	25%	33.3%	16.6%	0.8
score 1(n)	3	1	3	1	-
score 2 (n)	2	1	1	0	
Scleroderma pattern	0%	75%	0%	0%	0.0001
Early (n)	-	0	-	-	
Active (n)	-	50	-	-	
Late (n)	-	50	-	-	

AutoAb: autoantibody. * the percentage given is the percentage in each individual patient with the corresponding autoantibody type.

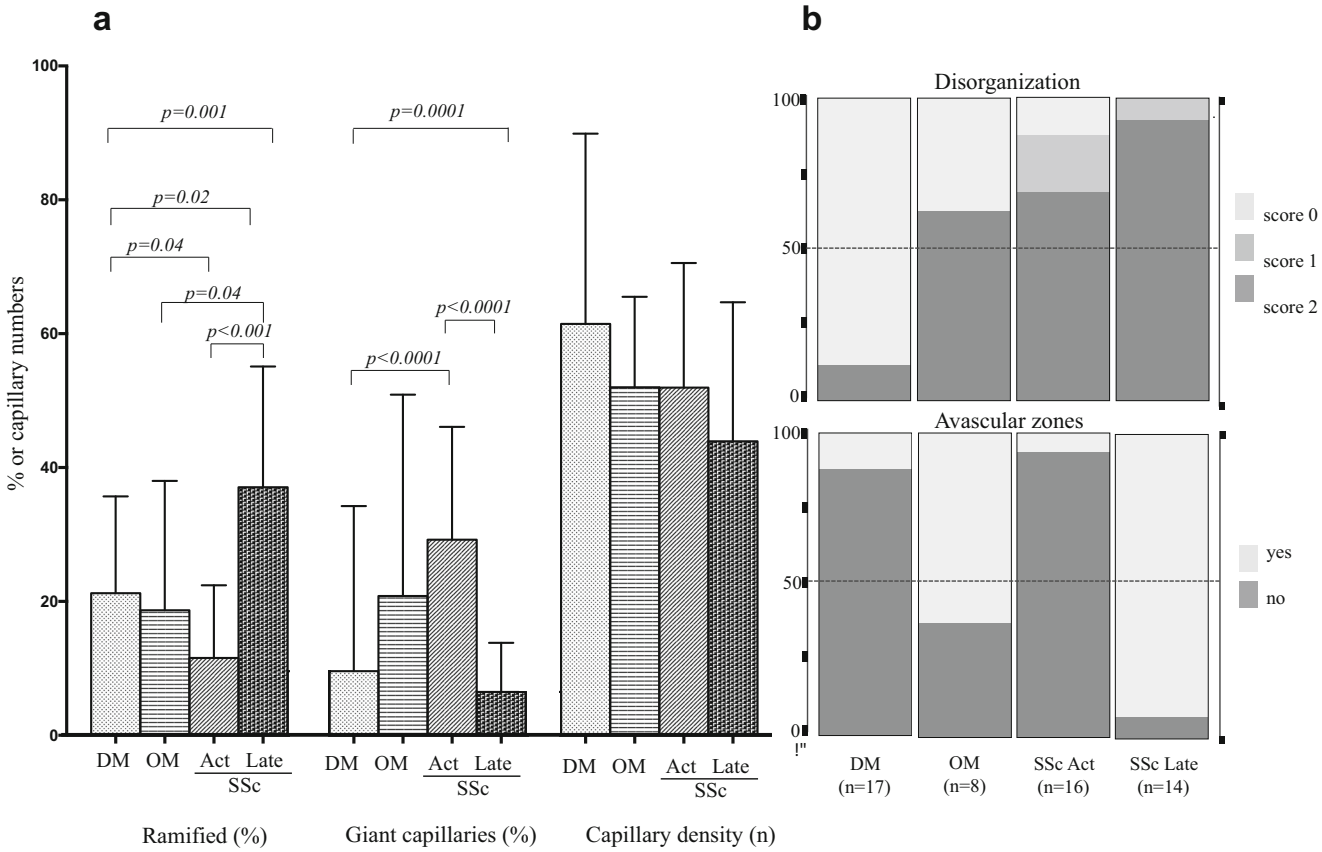

Fig. 2 **a**, **b** NVC abnormalities: comparison between OM, DM, and SSc patients. Act, active; n, numbers

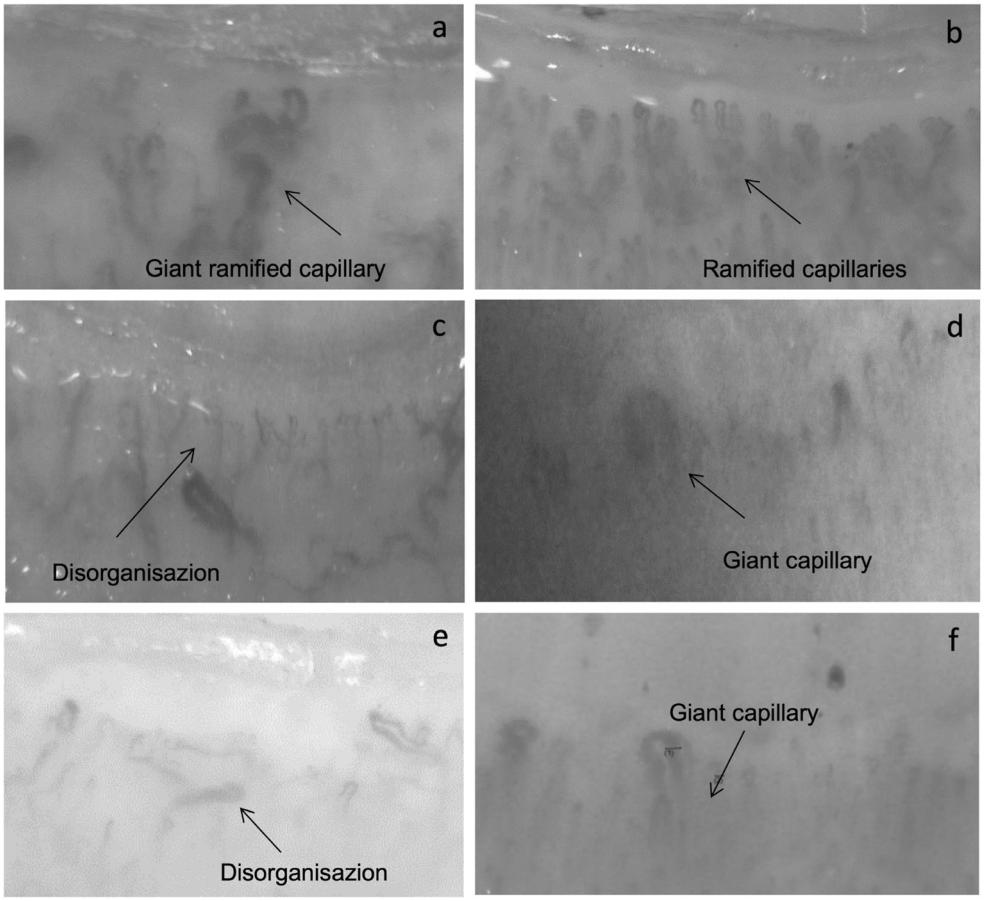

Fig. 3 NVC images in DM, OM, and SSc. DM (**a**, **b**). OM (**c**, **d**). SSc late state (**e**) and active state (**f**)

Here, only patients with OM and in a lesser extend patients with DM presented giant capillaries (respectively 50% and 17%), capillary disorganization (respectively 62.5% and 8%), or capillary loss (≤ 3 capillaries/mm) (respectively 25% and 11.8%). These findings are consistent with those of Kuboet al. who recently showed that MDA5+ and TIF1γ+ patients present more frequently giant capillaries than ASS patients [25]. The presence of a scleroderma pattern, either active or late state, was only observed in OM patients. Thus, when evaluating a patient with IMs, the presence of either giant capillaries, disorganization, or capillary loss will suggest the diagnosis of OM and possibly DM. The diagnosis of OM will be more probable if a scleroderma pattern, or a marked decrease of capillary density, is observed. Accordingly, most patients of the OM group presented with sclerodactyly or skin sclerosis changes. Only one of the two patients with OM and without skin sclerosis presented with a scleroderma pattern.

ASS patients can be individualized by clinical, serological, and pathological specific changes regardless of skin involvement [16]. In our study, ASS patients were different from OM and DM patients by the absence of giant capillaries, disorganization, avascular zones, and capillary loss. However, the rate of ramified capillaries, tortuosities, thrombosis, hemorrhage, and the capillary density was similar with DM. Selva-O'Callaghanet al. observed more frequent microhemorrhage and capillary enlargement in DM than in PM patients, but reported no differences between patients with ASS ($n = 16$) or PM/Scl ($n = 6$) antibodies [26]. Very recently, Sebastiani et al. reported that 62% of 190 patients with ASS presented NVC abnormalities, with an SSc-like pattern in 35% of patients [27]. Discrepancies between studies could be related to variation in the NVC analysis retrospective methodologies and a limited number of patients, with a longer disease duration in our study. The limited number of patient in each MSA subgroup did not allow to identify specific NVC abnormalities [25].

IMNM is a distinct subgroup of IMs characterized by the usual absence of extra-muscular manifestations and higher CPK levels. Muscular biopsy is characterized by muscle necrosis with absent or very few inflammatory cells. We report here for the first time that differences between IMNM patients and other IMs are mirrored by NVC, showing less ramified capillaries, tortuosities, thrombosis, and hemorrhage in IMNM than in DM, ASS, or OM patients.

DM has been reported to be associated with a scleroderma or a "scleroderma-like" pattern. Few studies have analyzed

separately OM and DM. In the study of Pavlov-Dulanovic et al., a scleroderma pattern was noted in 46% of patients with an overlap syndrome (all with SSc signs), less frequently than in DM patients (76%) [28]. However, the classification criterion used for IMs subtypes was not provided. From the review of Bertolazzi et al., studies in adult DM reported a scleroderma pattern varying from 63 to 89% of patients [13]. These results cannot easily be compared with ours for mainly two reasons. First, they are based on the Bohan and Peter classification. Second, the methodology used for NVC abnormality characterization was variable [18, 13]. Here, DM was not associated with a scleroderma pattern, contrary to OM. For this reason, we aimed to compare both OM and DM with SSc patients. We used for this comparison the same methodology as that of Manfredi et al. who reported that (1) SSc shows a particularly higher prevalence of giant capillaries and capillary loss; (2) in DM, ramified capillaries are slightly more frequent; and (3) giant-ramified capillaries were almost exclusively found in DM [29]. According to our study, giant capillaries were more frequent in SSc active state than in OM and DM. Disorganization and avascular zones were higher in OM and SSc and lower in DM. A scleroderma pattern is frequently observed in OM but not in DM patients. We conclude that OM NVC changes are close to SSc changes, and this reflects close clinical presentation with frequent sclerodactyly or skin sclerosis in this group of IM. A lower disease duration in DM patients could have influenced some of our observations, because previous studies reported that giant capillaries and capillary loss are observed before 6 month, and ramified capillaries later in DM [30–32]. DM patients with giant capillaries in this study had a disease duration of respectively12, 60, and 72 months before NVC analysis. No correlation between vascular muscle lesions and NVC findings in DM and OM patients were observed in this study, but this analysis was limited by the few numbers of patients analyzed.

We report here NVC abnormalities in DM, OM, ASS, and IMNM. Only patients with OM had NVC changes close to SSc patients. NVC, a non-invasive technique, can help to distinguish subgroups of patients with IMs. Further evaluations are needed on larger groups of patients, according to new pathophysiological classifications and MSA specificities, at different times of the disease.

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Compliance with ethical standards

The study was performed in accordance with the ethical standards of the Helsinki Declaration. According to the French law (no. 2004–806, August 9, 2004), and because the data were collected retrospectively and patient management was not modified, this study did not require a specific research ethics committee approval.

Disclosures Nones.

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