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Nailfold capillaroscopy and autoimmune connective tissue diseases in patients from a Portuguese nailfold capillaroscopy clinic

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Abstract

Raynaud's phenomenon (RP) is frequent in autoimmune connective tissue diseases (AICTD) and its approach includes nailfold capillaroscopy (NFC), as it is a non-invasive technique that permits direct visualization of the microcirculation. The aim of this study is to analyze and establish clinical correlations between NFC findings and particular aspects of autoimmune disorders. This is a retrospective study. Clinical data from patients attending our NFC clinic were reviewed. Inclusion criteria included AICTD previous diagnosis, which included systemic sclerosis (SSc), mixed connective tissue disease (MCTD), systemic lupus erythematosus (SLE), Sjögren syndrome, inflammatory idiopathic myopathies (IIM), rheumatoid arthritis, undifferentiated connective tissue disease and antiphospholipid syndrome (APS). Videocap® version 3.0 biomicroscope was used. NFC score was determined. For statistics, SPSS software was utilized. 384 patients were included; most of them were women, with mean age of 47 years. RP was present in 91% of the patients, with greater prevalence in SSc and MCTD. Scleroderma pattern was the most prevalent NFC pattern, mainly in SSc, MCTD and IIM. Mean capillary density was reduced in IIM, SSc and MCTD. NFC score was worse in SSc, IIM and MCTD. In patients with AICTD, RP is related to microvascular damage and worse NFC score. NFC scleroderma pattern correlates with SSc classification criteria score. In MCTD, scleroderma pattern relates to myositis. SLE and APS reveal significant hemorrhages, but not related to APS antibodies. This study highlights the possible role of NFC as biomarker of AICTD, particularly in SSc and IIM.

Keywords Raynaud's phenomenon · Nailfold capillaroscopy · Autoimmune disease · Biomarkers

Introduction

Raynaud's phenomenon (RP) is a frequent vasomotor phenomenon, occurring discoloration of extremities due to vasospasm provoked by cold or stress—biphasic RP; in some situations, there's a third phase, of hyperemia, due to reperfusion, which can be painful, and lasts a few seconds—three-phase RP. It is a common manifestation in autoimmune diseases (AICTD), with a prevalence as high as 19% [1]. Nailfold capillaroscopy (NFC) is as non-invasive, safe, simple and low-cost technique used in the evaluation of patients with RP. As it permits a direct visualization of the microcirculation, morphologic abnormalities can be easily detected.

NFC is usually performed with a videocapillaroscope with magnifications lens (up to ×100, ×200 and ×600), which enables detailed observations of the distal capillary row. A normal field of observations usually measures 1 mm². Normal capillaries have the shape of hairpin loops, parallel to the axis of the finger, with normal range of 7–12/mm² [2]. Qualitative assessment establishes the general pattern, allowing the distinction between primary and secondary RP, and scleroderma or non-scleroderma pattern, according to Cutolo et al. [3]. Three scleroderma patterns have been described: early, active and late. Early pattern presents few giant capillaries, few capillary microhemorrhages, normal density and absence of ramified capillaries; active pattern presents frequent giant capillaries and hemorrhages, moderate loss of capillaries and absent ramified capillaries; late pattern presents severe loss of capillaries, extensive avascular areas, intensive vascular plexus distortion and ramified capillaries [4]. Semi-quantitative assessment is obtained by measuring particular characteristics of individual capillaries and its general counting—number of capillaries per field,

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presence of dilated or giant capillaries, presence of hemorrhages, dimension of capillary limb or abnormally shaped capillaries (tortuosities, meandering, crossing, bifurcations or ramified branches, the latter representing "neoangiogenesis") [2]. NFC score rates the capillaroscopic abnormalities from 0 to 3, according to variations in density, dimension, morphology or hemorrhages [5]. Score zero defines no changes in NFC; score one (minor) defines mild changes (normal density, 10% longer capillaries, 50% of morphological changes, absence of hemorrhages); score two (major) defines major changes (normal or decreased density, 10% of elongated capillaries, 50% of morphological changes, presence of hemorrhages); score three (severe) defines severe changes (decreased density, 10% elongated capillaries, 75% morphological changes, presence of hemorrhages).

In AICTD, RP can be the earliest clinical manifestation, providing an opportunity to identify patients in an early stage of the disease and then implement an early treatment. NFC can also act as a predictor of RP severity in digital ulcerations, using Capillaroscopic Skin Ulcer Risk (CSURI) in Systemic Sclerosis (SSc), validated in 2012 [6].

The aim of this study is to compare the experience of our clinic to the findings already described for each AICTD. Secondary objectives include establishment of clinical correlations between particular NFC findings and phenotypical aspects of each of these diseases. As the majority of AICTD are rare disorders, disclosing information from different regions can contribute to a better understanding of microcirculation variations in distinct populations. To our knowledge, this is the most in-depth study in a Portuguese population.

Methods

A retrospective study was performed. Clinical data from patients attending the NFC clinic of an autoimmune diseases unit from 2011 through 2017 were obtained and then anonymized. Patients were referred to capillaroscopy clinic from several different hospitals and private medical practice. Requests included clinical aspects to justify NFC evaluation like RP+, associated or not (RP−) with an autoimmune connective tissue disease (AICTD), ischemic lesions, isolated positive autoantibody results or other systemic diseases with vascular involvement.

Inclusion criteria included previous diagnosis of connective tissue AICTD or antiphospholipid syndrome, based on validated international criteria (systemic sclerosis (SSc)—2013 ACR/EULAR SSc criteria; systemic lupus erythematosus (SLE)—1997 ACR criteria; mixed connective tissue disease (MCTD)—Alarcón-Segovia diagnostic criteria; rheumatoid arthritis (RA)—2010 ACR/EULAR Criteria; Sjögren Syndrome (SSj)—2016 ACR/EULAR criteria for primary SSj; antiphospholipid syndrome (APS)—2006 International Classification Criteria; Undifferentiated Connective Tissue Disease (UCTD)—classification criteria proposed by Mosca et al. in 1999; dermatomyositis and polymyositis—2017 EULAR/ACR Classification Criteria for Idiopathic Inflammatory Myopathies) [7–15]. Exclusion criteria included patients with other AICTD, including vasculitis, unfulfillment of diagnostic criteria, undiagnosed situations or missing data impossible to retrieve in patient's electronic file.

Analyzing variables comprised demographics (gender, age at the examination), presence/absence of RP, relevant clinical aspects, immunologic results, risk factors for RP non-related to AICTD (tobacco use, hormone therapy, finger microtrauma caused by professional occupation or hobbies), ongoing treatment and NFC result.

All patients stood in a 22 °C acclimatized waiting room before the exam, for at least 15 min, to avoid RP attacks. All NFCs were performed with a Videocap® biomicroscope version 3.0, magnification 200×, using sweet almond oil to smooth and improve visualization of the skin. NFC was performed on eight fingers, four fingers from each hand, excluding the thumbs (due to opponency's frequent trauma and thicker skin), capturing at least four images per finger. Results were validated by two different physicians attending the NFC clinic. Qualitative assessment criteria followed Cutolo et al. classification, dividing patterns as scleroderma and no scleroderma [16, 17]. Minor morphological abnormalities included tortuosities, crisscrossing and dilated loops; major abnormalities included giant, branched (neoangiogenesis) and twisting (meandering) capillaries. As for quantitative assessment, capillaries with distal loop $\geq 30\ \mu m$ were considered dilated; if mean diameter was $\geq 50\ \mu m$, capillaries were considered giant capillaries [16]. Elongated capillaries were considered if loops were longer than 300 μm [18]. Density was obtained calculating the mean capillary number in the distal row by mm^2. Normal density is considered normal between 7 and 12 capillaries/mm^2.

Descriptive statistical analysis used means and standard deviation (SD) for clinical and demographics characteristics, as well as frequencies and percentages for qualitative variables. Chi-square test with Yates's correction, Fisher exact test, independent T test not assuming equal variances and one-way ANOVA were used for correlation and variance analysis, with p value < 0.05. SPSS® software was used.

Results

About 1148 NCF were performed, but 764 results were excluded for lacking major relevant data, as immunologic profile, for example.

A total of 384 NCF were included in this study (Table 1), most of them in women (91%), with a mean age of 47 (± 17) years. Some patients accomplished diagnostic criteria for more than one disease, as secondary APS in SLE, accounting for both of them. The most frequent AICTD diagnosed at the moment of the exam was SSc (36%), followed by UCTD (16%) and SLE (15%). RP was present in approximately 91% of patients, with greater prevalence in SSc (100%) and MCTD (97%). The presence of RP was strongly related to an abnormal NFC result ($p < 0,001$) and a worst NFC score ($p < 0.001$).

Qualitative analysis disclosed scleroderma pattern in the majority of patients (54%), although non-scleroderma pattern was more frequent in SLE (79%), SSj (67%), RA (91%), UCTD (81%) and APS (67%). Quantitative assessment of NFC revealed decreased density of capillaries and more avascular areas in SSc, IIM and MCTD. Although dilated loops were frequently found in all AICTD, except for SLE, giant capillaries were predominant in SSc (94%), IIM (79%)

Table 1 Main characteristics of the study population, according to each previously diagnosed autoimmune disease

Variable	SSc	MCTD	SLE	SSj	IIM	RA	UCTD	APS	Total
n (%)	137 (35.68)	38 (9.90)	58 (15.10)	15 (3.91)	24 (6.25)	22 (5.73)	62 (16.15)	45 (11.72)	384 (100.00)
Mean age (years)	53.81 ± 15.80	39.95 ± 19.85	41.93 ± 14.42	49.53 ± 16.24	37.17 ± 22.01	53.32 ± 12.45	47.15 ± 15.26	42.69 ± 13.72	47.38 ± 16.98
Female (%)	93.43	86.84	93.10	100.00	91.67	90.91	87.10	91.11	91.15
RP + (%)	100.00	97.37	87.93	93.33	75.00	90.91	87.10	82.22	91.67
NFC pattern (%)									
Sclero-derma	94.16	68.42	12.07	33.33	83.33	4.55	14.52	28.89	53.65
Non-sclero-derma	5.84	28.95	79.31	66.67	8.33	90.91	80.65	66.67	39.06
Normal	0.00	2.63	8.62	0.00	8.33	4.55	4.84	4.44	3.65
NFC parameters									
Density									
Mean density (n/mm^2)	5.88	6.47	8.86	8.80	6.67	9.23	9.26	9.11	7.60
Avascular areas (%)	37.23	21.05	0.00	0.00	41.67	0.00	1.61	2.22	18.23
Dimensions									
Enlarged capillaries (%)	92.70	84.21	29.00	73.33	83.33	68.18	61.29	73.33	76.56
Giant capillaries (%)	94.16	68.42	12.07	33.33	79.17	13.64	16.67	28.89	53.65
Elongated (%)	5.11	5.26	12.07	26.67	8.33	18.18	24.19	13.33	10.94
Morphology									
Meandering (%)	9.49	15.79	39.66	26.67	8.33	31.81	16.67	17.78	32.03
Crossing (%)	56.20	73.68	93.10	100.00	50.00	100.00	95.16	91.11	76.30
Tortuosities (%)	85.40	97.28	98.28	100.00	75.00	100.00	93.55	100.00	91.67
Hemor-rhages (%)	87.59	63.16	51.72	46.67	83.33	59.09	41.93	64.44	67.19
Neoangio-genesis (%)	46.72	39.47	8.62	0.00	58.33	4.55	11.29	20.00	29.17
NFC score (mean)	2.41	1.97	1.59	1.67	2.34	1.82	1.45	1.64	1.96

NFC nailfold capillaroscopy, *SSc* systemic sclerosis, *MCTD* mixed connective tissue disease, *SLE* systemic lupus erythematosus, *IIM* inflammatory idiopathic myositis, *RA* rheumatoid arthritis, *UCTD* undifferentiated connective tissue disease, *APS* antiphospholipid syndrome, *RP+* Raynaud's phenomenon present

and MCTD (68%). Elongated capillaries were scarce, but more frequent in SSj (27%), UCTD (24%) and RA (18%). Minor abnormalities were frequent in every AICTD, with particular emphasis on tortuosities (92%). Hemorrhages and neoangiogenesis were present mainly in SSc, IIM and MCTD.

Considering each AICTD separately, all the selected SSc patients fulfilled the ACR/EULAR classification criteria, with a mean of 14.24 points/patient (≥ 9 points makes the diagnosis of SSc). RP [$n = 137$ (100.0%)], abnormal NFC findings [$n = 126$ (92.0%)] and sclerodactyly [$n = 108$ (78.8%)] were the most frequent criteria; anti-centromere antibody was the most prevalent autoantibody. Active scleroderma pattern was the most frequent result on qualitative assessment of NFC results.

Patients revealing a scleroderma pattern on NFC presented a higher score on 2013 ACR/EULAR classification, which means either more severe manifestations of the disease or greater disease activity. Greater severity of scleroderma pattern, as active or late pattern, strongly related to a higher classification criteria score ($p < 0.001$). No relation was found between each SSc autoantibody and a particular scleroderma pattern ($p > 0.05$), except for anti-RNA polymerase III antibody and active scleroderma pattern ($p = 0.04$).

In MCTD, hand edema was present in 25 (66%) patients, synovitis in 28 (74%), myositis in (26%), RP in 36 (95%) and acrosclerosis in 26 (68%). The main NFC pattern was scleroderma—early in 10 patients, active in 12 and late in 4. There was no relation between clinical aspects related to classification criteria of MCTD and the NFC pattern, except for myositis and scleroderma pattern (p value $= 0.04$).

In SLE patients, arthritis was the most frequent clinical criteria (50%, $n = 29$), followed by malar rash (47%, $n = 27$), photosensitivity (43%, $n = 25$) and renal disorder (33%, $n = 19$). As for immunologic markers, anti-nuclear antibody was positive in 98% ($n = 57$), anti-double-stranded DNA in 57% ($n = 33$), anti-cardiolipin antibody in 17% ($n = 10$), anti-beta-2 glycoprotein in 17% ($n = 10$) and lupus anticoagulant in 31% ($n = 18$) patients. The main NFC pattern was non-scleroderma (79%) and the most frequent capillaroscopy findings were minor abnormalities, like crossing (93%) and tortuosities (98%), and hemorrhages (52%). About 33% ($n = 19$) of patients were positive for Anti-SSA antibody (A-SSA+). The relation between antiphospholipid antibodies and hemorrhages was negative ($p = 0.64$). No relation was found between A-SSA+ and the presence of hemorrhages ($p = 0.85$); between RP+ and dilated loops ($p = 0.13$) or RP+ and hemorrhages ($p = 0.92$).

RP was present in 93% of SSj patients and non-scleroderma pattern was the most frequent NFC result. Crossing and tortuosity were observed in all patients. Most patients presented primary SSj (73%), while 27% had secondary SSj (associated with MCTD, overlap to primary biliary cirrhosis and Achenbach syndrome). Secondary SSj related to scleroderma pattern ($p < 0.001$) and hemorrhages ($p = 0.03$) in NFC. Scleroderma pattern was not related to RP ($p = 0.649$).

IIM included patients with polymyositis ($n = 3$), dermatomyositis ($n = 17$) and anti-synthetase syndrome ($n = 4$). All patients with DM and ASSD presented scleroderma pattern; all PM had non-scleroderma pattern. RP and scleroderma pattern were present in 75% and 83% patients, respectively. No significative association was established between scleroderma pattern and RP ($p = 0.116$), Gottron papules ($p = 0.855$) or anti-Jo1 antibodies ($p = 0.186$). Mean NFC score was 2,34.

RA patients revealed RP in 86%; non-scleroderma pattern was present in 82%. Crossing and tortuosities were also present in all patients. Seropositivity for RA (rheumatoid factor or anti-citrullinated C peptide) was not related to scleroderma NFC pattern ($p = 0.515$). Neoangiogenesis was not visualized in RA patients.

Raynaud's phenomenon was present in 87% UCTD patients and non-scleroderma pattern in 81%. No relation was found between RP and scleroderma pattern ($p = 0.414$).

In APS, RP was present in 82% of patients and non-scleroderma pattern prevailed on NFC results. Primary APS accounted for 36% of patients; secondary APS was mostly associated with SLE and MCTD. No correlation was found between primary or secondary APS and scleroderma pattern ($p = 0.959$) or presence of hemorrhages ($p = 0.887$). Hemorrhages were not associated with ongoing anticoagulation treatment ($p = 0.07$). However, the presence of microbleeding distributed symmetrically, the "comb-like" hemorrhages, was strongly associated with the diagnosis of APS ($p < 0.001$). Each antibody was tested for its association with hemorrhages: no relation was found with lupic anticoagulant ($p = 0.102$) or anti-β2-glycoprotein1 ($p = 0.084$); anti-cardiolipin antibody was associated with absence of hemorrhage ($p = 0.048$).

Tobacco use was present in 62 patients, mainly in SLE ($n = 23$) and SSc ($n = 15$) patients. No association was found between tobacco use and NFC Score ($p = 0.249$), or tobacco use and scleroderma pattern ($p = 0.757$). Analyzing specifically SSc patients, there was no association between tobacco use and worse NFC score ($p = 0.994$), scleroderma pattern ($p = 0.773$) or even worse scleroderma pattern ($p = 0.218$).

Discussion

This is a small and heterogeneous population, as only patients presenting an already-known AICTD at the exam were included. Strict fulfillment of the above-mentioned diagnostic criteria also reduced the population cohort. Furthermore, many patients were referred to NFC after a single

medical consultation, so that diagnostic workup was still ongoing. As NFC is part of the RP approach, there is a bias on the frequency found for RP in the included AICTD. So, the percentage of RP in our patients cannot be inferred as the relative frequency of RP in AICTD patients.

Women were more affected, as AICTD and RP are known to be more frequent on female gender [19]. This study confirms that autoimmune disorders clearly present NFC abnormalities and that RP is a frequent symptom, which, itself, relates to worse NFC score. Scleroderma pattern was the most frequent NFC pattern, but SSc and MCTD patients were also the most prevalent groups. NFC score was worse on SSc and IIM, as scleroderma pattern is also more frequent in these AICTD, as stated before. Findings as hemorrhages and neoangeogenesis were also more prevalent in SSc and MCTD, reflecting vascular instability of giant capillaries, which leads to spontaneous rupture, avascular areas and new ramified capillaries (neoangiogenesis).

In systemic sclerosis (SSc), RP is present in almost every patient, with prevalence higher than 95%, either in limited cutaneous SSc (lcSSc) or diffuse cutaneous SSc (dcSSc) [20]. NFC is particularly important in SSc, as giant capillaries account for classification criteria, scoring 2 points out of a minimum of nine [7]. The microvascular damage in SSc evolves by progressive dilation of the distal loop and decrease in its density, slow blood flow, hemorrhages and neoangiogenesis. We found that greater severity of NFC scleroderma pattern positively correlates with the number of SSc classification criteria—which, itself, already includes changes in NFC and vascular complications, as digital ulcers. NFC changes witness microvascular damage. Therefore, this result supports the assumption that NFC findings relate to systemic involvement and disease progression. SSc autoantibodies were only associated with active scleroderma pattern in anti-RNA polymerase III antibody.

In Mixed Connective Tissue Disease (MCTD), RP is also very frequent, with prevalence higher than 90%, although digital ischemia and ulceration are rare when compared with SSc [21]. RP is an important symptom in MCTD, often the only one present at the diagnosis, and accounts as classification criteria in Alarcon-Segovia, Sharp and Kasukawa criteria [22–24]. NFC usually reveals a scleroderma pattern, which has been associated with the development of internal organ damage [25]. In fact, MCTD patients mostly presented a scleroderma pattern, which in turn relates to myositis. To our knowledge, this is the first time this association is described and it clearly suggests microvascular damage in inflammatory idiopathic myositis, albeit the sample size.

Systemic lupus erythematosus (SLE) has a prevalence of RP of 18-40% and it may appear before or after the diagnosis [26, 27]. RP is associated with organ complications and positivity for anti-cardiolipin (IgG) antibody [28]. A recent systematic review concluded that SLE patients presented more

tortuous and abnormal capillaries, with more hemorrhages and higher NFC score than healthy controls [27]. It also related SLE disease activity with NFC abnormalities, but based on small sample cohorts. In this study, SLE NFC score particularly reaches level 2, probably due to the presence of hemorrhages. However, no relation was found between hemorrhages and APS autoantibodies. These hemorrhages could have been mistakenly interpreted as resulting from spontaneous rupture, instead of microtrauma. Nevertheless, all patients were carefully asked about their jobs, hobbies and even onychophagia, to more easily recognize traumatic hemorrhages. A possible explanation is that these patients present a great proportion of morphologic abnormalities, as crossing and tortuosities, and this capillary instability can more easily lead to spontaneous capillary rupture and consequent hemorrhages. SLE patients presented a predominance of cutaneous manifestations, which can be due to sensitivity of 1997 ACR diagnostic criteria. These criteria were chosen over the 2012 SLICC criteria, once great part of the patients was previously diagnosed using 1997 criteria [8].

RP is a common clinical sign in Sjögren's syndrome (SSj) and appears in up to one-third of patients, albeit digital ischemic complications are rare [29, 30]. NFC abnormalities range from non-specific findings, like crossing, to more specific ones, as hemorrhages, and even scleroderma-type changes, which are more frequent in patients with RP [31]. In our sample, secondary SSj positively relates to scleroderma patterns, but those patients had overlap syndromes, also presenting diseases as MCTD and PBC [32]. In these cases, one must relate the NFC results to primary or secondary diagnosis.

The frequency of RP in idiopathic inflammatory myopathies (IIM) is 20% in polymyositis (PM), 40% in dermatomyositis (DM) and 62% in anti-synthetase syndrome (ASSD) [33, 34]. NFC is usually more exuberant in DM. A study by Manfredi A et al. revealed that capillaroscopic findings (mainly capillary loss, giant, bushy and ramified capillaries) were clearly associated only to DM, while no significant difference was observed between PM and controls [35]. Recently, NFC abnormalities in ASSD were observed in up to 62% patients and scleroderma pattern was associated with positive anti-Jo1 autoantibody, but not to Raynaud's phenomenon [36]. In our IIM patients, results were in line with previous descriptions: all the DM and ASSD patients presented scleroderma pattern and all the PM's a non-scleroderma pattern.

RP is present in rheumatoid arthritis (RA) in 5–17%, depending on the series [37, 38]. Angiogenesis and tortuosity account for the most frequent NFC findings, according to a recent study including 430 RA patients [39]. RA patients presented mainly a non-scleroderma pattern, as predictable, and exuberant minor abnormalities, like crossing and tortuosities. In RA, microcirculation involvement can result from

inflammation, endothelial dysfunction or atherosclerosis [40, 41]. The fact that almost 91% of our patients revealed capillary abnormalities and dysfunction suggests that microcirculation in RA can also be involved and its pathology process has yet to be elucidated.

In undifferentiated connective tissue disease (UCTD), RP occurs in about half patients and was associated with esophageal dysmotility and anti-ribonucleoprotein antibodies [42, 43]. Patients presenting RP also present more NFC abnormalities, such as widened and irregular enlarged capillary loops. In this study, non-scleroderma pattern prevailed on UCTD patients, and no relation was found between RP and scleroderma pattern. However, the great proportion of patients with RP justifies a close follow-up and repeated NFC exams, to early detect any change that can disclose any disease evolving into a different AICTD.

RP has been described in association with APS in anecdotic reports and the prevalence of primary or secondary RP has not yet been established. Studies referring NFC in APS concluded that microhemorrhages appear to correlate to clinical manifestations, although it does not suffice for its diagnosis, due to relative low sensitivity and specificity [43]. A special pattern of microbleeding distributed symmetrically has been described in patients with APS—the "comb-like" hemorrhages [44, 45]. Analyzing all the patients from our population who presented comb-like hemorrhage, it strongly correlated with previous APS diagnosis. Again, this particular NFC finding can be a part of the APS clinical condition and NFC should be performed in all APS patients.

Tobacco is known for its association with microvascular damage [46]. In our study, only a small proportion of the patients with AICTD smoked and evidence was not found between tobacco use and worse NFC outcomes.

Our study has some weaknesses and strengths. As mentioned above, the missing data greatly reduced our population cohort, to strictly respect the classification criteria. Besides, as patients were frequently referred to our NFC clinic due to RP, there is a possible bias on its prevalence in the included AICTD. On the other hand, we carefully compared our findings to those already described and we believe we are sharing valuable information about microcirculation in AICTD, which are rare diseases. We describe, for the first time, an association between scleroderma pattern in MCTD and muscle involvement; our patients with RA and UCTD also revealed great NFC abnormalities, which justifies further research.

Conclusion

In conclusion, this small study emphasizes the importance of NFC as a possible biomarker on the approach of AICTD, as RP is a frequent symptom among them. As for SSc, the presented results suggest a correlation between NFC findings and systemic involvement, underlining the possible role of NFC to witness or even predict disease progression. In MCTD, a new correlation was found between scleroderma pattern and myositis. IIM, specially DM and ASSD, reveal profound microvascular damage, so that NFC should be inherent on regular clinical investigations. In RA, microvascular involvement has been disclosed and future research is needed to clarify its role in the disease development. UCTD patients should be carefully followed and monitored, as their disease can evolve, given the microcirculation involvement we have found. In APS, NFC can suggest but not establish the diagnosis, although it could be included in APS clinic approach. Larger studies are needed to obtain more statistically significant data.

Compliance with ethical standards

Conflict of interest Vera Bernardino, Ana Rodrigues, Ana Lladó and António Panarra declare that they do not have any conflict of interest.

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