Is Scleroderma Pattern Able to Address a Specific Diagnosis of Connective Tissue Diseases?

Serena Bonin[1,*], Giuseppe Stinco[2], Nicola di Meo[1], Laura Quaranta[1], Paraskevi Chatzikokkinou[1], Cinzia Buligan[2], Sara Trevisini[1] and Giusto Trevisan[1]

[1]*Department of Medical Sciences, Unit of Dermatology, University of Trieste, Trieste, Italy*

[2]*Department of Experimental and Clinical Medicine, Institute of Dermatology, University of Udine, Udine, Italy*

Abstract: *Introduction*: Nailfold videocapillaroscopy (NVC) is a non-invasive imaging technique widely used to investigate microvascular abnormalities in different connective tissue diseases (CTDs).

Methods: We conducted a retrospective study where we analysed 415 patients submitted to NVC. Patients with scleroderma-like pattern were selected to investigate if there are specific NCV changes, which discriminate among the different CTDs. Ninety-one patients met this requirement and had a diagnosis of CTD. For each patient the following abnormalities were observed: enlarged and giant capillaries, oedema, loss and rarefaction of capillaries, long loops and minor dystrophies.

Results: Multivariate analyses did not reveal any specific modification among the analysed co-variables for scleroderma (SS) and dermatomyositis (DM). For the others CTDs analysed in this study, logistic regression revealed that some of the capilloroscopic features could be indicative of specific diseases. Of note, the presence of megacapillaries with long loops in a scleroderma-like pattern seems to be highly indicative for a diagnosis of systemic lupus erythaematosus (SLE).

Conclusions: Our data showed that in CTDs with a scleroderma-like pattern, the NVC variables alone are not able to discriminate for a specific diagnosis of CTD. Nevertheless, there are some NVC features, which could strongly address the differential diagnosis toward a specific CTD.

Keywords: Nailfold videocapillaroscopy, connective tissues diseases, scleroderma-like pattern.

INTRODUCTION

Nailfoldvideocapillaroscopy (NVC) is a non-invasive imaging technique, which enables the analysis of microcirculation *in vivo*. This technique is widely used as a tool to investigate microcirculation in various connective tissue diseases (CTDs) such as systemic scleroderma (SS), dermatomyositis (DM), undifferentiated connective tissue disease (UCTD), overlap syndrome (OS) and systemic lupus erythaematosus (SLE) [1] and recently a novel approach has been proposed for quantitative analysis [2]. At the same time, NVC has been shown to be valuable in many other extra-rheumatic diseases [1, 3]. In normal conditions, the NVC microvascular pattern is characterized by a regular array of microvessels with large intra/interindividual variability. The presence of enlarged and giant capillaries (megacapillaries with a diameter >50 μm of both arteriolar and venular branches), haemorrhages, oedema, disorganization of the vascular array, ramified/bushy capillaries and loss of capillaries are the morphological aspects of the vascular damage observed by NVC [4, 5]. The peripheral microvascular damage involving more than 95% of patients affected by systemic sclerosis is an important diagnostic criterion and all the capillaroscopic changes are defined as “scleroderma pattern” [6]. The capillaroscopic aspects observed in other CTDs are generally reported with the term of “scleroderma-like pattern” [7]. NVC modification is not diagnostic alone for a specific CTD. To improve the diagnosis of this complex group of diseases, we conducted a retrospective study analysing the NVC parameters in patients affected by CTDs.

PATIENTS AND METHODS

Case histories of 415 patients addressing the Dermatology Unit of the University of Trieste from January 2008 to June 2011 to perform a NVC for a suspected CTD have been retrospectively analysed. We selected the medical records of patients whose complete data had been registered and made available. Consequently, patients who presented with a certain diagnosis of CTD, comprehending complete medical records (availability of videocapillaroscopic images, clinical conditions, physical examination and autoimmune serologic parameters), and a scleroderma-like pattern, according to Maricq *et al.* [8, 9] and Bergman *et al.* [10], on NVC were included in the study.

*Address correspondence to this author at the Department of Medical Sciences, Unit of Dermatology, Cattinara Hospital, Strada di Fiume 447, 34149 Trieste, Italy; Tel: +39 040 3996266; Fax: +39 040 3996247;
E-mail: sbonin@units.it

E-ISSN: 2310-9874/13 **© 2013 Synergy Publishers**

NVC capillaroscopy had been performed using a video capillaroscope (Videocap Microscope DS Medica, Monza, Italy). For visual investigation 200x magnification had been used. Images were collected and analysed using the VideoCap software (DS Medica, Monza, Italy). Morphologic evaluation of skin capillaries has been performed at the nailfold of 8 fingers, excluding thumbs, of both hands, following standard conditions [1].

For each patient the following abnormalities were recorded: enlarged and giant capillaries (semi-quantitatively divided into two groups: megacapillaries< 3 and equal or > 3), oedema, loss of capillaries (rarefaction), long loops (>400μm) and minor dystrophies, that include disorganization of the vascular array and ramified/bushy capillaries.

Statistical analysis was performed by means of the software Stata SE v. 12 (Stata Corporation, Texas, 2007). The Chi-square statistic and/or Fischer exact test were used to test the difference between nominal data tabulated in contingency tables. One-way analysis of variance and a multi-comparison test were used to assess differences in the patients' age among diagnostic groups. Multinomial logistic regression was performed in order to estimate the effect of the NVC patterns on the differential diagnosis of specific CTDs.

RESULTS

Of the overall 415 case histories we examined, 91 fulfilled the above-mentioned criteria. We excluded 324 patients: 170 did not present with any specific NVC pattern, 87 presented with a diagnosis of Raynaud's phenomenon (RP), 22 presented with a secondary RP, but not a scleroderma pattern, 24 were patients with SLE, without a sclerodermic-like pattern on NVC, 8 were DM without megacapillaries, 4 were OS without major dystrophies, 2 were affected by Sjögren syndrome, 2 patients had an Adamantiades-Behçet disease, and 4 patients presented with a sclerodermic-like pattern, but serological data were not available and diagnosis not certain.

Ninety-one patients with a diagnosis of CTD and a scleroderma pattern on NVC were evaluated in this study. Their median age was 64 years (25^{th} -75^{th}: 45-73), with a female/male ratio of 71/20. Of the 91 patients included in the study, 21 had a diagnosis of SS (median age 64 years, female/male ratio 16/5); 14 of DM (median age 63 years, female/male ratio 8/6); 9 of SLE (median age 61 years, female/male ratio 8/1); 20 of OS (median age 68.5 years, female/male ratio 17/3) and 27 of UCTD (median age 53 years, female/male ratio 22/5). There were no differences in the age of patients (p= 0.4) and gender distribution (p= 0.3) among the group defined by the diagnosis of CTDs. The frequencies of capillaroscopic changes detected in these patients are summarised in Table **1** and Figure **1**. The presence of minor dystrophies, of long loops>400 μm and capillary rarefaction resulted significantly different among the examined CTDs (p= 0.05, p=0.0001 and p= 0.02 respectively). In detail, the presence of minor dystrophies, such as ramified/bushy capillaries and disorganization of the vascular array were mostly present in DM (71%), but less frequent in patients with OS (20%) (p= 0.005 specifically). The presence of megacapillaries with long loops was characteristic of those cases of SLE, which presented with a scleroderma-like pattern on NVC (100%). Extensive loss of capillaries (avascular areas) in the nailfold were especially found in patients affected by SS (71%) and DM (64%) as compared to those affected by UCTD (26%) (p= 0.003 and p= 0.02, respectively). Neither the presence of oedema, nor the quantity of megacapillaries was distinctive for any CTDs (p= 0.5 and p= 0.3 respectively). However, considering separately the OS and the UCTD a significant difference was detected in the number of megacapillaries, showing that a higher number of megacapillaries (≥3) was mostly related to the OS compared to the UCTD (p= 0.04). There were no specific NVC changes to discriminate SS and DM from

Table 1: Summary Table of NVC Results: Variables are Divided Per Diagnosis of Connective Tissues Diseases

Diagnosis	Megacapillaries ≥3 (%)	Megacapillaries <3 (%)	Minor dystrophies (%)	Long loops (%)	Oedema (%)	Rarefaction (%)
SC	3 (14)	18 (86)	9 (42)	3 (14)	14 (67)	15 (71)
DM	2 (14)	12 (86)	10 (71)	4 (28)	11 (79)	9 (64)
SLE	1 (11)	8 (89)	5 (55)	9 (100)	5 (56)	3 (33)
OS	6 (30)	14 (70)	4 (20)	4 (20)	15 (75)	10 (50)
UCTD	2 (7)	25 (93)	12 (44)	10 (37)	15 (56)	7 (26)

the other CTDs (p= 0.3 and p= 0.06, respectively). Nevertheless, for DM the presence of minor dystrophies seems to be more closely related.

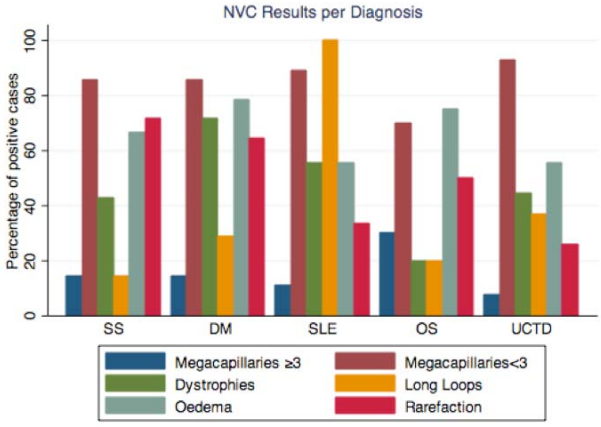

Figure 1: Nailfold capillarscopic variables per clinical diagnosis.

Regarding the examined cases of SLE with a sclerodermic pattern on NVC, the presence of megacapillaries with long loops resulted to be the most significant characteristic of this group of CTDs (confirmed by logistic regression). In OS group the detection of long loops and minor dystrophies seems to be an infrequent event as well as the presence of rarefaction areas in UCTD (Table **2**, Figure **1**).

Table 2: Results of the Logistic Regression Analysis. Only Significant Results and Variables are Reported

Diagnosis	p	Variables (p)
SS	0.2	none
DM	0.1	none
SLE	0.0000	Megacapillaries with long loops (0.000)
OS	0.06	Megacapillaries with long loops (0.06) Megacapillaries and dystrophies (0.03)
UCTD	0.04	Megacapillaries and rarefaction (0.006)

DISCUSSION

Nailfoldcapillaroscopy has been widely investigated in the evolution of rheumatic diseases, especially those related to connective tissues. Most studies have focused on primary and secondary RP and its evolution to more severe CTDs. Indeed, the early differential diagnosis between primary and secondary RP is the best advantage NVC may offer [11, 12]. In addition, interesting capillaroscopic changes have been observed in the CTDs: the term 'scleroderma pattern' includes, all together, the capillaroscopic changes typical of microvascular involvement in SS, but similar capillaroscopic aspects have also been found in other CTDs and are generally referred to as 'scleroderma-like pattern'. In the present study we focused on specific variables of the capillaroscopic analysis, associated with the sclerodermic pattern in order to investigate possible specific NCV changes, which could discriminate among the different CTDs characterized by scleroderma-like pattern. Multivariate analyses did not reveal any specific modification among the analysed co-variables for SS and DM, although in the latter the presence of minor dystrophies seems to be more characteristic. This feature was recorded in 71% of our patients with a clinical and serological diagnosis of DM and this is in agreement with Cortes *et al*. who reported the presence of budding and twisted enlarged capillaries in DM [13]. For the other CTDs analysed in this study the logistic regression revealed that some of the capilloroscopic variables could be highly indicative. Regarding SLE, the presence of megacapillaries with long loops seemed to be pathognomonic, since it was detected in 100% of the patients in this group. Therefore, this feature significantly discriminated SLE from the other CTDs examined in this study. However we recognize that those data are relevant only in a specific subgroup of SLE, which presents with a sclerodermic like pattern. Although subtle capillary changes such as mild disorganization can be detected in patients with SLE, a scleroderma-like pattern is rarely found [14]. In this study we have found for the first time that the presence of megacapillaries with long loops in a scleroderma-like pattern could be highly indicative for a diagnosis of SLE. At present we have no data on the meaning of this variable in terms of evolution of the disease; further analyses should be carried out to compare the clinical course of the SLE in patients with and without this particular capillary abnormality. Regarding OS and UCTD there is a strong connection with NCV and the specific CTD diagnosis. In this group of patients major abnormalities at the capillary level are expected to be found because this syndrome may present with an overlap of symptoms characteristic of SLE, DM and SS [12]. Our analysis, neighbouring only patients with a scleroderma–like pattern is focused on specific features of this pattern. Even though in OS the capillaroscopic pattern could be non-specific [4], here we found that, when a scleroderma-like pattern was individualized, the absence of long loops and minor dystrophies could represent a signature for this CTD. Undifferentiated connective tissue disease is referred to patients with a systemic disorder, which lacks specific characteristics

of any well define CTD [12]. It is well known that in UCTD the presence of capillary abnormalities may confer an increased risk for the development of a defined connective tissue disease [15]. In the present study we consider solely the UCTDs with a scleroderma-like pattern on the NVC and we found that these patients are mostly characterized by the absence of capillary rarefaction. However, further works are needed to determine precisely which capillaroscopic variable may predict the evolution of UCTD into another CTD.

Surely, possible limitations of our work are due to intra/inter-individual variability of NVC changes and their variation according to the disease chronicity. The recognition of different NVC morphological scleroderma-patterns (''early'', ''active'',''late'') and their correlation with specific CTDs could be enhanced in the future.

The conclusion is that the scleroderma pattern is often present in SS and DM, and that patients with other CTDs might occasionally exhibit this pattern. Our data showed that in CTDs with a scleroderma-like pattern the NVC variables are not able alone to diagnose a specific CTD, without a clinical diagnosis. However there are some features of NVC which could strongly address the differential diagnosis toward a specific CTD, such as in the case of long loops and SLE. Capillaroscopy, together with a clinical and serological data, seems to be therefore a useful tool for early selection of those patients who are potential candidates for developing connective spectrum disorders.

ACKNOWLEDGEMENTS

The authors are grateful to Dr Valentina Melita for the English revision of the manuscript.

CONFLICT OF INTEREST

None declared.

REFERENCES

[1] Gallucci F, Russo R, Buono R, Acampora R, Madrid E, Uomo G. Indications and results of videocapillaroscopy in clinical practice. Adv Med Sci 2008; 53: 149-57. http://dx.doi.org/10.2478/v10039-008-0038-4

[2] Goffredo M, Schmid M, Conforto S, Amorosi B, D'Alessio T, Palma C. Quantitative color analysis for capillaroscopy image segmentation. Med Biol Eng Comput 2012; 50: 567-74. http://dx.doi.org/10.1007/s11517-012-0907-7

[3] Stinco G, Lautieri S, Piccirillo F, Valent F, Patrone P. Response of cutaneous microcirculation to treatment with mometasone furoate in patients with psoriasis. Clin Exp Dermatol 2009; 34: 915-9. http://dx.doi.org/10.1111/j.1365-2230.2009.03298.x

[4] Cutolo M, Pizzorni C, Secchi ME, Sulli A. Capillaroscopy. Best Pract Res Clin Rheumatol 2008; 22: 1093-108. http://dx.doi.org/10.1016/j.berh.2008.09.001

[5] Cutolo M, Sulli A, Secchi ME, Paolino S, Pizzorni C. 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) 2006; 45 (Suppl 4): iv43-6.

[6] Bombardieri S, Medsger TA, Jr., Silman AJ, Valentini G. The assessment of the patient with systemic sclerosis. Introduction. Clin Exp Rheumatol 2003; 21: S2-4.

[7] Cutolo M, Sulli A, Secchi ME, Olivieri M, Pizzorni C. The contribution of capillaroscopy to the differential diagnosis of connective autoimmune diseases. Best Pract Res Clin Rheumatol 2007; 21: 1093-108. http://dx.doi.org/10.1016/j.berh.2007.10.001

[8] Carpentier PH, Maricq HR. Microvasculature in systemic sclerosis. Rheum Dis Clin North Am 1990; 16: 75-91.

[9] Maricq HR, LeRoy EC, D'Angelo WA, *et al*. Diagnostic potential of *in vivo* capillary microscopy in scleroderma and related disorders. Arthritis Rheum 1980; 23: 183-9. http://dx.doi.org/10.1002/art.1780230208

[10] Bergman R, Sharony L, Schapira D, Nahir MA, Balbir-Gurman A. The handheld dermatoscope as a nail-fold capillaroscopic instrument. Arch Dermatol 2003; 139: 1027-30. http://dx.doi.org/10.1001/archderm.139.8.1027

[11] Lambova SN, Muller-Ladner U. The role of capillaroscopy in differentiation of primary and secondary Raynaud's phenomenon in rheumatic diseases: a review of the literature and two case reports. Rheumatol Int 2009; 29: 1263-71. http://dx.doi.org/10.1007/s00296-009-1019-z

[12] Nagy Z, Czirjak L. Nailfold digital capillaroscopy in 447 patients with connective tissue disease and Raynaud's disease. J Eur Acad Dermatol Venereol 2004; 18: 62-8. http://dx.doi.org/10.1111/j.1468-3083.2004.00853.x

[13] Cortes S, Cutolo M. Capillarosecopic patterns in rheumatic diseases. Acta Reumatol Port 2007; 32: 29-36.

[14] Hasegawa M. Dermoscopy findings of nail fold capillaries in connective tissue diseases. J Dermatol 2011; 38: 66-70. http://dx.doi.org/10.1111/j.1346-8138.2010.01092.x

[15] Kabasakal Y, Elvins DM, Ring EF, McHugh NJ. Quantitative nailfold capillaroscopy findings in a population with connective tissue disease and in normal healthy controls. Ann Rheum Dis 1996; 55: 507-12. http://dx.doi.org/10.1136/ard.55.8.507

Received on 17-12-2013 Accepted on 10-01-2014 Published on 29-01-2014

DOI: http://dx.doi.org/10.12970/2310-9874.2013.01.02.2

© 2013 Bonin *et al*.; Licensee Synergy Publishers.
This is an open access article licensed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted, non-commercial use, distribution and reproduction in any medium, provided the work is properly cited.