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EDITORIAL

Nailfold capillaroscopy in rheumatology: ready for the daily use but with care in terminology

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The scleroderma pattern in systemic sclerosis

With the recent inclusion of nailfold capillaroscopy (NVC) in the 2013 ACR/EULAR classification criteria for systemic sclerosis (SSc), together with the assessed role in monitoring the progression of the disease and effects of treatments, its use and the need to learn the correct interpretation and representation in daily practice, as well as in research context by rheumatologists, is increasing worldwide [1, 2].

In rheumatology today, NVC is the mandatory tool for the evaluation of subjects affected by Raynaud's phenomenon (RP) because a "scleroderma pattern" has been validated and helps to differentiate primary from secondary RP associated with connective tissue diseases (CTDS), *in primis* SSc [2–5].

As a matter of fact, microvascular changes, characterised by progressive structural and functional damage of the microvessels, play a central role in the complex pathogenesis of autoimmune diseases and in particular in SSc [6, 7].

The first modern interpretation of the microvascular alterations in SSc was given by Maricq et al. in 1980, using the wide-field microscopy technique, describing it as a capillaroscopic pattern [8].

This classification was later adapted to the videocapillaroscopic technique in 2000 by Cutolo et al., introducing a new concept on the basis of the microvascular morphological characteristics associated with disease progression [9–12].

The microvascular lesions detected qualitatively by NVC in SSc patients follow three clearly distinct patterns that differ from the normal aspect and reflect various phases of capillary involvement with an evolutive trend from the "Early", to the "Active", until the "Late" [13–16].

The different SSc NVC patterns correlate with the disease duration and severity, as well as the associated clinical complications and autoantibody profile [17–19].

In addition, the NVC patterns have been found to change in patients with SSc with up to 4 years of combined therapy, in particular showing a progressive significant recovery in structure as well as function of microvasculature, linked to improved clinical outcomes, independent of disease severity [20–22].

Furthermore, reliability of the qualitative and semiquantitative NVC assessment in SSc cohorts between raters at different centres has been demonstrated [23]. Reliability of NVC assessment is essential for the use of this tool in multicentre SSc trials.

The quantitative analysis of the morphological changes observed at NVC today is widely validated and even automatic systems for the count of capillaries are available [24–27].

The scleroderma-like pattern in autoimmune connective tissues diseases

Other NVC patterns have been searched in other CTDs, and a NVC "scleroderma-like "pattern that consists of a cluster of alterations of the capillary distribution, shape, number, and dimension pattern (mixing together the aspects observed in detail in the three SSc NVC patterns) has been described in dermatomyositis (DM) and recently compared on the long-term follow-up to the SSc NVC pattern changes (DM) [28–30].

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Other studies described the association between microvessel array and inflammatory myositis (IIM), and often considering together DM and PM [31, 32].

Among the almost 80 papers reported in the literature concerning capillaroscopy and DM and evaluating different aspects and interactions, the most recent investigation published by Miossi et al. reported several correlations between morphological markers of the NVC "scleroderma-like" pattern and circulating angiogenetic factors (AF) in recent-onset DM [33].

The conclusion was that the increase of the serum AF angiogenin (ANG) in DM might represent a tool for the assessment of the role the angiogenesis process in DM which seems plausible with the very disturbed microvessel array observed in the "scleroderma-like" pattern.

The presence of capillaroscopic changes mixing the different NVC SSc pattern features (as described in the "scleroderma-like" pattern) was reported in another very recent investigation by Shenavandeh et al. in 33 DM patients (58.7%), and compared with the NVC patterns of 27 SSc patients (79.4%) as well as other CTDs, like mixed connective tissue disease (MCTD) and undifferentiated connective tissue disease (UCTD); however, possible overlaps were referred by the authors [34].

Of note, for the last two diseases (MCTD and UCTD), the number of patients analysed was not significant to draw any conclusion (3 and 2 patients, respectively).

The altered capillaroscopic findings when tested versus clinical aspects associated with CTDs, like the "Mechanic's Hands" (Gottron's papules), were found significantly correlated in 80.8% of CTD patients, including the concomitant presence of the RP.

Interestingly, in a previous study, the effect of treatment on capillaroscopic pattern in patients with DM showed that a rapid change of the NVC microvascular status during the time and treatment [35].

On the other hand, a recent multicentre investigation by Sebastiani et al. showed that NVC specific abnormalities are commonly observed in Antisynthetase Syndrome (AS), independently from the occurrence of RP [36].

Again, the presence of a NVC "scleroderma-like" pattern could allow the identification of a more defined AS subtype, possibly in the presence of inflammatory myopathy as a major clinical feature.

Interestingly, several studies analysed the NVC in systemic lupus erythematosus (SLE) [37].

Forty such studies were identified and displayed through a standardised language, more specifically the standard interpretation of capillaroscopic descriptions as consensed by the EULAR study group on microcirculation in rheumatic diseases (EULAR SG-MC see below).

When displaying the studies through a standardised representation language agreed by the EULAR SG-MC in rheumatic diseases, several NVC parameters were found to be significantly more prevalent in SLE patients when compared with healthy controls, such as tortuous capillaries, abnormal morphology and haemorrhages, whereas hairpin-shaped capillaries were found to be significantly less prevalent than in healthy persons.

The semi-quantitatively determined nailfold capillaroscopic score (NFC score) was also found higher in SLE patients. Some correlations between clinical parameters, like disease activity and NVC parameters (abnormal morphology, i.e. "meandering"), and NFC score were found in seven studies and in one study with haemorrhages. Frequent episodes of RP and gangrene were found significantly correlated with dilated capillaries. Conflicting results were found about other immune parameters.

On the other hand, "scleroderma-like" capillaroscopic changes can also be found in rheumatoid arthritis (RA) patients, with peripheral digital vasculitis, as recently summarised in a short article by Lambova et al. [38].

Interestingly, the authors conclude that these changes are not obligatory but possibly associated with an overlap syndrome. Further larger studies are required.

Very recently, several noninfectious vasculitides have been analysed by a systematic review by Bertolazzi et al. starting from the concept that vasculitis characterised by active involvement of vessels including capillaries might offer a large field of investigation for the use of NVC [39].

The vasculitides included Takayasu arteritis (TAO), giant cell arteritis, polyarteritis nodosa, Kawasaki disease, ANCA-associated vasculitis, microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatosis (GPA), crioglobulinemic vasculitis (MC), IgA vasculitis (IAV), Behçet disease (BD), Cogan's syndrome, lupus vasculitis, rheumatoid vasculitis and sarcoid vasculitis.

The authors did not explain in their methodologic section the definitions that had been used throughout the studies; hence, interpretability of the findings of this systematic review is not without sine cure. This is because same terminology may have different meaning by different authors.

Also, contrary to the systematic review on SLE (above), the authors of this manuscript did not use an upfront standard language (see below) to display the results of the manuscripts they had identified. This may be the reason that they found "a wide range of NVC changes" and inconclusive evidence for clinical impact of capillaroscopy.

We agree with the authors that future large-scale standardised studies are required to elucidate on the role of capillaroscopy in vasculitis.

The standardisation of the terminology in nailfold capillaroscopy

Since one of the major problems in analysing and reporting the morphological changes observed by NVC in

rheumatology is related to the need of a standardisation of the terminology, two consecutive recent studies reported on the reliability of simple capillaroscopic definitions in describing capillary morphology in rheumatic diseases [40, 41].

In these studies by the EULAR SG-MC in rheumatic diseases, a simple definition was proposed to describe the morphology of single capillaries as being normal or abnormal. A moderate reliability regarding these definitions was obtained between attendees of the sixth EULAR capillaroscopy course, held in 2014, and an excellent reliability after optimatisation of the definition, at the seventh EULAR capillaroscopy course held in 2016 in Genoa (Italy).

Attendees were rheumatologists with different levels of expertise in performing capillaroscopy (a large number of whom had no previous experience). The multicentre international study (37 countries) demonstrated that the reliability of the optimised simple capillaroscopic definition of normal and abnormal morphologies of capillaries is excellent, with a mean proportion of overall agreement of 91%, and a mean proportion of specific agreement for abnormal of 89% and for normal of 92%, even when used by rheumatologists with different levels of expertise in capillaroscopy.

This standardisation of evaluation of morphology of single capillaroscopic shapes has now been followed by a multicentre consensed "fast track algorithm" by the EULAR SG-MC in rheumatic diseases [42].

This latter study not only presented the EULAR consensed standard language to describe overall capillaroscopy and existing capillaroscopic manuscript in a standardised, uniform way (number of capillaries [density], dimension, abnormal shapes [morphology], presence/absence of haemorrhages) but also described for the first time an algorithm to discern scleroderma patterns from non-scleroderma patterns in a simple way and hence allowed novices as well as expert capillaroscopists to have a simple algorithm to discern scleroderma patterns form non-scleroderma patterns, as well as the golden standard.

This implies that the key role of capillaroscopy, more specifically to discern a scleroderma pattern from a non-scleroderma with the aim to distinguish a primary RP from a secondary RP due to SSc, is now made easy for a capillaroscopist of any level.

A more recent review article by Karbalaie et al. was addressed to identify different factors affecting the reliability and validity of the assessment in NVC [43].

The investigation concluded that minimisation of the impact of some artefacts should be obtained just by considering dedicated protocols before the examination and by using training and guidelines, also with the intention to reduce mistakes in the measurement and analysis of NVC images.

Following the EULAR and ACR-dedicated courses and study groups on teaching basic, applied and practical capillaroscopy to the rheumatologists, a recent investigation on consensus for the format and content of the report in capillaroscopy in Rheumatology by the PANLAR Capillaroscopy Study Group has been published by Bertolazzi et al. [44].

A Delphi questionnaire was sent to a South American panel including 25 rheumatological experts in capillaroscopy, asking them to rate their level of agreement or disagreement with each statement. The exercise consisted of three online rounds and a face-to-face (live meeting) held at the PANLAR 2018 congress in Buenos Aires, Argentina. At the end of the exercise, 46 recommendations were formulated as further effort for the standardization of technique of execution and interpretation of NVC.

The results of the report confirmed the conclusions of the earliest studies previously mentioned [40, 41], namely that the capillaroscopy examination and its use in a homogeneous form can help in the correct interpretation of findings in daily practice.

Against this background, the recent international consensus of worldwide experts to find a standard format to report capillaroscopic characteristics (density, dimension, abnormal shapes, haemorrhages) and to create an algorithm that makes interpretation of scleroderma pattern or not has been more than welcome and will be a working tool at an international level [42].

Conclusions

Finally, in order to further implement the already existing EULAR living courses and dedicated textbook started at the beginning of 2000s, the EULAR School of Rheumatology (ESoR) has now implemented preparations for an online course on Capillaroscopy and Microcirculation in Rheumatic Musculoskeletal Diseases (RMD).

In conclusion, nailfold capillaroscopy is an important, reliable and useful tool in rheumatology: it is ready for daily use but with care in interpretation and terminology.

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