Emerging nailfold capillaroscopic patterns in COVID-19: from acute patients to survivors

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INTRODUCTION

The SARS-CoV-2 infection causing the Coronavirus disease-19 (COVID-19) is characterized by a broad range of clinical manifestations, implicating microvascular damage with endothelial dysfunction and different organ involvement (1). SARS-CoV-2 directly binds to the angiotensin-converting enzyme 2 (ACE-2) receptor, which is expressed on endothelial cells, and not only on them, by using the S_1 subunit of viral receptor-binding domain. The S_2 subunit allows the virus to adhere to and enter the endothelium, disrupting the integrity of the endothelial barrier and starting a cascade of pro-inflammatory and pro-thrombotic events (2, 3). A recent autopsy-based study demonstrated the presence of endothelitis of small and medium-sized vessels in more than 90% of patients and (micro) thrombotic events in 30-60% of them, depending on the organ involved (4).

Nailfold videocapillaroscopy (NVC) is the best non-invasive tool to evaluate capillary morphology in a large spectrum of rheumatic and non-rheumatic diseases, including COVID-19, recognizing specific or non-specific patterns of autoimmune diseases (5).

THE GROWING EVIDENCE: ACUTE COVID-19 PATIENTS VERSUS COVID-19 SURVIVORS NON-SPECIFIC CAPILLAROSCOPIC PATTERNS

A first Italian NVC study evaluating 82 adult COVID-19 patients, of whom 28 during their hospitalization and 54 after recovery and hospital discharge, reported several abnormalities classifiable as non-specific pattern in 65% of them (6). In particular, COVID-19 patients during the acute infection, compared to recovered patients, showed a higher prevalence of micro-hemorrhages ($p=0.027$), microthrombi ($p<0.016$), and pericapillary edema ($p<0.001$). Conversely, COVID-19 recovered patients, evaluated an average of 31 days after healing, showed a higher frequency of dilated capillaries per linear millimeter ($p < 0.001$), loss of capillaries < 9 mm ($p = 0.002$), and of course, empty dermal papillae ($p = 0.006$). The authors suggested that the active COVID-19 patients versus recovered ones seemed characterized by a different distribution of non-specific NVC abnormalities which generally remind acute and post-acute microvascular damage.

The loss of capillaries consequent to COVID-19 disease was further confirmed by

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another detailed investigation, which evaluated the microvascular status in 61 adult COVID-19 survivors, investigated after an average of 103 days after healing and with past different disease severity, in comparison with age and sex-matched primary Raynaud's phenomenon (PRP, n = 31) patients and control subjects (CNT, n=30) (7). Interestingly, once again, the mean nailfold capillary number per linear millimeter was significantly lower in COVID-19 survivors when compared with PRP patients and CNT (8.2±1.15 in severe disease survivors, 8.4±0.75 in moderate/mild disease survivors, 8.7±0.68 in PRP subjects, 9.3±0.53 in CNT - univariate and multivariate analysis $p<0.001$). On the contrary, COVID-19 survivors showed significantly less isolated microhemorrhages than PRP patients and CNT (univariate and multivariate analysis, $p=0.005$ and $p=0.012$, respectively). Additionally, the study evaluated also possible effects of concomitant therapies (7). COVID-19 specific therapies showed an encouraging trend on saving capillary loss and are matter of further investigations. The study confirmed that in the post COVID-19 patients the most important non-specific pattern is characterized by a significant loss of capillaries when adequate controls are considered.

Furthermore, the presence of skin NVC microvascular changes in acute and post-acute (90 days after discharge) SARS-CoV-2 infection, was confirmed in a study involving 22 patients with acute COVID-19 infection who showed skin microvascular complications, such as thrombosis, microhaemorrhages and neoangiogenesis during active disease, which disappeared after 3 months from hospital discharge (8). A direct correlation between capillary density (skin n/mm^2) during the acute phase and lymphocyte number was detected ($r=0.49$, $p<0.05$), whereas once again a significant reduction of skin capillary density was observed after the acute COVID-19 phase (97.2±5.3 vs 75.81±3.9 n/mm^2, $p<0.05$), together with a significant inverse correlation with C-reactive protein ($r=0.44$, $p<0.05$).

The severity of capillary loss was found to be an important prognostic factor following the NVC evaluation of 32 adult COVID-19 patients treated in intensive care units (9). In fact, mean capillary density was 5.50±0.19/1 mm among deceased patients, 6.71±0.25/1 mm among survivors ($p=0.011$) and 8.55±1.12/1 mm in the non-COVID-19 controls ($p<0.001$). In this study, capillary density was already significantly reduced in the acute phase, probably reflecting a more aggressive form of the disease with super-imposed pro-inflammatory cytokine storm.

NVC has also been used in a pediatric cohort of patients (10). Thirty-one children diagnosed with COVID-19 and/or multisystem inflammatory syndrome following SARS-CoV-2 infection showed significantly more microhemorrhages ($p<0.001$) and neoangiogenesis ($p<0.001$) with capillary ramifications ($p<0.001$) than healthy controls, whereas again capillary density per linear millimeter (6 per linear mm vs 7 per linear mm, $p=0.002$) and capillary length ($p=0.002$) were found significantly lower in the patients' group. NVC examinations were performed a median of 73 days after the diagnosis (median date).

Therefore, the reactive hyperinflammatory status during the active SARS-CoV-2 infection, seems to result in endothelial dysfunction in both children and adults, considering that SARS-CoV-2 infects target cells by interacting with ACE-2, which is expressed on endothelial cells as well as on cells of various organs, including the lung, the heart, the kidney and the gut (11,12). The presence of microthrombosis which is frequently detected at NVC analysis during COVID-19 infection, was further confirmed also by conjunctival video capillaroscopy of the eye microcirculation in 17 adult COVID-19 patients with thromboprophylaxis, shortly after hospital discharge (9 days on average) (13). This observation agrees with the microvascular effects related to the SARS-CoV-2 infection, and earliest pathological studies have already shown that a diffuse microvascular thrombosis is indeed a common observation in the lungs of COVID-19 patients at post-mortem examination (14, 15).

EFFECTS OF ANTI-COVID-19 VACCINES

A very recent, intriguing study was performed to establish whether 18 patients who received a double dose of m-RNA anti-COVID 19 vaccines (13 Comirnaty® e 5 Spikevax®) might show changes in their oral microcirculation evaluated by videocapillaroscopy with a complete capillaroscopic mapping including cheek, labial, chewing-gingival and back of the tongue (16). This investigation showed an increase in mean upper labial capillary density in COVID-19 vaccinated patients (32.75 n/mm^2 for Comirnaty® and 27.79 n/mm^2 for Spikevax®) when compared to the reference mean capillary density value of the literature (12.80 n/mm^2). Even at the level of the lower lips, the mean value of capillary density in COVID-19 vaccinated patients was found higher (30.41 n/mm^2 for Comirnaty® and 25.97 n/mm^2 for Spikevax®, respectively) than the values found in the literature in healthy and non-vaccinated patients of the pre-COVID era (12.80 n/mm^2). This study analyzed the samples from the patients soon after the first and second doses of vaccine. The authors concluded that the significantly increased capillary density observed following the anti-COVID-19 vaccination can be related to an increased angiogenesis associated to the vaccine-induced inflammatory reaction. Therefore, the microvascular reactivity induced by anti-COVID-19 vaccination, seems to evocate the increased angiogenesis observed at NVC in patients with active SARS-CoV-2 infection, as reported in the other investigations above discussed.

As a matter of fact, the immune system activation and the inflammatory reaction play an important role in regulating angiogenesis, and many studies indicate that leukocytes and proinflammatory cytokines (mainly Tumor Necrosis Factor, interleukin (IL)-1, IL-8, Transforming Growth Factor) are able to induce microvascular proliferation (17). Furthermore, from the beginning of the pandemic, it was demonstrated that higher serum Vascular Endothelial Growth Factor (VEGF) concentrations were present in acute COVID-19 patients compared with healthy controls suggesting that VEGF plays a crucial role in SARS-CoV-2 infection-associated acute inflammation and angiogenesis (18). More recently, increased serum VEGF concentrations have been found in COVID-19 patients with chilblains and a significant positive correlation with capillary density and presence of abnormally shaped capillaries (ramifications) was observed, suggesting that VEGF could be a reliable modifier for capillary density (19).

CONCLUSIONS

We can conclude that two non-specific capillaroscopic patterns of NVC microvascular abnormalities may be recognized as consequence of the SARS-CoV-2 infection. An

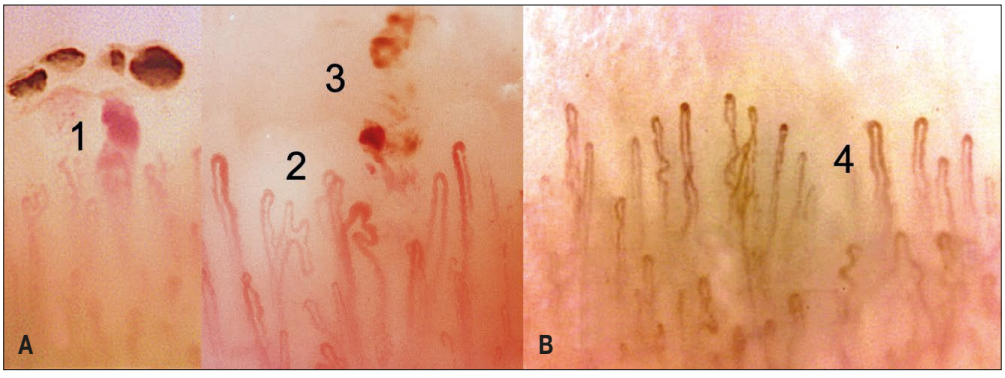

Figure 1 - An "early" non-specific pattern (A), during the immune/inflammatory reaction in acute COVID-19 patients and mainly characterized by angiogenesis (2) (abnormal shapes as ramifications), microhaemorrhages (3) and microthrombosis (1), followed by a "late" non-specific pattern (B), in COVID-19 survivors, mainly characterised by loss of capillaries (4) (magnification 200X *Videocap ADBiomicroscopy*).

"early" non-specific pattern appears in acute COVID-19 patients during the immune/inflammatory reaction and is mainly characterized by angiogenesis (abnormal shapes such as ramifications) microhaemorrhages and microthromboses, followed by a "late" non-specific pattern, in COVID-19 survivors, mainly characterised by loss of capillaries (Figure 1). "Late" capillaroscopic abnormalities have so far been identified in studies with different observation periods up to 3 months after healing, without differences in the concordance of the collected results.

The non-specific NVC abnormalities observed during and after COVID-19 seem to underline acute and post-acute microvascular damage and are reminiscent of some of the specific NVC abnormalities linked to the pathophysiology of systemic sclerosis (SSc) that is a progressive autoimmune self-amplifying process (20, 21). Similarly, the NVC features observed in SSc are related to the microvascular/endothelial damage and followed by the autoimmune response and inflammation, and finally result in the loss of capillaries (21).

Presently, the microvascular capillaroscopic changes identified in COVID-19 patients remain only partially explained, but they suggest a possible pathophysiological basis for the clinical organ complications that characterize the long-COVID.

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Disclosure of interest

All authors declare no conflicts of interest concerning this editorial.

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