Dermatology Practical & Conceptual

A Window into the Vascular Endothelium in Covid-19: Nails

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ABSTRACT

Introduction: Endothelial damage is associated with acute and long-term coronavirus disease 2019 (COVID-19) complications. Proximal nailfold capillaries and nail beds give important clues to microvascular changes associated with endothelial dysfunction.

Objective: We aimed to use dermoscopy to examine the proximal nailfold capillaries and nail bed of COVID-19 patients and identify microvascular changes.

Methods: A prospective study was designed to evaluate the dermoscopic features of proximal nail fold capillaries and nail bed in mild-to-moderate COVID-19 patients and healthy controls between June 2022 and December 2023. The patients underwent their initial dermoscopic examination two weeks after the onset of symptoms, followed by a follow-up evaluation 10-14 months later.

Results: The study included 46 patients with mild-to-moderate COVID-19 and 62 healthy controls. The presence of avascular areas (P <0.001), meandering capillaries (P = 0.016), microhemorrhages (P = 0.007), and enlarged capillaries (P = 0.009) in the proximal nail fold was significantly higher in COVID-19 patients than in healthy controls. The capillary architecture was disorganized (P = 0.002) and density reduced (P <0.001) in COVID-19 patients compared to healthy controls. In the follow-up examination, microvascular changes were observed to have regressed.

Conclusions: Proximal nailfold dermoscopy is an effective, low-cost, easily accessible method that enables observation of microvascular changes in COVID-19 patients.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has a broad range of clinical manifestations, from mild flu-like illness to severe, potentially fatal outcomes [1]. The first data providing an understanding of the pathogenesis of the disease were obtained from autopsies of patients who died with severe disease. It has been reported that endothelial damage caused by SARS-CoV-2 cell invasion and disturbance in inflammation and coagulation pathways may lead to microcirculatory disorders and multiple organ failure [2]. Over time, data showing that endothelial damage is present not only in severe disease but also in mild disease findings have been shared [3].

Several studies have focused on defining endothelial damage caused by COVID-19 in patients of varying severity [4-9]. It has been reported that some biomarkers such as Von Willebrand Factor (VWF), tissue-type plasminogen activator (t-PA), plasminogen activator inhibitor-1 antigen (PAI-1) antigen, and soluble thrombomodulin (sTM) can be used as indicators of endothelial dysfunction in COVID-19 patients [7-9]. These biomarkers are challenging to use routinely because they are not readily accessible or cost-effective in daily practice. As an alternative to these biomarkers, nailfold videocapillaroscopy has been used to demonstrate endotheliopathy in COVID-19 patients [10-16].

Nailfold video capillaroscopy (NVC) providing x 200 magnification is the gold standard for detecting nailfold capillary abnormalities. However, it requires special equipment and is not easily accessible [17]. Some studies have shown that the dermoscope, a more widely used, practical, and cheaper tool, can be used instead of NVC in cases that cause microvascular damage such as systemic sclerosis [17-19].

Objective

Our study aimed to describe the dermoscopic findings of the proximal nailfold and nail bed in COVID-19 patients. In addition, we aimed to identify potential microvascular abnormalities through dermoscopic observations.

Methods

Study Population

The study involved 46 mild-to-moderate COVID-19 patients at Pamukkale University between June 2022 and December 2023, along with 62 healthy controls. Patients who presented to the emergency services with symptoms suggestive of SARS-CoV-2 infection, such as fever, myalgia, or cough, and were diagnosed with the virus by real-time PCR examination of nasopharyngeal swab samples were included in the study. Patients were classified as mild or moderate based on the World Health Organization's definition of severity for cases of COVID-19. Patients with mild cases typically present with fever, cough, and fatigue, while those with moderate cases have difficulty breathing or evidence of pneumonia [15]. In line with these criteria, 38 patients exhibited mild disease severity, while eight demonstrated moderate disease severity.

Healthy controls were individuals who had no prior history of COVID-19 infection. Connective tissue diseases and any other conditions affecting microcirculation (such as smoking, diabetes, obesity, and hypertension) were considered exclusion criteria. The Ethics Committee of the Pamukkale University Training and Research Hospital, Denizli Turkey, approved the study. Written informed consent was obtained from all patients. The procedures followed were by the Declaration of Helsinki and institutional guidelines.

Dermoscopic Examination

The proximal fold and nail bed of all nails except the thumb (which are often difficult to visualize capillaries) of COVID-19 patients and healthy controls were evaluated in polarized light with contact mode using ultrasound gel as an interface with FotoFinder® Medicam 800 dermatoscope (FotoFinder Systems GmbH). Participants were assessed after resting at room temperature (20-25°C) for at least 15–20 minutes before the examination. Two dermatologists recorded dermoscopic images using x 20 and x 70 magnification.

A dermatologist experienced in dermoscopy and trained in capillaroscopy (OSKB) and a rheumatologist experienced in capillaroscopy (UB) evaluated the dermoscopic images of the nailfold capillaries in terms of their morphology, diameter, architecture, and density [1,2]. Throughout the evaluation, these two authors remained blinded. The capillary network is loop-shaped and runs parallel to the skin in healthy people (Figure 1). Capillary density is considered decreased if it is less than 7 per mm [2]. The first dermoscopic evaluation was conducted two weeks after the onset of symptoms in COVID-19 patients.

A follow-up dermoscopic evaluation of the patient group was performed after 10–14 months.

Statistical Analysis

Data were analyzed using IBM SPSS software (version 26; IBM, Armonk, New York, USA). The results of categorical measurements are expressed as numbers and percentages. The chi-square test was used for the analysis of two categorical variables. The numeric measurements are presented as mean ± standard deviation (SD). A p-value of <0.05 was considered statistically significant.

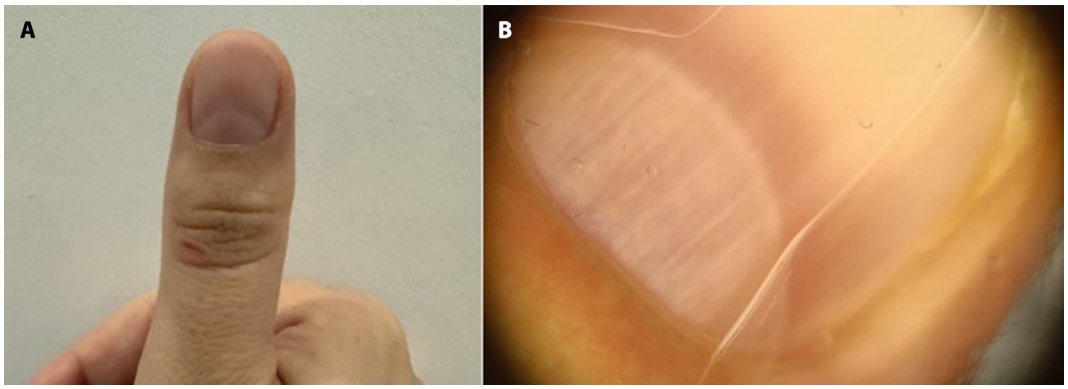

Figure 1. Red half-moon nail sign. (A) The distal margin of the lunula is surrounded by distally convex half-moon-shaped red bands. (B) On dermoscopy, the lunula was blurred and indistinct.

Results

The study included 46 patients with mild-to-moderate COVID-19 and 62 healthy controls. There was no statistically significant difference between the patient and control groups regarding age, sex, and vaccination status (P >0.05). The mean age of the patient group was 34.15 ± 11.35 and of the control group, 30.25 ± 9.42 years. In the patient group, 30 (65.2%) were female, and in the control group, 39 (63.9%) were female. Out of 108 participants, six had never been vaccinated, 46 had been vaccinated with BioNTech, 8 with CoronaVac (Sinovac), and 48 had both BioNTech and CoronaVac vaccines.

The patient cohort exhibited a prevalence of fever (40%), fatigue (77%), cough (26%), headache (21.7%), and anosmia (2.1%). We detected three cutaneous symptoms that may be associated with COVID-19: urticaria (n=1), telogen effluvium (n=1), and erythema multiforme (n=1). The red half-moon nail sign was seen on one patient's nail (Figure 2).

The presence of avascular areas (P <0.001) (Figure 3A), meandering capillaries (P = 0.016) (Figure 4 and Figure 5B), microhemorrhages (P = 0.007) (Figure 5), and enlarged capillaries (P = 0.009) (Figure 5A and Figure 6) in the proximal nail fold was significantly higher in COVID-19 patients than in healthy controls (Table 1). Branched capillaries were more common in COVID-19 patients than in the control group, but the difference was not statistically significant (P <0.05). The capillary architecture was disorganized (P = 0.002) and density decreased (P <0.001) in COVID-19 patients compared to healthy controls (Figure 3A). On the other hand, capillary tortuosity was detected more frequently in the healthy control group than in the patients with COVID-19 (Table 1). Although a higher rate of dilated nail bed capillaries (Figure 7) was found in COVID-19 patients, the difference was not statistically significant (P >0.05). We did not find any significant difference between the evaluations carried out at a magnification of x 20 and a magnification of x 70 (P >0.05).

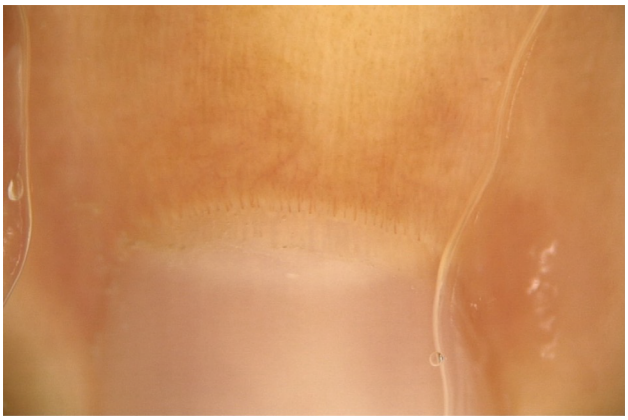

Figure 2. Nailfold capillaries in a healthy control. In healthy individuals, the capillaries in the proximal nail fold are loop-shaped and run parallel to the skin (×20).

After 10–14 months, we reconnected with 27 participants from the COVID-19 patient group for a follow-up dermoscopic examination conducted under identical conditions. Of these patients, 25 had had mild and two had had moderate disease severity. During follow-up, no significant capillary anomalies indicating microvascular damage was detected in the patients. In the initial evaluation, the capillary architecture was disorganized in six out of 27 patients, but all showed organized architecture in the follow-up. In four of these patients, the ramified capillary was initially present but disappeared, and in one patient, the ramified capillary appeared at the second evaluation. During the follow-up, microhemorrhage was initially present in 10 patients but disappeared in nine of them; it appeared in one patient at the second evaluation. Avascular areas were present in seven of 27 patients, all of which had resolved by follow-up (Figure 3B).

We did not detect any significant difference between COVID-19 patients with mild and moderate disease in all examinations.

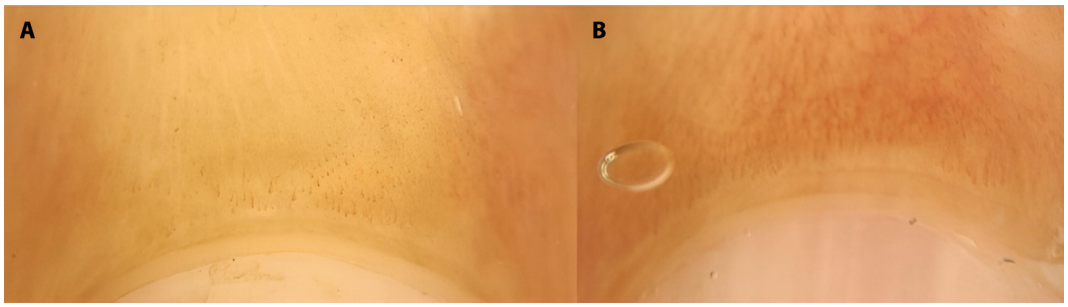

Figure 3. Architecture and density evaluation of proximal nailfold capillaries. (A) Dermoscopic image of COVID-19 patient showing avascular regions, reduced capillary density, and disorganized capillaries in the acute stage (× 20). (B) In the long-term follow-up of the same patient, neovascularization was observed, and avascular areas and irregularities disappeared (× 20).

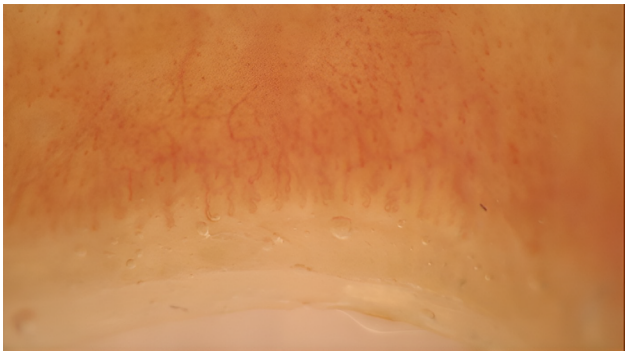

Figure 4. Meandering capillaries in a COVID-19 patient. Meandering capillaries were more common in COVID-19 patients than healthy controls (P = 0.016) (× 20).

Discussion

Capillaroscopy of the proximal nailfold provides important clues for the early detection of microcirculation changes [22]. Nailfold capillaroscopic abnormalities have been found in conditions linked to microvascular changes, such as connective tissue diseases, hypertension, and diabetes [20,23-25]. The videocapillaroscope is the main tool for capillaroscopic analysis, but a dermoscope, ophthalmoscope, or wide-field microscope can also be effective alternatives [22]. Dermoscopic findings of the nailfold have been reported in hemolytic uremic syndrome, psoriatic arthritis, rheumatoid arthritis, and connective tissue diseases [26-29]. The current study used dermoscopy to evaluate proximal nailfold capillaries in early and long-term follow-up of COVID-19 patients.

It is now well-known that endothelial dysfunction plays a crucial role in the pathogenesis of COVID-19 [30]. Microvascular changes due to endothelial dysfunction in COVID-19 patients have been reported in a few studies with NVC [10-16]. These studies included patients with varying disease severity, and pathological capillaroscopy findings were reported at different rates. In two studies on hospitalized COVID-19 patients, about 60% showed enlarged capillaries and around 50% had meandering capillaries and reduced capillary density [12,15]. In the study by Karahan et al. involving COVID-19 patients in need of intensive care, a similarly high rate of dilated capillaries (43.8%) and meandering capillaries (56.2%) were reported [14]. Our study findings revealed significant microvascular abnormalities in mild-to-moderate COVID-19 patients, with 39.1% showing decreased capillary density, 23.9% exhibiting enlarged capillaries, 34.8% microhemorrhage, and 19.6% meandering capillaries. A close relationship between endothelial dysfunction and proximal nailfold capillary density has been demonstrated in several diseases including scleroderma, diabetes mellitus, and essential hypertension [27]. SARS-CoV-2 uses the ACE2 receptor expressed by pneumocytes in the epithelial alveolar lining to infect the host, and the ACE2 receptor is also widely expressed in endothelial cells. Direct viral infection of the endothelium and subsequent inflammation can lead to apoptosis and widespread endothelial dysfunction [28]. Reduced capillary density is likely to reflect endothelial dysfunction in COVID-19. The impairment of microvascular tone causes the opening of endothelial junctions, which increases microvascular permeability and leads to progressive leakage, resulting in microhemorrhages [29]. Additionally, it has been suggested that hypoxia and inflammation that develop during COVID-19 may stimulate neoangiogenesis in the proximal nail fold [16]. The meandering capillaries observed in dermoscopy are representative of neoangiogenesis. Furthermore, local endothelial cells secrete vasodilator agents, such as prostacyclin and nitric oxide (NO), in response to hypoxia, which explains the presence of dilated capillaries [30].

Although the relatively higher rates of pathological NVC findings in previous studies suggest that disease severity may have an impact on capillaroscopic findings, in the study by Sulli et al., no difference was found in terms of NVC findings between severe disease and mild-moderate disease [11]. Technical differences certainly contribute to our relatively lower

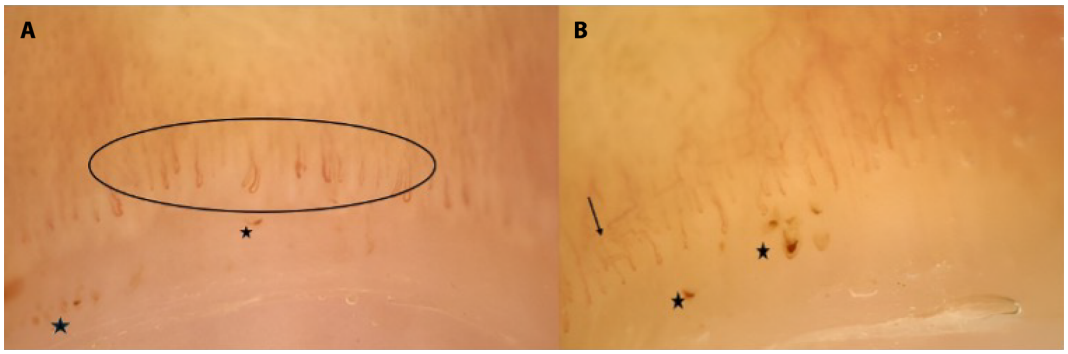

Figure 5. Microhemorrhages were more common in COVID-19 patients than healthy controls: (A) Microhemorrhages (stars) and enlarged capillaries (circle) in a COVID-19 patient (× 20). (B) Microhemorrhages (stars) and meandering capillaries (arrow) in a COVID-19 patient.

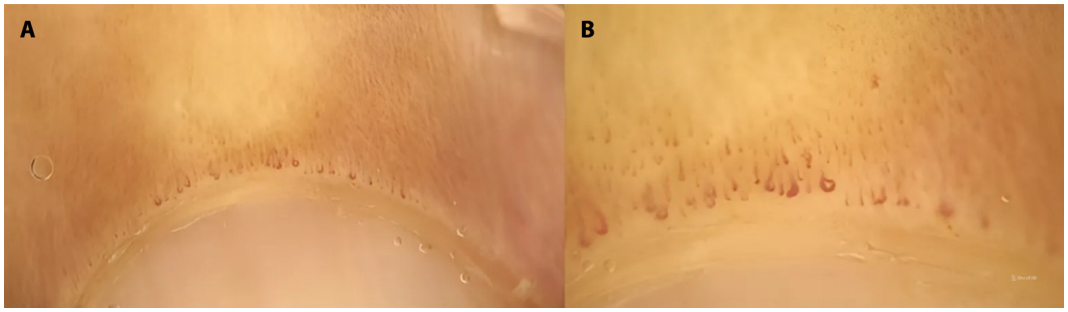

Figure 6. Enlarged capillaries. Enlarged capillaries were detected significantly more often in COVID-19 patients (P = 0.009). (A) × 20. (B). × 70.

Table 1. Dermoscopic Findings Observed in Proximal Nailfold and Nail Bed.

	COVID-19 Patients n (%)	Healthy Controls n (%)	p-value
Avascular area	15 (32.6)	4 (6.4)	**P<0.001***
Meandering capillaries	9 (19.6)	3 (4.8)	**P=0.016***
Microhemorrhages	16 (34.8)	8 (12.9)	**P=0.007***
Tortuous capillaries	16 (27.6)	19 (61.3)	**0.013***
Reduced capillary density	18 (39.1)	5 (8.1)	**P<0.001***
Disorganized capillaries	12 (26.1)	3 (4.8)	**P=0.002***
Enlarged capillaries	11 (23.9)	4 (6.4)	**0.009***
Branched capillaries	11 (23.9)	7 (11.3)	0.082
Dilated nail bed capillaries	19 (41.3)	17 (27.4)	0.130

*p-values with P<0.05 are written in bold.

rate of pathological capillaroscopic findings, but we believe the patient population included in the studies plays a greater role. In other studies, involving adult patients, the average age was around 60, whereas in our study, it was 34.15 ± 11.35. Furthermore, unlike previous studies which included patients with underlying conditions such as hypertension, diabetes, and smoking, which can lead to microvascular changes, our study specifically excluded individuals with these comorbidities. In their assessment of NVC in pediatric patients, Çakmak et al. found similar rates of microvascular changes as those in our study. This reinforces the notion that patient outcomes are influenced by their age and comorbidities. In the study, it was found that 22.5% of the patients had microhemorrhage, 29% had branched capillaries, and 38.7% had dilated capillaries [16].

Microvascular alterations have been a topic of interest throughout the COVID-19 pandemic, aimed at understanding the pathogenesis and at developing treatments [3,10,31-33]. The long-term consequences of acute endothelial damage have been the subject of a few studies [3,31,32]. Some studies

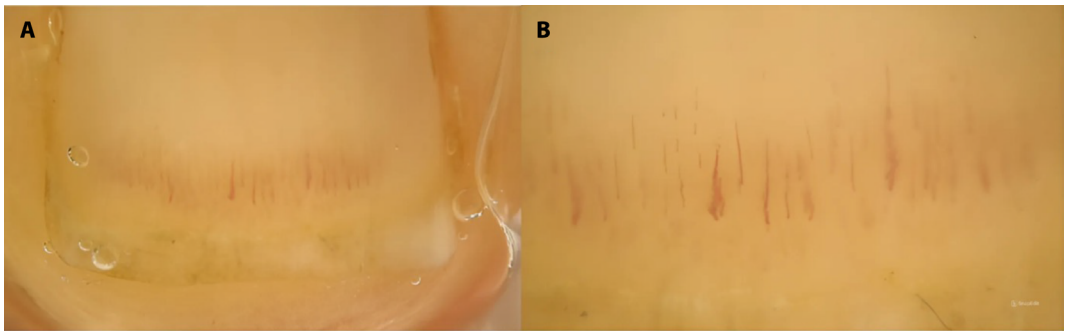

Figure 7. Dilated nail bed capillaries. It was determined that there were more dilated capillaries in the nail bed in COVID-19 patients, but the difference was not statistically significant (P >0.05). (A) × 20. (B) × 70.

report that in long-term follow-up after COVID-19, the elevation of endothelial biomarkers did not continue, and they found no evidence that endothelial dysfunction persisted [3,32]. However, Fan et al. reported that hypercoagulation, endothelial dysfunction, and inflammation could be detected in some patients approximately one year after recovery from COVID-19 [31]. In one of the studies on NVC, the follow-up capillaroscopy findings of the patients were reported. While Rosei et al. detected significant capillaroscopic findings of microvascular impairment in the acute phase, they observed that these findings disappeared after three months [10]. We reevaluated our patients at 10–14 months and found resolution of the pathological capillaroscopy findings.

The relatively small number of patients and the exclusion of patients with severe disease were limitations of our study. The strengths of this study include its prospective design, healthy comparator groups, and long-term follow-up data.

Conclusions

Despite advances in vaccines, antiviral drugs, and preventive measures, new infections with SARS-CoV-2 continue [35]. The virus continues its life with new mutations. In addition to the significant complications associated with COVID-19, the post-viral syndrome known as post-acute sequelae of SARS-CoV-2 infection, or "long COVID-19," continues to represent a significant public health concern [36]. Our findings could lead to new research aimed at explaining or predicting complications related to COVID-19.

We suggest that proximal nailfold dermoscopy is an easily accessible and cheaper technique that can be used as an alternative to NVC to detect microvascular changes in COVID-19 patients. We hope that early detection of microvascular changes and widespread screening, especially in at-risk patients, will protect them from complications that can have dangerous consequences.

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