ORIGINAL ARTICLE

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Evaluation of Coronavirus Disease-2019 Patients with Nailfold Capillaroscopy

Koronavirüs Hastalığı-2019 Hastalarının Tırnak Dibi Kapilleroskopisi ile Değerlendirilmesi

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ABSTRACT

Aim: Microvasculopathy is one of the suspected complications in Coronavirus disease-2019 (COVID-19). Nailfold capillaroscopy is a noninvasive method used to evaluate microvascularity. It can be a guide in detecting endothelial dysfunction and microvasculopathy in COVID-19 patients.

Materials and Methods: Severe acute respiratory syndrome-CoV-2 polymerase chain reaction positive 54 patients were evaluated. The 2nd-5th digits of both hands were investigated by nailfold capillaroscopy. Capillary density, capillary architecture and capillary morphology were recorded. Patients with abnormal and normal nailfold capillaroscopy findings were compared in terms of COVID-19 clinical symptoms.

Results: Of the patients included in the study, 72% were male and the mean age was 35.6±11.6 years. In total, 22 patients (41%) had at least 1 abnormal capillaroscopy change. Diffuse capillaroscopic abnormalities were as follows: pericapillary edema 43%, enlarged and dilated capillaries 24%, and tortiosteal capillaries 22%. Hyperinflammatory response was observed in 17% of the patients and intensive care was required in only 1 patient. The frequency of hyperinflammatory response, anticytokine use and thrombosis increased in patients with abnormal capillaroscopy.

Conclusion: Abnormal capillaroscopy findings were found to be frequent in COVID-19 patients. Higher rates of the hyperinflammatory response and anticytokine drug use in patients with abnormal nailfold findings suggest that there may be a relationship between hyperinflammation and microvasculopathy in COVID-19. Further studies are needed to evaluate the clinical relevance of nailfold abnormalities with clinical manifestations of COVID-19 disease.

Keywords: COVID-19, microangiopathy, nailfold capillaroscopy

ÖZ

Amaç: Mikrovaskülopati, Koronavirüs hastalığı-2019 (COVID-19) hastalığı komplikasyonlarında rol alan mekanizmalardan biridir. Tırnak dibi kapilleroskopisi (TDK) mikrovasküleriteyi değerlendirmede kullanılan non-invaziv bir yöntemdir. COVID-19 hastalarında endotel disfonksiyonu ve mikrovaskülopatinin saptanmasında yol gösterici olabilir.

Gereç ve Yöntem: Şiddetli akut solunum yolu sendromu-CoV-2 testi pozitif çıkmış 54 hastaya TDK yapıldı ve hastalar kapiller yoğunluk, mimari ve morfoloji açısından değerlendirildi. Anormal ve normal kapilleroskopi bulguları olan hastalar COVID-19 klinik semptomları açısından karşılaştırıldı.

Bulgular: Çalışmaya alınan hastaların %72'si erkek, yaş ortalaması ise 35,6±11,6 idi. Toplamda 22 hastada (%41) anormal kapilleroskopik değişikliklerden en az 1 tanesi vardı. Kapilleroskopik yaygın anormallikler ise sırasıyla, perikapiller ödem (%43), genişlemiş ve dilate kapil (%24), tortiyozite kapiller (%22) oldu. Hastaların %17'sinde hiperenflamatuvar yanıt görüldü ve 1 hastada yoğun bakım ihtiyacı oldu. Anormal kapilleroskopik değişliği olan hastalarda hiperenflamatuvar yanıt, antisitokin kullanımı ve tromboz sıklığı artmıştı.

Sonuç: COVID-19 hastalarında anormal kapilleroskopik bulgular sıklıkla gözlenmiştir. Anormal kapilleroskopik bulguları olan hastalarda hiperenflamatuvar yanıt ve antisitokin ilaç kullanımı sıklığının artması hiperenflamasyon ile mikrovaskülopati arasında bir ilişki olabileceğini düşündürmektedir. TDK'nın, COVID-19 hastalığı klinik tutulumları ile ilişkisini değerlendirmek için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: COVID-19, mikroanjiyopati, tırnak dibi kapilleroskopi

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INTRODUCTION

Severe acute respiratory syndrome- coronavirus-2 (SARS-CoV-2), as the causative agent of Coronavirus disease-2019 (COVID-19), caused a global pandemic following its first detection in Wuhan, China in December 2019[1]. The clinical course of COVID-19 may be asymptomatic or may progress with severe pneumonia by affecting the lower respiratory tract. In some patients, it can cause morbidity and mortality by causing disease in multiple organ systems[2]. The frequency of thrombosis has increased in the course of COVID-19[3]. Thrombosis in COVID-19 patients may be due to hyperinflammatory response, hypoxic injury, endothelial dysfunction, hypercoagulability and/or increased platelet activity[4]. Even in the early stages of COVID-19 disease, viral inclusion bodies can cause organ damage by causing apoptosis, inflammatory cell infiltration and microvascular thrombosis in endothelial cells. This microvasculopathy process in the course of COVID-19 may be responsible for the major thrombotic events[5,6].

Nailfold capillaroscopy (NFC) is a noninvasive method commonly used to evaluate microvasculopathy, especially in autoimmune connective tissue patients[7]. NFC is a bedside, easily applicable method which may also be helpful in detecting dysfunctional endothelial activation and microvasculopathy in patients with COVID-19[8,9].

In this study, we aimed to evaluate the nail fold of the fingers in hospitalized COVID-19 patients by NFC and compare the COVID-19 clinical course in patients with and without NFC changes.

MATERIALS AND METHODS

We included 54 consecutive COVID-19 patients, who were hospitalized for COVID-19 in Ankara City Hospital Infectious Diseases Clinic between 01 and 30 April 2020. Patients' SARS-CoV-2 tests were evaluated by reverse transcriptase-polymerase chain reaction taken from nasopharyngeal or oropharyngeal swabs and all patients gave informed consent. Patients under the age of 18 years, pregnant and having any comorbidity or using chronic medication were excluded from the study. Age, gender and smoking status of the patients, as well as the clinical features, complications, treatments, laboratory and radiological results of the COVID-19 disease, were recorded. Approval from Ankara City Hospital Ethics Committee was obtained for the study, along with the permission of the Ministry of Health and an informed consent form (no: E1-20-679, date: 30.09.2020).

All patients included in our study were examined by NFC (Dino-Lite Premier AM4113T) between the 3rd and 5th days of their hospitalization. As defined in previous studies, patients were rested at room temperature (22-25 °C) for at least 15 minutes prior to the examination[7]. All fingers of both hands except thumbs were examined by NFC by AE. Capillaroscopic changes were evaluated in terms of capillary density, capillary architecture, and capillary morphology.

Capillary density was recorded as the mean number of capillaries calculated from two areas in each finger examined (dividing the number of capillaries at 1 mm distance from the middle of the nail fold to each side) by two. The presence of at least 9 capillaries per 1 mm was considered normal capillary density[10].

All elongated, curved, dilated, giant capillaries and the presence of hemorrhages were noted. Avascular areas were defined as the loss of at least two consecutive capillaries in the dermal papilla. The presence of branching, bushy capillaries or ramified capillaries was classified as neoangiogenesis. The percentage of curved and elongated capillaries was determined by evaluating the same areas used to determine capillary density[10,11].

To identify abnormal NFC examination findings in COVID-19 patients, we used the definitions proposed by Ingegnoli et al.[12]. If more than 1 morphological abnormality (giant capillary or >50% convoluted or >10% elongated capillary or hemorrhage area or angiogenesis or avascular areas plus the presence of another capillaroscopy abnormality) was defined in at least 2 different fingers, the patient's NFC examination was accepted as abnormal.

Statistical Analysis

Statistical analysis was performed using SPSS 24.0 (IBM Corp., Armonk, NY, USA). The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Shapiro-Wilk test). Continuous data were defined as mean [±standard deviation (SD)] or median [interquartile range (IQR)] and categorical variables as percentages. The chi-square test was used to compare categorical variables. The Student's t-test or Mann-Whitney U test was used to compare continuous variables. A p value of <0.05 was considered statistically significant.

RESULTS

In this study, a total of 54 COVID-19 patients were included. Of them, 72% patients were male and the mean age was 35.6±11.6 years. Of the patients, 17% were active smokers and 6% were ex-smokers. The median (IQR) hospital stay of patients was 7 (4) days. All patients had a thorax computed tomography when hospitalized and ground glass opacity was observed in 85%, focal patchy infiltration in 4%, and normal findings in 11%.

COVID-19 symptoms of the patients were as follows: Cough 69%, fever 43%, shortness of breath 32%, myalgia 30%, sore throat 24%, arthralgia 20%, headache 15%, anosmia 13%,

nausea/vomiting 11%, diarrhea 7%, dysgeusia 6%, fatigue 6%, and abdominal pain 4%. Patients' COVID-19 treatments involved hydroxychloroquine 96%, azithromycin 57%, favipiravir 26%, glucocorticoid 2%, tocilizumab 6%, anakinra 6%, acetylsalicylic acid/dipyridamole 8%, colchicine 7%, and low molecular weight heparin 63%.

During the follow-up period, hyperinflammatory response was developed in 17% of the patients. Only 1 patient was admitted to the intensive care unit. In total, 2 thrombosis events, 1 being pulmonary thromboembolism and 1 being sinus vein thrombosis, developed in our COVID-19 patients during hospital stay. All patients with hyperinflammatory response and thrombosis were in the abnormal NFC group. No acute respiratory distress syndrome, myocarditis, sepsis, mechanical ventilation need, or mortality was seen in any of the COVID-19 patients.

NFC findings of all patients were shown in Table 1. In total, 22 patients (41%) had at least 1 of the described abnormal capillaroscopic changes. The evaluation of patients with and without abnormal NFC in terms of the COVID-19 disease course was shown in Table 2. Images of the NFCs of the patients with COVID-19 disease were shown in Figure 1.

DISCUSSION

In our study, 41% of 54 hospitalized COVID-19 patients had abnormal NFC findings. We found that the frequency of hyperinflammatory response and anticytokine drug use was increased in COVID-19 patients with abnormal NFC. This suggests that there may be a relationship between hyperinflammation and microvasculopathy in COVID-19 patients, but we could not find any association between abnormal NFC and mortality, and the need for mechanical ventilation.

Table 1. Nailfold capillaroscopy examination findings of patients with COVID-19 disease

Median (IQR) capillary density, number of capillaries/1 mm	9 (2)
Enlarged and dilated capillary, n (%)	13 (24)
Capillary tortuosity, n (%)	
≤50%	12 (22)
>50%	12 (22)
Elongated capillary, n (%)	
≤10%	7 (13)
>10%	11 (20)
Hemorrhage, n (%)	5 (9)
Pericapillary edema, n (%)	23 (43)
Branching capillary, n (%)	3 (6)
Bushy capillary, n (%)	0
Ramified capillary, n (%)	0
Avascular area, n (%)	0
Abnormal nailfold capillaroscopy, n (%)	22 (41)

IQR: Interquartile range, COVID-19: Coronavirus disease-2019

NFC examination is a simple method that may be used to demonstrate microvascular changes in capillaries. In clinical practice, it is mostly used as a diagnostic method in patients with systemic sclerosis and dermatomyositis with Raynaud's syndrome[7,13]. In the literature, abnormal NFC have also been found in primary vasculitides such as Behçet's disease, Henoch-Schönlein purpura, Takayasu arteritis and granulomatous polyangiitis[14-17]. It is also important that NFC may detect NFC changes at an early stage, especially in patients with systemic sclerosis[18].

The frequency of thrombosis has been increased in the course of COVID-19 disease[3]. Thrombosis in COVID-19 disease may be due to hyperinflammatory response, hypoxic injury, endothelial dysfunction, hypercoagulability and/or increased platelet activity[4,8]. Even in the early stages of COVID-19 disease, viral inclusion bodies can cause organ damage by causing apoptosis, inflammatory cell infiltration and microvascular thrombosis in endothelial cells. The microvasculopathic changes may be responsible for the major thrombotic events in the COVID-19 disease[5,6].

In the literature, there are not enough studies about the associations between abnormal NFC and COVID-19 disease yet. In our study, the median capillary density of all COVID-19 patients was found to be normal. Enlarged/dilated capillary was present in 13 patients and capillary hemorrhage was observed in 5 patients. Apart from these, 12 patients had >50% abnormal capillary tortuosity (total increased capillary tortuosity in 24 patients) and 10 patients had >10% elongated capillaries (total elongated capillaries in 18 patients).

No bushy capillary, ramified capillary or avascular area was detected in the NFC examinations. Branching capillary, which is one of the other common minor NFC changes, was observed in 3 patients and pericapillary edema was observed in 23 patients. In our study, as in the study of Natalello et al.[9], the frequency of minor NFC changes increased and the most common change was pericapillary edema. Giant capillary resembling scleroderma was not observed in any of the patients with COVID-19 disease. In this study, the incidence of pericapillary edema was 100% in the acute period of COVID-19 disease, while the rate of the cured patients was 70%. In another study, it was stated that papillary edema might indicate disease activity in Henoch-Schönlein purpura patients[15]. So pericapillary edema, being the most common finding in the early phase of the disease, may be considered as an indicator of active disease in our study.

In our study, comparing the patients with normal and abnormal NFC, there was no difference in terms of gender, age, and smoking status. The median capillary density of 22 patients

Table 2. Comparison of COVID-19 patients with and without capillaroscopic abnormalities			
	Abnormal capillaroscopy, (n=22)	**Normal capillaroscopy, (n=32)**	**p**
Male, n (%)	17 (77)	22 (69)	0.492
Age, year, mean±SD	38.5±13.1	33.4±10.1	0.104
Smoking, n (%) **Current** **Ex-smoker** **Never**	 4 (18) 2 (9) 16 (73)	 5 (16) 1 (3) 26 (89)	0.744
Capillary density, mean±SD	8.5±1.4	9.5±1.3	**0.022**
COVID-19 clinical features			
Fever, n (%)	12 (55)	11 (34)	0.141
Cough, n (%)	15 (68)	22 (69)	0.965
Dyspnea, n (%)	11 (50)	6 (19)	**0.015**
Arthralgia, n (%)	5 (23)	6 (19)	0.721
Myalgia, n (%)	6 (27)	10 (31)	0.753
Headache, n (%)	1 (5)	7 (22)	0.122
Sore throat, n (%)	3 (14)	10 (31)	0.199
Anosmia, n (%)	3 (14)	4 (13)	0.903
Dysgeusia, n (%)	2 (9)	1 (3)	0.560
Stomachache, n (%)	1 (5)	1 (3)	0.786
Nausea/vomiting, n (%)	3 (14)	3 (9)	0.671
Diarrhea, n (%)	1 (5)	3 (9)	0.638
Laboratory results			
Lymphocyte, median (IQR)	1450 (958)	1475 (800)	0.881
Hemoglobin, median (IQR)	14.0 (1.5)	14.7 (1.8)	0.659
Platelets, median (IQR)	213000 (115500)	214000 (68250)	0.685
Creatinine, median (IQR)	0.78 (0.33)	0.80 (0.26)	0.805
Aspartate aminotransferase, median (IQR)	22 (31)	19 (11)	0.062
Alanine aminotransferase, median (IQR)	24 (32)	27 (15)	0.359
Lactate dehydrogenase, median (IQR)	254 (121)	206 (63)	**0.010**
Creatinine kinase, median (IQR)	101 (209)	83 (49)	0.097
C-reactive protein, median (IQR)	18 (34)	7 (12)	0.369
Ferritin, median (IQR)	152 (331)	115 (113)	0.233
Fibrinogen, median (IQR)	3.7 (1.5)	3.3 (1.3)	0.279
D-dimer, median (IQR)	0.4 (0.5)	0.3 (0.3)	0.058
INR, median (IQR)	1.0 (0.1)	1.1 (0.1)	0.582
Troponin I, median (IQR)	2.5 (2.3)	2.5 (0.4)	0.578
COVID-19 clinical features			
Thorax computed tomography, n (%) **Ground glass opacity** **Focal infiltration/opacity** **Normal findings**	 19 (91) 0 2 (9)	 25 (81) 2 (6) 4 (13)	0.444
Hyperinflammatory response, n (%)	5 (23)	0	**0.008**
Thrombosis, n (%)	2 (9)	0	0.161
Length of stay in hospital, day, median (IQR)	8 (4.5)	7 (3.0)	0.131
Clinical complete recovery, day, median (IQR)	30 (52)	20 (48)	0.749

Tablo 2. Continued

	Abnormal capillaroscopy, (n=22)	Normal capillaroscopy, (n=32)	p
COVID-19 treatments			
Hydroxychloroquine, n (%)	21 (96)	31 (97)	0.786
Azithromycin, n (%)	9 (41)	22 (69)	**0.042**
Favipiravir, n (%)	9 (41)	5 (16)	**0.037**
Glucocorticoid, n (%)	1 (5)	0	0.407
Tocilizumab, n (%)	3 (14)	0	0.062
Anakinra, n (%)	3 (14)	0	0.062
Colchicine, n (%)	4 (18)	0	**0.023**
Acetylsalicylic acid/dipyridamole, n (%)	4 (18)	0	**0.023**
Low molecular weight heparin, n (%)	18 (82)	16 (50)	**0.023**

IQR: Interquartile range, COVID-19: Coronavirus disease-2019, SD: Standard deviation, INR: International normalized rate

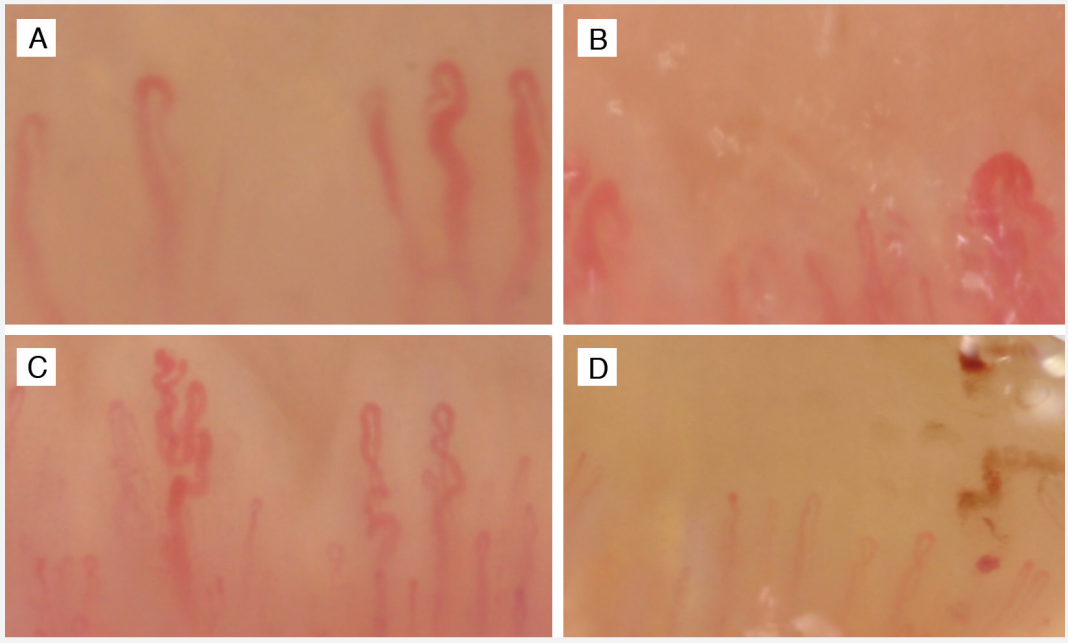

Figure 1. A) Elongated, dilated capillary and periungual edema, B) Dilated capillary, C) Capillary tortuosity, D) Capillary hemorrhage

with abnormal NFC was lower than that of 32 patients with normal NFC. Decreased capillary density, enlarged capillary and capillary tortuosity may also be seen in patients with diabetes mellitus and hypertension[10,19]. The exclusion of these comorbidities in our study suggests that the NFC changes detected could be due to COVID-19 disease.

In comparison of the COVID-19 clinical and laboratory features at the time of diagnosis, only the frequency of dyspnea and median lactate dehydrogenase levels were found to be higher in the group with abnormal NFC. In a meta-analysis review, elevated lactate dehydrogenase levels were associated with an increased incidence of COVID-19-related thrombosis[20]. In our patients, pulmonary-parenchymal involvement was similar between patients with and without abnormal NFC.

In the hospital follow-ups of the patients, a hyperinflammatory response was observed in 5 patients who were all in the abnormal NFC group. Thrombosis developed in 2 of these 5 patients (one sinus vein thrombosis and one pulmonary thromboembolism). In patients with normal NFC, there was no hyperinflammatory response or thrombosis. Apart from this, sepsis, acute respiratory failure or mortality, which can be a complication of COVID-19 disease, was not observed in any of the patients. Although the median hospital stay and clinical complete recovery time were higher in the group with abnormal NFC, this difference did not reach statistical significance. As a result of our findings, more hyperinflammatory response and thrombosis in COVID-19 patients with abnormal NFC changes is consistent with microvascular thrombotic processes that can be seen in the course of COVID-19 disease[21-23].

In our study, patients with abnormal NFC required more anticytokine, antiaggregant and antithrombotic drugs during the COVID-19 course. After the viremic phase at the onset of COVID-19, the excessive immune system activation increases the severity of the COVID-19 disease and reveals the need for anticytokine therapy[24]. Although the pathogenetic mechanisms are still unclear, the developing hyperinflammatory state may be directly related to the pathogenetic role of the viral agent causing endothelial activation in the early stages of the disease[25]. The need for more anticytokine therapy in the treatment management of our patients, who underwent a NFC examination in the first days of their hospitalization and who had abnormal NFC, is compatible with that in the severe COVID-19 disease course.

Study Limitations

There were several limitations in our study. The small number of patients and the absence of a control group are among the limitations of our study. That no NFC examinations were performed before the COVID-19 infection was another limitation of our study. Excluding patients with comorbidities and chronic drug use provides a homogeneity in our study but the lack of the objective COVID-19 severity scales is an important limitation.

CONCLUSION

In conclusion, increased abnormal NFC findings were detected in hospitalized COVID-19 patients in our study. The frequency of hyperinflammatory response and anticytokine drug use is increased in COVID-19 patients with abnormal NFC findings. In the light of these data, an association could be between hyperinflammation and microvasculopathy in COVID-19 patients. On the other hand, no association was observed between the presence of abnormal NFC findings in COVID-19 patients and mortality, and the need for mechanical ventilation. Therefore, in order to better demonstrate the clinical effect of abnormal NFC findings in COVID-19 disease and to confirm our findings, similar studies should be conducted with more patients and these patients should be followed up for a longer period of time.

Ethics

Ethics Committee Approval: Approval from Ankara City Hospital Ethics Committee was obtained for the study, along with the permission of the Ministry of Health and an informed consent form (no: E1-20-679, date: 30.09.2020).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.Ö., A.E., Concept: O.K., A.O., Design: B.A., O.K., A.O., A.E., Data Collection or Processing: B.Ö., A.A.A., E.A., Ö.K., Analysis or Interpretation: B.A., S.C.G., Literature Search: Ö.K., S.C.G., Writing: B.A., B.Ö.

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