CAPILLAROSCOPY IN COVID-19

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Abstract. *The infectious disease COVID-19, caused by the SARS-CoV-2 virus, is characterized by a wide range of clinical manifestations (pulmonary and extrapulmonary) and in some cases with post-infectious manifestations in persons who survived the infection. The vascular tropism of SARS-CoV-2 is the basis for the interest in using nailfold capillaroscopy to assess the microcirculation in children and adults who have recovered from COVID-19. Most often, non-specific changes are observed, without certain manifestations of microangiopathy and without a specific combination of microvascular findings, on the basis of which to define a specific capillaroscopic picture of the “COVID-19” type. The possibility that capillaroscopy in combination with other findings can be used for personalized approach and determination of prognosis in patients with post-COVID syndrome needs further studies.*

Key words: *capillaroscopy, COVID-19, post-COVID syndrome*

Introduction

The infectious disease COVID-19, caused by the SARS-CoV-2 virus, is characterized by a wide range of clinical manifestations (pulmonary and extrapulmonary) and in some cases with post-infectious manifestations in persons who survived the infection. The main clinical manifestations are on the part of the respiratory system, but other organs and systems can also be affected (nervous, endocrine, cardiovascular, excretory system, gastrointestinal tract, liver, eyes, etc.). In some patients, some symptoms may persist for weeks or months after the onset of infection (so-called “long COVID” and “post-COVID” syndrome/PCS) [1, 2, 3]. The symptoms and signs associated with an intense immune response are varied and can mimic some autoimmune and inflammatory diseases. Their severity ranges from mild, self-limiting to systemic, life-threatening. The pathogenesis of these manifestations is incompletely understood, with some appearing within two weeks of the onset of viral infection, and others developing in the late post-infectious phase. There is evidence of a relationship between COVID-19 and the development of systemic vasculitis, myositis, arthritis, skin manifestations (maculo-papular, urticarial lesions, chilblains, Raynaud’s phenomenon (RF), necrosis) [4, 5, 6], neurological involvement (Guillain-Barre syndrome, myelitis, optic neuritis) [4, 7], hematological, cardiovascular involvement (myocarditis, pericarditis), glomerulonephritis, thyroiditis, acute pancreatitis, ocular manifestations (anterior uveitis, conjunctivitis) [4, 8, 9, 10], symptoms characteristic of systemic lupus erythematosus, including cytopenias (lymphopenia, thrombocytopenia, hemolytic anemia), arthralgias, chilblains, serositis, positive antiphospholipid antibodies. In children, a multisystem inflammatory syndrome (MIS-C) has been described, characterized by clinical and laboratory manifestations similar to Kawasaki disease [4].

Vascular pathology in SARS-CoV-2 infection

The spike protein of SARS-CoV-2 binds to the angiotensin-converting enzyme-2/ACE-2 receptor, which is expressed on the surface of cells in a number of organs such as the lung, heart, kidney, neurons, and also on endothelial cells. In addition, secreted proinflammatory cytokines, hypoxia, and activated complement lead to endothelial damage and activation of the coagulation cascade [11, 12, 13].

The unique pathogenesis of SARS CoV-2 infection continues to pose new questions for clarification. Among these questions is whether it is possible to use capillaroscopy as an additional methodology for the assessment of vascular damage in COVID-19. The individual response to the infectious agent and the appearance of vascular pathology with different localization are among the factors that define COVID-19 as a multifaceted infection with an unpredictable prognosis.

A leading cause determining the severity of the clinical course and high mortality in COVID-19 are

thrombotic complications in severe forms, which leads to the universal use of anticoagulants in prophylactic and therapeutic doses in these cases [14]. Clinically, many of the patients with COVID-19 have elevated D-dimers as well as skin lesions on the extremities. Disseminated intravascular coagulopathy and large vessel thrombosis in COVID-19 are associated with development of multiorgan failure [15]. In addition, it is currently known that patients with COVID-19 also develop microthrombosis in the capillaries of various organs, including lungs, heart, kidneys [14]. Histological analysis of lung tissue from patients who died of COVID-19 showed the presence of wide-area thromboses with microangiopathy. Alveolar capillary microthrombosis was observed 9 times more often compared to patients who died from acute respiratory distress syndrome in influenza ($p < 0.001$) [15]. The coagulopathy that occurs in some patients is initiated by the state of intense systemic inflammation induced by the virus. In response to viral replication and cell lysis, numerous proinflammatory cytokines are released such as interleukins/IL (IL-1, IL-6, IL-7, IL-8, etc.), glycoproteins (G-CSF, GM-CSF, FGF, VEGF), acute-phase molecules (procalcitonin, C-reactive protein, fibrinogen, etc.) [14].

Capillaroscopy and Raynaud's phenomenon

RF is a common vascular syndrome in clinical practice characterized by a triphasic discoloration of the fingers and toes (whitening, cyanosis, and hyperemia) due to abnormal vasospasm of small arteries and arterioles, most often due to exposure to cold [16, 17, 18, 19]. It can be primary and secondary. In secondary RF due to rheumatic diseases, ischemic attacks are more frequent, more painful, and longer lasting, and digital ulceration or necrosis may develop [16, 18, 20, 21]. There are observations of the occurrence of RF after past SARS-CoV-2 infection in patients of different genders and ages with involvement of both upper and lower limbs [5, 6, 17, 18, 22]. Cases of digital necrosis have also been reported [18, 22]. Pathogenetic mechanisms of peripheral vascular ischemia in COVID-19 may include the development of vasculitis or thrombosis [22].

Video capillaroscopy is a valuable non-invasive diagnostic method for evaluating capillaries in the proximal nail fold area and the technique is key to differentiating primary from secondary RF. The non-invasive nature of the methodology and the high frequency of vascular involvement in SARS-CoV-2 virus infection motivated the initiation of capillaroscopic studies to assess the microcirculation during the COVID-19 pandemic [16, 23, 24, 25, 26].

The main capillaroscopic parameters that are analyzed are the number and shape of the capillaries [27, 28], arrangement, capillary diameters (of the arterial, venous arm and of the apical capillary loop) [27, 29]. The presence of dilated (arterial arm diameter greater than 15 μm or venous arm diameter greater than 20 μm) [30] and giant capillaries (diameter greater than 50 μm) [30, 31], avascular zones (distance between adjacent capillary loops greater than 500 μm for the distal row of capillaries and over 300 μm for the proximal row), presence of hemorrhages, neoangiogenesis (newly formed vessels) is assessed [30]. In healthy individuals, the arrangement is correct as the capillaries are oriented relative to each other. 1 to 3 capillary loops are observed in each dermal papilla. The number of capillary loops in healthy individuals is from 7 to 16 per millimeter, with the predominant number being hairpin-shaped with a convex apical part [30]. Hemorrhages may be an expression of local trauma, in which case they are not associated with giant capillaries or neoangiogenesis. In old traumatic damage, it is possible to observe single newly formed vessels (neoangiogenesis) with unchanged capillary density and arrangement of capillaries [27, 32]. Dilated, elongated (length ≥ 300 μm), short capillaries (length ≤ 100 μm) and single branched capillaries of atypical shape may also be found as a variation of the norm in healthy individuals [27, 32]. The subpapillary plexus, from which the capillaries of the nail fold originate, is visible in about 30% of healthy individuals [27, 28]. Variations in capillary shape in healthy individuals include capillaries with folded arms that do not cross each other and capillaries with arms that cross in one or two places [33]. Certain signs of microangiopathy, which are not found in healthy individuals, are giant capillaries and avascular zones, as well as neoangiogenesis in combination with low capillary density [27, 32, 34].

Videocapillaroscopy is currently widely used in the differential diagnosis of primary and secondary RF in rheumatic diseases [27, 28, 29, 30, 31]. The so-called „scleroderma“ and „scleroderma-like“ type of capillaroscopic findings are best studied. The „sclerodermic“ type of capillaroscopic picture is characterized by the presence of giant capillaries, hemorrhages, disorganization, avascular zones and neoangiogenesis. The initial stage of the „sclerodermic“ type of microangiopathy is characterized by the appearance of giant capillaries and single hemorrhages with a preserved capillary

arrangement, without avascular zones. In the so-called „active“ phase, there are a large number of giant capillaries and hemorrhages, a moderate loss of capillaries and a disorder in the arrangement. In the „late“ phase, extensive avascular zones and an advanced disorder in the arrangement are established, as well as numerous branched capillaries, which are an expression of neoangiogenesis [35, 36]. „Scleroderma-like“ type of capillaroscopic finding is observed in part of the patients with other systemic diseases of the connective tissue (undifferentiated collagenoses, overlapping syndromes, dermatomyositis, etc.) [27, 37, 38, 39, 40, 41].

Non-specific changes are mainly observed in patients with systemic lupus erythematosus, rheumatoid arthritis, Sjögren‘s syndrome. These changes include the presence of dilated, elongated capillaries, a prominent subpapillary plexus, hemorrhages, tortuous capillaries with altered morphology [27, 33, 42, 43, 44].

Cutaneous vascular involvement and COVID-19

There is growing interest in the application of capillaroscopic examination in COVID-19 with a view to monitoring peripheral vascular ischemia and skin involvement in some cases. There have been reports of pernions occurring with COVID-19, as well as cases of RF after experiencing infection [5, 6, 17, 18, 22, 23, 45]. and after vaccination against COVID-19 [46, 47].

Lisy et al. (2023) reported 19 cases of RF, of which 15 had a new onset of the syndrome after vaccination, with the initial manifestations of RF occurring after the first dose in 40% of cases, after the second in 33%, and after the third dose of the vaccine in 27%. Three out of four patients with prior RF reported worsening of symptom frequency and intensity [46].

Capillaryoscopy studies in COVID-19

Vascular tropism of SARS-CoV-2 is a basis for using nailfold capillaroscopy to assess the microcirculation in COVID-19. Various author teams have performed capillaroscopy in children and adults with COVID-19, reporting various non-specific findings, but without a specific capillaroscopy picture of the „COVID-19“ type [24, 25, 26, 48, 49, 50, 51].

In a capillaroscopic examination of 15 patients with COVID-19, Gualtierotti et al. (2023) found an increased incidence of microhemorrhages and thrombosis, with no difference in capillary density compared to healthy subjects [48].

Çakmak and colleagues conducted a study in 31 children, aged between 5 and 18 years, diagnosed with COVID-19 (25 patients) and MIS-C (6 patients) and compared capillaroscopy findings with those of healthy children (n = 58) matched by sex and age, without data on chronic disease, smoking or hand trauma. Children with chronic rheumatic diseases or RF were excluded from the study. Demographic data and disease characteristics (symptoms at the onset of COVID-19, duration of infection, clinical features, laboratory tests, therapeutic approach, comorbidities and complications) were analyzed. Infection is proved by PCR, chest imaging, or proven antibodies within the past three months. Among patients diagnosed with COVID-19, 19 (76%) had fever, 14 (56%) – sore throat, 28% – nausea and vomiting. Neurological involvement was found in seven cases, myalgias in seven, arthralgias in three (12%), headache in two (8%), cough in two, cardiac involvement in two patients and diarrhea in one (4%). The average length of hospitalization was 5.5 days (4-12), with 19 patients being followed up in the emergency department for one day. Three cases (12%) were treated with antiviral agents and two (8%) received enoxaparin and all recovered without complications [25]. All diagnosed with MIS-C had fever and cardiovascular symptoms (tachycardia, hypotension and shock) on admission. Five of them (83.3%) had gastrointestinal symptoms (nausea, vomiting, abdominal pain), four (16.7%) had hematological involvement (lymphopenia, thrombocytopenia) and two (33.3%) had cough. All patients received oxygen therapy and inotropic agents, two (33.3%) were treated with noninvasive ventilation, five (83.3%) were pulsed with methylprednisolone, and two with intravenous immunoglobulin. Median length of hospitalization was 5 days (4-7) and all recovered without complications. Laboratory data revealed lymphopenia in 15 patients with COVID-19 (60%) and 4 patients with MIS-C (66.7%), thrombocytopenia in 3 patients with MIS-C (50%), elevated CRP levels in 11 patients with COVID-19 (44%) and 6 MIS-C cases (100%), elevated ferritin levels in 4 MIS-C patients (66.7%), elevated procalcitonin levels in 6 MIS-C patients (100%), elevated D-dimer levels in 4 patients with COVID-19 (16%) and 6 patients with MIS-C (100%), elevated levels of NT-pro-BNP in 1 patient with COVID-19 (4%) and 6 cases with MIS-C (100%). Capillaroscopy was performed under standardized conditions, within an average of 73 days after diagnosis, with two images (a total of 62 patient images and 116 control images) of eight fingers of both hands (thumbs excluded). Capillary morphology, presence of pericapillary edema,

microhemorrhages, avascular zones and neoangiogenesis were analyzed. Significantly lower capillary density, shorter capillary length and greater intercapillary distance were found in patients compared to healthy volunteers. Patients have a higher frequency of capillary branching and tortuous capillaries, microhemorrhages and neoangiogenesis, without avascular zones and giant capillaries. A higher incidence of capillary branching and neoangiogenesis (stimulated by hypoxia, inflammation, and hypercoagulation during the course of the disease) was observed in children with MIS-C, while dilated capillaries were more common in children with COVID-19 [25].

Natalello et al. investigated capillaroscopic changes in adult survivors of COVID-19. Eighty-two patients, average age 58.8 ± 13.2 years, of which 28 – in the acute phase of the disease and 54 – in the recovery phase from COVID-19 pneumonia. The diagnosis was made through a laboratory test and chest imaging. Of the examined patients, 56 (68.3%) were men, 25 (30.5%) had arterial hypertension, 50 (61%) – overweight or obesity, 9 (11%) – diabetes mellitus, 4 (4.9%) – rheumatic disease (2 – rheumatoid arthritis, 1 – crystal-induced arthropathy, 1 – granulomatosis with polyangiitis), 11 (13.4%) were smokers. Eight patients (9.8%) reported acral symptoms associated with COVID-19 (RF – 1, acrocyanosis – 1, puffy hands – 1, distal paresthesia/dysesthesia – 5) and three patients reported RF with longer duration, which is not associated with other symptoms characteristic of systemic connective tissue diseases. In the first group of patients, capillaroscopy was performed during hospitalization, and in the second group, the examination was performed after the patients' clinical improvement and repeated negative tests were recorded. Data on initial symptoms of infection, duration of illness, clinical and radiological features of pneumonia, need for oxygen therapy, inflammatory and coagulation laboratory parameters, thrombotic or other complications, comorbidities, body mass index, concomitant therapy, and specific treatment for COVID-19 were analyzed. In patients evaluated during hospitalization, the mean time from symptom onset to examination was 7.5 ± 5 days. Seventeen patients (60.7%) were on oxygen therapy, two (7.1%) had evidence of pulmonary embolism (in one case associated with deep vein thrombosis), and four (14.2%) had isolated deep vein thrombosis. 14 (50%) were on hydroxychloroquine therapy, 7 (25%) received anticytokine therapy, 24 (85.7%) were on enoxaparin (in a prophylactic or therapeutic dose), four - on acetylsalicylic acid treatment. In patients in the acute phase, the frequency of active smokers and cases of diabetes mellitus is higher. In the patients examined after discharge from the hospital, the average time from the onset of symptoms to the capillaroscopy examination was 52.2 ± 7.1 days. During hospitalization, 30 patients (55.6%) required oxygen therapy and 5 (9.3%) were treated with mechanical ventilation in the intensive care unit. Three patients (5.6%) had pulmonary thromboembolism, and one was associated with deep vein thrombosis. Eight patients reported the onset of acral symptoms associated with COVID-19. All patients received antiviral medications and hydroxychloroquine, 14 were on anticytokine treatment, 15 – on enoxaparin (in prophylactic and therapeutic doses). During the capillaroscopic examination, 4 patients (7.4%) were on anticoagulants (warfarin, enoxaparin, edoxaban, apixaban), and 4 – on acetyl-salicylic acid. Cases with a history of hand microtrauma in the past two weeks were excluded from the study. All fingers except the thumbs were examined, and four different images were recorded for each finger (total of 32 images per patient). The presence of dilated (diameter > 20 μm and < 50), giant capillaries (diameter ≥ 50 μm), microhemorrhages, capillary density, capillary arrangement, capillary branching and capillaries with atypical morphology, tortuous capillaries with crossing arms of more than two sites, sludge phenomenon, pericapillary edema, visibility of subpapillary plexus, avascular zones, empty dermal papillae is assessed. If there are no changes, the score is 0, at < 33% changed capillaries = 1, at 33-66% changed capillaries = 2, over 66% changed capillaries = 3. A high frequency of non-specific capillaroscopic changes was found in 53 patients (64.6%), but no "scleroderma" type of capillaroscopic picture was observed. In the group of patients in the acute phase of the infection, the most frequent findings during capillaroscopy are pericapillary edema (100%), sludge phenomenon (78.6%) and arrangement disorder (50%). In 20 of the patients (71.4%), microhemorrhages were observed, and in 13 (46.4%) of them this change was on more than one finger, and their number was from 1 to 15 per patient. In the group of discharged patients, examined after recovery, non-specific capillaroscopic changes were observed in 25 (46.3%). The presence of dilated (85.2%), tortuous capillaries (81.4%), pericapillary edema (70.4%), capillary density below 9 capillaries per millimeter (63%) was most often found. Giant capillaries and avascular zones were rare findings, both observed in 3 cases. In 17 cases (31.5%) microhemorrhages or microthrombosis were found in at least one finger, and in 6 patients (11.1%) the changes were observed in more than one finger, and their number varied from 1 to 11 per patient [26].

Sulli et al. performed a capillaroscopy in 61 adults who had recovered from COVID-19, com-

paring the findings with 31 patients with primary RF and with 30 sex- and age-matched controls. Data on body mass index, smoking, comorbidities, concomitant drug therapy, pulmonary involvement (assessed by conventional radiography), D-dimers, C-reactive protein, PaO_2 and PaO_2/FiO_2 (by arterial blood gas analysis) were analyzed. The patients were divided into two subgroups according to the severity of the active infection: 34 with a mild and moderate course, without the need for oxygen therapy, and 27 patients with a severe form. Patients and controls with recent hand trauma as well as patients with chilblains after COVID-19 were excluded from the study. Capillaryoscopy was performed on average 126 ± 53 days after diagnosis of infection. Two photographs were taken of the nail bed of the fingers (excluding the thumbs). The presence of dilated (diameter 20-50 μm), giant capillaries (diameter ≥ 50 μm), microhemorrhages, capillary branching (neoangiogenesis) and capillary number per millimeter (normal density ≥ 7 capillaries) was assessed. Again, a semiquantitative scale was used to assess capillaroscopy findings: no change = 0; < 33% altered capillaries/reduced number = 1; 33 – 66% altered capillaries/reduced number = 2; > 66% altered capillaries/reduced number = 3. An additional analysis was performed in patients with severe COVID-19 to assess the effect of different medications on capillary density. None of the patients had manifestations of RF before the infection with COVID-19. Mean capillary density was significantly lower in patients with severe or moderate COVID-19 compared to patients with primary RF and controls. Survivors of COVID-19 showed nonspecific changes (dilated capillaries or isolated capillary branches), but these were not statistically more frequent than in patients with primary RF and controls. Giant capillaries were not found in any group. A positive effect on the preservation of capillary number was observed with the administration of antiviral agents and an anti-IL-6 receptor antagonist, while with treatment with continuous positive airway pressure/CPAP or mechanical ventilation, corticosteroids, anticoagulants and antibiotics no such trend was found. The results of the study indicate that the infection with the SARS-CoV-2 virus does not lead to the formation of a specific type of capillaroscopic picture of the “COVID-19” type, but in cases with a severe course, a loss of capillaries is found. Future studies comparing data before and after contracting COVID-19 are needed to confirm these results [24].

Another team of authors (Mostmans et al.) is conducting a study to evaluate COVID-19-associated chilblains believed to be type I interferon-induced microangiopathy. The purpose of the study is whether this microangiopathy of the skin vessels can be identified by measuring serum levels of vascular endothelial growth factor/VEGF and by nailfold capillaroscopy. The study included 17 patients with chilblains possibly induced by COVID-19. Inclusive criteria were: presence of chilblains-like lesions during the COVID-19 pandemic; no history of previous occurrence of chilblains; without cold exposure before their appearance; persistence of lesions over 48 hours; clinical and histopathological confirmation of chilblains; absence of systemic lupus erythematosus, progressive systemic sclerosis, photosensitive rash or other type of dermatosis in the affected area, antinuclear antibodies (ANA) ≤ 1:160. Capillaroscopic examination was performed in 14 patients, and the quantitative parameters were compared with 14 healthy controls similar in gender and age. Significantly lower capillary density, significantly higher frequency of pathologically shaped capillaries, capillary dilatations and microhemorrhages were found compared to controls. A positive correlation was found between patients’ age and capillary density in both studied groups. Serum VEGF levels in patients with chilblains and healthy controls did not differ significantly. In patients with chilblains, VEGF levels correlated positively with age and capillary density and negatively with the presence of capillary dilatations, the percentage of dilated capillaries, and the degree of visibility of the subpapillary plexus [49].

The presence of microvascular changes was also confirmed in 22 patients with acute infection with SARSCoV-2, in whom capillaroscopy was performed in the area of the nail fold and on the dorsal surface of the 4th finger (Rosei CA et al.). The presence of thrombosis, microhemorrhages and neoangiogenesis during active infection was observed. Changes disappear 3 months after discharge from hospital. Three months after the acute infection, a significant reduction in capillary density was found on the dorsal surface of the fingers. In the acute phase, a negative correlation was found between the capillary density and the values of C-reactive protein and lymphocytes [50].

Karahan et al. (Turkey) conducted a capillaroscopy study in COVID-19 patients treated in the intensive care unit (32 patients, of whom 20 men and 12 women; mean age 61 ± 5 years). Capillary density was significantly lower in the deceased (5.50 ± 0.19 per millimeter) compared to survivors (6.71 ± 0.25) and individuals who did not suffer from COVID-19 (8.55 ± 1.12), ($p < 0.001$) [51].

Table 1 summarizes the main results regarding capillaroscopy findings in patients with COVID-19.

Table 1. Capillaroscopy findings in patients with COVID-19

		Alberto Sulli et al. [24]				Figen Çakmak et al. [25]			Gerlando Natalello et al. [26]		Yora Mostmans et al. [49]	
		Control group (n = 30)	Primary Raynaud's phenomenon (n = 31)	Mild/moderate COVID-19 (n = 34)	Severe COVID-19 (n = 27)	COVID-19 (n = 25)	MIS-C (n = 6)	Healthy controls (n = 58)	Patients in the acute phase	Recovered	Healthy controls (n = 22)	Patients with chills (n = 18)
Capillary number	Normal	30 patients	31 patients	33 patients	22 patients	–	–	–	–	–	–	–
	< 33%	0 patients	0 patients	1 patient	5 patients							
Number of capillaries per mm		9,3 ± 0,53	8,7 ± 0,68	8,4 ± 0,75	8,2 ± 1,15	–	–	–	–	–	–	–
Number of dilated capillaries per mm		–	–	–	–	–	–	–	–	–	0,25*	1,03*
Number of dilated capillaries / total number of capillaries per mm		–	–	–	–	–	–	–	–	–	3,03 %*	16,69 %*
Abnormally shaped capillaries per mm		–	–	–	–	–	–	–	–	–	0,13*	0,40*
Crossed capillaries per mm		–	–	–	–	–	–	–	–	–	0*	0,06*
Capillary branches of mm		–	–	–	–	–	–	–	–	–	0*	0,12 *
Number of capillaries with concave apical part per mm		–	–	–	–	–	–	–	–	–	0,063 *	0,10*
Number of microhemorrhages		–	–	–	–	–	–	–	–	–	0*	0,09*
Visibility of the subpapillary venous plexus		–	–	–	–	–	–	–	–	–	0,38*	0,53*
Dearrangement		–	–	–	–	–	–	–	14 patients	25 patients	–	–
Capillary length		–	–	–	–	294 µm	319 µm	327 µm	–	–	–	–
Arterial arm		–	–	–	–	10 µm	10 µm	11 µm	–	–	–	–
Venous arm		–	–	–	–	13 µm	11 µm	13,5 µm	–	–	–	–
Apical loop		–	–	–	–	16 µm	14 µm	16 µm	–	–	–	–
Intercapillary distance		–	–	–	–	37 µm	31 µm	106 µm	–	–	–	–
Dilated capillaries	Normal	0 patients	0 patients	1 patient	0 patients	12 patients	0 patients	18 patients	4 patients	46 patients	–	–
	< 33%	19 patients	13 patients	23 patients	14 patients						–	–
	34-66%	11 patients	18 patients	10 patients	13 patients						–	–
	> 66%	0 patients	0 patients	0 patients	0 patients						–	–
Giant capillaries		30 patients	31 patients	34 patients	27 patients	0 patients	0 patients	0 patients	0 patients	0 patients	–	–
Avascular zones		-	-	-	-	0 patients	0 patients	0 patients	none	3 patients	–	–
Capillary branches	Normal	23 patients	27 patients	29 patients	19 patients	6 patients	2 patients	0 patients	8 patients	13 patients	–	–
	< 33%	7 patients	3 patients	4 patients	8 patients							
	34-66%	0 patients	1 patient	1 patient	0 patients							
Tortuous capillaries		–	–	–	–	2 patients	1 patient	0 patients	none	44 patients	–	–
Bushy capillaries		–	–	–	–	5 patients	3 patients	0 patients	-	-	–	–

Continuation of table 1

Microhemorrhages	Normal	16 patients	11 patients	23 patients	21 patients	6 patients	1 patient	0 patients	13 patients	6 patients	–
	< 33%	13 patients	19 patients	11 patients	6 patients						
	34-66%	1 patient	1patient	0 patients	0 patients						
	> 66%	0 patients	0 patients	0 patients	0 patients						
Microthrombosis		–	–	–	–	–	–	–	5 patients	1 patient	–
Pericapillary edema		–	–	–	–	1 patient	1 patient	0 patients	28 patients	38 patients	–
Sludge phenomenon		–	–	–	–	–	–	–	22 patients	22 patients	–
Empty dermal papillae		–	–	–	–	–	–	–	none	12 patients	–
Neoangiogenesis		–	–	–	–	5 patients	4 patients	0 patients	none	6 patients	–
Tortuous capillaries	< 50 %	–	–	–	–	3 patients	1 patient	29 patients	–	–	–
	> 50%	–	–	–	–	4 patients	1 patient	0 patients			
	None	–	–	–	–	18 patients	4 patients	29 patients			
Crossed capillaries	< 50 %	–	–	–	–	11 patients	4 patients	26 patients	–	–	–
	> 50%	–	–	–	–	0 patients	1 patient	0 patients			
	None	–	–	–	–	14 patients	1 patient	32 patients			

*Data expressed as median (minimum-maximum)

On the basis of the presented results from the current literature, it can be summarized that the observations of the presence of non-specific capillaroscopic changes in patients who experienced infection with SARS CoV-2 without the formation of a specific capillaroscopic picture of the „COVID-19“ type prevail [2, 24]. There is heterogeneity of the studies regarding the age of the patients, the time of conducting the capillaroscopy examination in relation to the onset of the disease. Nonspecific capillaroscopic findings observed during and after COVID-19 may be related to acute and late post-infectious microvascular damage. On the other hand, a more precise assessment is needed regarding the presence of dynamics of microvascular changes, which requires the follow-up of patient populations in longitudinal studies, taking into account the variations of the norm in nail fold capillaroscopy of healthy individuals. It is also of interest to study the clinical associations of microvascular capillaroscopic changes in patients with PCS [13].

In a recent review, Cutolo et al. (2022) analyzed the results of available capillaroscopy studies in COVID-19 patients [13, 24, 25, 26, 50, 51]. Based on the analysis, the authors hypothesize the presence of two phases of non-specific capillaroscopic changes as a consequence of SARS-CoV-2 infection – „early“ and „late“ phase. Cutolo et al. consider that the „early“ phase probably occurs in patients with acute COVID-19 and is characterized mainly by neoangiogenesis, capillary branching, microhemorrhages and microthrombosis and the „late“ phase non-specific changes is characterized by loss of capillaries, with the realized observations being up to three months after healing. Early and late non-specific changes in COVID-19 are associated with likely development of acute and late microvascular changes. An analogy with the evolution of the specific capillaroscopic changes in progressive systemic sclerosis has been proposed, in which the pathological changes are associated with an initial endothelial injury followed by an autoimmune response and inflammation and subsequent devascularization with a decrease in capillary number. Experts conclude that the microvascular changes in COVID-19, which are currently only partially understood, may underlie the pathogenetic changes in long-term COVID [13].

Conclusion

In conclusion, the acute respiratory virus SARS-CoV-2 that caused the COVID-19 pandemic is associated with a wide range of clinical manifestations, vascular tropism, and potential late complications

in the context of PCS in children and adults. In this regard, there is interest in using capillaroscopic examination to assess microcirculation in patients who have survived SARS-CoV-2 infection. At the present time, the presence of non-specific capillaroscopic changes (capillary branches, microhemorrhages and microthrombosis) as well as reduced capillary density after relapse up to the third month is known. No specific combinations of findings were observed that would enable the definition of a specific capillaroscopy picture of the „COVID-19“ type. Longitudinal studies, as well as data on the capillaroscopic picture before and after infection, are lacking, which requires clarifying the capabilities of the methodology in future studies.

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