

Nailfold Capillaroscopy and Retinal Findings in Patients with Systemic Sclerosis: Is There An Association?

Abstract

Introduction: Systemic sclerosis (SSc) is characterized by fibrosis and intimal proliferation of cutaneous and visceral small vessels. These architectural abnormalities can be visualized with nailfold capillaroscopy (NFC); the changes being quite characteristic. At the same time, morphological alterations in retinal vascular bed are expected but sparsely described. **Aim:** We aimed to characterize the frequency and type of retinal microvascular changes in patients with SSc and to analyze any association with NFC changes. **Patients and Methods:** With institutional ethical committee approval, we recruited 45 consecutive patients with SSc (diagnosed based on American College of Rheumatology and European League against Rheumatism [ACR/EULAR-2013] criteria). NFC was done for all of them with a Universal Serial Bus (USB) dermatoscope; additionally, funduscopy, fundus photography, and optical coherence tomography (OCT) were analyzed. Disease characteristics in patients with and without retinal disease were compared. **Results:** Among the 45 SSc patients, 12 (26.67%) had limited cutaneous SSc (lSSc) while 33 (73.33%) had diffuse cutaneous disease (dSSc). Retinal microvascular changes seen as mild arteriolar alteration and arteriovenous crossing changes were recorded in 13 patients (28.89%); mostly in those with dSSc (12/13). The NFC architectural changes were more severe in patients with retinal disease, though the difference was not statistically significant. **Conclusion:** Patients with SSc can often have retinal microvascular abnormalities commensurate with the vascular changes characteristic of SSc. The severity of retinal changes correlates with changes in NFC. NFC, which is now an essential tool for the management of SSc, could be a surrogate marker for retinal involvement in these patients.

Keywords: Eye, funduscopy, nailfold capillaroscopy, retina, systemic sclerosis

Introduction

Systemic sclerosis (SSc) is an autoimmune connective tissue disease (CTD) with multisystem involvement and varied manifestations.^[1-3] The pathophysiology involves fibroblast dysfunction and vascular abnormality leading to tissue hypoxia and altered immune responses.^[1-3] Intimal proliferation leading to obliteration of blood vessels is responsible for the involvement of various organ systems.^[1-3] The microvascular abnormalities and capillary morphological changes are characteristic of SSc and can be visualized in horizontally lying vessels in the vascular beds of the digital proximal nail folds (PNF) and the retina.

Nailfold capillaroscopy (NFC) is a noninvasive tool to study microvascular abnormalities in the PNF. It has been extensively studied in the setting of SSc.^[4-6]

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Retinal microvascular abnormalities have been extensively studied and reported in lifestyle diseases such as diabetes and arterial hypertension.^[7-10] However, the evaluation of retinal microvasculature in SSc has been sparsely reported. Most of the published data include case reports or small case series, that too in the Caucasian population, limiting the generalization of retinal findings to patients across the globe.^[7-11] Since SSc is known to affect the microvasculature (as evidenced by the NFC), there is a need to study the effect on retinal microvasculature as well. Hence, the present study was designed to evaluate the type and frequency of retinal microvascular changes in SSc and to compare the findings with NFC changes.

Patients and Methods

This observational descriptive study was carried out at a tertiary care center. The

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Deepak Jakhar,
Chander Grover,
Archana Singal,
G. K. Das¹

Departments of Dermatology and STD and ¹Ophthalmology, University College of Medical Sciences and GTB Hospital, New Delhi, India

Address for correspondence:

Dr. Chander Grover,
Department of Dermatology and STD, University College of Medical Sciences and GTB Hospital, New Delhi - 110 095, India.
E-mail: chandergroverkubba76@gmail.com

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study protocol was approved by the institutional review board. We included patients fulfilling the American College of Rheumatology and European League against Rheumatism (ACR-EULAR) criteria for the diagnosis of SSc.^[12] Patients with overlap syndrome or those with hypertension, diabetes mellitus, history of smoking, or drugs that can affect peripheral circulation were excluded from the study.

The hematological, biochemical, and autoantibody profiles including antinuclear antibody, anti-centromere antibody, SCL-70 and dsDNA were done for all recruited patients and recorded. The patients were evaluated clinically and subdivided into limited cutaneous SSc (lSSc) and diffuse cutaneous SSc (dSSc).^[12] Their disease severity was scored with the help of a modified Rodnan skin score (MRSS).

NFC was done with the help of a USB 2.0 videodermatoscope (Dinolite AM413ZT; 20-220X; 1.3 MP). It was performed by a single observer, while the images were stored, processed, and interpreted by two independent observers. Detailed examination for all 10 fingernails was performed after seating the patient comfortably at ambient room temperature for 15 min. They were asked to keep their hands at the level of heart on a dull non-refractive surface.^[4]

For each capillaroscopic image the following parameters were evaluated: linear capillary density (capillary number/mm), presence of micro hemorrhages, capillary drop out, avascular areas, and capillary morphology. The morphology of loops was considered normal or abnormal based on the definition by European League Against Rheumatism (EULAR).^[13] The capillary absolute number was obtained by a method suggested by Jakhar *et al.*^[14] The visibility of sub-papillary plexus was also recorded. The degree of capillary loss was evaluated on the scale proposed by Lee *et al.*^[15]

All patients underwent a complete ophthalmological evaluation by a single physician unaware of their clinical and laboratory profile. The best-corrected distant and near visual acuity (BCVA) was assessed by Snellen and Jaegler charts, respectively. Intraocular pressure (IOP) was measured by noncontact tonometry (NCT). Fundus examination by direct ophthalmoscope followed by fundus photography (Nikon NF-505) and optical coherence tomography (OCT) was also done. Retinal microvascular abnormalities were recorded as arteriolar narrowing, arteriolar nicking, vascular tortuosity, hemorrhages, exudates, and cotton wool spots. The patients were divided into two groups based on the presence or absence of retinal microvascular changes.

The data recorded were statistically analyzed using SPSS V 20. Continuous variables were expressed as the mean \pm standard deviation, whereas categorical variables were expressed as frequencies in percentages. The student's

t-test and Fischer's exact test were used to compare data. A *P* value of <0.05 was considered statistically significant.

Results

Of the 45 SSc patients recruited, 73.34% (33/45) patients had dSSc. There was a female preponderance (male: female ratio of 0.125:1), with the mean age being 33.40 ± 9.78 years (range 18–60 years). The mean age was higher in patients with lSSc (36 ± 8.79 years) as compared to dSSc (32.45 ± 10.07 years); however, the difference was not statistically significant. The average disease duration was 5.8 ± 4.94 years with the mean modified Rodnan score (MRS) being 17.49 ± 9.03 . The mean disease duration was higher in dSSc (6.57 ± 5.38 years) as compared to lSSc (3.67 ± 2.61 years). Similarly, the mean MRS was also higher in dSSc (21.09 ± 7.62) as compared to lSSc (7.58 ± 3.40).

The mean capillary density was 3.57 ± 1.36 capillaries/mm among our patients. It was marginally higher for patients with lSSc (4.30 ± 1.40 capillaries/mm) as compared to those with dSSc (3.30 ± 1.24 capillaries/mm), the difference being statistically significant ($P = 0.045$). The frequency of morphological capillary changes recorded in our patients is summarized in Table 1 [Figure 1a-d]. Abnormal morphology of capillaries was seen in all patients. Overall, changes were more frequent in patients

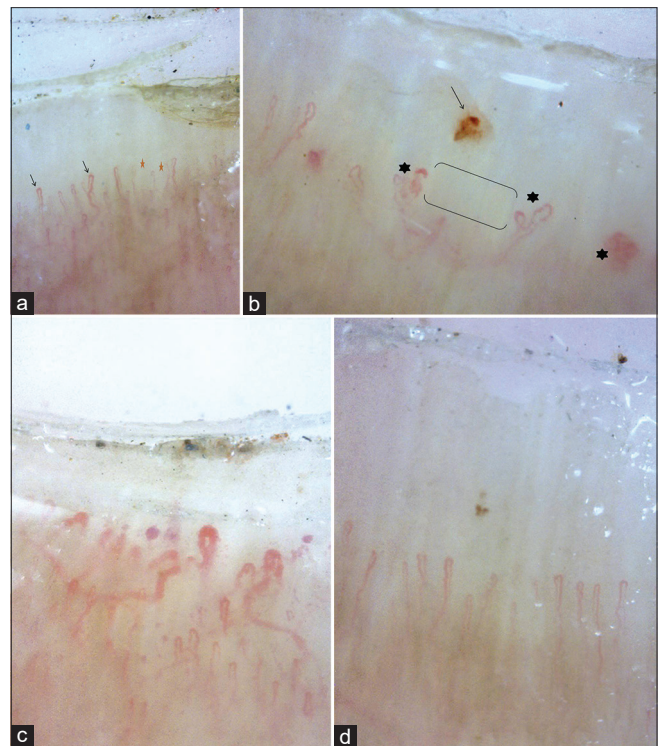


Figure 1: (a): Showing dilated capillaries (black arrows) and capillary dropouts (red stars) (50 \times). (b): Microhemorrhages (black arrow), avascular area (outlined by a black bracket) and bushy capillaries demonstrating neoangiogenesis (black stars) can be seen (150 \times). (c) Multiple bizarre and meandering capillaries [150 \times]. (d) Multiple tortuous capillaries (50 \times) (Dinolite AM413ZT, polarizing view under oil)

Table 1: Frequency of morphological NFC changes in study group participants (n=45)

NFC parameters	Total patients (n=45)		Limited SSc (n=12)		Diffuse SSc (n=33)		P
	n	Percentage	n	Percentage	n	Percentage	
Presence of dilated capillaries	44	97.8%	11	91.7%	33 (100%)	100%	0.27
Normal capillary morphology	1	2.2%	1	8.3%	0	0	0.00
Abnormal capillary morphology	45	97.8%	11	33.33%	33	63.63%	0.27
Evidence of capillary drop outs	22	48.9%	10	83.3%	12	36.4%	0.005*
Presence of avascular areas	36	80%	5	41.67%	31	93.93%	0.000*
Presence of micro hemorrhages	34	75.56%	9	75%	25	75.75%	1.000
Subpapillary plexus visibility	12	26.67%	5	41.67%	7	21.21%	0.254

*P<0.05 was taken as statistically significant; NFC=Nailfold capillaroscopy, SSc=Systemic sclerosis

with diffuse cutaneous involvement as compared to those with lSSc; however, a statistically significant difference could be observed only with respect to the presence of avascular areas (commoner in dSSc) and capillary dropouts (commoner in lSSc) (*P* < 0.05).

An ophthalmological evaluation revealed 40% (18/45) patients to have a low vision (visual acuity <6/18 in the better eye). The IOP was normal and OCT did not reveal macular edema and subretinal fluid; however, retinal microvascular changes were recorded in up to one-third patients (28.89%); being much more commonly detected in patients with diffuse cutaneous disease (36.36%) as compared to lSSc (8.3%) (*P* < 0.05). These were in the form of arteriovenous (AV) crossing changes and mild arteriolar attenuation [Figure 2]. The retinal changes are summarized in Table 2.

We also compared the baseline characteristics of SSc patients with and without retinal changes (13 vs 32 patients). The comparative features are summarized in Table 3; while various NFC findings in these two patient subgroups are shown in Table 4. The mean capillary density in patients with retinal changes was slightly lower (3.25 ± 1.18 capillary/mm) as compared to those without retinal changes (3.70 ± 1.42 capillary/mm) (*P* = 0.706). Almost all NFC morphological alterations were more common in patients with retinal disease although the differences were not statistically significant.

Discussion

NFC is an essential tool in the evaluation of microvasculature in CTDs, especially SSc [Figure 3]. Even in the early disease stage, before the tissue damage, NFC can detect microvascular changes reliably. The affection of the microvasculature in the retina does occur in SSc but has been sparsely studied. In our study, the mean capillary density for the 45 patients was reduced (3.57 ± 1.36 capillaries/mm) as compared to the expected normal (>6 capillaries/mm). A previous Indian study, evaluating 42 SSc patients, had reported the mean capillary density to be 5.3 ± 1.4 capillaries per mm, which was slightly higher than our patients.^[17] This could be due to the longer disease duration in our group of patients. Abnormal

Table 2: Retinal findings in SSc

Retinal findings	Number of patients showing changes (%)
Arteriolar narrowing	10 (22.22%)
Arteriovenous crossing changes	13 (28.89%)
Vascular tortuosity	8 (17.77%)
Hemorrhages	1 (2.22%)
Exudates	0
Cotton wool spots	0

Table 3: Comparative evaluation of SSc patients with and without retinal changes (n=45)

Parameters	SSc with retinal changes (n=13)	SSc without retinal changes (n=32)
Age (in years) ± SD	37.54±11.56	31.53±8.93
M:F ratio	2:11	3:29
BMI	21.51±2.96	21.40±2.21
Mean disease duration (in years) ± SD	8.77±4.23	4.59±4.75
MRSS±SD	21.38±7.18	15.91±9.32

BMI=Body mass index, MRSS=Modified Rodnan skin score, SD=Standard deviation

capillary morphology was seen in 97.8% of the patients. The commonest qualitative changes recorded by us were dilated capillaries (97.8%), avascular areas (80%), and micro hemorrhages (75.56%). Capillary tortuosity was recorded in 100% of cases. A similar frequency of NFC changes has been reported by Marciq *et al.*^[5] (83–93% of SSc patients). In the Indian scenario, similar frequency, as well as types of changes, were reported in 42 SSc patients with dilated capillaries (57.6%) and bushy capillaries (86.4%) being found commonly.^[17] Our study shows a comparably higher frequency of NFC changes among SSc patients as compared to the previous studies; however, our results are consistent with a recent study by Lambova *et al.*, where NFC changes were recorded in 97.2% of the patients. This could be because of the improved sensitivity and resolution of equipment used.^[6]

On comparing the NFC changes between the limited and diffuse cutaneous disease, it was seen that avascular areas were significantly more common in dSSc (*P* = 0.000), while capillary dropouts were more common in limited cutaneous

Table 4: Comparison of NFC features in SSc patients with and without retinal changes

NFC features	SSc with retinal changes (n=13)		SSc without retinal changes (n=32)		P
	n	Percentage	n	Percentage	
Presence of dilated capillaries	13	100%	32	100%	--
Normal capillary morphology*	0	0	1	3.1%	0.00
Abnormal capillary morphology	13	100%	31	96.9%	0.461
Evidence of capillary drop outs	13	100%	29	90.62%	0.372
Presence of avascular areas	12	92.30%	24	75%	0.249
Presence of micro hemorrhages	8	61.54%	26	81.25%	0.251
Sub-papillary plexus visibility	3	23.07%	9	28.13%	1.000

*P<0.05 was taken as significant^[16]



Figure 2: Arteriolar attenuation with arteriovenous crossing changes (green arrow) as visualized on funduscopy in a patient with diffuse cutaneous systemic sclerosis

variant ($P = 0.005$). The frequency of the remaining parameters didn't show statistically significant differences, although the frequency of abnormal capillary morphology was much more in patients with diffuse cutaneous disease.

Among our patients, 18 (40%) were found to have reduced visual acuity. IOP was normal, possibly because we excluded patients with hypertension. OCT is an *in-vivo* noninvasive technique to evaluate the choroid and retina.^[18] It measures the retinal thickness and macular edema and is mainly used in patients with diabetic retinopathy.^[18-20] A previous study by Ignenoli *et al.* had reported the reduction in the choroidal and retinal thickness in SSc patients and primary RP patients.^[18] However, in our study, there was no change in the retinal thickness in SSc patients, nor was there any evidence of macular edema/subretinal fluid. On the other hand, almost one-third of patients (13/45 or 28.89%) showed retinal microvascular changes in the form of mild arteriolar alteration and AV crossing. Previous studies have reported cotton wool spots, intraretinal hemorrhage and optic disc edema in SSc and have attributed these findings to malignant hypertension.^[21] We had excluded patients with hypertension, which may explain the absence of these findings in our study. The tortuosity, arteriolar attenuation, and AV crossing changes seen in our series



Figure 3: Clinical presentation of digital involvement in systemic sclerosis

were presumably a result of arteriosclerosis and vessel wall thickening.^[22] These probably reflect the characteristic microvascular damage of SSc.

The retinal disease was much more common in patients with dSSc (12/13 cases) ($P < 0.05$); probably because of the systemic nature of the disease process in this subset. The longer disease duration in dSSc could also contribute to the higher frequency of retinal microvascular changes. In an earlier study of 45 patients with SSc (27 with ISSc and 18 with dSSc), retinal microvascular changes were reported in a similar ratio.^[23] Ushiyama *et al.*^[11] in their study on 29 SSc patients found retinal changes in 10 patients (34%). The mean capillary density in SSc patients with and without retinal changes (3.25 ± 1.18 and 3.70 ± 1.42 capillaries/mm) was found to be comparable ($P = 0.280$). This finding was consistent with an earlier report by Ushiyama *et al.*^[11] The differences in qualitative NFC parameters among the two groups were also not significantly different statistically. Our finding was again in concordance with the previous study by Ushiyama *et al.*^[11] Though not statistically significant, our study does indicate that patients of SSc with the retinal disease have more severe NFC changes. Thus, this may be used as an indicator for retinal disease, further representing the systemic vascular changes, even possibly reflecting the involvement of the central nervous system vasculature. Cutolo *et al.* had reported focal or diffuse cerebral

hypoperfusion in their neurologically asymptomatic patients of SSc.^[24] Further studies are required to decide the significance of this possible association.

Limitations

A small sample size and limited time duration may have prevented the study to reach a statistically significant conclusion. In addition, we didn't have a healthy population group to compare our retinal findings. Fundus fluorescein angiography or evaluation for the dry eye could not be done due to resource constraints.

Conclusion

Our study substantiates the importance of NFC in the evaluation of SSc, both as a diagnostic as well as a prognostic tool. It also signifies the importance of detailed ophthalmologic evaluation, especially funduscopy of SSc patients as a fairly good number show retinal involvement. It seems particularly relevant for patients with diffuse cutaneous SSc.

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Conflicts of interest

There are no conflicts of interest.

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