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"Role of dermoscopy in detection of nailfold capillaroscopic changes in autoimmune connective tissue diseases "

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Abstract:

Background: Nail fold capillaries abnormalities are characteristic in some autoimmune connective tissue diseases. Recently, handheld dermoscope can be used to detect these abnormalities.

Aim of the study: To evaluate the nail fold capillaries pattern in different autoimmune connective tissue diseases using handheld dermoscope. Moreover, the relation between morphologic abnormalities and disease duration, activity, and severity were attempted.

Patients and Methods: This cross-sectional study was carried out over a period of six months on patients presenting to outpatient clinics of Alexandria main University hospital diagnosed with autoimmune connective tissue diseases. Sixty-seven females were included and were further categorized according to their primary connective tissue diseases. Disease specific markers and disease activity were assessed. Capillaroscopy was performed using DermLite® DL4 pocket dermoscope.

Results: The scleroderma pattern was detected in 100% of scleroderma and dermatomyositis, 71.4% of mixed connective tissue disease, 65.2 % of rheumatoid arthritis, and 52.9 % of systemic lupus erythematosus patients. There was a statistically significant relation between systemic lupus erythematosus disease activity index and abnormal morphology. There was no statistically significant relation between dermoscopic findings and any other disease activity markers, patients' age, or disease duration.

Conclusion/ recommendations: Dermoscopy is a helpful tool in assessment of nail fold capillaries abnormalities in autoimmune connective tissue diseases. Furthermore, in SLE patients, as abnormal morphology correlates with disease activity, dermoscopy could be a suitable screening test.

Keywords: Autoimmune connective tissue diseases, Capillaroscopy, Dermoscopy, Nailfold capillaries, Scleroderma pattern.

Introduction:

Nailfold capillaroscopy (NFC) is a sensitive, inexpensive, safe, and noninvasive imaging technique used in the morphological analysis of nourishing capillaries in the nailfold area [1]. In most areas of the finger, nutritional capillaries in dermal papillae are oriented at 90 ˚ to the skin surface so that only the tip of the loops can be seen as dots or commas. In nail folds, the capillary loops are parallel to the skin surface and in the last row they are seen in full length [2].

Nail fold capillaries morphological abnormalities are characteristic findings of some connective tissue diseases (CTD). NFC can be used for early diagnosis of CTD as well as distinguishing between primary and secondary Raynauds phenomenon [2]. Instruments that can be used for this purpose include stereomicroscope, opthalmoscope, dermoscope and videaocapillaroscopy [3].

So far, the gold standard for performing NFC has been nailfold videocapillaroscopy, which requires special equipment and settings, expensive, time-consuming, and not easily portable. Recently, the handheld low cost dermoscope was suggested to replace it in performing NFC [4,5].

First described by Maricq et al, in 1973, the scleroderma (SD) pattern of nailfold capillaries corresponds to a set of typical NFC changes characterized by the presence of dilated capillaries (ectasia and/or megacapillaries), loss of capillary loops, with consequent reduction in the number of capillaries, micro-bleeding and neoangiogenesis (branched capillaries). Two or more of these criteria in at least two nail folds were required to diagnose the SD pattern and any findings that fall short of this definition are diagnosed as non-specific [6].

The aim of this study was to evaluate NFC pattern in different autoimmune CTDs using the handheld dermoscope. Relations between the morphologic abnormalities and disease duration, activity and severity were attempted.

Patients and methods:

Study population

This cross-sectional study was carried out over a period of six months (between Jan and July 2021) on patients diagnosed with autoimmune connective tissue diseases from the attendants of outpatient clinics of Physical Medicine, Rheumatology and Rehabilitation and Dermatology departments, Alexandria Main University Hospital, Egypt. An informed consent was obtained from all participants, following the detailed explanation of the nature of the study. The institutional ethical committee approved the study (serial No: 0304243, IRB No: 0000-7555, FWA No: 00018699), and the research was conducted in accordance with the 1964 Helsinki Declaration and its later amendments.

Patients with any ungual or periungual disease were excluded. Smokers, diabetic, cardiac, hypertensive or cancer patients were also excluded.

Study Procedure

All patients underwent detailed history taking and musculoskeletal assessment. A specific marker was recorded according to each disease category; anti-citrullinated peptide antibody (ACPA) in RA patients, anti-double stranded *d*eoxyribonucleic acid (*a*nti-ds DNA*)* in SLE patients, antibodies against ribonucleoproteins (anti-U1-RNP) in MCTD and creatine phosphokinase (CPK) in DM. Disease severity was assessed according to each disease category; the 28 joint disease activity score-C-reactive protein (DAS28-CRP) in RA patients, SLE disease activity index (SLEDAI) in SLE patients, SSc activity score in SSc and myositis disease activity assessment tool *(*MYOACT*)* in DM [7]**.**

Capillaroscopic assessment:

Capillaroscopy was performed using handheld DermLite® DL4 pocket dermoscope (3Gen LLC, San Juan Capistrano, CA, USA). Examination was carried out using the polarized mode at tenfold magnification, with a liquid interface (ultrasound gel). Images were captured by iPhone® 8 plus camera (Apple, Cupertino, CA, USA) with

digital zoom up to 10x. Both devices were attached together by a connector allowing zooming in on details with further magnification.

Dermoscopy was performed on all fingers of each subject. The patient sat with the hand at the heart level, after a 15–20 min rest in room temperature, ultrasound gel was placed on proximal nail folds. The contact glass plate was removed to avoid blanching of nailfold capillaries. Ring, middle and little fingers showed the most prominent changes. The following parameters were evaluated: 1) capillary diameter, 2) microhemorrhages, 3) distribution, 4) capillary loss and 5) morphology. Capillaroscopic findings were accepted as abnormal if changes were observed in at least two fingers [4].

Statistical analysis

Data were analyzed using the IBM-SPSS software package version (20.0). (Armonk, NY: IBM Corp). Number and percent were used to describe qualitative data. Normality of distribution was verified by Shapiro-Wilk test. Significance of the obtained results was judged at the 5% level. Chi-square test was used for categorical variables, to compare between different groups. Fisher's Exact or Monte Carlo correction was used for correction for chi-square when more than 20% of the cells have expected count less than 5. Student t-test was used for normally distributed quantitative variables, to compare between two studied groups and Mann Whitney test for abnormally distributed quantitative variables.

Results:

Demographic and clinical characteristics of the studied groups:

Sixty-seven female patients with age ranging from 18-81 years were included. Patients had an established diagnosis of rheumatoid arthritis (RA) (27 cases, 40.3%), systemic lupus erythematosis (SLE) (21 patients, 31.3%), mixed connective tissue disease (MCTD) (8 patients, 11.9%), systemic sclerosis (SSc) (7 patients, 10.4%), and dermatomyositis (DM) (4 patients, 6%).

The mean age among patients was 37.12 ± 13.65 years (ranging from 18-81 years). Distribution of the studied patients according to different disease parameters in

each subgroup and the total patients is shown in (Table 1). The median disease duration of the total patients' population was 3 years ranging from 1 month to 20 years.

In RA patients, most had moderate and high disease activity (81.5%) with a mean DAS28-CRP of 4.17 ± 1.09. 10/27 (37%) were seronegative RA. 23/27 (85%) were on multiple conventional disease-modifying antirheumatic drugs (DMARDs), 1/27 was on leflunomide monotherapy, and 3/27 were on biological DMARDs (Etanercept).

In SLE patients, most patients had low and moderate disease activity (76.2%) with a median SLEDAI of 14 ranging from 4 to 51. 3/21 had associated antiphospholipid syndrome. All patients (100%) were on multiple conventional DMARDs, of which 6/21 were on mycophenolate mofetil.

The MCTD patients had a higher median anti-ds DNA level of 77.5 IU/mL compared to SLE patients, with most patients presenting with moderate and high disease activity (75%). Most patients with MCTD had predominantly SLE and SSc features. All patients (100%) were on multiple conventional DMARDs, of which 6/8 were on steroids.

Most SSc patients had moderate disease activity (85.7%), moreover 1/7 had limited type and another had CREST syndrome. Similarly, most **DM patients** had moderate disease activity (75%), with highly elevated CPK ranging from 900 to 1600 U/L.

Table 1. Distribution of the studied patients according to different disease parameters in each subgroup and total patients

	Total patient (n = 67)	**RA (n = 27)**	**SLE (n = 21)**	**Other CTD (n = 19)**
Disease duration (years)				
Min. – Max.	20.0–0.10	20.0–0.50	16.0–0.60	18.0–0.10
Median (IQR)	7.50)–3.0 (2.0	10.0)–3.0 (2.0	6.0)–4.0(2.0	6.50)–2.0(1.25
ACPA (u/ml)	(n = 27)	(n = 27)		
Min. – Max.	9587–4	9587–4	-	-
Mean ± SD.	1873.4±627.3	1873.4±627.3		
Median (IQR)	395.5)–73 (11.6	395.5)–73 (11.6		
DAS28 CRP	(n = 27)	(n = 27)		
Min. – Max.	6.15–1.94	6.15–1.94	-	-
Mean ± SD.	1.09±4.17	1.09±4.17		
Median (IQR)	4.95)–4.33 (3.46	4.95)–4.33 (3.46		
C3	(n = 29)		(n = 21)	(n = 8)
Min. – Max.	205–30	-	205–30	154–34
Mean ± SD.	50.11±92.66		54.13±95.29	39.97±85.75
Median (IQR)	110)–89 (59		112)–80 (59	107)–92.5 (49.5
C4	(n = 29)		(n = 21)	(n = 8)
Min. – Max.	45–4	-	40 –4	45–10
Mean ± SD.	10.64±21.38		9.01±19.76	13.88±25.64
Median (IQR)	25)–18.1 (13		25)–18 (13	40)–20.55 (14.5
Anti-ds DNA (IU/mL)	(n = 29)		(n = 21)	(n = 8)
Min. – Max.	298–10	-	298–10	200–32
Mean ± SD.	72.77±88.27		79.78±89.61	54.55±84.75
Median (IQR)	125)–75 (32		127)–66.1 (24	104.5)–77.5 (41
anti-RNP (U)	(n = 8)			(n = 8)
Min. – Max.	47–10	-	-	47–10
Mean ± SD.	12.86±27.1			12.86±27.1
Median (IQR)	35.5)–28.4 (16			35.5)–28.4 (16
SLEDAI	(n = 21)		(n = 21)	
Min. – Max.	51–4	-	51–4	-
Mean ± SD.	12.61±15.67		12.61±15.67	
Median (IQR)	19)–14 (8		19)–14 (8	
Disease activity	(n = 67)	(n = 27)	(n = 21)	(n = 19)
Rem	1 (1.5%)	1 (3.7%)	0 (0.0%)	0 (0.0%)
Low	15 (22.4%)	4 (14.8%)	8 (38.1%)	3 (15.8%)
Moderate	35 (52.2%)	15 (55.6%)	8 (38.1%)	12 (63.2%)
High	16 (23.9%)	7 (25.9%)	5 (23.8%)	4 (21.1%)

SD: Standard deviation n: number, IQR: Inter quartile range
SLE: systemic lupus erythematousis, CTD: connective tissue disease, RA rheumatoid arthritis,
ACPA: anti-citrullinated peptide antibody, DAS28-CRP: 28 joint disease activity score-C-reactive protein
Anti-dsDNA: anti-double stranded DNA, anti- RNP: antibodies against ribonucleoproteins
SLEDAI: SLE disease activity index, Rem: remission

Nail fold dermoscopic findings:

The nail fold capillaries were successfully visualized in 58/67 (86.6%) of patients. Patients with SSc had the highest rates of abnormal capillaroscopic findings, nearly 100% across all studied parameters, followed by MCTD, RA and finally SLE patients. Detailed description of the nail fold capillaries abnormalities in total patients and each disease category is shown in Table 2 (Figures 1-3). The scleroderma pattern was detected in 100% of SSc and DM patients, 71.4% of MCTD, 65.2 % of RA, and 52.9 % of SLE patients.

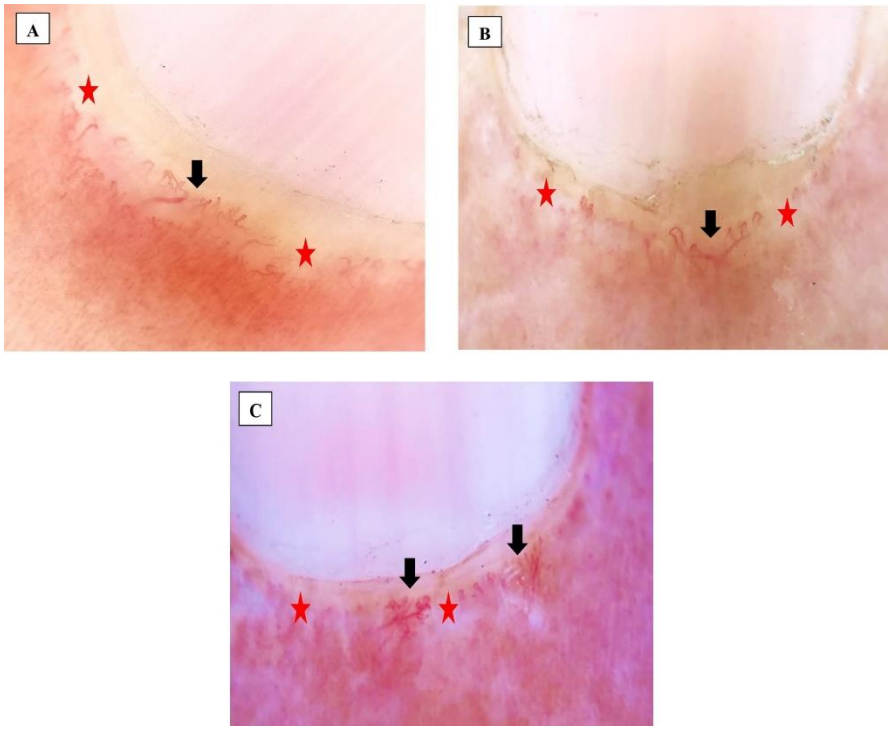

Figure (1): Nail fold capillaroscopy of three cases of systemic sclerosis (A, B and C) showing dilated, disorganized, branched capillary loops (black arrows) and extensive dropouts (red stars). (Dermlite 4, original magnification ×10)

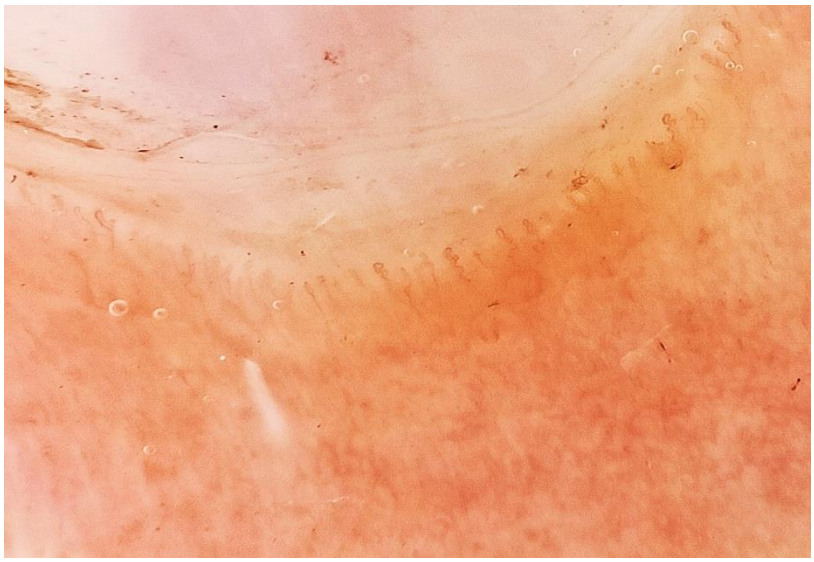

Figure (2): Nail fold capillaroscopy of a case of rheumatoid arthritis showing dilated tortuous capillary loops. (Dermlite 4, original magnification ×10)

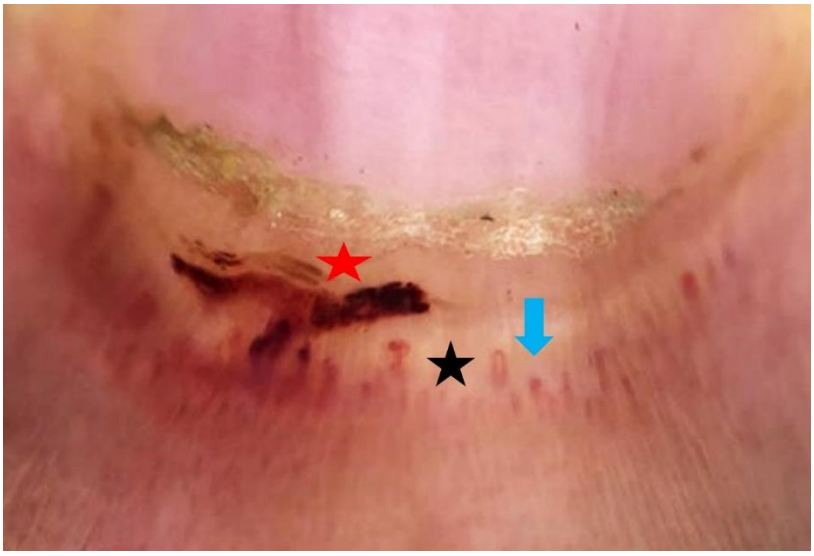

Figure (3): Nail fold capillaroscopy of a case of dermatomyositis showing extensive microhemorrhage (red star), dilated, tortuous capillaries (blue arrow) and dropouts (black star). (Dermlite 4, original magnification ×10)

Table 2. Distribution of patients according to proximal nail fold capillaries abnormalities by dermoscopy.

		Total patients (n = 58)		RA (n = 23)		SLE (n = 17)		Other CTD					
								MCTD (n = 7)		SSc (n = 7)		DM (n = 4)	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Morphology	Normal (Hairpin)	12	20.7	5	21.7	5	29.4	1	14.3	0	0.0	1	25.0
	Abnormal ±(Tortuous ramified)	46	79.3	18	78.3	12	70.6	6	85.7	7	100.0	3	75.0
Diameter	Normal	13	22.4	6	26.1	5	29.4	1	14.3	0	0.0	1	25.0
	Abnormal Giant)±(Dilated	45	77.6	17	73.9	12	70.6	6	85.7	7	100.0	3	75.0
Distribution	Organized	31	53.4	13	56.5	11	64.7	3	42.9	2	28.6	2	50.0
	Disorganized	27	46.6	10	43.5	6	35.3	4	57.1	5	71.4	2	50.0
Density	Normal	10	17.2	5	21.7	4	23.5	0	0.0	1	14.3	0	0.0
	Dropout	48	82.8	18	78.3	13	76.5	7	100.0	6	85.7	4	100.0
Micro hemorrhage	Negative	31	53.4	13	56.5	11	64.7	3	42.9	2	28.6	2	50.0
	Positive	27	46.6	10	43.5	6	35.3	4	57.1	5	71.4	2	50.0
Sub papillary plexus	Negative	48	82.8	21	91.3	14	82.4	5	71.4	5	71.4	3	75.0
	Positive	10	17.2	2	8.7	3	17.6	2	28.6	2	28.6	1	25.0

n: number, SLE: systemic lupus erythematousis, CTD: connective tissue disease, RA rheumatoid arthritis, MCTD: mixed connective tissue disease, SSc: systemic sclerosis, DM: dermatomyositis

Relations between capillaroscopic findings and clinical characteristics of patients:

There was no statistically significant relation between the capillaroscopic abnormalities (morphology, diameter, or density of nailfold capillaries) and age of patients, disease duration or disease activity (Table 3).

Table 3. Relation between age, disease activity and dermoscopic findings in total patients (n = 58)

	N	Age (years)	Disease duration	Disease activity		
		SD.±Mean	Median Max.)–(Min.	Low (n = 11)	Moderate (n = 31)	High (n = 16)
Morphology						
Normal (Hairpin)	**12**	12.17±36.25	7)–3 (0.5	3 (27.3%)	5 (16.1%)	4 (25.0%)
Abnormal ±(Tortuous ramified)	**46**	13.48±36.89	20)–3.5(0.1	8 (72.7%)	26 (83.9%)	12 (75.0%)
Test of Sig. (p)		t= 0.149,p=0.882	U=195,p=0.117	χ^2=1.117,^{MC}p=0.581		
Diameter						
Normal	**13**	12.07±31.46	20)–3 (1	4 (36.4%)	5 (16.1%)	4 (25.0%)
Abnormal Giant)±(Dilated	**45**	13.14±38.29	18)–3 (0.10	7 (63.6%)	26 (83.9%)	12 (75.0%)
Test of Sig. (p)		t= 1.679,p=0.099	U=277.5,p=0.778	χ^2=2.142,^{MC}p=0.295		
Density						
Normal	**10**	11.57±41.50	10)–2.5(0.5	1 (9.1%)	6 (19.4%)	3 (18.8%)
Dropout	**48**	13.32±35.77	20)–3 (0.1	10 (90.9%)	25 (80.6%)	13 (81.3%)
Test of Sig. (p)		t= 1.263,p=0.212	U=198,p=0.384	χ^2=0.56,^{MC}p=0.808		

U: **Mann Whitney test** **t: Student t-test** SD: **Standard deviation**

χ^2: **Chi square test** MC: **Monte Carlo**

p: p value for comparing between the different categories

*: Statistically significant at $p \leq 0.05$

In RA patients, there was no significant relation between disease duration, ACPA levels or DAS28 with morphology, diameter, or density of nailfold capillaries. However, there was a tendency for higher ACPA levels in patients with abnormal morphology, diameter, and reduced density of nailfold capillaries. **In SLE patients,** there was no statistically significant relation between disease duration or anti-ds DNA with morphology, diameter, or density of capillaries. However, there was a tendency of higher anti-ds DNA with abnormal morphology, dilated capillaries, and reduced density of nailfold capillaries.

There was a statistically significant relation between SLEDAI and abnormal morphology (p=0.019), being higher with abnormal morphology with a median of 17.5. Although the relation with diameter and density of capillaries insignificant, however, there was a tendency of higher SLEDAI with abnormal morphology and reduced density. Due to

the small number of patients, tests of significance could not be carried out for the MCTD group.

Discussion:

This cross-sectional study included 67 female patients with an age of 18 to 81 years. Patients were already diagnosed with RA (40.3%), SLE (31.3%), MCTD (11.9%), SSc (10.4%), and DM (6%). Nail fold capillaries demonstrated abnormal morphology in 79.3% of patients. Patients with SSc had the highest rates of abnormal capillaroscopic findings, nearly 100% across all studied parameters, followed by MCTD, RA and finally SLE patients. The scleroderma pattern was detected in 100% of SSc and DM patients, 71.4% of MCTD, 65.2 % of RA and 52.9 % of SLE patients.

Although some authors reported non-specific capillaroscopic findings in RA patients with absence of scleroderma pattern, [8,9] others reported evident capillaroscopic changes in RA patients in agreement with our results as the study by Rajaei et al, [10] which reported tortuosity and angiogenesis in up to 99.5% and 74.7% of RA patients respectively and scleroderma pattern in 20.9% of them.

The study by Beltrán et al [9] showed a typical SD pattern in 73% of cases of limited SSc and in 82% of cases of diffuse SSc. The study by Barbach et al, [11] reported the SD pattern in 75% of SSc, 47% of MCTD, 45% of DM, and 23.3% of SLE patients. Moreover, the study by Bergman et al, [12] reported it in 70.4% of SSc, 63.6% of DM, 50% of MCTD, and only 4.5% of SLE patients. Sundaray et al, [13] found that SD pattern was detected in 62.5% of patients with SSc and in 60% with MCTD. Non-specific pattern was found in 80% of SLE cases and 50% of dermatomyositis cases.

These variations could be attributed to the clinical diversity of CTDs where no patient has findings like the other either in organ affection or extent of involvement, also variation in disease duration may play a role, as these studies did not consider disease duration, and which was wide in our patients (0.1 to 20 years) with more than 75% of patients having established disease (disease duration >2 years) [14].

In the present study, tortuous, with or without ramified, capillaries were visualized in 100% of SSc, 85.7% of MCTD, 78.3 % of RA, 75% of DM and 70.6% of SLE patients. Dilated or giant capillaries were distributed as follows; 100% of SSc, 85.7% of MCTD, 75% of DM, 73.9% of RA and 70.6 % of SLE patients. Disorganized capillaries were seen in 71.4% of SSc, 57.1% of MCTD, 50% of DM, 43.5% of RA and 35.3% of SLE patients.

Dropouts were reported in 100% of MCTD and SSc, 78.3% of RA and 76.5% of SLE patients. Microhemorrhage was seen in 71% of SSc, 57.1% of MCTD, 50% of DM, 43.5% of RA, and 35.5% of SLE patients.

In agreement with our results, the study by Barbach et al [11] had reported the followings; disorganized capillaries in 59.3%of SSc, 27.5% of DM, 19.6% of SLE, 58.8% of MCTD patients. Dilated capillaries were seen in 46.8%of SSc, 25% of both DM and SLE, and 29.4% of MCTD. Tortuous capillaries were detected in 56.2% of SSc, 32.5% of DM, 31% of SLE, and 41% of MCTD. Microhemorrhage was visualized in 56.2% of SSc, 25% of DM, 30.3% of SLE, and 41.1% of MCTD. Finally, dropouts were seen in 37.5% of SSc, 12.5%of DM, 3.4% of SLE, and 23.5% of MCTD patients.

The present study had revealed that there was no statistically significant relation between the capillaroscopic abnormalities with neither the age of patients nor disease duration or activity.

In RA patients, there was no significant relation between disease duration, ACPA level or disease activity (DAS28-CRP) with the morphology, diameter, or density of nailfold capillaries. However, there was a tendency for higher ACPA and disease activity levels with abnormal morphology, diameter and reduced density, and a tendency for longer disease durations with abnormal morphology and reduced density. Although there is no direct link between RA pathogenesis and the detected changes in NFC, the autoantibody linked to the disease pathogenesis and progression may play a role in linking these findings [10].

In SLE patients, there was no statistically significant relation between disease duration or Anti-ds DNA and morphology, diameter, or density of capillaries. However, there was a tendency for longer disease duration and higher Anti-ds DNA with abnormal morphology, dilated capillaries, and reduced density of nailfold capillaries.

There was a statistically significant relation between SLEDAI and abnormal morphology, where abnormal morphology was detected in patients with high disease activity with a median of 17.50. Although the relation with diameter and density of capillaries was not significant, there was a tendency of SLEDAI being higher with abnormal morphology and reduced density.

Similarly, a study by Chojer and Mahajan,[5] supports our findings as several cutaneous and systemic organ involvements in SLE patients showed statistically significant relations with capillaroscopic findings. SLEDAI is a comprehensive disease activity

assessment tool in SLE involving multiple cutaneous and systemic organs, so one can conclude that both studies support that disease activity in SLE is associated with microvascular changes. A possible explanation that supports this finding is that the immune complexes implicated in the organ damage in SLE patients are also responsible for the vascular changes detected by the NPC [10,15]. On the contrary, Nagy et al,[8] reported no relevant association between the clinico-laboratory findings in SLE patients and capillaroscopic results.

Several studies have found relations between microvascular abnormalities evaluated by NFC and disease characteristics (duration and severity) in SSc [16,17] and DM patients [18]. On the contrary, the study by Shenavandeh et al,[19] could not find such association in DM patients. Surprisingly, Manfredi et al,[20] found that more severe changes were associated with shorter disease duration in DM. The study by Chanprapaph et al,[21] found that the presence of enlarged capillaries indicated higher SLE severity, but no specific finding was related to DM or SSc severity scores. In our study we could neither support nor decline such a link due to the small sample of SSc and DM patients enrolled, as tests of significance could not be carried out.

Study limitations:

The effect of medication and fluctuation in disease activity could not be assessed as this is a cross-sectional study. As CTDs have diverse pathogenesis and presentations this may have diluted the data. As all patients enrolled in this study were females so gender differences could not be assessed. Limited time period and small sample size are among the limitations of this study.

Conclusion and Recommendations:

In conclusion, handheld dermoscopy can be a useful modality in the assessment of nailfold capillary abnormalities in autoimmune connective tissue diseases. Furthermore, in SLE patients, as abnormal morphology correlates with disease activity, dermoscopy could be a suitable screening test.

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