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Nailfold capillary abnormalities in patients with familial Mediterranean fever

A. Dinç, M. Melikoğlu, C. Korkmaz, I. Fresko, H. Özdoğan, H. Yazici

Division of Rheumatology, Department of Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Turkey.

A. Dinç MD, Fellow; M. Melikoglu MD, Fellow; C. Korkmaz MD, Fellow; I. Fresko MD, Fellow; H. Özdogan MD, Professor; H. Yazici MD, Professor and Chief.

Please address correspondence to: Melike Melikoglu MD, Cumhuriyet sitesi, 7-8. kysym D31C D: 20, Ataköy, Istanbul Turkey
E-mail: tanverdi@veezy.com

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ABSTRACT

Objective

To determine the frequency and the degree of the nailfold capillary abnormalities in patients with familial Mediterranean fever (FMF).

Methods

We studied 67 (M/F: 28/39) patients with FMF. Thirty-seven healthy subjects (16/21), 19 patients (0/19) with systemic lupus erythematosus (SLE), and 8 patients (0/8) with scleroderma (PSS) were also studied. All participants were questioned for the presence of Raynaud's phenomenon (RP). Capillary loops of eight fingers were evaluated and scored with respect to avascular areas, tortuosity, enlargement and extravasations by the conventional capillary microscopy. Both FMF patients and healthy controls were examined in a blind manner.

Results

FMF patients differed from healthy controls by the presence of increased tortuosity and enlargement of capillary loops, but not by microhemorrhages. Being female and the presence of RP were the factors that correlated with the capillaroscopic findings.

Conclusion

Capillary abnormalities are seen in patients with FMF.

Introduction

Familial Mediterranean fever (FMF) is a recessively inherited disorder characterized by recurrent, self-limited attacks of fever and serositis (1, 2). Amyloid deposits surrounding capillaries may develop in FMF patients remaining untreated. Some patients with FMF also have associated vasculitis (1, 3).

Capillaroscopy is a simple tool that permits noninvasive *in vivo* study of the capillary network. Diverse diseases that have a vasculitic component cause changes in nailfold capillaries (4) and it is of great practical use when confronted a patient with Raynaud's phenomenon enabling an early diagnosis of scleroderma (5-9).

Based on the vasculitic features and the amyloid accumulation involving microvasculature in FMF as mentioned above, we looked at the nailfold capillaries in a group of FMF patients and suitable controls in a masked protocol.

Patients and methods

Sixty-seven consecutive FMF patients registered in our dedicated outpatient clinic constituted the probands. Thirty-seven healthy subjects, 19 consecutive patients with systemic lupus erythematosus (SLE) and 8 patients with progressive systemic sclerosis (PSS) were studied as controls. Patients younger than 13 years were excluded. This is the age when capillary maturation is completed (10).

All participants were questioned for the presence of RP. RP was defined as the presence of biphasic or uniphasic color changes plus paresthesias in response to cold exposure (11).

After excluding fingers with grossly deformed nailfolds, the rest of the digits other than the thumbs were examined. The examinations were performed at a comfortable temperature (24-28°C) after acclimatization of the patients for fifteen minutes. The subjects were seated in front of the microscope and their hands were placed on the microscope stage approximately at the level of heart. Both FMF patients and healthy controls were examined blindly via placing a cover between the physician and the individual. However, the evaluation for the diseased controls were not masked in that we reasoned most would anyhow be recognized by the appearance of their hands.

Nailfold capillaroscopy was performed using a stereomicroscope (Nikon SMZ-2 T). The initial 10-20 times magnification was used to ensure a wide field as described by Maricq (6). After evaluating the overall dominant pattern of the capillary bed, detailed observations of abnormal areas were accomplished under high power (40-60x). The nailfold with the highest score of capillary abnormalities was taken as the representative score for that proband or control. It was scored by the same physician (AD). Overall variability of the method was assessed by repeating the procedure one-month later in 21 FMF patients. No measurements of the distal row of capillaries or the individual loops were made. Table I shows the

capillaroscopic scoring criteria that were used.

The finger with the most severe capillary changes and the fourth digit was photographed in cases with abnormal and normal findings, respectively (Fig. 1. A, B). The photographs were coded and assessed by another observer reading a total of 82 prints from all groups.

All the data were recorded onto an electronic worksheet and statistical analyses were performed using a statistical software package (SPSS 4.5, SPSS Inc., USA). According to the data characteristics and its distribution, non-parametric statistical methods were chosen for evaluation. Chi-square, Fisher's exact and Wilcoxon's signed rank tests were used where appropriate and zero scores were included in all analyses. Alpha value was set to 0.05.

Results

The demographic data related to age, sex, and the presence of RP are shown in Table II. All FMF patients were using colchicine and mean disease duration from the onset of symptoms was 13.75 ± 8.32 years (range 2-37). Thirty-four patients (50.7%) had experienced an attack within the preceding six months. Proteinuria, suggesting the presence of amyloidosis was present in four patients. No FMF patient had experienced any clinical event suggestive of vasculitis.

Seven FMF patients and one healthy subject in whom capillaries could not be visualized due to uninterpretable nailfolds (*i.e.* scaled or thickened) were excluded. Features of scleroderma were encountered in a 54 year-old female FMF patient who had typical attacks of FMF for 35 years and had received colchicine for two years. This patient, who gave a history of RP for 15 years, was also excluded from the analysis of the results.

Table I. Capillaroscopic scoring.

A. Avascular areas (loss of more than two consecutive capillary loops)
   0 Absent
   2 Present

B. Tortuosity
   0 Normal (tortuosity in less than 10% of the loops)
   1 Slight (tortuosity in more than 10% of loops or focal crossed loops)
   2 Marked (frequent crossed loops or presence of bushy capillaries)

C. Enlargement
   0 Absent
   1 Focal enlarged capillaries or frequent apically enlarged capillaries
   2 Frequent enlarged capillaries or presence of megacapillaries

D. Extravasations (microhemorrhages)
   0 Absent or clearly traumatic
   1 Focal dotty microhemorrhages
   2 Clustered (more than 3 lesions) microhemorrhages or frequent dotty microhemorrhages.

Splinter hemorrhages were observed in only one FMF and one SLE patient. No avascular areas were detected in patients other than among those with PSS. Thus this parameter was also excluded from the formal analysis.

According to capillaroscopic scoring (Table III), all groups varied from each other in terms of tortuosity, enlargement and microhemorrhages ($p < 0.001$). When the data of the most abnormal group (PSS) were omitted, the statistical significance persisted ($p < 0.05$). All FMF patients with high scores were female. FMF patients differed from healthy controls with respect to tortuosity ($p = 0.057$) and enlargement ($p = 0.012$) but not to microhemorrhages ($p = 0.31$); on the other hand comparison of their corresponding subgroups lacking RP revealed the completely opposite results ($p = 0.357$, $p = 0.285$ and $p = 0.022$, respectively). In the same manner, excluding microhemorrhages, no differences were observed between FMF and SLE patients with respect to tortuosity and enlargement. This remained robust when the data related to patients with RP were omitted. The comparison of FMF patients with and without RP showed a significantly higher presence of all three categories of abnormality in the group with RP, however that was not the case for SLE patients (Table IV). Among four FMF patients with proteinuria; one had RP, two had a score of 2 and the remaining two patients had normal capilleroscopic findings.

There was no statistical difference between capillaroscopic versus photo-

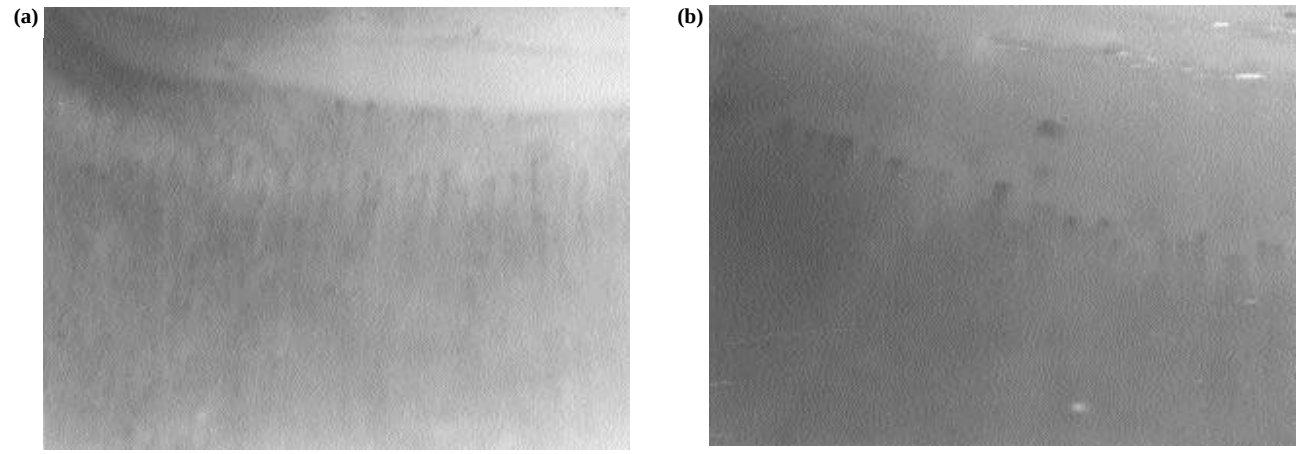

Fig. 1. (a) Normal hairpin shaped capillary loops (healthy subject); **(b)**. Frequent apically enlarged capillaries (FMF).

Table II. Demographic data and the frequency of RP.

Group	n	Age (yrs)	Sex (M:F)	RP
FMF	67	26.2 ± 8.7	28:39	10 (14.9%)
Healthy controls	37	31.0 ± 9.0	16:21	2 (5.4%)
SLE	19	33.1 ± 11.0	0:19	9 (47.4%)
PSS	8	38.8 ± 11.0	0:8	8 (100%)

Table III. The distribution of abnormal parameters.

Parameter	FMF n=59 (%)		Healthy n=36 (%)		SLE n=19 (%)		PSS n=8 (%)	
Scores*	1	2	1	2	1	2	1	2
Tortuosity	16(27.1)	1(1.7)	3(8.3)	0	9(47.4)	0	5(62.5)	2(25.0)
Enlargement	8(13.6)	1(1.7)	0	0	5(26.3)	0	0	8(100)
Extravasation	8(13.6)	6(10.2)	9(25.0)	2(5.6)	9(47.4)	0	1(12.5)	6(75.0)

* The zero scores were not shown.

Table IV. Comparison of FMF and SLE patients with and without RP.

	FMF patients*					SLE patients				
	With RP n = 10		Without RP n = 49		p (Chi-sq.)	With RP n = 10		Without RP n = 9		p (Fisher's)
Scores	1	2	1	2		0	1	0	1	
Tortuosity	6	1	10	0	0.002	4	6	6	3	>0.05
Enlargement	5	1	3	0	<0.001	6	4	8	1	>0.05
Extravasation	3	3	5	3	0.01	2	8	8	1	0.005

* The zero scores were not shown.

graphic interpretation of data evaluated blindly for tortuosity, enlargement and microhemorrhage scores of 82 cases belonging to all groups (p = 0.575, 0.093 and 0.076, respectively). Scores of two successive examination were similar in 21 FMF patients studied one month apart (tortuosity p = 0.735, enlargement p = 0.593 and microhemorrhages p = 0.345).

Discussion

The occurrence of vasculitis in FMF, mainly in the forms of Henoch-Schonlein purpura and polyarteritis nodosa (PAN) strongly suggests that the inflammation in FMF is not confined to serous membranes. Some microvascular abnormalities would also be expected because of the possibility of the development of secondary amyloidosis. However, we are unaware of previous studies focused on microvascular changes in FMF. Our results indicate that microvascular morphological alterations resembling those of SLE can be observed in patients with FMF. Capillary abnormalities were mainly seen in those patients with RP. However, the frequency of RP among FMF patients in general (14.9%) or among female patients (23%) was not different from the findings in our healthy controls, and from the findings in a previous hospital-based study conducted at a general medicine outpatient clinic in our hospital (12). The coexistence of capillary abnormalities and RP in FMF suggests that RP encountered in FMF patients may be a secondary phenomenon (11). Although it is beyond the scope of this study, the absence of a similar link between the extent of capillary abnormalities and the presence of RP may indicate that RP seen in SLE is related to not only capillary morphological changes, but also to altered microcirculatory hemodynamics (13).

Our FMF and healthy groups were age and sex matched, but diseased control groups consisted mainly of female patients. Since all FMF patients with high scores were female, we do not think the gender composition of our diseased control groups was a source of potential bias.

Some degree of tortuosity and extravasation was observed in our healthy controls, whereas capillary enlargement was confined to the disease groups. A recent study focused on individual capillary loop abnormalities revealed high frequencies of tortuosity, microhemorrhages and apical dilatation in healthy people aged 5 to 58 years old (14).

In conclusion capillary abnormalities exist in patients with FMF. Clinical and pathogenetic implications of this finding need to be further studied.

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