Title

Proximal nailfold microhemorrhage events are manifested as distal cuticular (eponychial) hemosiderin-containing deposits (CEHD) (syn. Maricq sign) and can aid in the diagnosis of dermatomyositis and systemic sclerosis

Journal

Dermatology Online Journal, 22(2)

Authors

McBride, Jeffrey D
Sontheimer, Richard D

Publication Date

2016

DOI

10.5070/D3222030078

Volume 22 Number 1
February 2016

Review

Proximal nailfold microhemorrhage events are manifested as distal cuticular (eponychial) hemosiderin-containing deposits (CEHD) (syn. Maricq sign) and can aid in the diagnosis of dermatomyositis and systemic sclerosis

Jeffrey D McBride MD PhD[1,2] and Richard D Sontheimer MD[3]

Dermatology Online Journal 22 (2): 1

[1]University of Oklahoma College of Medicine

[2]University of California, San Diego, Department of Internal Medicine

[3]University of Utah School of Medicine

Correspondence:

Richard D. Sontheimer, M.D.
Department of Dermatology
University of Utah School of Medicine
30 North 1900 East #4A 330
Salt Lake City, UT 84132
Phone: 801-581-6465
Cell phone: 801-889-9170
Fax: 801-581-6484
Email: richard.sontheimer@hsc.utah.edu

Abstract

Importance: Many patients present with cutaneous signs and symptoms that suggest a diagnosis on the autoimmune disease spectrum. During the "acute phase" of disease activity, patients with systemic sclerosis (SSc) and dermatomyositis (DM) have characteristic nailfold findings, including dilated capillaries, microhemorrhages, and hemosiderin deposits.

Objective: To review the literature on the presentation of microhemorrhages and to highlight the differences (in terms of terminology, characterization, and clinical relevance) between proximal microhemorrhage events and the distal products, often thought of as “hemosiderin deposits” located in the cuticle (eponychium). Because we found no studies directly showing these cuticular products are in fact “hemosiderin-containing,” we conducted a direct staining experiment in vivo using Prussian blue in order to increase our confidence that these products are indeed hemosiderin-containing and that the terminology is accurate for further use.

Evidence Review: In July-December 2014, the MeSH function in PubMed was used to identify approximately 165 articles relating to capillaroscopy. We reviewed these articles for mention of microhemorrhages and hemosiderin deposits. In addition, we used PubMed and Google Scholar searches for “hemosiderin + nail”, “Prussian Blue + nail”, and “hemosiderin deposit.” We found no papers reporting the use of Prussian Blue directly on nailfolds of patients with SSc and DM in vivo.

Findings: In our literature review, “microhemorrhages” and “hemosiderin deposits” were often used synonymously, yet they are clearly distinct entities. We present a case in which the presence of these deposits supported a diagnosis of amyopathic DM. We used Prussian blue staining solution to visualize the cuticular (eponychial) hemosoderin-containing deposits (CEHD) – distal

cuticular products that reflect previous proximal nailfold microhemorrhage events. CEHD can serve as an indicator of active autoimmune disease, particularly in SSc and DM.

Conclusions and Relevance: CEHD are in fact hemosiderin-containing deposits that can reflect the active inflammatory phase of microvascular injury occuring in autoimmune disorders such as DM and SSc. CEHD can be visualized and documented at the bedside with tools commonly available to any dermatologist (portable dermatoscope and compact digital camera).

Introduction

Nailfold cuticles (eponychium) of patients with certain autoimmune connective tissue diseases (ACTD) may provide a "window" into the progression of the disease. Capillary loop abnormalities, pericapillary "microhemorrhages," and avascular areas signifying capillary dropout are the primary finger nailfold capillaroscopy findings observed in systemic sclerosis (SSc) and DM [1]. Different combinations/patterns of these nailfold capillaroscopy findings are seen at different time points in the course of these diseases [2]. Table 1 summarizes the nailfold capillary findings observed at different time points in patients with SSc and DM.

Table 1. Nailfold capillaroscopy findings observed at different time points in the disease course of patients with SSc and dermatomyositis [2]

Early	
	Few giant capillaries, few "microhemorrhages"
	No loss of capillaries, preserved capillary distribution
Active	
	Frequent giant capillaries and "microhemorrhages" or CEHD (Maricq's sign)
	Moderate loss of capillaries, absent or mildly branched capillaries, mild disorganization of capillary architecture
Late	
	Giant capillaries and "microhemorrhages" virtually absent
	Severe loss of capillaries with extensive avascular areas
	Branched or bushy capillaries with severe disorganization of normal capillary array

Nailfold pericapillary hemorrhages, often referred to as "microhemorrhages," likely result from nailfold capillary damage caused by underlying vasculopathic mechanisms. This pattern of terminal microvascular damage allows red blood cells in the capillary loops to escape into the avascular space of the nailfold tissue. Little attention has been paid to the difference between the initial microhemorrhage event and the resulting "pigment deposits" that form distally in the nail cuticle.

Using 10X magnification dermoscopy, we observed discrete foci of red-brown to black deposits in the cuticle (eponychium) distal to the nailfold pericapillary microhemorrhages in lightly pigmented individuals with DM and SSc. The senior author has previously commented on this nailfold capillaroscopy finding in DM patients [3]. At times, multiple discrete foci of such deposits can be observed in the cuticle in a palisading array, running proximal-to-distal. These deposits are often visible to the unaided eye (Figure 1). Because of their size and dark color, we have observed that these cuticular deposits are typically the most visible component of nailfold microvascular changes to the unaided eye. It has been suggested vascular leak may be a universal feature of certain ACTD, such as SSc, and that hemosiderin deposition likely does not cause blood vessel damage [4]. Rather, these hemosiderin-containing deposits likely develop after vascular damage and leak.

In this report, we describe an unusual presentation of partially-expressed, clinically-amyopathic DM in which recognition of grossly-visible cuticular (eponychial) hemosiderin-containing deposits (CEHD) and dilated nailfold capillary loops observed under 10X dermoscopy were important clues to making the diagnosis. In addition, we present a series of color micrographs taken from different patients illustrating key morphologic features of CEHD. We are proposing the eponym "Maricq sign" to alternatively designate CEHD in honor of the pioneering contributions of Hildegard R. Maricq to our understanding of the clinical significance of the various in-vivo nailfold capillaroscopy findings in ACTD [5,6,7,8]. We show CEHD are indeed "hemosiderin-containing" using in vivo Prussian Blue staining. We then review the existing literature on CEHD as distinguished from nailfold pericapillary microhemorrhages occurring in the context of ACTD.

Case synopsis

A 75-year-old woman was referred to our clinic for further evaluation with a suspected diagnosis of delusions of parasitosis. Six months prior to our initial evaluation, the patient began to experience itching, burning, and crawling sensations in her scalp. These symptoms subsequently spread to involve other parts of her body including her upper and lower extremities. Four months prior to our evaluation, the patient had a punch biopsy of symptomatic skin that was reported to show only nonspecific findings. PAS stains were performed and failed to reveal evidence of microorganisms present in the skin biopsy specimen. She had a long history of Raynaud phenomena that worsened during the winter, for which she was taking oral nifedipine.

The patient's symptoms of severe persistent pruritus and resulting disturbed sleep had been treated with zolpidem (Ambien), alprazolam (Xanax), gabapentin, and capsaicin cream – all with little benefit. Her primary physicians treated her empirically for possible scabies with topical permethrin to which her symptoms failed to respond. Because of her ongoing symptoms and some unusual ideation by the patient relating to her symptoms, her physicians began to consider a diagnosis of delusions of parasitosis. During our initial evaluation the patient complained of severe burning sensations in her scalp and upper extremities. She described “little black spots” that she thought could be “bugs coming out” of the skin of her scalp. She denied other symptoms.

Our physical examination revealed confluent macular violaceous erythema of the entire scalp skin associated with generalized non-scarring hair thinning (Figure. 1A). Asymptomatic fingernail CEHD were grossly visible on multiple fingers of both hands (Figure. 1B). Nailfold telangiectasia were present on dermoscopy exam. Shown are magnified images of these changes at different time points in the patient’s disease course in our clinic (Figures. 1C-F). For comparison, we show CEHD and nailfolds present in other patients observed in the clinic (Figure 2). There were no other hallmark cutaneous manifestations of DM, including periorbital heliotrope erythema and Göttron papules. There was no evidence of digital ulcers, pitted digital scars, telangiectasia, cutaneous calcinosis, sclerodactyly nor other form of cutaneous sclerosis to suggest a cutaneous background of SSc. Examination of shoulder and hip girdle musculature suggested the presence of proximal weakness of shoulder girdle musculature, but we attributed little value to this weakness owing to the patient’s age and effort level during the physical examination and a history of spinal stenosis.

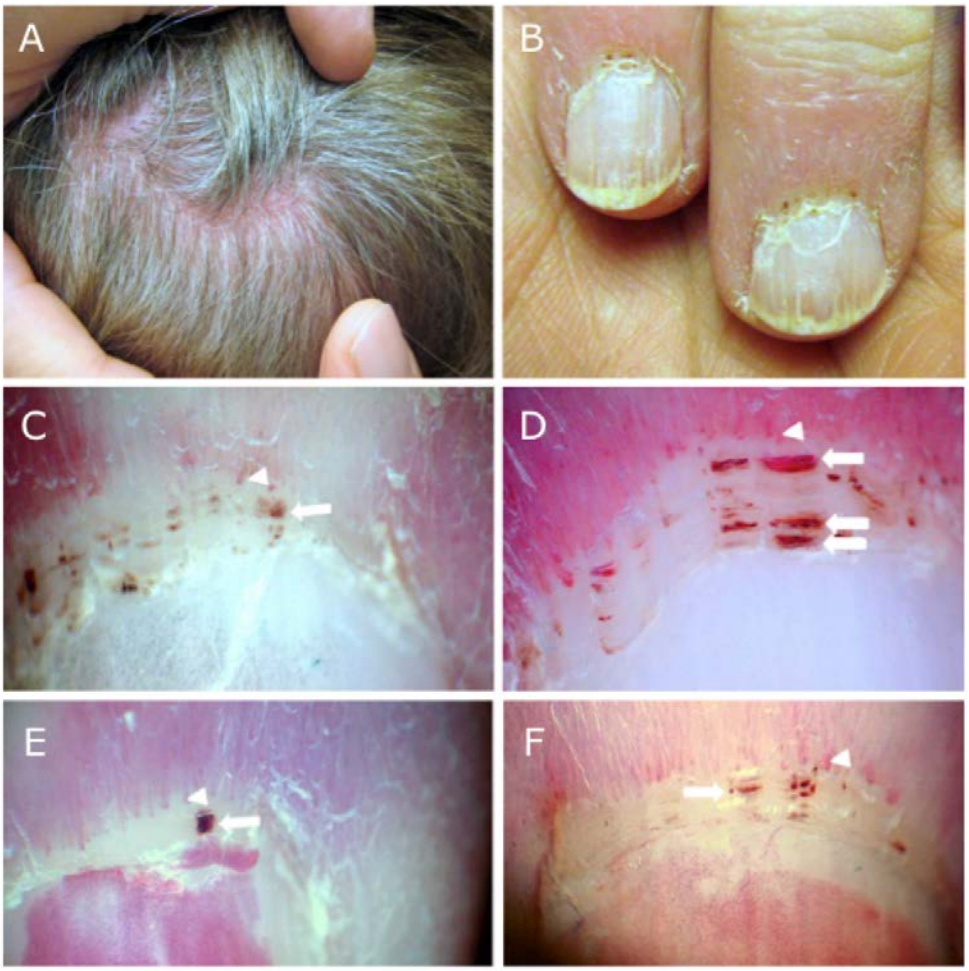

Figure 1. **CEHD in a patient with amyopathic dermatomyositis.** Panel A. Confluent violaceous erythema of the scalp in the subject of this case report. Panel B. Nailfold microvascular changes of same patient including grossly-visible cuticular (eponychial) hemosiderin-containing deposits (CEHD). Also notice the hyperplastic ragged-appearing cuticule overgrowth (Samitz sign). (Panel C-F) 10x digital micrographs of nailfold capillaroscopy changes observed at four different time points in the course of the patient described in this report. The photographs were taken of the finger displaying most prominent findings (typically the third or fourth finger of either hand). The white arrows indicate the CEHD

whereas the white arrowheads indicate the more proximal terminal nailfold capillaries. Panel C. November, 2010. Panel D. April, 2011. Panel E. April, 2012. Panel F. July, 2012.

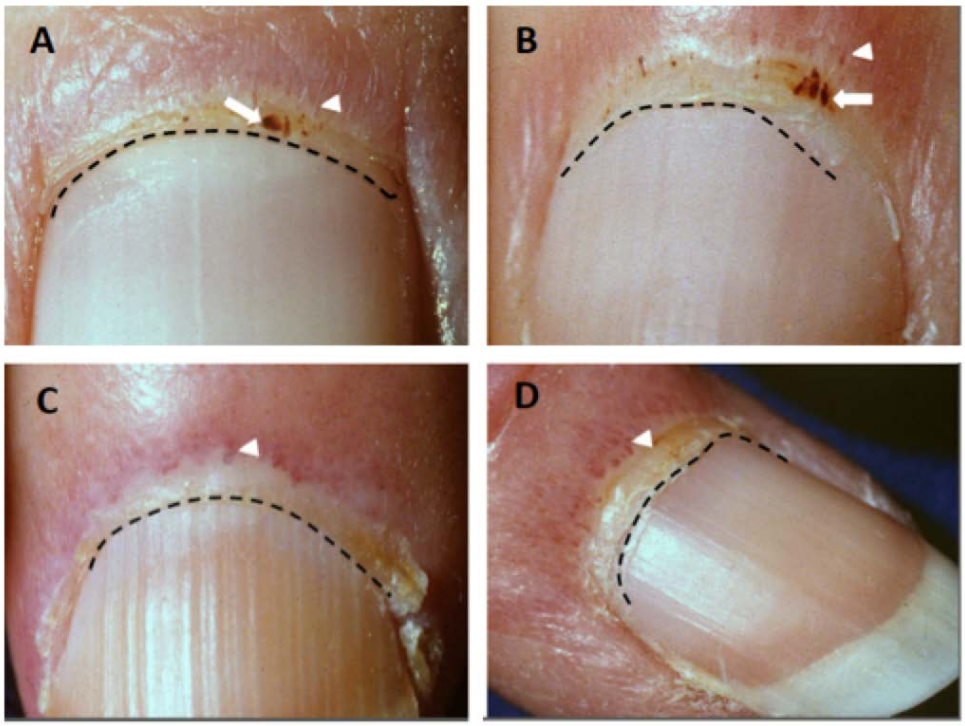

Figure 2. **Cuticles of patients with dermatomyositis.** Grossly-visible nailfold microvascular changes in four other dermatomyositis patients personally cared for by the senior author (A-D). The white arrows indicate the CEHD whereas the white arrowheads indicate the more proximal terminal nailfold capillaries. The hatched black lines indicate the junction of the distal edge of the cuticle and the nail plate. In Panels A and B, dilated terminal nailfold capillaries and CEHD are present together**.** In Panels C and D, no cuticular hemosiderin deposits are present.

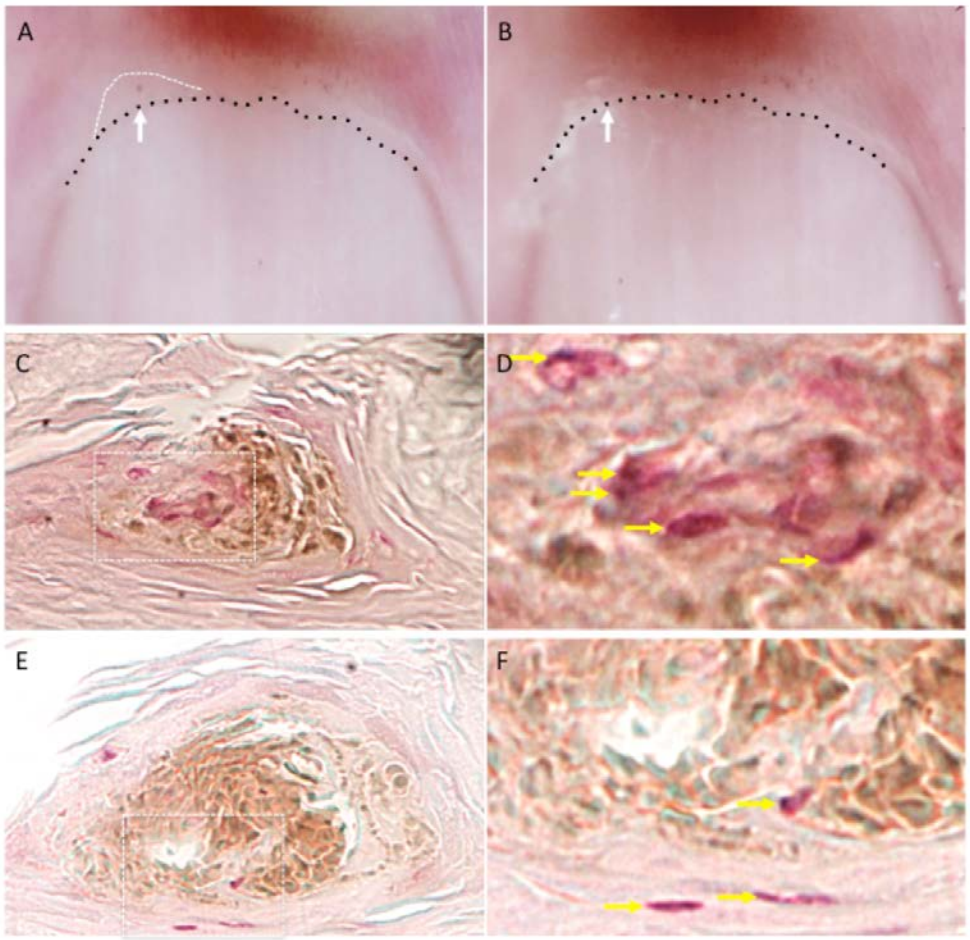

Figure 3. Biopsy and histology of CEHD containing hemosiderin in Prussian Blue-positive cells. (A) CEHD in the distal cuticle region of a patient suspected of having dermatomyositis. White arrow indicates CEHD; black dotted line delineates cuticle boundary; white line

delineates biopsy proximal boundary. (B) Biopsy of the CEHD shown in panel A. (C-F) Histology of CEHD (panel A), stained with Prussian blue (nuclear fast red counter stain). Yellow arrows = areas of Prussian-blue positivity. Panel D, F show higher magnification of C, E, respectively..

Punch biopsy of parietal scalp skin displaying violaceous erythema showed focal epidermal atrophy and a slight increase in interstitial mucin deposits, focal vacuolar interface changes along follicular infundibula, and an increase in telogen/catagen phase hair follicles. Antinuclear antibody assay was positive at a titer of 1:1280 with speckled, centromere, and homogeneous patterns. Screening for systemic lupus erythematosus (SLE)-related autoantibodies, including Ro/SS-A, La/SS-B, U1RNP, Sm and double-stranded DNA, was negative. Serum creatine kinase, aldolase, AST, and ALT levels were within normal limits. Because of these normal values, we did not test for anti-Mi-2 or anti-Jo-1 antibodies. Electromyogram was normal.

The patient was started on cetirizine and doxepin for the extreme pruritus and burning sensations in her skin. She was also given clobetasol spray to apply to the affected areas of her scalp. She was subsequently started on hydroxychloroquine. The patient admitted her adherence to this treatment regimen was erratic. The patient continued to experience pruritic, burning, crawling sensations in her scalp, and was instructed to follow the original treatment regimen more strictly. With better compliance to her prescribed oral antimalarial medical regimen, the patient slowly improved to the point of complete symptom relief.

The presence of fingernail CEHD in this case supported the diagnosis of cutaneous DM and provided an organic basis to this patient's presumed psychiatric symptoms. This was a great emotional relief to both the patient and her family.

Methods

In July - December 2014, we used PubMed to identify 165 articles discussing capillaroscopy, using the MeSH function searching "Microscopic Angioscopy" (instrumentation; methods; organization and administration; standards; statistics and numerical data; trends; and utilization)." We used PubMed and Google Scholar searches for "hemosiderin + nail", "Prussian Blue + nail", and "hemosiderin deposit" attempting to identify papers that utilized Prussian Blue staining method to assess the nature of nail chromonychia in cases of SSc and DM. We found no papers reporting the use of Prussian Blue directly on nailfolds of patients with SSc and DM in vivo.

Images in Fig. 1C-D were obtained using a Dermlite DL100 dermatoscope (3Gen) and a Canon PowerShot Elph 300 HS "point and shoot" compact digital camera. Figure 1 provides 10X color images viewed under a non-reflecting polarizing light. The telephoto zoom feature of the camera allows one to view the nailfold microvascular changes at different degrees of magnification. Manual effort is required to align the visual image. Post-processing of the digital images shown in the Figures 1-2 was performed using Picasa3 by Google to enhance the visibility of the cuticular findings.

To visualize if hemosiderin was present within the cuticles of patients, a sterile solution of 5% potassium ferrocyanide and 5% hydrochloric acid (1:1 ratio) was applied topically to the nailfolds/cuticles of human subjects, incubated for 20 minutes at room temperature then rinsed off with sterile water; CEHD were biopsied and stained with Prussian blue and nuclear-fast red as counterstain (Figures. 3A-F); gross images were captured using a DermLite DL3 dermatoscope and an iPhone 5s camera, manually aligned. In brief, histologic images were obtained after paraffin sections were deparaffinized and hydrated. They were immersed in Prussian blue "working solution" of 5% potassium ferrocyanide and 5% hydrochloric acid (1:1 ratio); heated in microwave for 30 seconds; rinsed in distilled water; immersed in nuclear-fast red for 5 minutes; washed in water; dehydrated, coverslipped, and imaged with light microscopy with digital camera. Protocols and written consent forms were approved by the Institutional Review Board at the University of Oklahoma.

Discussion

The significance of nailfold microvascular changes in ACTD has been increasingly recognized in the last half century. In 1955, nailfold changes were reported by Pagel et al in a case of diagnosed DM, in which "cutaneous changes were brown crusts around the cuticles of all the nails of both hands" and histological sections through the nail beds of patients showed "intra-epidermal bulla filled with fibrin and capillary haemorrhage in the core" [9]. In 1966, Ross stated "one or several nail folds may present a normal appearance…but positive findings in at least one nailfold would be of diagnostic significance; perniosis and idiopathic Raynaud's phenomenon may cause distortion of the capillaries and cause cuticular hemorrhage" [10].

Maricq garnered much attention to these nail changes in the more modern era, observing "palisades of extravasated red blood cells (RBC) grow out with the cuticle…" in patients with scleroderma (presumably SSc) and related disorders displaying traditional nailfold microvascular abnormalities [11]. Maricq pointed out that earlier workers, including Ehring had observed a similar phenomenon [12]. In 1988, Wong et al performed sequential nailfold capillary microscopy over 7 months in patients with

scleroderma or related disorders and found "recurrent episodes of extravasation from capillary loops, seen as deposits lying in the cuticle immediately distal to the involved capillary," and "loss of a capillary loop was often heralded by episodes of extravasation" [13]. In a report by Thompson and Maricq et al, it was stated "the most striking and consistent finding (on nailfold biopsy) was the presence of globular, eosinophilic, PAS-positive deposits in the cuticles of 14-15 patients (with scleroderma and related disorders) and none of the controls " [14]. They also indicated these globular eosinophilic cuticular deposits correlated positively with parakeratosis and negatively with nailfold capillary density. Thompson et al also reported serum protein exudates identified by immunofluorescence microscopy were associated with these cuticular globular eosinophilic deposits [14]. They pointed out Buchanan and Schnitzler had observed similar findings [15, 16].

Other diseases have varying probabilities of exhibiting CEHD. We and others have observed that SLE and cutaneous LE patients, for example, are much less likely to display microhemorrhages and CEHD in their nailfold areas. This was recently emphasized in a review by Hasagewa [1]. Another study reported in 1995 by Maeda et al 17 involved cuticular biopsies of patients with SSc and related disorders as well as normal controls. In this study, they used the term "bloody clots" to designate what we are referring to as CEHD. They observed these bloody clots in the middle cuticular layer predominately in scleroderma patients. These bloody clots and the three-layer configuration were seen much less commonly in SLE and DM patients studied (specifically, the bleeding clots of cuticle-proximal nailfolds were seen in 41 (65.1%) of SSc, 4 (44.4%) of DM, 1 (7.1%) of SLE and none of healthy controls) [17]. The bloody clots on closer examination were comprised of homogeneous eosinophilic globular deposits. They were observed to appear in and then disappear from the cuticle in a 1-2 week timeframe. The eosinophilic globular deposits were PAS positive but a melanin stain was negative. However, these workers did not present direct evidence via Prussian Blue staining that these eosinophilic globular deposits represented hemosiderin from degenerating blood resulting from more proximal pericapillary hemorrhage. These workers cited earlier studies in which the eosinophilic globular cuticular deposits had been referred to in different ways: 1) colloid [15]; 2) concretions of serum proteins, including immunoglobulins, complement components and fibrinogen [18] and 3) erythrocytes and extravasated serum.

In addition to SLE, other diseases associated with microvascular and connective tissue pathology may not show the characteristics nailfold changes seen in SSc and DM, as exemplified by the study showing sclerodermatous chronic graft-versus-host disease does not show the characteristic nailfold changes seen in SSc [19]. Diabetes mellitus may have capillary microvascular changes (such as capillary dilation), but these changes are likely to occur, if at all, in the latest stages of diabetes [20-22]. In a study of Bechet disease, dermoscopy was used to observe "microhaemorrhages" (appearing as what we label CEHD) [23]. Overall, the prevalence of CEHD in various diseases is still poorly characterized. In the senior author's experience, grossly-visible (non-magnified) CEHD are fleetingly rare in disorders other than SSc and DM (personal unpublished observation).

In several reports, the terms "microhemorrhages" and "hemosiderin deposits" are used interchangeably and synonymously to designate a visible surrogate marker for underlying disease activity. In Sambatero et al used videocapillaroscopy to count the number of "microhemorrhages (MHEs)" and "microthromboses (MTs)" and developed what they call a "NEMO score," correlating it with SSc "disease activity" [24]. They also described "erythrocyte extravasation following the rupture of capillaries…the consequent 'haemosiderin deposits' assume a round form." Their "NEMO score" represented the number of microhemorrhages (regardless of size) obtained via nail videocapillaroscopy (NVC) of 8 fingers per patient (in 107 SSc patients) and was a stronger indicator of disease activity (higher sensitivity and specificity for diagnosing SSc) compared to scores of "giant capillaries" and "dilated capillaries" using the European Scleroderma Study Group (ESSG) index as the gold standard [24]. A modified NEMO score (mNEMO) "defined by the presence of $\geq$ 6 MHE/MTs, or alternatively by the presence of three to five MHE/MTs plus at least three giant capillaries" exhibited the highest accuracy (88.7%) in correctly classifying patients with either moderate or highly active disease, with a sensitivity of 95.1% and a specificity of 84.8% [24]. This work encourages the potential use of CEHD visible by dermoscopy (as opposed to "MHE/MTs" visualized by NVC) as an endpoint for further studies relating to disease "activity" in ACTD.

In the review paper by Hasagewa [1], "microhemorrhages" are also referred to as "hemosiderin" when reviewing the "dermoscopy findings of nail fold capillaries in connective tissue diseases." Schlageri et al wrote that "(micro)haemorrhages were identified as haemosiderin extravasations," when studying the associations of nailfold capillary abnormalities and immunological markers in early Raynaud's phenomenon [25]. Bergman et al referred to what we are labeling CEHD as "extravasates" [26]. Jung et al went as far as labeling nailfold "bleeding" as "extravasal detection of erythrocytes or their degradation products," differentiating between "Type A: point-like microbleeding" and "Type B: larger confluent bleeding" [27]. Sulli et al refers to "microhaemorrhage" as a "dark mass due to haemosiderin deposit" in their paper discussing a scoring system for capillaroscopic analysis of SSc patients [28]. In this paper, Sulli et al report, after a mean follow-up of 72 months, the number of "haemorrhages" decreased from a baseline of 1.2 to 0.7 ($p<0.0001$) in SSc patients [28], suggesting the possibility that the number of CEHD on dermoscopy may change significantly over the course of the disease process.

We suspect that dermoscopy could simultaneously visualize a larger area of the cuticle/eponychium compared to videocapillaroscopy. Wu et al classified the severity of nailfold capillary hemorrhages on capillaroscopy in each finger of patients

with SSc, DM, SLE, and MCTD; they were classified as grade 1 (punctate hemorrhages <2/finger), grade 2 (punctate hemorrhages >2/finger), and grade 3 (confluent areas of hemorrhage) [29]. Inter-investigator variability is likely to remain the most consistent when looking at the presence of nailfold "hemorrhages," as Lambova et al found inter-investigator agreement was 100% consistent when comparing microhemorrhages, compared to 81% inter-investigator agreement for dilated capillaries [30].

In all of the previously described work, it has been assumed that hemosiderin and serum proteins exist in these cuticular deposits. We envisioned that when erythrocytes leak from the lumen of vessels into tissue and break down, releasing hemoglobin, macrophages convert hemoglobin into hemosiderin, a ferric ion-containing complex known to stain positive with Prussian Blue solution [31]. In certain parts of the nail such as the subungual space under the nail plate, Prussian Blue does not stain positively after bleeding events. This is likely owing to the inaccessibility of that region to phagocytic macrophages and the enzymatic processes required for conversion of hemoglobin to hemosiderin [32].

At least one prior case has been reported in which Prussian Blue was used to stain for hemosiderin in the distal nail matrix (post biopsy) to investigate the cause of chromonychia in patient. Using histological visualization of Prussian Blue, the authors concluded that the chromonychia in their case was likely the result of "hemorrhage from vessels" due to "benign capillary proliferation" [33]. This benign capillary proliferation may be analogous to the capillary changes seen in the nailfold region of ACTD during the "active" inflammatory phase of disease. To experimentally confirm that CEHD in our patients with ACTD contain hemosiderin, we used topical application of a Prussian Blue staining solution and visualized them with dermoscopy and subsequent histological analysis using Prussian blue (Figures. 3A-F). In brief, the reaction occurs during the topical treatment of tissue with a dilute acid solution of ferrocyanides. Ferric ions (+3) contained in hemosiderin combines with the ferrocyanide and results in the formation of a bright blue pigment called 'Prussian blue" or ferric ferrocyanide. Grossly, in vivo, it was difficult to see a significant change in color of CEHD, possibly owing to lack of penetration of the Prussian blue solution into the middle layer of the cuticle where the CEHD resides. Furthermore, only a small fraction of the CEHD may actually contain ferric iron. However, after biopsy and processing for histology with Prussian blue staining, it was clear that CEHD in fact contain hemosiderin-positive cells, likely representing phagocytic macrophages. The surrounding brown-to-yellow color within the cell-shaped structures in the CEHD likely represent the hemoglobin of lysed and nearly-lysed erythrocytes that have not been phagocytized. Thus, this other iron has likely not yet been converted to ferric iron.

Our patient in the case study illustrates the possibility that the presence of CEHD observed by routine dermoscopy could allow physicians at the bedside to more readily include AICD in the differential diagnoses. Our evaluation strongly suggested that the "crawling" sensations that our patient was experiencing were the result of inflammatory skin changes typical of DM rather than a psychiatric illness. We feel that the constellation of confluent macular violaceous erythema of the scalp skin, non-scarring alopecia, scalp skin biopsy showing an interface dermatitis with mucin infiltration, the long history of Raynaud's phenomenon, the grossly-visible CEHD and nailfold capillary abnormalities, hyperplastic cuticles (Samitz sign), and positive ANA in the absence of clinically-significant evidence of muscle inflammation was highly suggestive of a diagnosis of clinically-amyopathic DM [36, 37]. Some might argue that the diagnosis of cutaneous DM in a patient lacking both periorbital heliotrope erythema and Gottron papules would be suspect. It has been acknowledged that more study is needed to determine the minimal set of clinical, pathologic, and laboratory findings needed to diagnose cutaneous DM [35]. However, experienced clinicians will acknowledge that the disease-defining hallmark cutaneous manifestations of DM can be quite variably expressed from patient to patient with some individuals having quite limited but recognizable skin involvement.

Our patient was on two medications that we considered as potential contributors to her symptoms – anastrozole and lansoprazole. Anastrozole, a selective nonsteroidal aromatase inhibitor, is widely used as an adjuvant therapy for postmenopausal women with early hormone-sensitive breast cancer. This drug has been implicated as a trigger for drug-induced subacute cutaneous lupus erythematosus (SCLE) [38]. In addition, protein pump inhibiting drugs such as lansoprazole can serve as a drug trigger for other clinical forms of ACTD displaying an interface dermatitis such as SCLE [39]. Protein pump inhibitors such as omeprazole have been reported to be capable of triggering DM as a drug-induced phenomenon [40]. With reference to our case, both idiopathic and drug-induced forms of SCLE typically do not produce scalp inflammation, pruritus, or grossly-visible nailfold microvascular changes. In our case, the presence of CEHD was essential to recognizing the presence of amyopathic DM.

CEHD could be even more important to recognize in DM patients as recent studies have suggested the nailfold microvascular changes are more dynamic and change more quickly in DM compared to SSc [34].

The differential diagnosis of CEHD is quite limited. Periungual purpuric macules and papules resulting from small-vessel cutaneous leukocytoclastic vasculitis should be considered. Bywaters lesions of rheumatoid vasculitis typically appear in the lateral finger nailfold tissue whereas CHED are seen in the proximal nailfold tissue. In addition, Bywaters lesions can be seen on areas of skin of the fingers and hands other than the nailfolds. In addition, Bywaters lesions are typically larger and thus more easily seen with the unaided eye than are CEHD.

CEHD could possibly be confused with splinter hemorrhages in the proximal nailbed. The long axis of CEHD are typically oriented at 90° angles to the long axis of the finger (Figures.1-D and 1-F) whereas the long axis of splinter hemorrhages are characteristically oriented parallel to the long axis of the finger. In addition, close inspection will reveal splinter hemorrhages are located in the nailbed tissue under the nail plate whereas CEHD are located in the cuticular tissue above the nail plate.

The recognition of CEHD as being a separate and distinct entity from periungual microhemorrhages provides a new set of opportunities for capillaroscopy research. Studies that immediately come to mind include a population-based analysis of the diagnostic sensitivity and specificity for AICD of grossly-visible and dermoscopically-visible CEHD. Such studies might include a subcomponent in healthy controls to determine whether external trauma to the nailfold area can produce CEHD like trauma to the finger nails can produce splinter hemorrhages.

It would also be interesting to determine whether quantification of CEHD at different points in time might reflect changes in disease activity/response to treatment. Also, thought might be given to the idea of performing quantitative morphologic studies on CEHD to gain an appreciation of the temporal sequence of injury events that have occurred previously in the proximal terminal nailfold capillaries. As previously noted, one report indicated that CEHD appeared in and disappear from the cuticle within a 1-2 week time frame. Presuming that this is correct, multiple side-by-side linear CEHD present at the same location arranged 90° to the long axis of the finger as seen in (Figure. 1-D) would imply multiple discrete microbleeding episodes from the same affected periungual microvessel(s) over a 1-2 week time frame prior to the death and dropout of those vessels.

In summary, we have reviewed and further characterized the nature and clinical significance of CEHD that are seen predominately in the setting of active SSc and DM. We have illustrated how recognizing the presence of CEHD can aid in diagnosing amyopathic DM. We alternatively designate the presence of CEHD as “Maricq sign.” CEHD can be viewed as representing integration over time of earlier discrete capillary damaging events. SSc and DM are different diseases that merit a potential future study to delineate how hemosiderin deposits in SSc and DM might differ in presentation. For example, an unanswered question is whether or not the CEHD presentation in SSc and DM is different in terms of which nails are affected. More study is required to determine to what extent CEHD reflect disease status and any potential prognostic value they may provide to physicians managing patients with SSc and DM.

Acknowledgements

We would like to thank David R. Wright, M.D (Department of Dermatology, University of Wisconsin School of Medicine), for his assistance with the literature review component of this project at its inception. In addition, we would also like to express our appreciation to Tracy M. Frech, M.D. (Department of Internal Medicine (Rheumatology), University of Utah School of Medicine) for sharing her thoughts about this project and manuscript. We would like to thank Andrew John, M.D. for use of his dermatoscope and Geeta Patel, D.O., Jarad Levin, M.D., and Travis Blalock, M.D. for help with patient recruitment in Oklahoma. We thank Jeffery Smith at the OUHSC Histology Core for assistance with tissue processing and histology protocols.

References

1. Hasegawa M. Dermoscopy findings of nail fold capillaries in connective tissue diseases. The Journal of dermatology. Jan 2011;38(1):66-70. PMID: 21175758
2. Cutolo M, Sulli A, Pizzorni C, Accardo S. Nailfold videocapillaroscopy assessment of microvascular damage in systemic sclerosis. The Journal of rheumatology. Jan 2000;27(1):155-160. PMID: 10648032
3. Sontheimer RD. A portable digital microphotography unit for rapid documentation of periungual nailfold capillary changes in autoimmune connective tissue diseases. The Journal of rheumatology. Mar 2004;31(3):539-544. PMID: 14994402
4. Frech TM, Revelo MP, Drakos SG, et al. Vascular leak is a central feature in the pathogenesis of systemic sclerosis. The Journal of rheumatology. Jul 2012;39(7):1385-1391. PMID: 22660809
5. Maricq HR, LeRoy EC. Capillary blood flow in scleroderma. Bibliotheca anatomica. 1973;11:352-358. PMID: 4789062
6. Maricq HR, LeRoy EC. Patterns of finger capillary abnormalities in connective tissue disease by "wide-field" microscopy. Arthritis and rheumatism. Sep-Oct 1973;16(5):619-628. PMID: 4742842
7. Maricq HR, Downey JA, LeRoy EC. Standstill of nailfold capillary blood flow during cooling in scleroderma and Raynaud's syndrome. Blood vessels. 1976;13(6):338-349. PMID: 1016736
8. Maricq HR, Spencer-Green G, LeRoy EC. Skin capillary abnormalities as indicators of organ involvement in scleroderma (systemic sclerosis), Raynaud's syndrome and dermatomyositis. The American journal of medicine. Dec 1976;61(6):862-870. PMID: 1008072
9. Pagel W, Treip CS. Viscero-cutaneous collagenosis; a study of the intermediate forms of dermatomyositis, scleroderma, and disseminated lupus erythematosus. Journal of clinical pathology. Feb 1955;8(1):1-18. PMID: 14354022

10. Ross JB. Nail fold capillaroscopy--a useful aid in the diagnosis of collagen vascular diseases. The Journal of investigative dermatology. Oct 1966;47(4):282-285. PMID: 5954159
11. Maricq HR. Nailfold biopsy in scleroderma and related disorders. Dermatologica. 1984;168(2):73-77. PMID: 6698266
12. Ehring F. [Vital histological studies on microhemorrhages in a circumscribed skin area. 1. Vascular lesions]. Thrombosis et diathesis haemorrhagica. Mar 15 1962;7:129-158. PMID: 13889524
13. Wong ML, Highton J, Palmer DG. Sequential nailfold capillary microscopy in scleroderma and related disorders. Annals of the rheumatic diseases. Jan 1988;47(1):53-61. PMID: 3345105
14. Thompson RP, Harper FE, Maize JC, Ainsworth SK, LeRoy EC, Maricq HR. Nailfold biopsy in scleroderma and related disorders. Correlation of histologic, capillaroscopic, and clinical data. Arthritis and rheumatism. Jan 1984;27(1):97-103. PMID: 6691862
15. Schnitzler L, Baran R, Verret JL. [Proximal nail fold biopsy in connective tissue diseases. 26 cases studied under light and electron microscopy and direct immunofluorescence (author's transl)]. Annales de dermatologie et de venereologie. Aug-Sep 1980;107(8-9):777-785. PMID: 7004311
16. Buchanan IS, Humpston DJ. Nail-fold capillaries in connective-tissue disorders. Lancet. Apr 20 1968;1(7547):845-847. PMID: 4171334
17. Maeda M, Matubara K, Kachi H, Mori S, Kitajima Y. Histopathological and capillaroscopical features of the cuticles and bleeding clots in ring or middle fingers of systemic scleroderma patients. Journal of dermatological science. Jul 1995;10(1):35-41. PMID: 7577836
18. Chen Z, Maize JC, Silver RM, Dobson RL, Maricq HR, Ainsworth SK. Direct and indirect immunofluorescent findings in dermatomyositis. Journal of cutaneous pathology. Feb 1985;12(1):18-27. PMID: 3919071
19. Hofstee HM, de Waal TT, Zweegman S, et al. Nailfold capillary abnormalities in sclerodermatous chronic GVHD. Bone marrow transplantation. Nov 2013;48(12):1574-1577. PMID: 23892332
20. Greene RA, Scher RK. Nail changes associated with diabetes mellitus. Journal of the American Academy of Dermatology. May 1987;16(5 Pt 1):1015-1021. PMID: 3294936
21. Lambova SN, Muller-Ladner U. The specificity of capillaroscopic pattern in connective autoimmune diseases. A comparison with microvascular changes in diseases of social importance: arterial hypertension and diabetes mellitus. Modern rheumatology / the Japan Rheumatism Association. 2009;19(6):600-605. PMID: 19779765
22. Meyer MF, Pfohl M, Schatz H. [Assessment of diabetic alterations of microcirculation by means of capillaroscopy and laser-Doppler anemometry]. Medizinische Klinik. Feb 15 2001;96(2):71-77. PMID: 11253285
23. Aytekin S, Yuksel EP, Aydin F, et al. Nailfold capillaroscopy in Behcet disease, performed using videodermoscopy. Clinical and experimental dermatology. Jun 2014;39(4):443-447. PMID: 24825134
24. Sambataro D, Sambataro G, Zaccara E, et al. Nailfold videocapillaroscopy micro-haemorrhage and giant capillary counting as an accurate approach for a steady state definition of disease activity in systemic sclerosis. Arthritis research & therapy. 2014;16(5):462. PMID: 25296743
25. Schlager O, Kiener HP, Stein L, et al. Associations of nailfold capillary abnormalities and immunological markers in early Raynaud's phenomenon. Scandinavian journal of rheumatology. 2014;43(3):226-233. PMID: 24517537
26. Bergman R, Sharony L, Schapira D, Nahir MA, Balbir-Gurman A. The handheld dermatoscope as a nail-fold capillaroscopic instrument. Archives of dermatology. Aug 2003;139(8):1027-1030. PMID: 12925391
27. Jung P, Trautinger F. Capillaroscopy. Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG. Aug 2013;11(8):731-736. PMID: 23738531
28. Sulli A, Secchi ME, Pizzorni C, Cutolo M. Scoring the nailfold microvascular changes during the capillaroscopic analysis in systemic sclerosis patients. Annals of the rheumatic diseases. Jun 2008;67(6):885-887. PMID: 18037628
29. Wu PC, Huang MN, Kuo YM, Hsieh SC, Yu CL. Clinical applicability of quantitative nailfold capillaroscopy in differential diagnosis of connective tissue diseases with Raynaud's phenomenon. Journal of the Formosan Medical Association = Taiwan yi zhi. Aug 2013;112(8):482-488. PMID: 24016612
30. Lambova SN, Hermann W, Muller-Ladner U. Comparison of qualitative and quantitative analysis of capillaroscopic findings in patients with rheumatic diseases. Rheumatology international. Dec 2012;32(12):3729-3735. PMID: 22147109
31. Fischbach FA, Gregory DW, Harrison PM, Hoy TG, Williams JM. On the structure of hemosiderin and its relationship to ferritin. Journal of ultrastructure research. Dec 1971;37(5):495-503. PMID: 5136270
32. Ruben BS. Pigmented lesions of the nail unit: clinical and histopathologic features. Seminars in cutaneous medicine and surgery. Sep 2010;29(3):148-158. PMID: 21051008
33. Lee YB, Cho E, Park HJ, Cho BK. Proximal and lateral chromonychia with capillary proliferation on the distal nail matrix. Annals of dermatology. May 2012;24(2):240-241. PMID: 22577286
34. De Angelis R, Cutolo M, Gutierrez M, Bertolazzi C, Salaffi F, Grassi W. Different microvascular involvement in dermatomyositis and systemic sclerosis. A preliminary study by a tight videocapillaroscopic assessment. Clinical and experimental rheumatology. Mar-Apr 2012;30(2 Suppl 71):S67-70. PMID: 22691212
35. Schultz HY, Dutz JP, Furukawa F, et al. From Pathogenesis, Epidemiology, and Genetics to Definitions, Diagnosis, and Treatments of Cutaneous Lupus Erythematosus and Dermatomyositis: A Report from the 3rd International Conference on Cutaneous Lupus Erythematosus (ICCLE) 2013. The Journal of investigative dermatology. Jan 2015;135(1):7-12. PMID: 25501376

36. Euwer RL, Sontheimer RD. Amyopathic dermatomyositis (dermatomyositis sine myositis). Presentation of six new cases and review of the literature. Journal of the American Academy of Dermatology. Jun 1991;24(6 Pt 1):959-966. PMID: 1869684
37. Ghazi E, Sontheimer RD, Werth VP. The importance of including amyopathic dermatomyositis in the idiopathic inflammatory myositis spectrum. Clinical and experimental rheumatology. Jan-Feb 2013;31(1):128-134. PMID: 23190767
38. Trancart M, Cavailhes A, Balme B, Skowron F. Anastrozole-induced subacute cutaneous lupus erythematosus. The British journal of dermatology. Mar 2008;158(3):628-629. PMID: 18070201
39. Panting KJ, Pinto M, Ellison J. Lansoprazole-induced subacute cutaneous lupus erythematosus. Clinical and experimental dermatology. Aug 2009;34(6):733-734. PMID: 19508577
40. Pan Y, Chong AH, Williams RA, Green J, Sinclair R. Omeprazole-induced dermatomyositis. The British journal of dermatology. Mar 2006;154(3):557-558. PMID: 16445794