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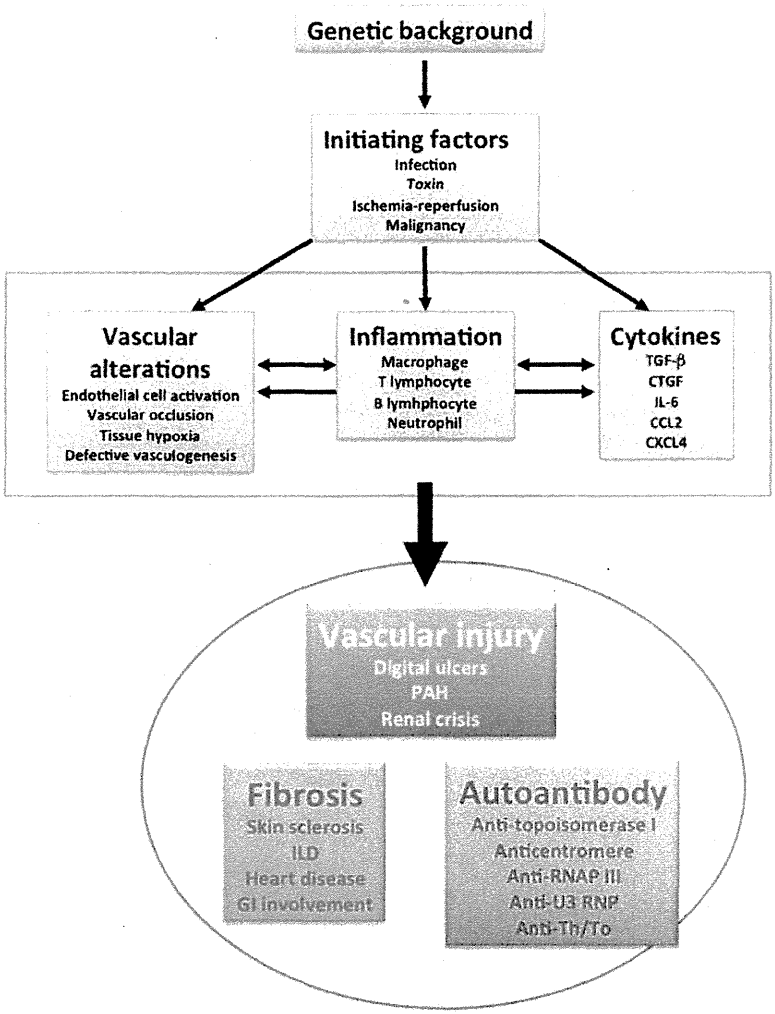

Fig. 1 Hasegawa M

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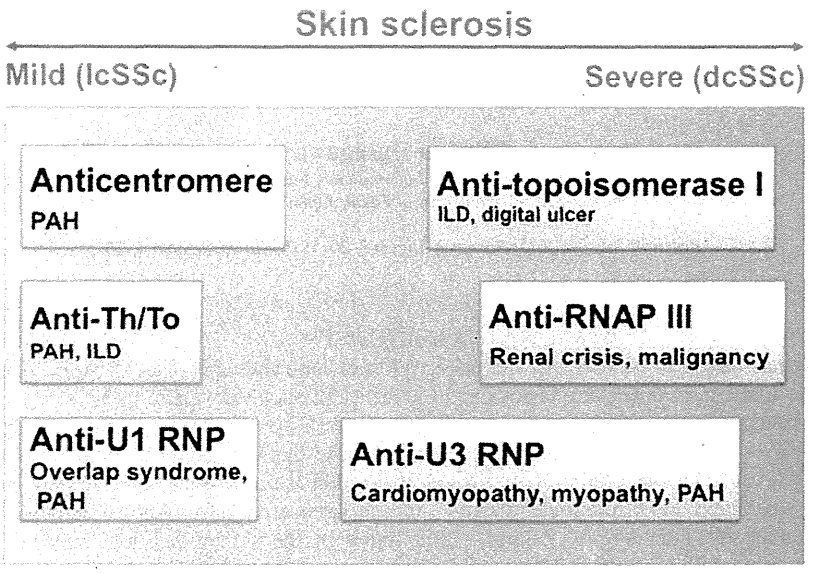

Fig. 2 Hasegawa M

254x190mm (72 x 72 DPI)

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Original Review Article: Open Access

Use of dermoscopy in the evaluation of connective tissue diseases

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ABSTRACT

Recently, dermoscopy has begun to be used for the observation of nailfold capillaries in connective tissue disease (CTD). However, dermoscopic features of other skin lesions and the utility of such information remains unclear. In this review, we summarize the typical dermoscopic findings of nailfold capillaries in CTD and discuss their significance. We compared the findings between dermoscopy and video capillaroscopy, and propose that dermoscopy could serve as a substitute to some extent for video capillaroscopy. The utility of dermoscopy for othe skin lesions of CTD remains unknown. However, dermoscopy findings may help to differentiate discoid lupus erythematosus from other skin disorders in patients with systemic lupus erythematosus. Interestingly, telangiectasia found in the skin other than nailfold resembles the nailfold capillary changes in patients with systemic sclerosis. Gottron's sign accompanied with punctate hemorrhage may reflect the existence of rapidly progressive interstitial pneumonia. We propose that daily use of dermoscopy could improve the clinical care of CTD patients, since it enables the recognition of vascular structures and other subtle features that are less visible to the naked eye. We hope that this review will promote increased use of dermosopy for clinical practice in patients with CTD, and believe that further investigation will yield additional valuable information in the near future.

KEYWORDS: Dermoscopy, Capillaroscopy, Systemic sclerosis, Lupus erythematosus, Dermatomyositis

ABBREVIATIONS: CTD, connective tissue disease; NVC, nailfold video capillaroscopy; SSD, scleroderma spectrum disorder; SSc, systemic sclerosis; DM, dermatomyositis; SLE, systemic lupus erythematosus; DLE, discoid lupus erythematosus; MDA, melanoma differentiation-associated protein.

INTRODUCTION

Connective tissue disease (CTD) causes various skin lesions that are composed of vascular tissue and inflammation. Dermoscopy has been widely used in differentiating malignant skin disorders. However, dermoscopy may be useful for evaluating nonpigmented skin disorders, since it provides an improved view of vascular structures and other subtle features that are usually not visible to the naked eye (1-4).

Much work has been done to show that nailfold video capillaroscopy(NVC) can distinguish the Raynaud's phenomenon associated with scleroderma spectrum disorder (SSD; systemic sclerosis (SSc) and its related diseases) from primary Raynaud's phenomenon (Raynaud's disease) (5-8). Distinct NVC patterns are also be useful in evaluating the severity and stage of SSD microvascular damage. Furthermore, NVC changes are as prevalent and as prominent in dermatomyositis (DM) as in SSD (9, 10). However, such findings are not found in patients with other connective tissue diseases. Routine use of NVC at the bedside has yet to become fully integrated into standard clinical practice, since the equipment is relatively expensive and not easily transported. Recently, it has been suggested that dermoscopy can replace NVC,to some extent, for detection of representative nailfold capillary abnormalities (11-15). However, dermoscopic finding and its significance of nailfold capillaries have not been summarized yet.

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Furthermore, there are few studies regarding the use of dermoscopy for other skin lesions of CTD and an overview of them is missing. In this review, we show some representative dermoscopic findings and pictures of skin lesions in CTD.,

Usage of dermoscopy for nailfold capillaries

NVC observation

Given a patient with Raynaud's phenomenon and no other symptoms, it is first important to determine whether the patient has "Raynaud's disease" or "Secondary Raynaud's phenomenon associated with CTD". Raynaud's phenomenon is most frequently found in patients with SSD, and is usually the first symptom of the disease. Therefore, the existence of SSD or other CTD must be determined. Blood examination for antinuclear antibodies, including CTD-specific autoantibodies, enable the most accurate diagnosis. However, NVC findings are also useful for early diagnosis of SSD, especially in patients negative for CTD-specific autoantibodies. When we use dermoscopy for evaluating CTDs the established findings of capillaroscopy are definitely useful. Therefore, we would like to review capillaroscopic findings of CTD before discussing our findings using dermoscopy.

Scleroderma NVC pattern

We used a video capillaroscopy system (Kekkan bijin, Kenkou Kagaku Kenkyu-kai, Co., Ltd, Kyoto, Japan). Diagnostic capillaroscopy patterns are grouped as follows: normal pattern, scleroderma pattern, and nonspecific pattern(12). Thenormal pattern in Figure 1A.shows homogeneous capillary distribution in the nailfold plexus without capillary loss (normal linear density: 30 capillaries per 5 mm) and no morphological alterations. The scleroderma pattern in Figures 1B-D is defined according to Maricq et al. (16, 17), with modifications according to Bergman et al. (13).Two or more of the following abnormalities are observed:①enlarged capillaries (Figures 1B and C);②hemorrhages (more than two punctuate hemorrhages per finger or confluent hemorrhage areas)(Figure 1C);③disorganization of the normal capillary distribution (Figure 1B-D);④moderate or extensive capillary loss (avascular areas)(Figure 1 D), and ⑤tortuous, crossed, and/or ramified capillaries (Figure 1D).The nonspecific pattern lacks the complete scleroderma pattern criteria.

Subclassification of scleroderma NVC pattern

The NVC scleroderma pattern is subdivided further as previously reported (18). The subclasses are as follows: (1) Early NVC pattern (Figure 1B): few enlarged/giant capillaries, few capillary hemorrhages, relatively well-preserved capillary distribution, and no evident loss of capillaries; (2) Active NVC pattern (Figure 1C): frequent giant capillaries, frequent capillary hemorrhages, moderate loss of capillaries with some avascular areas, mild disorganization of the capillary architecture, and absence of ramified capillaries; and (3) Late NVC pattern (Figure 1D): irregular capillary enlargement, few or absent giant capillaries, absence of hemorrhages, severe loss of capillaries with large avascular areas, severe disorganization of the normal capillary array, and frequent ramified/bushy capillaries. We have summarized the typical findings from each scleroderma pattern in Figure 1E (19). This subclassification has been useful for evaluation of activity and severity of vascular injury. In severe SSc cases with anti-topoisomerase I Ab present, the NVC pattern progresses quickly to the characteristic Late pattern, within two years of disease onset. On the other hand, mild SSc patients who have anticentromere Ab, gradually progress to the late pattern, more than 20 years after disease onset (20). NVC findings can be improved after treatment of SSc (21)(22).

NVC pattern in other CTD

NVC patterns are also found at high frequency in patients with DM and are generally similar to the patterns found in SSD patients [9], although the frequency of Raynaud's phenomenon is much lower. NVC patterns are referred to as a "scleroderma-like pattern" if thepattern is found in DM or disorders other than SSD. Although subtle capillary abnormality such as mild disorganization can be detected in patients with systemic lupus erythematosus (SLE), a typical scleroderma-like pattern is rarely found.

Nailfold capillary findings using dermoscopy

Nailfold capillaries may also be observed using dermoscopy. Although we use several types of dermoscopy, the picutres in this review were taken using dermoscopic camera lens with adaptor (Heine Optotechnik, Herrsching, Germany). We usually choose the third or fourth finger for examination. In a healthy person, we can see homogeneously-lined capillary distribution around the nailfold without hemorrhage (Figure 2A). Most specific NVC findings can also be detected by dermoscopy [11-15]. Our dermoscopic observations ofnailfold capillariesare as follows:

1) Disorganization of the capillary architecture

Disorganization of capillary loops can be found in patients with CTD including SSD (Figure 2B~2D), DM (Figure 2E~G), and SLE (Figure 2H).

2) Enlarged/giant capillaries

Enlarged capillaries can be found in patients with CTD-associated Raynaud's phenomenon. Extremely enlarged capillaries (giant capillaries) are specific for SSD (Figure 2C) and DM (Figure 2F). The enlarged/giant capillaries are considered to be an abnormal angiogenic response, secondary to peripheral ischemia.

3) Capillary hemorrhages

Dotted or lined microhemorrahges can be found located peripheral to capillaries in patients with SSD and DM. Single hemorrhages may rarely be found in healthy persons, but plural hemorrhages are specific for SSD (Figure 2C) and DM (Figure 2F). The hemorrhages likely reflect capillaryinjury caused by ischemia-reperfusion (Raynaud's phenomenon). Using dermoscopy, we can detect some microhemorrahges that are not visible to naked eye.

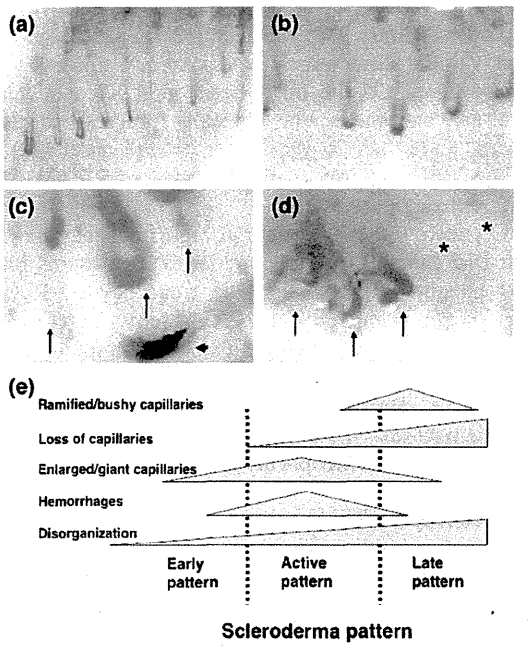

Figure 1 Hasegawa, et al.

Figure 1. Nailfold video capillary findings

a) Normal pattern (normal capillaries in healthy persons): lower side represents the peripheral direction (nail plate). Note homogeneous capillary distribution in the nailfold plexus without capillary loss and no morphological alterations.
b) Early scleroderma pattern: modestly enlarged capillaries and slight disorganization of capillaries.
c) Active scleroderma pattern: frequent giant capillaries (fine long arrows), frequent capillary hemorrhages (heavy short arrows), and moderate loss of capillaries.
d) Late scleroderma pattern: severe loss of capillaries with large avascular areas (asterisks), severe disorganization of the normal capillary array, and frequent ramified/bushy capillaries (fine long arrows).
e) The relationship between each NVC finding and scleroderma pattern.

4) Capillary loss or avascular areas

The existence of moderate to severe loss of capillaries (avascular areas) is characteristic for SSD (Figure 2D) or DM (Figure 2G). The severity reflects the peripheral circulatory disturbance of SSD or DM. SSD patients with severe capillary loss frequently develop intractable digital

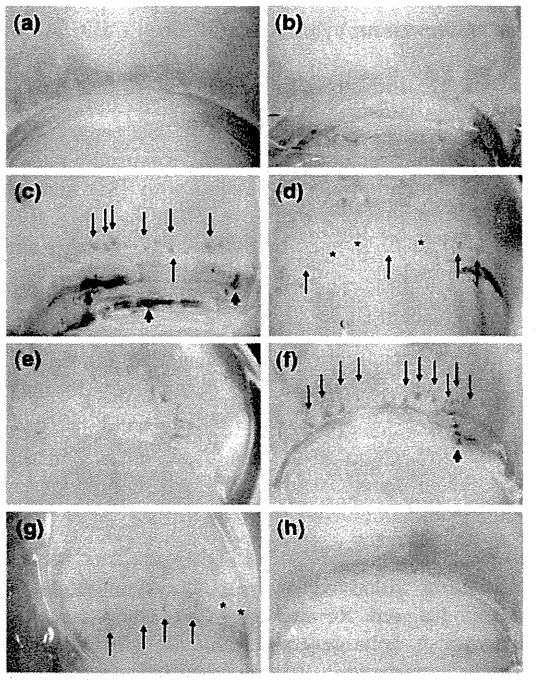

Figure 2. Hasegawa, et al.

Figure 2. Dermoscopy findings in healthy persons and systemic sclerosis and its related disease (SSD).

a) Normal capillaries in healthy persons.
b) Early pattern in patients with SSD: mild disorganization of the capillary architecture and modestly enlarged capillaries.
c) Active pattern in patients with SSD: enlarged/giant capillaries (fine long arrows) and hemorrhages (heavy short arrows).
d) Late pattern in patients with SSD: loss of capillaries with large avascular areas (astrisks) and ramified/bushy capillaries (fine long arrows).
e) Early pattern in patients with dermatomyositis: mild disorganization of the capillary architecture and modestly enlarged capillaries.
f) Active pattern in patients with dermatomyositis: enlarged/giant capillaries (fine long arrows) and hemorrhages (heavy short arrows).
g) Late pattern in patients with dermatomyositis: loss of capillaries with large avascular areas (astrisks) and ramified/bushy capillaries (fine long arrows).
h) Modestly enlarged capillaries in patients with SLE. This does not fit the criteria of scleroderma pattern, since other abnormalities are not detected.

5) Ramified/bushy capillaries

Ramified or bushy capillaries can be found in the hypovascular area of patients with SSc (Figure 2D) and DM (Figure 2G). This advanced vascular damage is an abnormal angiogenic response to the hypoxic state.

Usage of Dermoscopy for Skin Lesions of CTD

Dermoscopic findings in inflammatory skin diseases

Dermoscopic evaluation for inflammatory skin diseases should include the following: I. vascular morphology (dot, globule, linear, glomerulus-like); II. vascular arrangement (regular, clustered, patchy, peripheral, in rings); III. background color (dull-red, light red, yellowish).IV. scale colour (white, yellow); V. scale distribution (patchy, peripheral, diffuse, central); VI. presence of white crossing streaks (Wickham-striae) [1,23].

Systemic lupus erythematosus

Malar rash and discoid lupus erythematosus (DLE) are specific skin lesions of SLE. However, DLE is sometimes clinically difficult to distinguish from other skin diseases such as lichen planus, psoriasis vulgaris, nummular eczema, and cutaneous sarcoidosis.

The dermoscopic findings of DLE are not necessarily specific to the disease (Figure 3). The background colour is usually light red or orange, and often accompanies partial/whitish homogeneous lesions and/or white scales. Variously arranged dilated capillaries with varied morphology are highly visible. It has been reported that follicular keratin plugs, which correlate histologically with prominent hyperkeratosis in follicular openings, are detected only in active lesions (Figure 3B), not in scars or healed skin of DLE (Figure 3C) [24]. The finding of keratin plugs may therefore be useful as an estimate of disease activity or response to treatment in patients with DLE.

Regarding differential diagnosis of DLE, representative dermoscopic findings of psoriasis vulgaris are regularly distributed, dotted, globular, glomerular, or twisted loop-like vessels over a light red background and white scales (Figure 4A) [3,23,25]. The tortuous and dilated blood vessels within the elongated dermal papillae in psoriasis are present as regularty distributed red dots, red globules, glomerule-like vessels, and twisted red loops [2]. Dermoscopy of lichen planus shows diagnostic white crossing lines (Wickham striae) and red dotted or globular vessels at the periphery (Figure 4B) [25,26]. In eczematous lesions including nummular eczema, serum exudates can be seen dermoscopically as shiny yellow clods (Figure 4C) [27]. Cutaneous sarcoidosis as well as other cutaneous granuloma show dermoscopically translucent yellow to orange, globular-like or structureless areas associated with linear vessels (Figure 4D) [28].

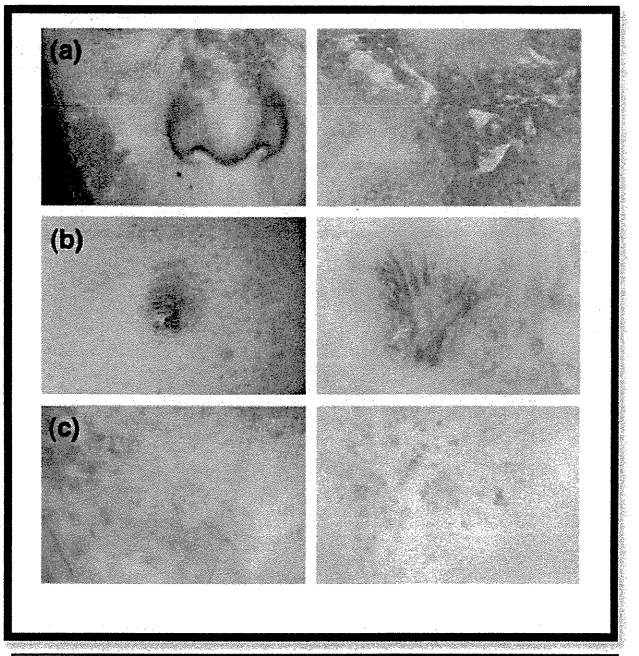

Figure 3. Dermoscopic findings in discoid lupus erythematosus (DLE). Clinical pictures and their dermoscopic counterparts are shown.

a) Active DLE at the cheek. Background is light red and mild pigmentation and depigmentation are mixed. Irregularly arranged enlaged ramified vessels are highly visible.
b) Active and prolonged (hypertrophic) DLE at the chest. Light red and white lesions are mixed in the background. Follicular keratin plugs and peripheral linear irregular vessels are found.
c) Healing stage of DLE at the forehead. Background is light red and mild partial depigmentation and white scales are found. Many dotted or hairpin-like vessels are highly visible.

Thus, although the dermoscopic findings of DLE are not entirely specific, dermoscopy can add important clues that help distinguish DLE from other skin disorders.

Systemic sclerosis

Telangiecatases are frequently detected on face, hand, mucous membranes, and other sites in patients with SSc. They are vascular lesions composed of vasodilated post-capillary venules without evidence of neovascularization or inflammation [29,30]. The mechanism by which telangiectases develop in SSc patients remains unknown. However, it may be the result of an aberrant attempt to increase blood perfusion to hypoxic tissues as a consequence of impaired circulation [31]. A recent study reported that

increased numbers of telangiectases strongly associated with the presence of pulmonary arterial hypertension in patients with SSc [31]. However, there are almost no studies that have investigated the findings in detail using dermoscopy. Morphologically, there are at least two kinds of telangiectases in SSc.

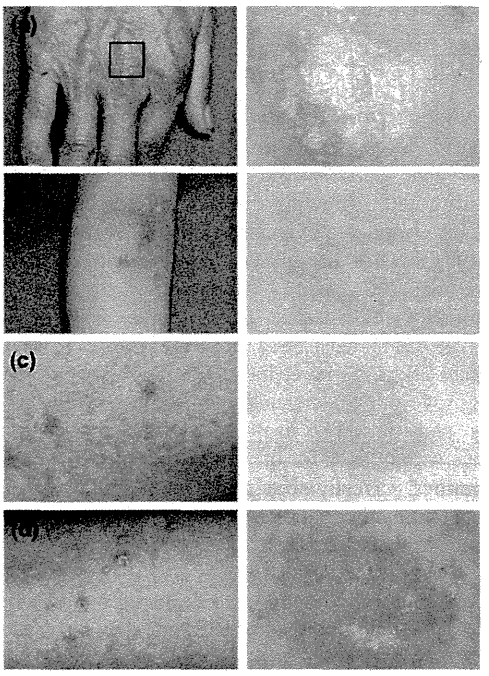

Figure 4. Hasegawa, et al.

Figure 4. Dermoscopic findings in skin disorders that should be differentiated from discoid lupus erythematosus (DLE). Clinical pictures and their dermoscopic counterparts are shown.

a) Psoriasis vulgaris at dorsal surface of the hand. Background is light red covered with white large scale. Dotted vessels are found outside of the scale.
b) Lichen planus on the arm. Diagnostic white crossing lines (Wickham striae) are detected.
c) Nummular eczema on the arm. Serum exudates can be seen dermoscopically, as shiny
yellow clods.
d) Cutaneous sarcoidosis on the arm. Yellow to orange structureless areas associated with
linear vessels

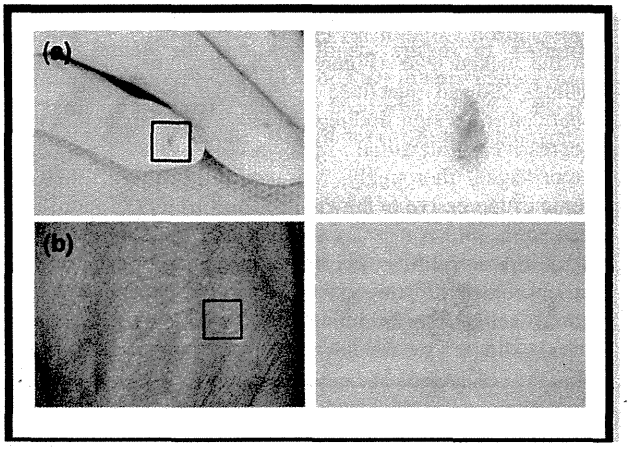

Figure 5. Dermoscopic findings in systemic sclerosis. Clinical pictures and their dermoscopic counterparts are shown.

a) Well-circumscribed dense telangiectases referred to as "matted" lesions.
b) Poorly-marginated light telangiectases referred to as "stellate" lesions.

The first are well-circumscribed dense telangiectases referred to "matted" lesions [31]. This type is frequently detected in patients with anticentromere Ab and the telangiectases are composed of enlarged capillaries (Figure 5A). The second are poorly-marginated light telangiectases referred to as "stellate" lesions [31]. This type is often found in patients with anti-topoisomerase I Ab. Here the telangiectases are composed of fine linear, tortuous, and/or ramified capillaries that are typically arranged in stellatepatterns (Figure 5B). Interestingly, the dermoscopic findings of enlarged capillaries are similar to giant capillaries/enlarged capillaries detected as the scleroderma active-pattern in the nailfold. On the other hand, the dermoscopic findings of fine capillaries are similar to that of tortuous, crossed, and/or ramified capillaries found as scleroderma late-pattern in the nailfold. However, the pathological and clinical significance of telangiectases remains unestablished, in contrast to nailfold capillary findings.

Dermatomyositis

Dermoscopic findings of Gottron's sign are not specific. Irregular arrangement of venules and scales are found on a light red background (Figure 6A and 6B). However and interestingly, the Gottron's sign observed by dermoscopy was impressive in one of our cases where anti- melanoma differentiation-associated protein 5 (MDA-5) Ab was present [32]. Anti-MDA-5 Ab is highly associated with the

development of rapidly progressive interstitial pneumonia [32]. Gottron's sign of her elbows were usual as determined by the naked eye (Figure 6C). However, dermoscope findings showed punctuate hemorrhage in addition to the usual Gottron's sign findings. In fact, she developed rapidly progressive interstitial pneumonia. The punctuate hemorrhage thoroughly disappeared after intensive immunosuppressive treatment and stabilization of interstitial pneumonia. Since it is known that DM patients with anti-MDA-5 Ab exhibit skin ulcer more frequently than patients without the Ab [33], we suspect the hemorrhage detected on Gottron's sign may be reflecting vascular injury associated with rapidly progressive interstitial pneumonia.

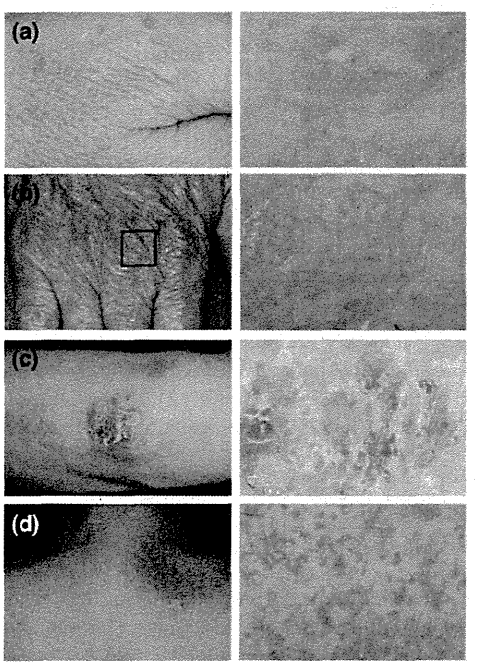

Figure 6. Hasegawa, et al.

Figure 6. Dermoscopic findings in dermatomyositis. Clinical pictures and their dermoscopic counterparts are shown.

a, b)Gottron's sign of the dorsal face of the hand. Background is light redaccompanied by white lesions. Linear irregular vessels are found.

c) Gottron's sign at the elbow. Dermoscopy findings showed punctuate hemorrhage in addition to usual Gottron's sign's findings. The patient developed rapidly progresive interestitial pneumonia.

d) Poikiloderma on the back. Enlarged, linear, irregular vessels are highly visible and pigmentation and depigmentation are mixed.

Another interesting finding was made by dermoscopy ofpoikilodermaskin lesions in patients with DM. Enlarged linear irregular vessels are visible and pigmentation and depigmentation are mixed (Figure 6D). Although poikiloderma is often detected in pateints with DM, but it is not specific for DM and usually detected by naked eyes. However, the confirmation using dermoscopy may be useful to distinguish poikiloderma from other skin lesions.

CONCLUSION

Our findings are preliminary and are not based on systematic studies of large numbers of patients. Nonetheless, we propose that dermoscopic observations are helpful for diagnosing and evaluating disease activity in some clinical situations. Improved visualization of vessels and color variations, that are difficult to recognize with the naked eye, can be observed using dermoscopy. A more detailed determination of specific dermoscopic features of skin lesions of CTD may be a valuable resource for clinical assessment. Furthermore, these findings may provide clues that improve our understanding of the pathogenesis of skin lesions and of CTD itself. We hope that dermoscopy becomes widely used for the evaluation of CTD and believe that further investigation will soon yield information valuable to the clinical practitioner.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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皮膚臨床 57(1)；19～22，2015

特集◆膠原病

各種末梢循環改善薬を併用し完治し得た全身性強皮症に伴う難治性足趾壊疽の1例

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長谷川　稔[*1,2]　藤本　学[*1,3]　竹原　和彦[*1]

要　約

33歳，女性。27歳時に全身性強皮症を発症。抗トポイソメラーゼI抗体陽性で高度の皮膚硬化を伴う。初診半年前に左足趾に潰瘍が出現，近医で足趾切断を提案されたが，保存的治療を希望し当科を紹介受診した。当科初診時，スキンスコアは51点中42点と高度皮膚硬化があり，左第2，4，5趾に壊疽を認めた。持続坐骨神経ブロックと各種末梢循環改善薬(ボセンタン，タダラフィル，アルプロスタジル，アルガトロバン，ベラプロストナトリウムなど)を併用し，12週間後治癒した。近年，強皮症皮膚潰瘍に対するエンドセリン受容体拮抗薬やPDE-5阻害薬の有効性が報告され，強皮症における難治性皮膚潰瘍の治療において有効であると考えた。

Key words：全身性強皮症，皮膚潰瘍，ボセンタン，タダラフィル

Ⅰ．はじめに

全身性強皮症では，しばしば指(趾)尖部や関節背面に皮膚潰瘍を生じ，難治で強い疼痛を伴い，患者のQOLを大きく低下させる。安易なデブリードマンや切断は，さらに潰瘍や壊疽を拡大させることが多く，可能な限り保存的治療を優先することが重要であることが近年知られている。今回，足趾壊疽とその疼痛に苦しんでいた患者に対し，坐骨神経ブロックと各種血管拡張薬を併用し，保存的に治癒し得たので，主に治療法の観点から報告する。

Ⅱ．症　例

患　者　33歳，女性

初　診　2013年4月

家族歴・既往歴　特記すべき事項なし。

現病歴　初診の5年前の第2子妊娠時から手指の腫脹，Raynaud現象を認め，全身性強皮症と診断された。3年前から皮膚硬化が進行し，手指に潰瘍を生じるようになった。半年前から足趾に潰瘍を生じ，近医に入院しアルプロスタジル3回/週，ボセンタン125 mg/日，クロピドグレル，シロスタゾールを投与されたが，潰瘍

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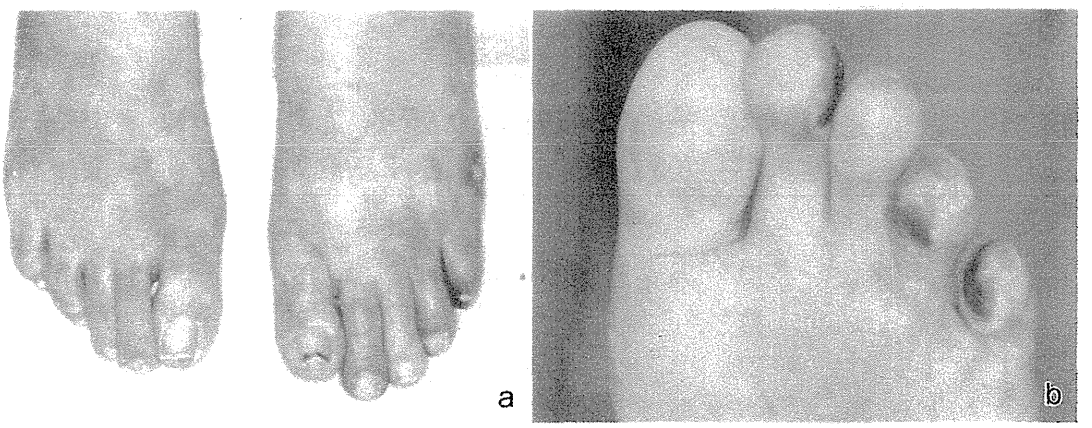

図1　入院時臨床像
a：両足背に暗紫色の網状斑がみられた。
b：左2，4，5趾尖部に壊疽を認め，激しい自発痛を伴っていた。

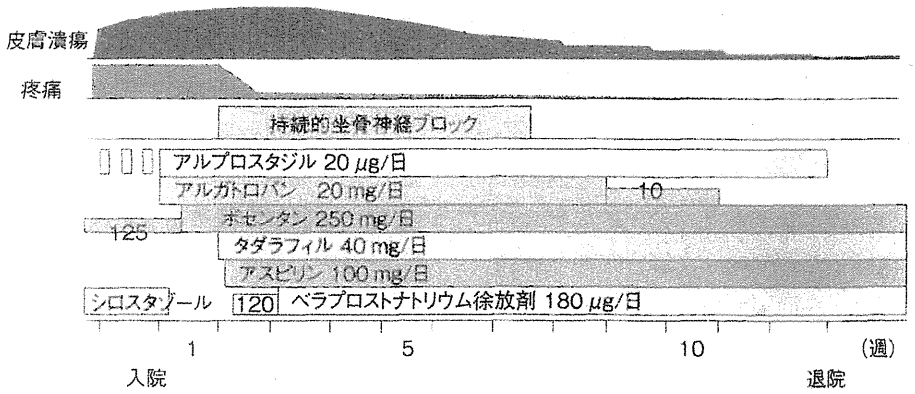

図2　臨床経過

は拡大，疼痛が強く不眠となった。近医にて足趾切断を提案されたが，保存的治療を希望し当科を紹介受診した。

現　症　両足背に暗紫色の網状斑がみられ，高度な皮膚硬化を認めた（図1-a）。左第2，4，5趾尖部に壊疽を認め，激しい疼痛を伴っていた（図1-b）。スキンスコアは51点中42点で，皮膚硬化は高度であった。

臨床検査所見　WBC 13610/μl，CRP 4.1 mg/dlと軽度上昇。抗核抗体640倍（homogeneous，nucleolar pattern），抗トポイソメラーゼI抗体が195.6 U/mlと高値陽性であり，その他の特異抗核抗体は陰性で，ループス抗凝固因子，抗カルジオリピン抗体，抗β_2-グリコプロテインI抗体は陰性であった。胸部CT検査では両下葉に軽度の網状影を認めたが，2年前の画像と著変はなかった。呼吸機能検査では，%VCは103.5%と正常で，%DLcoは64%と若干の拡散能低下を認めた。下肢動脈CT検査では閉塞狭窄は認めなかった。

鑑別診断　足趾に潰瘍を形成する疾患を鑑別に考えた。抗リン脂質抗体がいずれも陰性で，活性化部分トロンボプラスチン時間（activated partial thromboplastin time：APTT）延長もな

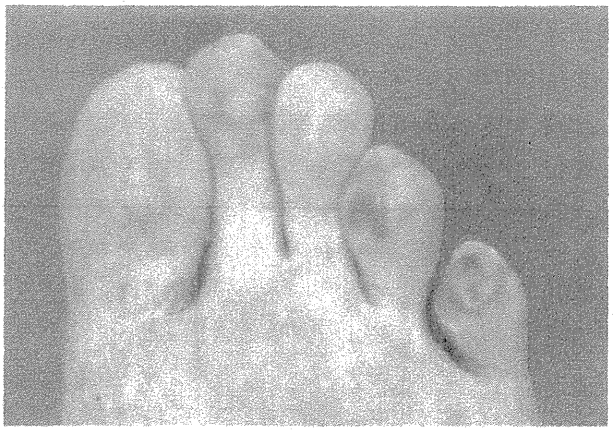

図3　12週間後の臨床像
入院12週間後にはほぼ完全に上皮化した。

く抗リン脂質抗体症候群は否定的と考えた。閉塞性動脈硬化症は，動脈の閉塞狭窄はなく除外した。以上から全身性強皮症に伴う足趾壊疽・潰瘍と診断した。

治療および経過（図2）　入院時から患部の安静とコタツによる保温に努めた。左足趾の疼痛に対し，オピオイドとプレガバリンの内服は効果が乏しいため，アナペイン持続的坐骨神経ブロックを施行した。ブロック施行後から疼痛は著明に改善し，処置時の疼痛や不眠の訴えはなくなった。局所の循環障害には，アルプロスタジル20 μg/日とアルガトロバン20 mg/日の点滴静注を開始し，ボセンタン250 mg/日へ増量，タダラフィル40 mg/日，アスピリン100 mg/日，ベラプロストナトリウム徐放剤180 μg/日を副作用の発生に注意しながら追加した。局所は毎日微温湯で洗浄し，壊死組織にはスルファジアンジン銀クリーム，壊死組織がない潰瘍にはプロスタグランジン E_1（以下 PGE_1）含有軟膏を外用した。入院後しばらくは壊死が拡大したが，徐々に上皮化が進み，壊死組織が浮いてきたところを少しずつ切除して保存的に治療したところ，入院12週間後にはほぼ上皮化し退院となった（図3）。

Ⅲ．考　察

全身性強皮症では，細動脈から小動脈，毛細血管が傷害されることで種々の皮膚症状を生じる。その機序は不明であるが，潰瘍・壊死を生じた指趾の固有動脈には壁の肥厚による内腔の狭小化・閉塞がみられる[1]。また，石川らの報告では，同側の複数指（趾）に潰瘍・壊疽が生じているか，あるいは同時に踵部などにも潰瘍が生じている3例では，中枢側の尺骨動脈や抗脛骨動脈にも閉塞や内腔の狭小化がみられ，これらの血管病変も強皮症によるものであるとした[2]。いずれにせよ，全身性強皮症で生じる潰瘍には大小さまざまな血管の狭小化・閉塞が関与していると考えられる。

本症例では，全身性強皮症に伴う循環障害に対し，血管拡張作用のある薬剤を複数投与した。プロスタグランジン製剤は一般的にもっともよく使用されていて，リポ PGE_1 は静注製剤で症例集積研究にてRaynaud現象の減少と指趾尖潰瘍に対する有用性が報告されている[3]。ただし，障害された血管よりも健常な血管拡張をきたすスチール現象が生じる可能性も報告されており[4]，投与後は循環障害の増悪がないか注意を要する。われわれは PGE_1 製剤投与前後でサーモグラフィ検査を行い，患肢のスチール

現象がないことを確認することにしている。ベラプロストナトリウムについては，多施設共同ランダム化比較試験において，プラセボと比較し指趾尖潰瘍の治療における有用性に関して有意な差は認められなかったが，虚血性指趾尖潰瘍の再発が少ない傾向があることがわかった[5]。抗トロンビン薬についても，清水らはアルガトロバンを投与し，難治性皮膚潰瘍が治癒した症例を報告している[4]。

本症例では，上記の血管拡張薬に加えてエンドセリン受容体拮抗薬とホスホジエステラーゼ5（以下PDE-5）阻害薬を投与した。エンドセリンは主として血管内皮細胞で産生されるペプチドであり，強力な血管収縮作用を有する。エンドセリンの受容体には，ETAとETBの2種類が存在するが，ボセンタンはその両方のエンドセリン受容体と拮抗することにより血管拡張をもたらす。全身性強皮症患者を対象にしたランダム化比較試験では，現存する皮膚潰瘍に対する有意な改善は認めないが，皮膚潰瘍の新生を抑制した[6][7]。症例集積研究では，潰瘍治療の有用性が示されている[8]。しかし，肝機能障害の頻度が高いことや，当施設の過去の報告では腹水を生じた2例があり[9]，投与開始後は，特に高齢者では副作用の発生に留意する必要がある。また，本邦では肺動脈性肺高血圧症にしか適応がなく，使用にあたっては慎重に適応を考慮する必要がある。

PDE-5阻害薬は，細胞内に存在するcGMPの分解を抑制することにより，血管が拡張する。PDE-5阻害薬は元来勃起不全治療薬として開発されたが，近年，肺動脈圧性高血圧症の適応を有するに至った。

本邦で使用可能なPDE-5阻害薬には，シルデナフィルとタダラフィルがある。シルデナフィルについては，強皮症患者16例を対象にしたランダム化クロスオーバー試験で，有意にRaynaud現象を抑制することが示された[10]。強皮症の皮膚潰瘍に対するこれまでの報告では，シルデナフィル投与により潰瘍数が有意に減少したというパイロット研究[11]と，タダラフィル投与により潰瘍の新生を抑制したとするランダム化クロスオーバー試験[12]がある。タダラフィルはシルデナフィルに比べて作用持続時間が長く，PDEのなかでもPDE-5に対する選択性が高いため，治療効果が期待でき，服薬コンプライアンス（タダラフィルは1日1回，シルデナフィルは1日3回）や副作用の点からも有用と考え，本例ではタダラフィルを選択した。また，エンドセリン受容体拮抗薬と同様に，本邦では肺動脈性肺高血圧症にしか適応がなく，使用にあたっては慎重に適応を考慮する必要がある。

以上のように，エンドセリン受容体拮抗薬やPDE-5阻害薬による強皮症皮膚潰瘍に対する治療効果は，今後も検討が必要である。しかし，本症例のように，これらの薬剤を複数組み合わせることで相乗効果を期待できると考えられた。

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