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Letter to the Editor

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Letter to the Editor (Case report)

Ameliorated nailfold capillary morphology of patients with pulmonary arterial hypertension in systemic sclerosis, treated with riociguat

Tomohiro Sugimoto [1,*], Yoshihiro Dohi[2], Yusuke Yoshida [1], Sho Mokuda[1], Shintaro Hirata [1]

[1]Department of Clinical Immunology and Rheumatology, Hiroshima University Hospital, Hiroshima, Japan
[2]Department of Cardiovascular Medicine, Kure Kyosai Hospital, Kure, Japan

*Correspondence to: Tomohiro Sugimoto, Department of Clinical Immunology and Rheumatology, Hiroshima University Hospital,1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan. E-mail: tsugimoto@hiroshima-u.ac.jp

Key message

- Nailfold videocapillaroscopy can be helpful in evaluating nailfold abnormalities and for monitoring pulmonary arterial hypertension.

Dear Editor, The long-term course of nailfold capillary abnormalities in patients with SSc and pulmonary arterial hypertension (PAH) has seldom been reported. Here, we report a case of SSc with PAH and nailfold capillary abnormalities that improved with triple vasodilatation therapy.

A 53-year-old woman with a history of hypertension presented with dyspnoea on exertion, that had persisted for 1 year. She also experienced an episode of RP during the same period. Electrocardiography indicated right heart overload, and the patient was referred for further work-up.

Upon examination, the patient had puffy fingers, fingertip-pitting scars and nail epithelial extension. ACAs were detected in blood samples, and the diagnosis of SSc was made. Serum anti-Scl-70 antibody, anti-RNA polymerase III antibody, anti-ribonucleoprotein antibody, anti-DNA antibody, anti-Sm antibody and anti-SS-A antibody tests were negative. The N-terminal prohormone brain natriuretic peptide (NT-proBNP) level was 477 ng/ml (normal range, 1–55 ng/ml). CT showed no co-morbid interstitial lung disease. The nailfold videocapillaroscopy (NVC) instrument (OptiPix Capillaroscopy; Optilia Instruments, Sollentuna, Sweden) facilitates a ×200 magnification of the observed area, allowing accurate evaluation of the nailfold capillaries. Based on previous reports, NVC testing was performed on eight fingers, excluding the thumb, and each finger was assessed on two images on either side of the centre [1]. NVC showed enlarged capillaries, giant capillaries and haemorrhages (Fig. 1a and d).

Echocardiography revealed an increased transtricuspid regurgitant pressure gradient of 53 mmHg. Right heart catheterization was performed and revealed a mean pulmonary artery pressure (mPAP) of 51 mmHg and a pulmonary artery wedge pressure of 13 mmHg, which was consistent with PAH.

We started oral combination therapy with selexipag and macitentan. The doses were adjusted and the treatment continued until follow-up (selexipag 3.2 mg and macitentan 10 mg daily, respectively). One year after initiation of treatment, the NVC showed worsening of the previous vasodilatation and haemorrhages (Fig. 1b and e). After 20 months of treatment, dyspnoea on exertion re-exacerbated, and oxygenation decreased, with a NT-proBNP level of 149 ng/ml. Re-evaluation using right heart catheterization revealed that the mPAP was 37 mmHg, an improvement from initiation of treatment, but the disease activity of PAH remained. Riociguat was then added to the patient's treatment regimen for oral triple therapy. The dose was increased gradually to 6 mg/day. The patient's symptoms, including dyspnoea on exertion, improved greatly. NVC performed at the 3-year follow-up showed that the vascular findings had normalized (Fig. 1c and f). The NT-proBNP level had decreased to 45 ng/ml and the mPAP to 27 mmHg. During the entire course, the patient was treated with vasodilators only, with no use of CSs or immunosuppressants.

In patients with SSc, nailfold capillary abnormalities are most likely to worsen over time [2]. Nevertheless, some reports show that immunosuppressive treatment can aid in improving nailfold capillary abnormalities [3, 4], and it has also been reported that drug therapy, such as bosentan, improves nailfold capillary abnormalities [4–6]. A previous study reported that the combined use of bosentan, an endothelin receptor antagonist, and iloprost, a prostacyclin analogue, improved capillary density on NVC [5]. Compared with iloprost monotherapy, concomitant use of bosentan and iloprost has shown enhanced improvement in capillary

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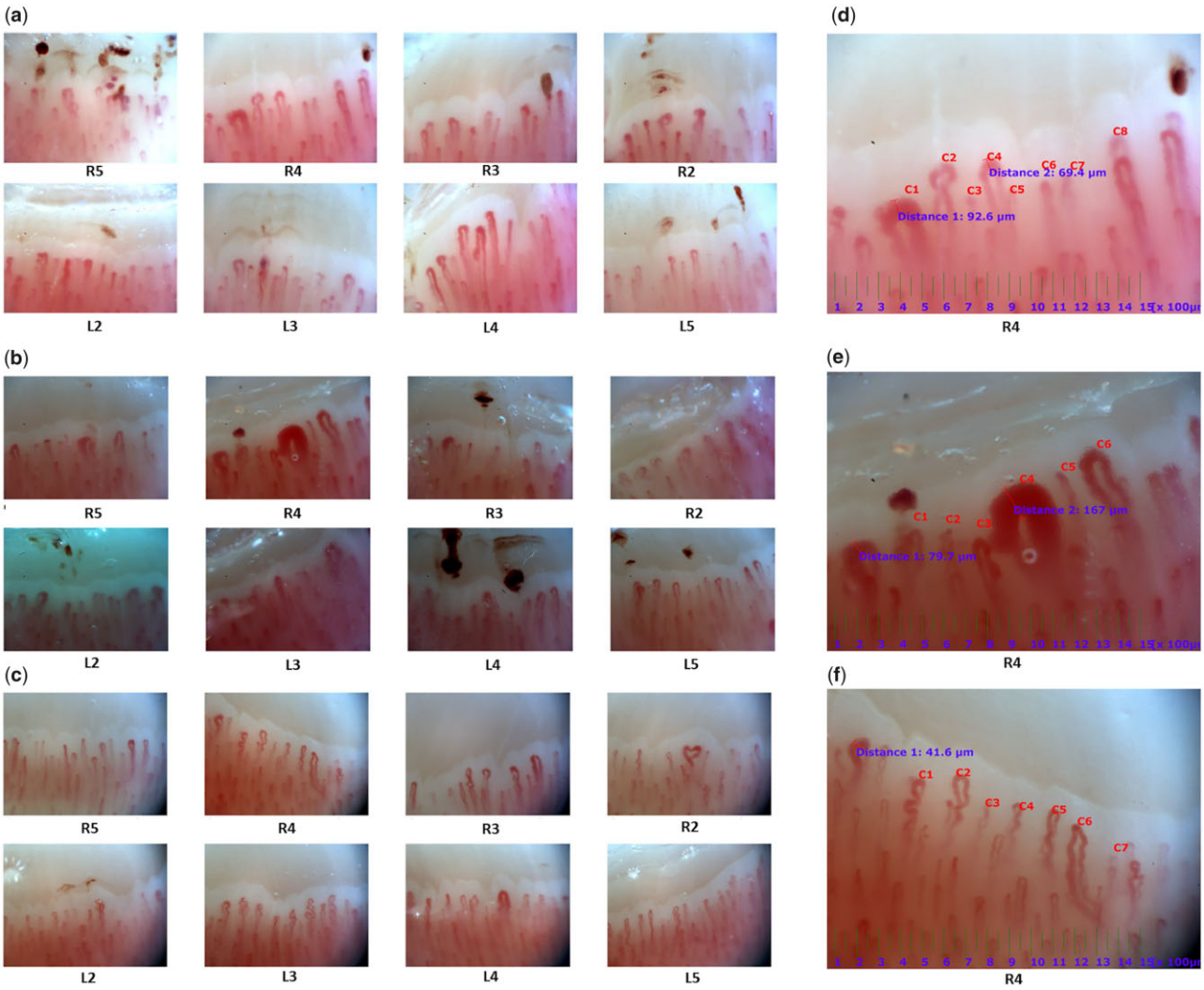

Figure 1. Nailfold videocapillaroscopy (NVC) showing the capillaries of eight fingers, excluding the thumbs, across both hands. (**a**) NVC image at the time of SSc diagnosis, before initiation of treatment. Enlarged capillaries, giant capillaries and haemorrhages are present. (**b**) Images after 1 year of treatment with selexipag and macitentan. Enlarged capillaries, giant capillaries and haemorrhages appear worse than those at the initial examination. (**c**) Three years after initiation of treatment, with the addition of riociguat as a triple therapy approach. Although some vasodilatation remains, the giant capillaries have disappeared and haemorrhage has improved. (**d**–**f**) Magnified images of the right ring finger at each stage. (**d**) Early pattern: multiple giant capillaries are present, and eight nailfold capillaries can be observed at intervals of 1 mm. (**e**) Active pattern: half of the nailfold capillaries are giant capillaries. A decrease in nailfold capillary density can be observed, with only six nailfold capillaries at 1 mm intervals. (**f**) Early pattern: enlarged capillaries have improved, and most of the giant capillaries have disappeared. The nailfold capillary density also appears to have improved, with seven capillaries observed at intervals of 1 mm. L2: left index finger; L3: left middle finger; L4: left ring finger; L5: left little finger; R2: right index finger; R3: right middle finger; R4: right ring finger; R5: right little finger

density on NVC [4]. The combined use of bosentan and sildenafil has also been reported to improve the activity pattern on NVC [6].

A decreased density of nailfold capillaries has been reported to be associated with the development of SSc-associated PAH [7]. Progression of the NVC pattern is also considered to be associated with the development of SSc-associated PAH [7]. In addition, although the impact of a reduction in capillary density on the SSc-associated PAH course is an important matter of interest, it remains unknown. This case report shows that the improvement of nailfold capillary abnormalities might be related to the improvement of SSc-associated PAH. Therefore, regular monitoring might be necessary not only before the diagnosis of SSc-associated PAH, but also after initiation of treatment.

Riociguat is a soluble guanylate cyclase (sGC) stimulant that binds to sGC and promotes cyclic guanosine monophosphate (cGMP) synthesis, independent of nitric oxide (NO). PAH is involved in endothelin, prostacyclin and NO–sGC–cGMP pathways [8]. The therapeutic advantage of combining riociguat with an endothelin receptor antagonist and prostanoids has been reported and implemented clinically [8]. In our case, no improvement in nailfold capillary abnormalities was observed, even after therapeutic intervention with selexipag and macitentan administration. PAH findings, shown by right heart catheterization, also did not improve sufficiently with the dual drug regimen. However, a marked improvement in nailfold capillary abnormalities and mPAP was observed with triple therapy. Our case showed that the use of riociguat, an sGC stimulant that engages the NO–cGMP pathway, can

possibly ameliorate PAH and vascular endothelial damage in patients with SSc-associated PAH.

In summary, long-term nailfold capillary follow-up examinations in SSc patients with PAH might be helpful in assessing the therapeutic efficacy of sGC stimulators.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Ethical statement: The study has been conducted in accordance with the 1964 Helsinki Declaration and its subsequent amendments.

Patient consent: Written consent was obtained from the patient regarding the publication of this case.

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