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Effect of Sildenafil on digital ulcers in systemic sclerosis – analysis from a single centre pilot study

Concise Report

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Abstract:
Objective: In this pilot study, the effect of sildenafil on digital ulcer (DU) healing and related clinical symptoms was analysed.
Methods: 19 systemic sclerosis (SSc) patients were treated with maximally tolerated sildenafil doses up to 6 months. Primary outcome was the healing of DU. Furthermore, changes in other clinical symptoms were evaluated.
Results: 49 DU were present at baseline that decreased to 17 ulcers ($p < 0.001$) at the end of sildenafil therapy. Furthermore, the visual analogue scale score for Raynaud's phenomenon (RP), pain, and activity improved ($p = 0.003$, $p = 0.002$, and $p = 0.05$, respectively). Nine patients developed 12 new DU during sildenafil therapy.
Conclusions: This study indicates an effect of sildenafil on DU healing in SSc patients, improvement of RP and associated symptoms that should be validated in controlled studies.

Introduction: Systemic sclerosis (SSc) is a devastating disease with a high impact on quality of life and prognosis. Vasculopathy is an early and prominent feature and is reflected by Raynaud`s phenomenon (RP), the presence of digital ulcers (DU) and pulmonary arterial hypertension (PAH, 1). Recent therapeutic advances suggest common pathogenic mechanisms and a role for endothelin receptor activation in SSc-associated vasculopathy (2). However, endothelin receptor blockers such as the dual endothelin receptor type A/B blocker bosentan are effective in the prevention of digital ulcers, but are not able to heal DU indicating different mechanisms for prevention and ulcer healing (3). Intravenous iloprost is often used for the treatment of DU, but its effect on the prevention of DU has not been studied so far. There is also a subgroup of patients that does not respond to iloprost therapy (4).
Reduced levels of nitric oxide have also been proposed to play a role in the pathogenesis of vascular disease in systemic sclerosis (5). Therefore, sildenafil as a selective inhibitor of cGMP-specific phosphodiesterase type 5 and potent agent to increase the endogenous NO levels is an attractive candidate for the treatment of SSc-associated vasculopathy. Indeed, sildenafil is approved by FDA and EMEA for the treatment of PAH. The highest dose of sildenafil recommended for the treatment of PAH is 60 mg daily, however; several studies suggest a higher effect by increasing the dose (6, 7). In a placebo-controlled cross-over study, 50 mg sildenafil twice daily for four weeks was shown to be effective for the treatment of Raynaud's phenomenon (8). Furthermore, some case reports suggest an effect on DU healing in SSc (9-10). Therefore, we conducted a pilot study analysing the effect of sildenafil on healing of SSc-associated DU refractory to other therapies.

Patients and Methods:
19 SSc patients (mean age 51 years) fulfilling the ACR criteria for systemic sclerosis, assessed according to the EUSTAR criteria (11), and suffering from severe rhagades (n = 1) or therapy-refractory digital ulcers (n = 18) were treated with the maximally tolerated sildenafil doses (up to 150 mg) for a maximum of 6 months. Inclusion criteria were stable therapy with vasoactive and immunosuppressive drugs for three months. Current smokers, patients with gangrene, a history of gastric ulcers during the last three months, cardiac ejection fraction below 25%, patients with severe organ involvement or other uncontrolled diseases were excluded. DUs were defined as a loss of both epidermis and dermis. The demographic data are shown in **table 1**.
The study was conducted between 2004 and 2007. Two patients were treated outside of the study with the intention to heal digital ulcers refractory to other therapies, the other 17 patients were treated as part of a prospective, open single

centre study. Here, the primary outcome parameter was DU healing. Secondary end points were effects on Raynaud's phenomenon by using a VAS scale, the prevention of new ulcers, changes in VAS scores for pain, activity and suffering from ulcers, the improvement of rhagades, SHAQ-indices, and the occurrence of sildenafil-related adverse effects. Drop out criteria/ final end points were any changes in the immunosuppressive therapies, no response on ulcer healing within one month, or escalation of medication with vascular effects. Relevant macrovasculopathy responsible for DU was excluded by angiography or duplex sonography (12). Nine patients treated for 6 months by sildenafil received a second angiography.
The study was approved by the local ethical committee (SDN-D-002G) and published as a clinical trial (NCT00624273). Patients signed an individual informed consent.

Statistics: Paired Wilcoxon-test was used to identify the effect of sildenafil on digital ulcers and VAS for clinical symptoms. Graph Pad Prism Version 3.02 (Graph Pad Software, San Diego, California) for Microsoft® Windows was used.

Results:
Three patients did not receive sildenafil for more than one month due to myositis requiring immunosuppression (n = 1), the re-occurrence of atrial fibrillation (n = 1), and infection of an ulcer with a multi-resistant staphylococcus (n = 1) and were excluded from further analyses. In the remaining 16 patients, the mean sildenafil dose was 114 mg/d, and the mean duration of therapy was 5.2 months. At baseline, 49 ulcers were present (mean 3.1/patient). Most patients showed a rapid response reaching a minimum of DU within three months without differences in the SSc subtype (**Fig. 1a, b, Fig. 2**). The minimal number of DU was achieved in each patient at different time points, minimally 9 DU were present (mean 0.6 ulcers/patients, $p < 0.001$ compared to initial numbers, **Tab.1**). At the end of sildenafil therapy, 17 digital ulcers were detectable (mean 1.1 /patient), which was different from the number of ulcers at baseline ($p < 0.001$, **Tab. 1**).

Tab 1. Patients characteristic and effects of therapies including previous and concomitant therapies. Abbreviations: * indicates male patients, SSc type: lim. = limited, diff. = diffuse SSc, DD means Disease Duration, Compl. Heal. stands for number of ulcers completely healed,+ indicates stop of the therapy due to side effects, ° indicates stop of therapy due to other events with possible impact on the effect of therapy (ulcer infection, cyclophosphamide use), # indicates patients with development of new digital ulcer or calcinosis and no significant improvement by therapy. Abbreviations for therapies: CCB = Calcium Channel Blockers, ACE = Angiotensin Converting Enzyme inhibitor, PC = intravenous ProstaCyclin (weeks with maximally tolerated dose for 6h/d), SL = SympathicoLysis, PX = PentoXyphylline, ASA = Acetyl Salicylic Acid, HQ = HydroxycloroQuine, AB = Alpha Blocker, SG = SurGery, ATB = AngioTensin receptor Blocker, AA = AutoAmputation, AZA = AZAthioprine, PP = PlasmaPhereses, AC = AntiCoagulation, CYC = CYClophosphamide, P = Prednisone (dose in mg/d). Abbreviations for side effects: AF = Atrial Fibrillation. Dys. = Dyspnea, BWI = Body Weight Increase, E = Edema, Fl = Flush, Pa = palpitations, Dizz: dizziness, RRR = reduction of RR medication, Rx = Reflux, Muscle Pain = MP.

					Therapy				Number of ulcers during therapy					
Pat. No.	Activity Score	SSc type	DD in years	Age in years	Previous and concomitant	Start	Duration in months	Dosage (mean in mg/d)	Start	Min.	End	Compl. Heal.	New	Side effects
1	4.5	Diff.	2	69	CCB, PC (4), PX	Jan.	2 #	50	1	0	0	1	0	no
2	2.0	Lim.	41	51	SL, CCB, PC (2), ASA	Oct.	1°	150	1	1	1	0	0	no
3	3	Lim.	0.5	40	PC (3.5), CCB, SL, P (7.5)	Sept.	3#	150	3	1	2	2	1	no
4	3.0	Diff.	25	54	ACE, CCB, ASS, P (2.5)	Febr.	6	50	1	0	0	1	0	no
5	2.5	Lim.	11	59	PX, PC (3), CCB, HQ, P (4),	Febr.	6	150	1	0	0	1	0	E, Fl, Pa, Dizz., Rx
6*	0.5	Diff.	5	55	PC (1.5), SG, CCB, AB, ACE	April	2.5+	75	2	0	0	2	0	Dys., E, WI
7	1.0	Lim.	0.5	39	PC (5), CCB, ATB. P (7)	Jan.	6	100	3	0	0	4	1	Fl, Pa, RRR, Rx
8	5.0	Diff.	5	58	AA, CCB, ACE, PC (4)	Oct.	6	150	2	0	1	2	1	Fl
9	1.0	Lim.	3	29	CCB, PX, ASA,	Jan.	6	150	2	1	1	1	0	E
10*	1.0	Lim.	6	70	PC (4), SG, CCB, ACE AZA, P (5),PX	Aug.	<1+	50	5	5	5	0	0	AF, Dizz
11	1.0	Lim.	6	48	PP, PC (2), PX, CCB, AC	Mai	<1°	75	2	2	2	0	0	no
12	2.5	Diff.	2	54	CCB, ACE, PC (2.5), AB, ATB	Mai	6	125	5	0	2	5	2	RRR
13	2.0	Diff.	11	43	PC (6), CCB, PX, P(5)	Aug.	6	50	2	0	3	2	3	E, Fl, Pa, MP
14	1.0	Diff.	7	43	PC (3), CCB, ASA, P(5)	April	6	75	4	1	2	3	1	WI, Pa, RRR
15	2.0	Lim.	9	60	SG, PC (3), CCB, ACE	Jan.	6	150	6	2	2	5	1	No
16	2.5	Diff.	22	51	SG, PC (3), PX, ASA	Febr.	4#	150	4	2	2	3	1	No
17	3.0	Diff.	17	65	PC (2), PX, CCB, CYC, P (10)	May	6	100	6	2	2	5	1	No
18	1.5	Lim.	14	38	SG, PC (5), CCB, PX, PP, P (7.5)	Mar.	6	150	5	0	0	5	0	No
19	2.0	Lim.	1	42	CYC, CCB, PC (2), AC	June	6	150	2	0	0	2	0	no

During sildenafil therapy, nine patients developed 12 new DU resulting in a stop of therapy in three patients. In one of these patients calcinosis was diagnosed. 12 patients were treated for 6 months. VAS score for RP, pain, and activity significantly improved ($p = 0.003$, $p = 0.002$, and $p = 0.05$, respectively) by sildenafil therapy (**Fig.1c-f**). There was also a tendency for changes in the disability score due to the digital ulcers ($p = 0.08$). SHAQ-DI scores available from 11 patients improved from a mean of 0.6 (SD 0.52) to 0.42 (SD 0.32) but failed to reach statistical significance ($p = 0.14$). In the 9 patients that received angiography before and after therapy, one responder showed an improvement of vascular pathology (not shown). Severe rhagades disappeared by sildenafil in the one affected patient. Of the 14 patients in which follow-up data were available, 7 patients developed 15 DU within 3 months, three patients have taken sildenafil outside from the study.
Mild side effects were common and were present in 9 out of 19 patients, but resulted in a discontinuation of the therapy only in the two male patients (**Tab. 1**). In three patients with arterial hypertension, the antihypertensive therapy was reduced during sildenafil therapy.

Discussion: In a previous single-centre placebo-controlled cross-over study, sildenafil was shown to improve the capillary blood flow and Raynaud's phenomenon. As suggested by a few patients suffering from DU, sildenafil could provide a useful therapeutic approach for DU healing. In this prospective open pilot study, maximally tolerated sildenafil doses seem to be effective in DU healing. The effect was rapid, and maximum benefit was reached in the first months. Furthermore, the study confirmed the beneficial effect of sildenafil on RP and microvasculopathy. DU are a very severe complication with a high impact on the quality of life in SSc patients. At present, there is no approved therapy for the healing of DU. The dual endothelin-1 receptor antagonist has failed to be effective in ulcer healing (3). However, different studies showed the effect of bosentan to prevent the development of new DU (3, 13). In the present study, sildenafil shows benefit in DU healing confirming case reports and initial observations in which sildenafil was given only for a few weeks (8). In our study, patients were treated for up to six months. Within this period, a significant proportion of patients developed new DU suggesting a failure of sildenafil to prevent new structural defects. Furthermore, only one patient had mild improvement by angiography. As already suggested by others, different pathogenetic mechanisms could be responsible for prevention or DU healing (2, 14). Therefore, as also discussed for the therapy of PAH, combination therapies targeting different pathogenic mechanisms could provide a more valuable and effective tool for further therapies.
A major limitation of this study is the lack of a placebo group. When compared to the placebo group of the RAPID-1 study in which about 10% of ulcers healed per month (3), the number of ulcers healed was higher in our sildenafil group. However, direct comparison with other trial data provide only limited information due to other study designs. Furthermore, most of the patients treated here had been refractory to previous therapies. Therefore, our study population could represent a subgroup of SSc patients truly responding to sildenafil therapy.
For treatment of PAH or erectile dysfunction, lower doses of sildenafil are usually used. In our study, maximally tolerated doses were given for the treatment of DU. Therapy was well tolerated and side effects were not dose related. The two male patients who discontinued the drug due to side-effects received low sildenafil doses (2 x 25 mg/d) suggesting a higher sensitivity to the drug apart from the use of unconventionally high doses. The incidence of peripheral edema, the presence of

dyspnea and re-occurrence of atrial fibrillation suggest increased blood flow and fluid overload in few patients. This remains to be further evaluated since phosphodiesterase-5 inhibitors were also successfully used to treat pulmonary edema (15).
In conclusion, this pilot study indicates beneficial and rapid effects in the therapy of DU. Moreover, sildenafil decreases the burden of RP and associated symptoms. The data encourage controlled studies and combining both a preventive as well as a curative therapy would be a valuable approach to treat DU in SSc patients.

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Competing interests: Gabriela Riemekasten received lecturers fees from Encysive, Actelion, GSK, and Phizer.

Figure legend:
Fig. 1: Effect of sildenafil therapy on the number of digital ulcers in diffuse (a) and limited (b) SSc patients during 6 months of therapy, on Raynaud`s phenomenon (c), burden of pain (d), daily activity (e), and on disease burden due to ulcers (f) measured by visual analogue scale (VAS). Paired Wilcoxon-test was used to calculate statistical significance; the median is illustrated as a horizontal line.

Fig. 2: Digital ulcer healing by sildenafil therapy as shown for three different patients. Digital ulcers before therapy are shown in figure a, c, d; figure b, d, and f show the effects of sildenafil therapy. Figure e and f come from a patient refractory to continuous intravenous iloprost therapy over two weeks requiring amputation and showing insufficient wound healing. Within a few days, patient remarked finger re-warming and subsequently progressive wound healing.

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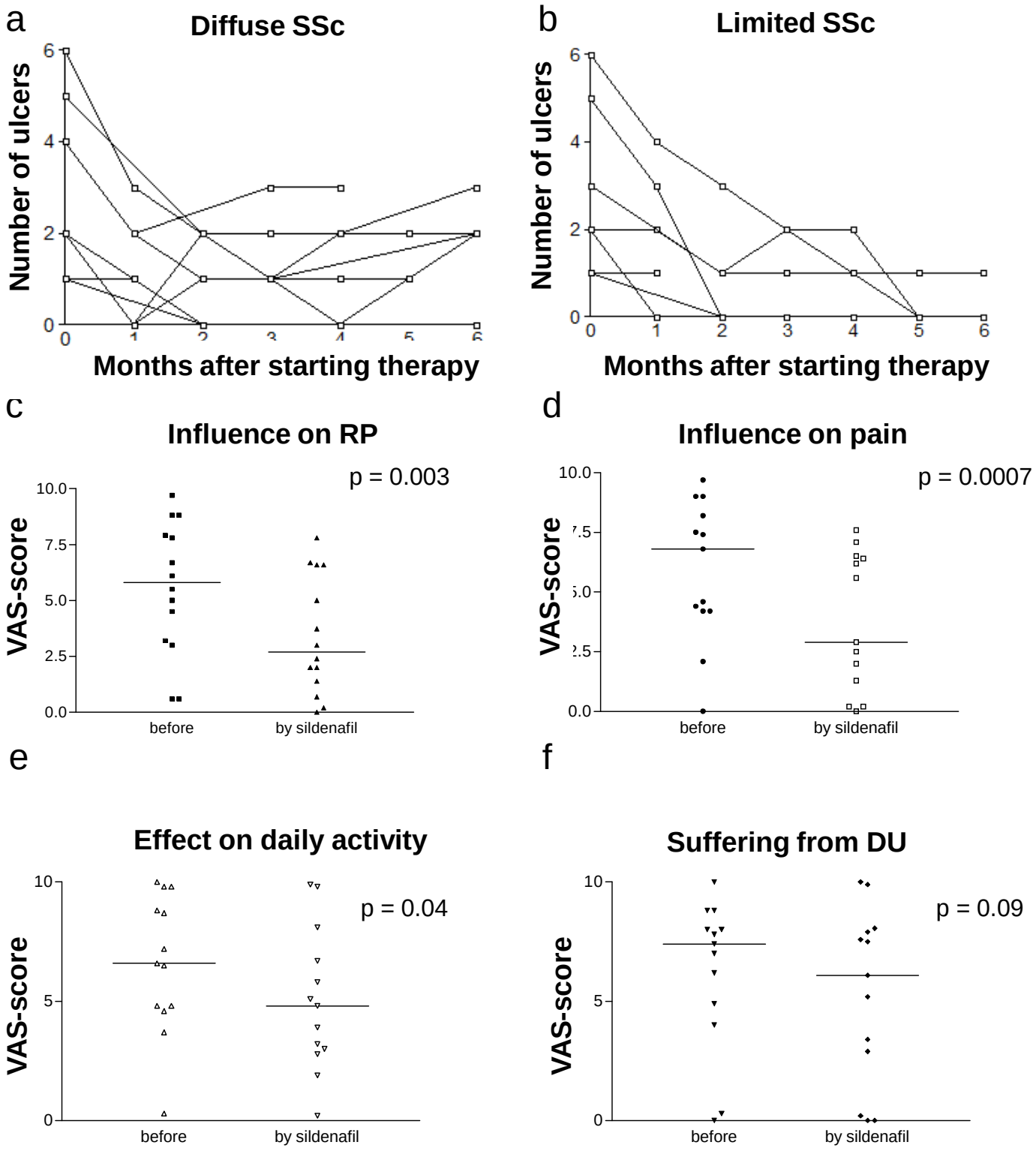
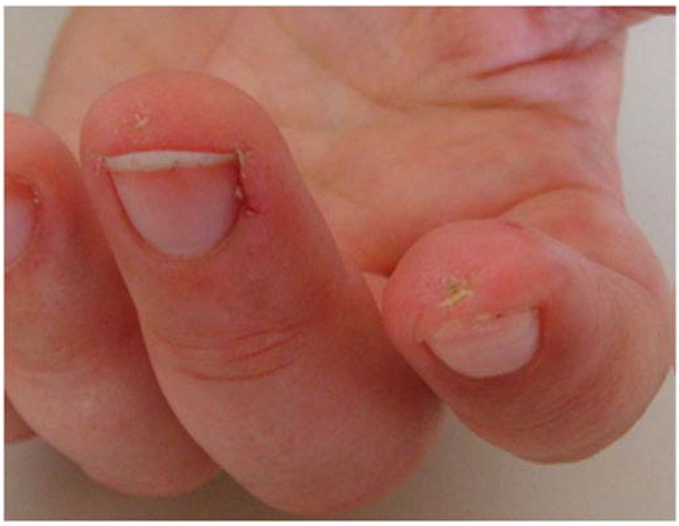


before

after sildenafil

a

b



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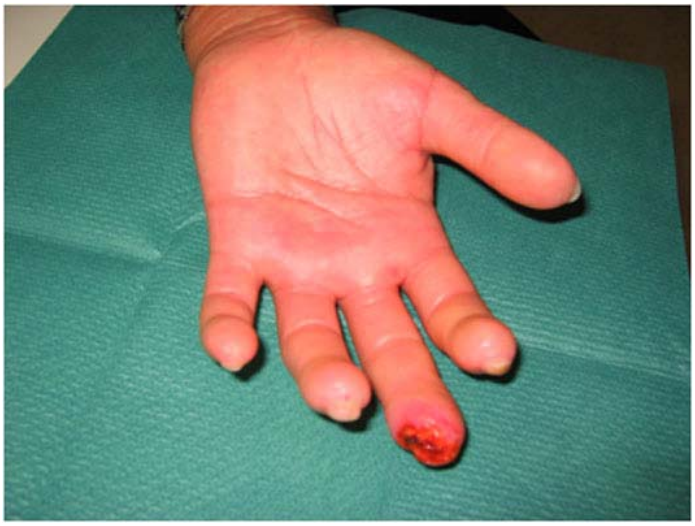

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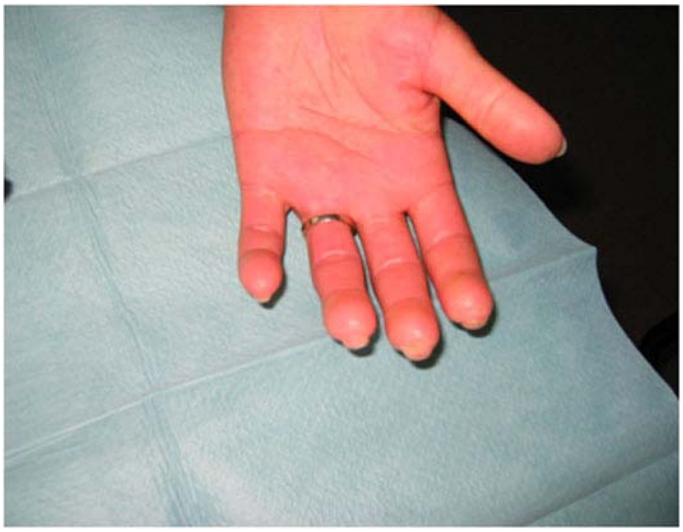

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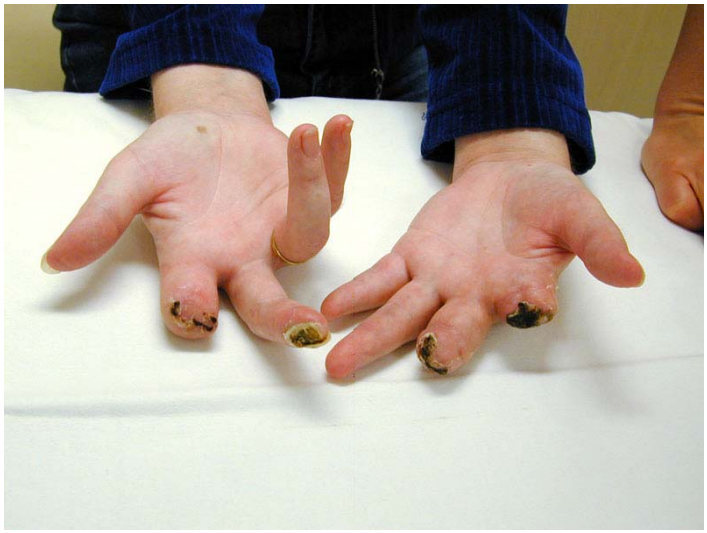

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