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# Prostaglandin E1 — salvage therapy in the treatment of difficult-to-heal ulcers in systemic sclerosis

## ABSTRACT

Involvement of blood vessels in the form of Raynaud's phenomenon and microcirculatory dysfunction as well as accompanying skin lesions of the fingers in patients with systemic sclerosis lead to easy skin damage and difficult-to-heal ulcers. Patient education regarding, among other things, the avoidance of injuries, exposure to cold or smoking and pharmacological treatment are becoming important. The choice of drugs listed in current recommendations depends on the clinical manifestation, i.e. the presence and severity of Raynaud's phenomenon, the treatment or prevention of ulceration and the response to previous treatment.

The paper presents a case of a 79-year-old woman with advanced necrotic lesions of the fingers in the course of systemic sclerosis diagnosed late in life. Due to the advancement of the lesions and the lack of improvement after first-line oral medications, the patient required intravenous prostaglandin. Six months of effective therapy and additional surgical treatment led to complete healing and inhibition of new ulcer formation. Intravenous prostaglandin is an effective alternative for the treatment of difficult-to-heal ulcers in the course of systemic sclerosis while preventing the formation of new lesions.

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**KEY WORDS: Raynaud's phenomenon; ulcers; systemic sclerosis; prostaglandin**

## INTRODUCTION

*Systemic sclerosis,* commonly known as scleroderma, is a chronic systemic connective tissue disease characterised by abnormalities in the morphology and function of blood vessels, progressive fibrosis of the skin and internal organs, and abnormalities in the immune system. Currently, the 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria are in force, which include and assign appropriate scores to lesions resulting from microcirculatory disorders such as Raynaud's phenomenon (3 points) and fingertip lesions (2 points — ulcerations, 3 points — scarring lesions) [1].

Lesions suggestive of angiopathy include Raynaud's phenomenon, telangiectasias, pulmonary arterial hypertension and renal dysfunction due to thickening of the vessel walls with an associated impaired vessel reactivity.

Raynaud's phenomenon is present in nearly 100% of patients with limited SSc (previously called the „CREST syndrome") and in > 90% of patients with diffuse SSc. It usually affects the fingers but can also affect the entire hands, feet and the skin around the nose. As a result of skin lesions passing successively through phases of oedema, sclerosis and atrophy, as well as microcirculatory dysfunction, fingers become susceptible to various types of damage with subsequent development of difficult-to-heal ulcers in an average of 1/4 of pa-

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tients. Chronic ischaemia and recurrent ulcerations can lead to the atrophy of the fingertips and shortening of the distal parts of the fingers [2]. Independent risk factors for finger ulcers in systemic sclerosis include the presence of avascular areas in capillaroscopy, elevated HAQ-DI and anti Scl-70 [3].

## CASE REPORT

On the example of a 79-year-old female patient diagnosed with systemic sclerosis (limited SSc) at the age of 77, the evolution of vascular lesions of the fingers and the applied treatment along with its effects will be presented.

Raynaud's phenomenon had been present in the patient's history for many years, while the first fingertip ulcers appeared less than a year before the diagnosis was made. Topical disinfectant and antibacterial treatment was applied at the time, without any improvement. After 6 months, due to necrosis of the second fingertip of the right hand, the patient was admitted to the Angiology Department, where the decision was made to implement conservative treatment and allow the necrotic lesions to demarcate. The patient consulted a rheumatologist and was diagnosed with advanced Raynaud's phenomenon, with no clinical signs of scleroderma. Echocardiography was performed, showing a low probability of pulmonary hypertension; moreover, COPD, hypertension, atherosclerosis of the carotid arteries and lower limb arteries with segmental obstruction and critical stenosis of the left superficial femoral artery were diagnosed — with eligibility for conservative treatment. The treatment included intravenous pentoxifylline followed by oral pentoxifylline, a calcium antagonist, sulodexide, pregabalin, morphinomimetics and topical nitroglycerin ointment. At discharge, outpatient follow-up at the Rheumatology Outpatient Clinic was recommended, which the patient did not do. Despite the treatment, the progression of necrotic lesions in the fingers was observed; the patient was still not eligible for surgical treatment and was once again referred for further rheumatological diagnostics.

In March 2020, the patient was admitted to the Rheumatology Department in overall average condition, cachexia (BMI 16 kg/m$^2$), with more severe hand pain, necrosis of three fingers with associated bacterial infection of the ulcers. Laboratory tests showed moderately elevated inflammatory markers, high positive RF, vitamin $D_3$ deficiency, ANA profile typical of SSc. Based on the overall clinical picture and the tests performed, systemic sclerosis was diagnosed. Sildenafil and hydroxychloroquine were added to the treatment and intravenous infusions of prostaglandin E1 were started at a total dose of 300 mcg, with good tolerance. In addition, targeted antibiotic therapy based on wound cultures was implemented, achieving a reduction in local inflammatory reaction. The patient required opioid medication due to increased pain. Referrals were issued to Pulmonology and Cardiology outpatient clinics for multi-specialty treatment. Multiple brachial plexus blocks were performed at the Pain Management Clinic, reducing the symptoms.

The patient was periodically admitted to the Department at monthly intervals for the continuation of prostaglandin (alprostadil alfadex) treatment with simultaneous cardiovascular, respiratory and renal function monitoring. She also remained under constant observation at the Vascular Surgery Outpatient Clinic. After about six months of effective therapy, a marked acceleration of ulcer healing and inhibition of the progression of necrotic lesions was observed. Thanks to the improvement in blood supply to the tissues and their regenerative properties, it was possible to carry out the amputation of necrotic fingers in a safe and effective manner, thus improving the physical and aesthetic comfort of the patient (Figs. 1–7).

**Figure 1.** Start of prostaglandin treatment

**Figure 2.** After 2 months of treatment

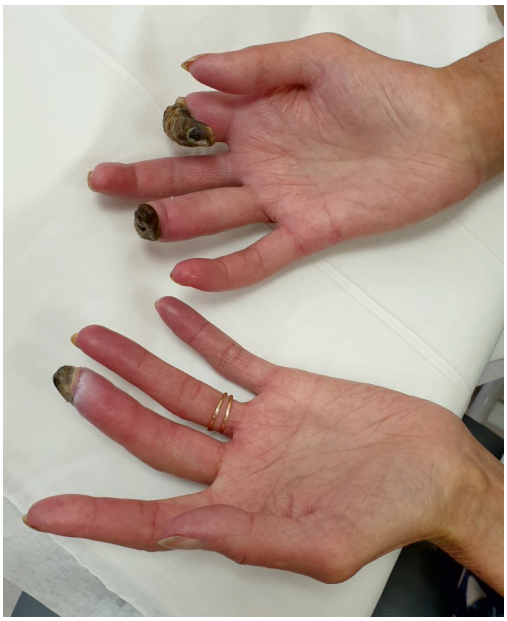

**Figure 3.** After 4 months of treatment

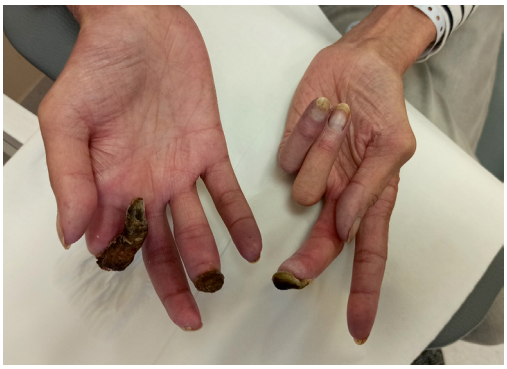

**Figure 4.** After 6 months of treatment

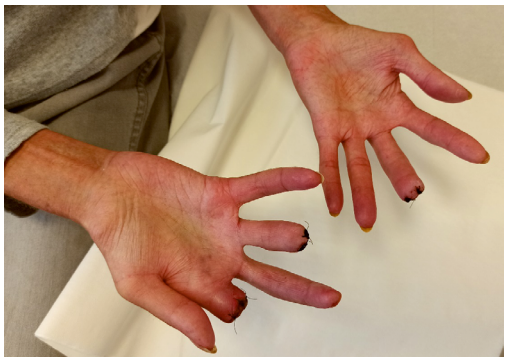

**Figure 5.** One week after amputation

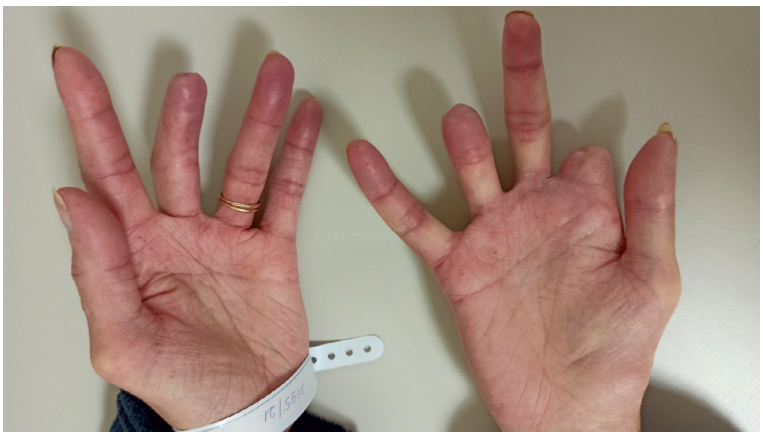

**Figure 6.** Six months after amputation

Prostaglandin treatment continued for a few more months. Subsequently, once the lesions were completely healed, it was decided to discontinue the therapy. Methotrexate was started with an assessment of efficacy and tolerability, and the continuation of treatment

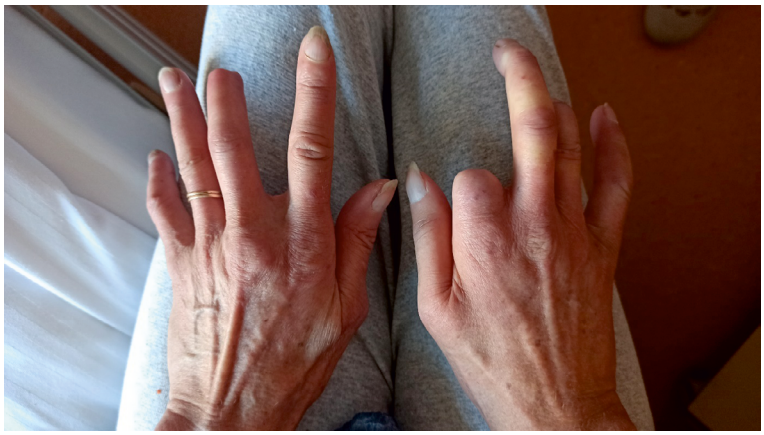

**Figure 7.** Nine months after amputation

with a phosphodiesterase type 5 inhibitor was recommended. The patient has remained under constant Rheumatological observation to this day with no recurrence of symptoms.

## DISCUSSION

The current 2017 EULAR guidelines for the treatment of systemic sclerosis (SSc) provide 16 recommendations for the pharmacological management of the various organ complications of the disease, while emphasising the importance of an individual and comprehensive approach to each patient, thus enabling early diagnosis of the disease, its complications and identification of patients at high risk of disease progression. As the clinical course varies considerably, management depends on the presence or risk of organ complications (the so-called organ-specific therapy). These recommendations should be considered as a tool to help an experienced specialist make a therapeutic decision based on a thorough analysis of the clinical case [4].

According to the recommendations for the treatment of Raynaud's phenomenon in the course of systemic sclerosis, a calcium channel blocker (dihydropyridine derivatives) should be considered first; other oral drugs are phosphodiesterase type 5 (PDE-5) inhibitors. It is believed that hypotension, dizziness, hot flashes, dependent oedema and headaches are fairly common side effects of calcium channel blockers. Side effects associated with the use of PDE-5 inhibitors include various vasomotor reactions, muscle pain, allergic reactions, chest pain, indigestion, a blocked nose and vision disorders. Given their long experience and good safety profile, experts recommend calcium channel blockers as first-line therapy for SSc-RP and PDE-5 inhibitors for SSc patients with severe RP and/or those who do not respond satisfactorily to calcium channel blockers [4]. In case of severe Raynaud's phenomenon and insufficient effectiveness of oral medication, intravenous iloprost should be considered. As most drugs used to treat RP can cause vascular side effects, experts recommend special attention if prostanoids are combined with other vasodilators [4]. Ca-blockers, PDE-5 inhibitors and prostanoids have the greatest strength of recommendation — A.

Another drug used in medical practice for the treatment of Raynaud's phenomenon is fluoxetine, which has the strength of recommendation C. Its efficacy and superiority over nifedipine was confirmed in only one clinical trial. According to experts, despite the relatively low quality of data published, this antidepressant could be an alternative in case of contraindications or lack of improvement after vasodilators.

Drugs with a strength of recommendation A for the treatment of finger ulcers in SSc patients include intravenous iloprost, a PDE-5 inhibitor and bosentan. Iloprost as well as PDE-5 inhibitors showed efficacy in healing already formed ulcers, while there is less evidence of their efficacy in preventing the formation of new lesions. Iloprost is reserved for patients with insufficient improvement after oral medication. In severe cases, combination therapy is also possible. A drug that should be considered for the prevention of new ulcers, especially in patients with a high number of ulcers despite the use of calcium channel blockers, 5-phosphodiesterase inhibitors or iloprost is bosentan, a non-selective endothelin receptor antagonist [4].

In 2 large clinical trials (RAPIDS-1 and RAPIDS-2), bosentan significantly reduced the number of new finger ulcers, especially in patients with multiple ulcers at baseline, but did not show efficacy in healing. Due to the risk of side effects, such as hepatotoxicity and teratogenicity, the use of bosentan should be restricted to patients in whom there was no improvement after other drugs. In addition, concomitant use of bosentan and hormonal contraceptives may reduce their efficacy through interference with the cytochrome P450 system [4].

Subsequent clinical trials (DUAL-1 and DUAL-2) have failed to demonstrate the beneficial effect and efficacy of other drugs in this group (macitentan) [5], so the endothelin receptor inhibitor — bosentan, remains the sole drug recommended for use.

Despite their absence from the updated EULAR recommendations for the treatment of systemic sclerosis, antithrombotic and anti-aggregation drugs, antibiotics, pharmacological or surgical sympathectomy and surgical treatment are also important in the treatment of fingertip ulcers [6]. Despite the potential benefits in terms of pain relief, ulcer healing and prevention of amputation, surgical sympathectomy with its relatively low risk of complications and need for reoperation appears to be performed rarely [7].

Pentoxifylline is often used for Raynaud's phenomenon, despite a lack of documented efficacy in clinical trials [6]. and topical nitroglycerin ointments. According to preliminary reports, immunosuppressive treatment may have a beneficial effect on microcirculation, but in the case of vascular complications such as ulcerations, it may favour the development of infections [8].

Alprostadil is a prostanoid, exogenous prostaglandin E1, registered for use in chronic peripheral artery occlusive disease in stages III and IV (according to the Fontaine classification) in patients who are not eligible for revascularisation or in whom revascularisation has failed. It is an alternative to iloprost due to less frequent side effects. Due to its pharmacodynamic properties, it exhibits a diverse mechanism of action. It increases blood flow as a result of diastolic effect on arteries and precapillary sphincters, improving impaired blood microcirculation; increases erythrocyte deformability and reduces their aggregation; inhibits changes in platelet shape, their aggregation, release of granular content and formation of thromboxane (substance stimulating platelet aggregation); in peripheral vessels, it reduces the number of activated vascular smooth muscle cells; inhibits cholesterol synthesis and reduces cholesterol uptake by the atherosclerotic vascular wall, increases LDL receptor activity in the liver; improves cell metabolism by increasing delivery and utilisation of oxygen and glucose in ischemic tissues; inhibits neutrophil activation, leading to reduced release of toxic metabolites. Thus, alprostadil counteracts one of the mechanisms causing tissue damage in inflammation and probably in ischaemia [9].

In the presented case report of a patient with systemic sclerosis, exogenous prostaglandin E1-alprostadil was used in the treatment of advanced finger ulcers, after previous ineffective therapy with oral vasodilators such as calcium channel blockers and PDE-5 inhibitors. Combination therapy with sildenafil showed greater efficacy without causing increased side effects.

The treatment of complications of microcirculatory disorders, including difficult-to-heal ulcers and necrosis of the fingers, becomes a difficulty and a challenge for every rheumatologist. The presence of fingertip skin ulcers, either currently or in the history, is an indicator of poorer prognosis and is associated with increased cardiovascular risk and thus reduced survival [10]. Patients with systemic sclerosis and finger ulcer complications require increased annual healthcare services, including hospitalisation, outpatient care, and emergency care in the emergency department compared to patients without these complications [11]. The choice of therapy should be guided by the good of the patient, bearing in mind that the lack of specific reimbursement indications or current recommendations for a particular drug does not constitute an absolute contraindication for its use.

## CONCLUSIONS

Based on the example of the described patient and observations of other patients, it can be concluded that treatment with Prostaglandin E1 is a lifesaver in the case of early or advanced necrotic lesions of fingers in the course of systemic sclerosis. Treatment with a standard drug such as sildenafil combined with cyclic prostaglandin infusions is an effective and safe therapeutic option and, in the opinion of the patients, is becoming the only way to improve their quality of life.

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