SUCCESSFUL COMBINATION THERAPEUTIC STRATEGY FOR TREATMENT OF DIGITAL NECROSIS IN SYSTEMIC SCLEROSIS

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Abstract. Currently, there are no randomized trials that assess combination treatments of digital ulcers in systemic sclerosis (SSc). Here, we present a clinical case of successful treatment of digital necrosis in SSc patient with diffuse cutaneous involvement with complete recovery for a period of 2 months, using combination therapeutic strategy (felodipine, intravenous iloprost, sildenafil, anticoagulant, local treatment). Treatment of severe digital ischemia in SSc is a challenge in rheumatology. However, complete and quick recovery including in cases with digital necrosis with minimal tissue loss could be achieved with close monitoring of the patients, providing complex care with the use of combination pharmacological therapy and local treatment.

Key words: systemic sclerosis, digital ulcers, combination therapy

INTRODUCTION

Systemic sclerosis (SSc) is a rare rheumatic disease characterized with unique pathogenesis among connective tissue diseases that includes angiopathy, fibrosis and autoimmune disturbances. Treatment is organ-oriented and the opportunities have improved significantly based on the increasing experience and the results from randomized clinical trials [1].

Raynaud’s phenomenon (RP) is one of the most frequent syndromes in SSc that is observed in over 95% of patients and frequently preceded other features of the diseases by years [2]. The endothelium takes part in the regulation of vascular tone, coagulation, fibrinolysis, smooth muscle proliferation, cell adhesion and inflammation. Endothelial damage is an early event in SSc [3]. Progressive vasculopathy in SSc is associated with the severe course of RP and development of digital ulcers [4]. Digital ulcers are observed in around half of SSc patients [5]. The time of healing of digital ulcers depends on their severity and on the time of medical intervention that is usually delayed [2]. Amanzi et al. (2010) have reported mean time to healing for pure ischaemic digital ulcers 76.2 days (range 7–810 days) and 93.6 days for digital ulcers associated with calcinosis (range 30–388 days) [6]. Major risk factor for development of ulcers in SSc is previous history of ulcer [2, 5]. Digital ulcers in SSc are associated with considerable pain, hand-related disability, reduced quality of life [7, 8]. In some cases, they may be complicated with infection of the underlying bone that could be detected early using magnetic resonance imaging [5].

The underlying pathogenic mechanisms for development of digital ulcers in SSc are different i.e., ischemic ulcers of the tips of fingers and toes, mechanical ulcers due to increased frictions around the extensor surface of the hand joints [2, 5], digital pitting scars i.e., small sized hyperkeratosis, digital gangrene [6], ulcers secondary to calcinosis [2, 5, 6]. Gangrene is defined as tissue death due to a total lack of blood supply, dark black in colour [6].

Large study based on database of the European League Against Rheumatism (EULAR) Scleroderma Trials and Research (EUSTAR) among 3656 SSc patients has shown significantly higher prevalence of digital ulcers in SSc patients with diffuse cutaneous involvement (42.7%) as compared with the cases with limited cutaneous involvement (32.9%, p < 0.001) [9]. Similar are the results of a 4-year follow-up performed by Amanzi et al. (2010) in 100 SSc patients (1614 digital lesions), who have found digital ulcers in 60.9% of patients with diffuse cutaneous involvement and in 47% of those with limited cutaneous form of the disease. Digital pitting scars and digital ulcers secondary to calcinosis were more common in patients with limited cutaneous involvement. Digital gangrene were rare finding (n = 7) that were more frequent in diffuse cutaneous form of SSc (0.9% vs 0.25% in cases with limited cutaneous involvement) [6]. In an own study (Lambova et al., 2013) that included 60 SSc patients, it has been also
observed that prevalence of digital ulcers is higher among scleroderma patients with diffuse cutaneous involvement vs limited cutaneous form of SSc [10].

Digital ulcers in SSc are more common at the hands as compared with the feet. La Montagna et al. (2002) have observed digital ulcers of the hands in 43% of cases vs 8% prevalence of the feet (p < 0.001) [11]. Similar are the results from an own study (Lambova et al., 2013), in which the prevalence of digital ulcers of the hands was 35% (21/60) vs 10% (6/60) – prevalence of the toes (p < 0.05) [10].

EULAR recommendations for treatment of SSc-related RP include use of dihydropyridine-type calcium blockers as a first-line option. Other approaches approved by the experts are administration of phosphodiesterase type 5 (PDE-5) inhibitors (sildenafil, tadalafil and vardenafil) and intravenous iloprost after insufficient effect from oral therapy. Fluoxetine also is suggested as an option for treatment of RP in SSc-RP. Regarding the treatment of digital ulcers in SSc, EULAR recommendation (2017) suggest the use of intravenous iloprost and PDE-5 inhibitors for treatment and bosentan for reduction of the number of new digital ulcers, especially in cases with multiple digital ulcers [12].

Despite recent enrichment in the therapeutic armamentarium for SSc, the therapeutic decision in each individual case is a challenge for the rheumatologists, requires personalized approach and expert opinion for achievement of successful outcome. Moreover, currently there are no randomized trials that assess combination treatments of digital ulcers in SSc [2, 5]. Here we present a clinical case of successful treatment of digital necrosis in SSc with complete recovery for a period of 2 months, using combination therapeutic strategy.

**CASE REPORT**

A 37-year-old woman presented in our department with digital necrosis of the 4th toe of the left foot with 2-month duration (Fig. 1A and B). The patient is with diffuse cutaneous form of SSc since childhood with vascular, pulmonary and articular involvement. The patient presents regularly for many years with recurrent ulcers – ischemic digital ulcers and mechanical around the extensor surfaces of the hand joints, elbows. Paramalleolar ulcers around the ankles were also treated in the last year. As a result of the recurrent severe ischemia of the upper extremity, the patient had developed gradual soft tissue and bony loss of the distal phalanges of the hands i.e., acroosteolysis of all fingers. The peripheral vascular syndrome of lower extremities in the disease course was less severe and acroosteolysis of the toes is not observed. At the time of appearance of the digital necrosis, the patient was on treatment with felodipine 10 mg daily, aspirin 100 mg, pentoxifylline 600 mg bid, pantoprazole 20 mg b.i.d. Upon admission, the patient received infusions with iloprost 20 µg daily for 5 days. The dose of felodipine was increased to 10 mg twice daily. In addition, sildenafil (at a dose of 50 mg b.i.d orally) and nadroparin 0.6 ml daily subcutaneously were added to the therapeutic scheme. Tramadol was used for pain relief on demand. There were no local and systemic signs of inflammation. X-ray of the foot ruled out bony involvement. CRP was within normal values. Thus, antibiotics were not indicated. Daily local antiseptic dressings were applied using jod povidone solution and ointment during the entire period of treatment.

Complex therapeutic approach that included combination of vasodilators, anticoagulant, local antiseptic treatment has lead to decreased pain and lower frequency of vasospastic attacks in 2 weeks. The patients was discharged and regular follow-up was continued in the ambulance once weekly. During the follow-up CRP was also monitored in order to assess development of inflammation. Two months after the adjustment of treatment with administration of combination of vasodilators and anticoagulant
that is 4 months after the appearance of the digital necrosis, auto-sequestration of the necrotic soft tissue, falling-off of the toenail of the affected digit and complete recovery with minimal tissue loss was observed (Fig. 2A and B).

**DISCUSSION**

Current recommendations for the use of calcium channel blockers in SSc-related RP are based mainly on clinical trials with nifedipine [12]. The efficacy of calcium channel blockers for improvement in the frequency and severity of ischemic attacks in RP has been confirmed in randomized clinical trials [13]. Of note, reduction in digital lesions (ulcers, fissures, paronychia) was observed under treatment with both nifedipine and iloprost [14]. Felodipine is a new highly vasoselective calcium channel blocker. It inhibits arteriolar smooth muscle contractile activity and lowers vascular resistance without significant effect on myocardial contractility [15]. Felodipine is used at daily doses 2.5, 5, 10 mg once or twice daily [16]. The vascular selectivity of calcium antagonists can be assessed in vitro as the ratio between drug concentration that is necessary to relax vascular smooth muscle to that required to depress myocardial contraction. In in vitro study, it has been demonstrated that the vascular selectivity of verapamil is 1.5, those of diltiazem is 7. The value for nifedipine is 14 and felodipine is over 100 times more potent as a vasodilator than as a negative inotrope [17]. In our experience, felodipine should be the preferred calcium channel blocker in SSc-related RP [10].

Prostacyclin is a potent vasodilator that inherits also antiplatelet activity. Intravenous iloprost is widely used synthetic prostacyclin analogue in severe peripheral ischemia. It is administered at a dose of 0.5ng/kg/min in a 6-hour intravenous infusion. Interestingly, body mass index is suggested to be a predictive factor of drug intolerance, as overweight patients have a 13-fold increased risk of developing adverse effects. Iloprost binds to prostacyclin and prostaglandin E2 receptors with equal affinity. Despite its short half-life, longer clinical activity is observed that lasts weeks after treatment course [18].

Sildenafil is a selective PDE-5 inhibitor that catalyses the hydrolysis of cyclic guanosine monophosphate (cGMP). The increase in cGMP levels is associated with increase in the level of endogenous NO and induces smooth muscle relaxation and vasodilation [18, 19]. After its initial approval for erectile dysfunction, its properties of vasodilator at micro- and macrovascular level through cGMP-dependent mechanism has been confirmed. It is now also indicated for the treatment of primary and secondary pulmonary hypertension [20]. Sildenafil has been used in different doses for the treatment of RP and digital ulcers in SSc [20, 21]. In a double-blinded, placebo-controlled, Fries et al. (2005) have evaluated the efficacy of sildenafil 50 mg b.i.d. for 4 weeks in 16 patients with secondary RP resistant to treatment. Mean capillary blood flow velocity measured by laser Doppler increased by more than 400% during sildenafil treatment. Significant improvement of symptoms of RP was registered. Improvement and complete healing of digital ulcers were also observed. The treatment was well-tolerated. Other vasodilatory drugs were discontinued before the study entry, while other medications for the treatment of the rheumatic disease remained unchanged during the study [20]. Hachulla et al. (2016) have performed randomised, placebo-con-

![Image](image1)

**Fig. 2A and B. Complete recovery 2 months after treatment with administration of combination of vasodilators and anticoagulant; 3 months after the appearance of the digital necrosis**
trolled study in 84 SSc patients to evaluate the efficacy on ischaemic digital ulcers healing of sildenafil 20 mg or placebo, three times daily for 12 weeks. Unexpectedly high healing rate (66%) in the placebo group was observed. However, a significant decrease in the number of digital ulcers were observed at weeks 8 and 12 in the sildenafil group as compared with placebo. Interestingly, analysis of a patient subgroup who received a combination of bosentan and sildenafil has shown significantly shorter period of healing vs patients who received bosentan and placebo. This suggests that the combination of sildenafil and bosentan might have a beneficial effect on the healing of digital ulcers in SSc [21]. Herrick et al. (2011) have observed reduction in the frequency of RP attacks in a double-blind, placebo-controlled study that included 57 SSc patients. Modified-release sildenafil was used at a dose of 100 mg once daily for 3 days followed by modified-release sildenafil 200 mg once daily for 25 days [22].

Among the main functions of the healthy endothelium is prevention of thrombus formation. There is increasing evidence that in SSc with secondary RP, enhanced activation and aggregation of platelets is present. In SSc, platelet activation markers were found to correlate with disease activity and severity [23]. The literature data addressing the therapeutic effect of antiplatelet agents and anticoagulants in SSc-related peripheral vascular syndrome are scarce [24]. We have previously reported personal experience with administration of subcutaneous low-molecular heparin for one month with switching on low-dose aspirin after documented improvement in SSc patients with digital gangrene [10]. Official recommendations about the administration of antiplatelet drugs (e.g., low-dose aspirin, clopidogrel) and anticoagulants (heparin) in the therapeutic protocol of digital ulcers in SSc are absent and their use is based on experts’ opinion [25, 26].

**Conclusion**

Successful treatment of severe digital ischemia in SSc is a challenge in rheumatology. However, complete and quick recovery including in cases with digital necrosis with minimal tissue loss could be achieved with close monitoring of the patients, providing complex care with the use of combination pharmacological therapy and local treatment.

**Библиография / References**