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Review

Two faces of the same coin: Raynaud phenomenon and digital ulcers in systemic sclerosis

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ABSTRACT

Systemic sclerosis (SSc) is characterized by wide-spread fibrosis, activation of immune system with production of autoantibodies and extensive vascular damage. Raynaud's phenomenon (RP) and digital ulcers (DU) represent two faces of the same coin in SSc vasculopathy. RP, the earliest manifestation of the vascular involvement, is due to an excessive vasospasm of digital arteries, precapillary arterioles and cutaneous arteriovenous shunts, usually in response to cold exposure or other stimuli. DU are a severe complication of microvessel involvement and also of the persistent vasospasm of RP. Thus, the management of RP and DU requires a multimodal approach using a combination of pharmacological, non-pharmacological, and surgical treatments. Currently, the treatment of these complications represents a great challenge for all physicians.

Contents

1. Introduction

Systemic sclerosis (SSc) is a severe multiorgan disease characterized by wide-spread fibrosis, activation of immune system with production of autoantibodies and extensive vascular damage [1]. The vascular involvement is clinically evident with Raynaud's phenomenon (RP) and digital ulcers (DU) that represent two faces of the same coin.

In SSc, microvessels, endothelial cell injury in microvessels and in small and medium arteries [2,3] may be triggered by vasculotropic viruses, inflammatory cytokines, granzymes, endothelial cell-specific autoantibodies or elevated levels of reactive oxygen species due to oxidative stress [4]. Vascular injury leads to structural changes, loss of capillaries (well demonstrated with nailfold capillaroscopy [5]), remodelling of the vessel wall with intimal and median layers hyperplasia and adventitial fibrosis resulting in progressive luminal narrowing and eventually occlusion. This proliferative intimal vasculopathy is mediated by molecules that regulate mainly cell apoptosis, proliferation and vasoconstriction including an increase production of endothelin (ET), a reduction of prostacyclin release and a reduced production of nitric oxide synthase. Moreover, there is an overexpression of adhesion molecules (E-selectin, P-selectin, VCAM-1, ICAM-1) [6]. The loss of capillaries in SSc is not compensated because of defective angiogenesis and vasculogenesis [7,8].

2. First face: Raynaud's phenomenon

The earliest manifestation of the vascular involvement is RP, the clinical expression of SSc in the acral parts characterized by episodic colour changes of the digits that classically turn white (ischemia), then blue (cyanosis) and red (reperfusion). RP is essentially due to an excessive vasospasm of digital arteries, precapillary arterioles and cutaneous arteriovenous shunts, usually in response to cold exposure or other stimuli resulting in impaired oxygenation of the distal

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extremities. Vasospasm without vascular injury is considered the leading cause for primary RP, it is entirely reversible and does not seem to progress to complications [9]. Secondary RP has a more severe course and in SSc it is frequently associated with development of DU and necrosis. The pathogenesis of RP secondary to SSc is supposed to be initiated primary by the injury of endothelial cells which plays a fundamental role in the pathogenesis and consequent tissue injury. Another key role in the pathogenesis of RP appears to be due to the dysfunction of the autonomic nervous system that, through the regulation of the release of neurotransmitters, controls the vascular tone. Although the contribution of the peripheral nervous system to SSc pathogenesis is poorly known, there are some evidences of the involvement of a variety of neurotransmitters and their receptors that are likely to be involved, relating to small sensory nerve fibers as well as to sympathetic vasoconstrictor and vasodilator nerves [10].

3. Second face: digital ulcers

DU are a frequent complication that affects almost half of the SSc patients, and about 75% of the affected patients have their first DU episode within 5 years from their first non-Raynaud symptom [11,12]. DU are persistent, difficult to heal and extremely painful, can cause tissue loss, autoamputation and impaired hand function, heavily impairing quality of life [13]. Moreover, DU are frequently infected and, if not treated early, may lead eventually to osteomyelitis, gangrene and septicaemia [14]. The frequent, persistent and severe nature of DU in SSc patient has been confirmed by data from disease registries [11,15]. Data from the French registry identified 44% of patients as having one or more ischemic DU, resulting in hospitalization for 33% of cases with 46% requiring systemic antibiotics [11].

The aetiology of DU is multifactorial and may differ depending on the DU localization. Fingertips DU are attributable not only for the presence of the underlying vasculopathy but also to the persistent vasospasm of RP. Another possible factor that could have a role in the development of DU is the intraluminal platelet activation with formation of clots and release of thromboxane, a potent vasoconstrictor, which may lead to vessels thrombosis [16]. Instead, DU on the dorsal aspect of the fingers are in the largest part of cases due to epidermal thinning and cutaneous retraction leading to cracks on the skin overlying the joints [17].

DUs may develop on the fingers or toes and can occur over the extensor surface of the joint, on the finger creases, under the nails and in the majority of cases on the fingertips. DU may also develop from a pre-existing calcinosis and sometimes from digital pitting scars [17].

DU may be considered also by the degree of involvement of damaged tissues. Thus, DU that present clinically as a shallow crater are superficial and involve only the epidermis, the intermediate ulcers also involve the subcutaneous tissue to the underlying fascia and may undermine the adjacent tissues, while those exceeding the fascia may affect muscles, supporting structures such tendons and joint capsules, and bone [17].

4. The management

Currently, there are several pharmacological therapies for the treatment and prevention for both RP and DU, including calcium channel blockers, antiplatelet and anticoagulant therapies, endothelin receptor antagonist, phosphodiesterase inhibitors and statins.

In Europe, although the high impact on patients' quality of life, there are no guidelines for the therapy of DU and only iloprost was approved for severe RP.

The management of DU include *non pharmacological therapy,* with the avoidance of all risk factors such as cold stimuli, emotional distress, nicotine exposure, repeated trauma of hands and some drugs [18], *pharmacological treatment* both local and systemic, and finally the *surgical treatment* [19].

Calcium channel blockers (CCBs) have been the elective treatment of RP until today. *Nifedipine* has a direct effect on vascular smooth muscles and inhibits platelet activation reducing the frequency and severity of RP attacks [20]. The efficacy of CCBs for DU has been reported only in a little study, but may provide a support for the use as background therapy in patients with DU [21].

Transdermal nitrates or nitroglycerin cream are NO donors, inducing local vasodilation, thus reducing severity and frequency of vasospastic episodes in patients with primary and secondary RP. There is no evidence in the DU healing but may play an important role as local combination therapy, especially in acute ischemic gangrene.

Prostaglandins are considered the most potent vasodilators currently available. Prostacyclin (PGI2) exerts not only a potent vasodilation, but also has an anti proliferative effect and inhibition of platelet aggregation. The efficacy of both *iloprost* (PGI2 analogue) and *prostaglandin E1*, have been widely demonstrated. In particular, a reduction in time to healing in more than half of patients treated with iloprost and a reduction of formation of new DU were demonstrated [22,23]. In SSc patients with severe manifestation such as DU and gangrene, iloprost is administered parenterally for a dose of 2 ng/kg/min, infused for 6 h/day, for 5 days. Even for *Treprostinil*, a prostacyclin analogue delivered by continuous subcutaneous infusion, there is some evidence of efficacy in the healing and prevention of DU [24].

Antiplatelet and anticoagulant can be considered in acute ischemic phases or when a thrombotic complication is suspected. In SSc, micro clots are formed and can create vascular occlusion. It may therefore be useful oral administration of *aspirin* 100 mg/day in all patients with a history of ischemic DU and gangrene or previous thromboembolic events.

Endothelin receptor antagonists. Endothelin levels are elevated in serum of patients with SSc, especially in those patients with DU and is considered a marker of vascular severity [25,26]. Two clinical trials have evaluated the efficacy of *bosentan,* a dual endothelin receptor antagonist, in SSc-related DU and it has been shown to reduce the number of new lesions especially in patients at risk of multiple ulcers. In patients treated with bosentan was also reported a significant improvement in functionality of the hand. Unfortunately there was no effect on the healing of existing DU [27–29]. *Sitaxsentan*, a selective antagonist of endothelin A receptor, could be a new alternative in addition to drugs already available for the treatment or prevention of DU. Currently there are no studies of efficacy of sitaxsentan, but only isolated cases in which it was demonstrated almost complete healing of existing ulcers, a significant reduction of pain and no formation of new ulcers after six months treatment with a dose of 100mg qd [30].

Phosphodiesterase 5 inhibitors such as *sildenafil*, have been studied for use in patients with RP and have shown a significant benefit in terms of frequency, duration and severity of attacks [31]. However, there was still no prospective studies on the efficacy on healing or prevention of DU. At present, there are only few publications of anecdotal use of sildenafil in SSc patients that have shown a reduction of time to healing of DU [32–34].

Statins have demonstrated efficacy in reducing the occurrence and the total number of digital ulcers, an improvement of RP, and finally a significant improvement of the vascular function by reducing serum levels of angiogenic factors and markers of vascular injury [35,36]. Due to its good tolerability and low cost of the drug, atorvastatin may considered valuable in early SSc vasculopathy or in patient with macrovascular involvement (i.e. radial and ulnar arteries).

In addition to these therapies oral antibiotics are essential in the treatment of DU for the control of infections in order to avoid its spreading to adjacent tissues or bone with possible evolution to septicemia. In these cases, amputation can be mandatory [16,18]. Patients with severe forms of RP, as well as patients with DU, require frequent prescription of NSAIDs, coxibs and opioids that can cause numerous side effects (heart and kidney function, intestinal block)

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and even abuse and therefore need to be used with follow up of gastrointestinal, renal and heart function.

Standard topical care treatment includes the maintenance of a warm and humid environment which encourages the healing processes, and the application of various medications such as hydrogel, hydrocolloid, paraffin gauze, antiseptic dressings like silver-coated medications that are able not only to heal infection but also to prevent it [17]. Local application of vitamin E gel has significantly contributed to reduce time to healing and a faster resolution of pain [23].

Surgical treatment include arterial bypass, digital arterial reconstruction, sympathectomies (peripheral and digital) and botulinum toxin injection [37,38]. These invasive therapies should be used only for patients with refractory nonhealing DU or in patients with intractable pain. Recently, local or intramuscular implantation of *mesenchymal stem cell* has been also suggested [39,40].

5. Conclusion

Currently, the treatment of RP and DU represents a great challenge for all physicians. First, we must recognize that both RP and DU are a sign of the result of underlying different processes. Second, vascular injury is itself a complex process mediated by many factors that can, in different ways, contribute to the dysregulation of the vascular tone and of the repair and regeneration processes. Thus, vascular structure and function are involved in SSc and both play a key role in the mechanism of tissue damage. In SSc, the repetitive vasospasm of RP and the structural changes of the digital vessels are the leading contributory causes of the incipient development of ischemic digital ulcers. The management of RP and DU require a multimodal approach using a combination of pharmacological, local and surgical treatments and should be inclusive of all the tools to prevent or modify trigger factors underlying the development of these complications. Research is required to better define the pathogenesis of DU and thus to define a treatment algorithm to promote healing and reduce the formation of new ulcers.

Take-home messages

- The vascular involvement is clinically evident with Raynaud's phenomenon and digital ulcers that represent two faces of the same coin in SSc.
- Secondary RP has a severe course in SSc and is frequently associated with DU and tissue necrosis.
- DUs are a frequent and extremely painful complication heavily affecting patient's quality of life.
- The aetiology of DU is multifactorial and may differ depending on the DU localization.
- The management of DU includes non-pharmacological therapy with the avoidance of all risk factors, pharmacological treatment (local and systemic) and surgical treatment.

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