Digital ulcer, Raynaud phenomenon and osteomyelitis of the fifth finger in patient with systemic sclerosis

Personal experience

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The authors report a case of recent observation of digital ulcer associated with vascular disease (Raynaud phenomenon) and osteomyelitis of the right fifth finger, in patient with systemic sclerosis (SSc). Raynaud phenomenon (RP) is an universal manifestation of SSc (95% of these patients are affected); in 30% of the patients resulted in digital ulcers (DUs). The authors emphasize the importance of early clinical and surgical management, because the effect on function (*functio laesa*) and quality of life of the SSc-DU is significant, and they are associated with pain, disability and disfigurement. In our case history, remarkable remission of digital ulcer (of the right fifth finger) was achieved with long-term administration of mepivacaine into the lesion, its toilette and addition of antibiotic ointment. Subsequently, the patient decided to perform a local sperimental treatment with bosentan, hesitated with good results, both locals that systemic. Despite a considerable clinical outcome, we do not exclude in the future to implement a surgical treatment to correct alterations no-reversible by clinical treatment with bosentan. Our patient has a good response to clinical treatment; currently the clinical of patient is in a stable phase. At last she has resolution specially of pain symptom, caused in part by persistent osteomyelitis, implementing her quality of life. The object of this paper is to discuss about definitions, origin, pathogenesis, diagnostic standards, clinical classification and therapy of secondary digital ulcer in SSc. The authors believe in the surgical treatment as only procedure to the cure of the patient, when the DUs are not clinically more tractable.

Key words: **Ulcer - Raynaud disease - Osteomyelitis - Scleroderma, systemic.**

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Systemic sclerosis (SSc) is a multisystem autoimmune complex disease of the connective tissue, of unknown aetiology, characterized by vasculopathy (microvascular damage) and extracellular excessive deposition of collagen matrix (fibrosis of the skin and various internal organs), leading to fibrosis and autoimmune processes.

SSc is often associated with Raynaud's phenomenon (earliest universal clinical manifestation occurring in 90% to 98% of patients), and together these can lead to digital ulcers (DUs) and hyperkeratosis, manifestations of the underlying vasculopathy (endothelial dysfunction leading to intimal proliferation and thrombosis) and fibrosis.[1]

The fibrosis, the thinning and the loss of elasticity of the skin associated to the characteristic vascular alterations, immunity reactivity, peripheral neurological damage, eventual drug assumption, sympathetically mediated vasospasm and vaso-occlusioning disease (in response to cold or other stim-

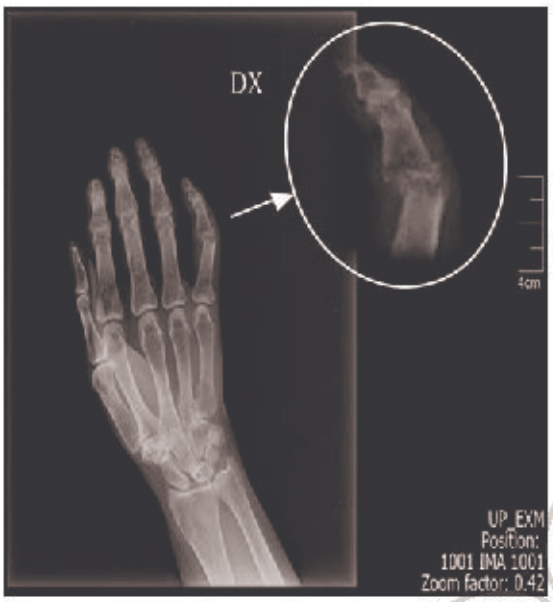

Figure 1.—The radiograph of the right hand shows in the fifth finger subcutaneous calcification, osteomyelitis, outcomes of synovitis, disuse osteoporosis and osteolysis, especially in the articulation of the proximal-medial phalanges.

uli), can reduce regenerative and reparative abilities, lead to the genesis of digital ischemic phenomenon or ulcer, more or less extended, often multiple with peripheral localization; the same can easy become chronic and infect, complicating still more the patient disease, rendering more difficult the cure often, ulcer evolves to gangrene, and in some cases, in amputation too.

Primary scope in ulcers therapy (local and systemic) is the prevention, in contrary case, therapy is based in alleviating the pain and rendering the quality of the life of the patient better.[2]

We report a case in which initially middle remarkable remission of digital ulcer (of the fifth finger of right hand) was achieved with long-term administration of mepivacaine into the DU-lesion and its toilette, as a means to alleviate pain and to improve circulation.

The same patient came to our attention after a month's absence from our local treatment, with DU-lesion hesitated with hyperkeratosis and slight improvement of the clinic; the reason of this clinical change was the bosentan treatment made in another hospital (accredited clinical trial conducted in Bologna-Italy).

Bosentan is a dual endothelin receptor antagonist licensed for the management of pulmonary hypertension and the prevention of DUs in SSc.

With the advance of the scleroderma disease, persistence of refractory hyperkeratosis/digital ulceration and pain secondary to osteomyelitis, our patient may be a candidate for additional clinical treatment with bosentan or surgical therapy (amputation of finger).

Case report

We report a case of systemic sclerosis associated with Raynaud phenomenon, ischemic digital ulceration and osteomyelitis of the fifth finger of the right hand, who responded successfully, at least initially, to bosentan local therapy.

A 50 year-old Caucasian housewife came to our attention in November 2011, with a history of SSc not under treatment, in clinical phase acro-localized, positive clinical for mild Raynaud's syndrome, mild sclerodactyly, recurrent myositis, acral sclerosis since 18 years and superficial DU (L: 2.1cm, W: 2.4 cm, D: <1 cm) started 8 months previously and persisted in her hand, associated with underlying osteomyelitis and pitting scars.

On clinical examination, the patient reported severe and persistent pain, combined with functional alterations and joint stiffness of the fifth finger.

Laboratory investigations revealed that she was positive for antinuclear antibodies (titre >1:180) without detectable auto-antigen specificity.

In other clinical and laboratory findings, we found untreated slight essential arterial hypertension and no alteration in pulmonary/renal parameters; the patient not taking medications for other diseases and she did not carry out any treatment to slow the progression of systemic sclerosis.

Chest radiograph showed no pulmonary fibrosis on the basis or other alterations.

The radiograph of the right hand, has shown, especially in the fifth finger, subcutaneous calcification, osteomyelitis and outcomes of synovitis, disuse osteoporosis and osteolysis, especially in the articulation of the proximal-medial phalanges (Figure 1).

Initially, remarkable clinical remission of digital ulcer (L: 1.2 cm, W: 1.4 cm and obvious active granulation) was achieved with long-term administration of mepivacaine (mepivacaina cloridrato 20 mg/mL, 10 mL/die/approximately every 5 days) into

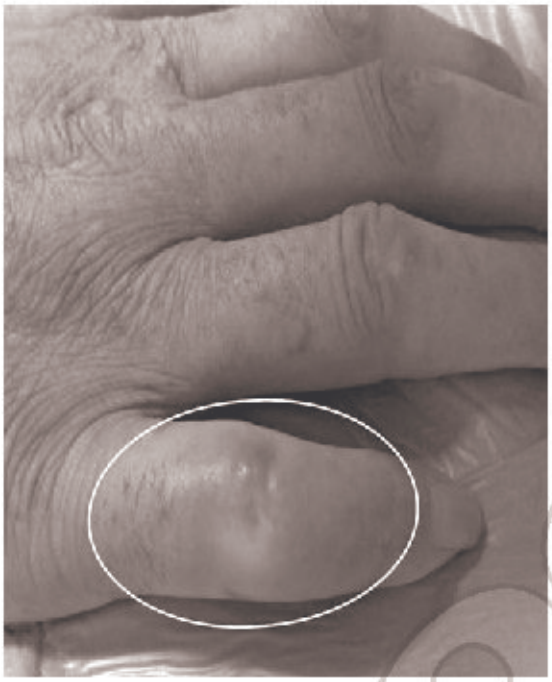

Figure 2.—Detail of the fifth finger of the right hand showing ischaemic digital ulceration in healing phase with hyperkeratosis after bosentan treatment, suggesting that treatment with bosentan delays the development of digital ulcer.

the lesion and its toilette, with addition of antibiotic ointment (gentamicin sulfate), as a means to alleviate pain, antagonize the osteomyelitis and improve circulation.

After three months of our local treatment, and given the slow improvements, the patient decided to perform a local sperimental treatment with bosentan (cpr 62.5 mg/bid, duration one month), in another hospital, with our prior agreement.

The European Medicines Agency (EMA) requested the establishment of a prospective registry of patients with ongoing digital ulcers associated with SSc as a licensing requirement for bosentan treatment; our patient is registered.[3]

At the time of writing (May 2012), after one month of bosentan treatment, the patient's clinical condition is satisfactory (NYHA functional class I, no dyspnoea, no evidence of right heart failure).

From a local clinical point of view, the patient returned to our attention with partial re-epithelialisation and presence of granulation tissue (where initially there was DU), overall reduction of Raynaud's phenomenon (Figure 2), no major side-effects of bosentan (tolerance of bosentan was good), overall improvement of telengectasia of the lower limbs and progressive improvement of damaged skin, suggesting that treatment with bosentan

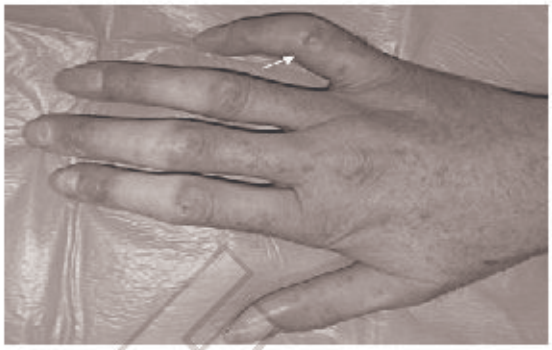

Figure 3.—Photo of the right hand shows improvement of the disease after bosentan treatment, with clinical evidence of phase acro-localized sclerosis of Ssc, ischaemic digital ulceration in healing phase (arrow), positive clinical for mild Raynaud's syndrome, mild sclerodactyly, recurrent myositis associated with underlying osteomyelitis and pitting scars; all factors that could lead the patient to choose surgery soon.

not only delays the development of digital ulcers, but slow down the natural history of systemic sclerosis.

Despite these improvements, for persistence of slight pain and numbness in the fifth finger of her right hand, reduced function caused by osteomyelitis, persistence of Raynaud phenomenon, occurrence or maintenance of small ischaemic digital ulceration (Figure 3) and psychological and physical discomfort, may bring the patient in the near future, to surgery treatment, implementing a metacarpal-phalangeal amputation and subsequent post operative rehabilitation.

Discussion

The initial triggers in SSc-related vasculopathy and fibrosis of the skin, blood vessels and visceral organs, are multifactorial and nonspecific: male sex, presence of pulmonary hypertension and/or lower DLCO (Diffusion Capacity of Carbon Monoxide), diffuse subset of the disease, early onset of SSc, presence of antitopoisomerase I antibodies like anti-topo I (or other specific subsets), smoking, etc., and pose various challenges in terms of risk factors, diagnosis, classification, therapy and morbidity.

RP, characterized by vasospasm in response to cold or stress, is the most common manifestation of the endothelial dysfunction SSc-related and, digital ulcers

(DUs), develop in over 90% of the patients with RP SSc-related.

Digital ulcers in SSc are defined as necrotic lesions that may occur on the fingers or toes and can manifest on the tips, the finger creases, over the extensor surfaces of the joints or in association with calcinosis.

The underlying phenomenon is compromise of the arterial lumen which occurs as a combination of major contributing factors: vascular wall structural (intimal proliferation) and functional (overproduction of vasoconstrictors) abnormalities, a variable degree of intraluminal thrombosis and ischemia, repetitive microtrauma, sclerodactyly, dry skin and calcinosis.

It is believed that smooth muscle cells migrate into the intimal layer of the microvasculature and differentiate into myofibroblasts that secrete collagen and an other extracellular matrix; this process leads to a fixed narrowing of the intravascular lumen which hinders the blood flow and causes chronic tissue ischemia.

Aside from the structural change, the endothelial cells are perturbed, possibly through ischemia-reperfusion injury or an autoimmune insult leading to an increate production of vasoconstrictors such as endothelin and an underproduction of vasodilators such as prostacyclin and nitric oxide.

Another proposed mechanism of endothelial injury is the presence of antiendothelial cell antibodies.

One other possible consequence of the endothelial damage is platelet activation with release of thromboxane which leads to intraluminal thrombosis.

The digital lesions were located more frequently on the second and third digit and mostly on the fingertip area and some of the DUs were hidden behind hyperkeratosis.

As a consequence of the progressive scarring and tissue loss that follow healing of ulcers, patients may exhibit permanent disability, with associated social and self-image problems.

With the development of disease, chronic digital ulcers can become infected, resulting in gangrene, osteomyelitis and amputation inevitable.

Major clinical problems of DUs are painful, heal slowly, and lead to a great deal of functional impairment and affect the quality of life significantly.

The DUs-vasculopathy in SSc is very similar to that observed in pulmonary arterial hypertension and renal crisis; Masson's Trichrome staining of the digital arteries of patients with SSc has revealed a striking fibrotic intimal hyperplasia, adventitial fibrosis and severely compromised arterial lumen[1].

These characteristics differ in frequency and severity depending on the SSc subtype and often are associated with systemic manifestations of SSc, included oesophagus dysmotility, gastrooesophageal reflux disease, mild pulmonary fibrosis and slight pulmonary hypertension.

Currently, there is no official algorithm for diagnosis and therapy of digital ischemia in SSc, and a multidisciplinary approach to the local management of DUs is required, using a combination of non-pharmacological care and antibiotics if an infection is suspected.

The aim of the treatment is to reduce the pathology DUs and their impact on quality of life, reducing pain, restoring hand function, improving digital circulation, preventing infection, promoting healing of established ulcers, inhibiting the formation of new ulcers and/or reducing the need for hospitalization and amputation.

The correct diagnosis of DUs is instrumental both in clinical practice and in clinical trials focused on digital ischemia.

It is crucial to clinically define the true ischemic lesion, because can be confused with DUs due to trauma or calcinosis; Amanzi et al. classified DUs as follows: pure ischemic DUs (48.6% of 1,614 analysed lesions), and DUs derived from pitting scars (44.1%), calcinosis (6.8%), or gangrene (0.8%).[4]

The measurement of the depth and length of DUs is not feasible due to the location of the ulcerations and the associated pain.

The only direct parameter remains the absolute healing of the DUs, which in-

cludes an anatomical (re-epithelialization of the area) and a physiological (pain cessation) component.

The DUs therapeutic approach include supportive therapies as a smoking cessation, suspension of all vasoconstrictors (cocaine, sympathomimetics) and anxiety management which potentially worsens the Raynaud's phenomenons (if present, treatment must be directed towards relieving vasospasm and restoring nutrient blood flow).

Pain and infection are common comorbidities that require supportive therapy.

The nonsteroidal antiinflammatory drugs are very efficient in pain management, they should be avoided in favor of acetaminophen or opiates due to their vascular side effects. Since the cause of the pain is tissue ischemia, the real solution is improving the oxygen delivery to the affected area[5].

Infections are common in SSc-DUs and heal slowly because of the poor circulation; simple gram positive coverage is usually very efficient.

If osteomyelitis is suspected, patients should be managed by a multidisciplinary team that includes infectious disease and orthopedic specialists. Antibiotic ointment (as in our case report) or intravenous antibiotics, hyperbaric therapy, and surgical amputation may be helpful.

Knowing in detail the pathogenesis of the DUs-disease, the underlying disease and its manifestations may be administered with treatment algorithm including one or more drugs, such as antiplatelet agents and vasoactive agents (vasodilators), calcium channel blockers, phosphodiesterase-5 inhibitors (sildenafil), endothelin receptor antagonists (bosentan), prostacyclin analogus (like epoprostenol, iloprost, beraprost, treprostinil or treprostinil diethanolamine), statins, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, n-acetylcysteine or/and Vitamin E.

Experimental medication that is giving the best results is bosentan, endothelin receptor antagonist[4].

The Digital Ulcers Outcome (DUO) Registry enrols patients with digital ulcer disease regardless of their treatment status; however, a large proportion are receiving bosentan[3].

The endothelial injury that is the hallmark of ischemic digital ulcers corresponds with an increase in levels of endothelin-1 (vasoconstrictive and profibrotic effects; ET-1).

Bosentan is a receptor antagonist with activity against both types of receptors, ET-A (receptors on vascular smooth muscle cells) and ET-B (receptors are found on both endothelial cells and vascular smooth muscle cells).

Bosentan may be helpful in reducing ulcer size or improving healing;[5] other studies have demonstrated an improvement in flow-mediated dilatation of microvasculature with bosentan therapy in patients with systemic sclerosis.[5]

One of the most precise definitions of SSc-DUs was described in the RAPIDS-1 clinical trial (digital ulcers are defined as a denuded area with well demarcated borders, involving loss of dermis and epidermis; they are located on the volar surface of the fingers, distal to the proximal interphalangeal joints),[1] also RAPIDS-1 trial analyzed the effect of bosentan on the prevention and treatment of existing digital ulcers.

In summary, long-term bosentan administration can efficiently prevent ischaemic complications in SSc, including DUs, pain and secondary infections; it may also delay the progression of SSc, and it has a role on prevention of episodes of Raynaud's syndrome (potential future indications).[5]

Often, such patients are resistant to vasodilator therapy, probably because the digital arterial circulation is fixed and unresponsive.

Surgical options are reserved for treatment of severe or refractory/recurrent DUs that are recalcitrant to medical therapy.

Available procedure is digital sympathectomy,[5] given that microsurgical revascularization of the hand is not applicable.

Sympathectomies are aiming to block the sympathetic nerve-mediated vasospasm which is thought to have an important role in digital ischemia. This pro-

cedure has been shown to help healing of SSc-DUs, improvement in pain, and prevention of new DUs for amean of 31 months after the surgery.[5] The long-term results of cervical sympathectomy have been discouraging.

Often on affected fingers suffering from ulcers, osteomyelitis and/or infections, only real therapeutic act that can be implemented, is surgical amputation, technique only really able to stop the disease process, pain and mental suffering of the patient.

Conclusions

Raynaud phenomenon and digital ulcers are an almost universal manifestations of SSc.

The authors emphasize the importance of early clinical and surgical management, because the effect on function (functio laesa) and quality of life of the SSc-DU is significant, and they are associated with pain, disability and disfigurement.

In our case history, remarkable remission of digital ulcer and underlying osteomyelitis (of the fifth finger) was achieved with long-term administration of mepivacaine into the lesion, its toilette and addition of antibiotic ointment; subsequently, the patient decided to perform a local sperimental treatment with bosentan, hesitated with good results, both locals that systemic.

The dual endothelin receptor antagonist-bosentan has demonstrated efficacy in healing of present ulcers, efficacy by the prevention of new DUs and improving quality of life. Bosentan is particularly effective in more severely affected patients.

Despite a considerable clinical outcome, we do not exclude in the future to implement, in our patient, a surgical treatment to correct the pathology no-reversible by clinical treatment with bosentan.

At last she has complete resolution specially of pain symptom, due to clinical therapy, implementing her quality of life.

The authors believe in the surgical treatment (amputation of finger) as only procedure to the cure of the patient, when the digital ulcers are not clinically more tractable.

A long-term follow-up observation is always needed for the case.

Riassunto

Ulcera digitale, fenomeno di Raynaud e osteomielite del quinto dito della mano destra con sclerosi sistemica. Esperienza personale

Gli autori riportano un caso di recente osservazione di ulcera digitale associata a malattia vascolare (fenomeno di Raynaud) e osteomielite del quinto dito della mano destra, in paziente con sclerosi sistemica (SSc). Il fenomeno di Raynaud (RP) è una manifestazione universale di SSc (95% di questi pazienti sono affetti); nel 30% dei pazienti predispone la formazione di ulcere digitali (DUS). Gli autori sottolineano l'importanza di una gestione clinica e chirurgica precoce; l'effetto negativo sulla funzione (functio laesa) e sulla qualità della vita della SSc-DU è significativo, essendo associato a dolore, disabilità e deturpazione. Nel nostro caso, la notevole remissione del quadro clinico è stato ottenuta secondariamente a somministrazione, per un lungo termine, di mepivacaina nella lesione e toilette della stessa, con aggiunta di pomata antibiotica. Successivamente, la paziente ha deciso di eseguire un trattamento locale sperimentale con bosentan, esitato con buoni risultati, sia locali che sistemici. Nonostante il notevole impatto clinico positivo, non escludiamo in futuro di attuare un trattamento chirurgico per correggere alterazioni non reversibili mediante trattamento clinico con bosentan. La paziente ha risposto bene al trattamento clinico; attualmente la clinica della paziente è in una fase stabile, con risoluzione del sintomo dolore, causato prima del trattamento dalla persistente osteomielite, implementando positivamente la sua qualità della vita. Lo scopo di questo lavoro è quello di discutere sulla definizione, origine, patogenesi, standard diagnostico, classificazione clinica e terapia dell'ulcera digitale secondaria a SSc. Gli autori credono nel trattamento chirurgico, come sola procedura capace di portare a cura il paziente, quando le ulcere digitali non sono più clinicamente trattabili.

Parole chiave: Ulcera - Malattia di Raynaud - Osteomielite - Scleroderma sistemico.

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