Reumatol Clin. 2012;8(5):270–277

Reumatología Clínica

www.reumatologiaclinica.org

Review Article

Raynaud, Digital Ulcers and Calcinosis in Scleroderma☆

Alejandro Nitsche

Specialist in rheumatology, Servicio de Reumatología, Hospital Alemán; Consultorio de Raynaud, Esclerodermia e Hipertensión Arterial Pulmonar, Sanatorio San José, Ciudad Autónoma de Buenos Aires, Argentina

ARTICLE INFO

Article history:
Received 26 December 2011
Accepted 29 February 2012
Available online 20 September 2012

Keywords:
Scleroderma
Raynaud
Digital ulcers
Calcinosis

ABSTRACT

Raynaud, digital ulcers and calcinosis are frequent manifestations of patients with systemic sclerosis. Digital ulcers are seen in more than half of the patients with scleroderma. Hospitalizations, ischemic complications and impairment of hand function are frequently observed in patients with digital ulcers, especially if treatment is delayed.

Rapid and intensive treatment escalation in patients with scleroderma and refractory Raynaud's phenomenon is one of the most effective preventive action available in order to avoid the development of digital ulcers and tissue loss.

Raynaud, úlceras digitales y calcinosis en esclerodermia

Palabras clave:
Esclerodermia
Raynaud
Úlceras digitales
Calcinosis

RESUMEN

En pacientes con diagnóstico de esclerodermia, el fenómeno de Raynaud, las úlceras digitales y la calcinosis son manifestaciones frecuentes. Las úlceras digitales se observan en más de la mitad de los pacientes. El tratamiento tardío o las secuelas que generan las úlceras digitales con o sin calcinosis conllevan a un deterioro de la capacidad funcional de estos pacientes y complicaciones que pueden requerir hospitalización.

El tratamiento escalonado y temprano de los pacientes con esclerodermia y Raynaud refractario constituye la medida preventiva más efectiva para evitar el desarrollo de úlceras digitales y pérdida tisular.

Introduction

Despite scleroderma being a rare disease, it is common for rheumatologists in daily practice to receive referrals of patients with Raynaud's phenomenon and underlying systemic sclerosis.[1]

Raynaud's phenomenon may precede by more than 10 years the clinical manifestations of the disease. Because these characteristics of scleroderma overlap with other connective tissue diseases, diagnostic delay is a problem. An early referral on the basis of questioning, physical examination, capillaroscopy and laboratory guide are of paramount importance for diagnosis.[1–3]

The purpose of this update is to analyze the pathogenic mechanisms and the impact on quality of life of patients with Raynaud's phenomenon, digital ulcers and calcinosis, as well as its possible treatments, with information from the literature, published guidelines and experience from observational studies.

We must not forget the difficulties reported by several authors at the time of incorporating patients with scleroderma in various controlled studies.[4,5]

Finally, treating physicians, within the scope of their practice, may apply the knowledge in the difficult management of these patients.[6–9]

Pathophysiology

Scleroderma is a complex autoimmune disease that potentially affects all organ systems.

The pathophysiology involves several cell lines, such as endothelium, fibroblasts, lymphocytes and their soluble mediators. These cells set the tone for an early vascular phase with an

☆ Please cite this article as: Nitsche A. Raynaud, úlceras digitales y calcinosis en esclerodermia. Reumatol Clin. 2012;8(5):270-7.

E-mail address: alejandro.nitsche@gmail.com

2173-5743/$ – see front matter

inflammatory infiltrate and finally fibrosis.[10] The vascular phase begins in the endothelium of small vessels throughout the body, although the primary event that triggers endothelial damage is unknown. Tissue hypoxia is one of the primary events that modify vascular tone.

Nitric oxide, prostacyclin and endothelin regulate the vascular tone our body. Both nitric oxide and prostacyclin are potent endogenous vasodilators that also have antiproliferative action. In contrast, the endothelin system acts as a counterweight for vascular tone, being a potent vasoconstrictor. Endothelin 1 (ET1) has 10 times the angiotensin[11] vasoconstrictor effect.

Endothelial cells are involved in vascular homeostasis by regulating both muscle tone and cell proliferation. Vasoconstriction is caused by an imbalance of the mediators listed above. Cellular inflammation and perivascular infiltrates with complement deposition and release of proinflammatory mediators complete the picture.

Endothelins are small peptides of 21 amino acids with a potent vasoconstrictor effect. The 3 isoforms of endothelins, ET1, ET2 and ET3, are produced by various cells.[11] Among them, endothelial cells and vascular smooth muscle, distributed in all organs, play a dominant role in the pathogenesis of scleroderma. ET2 and ET3 are distributed differently in kidney, intestine, placenta, uterus, myocardium, brain and to a lesser extent in the lung.[11]

From the viewpoint of pathogenesis, ET1's role explains the different events in the endothelial phase. ET1 is synthesized in endothelial cells and to a lesser extent in vascular smooth muscle cells. It is also synthesized in mesangial cells, liver cells and cells of the central nervous system.

The ET1 prehormone is activated by the endothelin converting enzyme, and its biosynthesis stimulated by mechanisms such as hypoxia, metabolic disorders and various procoagulants[11–14] disorders. It is increased in clinical situations, such as hypertension, atherosclerosis, heart failure and renal failure.

In addition to its potent vasoconstrictor, ET1 has proinflammatory action, promoting cell proliferation and fibrosis. The action of endothelin is genetically encoded by the transforming growth factor beta (TGF-beta), which, by binding to its tissue receptor overexpresses proteins called Smad, which are the genes encoding collagen. Different Smad proteins have different roles, either in the overproduction of collagen and in inhibiting the formation of collagen. This loss of balance is seen in patients with progressive systemic sclerosis.[10]

ET1 exerts its action through two receptors: ET1 A and ET1 B, both different and complementary in action.

The ET1 A receptor is located on smooth muscle cells of pulmonary vessels and favors proliferation,[11] vasoconstrictor action and activity.

The ET1 B receptor is located on endothelial cells and to a lesser extent in smooth muscle cells. The action on this receptor varies according to its location: in endothelial cells its vasodilatory action is mediated by the release of nitric oxide and prostacyclin, contributing to the purification of ET1 and inhibition of platelet aggregation. But in the smooth muscle cells, action on the B receptor is vasoconstriction with proliferation and fibrosis.[11]

It has been shown that, in general in scleroderma, both diffuse and limited, serum endothelin levels are increased significantly. This excess endothelin vasoconstriction creates an imbalance between initial and subsequent cell proliferation or remodeling. These events explain the positive correlation between increased levels of pulmonary pressures and elevated levels of endothelin. Thus the higher levels of endothelin, the higher the values of pulmonary systolic pressure. This supports the dramatic improvement in survival of patients with pulmonary arterial hypertension by blocking endothelin receptor.[15]

Once the endothelial phase of the disease is installed, baseline hypoxia activates the overproduction of endothelin. This excess disturbs the balance of endothelin with nitric oxide and prostacyclins, generating a potent vasoconstrictor action that is not countered, establishing a vicious circle in which the unresolved tissue ischemia leads to increased vasoconstriction, release of proinflammatory cytokines and platelet aggregation as well as stimulation of fibroblast activity. The increase of platelet aggregation with endothelial proliferation and secondary thrombosis promotes remodeling.

Nitric oxide and prostaglandins help maintain the vascular tone balance. Nitric oxide generated by the conversion of L-arginine to L-citrulline produces vasodilation, platelet antiaggregation and inhibition of cell proliferation mediated by cGMP. Prostaglandins, through the arachidonic acid pathway mediated by cAMP, produce vasodilatation with antiinflammatory action. These actions are balanced by a family of phosphodiesterases, which by inhibiting cGMP and cAMP counteract nitric oxide-mediated vasodilation and prostacyclins.[2,10]

Clinical Manifestations

Raynaud's Phenomenon

Raynaud's phenomenon is a transient reversible, vasospastic phenomenon, induced by cold or stress. It occurs in fingers, toes and, less frequently, nose, ears and nipples. It may be asymmetric and not affect all fingers.[2,6]

Typically, changes in skin color undergo 3 phases: initial pallor, cyanosis, and finally erythema as an expression of a compensatory vasodilatation phase. Analyzing the clinical manifestations of progressive systemic sclerosis, both diffuse and limited, Raynaud's is present in most patients.

The prevalence of Raynaud's occurs in less than 10% in the general population.

Secondary Raynaud can occur at any age, while the primary form usually refers to patients in their youth.

Digital Ulcers in Scleroderma

A study of 1614 patients with digital ulcers in scleroderma highlights that defining a digital ulcer can be difficult and complex.[16] This is especially important in relation to the inclusion of patients in various research protocols, in some of which digital ulcer are considered as a loss of the dermis equal to or greater than 2 mm of palmar location on the finger pads of an ischemic etiology.[17,18]

However, despite the different criteria, digital ulcers in patients with scleroderma may be simply defined as a loss of continuity in the epidermis and adjacent layers and of digital location.[9,16–18]

By contrast, ulcer healing involves the complete re-epithelialization of the same, irrespective of pain.[17]

Regarding digital ulcers, we must consider certain features: size, borders, bedding, exposure of tissue (bone, tendons) and presence of underlying calcinosis. An active ulcer is considered acute when its development occurs in less than 3 months, and chronic if lasting more than 6 months.

Digital ulcers in scleroderma patients can be seen in the hands and feet. So-called non-digital ulcers have also been described. Non-digital ulcers in patients with scleroderma are located on the shins, ankles, elbows and forefeet. The leg lesions are generally large and should undergo a differential diagnosis with vasculitis.