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Review

Large vessels vasculopathy in systemic sclerosis☆

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ABSTRACT

Vasculopathy in systemic sclerosis is a severe, in many cases irreversible, manifestation that can lead to amputation. While the classical clinical manifestations of the disease have to do with the involvement of microcirculation, proximal vessels of upper and lower limbs can also be affected. This involvement of large vessels may be related to systemic sclerosis, vasculitis or atherosclerotic, and the differential diagnosis is not easy. To conduct a proper and early diagnosis, it is essential to start prompt appropriate treatment. In this review, we examine the involvement of large vessels in scleroderma, an understudied manifestation with important prognostic and therapeutic implications.

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Vasculopatía de grandes vasos en la esclerosis sistémica

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RESUMEN

La vasculopatía en la esclerosis sistémica es una manifestación grave, y en muchas ocasiones irreversible, que puede llevar a la amputación. Si bien las manifestaciones clínicas clásicas de la enfermedad tienen que ver con la afectación de la microcirculación, también los vasos proximales de extremidades superiores e inferiores pueden afectarse. Esta afectación de grandes vasos puede tener un origen relacionado con la esclerosis sistémica, vasculítico o arteriosclerótico por lo que llegar al diagnóstico no es fácil pero sí fundamental para empezar cuanto antes un tratamiento adecuado. En esta revisión repasamos la afectación de los grandes vasos en la esclerosis sistémica, manifestación poco estudiada y con importantes repercusiones pronósticas y terapéuticas.

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Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by excessive collagen and other extracellular matrix components deposition on different organs. In general, 3 components are involved in the pathogenesis of SSc: vascular, in which the endothelium plays a major role; fibrotic, fibroblasts and myofibroblasts dependent; and the immune system, in which lymphocytes and their mediators play a main role. Somehow, these 3 components are interconnected and are responsible for the disease development.[1,2]

Vascular involvement in SSc is a challenge for clinicians due to its high morbidity and mortality and the lack of effective treatment options when vasculopathy is present. It is important to distinguish the concept of vascular disease and vasculitis: vasculopathy encompasses any disease that affects a vessel, while vasculitis is the inflammatory disease of a vessel due to an impaired immune system. In this review we will focus primarily on two uncommon manifestations of scleroderma, such as the involvement of large vessels and non-digital ulcers. The rarity of large vessel involvement and the importance of a correct differential diagnosis justifies this review.

Pathogenesis of vascular involvement in systemic sclerosis

Currently it is not known exactly what stimulus triggers vasculopathy in SSc. It is thought that different infectious agents could be involved, such as free radicals related to nitric oxide, endothelial cells antibodies or cytotoxic T cells. The point is that, from a *precipitating factor* a series of processes that result in changes

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that start in microcirculation and eventually end up in fibrosis are activated.[1–3]

This series of alterations can be summarized as follows: microcirculation impairment, endothelial dysfunction and pericyte involvement, abnormal angiogenesis and vasculogenesis, chronic activation of platelets and maintained vasoconstriction.

Impairment of microcirculation

The earliest, most frequent and severe SSc clinical manifestations, with increased morbidity and mortality, are the ones that result from changes in microcirculation. Hair loss and altered capillary structure: the basement membrane is thickened, the endothelial cells of the capillary wall increase in size and there is a loss of intercellular junctions so gaps are formed, vacuolization of the cytoplasm occurs and plasmalemma vesicles are lost. Parallel to all this process, intimal proliferation occurs by accumulation of proteoglycans in arteries and arterioles.[3–7]

Endothelial dysfunction and impaired pericytes

Endothelial damage occurs early in the SSc. Endothelial dysfunction triggers such an imbalance of vasoactive molecules that vasoconstrictors increase and vasodilators decrease. Increased von Willebrand factor in plasma as well as endothelin-1 point to endothelial dysfunction indicators. The increase in both results in platelet aggregation and vasoconstriction, which in turn produces continuous platelet adhesion and fibrin accumulation.[2] This contributes to an intravascular thrombus formation.[1,8–10] On the other hand, it is not clear that this process is associated to an apoptotic phenomenon affecting the endothelial cell, resulting in phagocytosis by antigen presenting cells and cytotoxic T lymphocytes exposure. Thus, an alternative complement and coagulation pathway favouring thrombus formation would be activated.[10–12]

Pericytes are contractile cells that wrap around the endothelial cells of capillaries and venules. They regulate vascular maturation and stabilization during angiogenesis. They express *cytokines* such as the β receptor of the platelet-derived growth factor and the melanoma associated antigen of high molecular weight. Elevated levels of these *cytokines* have been observed in patients with SSc, Raynaud's phenomenon and vascular lesions. In addition, pericytes can be differentiated to smooth muscle cells, fibroblasts and myofibroblasts, contributing to increase the thickness of the capillary.[13,14]

Impaired angiogenesis and vasculogenesis

Angiogenesis is the formation of new blood vessels from preexisting vessels. It depends on the activation, proliferation and migration of endothelial cells. It is caused by a stimulus that induces proteolytic enzymes that break the extracellular matrix. The loss of capillaries and small vessels in scleroderma patients suggests a defect in the angiogenesis process, due to the increase of proangiogenic and antiangiogenic agents.[1,15]

Vasculogenesis is the formation of a vessel from stem cells and its role in SSc is not so clear. Stem cells migrate to where there has been endothelial damage, but there is no optimal differentiation mechanism for these new endothelial cells to repair the damage.[16–19] This fact shows that there may be a defect in these patients vasculogenesis.

Chronic platelet activation and impaired platelet aggregation

A release of vasoactive agents that induce permanent vasoconstriction occurs. This leads to a proliferation of intimal and smooth muscle cells and, eventually, fibrosis.[20] In summary, obliterative vasculopathy combined with progressive fibrosis occurs in the SSc. It can affect capillaries, arterioles and, less frequently, medium and large calibre vessels.

Clinical manifestations of vasculopathy in systemic sclerosis

Raynaud's phenomenon and digital ulcers

The typical clinical manifestations of impaired microcirculation include Raynaud's phenomenon, telangiectasia, linear subungual bleeding or "splinter" haemorrhage and ulcer, as the most severe manifestation.

Raynaud's phenomenon is a transient, reversible vasospasm, triggered by cold, stress or spontaneous appearance. It is characterized by three phases: pallor, cyanosis and hyperaemia. It affects the acral areas and can be asymmetrical. Its prevalence in the general population is less than 10%, however, in patients with SSc, the prevalence increases to 90%.[2] If Raynaud's phenomenon is maintained over time, digital ulcer appears.

The digital ulcer in SSc is defined as an ischaemic-necrotic lesion with loss of dermoepidermal tissue substance located in the palmar surface of the fingers, distal to the proximal interphalangeal joint.[21,22] These ulcers can be active (less than 6 months) or chronic (more than 6 months). It is essential to consider certain aspects such as edges, size, bed, tissue exposure and the presence of subcutaneous calcinosis. The most important risk factor for its development is a maintained and refractory to treatment Raynaud.[2] In different studies with cohorts of SSc patients, it has been observed that other risk factors for developing digital ulcers are: male sex, presence of pulmonary hypertension and/or decreased diffusion, diffuse type systemic scleroderma, long term disease progression, presence of scl-70 antibody and smoking.[23,24]

The association between anticardiolipin antibodies and digital ischaemia has been researched, with conflicting data. Herrick et al.,[25] found no difference in the prevalence of anticardiolipin antibodies in patients with SSc and ischaemic ulcers (11/31) compared with those who did not present these conditions (16/31).

Nor did they find any differences among patients who required amputation (5/13) and those that didn't (22/55). However, in the Boin et al.[26] study, a positive correlation between anti-beta2-glycoprotein antibodies (specifically IgA subtype) and digital ischaemia was observed.

Almost 60% of the patients with SSc develop an ulcer throughout their illness. 30% of cases correspond to ulcers with loss of soft tissue or bone and 11% of cases have digital gangrene at 7 years of follow-up. It is noteworthy that 25% of patients with SSc have 2 or more digital ulcers in the first visit, that is, even before being diagnosed.[2,27–29]

Non digital ulcers

Although the prevalence of digital ulcers is well documented, this is not the case with non-digital ulcers. However, since the last century, case series highlighting the impact of these on morbidity and mortality of patients with SSc have been published.[30]

In the general population, the most frequent causes are non-digital ulcers with venous involvement (70%), followed by arterial (15%) and mixed cause (10%), for example by diabetes. Instead, the aetiology of non-digital ulcers in patients with SSc are mostly by arterial involvement and appear on extensor surfaces and bony prominences (metacarpophalangeal joints, proximal interphalangeal joints, elbows, ankles, pretibial and forefoot regions). Lower extremity ulcers are often extensive, making it necessary to perform a differential diagnosis in those of vasculitic origin.[2]

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