Can fibroblasts determine the late differing outcome between systemic sclerosis and primary hypertrophic osteoarthropathy (pachydermoperiostosis) ?

M. Matucci-Cerinic, A. Pignone, S. Generini, J.H. Korn

Department of Medicine, Section of Rheumatology, University of Florence, Italy; 1Section of Rheumatology, Boston University School of Medicine, Boston, Massachusetts, USA.

Please address correspondence and reprint requests to: M. Matucci-Cerinic, MD, Department of Medicine, Section of Rheumatology, viale Pieraccini 18, 50139 Florence, Italy.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2000.

The findings presented in this issue by Silveira et al. (1) that circulating vascular endothelial growth factor levels are increased in hypertrophic osteoarthropathy (HOA), in particular in its primary form (also referred to as pachydermoperiostosis), confirm the role that endothelial cells may play in the pathogenesis of primary HOA (2). Endothelial dysfunction has been previously suggested to be one of the fundamental steps in this pathogenesis (1, 2).

Both involvement of the microcirculation and the derangement of endothelial cells have been demonstrated in HOA by: evidence of capillary modifications (2); the increase of Weibel Palade bodies in the cytoplasm of endothelial cells and the reduplication of the basal membrane (2); and the increase in circulating levels of von Willebrand factor (3). Indeed, the serum of primary HOA patients has been shown to exert cytotoxic activity on endothelial cells (4).

This involvement of the microvessels and endothelium has led to a comparison of the pathogenesis of primary HOA to that of systemic sclerosis (SSc) (5), a disease characterised by extensive endothelial activation, injury and apoptosis with severe microvascular modifications (6). It must be noted, however, that the two diseases are characterised by a completely different outcome in terms of skin involvement in the long-term: primary HOA tends to evolve in its late stages toward a florid skin hypertrophy, while SSc evolves toward severe skin atrophy. This clinical observation should direct our attention not only to the vascular system, but also to the connective tissue and fibroblasts.

During the last two decades, the importance of fibroblasts in the pathogenesis of connective tissue diseases has been highlighted. SSc and primary HOA exhibit similar modifications not only in the microvascular system, but also in the connective tissue. In SSc fibroblasts are activated (7) and produce an impressive amount of collagen (8), leading eventually to tissue fibrosis. In primary HOA the fibroblasts proliferate abnormally (9) and produce a striking amount of collagen (10), which can be found in bundles in the dermis (2), together with large amounts of glycosaminoglycans (11).

This is the underlying cause of the unsightly hypertrophy of the skin that characterises HOA. Thus, primary HOA and SSc share not only the feature of endothelial derangement - an early event during the course of both diseases - but also the “activation” of connective tissue cells. Despite the similarity of their initial pathways, however, the ultimate fate of the two diseases is completely opposite. Although they are both marked by the increased production of collagen, SSc results in cutaneous atrophy with epidermal thinning, whereas primary HOA results in cutaneous hypertrophy with epidermal thickening. This striking discrepancy in the evolution of these diseases despite the common underlying event of collagen overproduction could shed light on the mechanisms leading to severe fibrosis, a fundamental problem in medicine.

The partially shared pathogenetic pathway of primary HOA and SSc may be summarised as follows (Fig. 1). In early SSc fibroblast activation and proliferation occur, probably by a mutual influence with endothelial cells (12,13); this leads to the production of an excessive amount of collagen and extracellular matrix (Fig. 2). In this phase the clinical picture is dominated by tissue edema. As the disease progresses, collagen production is maintained while the ratio of hyaluronic acid is lower, and dermatan sulphate (14) and other factors such as dermatopontin and gangliosides (15,16) are strikingly reduced. Thus, the dermis is filled with collagen and sparse fibroblasts, with a concomitant loss of skin appendages and, it has been suggested, of other components of the extracellular matrix. This phase is clinically expressed by tissue fibrosis.

In primary HOA, on the other hand, fibroblast growth and proliferation appear to persist over the entire disease course, in association with increased collagen and extracellular matrix production (Fig. 2). This results in cutaneous edema and a “never-ending”, progressive skin hypertrophy (thickening and puckering). Unlike in SSc, there is also epidermal proliferation and maintenance of the skin appendages such as sweat glands and hair follicles.

Thus, SSc and primary HOA seem to
Fig. 1. The shared early pathogenetic pathway of systemic sclerosis and primary hypertrophic osteoarthropathy is shown. In the late phase, however, where collagen production predominates, this pathway diverges due to the different levels of glycosaminoglycan (GAG) production in the two diseases. In SSc a decrease in GAG favours fibrosis, whereas in primary HOA a GAG increase induces marked edema.

share the same initial event - the impressive production of collagen - while in the late phases of the two diseases, it may be hypothesized, divergent pathways are taken, one toward a reduction and the other toward the maintenance of extracellular matrix production. This hypothesis could explain the strikingly different late clinical course of SSc and primary HOA, i.e. atrophy/fibrosis versus hypertrophy/edema (Fig. 1).

Comparative studies of the behaviour of SSc and primary HOA fibroblasts may lead to a better understanding of the different mechanisms regulating their activation and help to explain the completely different course of these two diseases.

References
5. KAHALEH BM: The role of vascular endothelium in fibroblast activation and tissue fibrosis, particularly in scleroderma (systemic sclerosis) and pachydermoperiostosis (primary hypertrophic osteoarthropathy). Clin Exp Rheumatol 1992; 10 (Suppl. 7): 51-6.

Fig. 2. Cell numbers and matrix and glycosaminoglycan production levels are compared for the different phases of primary hypertrophic osteoarthropathy (HOA) and systemic sclerosis (SSc).