Review paper

THE SKIN IN SYSTEMIC SCLEROSIS

M.L. Cagnoni and T. Lotti

ABSTRACT

Systemic sclerosis is a systemic disease of unknown etiology which has both cutaneous and systemic manifestations. This disorder is often preceded or accompanied by Raynaud's syndrome.

Patients affected by chronic systemic sclerosis may present many cutaneous manifestations like pigmentary changes and vascular lesions including panniculitis, erythema nodosum, livedo reticularis, atrophie blanche or ulcerations that are often indicative of a specific phase of the disease.

In very rare cases systemic sclerosis may occur without any cutaneous symptoms, while more frequently patients present different pattern of cutaneous involvement.

Cutaneous involvement has been divided into three groups: the first group is characterized by an involvement of acral regions, the second group includes disorders which start distally and the third group is characterized by generalized cutaneous sclerosis.

KEY WORDS

systemic sclerosis (SSc), skin, connective tissue.

INTRODUCTION

In this paper we discuss the most recent data concerning the affected skin in systemic sclerosis (SSc) as described in the recent issue of Clinics in Dermatology, reviewed by Lotti and Matucci-Cerinic. From the dermatological point of view patients have been divided into three groups according to the peculiar characteristics.

A GENERAL REVIEW AND OUR OBSERVATIONS

The first group includes over 50 % of the patients. Here the disease typically involves the skin of the acral portions of the extremities which show scleroatrophic lesions on the fingers and occasionally also on the toes (sclerodactyly) (Fig. 1). The forearms and the face can be affected and gradually the upper extremities can be involved. Frequently scattered

teleangiectasias are present, most often as stellate nevi on the face and upper chest.

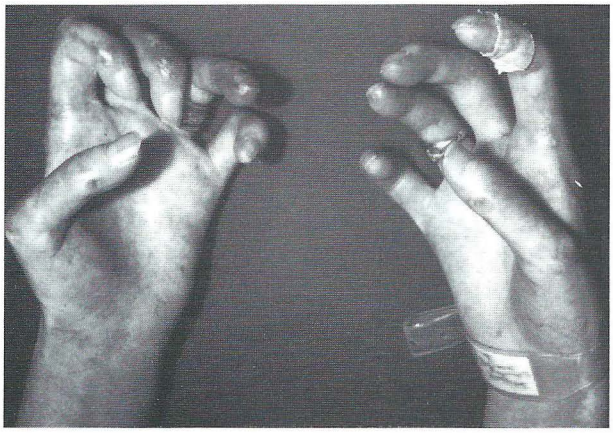

Fig. 1. Indurated skin appearing shiny and taut with developing contractures

In the second group the disease starts distally. Raynaud's phenomenon is observed and diffuse cutaneous sclerosis progresses centripetally with visceral and articular involvement (Fig. 2). Usually in this group no teleangectasias are evident. The scleroatrophic degeneration of the skin of the hands is usually preceded by a phase of fixed oedema which may last even months and which is followed by sclerodactyly and acrosclerosis. The skin of the face, of the forearms and of the upper portion of the chest is usually involved later (4).

The third group is less frequent. It is characterized by the early involvement of the trunk and by the successive centrifugal involvement of the extremities. This form is not necessarily preceded or accompanied by Raynaud's phenomenon, which is usually observed only in an advanced phase of the disease (5). It can lead to a whitish sclerosis of the whole skin surface, which is sometimes characterized by single, diffuse, confluent sclerodermic lesions (generalized morphea) to which a great number of teleangectasias are associated. It can also lead to an involvement of viscera, joints and muscles. Mild fever may be present (4). Teleangectasias (stellate nevi, macular or linear) are present in 75% of the patients affected by SSc and formed by vessels of a diameter between 0.2-20 mm. They are mostly present on the face, the lips, the mouth, the upper trunk, the palms and on the back of the hands. They can also involve the thighs.

In patients with acral cutaneous sclerosis (first group) the disease appears more often at a late age; its course is relatively benign and serious visceral involvement is less frequent. Usually the onset of the disease is preceded by manifestations as fatigue, headache, depression, fever and by Raynaud's phenomenon. In most cases the acral cutaneous sites are first involved. Fingers and the back of the hands, and later on, other cutaneous sites as the forearms, the neck and the face, undergo a two-stage transformation.

The first oedematous stage is characterized by oedematous swelling of the back of the hands (oedematous scleroderma) and by typical cyanosis of the fingertips with frequent loss of tissue. Such oedema is associated with morning fatigue, arthralgia and, occasionally, compression of the median nerve. The oedema may involve the arms, the face, and the trunk and is partially due to the deposit of hydrophilic glycosaminoglicans in the dermis. It can, however, also reflect a local inflammation, hydrostatic effects and microvascular alterations. It is still not clear today what causes the regression of this oedema.

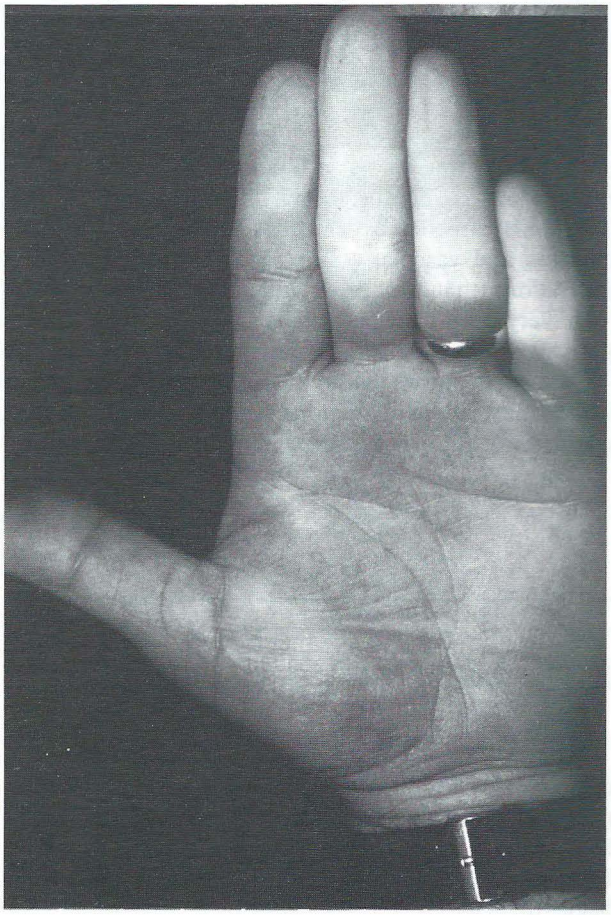

Fig. 2. Presence of Raynaud's phenomenon: well-markated blanching of the digit on exposure to cold

The second, atrophic stage becomes evident at an advanced stage of the disease and is characterized by atrophy of the skin and fragility of the superficial dermis. The skin of the fingers, toes and the back of the hands is taut, thickened and shiny, resulting in a reduction of the flexion and extension movements (6). Modifications of the pigmentation of the fingers and of the back of the hands accompany these atrophic alterations, as do teleangectasias on the palms. Moreover, ulcerative phenomenon of bony eminences are frequent and may be correlated with the trophic alterations of the fingers.

It has been seen that in this phase the total amount of collagen in the tissues is reduced whereas its density is normal (7).

The nail bed is most often erythematous and occasionally teleangectasias which are visible with the naked eye are present. Frequently enough the cuticle appears dishomogeneous. The examination of the nail bed may show bleeding and capillary infarcts which are followed by scarring and atrophic processes and which may result in the formation of large avascular areas. The gradual loss of parts of the fingertips may be accompanied by necrosis and by gradual resorption, especially of the periungueal area (8-10). The scleroatrophic regions may show a typically "cobbled" skin resulting in discontinuous scarring, dyschromias, lymphangiectasias and subcutaneous nodules (4). A palmar erythema on the tenar and hypotenar eminences may be characteristically associated with these manifestations.

In the serum of majority of these patients and in 50% of the patients having so-called CREST syndrome (Calcinosis, Raynaud's phenomenon, Esophageal dysfunction, Sclerodactyly, Teleangectasia) anticentromere antibodies (ACA) are present (11).

In the scleroatrophic areas typical little papules (deposits of amyloid substance) may be observed.

In the patients belonging to the second group Raynaud's phenomenon usually closely precedes or even closely coincides with the onset of the disease.

The cutaneous lesions extend rapidly involving the trunk and the arms (4). The incidence of clinically detectable pulmonary, renal or cardiac alterations is particular high. In some patients the hardening of the skin may be initially accompanied by a dark-red erythema. In many of these patients anti-topoisomerasis I autoantibodies are observed in the serum.

The non-constant presence of anti-fibrillarine autoantibodies is peculiar to the third form of the disease, which characteristically implies widespread cutaneous sclerosis and a great number of teleangectasias (12). In most cases the cutaneous manifestations precede the visceral involvement by several years but the opposite may also occur. Chronic systemic sclerosis is sometimes accompanied by a panniculitis which is clinically not unlike erythema nodosum. In fact, it manifests itself with a transient oedema covering dermal and hypodermal nodules (13).

In patients with SSc "white atrophy" (whitish-coloured scleroatrophic areas of vasculitis, sometimes striped for the presence of hyperchromic regions and crossed by teleangectasias) and "livedo reticularis" (skin erythematous, cyanotic and pigmented with reticular appearance) may arise on the lower third of the legs. At the site of the skin affected by "white atrophy" very painful ulcers may arise, which have little tendency to heal. These are caused partly by inflammation of the vessels and partly by mechanical phenomenons, namely compression by the sclerotic tissue (14)

Calcinosis, present in approximately 25% of the cases, occurs on the fingers, on the extensor surfaces of the forearms, especially on the palmar side of the terminal phalangeas, and is more frequent in women. These calcium deposits may break and expel calcareous material. The re-epithelisation of such lesions is very slow. Typical alterations of SSc in its limited form are calcinosis with simultaneous resorption of the bone of the phalanges (15).

Patients affected by SSc often show modifications of the pigmentation of the skin, most frequently on the face, on the lower third of the abdomen and on the thighs. These are probably expressions of post-inflammatory pigmentary alterations of the sclerotic areas (16-17). In most cases such are hyperpigmentations arising in isolated areas of sclerosis. Occasionally they may even precede the cutaneous sclerotic manifestations; sometimes they may be so intense and widespread that they resemble Addison's disease without, however, involving the mucosae (18). Manifestations resembling acanthosis nigricans may be observed at the flexor sites (4). Areas of depigmentation may arise in different sites of the body, even simultaneously, which wholly resemble vitiligo from both the clinical and the immunopathological standpoint (17).

Another cutaneous manifestation typical of the latest phase of systemic sclerosis is atrophy of the cutaneous appendages (pilo-sebaceous units, ducts and eccrine glands). Another is sclerodermal (atrophic) alopecia on the scalp (4).

In these patients affected by SSc, ivory-coloured subcutaneous nodules with diameter between 3-20 cm are occasionally evident. These nodules prevalently arise on the trunk and thighs (19) and are hystologically characterized by the presence of fibrinoid necrosis and fibromatous alterations.

THE FACE IN SYSTEMIC SCLEROSIS

The face is one of the first areas to be hit by the disease. In fact, at the onset of the disease a loss of expressiveness is commonly noticed: the face becomes an inexpressive mask (facies sclerodermica) and there is loss of the normal facial lines. The face seems tense with a sharp nose and has reduced dimensions because the skin is thinned and sclerotic. In an early oedematous phase a periorbital oedema can be observed in patients with few other cutaneous manifestations of SSc (20). The skin of the forehead can no longer rise in folds and that of the nose becomes thin and translucid. The patient can hardly completely open his mouth which has become smaller (microstomia). The lips are thin and fixed folds are present near the upper lip which extend in a typical radial way. The mobility of the eyelids is also reduced.

The sclerosis can successively extend to the neck. More rarely there is an involvement of the mucosae with a painful hardening of the gums and tongue (21).

HYSTOLOGICAL ASPECTS

The histopathological aspects of SSc vary according to the clinical stage. The epidermis may be normal (in the initial phases) or thickened or atrophic (later phases) with loss of the papillary pattern. Initially the dermis is oedematous and present swelling of the collagen fibers which successively undergo homogenization. The non-homogenized fibers are thickened and extend parallel to the skin surface (22).

In the first stage (inflammatory phase), there is a perivascular infiltrate which is mostly constituted by lymphocytes and by cells of the monocyte/macrophage line as well as by T-helper lymphocytes which express the HLA-DR. However, no HLA expression is observed in the keratinocytes of the affected skin, as is, on the contrary, seen in graft versus host disease (GVHD) (23). An infiltrate is also present among the collagen fibers of the dermis and the subcutaneous fat (septa). Here evidence of septal panniculitis with an infiltrate containing lymphocytes, plasmacells and eosinophils can be observed (24). In this phase the number of mastocytes has increased (25). At the sites of the teleangectasias, the presence of immunoglobulins and of complement was shown by immunofluorescence (26). In sclerotic areas on the other hand, this test was negative.

Successively the dermis thickens, and collagen fibrils become dense and sclerotic and lay parallel to the (derma-epidermal) junction. The number of fibroblasts is reduced and they are not easily identifiable (27). The pilo-sebaceous appendages (but not the errector muscles of the hair) and the dermal and hypodermal adipose tissue progressively dwindle until they disappear completely. In the late sclerotic phase, homogenized connective tissue replaces areas of subcutaneous adipose tissue. Even the sweat glands tend to disappear; only a few remain deep in the sclerotic mass (4).

In the sclerotic stage of the disease, in addition to the atrophy of the epidermis, to the hyalinisation of the collagen of the dermis and to the frequent loss of melanocytes, elastic tissue is also lost. The skin vessels of the patients who have only Raynaud's phenomenon display histopathological alterations of varying degrees, which are, however, not pathognomonic: capillary and lymphatic congestion depending on the cyanotic phase, thickening of the basal membrane and endothelial oedema (28-30) The capillaries of the affected skin have greatly reduced diameters, often leading to the occlusion of the lumen (31).

The increase in the serum levels of both factor VIII von Willebrand, antigen and coagulant, which is not, however, constant, and of the angiotensin converting enzyme, is correlated to the vascular lesions. So is the increase of the cutaneous and plasma fibrinolytic activity (32-33). Such activity may be normal.

The finding of normal values may indicate that the endothelial-articular-cutaneous area is mostly involved in the process. In this area, in fact, no fibrinolytic activity is evident. On the other hand, the cutaneous fibrinolytic hyperactivity which has occasionally been observed in SSc could be associated with hypoxia in the post-capillary compartment, caused by the partial occlusion of the arterioles.

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AUTHORS' ADDRESSES

Matteo L. Cagnoni, MD, Via Bolognese Vecchia 178, 50139 Firenze, Italy
Torello Lotti MD, professor of dermatology, same address