Localized and systemic forms of scleroderma in adults and children

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ABSTRACT

Systemic sclerosis (SSc) presents a great deal of variability in the extent and severity of skin and internal organ involvement. The diagnostic and prognostic significance of autoantibodies in SSc is undisputed and the patient's autoantibody profile represents a fundamental tool for clinicians. Scleroderma is a rare condition in children. Unlike adults, localized scleroderma is more frequent than the systemic sclerosis, nevertheless it represents a disabling condition. In both conditions, no validated outcome measures and proven effective treatment is available to date. Raynaud's phenomenon (RP) is one the most common and significant clinical symptoms of SSc and therefore in patients with RP a capillaroscopic analysis should be carried out as soon as possible. The actual and select advantage of the early nailfold videocapillaroscopic (NVC) analysis is to distinguish between the primary RP and the secondary RP and to allow the early detection of SSc.

Introduction

'Scleroderma', a word meaning hard skin, is a part of many syndromes including localized, limited, and generalized scleroderma. The group of syndromes called localized scleroderma includes morphoea (limited and guttate), linear scleroderma with the *en coup de sabre* variety, and generalized morphoea (1). These syndromes predominate in childhood and are almost never associated with systemic involvement but may demonstrate abnormal autoimmune serology and inflammatory histological changes in skin. Generalized scleroderma is called systemic sclerosis (SSc); the term is preferable to progressive systemic sclerosis because not all cases are progressive (2). SSc involves immunologic mechanisms, lymphocytic infiltration, vascular endothelial cell activation and/or injury, and activation of fibroblasts. This results in overproduction and excessive deposition of collagen and other extracellular matrix proteins, including fibronectin, tenascin, and glycosaminoglycans in the skin and internal organs. It embraces a clinical spectrum ranging from widespread skin thickening (diffuse scleroderma) to skin thickening either limited to the face and distal extremities (limited scleroderma) or absent (systemic sclerosis *sine* scleroderma). The term limited cutaneous systemic sclerosis is preferable to CREST (Calcinosis, Raynaud's, Esophageal dysphagia, Sclerodactyly, Telangiectasia syndrome), because cutaneous manifestations often extend beyond sclerodactyly and calcinosis may be present only late or radiologically (1, 2). Diffuse cutaneous systemic sclerosis is much more rapid in onset with organ failure often present within 5 years of the first symptoms.

Systemic sclerosis

SSc is a generalized disorder of connective tissue which is characterized by: (I) a distinctive vasculopathy affecting microvessels and small-sized muscular arteries; and (II) deposition of collagen and other constituents of the extracellular matrix in the skin and internal organs, notably gut, lung, heart, kidney, joints and muscles. The reported prevalence of SSc is between 19 and 75 per 100,000 persons, women being affected more often than men.

Patients with SSc present a high degree of variability as far as the extent of skin and internal organ involvement, the disease activity and severity and, consequently, the prognosis. In addition, the single patient during the course of his/her disease can present a variety of different clinical manifestations (1-5).

These disease aspects explain the differences registered among studies in

the prevalence and severity of internal organ involvement (6). In order to improve the comparability among studies, a consensus conference was held a few years ago, with the aim to define the clinical, laboratory and instrumental investigations devoted to assess the organ involvement in SSc (7). In particular, it was underlined that each clinical investigational study on any topic should be accompanied by a clear-cut definition of a number of epidemiological, serological and clinical items including the evaluation of disease activity by European Scleroderma Study Group Criteria (8) and that of severity by revised Medsger severity scale (9).
A cohort of 121 Italian patients affected by SSc prospectively studied describing the main clinical aspects, in particular the low prevalence of kidney disease, the high frequency of general complaints and the occurrence of a definite number of patients with end-stage organ disease, is reported in Table I (10).

Table I. Systemic sclerosis in an Italian cohort.

Sex (F/M)			108/13	
Age median (range 19-75)			51	
Disease duration median (range 1-55)			10.5	
ACR criteria fulfilled			121	
SUBSET				
limited cutaneous SSc			75	(62%)
diffuse cutaneous SSc			46	(38%)
AUTOANTIBODY PROFILE:				
ANA positive			121	(100 %)
ACA positive			47	(39.5 %)
Anti-Scl-70 positive			62	(51.2 %)
ACA and Anti-Scl-70 negative			11	(9.5 %)
ACTIVE DISEASE (ESSG activity index ≥ 3) (ref. 8)			38	(31.4 %)
ORGAN/SYSTEM INVOLVEMENT			SEVERITY (ref. 9) median	range
General	59	(47.8%)	0	0-4
Peripheral vascular	116	(95.9%)	2	2-4
Skin	110	(90.9%)	1	1-3
Joint/tendon	45	(37.2%)	0	0
Muscle	12	(9.1%)	0	0
GI tract	98	(81 %)	1	0-3
Lung	98	(81 %)	2	0-4
Heart	53	(43.8%)	0	1-4
Kidney	13	(10.7%)	0	0-2

Autoantibodies in SSc
In more than 90% of patients antibodies against cellular self components can be detected. Most of these autoantibodies are found in mutually exclusive subsets, each associated with a different clinical phenotype. The main mutually exclusive subgroups include anti-centromere antibodies (ACA), anti-topoisomerase I (anti-Scl-70), and anti-RNA polymerase III (anti-RNAP III) (11).
Anti-centromere antibodies. At least 6 centromeric nucleoproteins recognized by ACA+ SSc sera have been identified and there are no reports on clinical differences in targeting these different proteins. ACA occur in about 20-30% of patients, but the frequency varies according to ethnic differences. They are strongly associated with limited cutaneous involvement, ischemic digital loss and CREST syndrome. ACA+ patients show lower frequency of interstitial pulmonary fibrosis compared to anti-Scl-70+ patients and better survival rates. A major cause of death in this subset is pulmonary hypertension without radiological signs of fibrosis or restrictive lung disease on pulmonary function tests (12).
Anti-Scl-70. A chromatin-associated, nonhistone protein (Scl-70) was described to be recognized by sera from SSc patients and further studies have cleared that these autoantibodies target different epitopes on topoisomerase I. Anti-Scl-70 are specific for SSc and, like ACA, when a patient with Raynaud's phenomenon is found positive, there's a very high risk of developing the disease. This antibody is clinically associated with diffuse cutaneous disease, severe degree of lung fibrosis and high mortality rate due to pulmonary involvement. In Japanese patients, an association with scleroderma renal crisis was also reported (13).
Anti-RNA-polymerase I-III. There are three classes of RNAP (I-II-III) and they can all be target of autoimmune responses. In particular, autoantibodies against RNAP III, almost exclusively found in association with anti-RNAP I, are highly specific markers of SSc. Anti-RNAP I-III+ patients frequently have diffuse cutaneous involvement with higher skin scores than anti-Scl70+ patients. They also show a higher risk of cardiac and renal involvement, in particular scleroderma renal crisis (14, 15). Anti-RNAP I-III are detected in about 20-30% of patients from USA and UK while the frequency is lower in Italian patients. This may at least in part account for a lower occurrence of scleroderma renal crisis in Mediterranean countries (16).
Anti-snoRNPs. Small nucleolar ribonucleoproteins (sno-RNPs) are complexes of RNA and proteins, divided into three groups by conserved RNA sequences: box C/D, box H/ACA, RNase MRP/RNase P complexes (17). Sno-RNPs are influenced by many stressor agents like irradiation, mercury exposure and activation of death receptors, circumstances that actively participate in the setting of autoimmunity in SSc (18).
Anti-fibrillarin (AFA). Fibrillarin is shared by all box C/D sno-RNP components. AFA are frequently found in SSc. They identify a severe disease with diffuse skin sclerosis, esophageal involvement and a high risk of pulmonary hypertension and arthritis. Reactivity against the box C/D component U3-snoRNP alone can also be detected and it seems related to a milder course with diffuse cutaneous sclerosis but a less important visceral involvement (17).
Other autoantibodies. Other autoantibodies may be found in SSc sera with

different clinical relevance (Table II). Furthermore, a lot of studies have also reported many autoantibodies with a potential direct pathogenetic role. Anti-endothelial cells antibodies have been associated with an increased frequency of severe pulmonary fibrosis. They are able to mediate many effects *in vitro* (like vascular injury through antibody-dependent citotoxicity and induction on endothelial cells of the adhesion molecules), bringing a possible explanation to the vascular hyperreactivity and consequent mononuclear migration to the inflamed tissues (19).

Antibodies directed against matrix metalloproteinases can be found in SSc and may contribute to the development of fibrosis and to the vasculopathy through indirect inhibition on Vascular Endothelial Growth Factor (VEGF) and neoangiogenesis (20).

A recent study reported that autoantibodies to the Epidermal Growth Factor Receptor, overexpressed in SSc patients and possibly linked to the increased output of extracellular matrix (ECM) from fibroblasts, can be detected as well (21). ECM components like fibrillin-1 are other targets of autoantibodies in SSc (22).

Antibodies to membrane structures on fibroblasts have been described. They are able to induce fibroblast activation *in vitro*, with production of pro-inflammatory mediators and ICAM-1 up-regulation. These antibodies have been strongly correlated with anti-Scl-70, and anti-topoisomerase I themselves display anti-fibroblasts activity by reacting with an unidentified epitope on their membranes (23). Further studies should clarify whether this antigenic determinant cross-reacts with anti-topoisomerase I antibodies or the nuclear enzyme itself is brought to the cell surface. Anyway these results may represent a key point as for the potential pathogenic role of anti-Scl70 in SSc.

Localized scleroderma and antibodies.

Localized scleroderma (LSc) is a fibrosing disorder of skin and subcutaneous tissues. It is classified into three forms with a crescent grade of gravity: morphea, linear scleroderma and generalized morphea. The absence of Raynaud's phenomenon, acrosclerosis and visceral involvement differentiates it from SSc. An autoimmune background is certainly involved in its pathogenesis, and a wide variety of autoantibodies have been described (24).

Anti-histone antibodies, even if not specific, are considered a serological characteristic of the disease. Their presence is also related to the detection of other frequently observed autoantibodies: anti-ssDNA and anti-topoisomerase IIa. Rheumatoid factor IgM, but also IgG and IgA have been described to be frequently high in LSc subjects compared to healthy controls (25). For all these autoantibodies, generalized morphea shows the highest percentages of positivity and the highest titers. Serological abnormalities seem to follow disease course as well, being higher when lesions are active. Many other reactivities shared with other autoimmune disorders have been reported in a minority of patients, further confirming the immunomediated mechanisms underlying LSc.

Skin involvement in SSc

Among the first symptoms is a dyscoloration of the fingers upon mental, thermal (cold) or sometimes physical stress, Raynaud's phenomenon, which can appear months or even years before skin sclerosis. The disease itself manifests clinically by the sequential appearance of three phases of skin changes: an initial edematous phase, which begins distally in the extremities and advances proximally, a sclerotic or indurative phase and an atrophic phase often accompanied by teleangiectasias.

Two main subsets of clinical manifestations can be distinguished. In *limited cutaneous scleroderma* thickening is limited to distal extremities and progresses slower. In *diffuse cutaneous scleroderma*, a more generalized symmetric skin thickening develops rapidly. If this occurs in less than 3 to 4 years, it poses a greater risk of affecting the lungs, heart, or kidneys and influencing mortality (26). If no organ involvement has appeared during the first six years after initial symptoms, the probability of still developing visceral complication is low. The first 1 to 3 years will belong to the inflammatory stage. Usually, this is the period when the skin sclerosis progresses the most, followed, in general, by a stabilization of the sclerosis or even subjective improvements.

The involvement of the face leads to a mask like appearance with loss of wrinkles, microstomia, diminished facial expression and perioral wrinkles perpendicular to the thinned lips. Increased skin fibrosis may result in a loss of hair follicles, sweat glands or skin pigmentation around hair follicles resulting in the typical "salt-and-pepper" appearance and dryness. Especially patients with the limited cutaneous form of the disease can develop calcific deposits of considerable size intra- and subcutaneously. These will present mainly at finger pads, and extensor surfaces of elbows and knees. Teleangiectasias are frequently encountered over fingers, lips, face and oral mucosa.

Skin involvement evaluation. The most widely used assessment method for skin involvement is the Rodnan skin score, which has been modified since (26), now using measurements at 17 areas and requiring about 10 minutes to acquire. The skin is squeezed between two fingers and the degree of thickness is given scores from 0 (no detectable thickening) to 3 (strong thickening) and averaged over a certain area. The sum of all areas then leads to a maximum score of 51. In the face the area between the os zygomaticum and lower mandibule not the forehead is to be measured. On the fingers, hands and feet, only the dorsum is examined. The extremities are relaxed during examination and during thorax and abdomen scoring, the patient sits upright. Despite inter-observer variability, this has been shown to be a sufficiently reliable assessment method for follow-up tests.

New promising methods have been proposed: a skin durometer, an elastometer (28), a device measuring torsional stiffness or resistance to squeezing with a "plicometer" (29). The use of 22 MHz dermal ultrasound at 17 predefined anatomical locations has also been proposed (30). The investigator should also check for the presence of tendon friction rubs, which appear as a "leathery crepitus" while the joint is moved.

Table II. Major autoantibodies specifically associated with SSc and their most relevant clinical associations.

Autoantibody	Recognized epitope	Methods of detection	Clinical associations	Frequency in SSc (can vary according to ethnic differences)
Anti-Centromere Tan *et al*., Arthritis Rheum 1980	Centromeric nucleoproteins (CENP-A, 13 kD; -B, 80 kD; -C, 130 kD; -D, 50 kD; -E, 312 kD; -F, 400 kD)	IIF*, ELISA§	LcSSc[1]; CREST; isolated pulmonary hypertension	20-30%
Anti-Scl-70 Douvas *et al*., J Biol Chem 1979	Nuclear topoisomerase I (core and C-terminal domain)	ID°, ELISA	DcSSc[2]; pulmonary fibrosis; scleroderma renal crisis (?)	15-20%
Anti-RNA polymerase I-III Okano *et al*., Ann Intern Med 1993	RNA-polymerase I, RNA polymerase III	IP^, ELISA	DcSSc; cardiac and renal involvement (scleroderma renal crisis)	20-30%
Anti-RNA polymerase II Hirakata *et al*., J Clin Invest 1993	RNA-polymerase II phosphorylated (IIo) and unphosphorilated (IIa) plus a common sequence (IIc)	IP	DcSSc; usually associated with anti-RNA-polymerase I-III *or* anti-Scl70	~ 20%
Anti-fibrillarin Lischwe *et al*., J Biol Chem 1985	Fibrillarin, component shared by all of the box C/D sno-RNPs	IP	DcSSc; esophageal involvement; pulmonary hypertension; arthritis	4%
Anti-U3 snoRNP Van Eenennaam *et al*., Clin Exp Immunol 2002	U3-snoRNP, one of the box C/D components	IP	DcSSc; milder course compared to anti-fibrillarin + patients	10% among anti-nucleolar positive patients
Anti-Th/To Okano *et al*., Arthritis Rheum 1990	RNase MRP and RNase P	IP	puffy fingers; pulmonary fibrosis; scleroderma renal crisis	2-5%
Anti-hnRNP I Montecucco *et al*., Arthritis Rheum 1996	Polypirimidine-tract binding protein	IB#, ELISA	Pre-SSc	~ 50%
Anti-B23 Ulanet *et al*., Arthritis Rheum 2003	Nucleophosmin	IP, ELISA	Pulmonary hypertension	~ 10%
Anti-NOR90 Imai *et al*., Mol Biol Reports 1994	Human upstream binding factor (Nucleolus Organizer Region)	IB	LcSSc	rare
Anti-PM-Scl Reichlin *et al*., J Clin Immunol 1984	11-16 peptides with a range of MW from 20 to 110 kD and with PM-Scl-100 and -75 being the most antigenic	IB, ELISA	Polymyositis/scleroderma overlap syndrome, lcSSc	3%

* Indirect immunofluorescence
§ Enzyme-Linked ImmunoSorbent Assay
° Immunodiffusion
^ Immunoprecipitation
# Immunoblotting

[1] Limited cutaneous systemic sclerosis
[2] Diffuse cutaneous systemic sclerosis

Sclerosis of the skin is also a hallmark of localized forms of scleroderma like morphea. They show single or multiple plaques of skin induration but are not associated with organ complications and other disorders. Diffuse fasciitis with eosinophilia, Eosinophilia-myalgia syndrome (EMS), Scleromyxedema, Scleredema (scleredema adultorum of Buschke) or graft-versus-host disease especially after bone marrow transplantation differ in some critical characteristics like pattern of skin affection, autoantibodies or clinical history. Environmental agents involved may include silica dust, polyvinylchloride, epoxy resins and aromatic hydrocarbons such as benzine, toluene, trichloroethylene.

Treatment of the skin. Treatment of skin fibrosis and sclerosis is still difficult. Dryness of the skin should be reduced by avoiding detergent soaps and by application of bath oils. Regular physical exercise training should focus on improving joint extension to prevent contractures, resulting in gain of function and improved life-quality. Specialized massages improving lymph drainage and hand exercise against a resistant substance using a warm paraffine bath can help in increasing joint motility as well as peripheral blood flow (31). Although various treatments have been tried and many physicians still administer certain immunosuppressives like azathioprine, methotrexate, cyclophosphamide or others (32) during the early rapidly progressive inflammatory stage, no controlled studies exist proving their effectiveness. The first hints for the benefit of UV-therapy came from the treatment of localized scleroderma (33). The effectiveness of low and high-dose UVA1 phototherapy in systemic scleroderma has been reported as well, although still awaiting confirmation by larger controlled trials.

In severe cases, surgical correction of contractures can bring substantial improvement in the ability to perform everyday tasks (34).

Systemic and localized scleroderma in children

Juvenile scleroderma syndromes are autoimmune rheumatic diseases characterized by the presence of hard skin and onset before 16 years of age. They can be separated into two main categories: those with skin sclerosis but no vascular or internal organ involvement such as Localized Scleroderma (JLS), and those with diffuse skin sclerosis involving many sites of the body together with internal organ involvement such as Systemic Sclerosis (JSS).

Juvenile systemic sclerosis. JSS is characterized by sclerodermatous skin changes combined with fibrous changes in internal organs, such as esophagus, intestinal tract, heart, lungs and kidneys. Recently, by using a consensus and experts-based methodology, criteria for classification of patients with juvenile systemic sclerosis have been proposed (JSS). On this basis a child is classified as having systemic sclerosis in presence of diffuse skin sclerosis/induration and at least two minor criteria selected among 21 items grouped under 9 different organ systems (35) (Table III).

Cutaneous changes characteristically evolve in a sequence beginning with edema, followed by induration and sclerosis resulting in marked tightening and contracture, and finally eventuating in atrophy. Telangiectases, although specific, are quite rare in children.

Raynaud's phenomenon occurs in 80-90% of children and is often the initial symptom of the disorder, preceding other manifestations by years. It mainly involve the fingers but can be observed in toes and, occasionally, ears and tip of the nose.

Musculoskeletal symptoms are common in JSS. Among the 153 children with JSS included in the Padua International Database, 36% had musculoskeletal symptoms during the course of the disease (36). Arthralgia is usually mild and transient, joint contractures are most common at the proximal interphalangeal joints and elbows and muscle inflammation rarely occur. Gastrointestinal involvement is present in almost 40% of the patients during the course of the disease and dysphagia may be one of the presenting signs in 14 percent of children (36). Typically it consists in esophageal dysmotility and gastro-esophageal reflux. Cardiopulmonary disease, although uncommon at presentation, is a primary cause of morbidity among children with JSS. Severe cardiomyopathy, although rare, can be one of the causes of early death in these patients and requires prompt and aggressive immunosuppressive treatment (37). Pulmonary involvement can manifest as dry, hacking cough or dyspnea on exertion. Interstitial pulmonary fibrosis is rarely reported in children (36). High resolution computed tomography (HRCT) may reveal pulmonary disease even in the presence of a normal chest radiograph. In children the most frequent findings are groundglass opacification, subpleural micronodules and honey combing.

Antinuclear antibodies (ANA) are frequently demonstrated in the sera of children with JSS. The prevalence of ANA positivity is around 80%, a frequency lower than what has been reported in adults (36). The prevalence of Scl-70 ranges from 20 to 30% while anticentromere antibodies are much less common than in adults (7%) (36, 38).

The management of patients with JSS presents one of the most difficult and frustrating challenges. Methotrexate, a proven effective drug for juvenile idiopathic arthritis, has never been tested in JSS but only in JLS with encouraging results (39). Mycophenolate mofetil has recently been used for scleroderma. The apparent safety and tolerability of this drug makes it a potential choice as an immunomodulatory drug for maintenance (40). Raynaud's phenomenon can be safely treated by calcium channel blockers (CCB) or by intermittent infusions of prostacyclin or its analogues (41). The endothelin-1 receptor antagonist, bosentan, recently introduced for the treatment of pulmonary hypertension, has never been utilized in children with systemic sclerosis.

Juvenile Localized Scleroderma. Juvenile Localized Scleroderma (JLS) is a distinct entity from JSS due to its almost exclusive cutaneous involvement and, with some exceptions, absence of internal organ involvement. Although JLS is relatively uncommon, it is far more common than systemic sclerosis in childhood. It is believed to occur in up to 1 per 100,000 of the population.

The most widely used classification

Table III. Preliminary classification criteria for systemic sclerosis in children (Padua Consensus Conference 2004[1]).

MAJOR CRITERIUM	Presence of diffuse sclerosis/induration of the skin
MINOR CRITERIA	
Organ System	Signs and Symptoms
Skin	Sclerodactily
Vascular	Raynaud phenomenon Digital ulcers Nailfold capillary changes
Gastrointestestinal	Gastro esophageal reflux Dysphagia
Respiratory	Lung fibrosis (HRCT) Pulmonary hypertension Diffuse Lung Capacity for CO
Renal	Renal crisis New onset hypertension
Cardiac	Heart failure Arrhythmias
Neurological	Carpal-tunnel syndrome Peripheral Neuropathy
Musculo-Skeletal	Arthritis Myositis Tendon friction rubs
Serology	Antinuclear antibodies
SSc selective autoantibodies	(Scl-70, anti-Centromere, PM-Scl)

A patient can be classified as having Juvenile Systemic Sclerosis with the presence of diffuse sclerosis/induration of the skin (Major Criterion) and at least two minor criteria.

divides JLS into five general types: plaque morphea, generalized morphea, bullous morphea, linear scleroderma, and deep morphea (42) (Table IV).

Plaque morphea is characterized by oval or round circumscribed areas of induration with a central waxy, ivory color surrounded by a violaceous halo. It is confined to the dermis with only occasional involvement of the superficial panniculus. When individual plaques become confluent or multiply and affect three or more anatomic sites we have *generalized morphea*.

Linear scleroderma is the most common subtype in children and adolescents (43). It is characterized by one or more linear streaks that typically involve an upper or lower extremity sometimes causing significant deformities. When a linear lesion involves the face or scalp, it is referred to as *en coup de sabre* scleroderma (ECDS), so called because the lesion was reminiscent of the depression caused by a dueling stroke from a sword.

Deep morphea is the least common but most disabling variant. In this subtype the entire skin feels thickened, taut, and bound down sometimes with the appearance of a solitary, indurate plaque (44). Almost one fourth of JLS patients have been reported as having, during the course of the disease, one or more extra-cutaneous manifestations (45). Articular involvement is the most frequently reported complication of JLS and sometimes is unrelated to the site of the skin lesion.

In linear scleroderma involving the face, neurological involvement such as epilepsy or brain calcifications and ocular changes such as uveitis or episcleritis have also been described (45). These extra-cutaneous manifestations, usually mild, may suggest that localized scleroderma and systemic sclerosis likely represent two ends of a continuous spectrum of disease.

Antinuclear antibodies can be present in any of the morphea subtypes with a frequency ranging from 23-73% (46).

Therapy for JLS has been as challenging as in JSS. Morphea en plaque generally is of cosmetic concern only, and therefore treatments with potentially significant toxicity are not justified.

When there is a significant risk for disability, such as in linear and the deep subtypes, systemic treatment should be considered. Methotrexate (MTX) has been successfully used in children with localised scleroderma (39). The use of ultraviolet light therapy has been reported in a number of studies with some clinical benefit (47). Use of vitamin D or its analogues has been reported, again with encouraging results; however, in the only controlled trial, results indicated it was no more effective than placebo (48).

Table IV. The Mayo Clinic classification of localized scleroderma (Peterson LS *et al*. 1995).

Plaque Morphea
morphea en plaque
guttate morphea
Atrophoderma of Pasini and Perini
keloid morphea
Generalized morphea
Bullous morphea
Linear scleroderma
Linear morphea
En coup de sabre scleroderma
Progressive hemifacial atrophy (Parry-Romberg syndrome)
Deep morphea
Subcutaneous morphea
Eosinophilic fasciitis
Morphea profunda
Disabling pansclerotic morphea

Capillaroscopy

The role of capillaroscopy in the early diagnosis of secondary Raynaud's phenomenon. Microvascular involvement represents a key feature of Raynaud's phenomenon (RP) and several rheumatic diseases are characterized by the presence of RP. However, secondary RP is considered the earliest and most common clinical manifestation of scleroderma (systemic sclerosis, SSc) as well as being frequent in other connective tissue diseases (CTD) such as systemic lupus erythematosus (SLE). A secondary cause of RP is suggested by different findings including an age at onset of more than 30 years, episodes

that appear intense, symmetric, painful and/or associated with ischemic skin lesions, clinical aspects suggestive of a CTD, the presence of specific autoantibodies and evidence of microvascular alterations detected by microscopy of nailfold capillaries (49). Therefore, RP offers one of the best insight into the investigation of the early vascular steps in the pathogenesis of SSc and generally CTD.

The most common aspect of microvascular involvement assessed by capillaroscopy is secondary RP. The best technique currently available to study such microvascular involvement is the nailfold capillaroscopy (50).

It is usually suggested that all the fingers should be evaluated during the capillaroscopic analysis, however, the most accurate morphologic assessments are commonly performed on the 4th and 5th fingers, because of the greater transparency of the skin.

In normal conditions or in primary RP (except during the cold-exposure test) the normal nailfold capillaroscopic pattern shows a regular disposition of the capillary loops along with the nailbed (Fig. 1). On the contrary, in subjects suffering from secondary RP, one or more of the peculiar capillaroscopic findings should alert the physician to the possibility of a CTD not yet detected (51) (Fig. 2).

At this stage, the early detection of the following microvascular alterations allows the differential diagnosis between primary and secondary RP.

Giant capillaries. The presence of homogeneously and/or irregularly enlarged microvascular loops represents one of the earliest and striking features of secondary RP (Fig. 3). These ectasias show a characteristic shape which make them different in respect to those observed in other pathological conditions, such as diabetes mellitus and acrocyanosis. Capillaries with a normal shape and diameter, often coexist with enlarged or giant loops. Even the detection of a single loop with a circumscribed or homogeneous diameter > 50 micron should be considered as a potential marker of microangiopathy related to an early scleroderma-spectrum disorder. It has been suggested that microvascular dilatation (enlarged/giant capillaries) represents a local autoregulatory response to tissue hypoxia (52). In a recent study enlarged capillaries have been found in 100% of SSc patients, 86% of patients affected by dermato-

Fig. 1. The videocapillaroscopic analysis of the nailfold (NVC) is considered at the present time the most sophisticated and might detect also the blood flow at the level of the microvessels. In addition, the NVC is connected to efficient software that allows the computerized processing of the images and the storage of the data (Capillaroscopic Unit, University of Genova).

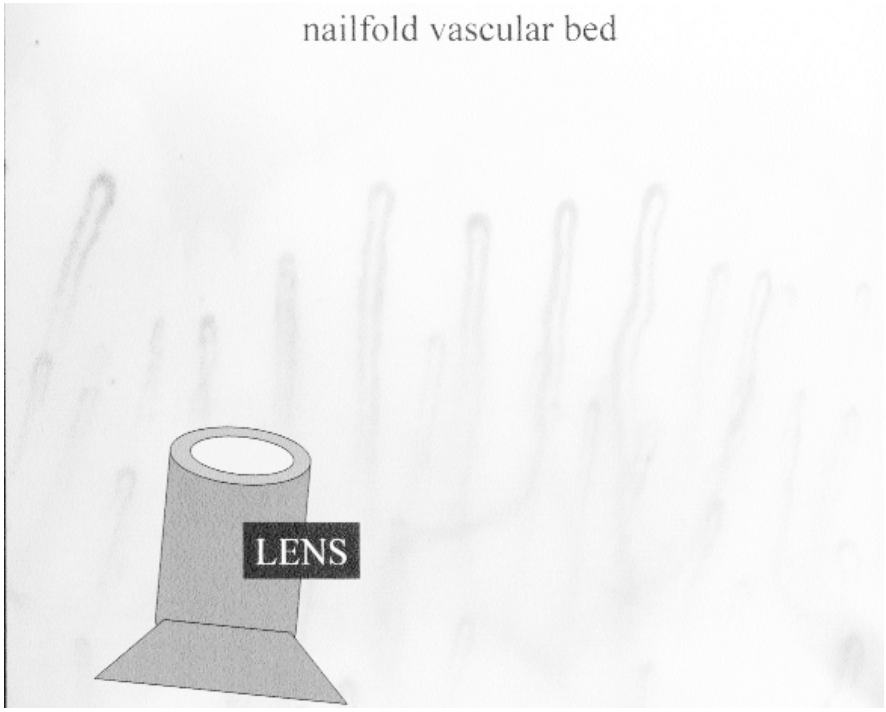

Fig. 2. Picture of a normal nailfold vascular bed as analyzed by NVC (magnification 200x).

myositis (DM) and 56% of patients affected by undifferentiated connective tissue disease (UCTD).

Angiogenesis. A large range of different morphologic features of capillary neoformation may be observed in patients with secondary RP. Highly tortuous and arborescent capillary loop clusters, often surrounded by dropout of normal capillary loops are a characteristic feature of angiogenesis. The main morphologic hallmark of angiogenesis is the clustering of tortuous capillaries with a pronounced shape heterogeneity, including thin or large meandering and bushy capillaries (ramified capillaries) (53).

In addition coiled capillaries are the morphologic hallmark of angiogenesis in the elongated papillae of psoriatic plaque. These aspects are also frequently observed in the classical pattern of DM.

Architectural derangement of the nailfold microvascular network. As previously stated, the general architectural arrangement of the skin microvascular bed is remarkably regular in healthy subjects. The nailfold capillaries on the last row are characterized by uniform distribution, shape and diameter. Most capillaries show a hairpin or a U-shaped aspect. A striking modification of the normal architectural arrangement represents an early morphological feature of SSc. In addition, in patients with recently onset RP, these changes may be patchy, unilateral or limited to a single finger making an early diagnosis important.

Loss of capillaries and/or avascular areas. A decreased number of loops (< 30 over 5 mm in the distal row of the nailfold) should be considered highly specific for secondary RP (54). Loss of capillaries may result in critical tissue hypoxia (55). The extensive disappearance of capillaries may generate large avascular areas with a "desert-like" appearance of the nailbed. In patients with even recently onset RP, the appearance of rapidly progressive capillary loss might represent the first dramatic capillaroscopic evidence of severe and progressive SSc. In fact, progressive loss of capillaries has been associated with more extensive skin involvement and with a poor prognosis (56).

Local microhaemorrages are also associated with early vascular damage and

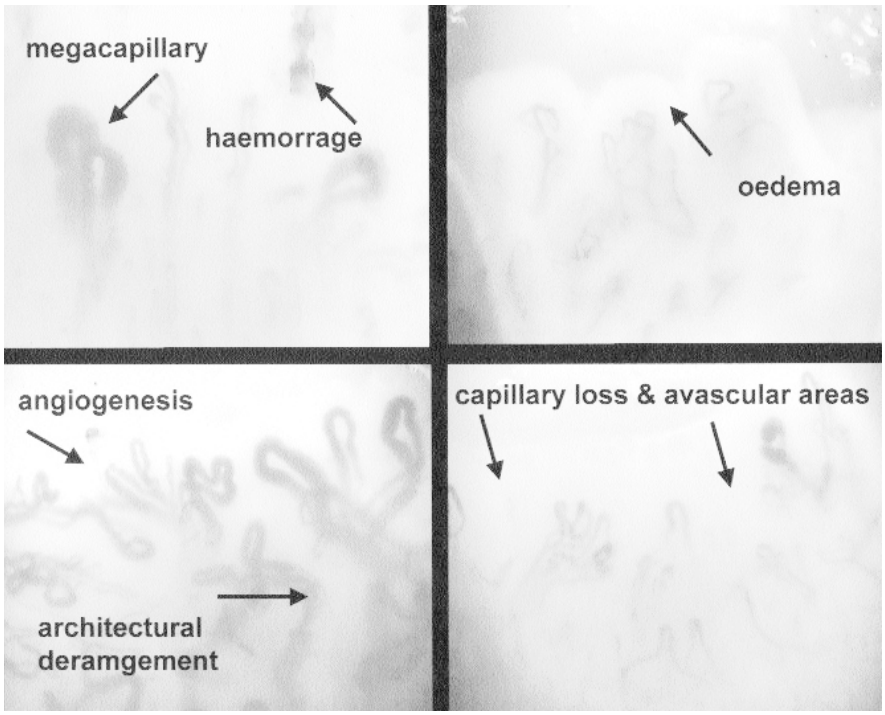

Fig. 3. The following major abnormal vascular parameters are considered during NVC analysys: presence of enlarged and giant capillaries, haemorrhages, oedema, loss of capillaries and /or avascular areas, disorganisation of the vascular array (magnification 200x).

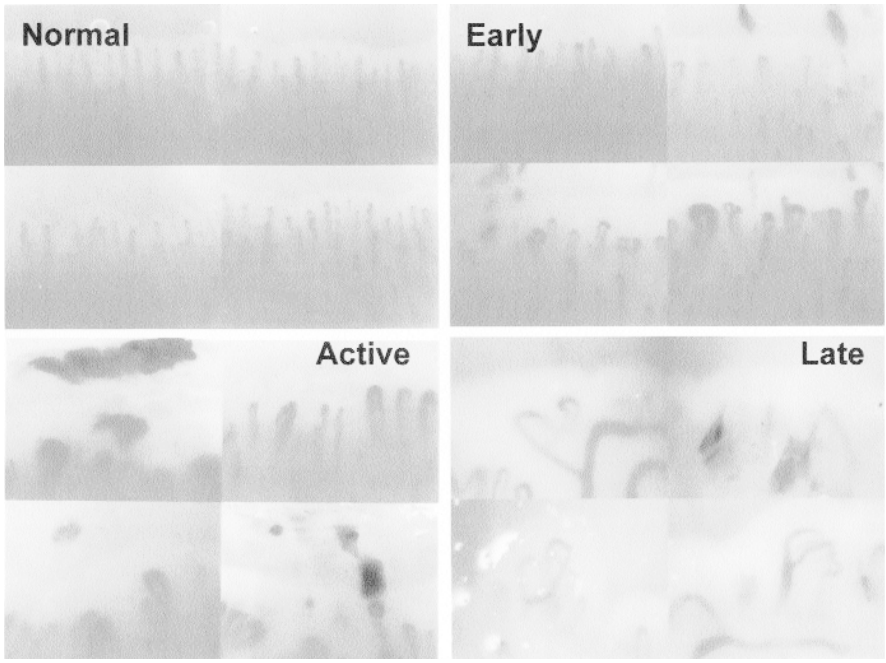

Fig. 4. The NVC patterns identified within the "scleroderma pattern" include: "Early" NVC pattern: few enlarged/giant capillaries, few capillary haemorrhages, relatively well-preserved capillary distribution, no evident loss of capillaries; "Active" NVC pattern: frequent giant capillaries, frequent capillary haemorrhages and oedema, moderate loss of capillaries, mild disorganisation of the capillary architecture, absent or mild ramified capillaries; "Late" NVC pattern: irregular enlargement of the capillaries, few or absent giant capillaries and haemorrhages, severe loss of capillaries with extensive avascular areas, disorganisation of the normal capillary array, ramified/bushy capillaries (magnification 200x).

are characterized by a wide range of different morphological presentations.

The scleroderma capillaroscopic pattern. Enlarged loops, architectural disorganization, loss of capillaries, haemorrhages, angiogenesis and avascular areas characterize more than 95% of patients with overt SSc. Therefore, the term "scleroderma pattern" includes all these sequential capillaroscopic changes typical of microvascular involvement in SSc and represents an important diagnostic criterium (57, 58). In a recent study, microvascular alterations as detected by capillaroscopy in patients with SSc, have been reclassified in three different patterns (59) (Fig. 4). The patterns identified within the "*scleroderma pattern*" include:

"Early" pattern: few enlarged/giant capillaries, few capillary haemorrhages, relatively well-preserved capillary distribution, no evident loss of capillaries;

"Active" pattern: frequent giant capillaries, frequent capillary haemorrhages, moderate loss of capillaries, mild disorganisation of the capillary architecture, absent or mild ramified capillaries;

"Late" pattern: irregular enlargement of the capillaries, few or absent giant capillaries and haemorrhages, severe loss of capillaries with extensive avascular areas, disorganisation of the normal capillary array, ramified/bushy capillaries.

The capillaroscopic aspects observed in DM and UCTD are generally reported as a "scleroderma-like pattern".

In conclusion, the presence of one of the above microvascular alterations indicates the a secondary RP and a CTD must be investigated.

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