Criteria for the Classification of Early Systemic Sclerosis

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ABSTRACT. We propose criteria for the early diagnosis and classification of systemic sclerosis that reflect the vascular and serological advances of the last 2 decades. (J Rheumatol 2001;28:1573–6)

Key Indexing Terms:
SCLERODERMA SYSTEMIC SCLEROSIS RAYNAUD'S PHENOMENON
CLASSIFICATION CRITERIA EARLY CONNECTIVE TISSUE DISEASE

The Preliminary Criteria for the Classification of Systemic Sclerosis proposed by a committee of the American Rheumatism Association in 1980[1] were intentionally designed to be specific rather than sensitive to minimize false positive diagnoses. Subsequently, improvements in the physiologic (cold induced digital artery vasospasm) and questionnaire (validated questions) detection of persons with Raynaud's phenomenon (RP), widespread use of wide-field nailfold microscopy, and more precise autoimmune serology using rapidly-dividing human cell substrates (HEp-2 cells, a rapidly-dividing human laryngeal epithelial cell carcinoma cell line used in indirect immunofluorescence assays to detect the centromere and topoisomerase-I autoantibodies) have identified many persons with features of SSc who do not fulfill these preliminary criteria (which require taut skin proximal to the metacarpophalangeal joints or multiple minor criteria).

Further distinctions between SSc patients with limited (lSSc) or diffuse cutaneous (dSSc) involvement (Table 1) make it intuitively apparent that limited cutaneous, as well as the absence of cutaneous, involvement need not prevent the diagnosis of SSc, which is a multisystem, multistage disorder marked by variable expression[2]. It is the purpose of this essay to propose criteria for the early diagnosis (and classification) of SSc that reflect the vascular and serological advances of the last 2 decades. The cornerstone of these criteria is the phenomenon originally described by Maurice Raynaud in 1862[3]. These criteria are presented to stimulate their validation (or refutation) in prospective series of early patients.

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Submitted August 10, 2000; revision accepted January 5, 2001.

Raynaud's Phenomenon (RP)

Criteria for the diagnosis of primary RP (pRP), which can be defined as episodic, bilateral, di- or triphasic (pallor, cyanosis, suffusion) vascular reactions of the fingers, toes, ears or nose, have been proposed[4]. There are a number of assistive devices one can use to diagnose RP, including validated questionnaires[5], color charts (which integrate pallor, cyanosis or suffusion with skin pigment)[6], a cold stimulus (extreme cold should be avoided, as it can induce vasodilatation via the hunting response of Lewis), the rewarming of skin after defined cold exposure (skin rewarming is delayed in RP)[7], or a quantitative measure of cold induced vasospasm (Nielsen test, laser Doppler ultrasound, thermography, skin thermistor measurements, thermosensitive crystals, and others)[8,9].

RP, when documented objectively, is proposed here as the single major criterion for the diagnosis of the most limited form of limited cutaneous SSc (see Table 2 for proposed definitions of lSSc and lcSSc, the latter synonymous with CREST — calcinosis, Raynaud's phenomenon, esophageal hypomotility, sclerodactyly, telangectasia). When RP is reported by history only, we propose the requirement that the patient be *both* capillary and serology positive (a serology selective for SSc). Two conditions, dermatomyositis and polyarteritis nodosa, can be associated with scleroderma-like nailfold capillary abnormalities and RP. The cutaneous features of these 2 diseases distinguish them from SSc[10]. It is likely that the experienced clinician's judgement regarding the presence or absence of RP is as powerful a tool as any of the technologies mentioned[11]. Serologies selective for connective tissue diseases (CTD) other than SSc — such as Sjögren's syndrome, systemic lupus erythematosus (SLE), or antineutrophil cytoplasmic autoantibody (ANCA) positive vasculitis — or nonselective serology (e.g., single stranded DNA autoantibodies) do not

Table 1. Constellations of criteria for diagnosis.

lSSc:	RP (objective documentation)	
	plus any one:	SSc-type nailford capillary pattern
		or
		SSc selective autoantibodies
	or	
	RP (subjective only)	
	plus both:	SSc-type nailfold capillary pattern
		and
		SSc selective antibodies (see Table 2)
lcSSc:	criteria for lSSc	
	plus:	distal cutaneous changes
dcSSc:	criteria for lSSc	
	plus:	proximal cutaneous changes
Diffuse fasciitis with eosinophilia (DFE):		
		proximal cutaneous changes without criteria for lSSc or lcSSc

qualify a patient for the diagnosis of lSSc, but may participate in the diagnosis of an overlap syndrome, where clinical features of 2 or more CTD are present.

The absence of RP in a patient suspected of having SSc must be viewed with suspicion and should be supported by a normal nailfold capillary examination. This introduces the related group of disorders called fasciitis (diffuse fasciitis with eosinophilia or eosinophilic fasciitis)[12]. These disorders are characterized by the absence of RP, by normal nailfold capillaries, and by sparing of the digits and often the hands, i.e., peripheral sparing of skin changes. Of course, there are many other conditions in which RP may be present and in which the nailfold capillary examination is normal, including hypertension, beta blocker therapy, diabetes mellitis, atherosclerosis, hyperviscosity syndromes, and fibromyalgia. These are beyond the purview of this essay. The reader is referred to standard rheumatologic texts and reviews[13-18]. The reassurance of patients with RP whose nailfold capillaroscopy and serology are negative is important from the individual and the socioeconomic standpoint. The unusual association of morphea and peripheral vasospasm (RP) in the same patient is not included here.

Conclusions

The original vascular hypothesis, as stated by Campbell, *et al* in 1975, has been incorporated into the diagnosis and management of SSc only to a limited degree[19]. The introduction of angiotensin converting enzyme inhibitors and their dramatic effects in the management of scleroderma renal crisis is a striking example of the benefits to the patient with SSc of vascular considerations[20]. We have attempted to incorporate microvascular and autoimmune techniques into the early diagnosis of the more limited forms of SSc. Validation of these preliminary criteria will be important for their further definition.

If patients with RP are followed for more than 10 years, about 1/10 develops a rheumatic or connective tissue disease. The obvious challenge is to predict the one in 10 at initial visit. Thus far, nailfold capillaroscopy and indirect immunofluorescence using HEp-2 cells as substrate are the 2 truly predictive variables of a transition to SSc, which represents three-fourths of all patients who undergo transition. The remaining fourth consists of patients who develop Sjögren's syndrome, lupus (SLE), rheumatoid arthritis, vasculitis, and myositis, in order of decreasing frequency. It is predicted that the strict definition of primary RP and the use of the limited subsets of SSc proposed here will reduce the number of patients with RP progressing to connective tissue disease 4-fold, to between 2 and 3% over 10 years. It is hoped that these suggestions will promote discussion and lead to formal validation of proven criteria for the diagnosis of early SSc.

Note Added in Proof:

In initial attempts to "test" these proposed criteria, earlier comments of one of us (TAM) are relevant: In 1985, the Pittsburgh experience (1972–83) of 639 patients with SSc included 315 diffuse (49%) and 324 limited. Of the latter group, 134 (21% of total SSc, 41% of limited SSc) did not fulfill the *major* preliminary ARA criterion of 1980, and 67 (10.5% of total SSc, 20% of limited SSc) did not satisfy either the major or 2 of the 3 minor criteria[23]. With present nailfold capillary and serologic capability, it is expected that most, if not all, of these 134 SSc patients would fall within either the lSSc or the lcSSc categories proposed.

A second paper "test" of these proposed criteria may also be relevant: Senecal, *et al* reviewed the records of 259 French Canadian patients, diagnosed as "definite SSc," of which 29 were considered diffuse (truncal skin involvement), 78 intermediate (not truncal, but otherwise proximal to metacarpophalangeal joints), and 152 limited (sclero-

Table 2. Proposed criteria for limited forms of SSc (lSSc).

Limited SSc (lSSc):

Raynaud's phenomenon (RP), objectively documented by

1. Direct observation of any 2 of
   - A. pallor (well demarcated whitening of acral skin)
   - B. cyanosis (dusky blueness, which disappears on rewarming)
   - C. suffusion (well demarcated redness)

or 2. Direct measurement of response to cold by
   - A. objective evidence of delayed recovery after cold challenge
   - B. Nielsen test[8] or equivalent (see text)

plus 1. abnormal widefield nailfold capillaroscopy (consisting of dilation and/or avascular areas)[21]

or 2. SSc selective autoantibodies (anticentromere, antitopoisomerase I, anti-fibrillarin, anti-PM-Scl, anti-fibrillin or anti-RNA polymerase I or III in a titer of 1:100 or higher)[22]

If RP is subjective only, both SSc capillary pattern and SSc selective autoantibodies (in titer > 1:100) are required to define lSSc. lSSc can overlap with any other disease.

Limited cutaneous SSc (lcSSc):

In addition to the criteria for lSSc, lcSSc patients must demonstrate cutaneous involvement distal to the elbows, knees, and clavicles. Put the other way round, skin tautness of the fingers, hands, forearms, legs, feet, toes, neck, and face in the absence of skin tautness of the arms, chest, abdomen, back, or thighs (which defines diffuse cutaneous SSc), in addition to the criteria for lSSc, defines lcSSc. Also, lcSSc can overlap with any other disease (including type I diabetes mellitus), CREST (calcinosis, RP, esophageal involvement, sclerodactyly, and telangectasia) is a synonym for lcSSc.

dactyly only plus Raynaud's). Two-thirds of the 152 patients with limited SSc did not fulfill 1980 ARA preliminary criteria. Nonetheless, 50% of limited patients were anticentromere antibody positive and two-thirds had significant nailfold capillary abnormalities. Thus a large proportion of the ARA preliminary criteria negative patients from Montreal would be included in the present lSSc category. By adding nailfold capillary findings and anticentromere serology, the sensitivity of ARA preliminary criteria was improved from 33% to 92%[24]. Somewhat different approaches to characterize SSc sine scleroderma[25] and undifferentiated connective tissue disease have been published recently[26].

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