

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)

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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 1980¹ 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 expression². 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 1862³. These criteria are presented to stimulate their validation (or refutation) in prospective series of early patients.

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 proposed⁴. There are a number of assistive devices one can use to diagnose RP, including validated questionnaires⁵, 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, telangiectasia). 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 SSc¹⁰. 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 mentioned¹¹. 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

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Table 1. Constellations of criteria for diagnosis.

ISSc:	RP (objective documentation) plus any one: SSc-type nailfold 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 ISSc plus: distal cutaneous changes
dcSSc:	criteria for ISSc plus: proximal cutaneous changes
Diffuse fasciitis with eosinophilia (DFE):	proximal cutaneous changes without criteria for ISSc or lcSSc

qualify a patient for the diagnosis of ISSc, 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 mellitus, atherosclerosis, hyperviscosity syndromes, and fibromyalgia. These are beyond the purview of this essay. The reader is referred to standard rheumatologic texts and reviews¹³⁻¹⁸. 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 degree¹⁹. 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 considerations²⁰. 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 criteria²³. 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 ISSc 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 (ISSc).

Limited SSc (ISSc):

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 test⁸ 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 ISSc. ISSc can overlap with any other disease.

Limited cutaneous SSc (lcSSc):

In addition to the criteria for ISSc, 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 ISSc, defines lcSSc. Also, lcSSc can overlap with any other disease (including type I diabetes mellitus), CREST (calcinosis, RP, esophageal involvement, sclerodactyly, and telangiectasia) 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 ISSc 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 scleroderma²⁵ and undifferentiated connective tissue disease have been published recently²⁶.

REFERENCES

1. Masi AT, Rodnan GP, Medsger TA Jr, et al. Subcommittee for Scleroderma Criteria of American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980;23:581-90.
2. LeRoy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988;15:202-5.
3. Raynaud, M. De l'asphyxie locale de la gangrène symétrique des extrémités [Local asphyxia and symmetrical gangrene of the extremities]. Paris: L. Leclerc, Rignaux; 1862. [see Selected Monographs; London: The Society; 1888].
4. LeRoy EC, Medsger TA Jr. Raynaud's phenomenon: a proposal for classification. *Clin Exp Rheumatol* 1992;10:485-8.
5. Weinrich MC, Maricq HR, Keil JE, McGregor AR, Diat F. Prevalence of Raynaud phenomenon in the adult population of South Carolina. *J Clin Epidemiol* 1990;43:1343-9.
6. Maricq HR, Weinrich MC. Diagnosis of Raynaud's phenomenon assisted by color charts. *J Rheumatol* 1988;15:454-9.
7. Lau CS, Khan F, Brown R, McCallum P, Belch JJ. Digital blood flow response to body warming, cooling, and rewarming in patients with Raynaud's phenomenon. *Angiology* 1995;46:1-10.
8. Nielsen SL. Raynaud phenomena and finger systolic pressure during cooling. *Scand J Clin Lab Invest* 1978;38:765-70.
9. Maricq HR, Weinrich MC, Valter I, Palesch YY, Maricq JG. Digital vascular responses to cooling in subjects with cold sensitivity, primary Raynaud's phenomenon, or scleroderma spectrum disorders. *J Rheumatol* 1996;23:2068-78.
10. Miller FW. Inflammatory myopathies: polymyositis, dermatomyositis, and related conditions. In: Koopman WJ, editor. *Arthritis and allied conditions. A textbook of rheumatology*. 13th ed. Baltimore: Williams & Wilkins; 1997:1407-31.
11. Silman AJ, Black CM, Welsh KI. Epidemiology, demographics, genetics. In: Clements PJ, Furst DE, editors. *Systemic sclerosis*. Baltimore: Williams & Wilkins; 1996:23-49.
12. Silver RM. Variant forms of scleroderma. In: Koopman WJ, editor. *Arthritis and allied conditions. A textbook of rheumatology*. 13th ed. Baltimore: Williams & Wilkins; 1997:1465-80.
13. Medsger TA Jr. Systemic sclerosis (scleroderma): Clinical aspects. In: Koopman WJ, editor. *Arthritis and allied conditions. A textbook of rheumatology*. 13th ed. Baltimore: Williams & Wilkins; 1997:1437-9.

14. Seibold JR. Connective tissue diseases characterized by fibrosis: scleroderma. In: Kelley WN, Harris ED Jr, Ruddy S, Sledge CB, editors. *Textbook of rheumatology*. 5th ed. Philadelphia: WB Saunders Co.; 1997:1133-62.
15. Black CM, Stephens C. Systemic sclerosis (scleroderma) and related disorders. In: Maddison PJ, Isenberg DA, Woo P, Glass DN, editors. *Oxford textbook of rheumatology*. 1st ed. Oxford: Oxford University Press; 1993:771-89.
16. Wigley FM. Raynaud's phenomenon and other features of scleroderma, including pulmonary hypertension. *Curr Opin Rheumatol* 1996;8:561-8.
17. Belch JF, Zurier RB, editors. *Connective tissue diseases*. New York: Chapman & Hall Medical; 1995.
18. Steen VD. Problems in the diagnosis of Raynaud's phenomenon. In: Klippel JH, Dieppe PA, editors. *Rheumatology*. 1st ed. St. Louis: Mosby; 1994:11.1-11.3.
19. Campbell PM, LeRoy EC. Pathogenesis of systemic sclerosis: a vascular hypothesis. *Semin Arthritis Rheum* 1975;4:351-68.
20. Whitman HH III, Case DB, Laragh JH, et al. Variable response to oral angiotensin-converting-enzyme blockade in hypertensive scleroderma patients. *Arthritis Rheum* 1982;25:241-8.
21. Maricq HR, LeRoy EC. Patterns of finger capillary abnormalities in connective tissue disease by "wide-field" microscopy. *Arthritis Rheum* 1973;16:619-28.
22. Tan EM. Antinuclear antibodies: diagnostic markers for autoimmune diseases and probes for cell biology. *Adv Immunol* 1989;44:93-151.
23. Medsger TA Jr. Comment on Scleroderma Criteria Cooperative Study. In: Black CM, Myers AR, editors. *Current topics in rheumatology: systemic sclerosis (scleroderma)*. New York: Gower Medical Publishing; 1985:16-7.
24. Lonzetti LS, Joyal F, Raynauld JP, et al. Updating the American College of Rheumatology preliminary classification criteria for systemic sclerosis: addition of severe nailfold capillaroscopy abnormalities markedly increases the sensitivity for limited scleroderma. *Arthritis Rheum* 2001;44:735-6.
25. Poormoghim H, Lucas M, Fertig N, Medsger TA Jr. Systemic sclerosis sine scleroderma: demographic, clinical, and serologic features and survival in forty-eight patients. *Arthritis Rheum* 2000;43:444-51.
26. Mosca M, Neri R, Bombardieri S. Undifferentiated connective tissue diseases: A review of the literature and a proposal for preliminary classification criteria. *Clin Exp Rheumatol* 1999;17:615-20.