Criteria for the Classification of Early Systemic Sclerosis

E. CARWILE LeROY and THOMAS A. MEDSGER Jr

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

Raynaud in 1862. 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 proposed. There are a number of assistive devices one can use to diagnose RP, including validated questionnaires, color charts (which integrate pallor, cyanosis or suffusion with skin pigment), a cold stimulus (extreme cold should be avoided, as it can induce vasodilation via the hunting response of Lewis), the rewarming of skin after defined cold exposure (skin rewarming is delayed in RP), or a quantitative measure of cold induced vasospasm (Nielsen test, laser Doppler ultrasound, thermography, skin thermistor measurements, thermosensitive crystals, and others).

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 SSc. 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.

Serologies selective for connective tissue diseases (CTD) other than SSc — such as Sjogren’s syndrome, systemic lupus erythematosus (SLE), or antineutrophil cytoplasmic autoantibody (ANCA) positive vasculitis — or nonselective serology (e.g., single stranded DNA autoantibodies) do not

The Preliminary Criteria for the Classification of Systemic Sclerosis proposed by a committee of the American Rheumatism Association in 1980 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. 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
qualify a patient for the diagnosis of lSSc, but may partici-
pate 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)\textsuperscript{12}. These disor-
ders are characterized by the absence of RP, by normal nail-
fold 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
reviews\textsuperscript{13-18}. The reassurance of patients with RP whose
nailfold capillaroscopy and serology are negative is impor-
tant 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, \textit{et al} in 1975, has been incorporated into the diagnosis and
management of SSc only to a limited degree\textsuperscript{19}. The intro-
duction 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\textsuperscript{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 transi-
tion. 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.

\textbf{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 \textit{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\textsuperscript{23}. With present
nailfold capillaroscopy 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, \textit{et al} reviewed the records of 259
French Canadian patients, diagnosed as “definite SSc,” of
which 29 were considered diffuse (truncal skin involve-
ment), 78 intermediate (not truncal, but otherwise proximal
to metacarpophalangeal joints), and 152 limited (sclero-

\begin{table}
\centering
\caption{Constellations of criteria for diagnosis.}
\begin{tabular}{ll}
\hline
lSSc: & 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 \\
deSSc: & criteria for ISSc \\
& plus: proximal cutaneous changes \\
Diffuse fasciitis with eosinophilia (DFE): & proximal cutaneous changes without criteria for ISSc or lcSSc \\
\hline
\end{tabular}
\end{table}
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, antitopoisoomerase 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 telangectasia) is a synonym for lcSSc.

REFERENCES


