When is scleroderma really scleroderma?

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*The Journal of Rheumatology* is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
In this issue of The Journal LeRoy and Medsger propose criteria for the early diagnosis of systemic sclerosis (scleroderma, SSc), arguing that new advances in medical technology provide the opportunity to detect disease in patients who do not meet current criteria for the classification of scleroderma established in 1980. This editorial addresses the value of establishing these new criteria for the classification of scleroderma.

Disease can be thought of as a continuous process that spans a varied clinical phenotype from asymptomatic biological abnormalities to a severe life threatening process. Early detection of a disease has many potential advantages including the opportunity to prevent disease progression. The challenge is to have sensitive and specific tools that accurately identify the disease correctly. Incorrect identification of a disease can lead the clinician into the wrong treatment pathway, the patient into a state of undue anxiety, and the scientist into a maze of misdirected efforts. Unfortunately, we often get fooled into the wrong decision in medicine by using our existing diagnostic tools because human disease is complex and the outcomes are unpredictable. An active biological process can be detected that never expresses itself as a clinical disease. For example, patients can have persistent autoantibodies in their serum consistent with an autoimmune process but never develop active disease. We also recognize that a well defined biological insult may cause different clinical problems. For example, hepatitis B infection can occur without symptoms or it can cause a transient rash and polyarthritis, an acute or chronic hepatitis, or a systemic vasculitis. We can also be fooled by tissue responses to different insults that may appear clinically the same. Tissue fibrosis can occur after exposure to certain drugs, infection, chemicals, autoimmune injury, or tissue hypoxia. Even a disease known to be secondary to a single gene defect can express itself differently among patients. For example, the level of fetal hemoglobin produced by the affected patient influences the severity of the expression of sickle cell anemia.

SSc (scleroderma) is a complex disease that has a highly variable expression and whose pathogenesis is still poorly understood. Our current bias is that the name “scleroderma” comprises 2 different categories. The most popular classification is to divide scleroderma into 2 subtypes (limited and diffuse) defined by the degree of skin involvement. The diffuse group has truncal and acral skin involvement. Several previous classifications would have further subdivided “limited scleroderma” into several different groups. Reviews of the merits of a 3-subtype versus 2-subtype classification suggest that patients with sclerodactyly alone are different than patients with more proximal skin changes. These patients have features of the CREST syndrome, have a strong and specific association with anticentromere antibody, have a better longterm survival rate, are more likely to have severe digital ischemia, and can present with isolated pulmonary hypertension in the absence of lung fibrosis. However, a panel of experts felt that there were no clear clinical distinctions among patients with limited skin changes to justify more than one group. Limited scleroderma, therefore, includes the CREST syndrome, the acrosclerosis types I and II scleroderma of Barnett, systemic sclerosis sine scleroderma, and other variations. It is also argued that the term “CREST syndrome” be replaced by “limited scleroderma” because many of the CREST patients do not have all the features of CREST, and patients with late diffuse cutaneous disease can develop calcinosis and telangiectasia. However, this classification issue should be reexamined in population based longitudinal studies. Not all patients with limited scleroderma have the striking features of CREST syndrome, and autoantibody associations are distinctly different among these patient groups. In addition, many of the patients with limited scleroderma do not meet American College of Rheumatology (ACR) criteria.

ACR criteria for a diagnosis of scleroderma insist that the patient have proximal scleroderma skin changes or specific physical findings. Scleroderma skin changes proximal to
the metacarpophalangeal or metatarsophalangeal joints were
found to be a sensitive (91%) and highly specific (99.8%)
criterion for the classification of definite scleroderma. In
fact, these criteria were designed for research purposes and
thus exclude individuals from investigations when the
disease is not fully expressed. These criteria assure that
different studies have comparable patients but may exclude
patients with early, mild, or limited disease. Roughly 75% of
patients with Barnett’s Type 1 or sclerodactyly alone meet
ACR minor criteria for scleroderma5. The current theory of
the pathogenesis of scleroderma is most often modeled after
the diffuse disease, and the majority of clinical interventions
target the skin disease as a primary outcome. The American
Rheumatism Association criteria for the classification of
definite scleroderma should continue to be recognized as the
standard for research while any new subclassification of
disease is studied further.

It seems logical to attempt to refine the current criteria
for classification of scleroderma. New technology allows
for sensitive testing that may identify patients who have
early scleroderma or a mild expression of the disease that
previously would not be recognized. Patients could be
regrouped according to specific autoantibodies, objective
testing of vascular disease, or longitudinal data rather than
by the consensus of experts defining clinical phenotypes.
Recent reports have reemphasized a group of patients
without scleroderma skin changes who have clinical
features and laboratory data consistent with a scleroderma
disease course12,13. Therefore, it is argued that by coupling
specific sensitive markers of disease with known clinical
features the definition of disease will be more inclusive and
therefore early scleroderma can be detected and treated.

There are 3 features of scleroderma that should be
present before suggesting that the patient has systemic sclero-
sis: tissue fibrosis, unique vasculopathy, and evidence of a
specific autoantibody response. The diagnosis is clear when
skin fibrosis or scleroderma is present. Fibrosis of other
organs (e.g., the lungs) is not specific and must be coupled
with one of the other features of scleroderma to consider the
diagnosis. The vascular disease almost always clinically
manifests itself as Raynaud’s phenomenon (RP) or cuta-
neous capillary abnormalities, best characterized at the nail-
fold14. However, the presence of RP or nailfold capillary
abnormalities is not specific for scleroderma.

RP is seen in 3–15% of the population and can be diag-
nosed by the observant clinician without complex diagnostic
studies15. It has been suggested that digital pressure
responses to cooling may distinguish primary from
secondary RP6, but such testing is not simple to perform
and longitudinal studies have not been conducted to define
its use in the diagnosis of early disease. RP and the presence
of specific risk factors predict patients who likely have a
connective tissue disease. These risk factors include the
presence of severe RP (particularly if digital ischemic events
occur), late onset of RP, a positive test for antinuclear anti-
bodies, and nailfold capillary abnormalities17. Patients who
have one or more of these risk factors clearly need to be
followed closely, but when do we make a diagnosis of a
specific disease like scleroderma?

Patients presenting with RP and symptoms of a connec-
tive tissue disease who have nailfold capillary loop abnor-
malities and/or abnormal serology can develop scleroderma.
One university based longitudinal survey found that about
20% of patients presenting with RP develop a definite diag-
nosis within a relatively short period of time18. Several cross
sectional surveys of patients with RP have suggested that
those patients with nailfold capillary abnormalities or
specific scleroderma autoantibodies (e.g., anti-centromere)
are more likely to have scleroderma17. However, population
based longitudinal studies are lacking and it is clear that
many patients stay in an undiagnosed category without
further disease expression.

So, why define new criteria for the diagnosis and classi-
fication for early scleroderma (ISSc) as proposed by LeRoy
and Medsger19? What is the value of making a new category?
A new category acknowledges that a group of scleroderma
patients may exist with subtle features of the disease. These
patients may progress to more serious disease or they may
benefit from scleroderma-specific therapy. This new sclero-
derma category would also allow for prospective investiga-
tions of these patients, which may help us understand the
disease and its course better. In addition, careful classifica-
tion will provide uniform standards that investigators and
clinicians can use as a standard reference.

What are the dangers of this early diagnosis? The main
danger is that they may not have “scleroderma.” Features of
“early scleroderma” that do not associate with disease
progression may not be relevant. As Drs. LeRoy and
Medsger suggest, predictors of the course of disease should
be validated by longitudinal studies before any new classifi-
cation is accepted. Patients and their doctors often attach
themselves to a diagnosis and fear the worst, even if they are
in a good prognosis group. Doctors may overdiagnose or
become too aggressive with therapy. Scientists may begin to
think all clinical subtypes are the same disease and not
appreciate important biological differences. There are
several reasons to sacrifice sensitivity in detection and
require more specific measures before making a definite
diagnosis. Patients should not be forced into a definite diag-
nosis prematurely because it may inappropriately imply a
specific prognosis or disease course. Withholding a definite
diagnosis gives us the opportunity to observe the natural
events before inappropriate treatment is given. Solid and
specific diagnostic criteria provide clarity for investigators
attempting to study and understand a disease process. There
is no doubt that the earlier the diagnosis, the better.
However, understanding the process may be more important
both clinically and scientifically.
Terms like “undifferentiated connective tissue disease with features of scleroderma” provide an opportunity to recognize the presence of a biological process that may never fully express a specific disease or declare a definite outcome. It keeps the clinical mind open to appreciate the complexity of the situation and recognize the varied course the process can take. At the same time, it alerts the patient and physician to the presence of a dangerous process that may need attention. Keeping an unclear clinical situation in the “undifferentiated” category also provides clarity for scientific investigations.

The progress we have made in understanding the biology of scleroderma emphasizes the complexity of the disease. While we have new tools to measure RP, to see the microvascular changes, and to measure autoantibodies, we must take great care before we lump patients with subtle findings into one diagnostic category. It seems that our classification of patients with features of early disease can best be served by calling these early patients undifferentiated connective tissue disease with features of scleroderma. This does not alter their clinical management, it does not alter the idea that they have a unique biological process, and it does not exclude them from scientific investigations. It just keeps them undiagnosed.

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REFERENCES