The Scleroderma Education Project™

"Diffuse"? "Limited"? "Overlap"? "Sine"?: Know Your Terms and Your Antibody Type

Background – 25 Years Ago

The names used for referring to the scleroderma family of disease are very confusing for a number of reasons. Historically, there were two known forms of systemic scleroderma: diffuse (originally called Progressive Systemic Sclerosis or PSS) and limited (originally called CREST Syndrome – see the *Scleroderma FAQ* for full details on the acronym "CREST"). The words "diffuse" or "limited" are associated with how much skin involvement is eventually likely to occur. In diffuse systemic scleroderma, the pattern of skin changes is "diffuse," potentially involving the entire body. In contrast, in limited systemic scleroderma, the skin changes are more "limited," usually just involving the face, hands, and feet.

Back 25 years ago, two antibodies were known to be associated with these two forms of systemic scleroderma. Scl-70 (anti-topoisomerase I) antibodies were associated with diffuse scleroderma, and anti-centromere (ACA) antibodies were associated with limited scleroderma/CREST. The association was strong but one-way. If you had anti-Scl70 antibodies, then assuming you had suitable other symptoms, you would be diagnosed with diffuse systemic scleroderma. However, you might have clear diffuse scleroderma symptoms and skin changes but not test positive for Scl-70 antibodies. In a similar manner, if you had positive anti-centromere antibodies and corresponding symptoms, you would receive a diagnosis of limited systemic scleroderma/CREST syndrome, but in some cases you would appear to have all the symptoms of CREST but test negative for anti-centromere antibodies.

Another related diagnosis used back then and now is MCTD (Mixed Connective Tissue Disorder), which is associated with a different antibody (U1-RNP). MCTD can have a number of symptoms commonly seen in scleroderma, e.g., Raynaud's and skin changes, but also has symptoms more commonly seen in lupus and rheumatoid arthritis. A fourth term – UCTD (undifferentiated connective tissue disease) was (and still is) used to describe patients who have symptoms and lab results that appear to be associated with some type of autoimmune disorder that might eventually turn into scleroderma, lupus, MCTD, rheumatoid arthritis, etc., but it just isn't clear yet which autoimmune diagnosis will eventually be appropriate.

Fast Forward to Today

We now know that the reason why some patients with clear diffuse scleroderma skin changes did not test positive for Scl70 antibodies is that there areat least two other antibodies associated with diffuse skin changes. RNA Polymerase III antibodies are about equally common with Scl-70 antibodies. U3-RNP (fibrillarin) antibodies are much less common but are also associated with diffuse skin changes. Similarly, there is a significantly less common antibody – Th/To – that is associated with a second form of scleroderma that is clinically similar to anti-centromere positive limited scleroderma, but with a slightly different symptom profile.

Researchers and an increasing number of clinicians are starting to look at scleroderma as a family of diseases based on specific antibody type. Depending on the research, there are at least nine or ten different antibodies associated with various variants of systemic scleroderma (plus ANA/antibody negative scleroderma – see Note 1 below). These antibodies are currently grouped into three broad categories, but different researchers place some of these antibodies into these categories a bit differently. Here is one category grouping that is fairly common:

Antibody	Estimated Prevalence	Classifi-cation*	Testing Available	Clinical Associations	Notes
Anti-centromere (ACA)	20 to 30%	Limited	Yes	CREST, PAH	Skin changes often delayed for many years
Anti-Scl-70 (Topoisomerase)	15 to 20%	Diffuse	Yes	ILD	Rapid skin thickening, early internal organ involvement
Anti-RNA Polymerase III	~ 20%	Diffuse	Yes	PAH, cardiac, kidney	Increased mortality
Anti-Th/To	2 to 5%	Limited	Yes	PAH, ILD	Worse prognosis than ACA
Anti-PM-Scl	2 to 3%	Overlap	Yes	Myositis (muscle)	Good prognosis, often responsive to steroids
Anti-U3-RNP (Fibrillarin)	~ 4%	Diffuse	Yes	Myositis, PAH, kidney, cardiac	Seen in younger patients with greater internal organ involvement
Anti-U1-RNP	~ 8%	Overlap	Yes	Myositis, ILD, joint	MCTD. More benign, often responsive to steroids
Anti-Ku	~ 2%	Overlap	Yes	Myositis, ILD	Limited cutaneous involvement
Anti-U11/U12-RNP	~ 3%	Diffuse / Limited	No	ILD	Severe lung fibrosis
Anti-RuvBL1/2	~ 2%	Overlap	No	Myositis	Diffuse cutaneous involvement

Note 1: Recent research literature indicates that about 6% of patients with clear systemic scleroderma symptoms test negative for ANA when done with the correct IFA method. The best guess is that while ANA testing by IFA can detect the presence of up to 150 different antibodies, there are probably some additional scleroderma-related antibodies that can't be detected using this testing method.

Note 2: it is VERY rare for patients to have more than one scleroderma-related antibody (about 2%) when antibody testing is done correctly. However, there is a significant false-positive problem with Scl-70 antibody testing using the two most common testing methods: ELISA and Multiplex. If you have a low-positive Scl-70 antibody result and a second different positive antibody result, the Scl-70 result is usually a false positive that should be ignored. (See the separate article in this series called "False-positive Scl-70 (Topoisomerase) Antibody

Testing: A Major Problem in Systemic Sclerosis Diagnosis" for more information on this important topic.)

"Sine" Scleroderma?

"Sine scleroderma" is a term that is used to describe cases of systemic scleroderma where there is internal organ involvement that is characteristic of scleroderma, but with no skin thickening. As mentioned above, in the research literature, the term that is mostly used to talk about the systemic forms of scleroderma is actually "systemic sclerosis" rather than "systemic scleroderma," as is commonly used in patient oriented literature. The reason for this is that "systemic sclerosis" better reflects that this is a systemic disease that involves "hardening" of connective tissue throughout the body (see the separate article titled "Yes – You DO Have Internal Organ Damage, But..." on this website.) Remember that the word "scleroderma" literally means "hard skin," so when researchers are describing this condition, they are using the full term "systemic sclerosis sine scleroderma" to mean that there is internal organ damage but no skin changes.

Sine scleroderma is described as a rare variant of scleroderma in a number of online articles about scleroderma, but the term rarely appears in scleroderma research literature. In some of the few studies that have looked at the characteristics of patients with sine scleroderma, it is mostly associated with limited forms of scleroderma, rather than diffuse forms, and is generally considered to have a good prognosis. While there can be skin abnormalities, such as telangiectasias and abnormal nailfold capillaries, the skin thickening which is the hallmark symptom of all forms of scleroderma is not present in these patients.

A number of researchers have concluded that so-called "sine scleroderma" is really nothing more than a symptom variant of either the limited or diffuse forms of scleroderma, in the same way that lung involvement is a symptom variant in both forms of the disease. Classically, with limited scleroderma it is very common for patients to have a symptom progression that begins with Raynaud's, is followed by "puffiness" of the fingers, especially in the morning, abnormal nailfold capillaries, and GI symptoms (primarily reflux) for a number of years before actual skin thickening is noted. Major internal organ damage is typically later with limited scleroderma as well, but can sometimes occur early in the disease process, creating the potential for the "sine" condition. In most cases, skin changes do eventually occur even with limited scleroderma, but in other cases they may never reach diagnostic significance during the overall course of the disease.

With the more rapidly progressing diffuse forms of scleroderma, skin changes typically occur earlier and progress more rapidly. However, clinically significant internal organ damage typically appears much earlier than with limited scleroderma, sometimes before even Raynaud's symptoms or skin changes are evident, so the sine state is possible here as well, although less often than with limited scleroderma.

The bottom line is that some clinicians use the term sine scleroderma and others do not, but practically speaking it makes little difference in which treatments are used.

Know Your Antibody!

So why is it important to know your specific antibody type? Basically, while there is still a lot of variability in symptom development and progression even for patients with the same antibody type, there are some very clear differences in symptom risk factors that can affect treatments and ongoing testing. For example, with anticentromere positive limited

scleroderma, there is an increased risk of developing pulmonary artery hypertension (PAH) as a long-term major complication. Regular monitoring of certain measures of lung functioning (DLCO and DLCO/VA in particular) via regular pulmonary function testing is important, since a drop in these measures to certain levels can be a leading indicator of future development of PAH. Another very important example is that for patients with anti-RNA Polymerase III antibodies (pointing to one of the diffuse variants of scleroderma), there is a significant risk of major kidney problems. For patients with this antibody, research suggests that prednisone is not effective as an overall treatment, but, more importantly, it is actually potentially quite dangerous since there is a dose-dependent risk of triggering scleroderma renal crisis – a very serious complication. In contrast, patients with antibodies for some of the overlap syndromes (e.g., U1-RNP (MCTD) or Pm-Scl) often are responsive to steroids without much increased risk of developing scleroderma renal crisis. If you have one of these antibodies, prednisone may be an appropriate treatment option for your doctor to consider.

In a separate article in this series on ANA and antibody testing ("How to Do Scleroderma ANA and Antibody Testing Correctly"), we discuss some major problems that can occur when doing ANA and antibody testing for patients with suspected systemic scleroderma. While we won't repeat most of the information here, below are some key points from that article:

- ANA testing for scleroderma must be done by a method called IFA (indirect immunofluorescence) to be accurate. Otherwise, there is a very significant chance of getting a false negative ANA result which can delay accurate diagnosis for a long period of time.
- With the exception of two reference labs (in the US) that do testing for almost all of the scleroderma related antibodies listed above (RDL and ARUP Reference labs), most testing labs offer very limited so-called "scleroderma antibody screening panels" that may only include one or two scleroderma related antibodies. If the ordering physician is not a scleroderma expert and gets a negative result on one of these limited scleroderma antibody screening panels, s/he may incorrectly infer that a patient does not have scleroderma.
- Any antibody testing for suspected systemic scleroderma should always start with the three most common antibodies: Scl-70, centromere, and RNA Polymerase III. If these are negative, then additional antibody testing for the less common antibodies should follow.