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Classification and Subsetting of Systemic Sclerosis: A Guide to the Natural History of Disease and Prognosis

CHRISTINE PEOPLES, MD

Research Fellow, Division of Rheumatology and Clinical Immunology

ROBYN T. DOMSIC, MD, MPH

Assistant Professor of Medicine, Division of Rheumatology and Clinical Immunology

THOMAS A. MEDSGER JR., MD

Professor of Medicine, Division of Rheumatology and Clinical Immunology

Introduction

Scleroderma (*sclero* = hard, *derma* = skin) is an umbrella term used to describe a group of diseases characterized by cutaneous inflammation and fibrosis. Scleroderma is classified as either localized (limited to the skin) or systemic (involving skin, but also capable of causing internal organ damage).

In this review, we discuss an approach for managing physicians to classify and stage systemic sclerosis, with clues to the natural history of the disease and prognosis.



A patient with systemic sclerosis demonstrating puffy fingers, telangiectasias, calcinosis, and digital tip ulceration.

Clinical Classification of Scleroderma

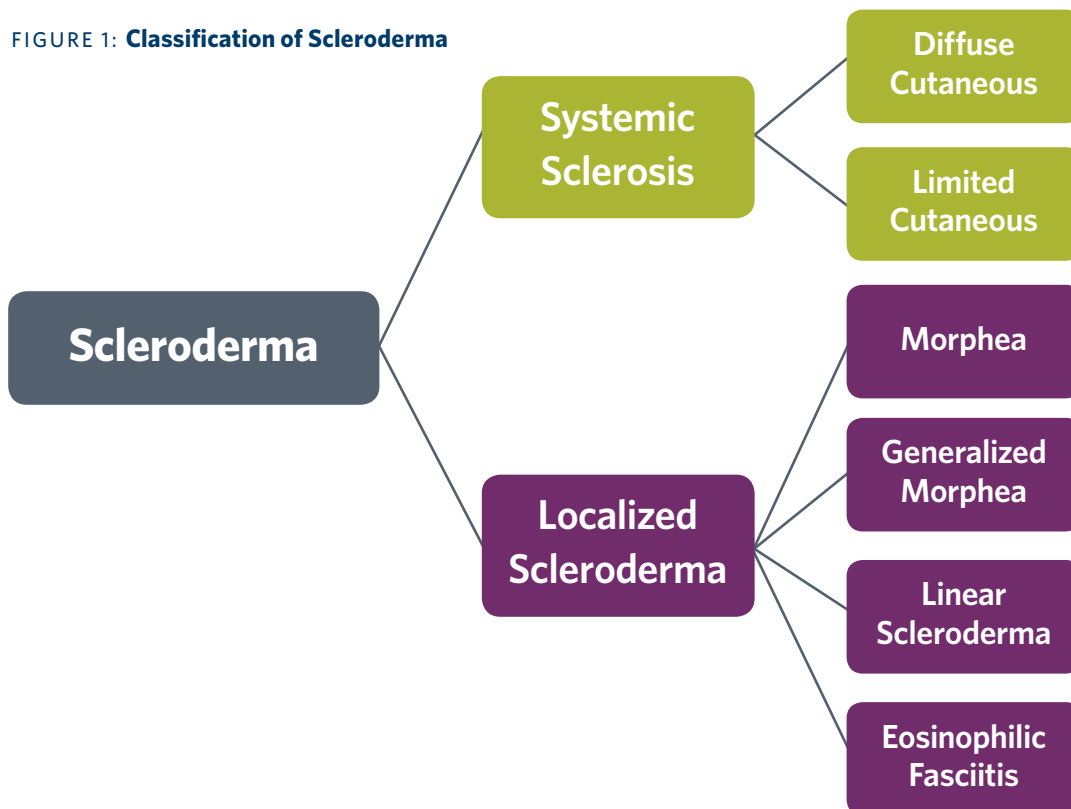
Localized scleroderma, also referred to as circumscribed scleroderma, includes several variants: morphea, generalized morphea, linear scleroderma, and eosinophilic fasciitis (Figure 1). In contrast, systemic sclerosis (SSc) is a complex, multisystem autoimmune disease which can affect the blood vessels and internal organs. The clinical course of SSc ranges from a slowly progressive or non-progressive disorder to a swiftly developing disease affecting multiple internal organs. SSc has the highest case-specific mortality among the rheumatic diseases.¹ The presenting features of SSc and its manifestations are extremely heterogeneous, suggesting that it is a family of closely related disorders rather than a single disease. Nevertheless, there is general agreement that there are two major clinical subsets of SSc.

Cutaneous Classification of Systemic Sclerosis

A patient is considered to have diffuse cutaneous SSc (dcSSc) if he or she has had skin thickening both distal (fingers, hands, forearms) and proximal (upper arms, thighs, chest, abdomen) to the elbows or knees at any time during the illness. Conversely, a patient with limited cutaneous SSc (lcSSc) has either no skin thickening (scleroderma sine scleroderma or ssSSc) or skin thickening that is restricted to the distal extremities (Figure 2). The older term CREST syndrome has now been replaced by lcSSc. Skin thickening involving the face or the neck can occur in either dcSSc or lcSSc and has not been found to influence disease classification.

The standard method for quantification of skin thickness in SSc patients is the modified Rodnan skin score (mRss),² in which 17 different cutaneous sites are graded from

FIGURE 1: **Classification of Scleroderma**



0 (no skin thickening) to 3+ (severe skin thickening). Practitioners should be familiar with the mRss, which can help to distinguish lcSSc from dcSSc and assist in staging of dcSSc (early vs. late, see Table 1).

Overlap syndromes occur in up to 10% of SSc patients, more frequently with lcSSc than with dcSSc. They pose a challenge to the clinician, as there are no strict definitions or accepted management guidelines. We consider an overlap syndrome to be present when a patient has definite SSc and also has clinical features that support an independent diagnosis of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), polymyositis (PM), or dermatomyositis (DM).

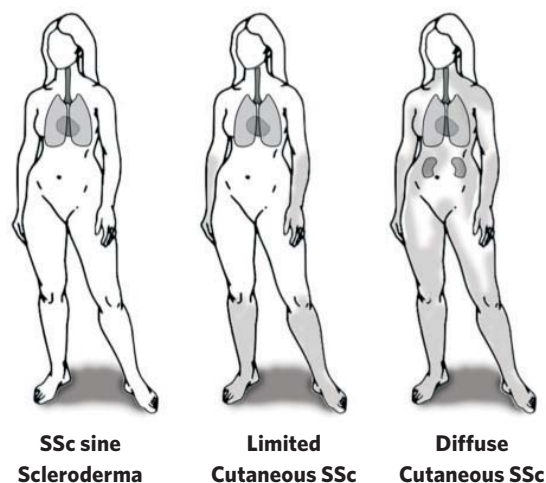
Clinical Manifestations, Staging, and Natural History of SSc

Diffuse Cutaneous SSc

Early in their disease, patients with dcSSc typically have a rapid increase in the mRss, with the majority experiencing a peak in skin score within 12 to 18 months of the first SSc symptom, with slow improvement in skin thickening thereafter. We have developed a method to measure the skin thickness progression rate (STPR),³ which can be calculated by history and skin thickness examination at the time of the first visit. A rapid STPR is an independent predictor of early mortality and risk of “renal crisis” in early dcSSc.³ In our Pittsburgh dcSSc cohort, more than 90% of organ system involvement (gastrointestinal tract, lung, heart, and kidney) is experienced within the first five years of disease and the majority of such complications occur in the first two years.

Most of the “action” in diffuse SSc occurs soon after disease onset in conjunction

FIGURE 2: Clinical Classification of SSc



RT Domsic

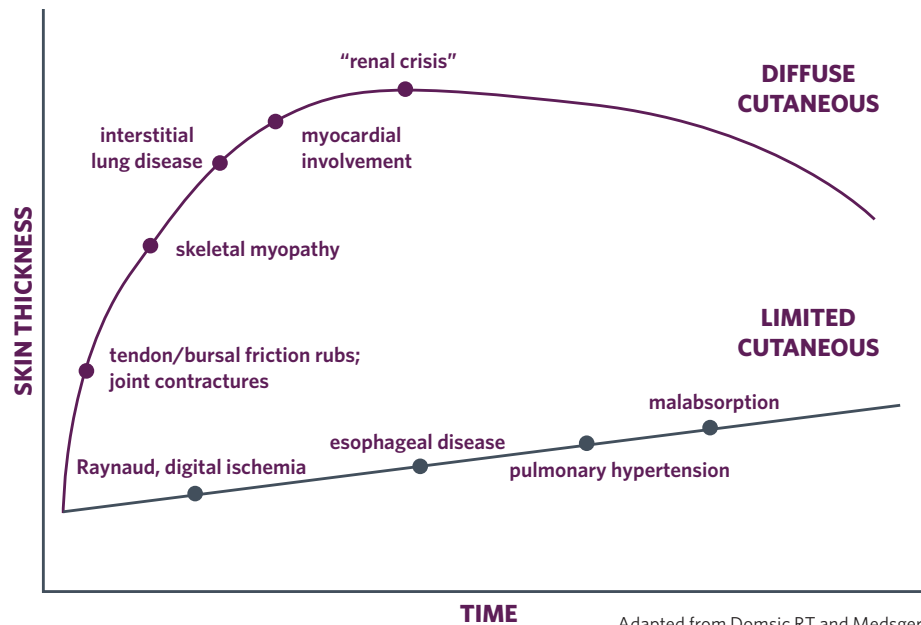
with rapid skin thickening (Figure 3, Page 4). Tendon and/or bursal friction rubs along with the development of contractures at the proximal interphalangeal (PIP) joints are two of the earliest physical exam findings. Other early features include skeletal myopathy, interstitial lung disease, myocardial involvement, and “renal crisis,” not necessarily in the order illustrated in Figure 3. With time, typically after two to three years, skin thickness peaks and slowly improves,

TABLE 1:

How do I know if my patient is developing diffuse cutaneous SSc?

Palpable tendon/bursal friction rubs
Skin thickening prior to the onset of Raynaud symptoms
Rapid progression of skin thickening (rapid STPR)
Generalized pruritus
Finger joint contractures within six months of disease onset
Serum autoantibody either anti-RNA polymerase III or anti-topoisomerase I (Scl-70)
Disease duration of less than 18 months at first visit

FIGURE 3: Natural History of SSc



Adapted from Domsic RT and Medsger, Jr, TA. Chapter 6: Disease Subsets in Clinical Practice. Scleroderma: From Pathogenesis to Comprehensive Management. London: Springer Science and Business Media, LLC; 2012.

accompanied by a considerably lower risk of new internal organ involvement. For these reasons, we define early dcSSc as up to two to three years after disease onset, and late dcSSc as five-plus years after onset.

Clues suggesting that a patient is developing diffuse SSc are listed in Table 1 (page 3). If one or more of these characteristics is present, the patient should be seen again within two to three months for reevaluation. If dcSSc is confirmed, serious consideration should be given to initiating immunosuppressive therapy or prompt referral to a scleroderma center where advice regarding aggressive treatment can be provided, and clinical trials for early dcSSc are likely to be available.

Limited Cutaneous SSc

Patients with lcSSc have a somewhat different spectrum of internal organ complications and better long-term survival compared to dcSSc patients. However, many patients will not see a physician for lcSSc symptoms or have the disease diagnosed during the first five years. The most frequent first symptom in lcSSc is Raynaud phenomenon, with or without

digital tip ulceration, followed after a variable period of time (usually two to 10 years) by puffy/swollen fingers. Symptoms of gastroesophageal reflux disease (GERD) or distal dysphagia for solid foods occur during this time period, but often do not prompt a patient to seek medical attention. In early lcSSc, internal organ involvement is uncommon and PIP joint contractures are infrequent, unless they are due to coexisting osteoarthritis. Thus, we define early lcSSc as the first five years after the onset of disease.

Late lcSSc

Late lcSSc is arbitrarily defined as more than 10 years after disease onset. After many years, patients with lcSSc develop matte-like telangiectasias (face, lips, fingers) and subcutaneous or intracutaneous calcinosis with greater frequency. The mRss remains low and skin thickening may disappear altogether. In contrast, digital ischemia with digital tip ulcerations tends to occur more frequently in late lcSSc. Esophageal symptoms also may worsen in late lcSSc, but the use of proton pump inhibitor therapy has reduced the frequency and severity of these problems and has

prevented development of distal esophageal strictures. The most serious potential complication of late lcSSc is pulmonary arterial hypertension (PAH), occurring in about 10% to 15% of patients. PAH can appear as late as three or four decades after disease onset and is more frequent in lcSSc patients with anti-centromere, anti-Th/To, or anti-U1RNP antibodies. Up to 5% of late lcSSc patients have small bowel involvement with diarrhea, weight loss, pseudo-obstruction, and/or malabsorption. New-onset ILD, myocardial involvement, or “renal crisis” are very infrequent in late lcSSc.

Importance of Clinical Classification and Staging

Classification and staging a patient with a new diagnosis of SSc is of utmost importance. If possible, each SSc patient should be classified clinically as dc or lc with an accompanying stage (early or late). Thus, the four categories: (1) **early dcSSc**, (2) **late dcSSc**, (3) **early lcSSc**, or (4) **late lcSSc**. Individuals with intermediate disease duration should be followed closely for several years to better determine their subtype and disease stage. Going through this process allows anticipation of possible future disease complications, more appropriate clinical and laboratory monitoring, and counseling of the patient. Individuals with early dcSSc should have thorough regular surveillance for internal organ involvement. In those with late dcSSc, such monitoring is most often not necessary, given the natural history of disease (Figure 3), although a small subset of patients with late dcSSc (10% to 15%) who have passed the peak of skin thickening will experience a flare of skin thickening. Caution must be exercised in this situation, as the risk of internal organ involvement is equal to that in early dcSSc.

Classifying SSc patients based on skin thickness is quite useful, but clinical outcomes in each group can still be diverse. One way to improve upon the clinical classification is to include serum autoantibody profile. Approximately 90% of SSc patients have one of nine SSc-associated serum autoantibodies. Each autoantibody is associated with different risks of internal organ system involvement. Hence, we can use a combined clinical-serologic classification system, which we describe below.

Initial Evaluation of the Patient with a New Diagnosis of SSc (Table 2)

Due to the substantial morbidity and mortality of SSc and its associated economic burden, quality care indicators for patients with SSc are needed. A recent publication, which represents the consensus opinions of SSc experts, addresses this.⁴ For a patient with a new diagnosis of SSc, serological testing for ANA and SSc-associated autoantibodies, including anti-topoisomerase I (Scl-70), anti-centromere,

TABLE 2:

Initial Evaluation of a Patient with a New Diagnosis of SSc

Serum autoantibody testing (ANA by IIF and specific autoantibodies including anti-topoisomerase I, anti-centromere, anti-RNA polymerase III)
Resting TTE with Doppler
Pulmonary function tests (full spirometry with DLCO)
HRCT if FVC or DLCO < 80% predicted
Serum creatinine and total creatinine kinase
Weekly blood pressure measurements if early SSc
Close follow-up (within 3 months) if tendon/bursal friction rubs on exam
Regular and objective assessment of physical function (activities of daily living, health assessment questionnaire-disability index, or self-report)

TABLE 3:

SSc-Associated Serum Autoantibodies⁷⁻¹⁰

Antigen	ANA Staining Pattern	ANA Titer	Commercial Availability
Scl-70 (topoisomerase I)	speckled; homogeneous; weak nucleolar	low-moderate	Yes
RNA polymerase III	fine speckled; nucleolar	low-moderate	Yes
Centromere	centromere	low-moderate	Yes
U3-RNP (fibrillarin)	nucleolar	moderate to very high	Few labs
U1-RNP	speckled (combined speckled and homogeneous)	moderate to very high	Yes
PM-Scl	nucleolar; homogeneous	moderate	Yes
U11/U12 RNP	nucleolar	moderate (rarely negative)	No
Ku	speckled	low-moderate	Few labs
Th/To	nucleolar	moderate-high	Few labs

and anti-RNA polymerase III antibodies, should be performed, given their important prognostic value. A resting transthoracic echocardiogram complete with Doppler should be done to screen for PAH, diastolic dysfunction, pericardial effusion, and cardiomyopathy. Pulmonary function tests (PFTs), including full spirometry with diffusing capacity of the lungs for carbon monoxide (DLCO), should be performed within 12 months of diagnosis. If the forced vital capacity (FVC) or the DLCO is below 80% of predicted, a high-resolution computed tomography scan (HRCT) should be pursued to define the presence and extent of pulmonary fibrosis. A serum creatinine and serum total creatine kinase (CK) should be obtained. Regular and objective assessments of an SSc patient's physical function are of paramount importance, both at the initial and subsequent visits. Exceptions for these recommendations are in early diffuse SSc patients, for whom we recommend more frequent testing: PFTs every six months for the first three years of disease and weekly blood pressure measurements to facilitate early detection of "renal crisis" as long as their skin continues to worsen. If a patient is found to have one or more tendon/bursal friction rubs on exam, he/she should have

close follow-up (within three months), as this finding indicates active disease and has been shown to predict subsequent increase in skin thickness and increased risk of new internal organ involvement.^{4,5}

Clinical and Serological Classification

Antibody Testing in Systemic Sclerosis

Detection of antinuclear antibodies (ANA) is an important screening tool when evaluating a patient for possible SSc. More than 95% of SSc patients have skin thickening, Raynaud phenomenon, and a positive ANA. Positive ANAs can be further classified into nine SSc-associated autoantibodies (Table 3). It is rare (~2%) for an SSc patient to have more than one of these autoantibodies, and antibody status does not change over time. Eight SSc-associated antibodies can be identified by commercially available testing. Specific clinical manifestations are associated with each autoantibody. Knowledge of the SSc patient's autoantibody should be incorporated into clinical practice and management.

Antibodies can be detected by a variety of different methods, including indirect immunofluorescence, double immunodiffusion, immunoprecipitation, enzyme-linked immunosorbent (ELISA), and multiplex systems. Classic detection of ANA utilizes indirect immunofluorescence (IIF), and approximately 95% of scleroderma patients will test positive for ANA using IIF testing. ELISA is now a popular technique due to automation, reduced cost, ability for widespread screening, and the availability of recombinant proteins for a wide range of autoantigen specificities. However, caution must be utilized when interpreting ELISAs, as there is potential for false-positive results due to non-specific binding of immunoglobulins. Newer, high throughput, solid-phase assays based on multiplex technology have begun to replace IIF in clinical practice. These assays are not as sensitive as IIF for the detection of autoantibodies, and there can be significant inter-assay variability regarding sensitivity. Nucleolar antigens, many of which are targeted by autoantibodies in SSc, are most often

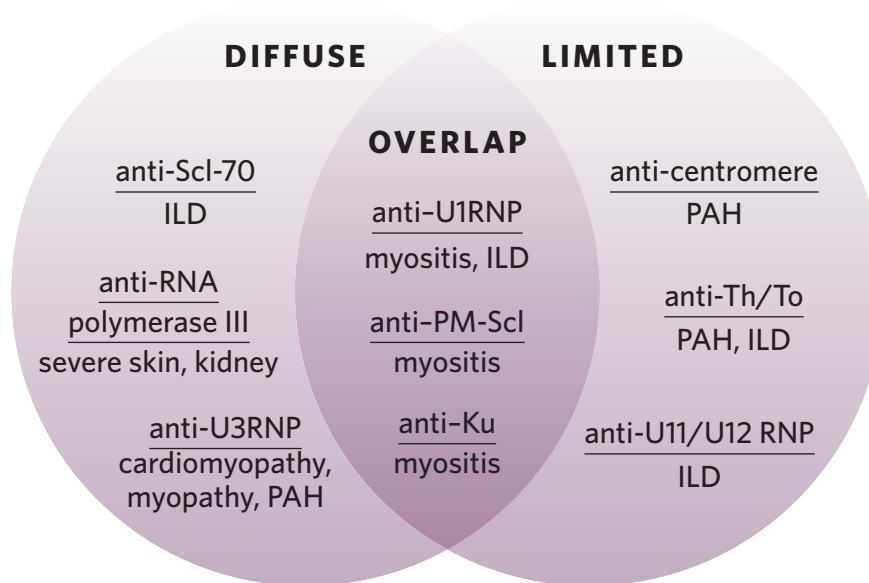
not coated onto beads. A recent retrospective study⁶ revealed that multiplex bead ANA testing failed to identify more than 40% of SSc patients, particularly those with RNA polymerase III and nucleolar IIF ANA staining. False negative tests with such multiplex assays could result in significant delays in referral and diagnosis. We recommend that IIF ANA testing be the screening test for patients with possible scleroderma or Raynaud syndrome alone. Rheumatologists should be proactive in insisting that screening for SSc and other connective tissue diseases be performed by IIF in their local laboratories.

Autoantibody Distribution by Clinical Classification

(Figure 4 and Table 3)

Diffuse Cutaneous SSc: The autoantibodies most commonly associated with dcSSc include anti-topoisomerase I (Scl-70) antibodies, anti-RNA polymerase III antibodies, and anti-U3RNP antibodies. Anti-topoisomerase I (topo I) antibodies are highly specific for SSc and are strongly

FIGURE 4: Clinical and Serological Classification of SSc



Adapted from Domsic RT and Medsger, Jr., TA. Chapter 6: Disease Subsets in Clinical Practice. Scleroderma: From Pathogenesis to Comprehensive Management London: Springer Science and Business Media, LLC; 2012.

associated with pulmonary fibrosis and digital ulcers. Anti-topo I antibodies also can be found in lcSSc, and, in this circumstance, have the same clinical associations. Anti-RNA polymerase antibodies also are highly specific for SSc and are found almost exclusively (>90%) in dcSSc. They are strongly correlated with the development of scleroderma “renal crisis”¹⁰ and severe skin thickening. Anti-U3RNP antibodies are specific for SSc and can be found with equal frequency in both dcSSc and lcSSc patients. They are disproportionately frequent in African-American SSc patients. Clinical associations of anti-U3RNP antibodies include cardiomyopathy, myopathy, and PAH.⁷

Limited Cutaneous SSc: lcSSc patients most often have anti-centromere antibodies (ACA), anti-Th/To antibodies, or anti-U11/U12 RNP antibodies. ACA are the most frequent autoantibodies found in SSc, particularly in post-menopausal Caucasian patients. They carry a higher risk for the development of PAH. In addition, they are associated with relative protection from SSc-associated pulmonary fibrosis and scleroderma “renal crisis.” ACA positive SSc patients have an increased risk of developing Sjogren syndrome and primary biliary cirrhosis. Anti-Th/To antibodies are specific for lcSSc and are associated with both PAH and ILD. Anti-U11/U12RNP antibodies are nearly 100% specific for SSc and 80% of patients with this antibody have ILD, even more frequently than with anti-topo I.

Overlap: The majority of patients with overlap syndromes have limited cutaneous SSc. The autoantibodies most commonly associated with overlap syndromes include anti-PM-Scl, anti-Ku, and anti-U1RNP antibodies. Anti-PM-Scl antibodies are associated with myositis and cutaneous changes of DM, such as Gottron sign. High rates of calcinosis, inflammatory arthritis, and ILD (most often mild) are found. Anti-Ku antibodies are uncommon, detected in about 2% of SSc patients, and are associated with overlap syndromes with features of SLE, myositis (both PM

and DM), and Sjogren syndrome. Anti-U1RNP antibodies are more frequently seen in lcSSc than dcSSc. Clinical associations include myositis and ILD along with features more commonly seen in SLE, such as inflammatory polyarthritis and leukopenia. Other autoantibodies not specific to SSc, such as anti-Ro/SSA, anti-La/SSB, and anti-Smith antibodies, also can be detected in anti-U1RNP positive patients.

Nailfold Capillaroscopy

Patients with SSc and other CTDs often demonstrate nailfold capillary abnormalities not found in normal individuals or those with primary Raynaud syndrome. There are three distinct features on nailfold capillary examination that are unique to CTDs: (1) enlarged [dilated] capillaries, (2) pericapillary hemorrhage, and (3) capillary loss or dropout.¹¹ Eighty percent of patients with Raynaud phenomenon who have abnormal findings on nailfold capillaroscopy at baseline and who also have an SSc-associated autoantibody will develop SSc over time.¹² Capillary abnormalities can be identified using widefield microscopy, videocapillaroscopy, a dermatoscope, or an ophthalmoscope with oil or immersion gel. A dermatoscope is a handheld, battery-powered instrument which uses a polarized light source that blocks reflections from the skin, thus eliminating the need for oil or immersion gel. The inter- and intra-rater reliability are higher, as compared to the use of an ophthalmoscope. Dermatoscopes are relatively inexpensive and user-friendly, with a mean capillaroscopic examination time of about 4 to 5 minutes. We recommend that all rheumatologists have and use one or another instrument for office assessment of nailfold capillaries.

Summary

We propose guidelines to aid managing physicians in clinically and serologically classifying and staging systemic sclerosis, which provides important clues to its natural history and prognosis. SSc-associated autoantibodies are valuable for managing physicians, clinical investigators, and basic/laboratory investigators alike, aiding in diagnosis, clinical subsetting, predicting natural history of disease (both skin and internal organ system involvement) and survival, and design of clinical and laboratory studies. We have tried to emphasize that early detection of internal organ involvement, which carries a high likelihood of progression to disability or death in SSc patients, allows the clinician to intervene at a crucial time. Early detection of scleroderma “renal crisis,” interstitial lung disease, and pulmonary hypertension can potentially be managed effectively with aggressive ACE inhibitor, anti-inflammatory, immunosuppressive, or other targeted therapy.

Case Scenarios

Case 1

A 54-year-old woman presents to her PCP in early March complaining of classic triphasic Raynaud symptoms experienced on several occasions during the past winter, and swollen hands, particularly in the morning, for two months. She reports that her hands feel stiff in the morning and tight throughout the day.

She is referred to a rheumatologist in May for evaluation. Review of systems is notable for generalized pruritus for six weeks, heartburn for three months, and mild dyspnea on exertion for one month. Physical exam: BP 110/75, HR 72, skin thickening of fingers (2-3+), hands (1+), and distal forearms (1+). She cannot completely extend her fingers. When making a fist there is a “squeaky” sensation in the

right palm to palpation. Labs from her PCP show a Hbg 11.2, WBC 8200, platelets 475,000, ESR 12 mm/hr, serum creatinine 0.8 mg/dL, ANA negative (performed by a multiplex assay), and anti-Scl-70 negative.

What testing would you order?

Comment: This patient has definite systemic sclerosis on physical examination with skin thickening (scleroderma) affecting the fingers, hands, and forearms. There has been a rapid progression of symptoms during the past six months. Although skin thickening is not present proximal to the elbows or knees, there are several findings suggesting that diffuse skin changes will appear soon (Table 1). She should therefore be classified as having probable early dcSSc and should be followed closely for the development of internal organ involvement. “Renal crisis” and gastric antral vascular ectasia (GAVE) with gastrointestinal bleeding are the two most likely serious early complications. Actions to be taken at this visit, for completeness, are: ANA by immunofluorescence; anti-RNA polymerase III antibody; pulmonary function tests, including DLCO, high-resolution CT scan of the lungs (without contrast); barium swallow; and transthoracic echocardiogram. CBC should be done every month, BP monitored weekly, and a return visit scheduled in two months or less.

Case 2

A 36-year-old Caucasian woman is referred to a rheumatologist by her PCP for management of Raynaud symptoms and digital tip ulcers. She reports that she has had Raynaud symptoms since age 20. She noticed that her fingers became puffy three years ago and she had to have her wedding ring resized. She has had small sores on the tips of her fingers periodically during the winter months for the last 10 years. This winter was far worse, with numerous digital tip areas of skin breakdown. She has been treated with

nifedipine and amlodipine in the past and is currently using nitroglycerin paste as needed. ROS is notable for heartburn for the past five years with rare, intermittent distal dysphagia. She denies dyspnea currently, does report dry eyes and dry mouth, mild to moderate fatigue, and about 30 to 45 minutes of morning stiffness. PE: puffy fingers with skin thickening (1-2+) bilaterally, digital pitting scars on several fingers, small (3 mm) nontender digital tip ulcers on the left ring finger with eschar formation, matte-like telangiectasias of fingers and face, a small calcific deposit over the right olecranon, tenderness to palpation over PIP joints and wrists bilaterally, and dryness of the mucosal membranes.

Tests that should be ordered and the results.

The ANA is positive at 1:320 with a centromere pattern, SSA positive, C3 normal, and low C4. There is mild leukopenia with WBC 3.8. ESR, CRP, and SPEP are normal. Formal dry eye exam confirms reduced tearing. Barium swallow shows mild distal esophageal hypomotility. TTE shows an estimated PA pressure of 38 mmHg. The FVC is 96% predicted and DLCO 88% predicted. HRCT is clear. Doppler ultrasounds reveal adequate flow at the radial and ulnar artery. At her one-year follow-up, she is doing well. At her five-year follow-up, she notes dyspnea on exertion for the past four months and leukopenia has resolved. Screening PFTs show a drop in DLCO to 52% predicted with FVC 94% predicted. TTE reveals an estimated PA pressure of 64 mmHg.

What is the next step in this patient's management?

Comment: She has late stage lcSSc with prominent digital ischemia and esophageal involvement as well as matte-like telangiectasias and subcutaneous calcinosis. She also has secondary Sjogren syndrome. She is at risk for the development of PAH, given her disease duration and anti-centromere

antibody positivity. Her FVC:DLCO% predicted ratio (94% to 52%) is 1.8, and an FVC:DLCO% predicted ratio of 1.6 or higher suggests PAH. She should now be referred for right heart catheterization. She also should be screened for small bowel involvement, asking about diarrhea, weight loss, and symptoms suggestive of pseudo-obstruction and/or malabsorption.

Case 3

A 55-year-old woman has had polyarthralgias for eight months, erythema and scaling over the elbows, knees, and MCP joints for six months, swollen fingers for four months, and Raynaud symptoms for 12 months. ROS includes heartburn for three months with intermittent distal dysphagia and no regurgitation, along with moderate fatigue without dyspnea. Physical exam reveals erythema of the upper eyelids, Gottron changes over elbows, MCPs, and PIPs, calcinosis over the ulnar surface distal to both elbows, sclerodactyly, abnormal nailfold capillary exam, reduced proximal muscle strength (4/5+), and clear chest. Labs include ANA 1:640 (nucleolar) and CPK elevated at five times the upper limit of normal. HRCT of the lungs shows mild basilar fibrosis. Esophagram and TTE are normal.

What autoantibody will she have?

Comment: She has features suggestive of an overlap syndrome. She has early SSc with limited cutaneous involvement and findings consistent with dermatomyositis. She has a nucleolar ANA (one of three autoantibodies is most likely, anti-U1RNP, anti-PM-Scl, or anti-Ku). The two former antibodies are commercially available and should be ordered. Given the DM features, anti-PM-Scl is most likely to be positive.

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ADDRESS CORRESPONDENCE TO:

**UPMC Rheumatology and
Clinical Immunology**
S718 Biomedical Science Tower
3500 Terrace St.
Pittsburgh, PA 15261
Telephone: 412-648-4701
Fax: 412-383-8753

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