# Chapter 6
# Disease Subsets in Clinical Practice

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## Why Classify Patients?

Disease classification has two primary purposes [1]. The first is to assure the reader of a journal article or book chapter that the author(s) are describing a group of patients with a single condition that can be distinguished from those without this condition(s). The second is to help categorize patients with a disease into subsets who may have different risk stratification levels, or behave differently from a clinical perspective. For the former, the object in systemic sclerosis (SSc) is to develop criteria which accurately classify groups of patients because they include clinical features which are frequent in SSc patients but are infrequent in patients with other closely related diseases. This is a particularly challenging task as SSc includes patients with a wide spectrum of clinical and laboratory manifestations.

Generally, classification refers to systematic placement into categories. Classification criteria are not the same as diagnostic criteria, although can represent of different areas along a continuum. Classification criteria were initially proposed to enhance research by developing a systematic approach to creating groups of similar patients. A goal of classification criteria development is to reach high levels of both sensitivity and specificity. However, in this circumstance, 100% sensitivity is rarely achieved. Neither is specificity 100%, as patients with other conditions may, on occasion, satisfy criteria. Diagnostic criteria refer to classification of the individual patient. If they are not satisfied, then a patient cannot be said to have the disease in question. If a patient falls short of satisfying a set of diagnostic criteria for "definite" disease, yet the disease remains the best available diagnosis, the patient may be said to have "probable" or "possible" disease.

The rationale for subsetting within disease is that in disorders with a broad spectrum of manifestations, the natural history is highly variable, and morbidity and mortality are can be different. Disease subsetting offers the opportunity to identify patients early in their disease who have a greater likelihood of developing one or another manifestation or complication of the disease, and may have a higher risk of mortality. Understanding these risks is important for the patient and the managing physician, as organ system surveillance and prompt identification of problems can result in appropriate intervention. SSc lends itself to subset classification.

## Disease Classification Criteria

The American Rheumatism Association (now American College of Rheumatology) Scleroderma Criteria Cooperative Study authors developed preliminary classification criteria for SSc which were published in 1980 [2]. This multicenter prospective study identified 264 rheumatologist-confirmed cases of SSc and compared them with three groups of patients with other

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connective tissue diseases [polymyositis/dermatomyositis (PM/DM), systemic lupus erythematosus and Raynaud disease]. The final criteria for definite SSc required one major criterion (skin thickening proximal to the metacarpophalangeal joints), or any two of three minor criteria (digital pitting scars, sclerodactyly [skin thickening restricted to the fingers only] or bibasilar pulmonary fibrosis on chest radiograph). The major criterion was present in 90% of SSc patients and the minor criteria accounted for an additional 7%, bringing the sensitivity to 97%. There was 98% specificity, as only 2% of the comparison patients satisfied the criteria. These criteria clearly show that skin thickening is a distinctive feature of SSc, occurring rarely in other closely related diseases.

Since their publication, these criteria have been criticized because they fail to identify a sizable portion of SSc patients with either limited cutaneous (lc) involvement or no skin thickening (SSc sine scleroderma or ssSSc) [3, 4], suggesting a lower sensitivity than initially reported. Since 1980, additional diagnostic tests have been developed which are in widespread use and which have the potential to contribute to both sensitivity and specificity of SSc classification criteria. They include SSc-associated serum autoantibody testing, widefield nailfold capillaroscopy, echocardiography, and high-resolution computerized tomography of the lungs. The addition of capillary microscopic abnormalities and anticentromere and other SSc-associated serum autoantibodies have been shown to increase sensitivity among lcSSc and ssSSc patients to over 90% [4, 5]. Currently a combined American-European committee has been charged by the ACR and European League Against Rheumatism (EULAR) with developing revised classification criteria for SSc [6].

Given the limitations of the ACR criteria, it is our recommendation that authors submitting manuscripts for publication or describing case series should not restrict their populations to those patients satisfying ACR criteria. This will likely omit or under-represent lcSSc or ssSSc patients who may add importantly to the research question being studied. Instead, it is preferable to include all patients diagnosed with SSc by the clinician authors and then to state what proportion of them satisfy ACR criteria, including why SSc is the correct diagnosis in those not satisfying the ACR criteria.

In SSc, it is unclear how often patients with other connective tissue diseases (CTDs) satisfy SSc classification criteria. This question has not been formally addressed in the medical literature. Using the University of Pittsburgh CTD database, we found that 87 of 1,499 (6%) definite SSc patients, excluding those diagnosed by one of our physicians with an "overlap syndrome," satisfied the 1982 revised classification criteria for SLE [7]. This high proportion is due to the relatively high percentage of SSc patients who had joint findings, serositis, and/or a positive ANA. Twenty three (1.3%) of the 1,499 SSc patients satisfied the 1975 Bohan and Peter diagnostic criteria for definite PM/DM [8].

## SSc Subset Classification

Although different classification systems have been proposed, the most widely accepted clinical method of dividing SSc patients into subsets is to separate them according to the distribution of skin thickening into diffuse cutaneous (dc) and limited cutaneous (lc) groups [9].

### *Diffuse and Limited Cutaneous SSc*

A patient who during the course of his/her disease has *ever* had skin thickening proximal to the elbows or knees (upper arms, thighs, chest, abdomen, back) is considered to have dcSSc. In contrast, patients with lcSSc have either no skin thickening (ssSSc) [10] or skin thickening restricted to the distal extremities, for example, fingers, hands, forearms. Facial and neck skin thickening can occur in either variant and does not influence classification. Several authors have proposed that three [11] or even four [12] cutaneous subsets are more appropriate, but these categories are not convincing because they do not include distinctive clinical, laboratory, or serologic features.

The dcSSc vs. lcSSc subset distinction is useful because the natural history of the degree and extent of skin thickening over time is different in these two subgroups (Fig. 6.1), as is the time during which patients tend to accumulate internal organ involvement [13]. The classic bedside method of semiquantitative measurement of skin thickness is the modified Rodnan skin score (mRss) [14], in which the examiner grades skin thickness in each of 17 surface anatomic areas as 0 (no skin thickening) to 3 (severe skin thickening). The maximal value is thus 51. Skin thickness is relatively easy to measure and has good inter-observer correlation [15]. The mRss correlates closely with the weight of a core dermal punch biopsy from the same site [16]. It should be noted, however, that skin in SSc patients which is not obviously thickened can be abnormal in other clinical respects (hyperpigmentation, telangiectasias). Fibroblasts from biopsies of apparently normal skin in SSc patients, have been shown to have a biochemical "profile" which more closely resembles scleroderma-affected skin than normal skin [17].

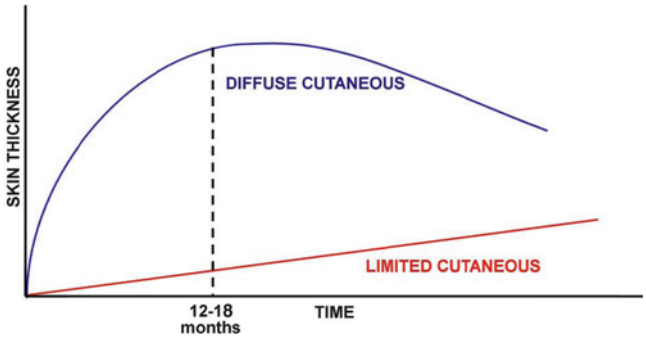


**Fig. 6.1** Schematic representation of skin changes over time in diffuse and limited cutaneous SSc. In the majority of patients, maximal skin thickness occurs within 12–18 months from the first symptom attributable to scleroderma

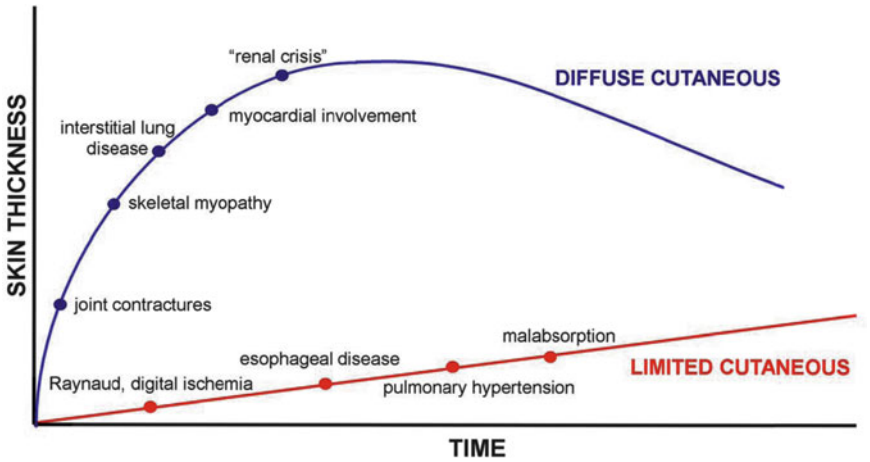


**Fig. 6.2** Usual timing of organ involvement in SSc

Patients with dcSSc have a rapid increase in mRss early in their disease. The skin score typically peaks 12–18 months after the onset of swollen fingers and improves slowly thereafter, although does not necessarily return to 0 (no skin thickening). The rate of skin thickening (defined as skin score divided by the time since the first symptom attributable to SSc) is an independent predictor of early mortality and risk of renal crisis in early dcSSc [18]. In our experience, over 90% of organ involvement (particularly of the gastrointestinal tract, lung, heart, and kidney) experienced within 5 years of disease onset occurs in the first 2 years after disease onset [19]. During the phase of rapidly increasing skin thickness in dcSSc, there is also a greater frequency of constitutional findings (fatigue, weight loss), arthralgias/arthritis, palpable tendon/bursal friction rubs, carpal tunnel symptoms, and development of finger joint contractures [20]. Ulcerations over contractures at the PIP joints are most often considered traumatic rather than ischemic in origin. Because these problems typically appear during the first 3 years of disease, one reasonable definition of early dcSSc is up to 3 years after the first symptom attributable to SSc (onset) and late dcSSc as 5+ years after onset.

Defining the time of dcSSc onset in staging of disease in individual patients is important in reporting groups of patients in the medical literature and in identifying "cut-offs" for enrollment of patients into clinical trials. A number of authors have used the time of first non-Raynaud symptom to define dcSSc onset [21–23]. Our opinion is that this is not a good method because Raynaud phenomenon is the first symptom in 40% of dcSSc patients. In our databank, the first non-Raynaud symptom occurs at a mean of 5 months after the first symptom attributable to SSc in dcSSc patients. Thus, if a clinical trial permits entry of patients up to 24 months after disease "onset," a considerable portion of patients will be past the peak of skin thickening, which occurs 7–13 months after the first non-Raynaud symptom (see Fig. 6.1).

It is incumbent on the managing physician to "stage" his/her patient as "early dcSSc," "late dcSSc," or, if uncertain, "intermediate SSc" in order to facilitate appropriate management and counseling of the patient (Fig. 6.2) [24]. For example, patients with early dcSSc should receive careful and routine surveillance for organ involvement, such as blood pressure monitoring for renal crisis. This would be unnecessary in an individual with late dcSSc. A minority of patients who have passed the peak of skin thickening have a "relapse" with redevelopment of increased skin thickening [25]. Such relapses carry all of the internal organ risks of the initial increase of skin thickening. The likelihood of later cutaneous exacerbations declines with time even in untreated patients, so that after 10 years, the risk is less than 5%.

In contrast to dcSSc, patients with lcSSc have restricted skin thickening distribution (fingers, dorsum of hands, sometimes distal forearms) which does not spread, regardless of how long they are followed, even many decades. In general, lcSSc patients have fewer internal organ complications and better long-term survival in published studies [26], but this generalization has significant limitations. Early lcSSc is arbitrarily defined as the first 5 years after the onset of disease. Many such patients will not have seen a physician or had a diagnosis of SSc made during these first 5 years. Raynaud phenomenon with or without digital tip ulceration is most frequently the first symptom, followed by swollen fingers after 1–3 years or even longer. Articular complaints and heartburn often begin during this time period but are typically of minor importance to the patient and not evaluated by the attending physician. Severe finger joint contractures are rare in lcSSc. Serious internal organ involvement in early lcSSc is uncommon. For example, pulmonary fibrosis occurs in fewer than 10% of early lcSSc patients, perhaps in part because many of these individuals have anticentromere antibody, which is seldom associated with interstitial lung disease. After 10 years of disease, it is more appropriate to use the term late lcSSc. The most obvious difference between late and early lcSSc is that over time, there is an increased frequency of mat-like telangiectasias (face, lips, fingers) and subcutaneous or intracutaneous calcinosis. Skin thickness scores continue to be low or sometimes skin thickness disappears completely. Hand disability in late lcSSc is primarily due to severe Raynaud phenomenon and digital ischemia with digital tip tissue loss and ulcerations. Esophageal symptoms (heartburn, distal dysphagia for solid foods) often persist or worsen as esophageal smooth muscle becomes more atrophic and dysfunctional. However, the advent of more effective acid-blocking medical regimens in recent decades has minimized these symptoms and sharply reduced the frequency of late distal esophageal strictures. Small bowel involvement with diarrhea, weight loss and episodes of pseudo-obstruction and malabsorption are uncommon but can occur in up to 5% of late lcSSc patients [27].

The most serious problem in late lcSSc is the development of pulmonary hypertension (PH) in a small minority of patients (approximately 10%). This complication most often occurs in SSc patients with long-standing disease (two or more decades) who have had few other disease-related problems. PH is disproportionately more frequent in SSc patients with anticentromere, anti-Th/To, and anti-U1RNP antibody [28, 29]. New appearance of interstitial lung disease, myocardial involvement, or "renal crisis" is rare in late lcSSc (Fig. 6.2).

In late lcSSc patients with coexisting autoimmune diseases, symptoms may be due to the latter conditions rather than due to SSc. Sjogren syndrome can be complicated by polyarthritis, vasculitis affecting the skin (palpable purpura), and peripheral neuropathy or mononeuritis multiplex; such patients most frequently have anti-SSA and/or –SSB antibodies and hypocomplementemia [30]. Autoimmune hypothyroidism and primary biliary cirrhosis also occur disproportionately frequently in late lcSSc patients [31, 32].

## *SSc Sine Scleroderma*

SSc sine scleroderma is an uncommon presentation of SSc with classic internal organ manifestations, but lacking skin involvement. These individuals almost all have Raynaud phenomenon and a SSc-associated serum antibody. The frequency of internal organ involvement and mortality is similar to those in patients with lcSSc [10], and it is felt by most authors that SSc sine SSc represents a portion of the spectrum of limited cutaneous SSc.

## *Overlap Syndromes*

It is commonly accepted that there is a subset of SSc patients who demonstrate distinctive features of SSc along with manifestations of other connective tissue diseases, for example, systemic lupus erythematosus, inflammatory myopathies, or rheumatoid arthritis. These patients have frequently been classified as having "overlap syndromes." The concept of "overlap syndrome" is a difficult one, as there are no accepted guidelines to help managing physicians or clinical investigators define overlaps. When does a SSc patient have SSc-associated polyarthritis and when an overlap with rheumatoid arthritis? When is polymyositis an integral part of SSc or a separate CTD? It has been our policy to say that an overlap exists when a patient with definite SSc also satisfies the published classification criteria for SLE [7] or RA [33] or the diagnostic criteria for PM/DM [8]. Although the existence of such patients provides indirect evidence that there are common pathogenic processes underlying these rheumatic conditions, further study of these clinically and serologically heterogeneous patients will be necessary for more appropriate classification.

## Classification Based on a Combination of Cutaneous Features and Serum Autoantibodies

Although the above described SSc skin thickness classification method is very useful, it is an imperfect system, limited by the fact that clinical outcomes are quite mixed within the two groups. Greater specificity regarding the future risk of internal organ involvement may be gained by using a combined cutaneous and serologic classification system. Serum autoantibodies in SSc are described in detail in Chap. 18. For purposes of this discussion, it is important to understand that 80–90% of SSc patients have one of nine SSc-associated serum autoantibodies and that seldom (2%) does a SSc patient have more than one of these antibodies. Second, antibody status does not change over time. Third, these antibodies are associated with different risks of internal organ system involvements.

We recommend using the diagram in Fig. 6.3 as a method of placing patients into cutaneous-serologic categories. For each antibody, we have listed those clinical features which are particularly frequent compared with their frequency in other autoantibody subsets. For example, anti-RNA polymerase III antibody is associated with dcSSc (90%), severe skin thickening (mean maximum mRss in dcSSc patients >30), and a high risk of renal crisis (25%) [34]. In contrast, anticentromere antibody patients almost all have lcSSc (95%) and 10% ultimately develop PH [28]. For some autoantibodies, the situation is somewhat more complex. Anti-topoisomerase I antibody positive patients with dcSSc have a higher risk of renal and cardiac involvement than do anti-topoisomerase I positive lcSSc patients, but the risk of interstitial lung disease is similar in anti-topoisomerase I positive dc and lc patients [35].

Clinical-cutaneous disease subsets are clearly associated with different short- and long-term cumulative survival. Table 6.1 depicts the previously unpublished 5- and 10-year cumulative survival rates (CSRs) for 2,500+ SSc patients first evaluated at the University of Pittsburgh Scleroderma Clinic during 1980–2005 from first physician diagnosis of SSc according to cutaneous-serologic subset. Some patients groups are small, making generalizations premature.

Further refinements of the lifetime risk of organ system involvement and the time of onset of these involvements according to autoantibody should be published in the future. These data will provide managing physicians important information concerning surveillance for complications, regardless of disease stage. Of greatest importance will be the early detection of internal organ involvements which have a high likelihood of progression to disability or death, such as "renal crisis," interstitial lung disease, and PH, and which can potentially be managed effectively with aggressive ACE inhibitor, anti-inflammatory, or immunosuppressive drug or other treatment plans.

## Typical Subset Patient Profiles

Below are brief patients summaries typical of the combined clinical-serologic profiles described above.

*Early diffuse SSc*: A 45-year-old woman develops swollen fingers and inflammatory arthralgias affecting the small joints of her hands. Three months later she notes Raynaud phenomenon. After an additional 2 months, the skin becomes thickened over the dorsum of her hands and forearms, and she notes proximal interphalangeal (PIP) joint contractures as well

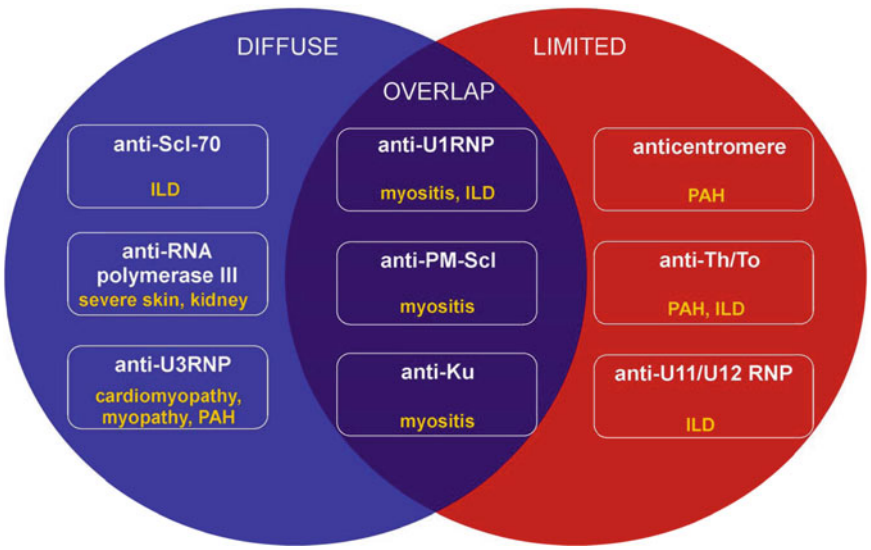


**Fig. 6.3** Clinical-serologic classification of SSc interstital lung disease (ILD)

**Table 6.1** Cumulative survival rates of University of Pittsburgh SSc patients calculated from first physician diagnosis of SSc according to cutaneous-serologic subset (first evaluation 1980–2005)

| | Diffuse | | | Limited | | |
|---|---|---|---|---|---|---|
| Autoantibody | *N* | 5 Years (%) | 10 years (%) | *N* | 5 Years (%) | 10 Years (%) |
| Topo I | 333 | 76 | 58 | 166 | 92 | 76 |
| RNA pol III | 471 | 82 | 73 | 57 | 78 | 70 |
| ACA | 35 | 89 | 77 | 457 | 85 | 74 |
| U1RNP | 20 | 90 | 79 | 91 | 91 | 83 |
| Ku | 7 | 57 | 29 | 8 | 100 | 69 |
| U3RNP | 47 | 72 | 58 | 41 | 79 | 59 |
| Th/To | 0 | 0 | 0 | 140 | 77 | 66 |
| PM-Scl | 21 | 100 | 88 | 50 | 100 | 91 |
| U11/U12 | 16 | 59 | 39 | 17 | 88 | 66 |

as heartburn and fatigue. Eight months after the onset of swollen fingers she sees her primary care physician, who does an ANA which is positive at 1:640 with speckled and nucleolar staining.

She is a referred to a rheumatologist who makes the diagnosis of systemic sclerosis 10 months after disease onset. Physical examination findings include a blood pressure of 120/75, and a mRSS of 33 with thickening involving the distal extremities as well as the upper arms, chest, and abdomen. The skin thickness progression rate is rapid at 46 per year (ref 18). She has palpable wrist extensor and anterior tibial tendon friction rubs, with PIP greater than metacarpophalangeal (MCP) joint contractures. Anti-RNA polymerase III antibody is positive. HRCT of the chest, echocardiogram, serum creatinine and urinalysis are all within normal limits. Cine esophagram reveals mild distal esophageal hypomotility.

*Late diffuse SSc*: A 62-year-old man relocates to another city and sees a new rheumatologist for the first time. Review of his medical records reveals that he developed Raynaud phenomenon at age 47, swollen fingers at age 48, and skin thickening described as "extensive, including the chest and abdomen" later that year. He noted flexion contractures of the PIP joints and occasional ulcerations over the dorsal surfaces of these joints. The ANA was positive at 1:1280 with speckled and nucleolar staining and the anti-topoisomerase I antibody was positive.

Records after this initial visit were not available. The patient recalls receiving "many medications, none of which seemed to help." He took partial disability for 6 months. He had been told of "a touch of scarring" in the lungs and had mild but non-progressive dyspnea on exertion. He said that "my esophagus was affected, but acid-blocking drugs controlled heartburn." After several years, skin thickening regressed. In general the patient feels well. He had has no fatigue and is able to work full-time as an accountant, including regular use of a computer.

On physical examination he was normotensive. There were faint bibasilar end-inspiratory rales audible. He had a mRSS of 6 with 2+ sclerodactyly and 1+ skin thickening over the dorsum of the hands bilaterally. There were numerous facial telangiectasias. There were several small non-tender digital pitting scars. The PIP joints lacked 20° of extension and there were healed ulcerations over these joints.

Laboratory studies confirmed the presence of anti-topoisomerase I antibody. The ESR and CRP were normal. A HRCT scan of the lungs revealed mild basilar fibrosis with slight honeycombing but without "ground glass" changes. The FVC was 68% predicted and DLCO 59% predicted. Echocardiogram did not show either left or right ventricular dysfunction and pulmonary arterial pressure was estimated to be 31 mmHg.

*Early limited cutaneous SSc*: A 42-year-old woman noticed blanching followed by bluish discoloration of her fingertips upon cold exposure beginning in the early fall. This was uncomfortable when it occurred. At New Year's Eve she had heartburn, which became more frequent over the next 2 months (although intermittent). In mid-February she developed a small ulceration at the tip of the right index finger. This was quite painful, and she went to her primary care physician. She denies any joint pain or muscle weakness, but is experiencing some mild hand stiffness for approximately 30–60 min in the morning. Her exam is remarkable for a blood pressure of 124/82, periungual erythema, and a small 0.7 cm ulceration on the tip of her right index finger. The physician notices blanching of several of the fingertips during the interview. Bloodwork shows a positive ANA and she is referred to a rheumatologist for further management. She is evaluated the following week. On this exam there are several matte-like telangiectasias on the dorsum of her hands, and mild skin thickening limited to the fingers only. Nailfold capillaroscopy reveals 3+ dilated capillaries with some areas of drop-out. There is a digital pitting scar on the left fourth finger tip. She has a normal Allen test. Serum testing reveals a positive anti-centromere antibody. Mild esophageal distal hypomotility is found on cine esophagram. Subsequently, pulmonary function tests, echocardiogram, and electrocardiogram were performed and all were normal.

*Late limited SSc*: A 54-year-old woman presents to a gastroenterologist for bloating after eating and intermittent bouts of diarrhea which have greatly impacted her quality of life. She has lost 21 lb over the past 6 months. On one occasion she

went to an Emergency Room because of severe abdominal distention. She was told that an abdominal film showed that she was "full of gas and stool." A laxative was prescribed and the symptoms resolved after 1 week. She also complains of almost daily heartburn for the last 10 years, improved by proton pump inhibitor use. Her past medical history is significant for mild hypertension, hypothyroidism and Raynaud phenomenon starting around age 40. On exam the gastroenterologist notes matte-like telangiectasias on the hands and face. Work-up reveals esophagitis/gastritis on EGD, as well as delayed gastric emptying and transit time on small bowel follow-through. The gastroenterologist refers her to a rheumatologist because of his concern for possible scleroderma as the cause of her dysmotility. Further history confirms the presence of systemic lupus erythematosus in a maternal aunt, and a first cousin with hypothyroidism. The patient notes some mild dyspnea on exertion, but attributes it to lack of exercise due to a demanding job. Exam reveals periungual erythema with visibly abnormal capillaries and sclerodactyly with 2+ skin thickening of the fingers bilaterally. She is found to be ANA positive (speckled and nucleolar pattern) with a mild restrictive pattern on pulmonary function tests. High-resolution chest CT shows mild interstitial fibrosis. Echocardiogram reveals no evidence of pulmonary arterial hypertension.

*SSc sine SSc*: A 43-year-old woman presents to her PCP for evaluation of dyspnea, progressive over 1 year. A full work-up shows that she had a reduced diffusion capacity on pulmonary function tests, and an echocardiogram reveals an elevated pulmonary arterial systolic pressure at 56 mmHg. She has normal systolic and diastolic heart function. Electrocardiogram is within normal limits. She is referred to a cardiologist who obtains the additional history that she has experienced Raynaud phenomenon beginning shortly after her second pregnancy at age 35. Serum testing reveals the presence of a positive ANA and she is referred to a rheumatologist.

The review of systems is positive for heartburn for 10 or more years, with only intermittent distal dysphagia for solid foods. She has had to increase her ring size over the last 5 years, but denies any skin thickening. Examination reveals periungual erythema with visibly abnormal nailfold capillaries, puffy fingers without sclerodactyly, cobblestoning in the back of the oropharynx, and an accentuated P2 sound on auscultation. ANA with immunofluorescence reveals a nucleolar pattern, and additional serum testing shows that she has a positive Th/To antibody. Esophageal hypomotility with spontaneous reflux is found on cine esophagram.

*Overlap syndrome*: A 21-year-old college student reported the onset of Raynaud phenomenon and inflammatory polyarthralgias 3 months prior to seeing her PCP. Her fingers look swollen to her, and she had been experiencing low grade fever and myalgias. The PCP finds no abnormalities on physical examination. A CBC with differential is normal. The ESR and CRP are moderately elevated. The SGOT is 52 units/dL (normal <40 units/dL), SGPT 69 units/dL (normal < 50 units/dL), and alkaline phosphatase normal. The ANA was positive 1:320 with nucleolar staining. She was referred to a gastroenterologist for possible autoimmune hepatitis. A liver biopsy was done which was normal.

Two months later she noted swelling of the PIP and MCP joints and a scaling rash over the upper eyelids, elbows, MCP joints, and knees. She was referred to a rheumatologist. She did not complain about muscle weakness, dyspnea, or heartburn. At that time she had MCP and PIP joint polyarthritis, sclerodactyly, and a rash consistent with dermatomyositis. The neck flexor and shoulder girdle muscles were weak. The CPK was elevated at 681 units/dL (normal < 200 unit/dL). An EMG suggested inflammatory myopathy and a deltoid muscle biopsy showed typical changes of dermatomyositis. The cine-esophagram was abnormal with mild distal esophageal hypomotility. Pharyngeal swallowing function was normal. A chest x-ray was normal, but a high-resolution CT scan of the lungs revealed bibasilar fibrosis. The FVC was 82% predicted and the DLCO 74% predicted. An echocardiogram was normal. Anti-PM-Scl antibody was positive.

## Future Directions

One current limitation of the combined clinical-serologic subset classification is that not all nine SSc-associated serum autoantibodies are available commercially for testing. It is our hope that this may be resolved in the future. Molecular methods such as gene expression profiling or genetic markers may provide additional information to further refine clinical subsetting and risk stratification in SSc.

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