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 that the author(s) are describing a group of patients with a single condition that can be distinguished from patients without this condition. The second is a phenotypic classification to help categorize patients with a disease into subsets which may have different risks for disease complications or mortality 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 they can reflect 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 the criteria 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 most likely diagnosis, the patient may be said to have "probable" disease.

The rationale for disease subsetting (or phenotyping) is that in disorders with a broad spectrum of clinical manifestations and severity, the natural history and risk of morbidity and mortality may be highly variable. 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 morbidity or mortality. Understanding these risks is important for the patient and the managing physician, as organ system surveillance and prompt identification of disease-associated problems can result in appropriate intervention. SSc lends itself to subset classification.

SSc 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]. 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). These criteria clearly showed that skin thickening is a distinctive feature of SSc. However, the 1980 criteria have been criticized because they fail to identify a group of SSc patients with either limited cutaneous (lc) involvement or no skin thickening (SSc sine scleroderma or ssSSc) [3, 4], resulting in a lower sensitivity than initially reported. In 2013 a joint ACR and European League Against Rheumatism (EULAR) committee published revised classification criteria for SSc [5, 6]. These new criteria (Table 4.1) improved upon the shortcomings of the earlier ACR criteria as they recognized post-1980 advances in the detection of SSc-associated autoantibodies and distinctive

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Table 4.1 Revised classification criteria for SSc

Item	Sub-item(s)	Weight/score[a]
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)		9
Skin thickening of the fingers (only count the higher score)	Putty fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions (only count the higher score)	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or interstitial lung disease (maximum score is 2)	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud phenomenon		3
SSc-related autoantibodies (anticentromere, anti-topoisomerase I [anti-Scl-70], anti-RNA polymerase III) (maximum score is 3)	Anticentromere	3
	Anti-topoisomerase I	
	Anti-RNA polymerase III	

[a]The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of ≥9 are classified as having definite SSc

SSc-abnormalities on nailfold capillaroscopy. All three hallmark features of SSc (fibrosis of the skin and/or internal organs, production of specific autoantibodies, and evidence of vasculopathy) are included. The new criteria have a sensitivity of 91 % and specificity of 92 %. The use of antibodies in the criteria underscores the growing importance of serologic classification, as we discuss later in this chapter [7].

In SSc, it is unclear how often patients with other established 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 [8]. 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 [9].

SSc Subset Classification

Cutaneous Classification

Although several different subset classification systems have been proposed, the most widely accepted clinical method of dividing SSc patients is to separate them based on the distribution of skin thickening into diffuse and limited cutaneous subsets [10]. 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 diffuse SSc. Thus, even patients who have had regression of the skin involvement to fit the limited SSc definition are still classified as having diffuse SSc. Patients with limited SSc have either no skin thickening (sine scleroderma) [11] or skin thickening present only distal to the elbows or knees. Facial and neck skin thickening can occur in either variant and do not influence classification. Several authors have proposed that three [12] or even four [13] cutaneous subsets are more appropriate, but these more complicated subsets do not include distinctive clinical, laboratory, or serologic features that convincingly function better than the simple diffuse versus limited SSc classification.

How Is the Diffuse and Limited SSc Classification Helpful?

The cutaneous distribution method is helpful because the natural history of these subsets is different for both skin and internal organ involvement. From a cutaneous standpoint, progression and extent of skin thickening over time is different (Fig. 4.1) in these two subgroups. Mirroring this, the at-risk time of new internal organ involvement is also different between the limited and diffuse SSc patients [14]. Patients with diffuse SSc tend to develop 90 % of their internal organ involvement during the first 2 years of disease (Fig. 4.2).

Assessment of Cutaneous Disease

The classic bedside method for semiquantitative measurement of skin thickness is the modified Rodnan skin score (mRss) [15], 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 interobserver correlation [16]. The mRss correlates closely with the weight of a core dermal punch biopsy from the same site [17]. It should be noted, however, that

skin in SSc patients which is not obviously thickened can be abnormal in other clinical respects (hyperpigmentation, telangiectasias). Furthermore, fibroblasts grown 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 [18].

Natural History and Disease Staging in Diffuse SSc

Patients with diffuse SSc have a rapid increase in mRss early in their disease. The skin score typically peaks 12–18 months after the first SSc symptom and improves slowly thereafter, although does not necessarily return to 0 (no skin thickening). The skin thickness progression rate, or STPR, is defined as the total skin score at the time of initial evaluation divided by the time since the first symptom attributable to SSc in years. The STPR is an independent predictor of early mortality and risk of renal crisis in early diffuse SSc [19]. In the Pittsburgh experience, the majority of internal organ involvement in diffuse SSc patients is early, and 90 % of the complications experienced within 5 years of disease onset occur in the first 2 years [20] (Fig. 4.2). The exception to this is pulmonary hypertension, which can occur later in disease. 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 [21].

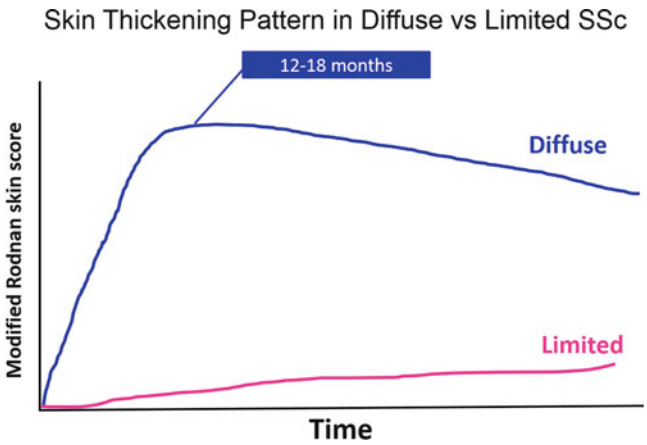

Fig. 4.1 Schematic representation of skin changes over time in diffuse and limited cutaneous SSc. In the majority of patients, maximal skin thickness occurs within 12–18 months from the first symptom attributable to scleroderma

Defining the time of diffuse SSc onset for staging of disease in individual patients is important in reporting groups of patients in the medical literature and in identifying "cutoffs" for enrollment of patients into clinical trials. A number of authors have used the time of first non-Raynaud symptom to define diffuse SSc onset [22–24]. 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 3 months after the first symptom attributable to SSc in diffuse SSc 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. 4.1).

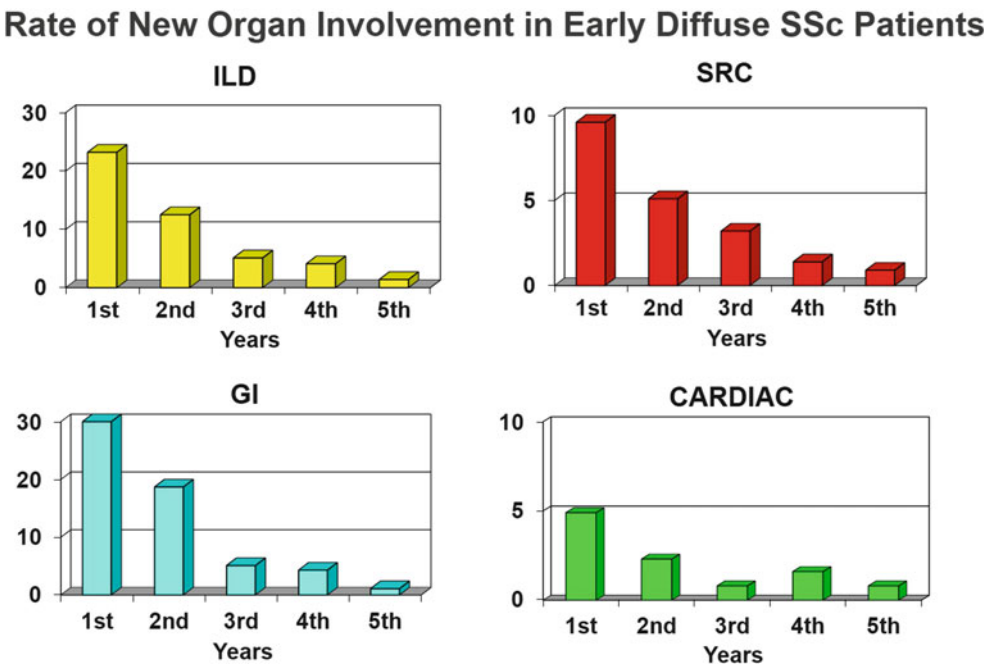

Fig. 4.2 Rate of new internal organ involvement in the first 5 years of diffuse disease. Patients presented with early diffuse SSc (<2 years of symptoms) to the UPMC and University of Pittsburgh Scleroderma Center, 1980–2007

As internal organ involvement typically appears during the first 2 years of disease, one reasonable definition of early diffuse SSc is up to 2 years after the first symptom attributable to SSc (onset) and late diffuse SSc as 5+ years after onset. However, as the majority of skin thickening occurs within the first 18 months of SSc symptoms, an alternative cutaneous-based definition of early diffuse SSc is the first 18 months.

It is incumbent on the managing physician to "stage" his/her patient as "early diffuse," "late diffuse," or, if uncertain, "intermediate diffuse SSc (2–5 years duration)" in order to facilitate appropriate management and counseling of the patient [25]. For example, patients with early diffuse SSc should have 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 [26]. Such relapses carry all of the internal organ risks associated with 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 approximately 5%. Pulmonary hypertension should be screened for in all diffuse SSc patients, regardless of stage.

Natural History and Disease Staging in Limited SSc

In contrast to diffuse SSc, patients with limited SSc have restricted skin thickening distribution (fingers, dorsum of hands, sometimes distal forearms) which does not spread, regardless of how long they are followed, even over decades. In general, limited SSc patients have fewer internal organ complications and better long-term survival in published studies [13]. Distinct from diffuse SSc, patients with limited SSc accumulate their internal organ involvement slowly, sometimes over decades (Fig. 4.3). This means that patients with limited SSc need to be screened for internal organ involvement regardless of how long they have their disease.

Early limited SSc 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 limited SSc. Serious internal organ involvement in early limited SSc is uncommon. For example, pulmonary fibrosis occurs in fewer than 10% of early limited SSc 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 limited SSc. The most obvious difference between late and early limited SSc is that over time, there is an increased frequency of matte-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 limited SSc is primarily due to severe Raynaud phe-

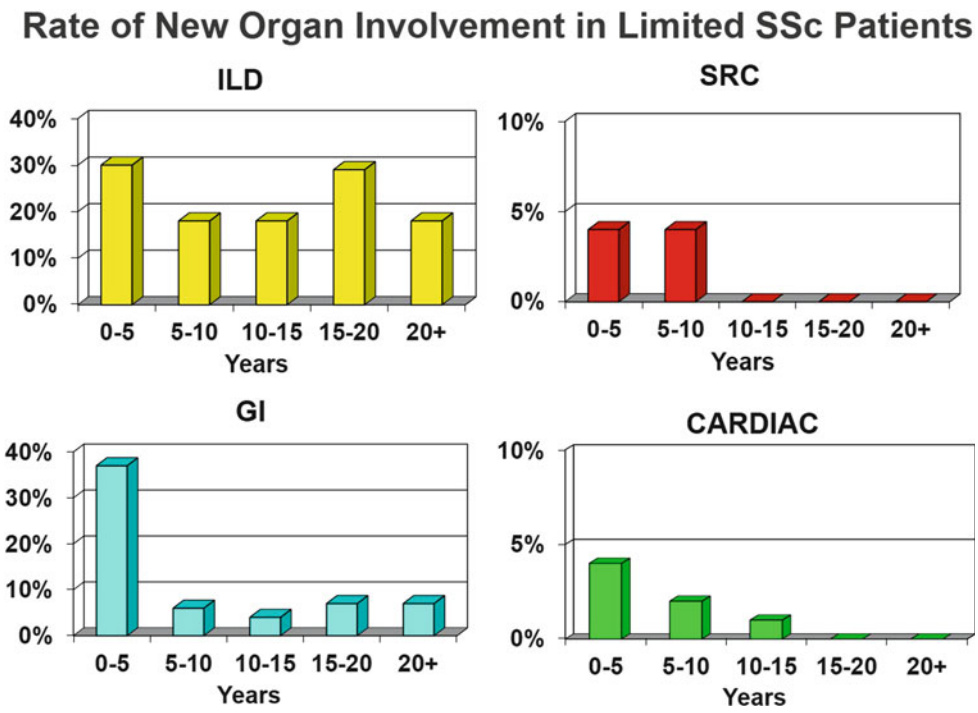

Fig. 4.3 Rate of new internal organ involvement in patients over 20+ years in limited SSc. Patients presented with early limited SSc (<5 years of SSc symptoms) to the UPMC and University of Pittsburgh Scleroderma Center, 1980–2007

nomenon 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 atrophic and dysfunctional. However, the advent of more effective acid-blocking medical regimens in recent decades has minimized these symptoms and has 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 limited SSc is the development of pulmonary hypertension (PH) in a small minority of patients (approximately 10 %). This complication can occur in SSc patients with long-standing disease (two or more decades) who have had few other disease-related problems.

In late limited SSc 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 sensory neuropathy or mononeuritis multiplex; such patients most frequently have anti-SSA and/or anti-SSB antibodies and hypocomplementemia [28]. Autoimmune hypothyroidism and primary biliary cirrhosis also occur disproportionately frequently in late limited SSc patients [29, 30].

SSc Sine Scleroderma

SSc sine scleroderma is an uncommon presentation of SSc with classic internal organ manifestations, but no skin thickening. This occurs in <5 % of individuals with SSc [11, 31]. These individuals almost all have Raynaud phenomenon and an SSc-associated serum antibody. The frequency of internal organ involvement and mortality are similar to those in patients with limited SSc [11], and it is felt by most authors that SSc sine scleroderma represents a portion of the spectrum of limited cutaneous SSc. Long-term follow-up of these patients suggests that approximately half will develop some limited skin thickening over time [31].

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, inflammatory myopathies, systemic lupus erythematosus (SLE), or inflammatory arthritides. 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 an SSc patient have SSc-associated polyarthritis and when an overlap with rheumatoid arthritis (RA)? When is polymyositis (PM) 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 [8] or RA [32] or the diagnostic criteria for PM/DM [9]. Although the existence of such patients provides indirect evidence that there are common pathophysiologic processes underlying these rheumatic conditions, further study of these clinically and serologically heterogeneous patients will be necessary for more appropriate classification.

Mixed Connective Tissue Disease

Mixed connective tissue disease (MCTD) was originally described in 1972 and defined by the presence of U1-RNP autoantibody. This was based on the principle that virtually all patients with a U1-RNP antibody had features of SSc, SLE, and PM. Several diagnostic criteria have been published for MCTD [33–37]. The criteria of Alarcon-Segovia and Kahn are felt to be the best. In both the presence of U1-RNP is required. In the Kahn criteria Raynaud plus two of the following is required: swollen fingers, synovitis, or myositis. In the Alarcon-Segovia criteria three of the following features are required (of which synovitis or myositis had to be present): swollen hands, synovitis, myositis, Raynaud, or acrosclerosis.

Although initially a point of debate, MCTD is now generally felt to represent a distinct clinical entity. One difficulty in establishing a diagnosis of MCTD is that the overlapping features can occur sequentially over time, rather than presenting together initially. This often delays a diagnosis of MCTD. The earliest feature is often Raynaud with constitutional symptoms of fatigue, arthralgias, and myalgias. This can lead to an initial differential of undifferentiated connective tissue disease, SLE, or RA. It is frequently later that the more distinctive features emerge (puffy fingers, synovitis, and/or myositis). It should be noted that patients with MCTD may develop prominent features of SLE such as lupus nephritis, although this is uncommon. From a scleroderma spectrum of disease viewpoint, these patients will have typical SSc nailfold capillaroscopy patterns and can develop interstitial lung disease (ILD), PH, and esophageal or small bowel dysmotility. In the case of MCTD, the U1-RNP positivity and SSc-like internal organ risks associated with it can be helpful in patient management.

Classification Based on a Combination of Cutaneous Features and Serum Autoantibodies

The above described SSc cutaneous classification method is very useful, but it is an imperfect system, as clinical organ involvement and outcomes are still heterogenous within the limited and diffuse subsets. 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 Chapter 18. For purposes of this discussion, the primary focus is that each of these antibodies is associated with a unique cutaneous subtype and risk profile for internal organ involvement. It is also important to consider that (1) 85–95 % of SSc patients have one of ten SSc-associated serum autoantibodies, (2) seldom (2 %) does a SSc patient have more than one of these antibodies, and (3) different antibodies do not appear over time. One must be cautious, however, with current commercially based ELISA and multiplex antibody assays as it has been our experience that there is a high false-positive anti-Scl-70 rate.

We recommend using the diagram in Fig. 4.4 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 diffuse SSc (90 %) with severe skin thickening (mean maximum mRss in dcSSc patients >30) and a high risk of renal crisis (25 %) [38]. In contrast, anticentromere antibody patients almost all have limited SSc (95 %) and 15 % ultimately develop pulmonary hypertension [39]. For some autoantibodies, the situation is somewhat more complex as they may not as clearly be associated with a cutaneous subtype. For example, anti-topoisomerase (Scl-70) positive patients with diffuse skin thickening have a higher risk of renal and cardiac involvement than do anti-Scl-70 positive limited SSc patients, but the risk of ILD is similar in anti-Scl-70 positive diffuse and limited patients [40].

Clinical-cutaneous disease subsets are clearly associated with different short- and long-term cumulative survival. Table 4.2 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 1980–2010 from first physician diagnosis of SSc according to cutaneous-serologic subset. Some patient 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 examined 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," ILD, and PH, and which can potentially be managed effectively with aggressive ACE inhibitor, anti-inflammatory, immunosuppressive drug, or vasodilator therapies, respectively.

Patient Profiles for SSc Disease Subsetting and Staging

Below are brief patient 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

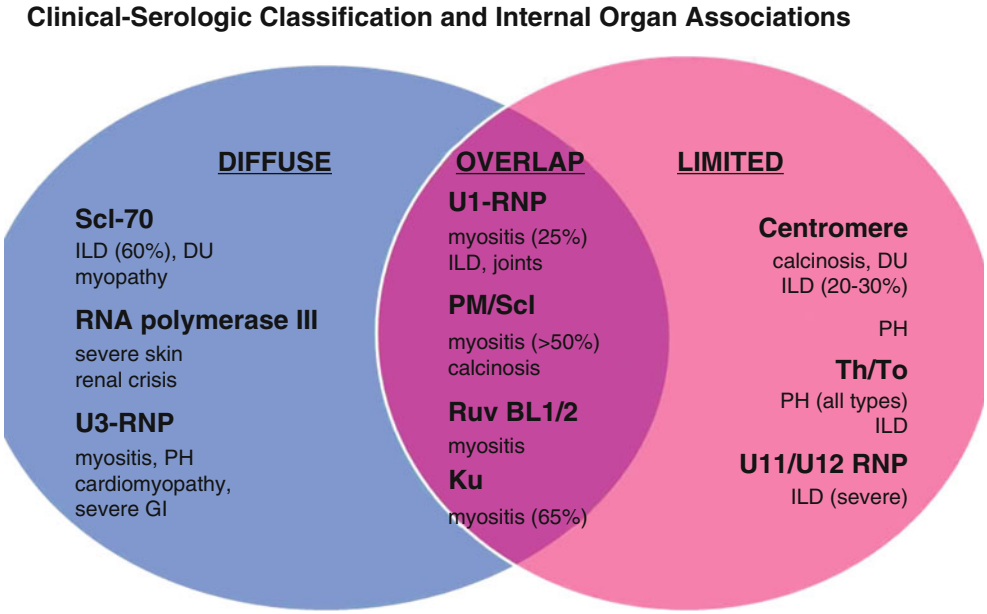

Fig. 4.4 Clinical-serologic classification and internal organ associations

ILD = interstital lung disease; DU = digital ulcers; PH = pulmonary hypertension; GI = gastrointestinal

Table 4.2 Cumulative unadjusted survival rates from the UPMC and University of Pittsburgh SSc Center. Survival calculated from SSc diagnosis and presented by cutaneous-serologic subset (first evaluation 1980–2010)

	Diffuse			Limited		
Autoantibody	*N*	5 years (%)	10 years (%)	*N*	5 years (%)	10 years (%)
Scl-70	368	76	57	200	93	78
RNA pol III	549	82	71	74	80	72
ACA	53	90	76	582	86	74
U1-RNP	30	90	78	124	90	82
Ku	10	60	30	12	75	58
U3-RNP	46	74	61	48	81	62
Th/To	4	75	50	180	77	67
PM-Scl	27	95	90	69	95	90
U11/U12	19	62	49	18	83	62

phenomenon. After an additional 2 months, the skin over the dorsum of her hands and forearms becomes thickened, and she has proximal interphalangeal (PIP) joint contractures. Heartburn and fatigue occur next. Eight months after the onset of swollen fingers, she sees her primary care physician, who does an ANA test which is positive at 1:640 with speckled and nucleolar staining.

She is referred to a rheumatologist who makes the diagnosis of SSc 10 months after her first symptom. Physical examination findings include a blood pressure of 120/75, and an mRss of 33 with thickening involving the distal extremities as well as the upper arms, chest, and abdomen. The STPR is rapid at 46 per year [19]. She has palpable wrist extensor and anterior tibial tendon friction rubs and PIP joint contractures. The anti-RNA polymerase III antibody test 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 had flexion contractures of the PIP joints and occasional ulcerations over the dorsal surfaces of the PIP joints. The ANA was positive at 1:160 with speckled and nucleolar staining, and the anti-Scl-70 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 nonprogressive 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 has had no fatigue and is able to work full time as an accountant.

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

Laboratory studies confirmed the presence of anti-Scl-70 antibody. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are normal. A high-resolution computed tomography (HRCT) scan of the lungs reveals mild basilar fibrosis with slight honeycombing but without "ground-glass" changes. The forced vital capacity (FVC) is 68 % predicted and DLCO 59 % predicted. Echocardiogram does not show either left or right ventricular dysfunction, and peak systolic pulmonary arterial pressure is estimated as 31 mmHg.

Early Limited Cutaneous SSc A 42-year-old woman noticed painful blanching followed by bluish discoloration of her fingertips on cold exposure beginning in the early fall. At a New Year's Eve party, she had heartburn, which was intermittent thereafter but became more frequent over the next 2 months. 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 denied any joint pain or muscle weakness, but attested to morning stiffness of the small joints of her hands for 30–60 min. Her exam was 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 primary care provider (PCP) noted blanching of several of the fingertips during the interview. Bloodwork shows a positive ANA, and she was referred to a rheumatologist who found several mat-like telangiectasias on the dorsum of her hands and mild skin thickening of the fingers only. Nailfold capillaroscopy revealed 3+ dilated capillaries with some areas of dropout. There was a digital pitting scar on the left fourth fingertip. Serum testing showed a positive anticentromere antibody. Mild esophageal distal hypomotility was 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 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 (14 years previously).

On exam the gastroenterologist notes matte-like telangiectasias on her hands and face. Workup reveals esophagitis/gastritis on esophagogastroduodenoscopy (EGD), as well as delayed gastric emptying and reduced 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 intestinal dysmotility. Further history confirms the presence of SLE in a maternal aunt, and a first cousin has hypothyroidism. The patient notes some mild dyspnea on exertion, but attributes it to lack of exercise due to a demanding job. Physical examination reveals periungual erythema with visibly abnormal nailfold capillaries and sclerodactyly (2+ skin thickening of the fingers bilaterally). She is found to be ANA positive. There is a mild restrictive pattern on pulmonary function tests. High-resolution chest CT shows 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 progressive dyspnea over the last year. She has a reduced diffusion capacity for carbon monoxide (DLCO) on pulmonary function tests, and an echocardiogram reveals an estimated peak pulmonary arterial systolic pressure of 56 mmHg (normal <40 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 of blanching of the fingertips with cold exposure starting after her second pregnancy at age 35. Serum testing reveals the presence of a positive ANA and she is referred to a rheumatologist.

Her review of systems is positive for 10+ years of heartburn and intermittent distal dysphagia for solid foods. She has had to increase her ring size over the last 5 years but denies any skin thickening. Physical examination reveals periungual erythema with visibly abnormal nailfold capillaries and puffy fingers without sclerodactyly. P2 sound is accentuated on auscultation. Additional ANA testing done by immunofluorescence reveals a nucleolar pattern, and the rheumatologist strongly suspects anti-Th/To antibody. Esophageal hypomotility with spontaneous reflux is found on cine esophagram.

Mixed Connective Tissue Disease A 21-year-old college student reported the onset of Raynaud phenomenon and inflammatory polyarthralgias 3 months prior to seeing her PCP. She also had been experiencing low-grade fever and myalgias. The PCP finds no abnormalities on physical examination and a CBC is normal. The ESR and CRP are moderately elevated. He attributes her symptoms to a viral syndrome. When her symptoms have not resolved 6 months later, she returns to her PCP. At this time her aspartate aminotransferase (AST) is abnormal at 52 units/dL (normal <40 units/dL), ALT 69 units/dL (normal <50 units/dL), and alkaline phosphatase normal. Hepatitis panels were negative, and she was referred to a gastroenterologist who ordered an ANA test that returned positive at 1:2560 with speckled nuclear staining. A liver biopsy was performed to evaluate for autoimmune hepatitis and this was normal.

Six months following the biopsy, she developed swelling of the *proximal interphalangeal* (PIP) *join* and *metacarpophalangeal* (MCP) joints. She was referred to a rheumatologist for evaluation of possible RA. She did not complain about muscle weakness, dyspnea, or heartburn. At that time she had MCP and PIP joint polyarthritis, puffy fingers, and skin thickening of the fingers. The neck flexor and shoulder girdle muscles were weak at 4/5. The creatine phosphokinase (CPK) was elevated at 577 units/dL (normal <200 unit/dL). An electromyogram (EMG) suggested inflammatory myopathy and a deltoid muscle biopsy showed changes typical of polymyositis. 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-U1-RNP was positive.

Future Directions

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

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