Chapter 7
Evolving Concepts of Diagnosis and Classification

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Keywords Classification • Clinical subsets of systemic sclerosis • Diagnosis • Evolving concepts • Limitations • Original LeRoy classification • Scleroderma sine sclerosis

Systemic sclerosis (SSc) is a rare connective tissue disease characterized by fibrosis of the skin and internal organs and a vasculopathy affecting the micro- and macro-vasculature. The pathogenesis of SSc involves the interplay between vascular injury and dysregulation of the immune response with resultant fibrosis of various target organs. More than 90% of patients with SSc suffer from Raynaud's phenomenon, a reversible vasospastic disorder induced by cold or stress, which results in typical white, blue, and red color changes of the distal extremities from decreased perfusion [1]. Other clinical features that are common in patients with SSc in addition to cutaneous sclerosis include pulmonary disease (interstitial lung disease and pulmonary hypertension), gastrointestinal dysmotility and malabsorption, digital ulcerations, inflammatory myositis and arthritis, cardiac and renal disease. There are two main subsets of SSc that are commonly recognized: limited cutaneous SSc and diffuse cutaneous SSc. The two subsets differ in manifestations and in prognosis, and presumably to some extent also in their pathogenesis. Although disease modifying therapies have demonstrated minimal efficacy in SSc [2–6], several organ-specific therapies have emerged over the past couple of decades resulting in improved survival and quality of life. These include angiotensin-converting enzyme (ACE) inhibitors for the treatment of scleroderma renal crisis (SRC) [7] and various agents for the treatment of pulmonary arterial hypertension (PAH), including prostacyclins, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors [8]. The development of successful disease-modifying therapies for SSc is hindered by the heterogeneous clinical manifestations of this disease, also making early diagnosis challenging. Patients with early disease are more likely to respond to targeted therapies, and irreversible organ damage may be prevented. For studying the effects of potential disease modifying drugs, and for more successful treatment in clinical practice, it is of paramount importance to recognize the presence of SSc early in the disease process. This is equally important for the diagnosis in clinical practice as well as for classification criteria used to include patients in clinical studies. If patients who are classified with SSc are similar to patients who are diagnosed with the disease, then it is straightforward to generalize evidence from clinical studies to those patients who have been diagnosed in practice. Therefore, classification and diagnosis in SSc should be developed toward recognition of SSc early in the disease process. This chapter will review the clinical subsets of SSc, the current American College of Rheumatology (ACR) classification criteria and its limitations, recently proposed classification criteria for SSc, and ongoing and future projects for revising and improving the ACR classification criteria.

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J. Varga et al. (eds.), *Scleroderma: From Pathogenesis to Comprehensive Management*,
DOI 10.1007/978-1-4419-5774-0_7, © Springer Science+Business Media, LLC 2012

Classification and Diagnosis

Classification criteria are not synonymous with diagnostic criteria but will almost always mirror the list of criteria that one uses for diagnosis. A clinical diagnosis results from a clinical evaluation for features that suggest the presence (absence) of disease, which ultimately results in the physician making his/her mind up over the probability of the disease (SSc) being present. Therefore, classification according to diagnosis and the diagnostic process in practice are regarded as different. Classification typically has a yes/no form, while diagnosis involves the concept of probability. As a result, classification criteria tend to exclude patients likely to have the disease in question (SSc). However, if classification criteria do not fully apply to the patients who are diagnosed with the disease in practice, evidence from studies using the criteria will not be applicable to all patients treated in practice. Therefore and ideally, diagnostic and classification criteria are the same, or to put it differently, classification criteria may become real diagnostic criteria.

Clinical Subsets of Systemic Sclerosis

Original LeRoy Classification

In 1988, an international panel of scleroderma experts convened to define subsets of SSc that are clinically distinguishable [9]. The two subsets were termed diffuse (dcSSc) and limited (lcSSc) cutaneous SSc, with the extent of cutaneous sclerosis as the primary differentiating feature. Patients with dcSSc have both truncal and acral skin involvement, whereas those with lcSSc have skin involvement that is limited to the hands, forearms, feet, legs below the knees, and face. The debate as to whether these subsets represent different diseases or a spectrum of the same disease has not entirely been settled. These two subsets follow different disease courses with particular organ manifestations [10, 11] and typically experience different outcomes, with poorer survival rates in patients with dcSSc [12]. Patients with dcSSc usually develop Raynaud's phenomenon within a year of onset of skin changes, whereas patients with lcSSc often experience symptoms of Raynaud's phenomenon for years before cutaneous or internal organ manifestations develop [10]. Together with the often rapid progression of cutaneous sclerosis in patients with dcSSc, tendon friction rubs and joint contractures commonly develop [9, 10]. Patients with dcSSc are also more likely to develop severe interstitial lung disease (ILD), SRC, or myocardial involvement during the first few years of disease than those with lcSSc, who typically have a late onset of pulmonary disease, particularly PAH [10]. These two subsets are also distinguished serologically, with the anti-centromere antibody (ACA) associated with lcSSc with a specificity of 93% and the anti-Scl-70 antibody associated with dcSSc with a specificity of 82% [13]. The CREST syndrome, an acronym for calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias, has been considered a subset of lcSSc because of the strong association with ACA [13, 14]. However, because patients with dcSSc can present with any of the five features of CREST, the use of this term as a subset of lcSSc can be confusing [15]. The classical two subset (dcSSc vs. lcSSc) classification scheme has been the most widely used in registries, clinical studies and therapeutic trials.

Three-Subset Cutaneous Model of SSc

The three-subset model of SSc based on extent of skin involvement was first described by Masi in 1988. This model included the following subsets: (1) lcSSc with sclerosis of fingers with or without sclerosis of the neck and/or face; (2) intermediate cutaneous SSc (icSSc) with sclerosis of upper and lower limbs, neck, and face, without truncal involvement; and (3) dcSSc with truncal and acral involvement as described by LeRoy et al. [9, 16]. Survival analysis in a cohort of Italian patients demonstrated that icSSc patients had survival rates that are midway between those of lcSSc and dcSSc [12]. However, a different study in a French Canadian population showed no significant difference in survival between lcSSc and icSSc, but did demonstrate a significant survival difference between patients with lcSSc and dcSSc [17]. In addition, anti-centromere antibodies have been found to perform best in predicting limited cutaneous involvement in SSc distal to the elbows and knees as opposed to fingers alone [13]. The icSSc subset becomes unnecessary when defining lcSSc more broadly, and therefore, the three-subset model has not been used in the majority of clinical studies. However, the three-subset model highlights the prognostic value of skin involvement, even within lcSSc or dcSSc.

Scleroderma Sine Sclerosis

In 1986, Giordano et al. proposed a four-subset cutaneous classification with the inclusion of a group of patients who lacked any evidence of cutaneous sclerosis but had other systemic features of SSc [18]. This group of patients has been termed SSc sine scleroderma (ssSSc) and has since been further characterized [19]. The largest study of patients with ssSSc performed at University of Pittsburgh defined these patients as follows: a clinical diagnosis of SSc with no skin thickening on physical examination and one or more of the following visceral involvements typical of SSc: distal esophageal or small bowel hypomotility, pulmonary fibrosis, PAH, cardiac involvement, or SRC [19]. In addition, Raynaud's phenomenon or a peripheral vascular equivalent (digital pitting scars, digital tip ulcers or gangrene, abnormal nailfold capillaries), a positive anti-nuclear antibody (ANA), and the absence of another defined connective tissue disease were considered necessary for the diagnosis of ssSSc. This study compared 48 patients with ssSSc to 507 patients with lcSSc as defined by LeRoy et al. No differences were found in the frequencies of individual internal organ involvements, laboratory features, SSc-specific autoantibodies, or survival between the groups. In this study, ssSSc patients were more likely to be ANA-positive with other non-SSc-specific autoantibodies than lcSSc patients. The authors concluded that ssSSc patients should be considered a form of lcSSc rather than a distinct subset [19].

Early SSc Versus Undifferentiated Connective Tissue Disease

Early in the disease course, patients with SSc may present with some symptoms or signs suggestive of the disease, as well as serologic abnormalities, without fulfilling the classification criteria for SSc. These patients may be described as undifferentiated or unclassified connective tissue disease (UCTD). The definition of UCTD includes patients with clinical manifestations suggestive of any CTD and the presence of at least one non-organ-specific autoantibody, such as antinuclear antibodies (ANA) or anti-extractable nuclear antigen antibodies (ENA) [20, 21]. Although the majority of patients with UCTD remain undifferentiated or remit, up to one-third of patients may develop an established CTD within 5 years of follow-up [22]. Evolution into SSc occurs in 8–39% of those UCTD patients who develop a definite CTD [22, 23]. The most frequent symptom at the onset of UCTD is Raynaud's phenomenon, and 10% of patients with isolated Raynaud's phenomenon have been shown to progress to SSc [20, 22]. Sclerodactyly and esophageal dysfunction at the onset of UCTD have been identified as significant predictors for evolution into SSc [23]. Therefore, a subset of patients with UCTD may represent those with early SSc, and the presence of sclerodactyly or esophageal dysfunction may be important features to include in classification criteria targeting those with early disease.

Evolution of Mixed Connective Tissue Disease into SSc

Mixed connective tissue disease was initially described by Sharp et al. in 1972 as a disorder displaying clinical features of SLE, SSc, and PM/DM in association with the presence of a high titer of anti-U1-ribonucleoprotein (RNP) antibodies [24]. Debate exists as to whether MCTD represents a distinct disease entity or a variant of individual CTDs [25]. Anti-U1-RNP antibodies occur in approximately 7–21% of SSc patients and can be present in other CTDs as well [26, 27]. In addition, 55% of patients initially classified as MCTD can be diagnosed as having one or a combination of two CTDs within 5 years of follow-up [28]. In one study, approximately one-third of MCTD patients evolved into SSc or an SSc overlap syndrome [28]. Therefore, a subset of patients with MCTD may in reality represent early SSc. The identification of predictive factors for the evolution of MCTD into SSc may be useful in recognizing patients who have early SSc.

American Rheumatism Association/American College of Rheumatology Classification Criteria

Study Design and Description

The intent of the 1980 ACR classification criteria for SSc was "to establish a standard for definite or certain disease in order to permit comparison of groups of patients from different centers and to assist in the proper evaluation of the results of clinical investigation and therapeutic trials" [29]. These criteria were not designed to aid in the diagnosis of early disease,

Table 7.1 Clinical and laboratory variables originally selected for criteria for classification of SSc

Clinical variables	Laboratory variables
Sclerodermatous skin changes	LE cell preparation
Any location	FANA, any titer
Sclerodactyly	Latex agglutination, any titer
Proximal scleroderma	X-ray findings
Face or neck	Digital tuft resorption
Bilateral hand edema	Calcinosis, subcutaneous
Digital pitting scars	Bibasilar pulmonary fibrosis
Hand deformity or contractures	Abnormal electromyogram
Abnormal skin pigmentation	Esophageal manometry
Raynaud's phenomenon	Abnormal proximal only
Telangiectasia, fingers	Abnormal distal only
	Abnormal proximal and distal
	Gastrointestinal X-ray
	Esophageal hypomotility proximal only
	Esophageal hypomotility distal only
	Esophageal hypomotility proximal and distal
	Duodenal loop dilatation
	Colonic sacculations
	Skin biopsy with dermal collagen thickening
	Anti-RNP
	Anti-Sm
	ESR
	Serum complement (C3)
	Urine creatine excretion
	SGOT

Modified from [29]
LE lupus erythematosus, *FANA* fluorescent anti-nuclear antibody, *RNP* ribonucleoprotein, *Sm* Smith, *ESR* erythrocyte sedimentation rate, *SGOT* serum glutamic oxaloacetic transaminase

Table 7.2 1980 American Rheumatism Association criteria for the classification of systemic sclerosis [29][a]

Major criterion: proximal cutaneous sclerosis
Induration of the skin proximal to the metacarpophalangeal or metatarsophalangeal joints, affecting other parts of the extremities, face, neck or trunk, usually bilateral, symmetrical, and almost always including sclerodactyly
Minor criteria
1. Sclerodactyly
2. Digital pitting scars of fingertips or loss of substance of the distal finger pad
3. Bibasilar pulmonary fibrosis

[a] One major criterion or two or more minor criteria provide a sensitivity of 97% and specificity of 98% for definite systemic sclerosis

but were based on patients who had a diagnosis of definite SSc that was made no longer than 2 years before entry into the study. The study included 264 cases of definite SSc and 413 comparison patients with systemic lupus erythematosus (SLE), polymyositis/dermatomyositis (PM/DM), and Raynaud's phenomenon. Twenty-nine rheumatology centers in the US, Canada, and Mexico were involved in this multicenter effort. Table 7.1 shows the clinical and laboratory variables originally selected for criteria analysis [29]. Using univariate and multivariate analyses, the goal was to find the fewest items that yielded the highest sensitivity and specificity for SSc.

The final classification criteria are listed in Table 7.2 [29]. Proximal scleroderma, defined as "sclerodermatous involvement proximal to the digits, affecting proximal portions of the extremities, the face, neck, or trunk" was found to be the most useful major criterion with a specificity of 99.8% differentiating SSc cases from comparison patients. Using multivariate analytic techniques, three minor criteria were identified: (1) sclerodactyly, (2) digital pitting scars of fingertips or loss of substance of the distal finger pad, and (3) bilateral basilar pulmonary fibrosis on chest X-ray. Either the one major criterion or [3]two minor criteria provided a sensitivity of 97% and specificity of 98% [29]. The proposed criteria were then externally validated using more than 1,300 case and comparison patients stored in the American Rheumatism Association Medical Information System (ARAMIS) database, yielding a sensitivity of 92% and a specificity of 96% [29].

Limitations

As mentioned above, the intent of the criteria was not specifically to identify patients with early SSc, and in fact, 35 patients with probable or early stage SSc were excluded from the analyses. Therefore, the population of patients who are most likely to benefit from therapeutic interventions, and who should be targeted for enrollment into clinical trials, is not represented by these classification criteria. Several studies have verified the low sensitivity of the ACR classification criteria for early SSc. A study comparing 240 SSc patients from the USA and 87 SSc patients from France showed sensitivities of 83% and 87% in the two populations, respectively [27]. Nadashkevich et al. reported an even lower sensitivity of 70% due to the exclusion of patients with early disease who had SSc-specific serologic markers and rapidly progressive disease [30].

In addition to excluding patients with early SSc, the current ACR classification criteria exclude a substantial portion of patients with established mild or limited cutaneous disease. An initial evaluation of the ACR classification criteria in the Pittsburgh SSc cohort found that 41% of lcSSc did not fulfill the major criterion, and 20% did not fulfill either the major or two of the three minor criteria [31]. Maricq and Valter reported that only 53% of their cohort, which included patients with diffuse and intermediate cutaneous involvement, sclerodactyly only, sine sclerosis, UCTD, and CREST, fulfilled the ACR criteria [32]. Ninety-six percent (77/80) of patients in the latter three categories with more mild disease were excluded [32]. Hudson et al. studied a group of SSc patients from the Canadian Scleroderma Research Group who had skin involvement distal to the metacarpophalangeal joints only. Of 101 patients, only 68 (67%) met the ACR classification criteria [33]. Lonzetti et al. reported an even poorer sensitivity with only one-third of French Canadian patients with lcSSc as diagnosed by expert clinicians fulfilling the 1980 ACR classification criteria [34].

Importance of Revising ACR Classification Criteria

There are several reasons why revision of the ACR classification criteria is necessary and timely. As described above, the poor sensitivity for patients with early SSc limits the identification of patients who may potentially have a greater response to treatment before irreversible damage ensues. Therefore, exclusion of these patients affects early diagnosis in clinical practice, as well as enrollment of appropriate patients in clinical studies and therapeutic trials. The low sensitivity for patients with lcSSc has also resulted in exclusion of a large portion of eligible patients in clinical trials. LcSSc patients may indeed benefit from treatments targeting cutaneous sclerosis, ILD, PAH, Raynaud's phenomenon and digital ulcerations, and should not be excluded from these studies. Technological advances in the past few decades provide an opportunity to improve the sensitivity of the current classification criteria. In particular, the development and widespread availability of tests for SSc-specific autoantibodies and nailfold capillary abnormalities have improved the detection of early SSc, and should be incorporated into the revised classification criteria. Data supporting the utility of these tests in the diagnosis of SSc will be discussed below.

Autoantibodies in the Diagnosis of SSc

Autoantibodies are detected in more than 95% of patients with SSc [35]. Seven SSc-specific autoantibodies have been described, but not all are widely clinically available (Table 7.3). These autoantibodies are rarely detected in patients with other CTDs and very infrequently observed in the general population [13]. These antibodies generally remain stable over time and are mutually exclusive in the majority of patients [13]. Autoantibody status (ACA vs anti-Scl-70 antibody positivity)

Table 7.3 Scleroderma-specific autoantibodies

Anticentromere[a]
Anti-Scl-70 (anti-topoisomerase I)[a]
Anti-PM/Scl[ab]
Anti-Th/To[b]
Anti-U3-ribonucleoprotein (antifibrillarin)[b]
Anti-RNA polymerase I/III[a]
Anti-U1-ribonucleoprotein[a]

[a] Clinically available at the majority of centers
[b] Associated with nucleolar staining pattern of anti-nuclear antibody

has been shown to supersede cutaneous subset (lcSSc vs dcSSc) in predicting the development of particular SSc organ manifestations [11]. Autoantibodies have also been shown to precede the onset of symptoms in SSc and other CTDs, such as SLE, and therefore, they are useful in the early diagnosis of disease [36, 37].

Anticentromere Antibodies

ACA have a high specificity for the limited cutaneous subset of SSc, but 5–7% of patients with dcSSc can have ACA [11, 35]. ACA have been associated with long disease duration at diagnosis with a mean of 8.7 years since first SSc symptom onset at the time of diagnosis [35]. Patients with ACA have a significantly higher prevalence of digital tip ulcers, gangrene, digital tuft resorption, and calcinosis than patients with other SSc-specific autoantibodies, but significantly lower prevalence of arthritis or muscle inflammation [35]. In addition, ACA are associated with the development of isolated pulmonary hypertension [11, 35].

As a diagnostic test for SSc, ACA detected by indirect immunofluorescence show a high degree of specificity, but fairly low sensitivity. Compared with healthy controls, the ACA has a specificity of almost 100%, but a sensitivity of 33% [13]. The sensitivity improves to 65% when comparing the frequency of ACA in patients meeting at least 2 of 5 CREST criteria to healthy controls. The sensitivity is 31% when diagnosing SSc compared with other CTDs, but the specificity remains high at 97.4%. When compared with patients with primary Raynaud's phenomenon, the sensitivity is 24.1% and specificity 90% [13]. Given the overall high specificity for diagnosing SSc and the strong predictive value in determining internal organ involvement, ACA appears to be a good candidate for inclusion in diagnosis or classification of SSc.

Anti-Scl-70 Antibodies

Anti-Scl-70 (also known as anti-topoisomerase I) antibodies are classically associated with diffuse cutaneous disease, however, 31–36% of SSc patients with anti-Scl-70 antibodies have lcSSc [11]. Anti-Scl-70 positivity is associated with a higher prevalence of arthritis, tendon friction rubs, severe pulmonary fibrosis, severe heart disease, and SRC than other SSc-specific autoantibodies, presumably due to the association of these organ manifestations with diffuse cutaneous disease [35]. Similar to ACA, anti-Scl-70 antibodies also confer a higher risk for compromise of the microvasculature with a high prevalence of digital tip ulcers, gangrene, and digital tuft resorption in patients with anti-Scl-70 antibodies [35]. Unlike diffuse cutaneous involvement, anti-Scl-70 positivity is associated with a higher prevalence of myocardial conduction block and diastolic dysfunction, but a lower prevalence of hypertension, than ACA positivity [11].

Similar to ACA, anti-Scl-70 antibodies detected by immunodiffusion have a very high specificity of 100% compared with normal controls; however, the sensitivity is only 20.2% [13]. Compared with patients with other CTDs or primary Raynaud's phenomenon the specificity remains high at 99.5% and 98%, with sensitivity of 26% and 28%, respectively [13]. The sensitivity improves to approximately 40% when compared with normal controls and other CTDs if immunoblotting techniques are used to detect anti-Scl-70 antibodies [13]. Further data on the diagnostic value of anti-Scl-70 antibodies detected by enzyme-linked immunosorbent assays (ELISA) is necessary. The high specificity of anti-Scl-70 antibodies, and the ability to predict organ involvement even better than the diffuse cutaneous subset, makes these antibodies important to consider in revised classification criteria for SSc.

Anti-nucleolar Antibodies

A nucleolar staining pattern of ANA on indirect immunofluorescence can be observed when any of the following SSc-specific autoantibodies is present: anti-PM-Scl, anti-Th/To, anti-U3-RNP (antifibrillarin), and anti-RNA-polymerase (RNAP) I, II, and III. The anti-RNAP antibodies, and in particular anti-RNAP III, demonstrate nucleolar staining only 30–44% of the time [38, 39]; therefore nucleolar staining on the ANA is not useful as a screening test for these autoantibodies, and they will be discussed separately. Immunodiffusion to detect anti-PM-Scl antibodies is commercially available, while the other nucleolar autoantibodies are typically detected by immunoprecipitation performed only at certain centers. However, a new ELISA for the detection of antibodies to fibrillarin and PM-Scl was recently described [40]. When evaluated in 50 SSc patients who were negative for ACA and anti-Scl-70 compared with 122 controls (42 SSc positive for ACA

or anti-Scl-70, 40 SLE, and 40 rheumatoid arthritis), the antifibrillarin ELISA had a sensitivity of 22% and specificity of 92.5%, and the anti-PM-Scl antibody had a sensitivity of 8% and specificity of 98.8% [40]. This study, however, did not compare the sensitivity and specificity of the ELISAs to immunoprecipitation.

Anti-PM-Scl antibodies are detected in 3–12.5% of patients with SSc and are associated with a high prevalence of muscle inflammation [27, 41]. Patients with anti-PM-Scl antibodies also have a high prevalence of severe pulmonary fibrosis and digital ulcers with a lower frequency of PAH [35, 41].

Anti-Th/To antibodies are associated with the limited cutaneous subset and have been reported in up to 24% of lcSSc patients compared with 2% of dcSSc patients [35]. Patients with these autoantibodies have a high prevalence of pulmonary fibrosis and pulmonary hypertension, as well as severe gastrointestinal involvement [35]. Compared with ACA, lcSSc patients with anti-Th/To antibodies have more subtle skin disease, less severe digital vasculopathy, and a higher prevalence of ILD [42]. The presence of anti-Th/To antibodies in patients with lcSSc portends a poorer prognosis than other SSc-specific autoantibodies [35, 42].

Anti-U3-RNP antibodies are present in 8% of patients with SSc and are associated with African American race [43]. These autoantibodies are associated with male gender and the diffuse cutaneous subset. SSc patients with these autoantibodies have a high prevalence of pulmonary fibrosis, cardiac, renal, and gastrointestinal involvement [35, 43]. Initial reports did not find an association between anti-U3-RNP antibodies and pulmonary hypertension, but a more recent study found an increased frequency of the combination of ILD and isolated pulmonary hypertension in patients with anti-U3-RNP antibodies [35].

Although anti-nucleolar antibodies have been reported in 15–40% of patients with SSc, few studies have reported the frequency of these autoantibodies in healthy controls or other CTDs [13]. A recent study indicated that anti-PM-Scl antibodies have a specificity of 96.9% for SSc when compared with healthy controls and other CTDs, but no patients with PM/DM were included in the comparison group [41]. Anti-Th antibodies have been shown to be 98.8% specific for SSc when compared with other CTDs [44]. However, one report evaluating for antifibrillarin antibodies by radioimmunoassay found that these antibodies were present in a large percentage of patients with MCTD, SLE, rheumatoid arthritis, and Sjogren's syndrome in addition to patients with SSc [45]. The lack of specificity of the radioimmunoassay for antifibrillarin antibodies may not apply to immunoprecipitation methods. Although anti-nucleolar antibodies may be specific for SSc, the variable sensitivity and the lack of widespread commercially available assays for these autoantibodies make them less useful for classification criteria.

Anti-RNA-Polymerase Antibodies

Anti-RNAP antibodies detected by immunoprecipitation have been reported in 4–25% of patients with SSc depending on the population studied [27, 39]. On indirect immunofluorescence, these antibodies typically display a fine-speckled nucleoplasmic stain with additional occasional bright dots, with or without concurrent punctate nucleolar staining [39]. Although anti-RNAP II antibodies are not specific for SSc and have been reported in 9–14% of patients with SLE and MCTD, antibodies to RNAP I and III detected by immunoprecipitation have a specificity of >99% for SSc when compared with other CTDs [46]. Anti-RNAP III antibodies are associated with diffuse cutaneous disease and a high prevalence of SRC, but a low frequency of severe pulmonary fibrosis [35]. In recent years, anti-RNAP III antibodies have been detected by ELISA and have become more widely available. Compared with immunoprecipitation, the ELISA has a sensitivity of 91–96% and specificity of 98–99% [39, 47]. As a diagnostic test for SSc, the sensitivity and specificity of the ELISA for anti-RNAP III have been reported as 11–17% and 98–99%, respectively [47, 48]. The relatively high sensitivity and specificity of anti-RNAP III antibodies for SSc, the strong predictive value of these antibodies for diffuse skin disease and SRC, and the increasing availability of the ELISA assay to test for these antibodies are all reasons that anti-RNAP III antibodies may be considered for inclusion in the revised ACR classification criteria.

Anti-U1-RNP Antibodies

As described above, anti-U1-RNP antibodies are present in high titers in patients with MCTD, but they can also be detected in 7–21% of patients with SSc [26, 27]. Clinical features associated with the presence of anti-U1-RNP antibodies in patients with SSc include a younger age at disease onset, vasospasm, arthritis, muscle inflammation, and ILD [26, 35]. In patients with lcSSc, the presence of anti-U1-RNP antibodies predicts a better survival when compared with other SSc-specific antibodies [35]. Given the high prevalence of anti-U1-RNP antibodies in patients with MCTD, overlap syndromes, and other CTDs, these antibodies may not be useful in classification criteria for SSc.

Nailfold Capillaroscopy in the Diagnosis of SSc

Nailfold Capillaroscopic Patterns in SSc

Since the 1970s, patients with SSc have been known to demonstrate a distinct pattern of nailfold capillary abnormalities when examined microscopically compared with patients with primary Raynaud's phenomenon and other connective tissue diseases [49, 50]. Maricq et al. initially described the scleroderma-pattern of capillary abnormalities using in vivo widefield capillaroscopic techniques. Enlarged and deformed capillary loops surrounded by relatively avascular areas were found in 82% of patients with SSc and 54% of patients with MCTD but only 2% of patients with SLE [50]. One of 11 patients with primary Raynaud's phenomenon showed these changes, but this patient developed SSc 5 months after the initial capillaroscopic examination. Another study found that the presence of the scleroderma-pattern of capillary abnormalities predicted the development of SSc in five of ten patients with Raynaud's phenomenon within 9 months to 5 years of follow-up [51]. A more recent study found that approximately 14% of patients with UCTD had the scleroderma pattern on nailfold capillaroscopy, and thus may be at higher risk of progressing to SSc or a related CTD [52].

During the past decade, nailfold videocapillaroscopic techniques have been used to describe three patterns of microangiopathy in SSc that correlate with disease duration: early, active, and late (Fig. 7.1) [53, 54]. The early pattern is characterized by few (fewer than four altered capillaries per millimeter) enlarged or giant capillaries, few capillary hemorrhages, relatively well-preserved capillary distribution, and no evident loss of capillaries. The active pattern demonstrates frequent (more than six altered capillaries per millimeter) giant capillaries, frequent capillary hemorrhages, 20–30% loss of capillaries, mild (between 4 and 6 altered capillaries per millimeter) disorganization of the capillary architecture, and absent or mild ramified capillaries. The late pattern shows irregular enlargement of the capillaries, few or absent giant capillaries and hemorrhages, and 50–70% loss of capillaries with large avascular areas, disorganization of the normal capillary array, and ramified or bushy capillaries [53, 54]. The late pattern was shown to be associated with older age and longer duration of Raynaud's phenomenon and SSc when compared with the early and active patterns [54]. Therefore, the early capillaroscopic changes of enlarged and giant capillaries, along with hemorrhages, likely represent the earliest microvascular changes observed in patients with SSc or related diseases, and may be useful in the early diagnosis of SSc.

Office Capillaroscopy

Although widefield microscopy and nailfold videocapillaroscopy provide detailed images of the nailfolds and have excellent inter- and intra-rater reliability in the detection of giant capillaries, microhemorrhages, and capillary loss [55], these modalities are not widely available and require specific training to use the instruments. The ophthalmoscope is a widely accessible instrument that has been used to assess for nailfold capillary abnormalities in the office setting with the application of a drop of oil or immersion gel to the nailfold surface. One study showed that the ophthalmoscope detected giant capillaries, severe avascular areas (loss of more than six capillaries), and bushy capillaries with 100% correlation with the stereomicroscope [56]. However, another study showed only moderate agreement between use of the ophthalmoscope and the microscope in detecting dilated and giant capillaries (kappa 0.63 and 0.52, respectively), with poor agreement in the detection of avascular areas (defined as any confluent area free of capillary loops) (kappa <0.1) [57]. The latter study also showed moderate inter- and intra-rater reliability for the ophthalmoscopic detection of dilated (kappa 0.43 and 0.61) and giant (kappa 0.54 and 0.56) capillaries with poor reliability for detection of avascular areas (kappa 0.19 and 0.31) [57].

The dermatoscope is a handheld, battery-powered instrument used by dermatologists to assess pigmented and other skin lesions. The most current models use a polarized light source that eliminates reflection from the skin surface, and therefore do not require the application of oil or immersion gel. When compared with the standard microscope, the dermatoscope has shown excellent agreement for the detection of dilated capillaries (kappa 0.93), megacapillaries (kappa 0.97), avascular areas (kappa 0.93), and microhemorrhages (kappa 0.94) [58]. The inter- and intra-rater reliability using the dermatoscope was better than that of the ophthalmoscope for detecting dilated (kappa 0.63 and 0.71) and giant (kappa 0.4 and 0.55) capillaries but was also poor for the detection of avascular areas (kappa 0.2 and 0.4) [57]. The dermatoscope is relatively inexpensive and is easy to use with a mean capillaroscopic examination time of 4 min [58]. When used to differentiate patients with SSc from healthy controls, the presence of two or more enlarged capillaries in one or more fingers as detected by the dermatoscope showed a sensitivity of 83% and specificity of 100% for the diagnosis of SSc [59]. Hudson et al. assessed the effect of the addition of capillaroscopic changes detected by the dermatoscope to the sensitivity

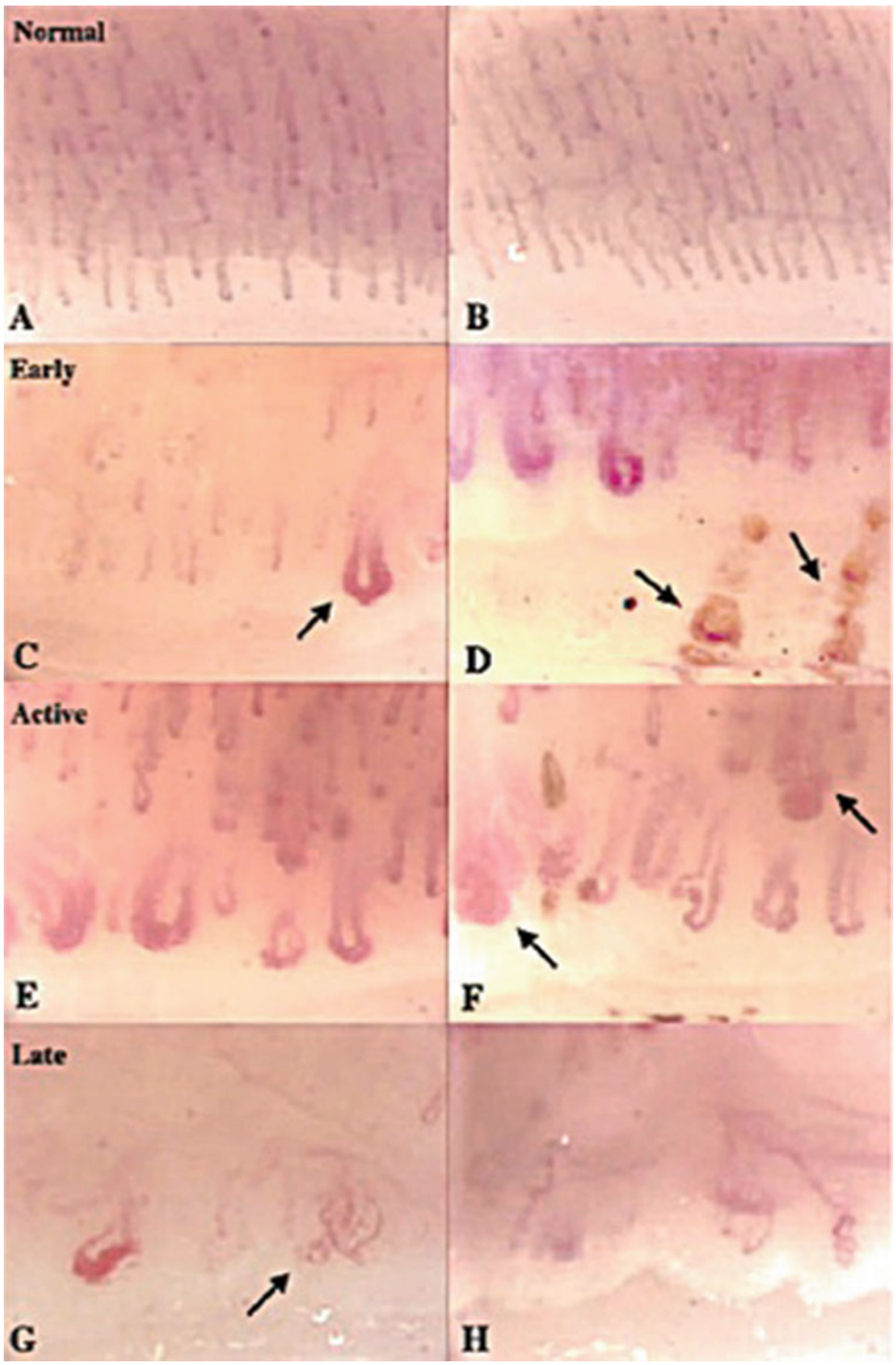

Fig. 7.1 Early, active, and late nailfold capillaroscopic patterns observed in systemic sclerosis

of the ACR criteria in a population of SSc patients with skin involvement distal to the metacarpophalangeal joints (with or without face involvement) [33]. They found that the sensitivity improved from 67% to 91%, with further improvement to 99% if visible mat-like telangiectasias were added [33]. Capillaroscopic evaluation using the dermatoscope may provide a feasible technique for clinicians and researchers to assess patients with early microvascular changes consistent with the scleroderma-pattern.

Autoantibodies and Capillaroscopic Abnormalities may Predict the Onset of SSc

Several studies have shown that the combination of autoantibodies and nailfold capillaroscopic abnormalities may be helpful in the early detection of SSc and related diseases in patients presenting with Raynaud's phenomenon. The annual incidence of transition from primary Raynaud's phenomenon to secondary Raynaud's phenomenon has been shown to be 1%, with ANA > 1:160 at presentation increasing the risk of developing secondary Raynaud's phenomenon by more than 68-fold [60]. In this study, after a mean follow-up period of 11.2 ± 3.9 years, the prevalence of transition from primary to secondary Raynaud's phenomenon was in 14.9% of cases [60]. Another study found that the addition of serial nailfold videocapillaroscopic examinations identified a similar percentage of patients transitioning from primary to secondary Raynaud's phenomenon over a shorter follow-up time of 29.4 ± 10 months [61]. Therefore, the addition of nailfold capillaroscopic examination to standard evaluations, including autoantibody assessments, likely permits the earlier detection of secondary Raynaud's phenomenon. Another study of 152 patients with sclerodactyly and Raynaud's phenomenon found that the addition of dilated capillaries visualized by stereomicroscope improved the sensitivity of ACR criteria for the diagnosis of SSc from 33.6% to 74.3% [34]. This was further improved to 82.9% with the addition of avascular areas detected by stereomicroscope, 88.8% with the addition of visible nailfold telangiectasias, and 91.5% with the addition of ACA [34]. A recent study evaluated a cohort of 586 patients with Raynaud's phenomenon and found that 12.6% ($n = 74$) of these patients progressed to definite SSc over a median follow-up time of 4.6 years [62]. Only 24 (32%) of these patients fulfilled the ACR criteria for SSc. The strongest independent predictors for the development of definite SSc were positive ANA, SSc-specific autoantibodies (anti-Scl-70, antiTh/To, ACA or anti-RNAP III), and a scleroderma pattern on nailfold capillaroscopy using stereomicroscope [62]. The combination of the presence of abnormal findings on nailfold capillaroscopy and SSc-specific autoantibody at baseline was associated with a 60-fold increased risk for the development of definite SSc, with a sensitivity of 47%. The presence of abnormal capillaroscopy and/or SSc-specific autoantibody at baseline improved the sensitivity to 89% with a negative predictive value of 98% [62]. In other words, patients with Raynaud's and normal findings on nailfold capillaroscopy and negative SSc-specific autoantibodies had a probability of only 1.6% to have SSc 10 years later; quite in contrast, patients with Raynaud's and SSc pattern on nailfold capllaroscopy and positive SSc-specific autoantibodies had a 73% probability to have developed SSc in the course of 10 years. This illustrates how the patient profile informs clinicians about the probability of SSc being present (becoming manifest). These studies support the usefulness of SSc-specific autoantibodies and nailfold capillaroscopic abnormalities in the early diagnosis of SSc and in the revised classification criteria.

Recently Proposed Classification Criteria for SSc

Multiple different classification criteria have been proposed for SSc over the past several decades [63, 64]. Here we will discuss the most widely accepted criteria proposed since 2000.

LeRoy and Medsger Criteria

In 2001, LeRoy and Medsger proposed an amended version of the classification criteria originally published by LeRoy in 1988 [65]. Taking advantage of the SSc-specific autoantibodies and nailfold capillaroscopy to detect vascular changes suggestive for connective tissue diseases, Leroy and Medsger suggested to extend the classification criteria to include "early" cases of SSc still without skin manifestations. Criteria for limited SSc (lSSc or "pre-SSc" or "unclassifiable SSc") can be fulfilled by patients with Raynaud's phenomenon plus a SSc-type nailfold capillary pattern and/or SSc-specific autoantibodies (Table 7.4A) [65]. Patients with lSSc must have either (1) objective documentation of Raynaud's phenomenon (direct observation or direct measurement of response to cold) plus either abnormal widefield nailfold capillaroscopy or SSc-specific autoantibodies (ACA, anti-Scl-70, anti-fibrillarin, anti-PM-Scl, anti-fibrillin or anti-RNAP I or III in a titer of 1:100 or higher); or (2) subjective symptoms of Raynaud's phenomenon plus abnormal widefield nailfold capillaroscopy and SSc-specific autoantibodies [65]. Patients with lSSc can have overlap features, thus capturing patients with UCTD and MCTD who have prominent sclerodermatous features. Patients with lSSc who also have cutaneous manifestations of SSc are again subdivided into the limited cutaneous (lcSSc) and diffuse cutaneous (dcSSC) forms (Table 7.4B) [65]. These subsets are differentiated from patients with diffuse fasciitis and eosinophilia who have proximal cutaneous changes but do not have Raynaud's phenomenon, abnormal nailfold capillaries, autoantibodies, or distal cutaneous changes. A small retrospective

Table 7.4 LeRoy and Medsger criteria for the classification of early systemic sclerosis (SSc)

A. Proposed criteria for limited forms of SSc (lSSc)
Raynaud's phenomenon (RP), objectively documented by
1. Direct observation of any two of:
(a) Pallor (well demarcated whitening of acral skin)
(b) Cyanosis (dusky blueness, which disappears on rewarming)
(c) Suffusion (well demarcated redness)
Or 2. Direct measurement of response to cold by:
(a) Objective evidence of delayed recovery after cold challenge
(b) Nielsen test or equivalent
Plus 1. Abnormal widefield nailfold capillaroscopy (dilation and/or avascular areas)
Or 2. SSc selective autoantibodies (anti-centromere, anti-Scl-70, antifibrillarin, anti-PM-Scl, anti-fibrillin, or anti-RNA polymerase I or III in a titer of 1:100 or higher)
If RP is subjective only, both SSc capillary pattern and SSc selective autoantibodies (in titer > 1:100) are required to define lSSc. LSSc can overlap with any other disease
B. Constellations of criteria for diagnosis of SSc
1. LSSc: defined in A above
2. LcSSc: criteria for lSSc + distal cutaneous changes
3. DcSSc: criteria for lSSc + proximal cutaneous changes
4. Diffuse fasciitis with eosinophilia (DFE): proximal cutaneous changes without criteria for lSSc or lcSSc

Modified from [65]

Table 7.5 Maricq and Valter proposed classification of scleroderma spectrum disorders

Group	Classification criteria definitions
I Diffuse scleroderma disorder[a]	Skin involvement proximal to elbows/knees; includes trunk
II Intermediate scleroderma disorder[a]	Skin involvement proximal to MCP/MTP, distal to elbows/knees; trunk not involved
III Digital scleroderma disorder	Sclerodactyly only; meets ACR minor criteria, but excludes those without skin involvement
IV Scleroderma sine sclerosis	Scleroderma-capillary pattern or pitting scars and visceral involvement; no ACA; no telangeictasias
V UCTD-scleroderma disorder	UCTD with scleroderma features; no ACA; no telangiectasias
VI "CREST"	No skin involvement or sclerodactyly only; telangeictasias required with one or more other acronyms; or ACA is required with any two or more acronyms

Modified from [32]
MCP metacarpophalangeal, *MTP* metatarsophalangeal, *ACR* American College of Rheumatology, *ACA* anticentromere antibodies, *UCTD* undifferentiated connective tissue disease, *CREST* calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias
[a]Groups I and II were subdivided into two categories: (a) without and (b) with CREST features

Swiss study found that 33/49 (67%) of SSc patients fulfilled the ACR classification criteria for SSc [66]. When using the amended LeRoy and Medsger criteria, this improved to 80% [66]. The study by Lonzetti et al. also included a group of 152 lSSc patients with Raynaud's phenomenon, but these patients also had sclerodactyly [34]. When adding nailfold capillary abnormalities and positive ACA to the ACR classification criteria, the sensitivity for diagnosis of SSc improved from 33.6% to 91.5% [34]. The amended LeRoy and Medsger criteria certainly improve the sensitivity of the ACR classification criteria but exclude a small percentage of patients with SSc who lack Raynaud's phenomenon. Studies indicate that approximately 10% of patients with SSc do not suffer from Raynaud's phenomenon [1, 32]. Patients most likely to be excluded by these criteria are those who do not have sclerodactyly or cutaneous sclerosis, but have internal organ disease consistent with SSc and SSc-specific autoantibodies or nailfold capillary abnormalities.

Maricq and Valter Criteria

In 2004, Maricq and Valter proposed another set of classification criteria for SSc with six different categories (Table 7.5) [32]. The first three groups are divided based on the extent of cutaneous sclerosis. The fourth category includes patients with scleroderma sine sclerosis who have internal organ involvement and scleroderma-pattern nailfold capillary changes or

Table 7.6 Nadashkevich, Davis, and Fritzler proposed criteria for systemic sclerosis (SSc)

Criterion	Comments
Autoantibodies	Anti-centromere, anti-Scl-70, or anti-fibrillarin
Bibasilar pulmonary fibrosis	Detected by chest radiograph
Contracture	Permanent limitation of joint motion
Dermal thickening proximal to wrists	Defined by the modified Rodnan skin score [68]
Calcinosis cutis	Detected by X-ray, crystallographic/chemical analysis
Raynaud's phenomenon	By patient's history or physician's observation
Esophageal distal hypomotility	Detected by cine/video barium esophagram or endoscopy
Sclerodactyly	Symmetric tightening of skin or nonpitting edema of digits
Telangiectasias	Common locations: digits, face, lips, tongue

Modified from [67]. Three or more of these criteria are necessary for a diagnosis of SSc

pitting scars but no ACA or telangiectasias. The fifth group includes patients with UCTD with sclerodermatous features but no ACA or telangiectasias. The last category includes patients who fulfill the CREST criteria with telangiectasias plus one or more of the other acronyms or ACA plus two or more of the acronyms [32]. Using these classification criteria, Maricq and Valter were able to capture 77/165 (47%) patients with mild or early forms of SSc who were excluded from the ACR classification criteria [32]. Unlike the LeRoy and Medsger criteria, these criteria do not require the presence of Raynaud's phenomenon, thus increasing the sensitivity for SSc. However, the Maricq and Valter criteria only include the assessment of one SSc-specific autoantibody (ACA), which may compromise sensitivity. In addition, these criteria have not been externally validated and have been criticized for being too complicated.

Nadashkevich, Davis, and Fritzler Criteria

Nadashkevich et al. proposed another set of classification criteria in 2004 through a three-phase study [67]. The first phase involved 752 Ukrainian patients assessed between 1987 and 1994 who were diagnosed with SSc ($n=170$, 38% dcSSc, 56% lcSSc, 6% overlap), SLE ($n=170$), RA ($n=170$), PM/DM ($n=20$), Sjogren's syndrome ($n=23$), isolated Raynaud's phenomenon ($n=88$), diabetes mellitus ($n=100$), eosinophilic fasciitis ($n=5$), and generalized morphea ($n=6$). In this cohort, the sensitivity of the ACR classification criteria for SSc was only 71.2% [67]. In the proposed criteria, classification as SSc was based on the presence of Raynaud's phenomenon and/or sclerodactyly or non-pitting digital edema plus one of 13 other SSc-related clinical manifestations. This phase identified 8 of the 15 clinical criteria as sufficient to identify all patients with SSc if at least 3 of the 8 criteria were fulfilled. None of the controls had more than two of the clinical criteria. Phase IIA of the study validated the initial set of 8 clinical criteria in an independent cohort of 99 Canadian SSc patients and 138 controls with SLE, RA, PM/DM, and Sjogren's syndrome evaluated between 1995 and 1997 [67]. In the external validation study, the criteria had a sensitivity of 99% (compared with a sensitivity of 69.7% using ACR criteria) and specificity of 100% for the diagnosis of SSc. In Phase IIB, various autoantibodies were assessed to add to the proposed criteria with the hopes of increasing sensitivity further. Ultimately, the presence of ACA (detected by indirect immunofluorescence), anti-Scl-70 antibodies (detected by double immunodiffusion), or antifibrillarin antibodies (detected by immunoprecipitation) was added as a final criterion [67]. Phase III of the study reviewed the SSc and isolated Raynaud's phenomenon patients in Phase I to develop the final set of classification criteria, requiring three or more criteria for a diagnosis of definite of SSc (Table 7.6) [67]. Although the authors demonstrate superb sensitivity and specificity of their proposed classification criteria, other independent validation studies have not been performed [30]. Although this set of classification criteria does account for patients without Raynaud's phenomenon, abnormal nailfold capillaroscopic examination and other SSc-specific autoantibodies (i.e., Anti-RNAP III) were not included in the criteria.

Criteria from the Canadian Scleroderma Research Group

In 2007, Hudson et al. proposed a revision to the ACR classification criteria using data from the Canadian Scleroderma Research Group (CSRG) [33]. The authors proposed the addition of nailfold capillary abnormalities as assessed by the handheld dermatoscope (dilated or giant capillary loops or avascular areas) plus visible mat-like telangiectasias to the ACR

classification criteria. Using the proposed criteria, the sensitivity to identify SSc patients with skin involvement distal to the metacarpophalangeal joints improved from 67% to 99% [33]. However this study did not include controls, and therefore the specificity of the proposed criteria was not assessed. Since SSc-specific autoantibodies and Raynaud's phenomenon were not included, the specificity of this classification system may be lower than other proposed criteria.

In 2010, Hudson, Fritzler and Baron published diagnostic criteria for SSc to aid the clinician in recognizing salient features of SSc rather than to classify patients for observational studies or clinical trials [69]. Of 1048 SSc patients from the CSRG, 127 (12%) did not fulfill the ACR classification criteria. Using regression tree analysis, the authors identified the presence of Raynaud's phenomenon, skin thickening proximal to the fingers, mat-like telangiectasias, and SSc-specific autoantibodies (ACA and anti-Scl-70) as providing 97% sensitivity for the diagnosis of SSc [69]. Again this study did not include controls to assess specificity. A combination of the two sets of criteria proposed by Hudson et al. might be useful in the revision of the ACR classification criteria.

Current Projects for Revising the ACR Classification Criteria

Very Early Diagnosis of Systemic Sclerosis (VEDOSS)

The very early diagnosis of systemic sclerosis (VEDOSS) project of the European League Against Rheumatism Scleroderma Trials and Research group (EUSTAR) aims at early diagnosis of SSc. Early SSc may be suspected on the basis of Raynaud's phenomenon, autoantibodies and SSc capillaroscopic pattern [65]. Presumably, also puffy fingers or early signs of sclerodactyly or one of the other early symptoms of SSc are to be considered in early diagnosis. For clinical purposes, the aim is to have criteria for the diagnosis of very early SSc. The criteria that are proposed are obviously provisional (Fig. 7.2) and need to be validated: (a) initially through a Delphi technique; (b) thereafter perhaps using already available datasets; but (c) of critical importance, through prospective studies [70]. Prospective studies are needed for validation of proposed diagnostic criteria. Moreover, prospective studies do inform the clinician what the exact probabilities are that a patient may or may not have (or develop) SSc. In the VEDOSS cohort, patients are included with an increased probability of SSc; patients with Raynaud's phenomenon and/or puffy fingers who are positive for ANA are considered to be at risk (Fig. 7.3). The other items that were judged as most relevant for the diagnosis of SSc were sclerodactyly, abnormal capillaroscopy, positive ACA, and positive anti-Scl-70 antibodies (Table 7.7). If a sufficient number of patients are included with a sufficiently long follow-up time (i.e., at least 5 years), then the best predictors and the probabilities of having/developing SSc can be determined.

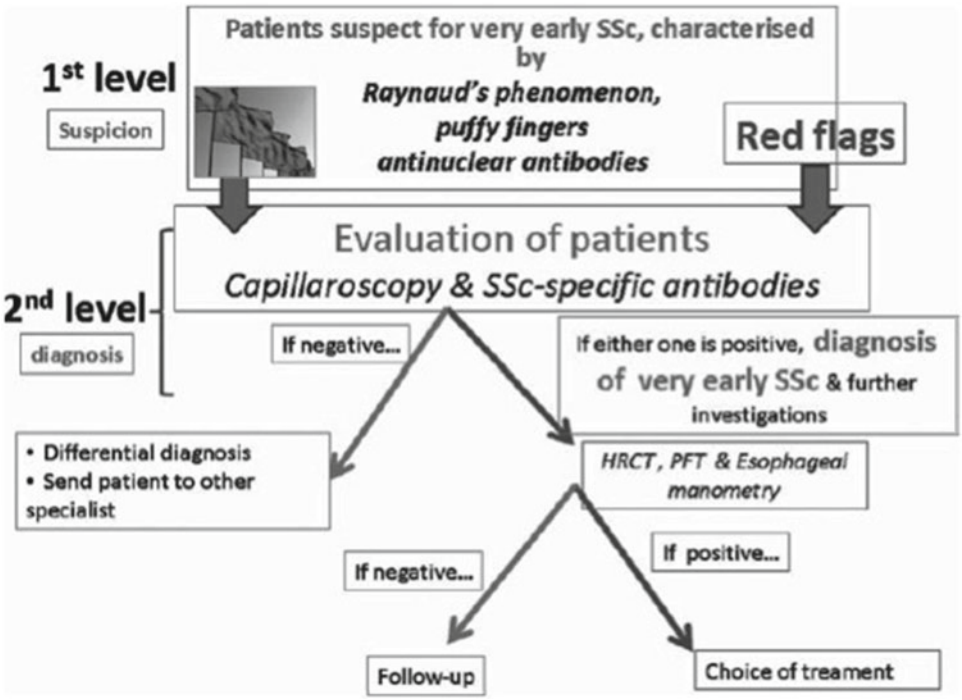

Fig. 7.2 Algorithm to diagnose patients with very early systemic sclerosis

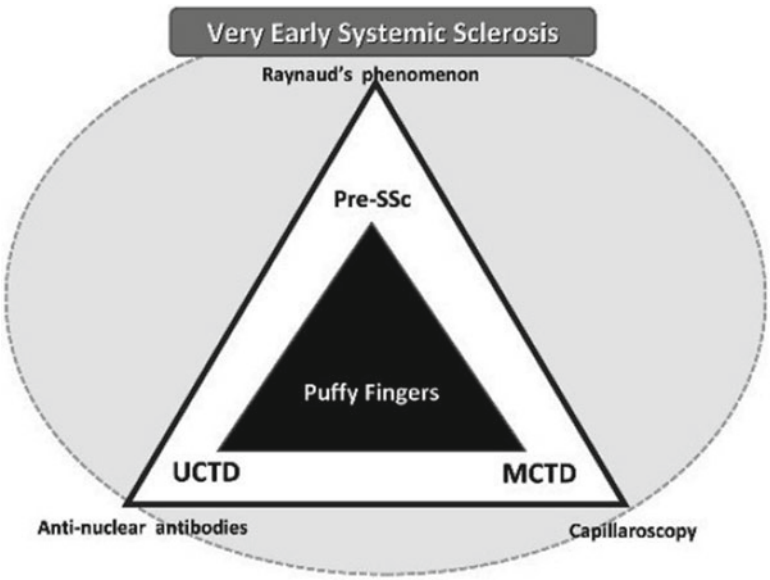

Fig. 7.3 Pyramid depiction of very early diagnosis of systemic sclerosis (SSc)

Table 7.7 Criteria for very early diagnosis of systemic sclerosis (SSc) determined by Delphi Consensus from EUSTAR[a]

	Criteria selected by experts
Criteria considered as having a high clinical relevance for the very early diagnosis of SSc	Raynaud's phenomenon
Criteria considered as leading to an early referral	Puffy swollen digits turning into sclerodactyly
	Abnormal capillaroscopy with scleroderma pattern
	Positive anticentromere antibodies
	Positive anti-topoisomerase I antibodies
	Raynaud's phenomenon
	Puffy fingers
	Positive antinuclear antibodies

Modified from [71]

[a] *EUSTAR* European League Against Rheumatism Scleroderma Trial and Research

ACR-EULAR Classification Criteria

The aim of the ACR/EULAR classification criteria for SSc working group is to arrive at a recommendation for SSc classification criteria, meant for inclusion of patients in clinical studies. To be an advantage over the existing ACR classification criteria and to meet the demands of early recognition of SSc, there are several prerequisites.

The revised classification criteria for SSc should include all patients who currently are regarded as having SSc. To reflect the pathogenic process in SSc, classification criteria presumably should include vascular, immunologic, and cutaneous symptoms and/or signs. Revised classification criteria for SSc should also acknowledge the main subtypes of SSc, notably "limited cutaneous SSc" and "diffuse cutaneous SSc." To be able to include all patients considered to have SSc, the classification criteria should be as close as possible to the diagnostic criteria used in clinical practice. That also means that the classification criteria should apply to patients early as well as late in the disease process. Last but not least, classification criteria for SSc should be feasible in daily clinical practice.

The process of development includes a Delphi procedure, testing in existing cohorts, opinion research, and testing in prospectively collected populations. While SSc is difficult to recognize early in the disease process, and while evidence is not complete, expert opinion and field opinion are important for developing the most sensitive and specific SSc classification criteria.

Conclusions

The pathogenesis of SSc is still quite unclear. However, there are three hallmark manifestations of the pathogenic process: a fibroblast dysfunction leading to fibrosis in skin and internal organs, vasculopathy of small vessels, and an immune response leading to production of autoantibodies [72]. It is clear that these hallmarks of the SSc pathogenic process play an important role in the recognition (diagnosis, classification) of SSc.

The currently used classification criteria for SSc are the 1980 "Preliminary criteria for the classification of systemic sclerosis (scleroderma)" by the ARA [29]. The ARA criteria were not intended for diagnostic purposes, did not include CREST-type patients, and made no attempt to deal with disease heterogeneity [72]. In 1988, it was proposed by LeRoy to subdivide SSc into limited and diffuse cutaneous forms, which was widely accepted [9, 72]. Although the difference between lcSSc and dcSSc is simply based on the extent of skin involvement, these subtypes differ in clinical course and in prognosis, and may differ to a certain degree in their pathogenesis. The latter is supported by the fact that different autoantibodies are strongly associated with each subtype of SSc.

The goal of revising the classification criteria is to improve the ability to distinguish patients with the disease in question (SSc) from those without the disease. This distinction may reflect differences in pathogenesis as well as differences in prognosis. Notably, an important aim of SSc classification criteria is to make a distinction between patients with SSc and patients with similar but distinct diseases. The purpose of classification criteria for SSc is to include patients with a similar clinical diagnosis (pathogenesis) for clinical (observational, experimental) studies. However, classification criteria are frequently used for diagnosis, even if they were not developed for that purpose.

The 1980 ACR classification criteria for SSc do not include all patients who are currently considered to have SSc, and do not make use of nailfold capillaroscopy and autoantibodies that were fully developed later. There are several proposals for new diagnostic or classification criteria for SSc, making use of the three hallmarks of disease. The LeRoy and Medsger criteria of limited- or pre-SSc, limited cutaneous SSc, and diffuse cutaneous SSc are the best known and widely accepted [65]. However, information from prospective clinical studies of patients that may have SSc is needed to know the frequency, and therefore the probability, with which SSc will be present. As SSc is a disease with low prevalence, it is critical to perform prospective studies of sufficient size. If several different studies using different populations are performed, this will add to the robustness of the findings. It is time "to cut the Gordian Knot" and to decide on criteria for classification or diagnosis of SSc and implement those in clinical studies and clinical practice [70].

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