Systemic Sclerosis

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Ada Man, M. Kari Connolly, and Robert W. Simms

Key Points

- Systemic sclerosis (SSc) is an autoimmune connective tissue disease with internal organ involvement that carries significant morbidity and mortality
- SSc is a disorder distinct from morphea, with a different presentation and graver prognosis; the two entities should not be conflated
- SSc patients must be monitored and treated for pulmonary, renal, gastrointestinal (GI), and cardiac involvement
- Highly specific autoantibodies may be present in SSc patients, with diagnostic and prognostic implications
- Recent therapeutic advances indicate that immunosuppressive therapy can prevent progression of severe systemic disease in SSc

Interdisciplinary Introduction

Systemic sclerosis (SSc, also called scleroderma) is an autoimmune connective tissue disease characterized by cutaneous sclerosis. It commonly progresses to involve fibrosis of one or more internal organs, with pulmonary involvement as the leading cause of death. In many ways, SSc is the prototype disease for which optimal management requires streamlined collaboration between multiple subspecialists, including dermatologists, rheumatologists, pulmonologists, nephrologists, gastroenterologists, nursing and support staff. Patients may be best served at academic centers with a focus on SSc patients, such as the Scleroderma Centers of Excellence, which may also offer participation in clinical trials. Rheumatologists often function as the coordinating physicians for these patients, while dermatologists have a role in managing cutaneous sclerosis, pruritus and digital ulcers.

To reflect the optimal interdisciplinary approach to SSc, this chapter reviews the classification, clinical features, pathogenesis, treatment and monitoring of SSc, with equal attention paid to all organ systems. The goal is to provide a text that may serve as a resource for physicians of all disciplines.

A. Man
University of Manitoba, Winnipeg, MB, Canada

M. K. Connolly (✉)
University of California San Francisco, Dermatology and Medicine, San Francisco, CA, USA
e-mail: Connolly@ucsf.edu

R. W. Simms
Boston University School of Medicine, Boston, MA, USA

A. Garg et al. (eds.), *Interdisciplinary Approaches to Overlap Disorders in Dermatology & Rheumatology*,
https://doi.org/10.1007/978-3-319-18446-3_6

Nomenclature

We draw a clear distinction between morphea and SSc, which are increasingly understood as separate entities rather than findings on a spectrum. Morphea is a disorder characterized by increased collagen deposition leading to localized cutaneous sclerosis that, unlike SSc, does not typically progress to involve internal organs, even when there is diffuse cutaneous disease. Misdiagnosis of morphea as SSc may expose patients to undue anxiety and unnecessary testing.

Clarity in the nomenclature surrounding these distinct entities is essential to facilitating diagnostic specificity. Unfortunately, the nomenclature is often confusing, as illustrated by the use of the terms "localized scleroderma" and "limited scleroderma." Localized scleroderma is synonymous with morphea; to avoid any confusion we will use the term "morphea" exclusively to describe this entity, as many dermatologists do. Limited scleroderma, by contrast, is a type of SSc that can progress to involve internal organs. It is also known as limited cutaneous (lcSSc) and was previously called CREST syndrome, an acronym standing for calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia. To avoid confusion, we will use the term limited SSc to describe this entity. (See Chap. 5 for a complete discussion on morphea.)

Epidemiology

Reliable epidemiological studies of SSc have been difficult to execute due to the rarity of the condition and heterogeneity in clinical presentation. Incidence is estimated at 3.7 to 23 cases per million people, while prevalence is estimated at 31 to 443 per million people. The wide range relates to variations in diagnostic criteria used, time period surveyed, and geographic location [1]. Moreover, prevalence estimates drawn from populations with milder and earlier disease, and in times with improved survival rates, may yield higher rates. Incidence and prevalence estimates from United States, Australia, and Southern Europe have been higher than those from Japan, Taiwan, and Northern Europe. Of note, there have been no new epidemiological surveys since the establishment of the 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for SSc [2]. These new criteria are expected to lead to higher estimates given their increased sensitivity and inclusion of earlier disease manifestations.

SSc affects people of all ages, though the peak age of onset is between 30 and 50 years [3]. As with many other autoimmune diseases, SSc disproportionately affects women, particularly women of reproductive age, with the female to male ratio ranging from 5:1 to 12:1 [4]. The reasons for this sex disparity are incompletely understood, but sex hormones, epigenetics, occupational exposures, and lifestyle differences may all play a role [4, 5]. Males who do develop SSc have been consistently shown to have a worse prognosis when compared to their female counterparts [6–8]. Males tend to have more diffuse disease and higher frequencies of digital ulcers, pulmonary arterial hypertension (PAH), heart failure, and all-cause mortality [9].

There are also variations in the epidemiology of SSc by race and ethnicity. Incidence and prevalence of SSc are greater among African-Americans than whites [6, 10, 11], with a younger age of onset (peak in the third decade of life) [12]. African-Americans are also almost twice as likely to have diffuse SSc, which is often associated with more severe disease [10, 11]. African-Americans with SSc have a higher frequency of autoantibodies to topoisomerase and U3 RNP, a higher risk of interstitial lung (ILD), and 1.8 times the risk of mortality as compared with Caucasians with SSc [6, 13, 14].

Hispanics with SSc have also been noted to have more diffuse skin involvement and digital ulcers than Caucasians [15]. There is a paucity of information on Asians with SSc, though estimates from China and Japan have placed prevalence rates between 21 and 100 cases per million [16, 17].

SSc Classification Criteria

The American Rheumatism Association (now the ACR) established criteria for the classification criteria of SSc in 1980 [18]. One major or two minor criteria were required for a diagnosis of SSc. The major criterion was skin thickening proximal to the metacarpal phalangeal joints, and the minor criteria included sclerodactyly, digital pitting scars, and bibasilar pulmonary fibrosis.

The 1980 ACR criteria were not sensitive enough to detect early disease and also excluded a large portion of limited SSc patients. To correct these deficits, the ACR collaborated with the EULAR to create new criteria, which were published in 2013 (Table 6.1) [2]. These criteria have higher sensitivity (91% as compared to 75% for the 1980 criteria) because they include more disease manifestations, including those that present early in the disease course. They also have improved specificity (92% as compared to 72%), likely due to the weighting of each item. The 2013 criteria are applicable to any patient considered for inclusion in a study on SSc. They do not apply to patients with skin thickening that spares the fingers or to patients who have a SSc-like disorder that better explains their manifestations (Table 6.2).

SSc Subsets

SSc is traditionally divided into two subsets: limited cutaneous SSc (lcScc) and diffuse cutaneous SSc (dcSSc) [19]. Classification is based on the

Table 6.2 Differential diagnosis of systemic sclerosis (SSc)

Generalized morphea
Scleredema
Scleromyxedema
Nephrogenic systemic fibrosis
Eosinophilic fasciitis
Lipodermatosclerosis
Malignancy-related palmar fasciitis
Chronic graft versus host disease
Diabetic cheiroarthropathy
Frostbite
Erythromelalgia
Lichen sclerosus et atrophicus

Table 6.1 The 2013 ACR/EULAR criteria for the classification of SSc [2]

Item	Sub-item(s)	Weight/score*
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(single criterion sufficient for diagnosis)*	–	9
Skin thickening of the fingers *(only count the higher score)*	Puffy 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's phenomenon	–	3
SSc-related autoantibodies *(maximum score is 3)*	Anticentromere Anti-topoisomerase I Anti-RNA polymerase III	3
Total score	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.

ACR American College of Rheumatology, *EULAR* European League Against Rheumatism, *SSc* systemic sclerosis

extent of skin involvement, with lcSSc being restricted to the face and distal extremities (distal to elbows and knees), and dcSSc also involving the skin proximal to the elbows and knees and/or the trunk. Hand involvement is characteristic of both subsets; without it, the diagnosis of SSc should be reconsidered.

The two SSc subsets tend to take distinct courses. Patients with lcSSc typically have a more prolonged and slower progression of disease: they may first develop Raynaud's phenomenon, and then years later progress to sclerodactyly with possible digital ulcers and pits, accompanied by facial skin thickening, telangectasias and/or calcinosis. Gastroesophageal reflux disease is common, and esophageal dysmotility may be seen. Pulmonary hypertension (PH) can occur in the lcSSc group even many years after stable disease. Many lcSSc patients also have ILD, although it may be milder than that seen in dcSSc and exacerbated by prolonged esophageal reflux, possibly related to recurrent silent aspiration of gastric acids. The lcSSc group is also characterized by positive anti-centromere antibodies, which are associated with improved survival.

Patients with dcSSc tend to have a much more acute and rapidly progressive course than those with lcSSc, including short duration of Raynaud's before the onset of other symptoms. They often develop edema and pruritus of the hands and legs as skin begins to thicken, which progresses from the distal extremities to the trunk within months. Arthralgias, arthritis, carpal tunnel syndrome, tendon friction rubs and constitutional symptoms are characteristic. Renal, cardiac, and intestinal involvement is more common for dcSSc than lcScc.

Beyond the limited and diffuse subsets, there is also a rarer subset called SSc sine scleroderma, which is defined by characteristic SSc-like internal organ involvement plus or minus SSc antibodies, but without cutaneous manifestations.

Individuals with SSc often also have features of other connective tissue diseases, such as myositis or SLE, in which case they would be considered to have an overlap syndrome or mixed connective tissue disease.

New classifications based on clinical features in combination with serological markers are an area of active research.

Clinical Features

SSc is a disease characterized by the triad of vasculopathy, fibrosis, and autoimmunity. These pathogenic categories provide a useful framework for considering the clinical features of the disease. In particular, vasculopathy and fibrosis are apparent in the majority of the organ manifestations, leading to irreversible organ dysfunction.

The natural history of SSc is for most organ involvement to occur within 2–5 years of onset. For dcSSc, peak skin thickness also occurs within 2–5 years, whereas it progresses less rapidly in lcSSc and never reaches as high a peak. After skin thickness peaks, the skin begins to soften. It is rare for new organs to become involved after this time, with the exception that PAH and gastrointestinal (GI) malabsorption may be late manifestations in lcSSc (Fig. 6.1). It is important to recognize that spontaneous skin softening is part of the natural history of SSc, a phenomenon sometimes misattributed to treatment effect.

Here we review clinical manifestations of SSc by organ system.

Cutaneous

In early SSc, an inflammatory, edematous phase often occurs before fibrosis is apparent. In this stage, the hands and fingers may appear puffy, characterized by widened digits with loss of skin creases. Edema may also involve the legs and feet. Pruritus is common during this phase secondary to the production of histamine and bradykinins and possibly irritation of nerve fibers.

After the inflammatory phase, patients typically develop progressive fibrosis over 2–5 years. Some patients may initially appear to have limited-type skin involvement but will progress

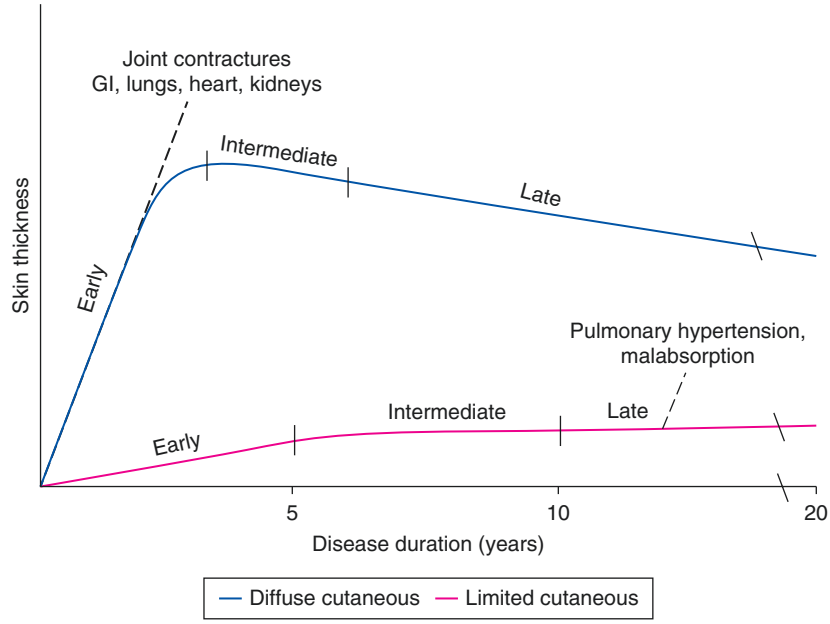

Fig. 6.1 Stages of systemic sclerosis (SSc) [20]. Schematic representation of the stages of diffuse and limited cutaneous SSc over time, including the usual relation between skin thickening and various organ system involvements. (GI, gastrointestinal)

during this period to have clinically apparent dcSSc. Progression of fibrosis usually occurs from distal to proximal, although patches of skin thickening can also occur outside this distribution. As the skin fibrosis progresses, sebaceous and eccrine glands may atrophy, resulting in xerosis and cracking of the skin. Hair loss in involved areas is also common. Rapid progression of skin thickening is associated with poor survival [21].

Skin thickening and tightening can develop in all parts of the body. Sclerodactyly, or thickening and tightening of the skin of the fingers, which are tapered distally, is the hallmark of SSc (Fig. 6.2). When the involved skin extends from the fingers to skin proximal to the metacarpophalangeal (MCP) joints, as reviewed above, this finding alone is enough for diagnosis of SSc (Fig. 6.3). Many SSc patients also have digital skin thickening only distal to the MCP joints, generally accompanied by other features that define the disease. Skin thickening proximal to the MCP joints without involvement of the fingers, by contrast, should prompt the consideration of an alternative diagnosis, including SSc mimics such as morphea or eosinophilic fasciitis. (See Table 6.2 for the differential diagnosis of SSc.) In long-standing SSc, skin on the fingers may become atrophic and appear thinner, sometimes becoming tethered to the underlying soft tissue (Fig. 6.4).

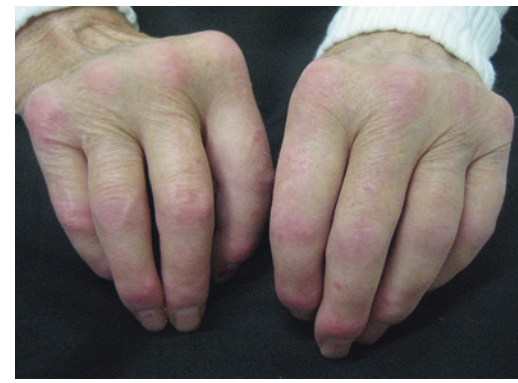

Fig. 6.2 Systemic sclerosis. Sclerodactyly. Thickening and tightening of the skin of fingers, which are tapered distally. (Courtesy of Amit Garg, MD)

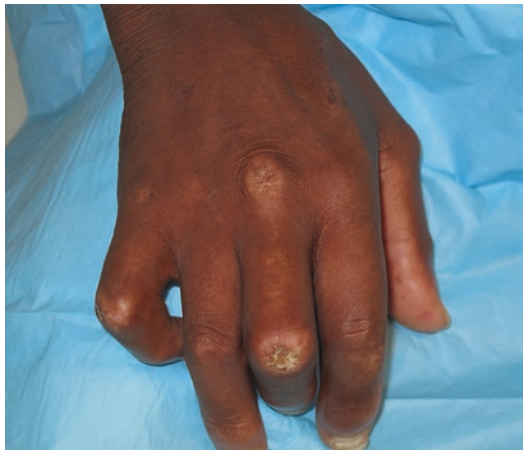

Fig. 6.3 Systemic sclerosis. Ulcerated cutaneous calcinosis involving the fingers over the metacarpophalangeal and proximal interphalangeal joints. (Courtesy of Amit Garg, MD)

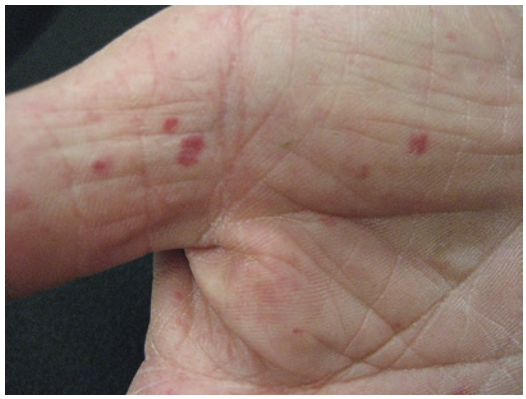

Fig. 6.4 Limited cutaneous systemic sclerosis. Matted telangiectasias on the palm of a patient with limited cutaneous systemic sclerosis. (Courtesy of Amit Garg, MD)

In lcSSc, skin thickening on the extremities occurs distal to the elbows and knees, while in dcSSc, it involves skin proximal to these joints, and may involve the trunk and back. Both subsets may have facial and neck involvement.

On the face, characteristic skin changes in SSc include tethering of the skin in the perioral area to create a wrinkled appearance, along with thinning of the lips and a reduced oral aperture (Fig. 6.5). Gum retraction may occur as well, leading to prominent front teeth. In the neck, Barnett's sign is characterized by a visible and palpable tight band over the platysma when the neck is extended [22]. On the chest and abdomen, the skin may be thickened in a band-like distribution along pressure areas, such as at the bra line and the waist.

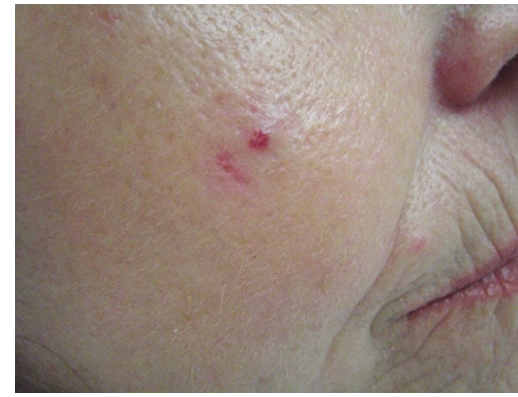

Fig. 6.5 Limited cutaneous systemic sclerosis. Telangiectasia, thinning of the lips and tethering of the skin in the perioral area to create a wrinkled appearance in a patient with limited cutaneous systemic sclerosis. (Courtesy of Amit Garg, MD)

Approximately 2–5 years into the course of SSc, the final stage of cutaneous disease is skin softening. This phenomenon occurs to some extent in most patients, though the skin may not always return to its baseline quality. Cutaneous improvement tends to begin in areas that have been affected last. Sweat and oil glands as well as hair follicles may return as well. Patients may note a decrease in fatigue, arthralgias, tendon friction rubs, and pruritus at this stage [23]. There is evidence that those who have significant improvement in skin thickening have improved survival [24]. Late exacerbations of skin thickening can rarely occur [23].

Beyond fibrosis and skin thickening, other cutaneous findings in SSc include hyperpigmentation, hypopigmentation, telangectasias, and calcinosis. Hyperpigmentation commonly occurs in skin creases, but pigmentary alterations may occur anywhere on the body and often have a "salt and pepper" appearance, due to perifollicular sparing of pigment loss (Fig. 6.6). Telangectasias are more common in lcSSc and are usually seen on the face, although they can also be found in other areas, such as the oral mucosa and the tongue. The presence of telan-

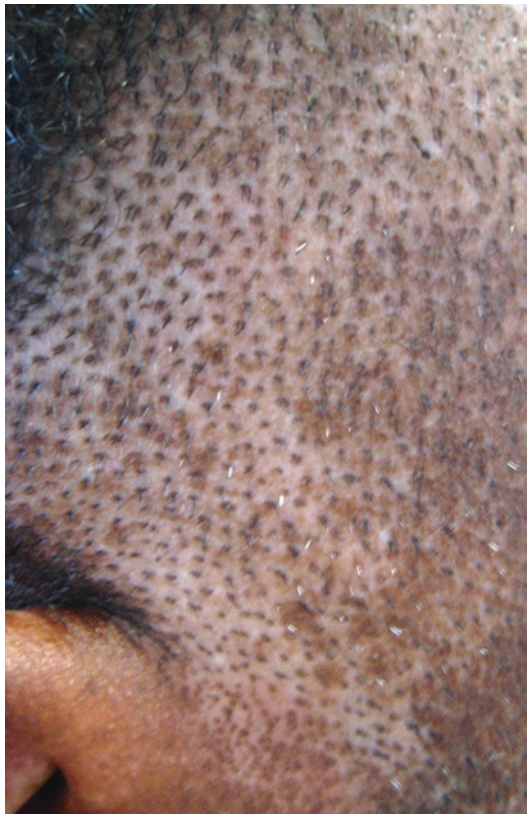

Fig. 6.6 Systemic sclerosis. Pigmentary alterations related to sclerosis often have a "salt and pepper" appearance due to perifollicular sparing of pigment loss. (Courtesy of Joseph Merola, MD)

gectasias in SSc may be associated with presence of PH [25]. Calcinosis, or the subcutaneous deposition of calcium hydroxyapatite, occurs both in lcScc and dcSSc and commonly involves the fingers and extensor surfaces of the limbs, possibly related to mechanical pressure and microtrauma. Involved areas may ulcerate and drain, and they may become infected.

Vascular

Raynaud's Phenomenon

Raynaud's phenomenon is present in greater than 95% of SSc patients. This finding is classically described as triphasic, where pallor of the fingers or toes is followed by ischemia, characterized by bluish duskiness, followed by reactive hyperemia with red erythema. However, many SSc patients do not report all three phases. The color changes typically end at a sharp cutoff at the proximal part of the fingers.

The mechanism behind Raynaud's phenomenon in SSc is thought to be vasospasm occurring in fixed, narrowed blood vessels. This is distinct from the vasospasm that occurs in normal caliber vessels among patients with primary Raynaud's disease. The typical trigger for Raynaud's is cold temperature, though stress or strong emotion may less commonly be implicated.

Digital Ischemia

The digital vasculopathy that precipitates Raynaud's phenomenon in SSc may also lead to persistent digital ischemia and poorly healing digital ulcers, acro-osteolysis (bony resorption of the terminal digital tufts seen on X-rays and shortened fingers seen clinically, loss of bulk from the finger pads, and occasionally gangrene and digital amputation (Fig. 6.7). Digital pits are common in SSc and represent ischemic insults presenting as tiny atrophic depressions at the fingertips. Digital ulcers also occur at the distal fingertips and may be seen in association with necrotic debris underneath the fingernail or overlying the knuckles. This debris is secondary to minor repeated trauma in the setting of poorly healing skin due to flexion contractures and tautness. Digital ulcers are very painful and can take a long time to heal, or they may not heal at all. They often become infected, requiring oral antibiotics. Experts differ in their opinions on whether or not debridement helps with healing. Uncommonly, severe ischemic disease may result in digital amputation [26].

The digital vasculopathy in SSc is mostly microvascular, although overlying macrovascular disease, such as within the ulnar arteries, may exacerbate the ischemic insult and should be ruled out, especially in cases of refractory ischemic complications.

Microvascular disease may be evident in characteristic nailfold capillary abnormalities observed with a widefield microscope or videocapillaroscopy, or a dermatoscope. Characteristic nailfold changes include dilated capillaries, loss of capillary loops ("drop-out"), architectural

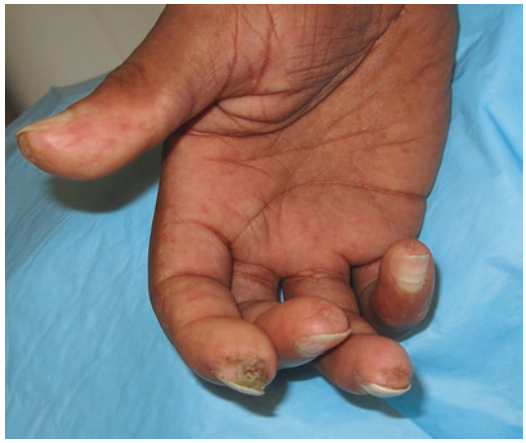

Fig. 6.7 Systemic sclerosis. Finger pad ulcers, pits and loss of bulk secondary to vasculopathy and persistent digital ischemia. (Courtesy of Amit Garg, MD)

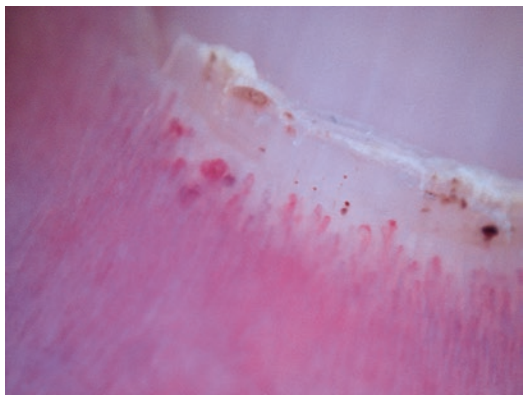

Fig. 6.8 Systemic sclerosis. Proximal nailfold changes including dilated capillaries, loss of capillary loops ("drop-out"), architectural derangement of capillaries, and microhemorrhages. (Courtesy of Joseph Merola, MD)

derangement of capillaries, and microhemorrhages (Fig. 6.8). Several studies have shown that detection of capillary abnormalities may allow for early SSc diagnosis when other SSc features are present. The presence of capillary abnormalities may also allow early differentiation of primary versus secondary Raynaud's. One study including 152 patients with sclerodactyly and Raynaud's phenomenon showed that the addition of visualized dilated capillaries improved the sensitivity of the 1980 ACR criteria for the diagnosis of SSc from 33.6% to 74.3% [27]. While capillaroscopy can clearly be useful, widefield microscopes and videocapillaroscopes are not readily available to most clinicians and require specific training for use. The ophthalmoscope has been used in their place with some success but still requires oil or immersion gel, which may hinder its use in clinical practice. Fortunately, a handheld dermatoscope may be used effectively to detect nailfold capillary changes, and dermatoscope-based studies have shown good concordance with standard methods [28, 29]. The dermatoscope is relatively inexpensive and mean examination time is only 4 minutes [30].

Gastrointestinal

The entire GI tract, anywhere from the mouth to the anus, may be involved in SSc. GI involvement is the most frequent internal complication of SSc, with a prevalence of up to 90% [31]. The pathogenesis of GI abnormalities relates to microvascular derangement, which is thought to lead to neurological dysfunction, causing smooth muscle malfunction with subsequent atrophy and fibrosis of the smooth muscles [32]. GI manifestations vary widely in severity, ranging from mild gastroesophageal reflux to severe malabsorption leading to death. Severe GI involvement affects about 8% of SSc patients and is associated with high mortality (9-year survival rate of 15%) [33].

Oropharynx

Oropharyngeal involvement in SSc begins with complications from a reduced oral aperture and rigidity of the facial skin and tongue, which may lead to difficulty with eating and maintaining dental hygiene. Reduced salivary flow, which can occur with SSc alone or from secondary Sjogren's syndrome, may exacerbate problems with dental health. Oropharyngeal dysphagia occurs in up to 26% of patients win SSc [34].

Esophagus

Esophageal involvement is common in SSc but can be clinically silent in up to 50% of affected patients [35]. Involvement of the smooth muscle of the lower two-thirds of the esophagus results

in loss of peristaltic action and symptoms of acid reflux symptoms and dysphagia. The upper third of the esophagus may also be affected in patients with myositis, which may be seen in SSc or overlap syndromes. A weakened lower esophageal sphincter compounds the problem, with acidic gastric contents refluxing into an esophagus that already has poor antegrade motility. Esophageal damage may ensue, manifesting as esophagitis and sometimes ulcers and GI bleeding. Long-term complications may include strictures and Barrett's esophagus, with a possible increase in the risk of esophageal malignancy [36]. In addition to reflux and dysphagia, patients may experience regurgitation, hoarseness, and weight loss.

Gastric

Gastric manifestations in SSc include delayed emptying and vascular abnormalities leading to bleeding. Delayed gastric emptying results in early satiety, nausea, bloating, and weight loss, and it may exacerbate existing reflux disease. Gastric vascular abnormalities include mucosal telangectasias in the stomach or gastric antral vascular ectasia (GAVE), both of which can lead to bleeding varying from occult to large amounts. GAVE is also known as "watermelon stomach" due to its unique endoscopic appearance, with erythematous blood vessels occurring in stripes from the pylorus to the antrum. Histologically, GAVE is characterized by mucosal capillary dilatations containing fibrin thrombi and fibromuscular hyperplasia [37].

Small Intestine

Impaired small intestine mobility can lead to distended bowel loops, manifesting as early satiety, bloating, cramping, nausea, and vomiting. A characteristic sign of small bowel SSc seen on barium studies is a "hide-bound" or "wire-spring" appearance caused by closely packed valvulae in dilated bowel. The intestinal stasis and pooling that occurs may also lead to small intestine bacterial overgrowth (SIBO), which can cause malabsorption, a serious complication in SSc patients. Patients with SIBO and malabsorption often suffer from diarrhea, steatorrhea, weight loss, and malnutrition. Small intestinal hypomotility may also provoke luminal dilatation and lead to pseudo-obstruction caused by functional ileus, which can present as abdominal pain, bloating, and vomiting. Patients may also develop pneumatosis cystoides intestinalis, or gas in the bowel wall, a finding often identified incidentally on abdominal CT performed for other reasons. In SSc, this is usually a benign process, but pneumoperitoneum is a potential complication.

Large Intestine and Anorectum

Involvement of the large intestine in SSc leads to reduced contractile activity and resultant constipation. Patients who have these findings comorbid with SIBO may present with diarrhea alternating with constipation. Refractory constipation can rarely lead to colonic perforation. Muscular atrophy of the intestinal mucosa can lead to characteristic wide-mouth diverticulae on the antimesenteric border, which can be detected on barium enema. Anorectal involvement leads to decreased compliance and reduced anal sphincter tone. These changes mirror the changes seen in the lower esophageal sphincter. Fecal incontinence, and less frequently, rectal prolapse can occur as a result.

Liver

The liver is rarely involved in SSc, although there is an association with primary biliary cirrhosis (PBC), especially among patients with lcSSc. SSc patients with PBC are often anti-centromere antibody positive; compared non-SSc patients with PBC, their hepatic disease tends to progress more slowly [38, 39].

Pulmonary

Pulmonary disease is the leading cause of morbidity and mortality in patients with SSc. The clinical presentation of pulmonary SSc may be completely silent or can include chronic cough and dyspnea on exertion. Severity ranges widely, from limited, non-progressive lung involvement to major pulmonary inflammation and fibrosis ultimately leading to respiratory failure and death.

The two most common pulmonary manifestations of SSc are ILD and PH. These complications may occur simultaneously, or PH can be a consequence of ILD. Less common pulmonary manifestations of SSc include pleuritis, malignancy, bronchiolitis obliterans, and bronchiectasis. SSc patients may also be at a higher risk of aspiration pneumonia due to oropharyngeal and esophageal dysfunction. In addition, patients with myositis due to SSc or overlap syndromes may develop respiratory muscle weakness.

Interstitial Lung Disease

In a recent report from the EULAR SSc Trials and Research database, the overall prevalence of ILD as identified on high resolution CT among patients with SSc was 51.9% [40]. ILD was present in 43.5% of patients with lcSSc and 64.1% of patients with dcSSc. On autopsy, however, the prevalence of ILD is as high as 80% [41].

ILD in SSc (or SSc-ILD) is characterized by basilar-predominant fibrosis, which is detectable on X-ray or high-resolution CT, the latter being a more sensitive imaging modality. The pattern seen on CT is usually consistent with nonspecific interstitial pneumonia (NSIP), or less commonly, usual interstitial pneumonia (UIP). UIP has findings consistent with end-stage fibrosis, including honeycombing and traction bronchiectasis, whereas NSIP presents with ground glass opacities and has a better prognosis [42]. Pulmonary function assessment in ILD demonstrates restrictive physiology with approximately equivalent decline in forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) [43, 44].

Risk factors for ILD include diffuse subset, presence of anti-topoisomerase I antibodies, and African-American ethnicity. Male sex, cardiac involvement and African-American ethnicity are additional poor prognostic factors for pulmonary disease [14]. Approximately 10–15% of patients with SSc will experience more severe ILD and progressive decline in lung function [14, 45]. SSc-ILD accounts for 33% of all SSc-related deaths [46].

Pulmonary Hypertension

In one report on patients with SSc, PH occurred in 21.1% of patients, with almost the same frequency in the limited and diffuse subsets [40]. PH in SSc can be of several different forms: (1) PAH due to SSc involvement of the small pulmonary arterioles (most common); (2) PH due to hypoxemia from advanced ILD; and (3) PH caused by myocardial dysfunction. Patients with PH may be asymptomatic in early stages. Later, there is increasing dyspnea on exertion, reduced exercise tolerance, and fatigue. Late-stage signs and symptoms include syncope, chest pain, jugular vein distention, and edema, indicating the development of right heart failure.

Isolated PAH can present even after years of mild, stable disease, highlighting the importance of long-term monitoring in these patients. Risk factors for PAH include greater than 10 cutaneous telangectasias, reduced capillary nailfold density, and the presence of anti-centromere antibodies [25, 47].

PAH associated with SSc is more aggressive than non-SSc PAH, with a median survival time of 1 year following diagnosis if left untreated. PAH accounts for 30% of deaths among SSc patients [48, 49]. SSc-ILD with PH has a much worse prognosis than SSc-ILD alone [50].

Cardiac

Cardiac involvement occurs frequently in both lcSSC and dcSSc but is more common in the latter. Risk factors include rapidly progressive skin disease, presence of anti-U3RNP antibodies, and presence of myositis. In the EULAR SSc Trails and Research (EUSTAR) database, 26% of SSc-related deaths were due to cardiac involvement, making it the third leading cause of death in SSc [51]. SSc may affect any part of the heart; however, pericardial disease, myocardial disease, and arrhythmias are the major SSc-related cardiac manifestations.

Pericardial disease results in symptomatic pericarditis and small or large pericardial effusions. The prevalence of clinically symptomatic cardiac involvement has been estimated at 30–35% [52]. However, pericardial abnormali-

ties may be observed in up to 78% of SSc patients at autopsy [53]. The presence of pericardial effusion can be a clue to impending SSc renal crisis, and when observed with PAH, it may be associated with poor prognosis.

With regard to myocardial disease, microvascular dysfunction leading to recurrent ischemic injury and myocardial fibrosis is thought to be the cause of systolic and diastolic dysfunction observed in SSc patients. In one study in 570 SSc patients, left ventricular systolic and diastolic dysfunction were present in 1% and 18%, respectively [54]. Recent studies have also indicated an increased risk of atherosclerosis and myocardial infarctions in SSc patients, for which the pathophysiology remains unclear [55, 56].

Ventricular and supraventricular arrhythmias are common in SSc and result in a range of symptoms, from transient palpitations to syncope and sudden death. Conduction abnormalities are thought to result from myocardial fibrosis and injury to the conduction system [53].

Renal

Scleroderma renal crisis (SRC) is the most important renal complication in SSc. Rarely, other abnormalities can occur, including interstitial nephritis, glomerulonephritis, chronic proteinuria and chronic renal vasculopathy [57].

SRC has a prevalence of 10% in the entire SSc population and occurs in approximately 20% of patients with dcSSc. It is defined as the new onset of rapidly progressive oliguric renal failure and/or accelerated hypertension. Patients may present with signs and symptoms of malignant hypertension, such as headache, dyspnea, visual disturbance, seizure, and lower extremity edema. However, because patients developing SRC may be normotensive, the diagnosis requires a high index of suspicion.

Additional features of SRC include microangiopathic hemolytic anemia on blood smear, retinopathy typical of acute hypertensive crisis, new onset hematuria, flash pulmonary edema, and renal biopsy with typical features (i.e., onion skin proliferation within the walls of intra-renal arteries and arterioles, fibrinoid necrosis, and glomerular shrinkage). SRC may sometimes be the presenting feature of SSc.

SRC results from renal vasculopathy rather than inflammation and is accompanied by a high renin state. Risk factors for SRC include diffuse subset, rapidly progressive skin thickening, anti-RNA polymerase III antibodies, and pericardial effusion. Poor prognostic factors include older age, male sex, and lower blood pressure at presentation. Prior to the introduction of angiotensin converting enzyme inhibitors (ACEi) for the treatment of this disease, SRC was the leading cause of mortality in patients with SSc. Outcomes have improved significantly with earlier diagnosis and prompt treatment, but SRC still carries a high mortality and morbidity rate: 1-year survival is estimated at 78%, and 40% of affected patients require chronic hemodialysis [58].

Musculoskeletal

The muscles, tendons, joints, and bones can all be involved in SSc. A large proportion of patients with SSc have arthropathy (46–97%) or myositis complicating their skin disease, which may contribute substantially to extremity dysfunction and disability [59–61]. The most common musculoskeletal manifestations are pain and joint contractures resulting from fibrosis around tendons and other periarticular structures. It is important to distinguish joint pain due to contractures from joint pain caused by true synovitis. Joint contractures most frequently involve the fingers, although larger joints including elbows, and knees may also be affected in dcSSc.

An erosive arthropathy involving the proximal and distal interphalangeal joints, resembling psoriatic arthritis, occurs in 15–20% of SSc patients [61]. In some cases, articular involvement may the presenting feature and result in diagnostic confusion, often with rheumatoid arthritis [60]. Further clouding the picture is the fact that up to 30% of SSc patients have a positive serum rheumatoid factor (though its presence does not distinguish those with articular manifestations from those without), and between 1% and 15% have serum anti-citrullinated peptide antibodies [61].

With regard to bones, approximately 20% of SSc patients develop acro-osteolysis, with resorption of bony tuft at the distal phalaynx [62]. As is the case for patients with other chronic inflammatory diseases, SSc patients are at higher risk of osteoporosis; this risk is compounded by immobility from the SSc itself.

Muscle weakness is a prominent symptom in SSc, although not all those with weakness have an identifiable myopathy. One type of SSc-associated myopathy is "bland" myopathy in which there is no significant necrosis or inflammation and creatine kinase levels are normal or only mildly elevated. The second type of SSc myopathy presents similarly to inflammatory myositis, in which patients have significant CK elevations and electrodiagnostic and biopsy findings suggestive of inflammatory myopathy.

Certain musculoskeletal findings can be early signs of SSc. Tendon friction rubs occur in up to 20% of patients with early dcSSc and appear to be associated with more rapid disease progression [63–66]. These can be felt and/or heard using a stethoscope over tendons of the fingers and wrists, elbows, knees, and ankles. Carpal tunnel syndrome is another common presenting manifestation of SSc; patients with bilateral carpal tunnel syndrome together with Raynaud's phenomenon should be evaluated for SSc.

Pathophysiology of Systemic Sclerosis

SSc is thought to result from the complex interplay of three principle pathophysiologic processes in a genetically susceptible individual: (1) vascular phenomena and vasculopathy; (2) autoimmunity or immune dysregulation; and (3) fibrosis [67]. We will review each of these proposed pathophysiologic mechanisms in detail.

Vascular Injury and the Initiation of SSc

The endothelial cell (EC) appears to play a key role in the initial cascade of molecular events that ultimately leads to both vascular damage or vasculopathy and tissue fibrosis in SSc [67, 68]. The prevailing pathophysiologic paradigm proposes that microvascular injury and subsequent EC activation incite increased expression of vascular cell adhesion protein (VCAM), intercellular adhesion molecule (ICAM) and E-selectin, which in turn promote inflammatory cell recruitment from blood into surrounding tissue [69–71]. The accumulation of these inflammatory cells in tissue leads to increased expression of profibrotic mediators, such as transforming growth factor beta (TGfβ), platelet-derived growth factor (PDGF), IL-1, and IL-6, which in turn stimulate increased extracellular matrix protein by tissue-residing myofibroblasts [69].

Progressive vascular injury results in activation and apoptosis of ECs with associated intimal thickening, smooth muscle proliferation, and vessel narrowing to varying degrees depending on the vascular bed [67, 72]. Endothelial cells release a variety of factors including the potent vasoconstrictor, endothelin 1 (ET-1), but also other cytokines, such as TGfβ, which work in concert to promote smooth muscle cell proliferation and luminal narrowing [68]. The role of inflammation in the early vascular events that characterize SSc is controversial but may be important in specific vascular complications such as PAH [73–76].

Modification of angiogenesis also appears to play an important role in the pathogenesis of vascular disease in SSc. Early in SSc, videocapillaroscopy has shown a proinflammatory state, leading to increased production of pro-angiogenic factors that stimulate angiogenesis, leading to new abnormal and tortuous capillaries [28, 77].

Later in disease, the early pro-angiogenic response is followed by loss of angiogenesis, resulting in a reduction in capillary density and development of extensive avascular areas that have been demonstrated by videocapillaroscopy. This latter pathogenic pattern appears to correlate with increased levels both of E-selectin and junctional adhesion molecules (JAMs). JAMs function in the regulation of leukocyte recruitment to sites of inflammation, ischemia reperfusion injury, vascular permeability and angiogenesis.

They appear to be critical in EC motility, EC directional movement and focal content formation during angiogenesis. In early SSc skin disease, JAMs appear to be upregulated in MVECs but have reduced expression in later stage disease, suggesting that JAMs play an important role in the modulation of angiogenesis in the different stages of SSc [78, 79].

Accumulating evidence suggests that deficiency of the transcription factor Friend leukemia integration factor-1 (Fli-1) plays a key role in the process of both skin fibrosis and microvascular injury in SSc. Fli-1 pathway interruption in SSc may connect both this early impairment of angiogenesis and the development of skin fibrosis, since Fli-1 is a transcription factor which appears to regulate many genes in both fibroblasts and ECs [80]. Fli-1 deficiency in dermal fibroblasts, for example, upregulates the expression of type 1 collagen, connective tissue derived growth factor (CTGF or CCN2) and alpha smooth muscle actin, facilitating the transition to predominance of myofibroblasts and uncontrolled deposition of ECM.

In microvascular ECs, Fli-1 deficiency leads to altered expression of a number of molecules involved in vascular homeostasis and angiogenesis, such as vascular endothelial (VE) cadherin, platelet-endothelial cell adhesion molecule (PECAM)-1, CXCL5, cathepsin V, CCN1 and cathepsin B, leading to loss of vascular integrity that manifests clinically as nailfold capillary abnormalities [81]. Asano and colleagues have shown that CCN1 expression in dermal microvessels in patients with SSc was markedly reduced and that Fli-1 deficiency plays a key role in the down-regulation of CCN1 [82]. Furthermore, lower circulating levels of CCN1 could be correlated with the presence of digital ulcers [82].

Autoimmunity

Several lines of evidence point to both innate and adaptive immune dysregulation or autoimmunity in SSc [71]. First, early in the disease, infiltrating immune effector cells (including CD4+ T cells, macrophages, activated B cells and plasmacytoid dendritic cells) consistently display a Type 1 interferon gene signature, a prominent marker of innate immune activation. Effector T cells, particularly Th17 and regulatory T cells (Treg), appear to be critical regulators of this initial inflammation; the presence of Th17 cells in particular has been shown to correlate with clinical parameters, such as disease duration and ILD score. An increase in activated T cells and a reduction in Treg is thought to cause excess production of cytokines that drive the synthesis of extracellular matrix proteins by fibroblasts, resulting in fibrosis [83]. While Th17 cells have been mostly found to be increased in SSc, Treg cells have been reported to be reduced in number or functionally defective in SSc [83, 84]. Additionally, Zhou and colleagues found elevated expression of Th17-related cytokines and receptors to be associated with skin lesion severity in early SSc. This included IL-17A, IL-21, IL-22, IL-26, IL-17RA, IL-21R and IL-22R, which correlated with modified Rodnan skin score (mRss) [85]. Thus recent evidence has revealed a crucial role for immune cells in the establishment and maintenance of fibrosis, with Th1 and Th2 cells contributing to the induction of pro-inflammatory and pro-fibrotic responses. These findings provide a rationale for therapy to decrease T cell activation.

Additional evidence pointing to the role of immune dysregulation in SSc includes evidence from genome wide association studies (GWAS), which have shown polymorphisms in *IRF5* (interferon regulatory factor 5) and *STAT 4* (signal transducer and activator of transcription 4), which are dysregulated in other autoimmune diseases [86–88]. Additionally, as reviewed in detail later in this chapter, SSc is associated with distinctive autoantibodies, such as anti-centromere, anti-Scl 70, and anti-RNA polymerase III, among others [89]. With the possible exception of antibodies to PDGF, the role of autoantibodies in the pathogenesis of SSc remains uncertain. Autoantibodies associated with SSc, however, do appear to have diagnostic importance [90–93].

Other evidence of immune activation in SSc includes elevation of Th2 cytokines such as IL-4, IL-13 and IL-6 [69, 94]. IL-6 in particular plays an important role in Th2-dominant immunity, inflammation and fibrosis [95]. IL-6 is a pleiotropic, pro-inflammatory, multi-functional cytokine produced by a variety of cell types, including lymphocytes, monocytes and fibroblasts [95]. IL-6 levels are elevated in the serum of patients with SSc, and isolated lymphocytes spontaneously produce elevated levels of IL-6 [96]. IL-6 induction of collagen gene expression appears to involve mechanisms dependent on STAT3, TGfβ and Smad 3, mediated through Gremlin-1 protein [95]. IL-6 could thus be considered a molecular target with biologic rationale in SSc; clinical trials of tocilizumab, a humanized monoclonal anti-IL-6 receptor antibody, are underway [97].

Fibrosis

Fibrosis as distinct from wound healing is a complex pathologic process characterized by the extracellular accumulation of a matrix made up of collagen, elastin, glycosaminoglycan and fibronectin [98]. In wound healing following injury, collagen and matrix deposition result in scar formation, which is then downregulated before excess accumulation of scar causes disruption of normal tissue [99–101]. The accumulation of this matrix, which permanently alters the tissue architecture, is the result of increased synthesis by activated fibroblasts or myofibroblasts as well as defective degradation [102–106]. Myofibroblasts may originate from several different locations, including from pericytes from the circulation and from transdifferention of telocytes and ECs. A recent study suggested that myofibroblasts populating fibrotic dermis also derive from adipocytic progenitors [107]. Increasing evidence suggests that matrix stiffness resulting from pathologic deposition of collagen in fibrosis induces a feedback loop via a process termed mechanotransduction, which further enhances fibroblast recruitment and activation at sites of fibrosis [108].

The molecular signaling events that characterize the fibrotic process in SSc have long been linked to TGfβ, considered the master cytokine of fibrosis and wound healing [109, 110]. Recent evidence suggests that, along with genes regulated by type I interferon, gene expression regulated by TGfβ drives the fibrotic process in SSc lung disease [109]. TGfβ is secreted as an inactive precursor bound to TGfβ binding protein by macrophages and other cells and converted to its biologically active form by integrins [111, 112]. Canonical signaling via phosphorylation of the type I TGfβ receptor (also known as ALK5) via the SMAD pathway eventually leads to increased profibrotic gene expression. TGfβ can also activate profibrotic gene expression via non-SMAD pathways via early growth response 1 (ERG1), ABL1 (previously known as c-ABL) and FAK, as well as by inactivation of transcriptional repressors such as peroxisome proliferator-activated receptor δ (PPAR δ), Fli-1 and kruppel-like factor family members. As indicated above, the transcription factor Fli-1 appears to play a particularly important function in SSc pathogenesis because of its dual role in preventing both fibroblast and EC gene transcription. Fli-1 deficiency has multiple downstream effects in fibroblasts and ECs that favor the development of fibrosis and vasculopathy in animal models and human disease [81].

In addition to TGfβ signaling, canonical Wnt signaling also appears to play a central role in fibrosis and has been implicated in pulmonary, renal and liver fibrosis in additional to keloid formation [113]. Wnt proteins stimulate the differentiation of resting fibroblasts into myofibroblasts and increase the release of ECM in vitro. In vivo, overexpression of Wnt 10b, stabilization of β-catenin, or inhibition of GSK3 β produce rapid and progressive skin fibrosis [113]. Wnt signaling is also closely linked to TGFβ-driven myofibroblast activation and upregulation of collagen gene expression: TGfβ induction of canonical Wnt signaling with β-catenin accumulation leads to matrix gene expression in murine skin and cultured fibroblasts, resulting in a negative feedback

loop that inhibits TGfβ, in turn reducing Wnt signaling.

PDGF is the term for a family of mesenchymal mitogens with important functions during the embryonal development and in the control of tissue homeostasis in the adult [114]. The PDGF isoforms exert their effects by binding to α–and β-tyrosine kinase receptors. Overactivity of PDGF signaling has been linked to the development of certain malignant and non-malignant diseases, including atherosclerosis and various fibrotic diseases, including SSc [114]. A causative role of PDGF receptor activity in SSc is suggested by the finding that tyrosine kinase inhibitors, e.g., imatinib, dasatinib and nilotinib, ameliorate symptoms in mouse models of SSc [114]. Activating autoantibodies against the PDGFα receptor have been demonstrated in the serum of patients with SSc [115], though this observation has been questioned in other studies [116, 117]. Another report noted PDGFα receptor autoantibodies in 29% of patients with SSc but found that these autoantibodies did not have any agonistic activity [118].

Connective tissue growth factor (CTGF, CCN2) is overexpressed in lung fibroblasts isolated from patients with SSc and ILD and is considered to be a molecular marker of fibrosis [119, 120]. Recent studies suggest that CTGF is important in lung tissue repair and fibrosis and indicate that CTGF-induced migration of lung fibroblasts to the damaged tissue is mediated via the IQGAP1 and MAPK signaling pathways, which are upregulated in SSc lung tissue [119]. IQGAP1 is a scaffold protein that plays a pivotal role in regulating migration of endothelial and epithelial cells. LPA-1, via CTGF, also appears to play a significant role in CTGF-mediated events governing tissue fibrosis [121].

Risk Factors for Systemic Sclerosis

Like many autoimmune diseases, SSc may in some cases be precipitated by an environmental trigger in a genetically susceptible individual. Here we review environmental and genetic risk factors identified to date.

Genetic Risk Factors

The genetic basis for SSc has not yet been fully elucidated. The twin concordance rate in SSc is only 4.7%, with no difference in concordance rates between monozygotic and dizygotic twins [122]. The disease occurs in only 0.4% of siblings [123], compared to 8% and 7% of siblings in RA and ankylosing spondylitis, respectively [124]. However, certain genetic susceptibility loci have been identified. The highest reported prevalence of SSc is in a Choctaw Native American group in Oklahoma, with a prevalence estimated at 4690 cases per million (based on 12 cases) [125]. Within the population who developed SSc, there was strong homogeneity of features, including diffuse disease, anti-topoisomerase I antibodies and pulmonary fibrosis. Several genetic loci were identified within this population that showed highly significant associations with SSc [126]. Further investigation in this vein may help shed light on the overall genetic basis for SSc [127].

Occupational and Environmental Risk Factors

Environmental factors have drawn particular attention in SSc, in part due to reports of geographic clustering. In a rural area in the province of Rome, for example, there were five patients with SSc in a village of 572 persons, while an additional 10 would have met criteria for SSc by today's definition [128]. Counting all 15, this would have represented a prevalence of 15/572, or 26,223 cases per million people, far greater than the expected prevalence based on population-level data. No disease-associated HLA antigen was observed, although there was a higher frequency of HLA B51 and DR2 haplotypes in the entire village population. Similar geographic clustering has been reported in the United Kingdom, Canada, and Australia [129–131]. In

the Australian cluster, SSc cases were noted mostly in male farm workers, raising the possibility of dust storm-related silica exposure as being a potential contributor.

Indeed, silica as a potential environmental factor has been a major focus of SSc epidemiological studies. Several countries, including Germany, South Africa, and Canada, consider silica-induced SSc an occupational disease covered under worker's compensation policies [132]. The first report of a possible association between silica exposure and SSc was in a 1914 series of nine Scottish patients, five of whom were stonemasons [133]. Subsequently, disease clustering was identified in miners from South Africa and coal miners from North America [134, 135]. Many other silica-associated cases have been reported, including one recent report of limited SSc in a French wine-grower who frequently filtered wine using diatomaceous earth, which is >80% silica [136]. A meta-analysis including 16 studies (9 case-control, 3 cohort, 4 other) examining the relationship between silica and SSc found the combined estimator of relative risk (CERR) in silica exposed versus non-exposed individuals to be 3.2 [137]. The risk was higher in males than females.

Organic solvents have also been implicated in precipitating SSc. A 2007 meta-analysis of 11 studies found that occupational exposure to solvents conferred an adjusted relative risk for developing SSc of 1.8, with male sex conferring excess risk [138]. These findings echo those of a prior study of 2227 patients, in which self-reported solvent exposure was associated with twice the risk of developing SSc [139]. Exposures to epoxy resins or pesticides have also been implicated as possible environmental triggers, but the evidence for these links is limited to case reports. For the majority of SSc cases, no occupational or environmental risk factors can be identified.

Autoantibodies

Several antibodies specific to SSc have been identified and are associated with particular clinical features. The presence of these antibodies provides further prognostic and clinical information beyond the limited and diffuse subsets. Prevalence of individual antibodies has varied by testing method used and differences in cohort characteristics, including ethnicity and country of origin.

In general, anti-nuclear antibodies, which are not specific for SSc, are present in up to 90% of SSc patients. The two most commonly observed SSc-specific antibodies are anti-centromere and anti-topoisomerase I antibodies, each occurring in approximately 30% of patients with SSc of all types [140]. Anti-centromere antibodies are more common among in lcSSc, whereas anti-topoisomerase I antibodies are more common among patients with dcSS. Both antibodies are widely available as commercial tests. Anti-RNA polymerase III antibodies are present in approximately 10% of SSc patients, and their presence correlates with renal crisis and malignancy risk [141, 142]. Anti-centromere, anti-topoisomerase I, and anti-RNA polymerase III are all included as part of the 2013 SSc classification criteria, as previously reviewed in detail.

Other antibodies related to SSc include those targeting Th/To, PmScl, U1 RNP, U3 RNP, Ku, U11/U12 RNP, and RuvBL1/2. Estimated prevalence for each of these antibodies in the SSc population as well as associated clinical features are described in Table 6.3.

Diagnostic Considerations

SSc is a clinical diagnosis based on the history, physical features, and laboratory findings. Skin biopsy is generally not needed for diagnosis. Diagnostic considerations of SSc should mirror the classification criteria (Table 6.1); however, these criteria were developed for research purposes and thus the classification criteria need not be met to make the diagnosis of SSc. For example, a patient with tendon friction rubs and calcinosis, items which are not part of the 2013 SSc classification criteria, may still be diagnosed as SSc if they have other features consistent with the diagnosis, such as Raynaud's and sclerodactyly. In the

Table 6.3 Autoantibody prevalence, clinical associations, and prognosis [3, 140, 143–145]

	Prevalence	Disease subset	Clinical associations	Prognosis
Anti-centromere	16–41%	Limited	Pulmonary hypertension, digital ulcers	Better
Anti-topoisomerase I	9–39%	Diffuse	Interstitial lung disease, cardiac involvement, digital ulcers	Worse
Anti-RNA polymerase III	2–25%	Diffuse	Renal crisis, tendon friction rubs, malignancy, GAVE	Worse
Anti-PM/Scl	0–9%	Limited/overlap	Myositis, calcinosis, digital ulcers	Better
Anti-U1 RNP	5–35%	Limited/overlap	Mixed connective tissue disease, myositis, arthritis, interstitial lung disease, pulmonary hypertension	Better
Anti-U3 RNP (fibrillarin)	1–10%	Diffuse	African-American patients, younger age of onset, pulmonary hypertension, gastrointestinal involvement, cardiac involvement, renal crisis	Worse
Anti-Th/To	1–7%	Limited	Interstitial lung disease, pulmonary hypertension	Worse
Anti-Ku	1–10%	Limited/overlap	Myositis, dysphagia, SLE overlap	–
Anti-U11/U12 RNP [146]	1–5%	Limited and diffuse	Severe interstitial lung disease, gastrointestinal involvement	Worse
Anti-RuvBL1/2 [143]	1–2%	Diffuse/overlap	Male patients, older age of onset, myositis	–

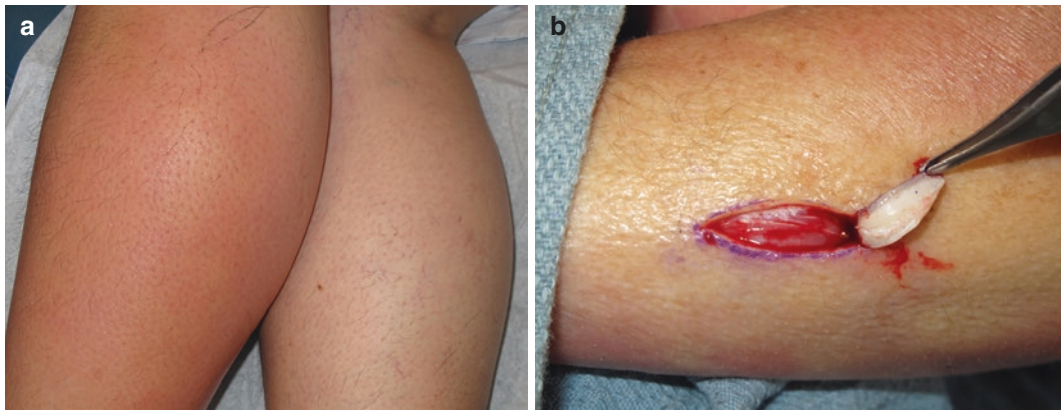

Fig. 6.9 (**a**, **b**) Eosinophilic fasciitis. (**a**) Erythema, swelling and induration of the lower extremity with the characteristic peau d'orange (orange-peel) appearance over the surfaces of the skin. (**b**) Gross specimen demonstrating significant thickening of the fascial layer due to inflammatory involvement with replacement of the subcutis. (Courtesy of Amit Garg, MD)

same way, patients may be diagnosed with SSc based on visceral manifestations and autoantibody profile, even when there is no skin thickening (SSc sine scleroderma). SSc should be suspected in patients with severe Raynaud's phenomenon, especially when there are digital ulcers and/or pits. Bilateral carpal tunnel syndrome may also be a presenting feature. Certainly, any patient with skin thickening and tightness, puffiness or swelling of the fingers should be suspected of having SSc.

Differential diagnosis of SSc includes diffuse morphea, scleredema, scleromyxedema, nephrogenic systemic fibrosis, eosinophilic fasciitis, lipodermatosclerosis, malignancy related palmar fasciitis and chronic graft versus host disease (Table 6.2) (Figs. 6.9, 6.10, and 6.11). A more common mimic of SSc is diabetic cheiroarthropathy, characterized by thickened waxy skin of the hands and fingers and sclerosis of the tendon sheaths with inability to fully flex or extend the

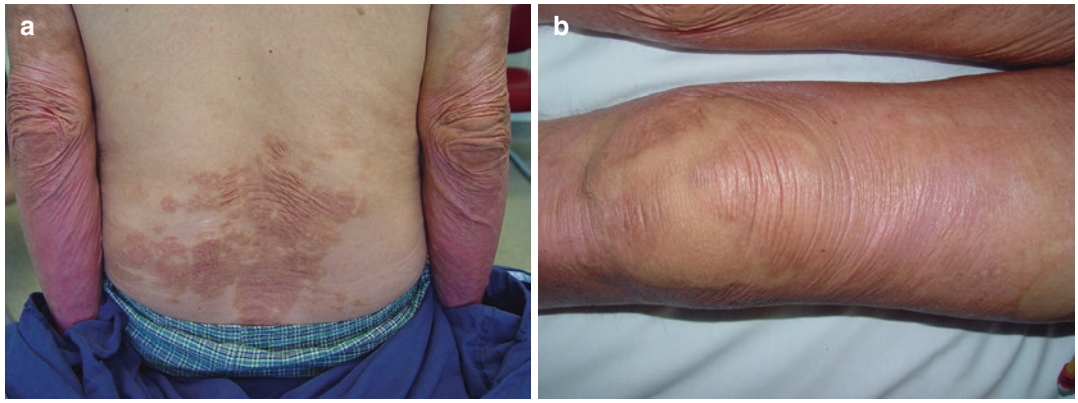

Fig. 6.10 (**a**, **b**) Nephrogenic systemic fibrosis. Symmetric, sharply demarcated, brawny plaques which are indurated and may have a cobblestone or texture. Thickened plaques typically involve trunk and extremities and usually spare the face. This patient has chronic kidney disease and has had imaging with Gadolinium containing contrast. (Courtesy of Amit Garg, MD)

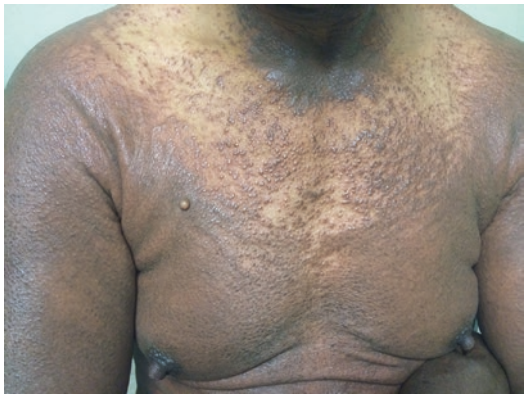

Fig. 6.11 Scleromyxedema. Numerous waxy appearing and firm discrete papules which are also coalescing to plaques on the trunk and extremities. (Courtesy of Amit Garg, MD)

fingers. Frostbite may cause SSc-like changes in a few, rather than all, fingers.

Physical Examination

On physical examination, the clinician should look for features unique to SSc, including puffy fingers (characterized by non-pitting edema), skin thickening and tightening (especially of the fingers, hands, neck, face, and perioral skin), digital pits, loss of digital pulp tissue (with skin often distally tethered to the nail), digital ulcers, telangectasias, and calcinosis. Examination of nailfold capillaries, especially of the fourth fingers, using a dermatoscope, widefield microscope, or videocapillaroscope is likely to aid in the diagnosis.

In addition to a cutaneous examination, careful evaluation of the cardiovascular and respiratory systems is essential to assess for cardiac, pulmonary and renal involvement. A thorough musculoskeletal examination is also needed to assess for joint contractures and synovitis as well as general mobility and joint range of motion.

Laboratory Testing

Routine laboratory testing, including complete blood count and differential, serum creatinine, urinalysis, and serum creatine kinase, may provide information about possible organ involvement. Serological tests including antinuclear, anti-topoisomerase I, anti-centromere, and anti-RNA polymerase III antibodies can support the diagnosis and provide prognostic information (Table 6.3). When there is suspicion of an alternative rheumatological diagnosis or overlap syndrome, other tests may be considered based on the specific presenting clinical features. Some of these may include rheumatoid factor, anti-citrullinated peptides, other extranuclear antigens, anti-double stranded DNA, and complement levels.

Table 6.4 Investigations for complications of SSc

Problem	Investigation
Dysphagia/reflux	Manometry, cine esophagogram, barium swallow, esophagogastroduodenoscopy, 24-hour pH monitoring
Gastric dysmotility	Gastric emptying study, esophagogastroduodenoscopy
Bacterial overgrowth	Glucose hydrogen breath test, D-xylose test, small bowel aspiration
Malabsorption/ Malnutrition	Malnutrition questionnaire, e.g. "Malnutrition universal screening tool," [148] hemoglobin, folic acid, serum carotene, vitamin B12, iron, zinc, vitamin D, INR, serum methylmalonic acid
Renal insufficiency	Blood pressure, blood smear, electrolytes and creatinine, urinalysis, hemolysis workup, consider renal biopsy

Cardiopulmonary Studies

Because ILD and PH are common in SSc and represent leading causes of morbidity and mortality in this population, the authors routinely perform high resolution computed tomography of the chest to evaluate for these conditions. A chest radiograph may be a reasonable first study to limit radiation exposure, but sensitivity is lower. SSc patients with respiratory symptoms and a negative chest radiograph should undergo additional testing. Pulmonary function tests should also be performed as a non-invasive screen for restrictive ventilatory defect and/or decrease in diffuse capacity for carbon monoxide (DLCO), the latter of which may be a sign of either ILD or PH. Echocardiography is also useful to evaluate for PH (in addition to cardiac involvement of SSc).

When echocardiography is suggestive of PH, right heart catheterization (RHC) may be performed to confirm the diagnosis. The most appropriate approach to selecting patients for RHC using other supportive information such as echocardiographic features, electrocardiography and NT-proBNP levels is being investigated [147]. In general, a pulmonary artery systolic pressure (PASP, estimated from echocardiogram) greater than 40 mmHg should trigger suspicion for PH. Other clinical features such as dyspnea, fatigue, reduced DLCO (especially if isolated or out of proportion to FVC reduction in cases of ILD, i.e., FVC%/DLCO% >1.6), and elevated NT-proBNP may warrant further investigation for PH, even when PASP is lower than 40 mmHg. Lastly, a baseline electrocardiogram should also be performed to screen for conduction abnormalities and arrhythmias.

Other Studies

Investigations for other organ involvement may be guided by patient symptoms. Table 6.4 lists some common tests performed for the unique symptoms and complications of SSc.

Disease and Comorbidity Assessment

Measurement of Disease Activity and Severity

The traditional disease activity measurement tool used in virtually all SSc clinical trials is the mRSS [149]. It measures the extent of skin involvement and has been shown to correlate well with internal organ involvement as well as survival. The mRSS assesses 17 body parts, including the face, anterior chest, abdomen, fingers, dorsum of the hands, forearms, upper arms, thighs, lower legs, and dorsum of the feet. In each area, skin with normal thickness is assigned a value of 0, while values of 1, 2 and 3 correspond to mild, moderate, and severe skin thickness, respectively. The total maximum score that can be assigned is 51. mRSS may be measured over time to track the skin thickness progression rate (STPR). A rapid STPR has been associated with reduced short-term survival and renal crisis

within 2 years of first evaluation [150]. The durometer has also been tested as a valid and responsive method to measure skin hardness [151]. It may have higher intraobserver reproducibility than mRSS [152], but its use may be limited by cost.

Multiple other SSc outcome measures have been used in clinical trials. These include both patient-reported and investigator-reported outcomes. Most are instruments that are also used for other diseases, such as Short Form-36 Health Survey, while some were specifically developed for SSc, such as the SSc health assessment questionnaire (SHAQ) [153], the UCLA SSc clinical trial consortium gastrointestinal instrument 2.0 [154], and the Raynaud's condition score [155]. Assessments of disease activity in individual organs utilize traditional organ-specific measures, such as FVC for pulmonary function assessment and tender joint count for musculoskeletal evaluation.

In the clinical setting, there are no widely and routinely used disease activity scales for SSc. The European SSc Study Group proposed a 10-point index based on organ system involvement and relevant laboratory findings [156]. However, the index has not yet been studied for early SSc and sensitivity for change in disease activity has not been established.

To assess disease severity, international SSc experts developed a revised Medsger severity index assessing 9 organ systems [157]. While individual item severity scores have been shown to predict survival [158], the entire severity index is not weighed and therefore it is not designed to render a total severity score.

Monitoring

In addition to regular cutaneous examinations, all patients with SSc require screening at routine intervals for the development of systemic manifestations, including pulmonary, cardiac, and renal disease. We recommend following patients with SSc at 3–6 month intervals. Review of systems at each visit should include assessment for difficulty swallowing, reflux, bloating, constipation, diarrhea, Raynaud's phenomenon, digital ulcers, dyspnea, fatigue, syncope, palpitations, chest pain, and blood pressure abnormalities.

For the first 5 years after the initial onset of symptoms, we obtain pulmonary function tests every 6–12 months and annual echocardiograms to assess for ILD and PH. Patients with mild respiratory impairment (FVC > 70%) or mild HRCT fibrosis (<20%) should have PFTs more frequently (every 3–6 months), until stabilization is documented on FVC and DLCO, especially during the first 3–5 years after disease onset. After 5 years, if there are no abnormal features (e.g. low DLCO, dyspnea, decreasing FVC), we decrease the frequency of pulmonary function testing. There are no clear guidelines with regards to frequency of echocardiography, as PH can occur many years after the onset of disease. Some experts choose to repeat echocardiography only in those who are symptomatic or at high risk for PH or with a decrease in DLCO, while others perform this exam on an annual basis indefinitely.

A yearly electrocardiogram is also advised to screen for cardiac involvement. For patients at high risk of renal crisis (male, African-American, anti-RNA polymerase III positive, with early disease, on prednisone), regular home blood pressure monitoring may be indicated.

Comorbidities

Comorbidities of SSc include increased cumulative risk of cardiovascular disease, including myocardial infarction and stroke [56, 159], deep vein thrombosis and pulmonary thromboembolisms [160], and malignancies (especially lung) [161]. A study using two large U.S. datasets to retrospectively assess comorbidities in SSc patients showed that they have a higher chronic disease burden, as defined by higher risks of overall cardiovascular, renal, hepatic, and neuropsychiatric disease [162]. The large epidemiological studies that have produced the above findings are limited by uncertainty with regard to their case and outcome definitions, as all of them

are based on administrative codes. Detection bias may also be an issue, as SSc patients have more medical care contact and undergo more testing than do healthy patients. In spite of these limitations, such findings are noteworthy, and more research is taking place to delineate the causes as well as mechanisms to prevent and/or improve outcomes for these comorbidities.

Management of SSc

No single approach to treatment has proven uniformly effective in SSc, and therapeutic studies are limited by the lack of adequate outcome measures and the variable natural history of the disease, including the tendency towards skin softening over time [163]. Future studies promise to utilize potentially more sensitive and specific biomarkers in the assessment of optimal therapeutic approaches [164–166].

Current therapeutic approaches largely focus on interventions tailored to specific organ involvement [86]. Therefore the essential first step in optimal management of SSc is to determine the disease phenotype and stage [167], because as reviewed above, limited and diffuse SSc differ in their natural history and complications. Later stage fibrotic disease of either phenotype may remain stable and therefore not require intervention [167].

Organ-Specific Therapy

Skin Disease

A large multicenter trial of methotrexate compared to placebo in patients with dcSSc showed a trend toward significance in skin score improvement in the methotrexate arm at the end of 24 months [168]. As a secondary outcome in the landmark Scleroderma Lung Study I (SLS I), the mRSS showed statistically significant improvement in patients with dcSSc treated with cyclophosphamide (CYC) as compared to controls, though the clinical significance of this finding was unclear [169]. Currently, there are several ongoing or recently completed studies of biologic therapies in SSc, both open label and randomized, in which changes in either mRSS or a gene expression biomarker in skin is a primary outcome (Table 6.5). Biologic therapies for skin disease alone should be considered experimental, and administration of these therapies is thus best conducted in the context of a clinical trial.

Vascular: Raynaud's Phenomenon and Digital Ischemic Ulcers

First line therapy for symptomatic Raynaud's phenomenon includes calcium channel blockers. Resistant or severe Raynaud's is best treated with PDE-5 inhibitors such as tadalafil or sildenafil, which have also shown to be of benefit in randomized trials of digital ischemic ulcers [170, 171]. ET-1 antagonists appear helpful in prevention of digital ischemic ulcers but not in healing established ulcers [172, 173].

Gastrointestinal

Treatment of GI complications of SSc focuses on symptom management. The mainstays of therapy are pro-motility agents (such as metachlopramide, octreatide, and erythromycin), antibiotics for bacterial overgrowth, and argon laser ablation for GAVE [174].

Table 6.5 Ongoing or recently completed trials of biologic therapy with mRSS or skin biomarkers as the primary outcome

Agent	Target	Design	NIH#
Fresolimumab	TGfβ	Phase I, open label	NCT01284322
Rilonacept	IL-1	Phase II, randomized, placebo controlled	NCT01538719
Abatacept	CTLA-4	Phase II, double blind, randomized, placebo controlled	NCT02161406
Tocilizumab	IL-6	Phase II/III randomized, double blind placebo controlled	NCT01532869
Anti-type I interferon	Type 1 interferon	Phase I, open label	NCT00930683

Pulmonary

Interstitial Lung Disease

ILD of all types has historically been difficult to treat. Recent efforts to treat SSc-associated ILD have focused on immune ablation with CYC. The SLS I was a pivotal trial comparing oral CYC to placebo over the course of 12 months in patients with SSc-associated ILD [169]. The trial showed a statistically significant benefit in FVC in patients treated with CYC, although a follow-up study showed that its benefit waned after 2 years [175].

Another randomized, placebo-controlled trial evaluated a regimen consisting of low-dose prednisolone with intravenous CYC monthly for 6 months followed by oral azathioprine for 6 months. It showed a trend toward statistical improvement in the treatment group, with change in FVC and single breath diffusion capacity for carbon dioxide (DLCO) as the primary outcomes [176].

SLS-II, a randomized, placebo-controlled trial of mycophenylate mofetil (MMF) versus oral CYC for 12 months, showed that MMF was equivalent to CYC in preventing FVC decline over the course of the trial, with lower toxicity. These results suggest that MMF should be considered standard of care in treating progressive ILD associated with SSc [177].

Other therapies currently under evaluation include pirfenidone (anti-fibrotic), palmolidomide (anti-fibrotic), nilotinib (anti-fibrotic) and rituximab (anti-CD20). The standard of care for SSc-associated ILD should involve assessment of stage and chronology of disease—i.e., stability or progression by imaging of the lung with high resolution CT scanning, and assessment of pulmonary function with spirometry and DLCO. Immunosuppressive therapy should then be considered for patients with disease progression or early stage disease. For end-stage progressive disease, lung transplantation may be required [178].

Pulmonary Arterial Hypertension

Virtually all trials of therapy of PAH include patients with SSc; however, to date there is only one randomized trial exclusively in patients with SSc-associated PAH [179]. Perhaps as a result, vasodilatory agents are the mainstay of therapy, in contrast to other manifestations of SSc, which are managed largely with immunomodulators. Still, therapy of PAH has undergone dramatic advances over the past several years.

There are two primary pharmacologic approaches to achieving vasodilation in PAH. The first approach is blocking the vasoconstrictive effects of ET-1. ET-1 antagonists include bosentan, ambrisentan and macitentan. The second approach is enhancing the vasodilatory effects of nitric oxide. Agents that accomplish this include phosphodiesterase (PDE) inhibitors (sildenafil and tadalafil), inhaled nitric oxide, and prostaglandin analogs (epoprostenol and treprostinil).

Both endothelin antagonists and PDE inhibitors have been shown to lead to statistically significant hemodynamic and symptomatic improvement in PAH. Only the most recent ET-1 inhibitor, macitentan, however, has shown a significant event-free survival (with event defined as death or hospitalization from PAH) as compared to placebo [180]. Recent studies suggest that combination therapies may offer improvements in efficacy when compared to monotherapies [181, 182].

The current standard of care for PAH patients falling into symptomatic New York Heart Association (NYHA) functional class II (mild to moderate impairment) is to begin an ET-1 inhibitor or PDE-5 inhibitor. For patients with advanced disease or in NYHA functional class III-IV, continuous intravenous infusion with prostacyclin derivatives such as epoprostenol is considered standard of care [183]. Lung transplantation may also be required for end stage disease [178].

Renal

Prior to the advent of angiotensin converting enzyme (ACE) inhibitors, SRC was associated with high risk of progression to end stage renal disease and high mortality secondary to complications of severe hypertension. ACE inhibitors have significantly improved outcomes in SRC, although the risk of progression to ESRD remains high even with early use of ACE inhibitors [184,

185]. Approximately 30% of patients with SRC who require renal replacement may be able to discontinue hemodialysis within a year if ACE inhibitors are continued during hemodialysis [186].

Musculoskeletal

Despite the frequent occurrence of musculoskeletal complications in SSc, there are no randomized controlled trials of SSc-associated arthropathy. Weekly methotrexate is considered standard of care, the first line disease-modifying therapy for musculoskeletal disease. Open label studies of anti-TNF agents as well as abatacept and tocilizumab suggest that these agents may also be of benefit [59, 167].

Low-dose prednisone may provide some symptomatic and functional benefit for both inflammatory arthritis and myositis. Prednisone at doses higher than 20 mg daily in patients with dcSSc, however, should generally be avoided due to concern about potentially precipitating SRC [187]. Physical and occupational therapy to maintain finger mobility are important adjunctive therapies.

Immune Modulation and Targeted Therapies

Beyond treating organ-specific manifestations, studies have shown benefit from immunomodulatory therapy in treating SSc overall. The 2014 Autologous Stem cell Transplantation International Scleroderma (ASTIS) trial showed that high-dose immunosuppressive therapy and autologous hematopoietic stem cell transplantation (HSCT) in patients with early diffuse SSc and poor prognosis (most of whom had either ILD or a history of renal crisis) conferred a significant survival benefit over lower level conventional immune suppression with monthly intravenous CYC [188]. This approach is not without substantial risk, however, given the 10% mortality associated with the stem cell transplantation [188]. HSCT should be viewed as a potential therapeutic option for patients with aggressive disease, but until treatment-associated mortality can be significantly reduced, it should not be considered a standard of care.

More targeted therapy is urgently needed in SSc, as conventional immunosuppression appears to confer modest benefit that wanes with time, and immune ablative approaches are risky. No such therapy yet exists, but there are number of promising therapies in development targeting potential drivers of disease pathogenesis, including fresolimumab (anti-TGfβ), rilonacept (IL1 inhibitor), tocilizumab (anti-IL6) and abatacept (T cell activation inhibitor).

Survival

Survival in SSc greatly depends on the clinical subtype and antibody profile, type of organ involvement, and patient demographics. Old age, male sex, African-American race, and poor socioeconomic status are associated with worse outcome. Other factors generally accepted as poor prognostic indicators include the diffuse cutaneous subset, anti-topoisomerase I antibody and presence of severe organ involvement (skin, lung, heart, GI tract, kidney) [33, 189]. In a recent analysis of 234 deaths in the EUSTAR database, the independent risk factors for mortality in SSc were proteinuria, PAH, restrictive pulmonary disease, dyspnea greater than NYHA Class II, decreased diffusion capacity, greater age of Raynaud's onset, and greater (mRSS) [51].

Encouragingly, survival in SSc has improved in the last few decades. In a large longitudinal study of a U.S. SSc cohort from Pittsburgh, PA, the 10-year survival rate improved from 54% in the 1970s to 66% in the 1990s [46]. More recent survival estimates in 1999–2010 report in a Brazilian cohort showed overall survival rate to be 90% over 5 years and 84% over 10 years [8]. The 10-year survival rate was lower for those with dcSSc (77%) vs. lcSSc (87%).

The improvement in SSc survival over time is largely attributable to the implementation of effective therapy for SRC, which historically had been the primary cause of death in SSc. Pulmonary fibrosis and PAH have since supplanted SRC as the leading causes of mortality

[46]. Additionally, more SSc patients are dying from non-SSc causes than in previous decades. In the EUSTAR database report, 55% of SSc deaths were directly related to SSc and 41% were secondary to non-SSc causes [51]. Top causes of non-SSc related deaths included infections, malignancies, and cardiovascular disease.

Summary

SSc is a debilitating connective tissue disease that disproportionately afflicts women and African-Americans and carries significant morbidity and mortality. However, recent therapeutic advances indicate that immunosuppressive therapy can prevent progression of severe cutaneous and visceral fibrosis. Patients must be evaluated for cutaenous, pulmonary, renal, GI, and cardiac involvement. Coordinated interdisciplinary care is essential in the evaluation and management of patients with systemic sclerosis.

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