CHAPTER 17

Systemic Sclerosis
A. Clinical Features

MAUREEN D. MAYES, MD, MPH

- Systemic sclerosis (scleroderma; SSc) is divided further into limited cutaneous disease and diffuse cutaneous disease on the basis of the extent of skin thickening.
- Limited disease is defined as skin thickening that only affects the extremities below the elbows and/or below the knees. Diffuse cutaneous disease is defined as skin thickening proximal to the elbows and/or knees in addition to distal extremity involvement. Truncal skin may also be involved in diffuse cutaneous systemic sclerosis (dcSSc).
- The face can be involved in both forms and has no bearing on subset designation.
- The clinical manifestations of SSc may be considered the result of three pathological processes: (1) a small vessel non-inflammatory obliterative vasculopathy; (2) the pathological accumulation of collagen in skin and other organs (fibrosis); and (3) autoimmunity.
- The obliterative small vessel vasculopathy is responsible for Raynaud's phenomenon, scleroderma renal crisis, and pulmonary artery hypertension.
- The fibrosing process results in thickened skin, pulmonary parenchymal disease, and gastrointestinal dysmotility.
- Tendon friction rubs, caused by an inflammation in the tendon sheath, are usually palpable on examination and sometimes cause pain with motion.
- A variety of autoantibodies occur in SSc, including those anti–topoisomerase III antibodies and anticentromere antibodies.
- Raynaud's phenomenon, usually the first manifestation of SSc, may precede the development of other features by months to years.
- Pulmonary disease is now the leading cause of death in SSc. Pulmonary fibrosis occurs in many SSc patients, with 20% ultimately requiring supplemental oxygen.
- Scleroderma renal crisis, the most common cause of death in SSc prior to the introduction of angiotensin-converting enzyme (ACE) inhibitors, remains an important source of patient morbidity in SSc.

From a clinical point of view, scleroderma is usually divided into two main forms, localized scleroderma and systemic scleroderma or systemic sclerosis (Figure 17A-1). Localized scleroderma includes the disease entities of morphea (one or more patches of thickened skin), linear scleroderma (a line of thickened skin affecting one or more extremities), and scleroderma en coup de sabre, which is a distinct subset of linear disease that affects the forehead and face [for review, see Piette (1)]. Although atrophy of the subcutaneous tissue underlying the lesions typically occurs in localized scleroderma, there is usually no associated internal organ or systemic involvement.

Systemic sclerosis (SSc), on the other hand, almost always has an element of internal organ disease (2). SSc is divided further into limited cutaneous disease (lcSSc) and diffuse cutaneous disease (dcSSc) on the basis of the extent of skin thickening. The terms *limited scleroderma* and *localized scleroderma* cause linguistic confusion, but these terms refer to very different conditions. In spite of a few reported cases of localized and systemic disease occurring in the same patient, this is a rare event and the two conditions should be thought of as two separate diseases with very different clinical pictures and prognosis.

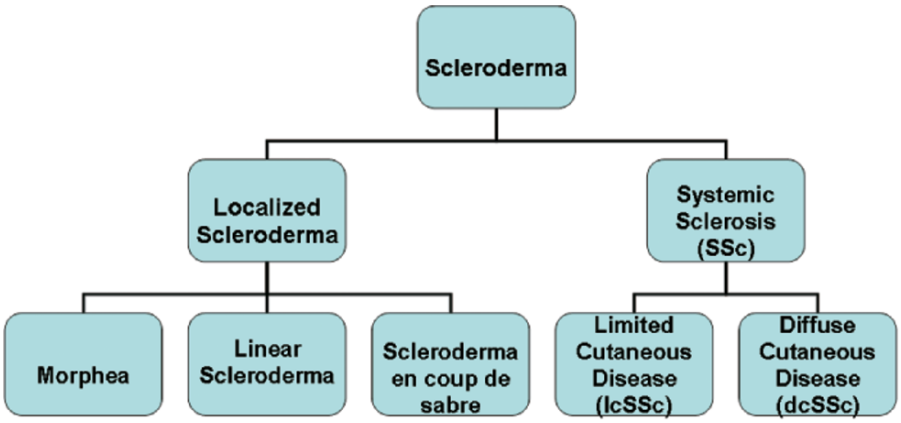
For rheumatologists, scleroderma is synonymous with systemic disease. Only SSc will be considered in the remainder of this chapter. In broad terms, the clinical manifestations of SSc may be considered the result of three pathological processes: (1) a small vessel non-inflammatory obliterative vasculopathy; (2) the pathological accumulation of collagen in skin and other organs (fibrosis); and autoimmunity (3). The mechanisms by which these three processes are linked are unclear.

VASCULOPATHY

The obliterative small vessel vasculopathy is responsible for Raynaud's phenomenon, scleroderma renal crisis, and pulmonary artery hypertension. In contrast, the

FIGURE 17A-1

Scleroderma is usually divided into two main forms, and then further subdivided.



fibrosing process results in thickened skin, pulmonary parenchymal disease, and gastrointestinal dysmotility. Some patients have an associated inflammatory component manifested by tendon friction rubs and synovitis. Other features such as calcinosis are less well understood.

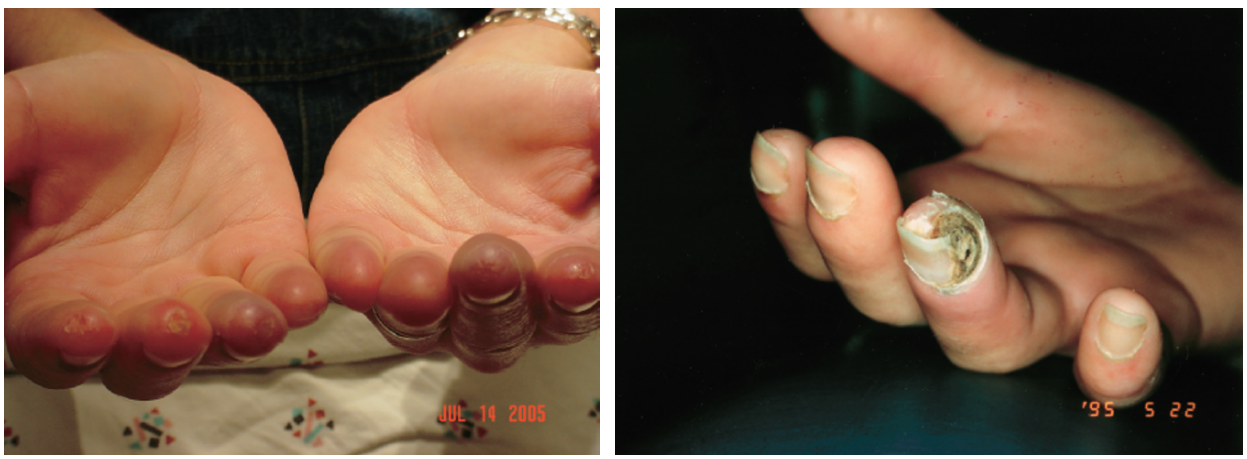
Raynaud's phenomenon is caused by vasospasm of the small vessels of the hands on cold exposure. This vasospasm, in turn, results in blanching, cyanosis, and then reactive hyperemia (rubor) as the affected area rewarms (4). An episode of Raynaud's phenomenon can be triggered by emotional stress, but the association with cold exposure must be present to make the diagnosis. Of the three phases—pallor, cyanosis, and rubor—rubor is the least frequent. The diagnosis is usually made on the basis of a compelling history rather than on attempts to recreate an episode under observation. This condition is common in the general population; approximately 5% to 10% or more of American adults will experience episodes of Raynaud's phenomenon (5,6). Most of these individuals have primary Raynaud's disease, not with a connective tissue disease. Primary Raynaud's disease does not result in tissue damage. Thus, digital ulcers or gangrene should not result from primary Raynaud's phenomenon.

Secondary Raynaud's phenomenon due to SSc, on the other hand, frequently results in irreversible tissue loss. In addition to the cold-induced vasospasm that occurs in such patients, the caliber of the blood vessels at baseline becomes narrowed by a vasculopathy. Chronic ischemia leads to reduction of the finger pad substance with consequent tapering of the fingers. Tender digital pitting scars are the result of more ischemia, leading to losses of small areas of tissue. Digital ulcers and digital gangrene are caused by even more severe degrees of ischemia [Figure 17A-2(A,B)]. Ulcers that spontaneously occur on the fingertips are due almost exclusively to ischemia, whereas those over the extensor surfaces of the proximal interphalangeal (PIP), metacarpophalangeal (MCP), ulnar styloid, and elbow joints are due to a combination of poor perfusion in areas of stretched skin and repeated minor trauma (Figure 17A-3).

Raynaud's phenomenon, usually the first manifestation of SSc, may precede the development of other features by months to years. In some cases, the delay

FIGURE 17A-2

(A, B) Digital ulcers and digital gangrene are caused by severe degrees of ischemia.



A B

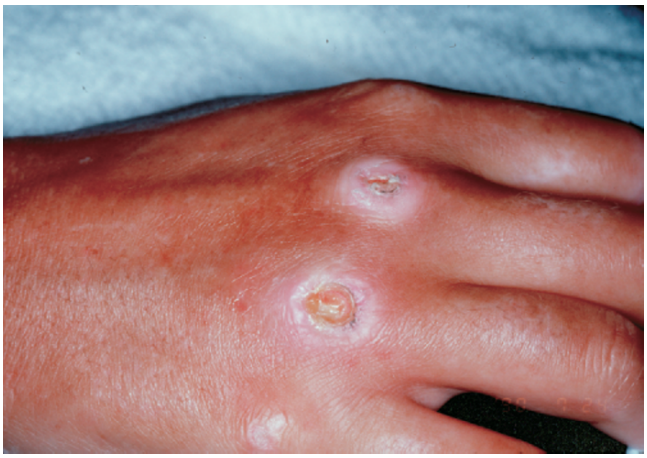


FIGURE 17A-3

Metacarpophalangeal ulcers are due to poor perfusion in areas of stretched skin or in areas of repeated minor trauma.

in diagnosis is due to the absence of full-blown SSc manifestations. In others, the diagnosis is delayed by the failure to realize that mild sclerodactyly (skin thickening limited to the fingers), gastroesophageal reflux, and other symptoms or signs of SSc are incipient indications of a broader systemic illness. Antinuclear antibodies (ANA) are usually present at the time of Raynaud's phenomenon onset. Indeed, the finding of a positive ANA in a patient with Raynaud's phenomenon suggests the need for further scrutiny of a possible connective tissue disorder.

The 1980 classification criteria for SSc, established by the American Rheumatism Society (now the American College of Rheumatology), consist entirely of clinical features (7). The single major criterion is the presence of thickened skin proximal to the MCP joints. There are three minor criteria, including sclerodactyly, permanent ischemic changes of the fingertips (loss of finger pad substance, digital pitting scars, or digital ulcers), and bibasilar pulmonary fibrosis. Classification of SSc is considered correct if proximal skin thickening is present, or if two of the three minor criteria are met. These classification criteria have a specificity of 98% and a sensitivity of 97%. However, this system may miss individuals who clearly have SSc by our current understanding. For example, individuals with only the CREST features (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias) do not meet this definition (8).

The division of SSc into limited cutaneous or diffuse cutaneous disease subsets has important prognostic implications and can be accomplished in a straightforward, clinically applicable approach. Limited disease is defined as skin thickening that only affects the extremities below the elbows and/or below the knees (8). Diffuse cutaneous disease (dcSSc) is defined as skin thickening proximal to the elbows and/or knees in addition to distal extremity involvement. Truncal skin may also be involved in dcSSc. The face can be involved in both forms and has no bearing on subset designation.

Limited cutaneous disease (lcSSc) typically begins with Raynaud's phenomenon, followed by the gradual development of other scleroderma-associated signs and symptoms including heartburn on a frequent, often daily, basis; tender digital pitting scars or ulcers; and thickening of the skin of the fingers, which may progress to include the dorsum of the hands and forearms. Later features include dyspnea related to pulmonary fibrosis; telangiectasias (initially on the hands and face); and, much later, the development of dyspnea related to pulmonary arterial hypertension.

In contrast, dcSSc has a more rapid onset, with skin changes shortly after or coincidental with the onset of Raynaud's phenomenon, and with internal organ involvement occurring during the first 2 years of disease. Skin involvement usually progresses over the first 1 to 5 years, then stabilizes, and can gradually improve but seldom totally resolves. Even if the extent and severity of skin disease recede with time, the designation of diffuse disease remains relevant because the course of the internal organ involvement does not parallel skin improvement. Fibrosis in the pulmonary, cardiac, and gastrointestinal (GI) systems fibrosis does not resolve. Individuals with dcSSc are at risk for progressive involvement in these organs. In addition, early dcSSc patients, especially in the phase of skin worsening, are at the highest risk of developing scleroderma renal crisis (SRC).

Inflammatory features are also prominent in this group of patients with early, diffuse disease. Such features include inflamed, reddened, and intensely pruritic skin, tendon friction rubs, and synovitis (which may be difficult to appreciate due to the thickened overlying skin). Although prednisone can provide symptomatic relief, doses of 15 mg per day or higher have been linked to the development of SRC.

In general, poor prognostic factors include diffuse skin involvement, late age of disease onset, African- or Native-American race, a diffusing capacity <40% of the predicted value, the presence of a large pericardial effusion, proteinuria, hematuria, renal failure, anemia, elevated erythrocyte sedimentation rate, and abnormal electrocardiogram (9,10).

Autoantibody status is also helpful in considering prognosis (11). Nearly all SSc patients are ANA positive. Those with a centromere pattern ANA usually have limited disease and a relatively good prognosis but are at an increased risk of developing pulmonary arterial hypertension, primary biliary cirrhosis, and severe digital ischemia. Antitopoisomerase antibodies (also known as anti–Scl 70) identify individuals with an increased risk of severe pulmonary fibrosis. Antibodies to RNA-polymerase (not to be confused with anti-RNP antibodies) are associated with increased risk of SRC.

TABLE 17A-1. KEY CLINICAL FEATURES OF SYSTEMIC SCLEROSIS.

Diffuse cutaneous systemic sclerosis (dcSSc)
- Proximal skin thickening involving the trunk, upper arms and thighs, in addition to symmetrical involvement of the fingers, hands, arms, and face/neck
- Rapid onset of disease following the appearance of Raynaud's phenomenon
- Significant visceral disease: lungs, heart, gastrointestinal, and/or kidneys
- Absence of anticentromere antibodies
- Variable disease course but overall poor prognosis, with survival 40% to 60% at 10 years

Limited cutaneous systemic sclerosis (lcSSc)
- Symmetrical skin thickening limited to the areas below the elbows and knees and involving the face/neck
- Progression of disease typically months or years after the onset of Raynaud's phenomenon
- Later and less severe development of visceral disease
- Late development of pulmonary arterial hypertension
- Association with anticentromere antibodies
- Relatively good prognosis with survival >70% at 10 years

Overlap syndromes
- Diffuse or limited systemic sclerosis with typical features of one or more of the other defined connective tissue diseases
- Mixed connective tissue disease: features of systemic lupus erythematosus, systemic sclerosis, and polymyositis in the presence of anti-U_1 RNP antibodies

Table 17A-1 provides a summary of key clinical features of the subsets of SSc. Although the recognition of limited and diffuse disease subsets is useful, SSc is a highly variable disorder. Severe internal organ disease can occur even in those in the lcSSc group.

SKIN MANIFESTATIONS

The hallmark feature of SSc is thickened skin. However, skin manifestations also include swollen hands (and sometimes feet), pruritus, hyper- and/or hypopigmentation, telangiectasias, calcinosis, dermal ulcers, digital tip pitting scars, and digital tip gangrene (12). Frequently, the first symptom following the onset of Raynaud's phenomenon is that of puffy hands; patients find that their rings no longer fit. This is followed by thickening of the skin beginning distally and progressing proximally, affecting the upper extremities more than the lower. Pruritus, a common feature, usually affects those with early diffuse disease and frequently predates clinically apparent skin thickening. Occasionally patients complain of sharp fleeting pains and superficial skin tenderness. Both the pruritus and the skin pain tend to be early symptoms and usually improve as the fibrosis becomes well established.

Diffuse hyperpigmentation is believed to be due to chronic inflammation in the skin. In time, the skin may develop a spotty hypopigmentation known as a salt-and-pepper appearance, caused by maintenance of pigment at the base of hair follicles but the loss of pigment in the surrounding skin. As time progresses, areas of pigment loss coalesce and may become quite extensive over the hands, face, and chest.

Telangiectasias most commonly occur over the fingers, palms, dorsum of the hands, and face (Figure 17A-4). By definition, telangiectasias blanch with pressure. The lesions, initially ≤1 mm in diameter, can enlarge over time and affect the upper extremities and trunk, as well as the vermilion border of the lips and oral mucosa. For reasons that are not clear, telangiectasias rarely affect the lower extremities. These lesions are cosmetically disturbing for many patients. When telangiectasias involve the GI tract extensively, they may be associated with significant blood loss. Otherwise, telangiectasias do not cause clinical problems.

Digital tip pitting scars, ulcers, and gangrene caused by ischemia are invariably painful. Ulcers over bony prominences (PIPs, MCPs, elbows, malleoli) are due to a combination of stretched and thickened skin, poor circulation in the microvasculature, and repetitive minor trauma. Although infection is not the primary cause of these ulcers, the areas can become secondarily infected due to their chronicity. Digital tip gangrene can occur suddenly and may require surgical intervention. Whenever possible from the standpoint of pain management, however, unsalvageable digital tissue should be allowed to undergo autoamputation rather than surgical

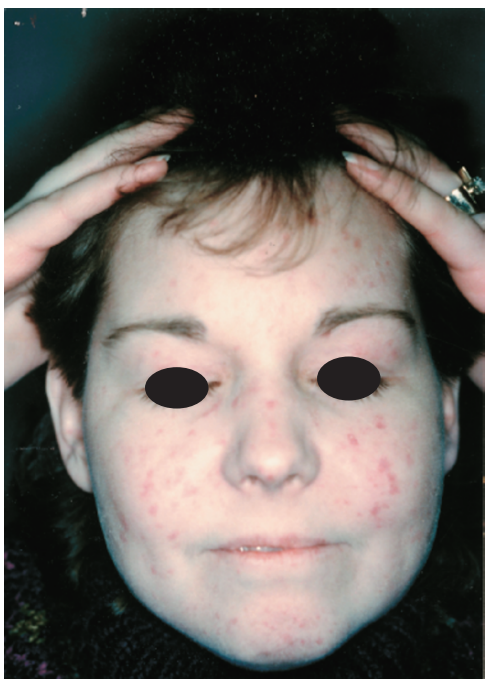


FIGURE 17A-4

Telangiectasias most commonly occur over the fingers, palms, dorsum of the hands, and face.

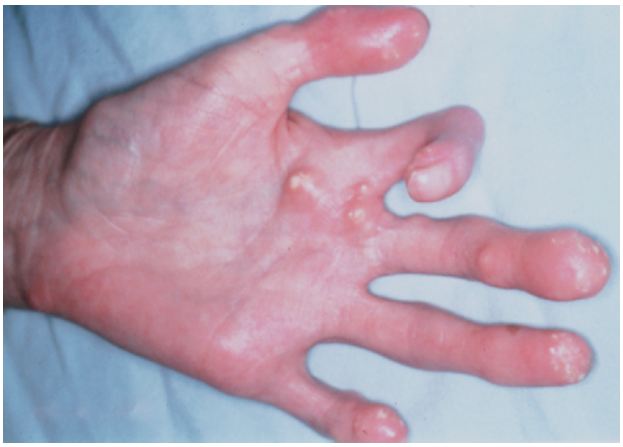


FIGURE 17A-5

Calcinosis can occur in the hands as well as in the forearms, elbows, knees, and legs.

removal, as surgical interventions generally lead to the loss of more tissue.

Calcinosis cutis, usually a late manifestation of SSc, occurs more frequently in limited disease but can occur in late diffuse disease, as well. Calcinosis can occur in the hands as well as in the forearms, elbows, knees, and legs (Figure 17A-5). These deposits can erupt through the skin, become secondarily infected, and pose major problems in management.

Although more than 95% of SSc patients have evidence of skin thickening, a small proportion will have scleroderma sine sclerosis, characterized by Raynaud's phenomenon, typical GI signs and symptoms, positive autoantibodies, and/or telangiectasias (13). The prognosis for these individuals, who have an increased risk for pulmonary arterial hypertension late in their course, is similar to those with limited cutaneous SSc. The diagnosis of SSc is usually quite delayed for this subtype due to the lack of thickened skin.

GASTROINTESTINAL MANIFESTATIONS

Next to skin involvement, the GI system is most commonly affected (14). Depending on the extent of involvement, signs and symptoms can include frequent heartburn, dysphagia, esophageal stricture formation, mucosal dysplasia (Barrett's esophagus), erosive esophagitis, gastritis, gastric antral vascular ectasia (GAVE or watermelon stomach), postprandial bloating, early satiety, weight loss, constipation, flatulence, and malabsorptive diarrhea.

The severity of GI tract disease is highly variable among individual patients. Most have some evidence of gastroesophageal reflux disease (GERD) due to lowered pressure of the gastroesophageal sphincter, but only a few develop severe GI dysmotility to the extent that hyperalimentation is required.

Gastrointestinal symptoms are related to dysmotility which, in turn, is related to smooth muscle atrophy and fibrosis. One current theory regarding SSc in the GI tract attributes gut dysfunction to early neural involvement with secondary muscular atrophy. In this scenario, fibrosis is a repair mechanism rather than the primary process (15).

Initially, there is incoordination of peristaltic waves in the esophagus. Over time, the esophagus may become totally aperistaltic. The sensation of dysphagia can occur on the basis of an esophageal stricture due to chronic reflux, or on the basis of disordered peristalsis such that food hangs up in one area, requiring several swallows to clear the material.

Chronic GERD can lead to mucosal erosions, dysplasia, stricture formation, and reactive airway disease due to nocturnal aspiration. GAVE, which is seen on upper endoscopy, is due to the thinning of the gastric mucosa such that the underlying parallel blood vessels in the antrum resemble the stripes of a watermelon. This condition, sometimes associated with blood loss, is amenable to endoscopic laser coagulation. Mucosal telangiectasias, which late in disease can develop throughout the GI tract, sometimes lead to occult, difficult-to-control blood loss.

Gastroparesis and small bowel dysmotility leads to early satiety, bloating, and flatulence. Bacterial overgrowth in the small intestine may cause malabsorption and diarrhea, requiring intermittent or rotating antibiotics. Decreased motility in the large bowel is associated with constipation, which can be severe. Radiographic contrast studies demonstrate wide-mouthed diverticuli as well as pneumotosis cystoides intestinalis. These latter two features are rarely of clinical consequence. Decreased pressure of the anal sphincter can also be seen in SSc, leading to stool incontinence.

Primary biliary cirrhosis (PBC) occurs in a small proportion of patients but at a rate that is greater than expected in the general population (16).

PULMONARY AND PULMONARY VASCULAR DISEASE

Pulmonary disease is now the leading cause of death in SSc (9). Pulmonary fibrosis occurs in many SSc patients, with 20% ultimately requiring supplemental oxygen. Patients with dcSSc are at higher risk of developing significant lung fibrosis compared to those with lcSSc. However, this distinction is not absolute, and pulmonary function test (PFT) monitoring is recommended for both groups. Early lung disease is frequently asymptomatic. Dry cough, a later symptom, is not specific for lung

disease and may be related to chronic GERD. Dyspnea on exertion may be a consequence of multiple factors.

Pulmonary function test that show a restrictive pattern is the most sensitive test for pulmonary parenchymal disease. Periodic testing is suggested. Decreases in the vital capacity, lung volumes, and/or diffusing capacity for carbon monoxide (DLCO) are indicative of restrictive changes. An isolated decrease in DLCO may also indicate pulmonary hypertension.

Computed tomography (CT) scans of the lung are more sensitive than radiographs for the detection of early fibrotic changes. High resolution CT views are required to detect a ground glass appearance, which is believed to represent inflammation or alveolitis. Bronchoalveolar lavage (BAL) showing neutrophils and/or eosinophils is suggestive of active inflammation. Patients who are positive for antitopoisomerase antibodies are at an increased risk for clinically significant pulmonary fibrosis, but this complication is not confined solely to this autoantibody subgroup.

Pulmonary hypertension can occur on the basis of two main pathologic processes: (1) those primarily involving destruction or obliteration of lung vasculature, such as pulmonary fibrosis, recurrent thromboembolic disease, or scleroderma vasculopathy; or (2) those associated with decreased cardiac output, for example, diastolic dysfunction, congestive heart failure, or valvular disease. *Pulmonary arterial hypertension* (PAH) is a term used to describe the first group of conditions.

As noted, PFTs in patients with PAH show an isolated decrease in DLCO with other parameters being normal, or a DLCO that is decreased out of proportion to the other measures. An echocardiogram is helpful in making the diagnosis, particularly if the right ventricular systolic pressure and/or the velocity of the regurgitant jet of the tricuspid valve are high. However, the echocardiogram is less reliable in borderline cases. In addition, the echocardiogram does not provide a measure of pulmonary capillary wedge pressure. Right heart catheterization should therefore be performed in patients suspected of PAH to confirm the diagnosis and obtain an accurate measurement of both the pulmonary artery and pulmonary capillary wedge pressures. Chronic thromboembolic disease must be excluded in patients with PAH.

In terms of symptoms, PAH is initially silent. Early symptoms can be nonspecific, for example, a sense of generalized weakness on exertion. Dyspnea is a later symptom and can be attributed to multiple other factors. PAH in SSc typically develops late in the course of patients with lcSSc. Many SSc patients with PAH are anticentromere antibody positive. However, in individuals with restrictive lung disease of mild or moderate severity, it is difficult to distinguish which patients have PAH secondary to their lung fibrosis and which patients have a combination of scleroderma lung disease with scleroderma pulmonary vasculopathy. The mortality risk in SSc patients with the combination of pulmonary fibrosis and PAH is similar to that of patients with isolated PAH and worse than those with pulmonary fibrosis alone (17).

The prevalence of PAH in the SSc patient population when measured by right heart catheterization is 8% to 12% (18,19). The prevalence of PAH by echocardiogram alone is more than double this figure (20) and emphasizes the point that right heart catheterization is necessary to confirm the diagnosis.

As echocardiography is being done more frequently in the SSc population, it is becoming clear that this condition is more common than believed previously, and that it can affect both lcSSc and dcSSc patients. Risk factors for progression to severe pulmonary hypertension include older age, limited skin disease, and elevated pulmonary artery pressures at the time of initial evaluation (21).

CARDIAC INVOLVEMENT

If cardiac involvement in SSc is defined as any change in the electrocardiogram (EKG), pericardium, or cardiac function, then heart disease in SSc is common (22). However, clinically apparent cardiac disease, usually a late finding associated with a poor prognosis, is relatively uncommon. When present, SSc cardiac disease is manifested by disturbances in the conduction system of the heart, arrhythmias, left ventricular or global heart failure, and pericarditis. Patchy fibrosis throughout the myocardium is the typical histological picture in SSc. Contraction band necrosis, characteristic of ischemia/reperfusion injury, has been described.

Asymptomatic small or moderate-sized pericardial effusions are frequently found, but tamponade is rare. Large pericardial effusions, however, are associated with a poor prognosis (23).

RENAL DISEASE AND SCLERODERMA RENAL CRISIS

Scleroderma renal crisis (SRC) was the most common cause of death in SSc prior to the introduction of angiotensin-converting enzyme (ACE) inhibitors (24). SRC still occurs, typically in the setting of early diffuse disease (<4 years from onset). In SRC, malignant hypertension can occur suddenly in individuals with previously normal blood pressure values. Clinical signs and symptoms are those of severe hypertension and can include headaches, stroke, and heart failure. The creatinine is elevated and urinalysis shows proteinuria and microscopic hematuria. Changes of microscopic angiopathy can be seen with anemia and thrombocytopenia, which resolve on normalization of the blood pressure. If treated early and aggressively with ACE inhibition (combined if necessary with other antihypertensives), the outcome is favorable, with return to normal or near normal renal function within several days of blood pressure normal-

ization. Good outcomes are dependent on lowering of the blood pressure to truly normal levels.

Factors predictive of SRC include diffuse skin disease, rapid progression of skin involvement, disease duration <4 years, anti-RNA polymerase III antibody, new anemia, new cardiac events, and antecedent high dose corticosteroid usage. In addition, prior use of cyclosporine has been linked to SRC.

Poor prognostic factors in SRC include a creatinine level >3 mg/dL at the time of diagnosis of SRC, delay in blood pressure normalization >3 days, male sex, older age, and presence of congestive heart failure. In one study, 55% of patients who initially required dialysis were able to discontinue dialysis at a mean of 8 months. It is therefore important to continue ACE inhibition and blood pressure control even after dialysis is initiated.

Normotensive renal crisis, characterized by a slow rise in creatinine in the absence of significant blood presssure elevation and without a microangiopathic picture, also has been described in SSc. Other causes for renal failure must be investigated thoroughly, and ACE inhibitors employed empirically.

MUSCULOSKELETAL DISEASE

Characteristics of musculoskeletal involvement include joint contractures, tendon friction rubs, myopathy, myositis, bone resorption, cutaneous calcifications, synovitis, and compression neuropathies (25).

In the absence of inflammatory synovitis, joint contractures are due to involvement of overlying skin that restricts motion. The degree of contractures reflects the extent of skin involvement. The hands, wrists, and elbows are the most commonly affected joints. Upper extremity involvement can interfere with normal hand and arm activities. Range of motion may also be reduced at the shoulders, hips, knees, and ankles. Lower extremity involvement can lead to marked gait impairment.

Tendon friction rubs, caused by an inflammation in the tendon sheath, are usually palpable on examination and sometimes cause pain with motion. If a patient complains of pain over the tendon with joint motion and no rub is palpated, it can usually be heard with the stethoscope. The most commonly affected tendon sheaths are those of the ankle dorsiflexors, the finger extensors, and the knee extensors. Tendon friction rubs may also be detected around the shoulders, wrists, and other joints.

In SSc, both a myopathy and a myositis can occur. Scleroderma myopathy is characterized by a relatively nonprogressive course; mild proximal muscle weakness; normal or slight elevations of creatine phosphokinase (CPK); and poor response to corticosteroids (26). Muscle biopsy shows replacement of muscle fibers with fibrosis, and lymphocytic infiltrates (if present) are scanty. In contrast, true myositis—a less common clinical finding—is characterized by progressive proximal muscle weakness, elevation of CPK, and typical electromyographic changes of inflammatory muscle disease. True myositis usually responds to immunosuppression.

Osteolysis or bone resorption of the digital tufts, seen in 40% to 80% of patients, is believed to be on the basis of chronic ischemia. Osteolysis of other bones is also seen but is much less common than digital tuft resorption. These sites include the ribs, the mandible, the distal clavicle, the humerus and the cervical spine.

Inflammatory synovitis of the peripheral joints, particularly those of the hands and wrists, is a frequent finding early in the disease course. Joint swelling can be difficult to appreciate under the thickened and taut scleroderma skin. The arthritis of SSc is nonerosive, usually responsive to anti-inflammatory agents (including methotrexate), and can resolve after several months.

In contradistinction to the above situation, some patients have an overlap of SSc and rheumatoid arthritis with positive rheumatoid factor, erosive joint disease, and progressive articular destruction. Treatment is the same as the treatment of idiopathic rheumatoid arthritis.

The most common compression neuropathy in SSc is carpal tunnel syndrome. This frequently occurs in the edematous phase of early disease. Other compression neuropathies, such as ulnar neuropathy, can occur as the skin becomes thickened and taut and as flexion contractures develop.

SCLERODERMA-LIKE DISORDERS

Several SSc-like disorders have been described (27). The most clinically relevant today include nephrogenic systemic fibrosis (NSF, previously called nephrogenic fibrosing dermopathy), eosinophilic fasciitis, scleredema, and scleremyxedema.

Nephrogenic systemic fibrosis (NSF) occurs in the setting of chronic renal insufficiency, usually but not always affecting individuals on dialysis (28). Features that distinguish this from SSc are the following: The fibrosis affects the lower extremities more than the upper extremities, occurs relatively rapidly, and tends to spare the hands. Raynaud's phenomenon is not associated with NSF, and renal transplantation has been reported to cause regression of this disease. Although the mechanism is not fully established, it is thought that circulating fibrocytes, derived from the bone marrow, are recruited to the skin, become activated and result in fibrosis.

Eosinophilic fasciitis (Shulman's disease) is characterized by fairly rapid onset of skin and fascial thickening with the early development of flexion contractures, particularly at the elbow. The skin has an orange peel or puckered appearance, sparing the hands and fingers. A deep biopsy that extends to the underlying fascia needs to be done in order to make the diagnosis. An eosinophilic infiltrate is seen on biopsy affecting the

fascia which is thickened. Peripheral eosiniphilia, unusual to any substantial degree in SSc, is common in eosinophilic fasciitis.

Scleredema (or scleredema diabeticorum) occurs, as its name suggests, as a complication of diabetes mellitus and causes induration and thickening of the skin of the neck, shoulder girdle area, proximal upper extremities, and back. The distribution is contrasts with the distal involvement of SSc and there is no Raynaud's phenomenon. A biopsy shows excess mucin as well as collagen. Scleredema can also be associated with a paraprotein or with multiple myeloma. Paraproteins are usually not demonstrated in the skin.

Scleromyxedema, on the other hand, is characterized by a more generalized cutaneous induration than that seen in scleredema. Scleromyxedema can involve the hands but there is also the presence of mucinous papules and nodules. This condition is also associated with a paraprotein. It can be distinguished by the presence of folded and pendulous skin, rather than the tight, hidebound character of SSc skin.

REFERENCES

1. Piette WW. Morphea or localized scleroderma. In: Clements PJ, Furst DE, eds. Systemic sclerosis. Philadelphia: Lippincott Williams & Wilkins; 2004:29–37.
2. Medsger TA Jr. Classification, prognosis. In: Clements PJ, Furst DE, eds. Systemic sclerosis. Philadelphia: Lippincott Williams & Wilkins; 2004:17–28.
3. Korn JH. Pathogenesis of systemic sclerosis. In: Koopman WJ, Moreland LW, eds. Arthritis and allied conditions. Philadelphia: Lippincott Williams & Wilkins; 2005:1621–1632.
4. Boin F, Wigley FM. Understanding, assessing and treating Raynaud's phenomenon. Curr Opin Rheumatol 2005;17: 752–760.
5. Fraenkel L, Zhang Y, Chaisson CE, et al. Different factors influencing the expression of Raynaud's phenomenon in men and women. Arthritis Rheum 1999;42:306–310.
6. Suter LG, Murabito JM, Felson DT, Fraenkel L. The incidence and natural history of Raynaud's phenomenon in the community. Arthritis Rheum 2005;52:1259–1263.
7. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee: preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23:581–590.
8. LeRoy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets, and pathogenesis. J Rheumatol 1988;15:202–205.
9. Steen VD, Medsger TA Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum 2000;43:2437–2444.
10. Bryan C, Knight C, Black CM, Silman AJ. Prediction of five-year survival following presentation with scleroderma: development of a simplet model using three disease factors at first visit. Arthritis Rheum 1999;42:2660–2665.
11. Cepeda EJ, Reveille JD. Autoantibodies in systemic sclerosis and fibrosing syndromes: clinical indications and relevance. Curr Opin Rheumatol 2004;16:723–732.
12. Clements PJ, Medsger TA Jr, Feghali CA. Cutaneous involvement in systemic sclerosis. In: Clements PJ, Furst DE, eds. Systemic sclerosis. Philadelphia: Lippincott Williams & Wilkins; 2004:129–150.
13. Poormoghim H, Lucas M, Fertig N, Medsger TA Jr. Systemic sclerosis sine scleroderma: demographic, clinical, and serologic features and survival in forty-eight patients. Arthritis Rheum 2000;43:444–451.
14. Weinstein WM, Kadell BM. The gastrointestinal tract in systemic sclerosis. In: Clements PJ, Furst DE, eds. Systemic sclerosis. Philadelphia: Lippincott Williams & Wilkins; 2004:293–308.
15. Goldblatt F, Gordon TP, Waterman SA. Antibody-mediated gastrointestinal dysmotility in scleroderma. Gastroenterology 2002;123:1144–1150.
16. Mackey RI. Autoimmunity and primary biliary cirrhosis. Baillieres Best Pract Res Clin Gastroenterol 2000;14:519–533.
17. Chang B, Wigley FM, White B, Wise RA. Scleroderma patients with combined pulmonary hypertension and interstitial lung disease. J Rheumatol 2003;30:2398–2405.
18. Hachulla E, Gressin V, Guillevin L, et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. Arthritis Rheum 2005;52:3792–3800.
19. Mukerjee D, St George D, Coleiro B, et al. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. Ann Rheum Dis 2003;62:1088–1093.
20. Wigley FM, Lima JAC, Mayes M, McLain D, Chapin JL, Ward-Able C. The UNCOVER study: prevalence of undiagnosed pulmonary arterial hypertension in subjects with connective tissue disease at the secondary healthcare level of community-based rheumatologists. Arthritis Rheum 2005;52:2125–2132.
21. Chang B, Wigley FM, White B, Wise RA. Scleroderma patients with combined pulmonary hypertension and interstitial lung disease. J Rheumatol 2006;33:269–274.
22. Follansbee WP, Marroquin OC. Cardiac involvement in systemic sclerosis. In: Clements PJ, Furst DE, eds. Systemic sclerosis. Philadelphia: Lippincott Williams & Wilkins; 2004:195–220.
23. Smith JW, Clements PJ, Levisman J, Furst D, Ross M. Echocardiographic features of progressive systemic sclerosis (PSS): correlation with hemodynamic and postmortem studies. Am J Med 1979;66:28–33.
24. Steen VD. Renal involvement in systemic sclerosis. In: Clements PJ, Furst DE, eds. Systemic sclerosis. Philadelphia: Lippincott Williams & Wilkins; 2004:279–292.
25. Pope JE. Musculoskeletal involvement in scleroderma. Rheum Dis Clin North Am 2003;52:391–405.
26. Clements PJ, Furst DE, Campion DS, et al. Muscle disease in progressive systemic sclerosis: diagnostic and therapeutic consideration. Arthritis Rheum 1978;21:62–71.
27. Mori Y, Kahari VM, Varga J. Scleroderma-like cutaneous syndromes. Curr Rheumatol Rep 2002;4:113–122.
28. Cowper SE, Boyer PJ. Nephrogenic systemic fibrosis: an update. Curr Rheumatol Rep 2006;8:151–157.

CHAPTER 17

Systemic Sclerosis
B. Epidemiology, Pathology, and Pathogenesis

JOHN VARGA, MD

- Systemic sclerosis (SSc) is a chronic, multisystem disease of unknown etiology characterized by autoimmunity and inflammation, functional and structural abnormalities in small blood vessels, and progressive fibrosis of the skin and visceral organs.
- Estimates of its incidence in the United States range from 9 to 19 cases per million per year. The only community-based survey of SSc yielded a prevalence of 286 cases per million population.
- SSc is more common in females, with women-to-men ratios of 3 to 5:1.
- African Americans have a higher incidence than whites, and disease onset occurs at an earlier age. Furthermore, African Americans are more likely to have the diffuse cutaneous form of the disease with interstitial lung involvement and worse prognosis.
- Some SSc patients (1.6%) have a first-degree relative with the disease [relative risk (RR) = 13], indicating an important genetic contribution to disease susceptibility.
- Among environmental factors, infectious agents (particularly viruses), exposure to environmental and occupational toxins, and drugs have been suspected of playing a role in the etiology of SSc.
- The distinguishing pathological hallmark of SSc is an obliterative vasculopathy of small arteries and arterioles, combined vascular and interstitial fibrosis in target organs. In patients with established SSc, these lesions occur in the absence of inflammation.
- In relatively early-stage disease, perivascular cellular infiltrates are detected in many organs prior to the appearance of fibrosis.
- The organs most prominently affected by obliterative vasculopathy are the heart, lungs, kidneys, and intestinal tract.
- Fibrosis is prominent in the skin, lungs, gastrointestinal tract, heart, tendon sheath, perifascicular tissue surrounding skeletal muscle, and in some endocrine organs, such as the thyroid gland.
- Multiple cell types and their products interact in the processes that underlie the diverse clinical manifestations of SSc.
- An integrated view of the pathogenesis of SSc must incorporate the development of vasculopathy, activation of the cellular and humoral immune responses, and progressive fibrosis of multiple organs.
- Autoimmunity, altered endothelial cell function, and vascular reactivity may be the earliest manifestations of SSc, leading to Raynaud's phenomenon years before other disease features are present. Complex interplay among these processes initiates, amplifies, and sustains aberrant tissue repair and fibrosis.

Systemic sclerosis (SSc) is a chronic, multisystem disease of unknown etiology characterized by autoimmunity and inflammation, functional and structural abnormalities in small blood vessels, and progressive fibrosis of the skin and visceral organs. The pathogenesis of SSc is highly complex and incompletely understood. Multiple cell types and their products interact in the processes that underlie the diverse clinical manifestations of SSc.

EPIDEMIOLOGY

Systemic sclerosis, an acquired, sporadic disease with worldwide distribution, affects all races. Estimates of its incidence in the United States range from 9 to 19 cases per million per year. Prevalence rate estimates range from 28 to 253 cases per million. The only community-based survey of SSc yielded a prevalence of 286 cases per million population (1). It is estimated that some

100,000 people in the United States have SSc, although this number may be significantly higher if patients who may have milder disease and do not meet formal classification criteria are also included. There does not appear to be a difference in incidence between warmer and colder climates within the United States. Studies from England, Australia, and Japan have shown lower rates compared to the United States (2).

Age, gender, and ethnicity are important factors determining disease susceptibility. Like other connective tissue diseases, SSc is more common in females, with women-to-men ratios of 3 to 5:1. The female predominance, most striking among patients aged 15 to 40 years, declines after menopause. The most common age of onset is in the 30 to 50 years range, and in contrast to localized forms of scleroderma, SSc is rare in children. African Americans have a higher incidence than whites, and disease onset occurs at an earlier age. Furthermore, African Americans are more likely to have the diffuse cutaneous form of the disease with interstitial lung involvement and worse prognosis. Increased disease severity and mortality of SSc in African Americans may be related to the greater frequency of severe disease subtypes and subtype-specific autoantibodies such as those directed against topoisomerase I (Scl-70) and U3-RNP (3).

Associations of SSc with specific human leukocyte antigen (HLA) haplotypes are generally weak. In contrast, specific autoantibodies are associated with particular HLA alleles. For instance, antitopoisomerase I antibodies show strong association with the HLA-DRB1*1101-1104 alleles in white and black Americans, and with DRB1*1502 in Japanese. Certain antibody–HLA associations differ among different ethnic groups. Among whites with SSc, the HLA-DQB1 molecule is associated with anticentromere antibodies.

GENETIC FACTORS

Systemic sclerosis is not inherited in a Mendelian fashion. Furthermore, monozygotic and dizygotic twin pairs show a similarly low rate of disease concordance (4). On the other hand, 1.6% of SSc patients have a first-degree relative with the disease [relative risk (RR) = 13], indicating an important genetic contribution to disease susceptibility. The risk of other autoimmune diseases, including systemic lupus erythematosus (SLE) and rheumatoid arthritis, is also increased in first-degree relatives of SSc patients. Among Choctaw Native Americans from Oklahoma, the prevalence of SSc may be as high as 4690 per million. Moreover, affected individuals in the Choctaw population display striking homogeneity of disease phenotype, with diffuse cutaneous involvement, pulmonary fibrosis, and antitopoisomerase I antibodies. Genetic investigations in SSc have focused on polymorphisms of candidate genes, particularly those involved in regulation of immunity and inflammation, vascular function, and connective tissue homeostasis. Weak associations of single nucleotide polymorphisms (SNPs) with SSc have been reported in genes encoding angiotensin-converting enzyme (ACE), endothelin 1, nitric oxide synthase, B-cell markers (CD19), chemokines (monocyte chemoattractant protein 1) and chemokine receptors, cytokines (interleukin 1 alpha, IL-4, and tumor necrosis factor alpha), growth factors and their receptors (connective tissue growth factor [CTGF] and transforming growth factor beta [TGF-beta]), and extracellular matrix proteins (fibronectin, fibrillin, and SPARC). The list continues to grow.

ENVIRONMENTAL FACTORS

The relatively low rates of twin concordance for SSc suggest the importance of environmental factors in disease susceptibility. Infectious agents (particularly viruses), exposure to environmental and occupational toxins, and drugs have been suspected. Patients with SSc have increased serum antibodies to human cytomegalovirus (hCMV), and antitopoisomerase I autoantibodies recognize antigenic epitopes that are present on the hCMV-derived UL94 protein. Because antibodies to UL94 induce endothelial cell apoptosis and activation of dermal fibroblasts—two of the pathophysiologic hallmarks of SSc—molecular mimicry may be a possible mechanistic link between hCMV infection and SSc. Other studies have implicated hCMV infection in the allograft vasculopathy that follows solid organ transplantation. This vasculopathy is characterized by vascular neointima formation and smooth muscle proliferation, reminiscent of the obliterative vasculopathy of SSc. Demonstration that hCMV can directly induce CTGF production in infected fibroblasts lends further rationale to the hypothetical connection between hCMV and SSc. Human parvovirus B19 infection has also been postulated to have a link with SSc.

Several reports of apparent geographic clustering of SSc cases suggest shared environmental exposures, but careful investigations have failed to substantiate these clusters. In the past two decades, two epidemics of multisystemic illnesses reminiscent of SSc have been reported. One of these, the toxic oil syndrome, was linked to contaminated rapeseed cooking oils in Spain. The other, eosinophilia–myalgia syndrome, was caused by the ingestion of a dietary supplement (L-tryptophan) in the United States. Both of these apparently novel syndromes, each of which affected more than 10,000 individuals, were characterized by chronic scleroderma-like skin fibrosis. Yet both showed clinical and pathological features that clearly distinguished them from

SSc. Some observers have noted an increased incidence of SSc among men with occupational exposure to silica, such as miners. Other occupational exposures tentatively linked with SSc include polyvinyl chloride, epoxy resins, and aromatic hydrocarbons (e.g., toluene and trichloroethylene). Drugs implicated in SSc-like illnesses include bleomycin, pentazocine, cocaine, and appetite suppressants (primarily derivatives of fenfluramine) associated with pulmonary hypertension. The occurrence of SSc in some women with silicone breast implants raised concern regarding a possible association, but careful epidemiologic investigations found no evidence of increased risk of SSc (5).

PATHOLOGY

The distinguishing pathological hallmark of SSc is an obliterative vasculopathy of small arteries and arterioles combined with interstitial fibrosis in target organs. In patients with established SSc, these lesions occur in the absence of inflammation. In relatively early-stage disease, however, perivascular cellular infiltrates are detected in many organs prior to the appearance of fibrosis. Cutaneous infiltrates are composed primarily of CD4+ T lymphocytes (6). In addition, CD8+ T cells, monocytes/macrophages, plasma cells, mast cells, and occasionally B cells are detected. In contrast to skin, the majority of T cells infiltrating the lungs are CD8+. Evidence of eosinophil degranulation is found in lesional skin and lungs in the absence of intact eosinophils.

The vascular lesion of SSc, characterized by bland intimal proliferation in the small and medium-sized arteries, results in luminal narrowing. The organs most prominently affected by obliterative vasculopathy are the heart, lungs, kidneys, and intestinal tract. Fibrosis is prominent in the skin, lungs, gastrointestinal tract, heart, tendon sheath, perifascicular tissue surrounding skeletal muscle, and in some endocrine organs, such as the thyroid gland. SSc-associated fibrosis is characterized by homogeneous-appearing connective tissue composed of type I collagen, fibronectin, proteoglycans, and other structural macromolecules. The process leads to progressive replacement of normal tissue, disruption of architecture, functional impairment, and (frequently) organ failure. In the skin, fibrosis is preceded by inflammatory cell accumulation. This causes massive dermal expansion with obliteration of the hair follicles, sweat glands, and other appendages (Figure 17B-1). Collagen accumulation is most prominent in the reticular dermis, and the fibrotic process invades the subjacent adipose layer with entrapment of fat cells. The epidermis is atrophic, and the rete pegs are effaced.

Pathological changes can be found in any part of the gartrointestinal tract, from the mouth to the rectum. The striated muscle in the upper third of the esophagus is generally spared. The lower esophagus is frequently involved, with prominent fibrosis of the lamina propria and submucosa, characteristic vascular lesions, and atrophy of the muscular layers. Lower esophageal dysfunction leads to gastroesophageal reflux in a high percentage of patients. Chronic reflux is associated with esophageal inflammation, ulcerations, and stricture formation, and may lead to Barrett's esophagus. Replacement of the normal intestinal tract architecture results in disordered peristaltic activity, dysmotility, and small bowel obstruction.

In the lungs, patchy infiltration of the alveolar walls with CD8+ lymphocytes, macrophages, and eosinophils is prominent in early disease. With disease progression, fibrosis and vascular damage dominate the pathological picture in diffuse SSc, often coexisting within the same lesions. In patients with limited cutaneous disease, vascular lesions predominate with little or no fibrosis. Intimal thickening of the pulmonary arteries, best seen with elastin stain, underlies pulmonary hypertension. At autopsy in such cases, multiple pulmonary emboli and evidence of myocardial fibrosis are often found. Pulmonary fibrosis is characterized by expansion of the alveolar interstitium, with accumulation of collagen and other connective tissue proteins. This pattern is classified histopathologically as nonspecific interstitial pneumonitis (NSIP). Progressive thickening of the alveolar septae results in obliteration of the air spaces and honeycombing, as well as loss of pulmonary blood vessels

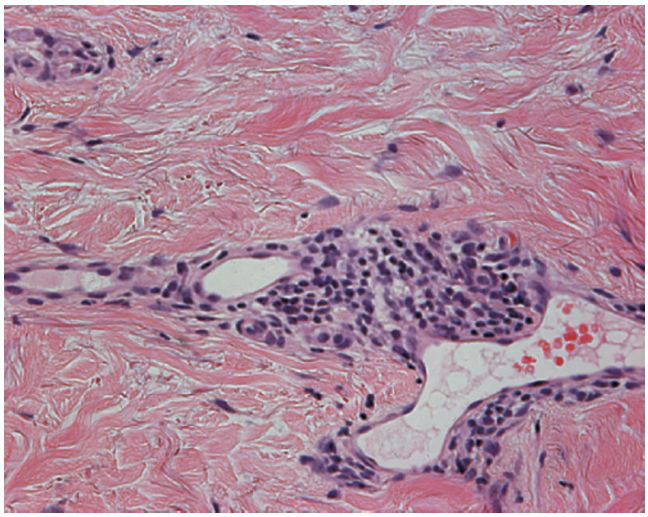


Figure 17B-1

Inflammation and fibrosis in the skin. This skin lesion from a patient with early systemic sclerosis shows a focal perivascular infiltrate composed on monocytes and lymphocytes, surrounded by densely packed collagen fibers in the deep layer of the dermis. Adnexal structures are encased by connective tissue. (Hematoxylin and eosin). (From Varga J, Abraham D. Systemic sclerosis: a prototypic multisystem fibrotic disorder, by permission of *J Clin Invest* 2007 117:557–67.)

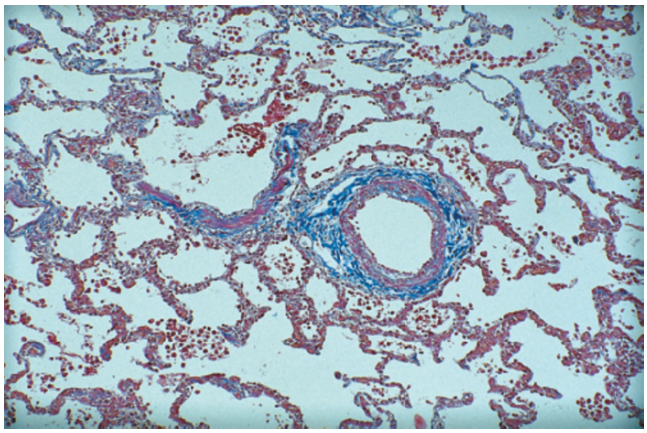


Figure 17B-2

Pulmonary artery. There is thickening of the intimal layer of a small pulmonary artery, leading to occlusion of vascular lumen. (Hematoxylin and eosin).

(Figure 17B-2). This process impairs gas exchange and contributes to worsening pulmonary hypertension.

The heart is frequently affected, with prominent involvement of the myocardium and pericardium. The characteristic arteriolar lesions of intimal proliferation and luminal narrowing are accompanied by contraction band necrosis, reflecting ischemia-reperfusion injury, and patchy myocardial fibrosis. The electrical system of the heart (bundle of His, Purkinje fibers) may be involved, leading to conduction disturbances.

In the kidneys, lesions of the interlobular arteries predominate. Glomerulonephritis is not characteristic of SSc. Chronic renal ischemia is associated with shrunken glomeruli. Patients with scleroderma renal crisis show dramatic changes in small renal arteries: reduplication of elastic lamina, marked intimal proliferation and narrowing of the lumen, and often thrombosis and microangiopathic hemolysis. The renal lesion in scleroderma renal crisis may be identical histopathologically to that of thrombotic thrombocytopenic purpura. Other organs may also be affected. Synovitis may be found in patients with early SSc, but with progression the synovium becomes fibrotic, as do tendon sheaths and fascia, producing audible tendon friction rubs. Inflammatory myositis and muscle fibrosis are common findings.

PATHOGENESIS

An integrated view of the pathogenesis of SSc must incorporate the development of vasculopathy, activation of the cellular and humoral immune responses, and progressive fibrosis of multiple organs (Figure 17B-3). Autoimmunity, altered endothelial cell function, and vascular reactivity may be the earliest manifestations of SSc, leading to Raynaud's phenomenon years before other disease features are present. Complex interplay between these processes initiates, amplifies, and sustains aberrant tissue repair and fibrosis (7).

ANIMAL MODELS OF DISEASE

No animal model reproduces all three cardinal features of human SSc (vascular damage, autoimmunity, and fibrosis), but some models recapitulate selected disease characteristics. The tight skin mouse (Tsk1/+) is a naturally occurring model of SSc characterized by spontaneous development of scleroderma-like skin changes. The mutation responsible for the mouse phenotype, an in-frame duplication in the gene responsible for Marfan's disease (fibrillin-1), results in defective matrix assembly and altered TGF-beta activation. However, corresponding mutations have not been found in human SSc. A chronic condition with fibrosis in the skin and lungs can be induced in mice by chemical exposure (bleomycin injections) or by transplantation of HLA-mismatched bone marrow or spleen cells (sclerodermatous graft versus host disease). Increasingly, manipulation of mice via mutagenesis or targeted genetic modifications such as knockout models or transgenesis have created new approaches to studying SSc and dissecting the roles of individual molecules in the underlying processes. For instance, genetic targeting of Smad3, an intracellular mediator for TGF-beta, and of the chemokine MCP-1, both resulted in mice that were resistant to bleomycin-induced scleroderma.

VASCULOPATHY

Vascular involvement is widespread in SSc and has important clinical implications. Raynaud phenomenon, an early disease manifestation, is characterized by an altered blood flow response to cold challenge. This initially reversible abnormality is due to alterations in the autonomic and peripheral nervous systems, with impaired production of neuropeptides, such as calcitonin gene-related peptide (from sensory afferent nerves) and heightened sensitivity of alpha 2-adrenergic receptors (on vascular smooth muscle cells). While primary Raynaud's phenomenon is a relatively benign, nonprogressive condition, in SSc irreversible morphological and functional changes in the circulation develop, leading to endothelial injury. Within the endothelium, there is altered production of and responsiveness to endothelium-derived factors that mediate vasodilatation (nitric oxide and prostacyclin) and vasoconstriction (endothelin 1). Microvessels show increased

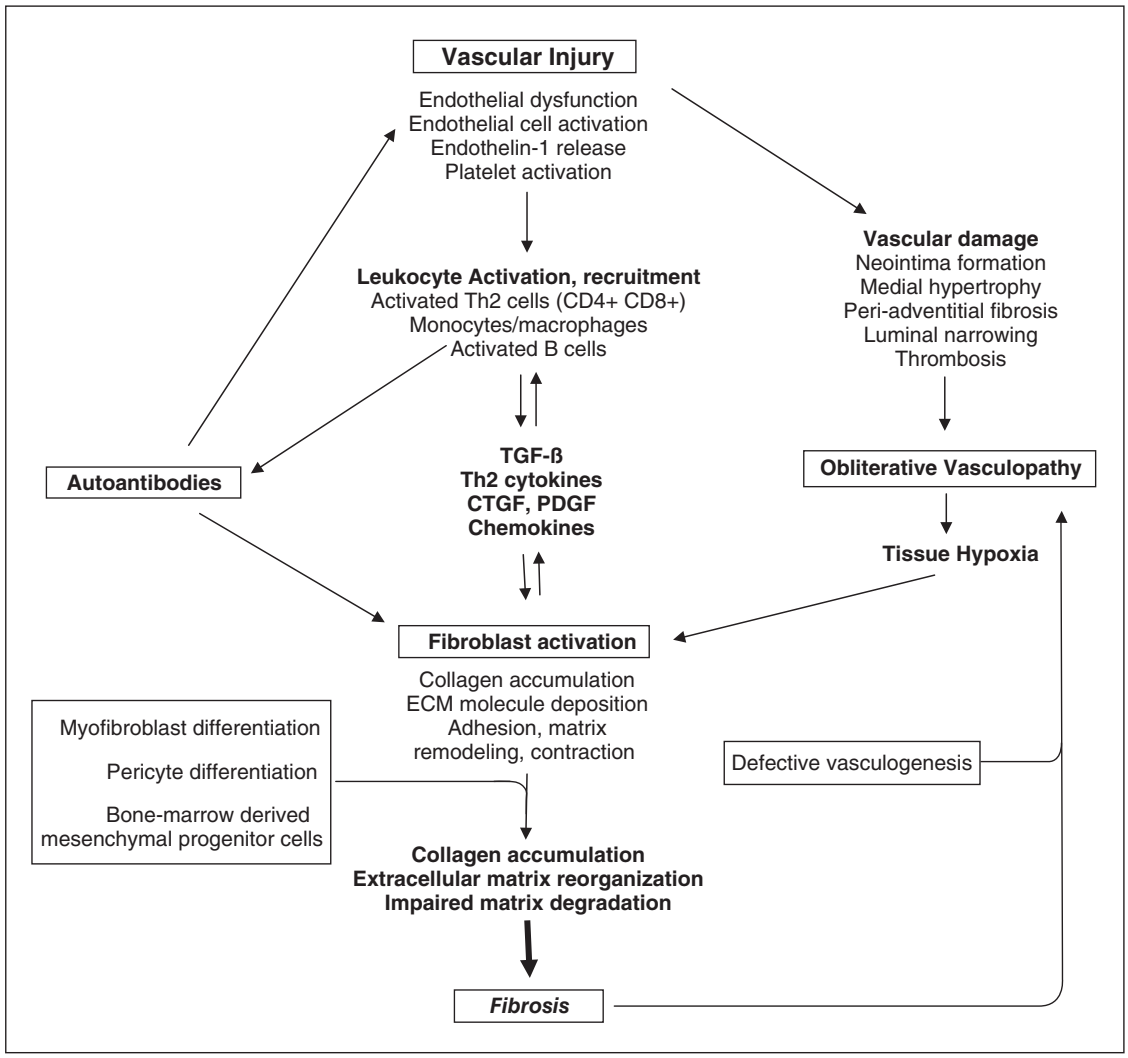


FIGURE 17B-3

Schematic representation of the complex pathogenesis of systemic sclerosis. Initial vascular injury in genetically susceptible individuals leads to functional and structural vascular alterations, inflammation, and the generation of autoimmunity. The inflammatory and immune responses then initiate and sustain fibroblast activation and differentiation, resulting in pathological fibrogenesis and irreversible tissue damage. CTGF, connective tissue growth factor; PDGF, platelet-derived growth factor; ECM, extracellular matrix.

permeability, enhanced transendothelial leukocyte diapedesis, activation of coagulation and fibrinolytic cascades, and platelet aggregation. These processes culminate in thrombosis. Endothelial cells show increased expression of intercellular adhesion molecule 1 (ICAM-1) and other surface adhesion molecules. Vasculopathy affects capillaries, arterioles, and even large vessels in many organs. Smooth muscle cell-like myointimal cells proliferate, the basement membrane is thickened and reduplicated, and adventitial fibrosis develops.

Progressive vascular luminal occlusion due to intimal and medial hypertrophy and adventitial fibrosis, combined with persistent endothelial cell damage and apoptosis, establish a vicious cycle. Angiograms of the hands and kidneys of patients with late-stage disease reveal a striking absence of blood vessels. Damaged endothelium promotes platelet aggregation and release of thromboxane, a potent vasoconstrictor, and platelet-derived growth factor (PDGF). Vascular compromise is aggravated further by defective fibrinolysis. Oxidative stress due to ischemia-reperfusion is associated with generation of free radicals that further contribute to endothelial damage through peroxidation of membrane lipids. Paradoxically, the process of revascularization that normally re-establishes blood flow to ischemic tissue appears to be defective in SSc. Failure of vasculogenesis occurs in the setting of elevated levels of angiogenic factors, such as vascular endothelial growth

factor (VEGF). In patients with SSc, the number of bone marrow–derived CD34+ CD133+ endothelial progenitor cells circulating in the system is reduced markedly; moreover, their differentiation in vitro into mature endothelial cells is impaired (8). Thus, widespread obliterative vasculopathy and failure to replace damaged vessels are hallmarks of SSc.

CELLULAR AND HUMORAL AUTOIMMUNITY

In the early stages of the disease, activated T cells and monocytes/macrophages accumulate in lesional skin, lungs, and other affected organs. Infiltrating T cells express activation markers such as CD3, CD4, CD45, and HLA-DR, and display restricted receptor signatures indicative of oligoclonal expansion in response to unknown antigens. Circulating CD4+ T cells also have elevated levels of chemokine receptors and express alpha 1 integrin (an adhesion molecule), accounting for their enhanced ability to bind to endothelium and to fibroblasts. Endothelial cells express ICAM-1 and other adhesion molecules that facilitate leukocyte diapedesis. Activated macrophages and T cells show a Th2-polarized response, and secrete interleukin 4 and interleukin 13. Both of these Th2 cytokines can induce TGF-beta, a powerful modulator of immune regulation and matrix accumulation (Table 17B-1). Because it can induce its own production, as well as that of CTGF (also termed CCN2) and other cytokines, TGF-beta establishes sustained autocrine/paracrine loops for activation of fibroblasts and other effector cells. DNA microarray studies of global gene expression in CD8+ T cells in bronchoalveolar lavage fluids from patients with SSc have demonstrated an activated Th2 pattern of gene expression, characterized by increased levels of IL-4 and IL-13, and reduced production of interferon gamma (IFN-gamma). Th2 cytokines promote collagen synthesis and other profibrotic responses. IFN-gamma inhibits collagen synthesis and blocks cytokine-mediated fibroblast activation.

TABLE 17B-1. SOLUBLE MEDIATORS OF FIBROBLAST ACTIVATION ELEVATED IN SYSTEMIC SCLEROSIS.

MOLECULE	CELLULAR SOURCE
TGF-beta	Inflammatory cells, platelets, fibroblasts
PDGF	Platelets, macrophages, fibroblasts, endothelial cells
CTGF	Fibroblasts
Insulinlike growth factor 1	Fibroblasts
IL-4, IL-13	Th2 lymphocytes, mast cells
IL-6	Macrophages, B cells, T cells, fibroblasts
Chemokines (MCP-1, MCP-3)	Neutrophils, epithelial cells, endothelial cells, fibroblasts
Fibroblast growth factor	Fibroblasts
Endothelin 1	Endothelial cells

ABBREVIATIONS: CTGF, connective tissue growth factor; IL, interleukin; PDGF, platelet-derived growth factor; TGF-beta, transforming growth factor beta. MCP, monocyte chemotactic protein.

Circulating autoantibodies are detected in virtually all patients with SSc. These mutually exclusive autoantibodies are highly specific for SSc, and show strong association with individual disease phenotypes and genetically determined HLA haplotypes. Autoantibody levels correlate with disease severity and their titers fluctuate to some degree with disease activity, albeit the precise temporal relationships between antibody titer and disease activity is imperfect. Some SSc-specific autoantibodies are antinuclear and directed against proteins involved in mitosis, such as topoisomerase I and the RNA polymerases. Others are directed against cell surface antigens or secreted proteins. The concordance rates for positive ANA in twin pairs in which one sibling has SSc are 85% (monozygotic) and 60% (dizygotic), indicating a major role for genetics in the SSc-specific immune response.

Although autoantibodies have well-established clinical utility as diagnostic and prognostic markers, their role in clinical manifestations of SSc remains uncertain. Topoisomerase I autoantibodies in SSc patients can directly bind to fibroblasts, and autoantibodies to fibroblasts, endothelial cells, fibrillin-1, and matrix metalloproteinase enzymes have all been described. Some of these autoantibodies may have direct pathogenic roles as mediators of tissue damage. Multiple potential mechanism(s) have been proposed to account for autoantibody generation in SSc. According to one theory, in SSc patients specific self-antigens undergo novel modifications, such as structural alterations due to proteolytic cleavage, increased expression level, or changes in subcellular localization, resulting in their recognition by the immune system. For example, cytotoxic T cells release the protease granzyme B, which cleaves autoantigens, generating novel fragments with potential neo-epitopes that break immune tolerance. Recent studies implicate B cells in both autoimmunity and fibrosis in SSc. In addition to their well-recognized role in antibody production, B cells can present antigen, produce cytokines, such as IL-6 and TGF-beta, and modulate T-cell and dendritic-cell function. B cells from SSc patients show intrinsic abnormalities, with elevated expression of the CD19 B-cell receptor, expansion in the naive B-cell

compartment, and reduced numbers of memory B cells and early plasma cells (9). Gene expression profiling of SSc skin biopsies has identified mRNA expression signatures characteristic of activated B cells.

FIBROSIS: CELLULAR AND MOLECULAR COMPONENTS

Fibrosis affecting multiple organs is a prominent hallmark, distinguishing SSc from other connective tissue diseases. Fibrosis is thought to be a consequence of autoimmunity and vascular damage. The process is characterized by progressive replacement of normal tissue architecture with dense acellular connective tissue, and accounts for substantial morbidity and mortality in SSc.

Fibroblasts and related mesenchymal cells are normally responsible for the functional and structural integrity of connective tissue in parenchymal organs. When activated by TGF-beta and related cytokines (Table 17B-2), fibroblasts proliferate, migrate, elaborate collagen and other matrix macromolecules, secrete growth factors and cytokines and express surface receptors for them, and differentiate into myofibroblasts. Together, these fibroblast responses facilitate effective repair of tissue injury. Under physiologic conditions, the fibroblast repair program is self-limited, terminating upon completion of healing. In pathological fibrotic responses however, fibroblast activation is sustained and amplified, resulting in exaggerated matrix remodeling and scar formation. Dysregulated fibroblast activation and matrix accumulation are the fundamental pathogenetic alterations underlying tissue fibrosis in SSc.

TABLE 17B-2. PROFIBROGENIC ACTIVITIES OF TRANSFORMING GROWTH FACTOR BETA POTENTIALLY IMPORTANT IN SYSTEMIC SCLEROSIS.

Recruits monocytes
Stimulates fibroblast synthesis of collagens, extracellular matrix, inhibitors of proteolytic enzymes; suppresses matrix metalloproteinase enzymes
Stimulates fibroblast proliferation, chemotaxis
Induces fibrogenic cytokine production: CTGF; autoinduction; blocks synthesis and activity of interferon gamma
Induces fibroblast mitogenic responses to PDGF
Promotes fibroblast–myofibroblast differentiation
Promotes monocyte–fibrocyte differentiation
Promotes epithelial–mesenchymal transition
Inhibits fibroblast apoptosis

ABBREVIATIONS: CTGF, connective tissue growth factor; PDGF, platelet-derived growth factor.

In addition to locally derived connective tissue fibroblasts, circulating mesenchymal progenitor cells of bone marrow origin also participate in fibrogenesis. Peripheral blood mononuclear cells expressing CD14 and CD34 have been shown to differentiate into collagen-producing alpha-smooth muscle actin-positive fibrocytes in vitro. This process is enhanced by TGF-beta (10). The factors that regulate the production of mesenchymal progenitor cells in the bone marrow and their trafficking from the circulation into lesional tissue, and promote their differentiation in situ into matrix-producing adhesive and contractile fibrocytes, remain unknown. Epithelial to mesenchymal cell transition (EMT), a process implicated in the development of fibrosis following injury in the lungs and kidney, may also be involved in organ fibrosis in SSc. Fibroblasts can differentiate into smooth muscle–like myofibroblasts. Both EMT and myofibroblast differentiation are mediated by TGF-beta. Although myofibroblasts can be transiently detected during normal wound healing, their persistence in tissue, possibly due to apoptosis resistance, indicates dysregulated repair during pathological fibrogenesis. Myofibroblasts contribute to scar formation via their ability to produce collagen and TGF-beta, and to generate contractile forces on the surrounding matrix, converting it into dense scar.

Fibroblasts explanted from lesional SSc tissues display an abnormal phenotype indicative of autonomous activation. Compared to normal fibroblasts, SSc fibroblasts in culture are characterized by variably increased rates of type I collagen gene transcription. Furthermore, they have smooth muscle actin stress fibers, enhanced synthesis of various extracellular matrix molecules, expression of chemokine receptors and cell surface adhesion molecules, secretion of PDGF, Akt-mediated resistance to apoptosis, and autocrine TGF-beta signaling. This abnormal scleroderma phenotype persists during serial passage in vitro. The mechanisms underlying the acquisition of the autonomously activated phenotype are unknown; persistent fibroblast activation via autocrine stimulatory loops involving TGF-beta, selection of activated fibroblast subpopulations driven by hypoxia or immune factors, intrinsic abnormalities in SSc fibroblasts, and altered cell–matrix interaction are some of the mechanisms under investigation. Recent reports indicate that intracellular blockade of TGF-beta signaling can abrogate the activated phenotype in SSc lesional fibroblasts, resulting in their partial normalization. Autocrine TGF-beta signaling, therefore, contributes to the persistence of the fibrogenic phenotype of SSc fibroblasts. Results from global transcriptome analyses of SSc fibroblasts show

differential expression of many ECM genes, including collagens, fibronectin, and fibrillins (11). A majority of the abnormally expressed genes could be mechanistically linked to TGF-beta responses, but other fibrogenic signaling pathways also operate in SSc.

Autocrine/paracrine TGF-beta and its intracellular signaling pathways play pivotal roles in the initiation and propagation of the fibrotic response in SSc. Intracellular TGF-beta signaling is a complex and cell type–specific process involving multiple primary and accessory receptors, stimulatory and inhibitory members of the Smad family of signal transducer proteins and other transcriptional factors, coactivators and repressors. Lesional fibroblasts secrete TGF-beta and exhibit TGF-beta hyper-responsiveness due to elevated expression of TGF-beta receptors and activation of latent TGF-beta. Inappropriate activation of the intracellular TGF-beta signal transduction pathways due to constitutive Smad3 phosphorylation and defective Smad-7–dependent negative feedback loops have been described in SSc. The nuclear coactivator protein p300 facilitates Smad-mediated collagen transcription and is an important locus of integration for multiple extracellular signals modulating fibroblast function. The cellular abundance of p300 appears to control the magnitude of its response to TGF-beta (12). Abnormalities in the expression, function, and interactions of Smads, p300, and other cellular proteins account for the persistence and progression of the scleroderma fibrogenic process by modulating target gene transcription.

REFERENCES

1. Maricq HR, Weinrich MC, Keil JE, et al. Prevalence of scleroderma spectrum disorders in the general population of South Carolina. Arthritis Rheum 1989;32:998–1006.
2. Mayes MD, Lacey JV Jr, Beebe-Dimmer J, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. Arthritis Rheum 2003;48:2246–2255.
3. Kuwana M, Kaburaki J, Arnett FC, Howard RF, Medsger TA Jr, Wright TM. Influence of ethnic background on clinical and serologic features in patients with systemic sclerosis and anti-DNA topoisomerase I antibody. Arthritis Rheum 1999;42:465–474.
4. Feghali-Bostwick C, Medsger TA Jr, Wright TM. Analysis of systemic sclerosis in twins reveals low concordance for disease and high concordance for the presence of antinuclear antibodies. Arthritis Rheum 2003;48:1956–1963.
5. Janowsky EC, Kupper LL, Hulka BS. Meta-analyses of the relation between silicone breast implants and the risk of connective-tissue diseases. N Engl J Med 2000;342:781–790.
6. Prescott RJ, Freemont AJ, Jones CJ, Hoyland J, Fielding P. Sequential dermal microvascular and perivascular changes in the development of scleroderma. J Pathol 1992;166:255–263.
7. Abraham DJ, Varga J. Scleroderma: from cell and molecular mechanisms to disease models. Trends Immunol 2005;26:587–595.
8. Kuwana M, Okazaki Y, Yasuoka H, Kawakami Y, Ikeda Y. Defective vasculogenesis in systemic sclerosis. Lancet 2004;364:603–610.
9. Sato S, Fujimoto M, Hasegawa M, Takehara K. Altered blood B lymphocyte homeostasis in systemic sclerosis: expanded naive B cells and diminished but activated memory B cells. Arthritis Rheum 2004;50:1918–1927.
10. Abe R, Donnelly SC, Peng T, Bucala R, Metz CN. Peripheral blood fibrocytes: differentiation pathway and migration to wound sites. J Immunol 2001;166:7556–7562.
11. Whitfield ML, Finlay DR, Murray JI, et al. Systemic and cell type-specific gene expression patterns in SSc skin. Proc Natl Acad Sci U S A. 2003;100:12319–12324.
12. Bhattacharyya S, Ghosh AK, Pannu J, et al. Fibroblast expression of the coactivator p300 governs the intensity of profibrotic response to transforming growth factor beta. Arthritis Rheum 2005;52:1248–1258.

CHAPTER 17

Systemic Sclerosis
C. Treatment and Assessment

MAYA H. BUCH, MBCHB, MRCP
JAMES R. SEIBOLD, MD

- Systemic sclerosis (SSc; scleroderma) targets several aspects of disease pathophysiology: vascular features that are currently highly treatable; inflammatory features that are currently partly amenable to therapy; fibrotic features for which therapies of modest efficacy (at best) exist; and atrophic, end organ damage for which only supportive therapy is available.
- The extent of skin involvement is neither a robust primary outcome measure for clinical trials nor a reliable guide to the therapy of individual patients.
- Regular pulmonary function testing is a cornerstone of assessment.
- Continuous intravenous epoprostenol, subcutaneous or intravenous treprostinil, and bosentan all have important roles in selected patients with pulmonary arterial hypertension.
- Early recognition of scleroderma renal crisis (SRC) and prompt treatment with angiotensin-converting enzyme (ACE) inhibitors has improved outcomes in SRC dramatically.
- Cyclophosphamide is a cornerstone of interstitial lung disease treatment in SSc, but the therapeutic gains from this agent are relatively small.
- Long-term proton-pump inhibition is highly effective in treating the gastroesophageal reflux. High doses, sometimes two to three times the normal therapeutic dose, are required to alleviate symptoms.

Systemic sclerosis (SSc, scleroderma) has one of the highest mortality rates among all connective tissue disorders. To date, no effective therapy that addresses the underlying disease process exists. Significant strides have been made in improving survival, however, largely through therapies directed at the treatment of specific organ complications. State-of-the-art management entails organ-based therapy with particular attention to lung and renal involvement, the major causes of morbidity and mortality. This strategy emphasizes the role of early detection of internal organ involvement, and the timely implementation of treatment. In simple terms, SSc includes vascular features that are eminently treatable; inflammatory features that are at least partly amenable to therapy, as well; fibrotic features for which therapies of modest efficacy (at best) exist; and atrophic, end organ damage for which only supportive therapy is available.

ASSESSMENT OF DISEASE

The extent of skin involvement is the basis for SSc subset classification and a major indicator of risk for certain internal organ complications. Unfortunately, skin involvement is neither a robust primary outcome measure for clinical trials nor a reliable guide to the therapy of individual patients. Monitoring for lung involvement with regular pulmonary function testing is a cornerstone of assessment, particularly in patients with early diffuse scleroderma. Reduction in forced vital capacity suggests the presence of interstitial lung disease, which is usually confirmed then by the demonstration of reticular or alveolar parenchymal disease on high resolution computed tomography (CT) of the chest.

Isolated or disproportionate reduction in diffusing capacity suggests pulmonary vascular pathology; namely, pulmonary arterial hypertension (PAH).

Doppler echocardiography can provide estimates of pulmonary artery pressures and is useful in serial follow-up, but right heart catheterization remains the gold standard for confirmation of that diagnosis (1).

Measures of renal function and blood pressure serve as prime indicators of scleroderma renal crisis in early diffuse disease. Creatinine phosphokinase and aldolase levels are sensitive indicators of myositis/myopathy. Specific serologies, including antitopoisomerase and anti-U1RNP antibodies, predict diffuse disease. In contrast, anticentromere antibodies predict limited SSc. Not all patients with scleroderma are positive for one of these autoantibodies (see Chapter 17A).

TREATMENT

When treating individual complications, a core set of principles applies, regardless of patients' subset and stage. Certain targeted treatment approaches may also address individual organ system components of disease. Disease subset and stage, however, are key in guiding initial treatment. Progression of skin changes in early, diffuse SSc signals the need for aggressive management to limit internal organ damage. The precise choice of therapy depends upon the specific organ system manifestations.

The natural tendency for skin involvement to improve by the second to third year complicates the assessment of treatment efficacies. Therapeutic strategies have evolved rapidly in recent years, but still permit relatively few evidence-based approaches (see Figure 17C-1). The next sections focus in turn on treatments of the vascular, inflammatory, and fibrotic components of scleroderma.

Vascular Therapy

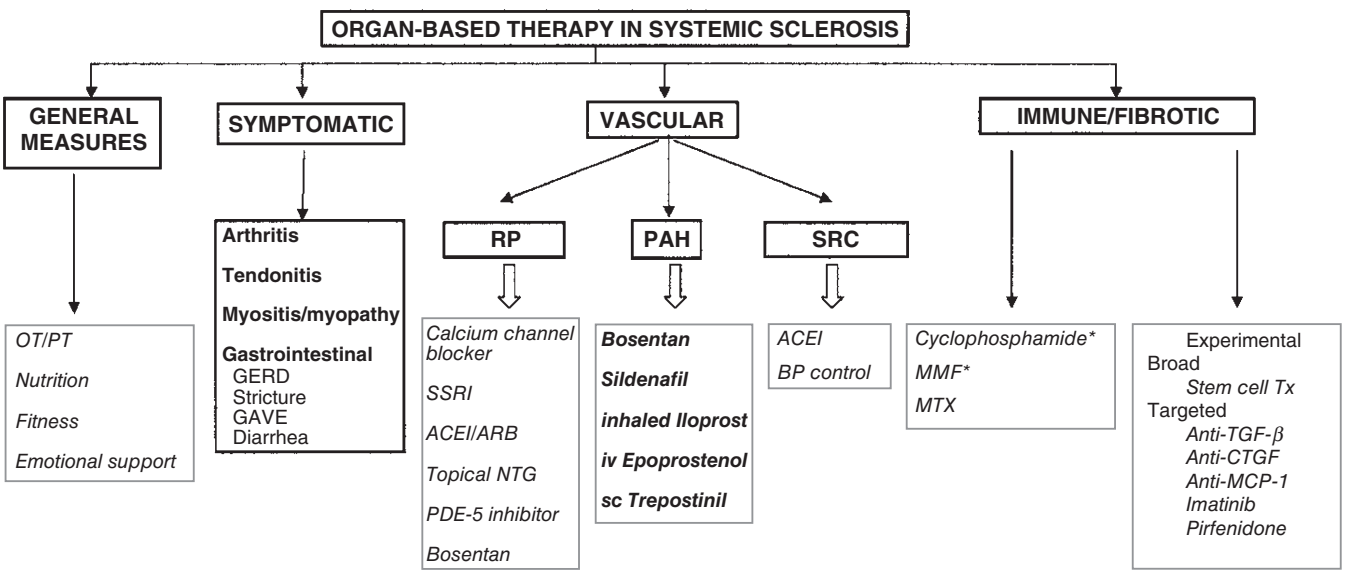
Complications of scleroderma that result clearly from vascular dysfunction include PAH, scleroderma renal crisis (SRC), and Raynaud's phenomenon (RP). Treatment approaches to these disease manifestations are evolving rapidly (2).

Pulmonary Arterial Hypertension

The endothelial dysfunction of PAH leads to increased endothelin and reduced nitric oxide and prostacyclin. Continuous intravenous epoprostenol (Flolan) and subcutaneous or intravenous treprostinil (Remodulin), both US Food and Drug Administration (FDA)–approved therapies, are consensus first-line treatments for PAH patients with World Health Organization (WHO) class IV disease. The delivery systems (indwelling catheters), associated risks (line infection), and

FIGURE 17C-1

A summary of organ-directed treatment in limited and diffuse scleroderma. Treatments in bold: FDA-approved. Cyclophosphamide*: Confirmed efficacy over placebo in a randomized, double-blind study in patients with interstitial lung disease. MMF×: No controlled studies. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CTGF, connective tissue growth factor; GAVE, gastric antral venous ectasia; GERD, gastroesophageal reflux disease; MCP-1, macrophage chemoattractant protein 1; MMF, mycophenylate mofetil; MTX, methotrexate; NTG, nitroglycerin; OT/PT, occupational therapy/physical therapy; PAH, pulmonary arterial hypertension; PDE-5, type 5 phosphodiesterase; RP, Raynaud's phenomenon; SRC, scleroderma renal crisis; SSRI, specific serotonin receptor uptake inhibitor; Stem cell Tx, stem cell transplantation; TGF-β, transforming growth factor beta.



other side effects (infusion site pain) have forced a search for alternative therapies.

The selectivity of prostacyclin's effects on pulmonary vasculature provided the rationale behind the development of inhaled therapy for PAH, which have the added potential advantage of avoiding some systemic side effects. Repeated inhalation of iloprost (Ventavis) has been shown to improve function and hemodynamics, and to slow the rate of clinical decline. The role of endothelin 1 in idiopathic PAH and SSc-PAH pathophysiology has led to the development of endothelin receptor antagonists (ERA). Bosentan (Tracleer), an oral, nonselective ERA, is considered a first-line therapy in WHO class III patients. Regular monitoring is required for possible abnormal liver function.

Other ERA therapies are under investigation. Type V phosphodiesterase (PDE-5) metabolizes cyclic guanine monophosphate (cGMP). Inhibition of cGMP metabolism with the PDE-5 inhibitor sildenafil (Viagra) enhances pulmonary vasodilation. Side effects include axial muscle cramps. To date, long-term studies examining mortality as the primary outcome are not available for any agent. Combination therapies using agents from each of the different classes are under active investigation.

Scleroderma Renal Crisis

Development of accelerated to malignant hypertension with microangiopathic hemolytic anemia is the definition of SRC. Until the availability of angiotensin-converting enzyme (ACE) inhibitors, the treatment of SRC was extraordinarily difficult despite the use of other antihypertensive approaches, and the onset of SRC nearly always signaled a terminal phase of the illness.

Early recognition of SRC and the prompt institution of ACE inhibition (at the maximum tolerable dose) has improved outcomes in SRC dramatically. Deaths from SRC are now decidedly rare, and fewer than 50% of patients in SRC progress to end-stage renal disease (ESRD) (3). If patients do progress to ESRD, ACE inhibition should be continued into the phase of dialysis; some patients demonstrate renal recovery even after several months of dialysis.

For patients with diffuse scleroderma—the subset at highest risk for SRC—prophylactic treatment with an ACE inhibitor is advisable. Although not yet tested in a rigorous fashion, angiotensin receptor blockade (ARB) therapies are also probably efficacious in SRC.

Raynaud's Phenomenon

A growing number of treatments are now available for RP. A cornerstone of the therapy of this complication, however, is the maintenance of a warm core body temperature. In addition to gloves, handwarmers, and other approaches to warming the extremities, patients are strongly advised to several layers of clothing over their entire bodies, particularly during cold months.

Calcium-channel blockers, such as amlodipine, nifedipine, or felodipine, are the initial medical treatment for RP. Low dose selective serotonin reuptake inhibitors (SSRIs) are also used because of their allegedly salubrious effects on platelet aggregation and activation. Among the SSRIs, fluoxetine (Prozac; Symbyax; Sarafem) is the best studied. Despite their striking effectiveness in SRC, ACE inhibitors and ARBs are not particularly effective for RP.

Digital ischemia and ulceration are often managed with intermittent intravenous iloprost, particularly during the winter months. In addition, therapies introduced originally for the management of PAH now are being applied to the treatment of recalcitrant RP. Two large, multicenter, controlled trials of bosentan confirmed a reduction in the development of new digital ulcers compared to placebo (4). Case series and reports have suggested improved RP control with the use of sildenafil. Despite the improved options for the treatment of RP now, therapy is expensive, access often limited, and the responses (albeit dramatic in some patients) frequently inconsistent.

Anti-Inflammatory Treatments

In addition to the vascular nature of some scleroderma-related problems, other manifestations of this disease, for example, interstitial lung disease and myositis, have clear inflammatory components. At the present time, anti-inflammatory therapies for scleroderma are less targeted than are those for vascular problems. An approach involving the use of nonspecific, broadly immunosuppressive agents assumes that immunological activation influences both the fibrotic and vascular components.

Cyclophosphamide

Cyclophosphamide (CYC) has been used as the primary therapeutic agent for interstitial lung disease in scleroderma. In a recent controlled trial (5), cyclophosphamide improved forced vital capacity (FVC) by only 2.9% compared to placebo. Although the demonstration of a modest benefit of CYC supports its continued use, the small effect suggests the need for a more targeted approach.

Autologous Stem Cell Transplantation

Immunoablation with immune reconstitution using autologous peripheral stem cells has been considered for severe diffuse scleroderma. Pilot studies have suggested robust effects on skin and patient function and neutral effects on internal involvement (6). Ongoing studies comparing stem cell transplantation with CYC treatments will determine the appropriateness of this strategy.

Methotrexate

A randomized, controlled trial evaluating efficacy of methotrexate in early diffuse scleroderma suggested greater disease stability compared with placebo (7). The precise advantages conferred in clinical practice remain uncertain. Methotrexate use is reserved generally for early diffuse cases with features limited to skin and musculoskeletal systems, including myositis.

Mycophenolate Mofetil

Mycophenolate mofetil has not been studied in any controlled trials. Current anecdotal evidence suggests it may be effective in early diffuse disease, including cases complicated by interstitial lung disease (8).

Antifibrotic Therapy

Despite the fact that fibrosis is a central component to the pathophysiology of scleroderma, no agent designed to prevent fibrosis has been proven effective to date. Nonspecific agents, including D-penicillamine (9) and recombinant human relaxin, have failed in clinical trials. The importance of transforming growth factor beta (TGF-beta) expression in the pathogenesis of scleroderma has prompted the evaluation of agents that either trap or block TGF-beta. Although the use of an anti–TGF-beta antibody has been suggested in early studies to be safe, clinical benefit remains to be observed. Other anticytokine therapies, all of which remain unvalidated in scleroderma, are included in Figure 17C-1.

Other Organ-Specific Therapies

Aside from therapies directed against disorders of the lung, kidneys, and peripheral vasculature in scleroderma, the gastrointestinal tract is a common focus for organ-specific therapy. Long-term proton-pump inhibition is highly effective in treating gastroesophageal reflux, often a chronic problem leading to significant complications in scleroderma. High doses, sometimes two to three times the normal therapeutic dose, are required to alleviate symptoms. Dilatation of esophageal strictures is undertaken where indicated. Watermelon stomach, also known as gastric antral venous ectasia (GAVE), is now considered the most common cause of gastrointestinal bleeding in scleroderma. GAVE is diagnosed and treated with endoscopy and laser photocoagulation.

With regard to gut function, smooth muscle atrophy results in gastroparesis and small bowel hypomotility. Prokinetic agents, including metoclopramide and domperidone (the latter not available in the United States), are used with variable effects. Intestinal pseudo-obstruction may be managed cautiously with subcutaneous octreotide, a somastatin analogue. Abdominal bloating and/or diarrhea suggest small bowel bacterial overgrowth. This is treated with antibiotics, often rotating courses, to circumvent antibiotic resistance. One- to two-week courses of metronidazole (250 mg t.i.d.) or ciprofloxacin (500 mg q.d.) are usually prescribed. Advanced scleroderma involvement of the gastrointestinal tract may be dominated by fecal incontinence and constipation. Antidiarrheal agents and behavioral therapy in the form of biofeedback is undertaken to manage incontinence. Stool bulking and softening agents are the mainstay of treatment in addressing constipation.

CONCLUSION

Modern management of scleroderma is characterized most appropriately as organ-based therapy. Specific gains in the treatment of scleroderma renal crisis and pulmonary hypertension have unequivocally improved overall outcome and survival. Continued progress in our understanding of the disease will lead to more targeted, effective treatments.

REFERENCES

1. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004;126:11S–34S.
2. Farber HW, Loscalzo J. Pulmonary arterial hypertension. N Engl J Med 2004;351:1655–1665.
3. DeMarco PJ, Weisman M, Seibold JR, et al. Predictors and outcome of scleroderma renal crisis. The high-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis trial. Arthritis Rheum 2002;46:2983–2989.
4. Korn JH, Mayes M, Matucci-Cerinic M, et al. Digital ulcers in systemic sclerosis—prevention by treatment with bosentan, an oral endothelin receptor antagonist. Arthritis Rheum 2004;50:3985–3993.
5. Tashkin DP, Elashoff R, Clements PJ, et al. The Scleroderma Lung Study: oral cyclophosphamide versus placebo for the treatment of scleroderma-related interstitial lung disease. N Engl J Med 2006;354:2655–2666.
6. McSweeney PA, Nash RA, Sullivan KM, et al. High-dose immunosuppressive therapy for severe systemic sclerosis: initial outcomes. Blood 2002;100:1602–1610.
7. Pope JE, Bellamy N, Seibold JR, et al. A randomized controlled trial of methotrexate versus placebo in early diffuse scleroderma. Arthritis Rheum 2001;44:1351–1358.
8. Stratton RJ, Wilson H, Black CM. Pilot study of anti-thymocyte globulin plus mycophenolate mofetil in recent-onset diffuse scleroderma. Rheumatology (Oxford) 2001;40:84–88.
9. Clements PJ, Furst DE, Wong W-K, et al. High-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis. Arthritis Rheum 1999;42:1194–1203.