

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/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.

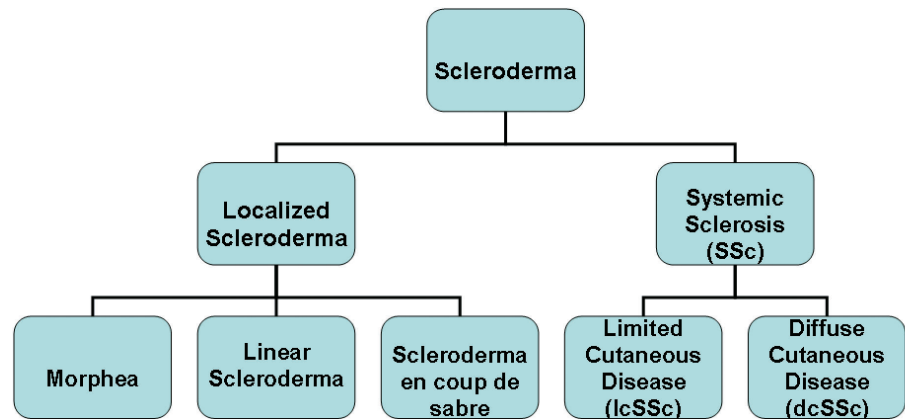
For rheumatologists, scleroderma is synonymous with systemic disease. Only SSc will be considered in the remainder of this chapter. In broad terms, the clinical manifestations of SSc may be considered the result of three pathological processes: (1) a small vessel non-inflammatory obliterative vasculopathy; (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 fibrosing

FIGURE 17A-1

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



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 associated with a connective tissue disease. Primary Raynaud’s disease does not result in tissue damage. Thus, in the absence of SSc, systemic lupus

erythematosus (SLE), or some other underlying connective tissue disease, 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 or in areas of repeated minor trauma (Figure 17A-3).

Raynaud’s phenomenon, usually the first manifestation of SSc, may precede the development of other

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.

features by months to years. In some cases, the delay 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 (lcSSc) 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/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, diffuse cutaneous disease (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 the first 2 years of disease. Skin involvement usually progresses over the first 1 to 5 years, then stabilizes, and then 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 renal crisis.

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 for scleroderma renal crisis.

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

Diffuse cutaneous systemic sclerosis (dcSSc)
<ul style="list-style-type: none">• 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 or even preceding 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)
<ul style="list-style-type: none">• 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
<ul style="list-style-type: none">• 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-U₁ 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, digital tip pitting scars, dermal ulcers, 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 vermillion 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 removal,



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.

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, 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 postulated to be 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 pneumatosis 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. Those 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 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 testing that shows a restrictive pattern is the most reliable 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 quite 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 antientomere 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 (<4 years from onset) diffuse disease. 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 normalization. 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 ACR 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 pressure elevation and without a microangiopathic picture, has also been described in SSc. Other causes for renal failure must be investigated thoroughly, and ACE inhibitors should be 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 degree 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 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 mild, relatively nonprogressive course; minor 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 is seen in 40% to 80% of patients, and 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 scleroderma 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 scleroderma-like disorders have been described (27). The most clinically relevant today include nephrogenic systemic fibrosis (NSF, previously called nephrogenic fibrosing dermopathy), eosinophilic fasciitis, sclerodema, and scleromyxedema.

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 transplant 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 eosinophilia, 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 neck, shoulder girdle, proximal upper extremities, and back. The distribution is quite different from 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. The distribution and histology are the same as that noted above. 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, hide-bound character of SSc skin.

REFERENCES

- Piette WW. Morphea or localized scleroderma. In: Clements PJ, Furst DE, eds. *Systemic sclerosis*. Philadelphia: Lippincott Williams & Wilkins; 2004:29–37.
- Medsger TA Jr. Classification, prognosis. In: Clements PJ, Furst DE, eds. *Systemic sclerosis*. Philadelphia: Lippincott Williams & Wilkins; 2004:17–28.
- Korn JH. Pathogenesis of systemic sclerosis. In: Koopman WJ, Moreland LW, eds. *Arthritis and allied conditions*. Philadelphia: Lippincott Williams & Wilkins; 2005:1621–1632.
- Boin F, Wigley FM. Understanding, assessing and treating Raynaud's phenomenon. *Curr Opin Rheumatol* 2005;17:752–760.
- 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.
- 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.
- 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.
- LeRoy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets, and pathogenesis. *J Rheumatol* 1988;15:202–205.
- Steen VD, Medsger TA Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. *Arthritis Rheum* 2000;43:2437–2444.
- Bryan C, Knight C, Black CM, Silman AJ. Prediction of five-year survival following presentation with scleroderma: development of a simplot model using three disease factors at first visit. *Arthritis Rheum* 1999;42:2660–2665.
- Cepeda EJ, Reveille JD. Autoantibodies in systemic sclerosis and fibrosing syndromes: clinical indications and relevance ••.
- 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.
- 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.
- 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.
- Goldblatt F, Gordon TP, Waterman SA. Antibody-mediated gastrointestinal dysmotility in scleroderma. *Gastroenterology* 2002;123:1144–1150.
- Mackey RI. Autoimmunity and primary biliary cirrhosis. *Baillieres Best Pract Res Clin Gastroenterol* 2000;14:519–533.
- Chang B, Wigley FM, White B, Wise RA. Scleroderma patients with combined pulmonary hypertension and interstitial lung disease. *J Rheumatol* 2003;30:2398–2405.
- Hachulla E, Gressin V, Guillemin L, et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. *Arthritis Rheum* 2005;52:3792–3800.
- 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.
- Wigley FM, Lima JAC, Mayes M, McLain D, Chapin JL, Ward-Able C. The UNCOVER study: prevalence of undiagnosed PAH in subjects with CTD at the secondary healthcare level of community-based rheumatologists. *Arthritis Rheum* 2005;52:2125–2132.
- Chang B, Wigley FM, White B, Wise RA. Scleroderma patients with combined pulmonary hypertension and interstitial lung disease. *J Rheumatol* 2006;33:269–274.
- Follansbee WP, Marroquin OC. Cardiac involvement in systemic sclerosis. In: Clements PJ, Furst DE, eds. *Systemic sclerosis*. Philadelphia: Lippincott Williams & Wilkins; 2004:195–220.
- 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.
- Steen VD. Renal involvement in systemic sclerosis. In: Clements PJ, Furst DE, eds. *Systemic sclerosis*. Philadelphia: Lippincott Williams & Wilkins; 2004:279–292.
- Pope JE. Musculoskeletal involvement in scleroderma. *Rheum Dis Clin North Am* 2003;52:391–405.
- Clements PJ, Furst DE, Campion DS, et al. Muscle disease in progressive systemic sclerosis: diagnostic and therapeutic consideration. *Arthritis Rheum* 1978;21:62–71.
- Mori Y, Kahari VM, Varga J. Scleroderma-like cutaneous syndromes. *Curr Rheumatol Rep* 2002;4:113–122.
- Cowper SE, Boyer PJ. Nephrogenic systemic fibrosis: an update. *Curr Rheumatol Rep* 2006;8:151–157.

1

Primer on the Rheumatic Diseases

Klippel, J.H.; Stone, J.H.; Crofford, L.e.J.; White, P.H.
(Eds.)

2008, XIX, 721 p., Softcover

ISBN: 978-0-387-35664-8