

## Clinical Features of Systemic Sclerosis

Michelle E. Eisenberg, DO

Binh Y. Nguyen, MD

Bernard M. Karnath, MD

**S**ystemic sclerosis, or scleroderma, is a rare connective tissue disease of unknown etiology. The word *scleroderma*, derived from the Greek words *scleros* for hard and *derma* for skin, refers to the hallmark finding of chronic hardening and thickening of the skin that occurs in this disease. The clinical manifestations of systemic sclerosis range from localized skin lesions affecting small areas (localized scleroderma) to systemic involvement in which multiple organ systems are affected. Systemic sclerosis is characterized by inflammation and fibrosis leading to changes in the blood vessels, skin, synovium, skeletal muscle, and internal organs. Morbidity and mortality in systemic sclerosis depend on the organ or system involved. Early recognition and diagnosis are important because effective therapies for many of the systemic manifestations are available, but timely treatment is required. This article reviews the clinical features of systemic sclerosis and provides a limited discussion on therapeutic options.

### BACKGROUND AND PATHOGENESIS

The prevalence of scleroderma is estimated to be between 4 and 253 cases per million persons.<sup>1</sup> Factors such as age, sex, genetic background, and environmental exposure may influence susceptibility. Women are affected 3 times as often as men, and the typical age of onset is in the 40s and 50s.<sup>1</sup> Family members of patients with systemic sclerosis are often affected by other connective tissue diseases, suggesting that a genetic factor may be significant in the expression of the disease. Although there is no direct evidence of an infectious etiology, viruses such as human parvovirus B19, cytomegalovirus, Epstein-Barr virus, and herpes simplex virus type 1 have been implicated in the development of systemic sclerosis.<sup>2</sup> Cases of systemic sclerosis also have been reported in individuals exposed to silica, organic solvents, vinyl chloride, bleomycin, L-tryptophan, and contaminated rapeseed oil.<sup>3</sup>

The structural damage that occurs in systemic sclerosis starts with small vessel endothelial activation and

### SYSTEMIC SCLEROSIS

- Systemic sclerosis is classified as limited or diffuse depending on the extent of skin involvement.
- Some patients with limited systemic sclerosis have the CREST syndrome (calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia).
- Raynaud's phenomenon occurs almost universally in systemic sclerosis and manifests as episodic pallor followed by cyanosis and then rubor.
- Pulmonary manifestations of systemic sclerosis include interstitial lung disease, pulmonary hypertension, pleuritis, pleural effusion, and aspiration pneumonia.
- Scleroderma renal crisis is characterized by an abrupt rise in blood pressure and rapid progressive renal failure.
- Anti-centromere antibodies are more likely associated with limited systemic sclerosis, whereas antibodies to topoisomerase-I (antiScl-70) are more likely to be associated with diffuse disease.

subsequent platelet activation, which lead to the release of the vasoconstrictors platelet-derived growth factor and thromboxane A<sub>2</sub>.<sup>2</sup> At the same time that vasoconstriction is occurring, other immune cells such as lymphocytes and monocytes migrate to injured tissue and blood vessels, producing cytokines and growth factors. In the blood vessel, intimal hyperplasia occurs, leading to vasculopathy and tissue ischemia. In addition, local

*Dr. Eisenberg is a rheumatology fellow, Dr. Nguyen is an internal medicine resident, and Dr. Karnath is an associate professor of medicine; all are in the Department of Internal Medicine, University of Texas Medical Branch at Galveston, Galveston, TX.*



**Figure 1.** The affected skin in scleroderma appears shiny, taut, and thickened, tightly adhering to the underlying cutis. This is most notable in the hands.



**Figure 2.** Telangiectasias scattered on the face.

fibroblasts increase synthesis of collagen and extracellular matrix components, producing the thickened skin and organ fibrosis that characterize systemic sclerosis.

### CLASSIFICATION OF SYSTEMIC SCLEROSIS

Systemic sclerosis is classified into subsets depending upon the extent of skin involvement. Limited systemic sclerosis is characterized by cutaneous thickening of the distal extremities (distal to the elbows and knees) and may involve the face and neck without truncal involvement. Limited systemic sclerosis is less likely to be associated with internal organ damage and has a better prognosis than the diffuse subtype. A subset of patients with limited systemic sclerosis have the CREST syndrome (calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia). Diffuse systemic sclerosis denotes more widespread skin involvement proximal to the elbows and knees and/or the trunk. Edematous skin, carpal tunnel syndrome, Raynaud's phenomenon, and painful joints may be the earliest manifestations. In the first few months, the skin may thicken rapidly, and



**Figure 3.** Palpable subcutaneous calcifications (arrow).

skin thickening continues for several years. After approximately 5 years, the skin typically softens. However, significant disability can result from severe fibrosis of the hands. Diffuse systemic sclerosis is more likely to involve the viscera, heart, lung, and kidney.

Other subtypes of systemic sclerosis include overlap systemic sclerosis, which is characterized by features of scleroderma and another connective tissue disease (eg, dermatomyositis or systemic lupus erythematosus), and systemic sclerosis sine scleroderma, which has the vascular features and visceral fibrosis of systemic disease without skin involvement.

### CLINICAL MANIFESTATIONS

#### Skin

The skin is almost always involved in systemic sclerosis. The earliest findings may be puffiness, swelling, and decreased flexibility of the joints and tendons. Subsequently, the affected skin appears shiny, taut, and thickened, tightly adhering to the underlying cutis (**Figure 1**). Skin thickening is frequently accompanied by hyperpigmentation, giving a salt-and-pepper appearance. As systemic sclerosis advances to the fibrotic stage, the skin becomes more thickened until atrophy occurs, especially over the bony prominences and extensor surfaces of the proximal interphalangeal joints. During the atrophic stage, the dermis may soften and revert to normal or below average thickness.

Other skin findings include nail-fold capillary alterations (dilated loops at the nail bed and distended venules), telangiectasias (**Figure 2**), painful ulcerations from ischemia (with or without necrosis), subcutaneous calcinosis, and Raynaud's phenomenon. When ulceration occurs, healing is slow with frequent secondary infection. Subcutaneous calcifications (**Figure 3**) composed of amorphous calcium hydroxyapatite occur mainly in periarticular tissues. Although radiographs are not necessary for a diagnosis of subcutaneous calcifications, they can show the radiopaque deposits (**Figure 4**).

### Raynaud's Phenomenon

Raynaud's phenomenon occurs almost universally in systemic sclerosis and is manifested by episodic pallor followed by cyanosis and/or rubor of the distal portions of the digits after exposure to cold. Raynaud's phenomenon often predates other manifestations in the limited subtype and is often found concurrently in diffuse systemic sclerosis.<sup>4</sup> Capillary nail-fold microscopic abnormalities seen in association with Raynaud's phenomenon predict later development of rheumatic disease. Although Raynaud's phenomenon occurs in approximately 4% to 15% of the general population, capillary nail-fold microscopy should reveal normal vasculature in these otherwise healthy persons.<sup>5</sup> Vascular occlusion can occur and has been associated with the anticardiolipin antibody, but this is very rare in systemic sclerosis.<sup>6</sup> Arterial occlusive disease can occur in extremities and may require amputation.

### Pulmonary

Pulmonary manifestations of systemic sclerosis include interstitial lung disease, pulmonary hypertension, pleuritis and pleural effusion, and aspiration pneumonia.<sup>7</sup> Dyspnea and nonproductive cough in a patient with systemic sclerosis should raise the possibility of lung disease, and a work-up for interstitial lung disease should be performed. However, chronic cough may be the only sign of pulmonary disease in systemic sclerosis.

Interstitial fibrosis is more likely to occur among persons with diffuse scleroderma than in those with limited scleroderma; it can occur without prior warning symptoms and can occur early in the disease course. On physical examination, end-inspiratory rales (fine or Velcro crackles) are often heard. Pulmonary function abnormalities can reveal a restrictive ventilatory defect, suggested by a reduction in forced vital capacity and decreased lung compliance and diffusing capacity. Chest radiograph shows reticular interstitial thickening in a linear or nodular pattern most evident in the lower lung bases. A high-resolution computed tomography (HRCT) scan is more sensitive and can detect early disease when chest radiographs are normal.<sup>8</sup> A "ground-glass" appearance is a feature of pneumonitis rather than fibrosis. This lung manifestation is seen more frequently with diffuse disease, in African Americans, and in those with antibodies to topoisomerase-I.<sup>8</sup>

Pulmonary hypertension is more frequently seen with limited systemic sclerosis than with diffuse disease and often occurs late in the disease course. A common presenting symptom of pulmonary hypertension is dyspnea on exertion. Physical examination may reveal accentuation of the S<sub>2</sub> and signs of right-sided heart failure



**Figure 4.** Radiographs showing subcutaneous calcifications as radiopaque deposits (arrows).

(elevated jugular venous pressure, pitting edema, right ventricular heave). An echocardiogram or right-sided cardiac catheterization can confirm the diagnosis. Pleuritis and pleural effusion can occur without symptoms. In late-stage systemic sclerosis, lung cancer can occur independent of tobacco use but is rare.<sup>9</sup>

### Cardiovascular

Patients with systemic sclerosis develop hypertension and atherosclerosis at similar or increased rates compared to those in the general population.<sup>10</sup> The major cardiac complications are pericarditis, constrictive pericardium, arrhythmias, and congestive heart failure. Autopsies may show degeneration of myocardial fibers with replacement by fibrosis that can be prominent in perivascular areas. Additionally, the pathologic finding of contraction band necrosis may be due to intermittent vascular spasm.<sup>11</sup>

### Renal

Scleroderma renal crisis is characterized by an abrupt rise in blood pressure over days to weeks and rapidly progressive renal failure if untreated, usually within the first 5 years of the disease.<sup>12</sup> It occurs virtually only in early diffuse systemic sclerosis. Risk factors in addition to diffuse disease include use of corticosteroids and cyclosporine A and the presence of anti-RNA polymerase III antibodies. The spectrum of presentation ranges from normal or mildly elevated blood pressure to malignant hypertension, causing elevated plasma renin levels, elevated serum creatinine (seen in 50% of patients), proteinuria, and microangiopathic hemolytic anemia (seen in 50% of patients). The urine sediment may show mild proteinuria and a few cells or casts. Renal disease in systemic sclerosis should be

diagnosed early since effective treatment exists. Successful management of this life-threatening complication involves aggressive use of angiotensin-converting enzyme (ACE) inhibitors, immediate control of blood pressure by adding other antihypertensives if needed, intravenous fluids, and close monitoring.

### **Gastrointestinal**

Gastrointestinal manifestations are common in systemic sclerosis, and the most common is esophageal dysfunction. Abnormal propulsive peristalsis and hypomotility resulting from selective atrophy of the circular smooth muscle layer cause dysphagia, reflux esophagitis, and the abnormal sensation of food “sticking,” which necessitates drinking of fluids for relief. Patients may experience retrosternal burning pain and acid regurgitation, especially when in a supine position. If reflux esophagitis remains untreated, a distal esophageal stricture may develop, requiring periodic dilatation. Chronic esophagitis also may lead to Barrett’s esophagus, but this complication seems to be diminishing with widespread use of proton pump inhibitors. Rarely, telangiectasias may cause bleeding in the stomach and result in a “watermelon stomach” visible as stripes on endoscopy.<sup>13</sup> Gastroparesis can aggravate reflux and contribute to bloating, abdominal cramps, and distention. These symptoms may lead to a functional ileus, which can be managed medically with nasogastric suction and bowel rest. Hypomotility of the intestines can lead to overgrowth of intestinal microorganisms, malabsorption, and cachexia.<sup>14</sup> Also, volvulus of the small intestine has been observed.<sup>15</sup> Patients who have colon involvement may present with constipation, which may be relieved by judicious use of increased dietary bulk, stool softeners, and increased fluid intake. In addition, wide-mouthed diverticuli in the transverse and descending colon may cause obstruction.<sup>16</sup>

### **Musculoskeletal**

The musculoskeletal symptoms of systemic sclerosis vary widely. Pain, arthritis, tendonitis, muscle weakness, and joint contractures are common. Flexion contractures usually occurring in the fingers, wrists, elbows, and ankles are due to tendon and periarticular fibrosis and shortening.<sup>17</sup> Myopathy with mild muscle weakness and slight elevation of creatinine kinase can occur. Patients with subcutaneous calcinosis also may develop calcification of the synovium and tendon sheaths.<sup>18</sup>

### **Other**

Disorders of the nervous system include depression, neuropathy from carpal tunnel syndrome, trigeminal

neuralgia, or other compressive phenomena. In patients with systemic sclerosis and Sjögren’s syndrome, vasculitis involving the skin and peripheral nervous system (sensory neuropathy) may occur.<sup>19</sup> Systemic sclerosis alone does not cause neuropathies other than compression neuropathies. Urogenital symptoms are rare, but histologic evidence of increased bladder wall connective tissue deposition and proliferative vascular lesions have been reported.<sup>20</sup> Vaginal symptoms such as tightness, dryness, and dyspareunia are common.<sup>21</sup> In men, erectile dysfunction due to reduced penile blood flow has been observed.<sup>22</sup>

### **DIAGNOSIS**

The diagnosis of systemic sclerosis is based on the identification of features that distinguish it from other disease, and thus a detailed history and careful physical examination are required. The American College of Rheumatology has proposed criteria to assist in identifying those affected with the condition.<sup>23</sup> Major criteria include scleroderma proximal to the metacarpophalangeal joints. Minor criteria are sclerodactyly, digital pitting scars, and bibasilar pulmonary fibrosis. To fulfill a diagnosis of systemic sclerosis, either 1 major or 2 minor criteria are needed.

Clinical evidence of active disease in systemic sclerosis must be investigated. Pulmonary complaints should prompt an evaluation with chest radiography, pulmonary function testing, or HRCT of the chest. Cardiac symptoms may prompt an electrocardiogram, echocardiogram, a stress test, or cardiac catheterization. Serial echocardiograms are routinely done in systemic sclerosis to screen for pulmonary hypertension, and if positive, right heart catheterization is performed. Symptoms of gastrointestinal involvement may require evaluation with endoscopy. Capillary microscopy may be indicated for complaints of Raynaud’s phenomenon.

### **Laboratory Findings**

Antinuclear antibodies have been detected in up to 90% of cases of systemic sclerosis.<sup>23</sup> Anti-centromere antibodies are more likely to be associated with limited systemic sclerosis, whereas autoantibodies to topoisomerase-I (anti-Scl-70) are more likely to be associated with diffuse systemic sclerosis. However, these tests have low sensitivity, with anti-centromere antibodies having a sensitivity of approximately 30% and anti-Scl-70 having a sensitivity of approximately 40%.<sup>24</sup> Hematologic studies are usually normal,<sup>25</sup> although autoimmune hemolytic anemia and neutropenia have been reported.<sup>26</sup> More commonly, anemia of chronic disease or iron deficiency anemia is seen; the latter is associated with

chronic bleeding in the gut from esophagitis or watermelon stomach or other telangiectasia. When systemic sclerosis overlaps with systemic lupus erythematosus, leukopenia may be present. Hypergammaglobulinemia can occur, but monoclonal gammopathy is rare.

## THErapy

Therapy in systemic sclerosis is directed at the organ/system involved. Localized skin lesions have been reported to respond to ultraviolet light therapy with improvement in skin tautness.<sup>27</sup> Other treatment modalities for skin lesions include high-dose topical corticosteroids, topical antibiotic ointments, and oral analgesics. D-Penicillamine may be effective in some cases, but strong evidence is lacking.<sup>28</sup> Management of Raynaud's phenomenon should be tailored to the severity of symptoms and the level of response. Conservative therapy includes avoiding exposure to cold, quitting smoking, and using relaxation techniques to control stress. Topical nitrates may be beneficial. Vasodilator therapy is prescribed when symptoms interfere with activity. Oral therapy includes the use of calcium channel blockers,  $\alpha$ -adrenergic blockers, and/or a phosphodiesterase inhibitor. More aggressive treatment may include intravenous infusion of prostaglandins, which are vasodilators and platelet aggregation inhibitors. Surgical sympathectomy may be considered for patients in whom conservative measures have failed or for those who have evidence of ischemic complications.

Lung disease in systemic sclerosis follows a variable course. Patients are more likely to respond to immunosuppressive therapy if there is evidence of active alveolitis or a ground-glass appearance on HRCT of the chest. Current data suggest that interstitial fibrosis may be preceded by inflammatory alveolitis.<sup>29</sup> A recent study has shown that patients with scleroderma treated with 1 year of oral cyclophosphamide had modest improvement in lung function, functional status, and health-related quality of life as well as reduced dyspnea compared with patients who received placebo.<sup>30</sup>

Therapies for primary pulmonary hypertension include intravenous, subcutaneous, or inhaled prostaglandins. Intravenous epoprostenol was shown to improve exercise capacity, hemodynamics, and dyspnea in systemic sclerosis patients with pulmonary hypertension.<sup>31</sup> Bosentan, an endothelin antagonist, is also available for therapy of severe pulmonary hypertension. If these therapies fail, consultation with a pulmonologist for lung transplantation should be considered. Additional antiplatelet therapy, such as daily aspirin or anticoagulation with low international normalized ratios, may be considered.

The use of ACE inhibitors has changed the prognosis of renal crisis in systemic sclerosis. Development of hypertension, microscopic hematuria or proteinuria, azotemia, or microscopic hemolytic anemia should prompt early aggressive therapy with an ACE inhibitor. Treatment of renal crisis requires ACE inhibitors, which reverse hyperreninemia and hypertension. ACE inhibitors should be used early and continued indefinitely to reduce morbidity and mortality from renal crisis. Other antihypertensives may be added as needed.

Management of the gastrointestinal manifestations of systemic sclerosis utilizes pharmacologic therapies that suppress acid production and treat gastrointestinal dysmotility. Proton pump inhibitors, histamine<sub>2</sub> blockers, and antacids are useful for reducing gastric acidity. In addition, reflux esophagitis can be minimized with nonpharmacologic measures, such as ensuring complete mastication during meals, eating frequent smaller-sized meals, remaining upright after food intake, and eliminating snacks after supper to decrease reflux. Prokinetic medications, such as erythromycin, metoclopramide, domperidone, and octreotide, can help with gastrointestinal dysmotility. Broad-spectrum antibiotics, such as ciprofloxacin, tetracycline, metronidazole, and erythromycin, can be used to treat bacterial overgrowth associated with dysmotility and malabsorption. Pseudoobstruction can be managed with nasogastric suction and bowel rest.

Other therapies include physical therapy, which can improve joint function, and nonsteroidal anti-inflammatory drugs and analgesics to reduce pain and stiffness. The efficacy of more recently developed and/or novel therapies in systemic sclerosis is being evaluated; these include cyclophosphamide, mycophenolate mofetil, methotrexate, autologous bone marrow transplant, thalidomide, anti-tumor necrosis factor- $\alpha$ , and interferon.

The 5-year survival rate for systemic sclerosis ranges from 34% to 73%.<sup>32</sup> Worse prognosis has been associated with being male, older age, and involvement of the lung, kidney and heart. It is likely that improved survival over the past few decades has occurred with the successful management of renal crisis, among other complications.<sup>33</sup>

## CONCLUSION

Systemic sclerosis is a rare chronic connective tissue disease of unknown etiology that can affect many organs and systems. Morbidity and mortality depend on the organ or system involved. Therapy in systemic sclerosis is directed at the organ or system involved. Worse prognosis has been associated with disease affecting the

lung, kidney, and heart. Patients with systemic sclerosis likely have better outcomes when referred to centers with expertise in diagnosis and treatment, especially of the many organ complications. **HP**

Corresponding author: Bernard M. Karnath, MD, 301 University Boulevard, Galveston, TX, 77555; [bm Karnath@utmb.edu](mailto:bm Karnath@utmb.edu).

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