Diagnosis and Management of Systemic Sclerosis

Case Study and Commentary, *Chris T. Derk, MD, MSc*

ABSTRACT

- *Objective:* To review the diagnosis and treatment of systemic sclerosis (SSc).
- *Methods:* Review of the literature.
- *Results:* SSc is a relatively rare disease predominantly seen in women between the ages of 25 and 55 years. SSc can be subclassified into limited and diffuse cutaneous forms based on skin findings and serological markers. The 2 main subtypes typically have differing courses and prognoses. The frequency and diverse nature of disease complications makes systematic assessment and long-term follow-up essential to good management of SSc. While there is no universally acceptable disease-modifying agent for treating SSc, there have been significant advances in the management of affected organ systems.
- *Conclusion:* Early recognition, diagnosis, and aggressive management can improve the prognosis of SSc. Lack of a universally acceptable disease-modifying agent for this disease makes treatment challenging.

Scleroderma (systemic sclerosis) is an autoimmune connective tissue disorder characterized by the triad of skin and visceral organ fibrosis, vascular dysfunction, and cellular and humoral immunity abnormalities [1]. Approximately 300,000 patients in the United States are affected by this disease, with two-thirds of patients having a localized form of the disease that predominantly involves the skin, and one-third of patients having the systemic form of the disease, which can involve visceral organs. Each year approximately 4000 to 5000 new cases are diagnosed [2]. It affects people of all ages and races, but it is more common in women; for every 4 women who have scleroderma, only 1 man has it. Age at onset of disease in most people is between 25 and 55 years of age. The incidence is 2 to 20 new cases per million per year.

No universally acceptable disease-modifying agent exists for treating scleroderma, and even though much basic research has been conducted and valuable insights into the molecular pathways of this disease have been obtained, randomized controlled clinical trials of disease-modifying agents have not been forthcoming [3]. Organ-specific therapies, in contrast, have been more successful, and therapies for the renal, pulmonary, and cardiac manifestations of this disease are currently available and in use. Early diagnosis and close follow-up with screening tests performed at regular intervals is important for timely initiation of treatment of the manifestations of systemic sclerosis and potentially improving morbidity and mortality.

CASE STUDY

Initial Presentation

A 42-year-old woman presents to her primary care physician for color changes of her fingers that began almost 5 years prior. She now notes puffiness of her hands and skin tightness of her fingers, and she has had difficulty putting on and taking off her rings.

History

About 5 years ago, the patient developed new-onset color changes of her fingers in cold weather where her digits would turn white, then bluish, and then a tingling bright red. She was diagnosed as having Raynaud's phenomenon and was instructed to avoid cold environments and to use heat when the symptoms become severe. No laboratory studies were performed during that visit. More recently she has noted increased fatigue and joint pains, specifically in her hands and feet. She has lost about 10 lb over the past 3 months and she is not trying to do so. She has noted difficulty with eating large meals, causing her bloating, abdominal pain, and increased symptoms of gastroesophageal reflux.

She takes medications for hypercholesterolemia as well as levothyroxine for hypothyroidism and has not made any changes to her medications in the past 2 years.

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Physical Examination

The patient's weight is 150 lb, blood pressure is 128/78 mm Hg, heart rate is 68 bpm, respiratory rate is regular at 14 breaths/minute, and temperature is 98.7°F. Head and neck examination reveals slightly dry oral mucosa and telangiectasias on the palate, lips, and face. She has fissuring of the skin around her mouth. Musculoskeletal examination reveals skin sclerosis from the metacarpophalangeal joints to the tips of the fingers, with slight flexion deformities of all of the fingers and telangiectasias observed in the palmar aspect of both hands. No digital ulcers are visible, and evaluation of the nailbed capillaries shows dilated blood vessels. She is unable to fully flex her fingers to make a fist. There is trace pedal edema in her lower extremities around her ankles.

Laboratory evaluation reveals the following:

- White blood cell count, 5500 cells/mm^3
- Hemoglobin, 9.8 g/dL
- Platelets, 350,000 cells/mm^3
- Creatinine, 0.9 mg/dL
- Blood urea nitrogen, 22 mg/dL
- Sodium, 138 mEq/L
- Aspartate aminotransferase, 30 U/L
- Alanine aminotransferase, 38 U/L
- Albumin 5.0 g/dL
- Erythrocyte sedimentation rate, 52 mm/h
- C-reactive protein, 2.8 mg/dL
- Antinuclear antibody positive at 1:1280 titer, centromere pattern
- Anti-topoisomerase 1 (Scl-70), negative
- Anti-SSA and anti-SSB, negative
- Rheumatoid factor, negative
- Anti-cyclic citrullinate protein, negative
- Creatine kinase, 90 U/L
- Urinalysis, normal

Radiographs of the hands are normal without bony erosions, joint space narrowing, or periarticular osteopenia, though there is diffuse soft tissue swelling.

Table 1. American College of Rheumatology Classification Criteria for Systemic Sclerosis

Major criterion
Proximal diffuse (truncal) sclerosis (skin tightness, thickening, non-pitting induration)
Minor criteria
Sclerodactyly (only fingers and/or toes)
Digital pitting scars or loss of substance of the digital finger pad (pulp loss)
Bilateral basilar pulmonary fibrosis

One major criterion or 2 minor criteria are 97% sensitive and 98% specific for systemic sclerosis diagnosis.

- **What are the characteristic findings in systemic sclerosis?**

Classification Criteria for Systemic Sclerosis

In 1980 the American College of Rheumatology defined a set of classification criteria to describe systemic sclerosis, and even though the criteria were developed mainly for research studies, they are often used as diagnostic criteria as well. The single major criterion is proximal diffuse (truncal) sclerosis (skin tightness, thickening, non-pitting induration), while the 3 minor criteria are (1) sclerodectyly (only fingers and/or toes), (2) digital pitting scars or loss of substance of the digital finger pads (pulp loss), and (3) bilateral basilar pulmonary fibrosis (**Table 1**). Systemic sclerosis is accepted as the diagnosis if patients fulfill the major criterion or 2 of the 3 minor criteria; using these criteria, the diagnosis is 97% sensitive and 98% specific. Also of note is that 90% to 98% of patients with systemic sclerosis have Raynaud's phenomenon [4].

Subclassification

Systemic sclerosis can be subclassified into limited and diffuse cutaneous forms based on skin findings and serological markers, although in practice it is a uniquely heterogeneous disease often with very different clinical and serological manifestations from patient to patient [4–6].

Limited cutaneous systemic sclerosis (**Table 2**) is characterized by Raynaud's development 5 to 10 years prior to the development of typical skin findings. The patient develops puffiness and pruritus of the skin in the hands and the feet that slowly progresses to skin tightness distal to the knees and elbows and that can involve the face. These

Table 2. Subsets of Systemic Sclerosis

Diffuse cutaneous systemic sclerosis
Onset of Raynaud's phenomenon with 1 year of skin changes
Truncal and acral skin involvement
Presence of tendon friction rubs
Early and significant interstitial lung disease, scleroderma renal crisis, gastrointestinal and myocardial involvement
Absence of anti-centromere antibodies
Nailfold capillary dilatation and capillary destruction
Anti-topoisomerase I antibodies (30% of patients)
Limited cutaneous systemic sclerosis
Raynaud's phenomenon for years
Skin involvement limited to the hands, face, feet, and forearms or absent
Significant late incidence of pulmonary hypertension, with or without interstitial lung disease, calcinosis and telangiectasias
High incidence of anti-centromere antibody (70%–80%)
Dilated nailfold capillary loops, usually without capillary dropout

findings are symmetric in nature and there is slow progression, with late appearance of internal organ manifestations. Anti-centromere antibody is positive in up to 70% to 80% of patients with the limited form of systemic sclerosis [4–6]. On nailfold capillaroscopy the capillaries are dilated but there is no dropout. The nomenclature previously used for limited cutaneous systemic sclerosis was *CREST* syndrome (*C*alcinosis, *R*aynaud's, *E*sophageal dysmotility, *S*clerodactyly and *T*elangiectasias), although this has fallen out of favor due to the fact that these 5 conditions are present in both the limited and diffuse forms. Patients with the limited form of disease tend to have a good prognosis (> 70% 10-year survival), although this does not prevent them from developing severe organ involvement.

Patients with diffuse cutaneous systemic sclerosis have rapid progression of skin findings, often within 1 year or less from the development of Raynaud's symptoms that advance rapidly from the distal extremities to above the knees and elbows to often involve the trunk, face, and neck. These patients typically have early and significant incidence of interstitial lung disease and can develop early scleroderma renal crisis as well as gastrointestinal and myocardial manifestations. On nailfold capillaroscopy the capillaries reveal both dilation and dropout [6]. Patients with the diffuse form of the disease tend to test negative for anticentromere antibodies and have early visceral organ involvement, which in turn translates to a poor prognosis, with 10-year survival being 40% to 60% [5].

Interstitial lung disease and lung involvement in general in systemic sclerosis is currently the most common cause of death, often related to pulmonary arterial hypertension due to the lung disease, though at times pulmonary arterial hypertension may also be seen in isolation [5].

- **What conditions can mimic systemic sclerosis?**

Several other disorders are also characterized by excessive skin fibrosis and phenotypic skin sclerosis.

Eosinophilic Fasciitis

This disease was first described by Shulman in 1974. Since that time, there have been many case reports and case series describing this condition, which has been characterized by woody induration of the skin. While systemic sclerosis begins from the dermis and goes down into the deeper tissues, this disease begins on the fascia and can spread both upwards towards the dermis but also go deeper than the fascia as well, causing a characteristic cobblestoning appearance of the involved skin. This condition has been described in relation to heavy exertional activities but also in relation to a monoclonal gammopathy. The hands and the face are typically not involved, and the patient does not have Raynaud's symptoms. Blood work may show a peripheral blood eosinophilia, elevated inflammatory markers, and a hypergammaglobulinemia, while some patients may have a low titer antinuclear antibody. When this diagnosis is suspected, a full-thickness skin to muscle biopsy is required, although MRI studies have also been successful in identifying fasciitis in these patients [7].

Scleromyxedema

Scleromyxedema is a scleroderma-like illness characterized by thickened but pendulous skin as compared with the sclerotic and atrophic skin that is bound closely to the underlying tissues in scleroderma. It can affect the upper extremities, face, and trunk, and patients can often have small skin lesions that excrete mucin, a clear gelati-

nous substance that deposits in the skin and leads to the scleroderma-like picture. At times it can involve visceral organs such as the lungs and the heart. When the patient has systemic involvement, the condition may imitate scleroderma, although patients typically do not have positive autoantibodies or Raynaud's symptoms, though they tend to have a paraproteinemia [8].

Scleredema of Buschke

This is typically a rapidly progressing process with edema of the neck, shoulders, face, and upper extremities. In contrast to scleroderma, the hands are not involved, and patients usually do not have Raynaud's symptoms or autoantibodies. It tends to occur in patients with aggressive forms of diabetes who are resistant to therapy and patients who had a recent infectious illness. In many cases, the process resolves without therapy over a 12-month period, although it can be chronic and resistant to therapy [8].

Nephrogenic Systemic Fibrosis

Over the years it has been observed that environmental factors may play a role in the development of scleroderma-like illnesses. Two outbreaks of scleroderma-like illness have been described prior to the current description of nephrogenic systemic fibrosis. In 1981 there was an outbreak of a scleroderma-like illness in Spain that has since been characterized as toxic oil syndrome. Rapeseed oil that was to be used for industrial purposes was denatured with 2% aniline, giving it an unpleasant odor so that it would not be used for consumption. This was then refined illegally to remove the aniline and sold on the market as cooking oil. Nearly 20,000 people developed myalgias, peripheral eosinophilia, and scleroderma-like skin changes, and many patients died within the first few years of the outbreak from pulmonary complications. A similar outbreak occurred in 1989 in the United States, later described as the eosinophilia-myalgia syndrome related to ingestion of contaminants in L-tryprophan supplements sold in the US market as sleep aids. The contamination was traced to a Japanese manufacturer where shortcuts had been taken in the purification process. Nephrogenic systemic fibrosis is the latest of such cases of environmentally induced scleroderma-like illness. This skin fibrotic illness was first described in patients on hemodialysis and was thought to be due to either the fact that the patients had renal failure or potentially some process in the hemodialysis. Patients have skin thickening with brawny hyperpigmentation, papules, and subcutaneous nodules typically seen in the extremities but sparing the fingers, neck, and face. Patients do not have Raynaud's symptoms, autoantibodies, or a paraproteinemia. Since its first description, it has been established that visceral organs can also be involved and also that the environmental trigger is a gadolinium dye used in MRIs and more specifically when used in patients with renal failure [8].

Other conditions that can mimic systemic sclerosis include:

- Generalized morphea
- Diabetic cheiropathy
- Hereditary telangiectasias
- Primary Raynaud's
- Graft-versus-host disease
- Palmar fasciitis
- Lichen sclerosis
- Progeria
- Porphyria

- **What laboratory studies and imaging studies can be helpful in patients with systemic sclerosis?**

When a patient presents with a scleroderma-like illness or Raynaud's with or without skin findings, it is of utmost importance to establish if the symptoms are related to an autoimmune process. In patients who have Raynaud's symptoms and no specific skin findings, it is important to perform a nailfold capillaroscopy, test for antinuclear autoantibodies (ANA), as well as measure erythrocyte sedimentation rate (ESR). Dilated capillaries on nailfold capillaroscopy or an elevated ANA or ESR are predictive of the patients Raynaud's symptoms being related to an underlying autoimmune connective tissue disorder [9]. In patients with established scleroderma-like skin findings, an ANA as well as testing for the systemic sclerosis–specific antibodies ant-Scl-70 and anti-centromere antibody is also helpful in establishing the presence of autoimmunity, while an anti-RNA polymerase III can suggest severe disease in patients with diffuse cutaneous systemic sclerosis. Patients who test positive for 1 of the 2 systemic sclerosis–specific antibodies are usually negative for the other. Many commercial laboratories use ELISA to perform their ANA, and

this test has a tendency to miss nucleolar antibodies; thus, an ANA immunofluorescence is recommended if systemic sclerosis is suspected.

As part of the initial evaluation and as part of routine follow-up (especially in patients with diffuse cutaneous systemic sclerosis), patients should have a complete metabolic panel, a complete blood count, urinalysis, and tests for inflammatory markers. On a yearly basis, even in the absence of any specific symptoms, a 2D echocardiogram should be performed to measure pulmonary artery pressure and pulmonary function studies to include spirometry and lung volumes and diffusing capacity should be done to evaluate for early cardiopulmonary involvement. If patients show abnormalities on these tests, then these should be followed more frequently. Follow-up assessments may include high-resolution computed tomography (CT) of the chest, a 6-minute walk, and, if needed, a right-sided cardiac catheterization to detect potential pulmonary arterial hypertension [10].

On a routine basis, patients should measure their blood pressure using a brachial artery blood pressure cuff. Scleroderma renal crisis is detected through blood pressure monitoring, and early detection and therapy averts morbidity and mortality.

- **What are the treatment options for patients with visceral organ involvement?**

While there is no universally acceptable disease-modifying agent for treating systemic sclerosis, there have been significant advances in the management of affected organ systems. Scleroderma renal crisis had been the most common cause of morbidity and mortality in the 1970s, but with the introduction of ACE inhibitors, the outcome of renal crisis has dramatically improved. Angiotensin receptor blockers (ARBs) have also been tried in these patients though without the same success rate [11–13].

Raynaud's Phenomenon

One of the most bothersome manifestations of this disease is the vascular manifestations and more specifically, the Raynaud's manifestations. While primary Raynaud's usually does not lead to tissue damage, secondary Raynaud's, and specifically the one seen in conjunction with systemic sclerosis, can lead to debilitating symptoms and poor quality of life. Patients may have digital ulcers and be unable to use their hands to perform activities of daily living. In the worst case, digital ischemia can lead to the loss of tissue or even digital amputation. The patient must be educated to keep their core body temperature high (wear stockings, headwear, and gloves in cold weather), avoid cold temperatures when possible, and reduce emotional stress, which can trigger digital vasospasm [14]. When symptoms persist even after conservative measures, then the treatment of choice is a calcium channel blocker, preferably a long-acting dihydropiridine [15]. Other agents that may have some success, although they have not been extensively studied, are ACE inhibitors, ARBs, and alpha blockers [16]. Antiplatelet therapy is also often added to the regimen to help with symptoms. Topical nitroglycerin may have some short-term results though side effects limit its use. Of great interest is the recent off-label use of phosphodiesterase-5 inhibitors to treat the manifestations of Raynaud's in scleroderma patients, although there has not been a large double-blind study to examine this [17]. Endothelin receptor blockers, while approved for pulmonary arterial hypertension, have also been extensively studied for digital ulcers in systemic sclerosis, and although they were not approved for this indication in the United States one such agent was approved for digital ulcers in scleroderma in Europe [18].

Calcinosis

Another cutaneous manifestation of the disease is tissue calcinosis, which is seen most often in the extremities. These calcium-based deposits in the soft tissue can be painful and may limit function. Excising the lesions can help. The different agents used to treat this, such as calcium channel blockers, bisphosphonates, colchicine minocycline and warfarin, have not been very successful [19].

Gastrointestinal Symptoms

Esophageal dysmotility, gastroparesis, and intestinal bacterial overgrowth are some of the most common gastrointestinal manifestations seen in patients with systemic sclerosis. Esophageal dysmotility can lead to gastroesophageal reflux, esophagitis, esophageal strictures and in rare cases, Barrett's esophagus. Acid suppressive therapy as well as lifestyle modifications can be used to treat symptoms, although at times more aggressive and invasive therapies may need to be undertaken. Esophageal strictures often require balloon dilatation during endoscopy, while esophageal dysmotility can be treated surgically or with botulin injections near the lower esophageal sphincter. Gastroparesis can be treated with promotility agents in

combination with acid suppressive therapy and frequent small meals, though intestinal bacterial overgrowth needs more aggressive therapy, with cycling of antibiotics every 2 weeks with the goal to normalize the intestinal flora [20]. Intestinal pseudoobstruction is another gastrointestinal manifestation seen in scleroderma patients. It is important for the clinician to be aware of this so as to avoid unnecessary surgery, since IV hydration and bowel rest can be effective in treating this [20]. A slow decline in hemoglobin should raise suspicion for intestinal bleeding. One of the most common causes of this in scleroderma patients is gastric antral vascular ectasias (GAVE); if persistent, it can be treated with laser cauterization.

Pulmonary Involvement

Lung disease is currently the leading cause of death in systemic sclerosis. The course of lung involvement in scleroderma patients is heterogeneous, with some patients having a subacute progression and others having recurrent exacerbations that can lead to fibrosis. It is important for the clinician to differentiate progressive disease versus stable chronic damage to the lungs and often the only way this can be evaluated is by serial pulmonary function tests or serial high-resolution CT of the chest. Rapidly progressive lung disease needs to be managed aggressively. The treatment of choice for active alveolitis is currently cyclophosphamide, with the Scleroderma Lung Study [21] showing a statistical significant benefit after 12 months of therapy (even though the absolute improvement in forced vital capacity was small). Other therapies evaluated in small studies that have suggested some benefit are mycophenolate mofetil and azathioprine, though large studies are needed to define the role of these agents [22].

Pulmonary arterial hypertension with or without a concomitant diagnosis of interstitial lung disease can be treated with at least 3 different classes of drugs, including prostacyclin analogues, endothelin receptor blockers, and phosphodiesterase-5 inhibitors. More agents are being studied. It is clear from the data currently available that systemic sclerosis–related pulmonary arterial hypertension appears to be more resistant to therapy than idiopathic pulmonary arterial hypertension [23]. Pulmonary arterial hypertension can be seen in 8% to 12% of patients with systemic sclerosis. Early detection is important since the survival rate for isolated pulmonary arterial hypertension in systemic sclerosis is 64% at 3 years, while patients with interstitial lung disease–associated pulmonary arterial hypertension have a 3-year survival of 39% [24].

- **What are the treatment options for systemic sclerosis?**

Many agents have been studied through the years for the treatment of systemic sclerosis, but none has been accepted as a definitive therapy for this disease. Early on in patients with new-onset diffuse cutaneous systemic sclerosis, some physicians will initiate low-dose prednisone (less than 15 mg per day) because of a described risk of scleroderma renal crisis with higher doses [13] and then add an immunosuppressive or antifibrotic agent. In patients with limited cutaneous systemic sclerosis, it is not customary to initiate such agents, so most of what is discussed under this heading will be in regards to patients with diffuse cutaneous systemic sclerosis of relatively recent onset [10]. While many agents have been studied for specific aspects of this disease, immunomodulatory agents such as mycophenolate mofetil [25], methotrexate [26] and cyclophosphamide [21] have been used by some to treat the disease as a whole even though there is no overwhelming data to support this. Other agents that are used at different institutions for their immunomodulatory effects are cyclosporine, IVIG, and tacrolimus [27]. Targeted immunotherapy has not been successful in the research work done for this disease, though use of rituximab and abatacept has been observed in some institutions specializing in systemic sclerosis. Antifibrotic agents have also had differing results among the studies performed and while some centers still use D-penicillamine as an antifibrotic, most centers no longer use this agent [28]. Research work with interferon alpha and gamma, relaxin, and anti-TGF-beta antibodies has not shown success [29].

Treatment of Case Patient

The patient was diagnosed with limited cutaneous systemic sclerosis and was prescribed a proton pump inhibitor to treat her gastroesophageal reflux disease as well as amlodipine 5 mg/day for Raynaud's. Because of her low hemoglobin, the patient underwent endoscopy that revealed gastric antral vascular ectasia. Cauterization was performed, leading to improved hemoglobin levels over the next 4 months. She was also sent to an occupational therapist for intensive hand therapy. After 4 months, she reported increased range of motion and grip strength.

- **What is the prognosis of systemic sclerosis?**

The 2 main forms of systemic sclerosis have different prognoses. Limited cutaneous systemic sclerosis typically is slowly progressive, often not causing significant visceral organ involvement until about a decade after the first symptoms. Diffuse cutaneous systemic sclerosis is usually rapidly progressive with significant visceral organ involvement, especially within the first 2 years after initial presentation of symptoms.

Survival in systemic sclerosis has dramatically improved over the decades. Ten-year cumulative survival in the longitudinal Pittsburgh scleroderma cohort was 66% in the 1990s as compared with 54% in the 1970s [30]. Among 5860 systemic sclerosis patients followed in the the *EU*LAR (European League Against Rheumatism) *S*cleroderma *T*rial *A*nd *R*esearch (EUSTAR) database, data was obtained for 234 of 284 deaths. In this cohort, 19% of patients died from pulmonary fibrosis, 14% from pulmonary arterial hypertension, 14% from systemic sclerosis–related myocardial disease, and 4% from scleroderma renal crisis [31].

- **When should a patient be referred to a specialist?**

Because of the rarity of the disease and the significant morbidity and mortality related to it, patients in whom this diagnosis is suspected should be referred to one of the many scleroderma centers in this country. The need for early recognition of the disease has been emphasized and primary care physicians as well as other physicians should be aware of the early signs of this disease such as puffy hands and Raynaud's symptoms and should refer appropriately [32].

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