*** no patient handout***

Scleroderma

Synopsis

General ManifestationsThis summary discusses scleroderma in adults. **Scleroderma in children** is addressed separately.

Scleroderma, or systemic sclerosis, is an autoimmune connective tissue disease that involves sclerotic changes of the skin and internal organs. While the etiology remains unknown, the disease is characterized by autoantibody production, collagen deposition, and vascular dysfunction. The disease is observed in all ages and is slightly more common in individuals of African descent and 3-4 times more common in women. The age of onset is usually between 30 and 50 years.

Scleroderma can affect the connective tissue of any organ, including the skin, gastrointestinal tract, lungs, kidneys, joints, muscles, heart, and blood vessels. Pulmonary disease is the leading cause of mortality. Additional common clinical features include esophageal fibrosis and dysmotility, arthralgias, and **Raynaud phenomenon**. Less common manifestations include hypertensive renal crisis, pulmonary hypertension and interstitial lung disease, and cardiomyopathy.

There are three major clinical subsets of scleroderma:

1) Limited cutaneous systemic sclerosis (distal skin sclerosis, Raynaud phenomenon, frequent severe late-stage complications such as pulmonary hypertension and gastrointestinal involvement). **CREST syndrome** (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias) refers to a subset of patients with limited scleroderma.

2) Diffuse cutaneous systemic sclerosis (proximal extremity or trunk skin sclerosis, Raynaud phenomenon of shorter duration, high risk of renal crisis, and cardiac and lung fibrosis).

3) Systemic sclerosis sine scleroderma (Raynaud phenomenon and systemic involvement without skin sclerosis).

The subsets are defined by the degree of skin involvement, so the classification does not predict systemic organ disease. The systemic sclerosis overlap syndrome is characterized by features of one of the scleroderma subsets with those of another autoimmune disease.

Patients of African descent tend to have an earlier onset (35-44 years compared with 45-55 years for all others), a more severe course, and increased mortality. This may be due to their being more likely to have diffuse, rather than limited, cutaneous systemic scleroderma. In addition, lung function is often worse. There is a greater prevalence of anti-topoisomerase I antibodies, anti-RNP, and anti-Ro antibodies in these patients, although the frequency of anticentromere antibodies is less compared with individuals of Northern European descent.

There are reports in the literature of drug-induced scleroderma. The majority of reports point to a scleroderma-like disease rather than true systemic scleroderma. See **drug-induced sclerodermoid reactions** for further details.

Codes

ICD10CM:
M34.9 – Systemic sclerosis, unspecified

SNOMEDCT:
89155008 – Scleroderma

Look For

Cutaneous changes include:

- Induration and taut, shiny skin. This is usually seen first in the fingers and hands and can lead to joint contractures. The "prayer sign" may be present, which is seen when individuals cannot perfectly oppose the palmar surfaces of their hands because of fibrosis of the fingers.
- Pigmentary changes including diffuse hyperpigmentation as well as depigmentation with sparing of perifollicular skin, giving a "salt-and-pepper" appearance. This is especially common on the back and legs.
- Flat telangiectasias that are most commonly seen on the lips, palms, and proximal nail folds. Mat-like telangiectases can be found on palms and lips. Prominent proximal nail fold capillaries are present in nearly all patients; they frequently have sausage-shaped vessels with magnification. Dermoscopy shows both loss of capillary and dilated capillaries.
- Calcinosis cutis of the fingers or other pressure points. This is an abnormal deposition of calcium in the tissues presenting clinically as hard nodules that may exude a white chalky substance if ruptured.
- Raynaud phenomenon resulting in cutaneous ulcers of the digits. Acutely, this can appear as transient red, blue, or white changes in the skin of the fingers or toes. This may be the earliest clinical sign of vascular involvement of systemic sclerosis.
- The face may develop a characteristic "beak-like" appearance. As the disease progresses there is a paucity of wrinkling to the nose and a reduced aperture of the mouth as the skin thickens.
- Intraoral findings include widening of the periodontal ligaments, bone lesions, and xerostomia.
- Sclerodactyly and joint contractures with loss of skin creases.

- Pterygium inversum unguis and parrot beak nails are seen in systemic sclerosis and are distinctive of the disorder. Of note, nail changes have been associated with more severe digital microangiopathy and esophageal disease.

- Hand x-rays may show acroosteolysis (resorption of the terminal digital tufts). This finding has been associated with digital ischemia and severe calcinosis.

Limited cutaneous scleroderma usually involves the distal extremities and may involve the face and neck. The diffuse form of scleroderma has additional sclerotic changes of the trunk and proximal extremities.

Diagnostic Pearls

Consider other clinical diseases that overlap with scleroderma. These include overlap with rheumatoid arthritis, systemic lupus erythematosus (SLE), polymyositis, and rarely vasculitis.

Differential Diagnosis & Pitfalls

- **CREST syndrome**

- Generalized **morphea** – Asymmetric induration, no Raynaud phenomenon, no systemic involvement.

- **Scleredema** – ANA negative, no Raynaud phenomenon, no systemic involvement.

- **Scleromyxedema** – ANA and anticentromere negative, no Raynaud phenomenon, no sclerodactyly.

- Generalized myxedema

- **Chronic graft-versus-host disease** – ANA negative, vascular abnormalities such as Raynaud phenomenon absent.

- **Eosinophilic fasciitis** – ANA negative, no Raynaud phenomenon, no facial involvement.

- **Nephrogenic systemic fibrosis** – Assess for recent history of radiologic imaging with gadolinium-based intravenous contrast in patients with renal insufficiency or renal transplant patient; ANA negative, no sclerodactyly, no Raynaud phenomenon.

- **Stiff-skin syndrome** – Characteristic sparing of the hands and feet, develops during early childhood, systemic involvement rare.

- **Porphyria cutanea tarda**

- **Phenylketonuria**

- Polyvinyl chloride exposure – ANA negative, cutaneous changes reverse with cessation of exposure.

- **Carcinoid syndrome**
- **Cutaneous T-cell lymphoma**
- **Amyloidosis**
- Bleomycin toxicity
- **Radiation effects**
- **Onchocerciasis** can produce similar "salt-and-pepper" skin changes if a patient is from an endemic area.
- **Vitiligo**

Best Tests

A skin biopsy is not required for diagnosis but may help.

The diagnosis of systemic sclerosis is clinical, and in 2013 the American College of Rheumatology and the European League Against Rheumatism produced a set of diagnostic criteria. The presence of sclerosis of the hands extending proximal to the metacarpophalangeal joints is sufficient to make the diagnosis. If this feature is absent, there are 7 other weighted criteria that can be used to make the diagnosis in combination: skin thickening of the fingers, lesions of the fingertips, telangiectasias, abnormalities of the nail folds, interstitial lung disease or pulmonary hypertension, Raynaud phenomenon, and autoantibodies associated with systemic sclerosis.

Autoantibodies in scleroderma are helpful in both diagnosis and prognostication. Antinuclear antibodies (ANA) are positive in about 95% of patients with systemic sclerosis. Anticentromere antibodies are associated with limited systemic sclerosis, and only about 5% of individuals with diffuse cutaneous systemic sclerosis have this antibody. Anti-DNA topoisomerase I (anti-Scl-70) antibodies are associated with diffuse cutaneous systemic sclerosis. Individuals with this antibody also have a high risk of interstitial lung disease. Anti-RNA polymerase III antibodies are seen in individuals with diffuse cutaneous systemic sclerosis who have rapidly progressive skin involvement. This antibody is also associated with an increased risk of renal crisis.

Other autoantibody tests may be useful, including anti-U3RNP, anti-fibrillin, and anti-PM-Scl. These antibodies are often associated with overlap syndromes.

Additional screening to consider includes:

- Urinalysis, blood urea nitrogen (BUN) test, creatinine clearance
- Pulmonary function tests and high-resolution CT
- Right heart catheterization

- Echocardiogram
- Esophagogastroduodenoscopy
- Barium swallow

Histopathology Findings:

- Epidermis normal or atrophic
- Closely packed thick hyalinized collagen bundles in dermis and subcutaneous fat
- Decreased adnexal structures and loss of adventitial fat resulting in entrapped eccrine glands
- Sparse deep (dermal-subcutaneous junction) lymphoplasmacytic infiltrate

Management Pearls

The approach to the patient with scleroderma should be multidisciplinary. A rheumatologist and a dermatologist should be involved. Depending on the manifestations and course of the disease, other specialties may need to be consulted (nephrology, pulmonology, gastroenterology, or hand surgery).

An experienced physician should be screening for and treating internal organ involvement because effective therapies exist, particularly for early pulmonary and renal disease. Internal organ changes include the following:

- Pulmonary hypertension and interstitial pulmonary fibrosis
- Hypertensive renal crisis
- Cardiomyopathy
- Esophageal dysmotility
- Sicca syndrome
- Myositis

Supportive measures are important. Patients should be kept warm to minimize Raynaud phenomenon. Any ulcers should be kept clean and dry. Encourage patients with dysphagia or reflux to eat smaller, more frequent meals. Advise smoking cessation, if applicable.

Hypertension from renal disease can be controlled in most cases with angiotensin converting enzyme (ACE) inhibitors.

Patients often require extensive occupational and physical therapy to maintain their range of motion and prevent contractures.

Long-term follow-up is required to ensure proper assessment of the extent of internal disease.

Therapy

Systemic complications of scleroderma should be managed in conjunction with a rheumatologist. Note that scleroderma is a challenging disease to treat, particularly the cutaneous manifestations. Therapies have demonstrated efficacy in treating the lungs and kidneys.

Besides oral glucocorticoids, the mainstay of treatment is methotrexate and mycophenolate mofetil. Cyclophosphamide may be used temporarily in patients with rapidly progressive disease. Cyclophosphamide may also be needed in cases refractory to methotrexate and mycophenolate mofetil. Methotrexate has been found to be effective for skin sclerosis, but has not been demonstrated to be effective in treating internal organ involvement. Mycophenolate mofetil has also been shown to be effective for skin sclerosis. Cyclophosphamide has been shown to be effective for interstitial lung disease and may also improve skin sclerosis. Rituximab may be used in refractory cases.

Adjunctive therapies such as phosphodiesterase-5 inhibitors, calcium channel blockers, endothelin receptor antagonists, and antihistamines may be used to treat other aspects of scleroderma.

In a randomized phase 2 trial, myeloablative CD34+ selected autologous hematopoietic stem-cell transplantation showed promise as an alternative to cyclophosphamide.

Example regimens:

- Corticosteroids: prednisone 2.5-5 mg once daily; increase as needed
- Immunosuppressants: mycophenolate mofetil 1-1.5 mg by mouth twice daily, OR cyclophosphamide 50-150 mg by mouth daily
- Antimetabolites: methotrexate 7.5-25 mg weekly
- Endothelin receptor antagonist: bosentan 62.5 mg by mouth twice daily for 1 month, then increase to 125 mg by mouth twice daily, OR ambrisentan 5 mg by mouth daily; increase up to 10 mg by mouth daily, if tolerated
- Phosphodiesterase type 5 inhibitor: sildenafil 20 mg by mouth 3 times daily (for severe Raynaud phenomenon, and to prevent digital necrosis and ulceration)
- Large preliminary studies show that low-energy extracorporeal shock-wave therapy may be effective in reducing digital ulcers.

Important treatment adjuncts include the following:

Raynaud phenomenon:

- Nifedipine XL (30 mg by mouth daily) or a different calcium channel blocker

Emollients and antihistamines for pruritus:

- Diphenhydramine hydrochloride (25, 50 mg tablets or capsules): 25-50 mg nightly or every 6 hours as needed
- Hydroxyzine (10, 25 mg tablets): 12.5-25 mg every 6 hours as needed
- Cetirizine hydrochloride (5,10 mg tablets): 5-10 mg per day
- Loratadine (10 mg tablets): once daily

Gastroesophageal reflux:

- Antacids (calcium carbonate)
- H2 blockers (ranitidine, famotidine)
- Proton-pump inhibitors (omeprazole, pantoprazole)

Hypertension:

- Patients should be aggressively monitored for hypertension and placed on an ACE inhibitor as soon as it is detected to prevent a renal crisis.