SCLERODERMA

Scleroderma is an autoimmune disorder of unknown etiology, characterized by fibrosis and microvascular injury in affected organs. The hallmark of the disease is thickening and tightness of the skin and of subcutaneous tissue. Scleroderma may be confined to the skin (localized) or it may be generalized (systemic sclerosis). In generalized involvement virtually all organ systems can be involved, most importantly the skin, blood vessels, lungs, kidneys, gastrointestinal tract, and the heart. Systemic sclerosis is further subdivided into limited and diffuse variants depending on the extent of cutaneous involvement (Table 1). The two variants differ in their clinical course and outcome.

Table 1: Classification of Scleroderma at presentation

<table>
<thead>
<tr>
<th>Presenting Feature</th>
<th>Scleroderma classification</th>
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<tbody>
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<td></td>
<td>Limited</td>
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<tr>
<td>Raynaud’s phenomenon</td>
<td>Long duration</td>
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<tr>
<td>Skin involvement</td>
<td>Distal limbs &amp; face</td>
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<tr>
<td>Tendon friction rubs</td>
<td>Absent</td>
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<td>Nailfold capillaries</td>
<td>Dilatation</td>
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<tr>
<td>Autoantigen</td>
<td>Commonly centromere</td>
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EPIDEMIOLOGY

In the USA, the prevalence of scleroderma in the general population has been reported in the range of 50 per 1000,000. The disease is very rare in childhood, with peak occurrence in the 30-40 years age group. Women are affected four times more often than men. Environmental factors seem to play a greater role than genetic factors in the aetiology; etiological agents implicated include viruses, silica exposure, vinyl chloride, organic solvents, bleomycin, and even smoking and alcohol intake. Genetic factors influence the clinical expression of the disease.
**PATHOLOGY AND PATHOGENESIS**

Small-vessel vasculopathy and fibrosis are the characteristic pathological findings of scleroderma. The vasculopathy is both proliferative and obliterative and involves small arteries, arterioles and capillaries. These changes are seen both in the skin and in viscera. The pathogenesis involves a complex interplay between endothelial cells, fibroblasts and the immune system triggered by an environmental factor.

**CLINICAL FEATURES**

Raynaud’s phenomenon is usually the initial symptom of scleroderma, either with or without puffiness of fingers. This is often accompanied by fatigue, early morning stiffness and musculoarticular pain. Up to 25% of patients may be initially mistaken for rheumatoid arthritis (RA). The hallmark of scleroderma is taut, hidebound skin, which may take several years to develop. In clinical practice, the following subsets are easily identified:

1. **Localized scleroderma.**
   
   Seen in dermatology practice in the form of morphoea and linear scleroderma. The former presents as plaques of fibrotic skin and subcutaneous tissue without systemic disease, while the latter occurs as linear fibrotic bands that occur over the extremities, involving skin and deeper tissue.

2. **Limited cutaneous systemic sclerosis**
   
   These sclerodermatous changes typically affect the face, neck and extremities distal to the elbows and knees. Involvement of the skin is the hallmark of systemic sclerosis, and there are usually three phases:

   (i) Edematous,
   
   (ii) Indurative, and
   
   (iii) Atrophic.

   The oedematous phase is characterized by the complaint of stiff hands with associated puffiness. Subsequently, the skin becomes thickened and tight, and it may develop a shiny appearance. Flexion contractures develop as a result of
skin thickening and tendon fibrosis. The trunk is never involved. Patients frequently complain of darkening of complexion. Peri-oral fibrosis leads to a “puckered mouth”. This, along with pinched nose and mask like face, constitutes the typical scleroderma facies. Patients may give a history of Raynaud’s phenomenon for 5-10 years before development of other features of scleroderma. Digital sores or pitted scars, pseudo-clubbing, finger contractures, ischaemic ulcers and telangiectasia over the face and nail folds are common findings. Calcinosis may occur. An occasional patient may present with the CREST syndrome (Calcinosis, Raynaud’s phenomenon, Esophageal involvement, Sclerodactyly and Telangiectasia). Late in the disease course, pulmonary hypertension may develop.

3. **Diffuse cutaneous systemic sclerosis**

This is characterized by extensive skin involvement extending proximal to the knees and elbows, and usually also affects the trunk. Although the cutaneous manifestations are the most easily recognized, generalized scleroderma is a systemic disorder that can affect virtually every organ system. It is therefore referred to as systemic sclerosis. There is often a rapid evolution of systemic disease after appearance of Raynaud’s phenomenon. Lungs, gut, heart and kidneys may all be involved. The clinical features are described in detail below.

**Raynaud’s phenomenon**

Isolated Raynaud’s phenomenon is far more common in the general population (approximately present in 5% of the population) than scleroderma. Strong indicators of underlying scleroderma are the onset after the age of 20, presence of antinuclear antibody and nailfold capillary abnormalities.

Attacks are triggered by exposure to cold and sometimes by emotion. The clinical presentation may include:
- Blanching
- Cyanosis
- Hyperaemia
- Numbness or pain in the affected digits.

With time, attacks may become more frequent and severe, causing frank gangrene. Terminal resumption of phalanges is a common finding.

**Skin involvement**
In addition to the involvement described under limited scleroderma, the trunk is also affected. “Salt and pepper” appearance may result from patchy hypo-and hyper-pigmentation, usually over the trunk.

**Musculoskeletal**
Generalized myalgias, arthralgias and frank arthritis are fairly common. Tendon friction rubs are quite characteristic of diffuse scleroderma. Muscle weakness is common and may result from disuse atrophy, overlap myositis, myopathy due to steroids or that due to D-penicillamine.

**Pulmonary**
Interstitial lung disease is present in almost all patients with diffuse scleroderma. It may be asymptomatic in half of them. Patients present with dry cough and dyspnoea on exertion. Bibasilar “Velcro” crepitations are characteristically heard on auscultation of the chest. The diagnosis can be confirmed with pulmonary function tests, HRCT (high resolution CT) or chest radiograph. The latter is quite insensitive in early disease. Pulmonary disease progresses for a few years and then tends to stabilize.

Other pulmonary complications of scleroderma include:
- Aspiration pneumonia (due to nocturnal gastro-oesophageal reflux)
- Pulmonary hypertension
- Pulmonary haemorrhage
• Pneumothorax
• Respiratory failure
• Increased risk of lung cancer.

Gastrointestinal
Dysphagia and heartburn are the most common gastrointestinal symptoms in patients with scleroderma. Reflux esophagitis is common and can lead to bleeding, stricture and Barrett’s metaplasia, hoarseness and atypical chest pain. Because of dysfunction of the lower part of the esophagus, patients may complain of a feeling of heaviness in the mid-chest. Similarly, delayed emptying of stomach leads to bloating, nausea and early satiety. Periodontal disease and loss of teeth is common in scleroderma. This, together with small oral aperture as well as sicca syndrome, can lead to poor nutrition and cachexia. Dysmotility of intestine could cause chronic diarrhoea, malabsorption and pseudo-obstruction.

Cardiac
Pathologically, myocardium, coronary vessels and pericardium are involved in the majority of patients with diffuse scleroderma, but clinical disease is either subtle or absent. Left ventricular failure is usually a late finding and a large pericardial effusion is a poor prognostic sign.

Renal
Renal disease, in the form of proteinuria, azotemia or hypertension may be seen in 20-30% of cases with diffuse scleroderma. The development of scleroderma renal crisis is of major concern. This complication comes on suddenly and is accompanied by severe hypertension, azotemia and microangiopathy. New, unexplained anaemia in a patient with diffuse scleroderma is an early warning sign for renal crisis. Kidney histology shows intimal hyperplasia, fibrinoid necrosis, medial thinning and adventitial fibrosis of the interlobular and intralobular arteries.
Miscellaneous

- Impotence
- Carpal Tunnel syndrome
- Hypothyroidism
- Secondary Sjögren’s syndrome
- Trigeminal neuralgia
- Depression.

Systemic sclerosis sine scleroderma is defined by the characteristic visceral, vascular, and serologic abnormalities, but without skin scleroderma changes. In overlap syndromes, one may see any of the aforementioned manifestations of systemic sclerosis with features of systemic lupus erythematosus (SLE), RA, inflammatory muscle disease, or Sjögren’s syndrome.

Undifferentiated connective tissue disease is reserved to classify those patient with Raynaud’s phenomenon and clinical or serologic features of systemic sclerosis without the characteristic skin or visceral involvement. When followed prospectively, however, many of these patients develop classic systemic sclerosis, at the rate of approximately 5% per year.

LABORATORY INVESTIGATIONS AND DIAGNOSIS

Baseline work up includes:

- Complete blood counts
- Erythrocyte sedimentation rate (ESR)
- Antinuclear antibody (ANA) testing
- Chest X-ray
- Urinalysis
- Blood urea and serum creatinine
- Barium swallow
- Pulmonary function tests (particularly, vital capacity and DLCO).
Patients with Raynaud’s phenomenon should be evaluated with an antinuclear antibody (ANA) and nailfold capillaroscopy. Nailfold capillaroscopy is a non-invasive means of detecting vascular changes characteristic of systemic sclerosis. The typical changes include giant (dilated) loops or a decreased number of capillary loops (avascularity). ANAs are detected in more than 95% of patients with systemic sclerosis. Primary Raynaud’s phenomenon (not associated with a connective tissue disease) can be diagnosed when physical examination (including pulses) and nailfold capillaroscopy are unrevealing, and the ANA and erythrocyte sedimentation rate are negative or normal. Abnormalities of any of these features may indicate the potential for development of a connective tissue disease in a patient with Raynaud’s phenomenon, which may evolve over many years (up to 20 years) following the onset of Raynaud’s symptoms.

Barium swallow or esophageal manometry may be helpful in detecting dysmotility and gastroesophageal reflux. Pulmonary function tests may reflect changes of restrictive lung disease indicative of interstitial fibrosis or a reduced diffusing capacity indicative of pulmonary hypertension. HRCT and bronchoalveolar lavage may detect early interstitial lung disease with ongoing active inflammation. Anticentromere antibody if found in 75% of cases with limited scleroderma while anti-Scl-70 (antitopoisomerase I) occurs in 50% of those with diffuse scleroderma.

Diagnosis of scleroderma can be clinically made at the bedside. The American College of Rheumatology (ACR) published criteria for the classification of systemic sclerosis in 1980. The major criterion is proximal scleroderma, defined as skin thickening proximal to the metacarpophalangeal or metatarsophalangeal joints. The three minor criteria are

(i) Sclerodactyly (cutaneous sclerosis distal to the metacarpophalangeal joints),
(ii) Digital pitting scars or the loss of subcutaneous tissue of the fingertips,
(iii) Chronic interstitial pulmonary changes on chest radiographs. Patients exhibiting the major criterion or two of the three minor criteria are considered to have systemic sclerosis.
Scleroderma can be quite frustrating to treat. Numerous therapeutic agents have been tried in pursuit of a disease modifying effect, but results have not been exciting. The list includes colchicine, D-penicillamine, DMSO, ketotifen, interferon, intravenous pulses of steroids, cyclosporine, methotrexate, chlorambucil, 5-FU and cyclophosphamide.

D-penicillamine is the most widely used agent in diffuse systemic sclerosis. It has been shown to improve the skin thickening. Even five-year survival was shown to improve in a retrospective study. It has an immunomodulating effect besides having the ability to interfere with collagen crosslinking. Doses varying from 500mg to 1000mg per day (to be taken early morning on an empty stomach) are recommended.

Raynaud’s phenomenon poses a great challenge to the clinician. For mild to moderate cases, measures such as avoidance of cold exposure, abstinence from smoking and protective warm clothing may suffice. Non-selective beta-blockers and vasoconstrictive agents such as ergot alkaloids, nicotine and amphetamine should be strictly avoided. For severe Raynaud’s phenomenon with digital infarcts/ulcers, vasodilator drugs such as nifedipine (30-12mg/d) and prazosin (3-20mg/d) are recommended. In addition, local treatment of ischemic ulcers, such as soaking the fingers or toes in half strength hydrogen peroxide followed by air drying and application of an antibiotic cream over the ulcers, promotes healing. Occasionally, debridement and parenteral antibiotics may be needed.

Sclerodermatous skin is prone to dryness and pruritus. Patients should be advised to avoid excessive use of detergents. Moisturizing creams containing lanolin are recommended. There is no satisfactory treatment for calcinotic nodules; low dose warfarin, probenecid and cardizen have been tried. Colchicine may be useful if there is a significant inflammatory component.

Gastrointestinal symptoms may be amenable to certain measures such as elevation of the head end of the bed, eating small frequent meals in the upright position and taking an early dinner. Proton pump inhibitors such as omeprazole have revolutionized the management of
reflux esophagitis. Cisapride and metoclopramide may also be useful. Esophageal strictures may need periodic dilatation. Chronic diarrhoea due to small bowel stasis and bacterial overgrowth responds to broad spectrum antibiotic.

Steroids and cyclophosphamide may arrest the progression of active interstitial lung disease. No specific treatment is recommended for mild non-progressive interstitial lung disease. Advanced lung fibrosis may demand nothing short of lung transplantation. Pulmonary hypertension is a dreaded complication of scleroderma and tends to be refractory to treatment.

Scleroderma renal crisis usually develops suddenly and requires prompt treatment. The drug of choice is an ACE inhibitor, because excessive stimulation of the renin-angiotensin system is the causative mechanism. This approach has dramatically changed the outcome from a non-year survival of 15% to 80%.

**PROGNOSIS AND SURVIVAL**

A poorer prognosis is seen in males and in patients with disease onset after the age of 45 years. Patients with lung, renal, or cardiac involvement have the worst prognosis. Patients with diffuse cutaneous involvement more frequently develop scleroderma renal crisis. Survival has been reported to be between 50% and 70% at 5 years and between 40% and 60% at 10 years. However, these reports predate the use of angiotensin-converting-enzyme (ACE) inhibitors and do not distinguish between diffuse and limited subsets. Renal disease formerly was the leading cause of morbidity and mortality in patients with systemic sclerosis. Since the introduction of ACE inhibitors, lung disease has become the major challenge.