

# Autoimmune Resource & Research



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## Scleroderma

Scleroderma is one of a group of chronic autoimmune diseases including systemic lupus erythematosus and Sjögren's syndrome. These diseases form a spectrum, and feature various combinations of the same set of symptoms. Skin thickening is the hallmark of the disease. Traditionally, the term "scleroderma" has encompassed two groups: "localised scleroderma", where problems are confined to the skin, and "systemic sclerosis", where internal organs and vessels are involved as well as the skin.

### Localised Scleroderma

Localised scleroderma includes a heterogeneous group of conditions characterised by circumscribed, patchy, or linear scleroderma without the typical serological and visceral manifestations of systemic sclerosis (see below). This condition should not be confused with limited cutaneous scleroderma (CREST), which is a systemic variety of scleroderma. Localised scleroderma primarily affects children and young adults, especially females.

### Morphoea

Localised scleroderma is characterised by one or more erythematous or violaceous areas of the skin which evolve to become sclerotic and waxy. Plaques may grow during the active phase up to several centimetres in diameter with violaceous inflammatory borders, before spontaneously softening after several months to a few years.

### Linear Scleroderma

In linear scleroderma, sclerotic lesions appear as linear streaks or bands, usually on the upper or lower extremities and less commonly on the trunk or forehead. If the fronto-parietal scalp is involved ("en coup de sabre"), disfiguring facial asymmetry and hemiatrophy may occur, while joint contractures and neurovascular involvement may occur if linear scleroderma crosses a joint.

Lesional histology in both of these conditions reveals excessive dermal collagen and cellular infiltration with lymphocytes, plasma cells and histiocytes. Inflammation and fibrosis may extend to the deep fascia, muscle, and rarely, underlying bone. During the active phase of disease, investigations may reveal a modest peripheral eosinophilia, antinuclear antibodies (especially anti-single-stranded DNA) and positive rheumatoid factor.

No treatment has been uniformly successful for these conditions. Transition from the localised variety to systemic sclerosis is very rare, as is co-existence of the two diseases.

### Systemic Sclerosis

Systemic sclerosis is a global disease with an incidence of 1-2 in 100,000 predominantly affecting women (female:male = 4:1) between the ages of 30 and 60 years. Patients and their relatives have detectable antinuclear antibodies, implying a genetic susceptibility that is probably related to HLA haplotypes. However, environmental factors are also important, as evidenced by the identification of certain chemical agents which cause scleroderma (Table 1). Augmentation mammoplasty was linked with scleroderma on the basis

of early anecdotal reports, but several large trials have recently argued against a strong link between the two entities.

Table 1: Chemical agents implicated in the development of scleroderma	
<ul style="list-style-type: none"> <li>• Organic chemicals               <ul style="list-style-type: none"> <li>○ aliphatic hydrocarbons (e.g. vinyl chloride, trichloroethylene)</li> <li>○ aromatic hydrocarbons (e.g. benzene, toluene)</li> </ul> </li> <li>• Epoxy resins</li> <li>• Toxic oil (aniline-treated rapeseed oil)</li> <li>• Silica, in stone masons, coal miners, gold miners</li> <li>• Foam insulation (urea-formaldehyde)</li> <li>• Drugs (e.g. L-tryptophan, bleomycin, cocaine, pentazocine, appetite-suppressants)</li> </ul>	

### Differential Diagnosis

It is important to consider many different conditions in the differential diagnosis of scleroderma which may cause similar clinical features (Table 2).

Table 2: Scleroderma-Like Syndromes	
Immunological/Inflammatory	<ul style="list-style-type: none"> <li>• Chronic graft-versus-host disease</li> <li>• Eosinophilic fasciitis</li> <li>• Overlap syndromes (eg with rheumatoid arthritis and SLE)</li> <li>• Undifferentiated connective tissue disease</li> </ul>
Metabolic	<ul style="list-style-type: none"> <li>• Scleroderma of Buschke with or without</li> <li>• Scleromyxoedema paraproteinaemia</li> <li>• Insulin-dependent diabetes mellitus (digital sclerosis)</li> <li>• Carcinoid syndrome</li> <li>• Amyloidosis</li> <li>• Acromegaly</li> <li>• Lichen sclerosis et atrophicus</li> </ul>

	<ul style="list-style-type: none"> <li>• Acrodermatitis chronica atrophicans</li> </ul>
Inherited	<ul style="list-style-type: none"> <li>• Phenylketonuria</li> <li>• Porphyrrias</li> <li>• Premature aging syndromes (eg progeria, Werner's syndrome)</li> </ul>
Localised	<ul style="list-style-type: none"> <li>• Idiopathic pulmonary fibrosis</li> <li>• Amyloidosis</li> <li>• Sarcoidosis</li> <li>• Infiltrating carcinomas</li> <li>• Infiltrating cardiomyopathy</li> <li>• Oesophageal and intestinal hypomotility syndromes</li> <li>• Lichen sclerosis et atrophicus</li> <li>• Acrodermatitis chronica atrophicans</li> </ul>

### Clinical Presentation

Typically, patients present with tight skin, Raynaud's phenomenon, and painful joints. Swallowing difficulties and gastro-oesophageal reflux may also occur early in the disease. The duration of symptoms and signs help to place the patient into one of the two major subsets, the relatively benign limited form or the aggressive diffuse form of systemic sclerosis (Table 3). A subgroup of patients present without skin changes and sometimes without Raynaud's, but with features associated with scleroderma and positive autoantibodies. These people with "scleroderma sine scleroderma" may present with oesophagitis, malabsorption, pseudo-obstruction, renal failure, cardiac arrhythmias, and interstitial lung disease. A minority of patients present with primary Raynaud's phenomenon associated with positive autoantibodies and abnormal nailfold capillaries. These "pre-scleroderma" patients may be developing more classical systemic sclerosis.

Table 3: Spectrum of Disease in Systemic Sclerosis	
Diffuse cutaneous systemic sclerosis	<ul style="list-style-type: none"> <li>• Onset of skin changes (puffy or hidebound) within 1 year of onset of Raynaud's phenomenon</li> <li>• Truncal and acral skin involvement</li> </ul>

	<ul style="list-style-type: none"> <li>• Tendon friction rubs</li> <li>• Early and significant incidence of interstitial lung disease, oliguric renal failure, diffuse gastrointestinal disease, and myocardial involvement</li> <li>• Nailfold capillary dilatation and capillary drop-out</li> <li>• Anti-topoisomerase I (Scl-70) antibodies in 30% Limited cutaneous systemic sclerosis (CREST)</li> <li>• Raynaud's phenomenon for years (occasionally decades)</li> <li>• Skin involvement limited to hands, face, feet, and forearms (acral) or absent</li> <li>• Significant late incidence (10-15 years) of pulmonary hypertension, with or without interstitial lung disease, skin calcifications, telangiectasia, and gastrointestinal involvement</li> <li>• High incidence of anti-centromere antibody (ACA) (70-80%)</li> <li>• Dilated nailfold capillary loops, usually without capillary drop-out</li> </ul>
Scleroderma <i>sine</i> scleroderma	<ul style="list-style-type: none"> <li>• Raynaud's phenomenon (may or may not be present)</li> <li>• No skin involvement</li> <li>• Presentation with pulmonary fibrosis, scleroderma renal crisis, cardiac disease, gastrointestinal disease</li> <li>• Antinuclear antibodies may be present (Scl-70, ACA, nucleolar)</li> </ul>
Pre-scleroderma	<ul style="list-style-type: none"> <li>• Raynaud's phenomenon plus nailfold capillary changes. Circulating autoantibodies (Scl-70, ACA, nucleolar)</li> </ul>

### Limited Cutaneous Systemic Sclerosis

Limited cutaneous systemic sclerosis is also known as CREST syndrome, an acronym referring to the combination of Calcinosis, Raynaud's, Esophageal dysmotility, Sclerodactyly, and Telangiectasia. Isolated Raynaud's may be present for years to decades before the insidious development of mild skin thickening limited to the distal extremities and face. Although the behaviour of CREST is generally far more benign than that of the diffuse variety, two important complications may occur after 10 to 15 years of disease: small bowel involvement producing malabsorption, and primary pulmonary hypertension. This occurs in about 10% of such patients and is not secondary to pulmonary fibrosis, which is rare in this patient subset. Mean survival after the detection of pulmonary hypertension is two years, with no effective therapy yet available.

## Diffuse Cutaneous Scleroderma

Whereas skin involvement in CREST is mild and gradual, diffuse scleroderma is characterised by rapid progression of significant skin thickening, especially over the first 1 to 3 years, after which progression slowly plateaus. This is accompanied by restriction of mobility in tendons, joints, and muscles, with contractures and ulceration, as well as impaired eye closure, mouth opening, and even respiration, through chest-wall involvement. Tendon friction rubs are an ominous sign which may antedate rapid skin thickening or visceral involvement. Gastrointestinal involvement can cause dry mouth (sicca), oesophageal dysmotility with reflux, gastroparesis and bowel hypomotility with malabsorption. 70% of patients develop some degree of pulmonary fibrosis, which is the commonest cause of death directly related to scleroderma. The pulmonary hypertension occurring secondary to interstitial lung disease is generally milder than the primary form seen in CREST. 15-20% of patients with diffuse disease develop scleroderma renal crisis, which tends to occur in the first five years of disease and is usually (but not always) heralded by the abrupt onset of malignant hypertension associated with microangiopathic haemolysis. Angiotensin-converting-enzyme (ACE) inhibitors play a vital role in the management of this complication. Less commonly, pericarditis, biventricular failure and arrhythmias can complicate the illness.

## Prognosis

After 5 years of illness (the "late" stage of diffuse disease), skin and musculoskeletal problems plateau and there is a reduced risk of new organ involvement, but existing visceral disease may still slowly progress. The five-year cumulative survival rate is about 70%, but this figure rises or falls depending on whether renal, lung, or heart disease co-exists.

## Pathophysiology

The exact cause of disease is unknown, but it is believed to be due to an interplay between immunological, vascular, and connective tissue abnormalities occurring in genetically predisposed individuals.

- **Immunological:** Over 80% of patients have detectable autoantibodies (Table 4). 50% of patients have dermal infiltration by T and B cells and macrophages.
- **Vascular:** Primary capillary abnormalities may induce platelet activation, thrombus formation, and vasculitis. There is capillary intimal proliferation and serological evidence of endothelial damage (e.g. raised levels of endothelin-I and Von Willebrands Factor). In scleroderma renal crisis, renal vessels display fibrinoid necrosis ("onion-skinning"). Nailfold capillaroscopy reveals capillary drop-out and dilatation.
- **Connective-Tissue:** Fibroblasts from these patients make excessive amounts of collagen in tissue culture. This may be related to cytokine imbalances, such as excesses of IL-1 and IL-2.
- **Genetic:** HLA associations exist (e.g. anti-centromere antibodies and HLA-DR1) but are relatively weak. The tightskin mouse, an animal model of scleroderma, has a mutation of chromosome 2.

## The Role of the Immunology Laboratory

In practical terms, anti-nuclear antibody (ANA), extractable nuclear antigens (ENA), and double-stranded DNA (dsDNA) antibodies should be requested. The ANA screen will be positive in over 80% of scleroderma patients. The detection of the extractable nuclear antigens RNP, Scl-70, and Pm-Scl will increase diagnostic specificity and provide prognostic information. For example, Scl-70 predicts an increased likelihood of pulmonary interstitial involvement. Antibody testing for dsDNA should be performed to exclude systemic lupus erythematosus, which may present with any of the above clinical features. The major types of autoantibodies and their associations are listed in Table 4.

Table 4: Major Autoantibodies in Scleroderma			
ANA Pattern	Antigen	Associations	Organ Involvement
Centromere (ACA)	Centromere (kinetochore)	CREST: 60% sensitive 98% specific	Pulmonary hypertension
Nucleolar -speckled	Scl-70 (topoisomerase-I)	Diffuse:38% sensitive 100% specific	Pulmonary fibrosis
- homogeneous	Pm-Scl (nucleolin)	Overlap with myositis	Myositis
-clumpy	Fibrillarin (U3RNP)	Overlap with myositis	Pulmonary hypertension Myositis
Speckled	U1RNP	Mixed Connective Tissue Disease	Raynaud's, myositis, serositis, arthritis

### Disease Management

The chronicity of this disease makes a holistic approach important. Problems in coping with the diagnosis and living with the fatigue and other inconveniences the disease brings should be anticipated. Patient support groups are often valuable for encouragement as well as education.

Raynaud's may be controlled by maintaining warmth, especially of the central body, as well as avoiding smoking,  $\beta$ -blockers, and other exacerbating factors. Sometimes calcium blockade, topical nitrates, and even parenteral vasodilators are required. Sympathectomy offers temporary relief in many cases. Scrupulous skin care and moisturisation is essential. ACE inhibitors play a major role in the management of scleroderma-related hypertension.

A number of agents have been shown to modulate disease in uncontrolled trials, including penicillamine, cyclosporin, methotrexate and colchicine. However, none of these agents are of proven efficacy, and all of them have significant potential side effects.

### References

1. The Oxford Textbook of Medicine. Weatherall DJ, Ledingham JGG, Warrell DA. Oxford University Press 1996. Volume 3, p.3027
2. Primer on the Rheumatic Diseases, 9th Edition. Arthritis Foundation, Atlanta, Georgia, 1988.p.111

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