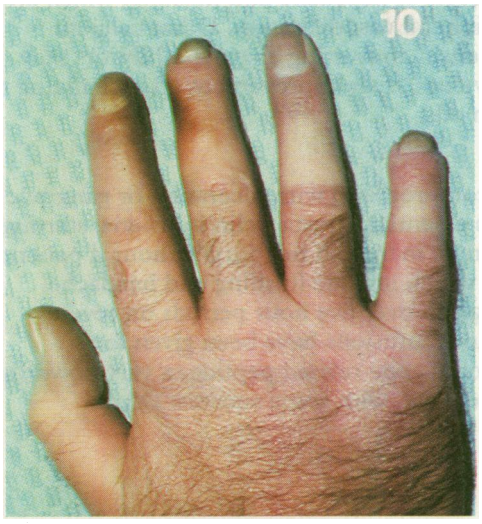
RAYNAUD'S PHENOMENON, SCLERODERMA, AND OVERLAP SYNDROMES

David A Isenberg, Carol Black

Raynaud's phenomenon



Well defined blanching of skin characteristic of Raynaud's phenomenon.

Several rheumatological conditions are linked to impaired peripheral circulation. These abnormalities may take various forms, including chilblains, acrocyanosis, and Raynaud's phenomenon. This last condition, described by the French clinician Maurice Raynaud in 1862, occurs in up to 5% of an otherwise healthy population, but may be a link between certain autoimmune rheumatic diseases. Raynaud's disease refers to the development of trophic changes as a result of microcirculatory damage and prolonged local ischaemia. Fortunately, gangrene is relatively rare, and, because patients are often young, recovery may be remarkable.

Disturbances of peripheral circulatory system

Chilblains—Painful, burning or itching erythematous lesions of hands or feet (rarely ulceration) precipitated by damp and cold (especially if inadequate clothing worn)

Acrocyanosis—Persistent cold, blue, and rather sweaty appearance, usually of hands

Raynaud's phenomenon—Episodic, clearly demarcated two or three phase colour change—white (ischaemia), then often blue (stasis), then red (reactive hyperaemia)—of fingers and sometimes toes (rarely nose, tongue, or ears) in response to cold or, less often, emotion

Prevalence of Raynaud's phenomenon in autoimmune rheumatic diseases

Rheumatoid arthritis	<5%
Systemic lupus erythematosus	20-30%
Sjögrens syndrome	20-30%
Myositis	25%
Scleroderma	>95%

Raynaud's phenomenon as a predictor of autoimmune rheumatic disease

Over 90% of patients with Raynaud's phenomenon are female and, at the time of presentation, are often aged under 25. Up to 5% of patients presenting with the condition eventually develop an autoimmune rheumatic disease. The presence of abnormal nail fold capillaries (detected by capillaroscopy) and antinuclear antibodies are of particular value in predicting this development.

Points to consider when looking for underlying cause of Raynaud's phenomenon

- Occupation—working outdoors, using vibrating tools, exposure to chemicals such as vinyl chloride
- Examination of peripheral and central vascular system for proximal vascular occlusion
- Drugs—such as β blockers, ergotamines, oral contraceptives, bleomycin
- Symptoms of other connective tissue disorders:

Arthralgia or arthritis	Alopecia	Skin rashes
Cerebral symptoms	Photosensitivity	Dry eyes or mouth
Mouth ulcers	Muscle weakness	Respiratory or cardiac problems

Investigations of patients with Raynaud's phenomenon to test for autoimmune rheumatic disease

- Full blood count and erythrocyte sedimentation rate
- Total immunoglobulin and electrophoresis strip
- Urine analysis
- Renal and liver function tests
- Nail fold capillaroscopy
- Test for antinuclear antibody
- Chest *x* rays
- Hand *x* rays

Primary and secondary Raynaud's phenomenon are distinguished by a combination of clinical examination and laboratory investigations. Physical examination should include assessment of peripheral pulses, measurement of blood pressure in both arms, and examination of the neck for the tenderness often associated with a cervical rib. A negative test for antinuclear antibody in an otherwise healthy patient is reassuring but does not completely exclude subsequent development of an autoimmune rheumatic disease. Different types of antinuclear antibody may be specific for certain diseases and so may help in diagnosis. Plethysmography, Doppler ultrasonography, and laser Doppler flowmetry with direct capillaroscopy and thermal entrainment have been used to measure vascular phenomena objectively.

Patient support organisations

The Raynaud's and Scleroderma Association Trust

- 112 Crewe Road, Alsager, Cheshire ST7 25A
Telephone (01270) 872776

The Scleroderma Society

- 61 Sandpit Lane, St Albans, Hertfordshire AL1 4EY
Telephone (01727) 55054

Drugs for treating Raynaud's phenomenon

- Nifedipine (Adalat Retard 20 mg daily)
- Diltiazem hydrochloride 60 mg thrice daily
- Nicardipine hydrochloride 20 mg thrice daily
- Felodipine 5-10 mg daily
- Isradipine 1 mg twice daily, increasing to 2 mg twice daily after four weeks if necessary
- Concentrated fish oils (Maxepa 5 capsules twice daily)
- Gamolenic acid (Epogam 4-6 capsules twice daily)
- Captopril 6·25 mg daily, increasing to 18·75 mg or 25 mg daily if necessary

Management

Raynaud's phenomenon can be helped by general measures, most importantly by stopping smoking. Patients should also avoid known exacerbating factors such as exposure to cold (patients should wear very warm gloves and socks) and use of vibrating tools. A variety of warming devices such as electrically heated gloves are available, and relevant information can be obtained from patient support organisations.

Some patients with primary Raynaud's phenomenon and most with the condition secondary to an underlying autoimmune rheumatic disease require drug treatment. Nifedipine, a calcium channel blocker, is often helpful. The modified release preparation is preferable as it reduces the common side effects of headache and flushing, which are due to central as well as peripheral vasodilatation. Other calcium channel blockers and angiotensin converting enzyme inhibitors may also help. Some patients have noted an improvement after changing to diets supplemented with fish oils.

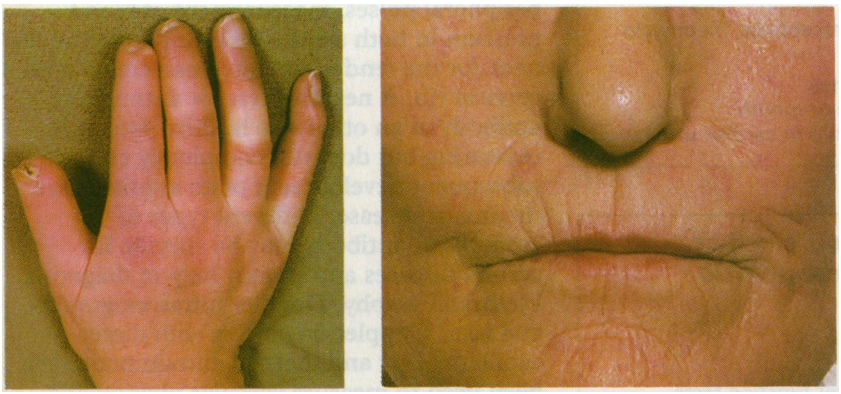
When tissue nutrition is compromised with ulceration or gangrene intravenous vasodilatation is essential. Prostacyclin infusions, starting with about 5 μg/kg/hour, can be increased to 15 μg/kg/hour if patients can tolerate the side effects, which include flushing and headache. These infusions are usually given over five hour periods on several successive days, but continuous infusions have been given for impending gangrene. Calcitonin gene related peptide, a very powerful vasodilator, is currently under trial, with some success. Digital sympathectomy may also be of value.

Scleroderma (systemic sclerosis)

Characteristic findings and suggested treatment for limited cutaneous scleroderma

Early stage (≤10 years after onset)
Constitutional symptoms—None
Skin thickening—No or minimal progression
Organs affected—Raynaud's phenomenon, ulcers of digital tips, oesophageal symptoms
Treatment—Vascular treatment (oral or intravenous) with or without digital sympathectomy, removal of calcinosis, treat oesophageal problems

Late stage (>10 years after onset)
Constitutional symptoms—Secondary to complications below
Skin thickening—Stable
Organs affected—Raynaud's phenomenon, ulcers of digital tips. calcinosis, oesophageal structure, small bowel malabsorption, pulmonary hypertension
Treatment—Vascular treatment (oral or intravenous) with or without digital sympathectomy, removal of calcinosis, treat oesophageal and midgut problems



Characteristic features of limited cutaneous scleroderma: (left) puffy fingers, tight skin, Raynaud's phenomenon, loss of distal digits, and ulceration of tips of digits; (right) microstomia and telangiectasia.

The term scleroderma encompasses a spectrum of disorders that includes localised scleroderma (morphea), which mainly causes dermal fibrosis; juvenile scleroderma, which is usually localised but can present with systemic disease; and scleroderma-like disorders. The diagnosis of scleroderma should be doubted in the absence of Raynaud's phenomenon. There are two main subsets of scleroderma according to the duration of Raynaud's phenomenon before the start of symptoms and signs suggestive of scleroderma.

Limited cutaneous scleroderma

Patients who develop this condition (previously called CREST) may have Raynaud's phenomenon for years before the appearance of the condition's characteristic symptoms: calcium deposits in the skin, painful digital scars and ulcers, dilated blood vessels (telangiectasia), and oesophageal dysmotility and reflux. There are few if any constitutional symptoms, and skin fibrosis is often restricted to sclerodactyly and microstomia, with minimal progression. Raynaud's phenomenon, pitting scars, digital ulcers, and telangiectasia can all be troublesome, and oesophageal symptoms are common. Patients may not be aware of the thickening of their fingers, but unsightly puckering, wrinkling and tightening of the skin around the mouth are soon noticed.

Characteristic findings and suggested treatment for diffuse cutaneous scleroderma

Early stage (≤5 years after onset)

Constitutional symptoms—Fatigue, weight loss

Skin thickening—Rapid progression

Organs affected—Risk of renal, cardiac, pulmonary (fibrosis), gastrointestinal, articular, and muscular damage

Treatment—Immunosuppression, antifibrotic treatment, vasodilation, physiotherapy, and occupational therapy as appropriate

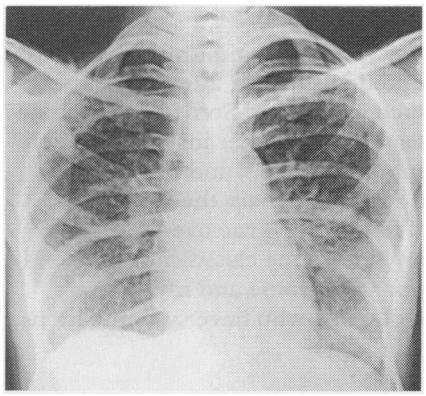
Late stage (>5 years after onset)

Constitutional symptoms—None

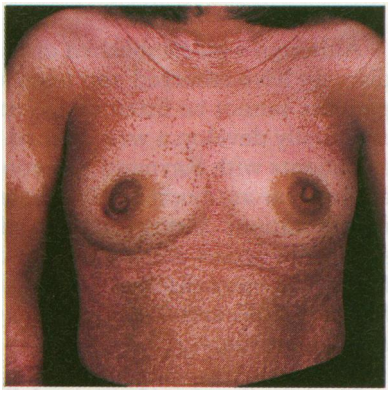
Skin thickening—Stable or regression

Organs affected—Musculoskeletal defmormities, progression of existing visceral diseases but reduced risk of new conditions

Treatment—Treat complications, reduce antifibrotic treatment, continue vascular treatment



Chest radiograph of diffuse interstitial lung disease in patient with scleroderma.



Hypopigmentation caused by diffuse cutaneous scleroderma.

Subsets of scleroderma

Limited cutaneous scleroderma

- Raynaud's phenomenon for years (sometimes decades) before start of scleroderma
- Skin is affected only at the extremities (hands, face, feet, and forearms) or is not affected
- Substantial proportion of patients develop pulmonary hypertension of late onset (after 10-15 years) with or without interstitial lung disease, skin calcifications, telangiectasia, and gastrointestinal symptoms
- High prevalence of anticentromere antibodies (70-80%)
- Dilated capillary loops of nail folds, usually without capillary dropout

Diffuse cutaneous scleroderma

- Start of skin changes (puffy or hidebound) within one year of start of Raynaud's phenomenon
- Skin of trunk and extremities affected
- Presence of tendon friction rubs
- Substantial proportion of patients have early onset of interstitial lung disease, oliguric renal failure, diffuse gastrointestinal disease, and myocardial disease
- Dilated capillaries of nail folds and capillary dropout
- Antibodies to scleroderma-70 (topoisomerase-1) in 30% of patients

"Scleroderma sine scleroderma"

- Raynaud's phenomenon may or may not be present
- Skin not affected
- Presents with pulmonary fibrosis, scleroderma renal crisis, cardiac disease, and gastrointestinal disease
- Antinuclear antibodies (scleroderma-70, anticentromere, and antinucleolar antibodies) may be present

In the last stage of this condition the vascular disease often worsens, with widespread telangiectasia, ulcers and calcinosis, and pulmonary hypertension. Pulmonary interstitial disease may occur as a late complication. Visceral symptoms can worsen, with development of oesophageal strictures, small bowel disease, malabsorption, pseudo-obstruction, and anal incontinence. About half of all patients with scleroderma have the anticentromere antibody, but it is much more common with limited cutaneous scleroderma.

Diffuse cutaneous scleroderma

Patients destined to develop this condition often have a short history and abrupt onset of Raynaud's phenomenon, and their skin is oedematous and itchy. During the first five years of diffuse disease (early phase), patients are weary and ill and lose weight. Arthritis, myositis, and tendon involvement are common. The fibrotic phase rapidly follows and can extend to affect most areas of skin except for the middle and lower back and buttocks. Hyperpigmentation and hypopigmentation may occur, the latter being more obvious in non-white patients. Rapid progression of skin disease is accompanied by increased risks of renal failure (often presenting as hypertensive renal crisis) and of pulmonary interstitial, early cardiac, and gastrointestinal disease.

After about five years (late phase) the constitutional symptoms usually subside. This atrophic phase may last for many years; musculoskeletal problems lead to deformity and wasting and existing visceral disease often progresses, though the risk of new organs being affected is reduced. Antibodies to scleroderma-70 (topoisomerase-1) are found in 25% of patients overall but are more characteristic of diffuse cutaneous scleroderma.

"Scleroderma sine scleroderma"

Some patients have scleroderma without their skin being affected, although they may have Raynaud's phenomenon. Patients present with complications of an internal organ such as restrictive pulmonary disease, cardiac failure, hypertensive renal crisis, or malabsorption and pseudo-obstruction. The presence of anticentromere, scleroderma-70, or antinucleolar antibodies can be helpful in making a definitive diagnosis.

Treatment

Although there is no cure for scleroderma, management tailored to the stage and subset of the disease can improve quality and length of life. Treatments include those for Raynaud's phenomenon itself, angiotensin converting enzyme inhibitors (such as captopril) for hypertension, omeprazole for oesophageal reflux, and digital sympathectomy for a critically ischaemic finger.

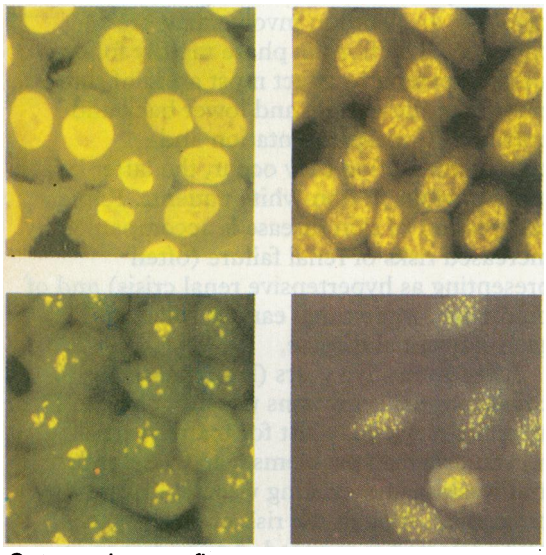
Management of scleroderma

- Explanation and support—scleroderma is chronic and distressing for patients and their families
- Treat vascular abnormalities as for Raynaud's phenomenon
- Treat individual symptoms (such as omeprazole for oesophagitis)
- In early phase of diffuse form use immunosuppressive drugs (cyclophosphamide, methotrexate, antihymocyte globulin)
- In later stages consider antifibrotic drugs (such as penicillamine, interferon)

If the diffuse form of the disease is identified in its early oedematous stage, immunosuppressive agents such as cyclophosphamide, methotrexate, and antithymocyte globulin are probably appropriate, followed by an antifibrotic drug such as penicillamine or interferon alfa or beta. Some of these drugs are used only in specialist centres in clinical trials, and early referral to such centres is strongly recommended. Fibrosis in the lungs, heart, and gut may develop after the skin changes stop progressing, which argues for long term use of an antifibrotic drug. The drug should not be withdrawn until the disease has been quiescent for at least a year.

The complications associated with internal organs being affected—such as cardiac arrhythmias, hypertensive renal crisis, pulmonary vascular disease, bacterial overgrowth, and oesophageal reflux—must be treated individually. Scleroderma is usually a lifelong and potentially life threatening disease. It requires accurate staging, suitable treatment, and sympathetic management, with emotional and physical support for patients and their families.

Overlap syndromes



Common immunofluorescent patterns seen on testing for antinuclear antibodies: (top left) *homogeneous*—typical of antibodies to DNA, with or without histones; (top right) *speckled*—typical of antibodies to Ro, La, Sm, and RNP; (bottom left) *nucleolar*—typical of scleroderma; (bottom right) *centromere*—mainly found with limited cutaneous scleroderma.

Links between various antinuclear antibodies and autoimmune rheumatic diseases

Antibodies to Jo-1
Jo-1 antigen is a tRNA histidyl synthetase
Antibodies are present in about 30% of patients with myositis

Antibodies to scleroderma-70
Antigen is topoisomerase-1, a DNA charging enzyme
Antibodies are present in about 25% of patients with scleroderma

Antibodies to Sm, RNP, Ro, and La
Antigens are varying combintions of RNA and protein
Antibodies to Sm are present in 5-30% of patients with systemic lupus erythematosus
Antibodies to Ro and La are present in many patients with systemic lupus erythematosus or Sjögrens syndrome

Antibodies to RNA
Antibodies are not disease specific

Although well established criteria for various autoimmune rheumatic diseases have emerged and been accepted in the past 20 years, some patients cannot be fitted easily into such categories. Some patients may eventually develop a well defined disease, but in other instances—such as patients with Raynaud's phenomenon, arthralgia, and presence of antinuclear antibodies only—isolated features remain the sole manifestations during long periods of follow up. True overlap syndrome occurs when a patient clearly meets the classification criteria for two or more diseases. Thus, Sjögen's syndrome and myositis are found in 20% and 5% respectively of patients who have systemic lupus erythematosus.

Historically, classification of disease has been based on particular clinical features, which are later supported by autoantibody or biochemical markers. The only exception to this general rule was the attempt made some 20 years ago to distinguish a group of patients primarily by their high titres of antibodies to ribonucleic protein. This condition—termed mixed connective tissue disease—was thought to represent a distinct rheumatic disease, with patients having a combination of arthralgias, swollen hands, Raynaud's phenomenon, oesophagitis, and myositis but lacking cerebral, pulmonary, or renal involvement. It has since become clear that many patients have antibodies to ribonucleic protein but lack these particular clinical features. In addition, other patients have these clinical features but lack this antibody specifically, and many patients who initially seem to fit this classification eventually develop scleroderma (usually) or systemic lupus erythematosus (occasionally). For this reason the term undifferentiated autoimmune rheumatic disease (or undifferentiated connective tissue disease) is often preferred.

Treatment of patients with overlapping autoimmune rheumatic diseases is largely based on each individual's symptoms. Raynaud's phenomenon that occurs in these patients is treated no differently from severe idiopathic disease or Raynaud's phenomenon complicating other autoimmune rheumatic problems. Similarly, myositis in these patients will be treated by the conventional corticosteroids and other immunosuppressive drugs (notably azathioprine, methotrexate, or cyclophosphamide). Oesophagitis in these patients is treated in the same way as in those who have sclerodactyly or scleroderma.

The box of subsets of scleroderma is adapted from E C LeRoy *et al, J Rheumatol* 1988;15:202-5.

David A Isenberg is professor of rheumatology in the division of rheumatology, University College London, and Carol Black is professor of rheumatology in the division of rheumatology, Royal Free Hospital, London.

The ABC of Rheumatology is edited by Michael L Snaith, senior lecturer in rheumatology at Nether Edge Hospital, Sheffield.