Regressive systemic sclerosis

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SUMMARY Systemic sclerosis is a disease which usually progresses or reaches a plateau with persistence of symptoms and signs. Regression is extremely unusual. Four cases of established scleroderma are described in which regression is well documented. The significance of this observation and possible mechanisms of disease regression are discussed.

Systemic sclerosis is a multisystem disease the prognosis of which is difficult to assess because of its episodic nature, protean presentations, and clinical features.¹

The usual course of the condition is one of progression for several years after the onset, especially in the skin, soft tissues, and gastrointestinal tract. In many cases it seems to reach a plateau with little or no further change but persistence of the features that have developed; in others it continues to worsen, hence the synonym 'progressive systemic sclerosis' was in common usage until recently.²

We report four cases in which the disease has got better after reaching an initial plateau. In each case the signs of systemic sclerosis receded dramatically over a period of years. Their condition might reasonably be called 'regressive systemic sclerosis'. It is important to recognise that this disease can improve spontaneously in a small percentage of patients.

Case reports

CASE 1

A female patient developed scleroderma in 1944 at the age of 26. When first seen by one of us (FDH) in 1948 she had advanced sclerotic changes affecting fingers, hands, arms, feet, legs, face, neck, and chest wall. Her knees were fixed in 90° flexion, the fingers clawed, the skin tight, shiny, and atrophic, and scarred by continuing extrusion of calcified material (Fig. 1). She was largely confined to bed and chair, was unable to walk, and suffering from mild dysphagia. She was illustrated in Copeman's

Textbook of the Rheumatic Diseases and was the author's most severe case.³

From 1948 onwards she slowly and steadily improved on regular exercise, olive oil massage of the extremities, and general health measures. No drugs were used except for simple analgesics. Her dysphagia had disappeared by 1952.

By 1969 she had lost her flexion contractures of the knees, her fingers flexed and extended almost completely (Fig. 2), and she could walk upstairs and resume a normal life. Her main concern then was her diabetes mellitus, which developed in 1960, and her cataracts. 'My sclerosis' she said 'is no trouble'.

CASE 2

A 25 year old man presented in 1972 with a six week history of increased thickness of the skin of his hands and lower legs, typical of scleroderma. He had no Raynaud's phenomenon, calcinosis, or systemic manifestations. Skin biopsy specimens had an appearance consistent with a diagnosis of diffuse scleroderma. Autoantibodies at this time were negative. The condition progressed, the patient complained of Raynaud's disease and arthralgia, became stiffer, and atrophic changes developed on his legs. He was given a short course of systemic corticosteroids, but this was ineffective. Six months after presentation his total range of wrist movement was restricted to 30°. He was started on D-penicillamine 125 mg daily. One year after the onset of the condition he developed small nodules over both elbows, which on biopsy showed oedematous collagenous tissue with focal accumulations of lymphocytes, plasma cells, and histiocytes, features compatible with the early phase of scleroderma. He failed to respond to penicillamine, which was discontinued when he developed proteinuria after

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Fig. 1 The hands of patient No 1 in 1948, showing the severe flexion deformity of the fingers, tight scleroderma skin, and scarring from the extension of calcific material.

12 months' treatment. At this time his antinuclear factor (ANF) became positive (1/320). He has been kept under observation without any treatment over the last 10 years, during which his condition has gradually improved. His antinuclear antibody (ANA) titre is now 1/40 with a speckled pattern on immunofluorescence. He is in complete remission with no detectable abnormality of his skin.

CASE 3

Case No 3 (female) first developed Raynaud's phenomenon in November 1961 at the age of 23. Six

months later she noted thickening of the skin of the arms, neck, and thighs with generalised pruritis. She had polyarthrititis, myalgia, and intermittent dysphagia. In August 1962 she was admitted to hospital with fever, pruritic pain, and nail bed vasculitis. Skin changes involved the arms, neck, thighs, and face but spared the hands. There were flexion contractures at the elbows. The appearance of skin biopsy specimens taken from the left inner forearm was compatible with scleroderma. She had a mild restrictive pattern on lung function tests, with reduced carbon monoxide transfer factor. Proximal

Fig. 2 The hands of patient No 1 in 1969. Note the improved extension of the fingers and normal appearance of the skin.

muscle weakness and tenderness were noted clinically, and an electromyograph (EMG) was compatible with myositis. A barium swallow and renal function tests were normal and the ANF was negative. She was given high dose steroids, her systemic manifestations quickly resolved, and prednisone was discontinued after several months. Some five months later, in August 1963, she noted an increase in her skin thickness and flexion contractures at the elbows. She was given a six months course of ϵ -aminocaproic acid, with marked symptomatic and clinical improvement. She remained well, apart from persistent Raynaud's disease. In 1966 she was admitted for bilateral sympathectomy. A skin biopsy from the opposite forearm was performed at that time and was described as normal, as were the pulmonary function tests, electrocardiogram, and EMG. It was commented that there were no signs of scleroderma. Her Raynaud's disease responded well to the bilateral sympathectomy. Regular follow up was discontinued. In 1979 she was reviewed and found to be working full time, and asymptomatic apart from very mild Raynaud's disease. Clinically there was no evidence of systemic sclerosis and all serological studies were negative, except for weak ANA positivity and a speckled pattern of immunofluorescence on HEP₂ cells. A further review in 1983 showed her to be in complete remission.

CASE 4

A 20 year old man presented in 1973 with a 15 month history of gradually increasing stiffness of the hands. On examination he had typical sclerodactyly, with thickening of the skin, areas of pigmentation, and flexion deformities of the proximal interphalangeal joints. Wrist flexion and extension was reduced to 30° and grip strength was impaired. He had no Raynaud's disease at presentation, but this developed after six months. Telangiectasia and calcinosis were absent and there were no systemic features except a history of mild intermittent diarrhoea. Barium studies were normal. Investigations included a negative autoantibody screen. A skin biopsy of the left forearm showed thickened, hyalinised subepidermal collagen but no inflammation. The changes were consistent with scleroderma. He was treated with D-penicillamine 750 mg daily for the next six years. His scleroderma improved somewhat while on therapy but continued to regress after the drug was discontinued. He has now been off all therapy for five years and is completely free of all symptoms and signs of the disease. He has no skin thickening or restriction of joint movement, and grip strength is normal. A repeat forearm skin biopsy showed a normal dermis.

Discussion

Scleroderma is normally a disease in which irreversible changes occur in the structural elements of the connective tissue, and which once established persist even if they do not progress. Fibrosis is the ultimate hallmark of the disorder.¹ The signal for fibroblast proliferation and activity is not known, although genetic factors,^{4,5} endothelial damage,⁶ and environmental chemical factors^{7,8} have all been implicated.

The four cases described fulfilled the preliminary American Rheumatism Association criteria for systemic sclerosis.⁹ In addition, three of the four patients had confirmatory skin biopsies. All had an initial progressive phase which appeared to last for two to four years. This was followed by regression over a period of eight to 30 years, leading to resolution. The available clinical information is summarised in Table 1.

All shared the common clinical features of the disease such as sclerodactyly and Raynaud's phenomenon, though they did not all have the common serological markers. Circulating antinuclear antibodies are common in scleroderma,¹⁰ but in one of the three cases in which information is available no autoantibodies were detected at any stage of the disease. In the other two, testing with HEP₂ cells showed a speckled pattern of immunofluorescence, but no antibody to anticentromere or SCL-70 as described in a proportion of patients with CREST (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, telangiectasia) syndrome.¹⁰ Tissue typing was obtained in three cases (Table 1), two of whom carried the DR5 antigen, which is one of those associated with classical systemic sclerosis.¹¹

Excess production of collagen is responsible for many of the clinical factors observed in these patients.¹² In vitro fibroblast culture studies have shown that collagen production is susceptible to many cellular and serum factors.^{13,14} It is therefore possible that a vascular, serum, or environmental factor may have triggered the disease in these patients and then been removed. These cases could be analogous to polyvinyl chloride disease, in which there is slow regression of the cutaneous fibrosis and Raynaud's phenomenon after removal of a toxin which induces disease in a genetically susceptible host.¹⁵

There are two case reports of spontaneous improvement of the skin in acute scleroderma. In one case resolution occurred after haemodialysis,¹⁶ but in the other case no obvious factor was implicated and only skin signs resolved.¹⁷ Complete remission

Table 1 Clinical and serological data in four patients with 'regressive sclerosis'

Case No	Sex	Age of onset (years)	Progression of disease (No of years)	Regression period (years)	Skin	Drug	Autoantibody status	Tissue typing
1	F	26	4	30	Not done	None	Not known	Not known
2	M	25	2	10	Positive at onset	Steroids (6/12), D-Penicillamine (one year)	Anticentromere and anti SCL-70 negative. Became ANA positive (1/320) during disease activity. Now 1/40 positive, with fine speckled pattern	A2, A3, B44, B35, DR5
3	F	23	4	17	Positive at onset. Normal at five years	Steroids (9/12)	Weak positive ANA on HEP; cells with fine speckled pattern. No anticentromere or SCL-70 antibody	A30/31, A32/33, B17, B13, Cw3, C26, DR3
4	M	19	4	8	Positive at onset. Subsequently normal	D-Penicillamine (six years)	All serology negative throughout	A1, A2, B44, B37, Cw5, Cw6, DR4, DR5

of systemic sclerosis, with prolonged follow up has not previously been recorded.

Is there any logical explanation for the regression? Three of the four patients received a variety of drugs which could have altered the course of the disease. Only one patient (case 4), however, received prolonged therapy with a drug thought to be effective, but even he continued to improve after drug therapy was stopped.

The identification of patients with 'regressive systemic sclerosis' is important for two reasons. First, the occasional case of improvement during therapeutic trials cannot necessarily be attributed to therapy. Secondly, such cases may provide important clues to the aetiology and pathogenesis of this disorder, and perhaps of other fibrosing diseases. Critical sequential assessments are necessary in all patients if the relevant genetic, immunological, biochemical, and environmental factors are to be identified.

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