Systemic sclerosis: clinical features and management

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Abstract

There have been substantial recent advances in understanding the pathogenic mechanisms underlying systemic sclerosis (SSc) and this has facilitated more logical treatment approaches. There have been positive clinical trials for immunosuppression in SSc lung fibrosis, in digital vasculopathy and in pulmonary arterial hypertension. Advances in management have occurred for many of the organ-based complications of SSc. However, it remains a challenging and clinically diverse disease with a high mortality and substantial morbidity. Systemic sclerosis forms an important part of the scleroderma spectrum of disorders that includes localized forms of scleroderma and overlap syndromes that include clinical features of other autoimmune rheumatic diseases. Systemic sclerosis should not be considered untreatable and patient and physician education about potential treatments is an important aspect of management. Therapies must however be carefully matched to disease subset and to the stage of disease.

Keywords scleroderma; systemic sclerosis; pulmonary fibrosis; pulmonary arterial hypertension; autoantibodies; renal crisis

Systemic sclerosis (SSc) is a heterogeneous rheumatic disease within the scleroderma spectrum of disorders. Although the terms scleroderma and systemic sclerosis are often used synonymously, a distinction is appropriate, with the latter describing a family of conditions in which fibrosis of the skin and internal organs together with a microvasculopathy. The high case-specific mortality and similarities with much commoner forms of organ-based fibrosis make SSc important despite its relative rarity. These diverse conditions share a number of common clinical features, in particular thickening of the skin resulting from dermal fibrosis and a high frequency of episodic peripheral vasospasm (Raynaud's phenomenon). These shared features make it likely that common pathogenetic processes underlie the various disorders.[1]

Localized scleroderma – at one end of the spectrum is the localized form of scleroderma including linear scleroderma and morphoea. Although adult-onset morphoea may be a fairly mild complaint, primarily of cosmetic significance, some cases are severe and extensive with multiple areas, or plaques, of involved skin. This form of scleroderma is termed generalized morphoea and may necessitate treatment with systemic immunosuppression, although phototherapy or topical treatments including tacrolimus are also employed. Another context in which localized scleroderma is of major consequence is in childhood onset disease. There is often defective growth of underlying structures with substantial morbidity. Although optimal management remains unclear the need for effective treatment of affected children is widely appreciated. At present a combination of systemic steroids and methotrexate are the most frequently used systemic therapies.[2]

Systemic sclerosis – the systemic forms of scleroderma are most appropriately designated systemic sclerosis, although the two terms are often used synonymously. Further subclassification of systemic sclerosis is generally made according to the extent of skin involvement. Two major subsets are designated limited and diffuse cutaneous systemic sclerosis. Other forms include overlap syndromes in which there are features of other connective tissue disorders such as SLE, polymyositis or arthritis and forms in which there is little of no skin sclerosis despite other features of systemic sclerosis. These cases are designated systemic sclerosis sine scleroderma.[3] Almost all patients with systemic sclerosis manifest Raynaud's phenomenon. It is conventional therefore to include other forms of isolated Raynaud's phenomenon within the scleroderma spectrum. It can best be considered that one end of the spectrum manifests purely sclerotic pathology (localized scleroderma), the other only vasospasm (Raynaud's) and that coexistence of these two processes occupies the central scleroderma spectrum. Disorders that are included in the scleroderma spectrum are summarized in Table 1.

Clinical features

Systemic sclerosis has been classified according to a number of different systems but the most widely used is based upon the extent of skin sclerosis and recognizes two major subsets. The clinical features are as follows.

Limited cutaneous systemic sclerosis – typically presents with a long history of antecedent Raynaud's phenomenon, often severe and associated with recurrent digital ulceration. Other manifestations include oesophageal dysmotility and gastro-esophageal reflux. Skin involvement is limited to areas distal to the knees and elbows, and often to the wrists and ankles. Additional changes in the face and neck are usually present. Other hallmark features include cutaneous telangiectasis, often seen clearly on the palms and around the mouth, subcutaneous calcinosis. The constellation of calcinosis, Raynaud's phenomenon, oesophageal involvement and sclerodactyly has been termed CREST syndrome. This is potentially misleading as it ignores some important manifestions including mid-gut disease, pulmonary fibrosis and isolated pulmonary hypertension and the term limited cutaneous systemic sclerosis is preferred. Many patients carry anti-centromere antibodies although other hallmark reactivities including anti-fibrillarin, anti-topisomerase-1 and anti-RNA polymerase may also be present. Typical features of lcSSc are shown in Figures 1 and 2.

Diffuse cutaneous systemic sclerosis – there are a number of characteristics separating diffuse cutaneous SSc from lcSSc. The presenting features are often of abrupt onset and manifests as inflammatory changes in the skin and other structures. Pain and

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The spectrum of scleroderma and scleroderma-like disorders

Systemic sclerosis
- Limited systemic sclerosis*
- Limited cutaneous systemic sclerosis
- Diffuse cutaneous systemic sclerosis
- Systemic sclerosis sine *scleroderma*
- Scleroderma overlap syndromes

Localized scleroderma
- Plaque morphoea
- Generalised morphea
- Linear scleroderma
- *En coup de sabre*
- *Hemifacial atrophy* (*Parry-Romberg syndrome*)

Raynaud's phenomenon
- Primary
- Autoimmune*

Scleroderma-like disorders
- Eosinophilic fasciitis
- Scleromyxoedema
- Scleroedema of Buschke
- Scleroedema diabeticorum
- Graft versus host disease

*Limited systemic sclerosis implies presence of a specific scleroderma associated autoantibody and capillary damage and overlaps with autoimmune Raynaud's phenomenon in which ANA may be non-specific or characteristic of another autoimmune rheumatic disease.

Table 1

swelling of the extremities often occurs and may be mistaken for an inflammatory arthropathy. Expansion of tissues around the wrist is often associated with symptoms of median nerve compression and in some cases early scleroderma may cause bilateral carpal tunnel syndrome. Affected skin is often intensely pruritic

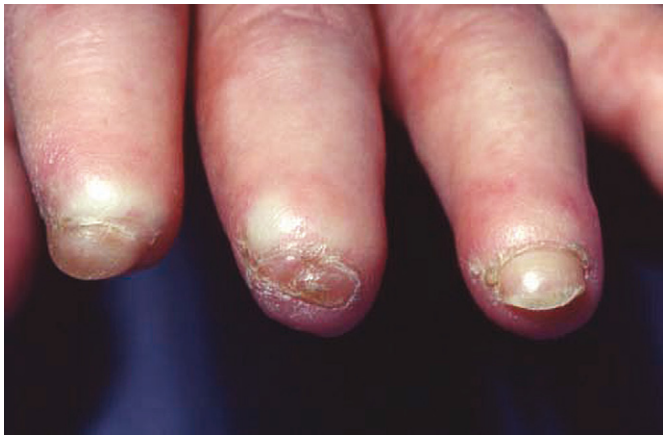

Figure 1 Sclerodactyly with digital pulp loss in established limited cutaneous systemic sclerosis.

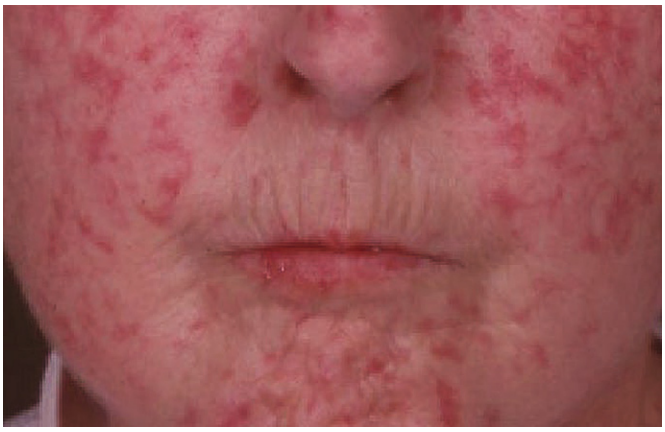

Figure 2 Perioral skin changes and widespread telangiectasis in limited cutaneous systemic sclerosis.

and there is loss of specialised skin structures leading to changes in the pattern of perspiration and loss of hair growth.

Symptoms of Raynaud's phenomenon are almost universal in dcSSc but may develop simultaneously with other features or once the disease is established. Although the clinical pattern of dcSSc is very distinct often including tendon friction rubs and skin inflammation it is sclerosis proximal to the elbows or knees in the limbs or affecting the trunk that ultimately determine classification as diffuse disease. Oesophageal involvement is almost always present and severe internal organ complications tend to occur earlier in dcSSc than in limited disease and lung fibrosis or hypertensive renal crises are relatively frequent. Many patients carry hallmark reactivities including of systemic sclerosis including anti-topisomerase-1, anti-RNA polymerase I and III anti Pm-scl, anti-fibrillarin or anti-nRNP. Features of dcSSc are shown in Figures 3 and 4.

Systemic sclerosis sine scleroderma – a small number of patients demonstrate typical vascular and serological features of SSc together with visceral complications such as lung fibrosis, hypertensive renal crisis or severe bowel involvement, but without any evidence of skin fibrosis. This group is termed SSc sine scleroderma and probably accounts for less than 1 % of cases although it may well be under diagnosed.

Limited systemic sclerosis – it is widely appreciated that the preliminary classification criteria of the American College for

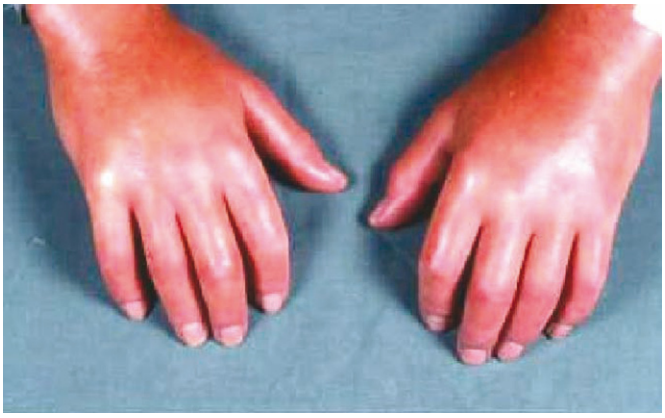

Figure 3 The hands of a patient in early stage diffuse cutaneous systemic sclerosis.