Systemic sclerosis: clinical features and management

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Abstract

Systemic sclerosis (SSc) is an autoimmune rheumatic disease within the scleroderma spectrum of disorders. It is the prototypic multi-system fibrotic disease with important complications that also result from vasculopathy and inflammation. There have been substantial recent advances in understanding the pathogenic mechanisms underlying SSc, which has facilitated more logical treatment approaches. While it remains the rheumatic disease with the highest case-specific mortality, there have been important advances in the management of organ-specific complications, with emerging clinical evidence supporting the use of immunosuppression, and novel therapeutic approaches for the management of pulmonary arterial hypertension (PAH). Systemic sclerosis should not be considered untreatable, and patient and physician education about potential treatments is an important aspect of management. However, therapies must be carefully matched to disease subset and to the stage of disease.

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

What's new?

- Modern molecular biology and genetics techniques have contributed significantly to the understanding of disease pathogenesis
- Preclinical studies on the involvement of inflammatory cytokine IL-6, are being translated into clinical trials using IL-6 receptor inhibition
- Modern management of pulmonary arterial hypertension using targeted therapies has dramatically improved prognosis
- Stem cell transplantation has emerged as a treatment option for some patients with early and severe disease
- Several therapeutic options for treatment-resistant digital ulcers are now available

The 'scleroderma spectrum' encompasses a diverse range of disorders that share clinical features, in particular, thickening of the skin caused by dermal fibrosis and, in many cases, episodic peripheral vasospasm (Raynaud's phenomenon). These shared features make it likely that common pathogenetic processes underlie the various disorders.[1] The spectrum ranges from purely sclerotic manifestations (localized scleroderma) to purely vascular features with cold-induced vasospasm (Raynaud's); coexistence of these two processes occupies the central scleroderma spectrum. Although the terms scleroderma and systemic sclerosis (SSc) are often used synonymously, a distinction is appropriate, with the latter describing a family of heterogeneous conditions in which fibrosis of the skin and internal organs occurs together with microvasculopathy and inflammation.

Localized scleroderma — adult-onset linear scleroderma and morphoea are usually considered to be primarily of cosmetic significance. Phototherapy and topical immunosuppression using tacrolimus are useful therapies, though some cases warrant systemic immunosuppression, particularly generalized morphoea, when multiple plaques involve large areas of skin.

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Localized scleroderma is also of major consequence in children. There is often defective growth of underlying structures with substantial morbidity and the need for effective pharmacological treatment is widely appreciated. At present, a combination of systemic corticosteroids and methotrexate is the most frequently used therapy.[2]

Raynaud's phenomenon — almost all patients with SSc manifest Raynaud's phenomenon. It is therefore conventional to include other forms of isolated Raynaud's phenomenon within the scleroderma spectrum.

Systemic sclerosis — Despite its relative rarity, SSc is an important clinical condition because of its high case-specific mortality and pathological similarity to more common organ-based fibrotic diseases. The two major subsets are designated limited and diffuse cutaneous SSc, according to the extent of skin involvement, though both forms are associated with internal organ involvement. Other forms include overlap syndromes, in which there are features of other connective tissue disorders, such as systemic lupus erythematosus, polymyositis or inflammatory arthritis, and forms in which there is little or no skin sclerosis despite other features of SSc (designated systemic sclerosis sine scleroderma).[3]

Epidemiology of systemic sclerosis

The relative rarity and clinical heterogeneity of SSc have made formal epidemiological studies difficult. The estimated prevalence from population-based studies is between 1 and 2 per 10,000 population, with a higher estimated prevalence in North America. An incidence of 1 in 100,000 per year is considered reasonably accurate.[4] There are two peaks of disease onset — the early 30s and mid50s — and, in common with most other autoimmune diseases, there is a female predominance. One exception to this is environmentally induced disease (for instance, due to organic solvent exposure) which has a number of clinical differences from idiopathic SSc.[5]

Evidence exists to support a genetic predisposition, though genetic associations relate more to clinical phenotype than susceptibility to the disease *per se*. As in other complex diseases, there are many conflicting reports of gene associations and it is possible that ethnic or geographical factors confound the demonstration of unifying genetic associations. The strongest

genetic links are with autoantibody profiles and appear to relate to class II MHC haplotype (reviewed in Romano et al.[6]). Many of the gene products discovered are relevant to disease pathogenesis. For instance, studies of a genetically isolated Native American population with a strikingly high frequency of the disease show linkage to the fibrillin-1 locus and association of fibrillin SNP haplotypes; together with similar findings in some patients with idiopathic SSc, this strengthens the case for the involvement of this gene in SSc. Familial associations of SSc are statistically significant, though the absolute risk for any relative of a patient remains less than 1%.[7,8]

Pathogenesis of systemic sclerosis

The pathogenesis of SSc involves the immune system, fibroblasts, the vasculature and epithelial structures in specialized organs. All forms of SSc seem to involve these processes, though their relative contribution can vary depending on disease subset and antibody profile. Fibrosis represents a common pathological process and SSc is often regarded as a prototypic fibrotic disease. The aetiology of SSc is multifactorial: whereas genetics do have a role, environmental factors are also required and the correct genetic/environmental combination occurs infrequently.

Subsets of systemic sclerosis

Limited cutaneous systemic sclerosis (lcSSc)

Skin involvement is limited to areas distal to the knees and elbows, and often just to the wrists and ankles. Additional changes in the face and neck are usually present. There is typically a long antecedent history of Raynaud's phenomenon, often severe and associated with recurrent digital ulceration and infarction. Other manifestations include oesophageal dysmotility and gastro-oesophageal reflux, and the hallmark features of cutaneous telangiectasia, generally seen on the palms and around the mouth, and subcutaneous calcinosis. The term lcSSc is preferred to CREST syndrome as it does not ignore the important internal organ manifestations of mid-gut disease (small bowel bacterial overgrowth), pulmonary fibrosis and pulmonary arterial hypertension (PAH).

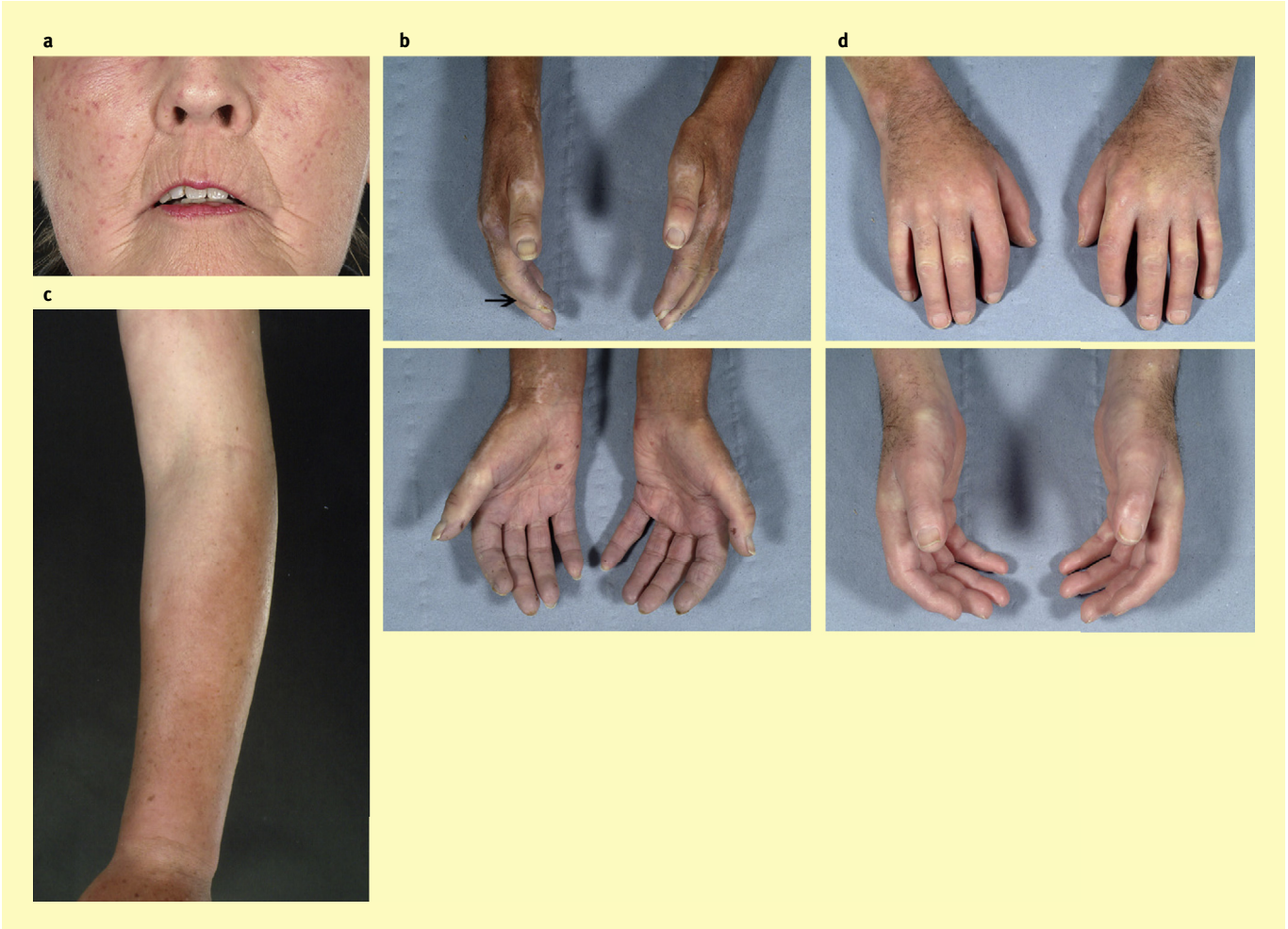

Figure 1 Clinical features of limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc). (**a**) Typical facial features of lcSSc: there is microstomia and accompanying radial furrowing with facial telangiectasia. (**b**) Typical features of established lcSSc. There are skin colour changes in the digits due to vasospasm, alterations in pigmentation particularly over the metacarpo-phalangeal joints (MCPs), nail dystrophy, sclerodactyly and areas of calcinosis (arrow). Pitting of the finger pulps has occurred at areas of previous ulceration. There is prominent palmar telangiectasia. (**c**) Skin thickening in dcSSc extends proximally to the elbows and knees. (**d**) Typical features of dcSSc. Note the generalized skin tightening, inflammation, altered hair growth and skin dryness in early dcSSc. Skin thickening and tendinopathy contribute to the development of fixed flexion deformities.