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19.11.3 Systemic sclerosis (scleroderma) 4513 Bentham J, Vyse TJ (2013). The development of genome-wide associ- ation studies and their application to complex diseases, including lupus. Lupus, 22, 1205–13. Bosma A, et al. (2012). Lipid antigen-presentation by CD1d(+) B cells is essential for the maintenance of invariant natural killer T cells. Immunity, 36, 477–90. Boumpas DT, et al. (1992). Controlled trial of methyl prednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. Lancet, 340, 741–5. Casciola-Rosen LA, Anhalt G, Rosen A (1994). Autoantigens targeted in systemic lupus erythematosus are clustered in two populations of surface structures on apoptotic keratinocytes. J Exp Med, 179, 1317–30. Cervera R, et al. (1993). Systemic lupus erythematosus—clinical and immunologic patterns of disease expression in a cohort of 1000 pa- tients. Medicine (Baltimore), 72, 113–21. Contreras G, et al. (2005). Sequential therapies for proliferative lupus nephritis. N Engl J Med, 350, 971–8. Datta SK, et al. (2005). T-helper cell intrinsic defects in lupus that break peripheral tolerance to nuclear antigens. J Mol Med, 83, 267–78. Ginzler EM, et al. (2010). Non-renal disease activity following mycophenolate mofetil or intravenous cyclophosphamide as induc- tion treatment for lupus nephritis: findings in a multi-prospective randomised open-label parallel-group clinical trial. Arthritis Rheum, 62, 211–21. Hahn BH (2003). Systemic lupus erythematosus and accelerated ath- erosclerosis. N Engl J Med, 349, 2379–80. Hanly J, et al. (2010). Prospective analysis of neuropsychiatric events in an international disease inception cohort of patients with systemic lupus erythematosus. Ann Rheum Dis, 69, 529–35. Isenberg DA, et al. (2007). 50 years of anti-dsDNA antibodies—are we approaching journey’s end? Rheumatology, 46, 1052–6. Kalaaji M, et al. (2007). Glomerular apoptotic nucleosomes are central target structures for nephritogenic antibodies in

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section 19 Rheumatological disorders 4514 blurring of vision, and significant hypertension is a medical emer- gency, portending scleroderma renal crisis and requiring immediate action. Significant visceral disease is common, affecting oesophagus (60% of cases), lungs (pulmonary fibrosis 41%, pulmonary hyperten- sion 17%), kidneys (18%), and heart (12%). Management Immunosuppressive and other treatments—broad spectrum immuno- suppression remains the current mainstay of treatment for diffuse cutaneous systemic sclerosis. The most commonly used agents are methotrexate (particularly for skin manifestations), cyclophos- phamide (for which there is strongest evidence of efficacy) and mycophenolate mofetil. Intensive immunosuppression combined with autologous stem cell rescue has been performed. Gastrointestinal symptoms—most patients with systemic sclerosis have at least one gastrointestinal manifestation, usually oesophageal dysmotility and associated reflux oesophagitis that often responds dramatically to treatment with proton pump inhibitors. Raynaud's phenomenon and digital vasculopathy—treatment ranges from simple measures (e.g. hand warmers) to simple vasodilators (e.g. calcium channel blockers) to advanced vascular therapy (e.g. prostacyclin analogues, phosphodiesterase inhibitors, endothelin re- ceptor antagonists). Prognosis and complications The most frequent cause of death related to systemic sclerosis is pul- monary disease, either interstitial fibrosis or pulmonary vascular disease. Fibrosing alveolitis—all patients with systemic sclerosis should be screened for lung fibrosis, but not all patients with abnormalities on high-resolution computed tomography will develop significant or progressive disease. For those that do, treatment is with corticoster- oids or cyclophosphamide. Pulmonary arterial hypertension—regular screening for this compli- cation is an important aspect of management. Treatment is with pros- tacyclin analogues, phosphodiesterase inhibitors, and endothelin receptor antagonists, singly or in combination. Scleroderma renal crisis—this may be the first manifestation of sys- temic sclerosis and typically presents with accelerated phase hyper- tension, acute kidney injury, and microangiopathic haemolysis. Treatment is with angiotensin-converting enzyme inhibitors, which have reduced mortality from over 75% to around 15%. Prognosis—survival in systemic sclerosis has improved to more than 80% at five years, even in the diffuse cutaneous subset. The thera- peutic nihilism that was once prevalent is no longer appropriate—the disease should be regarded as often treatable, if not curable. Introduction Systemic sclerosis (SSc) is an autoimmune rheumatic disease falling within the scleroderma spectrum of disorders that includes several diseases with similar clinical and pathological features, and which have Raynaud's phenomenon or skin sclerosis in common. Among these conditions systemic sclerosis is especially important due to a high clinical burden, unmet need for treatment, and high mortality due to severe internal organ manifestations. A hall- mark of systemic sclerosis is clinical heterogeneity that adds to the challenge of diagnosis and also requires an individualized ap- proach to management that takes into account the stage and clin- ical subset. Updated classification criteria were developed in 2013 and represent a major advance compared to previous classification approaches (Table 19.11.3.1). Those disorders included within the scleroderma spectrum are described in Table 19.11.3.2. The term 'prescleroderma' can be applied to the subgroup of patients with autoimmune Raynaud's phenomenon who manifest an abnormal microcirculation and scleroderma hallmark autoantibodies (anti-centromere anti- bodies, anti-topoisomerase, or anti-RNA polymerase III). Recent efforts to identify those cases that are developing systemic scler- osis have led to establishment of VEDOSS criteria (Very Early Diagnosis of Systemic Sclerosis) shown in Box 19.11.3.1. It is im- portant to make a clear distinction between systemic sclerosis and of the localized scleroderma conditions that are summarized in Table 19.11.3.3. The importance of distinguishing between these conditions and their subsets lies in the different clinical features, natural history, and patterns of visceral

involvement that are char- acteristic of each subgroup. Localized scleroderma is especially important when it develops in childhood due to associated im- pact on regional skeletal and soft tissue growth but all forms of Table 19.11.3.1 The 2013 ACR/EULAR criteria for the classification of systemic sclerosis Item Subitem(s) Weight/scorea Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion) – 9 Skin thickening of the fingers (only count the higher score) Puffy fingers 2 Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints) 4 Fingertip lesions (only count the higher score) Digital tip ulcers 2 Fingertip pitting scars 3 Telangiectasia – 2 Abnormal nailfold capillaries – 2 Pulmonary arterial hypertension and/or interstitial lung disease (maximum score is 2) Pulmonary arterial hypertension 2 Interstitial lung disease 2 Raynaud's phenomenon – 3 Systemic sclerosis- related autoantibodies (anticentromere, anti- topoisomerase I [anti-Scl-70], anti-RNA polymerase III) (maximum score is 3) Anti-centromere 3 Anti-topoisomerase I Anti-RNA polymerase III a Patients with a total score of ≥9 are classified as having definite systemic sclerosis. Arthritis Rheum. 2013;65:2737–47 Ann Rheum Dis. 2013;72:1747–55 Reprinted with permission fromHoogen F et al. (2013). 2013 Classification Criteria for Systemic Sclerosis: An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. Arthritis Rheum, 65, 2737–2747.

19.11.3 Systemic sclerosis (scleroderma) 4515 localized disease may occur in adults (Fig. 19.11.3.1). Localized forms of scleroderma are not associated with internal organ complications or significant vascular manifestations although it is now recognized that localized scleroderma may coexist with systemic disease in some cases. There is no evidence that one condition progresses to the other but there may be some shared aetiopathogenic features. There have been important developments in understanding the pathogenesis, clinical diversity, and management of the sclero-derma spectrum disorders over the last few years. This progress has occurred in parallel with improvements in the management of many of the organ-based complications of the condition. Thus outcomes have improved, including survival for the most severe forms of the disease, and there is a growing evidence base to support treatments for complications and manifestations such as skin fibrosis and lung disease. Other areas remain very challen- ging, but advances in clinical trial design as well as growing under- standing of pathogenic pathways that will allow logical selection of candidate therapies for evaluation. Aetiology Systemic sclerosis is an uncommon complex and heterogeneous condition, suggesting that aetiology is multifactorial and that the events or mechanisms leading to development of systemic scler- osis occur infrequently. Although emerging studies confirm po- tential genetic aspects to aetiology, these probably represent a relatively small component of the disease. This is supported by the low overall frequency of familial systemic sclerosis, and also the fact that many of the genetic susceptibility factors seem to only account for a small amount of risk and are shared with many other autoimmune or rheumatic diseases. Thus, there is likely to be a common genetic background, but other specific factors that de- termine the triggering or progression of systemic sclerosis. Recent genetic studies have identified possible factors that modify the severity or pattern of systemic sclerosis, and these factors may shed more light on specific disease mechanisms. Outside the im- mune system there is much more variability in the genetic results that suggests there is more redundancy and complexity governing nonimmune aspects of the disease. Table 19.11.3.2 The scleroderma spectrum of disorders Localized cutaneous scleroderma Morphoea Localized One or more skin lesions, often on truncal areas Generalized Widespread skin lesions can be reminiscent of diffuse cutaneous systemic

sclerosis, but Raynaud’s phenomenon is unusual, there is no visceral manifestations, and skin changes are less likely to be acral Linear scleroderma The most common form occurring in childhood. Skin changes follow a dermatomal distribution, especially on the limbs and lead to important secondary growth defects En coup de sabre Midline or parasagittal variant of linear scleroderma, which manifests in childhood and is often associated with defects in underlying fascial and skeletal structures Systemic sclerosis Limited cutaneous systemic sclerosis Skin sclerosis distal to the wrists (or ankles), over the face and neck Often longstanding Raynaud’s phenomenon Diffuse cutaneous systemic sclerosis Truncal and acral skin involvement. Presence of tendon friction rubs. Onset of skin changes (puffy or hide-bound) within 1 year of onset of Raynaud’s phenomenon Overlap syndromes Features of systemic sclerosis together with those of at least one other autoimmune rheumatic disease (e.g. SLE, RA, or polymyositis) Systemic sclerosis sine scleroderma Vascular or fibrotic visceral features without skin sclerosis (less than 1% cases) Raynaud’s phenomenon Raynaud’s phenomenon with positive ANA Raynaud’s phenomenon associated with antinuclear antibodies (or other systemic sclerosis-associated autoimmune serology), usually also abnormal nailfold capillaroscopy. Some patients later develop systemic sclerosis especially cases fulfilling VEDOSS criteria (see textbox 1). Others remain undifferentiated and may be termed ‘autoimmune Raynaud’s phenomenon’ Primary Raynaud’s phenomenon Vasospastic symptoms with normal nailfold capillaroscopy and negative autoimmune serology and no other underlying medical/mechanical cause Box 19.11.3.1 Proposed criteria for the diagnosis of Very Early Systemic Sclerosis (VEDOSS) Proposed by EULAR Scleroderma Trial & Research group (EUSTAR) Definite diagnosis of very early systemic sclerosis will be achieved when at least three major criteria are satisfied, or two major plus one additional criteria are satisfied Major criteria Raynaud’s phenomenon, autoantibodies (ANA, ACA, Topo I, ARA), diag- nostic nailfold videocapillaroscopy Additional criteria Calcinosis, puffy fingers, digital ulcers, dysfunction of the oesophageal sphincter, teleangectasia, ground-glass abnormalities on chest high- resolution computed tomography Definition of terms ANA—antinuclear antibody ACA—anti-centromere antibody ATA—anti-topoisomerase-1 antibody (Scl-70) ARA—anti RNA polymerase III antibody Diagnostic nailfold capillaroscopy means early or active scleroderma- pattern abnormalities

section 19 Rheumatological disorders 4516 Among the autoimmune rheumatic diseases, systemic scler- osis is remarkable for the large number of environmental agents or factors that are implicated in disease development. This includes various chemicals, especially silica and organic solvents. Some of the clinical syndromes associated with exposure may fall within the scleroderma-like category rather than typical systemic sclerosis, but there are sufficient shared features with the commoner forms of sys- temic sclerosis to make these factors highly relevant. The concept of an environmental trigger in a genetically and im- munologically susceptible individual is attractive. The timing and frequency of systemic sclerosis developing in adulthood suggests that several events occurring over time may be important, plaus- ibly a burden of events that occurs over time. There has long been suggestion that some cases may be associated with infection. It is possible that common immunological stimuli are relevant and that exposure to a triggering agent or event is only relevant in a par- ticular context. Recent studies of concurrence of systemic sclerosis and cancer has renewed interest in tumour antigen expression, immune-editing, and cross-reactivity between mutant and wildtype protein antigens as relevant to aetiology of systemic sclerosis, especially some cases occurring in the context of specific autoantibody reactivity such as anti-RNA polymerase III. An attractive framework for systemic sclerosis is that the disease represents a syndrome of dysfunctional connective tissue repair with associated immunological, epithelial, and

vascular pathology. This would be consistent with many of the descriptive mechanisms that operate and also explain pathological similarities with other fibrotic processes in the skin (keloids) and internal organs. Taking this further it might be considered that sys- temic sclerosis is an almost inevitable consequence of having a func- tional tissue repair mechanism, and that natural variability in this process might have some selective advantage that leads it to persist within the population. Current models suggest that initiating events involve changes in the vasculature and immune system, with subsequent interplay of vascular, inflammatory, and fibrotic processes. It has been suggested that stimulatory autoantibodies against platelet-derived growth factor, which can activate collagen expression in fibroblasts, may be an important link between the immune system and fibrosis, but this is not certain. These are among other potentially important me- diators of intercellular cross-talk that have been identified, which (hopefully) will ultimately suggest logical target factors or signalling pathways for therapeutic intervention. The culmination of these processes eventually leads to the establishment of a fibrogenic popu- lation of interstitial fibroblasts that produce increased amounts of extracellular matrix. Disruption of normal tissue architecture and Table 19.11.3.3 Localized scleroderma in adults and children Pattern of disease Clinical features Treatment Prognosis Plaque morphoea One or a few circumscribed sclerotic plaques with hypo or hyperpigmentation and an inflamed violaceous border Often unnecessary. Topical steroids or immunosuppression (e.g. tacrolimus) or phototherapy (PUVA, UVA1) may be considered. Severe or multiple plaques may require systemic corticosteroids and methotrexate or other immunosuppressive therapy. Serial measurement to assess progress Good prognosis; lesions less active within 3 years but pigmentary changes often persist Generalized morphoea Widespread pruritic lesions, often symmetrical and following the distribution of superficial veins Suppress inflammatory component using corticosteroids: in children oral doses up to 15 mg/day have been used. Intravenous infusions often effective Methotrexate or other immunosuppressive maintenance therapy often used, although benefit not proven in controlled trials. Vitamin
D-containing creams may be useful Topical corticosteroids rarely helpful. PUVA and UVA1 has been used Internal organ pathology very rare; Raynaud’s phenomenon sometimes associated and antinuclear antibody present in 5% of cases. This does not necessarily imply systemic pathology Generally improves within five years of onset, although textural and pigmentary changes may persist Linear morphoea Sclerotic areas occurring in a linear distribution often on limbs and asymmetrical; in childhood can lead to growth defect. MRI confirms the depth of lesions and associated musculoskeletal defects. Serial measurements of limb length and girth essential to monitor progression Suppress inflammatory component using corticosteroids: in children oral doses up to 15 mg/day have been used. Intravenous infusions often effective Methotrexate or other immunosuppressive maintenance therapy often used, although benefit not proven in controlled trials. Vitamin
D-containing creams may be useful Physiotherapy and appropriate regular exercise important to minimize growth defect in childhood-onset disease Surgical correction of limb defects may be considered when disease is inactive Long-term effects of childhood-onset form are minimized by effective suppression of the inflammatory process and by good physiotherapy Ultimately the disease tends to resolve, but it can remain active for many years En coup de sabre Linear scleroderma affecting the face or scalp, often involving the underlying subcutaneous tissues, muscles, periosteum, and bone. Cerebral abnormalities also reported including intracranial calcification Therapeutic options as for linear scleroderma; systemic treatment only for active inflammatory lesions Scarring, growth defects, and alopecia persist but the inflammatory component usually resolves

19.11.3 Systemic sclerosis (scleroderma) 4517 secondary mechanisms such as ischaemia produce the pathological and clinical features. Epidemiology Systemic sclerosis is a sporadic disease that has a worldwide distribu- tion and occurs in every ethnic group. No seasonal or geographical clustering of cases has been convincingly documented. The epidemi- ology of systemic sclerosis has proven difficult to establish, reflecting the clinical diversity of the disease, absence of widely accepted cri- teria for diagnosis or classification, and the methodological chal- lenges associated with population-based case ascertainment. In the United Kingdom there are approximately 300 new cases of systemic sclerosis per year and the population prevalence has been estimated to be 100 per million. Both these figures are significantly lower than estimates of disease frequency in the United States of America. Recent epidemiological survival analyses of patients with sys- temic sclerosis suggest a reduction in mortality compared with earlier studies, but this may partly be accounted for by the greater awareness of milder forms of the disease. The disease most often de- velops in the fifth decade of life, and affects women approximately four times as often as men, with this ratio increasing during the child-bearing years. Appreciation that some cases of systemic scler- osis may develop after a long preceding occurrence of Raynaud's phenomenon or other relevant clinical features makes definition of the incidence challenging. systemic sclerosis is an uncommon dis- ease that falls within the designation of an orphan disease for the purposes of drug development and regulation. Familial cases of systemic sclerosis are well recognized but rare, and the only twin study did not show greater concordance in mono- zygotic (MZ) twins suggesting that although genetic factors are relevant to the disease they are not necessarily very specific. This is consistent with the studies of genetic susceptibility loci that have Fig. 19.11.3.1 Variants of localized scleroderma: (a) limited forms of morphoea (plaque type); (b) linear forms of morphoea (linear type, en coup de sabre, Parry–Romberg syndrome); (c) generalized forms of morphoea (generalized disabling form of morphoea). Reproduced from Watts RA et al. (eds) (2013). Oxford Textbook of Rheumatology, 4th edn, by permission of Oxford University Press.

section 19 Rheumatological disorders 4518 mainly found alleles that are also implicated in development of other autoimmune diseases. High frequency of systemic sclerosis in some isolated populations such as the Oklahoma Choctaw Indians is not- able, although the number of affected cases is relatively few and dili- gent attempts to define genetic factors have been challenging. Clear environmentally triggered systemic sclerosis cases are of interest and may explain some of the rare clusters that have occurred. There may be overlap with occupational cases of systemic sclerosis and scleroderma-like condition including toxic oil syndrome and vinyl chloride disease. The recent description of nephrogenic sys- temic fibrosis is interesting as it is associated with use of linear gado- linium contrast agents in patients with renal impairment. It may be that the gadolinium is retained in these cases and leads to dissemin- ated vascular injury or extravasation of profibrotic cells. The lesions developed in nephrogenic systemic fibrosis have some biochemical features of systemic sclerosis, but clinically the syndrome is more similar to a diffuse fasciitis than systemic sclerosis. The condition has become less common since triggering contrast reagents were identified and their use limited, especially in patients with signifi- cant renal impairment. Pathogenesis/Pathology Pathogenesis of systemic sclerosis involves the interplay between dif- ferent cell types, as summarized in Fig. 19.11.3.2. Many molecular intermediates have been shown to be expressed or function in an altered way in systemic sclerosis. Interaction between the immune, vascular, and mesenchymal compartments is central to the devel- opment of typical systemic sclerosis lesions, but there are also hall- mark changes in specialized epithelial and other structures in skin and affected organs that may be highly relevant. A plausible model of

pathogenesis is that there is defective connective tissue repair in response to injury. Perturbed cellular interactions in pathogenesis systemic sclerosis KEY Cytokines/growth factors e.g. ET-1, CCL2, CCL7, IL-6, IL13, IL-4 TGFβ, CTGF, PDGF, IFN, TNFα Cell-matrix, integrin and matricellular protein function (αvβ6 integrin, COMP, TSP1) Functional auto-antibodies modifying cytokine or cell signalling Cytokine-matrix interaction and activation–latent TGFβ, fibrillin-1 Early disease Extracellular matrix excess –fibrotic response to inflammatory injury epithelium myofibroblast Connective tissue atrophy–defective repair/regeneration Late disease Interstitial fibroblast Extracellular matrix IgG Monocyte- macrophage B cell T cell microvascular endothelial cell fibrocyte pericyte NK cell EPITHELIAL COMPARTMENT Keratinocyes Lung, kidney, and gut epithelium Epithelial-mesenchymal transition VASCULAR COMPARTMENT Endothelial cells Pericytes Smooth muscle cells CONNECTIVE TISSUE COMPARTMENT Fibroblasts and myofibroblasts IMMUNO-INFLAMMATORY COMPARTMENT Innate and adaptive immune system platelets Fig. 19.11.3.2 Perturbed cellular interactions in pathogenesis of systemic sclerosis. Currently the most compelling pathogenetic framework for systemic sclerosis is one of dysfunctional connective tissue repair with altered interactions between vascular, immune, and mesenchymal cells leading to overproduction of extracellular matrix and vascular injury. At later stages connective tissue atrophy and defective epithelial repair may also be important. Genetic studies suggest that inherent abnormalities in immune function are important in susceptibility to systemic sclerosis and a variety of environmental factors may trigger or amplify injury at early stages of the disease. Altered cell-matrix and cytokine-matrix interaction may contribute to disease development. Some candidate cytokines, growth factors, and other proteins implicated as mediators in pathogenesis are included in this schematic. More detailed description is provided in the text.

19.11.3 Systemic sclerosis (scleroderma) 4519 The key issue of triggering and mechanisms of the injury have just been discussed, but once the disease is established there is multicompartmental abnormal cellular interaction. It is notable that many of the features of systemic sclerosis are similar to those occurring in normal tissue repair or regeneration, but that these seem to occur without appropriate regulation. It is also now appreci- ated that many of the key repair pathways represent reactivation or recapitulation of pathways and processes involved in normal tissue growth and development, hence lessons and mechanisms derived from developmental biology have fuelled much of the recent growth in understanding of systemic sclerosis cell and molecular pathology. This is important as it provides key insights into possible pathways and mediators that may be pivotal to the development of systemic sclerosis and which might be targets for therapy that could tackle the disease directly and be truly disease-modifying. Although traditionally viewed as a multiorgan fibrotic disease, the pathology of systemic sclerosis is more diverse that simply an excess of extracellular matrix. There are clear similarities in the pathology of vascular damage occurring in multiple organ beds in systemic sclerosis. Neointimal formation, medial thickening and proliferation/hypertrophy, and adventitial fibrosis, are all later fea- tures of vasculopathy in the pulmonary, renal, and digital vascula- ture. Similar features have been seen in other affected organ beds including the gut, penile arteries, and coronary circulation. A key question remains why different vascular beds are targeted and how these organ-based complications associate with other aspects of the disease. Strong association with immunological aspects of sys- temic sclerosis, especially hallmark antinuclear antibody (ANA) reactivity, suggest that immune or immunogenetic factors may be fundamental. At later stages of systemic sclerosis, connective tissue atrophy and failure of epithelial repair become more prominent and there is emerging evidence to support a model of abnormal differentiation of progenitor cells that would normally be involved in connective

tissue repair. Thus adipocyte progenitors appear to be defective and may differentiate preferentially into myofibroblasts that con- tribute to fibrosis, rather than into adipocytes that can regenerate appropriate subcutaneous tissue, and also contribute to the hallmark of calcinosis cutis that occurs mostly at sites of ongoing tissue is- chaemia or damage, but is usually a feature of later stage disease. Calcinosis represents a forms of dystrophic calcification that may derive from abnormal progenitor cell differentiation and the in- appropriate deposition, synthesis, or mineralization of bone matrix. Clinical features The clinical features of systemic sclerosis include some that are al- most universally present at the time of diagnosis, such as Raynaud's phenomenon, gastro-oesophageal reflux, dysphagia and skin changes affecting the extremities, and others that develop later or are present only in certain stages or subgroups of patients. It is important to con- sider the clinical features in the context of the stage and duration of disease, and with regard to the clinical subsets outlined next. Classification and diagnosis Having robust and relevant classification criteria for systemic sclerosis underpins clinical research and also facilitates diagnosis. Although not designed for diagnosis, classification criteria are rele- vant and are generally used for this purpose with the proviso that they have been developed for specificity rather than sensitivity, hence failure to fulfil criteria does not preclude diagnosis. This is of practical importance in healthcare systems where fulfilment of clas- sification criteria is required for access to therapy. However, the 2013 ACR/EULAR criteria were a major step forwards and were devel- oped using robust methodology. They replaced the 1980 preliminary criteria that had never been fully validated. A major problem with these earlier criteria was lack of sensitivity, especially for limited cu- taneous systemic sclerosis. The new criteria incorporate many more relevant features and were developed specifically to allow a points- based system for classification of definite disease (Table 19.11.3.1). Systemic sclerosis is divided into clinical subsets that are helpful in management as they highlight the distinct patterns of disease. A traditional subgrouping based upon the extent of skin sclerosis defines limited and diffuse cutaneous systemic sclerosis subsets, and in theory all cases can be allocated to one of these subsets. However, there are other cases that have no skin involvement and these are designated systemic sclerosis sine scleroderma. The definition of these cases is more challenging and they may include patients that might also be labelled as pre-scleroderma as just discussed. Although the two major subsets are defined by skin extent, there are other hallmarks that differentiate them. The systemic sclerosis- specific antinuclear antibodyreactivities provide additional informa- tion that can be used for subsetting, especially as they cross the two skin-based categories. Modern molecular classification approaches are also emerging. Intrinsic skin phenotypes are being defined based upon clusters of genes analysed by microarray or nano-string plat- forms, and these provide additional information that may eventually also aid management or help with treatment choice. All of these ap- proaches lead to better risk stratification of systemic sclerosis so that those at increased risk of specific complications or more likely to benefit from specific treatment approaches can be identified earlier. Clinical diagnosis and differential diagnosis Although thorough baseline and longitudinal investigation of patients with scleroderma spectrum disorders is central to their management, the diagnosis of scleroderma is essentially clinical. Several other causes of skin sclerosis or poor peripheral circulation must be con- sidered in the differential diagnosis (summarized in Box 19.11.3.2). Marked differences between the main subsets of systemic sclerosis in the pattern and time course of clinical features allow most patients to be characterized into the appropriate subset. Patients with diffuse, cutaneous systemic sclerosis typically pre- sent over 1 to 3 years with widespread changes in skin texture, puffy oedematous extremities, generalized pruritis, and profound constitutional and inflammatory symptoms. Vasospastic symp- toms are not usually

prominent during the early stages, although within 18 months of their onset most patients will describe definite Raynaud’s phenomenon. By contrast, the cutaneous and vasospastic symptoms of limited cutaneous systemic sclerosis are very different. The onset of skin changes is more gradual, often preceded by several years of Raynaud’s phenomenon, often becoming progressively more severe, with skin sclerosis limited to the face, neck, and hands distal to the wrists. The main differences between the subsets of systemic sclerosis are sum- marized in Table 19.11.3.4.

section 19 Rheumatological disorders 4520 Limited cutaneous systemic sclerosis This was formerly termed ‘CREST’ (calcinosis circumscripta, Raynaud’s, oesophagus, sclerodactyly, and telangiectasia) and is the most common form of systemic sclerosis, accounting for over 60% of cases. Patients are usually women, aged between 30 and 50 years, with longstanding Raynaud’s phenomenon. Early in the disease there is nonpitting oe- dema of the fingers (sausage-shaped fingers), which—after several weeks or months—is gradually replaced by thickened and shiny skin. This is not usually so closely adherent to underlying structures that mobility is severely impaired, which is in sharp contrast to the find- ings in those with diffuse disease. Skin involvement does not spread proximally on to the trunk, but the face should be examined carefully for thin, tightly pursed lips, with furrowing and puckering of the sur- rounding skin, and microstomia. The most striking cutaneous finding is digital and facial telangiectasia caused by dilated capillary loops and venules (Fig. 19.11.3.3). Other evidence of structural vascular change is to be seen in the fingertips, where small areas of ischaemic necrosis or ulceration are common, often leaving pitting scars and pulp atrophy. Loss of the tufts of the terminal phalanges, confirmed on radiography, is also presumed to be due to ischaemia. Patients with limited cuta- neous disease often develop intracutaneous and subcutaneous calcifi- cation. These deposits frequently occur in the fingers, particularly the digital pads, and in periarticular tissues such as the prepatellar area and olecranon bursa. The calcinotic masses vary in size and are often complicated by ulceration of the overlying skin, extrusion of calcific material, and secondary bacterial infection. Patients may complain of dyspepsia from reflux oesophagitis: this and other visceral complica- tions are discussed in detail next. Diffuse cutaneous systemic sclerosis By contrast to limited cutaneous systemic sclerosis, the onset of diffuse disease is often abrupt. It may present with widespread, Box 19.11.3.2 Differential diagnosis of scleroderma Skin sclerosis Infiltrative disorders • Amyloidosis • Scleromyxoedema • Scleroderma of Buschke • Lichen sclerosis et atrophicus Metabolic disorders • Myxoedema • Porphyria cutanea tarda • Congenital porphyrias • Acromegaly • Phenylketonuria Inflammatory disorders • Overlap connective tissue diseases • Eosinophilic fasciitis • Chronic graft-vs-host disease • Sarcoidosis Acral vasospasm Raynaud’s phenomenon • Primary Raynaud’s phenomenon • Other autoimmune rheumatic disorders: — Systemic lupus erythematosus — Rheumatoid disease — Dermato-/polymyositis Other vascular disease • Haematological : — Cryoglobulinaemia — Cold-agglutinin disease — Hyperviscosity syndrome • Systemic vasculitis • Macrovascular disease Table 19.11.3.4 Contrasting clinical features of the major subsets of systemic sclerosis (SSc) Diffuse cutaneous SSc (dcSSc) Limited cutaneous SSc (lcSSc) 33% of patients Inflammatory features more prominent at onset Raynaud’s phenomenon may develop later Skin sclerosis proximal to wrists/elbows and truncal areas Prominent pruritus and constitutional symptoms Tendon friction rubs associated with progressive disease Significant visceral disease more frequent than in lcSSc: renal, pulmonary fibrosis, pulmonary hypertension, cardiac, gut Disease activity appears to be maximal in the first three years from onset, then often plateaus, and skin involvement may stabilize or improve 66% of patients Longstanding Raynaud’s phenomenon Skin changes: hands, face, neck Compared with dcSSc, renal disease less frequent, pulmonary

hypertension, severe gut disease, and interstitial lung fibrosis (if antitopoisomerase-1 present) Florid telangiectasis and calcinosis (especially anticentromere antibody positive) Disease activity appears to remain fairly constant over many years, with prominent vasculopathy Prevalence of organ-based complications in the main systemic sclerosis subsetsa Clinical feature lcSSc (%) dcSSc (%) Overall (%) Raynaud’s phenomenon 99 98 99 Skeletal myopathy 11 23 15 Oesophageal 74 60 69 Other severe gastrointestinal 7 8 8 Cardiac 9 12 10 Pulmonary fibrosis 26 41 31 Pulmonary hypertension 21 17 20 Renal (overall) 8 18 12 Renal (crisis) 2 10 5 a Data from patients attending The Royal Free Hospital Centre for Rheumatology.

19.11.3 Systemic sclerosis (scleroderma) 4521 symmetrical, sometimes itchy, painful swelling of the fingers, arms, feet, legs, and face. Rapid weight loss and constitutional symptoms of fatigue or weakness are frequent. The clinical findings in diffuse scleroderma depend on the stage of the disease. At onset, examin- ation of the skin will usually reveal cold, painful, swollen hands, with swelling and stiffness already extending to the arms, feet, lower legs, face, and trunk. This oedematous phase is usually replaced within a few months by one of induration, when the skin becomes tight, shiny, and bound to underlying structures. Pigmentary changes (hyperpigmentation or hypopigmentation) accompany skin thick- ening in many patients. Skin involvement in diffuse scleroderma is quite different from that in the limited form of the disease, and can be mapped semi- quantitatively by measuring the degree and extent of cutaneous thickening at multiple sites, from which is derived a skin score. In diffuse scleroderma this score increases rapidly at first, often peaking after one to three years, and is accompanied by impaired mobility of tendons, joints, and muscles that is clinically all too apparent. Contractures and stretching of the skin over bony points often lead to painful ulcers that are slow to heal, particularly over the proximal interphalangeal joints, elbows, and ankle malleoli. In its earliest stages, diffuse scleroderma can be confused with an acute inflammatory arthropathy, particularly if Raynaud’s phenom- enon is absent. The oedematous puffy skin is often accompanied by symmetrically stiff, painful joints (hands, feet, knees, ankles, and wrists), but the classic synovitis of rheumatoid arthritis is usually absent. The clinical sign of tendon friction rubs should carefully be sought in this group of patients: these have a distinctive leathery crepitus and can be elicited during joint movement over elbows, knees, fingers, wrists, and ankles. They frequently antedate a rapid increase in cutaneous involve- ment, or the onset of visceral disease. Signs of carpal tunnel syndrome may be present, due to flexor tenosynovitis at the wrist. Mild muscle disease is common and can be detected on exam- ination, but is not usually accompanied by an increase in plasma creatine kinase or inflammatory changes on muscle biopsy. It is gen- erally nonprogressive. The few patients with florid changes of poly- myositis are usually classified as having an overlap syndrome. As with limited disease, evidence of structural vascular damage— sometimes extensive—may be found in the nailfold capillaries (Fig. 19.11.3.4) and the digital pads. Fig. 19.11.3.3 This patient shows the typical facial features of limited cutaneous systemic sclerosis. Microstomia, furrowing, and puckering of the skin around the mouth, beaking of the nose, and telangiectasia on the lips and face. Fig. 19.11.3.4 Nailfold capillaroscopy with early, active, and late patterns of systemic sclerosis. Reproduced from Watts RA et al. (eds) (2013). Oxford Textbook of Rheumatology, 4th edn, by permission of Oxford University Press. Courtesy of Dr Kevin Howell, RFH Microvascular Laboratory.

section 19 Rheumatological disorders 4522 Scleroderma sine scleroderma These patients constitute less than 2% of those with systemic scler- osis, but they are the most difficult group to recognize. They may or may not have Raynaud’s phenomenon, but by definition they never have

the skin changes of scleroderma; common presenting problems include oesophagitis, malabsorption, pseudo-obstruction, renal failure, cardiac arrhythmias, and interstitial lung disease. Overlap syndromes There are patients whose disease is not easy to define: around one- fifth of cases of systemic sclerosis have significant overlap features, most often myositis or arthritis. They may well fulfil criteria for rheumatoid arthritis or idiopathic inflammatory myopathy as well as systemic sclerosis. It should be noted that the 2013 EULAR-ACR criteria for classification of systemic sclerosis do not preclude the presence of more than one diagnosis, although the clinical diagnosis rather than classification criteria should be used in designating overlap, and if there are no features of systemic sclerosis then an al- ternative diagnosis should be used. Cases that have some features of systemic sclerosis or other autoimmune rheumatic diseases but which do not fulfil the criteria for a defined disease are best termed undifferentiated connective tissue disease. Investigation Autoimmune serology Most patients with scleroderma exhibit a hallmark autoanti- body, and almost all have antinuclear reactivity, often with an antinucleolar pattern on Hep2 cells. Three generally (although not always) mutually exclusive reactivities are seen: anticentromere, antitopoisomerase-1 (anti-Scl 70), and anti-RNA polymerase III. Rarer specificities include fibrillarin (U3RNP), PM-Scl, and anti- Th/To. Each serologically defined group shows somewhat different clinical features, which is of some value in risk stratification for management. There are also well- established class II major histo- compatibility complex (MHC) associations with the various auto- antibodies, although some differences in association occur in different racial groups. Clinical and immunogenetic associations of systemic sclerosis hallmark antinuclear antibodyreactivities are shown in Table 19.11.3.5. Some studies that suggest that autoantibodies directed against vascular structures and antigens may be present, and that reactivities against cell surface receptors may be relevant to pathogenesis. Less specific serological abnormalities are also found in scleroderma, including hypergammaglobulinaemia, the presence of immune complexes, low concentrations of com- plement components, and a weakly positive rheumatoid factor. Antibodies to SSA/Ro and SSB/La are found in 50% of patients with scleroderma who also have Sjögren’s syndrome, and are nearly always found in those with glandular lymphocytic infiltra- tion rather than fibrosis. Management—general approach Disease management starts with diagnosis and classification: when faced with a patient with a scleroderma spectrum disorder the first consideration is to determine whether they have features of localized disease or systemic sclerosis. The simplest discrimin- ators are the presence of vascular symptoms, including Raynaud’s phenomenon, and internal organ manifestations, of which the earliest is often reflux oesophagitis or dysphagia, but unfortunately both Raynaud’s phenomenon and gastro-oesophageal reflux are common in otherwise healthy individuals (Fig. 19.11.3.5). Table 19.11.3.5 Clinical and immunogenetic associations of systemic sclerosis hallmark antinuclear antibodyreactivities Target antigen Frequency (%) Staining pattern Clinical association Genetic association Centromere (ACA) 15–40 Kinetochore lcSSc, PAH HLA-DQB1 TNF-863A GRB10 NOTCH4 Topoisomerase-1 (Scl70) 10–40 Speckled dcSSc, lung fibrosis HLA-DPA1/B1 HLA-DPB2 HLA-DRB1 RNA polymerase III (ARA) 4–25 Fine speckled/nucleolar dcSSc, Renal crisis, malignancy, PAH HLA-DRB1 HLA-DRB3 HLA-DRB4 HLA-DQB4 EDNRA Fibrillarin (U3RNP) 1–5 Nucleolar/coilin PAH, cardiac, myositis HLA-DQB1 Pm-Scl 3–6 Nucleolar Myositis overlap None reported U1RNP 5–35 Speckled Overlap features HLA-DRB1 HLA-DPB1 Th-To 1–7 Nucleolar lcSSc, PAH, lung fibrosis None reported U11/U12 1–5 Nucleolar Lung fibrosis None reported dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis; PAH, pulmonary arterial hypertension; RNP, ribonucleoprotein; SLE, systemic lupus erythematosus. Other rarer antinuclear antibodyreactivities have been described that may also associate with specific complications although the frequency of these reactivities is less than

more established patterns.

19.11.3 Systemic sclerosis (scleroderma) 4523 The pattern and distribution of skin involvement provide crit- ical information about subset and classification: asymmetrical in- volvement and acral sparing are typical of localized scleroderma, whereas acral involvement is almost universal in systemic forms. Of the available laboratory investigations, autoantibody testing is per- haps the most useful, and provides additional information about likely subset and possible organ-based disease in systemic sclerosis. An additional clinical investigation that helps to discriminate pri- mary Raynaud's phenomenon from early connective tissue disease is nailfold capillaroscopy. There are classic morphological changes in systemic sclerosis, including capillary drop-out and dilatation, whereas capillaroscopy is usually entirely normal in cases of local- ized scleroderma. The underlying pathogenesis of systemic sclerosis involves inter- play between immune dysfunction, vasculopathy, and fibrosis, as just discussed, and it is likely that effective disease modification de- pends upon management of these facets. However, there is interplay between the pathologies and so treatment of one aspect of the dis- ease is likely to affect other processes, hence immunomodulatory approaches appear to have benefits for fibrosis in skin and lung, and there is evidence that immune mediated mechanisms may be im- portant in some aspects of vasculopathy. Broad spectrum immunosuppression remains the current main- stay of treatment for diffuse systemic sclerosis: currently used strat- egies are summarized in Table 19.11.3.6. In general, all patients with active dcSSc should be considered for immunosuppressive treatment, with the modality and intensity of treatment dictated by assessment of disease severity or activity. Evidence from placebo- controlled clinical trials supports efficacy of methotrexate for skin, although this was modest. Data regarding mycophenolate mofetil come from observational cohort studies or small trials, but the most robust evidence base is for cyclophosphamide. The SLS-I study was placebo controlled and showed statistical benefit for lung function and several key secondary end points, including skin sclerosis, in dcSSc subjects. The treatment effect persisted to 18 months for lung function, but then diminished, suggesting longer-term immunosup- pression is needed. The FAST study in United Kingdom suggested comparable treatments effect for intravenous cyclophosphamide, but was substantially smaller. In general, patients with overlap myositis or arthritis and without major lung fibrosis are started on methotrexate, whereas mycophenolate mofetil is used first line if skin or lung fibrosis are the main manifestations requiring treatment. Cyclophosphamide may be considered for severe or clearly progressive lung fibrosis: treat- ment is most often given monthly for 6 months and then oral mycophenolate mofetil substituted for a minimum of two to three years. However, some physicians favour longer term intravenous cyclophosphamide and have reported favourable results over 12– 18 months. The SLS-II study compared oral cyclophosphamide over 12 months with mycophenolate mofetil given for 24 months, and preliminary results seem to show mycophenolate mofetil treatment effects are similar over the first six months, which may impact on use of cyclophosphamide, although no formal comparison with paren- teral cyclophosphamide has been made. The potential value of more intensive immunosuppression with autologous stem cell rescue has been explored in registries and more robustly in controlled trials. The results of these studies suggest that there may be long-term benefit from autologous stem cell rescue, but that needs to be balanced against early treatment related mor- tality. In the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) study there was long-term survival benefit in the autologous stem cell rescue treated cases compared to those re- ceiving 12 months of IV cyclophosphamide, but the advantage was only seen after 2 years follow up post-transplant due to up to 10% early treatment related

mortality. In addition, there is evidence that some cases of systemic sclerosis are doing well with less intensive regimens, hence the key challenge remains case selection for autolo- gous stem cell rescue. Pathways to evaluate cases of poor prognosis systemic sclerosis have been proposed, and it will be important to take this potentially important treatment forwards in appropriate cases. There is particular interest in less cardiotoxic conditioning strategies that avoid very high doses of cyclophosphamide. Management of organ-based complications Despite the usefulness of an accurate subset classification of patients with systemic sclerosis, management requires that an organ-based approach be taken once the subset has been assigned. This ensures that important complications, which occur with different frequen- cies in the different subsets, are not missed. Vascular manifestations Raynaud's phenomenon Episodic acral vasospasm, precipitated by cold or emotional stress (Raynaud's phenomenon), is almost universally present in patients with systemic sclerosis, although its prominence varies considerably between cases. The pathogenic mechanism is uncertain, but prob- ably represents an imbalance between vasoconstrictor and vaso- dilator mechanisms in small blood vessels, or an exaggerated release of vasoconstrictor mediators in response to physiological levels of dcSSc lcSSc Manage according to severity and activity of overlap features– arthritis, myositis, lupus Therapy– Vascular Identification and treatment of organ-based complications Therapy- Vascular Immunosuppressive (Antifibrotic) SYSTEMIC SCLEROSIS Overlap SSc Fig. 19.11.3.5 Overall management strategy for patients with systemic sclerosis. Once diagnoses all cases of systemic sclerosis should undergo baseline clinical assessment for stage and subset determination. The presence of overlap features should be sought and cases stratified for risk of specific complications. Early diffuse systemic sclerosis or major organ-based complications usually require immunosuppressive therapy. All cases should have symptomatic treatment of gastro-oesophageal reflux, Raynaud's phenomenon, and other complications.

section 19 Rheumatological disorders 4524 stimulation by cold or emotion. Raynaud's phenomenon is common in otherwise healthy individuals, with some series estimating its prevalence to be up to 15% in women, with a much lower frequency in men. It may precede the onset of systemic sclerosis, especially the limited cutaneous subset, by many years, whereas in diffuse cuta- neous systemic sclerosis it generally first becomes manifest around the time of the onset of other features of the disorder, or afterwards. Current approaches to the management of patients with Raynaud's phenomenon are summarized in Table 19.11.3.7. Although Raynaud's is a feature of many autoimmune rheumatic diseases it is especially prominent in systemic sclerosis, when there are more complications. This may reflect the associated structural vasculopathy that leads to fixed vascular insufficiency. Treatment follows the principles of other situations with lifestyle adjustments, avoidance of precipitants, and use of vasodilator agents, which may be used in combination, especially for agents working on different pathways. Interestingly, some agents that are effective in organ- based vasculopathy such as endothelin receptor antagonists and ACEi have not been shown to benefit Raynaud's in clinical trials. In contrast, PDE5 inhibitors have been helpful and can be con- sidered in severe Raynaud's, especially when complications of digital ischaemia occur. In practice, Raynaud's is one component of a more significant problem of ischaemic digital vasculopathy in systemic sclerosis, which likely reflects multiple processes including vasospasm, structural vascular damage, altered tissue repair and healing, (probably) intravascular thrombosis, and (occasionally) vasculitis. These problems lead to digital ulceration and also to critical is- chaemia with complications such as gangrene, cellulitis, and osteo- myelitis (Fig. 19.11.3.6). In the past autoamputation was common, but more aggressive management has improved outcome in many cases. A mixture of local management, treatment of Reynaud's, and

Table 19.11.3.6 Management of Raynaud’s phenomenon and digital vasculopathy in systemic sclerosis Treatment Examples Comments Simple measures Nondrug Hand warmers Protective clothing Universally helpful; also useful to minimize cold exposure and ambient temperature changes in work environment Pharmacological Evening primrose oil Fish oil capsules Antioxidant vitamins Evening primrose oil has been shown to be effective in controlled clinical trials Theoretical benefit due to increased synthesis of vasodilator prostanoids Potentially reduces oxidant stress which may contribute to Raynaud’s phenomenon symptoms and pathology Simple prescription vasodilators Calcium channel blockers Nifedipine Amlodipine Diltiazem Variable and differential response to different agents. Slow titration of dose reduced the severity of side effects. Try each drug for at least 3 weeks if possible Serotonin antagonists Fluoxetine Serotonin reuptake inhibitor: readily available. Fewer vasodilatory side effects than calcium channel blockers. Depletes platelet 5HT levels Angiotensin receptor blockers Losartan Well tolerated, potential remodelling by blocking fibrogenic effects of angiotensin II. ACEIs not effective in RP (QUINS trial) Topical vasodilators Topical nitrates Shown to be effective in short-term use but systemic effects often cause headaches. New formulations under evaluation Advanced vascular therapy Parenteral vasodilators Prostacyclin analogues Effective at healing ulcers and reducing severity and frequency of Raynaud’s phenomenon attacks. Expensive and limited long-term duration of benefit. Most data for iloprost but epoprostenol and other prostacyclin analogues also used Phosphodiesterase inhibitors Sildenafil, Tadalafil Potentiate nitric oxide (NO) signalling by reducing breakdown of cGMP. Not co-administered with nitrates Endothelin receptor antagonists Bosentan Used to reduce digital ulcer formation but no robust evidence of benefit for uncomplicated Raynaud’s Other systemic therapy Antibiotics Flucloxacillin Erythromycin Teicoplanin Important adjunct to vasodilator therapy for secondary infection of digital ulcers. Prolonged systemic treatment necessitated by poor tissue perfusion especially for severe cellulitis or osteomyelitis Pain control Simple analgaesics Opiods neuromodulators Careful management of pain related to infection, digital ulceration, or tissue ischaemia using combinations of oral and transcutaneous agents. Neuromodulators (e.g. gabapentin) often helpful for ischaemic pain Surgical procedures Lumbar sympathectomy Radical microarteriolysis Debridement, amputation Chemical or surgical Division of adventitia of digital arteries.
Sometimes termed digital sympathectomy Surgical or autoamputation For severe lower limb Raynaud’s phenomenon Useful treatment for individual critically ischaemic digits Surgery should be as conservative as possible to allow maximum possibility of spontaneous healing Botulinum toxin Botox® Local injection around digital arteries can improve digital blood flow and relieve pain—sometimes termed medical sympathectomy 5 HT, 5-hydroxytryptamine (serotonin); ACEI, angiotensin converting enzyme inhibitor.

19.11.3 Systemic sclerosis (scleroderma) 4525 comorbidity seems important. There is increased interest in digital ulceration as a therapeutic target, and licensed therapies and treat- ment pathways have been established. In the United Kingdom an approved policy is now in place that recommends sildenafil ini- tially for digital ulceration, and then intravenous prostacyclin. Bosentan is licensed for digital ulceration as a therapy that reduces new ulcer formation, but has not been shown to increase healing of established ulcers. Macrovascular disease There have been several reports that macrovascular disease is in- creased in patients with systemic sclerosis, and there is evidence of altered vessel biomechanical properties. However, although asso- ciated macrovascular disease is important and should be explored in any case where there are risk factors or clinical pointers such as asymmetrical or sudden tissue ischaemia, it seems likely that the ex-

cess of macrovascular disease seen in other rheumatic diseases is not a feature of systemic sclerosis, and this certainly seems the case for ischaemic heart disease that has not been shown to be excessive compared with nonsystemic sclerosis cohorts. Skin manifestations Scleroderma means ‘hard skin’ and is the hallmark of the sclero- derma spectrum disorders. The skin lesions of scleroderma differ between diffuse and limited cutaneous subsets, not only by their extent and distribution, but also by the greater tendency for there to be induration and oedema of affected tissues in diffuse cutaneous systemic sclerosis, which may reflect a local release of cytokines or altered endothelial permeability. The inflammatory phase evolves into established fibrosis, sometimes leading to sheets of thickened skin or a hide-bound texture. The skin sclerosis score (skin score) is a validated method for as- sessing the extent of skin involvement and has been shown to predict survival and to correlate with some other disease features (e.g. a rap- idly increasing skin score is associated with an increased occurrence of scleroderma renal crisis). Although baseline skin score associates with outcome in many systemic sclerosis clinical trials, the relation- ship between skin extent and organ-based complications is less clear. The high frequency of severe pulmonary arterial hypertension in cases of limited cutaneous systemic sclerosis exemplifies this. In dif- fuse cutaneous systemic sclerosis many patients have their peak skin score within 12–18 months of disease onset (defined by first definite non-Raynaud’s phenomenon manifestation of systemic sclerosis), thus by the time they obtain specialist help such patients are often in a stable or improving phase of skin involvement, which has major implications in trying to assess treatment response in the skin. Pulmonary disease Lung complications are important and frequent in systemic sclerosis (Table 19.11.3.8). Table 19.11.3.7 Respiratory tract complications of systemic sclerosis Lung disease Pathology Frequency Clinical features Investigation Treatment Pulmonary fibrosis Predilection for lung bases. Inflammatory infiltrate precedes development of established fibrosis. At biopsy most patients show an NSIP histological pattern Significant fibrosis in around 25% of SSc. Strongly associated with antitopoisomerase-1 autoantibody. Occurs in both major SSc subsets Dry cough, exertional dyspnoea, bibasal crepitation. Finger clubbing uncommon Restrictive pattern of PFT (low FVC and DlCO). HRCT essential investigation. DTPA clearance accelerated, serum KL-6 may be elevated. Thoracoscopic lung biopsy in atypical cases Recent studies suggest modest benefit from immunosuppression with cyclophosphamide or azathioprine. Other agents under evaluation Pleural disease Effusions and pleurisy uncommon except in overlap syndromes or renal crisis Rare Chest pain, dyspnoea Chest radiograph NSAIDs or low-dose prednisolone Pneumothorax Rupture of cyst into pleural cavity Rare Chest pain, dyspnoea Chest radiograph Intercostal drainage. Expansion may be poor, especially if lung fibrosis. Pleuradesis Bronchiectasis Suppurative inflammation of airways Rare Chronic productive cough CT scan Antibiotics, postural drainage Lung carcinoma Overall probably increased risk, especially scar type (alveolar cell) Rare Variable Contiguous CT scan/ bronchoscopy. Biopsy Poor prognosis. Late diagnosis often due to associated lung pathology. Chemotherapy and radiotherapy may aggravate SSc Pulmonary hypertension Most often precapillary (Group I) PAH (60%) but also postcapillary (Group II) with elevated PAWP), or associated with lung fibrosis (Group III). PVOD and thromboembolic PH also occur 10–15% overall Exertional breathlessness, chest pain, loud pulmonary P2, syncope, right heart failure ECG, PFT (low DlCO preserved FVC in isolated PHT), Doppler echocardiography to estimate peak PAP. Nt-pro BNP, Right heart catheter study essential for diagnosis and classification Manage according to consensus recommendations (Galiè 2009). Oral PAH specific therapy or inhaled and parenteral prostacyclin analogues according to clinical severity BAL, bronchoalveolar lavage; DlCO; CO diffusion coefficient; DTPA, diethylenetriaminepentaacetic acid; FVC, forced vital capacity; HRCT, high-resolution CT; NSAID,

nonsteroidal anti-inflammatory drug; NSIP, nonspecific interstitial pneumonia; PAP, pulmonary artery pressure; PFT, pulmonary function test PHT, pulmonary hypertension SSc, systemic sclerosis; PAWP—pulmonary artery wedge pressure

section 19 Rheumatological disorders 4526 Fig. 19.11.3.6 Typical clinical features in the hands of patients with systemic sclerosis. Reproduced from Watts RA et al. (eds) (2013). Oxford Textbook of Rheumatology, 4th edn, by permission of Oxford University Press. Table 19.11.3.8 Investigation and management of cardiac manifestations of systemic sclerosis Cardiac complication Pathology Frequency (%) Clinical features Investigation Treatment Arrhythmias Extrasystoles, paroxysmal tachyarrhythmias 30 Palpitations,
syncope ECG (including 24-h tape or telemetry); exercise stress test Treat if haemodynamically significant Conduction defects Fibrosis of conduction tissue 15 Syncope, hypotension ECG Pacemaker may be required Pericardial involvement Pericarditis Pericardial effusion 10% clinically 35–50% at post-mortem examination Usually asymptomatic Haemodynamic effects rare ECG, echocardiogram Often none required Occasionally pericardiocentesis if diastolic collapse on Echo NSAIDs for pericarditis Myocardial involvement Myocarditis Myocardial fibrosis Rare 30–50% dcSSc Congestive cardiac failure, arrhythmias Congestive cardiac failure ECG, echocardiogram, stress echocardiogram, cardiac enzymes (CK-MB), troponin levels, Nt-pro—BNP, MRI with gadolinium, CT angiogram, MUGA, or other nuclear medicine studies Left heart catheterization Endomyocardial biopsy Myocarditis treated with prednisolone. And cyclophosphamide or other immunosuppressive agent. Diastolic heart failure managed with diuretics, systolic heart failure with ACEIs, carvedilol, β-blockers may be considered (care in Raynaud’s). ICD considered if high risk of ventricular tachyarrhythmia. Pacemakers for bradyarrythmia and systolic heart failure

19.11.3 Systemic sclerosis (scleroderma) 4527 Parenchymal lung disease with fibrosis is very common, but not always severe and progressive. The other most important com- plication affecting the lung is pulmonary vascular disease, which can lead to pulmonary hypertension. There appears to be a sus- ceptibility phenotype for this complication, with 1–2% of cases developing pulmonary hypertension per annum under long-term follow up. Recent progress in the assessment of pulmonary disease in pa- tients with systemic sclerosis has refined diagnosis and classifica- tion, and will almost certainly result in different treatment strategies for particular subsets of patients. Parenchymal lung disease The most prevalent type of parenchymal lung disease is intersti- tial lung fibrosis with a pattern typical of nonspecific interstitial pneumonia (NSIP) at biopsy or based upon the high-resolution computed tomography appearance (Fig. 19.11.3.7). A minority of lung fibrosis cases show a pattern of usual interstitial pneumonia (UIP). Other forms of interstitial lung disease may occur and need to be considered in assessment and diagnosis. This is espe- cially seen in patients with systemic sclerosis overlap syndromes where the lung pathologies of associated conditions may occur. These include organizing pneumonia associated with polymyo- sitis or complications such as alveolitis, alveolar haemorrhage, or alveolar proteinosis associated with other autoimmune rheumatic diseases. Pulmonary interstitial fluid may be present, associated with cardiac failure or hypertensive renal crisis, or features of superadded infection. Pulmonary sarcoidosis occurs sometimes in patients with systemic sclerosis and may need to be considered in the differential diagnosis of parenchymal lung disease in this condition. Although all patients with systemic sclerosis should be screened for lung fibrosis, it appears to affect only around 25% of those with limited cutaneous disease and up to 40% of those with the dif- fuse cutaneous form. It is strongly predicted by the presence of antitopoisomerase-1 autoantibodies and by associated major

histo- compatibility complex genotypes. Other reactivities such as anti U11/U12, anti-Th-to and anti fibrillarin may also associated with development of lung fibrosis although these associations have not reached statistical significance in cohort studies. The presence of anticentromere antibodies is associated with a reduced risk. These tests are therefore of clinical value in planning the frequency and intensity of lung screening tests. While the overall frequency of lung fibrosis in systemic sclerosis is high, not all patients with abnormalities on high-resolution computed tomography will develop significant or progressive disease. The most widely used staging system recommends brief initial assessment of the high-resolution computed tomography to determine whether there is trivial (less than 10% of the lung affected) or severe (more than 40%) disease, and if indeterminate then lung function tests with an forced vital capacity (FVC) threshold of 70% predicted can be used to separate those cases that on average have more or less than 20% of the lung affected on formal high-resolution computed tomography assessment. This has proven very helpful. Cases of mild disease should have rigorous follow up and any trend to deterioration or progression should prompt treatment. In diffuse disease a substantial propor- tion of those developing severe lung fibrosis do so within three years of onset of disease. There has been interest in developing additional independent pre- dictors of respiratory decline to allow better targeting of treatment. Bronchoalveolar lavage does not add to the staging information from high-resolution computed tomography. Likewise, lung bi- opsy is generally not considered helpful in typical cases of systemic sclerosis-associated lung fibrosis, although it remains important in cases that have atypical features, especially if an inflammatory pathology is suspected that may be steroid responsive. The nuclear medicine test of diethylenetriaminepentaacetic acid (DTPA) clear- ance scans or serum KL-6 levels have proved informative in research studies and may provide information that adds to that provided by lung function tests or high-resolution computed tomography (CT). Serum KL-6 is in use in some countries in management of idiopathic lung fibrosis, but its use in longitudinal follow up and validity as a test for routine clinical practice remains to be determined. DTPA scans, particularly serial studies, may become useful predictors of progression or improvement. The mainstay of therapy for systemic sclerosis-associated inter- stitial lung disease has long been corticosteroids or cyclophospha- mide, given orally or as intermittent intravenous boluses. Evidence supporting use of cyclophosphamide is underpinned by the FAST trial of IV cyclophosphamide and the scleroderma lung study (SLS-I) performed in North America. Both showed marginal su- periority of active treatment over placebo, and the recent SLS-II Fig. 19.11.3.7 High-resolution computed tomography appearance of lung fibrosis in systemic sclerosis. (a) A thin-section CT scan illustrating the ground-glass appearance of early pulmonary involvement posteriorly. A chest radiograph taken at the same time was normal. (b) A thin-section CT scan illustrating extensive honeycomb shadowing and cystic air spaces involving both lower lobes. The chest radiographic appearances at the same time were of advanced interstitial lung disease (bibasilar reticulonodular shadowing). Both images with grateful acknowledgement to Professors A. Wells, R. du Bois, and B. Strickland, Departments of Respiratory Medicine and Radiology, Royal Brompton National Heart and Lung Hospitals.

section 19 Rheumatological disorders 4528 is providing further support for the use of mycophenolate mofetil (MMF). Treatment needs to be continued for at least 3 years to maintain improvement. In cases that have not responded to standard immunosuppression there are emerging data to support use of rituximab. In idiopathic pulmonary fibrosis, recent clinical trials of pirfenidone, nintedanib and Mucodyne (acetylcysteine) have shown some efficacy, and these three agents are all licensed for treatment of this condition in some countries. Clinical studies are

underway, but at present they are not in routine use in the United Kingdom for systemic sclerosis. Lung transplantation may be an option for selected cases of sys- temic sclerosis with advanced pulmonary involvement. Pulmonary hypertension Precapillary pulmonary arterial hypertension, designated group I, is the most frequent form of pulmonary hypertension that occurs in systemic sclerosis. This is diagnosed by right heart catheteriza- tion and direct measurement of the pulmonary arterial pressure, with pulmonary hypertension defined by mPAP of 25 mm Hg or above, coupled with a normal pulmonary arterial wedge pressure (by definition <15 mm Hg). Postcapillary pulmonary hypertension (Group II), reflecting cardiac involvement from systemic sclerosis, is associated with elevation of wedge pressure. Group III pulmonary hypertension is associated with another lung diseases, which in sys- temic sclerosis is generally lung fibrosis. Thromboembolic disease and pulmonary venous occlusive disease may also occur, but less frequently. The latter is a particular challenge as biopsy is rarely per- formed (contraindicated|) and the compatible CT appearances are common in systemic sclerosis. It is likely that multiple mechanisms coexist in some cases, which may underlie the poor outcome in pa- tients with systemic sclerosis who have pulmonary hypertension. Patients with lung fibrosis and pulmonary hypertension seem to have especially poor survival. Regular screening of patients with systemic sclerosis for pul- monary hypertension is an important aspect of management, al- though the precise nature and frequency of screening tests remains debated. Annual assessment of symptoms, echocardiography with Doppler assessment of tricuspid regurgitant jet velocity, and lung function tests to assess the presence or selective decline in DLco is generally recommended. Screening programmes lead to the iden- tification of cases with borderline elevation of mPAP (between 21 and 24 mm Hg). These have markedly increased risk of progression to pulmonary hypertension over the next 1–3 years and are a highly enriched population for regular screening and assessment. The first evidence of treatment benefit for pulmonary arterial hypertension specific therapies came from a short-term trial of epoprosteol in systemic sclerosis. Over 24 weeks there was im- proved exercise capacity, although no gain in survival. The devel- opment of oral treatments for pulmonary arterial hypertension has been a major advance. Bosentan was the first licensed oral therapy, but other endothelin receptor antagonists have followed, also drugs that act on the nitric oxide pathway. First of these were selective PDE5 inhibitors that slow the breakdown of cGMP, a key secondary mediator of nitric oxide intracellularly, and more recently soluble guanylate cyclase agonists have been developed that also appear beneficial. There are now prostacyclin analogues that can be given subcutaneously, by inhalation and orally, but these have not yet been shown effective in systemic sclerosis-associated pulmonary arterial hypertension. Since the licensed therapies act on three different pathways it is lo- gical that they can be combined. Sequential benefit has been demon- strated in several robust clinical trials, and recent data also suggest that initial combination therapy of a PDE5 inhibitor and endothelin receptor antagonist may have greater benefit than monotherapy. Oral anticoagulation is no longer used in pulmonary arterial hypertension associated with systemic sclerosis unless there is clear evidence of associated thromboembolic disease, since co- hort studies suggest that survival is worsened by concomitant use of oral anticoagulation in this condition (likely due to associated comorbidity such as intestinal vascular disease). In advanced pulmonary arterial hypertension (PAH) surgical intervention may be useful for symptom control (septostomy) or long-term benefit (lung transplantation), but these approaches are suitable for only a few cases. Cardiac involvement Investigation and management of the cardiac manifestations of sys- temic sclerosis being summarized in Table 19.11.3.9. Post- mortem studies have identified at least three patterns of myocardial involvement in systemic sclerosis, with up to 50% of patients showing features of myocardial fibrosis. This may be dif- fuse,

in which case it may be very hard to discern noninvasively, or focal that can be detected best on MRI scan with late gadolinium enhancement. Other histological patterns of cardiac disease include contraction-band necrosis and, less frequently, inflammatory car- diomyopathy, the latter probably occurring most often in those with an inflammatory skeletal myopathy. Pericarditis and pericardial effusions are well recognized as com- plications of systemic sclerosis. They are seen particularly in the context of severe diffuse cutaneous disease and seem to be most fre- quently encountered in patients with an established or imminent scleroderma renal crisis. Echocardiographic studies often reveal small, haemodynamically insignificant effusions in patients with scleroderma. Electrophysiological cardiac abnormalities are commonly seen in patients with scleroderma, especially Q–Tc prolongation on the 12-lead electrocardiogram (ECG). Later, conduction tissue fibrosis may lead to varying degrees of heart block, including first- and second-degree block, or complete heart block necessitating pace- maker implantation. Bundle-branch blocks may reflect abnormal- ities in the conducting tissues or be complications of ventricular strain. Paroxysmal arrhythmias in those with occult cardiac disease are probably an important cause of unexplained death in patients with systemic sclerosis. Serum measurement of creatine kinase (CK), troponin, and BNP/ Nt-pro-BNP have all been used in the assessment of cardiac involve- ment. In general, the principles of management of other forms of cardiac failure are applied. Systolic dysfunction is treated with drugs to optimize function and reduce afterload, including ACEi and sometimes carvedilol or β-blockers (although these may worsen Raynaud’s). Diastolic heart failure is treated mainly by diuresis and preload reduction. Devises such as implantable cardioverter defib- rillators should be considered if there is documented arrhythmia, especially if these are associated with reduced systolic function and focal wall fibrosis.

19.11.3 Systemic sclerosis (scleroderma) 4529 Renal disease Several patterns of renal pathology are recognized in patients with scleroderma: all involve vascular abnormalities. The most clearly defined is the scleroderma renal crisis, which describes the occurrence of acute kidney injury in a patient with sclero- derma, usually associated with accelerated hypertension (fur- ther compounding the renal pathology), and in whom no other cause for nephropathy is present. However, in addition to a scleroderma renal crisis, many patients demonstrate less severe renal complications, probably associated with reduced renal blood flow and the consequent reduction in glomerular filtra- tion rate. The mechanism of this slowly progressive form of chronic renal disease is unclear. A few patients develop significant glomerulonephritis. Scleroderma renal crisis Scleroderma renal crisis occurs in 10 to 15% of patients with dif- fuse cutaneous systemic sclerosis and 1 to 2% of those with limited cutaneous systemic sclerosis. Many cases occur within the first 12 months of disease, and in up to a quarter of patients with sclero- derma renal crisis the diagnosis of systemic sclerosis is made at the time of the renal presentation. Typical presentation is with ac- celerated phase hypertension and progressive renal impairment. End-organ damage can result in encephalopathy with generalized seizures. Microangiopathic anaemia is common and disseminated intravascular coagulation sometimes develops. Before the late 1970s, renal complications were a major cause of sys- temic sclerosis-associated death, and scleroderma renal crisis was al- most always fatal. However, the routine use of angiotensin-converting enzyme inhibitors (ACEIs) has transformed outcome, with early case–control studies suggesting a fall in the 12-month mortality rate from 76% to less than 15%, although it is less clear whether these drugs, or related agents such as angiotensin receptor blockers (ARBs), are effective in preventing or abrogating the effects of scleroderma renal crisis. In several independent studies the mortality or renal outcome of scleroderma renal crisis occurring in systemic sclerosis cases already on ACEi at

the time of diagnosis appears to be worse than those not on ACEi, which means that any use as a preventative strategy should be cautious. Certain drugs, including ciclosporin and corticosteroids, have been implicated as precipitants of scleroderma renal crisis. The high risk of sudden deterioration such as renal failure, pul- monary oedema, or encephalopathy means that all patients with scleroderma renal crisis should have hospital-based treatment. Management is with ACEIs, increasing the dose every day to achieve a blood pressure reduction of 10 to 20 mm Hg systolic per 24 h, even if there is continued deterioration in renal function. Patients are also routinely given continuous low-dose prostacyclin, which may help control blood pressure and has potentially beneficial effects on renal blood flow, endothelial cell function, and production of proinflammatory or profibrotic factors, although this treatment has not formally been proved effective. Additional antihypertensive agents may be useful, including com- binations of ARBs and ACEIs or calcium channel blockers, nitrates (especially if there is pulmonary oedema), or other vasodilator agents such as doxazocin. However, vasodilatation may be associ- ated with relative hypovolaemia, so care must be taken to monitor cardiac function closely. Table 19.11.3.9 Gastrointestinal tract manifestations of systemic sclerosis Site Disorder Symptom Investigation Treatment Mouth Tight skin Dental caries Sicca syndrome Cosmetic Toothache Dry mouth None Dental radiograph Salivary gland biopsy Facial exercises Coleman fat transfer procedure can be helpful Dental treatment Artificial saliva Oesophagus Dysmobility/ oesophageal spasm Reflux oesophagitis Stricture Dysphagia Heartburn Dysphagia Barium swallow Oesophageal scintigraphy Manometry Endoscopy Proton pump inhibitors Minimize NSAID and calcium channel blocker use Elevate head of bed Avoid late meals Stomach Gastric paresis NSAID-related ulcer Anorexia Nausea Early satiety Endoscopy Scintigram Barium meal Proton pump inhibitors Metoclopramide, Domperidone Small bowel Hypomotility Stasis Bacterial overgrowth Malnutrition Pseudo-obstruction Pneumatosis intestinalis Weight loss Postprandial bloating Malabsorption Steatorrhoea Abdominal pain Distension Diarrhoea with blood; benign pneumoperitoneum Barium follow-through MRI studies Hydrogen breath test Jejunal aspiration Faecal microscopy Plain abdominal radiograph Plain abdominal radiograph Rotational antibiotics Erythromycin Metoclopramide Oral nutritional supplements Home parenteral nutrition for severe cases Percutaneous gastrostomy or jejunostomy if gastro-oesophageal disease severe Conservative management: ‘drip and suck’ Large bowel Hypomotility Colonic pseudodiverticula Pseudo-obstruction or volvulus (caecal/sigmoid) Alternating constipation and diarrhoea Rare perforation Abdominal pain Distension Barium enema Barium enema Plain abdominal radiograph Dietary manipulation Stool expanders for constipation Loperamide for diarrhoea (resection and colostomy as a last resort) Conservative management: ‘drip and suck’ Anus Sphincter involvement Faecal incontinence Rectal manometry Endoanal ultrasonography MRI Protective measures Sphincter enhancement Treat comorbidity (e.g. rectal prolapse) Sacral nerve stimulation

 After control of blood pressure has been achieved, there is a good case for pursuing renal biopsy, which can confirm the diagnosis, provide prognostic information, and may occasionally reveal cases of systemic sclerosis with inflammatory glomerular pathology that potentially requires very different treatment to that for a classic scleroderma renal crisis. Although improved by the treatment described, the outcome of a scleroderma renal crisis remains inadequate. About two-thirds of cases presenting to specialist centres will require renal replacement therapy, of which about half will eventually recover sufficiently to discontinue dialysis. This can occur up to 24 months after the crisis, so decisions about renal transplantation should be postponed until that time. Chronic nephropathy Patients who survive a scleroderma renal crisis

may develop similar but less florid proliferative changes in the interlobular and arcuate arteries. Even those who have never had a renal crisis may show re- duplication of elastic fibres, sclerosed glomeruli, tubular atrophy, and interstitial fibrosis, presumably reflecting the chronic changes of scleroderma. Glomerulonephritis There are a few case reports of glomerulonephritis occurring in systemic sclerosis, including a progressive crescentic glomer- ulonephritis in association with positive antimyeloperoxidase autoantibodies. More commonly, biopsy reveals coincident path- ologies such as drug-induced injury or overlap syndromes with fea- tures of other connective tissue disorders such as systemic lupus erythematosus. Gastrointestinal complications The most common gastrointestinal manifestation in systemic scler- osis is oesophageal dysmotility and associated reflux oesophagitis. This is almost universally present at diagnosis but fortunately often shows good symptomatic response to acid suppressive therapy with proton pump inhibitors. High doses or combination of different drug classes may be needed in refractory cases. Gastrointestinal involvement can also occur at other sites: these are described in Table 19.11.3.10, together with current management approaches for each complication. Gastric involvement typically leads to slow gastric emptying and symptoms of postprandial fullness. This, together with sicca symp- toms and difficulty swallowing, encourages poor nutritional intake and is a significant contributor to the weight loss observed in pa- tients with this disease. The earliest feature of small bowel involve- ment is also dysmotility, leading to increased intestinal transit time, which together with a propensity to form wide-mouthed jejunal diverticula leads to stagnation of the luminal contents and small intestinal bacterial overgrowth. This may in turn lead to bloating, flatulence, malabsorption, and chronic diarrhoea. End stage in- volvement of the small bowel leads to profound malabsorption and malnutrition and is a significant cause of miserable scleroderma- associated death. Large- bowel manifestations include constipation and anorectal incontinence. Alternating constipation and diar- rhoea is common and complicates management, which is generally empirical. Nutritional failure and weight loss is very frequent. It is im- portant to carefully assess the nutritional status and optimize oral intake in the context of reduced appetite, dysphagia, mouth and dental problems, and other symptoms such as bloating or diarrhoea or constipation that may all reduce nutritional intake. Enteral supplementation or tube feeding, especially jejunal tube feeding, can be given, but some cases will need home parenteral feeding. Although challenging in systemic sclerosis this can be a successful approach. Vascular manifestations in the gastrointestinal tract can be com- plicated by haemorrhage and anaemia. Gastric antral vascular ectasia is classically associated with intermittent severe anaemia and the need for regular transfusion or parenteral iron administration: it may be treated by photocoagulation. Musculoskeletal complications Musculoskeletal features are almost universal in established systemic sclerosis, although often relatively well tolerated. Arthralgia and stiffness are the most frequent symptoms. Most patients with diffuse disease experience muscle weakness, although prominent myositis is unusual. Flexion contractures of the interphalangeal joints are common and can be very debilitating. Surgical intervention can be valuable, but should focus on functional rather than cosmetic gain. Frank arthritis is uncommon and points towards an overlap syn- drome. Other musculoskeletal manifestations include carpal tunnel Table 19.11.3.10 Immunosuppressive strategies used in systemic sclerosis Agent Clinical trial data Methotrexate Two placebo-controlled trials suggest possible benefit for skin sclerosis, although this may not be clinically significant Cyclophosphamide Substantial uncontrolled evidence of efficacy for skin and lung disease. Recent placebo-controlled trials of oral or intravenous therapy are suggestive of limited benefit for lung fibrosis Mycophenolate mofetil Large experience in uncontrolled studies suggests that this drug is well tolerated and not inferior to other potent immunosuppressive agents. Small series point to benefit

in lung fibrosis Intensive immunosuppression with autologous peripheral stem cell transplantation Encouraging registry data have bene supported by the results of two controlled trials that suggest for some patients there may be benefit of agitated saline contrast test (ASCT) over intravenous cyclophosphamide but
at a cost of significant treatment related mortality of up to 10% Abatacept®, Antithymocyte globulin (ATG) Case series and cohort studies suggest potential benefit for skin disease Rituximab Case series suggest possible benefit for lung and skin fibrosis but formal evidence is lacking Tocilizumab One phase II controlled clinical trial suggests possible benefit for skin and lung disease in early diffuse SSc

19.11.3 Systemic sclerosis (scleroderma) 4531 syndrome, tendonitis (with friction rubs—most often in diffuse cu- taneous disease), and the consequences of contractures—especially affecting the hands, but also more proximal joints in diffuse Other organ involvement Neurological involvement is uncommon, but in the late stages of limited cutaneous disease a small but significant proportion of patients develop unilateral or bilateral trigeminal neuralgia. Impotence is a problem for men, usually occurring 1 to 2 years after disease onset: it is thought to have a neurovascular cause, and is refractory to treatment. Dryness of the mucous membranes is common, leading to dyspareunia. Hypothyroidism occurs in as many as 50% of patients with systemic sclerosis and is frequently missed: some patients have anti-thyroid antibodies, but lympho- cytic infiltration in the gland is uncommon, fibrosis being the more typical finding. Prognosis/Outlook As the clinical course of particular subsets of systemic scler- osis can to a great extent be predicted, appropriate classification within the scleroderma spectrum is valuable in planning disease management. Patients with limited disease have an ‘early phase’ that lasts about 10 years, when the picture is usually dominated by vascular problems such as Raynaud’s phenomenon, pitting scars, digital ulcers, and telangiectasias. Later there may be worsening of the vascular disease, both cutaneously and in the pulmonary circulation. Pulmonary interstitial disease, usually more indolent than that seen in the dif- fuse form, can also occur as a late complication. Gut involvement may worsen with time, and oesophageal strictures, malabsorption, pseudo-obstruction, and anal incontinence are all possible late and troublesome events in this subset. During the early phase of diffuse disease (the first five years), the patient is fatigued and loses weight. Hypertensive renal crisis is a real risk, and rapid progression of pulmonary and cardiac disease may occur. Arthritis, myositis, and tendon involvement can be most marked at this time. After 5 years, considered to be the late stage of diffuse disease, the constitutional symptoms settle down, the skin and musculoskeletal problems have usually reached a plateau, and there is progression of existing visceral disease but a reduced risk of new organ involvement. There have been several studies of survival in the past 50 years, and the five-year cumulative survival rate ranges from 34% to 73%. Even prolonged survival does not protect against an increased mortality risk, which continues for at least 15 years. Factors that adversely af- fect outcome are increasing age, being male, extent of skin involve- ment, and heart, lung, and renal disease. Most recent studies point to a substantial improvement in survival over the last 20 years: this is likely to be attributable to the treatment of renal crisis—previously almost invariably fatal—and perhaps to better detection and treat- ment of other major complications. In a recent single centre cohort study it was shown that over a decade from the early 1990s to the early 2000s there was significant improvement in five-year survival for unselected diffuse systemic sclerosis cases from 69% to 84%, possibly related to better ascertainment of lung complications, the commonest cause of systemic sclerosis-related death now being cardiorespiratory disease, especially pulmonary hypertension and severe lung fibrosis. Knowledge gaps and future developments Although there has been substantial progress in

understanding of pathogenesis and clinical assessment of systemic sclerosis, a better appreciation of the heterogeneity of disease, and improvements in treatment and outcome of specific complications, the knowledge gap remains one of the most challenging of the autoimmune rheumatic disease. There remain real gaps in understanding about the aetiology of the disease. This is because it has become apparent that the disease is genuinely heterogeneous. It seems plausible that a multihit mech- anism of environmental factors in a specific context will explain the condition, but some of these factors may be commonplace in com- parison to the rarity of systemic sclerosis and this is a real challenge in defining aetiology. Some of the gaps in understanding systemic sclerosis pathobiology may be filled from analysis of clinical trials data rather than discovery science in the laboratory. Understanding the genetics of the disease is highly relevant but will depend on epi- genetic and whole gene sequence analysis. There is real unmet need for treatments, despite new treatments that have emerged. Response to drugs is often incomplete and there has been a tendency to focus on life-threatening aspects of the dis- ease, whereas for patients the nonlethal burden of morbidity is often of more immediate relevance. Calcinosis, pruritus, fatigue and ano- rectal incontinence are common and very challenging manifestation in urgent need of treatment options. It seems likely that better stratifi- cation of cases, a more precise use of available treatment approaches, and improved evaluation including the integration of serum or gen- etic biomarkers with clinical tests will be possible. Paradoxically it is possible that rare but well defined diseases like systemic sclerosis may lead the way in stratified medicine and inform management of commoner diseases. FURTHER READING Bhattacharyya S, Wei J, Varga J (2011). Understanding fibrosis in
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