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HARRISON'S PRINCIPLES OF INTERNAL MEDICINE

CHAPTER 353

Systemic Sclerosis (Scleroderma) and Related Disorders

SAMPLE CHAPTER

Mc Graw Hill Education

MASTER MODERN MEDICINE

353 Systemic Sclerosis (Scleroderma) and Related Disorders

John Varga

DEFINITION AND CLASSIFICATION

Systemic sclerosis (SSc) is a complex and clinically heterogeneous orphan disease with protean clinical manifestations, a chronic and frequently progressive course, and significant disability, disfigurement and mortality. Virtually every organ can be affected **(Fig. 353-1)**.

There is marked variability among SSc patients in patterns of skin involvement, organ complications, rates of disease progression, response to treatment, and survival. The early stages of SSc are associated with prominent inflammatory features; however, over time, structural alterations in multiple vascular beds and progressive visceral organ dysfunction due to fibrosis and atrophy come to dominate the clinical picture. Classification criteria for diagnosis of SSc are shown in **Table 353-1**.

Although thick and indurated skin (*scleroderma*) is the distinguishing hallmark of SSc, skin changes also occur in localized forms of scleroderma, along with multiple metabolic, inherited and autoimmune disorders **(Table 353-2)**. Patients with SSc can be broadly segregated into two major subsets defined by the pattern of skin involvement, clinical and laboratory features, and natural history **(Table 353-3)**. Diffuse cutaneous SSc (dcSSc) is typically associated with extensive skin induration starting in the fingers (sclerodactyly) and ascending from distal to proximal limbs and the trunk. In these patients, interstitial lung disease (ILD) and acute renal involvement develop relatively early. In contrast, in patients with limited cutaneous SSc (lcSSc), Raynaud's phenomenon generally precedes other disease manifestations, sometimes by years. In these patients, skin involvement remains confined to the fingers, distal limbs, and face, while the trunk is spared. The constellation of calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia, was historically termed the *CREST syndrome*. In lcSSc, visceral organ involvement tends to show insidious progression, and digital ischemic ulcers, pulmonary arterial hypertension (PAH), hypothyroidism, and primary biliary cirrhosis may occur as late complications. In some patients, Raynaud's phenomenon and characteristic clinical and laboratory features of SSc occur in the absence of detectable skin thickening. This syndrome has been termed *SSc sine scleroderma.*

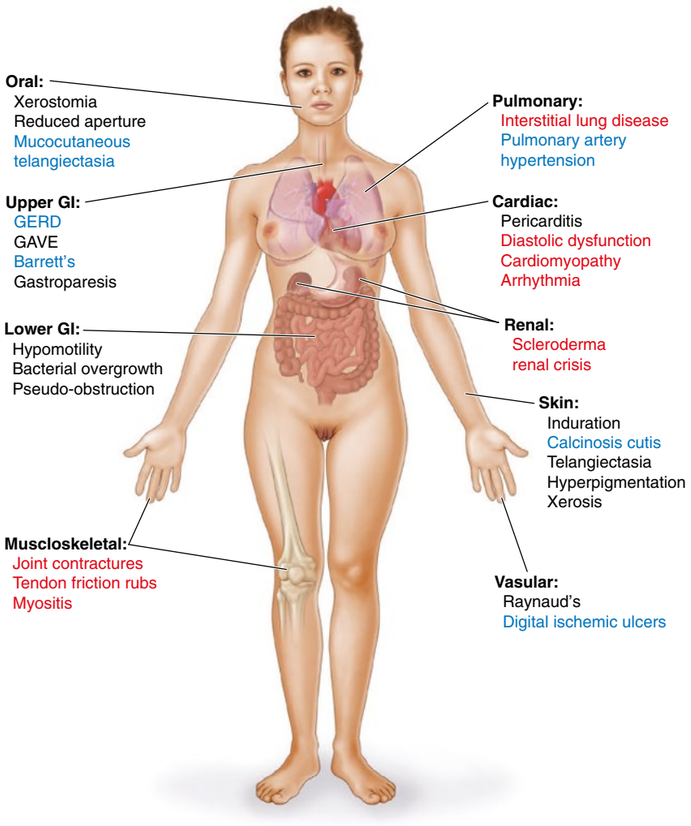


FIGURE 353-1 Multi-organ involvement in systemic sclerosis. Prominent complications more common in diffuse cutaneous SSc are shown in red; more common in limited cutaneous SSc in blue; and common in both forms of SSc shown in black.

INCIDENCE AND PREVALENCE

SSc is an acquired sporadic disease with a worldwide distribution and affecting all races. In the United States, the incidence is 9–46 cases per million per year. There are an estimated 100,000 U.S. cases, although this number may be significantly higher if patients who do not meet classification criteria are also included. There are large regional variations in incidence rates, potentially reflecting differences in case definition, environmental exposures or susceptibility genes in populations with different ancestries. Prevalence rates in England, Europe, and Japan appear to be lower than in North America and Australia. Age, sex, and ethnicity influence disease susceptibility, and blacks have higher age-specific incidence rates. In common with other connective tissue diseases, SSc shows a strong female predominance (4.6:1), which is most pronounced in the childbearing years and declines after menopause. An additional risk factor is having an affected first-degree family member, which increases disease risk 13-fold. Although SSc can present at any age, the peak age of onset in women with both lcSSc and dcSSc is 65–74 years, although in blacks, disease onset occurs at an earlier age. Furthermore, blacks with SSc are more likely to have dcSSc, ILD, and a worse prognosis.

GENETIC CONTRIBUTION TO DISEASE PATHOGENESIS

SSc is a polygenic disease. In general, the genetic associations of SSc identified to date make only a small contribution to disease susceptibility. Disease concordance rates are low (4.7%) in monozygotic twins, although concordance for antinuclear antibody (ANA) positivity is significantly higher. On the other hand, evidence for genetic contribution to disease susceptibility is provided by the observation that 1.6% of SSc patients have a first-degree relative with SSc, a prevalence rate markedly increased compared to the general population. The risk of Raynaud's phenomenon, ILD, and other autoimmune diseases, including systemic lupus erythematosus (SLE) **(Chap. 349)**, rheumatoid arthritis **(Chap. 351)**, and autoimmune thyroiditis **(Chap. 375)**, is also increased in first-degree relatives. Current approaches to uncover genetic factors in SSc include DNA sequencing and single nucleotide polymorphism (SNP) analysis of candidate genes, and SNP analysis of the entire genome in a hypothesis-free manner. Genome-wide association studies (GWASs) involve large multi-center and multi-national cohorts. A majority of the robustly validated susceptibility loci for SSc are genes involved in innate and adaptive immune responses, highlighting the importance of autoimmunity as the initial trigger for the disease. Genetic studies have shown associations with common (small effect size) variants related to B and T lymphocyte activation and signaling (*BANK1, BLK, CD247, STAT4, IL2RA, CCR6, IDO1, TNFSF4/OX40L, PTPN22*, and *TNIP1*). In addition, candidate gene studies and GWASs identified a strong association with human leukocyte antigen (HLA)-Class II haplotypes on chromosome 6, including *HLA-DRB1*11:04, DQA1*05:01*, and *DQB1*03:01*, and the non-HLA genes histocompatibility complex (MHC) genes *NOTCH4* and *PSORSC1*. Other genetic variants associated with SSc are involved in innate immunity and the interferon pathways (*IRF5, IRF7, STAT4, TNFAIP3/A20, GSDMA, PRDM1 (BLIMP1), TNFAIP3*, and *TLR2*). Additional associations with *IL12RB2, IL-21*, the apoptosis-related genes *DNASE1L3* and *SOX5*, and the fibrosis-related genes *CSK, CAV1, PPARG,* and *GRB10* have been reported. In addition to disease susceptibility, some of these genetic loci are associated with particular disease manifestations or serologic subsets, including ILD (*CTGF, CD226*), PAH (*TNIP1*), and scleroderma renal crisis (*HLA-DRB1**). While the functional consequences of these gene variants and their potential roles in pathogenesis are currently not well understood, it seems likely that in combination they cause a state of altered immune regulation, leading to increased susceptibility to autoimmunity and persistent inflammation. Of note, many of the genetic variants associated with SSc are also implicated in other autoimmune disorders, including SLE, rheumatoid arthritis, and psoriasis, suggesting common pathogenic pathways shared among these phenotypically dissimilar conditions. The genetic associations identified to date only explain a fraction of the heritability of SSc, and GWASs, and whole exome sequencing to identify additional genetic susceptibility factors in SSc, particularly rare (and potentially causal) variants, are currently ongoing.

TABLE 353-1 Classification Criteria for Diagnosis of Systemic Sclerosis

ITEM	SUB-ITEM	WEIGHT/SCORE
Skin thickening (bilateral)—fingers extending proximal to MCP joints		9
Skin thickening of fingers only	Puffy fingers	2
	Sclerodactyly (skin thickened distal to MCP joints)	4
Fingertip lesions	Digital tip ulcer or pitting scar	2
		3
Mucocutaneous telangiectasia		2
Abnormal nails capillary pattern		2
Lung involvement	PAH	2
	Interstitial lung disease	2
Raynaud's phenomenon		3
SSc-specific autoantibodies	ACA	3
	Scl-70	
	RNA polymerase III	

Abbreviations: ACA, anterior cerebral artery; MCP, metacarpophalangeal joint; PAH, pulmonary arterial hypertension.

TABLE 353-2 Conditions Associated with Skin Induration

Systemic sclerosis (SSc)
Limited cutaneous SSc
Diffuse cutaneous SSc
Localized scleroderma
Guttate (plaque) morphea, bullous morphea
Linear scleroderma, coup de sabre, hemifacial atrophy
Pansclerotic morphea
Overlap syndromes
Mixed connective tissue disease
SSc/polymyositis
Diabetic scleredema and scleredema of Buschke
Scleromyxedema (papular mucinosis)
Chronic graft-versus-host disease
Diffuse fasciitis with eosinophilia (Shulman's disease, eosinophilic fasciitis)
Stiff skin syndrome
Pachydermatoperiostosis (Primary hypertrophic osteoarthropathy)
Chemically induced and drug-associated scleroderma-like conditions
Vinyl chloride–induced disease
Eosinophilia-myalgia syndrome (associated with L-tryptophan contaminant exposure)
Nephrogenic systemic fibrosis (associated with gadolinium exposure)
Paraneoplastic syndrome

TABLE 353-3 Subsets of Systemic Sclerosis (SSc): Features of Limited Cutaneous SSc versus Diffuse Cutaneous Disease

CHARACTERISTIC FEATURE	LIMITED CUTANEOUS SSc	DIFFUSE CUTANEOUS SSc
Skin involvement	Indolent onset. Limited to fingers, distal to elbows, face; slow progression	Rapid onset. Diffuse: fingers, extremities, face, trunk; rapid progression
Raynaud's phenomenon	Antedates skin involvement, sometimes by years; may be associated with critical ischemia in the digits	Onset coincident with skin involvement; critical ischemia less common
Musculoskeletal	Mild arthralgia	Severe arthralgia, carpal tunnel syndrome, tendon friction rubs; small and large joint contractures
Interstitial lung disease	Slowly progressive, generally mild	Frequent, early onset and progression, can be severe
Pulmonary arterial hypertension	Frequent, late, may occur as an isolated complication	Often occurs in association with interstitial lung disease
Scleroderma renal crisis	Very rare	Occurs in 15%; onset may be fulminant; generally early (<4 years from disease onset)
Calcinosis cutis	Frequent, prominent	Less common, mild
Characteristic autoantibodies	Anti-centromere	Anti–topoisomerase I (Scl-70), anti-RNA polymerase III

ENVIRONMENTAL AND OCCUPATIONAL RISK FACTORS

Given the relatively modest genetic contribution to disease susceptibility in SSc, environmental factors, such as infectious agents, intestinal microbiota, and occupational, dietary, lifestyle, and drug exposures, are likely to play a major role. Some evidence suggests potential roles for parvovirus B19, Epstein-Barr virus (EBV), cytomegalovirus (CMV), and *Rhodotorula glutinis* and other microorganisms. An epidemic of a novel syndrome with features suggestive of SSc occurred in Spain in the 1980s. The outbreak, termed *toxic oil syndrome*, was linked to use of contaminated rapeseed oil for cooking. Another epidemic outbreak, termed *eosinophilia-myalgia syndrome* (EMS), was linked to consumption of L-tryptophan-containing dietary supplements. Exposure to gadolinium contrast material in patients with renal compromise undergoing magnetic resonance scanning has been associated with nephrogenic systemic fibrosis. While each of these novel toxic-epidemic syndromes was characterized by chronic indurative skin changes and variable visceral organ involvement, the constellation of associated clinical, pathologic, and laboratory features distinguishes them from SSc. Occupational exposures tentatively linked with SSc include particulate silica (quartz), polyvinyl chloride, epoxy resins, welding fumes, and organic solvents and aromatic hydrocarbons including pain thinners, toluene, xylene, and trichloroethylene. These exposures might elicit

stable and heritable epigenetic changes such as DNA methylation and histone modification underlying pathogenic alterations in gene expression. Drugs implicated in SSc-like illnesses include bleomycin, pentazocine, and cocaine, and appetite suppressants linked with PAH. Radiation therapy for cancer has been linked with *de novo* onset of SSc as well as with exacerbation of pre-existing SSc. In contrast to rheumatoid arthritis, cigarette smoking does not increase the risk of SSc. Although case reports and series of SSc in women with silicone breast implants had raised concern regarding a possible causal role of silicone in SSc, large-scale epidemiologic investigations found no evidence of increased prevalence of SSc.

PATHOGENESIS

Three cardinal pathomechanistic processes underlie the protean clinical manifestations of SSc: (1) diffuse microangiopathy, (2) inflammation and autoimmunity, and (3) visceral and vascular fibrosis in multiple organs (Fig. 353-2). While all three processes are concurrently operative in SSc patients, their activity, relative severity, and contribution to the overall clinical picture vary among individual patients and over time. In general, autoimmunity and altered vascular reactivity occur early, while fibrosis and atrophy occur later in the disease. Complex and dynamic interplay among these processes initiates and sustains the fibrotic process and tissue damage.

ANIMAL MODELS OF DISEASE

No single animal model of SSc fully reproduces the three cardinal processes that underlie pathogenesis, but some recapitulate selected aspects of the human disease. Tight-skin mice (Tsk1/+) spontaneously develop skin fibrosis due to a mutation in the fibrillin-1 gene. Mutant fibrillin-1 protein disrupts extracellular matrix assembly and causes aberrant activation of transforming growth factor β (TGF-β). Fibrillin-1 mutations in humans are associated with Marfan's disease and stiff skin syndrome, but have not been reported in SSc. Skin and lung fibrosis accompanied by variable vasculopathy and autoimmunity can be elicited in mice by injection of bleomycin or Angiotensin II, or by transplantation of HLA-mismatched bone marrow or spleen cells. Targeted genetic modifications in mice give rise to new disease models for investigating the pathogenetic roles of individual molecules, pathways, and cell types. For example, mice lacking IRF5, Smad3, uPAR, or peroxisome proliferator-activated receptor (PPAR)-γ, or constitutively overexpressing β-catenin, Wnt10b, sirtuin 3, Fra-2, TGFB1, PDGFRα, or adiponectin are either resistant or hypersensitive to experimental scleroderma, or spontaneously develop fibrosis. These disease models can contribute to understanding specific aspects of SSc pathogenesis, and to discovery and validation of novel targets for therapy.

MICROANGIOPATHY

Vascular injury is an early and possibly primary pathogenic event in SSc that leads to protean clinical manifestations of small vessel vasculopathy (Fig. 353-3).

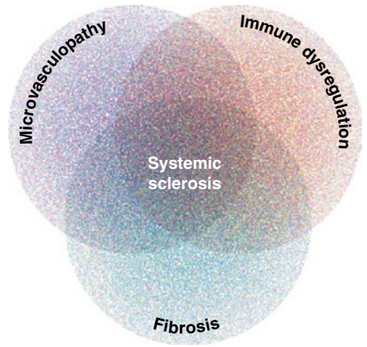


FIGURE 353-2 The characteristic constellation of vasculopathy, autoimmunity/inflammation and fibrosis underlies the protean clinical manifestations of systemic sclerosis.

Prominent microangiopathy in multiple vascular beds has important clinical sequelae including mucocutaneous telangiectasiae, Raynaud's phenomenon, ischemic digital ulcers, scleroderma renal crisis, myocardial involvement, and PAH. Raynaud's phenomenon is characterized by altered blood-flow response to cold challenge in small digital arteries. This initially reversible functional abnormality is associated with autonomic and peripheral nervous system alterations, including impaired production of the neuropeptide calcitonin gene-related peptide from sensory afferent nerves and heightened sensitivity of α_2-adrenergic receptors on vascular smooth-muscle cells. Isolated (primary) Raynaud's disease is common, generally benign and non-progressive. In contrast, secondary Raynaud's phenomenon in SSc is often progressive and complicated by irreversible structural changes, culminating in ischemic digital ulcers, necrosis, and amputation.

Viruses, cytotoxic factors, and chemokines thrombogenic microparticles, alternate complement pathway activation and autoantibodies targeting endothelial cells, phospholipids, and β2 glycoprotein I (β2GPI) are implicated as potential triggers of endothelial cell injury. Endothelial damage results in dysregulated production of vasodilatory (nitric oxide and prostacyclin) and vasoconstricting (endothelin-1) substances, as well as upregulation of intercellular adhesion molecule 1 (ICAM-1) and other surface adhesion molecules. Microvessels show enhanced permeability and transendothelial leukocyte diapedesis, abnormal activation of coagulation cascades, elevated thrombin production, and impaired fibrinolysis. Spontaneous platelet aggregation causes release of serotonin, platelet-derived growth factor (PDGF), and platelet alpha granules including thromboxane, a potent vasoconstrictor. Smooth-muscle cell–like myointimal cells in the media proliferate, the basement membrane is thickened and reduplicated, and perivascular adventitial fibrosis develops. The vasculopathic process affects capillaries, as well as arterioles, and less commonly even large vessels in many organs, resulting in reduced blood flow and tissue ischemia. Progressive luminal occlusion due to intimal and medial hypertrophy, combined with persistent endothelial cell damage and adventitial fibrosis, establish a vicious cycle that culminates in the striking absence of small blood vessels (rarefaction) in late-stage disease. Recurrent ischemia-reperfusion generates reactive oxygen species (ROS) that further damages the endothelium through peroxidation of membrane lipids. Paradoxically, the process of revascularization that normally reestablishes blood flow to ischemic tissue is defective in SSc despite elevated levels of other angiogenic factors. Moreover, bone marrow–derived circulating endothelial progenitor cells are reduced in number and impaired in function. Widespread capillary loss, obliterative vasculopathy of small and medium-sized arteries, and impaired ability to repair and replace damaged vessels are hallmarks of SSc.

INFLAMMATION AND AUTOIMMUNITY

Cellular Immunity The following observations provide support for the inflammatory/autoimmune nature of SSc: near-universal presence of circulating autoantibodies with defined specificities; familial clustering of SSc with other autoimmune diseases; detection of activated immune cells, including T cells with oligoclonal antigen receptors and T follicular helper-like cells, in target organs; prominent type I interferon (IFN) signatures, characterized by elevated expression of IFN-regulated genes, in a variety of cell types; elevated circulating levels and spontaneous secretion from mononuclear cells of cytokines and chemokines such as interleukin-6 (IL-6); tumor necrosis factor, IL-4, IL-10, IL-17, IL-33, CCL2, and CXCL4; genetic association of SSc with variants of MHC and other genes functionally implicated in the immune response; and the rapid clinical response, fibrosis resolution, and vascular regeneration observed in some SSc patients treated with immunomodulatory or immunoablative therapies. Genetic studies reveal strong associations with MHC locus alleles, as well as non-HLA-linked genes encoding mediators of both adaptive and innate immune responses (*CD247, STAT4, IRF5, CD226, TNFAIP3/A20*, and *TNFSF4*).

Circulating monocytes from SSc patients overexpress IFN-regulated genes such as Siglec-1, have reduced levels of caveolin-1, and exhibit an inherently profibrotic phenotype. In early (edematous) stage SSc,

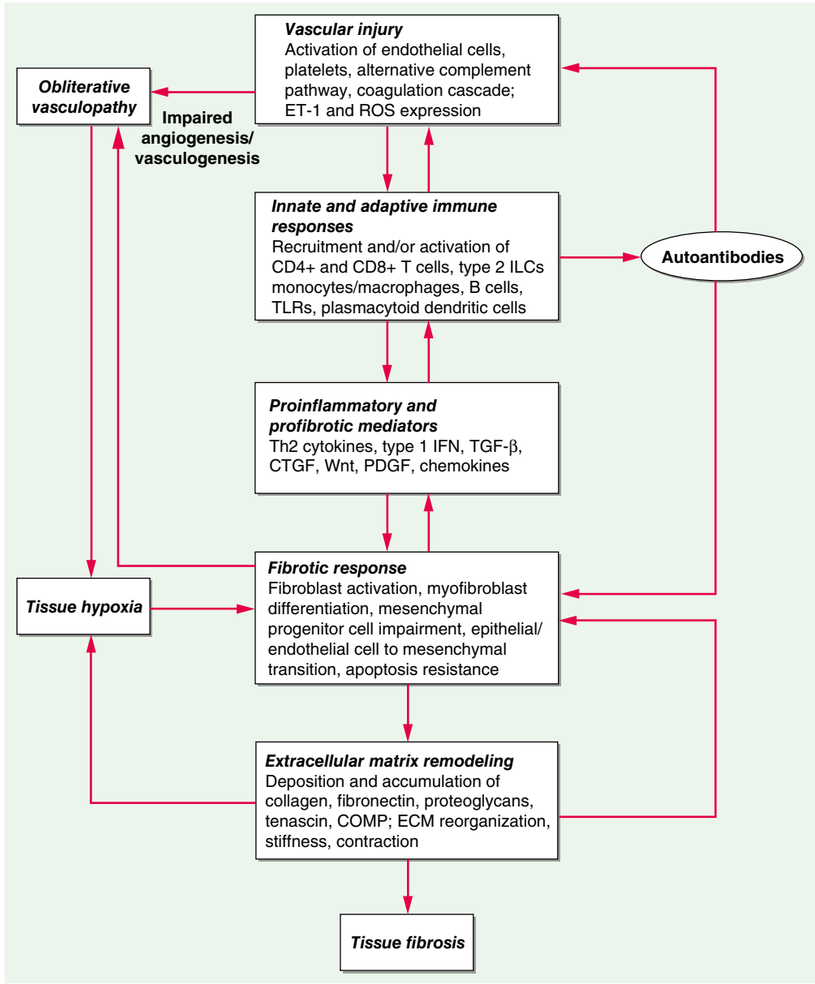


FIGURE 353-3 Initial vascular injury in a genetically susceptible individual triggers functional and structural vascular alterations, inflammation and autoimmunity, culminating in fibrosis. Inflammatory and immune responses initiate and sustain fibroblast activation and differentiation, resulting in pathologic fibrogenesis and irreversible tissue damage. Vascular damage results in tissue ischemia that further contributes to progressive fibrosis and atrophy. COMP, cartilage oligomeric matrix protein; CTGF, connective tissue growth factor; PDGF, platelet-derived growth factor; ROS, reactive oxygen species; TGF-β, transforming growth factor β; TLR, toll-like receptor.

mononuclear cell infiltrates comprised of activated T cells, monocytes/macrophages, and dendritic cells can be seen in skin, lungs, and other affected organs prior to appearance of fibrosis or vascular damage. Dendritic cells can be found in close proximity to activated fibroblasts and myofibroblasts and express toll-like receptors (TLR) and secrete IFN, IL-10, thymic stromal lymphopoietin (TSLP), and CXCL4, shaping the adaptive immune response and contributing to loss of immune tolerance. Tissue-infiltrating T cells express CD45 and HLA-DR activation markers and display restricted T cell receptor signatures indicative of oligoclonal expansion in response to recognition of as-yet unknown antigen. Of note, in patients diagnosed with SSc in close temporal association with cancer who are RNA polymerase III antibody-positive, the tumor may show mutations in RNApol3 autoantigen, which results in the generation of mutant-specific T cell immunity and cross-reactive antibodies. These findings support the premise that an abnormal antigen might act as initial trigger for the autoimmune response in SSc.

Circulating T cells in SSc express chemokine receptors and α_1 integrin, accounting for their enhanced binding to endothelium and to fibroblasts, while endothelial cells express ICAM-1 and other adhesion molecules that facilitate leukocyte diapedesis. Activated T cells show a T_H2-polarized immune response driven by dendritic cells. The T_H2 cytokines IL-4, IL-13, IL-33, and TSLP induce fibroblast activation, whereas the T_H1 cytokine interferon γ (IFN-γ) blocks cytokine-mediated fibroblast activation and exhibits anti-fibrotic properties. Evidence for altered Th17 and regulatory T cell (Treg) numbers and function in SSc has been reported. Type 2 innate lymphoid cells (iLCs), a recently discovered lymphoid cell population implicated in type 2 immunity and tissue remodeling, are also elevated in SSc skin biopsies. Alternately activated M2 macrophages, which produce TGF-β and promote angiogenesis and tissue remodeling, are increased in the skin in SSc. Although the frequency of regulatory T cells that enforce immune tolerance is elevated in the circulation and tissues, their immunosuppressive function appears to be defective. Some evidence implicates altered B cell homeostasis and function in SSc. Circulating B cells show elevated CD19 and co-stimulatory molecules CD80 and CD86, suggesting B cell chronic activation. Serum levels of a proliferation-inducing ligand (APRIL) and

B cell activating factor (BAFF), members of the TNF superfamily with potent effects on B cell activation, are elevated in SSc, and associate with extent of skin and lung involvement. B cells secrete IL-6, TGF-β, and other profibrotic cytokines implicated in pathogenesis. Thus, B cell hyperactivity in SSc might directly contribute to the inflammatory and fibrotic processes, as well as generation of autoantibodies. Microarray analysis identifies a distinct subset of SSc skin biopsies with elevated expression of inflammation-related genes. Evidence of innate immune and TLR signaling, reflecting activation by type 1 IFN from plasmacytoid dendritic cells, is prominent in peripheral blood cells and target organs.

Humoral Autoimmunity Circulating ANAs can be detected by indirect immunofluorescence in virtually all patients with SSc, even in early stages of disease. In addition, several SSc-specific autoantibodies with distinct patterns of immunofluorescence show strong associations with unique disease endophenotypes (Table 353-4). These antibodies are directed mostly against intracellular proteins associated with transcription, DNA repair, and RNA processing. Owing to their high specificity, mutual exclusivity and association with unique disease manifestations, SSc-associated autoantibodies have substantial utility in clinical practice as diagnostic and prognostic markers, while their role in monitoring disease activity remains uncertain. Moreover, antibodies directed against fibrillin-1, matrix metalloproteinases, cell surface markers Angiotensin II receptor, endothelin-1 receptor, muscarinic 3 receptor, or the PDGF receptor, have been described in patients with SSc, although their clinical relevance is not yet established. These antibodies manifest functional receptor agonist activity and might have direct pathogenic roles.

A variety of mechanisms have been proposed to account for the generation of SSc-associated autoantibodies. Proteolytic cleavage, increased expression or altered subcellular localization of normal proteins, or their alterations due to mutation in the case of certain tumors, could lead to immune recognition as neoepitopes, resulting in the breaking of immune tolerance.

TABLE 353-4 Major Systemic Sclerosis-Specific Autoantibodies and Principal Associated Features

TARGET ANTIGEN	SSc SUBSET	PROMINENT CHARACTERISTIC CLINICAL ASSOCIATION
DNA Topoisomerase I (Scl-70) Speckled pattern	dcSSc	Tendon friction rubs, digital ischemic ulcers, scleroderma, extensive skin involvement, early ILD, cardiac involvement, scleroderma renal crisis
Centromere proteins Discreet speckled (centromere) pattern	lcSSc	Digital ischemic ulcers, calcinosis cutis, isolated PAH; renal crisis rare
RNA polymerase III Speckled pattern	dcSSc	Rapidly progressive skin, tendon friction rubs, joint contractures, GAVE, renal crisis, contemporaneous cancers; digital ulcers rare
U3-RNP (fibrillarin) Nucleolar pattern	dc/lcSSc	PAH, ILD, scleroderma renal crisis, GI tract involvement, myositis
Th/T_0 Nucleolar pattern	lcSSc	ILD, PAH
PM/Scl Nucleolar pattern	lcSSc	Calcinosis cutis, ILD, myositis overlap
Ku Speckled pattern	Overlap	SLE, myositis overlap
U1-RNP Speckled pattern	MCTD	PAH, inflammatory arthritis, myositis overlap
U11/U12 RNP Speckled pattern	dc/lcSSc	ILD

Abbreviations: dcSSc, diffuse cutaneous SSc; GAVE, gastric antral vascular ectasia; ILD, interstitial lung disease; lcSSc, limited cutaneous SSc; MCTD, mixed connective tissue disease; PAH, pulmonary arterial hypertension; SLE, systemic lupus erythematosus.

FIBROSIS

Fibrosis affecting multiple organs is a distinguishing feature of SSc. The process is characterized by replacement of normal tissue architecture with dense, rigid, avascular, and relatively acellular connective tissue. Fibrosis in SSc follows, and is a consequence of, inflammation, autoimmunity, and microvascular damage (Fig. 353-3). Fibroblasts are mesenchymal cells primarily responsible for the functional and structural integrity of connective tissue. Upon their activation by extracellular cues, fibroblasts proliferate, migrate, secrete collagens and other matrix molecules, growth factors, chemokines, and cytokines, and transdifferentiate into contractile myofibroblasts. Under normal conditions, these self-limited responses accomplish physiologic repair and regeneration of tissue. In contrast, when these responses become sustained and amplified, pathologic fibrosis results. Stimulatory signaling by endogenous TGF-β and paracrine fibrotic mediators including IL-6, IL-13, Wnt ligands, connective tissue growth factor (CTGF), PDGF, lysophosphatidic acid, endothelin-1, hypoxia, ROS, thrombin, and mechanical forces are responsible for sustained fibroblast activation underlying non-resolving fibrosis in SSc. Buildup of damage-associated endogenous ligands for TLR4 (EDA-fibronectin, high mobility group B1 [HMGB1] and Tenascin-C) and for TLR9 (mitochondrial DNA) within the fibrotic microenvironment further contributes to non-resolving fibrosis.

In addition to tissue-resident fibroblasts and transformed myofibroblasts, bone marrow–derived circulating mesenchymal progenitor cells also contribute to fibrosis. The factors that regulate the differentiation of mesenchymal progenitor cells and their trafficking from the circulation into lesional tissue are unknown. Epithelial and endothelial cells, mesenchymal progenitor cells, preadipocytes and tissue fibroblasts have all been proposed as sources of myofibroblasts in fibrosis. Although myofibroblasts are transiently found in normal wound healing, their persistence in fibrotic tissue, possibly due to resistance to apoptosis, contributes to scar formation.

Explanted SSc fibroblasts display an abnormally activated phenotype ex vivo, with variably increased rates of collagen production, spontaneous ROS generation, prominent stress fibers, and constitutive expression of alpha smooth-muscle actin. Persistence of the "scleroderma phenotype" during serial ex vivo passage of SSc fibroblasts may reflect autocrine TGF-β stimulatory loops, deregulated microRNA expressions, or stable acquired epigenetic modifications in these cells.

PATHOLOGY

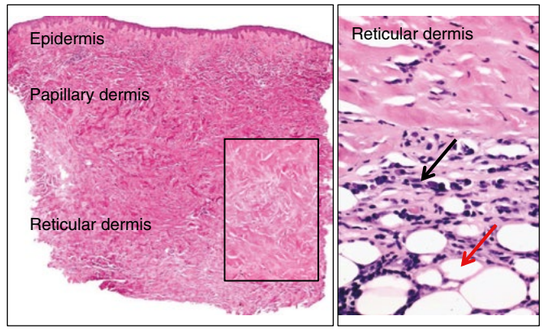
While pathological findings in SSc vary across anatomic sites, the distinguishing hallmark of SSc irrespective of the organ system is the triad of widespread capillary loss and obliterative microangiopathy, combined with fibrosis in the skin and internal organs. In early-stage disease, perivascular inflammatory cell infiltrates composed of T and B lymphocytes, activated monocytes and macrophages and mast cells may be detected in multiple organs. A non-inflammatory obliterative microangiopathy is a prominent late finding in the heart, lungs, kidneys, and gastrointestinal tract. Fibrosis is found in the skin, lungs, cardiovascular and gastrointestinal systems, tendon sheaths, perifascicular tissue surrounding skeletal muscle, and some endocrine organs. Excessive accumulation of collagens, proteoglycans, COMP and other structural matrix macromolecules progressively disrupts normal architecture, resulting in impaired function and failure of affected organs.

SKIN

The dermis is thickened, and accumulation of broad bundles of homogenized collagen oriented parallel to the epithelium is seen (Fig. 353-4*A*). Adnexal glands are atrophic, and loss of periadnexal and intradermal white adipose tissue and its replacement with collagen can be striking. While perivascular mononuclear cell infiltrates may be seen early, established skin fibrosis generally shows absence of inflammation. These findings are histologically indistinguishable from those in localized scleroderma.

LUNGS

Autopsy studies in SSc universally show evidence of lung involvement. Most common is a nonspecific interstitial pneumonia (NSIP) pattern characterized by variable interstitial fibrosis and mild chronic inflammation. Patchy infiltration of the alveolar walls with T lymphocytes, macrophages, and eosinophils may occur in early disease. With progression, interstitial fibrosis and vascular damage dominate, often coexisting within the same biopsy. The usual interstitial pneumonia (UIP) pattern of spatial/temporal heterogeneity of inflammation, fibrosis and fibrotic foci seen in idiopathic pulmonary fibrosis is less common in SSc (Fig. 353-4*B*). Fibrosis of the alveolar septae results in obliteration of the airspaces and loss of pulmonary blood vessels. This process impairs gas exchange and contributes to pulmonary hypertension. Intimal thickening of the pulmonary arteries, best seen with elastin stain, underlies SSc-associated PAH (Fig. 353-4*C*) and, at autopsy, is often associated with multiple pulmonary emboli and myocardial fibrosis. Patients may also show fibrosis and intimal proliferation in preseptal venules and veins in the lung, accounting for veno-occlusive disease. Lymphocytic bronchiolitis involving the submucosa of the terminal bronchioles may also be seen.



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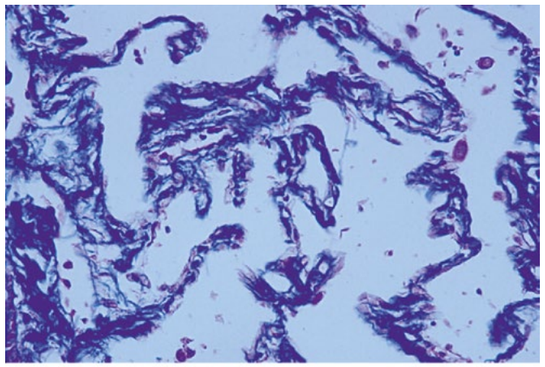

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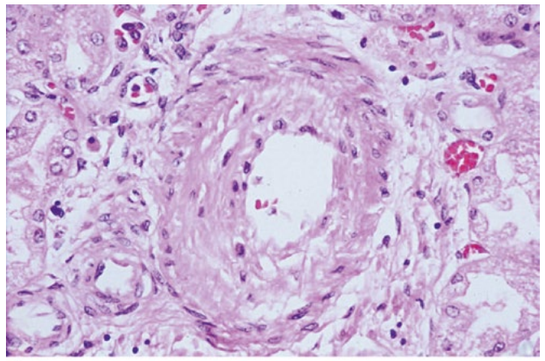

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FIGURE 353-4 Pathologic findings in systemic sclerosis (SSc). ***A. Left panel:*** The skin is thickened due to expansion of the dermis. Inset, higher magnification showing thick hyalinized collagen bundles replacing skin appendages. ***Right panel:*** Mononuclear inflammatory cells within the intradermal adipose tissue. Black arrow, collagen; red arrow, dermal adipocytes. ***B.*** Early SSc-ILD. Diffuse fibrosis of the alveolar septae and a chronic inflammatory cell infiltrate. Trichrome stain. ***C.*** Pulmonary arterial obliterative vasculopathy. Striking intimal hyperplasia and luminal narrowing of small pulmonary artery, with little inflammation and minimal interstitial fibrosis, in a patient with SSc-PAH.

GASTROINTESTINAL TRACT

Pathologic changes can be found at any level from the mouth to the rectum. Atrophy and fibrosis of the muscularis propria and characteristic vascular lesions are prominent in the lower esophagus, while striated muscle in the upper third of the esophagus is generally spared. Collagenous replacement of the normal intestinal tract architecture results in impaired smooth muscle contractility and diminished peristaltic activity, with dysmotility, bacterial overgrowth, small-bowel obstruction, and perforation. Chronic gastroesophageal reflux is associated with esophageal inflammation, mucosal ulceration, and stricture formation and may lead to Barrett's metaplasia with attendant risk of adenocarcinoma. Esophageal dilation and reflux are associated with ILD due to chronic microaspiration.

KIDNEYS

In the kidneys, vascular lesions affecting the interlobular and arcuate arteries predominate. Chronic renal ischemia is associated with shrunken glomeruli. Patients with scleroderma renal crisis show acute fibrinoid necrosis of afferent arterioles, followed by intimal proliferation (onion-skin pattern), and ischemic collapse of glomeruli. These changes are reminiscent of thrombotic microangiopathies such as atypical hemolytic-uremic syndrome (see Chap. 304), and are accompanied by complement deposition, thrombosis, thrombocytopenia due to platelet consumption, and intravascular hemolysis. Extensive vascular thrombosis, glomerular collapse and sclerosis, and peritubular capillary deposits in renal biopsy are associated with irreversible renal failure.

HEART

Subclinical cardiac pathology is common, with prominent involvement of the myocardium and pericardium. The characteristic arteriolar lesions are concentric intimal hypertrophy and luminal narrowing, accompanied by patchy contraction band necrosis, loss of cardiac myocytes, and myocardial fibrosis due to microvascular involvement and ischemia-reperfusion injury. Fibrosis of the conduction system is common, especially at the sinoatrial node. The frequency of epicardial atherosclerotic coronary artery disease may be increased compared to the general population, similar to other systemic inflammatory diseases. Pericardial involvement with chronic inflammatory infiltrates and fibrinous exudates is common and may be associated with pericardial effusions.

PATHOLOGY IN OTHER ORGANS

Synovitis may be found in early SSc; with disease progression, the synovium becomes fibrotic, and in contrast to rheumatoid disease, pannus formation or bone resorption are uncommon. Fibrosis of tendon sheaths and fascia, sometimes accompanied by calcifications, produces palpable and sometimes audible tendon friction rubs. Inflammation and, in later stages, atrophy and fibrosis of skeletal muscles are common findings, and are similar to those in polymyositis. Fibrosis of the thyroid gland and of the minor salivary glands may be seen. Placentas from SSc pregnancies show decidual vasculopathy, which is associated with poor perinatal outcomes and fetal death.

CLINICAL FEATURES

OVERVIEW

SSc can affect virtually any organ (Fig. 353-1 and Table 353-5). Although a dichotomous approach stratifying SSc into diffuse and limited cutaneous subsets (Table 353-2) is useful, disease expression is far

TABLE 353-5 Frequency of Clinical Organ Involvement in Limited Cutaneous and Diffuse Cutaneous Systemic Sclerosis (SSc)

FEATURES	LIMITED CUTANEOUS SSc (%)	DIFFUSE CUTANEOUS SSc (%)
Skin involvement	90[a]	100
Raynaud's phenomenon	99	98
Ischemic digital ulcers	50	25
Esophageal involvement	90	80
Interstitial lung disease	35	65
Pulmonary arterial hypertension	15	15
Myopathy	11	23
Clinical cardiac involvement	9	12
Scleroderma renal crisis	2	15
Calcinosis cutis	—	—

[a]Approximately 10% of patients have SSc *sine* scleroderma.

more complex, and multiple distinct endophenotypes with unique patterns of manifestations can be recognized within each subset. Unique endophenotypes associate with autoantibodies with distinct and mutually exclusive specificities (Table 353-4). Patients with SSc "overlap" have typical features coexisting with clinical and laboratory evidence of another autoimmune disease, most commonly polymyositis, Sjögren's syndrome, polyarthritis, autoimmune liver disease, or SLE.

INITIAL CLINICAL PRESENTATION

Characteristic initial presentation is quite different in patients with the diffuse (dcSSc) versus limited (lcSSc) cutaneous forms of the disease. In dcSSc, the interval between Raynaud's phenomenon and onset of other disease manifestations is brief (weeks to months). Soft tissue swelling, puffy fingers, and intense pruritus are signs of the early inflammatory "edematous" phase. The fingers, distal limbs, and face are usually affected first. Diffuse hyperpigmentation of the skin, carpal tunnel syndrome arthralgias, muscle weakness, fatigue, and decreased joint mobility are common. During the ensuing weeks to months, the inflammatory edematous phase evolves into the "fibrotic" phase, with skin induration associated with hair loss, reduced production of skin oils, and decline in sweating capacity. Progressive flexion contractures of the fingers ensue. The wrists, elbows, shoulders, hip girdles, knees, and ankles become stiff due to fibrosis of the supporting joint structures. While advancing skin involvement is the most visible manifestation of early dcSSc, important and clinically silent internal organ involvement commonly occurs during this stage. The initial 4 years from disease onset is the period of most rapidly evolving pulmonary and renal damage. If organ failure does not occur during this phase of dcSSc, the systemic process may stabilize.

Compared to dcSSc, the course of lcSSc tends to be more indolent. The interval between onset of Raynaud's phenomenon and disease manifestations such as GERD, cutaneous telangiectasia, or soft tissue calcifications can be as long as years. Scleroderma renal crisis, significant ILD, and tendon friction rubs occur rarely in lcSSc, while PAH, and overlap with keratoconjunctivitis sicca, polyarthritis, cutaneous vasculitis, and biliary cirrhosis can develop many years after disease onset.

ORGAN INVOLVEMENT

RAYNAUD'S PHENOMENON

Raynaud's phenomenon, the most frequent extracutaneous complication of SSc, is characterized by episodes of reversible vasoconstriction in the fingers and toes, sometimes also affecting the tip of the nose and earlobes. Attacks, triggered by a decrease in temperature, as well as emotional stress and vibration, typically start with pallor, followed by cyanosis of variable duration. Hyperemia ensues spontaneously or with rewarming of the digit. The progression of the three color phases reflects the underlying vasoconstriction, ischemia, and reperfusion. Up to 5% of the general population has Raynaud's phenomenon. In the absence of signs or symptoms of an underlying condition, Raynaud's

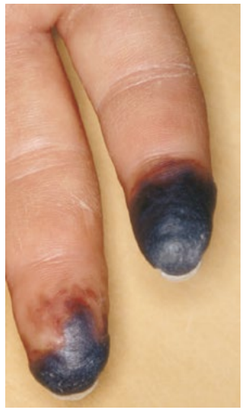


FIGURE 353-5 Digital necrosis. Sharply demarcated necrosis of the fingertip secondary to ischemia in a patient with limited cutaneous systemic sclerosis (SSc) associated with severe Raynaud's phenomenon.

phenomenon is classified as primary (Raynaud's disease), which represents an exaggerated physiologic response to cold. Secondary Raynaud's phenomenon occurs in SSc and other connective tissue diseases, hematologic and endocrine conditions, and occupational disorders, and can complicate treatment with beta blockers and anticancer drugs such as cisplatin and bleomycin. Distinguishing primary Raynaud's disease from secondary Raynaud's phenomenon can present a diagnostic challenge. Raynaud's disease is supported by the following: absence of an underlying cause, a family history of Raynaud's phenomenon, absence of digital tissue necrosis or ulceration, and a negative ANA test. Secondary Raynaud's phenomenon tends to occur at an older age (>30 years), is more severe (episodes more frequent, prolonged, and painful), and is associated with ischemic digital ulcers and loss of digits (Fig. 353-5).

Nailfold capillaroscopy using a low-power stereoscopic microscope or opthalmoscope permits visualization of nailbed cutaneous capillaries under immersion oil (Fig. 353-6). Raynaud's disease is associated with evenly spaced parallel vascular loops, whereas in secondary

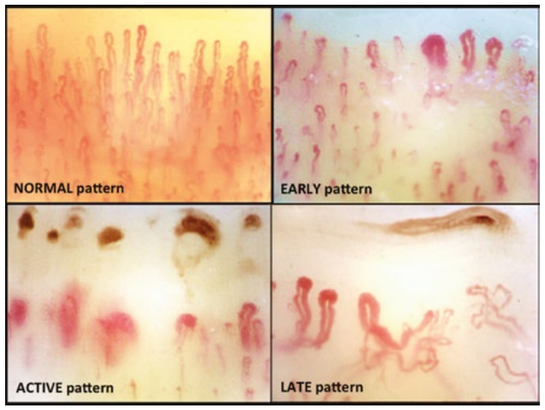


FIGURE 353-6 SSc-associated nailfold capillary alterations. Normal nailfold pattern in healthy subjects. Note regularly-arrayed and uniform-size "hairpin" microvessels; "early pattern" showing dilations of microvessels and symmetrically increased microvessels (giant capillaries) representing the first morphological sign of systemic sclerosis; "active pattern" with giant capillaries, collapse with microhemorrages and loss of capillaries; "late pattern" showing massive loss of capillaries, fibrosis (white/yellow background) and neoangogenesis with secondary dilations (nailfold videocapillaroscope VIDEOCAP; magnification 220×). *(Courtesy of Professor Maurizio Cutolo, University of Genoa.)*

Raynaud's phenomenon, nailfold capillaries are distorted with widened and irregular loops, dilated lumen, microhemorrhages, and areas of vascular "dropout." Thus, nailfold capillaroscopy can be helpful in differentiating primary from secondary Raynaud's phenomenon and in establishing the early diagnosis of SSc.

SKIN FEATURES

Bilateral symmetrical skin thickening is the hallmark of SSc that distinguishes it from other connective tissue diseases. Skin involvement starts in the fingers and characteristically advances from distal to proximal extremities in an ascending fashion. Some patients note diffuse tanning in the absence of sun exposure as a very early manifestation. In dark-skinned individuals, vitiligo-like hypopigmentation may occur. Because pigment loss spares the perifollicular areas, the skin may have a "salt-and-pepper" appearance, most prominently on the scalp, upper back, and chest. Dermal sclerosis obliterating hair follicles, sweat glands, and eccrine and sebaceous glands cause hair loss, decreased sweating, and dry and itchy skin on the extremities. Transverse creases on the dorsum of the fingers disappear (Fig. 353-7). Fixed flexion contractures of the fingers cause reduced hand mobility and lead to muscle atrophy. Skin and subjacent tendon fibrosis accounts for fixed contractures of the wrists, elbows, and knees. Thick ridges at the neck due to firm adherence of skin to the underlying platysma muscle interfere with neck extension.

In established SSc, the face assumes a characteristic "mauskopf" appearance with taut and shiny skin, loss of wrinkles, and occasionally an expressionless facies due to reduced mobility of the eyelids, cheeks, and mouth. Thinning of the lips with accentuation of the central incisor teeth and prominent perioral radial furrowing (rhytides) complete the picture. Reduced oral aperture (microstomia) interferes with eating and oral hygiene. The nose assumes a pinched, beak-like appearance. In late-stage disease, the skin becomes thin and atrophic, and is firmly bound to the subcutaneous fat (tethering). Dilated skin capillaries 2–20 mm in diameter (telangiectasiae), reminiscent of hereditary hemorrhagic telangiectasia, are frequently seen on the face, hands, lips, and oral mucosa (Fig. 353-8). The number of telangiectasias correlates with the severity of microvascular disease, including PAH. Breakdown of atrophic skin leads to chronic ulcerations at the extensor surfaces of the proximal interphalangeal joints, the volar pads of the fingertips, and bony prominences such as elbows and malleoli. Ulcers are often painful, heal slowly, and become secondarily infected, resulting in osteomyelitis. Healing of ischemic fingertip ulcerations leaves characteristic fixed digital "pits." Loss of soft tissue at the fingertips due to ischemia may be associated with striking resorption of the terminal phalanges (acro-osteolysis) (Fig. 353-9).

Dystrophic calcifications in the skin, subcutaneous, and soft tissues (calcinosis cutis) in the presence of normal serum calcium and phosphate levels occur in up to 40% of patients, most commonly in those

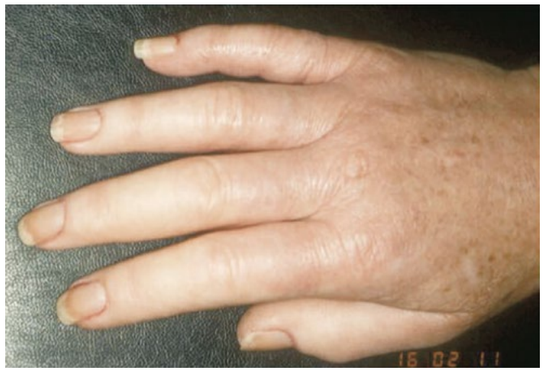
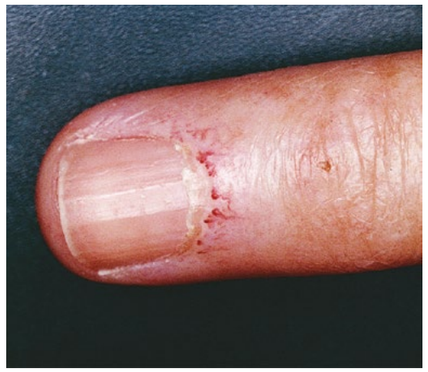


FIGURE 353-7 Sclerodactyly. Note skin induration on the fingers, and fixed flexion contractures of proximal interphalangeal joints, in a patient with limited cutaneous systemic sclerosis (lcSSc).



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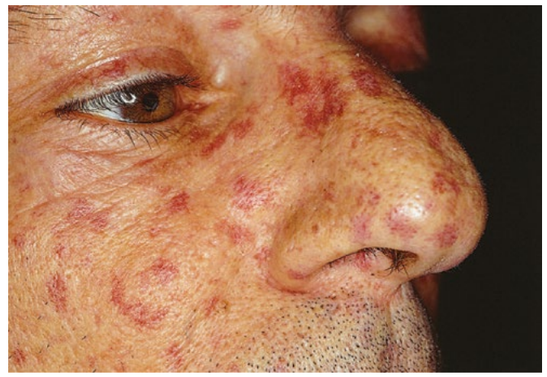


B

FIGURE 353-8 Cutaneous vascular changes. *A.* Vascular changes at the nailfold in lcSSc. ***B.*** Telangiectasia on the face.

with long-standing anti-centromere antibody-positive lcSSc. Calcific deposits, composed of calcium hydroxyapatite crystals, vary in size from tiny punctate lesions to large conglomerate masses can be readily visualized on plain radiographs, or dual-energy CT. These deposits occur when calcium precipitates in tissue damaged by inflammation,

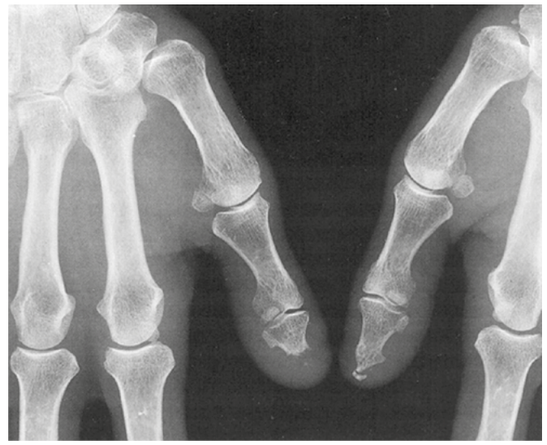


FIGURE 353-9 Acro-osteolysis. Note dissolution of distal terminal phalanges, commonly associated with ischemia, in a patient with long-standing limited cutaneous systemic sclerosis (lcSSc) and Raynaud's phenomenon.

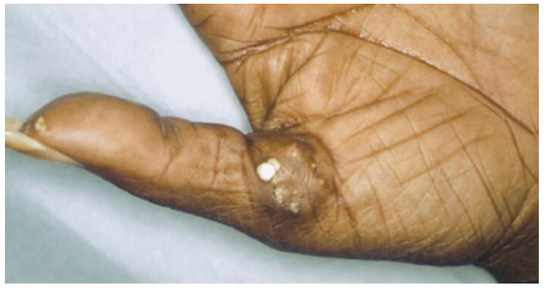


FIGURE 353-10 Calcinosis cutis. Note soft tissue calcific deposit breaking through the skin in a patient with limited cutaneous systemic sclerosis (lcSSc).

hypoxia, or local trauma. Common locations include the finger pads, palms, extensor surfaces of the forearms, and the olecranon and prepatellar bursae (Fig. 353-10). They can cause pain and nerve compression, ulcerate through the overlying skin with drainage of chalky white material, and secondary infections. Paraspinal sheet calcifications may cause neurologic complications.

PULMONARY FEATURES

The two principal forms of lung involvement in SSc, ILD, and pulmonary vascular disease are frequent and account for a majority of SSc-related deaths. Survival is particularly poor in SSc patients with concurrent presence of these two processes. Less common pulmonary complications of SSc include aspiration pneumonitis complicating chronic gastroesophageal reflux, pulmonary hemorrhage due to endobronchial telangiectasia, obliterative bronchiolitis, pleural reactions, restrictive physiology due to chest wall fibrosis, spontaneous pneumothorax, and drug-induced lung toxicity. The incidence of lung cancer is increased in SSc.

Interstitial Lung Disease While evidence of ILD can be found in up to 65% of SSc patients by high-resolution computed tomography (HRCT), clinically significant ILD develops in 16–43%; the frequency varies depending on the detection method used. Risk factors for ILD include male sex, African-American race, diffuse skin involvement, severe gastroesophageal reflux, and the presence of topoisomerase I autoantibodies; in contrast, anti-centromere antibody-positive patients have a reduced risk of ILD. Additional risk factors include low forced vital capacity (FVC) or single-breath diffusing capacity of the lung for carbon monoxide (DLco) at initial presentation. Esophageal dilation with chronic acid reflux in SSc cause micro-aspiration, a risk factor for the development and progression of ILD. The most rapid progression in ILD generally occurs early in the disease course (within the first 3 years), when the FVC can decline by 30% per year.

Pulmonary involvement can remain asymptomatic until it is advanced. The most common presenting respiratory symptoms—exertional dyspnea, fatigue, and reduced exercise tolerance—are subtle and slowly progressive. A chronic dry cough may be present. Physical examination may reveal fine inspiratory "Velcro" crackles at the lung bases. Pulmonary function testing (PFT) is relatively sensitive for detecting early pulmonary involvement, and typically shows a restrictive ventilatory defect (FV<70% predicted and/or FEV1/FVC ratio >0.8), reduced total lung capacity (TLC) and diffusing capacity (DLco). A reduction in DLco that is significantly out of proportion to the reduction in lung volumes should raise suspicion for pulmonary vascular disease, but may also be due to anemia. Oxygen desaturation with exercise is common.

Chest radiography can be used as an initial screening tool to rule out infection and other causes of pulmonary involvement; however, compared to HRCT, it is relatively insensitive for detection of early ILD. It may demonstrate lower lobe subpleural reticular linear opacities and ground-glass opacifications, even in asymptomatic patients with normal PFTs (Fig. 353-11). Additional HRCT findings include mediastinal lymphadenopathy, pulmonary nodules, traction bronchiectasis, and

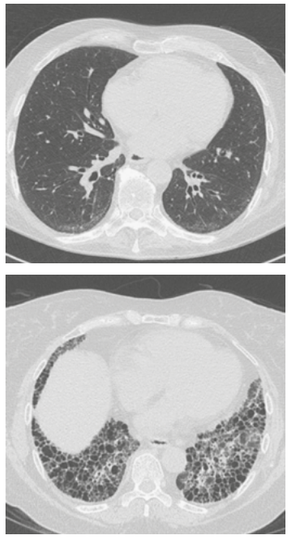


FIGURE 353-11 Chest CT in systemic sclerosis. ***Top panel:*** Early interstitial lung disease with subpleural reticulations and ground glass opacities in the lower lobes. Patient in supine position. ***Bottom panel:*** Extensive lung fibrosis with coarse reticular honeycombing, and traction bronchiectasis. Note dilated esophagus. *(Courtesy of Rishi Agrawal, Northwestern University.)*

uncommonly, honeycomb changes. The extent of interstitial changes on chest HRCT is a predictor of ILD progression and mortality. Bronchoalveolar lavage (BAL) can demonstrate inflammatory cells in the lower respiratory tract, and may be useful for ruling out tuberculosis and other infections. However, BAL does not appear to be useful for SSc diagnosis or for identifying reversible alveolitis, and is used primarily for research. Lung biopsy is indicated only in patients with atypical findings on chest radiographs. The histologic pattern on lung biopsy may predict the risk of progression of ILD, with NSIP, carrying a better prognosis than UIP.

Pulmonary Arterial Hypertension PAH resulting from vascular remodeling of small (<500 μm) pulmonary arteries develops in 8–12% of patients with SSc, and occurs as an isolated abnormality or in association with ILD. PAH is defined hemodynamically as a mean pulmonary artery pressure ≥25 mmHg with a pulmonary capillary wedge pressure ≤15 mmHg and pulmonary vascular resistance >3 Wood units. The natural history of SSc-associated PAH is variable, but often follows a downhill course with onset of right heart failure. The 3-year survival of SSc patients with untreated PAH is <50%. Risk factors include lcSSc, high numbers of cutaneous telangiectasia, older age at disease onset, and the presence of antibodies to centromere, U1-RNP, U3-RNP (fibrillarin), and B23. Mutations in the BMPR2 gene associated with idiopathic PAH are not found in patients with SSc-PAH.

Although patients with PAH are often asymptomatic in early stages, they may present with nonspecific symptoms of exertional dyspnea and reduced exercise capacity. With progression, angina, near-syncope, and symptoms and signs of right-sided heart failure appear. Physical examination may show tachypnea, a loud pulmonic component of the S_2 heart sound, pulmonic/tricuspid regurgitation murmur, palpable right ventricular heave, elevated jugular venous pressure, and dependent edema. Doppler echocardiography provides a noninvasive screening method for estimating the pulmonary arterial pressure. In light of the poor prognosis of untreated PAH and better therapeutic response in patients with early diagnosis, all SSc patients should be screened for PAH at initial evaluation, followed by annual evaluation. Estimated pulmonary artery systolic pressure >40 mmHg at rest or tricuspid regurgitation jet velocities >3 m/sec suggest PAH. PFT may show a reduced DLco in isolation or out of proportion with the severity of restriction. Because echocardiography can over- or underestimate pulmonary artery pressures, cardiac catheterization is the gold standard required to confirm the diagnosis of suspected PAH, to assess its severity, including the degree of right heart dysfunction, to rule out veno-occlusive disease and other cardiac (post-capillary) causes of pulmonary hypertension, and to provide prognostic parameters. Yearly echocardiographic screening for PAH is recommended in most patients; an isolated decline in DLco may also be indicative of developing PAH. Distinguishing PAH from pulmonary hypertension secondary to pulmonary fibrosis and hypoxia in SSc can be difficult. Serum levels of N-terminal pro-brain natriuretic peptide (NT proBNP) correlate with the presence and severity of PAH in SSc, as well as survival. While NT proBNP measurements can be useful in screening for PAH and in monitoring the response to treatment, elevated levels are not specific for PAH and also occur in other forms of right and left heart disease. Despite more favorable hemodynamics, the prognosis of SSc-associated PAH is worse, and treatment response poorer, than that of idiopathic PAH, most likely due to frequent concurrence of ILD and cardiac complications in these patients.

GASTROINTESTINAL INVOLVEMENT

Involvement of the gastrointestinal tract, which can affect any level, occurs in up to 90% of SSc patients with both lcSSc and dcSSc disease (Table 353-6). The pathologic findings of fibrosis, smooth muscle atrophy, and obliterative small-vessel vasculopathy are similar throughout the length of the gastrointestinal tract, and contribute to reduced quality of life, malnutrition, and increased mortality.

Upper Gastrointestinal Tract Involvement. Decreased oral aperture interferes with regular dental hygiene. Teeth are loosened due to loss of periodontal ligament attaching teeth to the alveolar bone. Additional oropharyngeal manifestations due to a combination of xerostomia, shortened frenulum, and resorption of the mandibular condyles are frequent and cause much distress. Most patients have symptoms of gastroesophageal reflux disease (GERD): heartburn, regurgitation, and dysphagia. A combination of reduced lower esophageal sphincter pressure resulting in reflux, impaired esophageal clearance of refluxed gastric contents due to diminished motility, and delayed gastric emptying accounts for GERD. Calcium channel antagonists and phosphodiesterase inhibitors used to treat Raynaud's phenomenon can further aggravate reflux. Esophageal manometry shows abnormal motility in most patients, even in the absence of symptoms. Extra-esophageal manifestations of GERD include hoarseness, chronic cough, and microaspiration, which can result in infections and may aggravate underlying ILD. Chest CT characteristically shows a dilated patulous esophagus with intraluminal air. Endoscopy may be necessary to rule out opportunistic infections with *Candida*, herpes virus, and CMV. Severe erosive esophagitis may be found on endoscopy in patients with minimal symptoms. Esophageal strictures and Barrett's esophagus may complicate chronic GERD. Because Barrett's metaplasia is associated with increased risk of adenocarcinoma, SSc patients with Barrett's require regular surveillance endoscopy with biopsy.

Gastroparesis with early satiety, abdominal distention, and aggravated reflux symptoms are common. Barium contrast studies are neither sensitive nor specific for evaluation of gastric involvement in SSc. Gastric antral vascular ectasia (GAVE) in the antrum may occur. These subepithelial lesions, reflecting the diffuse small-vessel vasculopathy of SSc, are described as "watermelon stomach" due to their endoscopic appearance. Patients with GAVE can have recurrent episodes of gastrointestinal bleeding, resulting in chronic unexplained anemia.

TABLE 353-6 Prominent Gastrointestinal Manifestations of SSc and Their Management

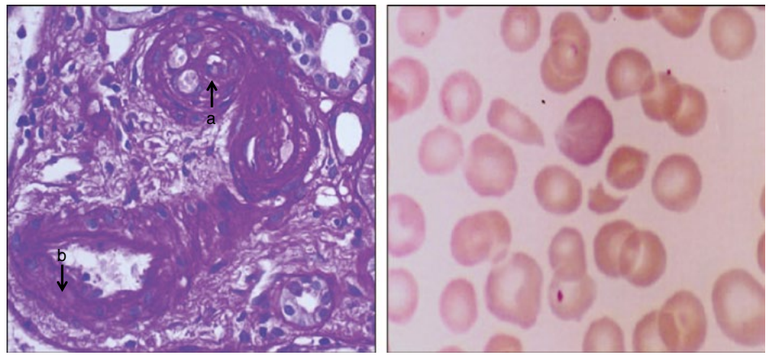
SITE	PRINCIPAL MANIFESTATION	MANAGEMENT
Oropharynx	Diminished oral aperture Dry mouth Periodontitis, gingivitis swallowing	Periodontal care Artificial saliva Swallowing therapy
Esophagus	Reflux Dysphagia Strictures Barret's metaplasia	Lifestyle modifications Prokinetic drugs proton pump inhibitors Endoscopic procedures
Stomach	Gastroparesis Gastric antral vascular ectasia (GAVE, watermelon stomach)	Prokinetic agents Endoscopic laser cryotherapy
Small and large intestines	Bacterial overgrowth Diarrhea/constipation Pseudo-obstruction Pneumatosis intestinalis Malabsorption Colonic pseudodiverticula	Laxatives Prokinetic agents Rotating antibiotics Octreotide Parenteral nutritional support
Anorectum	Sphincter incompetence	Biofeedback, sacral nerve stimulation, surgery

Lower Gastrointestinal Tract and Anorectal Involvement Weight loss and malnutrition due to impaired intestinal motility, malabsorption, and chronic diarrhea secondary to bacterial overgrowth are common. Fat and protein malabsorption and vitamin B_{12} and vitamin D deficiencies ensue, and may be further exacerbated by pancreatic insufficiency. Disturbed intestinal motor function can also lead to intestinal pseudo-obstruction, with symptoms that are indistinguishable from those of delayed gastric emptying. Patients present with recurrent episodes of acute abdominal pain, nausea, and vomiting, and radiographic studies show acute intestinal obstruction. A major diagnostic challenge is differentiating pseudo-obstruction, which responds to supportive care and intravenous nutritional supplementation, from mechanical obstruction. Colonic involvement may result in severe constipation, occasionally complicated by sigmoid volvulus. Fecal incontinence, gastrointestinal bleeding from telangiectasia, and rectal prolapse, can occur. In late-stage SSc, wide-mouth sacculations or diverticula occur in the colon, occasionally causing perforation and bleeding. An occasional radiologic finding is pneumatosis cystoides intestinalis due to air trapping in the bowel wall that may rarely rupture and cause benign pneumoperitoneum. Although the liver is rarely affected, primary biliary cirrhosis may coexist with SSc.

RENAL INVOLVEMENT: SCLERODERMA RENAL CRISIS

Scleroderma renal crisis presents with accelerated hypertension accompanied by acute kidney injury and progressive failure. This acute life-threatening complication of SSc occurs in 10–15% of patients, generally within 4 years of disease onset. Rarely, scleroderma renal crisis can be the initial presenting manifestation of SSc. Prior to the advent of angiotensin-converting enzyme (ACE) inhibitors, short-term survival in scleroderma renal crisis was <10%. The pathogenesis involves obliterative vasculopathy and luminal narrowing of the renal arcuate and interlobular arteries, with consequent intravascular hemolysis, along with evidence of activation of the complement pathways (Fig. 353-12). Progressive reduction in renal blood flow, aggravated by vasospasm, leads to juxtaglomerular renin secretion and activation of Angiotensin II, with further renal vasoconstriction resulting in a vicious cycle that culminates in accelerated hypertension. Risk factors for scleroderma renal crisis include African-American race, male sex, and diffuse or progressive skin involvement. Up to 50% of patients with scleroderma renal crisis have anti-RNA polymerase III antibodies, whereas patients with anti-centromere antibodies appear to be protected from this complication. Palpable tendon friction rubs, pericardial effusion, new unexplained anemia, and thrombocytopenia may be harbingers of impending scleroderma renal crisis. High-risk patients with early SSc should monitor their blood pressure daily. Because glucocorticoid use is associated with scleroderma renal crisis, prednisone in high-risk SSc patients should be taken only when absolutely required and at low doses (<10 mg/d).

Patients characteristically present with accelerated hypertension (generally >150/90 mmHg) and progressive oliguric renal insufficiency. However, ~10% of patients with scleroderma renal crisis present



A B

FIGURE 353-12 Renal changes in scleroderma renal crisis. *A.* Renal biopsy demonstrating intimal proliferation and myxoid changes in medium-sized renal arteries (*arrows*). ***B.*** Fragmentation of red blood cells due to intravascular hemolysis in scleroderma renal crisis. (*Courtesy of Drs. Edward Stern and Christopher Denton, Royal Free Hospital, London, UK.*)

with normal blood pressure. Normotensive renal crisis is generally associated with a poor outcome. Headache, blurred vision, congestive heart failure, and pulmonary edema may accompany elevation of blood pressure. Urinalysis typically shows mild proteinuria, granular casts, and microscopic hematuria; moderate thrombocytopenia and microangiopathic hemolysis with fragmented red blood cells can be seen. Progressive oliguric renal failure over several days generally follows. Scleroderma renal crisis is occasionally misdiagnosed as thrombotic thrombocytopenic purpura (TTP) or other forms of thrombotic microangiopathy. In such cases, renal biopsy and measuring vWF-cleaving protease activity may be of some benefit. Oliguria or a creatinine >3 mg/dL at presentation predicts poor outcome (permanent hemodialysis and mortality), as do biopsy findings of vascular thrombosis and glomerular ischemic collapse. Rarely, crescentic glomerulonephritis occurs in the setting of SSc and may be associated with myeloperoxidase-specific antineutrophil cytoplasmic antibodies. Membranous glomerulonephritis may occur in patients treated with D-penicillamine. Asymptomatic renal function impairment occurs in up to half of SSc patients. Such subclinical renal involvement is associated with other vascular manifestations of SSc and rarely progresses.

CARDIAC INVOLVEMENT

Although it is often silent, variable cardiac involvement in SSc is detected in 10–50% of patients screened with sensitive diagnostic tools. Clinical cardiac involvement, more frequent in dcSSc than in lcSSc, may be primary or secondary to PAH, ILD, or renal involvement, and is associated with poor outcomes. The endocardium, myocardium, and pericardium may each be affected separately or together. Pericardial involvement is manifested as pericarditis, pericardial effusions, constrictive pericarditis, and rarely, cardiac tamponade. Conduction system fibrosis occurs commonly and may be silent or manifested by heart block. Arrythmias including premature ventricular contractions, atrial fibrillation, and supraventricular tachycardia are common. Microvascular involvement, recurrent vasospasm, and ischemia-reperfusion injury contribute to patchy myocardial fibrosis, resulting in asymptomatic systolic or diastolic left ventricular dysfunction that may progress to overt heart failure. Acute or subacute myocarditis leading to left ventricular dysfunction may occur, and diagnosis requires cardiac magnetic resonance imaging (MRI) or endomyocardial biopsy. While conventional echocardiography has low sensitivity for detecting preclinical heart involvement in SSc, newer modalities such as tissue Doppler echocardiography (TDE), cMRI, and nuclear imaging (single photon emission CT [SPECT]) reveal a high prevalence of abnormal myocardial function or perfusion. The serum levels of N-terminal pro-BNP, a ventricular hormone elevated in SSc-PAH, may also have utility as markers of primary cardiac involvement.

Musculoskeletal Complications

Musculoskeletal complications are very common in SSc. Carpal tunnel syndrome may be a presenting disease manifestation. Generalized arthralgia and stiffness are prominent in early disease. Mobility of both small and large joints is progressively impaired, and fixed contractures develop at the proximal interphalangeal joints and wrists. Large joint contractures, seen in patients with dcSSc, are frequently accompanied by tendon friction rubs characterized by coarse leathery crepitation heard or palpated upon passive joint movement, that are due to extensive fibrosis and adhesion of the tendon sheaths and fascial planes at the affected joint. Tendon friction rubs are associated with increased risk for renal and cardiac complications and reduced survival. Synovitis detected by ultrasound or MRI is common; occasional SSc patients develop erosive polyarthritis in the hands, and some have a seropositive rheumatoid arthritis overlap. Muscle weakness is common and multifactorial: deconditioning, disuse atrophy, malnutrition, inflammation, and fibrosis may all contribute. A chronic non-inflammatory myopathy characterized by atrophy and fibrosis with mildly elevated muscle enzymes can be seen in late-stage SSc. Bone resorption in the terminal phalanges causes loss of the distal tufts (acro-osteolysis) (Fig. 353-9). Resorption of the mandibular condyles can lead to bite difficulties. Osteolysis can also affect the ribs and distal clavicles.

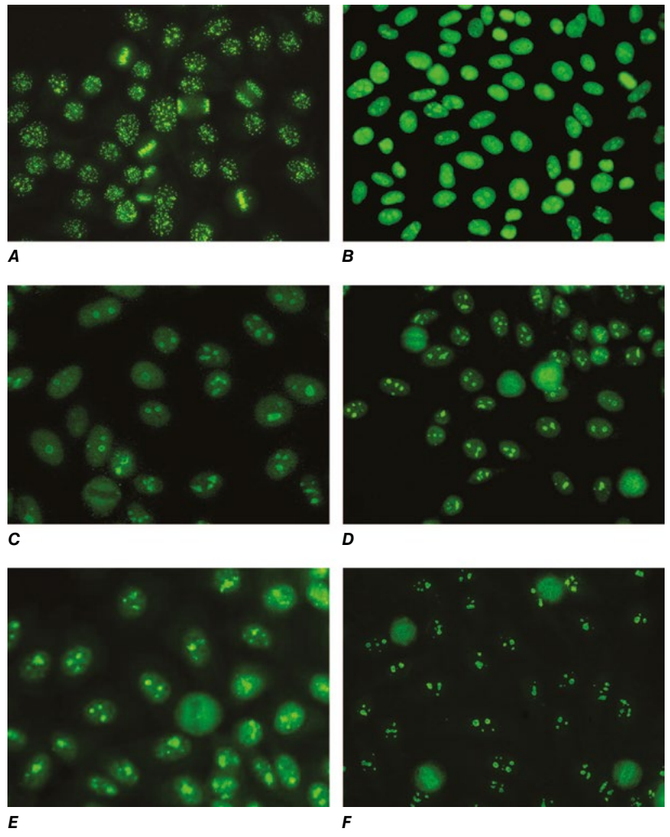
LESS RECOGNIZED DISEASE MANIFESTATIONS

Dry eyes and dry mouth (sicca complex) are common in SSc. Biopsy of the minor salivary glands shows fibrosis rather than focal lymphocytic infiltration characteristic of primary Sjögren's syndrome (Chap. 354). Hypothyroidism resulting from Graves' or Hashimoto's disease is common, particularly in lcSSc, and may be under-recognized. Whereas the central nervous system is generally spared, unilateral or bilateral sensory trigeminal neuropathy can occur. Erectile dysfunction is a frequent, and occasionally initial, disease manifestation. Inability to attain or maintain penile erection is due to vascular insufficiency and fibrosis of corporeal smooth muscle. Sexual performance is also adversely affected in women. While fertility is not impaired in SSc, pregnancy is associated with higher risk of adverse fetal outcomes. Furthermore, cardiopulmonary involvement may worsen during pregnancy, and new onset of scleroderma renal crisis has been described.

Cancer Epidemiologic studies indicate an increased cancer risk in SSc. Lung cancer and esophageal adenocarcinoma typically occur in the setting of long-standing ILD or GERD and may be caused by chronic inflammation and repair. In contrast, breast, lung, and ovarian carcinomas and lymphomas tend to occur in close temporal association with the onset of SSc, particularly in patients who have autoantibodies to RNA polymerase III. In this scenario, SSc may represent a paraneoplastic syndrome triggered by the anti-tumor immune response.

LABORATORY EVALUATION AND BIOMARKERS

Mild microcytic anemia is frequent and may indicate gastrointestinal bleeding caused by GAVE or chronic esophagitis. Macrocytic anemia may be caused by folate and vitamin B_{12} deficiency due to small-bowel bacterial overgrowth and malabsorption or by drugs such as methotrexate. Microangiopathic hemolytic anemia caused by mechanical fragmentation of red blood cells during their passage through microvessels coated with fibrin or platelet thrombi is a hallmark of scleroderma renal crisis. The erythrocyte sedimentation rate (ESR) is generally normal; an elevation may signal coexisting myositis or malignancy.



A B C D E F

FIGURE 353-13 SSc-associated autoantibodies: immunofluorescence patterns. Indirect immunofluorescence on HEp-2 substrate shows distinct patterns: ***A.*** anti-centromere; ***B.*** anti-Scl-70/topoisomerase I; ***C.*** anti-PM/Scl; ***D.*** anti-Th/To; ***E.*** anti-RNA polymerase III; ***F.*** anti-fibrillarin/U3RNP antibodies. Except for anti-centromere (discrete dots in metaphase nucleus), variations of nucleolar staining are clues to autoantibody specificity. However, immunoassays employing purified autoantigens are recommended to confirm specificity of these autoantibodies. *(Courtesy of Marvin Fritzler and Susan Copple, Inova Diagnostics Inc., San Diego, California.)*

Antinuclear autoantibodies are detected in almost all patients with SSc. Anti-topoisomerase I (Scl-70) and anti-centromere antibodies are mutually exclusive and each is highly specific for SSc. Topoisomerase I antibodies are associated with increased risk of ILD and poor outcomes. Anti-centromere antibodies are associated with PAH, but only infrequently with significant cardiac, pulmonary, or renal involvement. Nucleolar immunofluorescence pattern may indicate antibodies to U3-RNP (fibrillarin), Th/To, or PM/Scl, whereas speckled immunofluorescence indicates antibodies to RNA polymerase III (Fig. 353-13).

DIAGNOSIS, STAGING, AND MONITORING

The diagnosis of SSc is made primarily on clinical grounds and is generally straightforward in patients with established disease. The presence of skin induration with a characteristic symmetric distribution pattern associated with typical visceral organ manifestations establishes the diagnosis with a high degree of certainty. In lcSSc, a history of Raynaud's phenomenon and GERD symptoms, coupled with sclerodactyly and nailfold capillary changes, often in combination with cutaneous telangiectasia and calcinosis cutis, help to establish the diagnosis. Primary Raynaud's disease is a benign condition that must be differentiated from early or limited SSc. Nailfold microscopy is particularly helpful in this situation, because in contrast to SSc, nailfold capillaries are normal. Diagnosing SSc at an early stage may be a challenge. In dcSSc, initial symptoms are often nonspecific, Raynaud's phenomenon may be absent, and physical examination may only show upper extremity edema and puffy fingers. Patients with early SSc might be diagnosed as arthritis, SLE, myositis, or, most commonly, undifferentiated connective tissue disease. Within weeks to months, Raynaud's phenomenon and advancing skin induration appear. SSc-specific autoantibodies provide a high degree of diagnostic certainty. Raynaud's phenomenon with fingertip ulcerations or other evidence of digital ischemia, coupled with telangiectasia, distal esophageal dysmotility, unexplained ILD or PAH, or accelerated hypertension with renal failure in the absence of clinically evident skin induration, suggests the diagnosis of SSc *sine* scleroderma.

APPROACH TO THE PATIENT

Management of Systemic Sclerosis

OVERVIEW: GENERAL PRINCIPLES

To date, with the possible exception of hematopoietic stem cell therapy (HSCT), no therapy has been shown to significantly alter the natural history of SSc. In contrast, multiple interventions are highly effective in alleviating the symptoms, slowing the progression of the cumulative organ damage, and reducing disability. A significant reduction in disease-related mortality has been noted during the past 25 years. In light of the marked heterogeneity in disease manifestations, and natural history, the management of SSc mandates a "personalized medicine" approach that is specifically tailored to each individual patient's unique needs.

TABLE 353-7 Key Principles in Management

- Establish early and accurate diagnosis.
- Detect and evaluate internal organ involvement.
- Define clinical disease stage and activity.
- Tailor individualized therapy to each patient's unique needs.
- Assess treatment response, and adjust therapy as needed; monitor for disease activity, progression and new complications.

The following general principles should guide management **(Table 353-7)**: prompt and accurate diagnosis; classification and risk stratification based on clinical and laboratory evaluation, including prognostic and predictive biomarkers; early recognition of organ-based complications and assessment of their extent, severity, and likelihood of deterioration; regular monitoring for disease progression, new complications, and response to therapy; adjusting therapy; and patient education. In order to minimize irreversible organ damage, management should be proactive, with regular screening and initiation of appropriate, intervention at the earliest possible opportunity. In light of the complex and multisystemic nature of the SSc, a team-oriented management approach integrating appropriate specialists should be pursued. Generally, a combination of drugs that impact different aspects of the disease is used. Patients should be encouraged to become familiar with potential complications and understand therapeutic options, including interventional trials, and natural history, and empowered to partner with their treating physicians. This requires a long-term relationship between patient and physician, with ongoing counseling, encouragement, and two-way dialogue.

DISEASE-MODIFYING THERAPY: IMMUNOSUPPRESSIVE AGENTS

Immuno-suppressive agents used in other autoimmune diseases have generally shown modest or no benefit in SSc. Glucocorticoids alleviate stiffness and aching in early inflammatory-stage dcSSc, but do not influence the progression of skin or internal organ involvement. Since their use is associated with an increased risk of scleroderma renal crisis, glucocorticoids should be given only when absolutely necessary, at the lowest dose possible, and for brief periods only.

Cyclophosphamide has been extensively studied in light of its efficacy in the treatment of vasculitis **(Chap. 356)**, SLE **(Chap. 349)**, and other autoimmune diseases **(Chap. 348)**. Both oral and intravenous cyclophosphamide have been shown to reduce the progression of SSc-associated ILD, with stabilization and, rarely, modest improvement of pulmonary function, HRCT findings, respiratory symptoms, and skin induration. The benefits of cyclophosphamide need to be balanced against its potential toxicity, including bone marrow suppression, opportunistic infections, hemorrhagic cystitis and bladder cancer, premature ovarian failure, and late secondary malignancies.

Methotrexate had modest effect on SSc skin involvement in small studies. Mycophenolate mofetil was evaluated in both open label and randomized control trials. Both skin induration and ILD improved in patients treated with MMF, and the drug was well tolerated. Tocilizumab, a monoclonal antibody directed against the IL-6 receptor that blocks IL-6 signaling, also showed benefit in randomized SSc trials. Open-label studies and small trials provide support for the use of rituximab, a monoclonal antibody directed against the mature B cell marker CD20, along with extracorporeal photopheresis and IV immunoglobulin. Randomized trials in SSc evaluating the efficacy of abatacept, a fusion protein that inhibits T cell co-stimulation and function, are on-going. The use of cyclosporine, azathioprine, plaquenil, thalidomide, and rapamycin is currently not well supported by the literature. Intensive immune ablation using high-dose chemotherapy, (myeloablation) alone, or combined with total body irradiation, followed by autologous stem cell reconstitution has been evaluated in patients with severe early-stage SSc. In selected patients this intensive intervention was associated with durable remission and improved long-term survival in multiple small randomized clinical trials. Since this regimen has been associated with significant morbidity and even treatment-related mortality, its use currently should be restricted to SSc patients with severe, or treatment-refractory, disease.

Antifibrotic Therapy Because tissue fibrosis underlies organ damage in SSc, drugs that interfere with the fibrotic process represent a rational therapeutic approach. In older retrospective studies, D-penicillamine was shown to stabilize skin induration, prevent new internal organ involvement, and improve survival. However, a randomized-controlled clinical trial in early active SSc found no difference in the extent of skin involvement between patients treated with standard-dose (750 mg/d) or very low-dose (125 mg every other day) D-penicillamine. Recent clinical trials show benefit of pirfenidone and of nintedanib in patients with idiopathic pulmonary fibrosis, with significant slowing of the loss of lung function. Whether these anti-fibrotic drugs have comparable efficacy and tolerability in patients with SSc-associated ILD and other fibrotic manifestations of the disease is under investigation.

Vascular Therapy The goal of Raynaud's therapy is to control episodes, prevent and enhance the healing of ischemic complications, and slow the progression of obliterative vasculopathy. Patients should dress warmly, minimize cold exposure, and avoid drugs that precipitate or exacerbate vasospastic episodes. Extended-release dihydropyridine calcium channel blockers such as amlodipine and diltiazem ameliorate Raynaud's phenomenon, but their use is often limited by side effects (palpitations, dependent edema, worsening gastroesophageal reflux). While ACE inhibitors do not reduce the frequency or severity of episodes, Angiotensin II receptor blockers such as losartan are effective and well tolerated. Patients with Raynaud's phenomenon unresponsive to these therapies may require the addition of α_1-adrenergic receptor blockers (e.g., prazosin), 5-phosphodiesterase inhibitors (e.g., sildenafil), topical nitroglycerine, and intermittent IV infusions of prostaglandins. Low-dose aspirin and dipyridamole prevent platelet aggregation and may have a role as adjunctive agents. In patients with ischemic digital tip ulcerations, the endothelin-1 receptor antagonist bosentan reduces the risk of new ulcers. Digital sympathectomy and intradigital injections of botulinum type A (Botox) may be considered in patients with severe on-going ischemia. Empirical long-term therapy with statins and antioxidants may retard the progression of vascular damage and obliteration. There is limited evidence-based information for the treatment of cardiac complications of SSc, which should be guided by specialists experienced in their diagnosis and management. While selective beta blockers such as metoprolol can precipitate vasospasm, non-dihydropyridine calcium channel blockers can be used for rate control in atrial arrhythmias, and non-selective alpha/beta blockers such as carvedilol for improving myocardial perfusion and left ventricular systolic function.

TREATMENT

TREATMENT OF SSc-ASSOCIATED ILD

ILD is a leading cause of death in patients with SSc. However, as SSc-associated ILD is not necessarily progressive, it is important to identify patients who are at high risk for disease progression in the absence of treatment. The extent of ILD on HRCT and the FVC at initial evaluation, and decline in PFTs during the preceding 12-month period, are helpful in identifying these patients. Patients at high risk for ILD should be monitored by performing PFTs every 6 months; serial HRCT imaging is not recommended. Cyclophosphamide, given IV or orally for 6 to 12 months, and mycophenolate mofetil slow the decline in lung function and improve respiratory symptoms; however, cyclophosphamide is associated with more frequent side effects. The safety and efficacy of anti-fibrotic drugs recently approved for idiopathic pulmonary fibrosis in the treatment of SSc-associated ILD are currently under investigation. In certain patients who show continued progression of ILD despite medical therapy, lung transplantation might be considered as a life-prolonging procedure, although significant GERD is a concern in SSc. Recurrence of SSc-ILD in transplanted lung allografts has not been reported.

TREATMENT OF GASTROINTESTINAL COMPLICATIONS

Because oral problems including decreased oral aperture, decreased saliva production, gum recession, periodontal disease, and teeth loss are common, regular dental care is recommended. Gastroesophageal reflux is very common and may occur in the absence of symptoms. Patients should be instructed to elevate the head of the bed, eat frequent small meals, and avoid alcohol, caffeine, and known reflux exacerbants, or meals before bedtime. Proton pump inhibitors reduce acid reflux and in patients with SSc may need to be given in relatively high doses. Prokinetic agents such as metoclopramide, erythromycin (a motilin agonist), and domperidone may occasionally be helpful, but are frequently associated with side effects. Botulinum toxin injection sometimes ameliorates impaired gastric emptying. Anti-reflux procedures such as Nissen fundoplication can result in secondary achalasia and generally should be avoided. Episodic bleeding from GAVE (watermelon stomach) may be amenable to treatment with endoscopic ablation using laser or argon plasma photocoagulation, although bleeding frequently recurs. Some patients may require enteral feeding and/or decompression via percutaneous gastrostomy or jejunostomy. Small bowel bacterial overgrowth secondary to dysmotility causes abdominal bloating and diarrhea, and may lead to malabsorption and severe malnutrition. Treatment with short courses of rotating broad-spectrum antibiotics such as metronidazole, erythromycin, and rifaximin can eradicate bacterial overgrowth. Small bowel hypomotility may respond to octreotide; however, pseudo-obstruction is difficult to treat. Fecal incontinence, a frequent and under-reported complication, may respond to anti-diarrheal medication, biofeedback therapy, sphincter augmentation, and sacral neuromodulation. Potential malnutrition should be routinely assessed.

TREATMENT OF PAH

In SSc, PAH carries an extremely poor prognosis and accounts for 30% of deaths. Because PAH is asymptomatic until advanced, patients with SSc should be screened at initial evaluation, and regularly thereafter. Treatment is generally started with an oral endothelin-1 receptor antagonist such as bosentan or a phosphodiesterase 5 inhibitor such as sildenafil. Recently, the soluble guanylate cyclase stimulator riociugat, which acts by increasing the production of nitric oxide, and the selective IP prostacyclin receptor agonist selexipag, were shown to improve PAH symptoms and survival. Patients may also require diuretics and digoxin. If hypoxemia is documented, supplemental oxygen should be prescribed in order to avoid secondary pulmonary vasoconstriction. Prostacyclin analogues such as epoprostenol or treprostinil can be given by continuous IV or SC infusion, or via intermittent nebulized inhalations. Combination therapy with different classes of agents acting additively or synergistically is often necessary. Lung transplantation remains an option for selected SSc patients with PAH who fail medical therapy, and 2-year survival rates (64%) are comparable to those of idiopathic ILD or PAH.

MANAGEMENT OF RENAL CRISIS

Scleroderma renal crisis is a medical emergency. Since the outcome is largely determined by the extent of renal damage at the time that aggressive therapy is initiated, prompt recognition of impending or early scleroderma renal crisis is essential, and efforts should be made to avoid its occurrence. High-risk SSc patients with early disease, extensive and progressive skin involvement, tendon friction rubs, and anti-RNA polymerase III antibodies should be instructed to monitor their blood pressure daily and report significant alterations immediately. Potentially nephrotoxic drugs should be avoided, and glucocorticoids should be used only when absolutely necessary and at low doses. Patients presenting with scleroderma renal crisis should be immediately hospitalized. Once other causes of renal disease are excluded, treatment should be started promptly with titration of short-acting ACE inhibitors, with the goal of achieving rapid normalization of the blood pressure. In patients with persistent hypertension, addition of angiotensin II receptor blockers, calcium channel blockers, endothelin-1 receptor blockers, prostacyclins, and direct renin inhibitors should be considered. Up to two-thirds of patients with scleroderma renal crisis will require dialysis. Substantial renal recovery can occur, and dialysis can be discontinued in 30–50% of the patients. Kidney transplantation is appropriate for patients unable to discontinue dialysis after 2 years. Survival of transplanted SSc patients is comparable to that of other diseases, and recurrence of renal crisis is rare.

SKIN CARE

Because skin involvement in SSc is never life-threatening and it stabilizes and may even regress spontaneously, disease management should not be dictated by its cutaneous manifestations. The inflammatory symptoms of early skin involvement can be controlled with antihistamines and short-term use of low-dose glucocorticoids (<5 mg/d of prednisone). Cyclophosphamide and methotrexate have modest effects on skin induration. Because the skin is dry, the use of hydrophilic ointments and bath oils is encouraged, and regular skin massage is helpful. Telangiectasia, which presents a cosmetic problem, especially on the face, can be treated with pulsed dye laser. Ischemic digital ulcerations should be protected by occlusive dressing to promote healing and prevent infection. Infected skin ulcers are treated with topical antibiotics and surgical debridement. While no therapy has been shown to be effective in preventing soft tissue calcific deposits or promoting their dissolution, reports support the use of diltiazem, minocycline, bisphosphonates, and topical or IV sodium thiosulfate (STS). Other therapies that have been used for calcinosis include carbon dioxide laser, extracorporeal shock-wave lithotripsy, and surgical high-speed microdrilling.

TREATMENT OF MUSCULOSKELETAL COMPLICATIONS

Arthralgia and joint stiffness are very common and distressing manifestations in early-stage disease. Short courses of nonsteroidal anti-inflammatory agents, methotrexate, and cautious use of low-dose glucocorticoids alleviate symptoms. Physical and occupational therapy can be effective for preventing loss of musculoskeletal function and joint contractures, and should be initiated early.

COURSE

The natural history of SSc is highly variable and difficult to predict, especially in early stages of the disease. Patients with dcSSc tend to have a more rapidly progressive course and worse prognosis than those with lcSSc. Inflammatory symptoms of early dcSSc, such as fatigue, edema, joint pain and pruritus subside, and skin thickening reach a plateau at 2–4 years after disease onset. It is during the early edematous/inflammatory stage that life-threatening visceral organ involvement may develop. While existing visceral organ involvement, such as ILD, may progress even after skin involvement peaks, new organ involvement is rare. Scleroderma renal crisis generally occurs within the first 4 years of disease. In late-stage disease (>6 years), the skin is usually soft and atrophic. Skin regression characteristically occurs in an order that is the reverse of initial involvement, with softening on the trunks followed by proximal and finally distal extremities; however, sclerodactyly and fixed finger contractures generally persist. Relapse or recurrence of skin thickening after peak skin involvement has been reached is uncommon. Patients with lcSSc follow a clinical course that is markedly different than that of dcSSc. Raynaud's phenomenon typically precedes other disease manifestations by years or even decades. Visceral organ complications such as PAH generally develop late and progress slowly.

PROGNOSIS

SSc confers a substantial increase in the risk of premature death. Age- and gender-adjusted mortality rates are fivefold to eightfold higher compared to the general population, and more than half of all patients

with SSc die from their disease. In one population-based study of SSc, the median survival was 11 years. In patients with dcSSc, 5- and 10-year survival rates are 70% and 55%, respectively, whereas in patients with lcSSc, 5- and 10-year survival rates are 90% and 75%, respectively. The prognosis correlates with the extent of skin involvement, which itself is a surrogate for visceral organ involvement. Major causes of death are PAH, pulmonary fibrosis, gastrointestinal involvement, and cardiac disease. Scleroderma renal crisis is associated with a 30% 3-year mortality. Lung cancer and excess cardiovascular deaths also contribute to increased mortality. Markers of poor prognosis include male gender, African-American race, older age at disease onset, extensive skin thickening with truncal involvement, palpable tendon friction rubs, and evidence of significant or progressive visceral organ involvement. Laboratory predictors of increased mortality at initial evaluation include an elevated ESR, anemia, proteinuria, and anti–topoisomerase I antibodies. In one study, SSc patients with extensive skin involvement, vital capacity <55% predicted, significant gastrointestinal involvement (pseudo-obstruction or malabsorption), clinical evidence of cardiac involvement, or scleroderma renal crisis had a 9-year survival of <40%. The severity of PAH predicts mortality, and patients with mean pulmonary arterial pressure ≥45 mmHg had a 33% 3-year survival. The advent of ACE inhibitors in scleroderma renal crisis had a dramatic impact on survival, increasing from <10% at 1 year in the pre–ACE inhibitor era to >70% 3-year survival at the present time. Moreover, 10-year survival in SSc has improved from <60% in the 1970s to >66–78% in the 1990s, a trend that reflects both earlier detection and better management of complications.

LOCALIZED SCLERODERMA

The term *scleroderma* describes a group of localized skin disorders (Table 353-1). These occur more commonly in children than in adults, and in marked contrast to SSc, are generally not complicated by Raynaud's phenomenon or significant internal organ involvement. Morphea presents as solitary or multiple circular patches of thick skin or, rarely, as widespread induration (generalized or pansclerotic morphea); the fingers are generally spared. Linear scleroderma may affect subcutaneous tissues, leading to fibrosis and atrophy of supporting structures, tendons, muscle, and even bone. In children, the growth of affected long bones can be retarded. When linear scleroderma crosses large joints, significant contractures can develop.

MIXED CONNECTIVE TISSUE DISEASE

Patients who have lcSSc coexisting with features of SLE, polymyositis, and rheumatoid arthritis may have mixed connective tissue disease (MCTD). This overlap syndrome is generally associated with the presence of high titers of autoantibodies to U1-RNP. The characteristic initial presentation is Raynaud's phenomenon associated with puffy fingers and myalgia. Over time, sclerodactyly, soft tissue calcinosis, and cutaneous telangiectasia may appear. Skin rash suggestive of SLE (malar erythema, photosensitivity) or dermatomyositis (heliotrope rash on the eyelids, erythematous rash on knuckles) occur. Arthralgia is common, and some patients develop erosive polyarthritis. Pulmonary fibrosis and isolated or secondary PAH may develop. Other manifestations include esophageal dysmotility, pericarditis, Sjögren's syndrome, and renal disease, especially membranous glomerulonephritis. Laboratory evaluation shows elevated ESR and hypergammaglobulinemia. While anti-U1RNP antibodies are detected in high titers, SSc-specific autoantibodies are absent. In contrast to SSc, MCTD often responds to glucocorticoids, and the long-term prognosis is better than that of SSc. Whether MCTD is truly a distinct entity or is a subset of SLE or SSc, remains controversial.

EOSINOPHILIC FASCIITIS (DIFFUSE FASCIITIS WITH EOSINOPHILIA)

Eosinophilic fasciitis is a rare idiopathic disorder of adults associated with abrupt skin induration. The skin characteristically shows a coarse cobblestone "peau d'orange" appearance. In contrast to SSc, Raynaud's phenomenon and SSc-associated internal organ involvement and autoantibodies are absent. Furthermore, skin involvement spares the fingers. Full-thickness biopsy of the lesional skin reveals fibrosis of the subcutaneous fascia, with variable inflammation and eosinophil infiltration. In the acute phase of the illness, peripheral blood eosinophilia may be prominent. MRI appears to be a sensitive tool for the diagnosis of eosinophilic fasciitis. Eosinophilic fasciitis can occur in association with, or preceding, various myelodysplastic syndromes or multiple myeloma. Although glucocorticoids cause prompt resolution of eosinophilia, the skin shows slow and variable improvement. The prognosis of patients with eosinophilic fasciitis who do not develop hematological complications is generally good.

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354 Sjögren's Syndrome

Haralampos M. Moutsopoulos

DEFINITION, INCIDENCE, AND PREVALENCE

Sjögren's syndrome is a chronic, slowly progressing autoimmune disease characterized by lymphocytic infiltration of the exocrine glands resulting in xerostomia and dry eyes (keratoconjunctivitis sicca). The syndrome has unique features since it presents with a wide clinical spectrum from organ-specific autoimmune exocrinopathy to systemic disease. A small but significant number of patients develop malignant lymphoma. The disease can present as an entity alone or in association with other autoimmune diseases (Table 354-1). Finally, the histopathologic lesion in the labial minor salivary glands is easily accessible aiding the diagnosis, prognosis and disease pathogenesis.

Middle-aged women (female-to-male ratio, 9:1) are primarily affected, although Sjögren's syndrome may occur at any age, including childhood. The prevalence of primary Sjögren's syndrome is ~0.5–1%, while 5–20% of patients with other autoimmune diseases suffer from Sjögren's syndrome (secondary).

PATHOGENESIS

Sjögren's syndrome is characterized by both lymphocytic infiltration of the exocrine glands and B lymphocyte hyperreactivity. An oligomonoclonal B cell process, which is characterized by cryoprecipitable

TABLE 354-1 Association of Sjögren's Syndrome with Other Autoimmune Diseases

Rheumatoid arthritis
Systemic lupus erythematosus
Scleroderma
Mixed connective tissue disease
Primary biliary cirrhosis
Autoimmune thyroid disease
Chronic active hepatitis