TABLE 382-3 AUTOANTIBODIES AND ASSOCIATED FEATURES IN SYSTEMIC SCLEROSIS (SSC)

Target Antigen	SSc Subset	Characteristic Clinical Association
Topoisomerase I	dcSSc	Tendon friction rubs, early ILD, cardiac involvement, scleroderma renal crisis
Centromere proteins	lcSSc	Digital ischemic ulcers, calcinosis cutis, isolated PAH, overlap syndromes; renal crisis rare
RNA polymerase III	dcSSc	Rapidly progressive skin involvement, tendon friction rubs, joint contractures, GAVE, renal crisis, contemporaneous cancers
U3-RNP (fibrillarin)	dcSSc	PAH, ILD, scleroderma renal crisis, myositis
Th/T0	lcSSc	ILD, PAH
PM/Scl	lcSSc	Calcinosis cutis, ILD, myositis overlap
Ku	Overlap	SLE, myositis
U1-RNP	MCTD	PAH, arthritis, myositis

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.

Circulating T cells have elevated levels of chemokine receptors and α_1 integrin adhesion molecules, accounting for their enhanced binding to endothelium and to fibroblasts. Endothelial cells express ICAM-1 and other adhesion molecules that facilitate leukocyte diapedesis. Activated macrophages and T cells show a T_H2-polarized type 2 immune response driven by dendritic cells and thymic stromal lymphopoietin. T_H2 cytokines such as IL-4 and IL-13 induce fibroblast activation and alternate M2 macrophage polarization, whereas the T_H1 cytokine interferon γ (IFN-γ) blocks cytokine-mediated fibroblast activation. Alternately activated M2 macrophages produce TGF-β and promote fibrosis. Although the frequency of circulating regulatory T cells that enforce immune tolerance is elevated in SSc, their immunosuppressive function is defective. Molecular characterization of SSc skin biopsies using DNA microarrays identifies a subset showing markedly elevated expression of inflammation-associated genes, particularly chemokines and their receptors, interferon response genes, and mediators of innate immunity. Evidence of activated innate immunity and toll-like receptor signaling, indicative of activation by type 1 interferon produced by plasmacytoid dendritic cells, is prominent in peripheral blood cells.

Humoral Autoimmunity Circulating ANAs can be detected in virtually all patients with SSc. In addition, a number of SSc-specific autoantibodies have been described. These SSc-specific antibodies show strong association with distinct disease endophenotypes (Table 382-3). While most are directed against intracellular proteins associated with cell proliferation, such as topoisomerase I and RNA polymerases I, II, and III, others are directed against cell-surface antigens, receptors, or secreted proteins. Autoantibodies have clinical utility as diagnostic and prognostic biomarkers in SSc, and some, such as antibodies directed against the angiotensin II receptor or the PDGF receptor, may have a direct pathogenic role.

A variety of mechanisms have been proposed for the development of autoantibodies in SSc. Proteolytic cleavage, increased expression, or altered subcellular localization of certain cellular proteins in SSc could lead to their recognition as neoepitopes by the immune system, resulting in breakdown of immune tolerance. B cells are implicated in both the autoimmune and fibrotic process in SSc. In addition to antibody production, B cells also present antigen, secrete IL-6 and TGF-β, and modulate T cell and dendritic cell function.

FIBROSIS

Fibrosis affecting multiple organs, a distinguishing feature of SSc, is characterized by progressive replacement of normal tissue architecture with dense, stiff, and acellular connective tissue. Fibrosis characteristically follows, and is thought to be a consequence of, inflammation, autoimmunity, and microvascular damage. Fibroblasts are mesenchymal cells responsible for maintaining the functional and structural integrity of connective tissue. Upon activation by TGF-β and other extracellular cues, fibroblasts proliferate; migrate; secrete collagens, growth factors, chemokines, and cytokines; and transdifferentiate into contractile myofibroblasts. Under normal conditions, these fibrotic responses constitute self-limited physiologic remodeling necessary for tissue repair and regeneration. When these responses become sustained and amplified, pathologic fibrosis results. Autocrine stimulatory signaling by endogenously produced TGF-β and fibrotic mediators such as hypoxia, ROS, thrombin, Wnt ligands, connective tissue growth factor (CTGF), PDGF, lysophosphatidic acid, endothelin-1, mechanical forces, and endogenous ligands for toll-like receptors are responsible for maintaining sustained fibroblast activation underlying progressive fibrosis in SSc.

In addition to tissue-resident fibroblasts and transformation of epithelial cells into fibroblasts, 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, and tissue fibroblasts can differentiate into smooth-muscle-like myofibroblasts. Although myofibroblasts can be detected transiently during normal wound healing, they persist in fibrotic tissue, possibly due to resistance to apoptosis, and contribute to scar formation via production of collagen and TGF-β and contraction of the surrounding extracellular matrix.

Explanted SSc fibroblasts may display an abnormally activated phenotype ex vivo, with variably increased rates of collagen gene transcription, spontaneous ROS generation, and constitutive expression of alpha smooth-muscle actin stress fibers. The persistence of the "scleroderma phenotype" of these cells during their serial passage in vitro may reflect autocrine TGF-β stimulatory loops, deregulated microRNA expressions, histone acetylation, and other epigenetic modifications.

PATHOLOGY

The distinguishing pathologic hallmark of SSc is the combination of widespread capillary loss and obliterative microangiopathy, together with fibrosis in the skin and internal organs. In early disease, perivascular inflammatory cell infiltrates composed of T lymphocytes, monocytes/macrophages, plasma cells, mast cells, and occasionally B cells may be detected in multiple organs. A bland noninflammatory obliterative vasculopathy as a late finding is prominent in the heart, lungs, kidneys, and intestinal tract. Fibrosis is found in the skin, lungs, gastrointestinal tract, heart, tendon sheaths, perifascicular tissue surrounding skeletal muscle, and some endocrine organs. In these tissues, accumulation of collagens, fibronectin, proteoglycans, tenascin, cartilage oligomeric matrix protein (COMP), and other structural macromolecules progressively disrupts normal architecture, resulting in impaired function of affected organs.

SKIN

In the skin, fibrosis causes dermal expansion and obliteration of the hair follicles, eccrine glands, and other appendages (Fig. 382-2*A*). Collagen fiber accumulation is most prominent in the reticular dermis, and the fibrotic process invades the subjacent adipose layer with entrapment of adipocytes. With disease progression, the intradermal adipose layer is diminished and may completely disappear. The epidermis is atrophic, and the rete pegs are effaced.

LUNGS

Patchy infiltration of the alveolar walls with T lymphocytes, macrophages, and eosinophils occurs in early disease. With progression, interstitial fibrosis and vascular damage dominate the pathologic picture, often coexisting within the same lesions in patients with dcSSc. Pulmonary fibrosis is characterized by expansion of the alveolar interstitium, with accumulation of collagen and other matrix proteins. The most common histologic pattern in SSc-associated ILD is nonspecific interstitial pneumonia (NSIP), distinct from the usual interstitial pneumonia (UIP) pattern characteristically seen in patients with