and periadventitial fibrosis. Vascular changes are seen in the skin and may occur in the pulmonary, cardiac, and renal blood vessels, affecting arteries, arterioles, and capillaries. True vasculitis is conspicuously absent.

Cutaneous inflammatory infiltrates consist of activated mononuclear cells, T lymphocytes, and monocytes in the dermis, often occurring in a perivascular distribution. Dermal thickening is accompanied by excessive deposition of collagen fibrils and fibrous replacement of subcutaneous fat and secondary skin appendages such as hair follicles and sebaceous glands.

The interplay between the vascular, immunologic, and connective tissue changes is complex. Most hypotheses focus on interactions between early vascular and immunologic events leading to activation of fibroblasts, which are thought to be the effector cells in this disease. Fibroblasts are found in increased numbers in the skin and other tissues, and they develop an SSc phenotype when grown in vitro, producing an overabundance of collagen and living longer in tissue culture. Fibroblast persistence in culture suggests a perpetuated abnormality not requiring continued immune stimulation.

Other factors that may contribute to fibrosis include hypoxia and local cytokine changes. Early vascular involvement consists of an imbalance between vasodilatory and vasoconstrictive factors, endothelial cell activation with resultant leukocyte migration, smooth muscle cell proliferation, and defective vasculogenesis. Vascular activation can induce fibrosis by interleukin-mediated mechanisms.

Immune system activation is evident in several respects. First, serum levels of inflammatory markers (based on the sedimentation rate) and circulating cytokines are increased. Second, serum autoantibodies are detected in more than 95% of patients with SSc. One of nine autoantibodies is relatively specific for the disease. All of the antibodies are directed against distinct nuclear antigens. They are helpful in classifying patients, but their pathogenic role has not been elucidated. Third, there is evidence of T-cell activation, with a T_H2-predominant cytokine profile. Elevated levels of interleukins (i.e., IL-1, IL-2, IL-2R, IL-4, IL-8, IL-13, and IL-17) and interferon have been reported. The role of T_H17 cells is not understood, but studies suggest that dysregulation of these proinflammatory T cells contributes to disease pathogenesis. Fourth, there is increasing evidence of innate immune dysregulation in the setting of activated macrophages and altered expression and function of toll-like receptors.

CLINICAL PRESENTATION

Patients with SSc can have several clinical presentations, although Raynaud's phenomenon is the most common symptom. Distinctive phenotypes may manifest differently. SSc can have many internal organ manifestations, producing various clinical presentations and requiring tailored work-up protocols.

Classification by Cutaneous Features

Historically, SSc has been separated into two major clinical subsets defined by the degree and extent of skin involvement: limited cutaneous (lc) and diffuse cutaneous (dc) disease. Patients with lcSSc experience skin thickening limited to the distal extremities (i.e., below the elbows and knees). The dcSSc patients have similar distal changes in addition to involvement of the upper arms, thighs, or trunk at some time during the disease course. Few patients (<1%) have no skin thickening but have one or more typical SSc visceral manifestation.

The term *scleroderma sine scleroderma* has been used to describe dcSSc patients whose clinical course resembles that of individuals with lcSSc. The distinct cutaneous patterns are important, because patients with dcSSc are more likely to develop internal organ complications (e.g., renal crisis, cardiac involvement) early in their illness, whereas those with lcSSc can develop internal organ involvement throughout their disease, even decades after the initial symptoms (Table 80-1). Some patients with lcSSc or dcSSC may have typical features of another connective tissue disease (most commonly polymyositis, SLE, or rheumatoid arthritis-like features), and they are considered to have *SSc in overlap*.

Serologic Classification

Serologic classification refers to SSc-associated serum autoantibodies. Patients with the same autoantibody tend to have a similar cutaneous pattern, natural history of disease, and risk of internal organ involvement.

TABLE 80-1 MANIFESTATIONS OF SYSTEMIC SCLEROSIS BY CLINICAL CLASSIFICATION

MANIFESTATIONS	DIFFUSE (*N* = 1434)	LIMITED (*N* = 1718)
CUTANEOUS		
Puffy fingers	82%	78%
Skin induration, thickening	Widespread: trunk, face, extremities	Face, below the elbow and knee
Telangiectasias	58%	70%
Calcinosis	14%	22%
PERIPHERAL VASCULAR		
Raynaud's phenomenon	95%	97%
Digital ulcerations	42%	39%
PULMONARY		
Interstitial lung disease	37%	34%
Pulmonary arterial hypertension	5%	16%
CARDIAC		
Arrhythmias	16%	14%
Diastolic dysfunction	4%	5%
Myocarditis	6%	2%
Pericarditis	4%	3%
RENAL		
Renal crisis	18%	2%
GASTROINTESTINAL		
Esophageal hypomotility, reflux	79%	77%
Small intestine dysmotility	18%	13%
Malabsorption	11%	9%
Incontinence	2%	2%
JOINT AND MUSCULOSKELETAL		
Tendon friction rubs	53%	5%
Joint contractures	88%	38%
Myositis	10%	6%
Bland myopathy	2%	1%

Data from the University of Pittsburgh Scleroderma Databank, 1980-2012.