Localized and Systemic Scleroderma

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Scleroderma is a broad term encompassing both localized and systemic sclerosis. Localized scleroderma is a cutaneous limited fibrosis that manifests as plaque morphea, generalized morphea, linear scleroderma, and deep morphea. Systemic scleroderma (sclerosis) can manifest as either limited or diffuse disease. Limited systemic sclerosis is typically preceded by Raynaud's phenomenon, involves cutaneous sclerosis distal to the elbows, with gastrointestinal and pulmonary fibrosis, and anticentromere antibody positivity. Diffuse systemic scleroderma is characterized by simultaneous Raynaud's phenomenon, cutaneous skin involvement proximal to the elbow with gastrointestinal, pulmonary, renal and cardiac fibrosis, and positive serology for antitopoisomerase and anti-RNAP III antibodies. This article discusses the classification, epidemiology, pathogenesis, clinical manifestations, treatment, and prognosis of the scleroderma.

IN ITS EARLY HISTORY, scleroderma was confused with leprosy, ichthyosis, and keloids.[1] The first documented case of the disease, which occurred in Naples in 1752, was described as an ichthyosis corii.[1] In 1847, Gutrac coined the term "scleroderma," and Erasmus Williams is credited with designating localized scleroderma as morphea later in the same century.[1] Initially, the visceral manifestations of systemic sclerosis were believed to be unrelated to the cutaneous disease. However, in 1945 Goetz advanced the concept of systemic scleroderma as a multisystem disease, and in 1964, Winterbauer described the CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome.[2]

DEFINITION AND CLASSIFICATION

The term "scleroderma" refers to a rare spectrum of disorders characterized by cutaneous sclerosis. This develops because of fibrosis of involved tissue via the over-production and accumulation of collagen and extracellular matrix proteins. Patients can have either primary or secondary cutaneous sclerosis (Table 1). Primary cutaneous sclerosis occurs in idiopathic inflammatory disorders, and is often associated with features of humoral autoimmunity. Secondary cutaneous sclerosis, on the other hand, arises in the context of different disease processes with widely varying causes. They include sclerodermoid reactions to chemical/toxin/medication exposure, trauma, malignancy, internal disease, and radiation exposure.[3]

There are 2 distinct clinical categories of primary scleroderma: localized scleroderma (LSc) and systemic scleroderma (SSc). LSc occurs in the skin and subcutaneous tissue, and rarely progresses to systemic disease. The major variants of localized scleroderma are plaque morphea, generalized morphea, deep morphea, and linear scleroderma.[4]

SSc, on the other hand, involves the skin, blood vessels, and skeletal muscles, with the addition of internal organs including the gastrointestinal tract, lungs, heart, and kidneys. In 1980, the American College of Rheumatology (ACR) set forth its criteria for the diagnosis of systemic sclerosis.[5] The major criterion is skin thickening proximal to the metacarpophalangeal or metatarsophalangeal joints. The 3 minor criteria are 1) sclerodactyly, 2) digital pitting scars or loss of subcutaneous tissue of the fingertips, and 3) bibasilar pulmonary fibrosis on chest radiograph. Presence of the major criterion or 2 of the minor criteria are sufficient for diagnosis.[5] In patients with SSc, the degree and rate of involvement of organ systems differs, as does the prognosis and rapidity of disease progression. The 2 major patient subsets, limited (LSSc) and diffuse systemic scleroderma (DSSc), can be identified based on the anatomic extent of skin changes (Table 2). Earlier systems for classifying systemic sclerosis labeled diffuse disease as progressive systemic sclerosis and limited disease as CREST syndrome.

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Table 1. Primary Versus Secondary Cutaneous Sclerosis

Primary cutaneous sclerosis:
Localized scleroderma
Morphea
Linear scleroderma
Deep morphea
Systemic scleroderma
Limited
Diffuse
Cutaneous sclerosis as a component of an overlap syndrome
Mixed connective tissue disease
Undifferentiated connective tissue disease
Other
Secondary cutaneous sclerosis (pseudoscleroderma or sclerodermoid conditions) arises in the context of 1 of the following diseases. Systemic sclerosis or involvement may or may not be present.
Chronic graft versus host disease
Drug associated
Chemical/toxin exposure associated
Traumatic
Metabolic disorders
Genetic disorders
Mucinoses
Malignancy
Radiation exposure
Neurologic
Postinfectious

Data from reference 3.

This earlier classification system has been abandoned because it does not accurately describe and specify the disease types.[6]

Additional primary cutaneous scleroses include overlap syndromes such as mixed and undifferentiated connective tissue disease. Patients with undifferentiated connective tissue disease have Raynaud's phenomenon and other clinical features of SSc without the characteristic skin and internal organ manifestations.[2] Patients with other overlap syndromes present with the features of systemic sclerosis in addition to the characteristic features of other autoimmune diseases, such as systemic lupus erythematous, rheumatoid arthritis, inflammatory muscle disease, or Sjoren's syndrome.[2]

EPIDEMIOLOGY

Localized

In the only population-based study of LSc, Peterson et al[7] examined the prevalence and incidence of morphea from 1960-1993 in Olmstead County, Minnesota (Table 3)[6-9]. The ratio of females to males was 2.6:1, except in linear scleroderma in which the sex distribution was approximately even. The majority of patients had plaque morphea (56%), followed by linear scleroderma (20%), generalized morphea (13%), and deep morphea (11%). The average age at diagnosis was 33 years; however, most patients with linear scleroderma, a primarily pediatric disease, were diagnosed before the age of 18.[7]

Systemic

SSc is less common than LSc[6] (Table 3). The average age at diagnosis of SSc is approximately 49 years, with diffuse disease generally occurring at a younger age than limited disease. A retrospective cohort study by Laing et al[10] found that in addition to African American women having a higher incidence of SSc, they were more likely to develop diffuse disease at a younger age and have a lower survival rate than Caucasian women.[10] African American men are similarly more susceptible to SSc than their Caucasian counterparts.[6] Ethnic background appears to play a role in both disease and antibody expression. The anti-RNAP III antibody, which is associated with DSSc, is more common in African American than Caucasian scleroderma patients. The anticentromere antibody, which is associated with LSSc, is more common in Caucasian patients.[10] LSSc is more common than

Table 2. Classification of Diffuse and Limited Systemic Sclerosis

	Limited	Diffuse
% of Total SSc	~80%	~20%
Extent of skin involvement	Distal extremities, face	Distal/proximal extremities, face, trunk
Raynaud's phenomenon	May precede by 10-15 years	Onset within 1 year or at time of cutaneous sclerosis
Internal organ involvement	Gastrointestinal, pulmonary, musculoskeletal	Gastrointestinal, pulmonary, musculoskeletal, renal, cardiac
Antinuclear antibody	95%	95%
Anti-centromere antibody	50%	<5%
Anti-topo I antibody	15%	30%
Anti-RNAP III antibody	2%	45%

Data from references 11, 15, and 30.

Table 3. Epidemiology of Localized and Systemic Scleroderma

	Localized Scleroderma	Systemic Scleroderma
Incidence rate/100,000	2.7	1.9
Prevalence rate/100,000	50-220	0.4-29
Racial predisposition	Caucasians	African Americans
Female:Male ratio	3:1	5:1
Average age at diagnosis	33	49

Data from references 6-9.

DSSc. Englert et al[11] found that limited disease accounted for 79% of cases of SSc.

Comparison of American studies to those from other countries suggests a regional variation in SSc incidence, with the United States ranking higher than Great Britain, Iceland, or Japan presumably because of differences in disease susceptibility and/or environmental factors.[6] In the United States, the SSc mortality rates are higher in the Southeastern United States because of local clusters of concentrated mortality.[12] The Choctaw Indians, who reside in southern Oklahoma, appear to be particularly susceptible to SSc. Their estimated minimal prevalence is 469 of 100,000.[13]

PATHOGENESIS

Localized

Although the origin of LSc is unknown,[2] it is postulated that the disease process for LSc involves damage to the vasculature, immune activation, and connective tissue dysregulation.[4] Vascular damage, T-cell infiltration and activation, and increased levels of adhesion molecules and cytokines are seen early in the disease process.[8,14] Later in the disease process there is increased expression of type 1 collagen by fibroblasts, leading to a cutaneous sclerosis.[14] Skin biopsy specimens from patients with localized and systemic disease are indistinguishable. They both show homogenization of collagen bundles, diminished interbundle spaces, and few fibroblasts.[4,8]

The tick-borne spirochete *Borrelia burgdorferi* has been implicated in the pathogenesis of LSc in Europe and Japan, where *B burgdorferi* antibodies have been found in the serum of patients with LSc.[8] However, North American studies have failed to detect *B burgdorferi* DNA in skin biopsy samples, and therefore, it is not believed to be involved in the pathogenesis of LSc in the United States.[4,14]

Systemic

As is true in the LSc, the SSc disease process involves damage to the vascular epithelium, immune and inflammatory activation, and dysregulated extracellular matrix production by fibroblasts.[8] It is also postulated that microchimerism and genetics play a role. Vascular damage involving the small arteries, arterioles, and capillaries is typically the initial event in SSc. Injuries to the endothelial cells and basal lamina occur early, followed by narrowing of the lumen and obliteration of the vessel.[15]

Several mechanisms for the initial endothelial cell damage in SSc have been proposed. Granzyme A, an endothelial cytotoxic factor secreted by T cells, has been found in some patients with SSc, and may mediate endothelial cell growth inhibition.[16] Antiendothelial cell antibodies (AECA) found in patients with SSc have also been associated with vascular involvement. A recent study by Ihn et al[17] found that 54% of patients with SSc had AECA versus none of the control subjects. They also found that pulmonary fibrosis and cardiac involvement were significantly more frequent in patients with AECA. Increased vasoconstriction also contributes to endothelial cell damage via reperfusion injury. Danese et al[18] showed that levels of endothelin-1, a potent vasoconstrictor released on cold exposure, were significantly higher in patients with SSc than controls. Damage to the endothelial cells is reflected by elevated serum levels of Factor VIII/von Willebrand factor in many patients with SSc.[8,15] The binding of von Willebrand factor to subendothelium mediates platelet activation. Activated platelets, in turn, release platelet derived growth factor and transforming growth factor B, which stimulate fibroblast division and collagen production.[8,15]

Cell mediated immunity appears to be involved in the initiation and perpetuation of SSc. T cells, predominantly CD4+ cells, infiltrate the skin early in the disease process.[8] Elevated levels of interleukin 2 (IL-2), IL-2 receptors (IL-2R), IL-4, IL-6, and IL-8 are all found in patients with SSc.[2,8,15] Elevated levels of serum soluble IL-2R are associated with diseases progression.[4] IL-4 stimulates fibroblast proliferation and collagen synthesis.[15] IL-6 plays a role in IL-2 and IL-2R induction and immune activation.[15] T-cell interaction with endothelial cells is mediated by adhe-

sion molecules including E-selectin, P-selectin, intercellular adhesion molecule I, and vascular cell adhesion molecule 1.[15,19] Sato[19] notes that the abnormally high expression of adhesion molecules may lead to higher recruitment of T cells, higher fibroblast activation, and eventual fibrosis via a complex mechanism.

Humoral immunity may also play a role in SSc. Antinuclear antibodies are present in the majority of patients with SSc. Although no evidence exists showing that antinuclear antibodies are the cause of pathogenic changes seen in the disease, they are clearly useful in predicting clinical expression, disease course, and overall severity of the disease.[2,15,20] Rosen et al[21] postulated that the autoantibody response is the immune marker of metal dependent fragmentation of autoantigens. They suggest a role for abnormal cellular metal accumulation in the pathogenesis of SSc, and postulate that metal abnormalities may influence vascular reactivity, initiate a cycle of damage through reactive oxygen species, and create an environment that allows self-sustaining vascular injury.

Strehlow et al[22] reviewed the biology of the SSc fibroblast, and presented evidence for the three main explanations for abnormalities of matrix biosynthesis. First, it is hypothesized that increased matrix production may result from overproduction or malproduction of a matrix component by the fibroblast due to a mutant fibrillin gene. Second, fibroblasts of SSc patients have more receptors for a potent fibroblast activator, transforming growth factor-Beta, which may result in abnormal activation of the fibroblast. The third hypothesis is that the abnormality may result from abnormal selection of high collagen producing fibroblasts.

Fetal microchimerism, or the mixing of low levels of nonself cells between the fetus and the mother during gestation, has been postulated to play a role in the multifactorial pathogenesis of SSc.[23] This concept is similar to human chimerism initiating sclerosis in chronic graft versus host disease. Extensive fibrosis and mononuclear cell infiltration of affected tissue, as well as the presence of antinuclear antibodies characterize both diseases. This theory is based on the finding that fetal progenitor cells persist in maternal blood for as many as 27 years postpartum, and is consistent with the high female to male ratio of the disease, and the increase in disease prevalence after childbearing years.[23,24] Recent work has showed that male fetal DNA is found in blood and skin biopsy samples more frequently and in larger quantities in women with systemic sclerosis than in healthy women (ie, more microchimerism in patients with SSc).[23]

There are several concerns with the microchimerism model in the development of scleroderma. First, persistent fetal microchimerism does not explain the occurrence of SSc in men or nulliparous women. Second, there is a low ratio of host to nonhost cells in patients with SSc versus patients who have undergone bone marrow transplantation. It is unclear how the low ratios of host to nonhost cells (approximately 1 in every 1 million white blood cells) found in SSc could initiate a graft versus host disease (GVHD) type reaction.[25] Third, while GVHD and SSc are clinically similar, there are notable clinical and histopathological differences, including the absence of Raynaud's and renal disease in patients with GVHD.[23]

Genetic factors also appear to play a role in the pathogenesis of the disease. A retrospective cohort study by Englert et al[26] found that first degree family members were affected in 10 of the 710 positive SSc cohort families versus none of the 371 negative cohort families studied. The absolute risk of systemic sclerosis among first degree family members is therefore 1.4% versus 0.009% in the general population.

In SSc, certain human leukocyte antigen (HLA) alleles occur with an increased frequency. Specifically, the major histocompatibility complex (MHC) Class I alleles, A1, A3, and B8, and the MHC Class II alleles DR1, DR3, DR5, DRw8, and DRw52. HLA-DR associations are even stronger when looking at autoantibody defined subsets of SSc.[20] A case controlled study showed that Choctaws with SSc possess HLA-DRB1:1602; DQA1*0501;DQB1*0301, and that this is significantly associated with SSc.[13] In addition, Tan et al[27] identified a 2-cM haplotype on chromosome 15q that contains markers for the fibrillin 1 gene, and is associated with SSc in the Choctaw Native American population.

CLINICAL MANIFESTATIONS

Localized

LSc can be subdivided into plaque morphea and its subtypes, as well as generalized morphea, linear scleroderma, and deep morphea. Plaque mor-

phea is the most common form of LSc. It is characterized by the onset of 1 or more circumscribed plaques of skin hardening with variable dyschromia.[28] The plaques are initially erythematous and edematous; they then become indurated, but not bound to underlying structures.[8] These plaques are more common on the trunk than the extremities.[28] Guttate morphea is characterized by multiple yellowish-white, oval plaques that are similar, but smaller and more numerous than en plaque lesions. Guttate morphea may be associated with lichen sclerosis et atrophicans.[4,28] Bullous morphea is a rare form of morphea characterized by taut subepidural bullae.[28] It may occur in any subtype of LSc.[4] Generalized morphea occurs when more than 2 anatomical sites are affected by morphea.[8] It typically begins as individual plaques on the trunk that gradually grow and merge together.[4] The absence of Raynaud's disease, sclerodactyly, and internal organ involvement distinguishes generalized morphea from SSc.

Linear scleroderma presents as band-like lesions of skin hardening (Fig 1). There is deep atrophy, which often involves underlying muscle and bone. This can cause significant loss of function and mobility of the involved extremity.[2] Linear scleroderma most commonly develops in the first or second decades of life, and involves the extremities, face or scalp.[2,4] Linear scleroderma resulting in atrophy of the face is called "en coup de sabre," and Parry-Romberg syndrome occurs when there is progressive facial hemi-atrophy in the absence of the en coup de sabre deformity.[4,28]

LSc may also involve deeper structures such as subcutaneous tissue, muscle, bone, synovium, and vasculature.[4] Deep morphea is divided into 4 subtypes depending on the extent of involvement. Subcutaneous morphea develops rapidly with involvement of the panniculus or fascia forming hyperpigmented symmetric irregular plaques. Morphea profunda involves the panniculus and fascia forming diffusely taut and bound down skin lesions. Disabling pansclerotic morphea of children is a mutilating painful sclerosis of the dermis, fat, fascia muscle, and bone developing in preadolescence with unremitting progression.[4] The fourth type of deep morphea, eosinophilic fasciitis, is characterized histopathologically by severe fibrosis of the fascia, often extending to the underlying muscle. It is characterized clinically by symmetric skin induration, accompanied by edema of the extremities, joint contractures, and eosinophilia.[4,29] The origin of eosinophilic fasciitis is unknown, but it is occasionally associated with vigorous exercise.[29] It is a disorder of adults, has no Raynaud's phenomenon or internal involvement, and gives a characteristic cobblestone or rippled appearance to the skin of the extremities with no epidermal change.[15] Eosinophilic fasciitis responds to treatment with oral corticosteroids.[28]

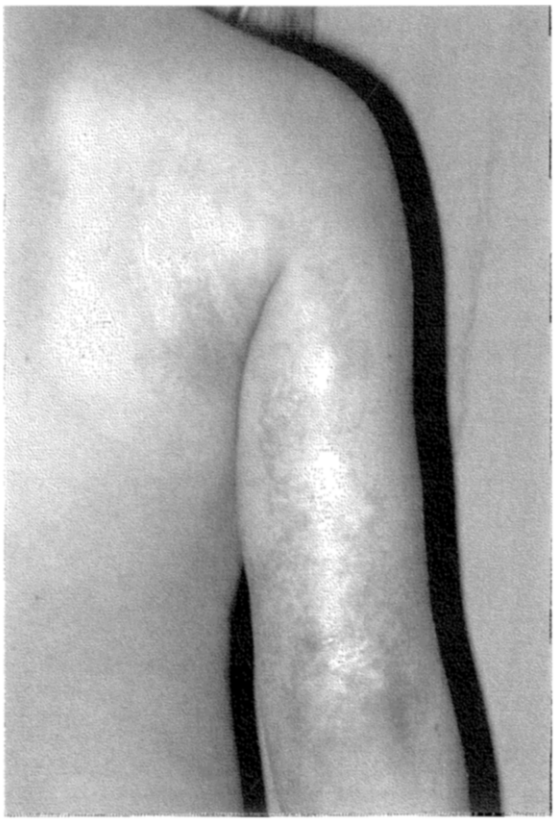

Fig 1. Linear scleroderma. (Photo from the teaching files of the University of Virginia Dept. of Dermatology.)

Systemic

The clinical manifestations of SSc include Raynaud's phenomenon (Fig 2), as well as fibrotic complications of the skin, musculoskeletal, gastrointestinal system, pulmonary, renal, and cardiac systems. Between 70% and 95% of scleroderma patients eventually experience Raynaud's phenomenon, a disorder characterized by cyanosis and blanching of the digits resulting from digital arterial vasoconstriction.[2] For some patients, Raynaud's phenomenon is also associated with

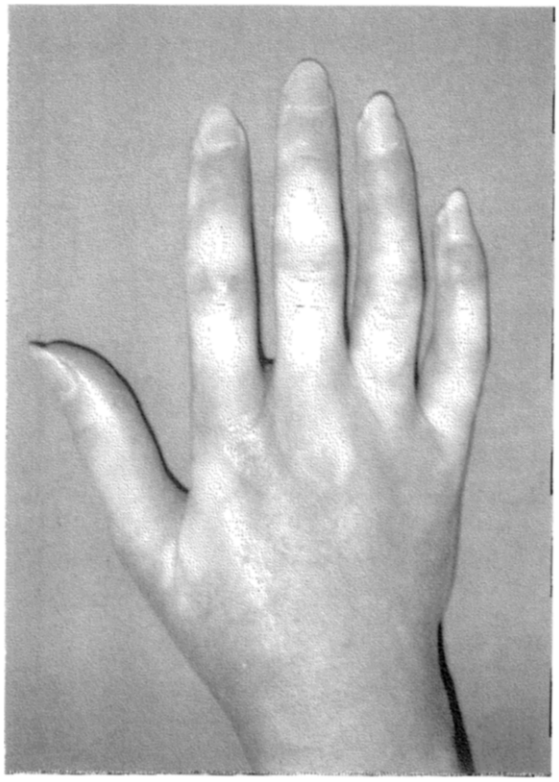

Fig 2. Raynaud's phenomenon. (Photo from the teaching files of the University of Virginia Dept. of Dermatology.)

digital pitting scars, nailfold infarcts, or digital ulcers.[2,30] Raynaud's phenomenon is more common in limited than diffuse SSc; in limited SSc, it can precede the development of other symptoms by 10 to 15 years.[15]

Skin thickening in systemic sclerosis always begins in the fingers. In LSSc, the thickening may spread, but is confined to the face and distal extremities, below the elbow or knees.[2,6] In DSSc, the thickening progresses from the hands to the distal and proximal extremities, trunk, and face.[2,6] Most of the skin thickening occurs in the first 3 to 5 years of the illness and is often followed by some spontaneous improvement.[15,30] Other skin manifestations of the disease include telangiectasias, xerosis, pruritis, alopecia, and pigmentation changes.[2,30] In African Americans, the characteristic pigmentary change is hypopigmentation of the skin with persistent perifollicular hyperpigmentation[3] (Fig 3).

Musculoskeletal manifestations are common but variable in expression.[2] In DSSc, rapid fibrosis often leads to flexion contractures of the hands, sclerodactyly (Fig 4), carpal tunnel syndrome, and coarse leathery friction rubs.[2,30] Polyarthritis, morning stiffness, fibrotic myopathy, and inflammatory myositis occur in both LSSc and DSSc.[2,30]

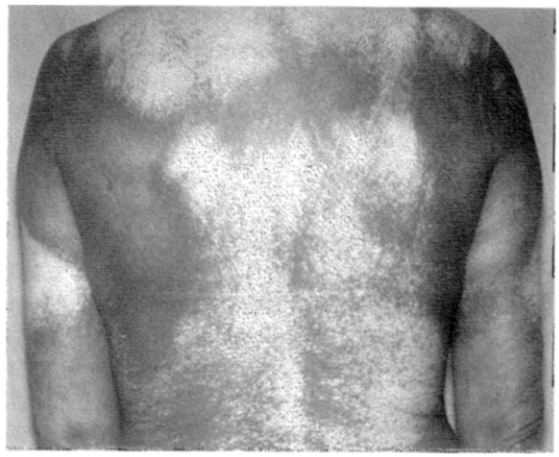

Fig 3. Systemic scleroderma aberrant pigmentation pattern. (Photo from the teaching files of the University of Virginia Dept. of Dermatology.)

Gastrointestinal tract involvement occurs in almost all patients with SSc, and is clinically manifested as gastroesophageal reflux and dysphagia. Distal esophageal motor dysfunction is the most common finding, occurring in 90% of patients.[8] It can lead to strictures, ulcerations, gastroparesis, pseudo-obstruction, infections with development of nausea and vomiting, anorexia, and malnutrition.[2,15,30]

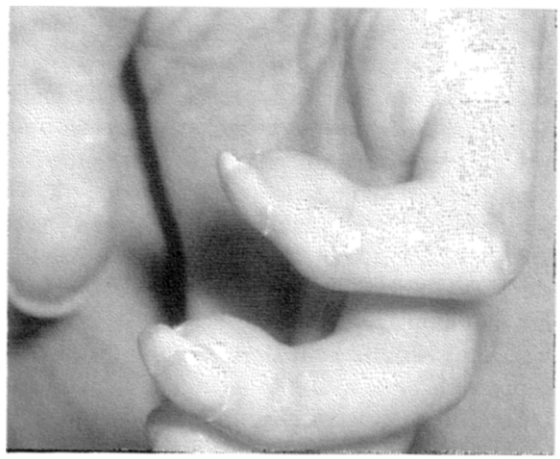

Fig 4. Sclerodactyly with calcifications of systemic scleroderma. (Photo from the teaching files of the University of Virginia Dept. of Dermatology.)

Approximately 45% of patients with SSc have kidney involvement.[8] Whereas a few patients experience progressive uremia, patients more commonly have acute renal crisis associated with malignant hypertension. Renal crisis was once the most fatal complication in scleroderma; now, however, prompt treatment with angiotensin converting enzyme (ACE) inhibitors has greatly improved survival.[30] However, progression to anuric renal failure with hemodialysis requirements can occur.[2] Symptoms of patients in renal crisis include headache, encephalopathy, seizure, and retinopathy.[15]

Pulmonary interstitial fibrosis is currently the most common cause of death in SSc.[2,30] Pulmonary function tests of patients with pulmonary interstitial fibrosis reveal a restrictive pattern with decreased forced vital capacity, and chest radiographs show bibasilar fibrosis. Pulmonary hypertension is the most fatal complication of SSc, with most patients dying within 2 years of diagnosis. It is characterized by a decrease in the diffusing capacity for carbon monoxide, severe dyspnea, and subintimal hyperplasia of pulmonary arteries.[30] This manifests as fatigue, dyspnea on exertion, cough, and chest pain.[2,8]

Although clinical evidence of myocardial involvement is seen in less than 10% of patients with SSc, pathological findings and cardiac tests show evidence of asymptomatic left ventricular dysfunction, conduction defects, arrythmias, or pericardial effusions in a high proportion of patients.[15,30] Clinically asymptomatic angina and sudden death have occurred.[2]

DIAGNOSIS

Localized

Because of its unique presentation, LSc is often diagnosed clinically. Diagnostic tests to confirm localized scleroderma may include skin biopsy, radiographic examination of affected extremities, and serologic testing.[4] Serum autoantibodies are common in LSc, particularly in linear scleroderma. Antinuclear antibodies can be found in 20% to 50% of patients with localized scleroderma, and rheumatoid factor can be found up to 40% of patients.[28]

Systemic

Diagnostic tests to confirm SSc include skin biopsy, chest X-ray, renal function tests, electrocardiogram, upper gastrointestinal motility studies, and serologic testing for disease classification.[3] The majority of patients with SSc have autoantibodies to intracellular antigens.[20] The 3 main autoantibody subgroups are anticentromere antibodies, anti-DNA topoisomerase I (anti-topo I) antibodies (ie, anti-Scl-70), and anti-RNA polymerase III (RNAP III) antibodies (Table 2).[20,30] These 3 subgroups are generally considered to be mutually exclusive; however, each subgroup may be accompanied by other autoantibody specificities.[20] For example, patients with anti-topo I antibodies may also have autoantibodies to RNAP II.[20] Minor serologic subgroups also exist and may provide additional prognostic information. For example, a 1999 study by Ihn et al[31] found that 8% of SSc patients were positive for anti-U1RNP, and that the presence of the anti-U1RNP antibody was correlated with LSSc, pulmonary fibrosis, and joint involvement.

The 3 main subgroups of antinuclear antibodies are useful in diagnosing SSc, as well predicting disease course and severity. Anticentromere antibodies are found in approximately 26% of SSc patients and are associated with the greatest likelihood of developing LSSc, the longest cumulative survival times, and the lowest frequency of DSSc, pulmonary and renal disease.[20,30] Anti-topo I antibodies are found in 22% of SSc patients.[20] They are associated with a high frequency of pulmonary interstitial fibrosis, and intermediate cumulative survival times, intermediate frequency of DSSc.[20,30] Anti-RNAP III antibodies are found in 18% of SSc patients.[20] These patients carry the greatest risk of DSSc and renal disease, the highest maximum skin thickness scores, and the shortest cumulative survival times.[20,30] Available data suggest that there may be 3 distinct disease processes, each with certain key pathologic factors that result in the production of a specific set of autoantigens.[20]

TREATMENT

Localized

The available treatment options for LSc are often supported only by anecdotal evidence. Because of the rarity of the disease, there have been few randomized, controlled trials of therapeutic agents. The trials that do exist use different endpoints, which makes it difficult to compare results

across trials.[14] Further complicating the evaluation of current therapies is the tendency for scleroderma lesions to spontaneously resolve.[2] An epidemiological study by Peterson et al[7] found that 50% of patients with localized scleroderma had softening or other evidence of disease resolution after 3.8 years.

Because of the self-limiting nature of the disease, the majority of cases of LSc can be treated with topical therapies and intralesional corticosteroids.[3] Physical therapy is indicated if there is significant disability secondary to linear scleroderma. Surgical procedures, although rare, may also be indicated.[4,14]

Topical therapeutic modalities for LSSc include potent topical steroids, occlusive steroid dressings, intralesional steroid, daily lubrication, topical calcipotriene, and topical capsaicin for pruritic lesions.[4,14] A recent open label study of topical calcipotriene 0.005% ointment (Dovonex; Westwood-Squibb, Buffalo, NY) used in 12 patients with active morphea or linear scleroderma showed improvement in all 12 patients over the 3-month study period.[32]

For patients with severe, rapidly progressing disease, a more aggressive therapy including non-topical pharmacologic agents may be indicated.[4,14] Nontopical pharmacologic agents include vitamin E, vitamin D3 (oral calcitrol), aminobenzoate potassium, penicillin, retinoids, interferon gamma, immunosuppressive therapy, and UV therapy.[4,14] To date, most of these therapies have been studied in open trials with no controls; therefore, it is not clear whether the observed improvements in fibrosis occurred as a result of treatment or were attributable to spontaneous remission. In terms of mechanism of action, vitamin E is postulated to influence collagen metabolism, aminobenzoate potassium (Potaba; Glenwood, Tenafly, NJ) to effect collagen deposition, penicillin to influence collagen fibrillogenesis and cross-linking, retinoids to influence the fibroblast synthesis complex, and vitamin D3 (Rocaltrol; Roche, Nutley, NJ) to effect fibroblast differentiation.[14] Interferon gamma (Actimmune; Intermune Pharmaceuticals, Palo Alto, CA) is a cytokine with a strong inhibitory effect on collagen synthesis. Hunzelmann et al[33] compared use of intralesional injections of interferon-gamma to placebo patients with LSc. They found no statistically significant difference in the size or fibrosis of existing lesions; however, there was a reduction in the total number of lesions.

Oral immunosuppressive therapies that have been used for treatment of LSc include oral steroids, hydroxychloroquine, methotrexate, salazopyrine, D-penicillamine, cyclosporine, and cyclophosphamide.[4,14] In a study of D-penicillamine (Cuprimine, Merck & Co Inc, West Point, PA) in 11 patients with severe LSc, 6 improved over the study period, but there were significant adverse side effects including allergic and renal complications.[34] Seyger et al[35] looked at the use of low-dose methotrexate (Methotrexate; Immunex Corp, Seattle, WA) in a noncontrolled study of 9 patients with LSc. There was improvement in the Modified Skin Scores in 6 of 9 patients, and in the Visual Analog Scale (a measure of overall well being) in 7 of 10 patients. Adverse events included nausea and elevated liver enzyme levels.

UVA irradiation, in the form of bath and oral psoralen (PUVA—Oxysoralen Ultra; ICN, Costa Mesa, CA), as well as high and low dose UVA1 therapy, has been applied to the treatment of LSc. UVA irradiation is postulated to increase the activity of metalloproteinases, and modulate expression of cytokines that participate in connective tissue remodeling.[13] Kerscher et al[36] treated 20 patients with severe LSc with UVA1 irradiation. During the 12-week study period, 80% of lesions treated with UVA 1 disappeared or improved.[36] In a noncontrolled study of PUVA bath therapy, there was disappearance or improvement of sclerotic lesions in 13 of the 17 study patients.[37] Morrison et al[38] published a series of 4 patients with LSc who were treated with PUVA. He found that the therapy stopped progression of morphea and reversed inflammatory changes.[38] Five patients with LSc found regression of lesions with topical photodynamic therapy, when treated with 3% 5-aminolevulinic acid gel after irradiation with and incoherent light source (PDT 1200, Waldmann, Germany—light dose 40mW/cm^2 and power density 10J/cm^2) for 3 to 6 months once to twice weekly.[39]

Systemic

As in LSc, the natural history of sclerotic lesions of the skin is improvement over time, which complicates the evaluation of therapeutic interventions. Whereas some of the proposed disease modifying agents have been shown to improve skin

scores, their side effect profiles preclude their use for this purpose alone.[40] Pruritus is especially problematic in early active lesions of SSc. Topical corticosteroids and PUVA can provide some relief.[40] Telangiectasias can be easily treated for cosmetic reasons by laser surgery.[40]

Most patients with SSc are secondarily affected with Raynaud's phenomenon. Nonpharmacologic therapies like cold avoidance tend to be less effective in patients with Raynaud's secondary to SSc than in those who have primary Raynaud's; however, they can still provide some relief.[40] The short-acting calcium channel blocker, nifedipine (Procardia; Pfizer, New York, NY), is considered first line therapy for treatment of Raynaud's.[40] For patients who are refractory to calcium channel blockers, the use of IV prostaglandins has been suggested; however, recent studies of the prostaglandin, iloprost (not available in the United States), indicate that it is no more effective than placebo in the treatment of Raynaud's phenomenon secondary to scleroderma.[41,42]

Although much progress has been made in treating the symptoms of scleroderma, the development of disease modifying therapies has been less successful.[43] Disease modifying agents used in treating SSc focus on the fibrotic and inflammatory processes associated with the disease; however, no therapy has been proven to alter the overall course of SSc.[44] A promising placebo-controlled study on recombinant human Relaxin (Connetics Corp, Palo Alto, CA), a new disease modifying therapy for SSc, was recently conducted by Seibold et al.[45] Relaxin is a hormone produced by the corpus luteum during pregnancy that has been shown to increase skin elasticity in animal models. The study included 68 patients who had stable, DSSc of less than 5-years duration. In this trial, the patients who received 25 ug/kg of human recombinant Relaxin per day had decreased skin scores, improved mobility, improved vital capacity, and improved functional status assessment in relation to controls.

Clinical trials have shown that interferon gamma is of limited effectiveness in the treatment of SSc, especially when considering the cost and influenza-like side effect profile associated with the drug.[46,47] Trials of photophoresis have similarly shown little skin improvement. Enomoto et al[48] conducted a 2-year study of photophoresis in 19 patients with SSc. They concluded that photophoresis produced a statistically and clinically insignificant change in average skin score and visceral organ status, and therefore, did not justify the duration, intensity, and cost of treatment. Minocycline (Minocin; Lederle Labs, Division of Am. Cyanamid Corp, Pearl River, NY) has also been used to treat SSc, but it has not been studied in placebo-controlled trials. An open trial by Lee et al[49] looked at the use of minocycline in the treatment of 11 patients with early DSSc. Of the 11 patients, 4 had complete resolution of the cutaneous manifestations of the disease, 2 had no improvement, and 5 dropped out.

Allogenic bone marrow transplantation (BMT) has been proposed as a potential therapy for patients with life threatening SSc because of evidence indicating that immune dysregulation is an important factor in the pathogenesis of scleroderma.[50,51] Allogenic bone marrow transplantation (BMT) after high dose cytotoxic therapy destroys the cells of the host immune system and replaces them with donor cells. Although BMT for SSc has yet to be studied in a clinical trial, a case report by Tyndall et al[51] describes their experience treating a 37-year-old woman with DSSc with immune ablation followed by autologous hematopoietic stem cell transplantation. The procedure was successful, and at 6 months follow-up, the patient had more energy, less joint stiffness and pain, less skin tightness, and an improved skin score.[51]

COURSE/PROGNOSIS

Localized

Survival rates for LSc are no different than that of the general population.[6,7] However, LSc may be associated with morbidity. Peterson et al[7] noted in a review of 82 patients with LSc, 11% of patients developed substantial disability resulting from their disease, with up to 44% of patients with deep morphea.[7] Pediatric patients in particular are at increased risk for major disability, including limb and facial asymmetry, flexion contractures, growth retardation, and psychological disability.[4]

Systemic

Unlike the local variant, SSc is associated with significant morbidity; however, mortality rates from the disease appears to be decreasing because of improved treatment options, particularly for renal complications of the disease. Most recent studies

indicate that 5-year survival is approximately 80% or higher for SSc.[52,53] However, DSSc is more often associated with poorer outcomes then LSSc.[52-54]

A recent prospective analysis of 280 patients with systemic scleroderma by Bryan et al[54] indicated that diffuse disease is associated with 73% excess mortality compared with limited disease. They also found that extent of skin involvement, decreasing lung capacity, presence of anti-topo I antibody, and cardiac abnormality on electrocardiogram were associated with significantly increased mortality rates. A logistic regression model of the data, validated by Monte Carlo simulation, found proteinuria, elevated Erythrocyte Sedimentation Rate, and low carbon monoxide diffusing capacity to be over 80% accurate in predicting mortality.[52] Of interest, is the absence of these feature were associated with 93% survival. Three recent studies have all shown that extent of skin and pulmonary involvement is also important prognostic indicators for SSc.[52,53,55]

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