Scleroderma

Disease Definition and Classification

Scleroderma, or systemic sclerosis, is a rare rheumatic disorder characterized by deposition of fibrous connective tissue in skin and other organs; microvascular lesions, especially in the skin, lungs, and kidneys; and autoimmunity and inflammation. No cure is known, but effective therapies for some scleroderma-related manifestations have recently been developed.

Scleroderma may be either systemic or localized. The systemic illness may occur in either diffuse or limited patterns or as part of an overlap inflammatory rheumatic disease with features of lupus, myositis, or arthritis. The limited cutaneous form of systemic scleroderma, formerly termed CREST syndrome (an acronym for calcinosis, Raynaud phenomenon, esophageal involvement, sclerodactyly, and telangiectasias), involves internal organs less often than diffuse systemic scleroderma does. Systemic scleroderma can be fatal; except when pulmonary arterial hypertension (PAH) is present, patients with the limited cutaneous form have a better prognosis than those with the diffuse form [see Table 1]. A systemic form of sclerosis, characterized by scleroderma-like internal organ involvement and autoimmunity without skin fibrosis (referred to as systemic sclerosis sine scleroderma), is an uncommon form of this rare condition.

Localized scleroderma is confined to the skin, subcutaneous tissue, and muscle. It is not accompanied by Raynaud phenomenon, acrosclerosis, or visceral involvement. There are two major groupings: morphea, which may occur as plaques of skin induration, generalized morphea, or deep morphea; and linear scleroderma, which presents as bands of skin induration on the face or a single extremity. In morphea, the lesions may persist for months or years, after which improvement may occur [see Table 1]. Linear scleroderma may be associated with muscle atrophy and involvement of the underlying bone. It usually afflicts children or young adults and may lead to significant growth impairment of the involved part. Some patients with localized morphea test positive for autoantibodies. Although there is a possibility of disfigurement, localized scleroderma is not typically a severe illness, and patients generally have a normal life span.

Epidemiology

Raynaud phenomenon, a cardinal feature of scleroderma, usually presents as a prelude to clinical disease [see Diagnosis, Clinical Manifestations, below]. Primary Raynaud phenomenon (i.e., Raynaud phenomenon occurring with underlying disease) occurs frequently and remits commonly. It has a prevalence of 7.8% and 10.9% in men and women, respectively; in nearly two thirds of cases, all symptoms are found to have resolved on follow-up. The transition from Raynaud phenomenon to a defined inflammatory rheumatic disease (e.g., scleroderma or lupus) occurs at the rate of 3.2 cases per 100 patient-years of observation; an inflammatory rheumatic disease eventually occurs in 12.6% of individuals with Raynaud phenomenon. The best predictor that an inflammatory disease will eventually develop is an abnormal nail-fold capillary pattern—a finding that has a predictive value of 47%; antinuclear antibody has a positive predictive value of only 30%.

Racial, genetic, and environmental factors may influence the epidemiology and disease pattern of scleroderma. In the United States, the overall annual incidence of scleroderma is approximately 18.7 cases per one million population, with higher rates occurring in women than in men. Patients of African descent experience diffuse scleroderma nearly twice as often as patients of European descent; patients of European descent are more often diagnosed with limited cutaneous scleroderma. The prevalence of scleroderma in the United States is approximately 24.2 to 28.6 per 100,000 population, which is several times the prevalence in other countries. Prevalence estimates of scleroderma in the United Kingdom and France are one third to one half that of the United States, with the limited cutaneous form being two to four times more prevalent than the diffuse form.

Etiology/Genetics

Scleroderma is a complex disorder of uncertain etiology involving random or environmental events acting in conjunction with the effects of multiple genes that individually confer modest risk. Environmental risk factors include exposure to paint thinners and paint removers, silica, and vibrating tools. Some investigators have suggested that infection with retroviruses or human cytomegalovirus may cause scleroderma. Silicone breast implants have been found not to be associated with scleroderma. For most cases of scleroderma, no environmental trigger can be identified.

Hereditary factors contribute in a strong way to the pathogenesis of scleroderma. A positive family history is the strongest known risk factor. In the United States, the frequency of scleroderma in relatives of persons known to have scleroderma is about 1.6%, a prevalence over 60-fold higher than in the general population. Although the evidence is not conclusive, the current pathogenetic explanation—that scleroderma stems from the interaction of autoimmune-inflammatory, extracellular matrix, and vascular processes—appears to be supported overall by various studies of genetic association.

Pathophysiology and Pathogenesis

The common pathologic features of scleroderma are severe progressive fibrosis, microvascular abnormalities, and chronic inflammation. Fibrosis involves an accumulation of excessive...
collagen and other extracellular matrix constituents, such as glucosaminoglycans and fibronectin. The vascular abnormalities involve intimal hyperplasia with collagen deposition and adventitial fibrosis, capillary dropout, dilatation, tortuosity, and fibrotic atherosclerosis. The inflammatory changes may include cellular infiltration. These pathologic characteristics are believed to be the result of three or more interacting components: autoimmunity and inflammation, an endothelial abnormality, and a skin fibroblast lesion. The conclusions of in vitro and animal-based studies suggest that the autoimmune response, vascular injury, and endothelial dysfunction precede and may trigger the activation of fibroblast-dependent processes. An alternative explanation is that the characteristics of scleroderma stem from a disease process akin to graft-versus-host disease.

**Immune Cell, Inflammation, and Cytokine Abnormalities**

Activated thymus-derived lymphocytes predominate among the cells that infiltrate involved tissues; other activated inflammatory cells are also present. The activated cells release a plethora of cytokines and soluble mediators that lead to fibrotic and microvascular lesions. Predominant among the released mediators are profibrotic cytokines and chemokines that are characteristic of a type 2 helper T cell response, particularly connective tissue growth factor (CTGF) and transforming growth factor-β (TGF-β). B cells are also activated in patients with scleroderma, and over 90% of patients have at least one serum autoantibody. Newly described autoantibodies directed toward endothelial cell targets, fibrillin-1, matrix metalloproteinases, and platelet-derived growth factor (PDGF) receptor may mediate tissue damage. In particular, scleroderma-associated anti-PDGF-receptor autoantibodies have been shown in studies of tissue culture to mediate intimal hyperplasia by directly injuring endothelial cells and upregulating CTGF and, in turn, PDGF. Platelets may then adhere to injured endothelium and initiate thrombosis and fibrin deposition; cytotoxic mediators may also injure endothelial cells directly. Microvascular dilation is impaired because of a relatively deficient number of vasodilators (i.e., prostanycin, nitric oxide, and calcitonin-gene-related protein [CGRP]) and an excessive quantity of endothelin-1, a potent vasoconstrictor. Endothelial cells express increased numbers of cellular adhesion molecules. Capillaries become obliterated but are not replaced; involved tissues may become ischemic and then reperfused. Raynaud phenomenon [see Diagnosis, Clinical Manifestations, below] reflects structural and functional abnormalities of the vasculature; it also is evidence of neuroregulatory lesions (e.g., reduced nerve release of CGRP and excessive response mediated through alpha2c-adrenergic receptors) and intravascular abnormalities (e.g., platelet activation, hyperviscosity, reduced fibrinolysis, and oxidant stress). In scleroderma, small arteries develop concentric intimal fibrosis and narrowing that, in turn, greatly increases the effects of vascular reactivity.

**Vascular Abnormalities**

Vessels in involved tissues show disrupted pattern and function, characterized by altered endothelial permeability, adhesion of platelets and leukocytes to endothelium, and the presence of fibrosis and inflammatory cells. Some cytokines, such as TGF-β, may injure endothelial cells and upregulate CTGF and, in turn, PDGF. Platelets may then adhere to injured endothelium and initiate thrombosis and fibrin deposition; cytotoxic mediators may also injure endothelial cells directly. Microvascular dilation is impaired because of a relatively deficient number of vasodilators (i.e., prostanycin, nitric oxide, and calcitonin-gene-related protein [CGRP]) and an excessive quantity of endothelin-1, a potent vasoconstrictor. Endothelial cells express increased numbers of cellular adhesion molecules. Capillaries become obliterated but are not replaced; involved tissues may become ischemic and then reperfused. Raynaud phenomenon [see Diagnosis, Clinical Manifestations, below] reflects structural and functional abnormalities of the vasculature; it also is evidence of neuroregulatory lesions (e.g., reduced nerve release of CGRP and excessive response mediated through alpha2c-adrenergic receptors) and intravascular abnormalities (e.g., platelet activation, hyperviscosity, reduced fibrinolysis, and oxidant stress). In scleroderma, small arteries develop concentric intimal fibrosis and narrowing that, in turn, greatly increases the effects of vascular reactivity.

**Fibroblast Abnormalities**

The final pathogenetic component of scleroderma is overactive fibrosis-related processes. Matrix-producing fibroblasts and myofibroblasts in scleroderma tissues may arise not only from resident tissue fibroblasts but also from other sources, such as bone marrow and circulating cells, epithelial cells subjected to cytokine influences, and vascular pericytes. As with lymphocytes and macrophages, such fibroblasts are metabolically activated. The cells overproduce collagen, other extracellular matrix molecules, and cellular adhesion molecules. Cytokines from inflammatory cells, such as interleukin-4 (IL-4) and TGF-β, may activate collagen gene transcription and collagen production persistently. TGF-β acts in large part through specific receptors, leading to activation of SMADs, a family of second messenger/transcription factor proteins.

**Chimerism and Microchimerism**

Another potential explanation for the pathogenesis of scleroderma is that the disease is mediated by engrafted foreign cells. Chimerism denotes a state in which a person has cells derived from one or more genetically distinct people. In individuals who
Clinical Manifestations

Skin  Cutaneous manifestations include thickening, tightness, telangiectasias, calcinosis, altered pigmentation, and Raynaud phenomenon. Skin involvement is characterized by three phases: edematous, indurative, and atrophic. The first sign is typically swelling of the fingers and hands. Later, skin on the hands and fingers may thicken and tighten; this phase may or may not involve the face. Still later in the illness, other areas may become thickened.1 Itching may be prominent. During the indurative phase, which may begin several months after onset and last for several years, the skin continues to thicken. The thickening then ceases and may recede, giving the impression that the skin is softening. Over subsequent years, skin atrophy occurs with concomitant loss of hair, sebaceous glands, and sweat glands, as well as a loss of pliability. In addition, the skin becomes hidebound—tightly drawn and bound to subcutaneous tissues. Frequently, the facial skin tightens, resulting in decreased skin lines, a pursed appearance, and a diminution in the oral aperture.

Sclerodactyly, which is the symmetrical thickening, tightening, and induration of the digits, can prove debilitating. The skin tightness may limit mobility, especially in the fingers; the reduced ability to flex the fingers fully is the result of the increased distance from fingertip to palm [see Figure 1]. Telangiectasias occur frequently, may be numerous [see Figure 2], and are often most prominent on the face, hands, and oral mucosa. Calcinosis—the deposition of hydroxyapatite crystals within or under the skin—occurs in 22% of patients; it may be limited or widespread and is usually located on finger pads or around joints [see Figure 3]. A diffuse hyperpigmentation may extend over the entire involved skin surface; areas of hypopigmentation are also commonly seen over bony prominences, such as the eyebrows and clavicles.

Raynaud phenomenon is not specific to scleroderma, but it is nearly always present. Almost all patients (95%) with diffuse or limited scleroderma experience Raynaud phenomenon at some time; it usually precedes the onset of limited cutaneous scleroderma by several years, but it sometimes follows the onset of diffuse scleroderma.2 The Raynaud phenomenon is an episodic numbness or pain accompanied by a two- or three-phase color change in the digits. Each episode typically begins with pallor, followed by cyanosis; finally, redness occurs as a result of reactive hyperemia [see Figure 4]. The changes are triggered by cold temperatures or emotional stress and are relieved by warming; in severe cases, however, the relation to ambient temperature may be less obvious. The phenomenon is found in patients with other inflammatory rheumatic disorders; it is also associated with the use of certain drugs (e.g., bleomycin, ergot derivatives, beta blockers, and methysergide) and occupational exposure to vinyl chloride, cold temperatures, and vibrating tools. Raynaud-related ischemia may lead to digital ulceration and even gangrene that, when healed, may result in digital pitting scars and loss of digital pad substance.

Musculoskeletal system  Arthritis, flexion contractures, tendon friction rubs, osteolysis, and muscle disorders occur in scleroderma. A mild, usually symmetrical, inflammatory arthritis occurs in 12% to 19% of scleroderma patients. Juxta-articular bone erosions occur frequently, especially in the distal interphalangeal joints; however, they are not as prominent as in rheumatoid arthritis. Flexion contractures of the fingers often develop and are most likely related to fibrosis of tendons and joint capsules. Crepitus and friction rubs are characteristic findings reflecting fibrotic changes of underlying tissues. Another feature is acral osteolysis, characterized by the resorption of the terminal phalanges and surrounding soft tissue with consequent shortening of digits [see Figure 5]. Patients with scleroderma may manifest one or more muscle disorders, such as fatigue without objective evidence of muscle damage, a simple myopathy with proximal weakness, or clear-cut inflammatory myositis (occurring in 4% to 6% of cases).
Scleroderma-related features are dominated by renal crisis. Chronic mild proteinuria and mild hypertension are common effects of scleroderma but typically do not result in clinically significant renal dysfunction. Renal crisis consists of the rapid development of malignant hypertension or higher-than-usual blood pressure, hyperreninemia, microangiopathic hemolytic anemia, and oliguric renal failure.
Other organ systems Although scleroderma rarely involves the central nervous system, peripheral neuropathy may occur. The most frequent form is unilateral or bilateral trigeminal neuropathy in one or more of the three branches; this neuropathy presents as progressive numbness and pain. Widespread autonomic nervous system dysfunction underlies the propensity for Raynaud phenomenon and intestinal involvement. Hematopoietic effects of scleroderma are uncommon. Sjögren syndrome, which causes dry eyes and dry mouth, occurs in about one third of patients with scleroderma; it is more common in patients with limited cutaneous scleroderma than in those with the diffuse form of the disease. Constitutional symptoms of fatigue and malaise are common. Finally, because scleroderma can be such a debilitating illness, the clinician must be alert for poor nutrition, weight loss, and significant affective symptoms.

Physical Examination Findings

Skin and vasculature The examiner should characterize the extent of skin involvement, as well as the distribution; nailfold capillaries should be examined; and signs of calcinosis, telangiectasias, and stigmata of Raynaud phenomenon should be sought. It is important to note the presence and distribution of nonpitting edema and the degree of cutaneous thickening and tightening. Other features that may be noted are the loss of normal skin wrinkles and skin folds, changes in skin pigmentation, diminished oral aperture (less than the breadth of two or three fingers), skin atrophy, and contractures. A critical distinction is whether skin involvement is proximal to knees and elbows; proximal involvement is consistent with diffuse rather than limited cutaneous scleroderma and thus carries a higher risk of visceral involvement and a poorer prognosis. Nailfold capillaries should be inspected using a magnifying lens, such as that on a standard ophthalmoscope; microscope immersion oil may reduce interfering reflections. Patients with underlying scleroderma may exhibit loss or dilatation of periungual capillaries; this finding may indicate diffuse scleroderma and its associated risk of visceral involvement. Calcification is found by inspecting and palpating for intracutaneous deposits over joints. Telangiectasias, which are dilated small vessels visible to the unaided eye, may be present anywhere on the skin, including oral mucosal surfaces. Raynaud phenomenon may be apparent during examination; the examiner should inspect the digits for the presence of necrotic or ulcerated areas (active or healed), loss of digital pads, and digital amputations.

Musculoskeletal system Arthritis, tendon friction rubs, and weakness may be evident on examination. Evidence of symmetrical joint swelling and tenderness may indicate inflammatory arthritis. A tendon friction rub, which is a palpable leathery crepitus over flexor or extensor tendons, may be noted on joint
palpation during active or passive motion. Neck flexion, as well as shoulder and hip girdle muscular strength, should be tested.

**Lungs and heart** Lung and heart involvement may be suggested by a reduction in exercise tolerance and findings of interstitial fibrosis. The clinician should determine whether the patient experiences dyspnea and fatigue after minimal or no physical effort; such findings are consistent with New York Heart Association functional class III or IV. When interstitial fibrosis is present, fine crackles may be audible during auscultation over the posterior lung fields. If PAH is present, the cardiac findings may include an accentuated pulmonic component to S2, a right-sided S3, or a tricuspid insufficiency murmur, as well as other features relating to right heart failure. Cardiac signs of heart failure and arrhythmia may be detected. The distance walked during a submaximal exercise test (i.e., a 6-minute walk) and oximetry may be helpful in determining baseline status and in serial comparisons. Resting tachycardia may indicate autonomic involvement, and signs of heart failure or valvular insufficiency may be apparent.

**Other organ systems** If renal crisis has ensued, hypertension of serious degree will be found; alternatively, blood pressure may be well above a lower baseline value.
mm Hg or more. Screening is generally effective for severe PAH, but it is less effective for mild and moderate hypertension, because of technical limitations in detecting tricuspid regurgitation and human error in interpreting pressure estimates (i.e., the values may be underestimated in cases of severe PAH and somewhat overestimated in cases of mild to moderate hypertension).

**Radiographic imaging** Imaging studies can aid in determining the extent of scleroderma-related involvement; they are also useful in excluding potentially complicating illnesses. Chest roentgenograms may show linear and reticular fibrosis in the lungs and underlying illnesses. High-resolution computed tomography is favored for the diagnosis of interstitial disease; alveolitis may appear as patchy areas with a ground-glass appearance, and fibrosis as reticular or reticulonodular opacification. Ventilation-perfusion lung scanning may aid in screening for thromboembolic disease. Imaging studies, such as esophagrams or small bowel series, may also show evidence of scleroderma involvement.

**DIFFERENTIAL DIAGNOSIS**

Many disorders may resemble the cutaneous presentations of scleroderma in some manner. These include disorders characterized by mucin deposition, papulonodular skin changes with dermal deposits, monoclonal gammopathy, eosinophilia (as with eosinophilic fasciitis); some endocrine abnormalities (e.g., the cheiropathy found with diabetes mellitus); graft-versus-host disease; some allergic conditions resulting from drug, chemical, and physical exposures; and certain hereditary conditions. Overall, scleroderma differs from other diseases by characteristic features and hand and finger involvement, the presence of Raynaud phenomenon, nailfold capillary abnormalities, and, often, internal organ involvement. Nonepisodic finger cyanosis simulating the cyanosis of Raynaud phenomenon may also occur with small arterial disorders, such as occlusions, clots, and emboli.

**TREATMENT**

Management of scleroderma is often a serious challenge, but it includes several potentially life-saving interventions. The clinician should screen each scleroderma patient for probable serious involvement and consult with rheumatologists and other subspecialists (in pulmonary medicine, cardiology, and radiology in particular) to determine the optimal management of most scleroderma patients [see Table 3].

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**Table 2 Antinuclear Antibodies in Scleroderma**

<table>
<thead>
<tr>
<th>Antigens</th>
<th>Clinical Pattern</th>
<th>Approximate Frequency (%)</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleolar ribonucleoproteins (nRNP)</td>
<td>Diffuse or limited scleroderma</td>
<td>50</td>
<td>Moderate</td>
</tr>
<tr>
<td>RNA polymerases I, II, and III</td>
<td>Diffuse scleroderma</td>
<td>23</td>
<td>High</td>
</tr>
<tr>
<td>Nuclear proteins PM-1 (PM-Scl) and Ku</td>
<td>Scleroderma-polymyositis overlap</td>
<td>&lt;5</td>
<td>High, for scleroderma and polymyositis</td>
</tr>
<tr>
<td>Fibrillarin (U3 snRNP)</td>
<td>Diffuse scleroderma</td>
<td>12</td>
<td>High</td>
</tr>
<tr>
<td>Centromeric (large speckles)*</td>
<td>Centromere proteins (CENP-A, CENP-B, and CENP-C)</td>
<td>Usually in limited scleroderma (CREST syndrome)</td>
<td>50 (of patients with CREST syndrome)</td>
</tr>
<tr>
<td>Diffuse (fine speckles)</td>
<td>DNA topoisomerase I (Scl-70)</td>
<td>Diffuse scleroderma</td>
<td>20–33</td>
</tr>
</tbody>
</table>

*Requires a human epithelial carcinoma cell line (HEp-2).

**Renal Crisis**

Renal crisis is a rare but serious complication, and appropriate management may alter outcome. Before angiotensin-converting enzyme (ACE) inhibitor therapy, renal crisis was the most common cause of scleroderma-related death. Still, once renal crisis occurs, even the best current management may not prevent progression to chronic renal failure or dialysis; the percentage of patients who have poor outcomes after renal crisis is estimated to be 39%; in one study, survival was 50%. Those patients at greatest risk for renal crisis have features more consistent with diffuse scleroderma, such as rapid progression of skin disease, large-joint contractures, heart involvement, recent high-dose corticosteroid therapy, or autoantibodies directed toward RNA polymerase III. For this reason, a clinician should instruct each patient with early diffuse scleroderma about the importance of regular self-monitoring of blood pressure and of promptly contacting the physician when an elevation in blood pressure is detected. Renal crisis is recognized by diminished renal function accompanied by new-onset hypertension (or a systolic increase of 30 mm Hg and a diastolic increase 20 mm Hg above a baseline level), microscopic hematuria, and proteinuria. Treatment of this medical emergency with ACE inhibitors (or angiotensin receptor blockers) and other potent antihypertensive drugs may arrest the deterioration in renal function. In about half of those who initially require dialysis, treatment may restore enough renal function to make further dialysis unnecessary. However, ACE-inhibitor therapy has been shown to be more beneficial when initiated before serum creatinine levels have exceeded 3 mg/dl. In other patients, renal failure progresses despite good control of blood pressure, necessitating permanent dialysis and possibly renal transplantation.

**Pulmonary Involvement**

The clinician’s focus is on discerning early clinically important lung disease and arranging referral of the patient to a specialty center when appropriate. Scleroderma patients should receive influenza and pneumococcal immunizations; they should also be counseled regarding cigarette smoking and other potentially harmful exposures (e.g., use of solvents or travel to high altitudes). When hypoxemia is present, supplemental oxygen is appropriate.

Patients with scleroderma who are asymptomatic are at high risk for PAH and interstitial fibrosis, and such patients should be screened for these disorders. If baseline evaluation or ongoing screening suggests serious involvement or if pulmonary symp-
compared with placebo. Various prostaglandins are also helpful in therapy for PAH. The currently available prostaglandins include continuous intravenous epoprostenol (Flolan, or prostacyclin), continuous subcutaneous treprostinil (Remodulin), and the inhalant iloprost (Ventavis). The most dramatic therapeutic development has been bosentan (Tracleer), an orally administered endothelin-1 antagonist. Bosentan therapy leads to improvement in exercise capacity, symptoms, and hemodynamic effects; however, hepatotoxicity is a concern. In one study, patients with scleroderma or related illnesses who were treated with bosentan had stable exercise tolerance and improved survival, whereas patients receiving placebo deteriorated. The most beneficial current therapies for severe PAH are costly (annual cost of sildenafil, $10,000; bosentan, $40,000; epoprostenol, $72,000; and treprostinil $93,000).

A patient with PAH should also undergo screening for significant pulmonary interstitial fibrosis and should be referred to a specialty center for treatment. Screening should begin at diagnosis with pulmonary function studies, exercise tolerance, and CT scanning (see Table 3). In scleroderma patients with interstitial lung disease, the best current evidence shows that progression may be slowed or halted by long-term therapy with oral cyclophosphamide and low-dose prednisone (< 10 mg/day). Patients treated with cyclophosphamide have shown modest improvement in lung function and symptoms, skin thickening, and quality of life. Cyclophosphamide is a powerful immunosuppressive medication; its use is sometimes associated with adverse events, such as bacterial infections, varicella-zoster virus infection, interstitial cystitis, and malignancies (e.g., bladder transitional cell carcinoma). Such patients warrant prophylaxis against Pneumocystis jiroveci (e.g., with a regimen of trimethoprim-sulfamethoxazole, 160/800 mg three times a week); their management should also include monitoring of leukocyte counts and urinalysis for microscopic hematuria every 3 to 4 weeks. Mycophenolate mofetil, as an alternative to cyclophosphamide, appears safe, reduces pulmonary fibrosis, and improves survival, but it does not yet have the same robust support as cyclophosphamide in prospective, double-blind clinical trials.

For the unfortunate scleroderma patients with rapidly progressive or severe and nonresponsive lung disease (i.e., either PAH or interstitial fibrosis), the clinician may consider referral of the patient to a specialty center for evaluation for lung transplantation. International guidelines list among absolute contraindications to transplantation the presence of advanced dysfunction of other major organs (i.e., heart, liver, or kidney); each

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prospective transplantation candidate requires individualized consideration.44

**Cutaneous Involvement**

The goals of therapy for patients with cutaneous involvement include reducing symptoms, such as pruritis, and minimizing episodes and stigmata of Raynaud phenomenon. For itching, doxepin may prove effective; the initial dose of 10 mg each evening may be increased to 50 mg to achieve an antipruritic effect. Hydroxyzine (10 to 25 mg four times daily) may also prove useful in reducing itching. Many, if not most, patients with Raynaud phenomenon may be managed with such simple measures as avoidance of exposure to cold. Instructions to wear warm clothing, gloves, and a hat when exposed to a cold environment may be sufficient. Current cigarette smokers bear a fourfold risk of serious digital vascular complications; therefore, smoking cessation is a key instruction. In addition, patients should avoid vasoconstrictive agents (e.g., decongestants, caffeine, amphetamines, beta blockers, and ergot alkaloids). For persons with Raynaud attacks so frequent or so severe as to interfere with daily activities or to put them at risk for developing digital ulcers, pharmacologic therapy may be employed. Low-dose aspirin (81 mg daily) is recommended. The calcium channel blocking agents promote vasodilatation and generally reduce the frequency and severity of the Raynaud phenomenon, not only in scleroderma but also in primary Raynaud phenomenon.45 Although nifedipine in daily doses of 30 to 60 mg has been effective for most patients, approximately one third do not respond, and some patients experience adverse effects. Other calcium channel blockers have also shown efficacy for the Raynaud phenomenon; these agents include amlodipine (5 to 10 mg daily) and felodipine (5 to 10 mg daily). A small but remarkably positive study suggests that sildenafil, taken in doses of 50 mg twice daily for 4 weeks (at a cost of approximately $685) reduces Raynaud phenomenon frequency and severity.46 Ischemic digital ulcerations may be difficult to treat and may progress to gangrene of the fingertips; prostanoids may be useful in critical digital ischemia. Bosentan taken in doses of 62.5 mg twice daily for 4 weeks, then 125 mg twice daily for 8 weeks (at a cost of approximately $11,700) reduces the frequency of new ulcers by nearly half, even in those patients who already have digital ulcers; such therapy also improves hand function.48 Sympathectomy should be reserved for severe ischemic crises.

**GI Tract Involvement**

The aim of management for patients with gastrointestinal involvement is to reduce morbidity resulting from intestinal issues—chiefly, esophageal reflux. Because gastroesophageal reflux is so prevalent in scleroderma patients,27 clinicians typically instruct patients about diet and life-style modifications, such as eating multiple small meals and elevating the head of the bed six inches. Also, management of such patients usually includes anti-secretory agents (i.e., proton pump inhibitors). In scleroderma patients, the dosage of omeprazole and possibly other proton pump inhibitors may need to be twice or even four times the normally recommended dose of 20 mg daily. Such measures are intended not only to relieve symptoms (e.g., dyspepsia and water-brash) but also to reduce complications. A clinician must therefore educate such patients that the antireflux measures must be employed even if symptoms abate or were never present. Esophageal motility may be enhanced and esophageal sphincter pressure raised by metoclopramide or erythromycin use. Esophageal dilatation may be required if strictures are present, but surgical intervention is relatively contraindicated. Gastric involvement with significant symptoms occurs in 15% of scleroderma patients. Such individuals may have gastric dysmotility and weight loss. Patients with diminished gastric emptying may be instructed regarding the advisability of frequent small meals; management may also include nutritional support (vitamins and low-residue diet) and the use of prokinetic medications such as metoclopramide or erythromycin. Small bowel motility may manifest as pain, distention, and vomiting; most cases can be managed by increasing dietary fiber and avoiding medications that affect motility (e.g., opiates). For bacterial overgrowth with malabsorption, rotating or intermittent empirical antibiotic therapy (using such agents as tetracycline, amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, or a cephalosporin) is recommended. Colonic involvement is usually clinically insignificant, but diarrhea or constipation may occur. Surgical intervention is to be avoided unless obstruction or perforation occurs.28

**Potential Disease-Modifying or Curative Therapies**

Many medications have been investigated for disease-modifying or curative effects in scleroderma patients, and none have as yet proved successful. Penicillamine and methotrexate have failed to show benefit. A monoclonal antibody blocker directed toward TGF-β1 failed to show efficacy in a pilot study.49 Autologous hematopoietic stem cell transplantation is currently under study for use in severely affected scleroderma patients.50 A truly effective disease-modifying therapy is not yet available.

**Prognosis**

The prognosis for patients with limited cutaneous scleroderma is generally favorable unless viscera are involved. The 7-year survival rate from onset of Raynaud phenomenon is 87%; and from the time of scleroderma diagnosis, 81%. Overall, the course tends to be unremitting and slowly progressive in most patients, although the progression may be more rapid. When severe PAH occurs, the survival rate for patients who do not receive treatment is less than 10%; with treatment, the 2-year survival rate may be as high as 73%. In patients with limited cutaneous involvement who test negative for antitopoisomerase I antibody and who have no renal, cardiac, or lung disease for at least 3 years, the scleroderma mortality is the same as for the general population. Internet resources provide information about evolving therapies; they may also prove useful in identifying local specialists and support programs available to scleroderma patients [see Sidebar Internet Resources for Information on Scleroderma]. Overall, diffuse scleroderma has a worse outlook. Because diffuse scleroderma is highly variable in its course and manifestations, the progression rate is difficult to predict. With the exception of some scleroderma-like changes in mixed connective tissue disease, diffuse scleroderma rarely remits completely. The 7-year survival rate for patients with diffuse scleroderma is approximately 72%.23 The adverse indicators are visceral involvement, such as the involvement of the heart (odds ratio [OR], 2.8), lungs (OR, 1.6), or kidney (OR, 1.9), and the presence of antitopoisomerase I antibody (OR, 1.3). Although the adverse factors tend to cluster, they are statistically independent (that is, the risks associated with individual factors are multiplicative). Life-threatening complications of diffuse scleroderma—severe skin involvement, pulmonary fibrosis, and renal crisis—usually occur within the first 3 years after disease onset. Given the efficacy of current therapies, the 2-year survival rate of patients with pul-

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monary fibrosis is about 70%.

10. Lung involvement (either PAH or interstitial fibrosis) represents the most common scleroderma-related cause of death. 10 Gastrointestinal involvement does not seem to affect mortality but certainly contributes to morbidity.

Eosinophilic Fasciitis

Eosinophilic fasciitis can superficially resemble scleroderma. It is characterized by pain, swelling, and tenderness of the extremities, after which induration of the skin and subcutaneous tissues occurs. Joint motion may be limited, but Raynaud phenomenon, sclerodactyly, and other manifestations of scleroderma are not seen. Laboratory testing reveals peripheral blood eosinophilia, which may be marked; elevation of the erythrocyte sedimentation rate; and hypergлюбулинемия. Antinuclear antibody and rheumatoid factor test results are negative. Biopsy specimens of involved areas have shown inflammation and thickening of the fascia deep to the subcutaneous tissues. The skin appears normal, but the underlying deep fascia is infiltrated with lymphocytes, plasma cells, histiocytes, and sometimes eosinophils. Eosinophilic fasciitis seems to be either self-limited or responsive to low doses of glucocorticoids. Its etiology remains unknown, but several cases have been reported after strenuous muscle exertion.

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References


Internet Resources for Information on Scleroderma*

National Institute of Arthritis and Musculoskeletal and Skin Diseases Information Clearinghouse
http://www.niams.nih.gov

This clearinghouse provides information about various forms of rheumatic and dermatologic diseases, distributes patient and professional education materials, and refers people to other sources of information.

American College of Rheumatology
http://www.rheumatology.org

This association provides referrals to doctors and health professionals who work on arthritis, rheumatic diseases, and related conditions. The association also provides educational materials and guidelines.

Scleroderma Foundation
http://www.scleroderma.org

The foundation publishes information on scleroderma and offers patient education seminars, support groups, physician referrals, and information hotlines.

Scleroderma Research Foundation
http://www.srfcure.org

The foundation’s goal is to find a cure for scleroderma by funding and facilitating the most promising, highest-quality research and by placing the disease and its need for a cure in the public eye. The foundation distributes patient handbooks and a twice-yearly, research-related newsletter.

Arthritis Foundation
http://www.arthritis.org

The foundation is a voluntary organization devoted to supporting research on arthritis and other rheumatic diseases, including scleroderma. It also provides up-to-date information on treatments, nutrition, alternative therapies, and self-management strategies. Chapters nationwide offer exercise programs, classes, support groups, physician referral services, and free literature.

*Descriptions of Web sites are derived from www.niams.nih.gov.
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