Diagnosis and Treatment of Scleroderma

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ABSTRACT

Scleroderma is a rare disease. Approximately 80% of patients are females, and one-half present before the age of 40. Some studies suggest a higher incidence and severity of disease in black females than in whites. Scleroderma affect approximately 20 new patients per million per year and has an estimated prevalence of approximately 250 patients per million in the United States, the synonyms from this desease including Progressive systemic sclerosis (PSS), or diffuse scleroderma. Scleroderma is a multisystem disorder characterized by skin thickening and vascular abnormalities. Causes of scleroderma remain mysterious. Immunologic abnormalities are suggested by the presence of characteristic autoantibodies such as ANA,anticentromere, and anti-Scl-70 antibodies. In addition to skin, the most commonly affected organs are lung and kidney. Three major diseases subsets are recognized based on the extent of skin disease. Limited disease is defined as skin fibrosis in distal extremities and some areas of face and neck. Limited diseases are also known as CREST syndrome. Diffuse disease includes patients with skin abnormalities extending to the proximal extremities (i.e., above the elbow or knee) and trunk. Localized disease manifests as patches (morphea) or bandlike (linear scleroderma) areas of skin thickening.

Key words: *scleroderma, systemic autoimmune, multiple organ, skin fibrosis.*

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INTRODUCTION

Scleroderma is derived from the Greek words *skleros* (hard or indurated) and *derma* (skin). Hippocrates first described this condition as thickened skin. Systemic sclerosis (scleroderma) is a chronic multisystem disease characterized by skin thickening and vascular abnormalities.[1] This desease belongs to the family of systemic autoimmune disorders. In addition to skin, the most commonly affected organs are lung and kidney. Localized disease manifests as patches (morphea) or band-like (linear scleroderma) areas of skin thickening.[1-4]

The finding of various subtypes of scleroderma among different ethnic or racial groups, the presence of familial clustering, and the appearance of specific autoantibodies that are associated with specific human leukocyte antigen types define genetic influences on disease expression. Certain environmental factors are also thought to play etiologic roles. For example, characteristic antibodies and scleroderma disease manifestations can develop in coal miners exposed to high levels of silica.[5]

ETIOLOGY

Causes of scleroderma remain mysterious. Immunologic abnormalities are suggested by the presence of characteristic autoantibodies such as ANA, anticentromere, and anti-Scl-70 antibodies. In addition, other striking abnormalities are seen in small- to medium-sized blood vessels, which show immunologically bland fibrotic change. The theory that the vasculature is the primary target is supported by significant experimental data. In addition to these intrinsic abnormalities, the association of scleroderma-like syndromes with epidemic exposures to toxins (e.g., toxic oil syndrome, eosinophilia-myalgia syndrome) suggests that an environmental trigger may start the process in a susceptible individual.[4,5]

PATHOLOGY

Vascular dysfunction is one of the earliest alterations of systemic sclerosis and may represent the initiating event in its pathogenesis. Severe alterations in small blood vessels of skin and internal organs, including fibrosis and perivascular cellular infiltration with activated T cells, are almost always present in systemic sclerosis. Small arteries in the skin, lung, and kidney show proliferation of subintimal tissues and fibrotic change.

Small thrombi may form on the altered intimal surfaces. Luminal narrowing or occlusion characterizes these small vessels, with a lesser role by vasospasm. Increased accumulation of fibrotic tissue, primarily collagen, is seen in the dermis and is accompanied by loss of normal skin appendages such as hair follicles. Skeletal muscle and myocardium may show atrophy of the muscle fibers and replacement by fibrotic tissue. Infrequently, histologic myositis is seen.

Systemic sclerosis is a systemic disease that affects many organ systems. It is most obvious in the skin; however, the GI tract; the respiratory, renal, cardiovascular, and genitourinary systems; and numerous vascular structures are frequently involved. The symptoms result from inflammation and progressive tissue fibrosis and occlusion of the microvasculature by excessive production and deposition of types I and III collagens. The levels of other macromolecules found in the connective tissue (eg, glycosaminoglycans, tenascin, fibronectin) are also increased.

DEMOGRAPHICS

Scleroderma is a rare disease. Approximately 80% of patients are females, and one-half present before the age of 40. Some studies suggest a higher incidence and severity of disease in black females than in whites. A much higher prevalence is seen in the United States than in northern Europe or in Asia, a difference that at present remains unexplained.[5]

CLINICAL FINDINGS

Skin

Skin changes are the hallmark of this disease in most patients. Thickening of the skin is the most easily recognizable manifestation of scleroderma but is not prominent in all patients. Normal skinfolds (e.g., over the knuckles) may be obliterated, and hair no longer grows over sclerodermatous skin. The lack of facial wrinkling may make patients appear younger than their actual age. Skin changes are often accompanied by Raynaud phenomenon, and fingertips may be cool and dusky, with loss of the usual digital pulp.[1,3] In vitro studies show that dermal fibroblasts derived from patients with scle-roderma overproduce extracellular matrix that leads to increased tissue collagen deposition in the skin. Collagen cross-linking then causes progressive skin tightening. In the later stages of the disease, the involved skin becomes atrophic, dry, and scaly because of the loss of its natural oils (sebaceous gland damage). These dry thickened areas of skin are often intensely pruritic, causing the patient to excoriate the skin, which leads to more damage and thickening (lichenification).[3]

The amount of skin thickening can be quantified by performing a "skin score," in which the skin is pinched between the examiner's thumbs in 17 specified areas of the patient's body, scoring the thickness of the skin from 0 (normal) to 3 (very thick). The skin score provides a systematic approach to longitudinal disease evaluations and is commonly used in clinical trials to assess treatment efficacy.[1,3]

Vascular

Involvement of the vasculature is ubiquitous among patients with scleroderma. A diffuse vasculopathy of peripheral arteries is manifested pathologically by intimal proliferation, activation of the arterial smooth muscle and endothelium, and narrowing or occlusion of the vessel lumen. Critical ischemia occurs in the tissues when vasoconstriction occludes these diseased vessels.[3]

Raynaud phenomenon is the first manifestation of the disease in almost every patient. Stress and cold temperatures induce an exaggerated vasoconstriction of the small arteries, arterioles, and arteriovenous shunts of the skin of the digits. Clinical features found to be predictive of an autoimmune rheumatic disease among patients with Raynaud phenomenon include the presence of antinuclear antibodies (ANAs) and abnormal nailfold capillaries.[1, 3]

Musculoskeletal

Arthralgias and joint stiffness are common if areas around the tendons are involved, active and passive range of motion of the joints are limited and painful. Uncommonly, patients may initially display rheumatoid like synovitis, with subsequent development of sclero-dermal skin findings. Palpable tendon friction rubs are best felt over the flexor and extensor surface of the wrists, knees, or above the ankles and produce a palpable grating sensation with movement. Tendon friction rubs may be seen early in diffuse disease and are associated with increased incidence of organ involvement. Muscle weakness may be from muscle atrophy, fibrosis, or less commonly frank myositis.[1,4]

GI

Gastrointestinal disease in scleroderma usually involves both the upper and lower gastrointestinal tract but is highly variable in its clinical expression.Esophageal dysmotility with substernal dysphagia is common. Incompetence of the gastroesophageal sphincter leads to symptomatic reflux esophagitis. Common symptoms are heartburn and a sensation that food or pills are lodged in the chest behind the sternum. If left untreated, the upper gastrointestinal disease can cause esophagitis, esophageal ulceration with bleeding, esophageal stricture, or Barren esophagus. The small and large intestines can also be affected by smooth muscle atrophy of the bowel wall causing abnormal motility of the gut. Involvement of the small bowel is less common and can produce a malabsorptive or blind loop syndrome. Colon abnormalities may contribute to constipation. Wide-mouthed diverticula commonly occur in the large intestine.[1,4]

Cardiopulmonary

Two main forms of lung disease occur in patients with scleroderma: inflammatory alveolitis leading to interstitial fibrosis and pulmonary arterial hypertension. Insidious development of interstitial lung involvement is common early in the course of diffuse disease and may lead to a restrictive defect seen on pulmonary function testing. Pulmonary vascular disease with or without fibrosis can lead to pulmonary arterial hypertension and ultimately right heart failure. Estimates of the prevalence of pulmonary arterial hypertension among patients with scleroderma vary, but may be as high as 25%, although severe disease is only seen in roughly 10-15%.[2,3]

Renal

Clinically significant kidney disease occurs in only a minority of patients, but when it develops, renal disease poses a major threat to life. Scleroderma renal crisis (SRC) develops in approximately 10% of patients. It is characterized by the sudden onset of malignant hypertension that, if untreated, can lead rapidly to renal failure and death. This syndrome includes very high blood pressure, headaches, visual disturbances, and heart failure. There is intimal hyperplasia and vasospasm of cortical arteries. This leads to activation of the renin-angiotensin system and accelerated hypertension, proteinuria, microscopic hematuria, and microvascular hemolysis (schistocytes on peripheral blood smear). Before the use of the ACE inhibitors, this syndrome was uniformly fatal. The more widespread use of ACE inhibitors has dramatically reduced the numbers of renal deaths in diffuse scleroderma. More than half of patients with renal crisis do well and avoid longterm dialysis; <20% die of this infrequent complication.[1,6]

Thyroid

Hypothyroidism, present in approximately one-fourth of patients, is often clinically unrecognized. The thyroid gland shows fibrotic change. Hyperthyroidism is rare.[1]

LABORATORY FINDINGS

There is no single laboratory study or test that confirms the diagnosis of scleroderma. The diagnosis is made largely by history and physical examination. Laboratory information may provide supportive or prognostic information. More than 90% of patients are positive for ANAs. The nucleolar ANA pattern is common in patients with diffuse scleroderma, and the cen-tromere pattern is characteristic of the limited (CREST syndrome) variant. Antibodies to Scl-70 are directed against topoisomerase-1 and are associated with the diffuse form. Patients tend to have either anticentromere (limited disease) or anti-Scl-70 (diffuse disease) antibodies but not both. Periodic pulmonary function testing, including the force vital capacity and diffusion capacity, is indicated in patients with diffuse disease and is an effective measure of interstitial lung disease. Routine hemogram, chemistries, and urinalysis are most often indicated as part of drug monitoring.[1,4,5]

Table 1. Autoantobodies associated with scleroderma[3]

Autoantibody	Prevalence	Associated Clinical Features
Antinuclear antibody	>95%	—
Anti-Scl-70 (anti-topoisomerase 1)	20-40%	Lung disease, diffuse skin involvement. African Americans, worse prognosis
Anti-centromere	20-40%	CREST syndrome, digital ulcerations/digital loss
Anti-RNA polymerases	4-20%	Diffuse skin involvement, scleroderma renal crisis, cardiac disease, worse prognosis
Anti-B23	10%	Pulmonary hypertension
Anti-Pm-Scl	2-10%	Limited cutaneous involvement, myositis
Anti-U3-RNP (anti-fibrillarin)	8%	Lung disease, diffuse skin involvement, African-American males
Anti-U1-RNP	5%	Mixed connective tissue disease
Anti-Th/To	1-5%	Limited cutaneous involvement, pulmonary disease

CREST, calcinosis. Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and felangiectasias; RNP, ribonucleoprotein.

IMAGING STUDIES

Chest radiographs should be performed to evaluate pulmonary symptoms and may aid in diagnosis of pulmonary fibrosis. High-resolution CT scans may be used to further evaluate pulmonary fibrosis and may show a honeycomb (with pulmonary fibrosis) or ground-glass (with alveolitis) appearance. Radiographic testing for evaluation of upper gastrointestinal disease is not often required unless patients have atypical symptoms or do not respond to standard treatments. Esophageal studies such as barium swallow with a cine-esophagram can identify lower esophageal dysmotility.[1,3]

DIAGNOSTIC CRITERIA

The American College of Rheumatology diagnostic criteria for scleroderma include either thickened (sclerodermatous) skin changes proximal to the metacarpophalangeal joints or at least two of the following:

- Sclerodactyly.
- Digital pitting (residual loss of tissue on the finger pads due to ischemia).
- Bibasilar pulmonary fibrosis.

A diagnosis of scleroderma can also be made if the patient has three of the five features of the CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and felangiectasias). Patients with definite Raynaud phenomenon who have abnormal nailfold capillary loops and the presence of autoantibodies known to be associated with scleroderma may be considered to have early scleroderma or a mild expression of the disease.[1,4]

THERAPY

Raynaud phenomenon: treatment of Raynaud's phenomenon should include care to keep hands and feet warm with gloves or other coverings; these may be required at night as well as during the day. Vasodilating agents may be used, especially long-acting calcium channel blockers such as nifedipine. High blood pressure is best treated with angiotensin-converting enzyme inhibitors.[1,3]

Corticosteroids: in the early stages of diffuse disease, when hands appear puffy or edematous, low doses of prednisone may be useful. However, data suggest that high doses of corticosteroids can lead to renal crisis or failure. Thus, steroids should be avoided in most patients.[1,3,6]

Penicillamine: data from several uncontrolled studies show a reduction in skin thickening with penicillamine treatment. Beneficial effects on pulmonary and GI abnormalities have also been reported in retrospective studies. Thus, penicillamine is generally recommended in patients with early disease who manifest progressive skin changes, pulmonary compromise, or renal disease. A recent study did not show any clinical difference between low-dose (250-750 mg/day) and high-dose (1,000-1,500 mg/day) penicillamine. Unfortunately, a placebo-treated group was not included. [1,3,6]

Others: use of other immunosuppressive drugs is not promising; no controlled trials suggest their benefit. Some investigators anecdotally advocate the use of cyclophosphamide with progressive pulmonary fibrosis and cyclosporine for rapidly advancing early disease. Agents such as chlorambucil, MTX, recombinant human relaxin, extracorporeal photopheresis, antithymocyte globulin, interferon alpha, minocycline, and potaba (potassium aminobenzoate) have been tried but remain unproven. The efficacy and safety of autologous stem cell transplantation in scleroderma is under study.[1,3,6]

CONCLUSION

The outcome is most closely related to the extent of significant organ involvement, especially lung and kidney. In one study, 5-year survival in patients without organ involvement was >90%; patients with pulmonary or renal involvement had survival rates of 70% and 50%, respectively.[2,3] Patients with diffuse skin involvement show shorter survival times than those with limited involvement. Patients with diffuse disease are at risk of early progressive end-organ damage, and those with limited disease are at a small but significant risk of developing pulmonary hypertension or small bowel malabsorption.[1,5]

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