reduced the extent and progression of skin induration; however, these benefits could not be substantiated in a controlled prospective trial. Cyclophosphamide and methotrexate have modest effects on skin induration. Because the skin is dry, the use of hydrophilic ointments and bath oils is encouraged. Regular skin massage is helpful. Telangiectasia may present a cosmetic problem, especially on the face. Treatment with pulsed dye laser may have short-term benefit. Ischemic digital ulcers should be protected by occlusive dressing to promote healing and prevent infection. Infected skin ulcers are treated with topical antibiotics. Surgical debridement may be indicated. No therapy has been shown to be effective in preventing the formation of calcific soft tissue deposits or promoting their dissolution.

TREATMENT OF MUSCULOSKELETAL COMPLICATIONS Arthralgia and joint stiffness are common and distressing manifestations most prominent in early-stage disease. Short courses of nonsteroidal anti-inflammatory agents, weekly methotrexate, and cautious use of low-dose corticosteroids may alleviate these symptoms. Physical and occupational therapy can be effective for maintaining musculoskeletal function and improving long-term outcomes.

COURSE

The natural history of SSc is highly variable and difficult to predict, especially in early stages of the disease, when the specific subset—diffuse or limited cutaneous form—is not clear. Patient with dcSSc tend to have a more rapidly progressive course and worse prognosis than those with lcSSc.

In dcSSc, inflammatory symptoms such as fatigue, edema, arthralgia, and pruritus tend to subside, and the extent of skin thickening reaches a plateau at 2–4 years after disease onset, followed by slow regression. It is during the early edematous/inflammatory stage, generally lasting <3 years, that important visceral organ involvement occurs. While existing visceral organ involvement, such as pulmonary fibrosis, may progress even after skin involvement peaks, new organ involvement is rare. Scleroderma renal crisis almost invariably occurs within the first 4 years of disease. In late-stage disease (>6 years), the skin is usually soft and atrophic. Skin regression characteristically occurs in an order that is the reverse of initial involvement, with softening on the trunks followed by proximal and finally distal extremities; however, sclerodactyly and finger contractures generally persist. Relapse or recurrence of skin thickening after the peak of skin involvement has been reached is uncommon. Patients with lcSSc follow a clinical course that is markedly different than that of dcSSc. Raynaud's phenomenon typically precedes other disease manifestations by years or even decades. Visceral organ complications such as PAH and ILD generally develop late and progress slowly.

PROGNOSIS

SSc confers a substantial increase in the risk of premature death. Age- and gender-adjusted mortality rates are fivefold to eightfold higher compared to the general population, and more than half of all patients with SSc die from their disease. In one population-based study of SSc, the median survival was 11 years. In patients with dcSSc, 5- and 10-year survival rates are 70% and 55%, respectively, whereas in patients with lcSSc, 5- and 10-year survival rates are 90% and 75%, respectively. The prognosis correlates with the extent of skin involvement, which itself is a surrogate for visceral organ involvement. Major causes of death are PAH, pulmonary fibrosis, gastrointestinal involvement, and cardiac disease. Scleroderma renal crisis is associated with a 30% 3-year mortality. Lung cancer and excess cardiovascular deaths also contribute to increased mortality. Markers of poor prognosis include male gender, African-American race, older age at disease onset, extensive skin thickening with truncal involvement, palpable tendon friction rubs, and evidence of significant or progressive visceral organ involvement. Laboratory predictors of increased mortality at initial evaluation include an elevated ESR, anemia, proteinuria and anti–topoisomerase I antibodies. In one study, SSc patients with extensive skin involvement, lung vital capacity <55% predicted, significant gastrointestinal involvement (pseudoobstruction or malabsorption), evidence of cardiac involvement (arrhythmias or congestive heart failure), or scleroderma renal crisis had a cumulative 9-year survival <40%. The severity of PAH is strongly associated with mortality, and SSc patients who had a mean pulmonary arterial pressure ≥45 mmHg had a 33% 3-year survival. The advent of ACE inhibitors in scleroderma renal crisis had a dramatic impact on survival, increasing from <10% at 1 year in the pre–ACE inhibitor era to >70% 3-year survival at the present time. Moreover, 10-year survival in SSc has improved from <60% in the 1970s to >66–78% in the 1990s, a trend that reflects both earlier detection and better management of complications.

LOCALIZED SCLERODERMA

The term *scleroderma* is commonly used to describe a group of localized skin disorders (Table 382-1). These occur more commonly in children than in adults. In contrast to SSc, localized scleroderma is rarely complicated by Raynaud's phenomenon or significant internal organ involvement. Morphea presents as solitary or multiple circular patches of thickened skin or, rarely, as widespread induration (generalized or pansclerotic morphea); the fingers are spared. Linear scleroderma—streaks of thickened skin, typically in one or both lower extremities—may affect the subcutaneous tissues, leading to fibrosis and atrophy of supporting structures, muscle, and bone. In children, the growth of affected long bones can be retarded. When linear scleroderma lesions cross joints, significant contractures can develop.

MIXED CONNECTIVE TISSUE DISEASE

Patients who have lcSSc coexisting with features of SLE, polymyositis, and rheumatoid arthritis may have mixed connective tissue disease (MCTD). This overlap syndrome is generally associated with the presence of high titers of autoantibodies to U1-RNP. The characteristic initial presentation is Raynaud's phenomenon associated with puffy fingers and myalgia. Gradually, lcSSc features of sclerodactyly, calcinosis, and cutaneous telangiectasia develop. Skin rashes suggestive of SLE (malar rash, photosensitivity) or of dermatomyositis (heliotrope rash on the eyelids, erythematous rash on the knuckles) occur. Arthralgia is common, and some patients develop erosive polyarthritis. Pulmonary fibrosis and isolated or secondary PAH may develop. Other manifestations include esophageal dysmotility, pericarditis, Sjögren's syndrome, and renal disease, especially membranous glomerulonephritis. Laboratory evaluation indicates features of inflammation with elevated ESR and hypergammaglobulinemia. While anti-U1RNP antibodies are detected in the serum in high titers, SSc-specific autoantibodies are not found. In contrast to SSc, patients with MCTD often show a good response to treatment with glucocorticoids, and the long-term prognosis is better than that of SSc. Whether MCTD is a truly distinct entity or is, rather, a subset of SLE or SSc remains controversial.

EOSINOPHILIC FASCIITIS

Eosinophilic fasciitis is a rare idiopathic disorder associated with induration of the skin that generally develops rapidly. Adults are primarily affected. The skin has a coarse cobblestone "peau d'orange" appearance. In contrast to SSc, internal organ involvement is rare, and Raynaud's phenomenon and SSc-associated autoantibodies are absent. Furthermore, skin involvement spares the fingers. Full-thickness excisional biopsy of the lesional skin reveals fibrosis of the subcutaneous fascia and is generally required for diagnosis. Inflammation and eosinophil infiltration in the fascia are variably present. In the acute phase of the illness, peripheral blood eosinophilia may be prominent. MRI appears to be a sensitive tool for the diagnosis of eosinophilic fasciitis. In some patients, eosinophilic fasciitis occurs in association with, or preceding, myelodysplastic syndromes or multiple myeloma. Treatment with glucocorticoids leads to prompt resolution of the eosinophilia. In contrast, skin changes generally show slow and variable improvement. The prognosis of patients with eosinophilic fasciitis is good.