breast, lung, and ovarian carcinomas and lymphomas tend to occur in close temporal association with the clinical onset of SSc, particularly in patients who have autoantibodies to RNA polymerase III. In these cases, SSc may represent a paraneoplastic syndrome triggered by the antitumor immune response.

LABORATORY EVALUATION AND BIOMARKERS

A mild normocytic or microcytic anemia is frequent in patients with SSc and may indicate gastrointestinal bleeding caused by GAVE or chronic esophagitis. Macrocytic anemia may be caused by folate and vitamin B_{12} deficiency due to small-bowel bacterial overgrowth and malabsorption or by drugs such as methotrexate or alkylating agents. Microangiopathic hemolytic anemia caused by mechanical fragmentation of red blood cells during their passage through microvessels coated with fibrin or platelet thrombi is a hallmark of the thrombotic microangiopathy associated with scleroderma renal crisis. Thrombocytopenia and leukopenia may indicate drug toxicity. In contrast to other connective tissue diseases, the erythrocyte sedimentation rate (ESR) is generally normal; an elevation may signal coexisting myositis or malignancy.

Antinuclear autoantibodies are present in almost all patients with SSc and can be detected at disease onset. Autoantibodies against topoisomerase I (Scl-70) and centromere are mutually exclusive and quite specific for SSc (Table 382-3). Topoisomerase I antibodies are detected in 31% of patients with dcSSc, but in only 13% of patients with lcSSc. They are associated with increased risk of ILD and poor outcomes. Anticentromere antibodies are detected in 38% of patients with lcSSc, but in only 2% of patients with dcSSc and rarely in patients with Raynaud's phenomenon and Sjögren's syndrome. Anticentromere antibodies in SSc are associated with PAH, but only infrequently with significant cardiac or renal involvement or ILD. Nucleolar immunofluorescence pattern on serologic testing reflects antibodies to U3-RNP (fibrillarin), Th/To, or PM/Scl, whereas a speckled immunofluorescence pattern indicates antibodies to RNA polymerase III. Although antibodies to β2GPI occur in antiphospholipid antibody syndrome and are not specific for SSc, their presence in SSc is associated with an increased risk of ischemic lesions in the fingers.

DIAGNOSIS, STAGING, AND MONITORING

The diagnosis of SSc is made primarily on clinical grounds and is generally straightforward in patients with established disease. The presence of skin induration, with a characteristic symmetric distribution pattern associated with typical visceral organ manifestations, establishes the diagnosis with a high degree of certainty. Although the conditions listed in Table 382-1 can be associated with skin induration, the distribution pattern of skin lesions, together with the absence of Raynaud's phenomenon or typical visceral organ manifestations or SSc-specific autoantibodies, differentiates these conditions from SSc. Occasionally, full-thickness biopsy of the skin is required for establishing the diagnosis of scleredema, scleromyxedema, or nephrogenic systemic fibrosis. In lcSSc, a history of antecedent Raynaud's phenomenon and gastroesophageal reflux symptoms, coupled with the presence of sclerodactyly and capillary changes on nailfold capillaroscopy, often in combinations with cutaneous telangiectasia and calcinosis, helps to establish the diagnosis. The finding of digital tip pitting scars and radiologic evidence of pulmonary fibrosis in the lower lobes are particularly helpful diagnostically. Primary Raynaud's phenomenon is a common benign condition that must be differentiated from early or limited SSc. Nailfold microscopy is particularly helpful in this situation, because in primary Raynaud's phenomenon, the nailfold capillaries are normal, whereas in SSc, capillary abnormalities, as well as serum autoantibodies, can be detected even before other disease manifestations.

Establishing the diagnosis of SSc at an early stage of the disease may be a challenge. In dcSSc, initial symptoms are often nonspecific and relate to inflammation. Patients complain of fatigue, swelling, aching, and stiffness, and Raynaud's phenomenon may initially be absent. Physical examination may reveal diffuse upper extremity edema and puffy fingers. Patients at this stage are sometimes diagnosed as early rheumatoid arthritis, SLE, myositis, or, most commonly, undifferentiated connective tissue disease. Within weeks to months, Raynaud's phenomenon and characteristic clinical features appear accompanied by advancing induration of the skin. The presence of antinuclear and SSc-specific autoantibodies provides a high degree of diagnostic specificity. Raynaud's phenomenon with fingertip ulcerations or other evidence of digital ischemia, coupled with telangiectasia, distal esophageal dysmotility, unexplained ILD or PAH, or accelerated hypertension with renal failure in the absence of clinically evident skin induration, suggests the diagnosis of SSc sine scleroderma. These patients may have anticentromere antibodies.

TREATMENT SYSTEMIC SCLEROSIS

OVERVIEW: MANAGEMENT PRINCIPLES To date, no therapy has been shown to significantly alter the natural history of SSc. In contrast, multiple interventions are highly effective in alleviating the symptoms, slowing the progression of the cumulative organ damage, and reducing disability. A significant reduction in disease-related mortality has been noted during the past 25 years. In light of the marked heterogeneity in disease manifestations, organ complications, and natural history, treatment must be tailored to each individual patient's unique needs.

A thorough investigation should be undertaken at baseline. Optimal management incorporates the following principles **(Table 382-5)**: prompt and accurate diagnosis; classification and risk stratification based on clinical and laboratory evaluation; early recognition of organ-based complications and assessment of their extent, severity, and likelihood of deterioration; regular monitoring for disease progression, activity, new complications, and response to therapy; adjusting therapy; and continuing patient education. In order to minimize irreversible organ damage, the management of life-threatening complications must be proactive, with regular screening and initiation of appropriate intervention at the earliest possible opportunity. In light of the complex and multisystemic nature of the SSc, a team-based management approach integrating multiple specialists should be pursued whenever possible. Most patients are treated with combinations of drugs that impact different aspects of the disease. We encourage patients to become familiar with the spectrum of potential complications and understand therapeutic options and natural history, and empower them to partner with their treating physicians. This requires a long-term relationship between patient and physician, with ongoing counseling and encouragement.

DISEASE-MODIFYING THERAPY: IMMUNOSUPPRESSIVE AGENTS Immunosuppressive agents used in the treatment of other autoimmune or connective tissue diseases have generally shown modest or no benefit in SSc. Glucocorticoids may alleviate stiffness and aching in early-stage dcSSc but do not influence the progression of skin or internal organ involvement, and their use is associated with an increased risk of scleroderma renal crisis. Therefore, glucocorticoids should be given only when absolutely necessary, at the lowest dose possible, and for brief periods only. The use of cyclophosphamide has been extensively studied in light of its efficacy in the treatment of vasculitis **(Chap. 385)**, SLE **(Chap. 378)**, and other autoimmune diseases **(Chap. 377e)**.

Both oral and intermittent IV cyclophosphamide were shown to reduce the progression of SSc-associated ILD, with stabilization and, rarely, modest improvement of pulmonary function and HRCT findings after 1 year of treatment. Improvement in respiratory symptoms and skin induration was also noted. These beneficial effects wane upon discontinuation of therapy. The benefits of cyclophosphamide need to be balanced against its potential toxicity, including bone marrow suppression, opportunistic infections, hemorrhagic cystitis and bladder cancer, premature ovarian failure, and late secondary malignancies.

TABLE 382-5 KEY PRINCIPLES IN MANAGEMENT

- Establish early and accurate diagnosis.
- Evaluate internal organ involvement.
- Define clinical disease stage and activity.
- Tailor individualized therapy to each patient's unique needs.
- Assess treatment response, and adjust therapy as needed; monitor for disease progression and new complications.