Clinical aspects of systemic and localized scleroderma

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After the skin, the gastrointestinal tract is the most frequently affected organ in systemic sclerosis. Gastrointestinal symptoms already may be present early in the course of the disease and do not necessarily correlate with objective findings. Esophageal dysmotility is not specific for systemic sclerosis but occurs in other connective tissue diseases as well. Peripheral macrovascular disease was shown to be increased in patients with limited cutaneous sclerosis; signs of autonomic dysfunction were found in patients with the CREST (calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) variant. Pulmonary involvement was shown to be moderately or severely decreased in 40% of a large cohort of scleroderma patients. In one study, no support was found for the association between pulmonary involvement and gastroesophageal reflux. Peripheral nerve involvement is often subclinical and might be associated with anti-U1-RNP and anti–topoisomerase I antibodies. Internal organs are seldomly affected in localized scleroderma. When occurring in childhood and involving an extremity, localized scleroderma can cause growth failure, resulting in long-term functional disability.

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Systemic sclerosis

Survival

The natural course of systemic sclerosis may vary widely. Some patients experience spontaneous remission, but the majority undergo progression of skin and internal organ involvement, leading to considerable morbidity and mortality. The cumulative survival rate has been shown to be as little as 30% at 12 years. Internal organ involvement, presence of antitopoisomerase autoantibodies, and diffuse skin involvement are known to adversely affect outcome. Because renal crisis can now be treated successfully in most cases with angiotensin-converting enzyme (ACE) inhibitors, the leading cause of death in patients with systemic sclerosis is cardiopulmonary disease. The improved outcome of patients with renal crisis was reviewed by Steen [1]. An increase in both incidence and mortality during the past decades may be the result of improved case detection rather than a true increase, as discussed by Medsger [2].

In a nationwide epidemiologic study from Iceland, a low incidence of systemic sclerosis (3.8 per million) and a high proportion of patients with limited cutaneous involvement was found, which might account for the observed 10-year survival rate of 81% [3].

Malignancy

In the past, several reports emphasized the coincidence of systemic sclerosis and malignancy, especially cancer of the lung and breast. Patients with older age at diagnosis and who test positive for anti–topoisomerase I antibodies were found to be at particular risk for developing cancer [4,5]. A case of ductal carcinoma of the prostate was reported in a patient with rapidly progressive systemic sclerosis [6]. The possible pathogenetic interrelationships between systemic sclerosis and malignancy are as yet unknown.

Gastrointestinal involvement

After the skin, the gastrointestinal tract is the second most commonly affected organ in systemic sclerosis. Gastroesophageal reflux, small-bowel bacterial overgrowth, malnutrition, and intestinal pseudoobstruction are the main clinical manifestations. An excellent review of the literature concerning pathophysiology, clinical features, diagnostic procedures, and possible treatments of gastrointestinal involvement in systemic sclerosis was provided by Sjogren [7••], who emphasized that many patients with systemic sclerosis and without gastrointestinal symptoms do have gastrointestinal abnormalities on careful examination. The author also hypothesized that progressive gastrointestinal dysfunction is the result of an orderly series of steps. First, the earliest lesions could be induced by neural dysfunction, either due to arteriolar changes in the vasa nervorum or to compression of nerve fibers by collagen deposits. The next lesion is smooth-muscle atrophy, superimposed on the already existing neural dysfunction. Finally, muscle fibrosis occurs, which is essentially irreversible.

In a prospective survey, gastrointestinal manifestations of systemic sclerosis were found in 82% of 262 patients [8••]. The most common findings were esophageal dysmotility, lower esophageal sphincter laxity, bacterial overgrowth, and wide-mouth diverticula. No significant correlations were found between gastrointestinal involvement and gender, age at diagnosis of systemic sclerosis, or subtype of disease (diffuse-limited).

Abbreviations

ACE—angiotensin-converting enzyme; **CREST**—calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia; **^{99m}Tc-DPTA**—technetium-labeled diethylene-triamine pentacetate.

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It was found that upper-gastrointestinal symptoms develop early in the course of the disease and do not necessarily correlate with objective findings.

In an Italian study [9], the prevalence and pattern of esophageal motility disorders was examined in 150 patients with systemic sclerosis and other rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, poly- and dermatomyositis, and unclassified connective tissue diseases. Although motility disorders of the esophageal body and lower esophageal sphincter statistically occur more frequently in systemic sclerosis, they are not specific to systemic sclerosis. The lack of consistent correlations between a specific pattern of esophageal dysfunction and Raynaud's phenomenon suggests that esophageal dysfunction and Raynaud's phenomenon may not have a common pathogenetic mechanism.

A rare but important condition associated with systemic sclerosis is small-bowel telangiectasia, as exemplified by the case of a 47-year-old woman with systemic sclerosis and excessive gastrointestinal bleeding due to multiple telangiectases throughout the whole small intestine [10].

Cardiovascular disease

Heart involvement in systemic sclerosis consists of pericarditis, congestive failure, and arrhythmias, and was reviewed by Clements and Furst [11]. Also, a patient with limited scleroderma complicated by a pericardial effusion sufficient to cause hemodynamic compromise was described recently [12].

Autonomic dysfunction was examined in nine patients with diffuse scleroderma and in eight with CREST (calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) syndrome; results of a short-term analysis of heart-rate variability in these patients were compared with those for healthy controls [13]. An abnormal heart-rate variability was found in patients with CREST syndrome; these results differed significantly from those of patients with diffuse cutaneous disease, suggesting that parasympathetic control of the heart rate is decreased in patients with CREST syndrome.

The prevalence of macrovascular disease was studied in a retrospective cohort of patients with limited systemic sclerosis [14•]. Peripheral macrovascular disease occurred in 58% of the patients, compared with only 3% of well-matched controls. Macrovascular disease occurred mainly in the abdominal arteries and arteries of the lower extremities; no significant increase in the prevalence of coronary artery or cerebrovascular disease was observed. In the majority of patients, macrovascular disease was symptomatic and required surgical intervention.

Microvascular endothelial injury is a prominent feature in systemic sclerosis. In a study set up to examine the significance of circulating levels of endothelin-1 in relation to vascular damage and fibrosis, a relationship was found between circulating levels of endothelin-1 and other markers of fibrosis and vascular damage such as angiotensin-converting enzyme and von Willebrand factor [15].

Hypotheses on the pathogenesis of Raynaud's phenomenon, which occurs in up to 90% of patients with systemic sclerosis, were reviewed by Kahaleh and Matucci-Cerinic [16•], who discussed the possible etiopathogenetic role of neuropeptides, which are found in abundance in human skin and are involved in the control of skin blood flow.

Serial nailfold capillary microscopy was performed in patients with primary Raynaud's phenomenon and systemic sclerosis [17]. Gradually decreasing numbers of capillary loops and increasing numbers of widened and giant loops were found in the following conditions in the following order: primary Raynaud's phenomenon, possible systemic sclerosis, and systemic sclerosis, suggesting that these disorders are part of a continuing spectrum of Raynaud's phenomenon.

Pulmonary involvement

Pulmonary involvement occurs in 60% to 80% of patients with systemic sclerosis. Clinical manifestations consist of dyspnea, pleurisy, pulmonary fibrosis, and pulmonary hypertension. Lung disease is associated with decreased survival. To identify risk factors for developing severe restrictive lung disease and to determine the time of onset and rate of progression in patients with systemic sclerosis, Steen *et al.* [18••] used the University of Pittsburgh Scleroderma Databank to group 890 patients according to their lowest forced vital capacity value: greater than 75% predicted, 50% to 75% predicted, and less than 50% predicted. They also analyzed serial pulmonary function test results in patients with restrictive lung disease to assess the rate of deterioration of lung volume over time. Only 13% of the patients appeared to have severe restrictive lung disease, with forced vital capacity less than or equal to 50% predicted; 27% had moderate restrictive lung disease, with a forced vital capacity of 50% to 75% predicted; and 60% of the patients had no or minimal restrictive lung disease (forced vital capacity ≥75%). Multiple logistic regression showed that black race, male gender, early disease, and primary cardiac involvement due to systemic sclerosis were the characteristics most frequently associated with severe lung disease. Of interest, scleroderma subtype (limited or diffuse) and anti–topoisomerase I antibody, which is known to be associated with poor prognosis, were not differentiating factors between moderate and severe restrictive disease.

Pulmonary function in systemic sclerosis may be the result of gastroesophageal reflux, most presumably by microaspiration of refluxed material into the lungs. The relationships between esophageal dysfunction, gastroesophageal reflux, and lung involvement in systemic sclerosis were studied by Troshinshky *et al.* [19•], who grouped 39 patients according to the presence or absence of abnormal distal or proximal gastroesophageal acid reflux and the presence or absence of distal esophageal peristalsis. Esophageal manometry, dual-probe (distal and proximal) esophageal 24-hour pH measurements, and pulmonary function tests were performed in all patients. The results did not support an association between pulmonary function impairment and abnormal proximal or distal esophageal pH.

The value of the clearance rate of inhaled technetium-labeled diethylene-triamine pentacetate (^{99m}Tc-DPTA) in detecting early pulmonary involvement was studied prospectively in 16 patients with systemic sclerosis without pulmonary symptoms and chest radiography abnor-

malities [20]. In six patients, an abnormal ^{99m}Tc-DPTA clearance was found, and in five of these patients, it was associated with pathologic findings on high-resolution computed tomography, suggestive of early interstitial lung disease. This finding indicates that ^{99m}Tc-DPTA lung scintigraphy may allow early detection of subclinical pulmonary involvement in systemic sclerosis.

The results of a study in which bronchoalveolar lavage findings were related to computed tomographic appearance of fibrosing alveolitis in systemic sclerosis indicated that in systemic sclerosis, bronchoalveolar lavage neutrophilia is generally associated with extensive fibrotic disease, whereas bronchoalveolar lavage eosinophilia is often observed in less-advanced disease, especially when computed tomographic appearances suggest pulmonary inflammation [21].

Features of small-airways dysfunction were observed in four of four patients with limited scleroderma and in three of seven patients with diffuse scleroderma [22]. It was concluded that small-airways disease may be an early feature of systemic sclerosis, especially in patients with limited scleroderma. This conclusion was questioned [23], because the high incidence of small-airways disease found in this study differed from the findings of a previous study [24].

Several aspects of pulmonary hypertension as a complication of connective tissue disease, particularly systemic sclerosis, were addressed in an editorial [25]. In an open study, the same group of investigators reported improved exercise tolerance and quality of life in patients with severe pulmonary hypertension associated with systemic sclerosis ($n = 3$) and primary antiphospholipid antibody syndrome ($n = 2$) after treatment with continuous iloprost infusion [26]. These results warrant confirmation in further controlled trials.

Renal involvement

Renal crisis, once the major cause of death in patients with systemic sclerosis, can be successfully treated with ACE inhibitors in the majority of patients. Discontinuation of dialysis even after a prolonged period has been observed after treatment with ACE inhibitors. As pointed out by Steen [1], prompt diagnosis and early aggressive treatment of scleroderma renal crisis with ACE inhibitors are mandatory for an optimal outcome.

Molina *et al.* [27] reported the development of renal crisis in a patient with systemic sclerosis sine scleroderma, who presented with symmetric polyarthritis. Scleroderma renal crisis, with malignant hypertension and cardiac and renal failure, was histologically confirmed. Anti-RNA polymerase III antibodies were positive. These autoantibodies are highly specific for systemic sclerosis [28] and are associated with renal involvement [29].

Nervous system

Signs and symptoms of neurologic involvement are rare in patients with systemic sclerosis, although subclinical peripheral nerve involvement has been demonstrated in a considerable proportion of patients [30]. A case of systemic sclerosis complicated by peripheral neuropathy associated with vasculitic change on biopsy was described [31]. The possible contribution of anticardiolipin antibodies to vasculitis in this patient is briefly discussed. The same group of investigators described two patients with limited systemic sclerosis and mononeuritis [32]. Because both patients had severe digital ischemia, it was presumed that inflammatory blood vessel wall changes might have been an etiologic factor in the neuropathy.

An association of anti-U1-RNP and anti–topoisomerase I antibodies with neurologic manifestations was suggested by Hietarinta *et al.*[33]. They examined 31 scleroderma patients, 11 of whom had neurologic findings such as trigeminal neuropathy and polyneuropathy. Eight of these 11 patients had either anti-U1-RNP or anti–topoisomerase I antibodies in their sera.

Autoantibody associations

The association of specific autoantibodies with the clinical features and disease course of scleroderma was extensively reviewed by Wigley [34] in the November 1994 issue of *Current Opinion in Rheumatology.*

In the past year, two studies reported on the clinical correlations of anticentromere antibodies. Although anticentromere antibodies are associated with limited scleroderma, their occurrence in other autoimmune-mediated diseases is well known. In a study from Taiwan [35], anticentromere antibodies were found in patients with Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, immune thrombocytopenic purpura, and Graves' disease. A retrospective survey of patients with anticentromere antibodies detected during routine antinuclear antibody testing [36] showed that in only 29% a diagnosis of systemic sclerosis could be made.

Herrick *et al.* [37] found no support for an association between anticardiolipin antibodies and severe ischemia in systemic sclerosis but confirmed the association between anticentromere antibodies and severe peripheral ischemia and found an association between anti–topoisomerase I antibodies and severe ischemia.

Localized scleroderma

Based on the morphologic features and distribution of skin lesions, localized scleroderma is classified into three subtypes: morphea, generalized morphea, and linear scleroderma. Localized scleroderma is rare, with lesions that are usually confined to the skin and underlying subcutaneous tissue. Internal organ involvement, such as occurs in systemic sclerosis, is seldom observed. The frequency, prognosis, and predictors of internal organ involvement were studied in a group of 53 patients with morphea with or without linear scleroderma [38•]. Systematic examination revealed internal involvement in 16 patients. The abnormalities found were mostly asymptomatic, consisting of esophageal dysfunction and slightly impaired carbon monoxide diffusion in the lung. After a median follow-up of 48 months, prognosis was not influenced by such involvement. Only two of these 16 patients, one of whom developed systemic sclerosis, had symptomatic and severe visceral disease. Parameters that were found to be associated with internal involvement were male gender, increasing number of skin lesions, and hypergammaglobulinemia at first ex-

amination. This study emphasizes that localized scleroderma and systemic sclerosis behave as two different diseases and that routine screening for internal involvement is not justified in asymptomatic patients with localized scleroderma.

Despite the low prevalence of visceral abnormalities in localized scleroderma, it can result in long-term functional disability. This is especially true in linear scleroderma, which mainly occurs in childhood. Thirty cases of localized scleroderma in children were reported by Uziel *et al.* [39•]; five of 19 patients with linear scleroderma that involved an extremity had growth failure in that limb, and one patient required surgery. Growth failure resulted from the extension of fibrosis from the skin into subcutaneous tissue, muscle, and even bone. The authors also reviewed the literature concerning drug therapy in localized scleroderma. Although many drugs are advocated for use in localized scleroderma, none of these drugs have been proven effective. Clinical studies aimed toward evaluation of drug therapy are hampered by the lack of disease activity parameters. Clinical evaluation of the skin lesion was found to offer the only possibility for monitoring disease activity.

Treatment with oral prednisone (starting dose ranging from 0.5 to 1.0 mg/kg/d; duration of treatment for at least 6 weeks) in 17 patients with localized scleroderma resulted in complete disappearance of skin lesions in four patients [40]. A favorable effect on the disease course was observed in 13 other patients. Six patients experienced a relapse after treatment discontinuation. In another study, great improvement in skin sclerotic lesions and joint mobility was seen in one patient who was treated with the antiallergy drug tranilast [41]. Such findings should be critically examined, because in the majority of patients, localized scleroderma is a self-limited disease. It is preferable that the efficacy of any drug treatment be assessed in placebo-controlled trials.

The etiology of localized scleroderma is unknown. The resemblance of morphea to acrodermatitis chronica atrophicans has been the focus of a possible association of *Borrelia burgdorferi* with localized scleroderma. Several studies of this association did not lead to unequivocal results. Wienecke *et al.* [42•] analyzed skin biopsy specimens from 30 patients with localized scleroderma for the presence of *B. burgdorferi* using three different polymerase chain reaction systems for amplification of segments of borrelial genes. Borrelial DNA was not detected in any of the biopsy specimens, a finding that does not support the concept of the presence of *B. burgdorferi* in active lesions of localized scleroderma. However, *B. burgdorferi* still may be present in early sclerotic lesions and initiate changes in connective tissue that lead to morphea. It also may be possible that the positive association of localized scleroderma with *B. burgdorferi* is confined to endemic areas [43].

The occurrence of multiple morphea-like changes in a patient with eosinophilic fasciitis is rare. One such case was described by Castanet *et al.* [44]. The patient also had antiphospholipid antibodies, neurologic symptoms, and livedo-like cutaneous lesions. The cooccurrence of either morphea or eosinophilic fasciitis and antiphospholipid antibodies has never been reported in the literature before. Lipomembranous (membranocystic) changes in adipose tissue, known to occur in a number of diseases including discoid and systemic lupus erythematosus, were reported in three patients with localized scleroderma [45].

Scleroderma-like lesions and juvenile scleroderma

Castanet *et al.* [46] reported the case of a 74-year-old man with porphyria cutanea tarda, who presented with inflammatory sclerodermatous plaques and dermatohelios of 2-years' existence. During repeated phlebotomies, sclerodermatous lesions simultaneously improved, with the reduction of urinary uroporphyrin and ferritin levels.

In children, mostly localized forms of scleroderma are seen, although systemic disease can occur. Approximately 3% of all scleroderma cases are juvenile [47]. The prognosis, management, and current therapeutic options for scleroderma and scleroderma-like disorders in children recently were reviewed by Black [48].

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