Systemic Sclerosis
An Update

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Abstract
Systemic sclerosis (SSc) is a complex and heterogeneous chronic illness characterized by substantial patient to patient variability in clinical manifestations, internal organ involvement, and outcome. Genetic factors contribute to disease susceptibility, but environmental influences also play a significant role. The pathogenesis of SSc encompasses vascular, immunological, and fibrotic processes, which contribute to clinical manifestations and morbidity and must be addressed in the treatment plan. Although vascular interventions appear to reduce the frequency and severity of complications, such as scleroderma renal crisis and pulmonary hypertension, current therapies generally target the immune component of SSc in a non-selective fashion and have largely failed as diseases-modifying interventions. Newer insights into the mechanisms underlying autoimmunity, vascular injury and destruction, and particularly tissue fibrosis provide novel potential targets for therapy. Transforming growth factor-β is a ubiquitous cytokine that appears to contribute to fibroblast activation, collagen overproduction, and pathological tissue fibrosis. Neutralizing antibodies and small molecules that block TGF-β activation or function are effective in shutting down TGF-β signaling and selectively inhibit the progression of fibrosis and may be entering clinical trials for the treatment of SSc.

Systemic sclerosis (SSc) is a chronic multisystem autoimmune disease that is highly heterogeneous and has multiple overlapping and poorly defined clinical subsets. The two widely recognized subsets of SSc are limited cutaneous and diffuse cutaneous SSc with divergent patterns of organ involvement, tempo, autoantibody profiles, and survival. The prominent features of the disease reflect the characteristic pathophysiologic triad of autoimmunity and inflammation, vascular damage, and fibrosis. SSc affects 1 in 4,000 adults in the United States, shows a female preponderance, and is more frequent in African-Americans than Caucasians. Systemic sclerosis has the highest case-fatality among the connective tissue diseases, with a 10-year survival of 55%. However, survival during the past decade has shown improvement in some studies. Survival correlates with internal organ involvement; baseline predictors of increased mortality include truncal skin involvement, abnormal EKG, reduced diffusing capacity (DLCO), elevated erythrocyte sedimentation rate (ESR), and the presence of antibody to topoisomerase I.

Systemic sclerosis must be differentiated from other conditions associated with skin fibrosis, including localized scleroderma, scleredema, scleromyxedema, and eosinophilic fasciitis, as well as rare conditions (e.g., porphyria, cutaneous amyloidosis, progerias, and the stiff skin syndrome). A skin biopsy as well as the clinical presentation generally permits accurate diagnosis. Of note, toxico-epidemic conditions with scleroderma-like features have been described, including the toxic oil syndrome (early 1980s), the eosinophilia-myalgia syndrome (early 1990s), and the nephrogenic fibrosing syndrome (current decade). These conditions have been linked to exposure to rapeseed oil, L-tryptophan, and gadolinium-containing contrast agents, respectively.

Etiology
While some evidence links SSc with exposures to silica, vinyl chloride, and organic solvents, the etiology remains largely unknown. Cytomegalovirus (CMV)-specific antibodies are elevated in some SSc patients. Cytomegalovirus infection in rodents can induce vascular lesions reminiscent of SSc vasculopathy. However, lesional tissue from SSc patients

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could not be shown to contain viral mRNA. Small numbers of circulating cells of maternal origin (maternal microchimerism) can be detected by polymerase chain reaction (PCR) in 22% of healthy individuals and 72% of females with SSc. In SSc, these microchimeric cells appear to infiltrate the skin and other affected tissues. Because there are clinical similarities between SSc and graft-versus-host disease following allogeneic stem cell transplantation (iatrogenic microchimerism), it has been speculated that microchimerism may play a role in SSc.

Genetic Factors
The influence of genetics in SSc has been investigated. Although 1.6% of patients have a first-degree relative with SSc (relative risk equals 13), the low concordance rate among twins (4.6% for both monozygotic and dizygotic) argues against a strong genetic component. In contrast, concordance rates for antinuclear antibody (ANA) are near 100% in monozygotic twins. Scanning the entire genome in SSc has identified informative single nucleotide polymorphisms, or SNPs. Particular alleles in the genes for transforming growth factor-β (TGF-β), monocyte chemoattractant protein-1 (MCP-1), IL-1α, tumor necrosis factor, allograft inflammatory protein-1 (AIF1), and angiotensin converting enzyme (ACE) have been linked to disease susceptibility. A recent study from the United Kingdom indentified SNP associations in the gene for connective tissue growth factor (CTGF), with susceptibility to SSc and associated lung disease. Furthermore, distinct HLA allele associations with disease or with a particular autoantibody response have been reported in different ethnic groups. Microsatellite chromosome mapping has identified markers near the genes for secreted protein acidic and rich in cysteine (SPARC) and fibrillin-1, a binding protein for TGF-β, to be associated with SSc. The latter is particularly intriguing because some SSc patients have anti-fibrillin autoantibodies and a duplication mutation in the fibrillin-1 gene is linked to the tight skin (Tsk) phenotype in a putative mouse model of scleroderma. Fibrillin-1 mutations in certain inherited fibrosing conditions in humans are under investigation.

Pathophysiology: Emerging Insights

Inflammation
During the past decade, the application of powerful new research methods, such as DNA microarrays, population-based genetic studies, gene targeting in animal models, and cellular biology, has brought the pathophysiology of SSc into sharper focus. It is now generally accepted that vascular injury (possibly caused by virus, autoantibody, granzyme, or oxidation products) is a very early event. The resulting endothelial cell activation and apoptosis lead to inflammation and activation of T cells, B cells, and macrophages. There is evidence for involvement of both innate and adaptive arms of the immune response. Lesional T cells show Th2 polarization and oligoclonality suggestive of an antigen-driven response. Recent studies also implicate the Th17 subset of T-cell cytokines, such as IL-17 and IL-23, in the development of fibrosis. The early inflammatory phase of SSc is self-limited, and lesional tissues or bronchoalveolar lavage (BAL) fluid from patients with established disease show a paucity of immune cells.

Fibrosis
Cytokines and growth factors, such as TGF-β, CTGF, PDGF (platelet-derived growth factor) and endothelin-1 (ET-1), secreted in the skin and lungs activate resident fibroblasts, promoting accumulation of collagen, proteoglycans, fibronectin, tenasin, and elastin. Furthermore, TGF-β induces the differentiation of fibroblasts into smooth muscle cell-like myofibroblasts in situ. Because myofibroblasts are also capable of enhancing the stiffness of the extracellular matrix (ECM), elaborating matrix molecules and profibrotic cytokines, and are relatively resistant to apoptosis, their accumulation and persistence within lesional tissue contributes to the progression of the fibrosis. The fibroblast population within lesional tissue is expanded by the arrival of bone marrow-derived mesenchymal progenitor cells, called fibrocytes, which then further contribute to connective tissue accumulation. The signals that instruct the bone marrow to mobilize progenitor cells and govern their homing and engraftment in lesional tissue, remain unknown. A recent report demonstrated that SSc patients have circulating antibodies directed against the PDGF receptor that are capable of triggering activation of fibroblasts. Once collagen is secreted into the extracellular space, it undergoes cross-linking and maturation, resulting in a highly stable matrix that accounts for the stiffness of fibrotic skin and other tissues. The stiff matrix may itself serve as a strong stimulus for integrin-mediated TGF-β activation and increasing fibrosis.

TGF-β
TGF-β is detected in early lesional tissue and is elevated in BAL fluid. In normal fibroblasts, TGF-β induces a gene activation signature that is virtually identical to the phenotype of SSc fibroblasts. Furthermore, animal models provide strong support for the critical pathogenetic role of TGF-β in the fibrotic process in the skin and lungs. The stimulation of ECM molecules by TGF-β involves a complex intracellular signal transduction mechanism consisting of activation of Smad2/3, along with MAP kinases and Egr-1. c-Abl, a tyrosine kinase implicated in chronic myelogenous leukemia (the Philadelphia chromosome), appears to be activated in patients with SSc, perhaps reflecting TGF-β and/or PDGF stimulation. c-Abl inhibition by imatinib mesylate (Gleevec) blocks TGF-β responses. Furthermore, Gleevec also blocks signaling downstream of the PDGF receptor and c-Kit. In a mouse model of fibrosis, Gleevec prevented lung fibrosis, but failed to treat...
established fibrosis. The anti-fibrotic potential of Gleevec provides the rationale for current clinical trials evaluating its efficacy in SSc.

**Vasculopathy**

Vascular damage is prominent in the small and medium-sized vessels of the digits, lungs, heart, and gastrointestinal tract. Changes progress through three distinct phases: 1. endothelial cell activation, with increased production of ET-1 and decreased prostacyclin release, causing functional changes with initially reversible vasocostriction; 2. upregulation of adhesion molecules; and 3. generation of reactive oxygen species. Vascular wall remodeling follows with intimal proliferation, medial hypertrophy, and adventitial fibrosis; ultimately, platelet aggregation occurs and in situ thrombosis. The late vascular lesions are indistinguishable from the obliterator vasculopathy seen in organ transplant-associated allograft vasculopathy.

Patients with long-standing SSc demonstrate vascular rarefaction, i.e., paucity of small blood vessels, despite high levels of vascular endothelial growth factor (VEGF) and other angiogenic factors. Progressive obliteration of blood vessels results in tissue hypoxia, which is itself a potent stimulus for production of TGF-ß and fibroblast activation, further enhancing the fibrotic process. Recent studies suggest that depletion of bone marrow-derived endothelial vascular progenitor cells in SSc may impair the ability to repair vascular damage.

The Spectrum of Clinical Manifestations

Systemic sclerosis is extremely heterogeneous in its clinical manifestations, autoantibody responses, patterns of organ involvement, natural history, and survival. Patients are grouped into limited cutaneous (lc) or diffuse cutaneous (dc) SSc subsets based on the pattern of skin involvement. During the past decade, the lung has emerged as a critical target organ in SSc. Over 90% of patients have evidence of interstitial lung disease (ILD) at autopsy, and 40% show restrictive changes on pulmonary function tests (PFTs). Survival is inversely related to the severity of restrictive lung disease. The earliest changes occur in the posterior lower lobes. Because the greatest loss of lung function (measured by FVC, forced vital capacity) generally occurs within the first few years, patients at high risk for progressive disease need to be identified and effective therapy initiated early.

Raynaud’s phenomenon is a prominent early vascular feature, and in some patients progresses to severe digital ischemia. In the kidneys, injury to the medium-sized arteries can precipitate scleroderma renal crisis (SRC) with malignant hypertension and hyperreninemia, microangiopathic hemolytic anemia, and rapidly progressive renal failure. Scleroderma renal crisis develops in up to 15% of patients with deSSc, almost always within the first 4 years of the disease. Major risk factors include extensive and advancing skin involvement, large joint contractures, and tendon friction rubs, along with the presence of autoantibodies to RNA polymerase III. Normotensive SRC, occurring in a minority of SSc patients, is associated with a worse outcome. Corticosteroids, even at relatively low doses, appear to increase the risk of SRC. In the pre-ACE inhibitor era, SRC was uniformly fatal. Although ACE inhibitors do not prevent SRC, they are effective in its treatment, especially if started early. Because chronic dialysis can be avoided if aggressive intervention with ACE inhibitors is initiated before serum creatinine exceeds 3 mg/dl, SRC is a medical emergency. The 5-year survival of patients requiring permanent dialysis due to SRC is only 40%.

Pulmonary arterial hypertension (PAH), defined as mean pulmonary artery pressure greater than 25 mmHg at rest or greater than 30 mmHg during exercise, is a major SSc complication, and is a leading cause of death. PAH develops in 40% of SSc patients, generally late in the disease, and occurs more frequently in dcSSc, where it may be indistinguishable pathologically from primary PAH. Risk factors include older age of disease onset and the presence of antibodies to fibrillarin/U3RNP or B23, whereas topoisomerase-1 antibodies may be protective. While early PAH is asymptomatic, with progression, increasing right ventricle hypertrophy and failure develops. In a recent study, 5-year survival of SSc patients with isolated PAH was 10%, substantially worse than of patients with primary PAH. Cardiac involvement in SSc is frequent, and is often clinically silent or can be associated with left ventricular (LV) diastolic dysfunction. Heart involvement in SSc may be due not only to PAH but also cardiac fibrosis. The use of MRI imaging has greatly enhanced the sensitivity of detecting myocardial involvement.

**Evaluation**

The challenge of evaluation includes accurate early diagnosis and classification, staging, and serial monitoring for either progression or response to therapy. Because dyspnea is not a sensitive symptom of either early ILD or PAH, all patients should have screening PFTs to measure FVC and DLCO. In ILD, these two parameters tend to decline in parallel, whereas in isolated PAH, the DLCO shows a disproportionate decline. High-resolution CT is more sensitive than a radiograph, and should be used for screening. Alveolitis is usually associated with ground-glass opacification. However, since this pattern may occur in infection, pulmonary congestion and other forms of lung injury, many centers incorporate BAL into their evaluation protocol. The presence of greater than 2% to 3% eosinophils or polymorphonuclear leukocytes in BAL fluid at initial evaluation is correlated with severity, and in some studies with progressive decline in FVC.

Recent studies have questioned the prognostic utility of BAL in the evaluation of SSc-associated ILD. Lung biopsy is rarely necessary. Patients with early SSc and documented
ILD should have PFTs every 3 to 6 months during the first 5 years. PAH often remains undetected until it is advanced. Traditional diagnostic methods include measurement of DLCO and echocardiography (transesophageal or Doppler), which estimates PA pressure based on the velocity of the tricuspid or pulmonic regurgitant jet. However, echocardiography can under- or overestimate PA pressure. A recent analysis of 137 SSc patients showed that a noninvasive evaluation (tricuspid gradient greater than 45 mmHg, or DLCO less than 55% predicted) was moderately sensitive and specific for screening early PAH. It is recommended that Doppler echocardiography be performed on a yearly basis. The 6-minute walk test is an independent predictor of survival in PAH. The diagnostic gold standard, cardiac catheterization, is required to directly measure baseline PA pressures and cardiac output and rule out left ventricular dysfunction.

The autoantibody profile in SSc is highly specific and useful for establishing the diagnosis, for subsetting, and for monitoring disease activity. Anti-topoisomerase I antibodies associated with dSSc show fluctuations with disease activity and correlate with skin score. Antinucleolar antibodies against PM/Scl, B23, small ribonucleolar protein, or RNA polymerase III occur in 15% to 40% of SSc patients and show intriguing associations with specific clinical patterns of SSc, such as SRC (RNA polymerase III), hypothyroid (Th), or malignancy (B23). Recent studies suggest that SSc-specific autoantibodies may directly contribute to disease-associated injury and tissue damage.

Management

Until recently, therapeutic options for SSc were few. Clinical heterogeneity and low prevalence, lack of validated severity, activity and outcome measures, or biomarkers, and limited interest from the pharmaceutical industry all contributed to a dearth of intervention trials. In contrast, the last few years have witnessed the introduction of novel treatments, and now we have a rich therapeutic pipeline. Because SSc is a heterogeneous disease with an unpredictable course, treatment must be individualized for each patient. Ideal disease-modifying therapy should address the inflammatory, vascular, and fibrotic aspects of the disease.

Immunosuppression

Immunosuppressive therapies historically have not been highly effective. In particular, corticosteroids failed to influence the course of skin or lung deterioration. A recent study demonstrated clinical benefit in patients treated with high-dose immunosuppression using lymphoablative doses of cyclophosphamide. Autologous hematopoietic stem cell transplantation (HSCT) induces marked improvement or complete remission in animal models of autoimmunity and in some patients with lupus and rheumatoid arthritis. These encouraging results provide the rationale for clinical trials of HSCT in SSc. HSCT involves mobilization of stem cells using cyclophosphamide and G-CSF, followed by conditioning with high-dose cyclophosphamide (100 to 200 mg/kg); in some centers, patients also receive radiation. In a multicenter European study, 58 patients with severe SSc underwent HSCT. Skin scores showed improvement in 50% of evaluable patients at a median follow-up of 12 months, and lung function stabilized. However, 15% of the patients relapsed following initial improvement and there were 11 deaths, seven of which appeared to be procedure-related. In a recent smaller U.S. trial, 12 of 19 patients showed improved skin scores, and internal organ involvement stabilized. Revascularization of ischemic skin tissue has also been described. Mortality was 17%, due to radiation-induced pulmonary complications, lymphoproliferative disease, and other complications. Multiple clinical trials comparing HSCT versus monthly cyclophosphamide in patients with severe SSc is currently underway in the U.S.

PAH

PAH is a leading cause of death in lcSSc. Three prostacyclin analogues are currently FDA-approved for SSc-associated PAH. Due to their short half-life, they must be administered by continuous infusion or frequent inhalation (iloprost). Epoprostenol is given intravenously, and treprostinil is given subcutaneously. Both have been shown to improve 6-minute walk distance, but are expensive and are associated with complications, including line infections and infusion site pain. The orally administered nonselective ET-1 receptor antagonist bosentan has been shown to improve exercise tolerance and slow clinical deterioration. Abnormal liver function, edema, and anemia are among potential complications. A selective ET-1A receptor antagonist, ambrisentan, has been demonstrated to improve exercise capacity and cardiopulmonary hemodynamics. Inhibitors of phosphodiesterase-5, such as sildenafil, cause pulmonary vasodilation, improve exercise tolerance, and may have a role in the treatment of SSc-associated PAH as monotherapy or in combination with ET-1 antagonists or prostacyclin analogues. Unfortunately, the survival benefit of prostacyclin drugs in SSc patients is less than in patients with primary PAH, possibly due to concurrent ILD. Whether treatment of early PAH could halt its progression remains to be determined. We generally start treatment with an ET-1 antagonist and add additional agents, such as sildenafil or inhaled iloprost, in patients with inadequate response. The role of statins is controversial. Recent studies suggest that statin therapy in SSc enhances endothelial vascular progenitor cell mobilization and maturation, thereby contributing to vascular repair.

Lung Involvement

When ILD is present, the goal of therapy is to stabilize fibrosis in patients with progressive disease and avoid unnecessary therapy in those with inherently stable disease. Since most pulmonary deterioration occurs within the first 5 years,
treatment must be instituted early. Uncontrolled studies showed that cyclophosphamide, given orally or intravenously, stabilizes PFTs and high resolution computed tomography (HRCT) abnormalities, and may also improve survival. Results from a multicenter, placebo-controlled study of oral cyclophosphamide (SLS) have indicated a modest but statistically significant benefit at 12 months of treatment that persisted at 18 months but not at 24 months. The role of adjuvant corticosteroids and the optimal duration of cyclophosphamide therapy are unknown. The antifibrotic cytokine interferon-gamma showed promise in a small study of idiopathic pulmonary fibrosis, but a recently completed large clinical trial failed to show benefit. Bosentan is currently undergoing evaluation in SSc patients with ILD. Mycophenolate has been used with modest benefit in multiple small studies; a multi-center controlled clinical trial is planned. Clinical trials of biological therapies with antibodies directed against TGF-ß, CTGF, IL-13, and MCP-1 are planned.

Raynaud Disease and Renal Crisis

Widely used agents for Raynaud phenomenon include vasodilators, such as calcium channel blockers and nitrates, and inhibitors of vasoconstriction, such as angiotensin-receptor blocker (ARB) losartan, and ACE inhibitors. Newer therapies include ET-1 receptor blockers, phosphodiesterase-5 inhibitors, prostanoids, antioxidants, and low-molecular weight heparin. In patients with severe digital ischemia, prostacyclin infusion and stellate ganglion blockade may be helpful. A recent study demonstrated that bosentan reduced the occurrence of ischemic digital ulcers. Although ACE inhibitors do not prevent SRC, they are effective in its treatment. Treatment with an ACE inhibitor must be started promptly once the diagnosis is made and then be continued, even when blood pressure is stabilized. The role of ARB therapy in the management of SRC is unknown. Appropriately treated patients may recover renal function and discontinue dialysis for up to 2 years after onset of SRC.

Skin Fibrosis

Skin fibrosis remains a vexing therapeutic problem. Despite the fact that D-penicillamine has been in widespread use for decades, a multicenter placebo-controlled trial failed to show significant difference between high dose and low dose D-penicillamine. Small studies have suggested clinical utility for methotrexate and for mycophenolate mofetil. Relaxin and minocycline, reported to be effective in small open-label studies, showed no beneficial effect in controlled trials. Ultraviolet A light therapy appears safe and effective for localized forms of scleroderma. There is also interest in trials of small molecule kinase inhibitors including imatinib, an inhibitor of Bcr-Abl and of the PDGF receptor.

Disclosure Statement

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