

Advances in Therapy of Systemic Sclerosis

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Systemic sclerosis (SSc) is a chronic autoimmune disorder, characterized by microvascular abnormalities, inflammatory cell infiltrate and an excessive collagen deposition in the dermis and internal organs, leading to excessive fibrosis. Not many large series have been reported from India of this disease. The spectrum of the disease is no different than seen elsewhere in the world. However, there are reports suggesting a much higher prevalence of the diffuse form of the disease as compared to the West.¹ Another study from south India in 98 patients has showed a lower prevalence of the diffuse form of the disease.²

There is a dysregulated collagen production in SSc in both forms of the disease; the limited and the diffuse cutaneous variants. In the former, the skin involvement is limited to the acral distal parts, while in the latter form, there is widespread involvement of the skin, gastrointestinal tract, lungs, heart and the kidneys. In both, there occurs Raynaud's phenomenon (three phase colour change of finger and toes on exposure to cold) which precedes skin involvement by several months to years. This and the capillary loop abnormalities that occur before the skin involvement suggest that initial vascular events clearly play an important role in establishing the disease. The disease is believed to be due to a complex interaction between the activation of the immune system and microvascular injury which results in dysregulated collagen production.

Environmental agents like drugs and toxins (vinyl chloride, silica, and contaminated oil), occupational agents (like vibrational tools etc) have long been implicated as aetiological agents in susceptible individuals.

In this review, we will summarize the progress done in the last 5 years on the pathogenesis and treatment of this disease.

ROLE OF GENETICS

Fibrillin-1 is a major component of elastic microfibrils found in extracellular matrix (ECM) and is an important structural protein expressed in many tissues, including skin. Murine genetic model for the SSc (tight skin mice, *tsk/+*) has recently been shown to have genomic duplication of fibrillin-1 gene.³ This mutated gene produces a larger protein at the same level as the normal protein. This enlarged fibrillin-1 monomer assembles into homopolymers that are distinct from the normal microfibrils. Genetic linkage of human SSc to the fibrillin-1 gene on chromosome 15 has also been established in the Choctaw Native Americans.⁴ Preliminary metabolic labeling indicates that fibrillin-1 containing microfibrils from SSc fibroblasts are unstable and easily degraded.⁵ Abnormal

fibrillin protein might lead to defective matrix which may bind to increased amounts of growth factors, such as TGF beta⁶ which in turn is slowly released and causes proliferation of fibroblast and increased matrix biosynthesis. It may also unmask cryptic epitopes against which antibodies have been detected in SSc.⁷

Fibronectin is involved with interaction of cells with collagen. Certain restricted fragment length polymorphisms in the fibronectin gene are found more frequently in SSc patients with pulmonary fibrosis.⁸ A protease, nexin I, thrombin and urokinase inhibitor made by fibroblasts, is overexpressed at the mRNA and protein level in SSc lesional skin.⁹ This may promote collagen gene transcription. In SSc, there is a disruption of the normal negative regulation of the matrix production leading to excessive tissue fibrosis. TNF and IFN gamma are the negative regulators of collagen gene expression. Induction of the transcription factor NF-kB by TNF alpha has been shown to inhibit collagen transcription by interfering with Sp-1 mediated activation.¹⁰ Understanding of this negative regulatory pathway may lead to development of novel antifibrotic drugs.

Non-collagen genes may also be important. Tenascin C, a normal ECM protein expressed during embryonic life, is normally silent in adults. It is increased in SSc skin and its promoter elements have been shown to be important in the context of this disease.¹¹

The association of various HLA genes with SSc is rather weak. Familial aggregations of SSc have been seen as exemplified by the classical Choctaw Indians tribe.¹² Non-HLA associations like TNF polymorphisms¹³ have also been inconsistently reported.

MICROCHIMERISM

Chronic graft versus host disease following allogeneic bone marrow transplantation mimics systemic sclerosis. This has led to a hypothesis based on microchimerism with persistence of foetal cells in mother, especially if they were HLA class II incompatible with the child, might lead to a graft versus host reaction and SSc. This may also explain the high female incidence and relation with immediate post-partum period of the disease. HLA disparate maternal cells could also persist in the male offspring. This 'microchimerism' may explain disease occurrence in male patients.¹⁴

TGF beta and fibroblast proliferation

The central player in this excess fibrosis production is the fibroblast, which in SSc has been shown to produce a 2-3 fold excess collagen as compared to normal skin fibroblast. This could be either be due to a genetic defect, or induced by cytokines from immune or endothelial cells.¹⁵ TGF beta is the key cytokine that stimulates the excessive collagen production. High levels of TGF beta receptors have been demonstrated on

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the fibroblasts.¹⁶ TGF beta leads to an induction of the collagen gene expression. TGF beta inhibits proliferation of epithelial, endothelial and haematopoietic cells while stimulating the synthesis of ECM, like collagen. Much of the delayed increase in collagen synthesis is at transcriptional level and increased transcription factors like c-myc¹⁷ that activates IL4, have been found. IL4 in SSc increases fibroblast proliferation.¹⁸ Further, IL 4, an activator as potent as TGF beta,¹⁹ has been found to be overexpressed in scleroderma skin and also enhance another matrix component, tenascin.²⁰

Autoantibodies and T cells

Antinuclear antibodies are positive in about 95% of patients with SSc on HEp2 substrate. A wide variety of antigenic targets have been established namely centromere, topoisomerase, U3 RNP (fibrillarin), RNA polymerase I/III, U1RNP and PM/Scl,²¹ but none of these can explain an etiologic role. Anti-endothelial cell antibodies, which may reflect vascular injury, has been shown to activate endothelial cells, causing upregulation of adhesion molecules²² and apoptosis.²³ Our recent observations of antineutrophil cytoplasmic antibody positivity with specificity against BPI and cathepsin G antigens in SSc patients may also have pathogenetic implications.²⁴

Like rheumatoid arthritis, T cells may play an important role in the pathogenesis. There are increased number of CD4 cells, increased ratio of CD4/CD8 cells and increased T cell cytokines (IL 2 and IL 2R). T cell-endothelial cell interaction may actually lead to endothelial injury thus implicating T cell as the main culprit in pathogenesis. On the other hand, T cell-fibroblast interactions may also lead to increased fibroblast activation.

Vascular injury

The normal vascular tone is maintained by factors released by endothelial cells, platelets and the nervous system. Endothelins, endothelial-derived relaxation factor, nitric oxide and prostacyclin are secreted from endothelial cells whereas serotonin and platelet activation factor 4 (PF 4) are released by platelets. In addition, there is contributory effect of sympathetic nervous system (neuropeptide Y (NPY), noradrenalin (NA)), parasympathetic nervous system (vasoactive intestinal peptide (VIP) and acetylcholine) and sensory nervous system (calcitonin gene related peptide (CGRP), and substance P (SP)). While NPY, NA, serotonin and PF 4 act as vasoconstrictors, CGRP, VIP, SP and NO are vasodilators. In SSc, this normal control is defective with increase in vasoconstrictors compared from vasodilators leading to vascular injury.

Free radical injury

An ischaemic act is superadded upon by the reperfusion injury causing generation of oxygen free radicals, which aggravates vascular damage.²⁵ It has been shown that in Raynaud's phenomenon secondary to SSc, there is an increase in oxidized lipoproteins, increased susceptibility to oxidation of LDL, decrease in antioxidants (Vit E, carotene, ascorbic acid) and increase in plasma superoxide dismutase levels. Initially, endothelial cells have the capacity to respond to oxidative stress by synthesizing stress inducible proteins. When this capacity is exhausted, there is endothelial injury and progression to SSc.

Recent studies have suggested a central role played by the heavy metals and increase in reactive oxygen species generated during ischaemia-reperfusion phases, in the pathogenesis of scleroderma. It has been seen that the autoantigens targeted

in systemic sclerosis like topoisomerase I, RNA polymerase, fibrillarin, CENPs, etc, are unified by their enrichment in the nucleoli during physiological conditions,²⁶ and are susceptible to modification at highly specific sites in a reaction that requires metal binding and the presence of oxygen free radicals.²⁷ This modification leads to fragmentation of various potential autoantigens. The novel scleroderma autoantigens that are thus generated break tolerance to the intact self molecules and thus an immune response is mounted.

Newer modalities in diagnosis of vascular insufficiency

As against the traditional method of nail fold capillary microscopy to visualize microvascular changes, microcirculatory vasodilatation can now be assessed by iontophoresis (a non-invasive method to study vascular tone control, in which the transcutaneous delivery of pharmacological substances may stimulate the endothelium to release vasodilating factors via an endothelium dependent or may directly stimulate smooth muscle cells causing vasodilation via an endothelium independent mechanism), laser Doppler flow velocimetry, strain gauge plethysmography, and finger skin temperature via computed thermography. These newer diagnostic modalities may help in differentiating primary from secondary Raynaud's and hence, an indication to a definite connective tissue disease evolution.

Measuring disease activity, severity, damage and functional quality

Efforts have been made to find out disease severity and damage in this chronic, 'inactive', disease. A 9-organ disease severity scale has been published.²⁸ This may be useful in comparing patient populations, assessing disease severity status at a given time as well as longitudinally and in strengthening clinical trials. Attempts to develop disease activity index are also on and parameters as rapid increase in skin thickness to include proximal extremities, palpable tendon friction rubs, myositis, alveolitis, new congestive heart failure and new renal crisis may be included.

Similar on the lines of RA, a HAQ-disability index has been proposed.²⁹ This 20 item index was evaluated and increased baseline HAQ-DI was correlated with reduced fist closure, reduced hand spread, elevated platelet count, presence of tender joints, older age and female sex. In this study, the most important contributor to functional impairment was hand dysfunction. Even after first 18 month of disease onset, moderate to severe functional impairment was frequent in this group of patients.

A number of soluble serum markers of disease activity may be useful. These include IL2, 4, 6, 8,³⁰ TGF-β and TGF beta receptor, E selectin,³¹ von Willebrand factor,³² endothelin 1,³³ and procollagen III breakdown products,³⁴ and nitric oxide synthetase levels. Laminin-P1 (a component of basement membrane) has been found to be associated with poor renal outcome, and KL6 (a protein from type II pneumocytes) levels, correlate with interstitial lung disease (ILD).³⁵

ADVANCES IN TREATMENT

Raynaud's phenomenon

Besides preventive aspects like protection from cold, agents like calcium channel blockers have been used for the last several years. Nifedipine, diltiazem and ACE inhibitors have also been used. In patients not responding to these above

methods, trial of surgical or chemical sympathectomy has been tried with variable results. Recent studies have shown the role of intraarterial agents like alpha antagonists, oral prostacyclin and its analogues,³⁶ antiplatelet agents, and tissue plasminogen activators.³⁷ Experimental therapies like nitric oxide donors are also being tried. Few studies also have suggested the role of direct acting nerve stimulants like capsaicin. With the role of free radical injury in pathogenesis, free radical scavengers and antioxidants are being tried.³⁸

Impending gangrene

Such patients have been treated with sympathectomy with poor results or may require repeated interventions. Other modalities of treatment that have been tried are local application of vasodilators like nitroglycerine patches, however this leads to increased incidence of side effects like headache and problems of tachyphylaxis. Therapeutic angiogenesis has been tried in which endothelial cell precursors or angioblasts isolated from human peripheral blood are used to augment collateral vessels growth to the ischemic tissue.³⁹ Other experimental modalities of therapy also include the potential use of angiogenic growth factors coated on angioplasty balloon. These are coated with gel containing DNA of a gene encoding for vascular endothelial growth factor.⁴⁰

Skin

With not more than a third of treated patients responding to d penicillamine in their skin thickening, agents such as recombinant human relaxin have been of greater benefit in a few recent studies.⁴¹ Relaxin, a pregnancy related hormone from placenta, has tissue remodeling and antifibrotic effects.

ILD and pulmonary arterial hypertension

After the use of ACE inhibitors, renal crisis has been a less common cause of morbidity and mortality. On the other hand, primary PAH and ILD continue to have an upper hand. No drug has actually shown any significant benefit in it. Traditional agents like d-penicillamine have shown success in about 20% of patients. Considering the pathogenetic effect of T- cells in SSc, immunosuppressive agents are also being utilized. Among the various drugs, high doses of cyclophosphamide has been found to be beneficial in a few recent studies,⁴² especially in cases with early diffuse SSc, although other agents like cyclosporine and azathioprine have also been tried. The potential role of bone marrow transplantation is also aimed at achieving similar effect. PAH, a dreaded complication of limited SSc, has now been successfully managed with continuous iv administration of prostacyclin.⁴³ Other potential agents may include anti-vasoconstrictors like antiendothelins, and vasodilators like adenosine and NO. Prostacyclin analogues have been used via subcutaneous and inhaled routes with good results.⁴⁴

Gastrointestinal tract

Is another manifestation causing a significant morbidity. Therapy has been at best symptomatic. Besides advice regarding small, frequent feeds and head end elevation, prokinetic agents like cisapride and mosapride have been used with varying results. Blind loop syndrome has been treated with antibiotics.

In summary, although the last few years have witnessed significant progress in our understanding of the pathogenesis of this disease, treatment of this disease remains far from satisfactory.

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