Review

Pathogenesis of Scleroderma

Current Concepts

EDWARD B. LEE, M.D., GRANT J. ANHALT, M.D., JOHN J. VOORHEES, M.D., AND LUIS A. DIAZ, M.D.

From the Department of Dermatology, The University of Michigan School of Medicine and the Veterans Administration Medical Center, Ann Arbor, Michigan

The term "scleroderma" traditionally has been utilized to describe the cutaneous changes of a heterogeneous group of disorders involving hardening, tightening, and decreased elasticity of the skin.[1] Two extreme forms have been identified—localized and diffuse.

The localized form, specifically morphea, is characterized by well-circumscribed, sclerotic plaques with an ivory-colored center and a surrounding violaceous halo. The violaceous halo implies active disease. Visceral involvement is not observed and, therefore, prognosis is generally favorable.[2]

In sharp contrast is the diffuse type, or progressive systemic sclerosis (PSS), which is correlated with widespread sclerosis, Raynaud's phenomenon, and multisystem involvement.[2-4] Prognosis is poor, with death often secondary to renal failure or pulmonary fibrosis.[5]

Between these two extremes are intermediate forms, with generalized morphea representing a form of localized scleroderma and acrosclerosis and the CREST syndrome representing a form of PSS.[1,6]

Formulating a definition of the full spectrum of PSS necessitates an understanding of the etiology and pathogenesis. This, in turn, may clarify the interrelationship between progressive systemic sclerosis, morphea, and the intermediate varieties.

According to Lever and Schaumberg-Lever, histologic differentiation of the skin lesions in morphea versus PSS is usually impossible; however, they identify two stages: (1) early inflammatory; and (2) late sclerotic.[7] During the early inflammatory stage, the dermis reveals closely packed, thick collagen bundles in conjunction with a mild, predominantly lymphocytic, inflammatory infiltrate that is located in the perivascular spaces and between the collagen bundles. This infiltrate appears to be much more pronounced in its distribution in the subcutaneous tissue and is accompanied by deposition of new collagen in these areas. In the late sclerotic stage, the inflammatory infiltrate almost completely disappears, with concurrent replacement of the subcutaneous tissue by collagen.

Three predominant theories have emerged in the investigation of the pathogenesis of PSS. The first theory advocates evolution of the primary lesion within the blood vessel.[8] The second postulates an autoimmune basis for the disease.[9] The third considers the primary event an abnormality of collagen metabolism, manifested by fibrosis.[5]

The true pathogenesis of PSS is essentially unknown at present. The separation of these theories is artificial and merely facilitates the discussion of pathogenesis. One may speculate that the three theories, rather than existing independently, might be somehow interdependent and interrelated.

The Vascular Theory

The vascular manifestations of PSS include its early edematous phase, Raynaud's phenomenon, telangiectasias, capillary abnormalities detectable through both nailfold and ultrastructural microscopy, and widespread multisystem vascular disease.[10] The most striking histologic abnormalities occur in the small blood vessels—the small arteries, arterioles, and capillaries—with occasional involvement of the major arteries.[11,12] The primary vascular lesion is believed to be manifest by a distinctive intimal proliferation, with cells arranged con-

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Address for reprints: John Voorhees, M.D., Department of Dermatology, The University of Michigan School of Medicine, Ann Arbor, MI 48109.

centrically in a matrix of ground substance.[13] This pattern is referred to as fibromucinous endothelial change."[8]

Recent electron microscopic studies by Fleischmajer and Perlish[14] reveal the earliest change in PSS capillaries to be large gaps between endothelial cells. These researchers hypothesize that the gaps would allow extravasation of plasma fluids into the extracellular matrix, thereby creating the early edematous features of the disease that precede the characteristic fibrotic phase. They also document that after development of these endothelial cell gaps, cells undergo swelling and subsequent destruction, with release of organelles into the lumen. Capillary obstruction frequently results. This repeated pattern of endothelial cell destruction is believed responsible for the observed replication of the basal laminae,[14] with each basal lamina layer corresponding to the residual of one endothelial cell regeneration.[15]

What, then, is the etiology of the actual endothelial cell destruction? Could ischemia be implicated? It is known that Raynaud's phenomenon is often the presenting sign of PSS and that endothelial cell damage may occur in response to hypoxia.[16] In addition, Kristensen and Henriksen[15] report decreased compliance of extravascular tissue in PSS. Diminished circulation, which may occur as a result of this decreased compliance, may also contribute to hypoxia.[17] Kahaleh et al[10] have demonstrated the existence of an endothelial cell-specific cytotoxic factor, demonstrating its occurrence in 31 of 52 patients with PSS. The factor is characterized as heat-stable, nondialyzable, and able to migrate with albumin on gel filtration.

Vibrational energy also has been associated with endothelial cell damage. People who work with vibrating tools have been known to develop scleroderma-like changes.[18,19]

In addition to these ongoing destructive processes, some vessels exhibit discrete areas in which endothelial cells remain intact, with their nuclei in prophase.[20] In vitro autoradiography with ^{3}H-thymidine demonstrates a marked increase in endothelial and pericyte cell labeling in these areas.[20] The significant decrease in the number of capillaires observed in the papillary layer of PSS patients may be the result of an overwhelming predominance of endothelial cell destruction, rather than proliferation.[14]

Why does proliferation occur at all? Fleischmajer et al[20] offer several interpretations. Proliferation may simply be a reparative process in response to endothelial cell destruction. What is detected as proliferation may actually be a measure of the differentiation of endothelial cells into fibroblast or fibroblast-like cells. Or, endothelial cell proliferation may produce enlargement of existing capillaries with resultant telangiectasias.

In this context, it is interesting to note that the telangiectasias observed in PSS usually occur in sites where Raynaud's phenomenon has been documented—the face, tongue, lips, upper chest, and hands.[21] It may therefore be valid to hypothesize that ischemia triggers endothelial cell destruction, which in turn stimulates a reparative process responsible for endothelial cell proliferation, with subsequent telangiectasia formation.

Changes in the microvasculature in PSS as well as in other connective tissue diseases have been investigated by Maricq et al,[22] who employed the technique of wide-field capillary microscopy. Applied to PSS patients, this technique has uncovered a distinctive microvasculature pattern consisting of dilated and distorted capillary loops alternating with avascular areas. Additionally, these authors have found a positive correlation between the degree and extent of abnormal microvasculature patterns and the scope of multisystem involvement.

A perivascular cellular infiltrate has been associated with the above-mentioned vascular changes.[20] This infiltrate comprises lymphocytes, plasma cells, macrophages, and monocytes. The causative mechanism for this cellular response is unknown at present.

The observed perivascular fibrosis may be secondary to the proliferating endothelial cells, pericytes, or perivascular fibroblasts, all of which reveal a prominent rough endoplasmic reticulum on electron microscopic examination suggesting that these cells may be implicated in increased collagen synthesis.[20]

Abnormal responsiveness of the blood vessels of PSS patients to catecholamines and serotonin has also been scrutinized, with conflicting results.[23–30]

The Immune Theory

It has been proposed that PSS may be of autoimmune etiology because of the immunologic abnormalities that are observed along with the presence of cellular infiltrates composed of lymphocytes, plasma cells, and macrophages.[31] This theory is further supported by the association of PSS with other diseases of possible autoimmune etiology, such as Hashimoto's thyroiditis, Sjögren's syndrome, systemic lupus erythematosis (SLE), dematomyositis, biliary cirrhosis, and MCTD.[32–39]

Although the number of circulating B lymphocytes has been found to be normal,[35] serum protein electrophoresis reveals a polyclonal gammopathy in one-half of PSS patients.[36] Approximately one-half of patients have a positive test for antinuclear antibodies.[37] Antibody to Scl-70 antigen, antibody to centromere, and antinucleolar antibody are highly specific for PSS.[40] The anticentromere antibody appears to be highly selective for the CREST variant of PSS. This antibody occurs in approximately 57% of patients with the CREST syndrome, compared with approximately 8% in patients with PSS. Twenty to thirty percent of patients exhibit low titers of rheumatoid factor.[9] Sixty-six percent of patients have anti–smooth-muscle antibody.[38] Five percent have pos-

itive LE test results but show a negative direct immunofluorescence in contrast to SLE.[41] N-DNA antibodies and cryofibrinogen are also present.[42,43] Immune complexes and complement deposition have been demonstrated in the glomeruli and intralobular arteries of the sclerodermatous kidney.[44] Antibodies directed against interstitial (Type I) and basement membrane (Type IV) collagens in the sera of patients with PSS also have been observed[45] (Table 1).

Hughes et al[46] recently reported a decrease in the number of circulating T cells in patients with PSS. Utilizing antisera specific for B and T cells, it has been demonstrated that T lymphocytes comprise the majority of the lymphocytic infiltrate seen in the dermis and the subcutaneous tissue during the inflammatory stage.[47] The reduction in the number of circulating T cells has been correlated with the magnitude of visceral involvement: patients with lower T cell counts show more extensive disease.[46] Kondo et al[47] found that lymphocytes of PSS patients respond to extracts of both normal and sclerodermatous skin in the migration inhibition assay, implying that the lymphocytes are sensitized to a cutaneous antigen present in these patients. Because of the crude extracts they used, however, it was impossible to ascertain the exact nature of this antigen from the study. Johnson and Ziff[48] documented that in vitro stimulation of lymphocytes by phytohemagglutinin resulted in the release of a lymphokine. This, in turn, stimulates production of collagen by fibroblasts. This lymphokine, which is nondialyzable and stable at −70 C, may be the basis of lymphocyte–fibroblast interaction in PSS.

Although several functional studies of the immune system have been undertaken,[17–49] results to date are inconclusive. The major drawback in the autoimmune hypothesis lies in the lack of correlation between immune alterations and the duration of the disease, the clinical severity of the disease, and the presence of cellular infiltrates in the skin.[50]

Perhaps an understanding of these immune alterations and even the pathogenesis of PSS will be discovered in the principles of the graft-versus-host (GVH) reaction.

There are three theoretic requirements for the GVH reaction to occur: (1) the graft must consist of foreign, lymphoid, immunocompetent cells in sufficient quantities; (2) the host must be in a state of immunologic compromise; and (3) there must be histocompatability differences between the host and the graft.[51]

GVH has been separated into acute and chronic phases.[51–53] The late chronic phase involves cutaneous alterations that are indistinguishable both clinically and histologically from scleroderma. The current literature implicates both humoral and cell-mediated mechanisms in GVH pathogenesis.[51] What makes GVH disease so exciting is that, for the first time, we have an experimental human or animal model to study the pathogenetic mechanisms involved in scleroderma. One may therefore speculate that unraveling the complexities of the GVH reaction may lead to a clearer concept of the pathogenesis of PSS.

TABLE 1. *Serologic Abnormalities in Progressive Systemic Sclerosis*

Polyclonal gammopathy
ANA-Scl-70, centromere, nucleolar
Rheumatoid factor
Anti–smooth-muscle antibody
Positive LE test result
N-DNA antibodies
Cryofibrinogen

Abnormality of Collagen Metabolism Theory

Clinically, the most striking feature of PSS is the thickening and severe rigidity of the skin. Because the structural stability of the skin is almost totally dependent upon the fibrous protein collagen, qualitative and quantitative changes in collagen could conceivably lead to the signs and symptoms observed in PSS.[54] This concept has led the way for a vast amount of research concerning collagen and its role in the pathogenesis of PSS.

In PSS, fat is replaced by collagen both in the subcutaneous tissue and in tissue surrounding the eccrine sweat glands.[55] Fleischmajer points out that at light-microscopic examination, the dermis exhibits compact connective tissue due to a reduction in the interfascicular spaces. Additionally, collagen in these areas is composed of thick bundles that stain normally with trichome stains.[5] This is in contrast to the hyalinized connective tissue of the subcutaneous fat, which consists of fine fibers and stains lightly with trichome stains.

At electron-microscopic examination, the upper dermis reveals thick aggregates of collagen fibrils. Normally, these fibrils have a diameter of 900–1100 A and a periodicity of 640 A. In the lower dermis and subcutaneous tissue, there are large areas of fine collagen fibrils 200–400 A in diameter with normal periodicity.[56] Areas with bimodal distribution are also present, in which fibril diameter is 350–950 A.[55] In the fat trabeculae, in addition to fibrils 200–400 A in diameter, there occur well-circumscribed regions of fibrils 100 A in diameter without discernable periodicity.[5] Therefore, one may observe areas in the upper dermis that appear to be composed of normal, mature collagen, whereas the lower dermis and subcutaneous tissue are replaced by what appears to be immature collagen.

Experimentally, it has been demonstrated that a high ^{3}H-proline uptake occurs by the large numbers of fibroblast-like cells in the hyalinized areas of the subcutaneous tissue.[20] Correlation of this finding with the electron-microscopic findings imply that subcutaneous

tissue fibroblasts are engaged in collagen synthesis; however, this cannot be substantiated, because proline is incorporated into proteins other than collagen.[5]

Although the concentration of collagen is normal in PSS,[57] a net increase in collagen occurs that is directly proportional to the increase in skin thickness.[5,58] This net increase may be due to an accelerated rate of fibroblast collagen synthesis.[59] Findings in support of this hypothesis include: (1) an increase in prolylhydroxylase activity[60]; and (2) accelerated incorporation of radioactive proline and the synthesis of radioactive hydroxyproline in skin collagen biopsies obtained from PSS patients when compared with biopsies from normal controls.[61]

Another rationalization for this net increase in collagen may be that fibroblasts that assume a normal rate of collagen production may have defective negative feedback mechanisms. They are, essentially, unable to turn off.[62] This might account for the net increase in collagen despite the normal production rate.

Perlish et al[2] found that fibroblasts that originate in involved areas undergo a rate of collagen synthesis equal to or less than fibroblasts isolated from adjacent, clinically noninvolved sites. It is apparent that, in PSS, there are discrepancies concerning the rate of fibroblast collagen synthesis. Attempting to reconcile these discrepancies, Perlish et al postulated that experimental design, ie, the culture method, may be responsible. Investigators employing different media obtained conflicting results. One group of results is based on short-term, 24-hour studies, while other data are founded on long-term, 3-day experiments. These authors speculated that another significant factor and experimental design variable is the site of biopsy. They postulated that the cells in the center of the sclerodermatous plaque might be inactive or metabolically suppressed because of their environment. They might be incapable of synthesizing protein or collagen to any significant degree. In contrast, the cells at the lesion's periphery actively synthesize collagen, thus accounting for the increased plaque diameter observed in active lesions. It has also been demonstrated that fibroblasts obtained from the lower portions of involved dermis accumulate significantly more collagen than those from the upper portions.[63,64] The author's final factor responsible for experimental discrepancy involves the stage of the disease. Herbert et al[54] in studying the biosynthesis and maturation of skin collagen in scleroderma, showed that collagen isolated from sclerodermatous skin contains reducible cross-links. This implies that new collagen is being deposited in the skin; however, the absence of reducible cross-links in the center of the older plaques and from patients with inactive disease implies that no new collagen is being deposited.

On the basis of the above information, Perlish et al[62] proposed two distinct fibroblast populations in PSS. The first is trapped within the collagen matrix of the lesion and is consequently metabolically inactive. The second is composed of cells located in the periphery as well as underlying the lesion. These fibroblasts actively synthesize collagen but may be similar metabolically to fibroblasts within the normal population. In addition, Fleischmajer et al[65] recently reported great heterogeneity among scleroderma fibroblasts regarding collagen synthesis.

A decrease in the concentration of collagenase also may cause a net increase in collagen. This decrease has been confirmed by some authors but rejected by others.[66]

The net increase in collagen may be a result of: (1) an increase in the rate of fibroblast collagen synthesis; (2) a normal rate of collagen synthesis but defective regulatory mechanisms; (3) increased fibroblast proliferation at the site as reflected in increased endothelial cell labeling; and/or (4) a decrease in the concentration of collagenase.

Conclusion

There are numerous theories on the pathogenesis of PSS. At present, no unifying hypothesis can satisfactorily explain all of the abnormalities observed in the disease. Perhaps in the future, a clearer understanding of the etiology and pathogenesis of progressive systemic sclerosis will emerge.

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