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REVIEWS IN MEDICINE

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Ocular Manifestations of Scleroderma

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Abstract. Systemic sclerosis is a chronic multi-system disorder predominantly affecting the skin, musculoskeletal, gastrointestinal, pulmonary, and renal systems. Although the exact etiology is unknown, recent evidence suggests that immune activation play a pivotal role in the pathogenesis. Ocular involvement in systemic sclerosis has been documented; however, due to the rare nature of the disease, most papers have been single case reports or small case series. This review paper aims to consolidate the findings of previous papers with a view to providing a comprehensive review of the ocular manifestations of systemic sclerosis. (**Surv Ophthalmol** 54:292–304, 2009. © 2009 Elsevier Inc. All rights reserved.)

Key words. pathogenesis • scleroderma • systemic sclerosis

Scleroderma or systemic sclerosis (SSc) is a chronic multi-system disorder of unknown etiology. To date, there has been a significant number of papers published documenting the various ocular manifestations of systemic sclerosis. However, due to the rare nature of the condition, most of these have been single case reports or small case series. This review paper aims to consolidate the findings of previous papers with the awareness of the difficulty in drawing general conclusions in view of the limited published data. It is hoped this review will provide a useful summary when dealing with this disorder.

Epidemiology

SSc has a worldwide distribution. The peak incidence appears in individuals between 30 and 50 years of age. In terms of sex distribution, women are affected three times more often than men and this ratio increases during mid–late childbearing years to approximately 8:1.[21] Black patients are affected twice as frequently as white patients, at a lower age of onset, and are more likely to develop diffuse cutaneous involvement and pulmonary fibrosis.[21,43] In the U.S., the prevalence has been estimated to be 276 cases per million with an annual incidence of 19.3 new cases per million adults per year.[43]

Pathogenesis

SSc is characterized by three principle features, which are believed to occur in the following sequence: immune activation, vasculopathy, and excessive and widespread fibrosis.[63]

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IMMUNE ACTIVATION

For many years, it was believed that fibroblasts were the main culprit in the pathogenesis of SSc. However, activation of these cells is not intrinsic but orchestrated by the immune system.[34,35,91] There appear to be two phases associated with immune activation: an inflammatory phase and a fibrotic phase.[55]

In the inflammatory phase, the role of autoantibodies in the etio-pathogenesis has been uncertain. Over the last decade, studies have identified subsets of antinuclear antibodies (ANA) that are selectively associated with specific phenotypes of SSc (Table 1) and hence prognosis. However, research has not proven whether these antibodies have a direct pathogenic role or represent markers of a particular SSc phenotype.[9]

More recently, a class of autoantibodies that recognize cellular or extracellular matrix antigens have been identified. Of importance, these antibodies may have a role in immune initiation and the activation of pathways that precede the inflammatory cascade, which ultimately leads to vascular damage and tissue fibrosis.[9] Although a detailed description of these antibodies is beyond the scope of this paper, they are summarized in Table 2.

TABLE 1

Autoantibodies and Associated Phenotypes in Scleroderma

Antigen	Subtype of SSc	Clinical Phenotype
Topoisomerase 1	Diffuse	Pulmonary fibrosis, cardiac involvement
Centromere	Limited	Severe digital ischemia, PAH, sicca syndrome and calcinosis
RNA polymerase III	Diffuse	Severe skin disease, renal crisis (+/− sine scleroderma)
U3-RNP (fibrillarin)	Diffuse/limited	Primary PAH, esophageal, cardiac, and renal involvement and muscular disease
Th/To	Limited	Pulmonary fibrosis, renal crisis
B23	Diffuse/Limited	PAH, lung disease
Cardiolipin, B2 Glycoprotein 1	Limited	PAH, digital loss
PM/Scl	Overlap	Myositis, pulmonary fibrosis
U1-RNP	Overlap	SLE, inflammatory arthritis, pulmonary fibrosis

From Boin-Francesco.[9] PAH = pulmonary artery hypertension; SLE = systemic lupus erythematosus.

Molecular mimicry has been shown to be one of the mechanisms that accounts for the link between infection and autoimmunity.[14,93] Of particular relevance to systemic sclerosis is the cytomegalovirus (CMV), which has been shown to infect endothelial cells and macrophages, upregulate fibrogenic cytokines, and induce immune disregulation.[53] Lunardi et al identified a peptide that shares homology with autoantigens (identified in patients with systemic sclerosis) and with the CMV protein UL94.[39] Additionally, immunoglobulin G antibodies against the peptide from the sera of patients with systemic sclerosis specifically recognized the CNV protein UL94 and autoantigens, and such antibodies induced endothelial cell apoptosis. Hence, this study demonstrated that antibodies against CMV cause apoptosis of endothelial cells, a pathological process considered to be the initial pathogenic event of systemic sclerosis.[68]

At the onset of clinically apparent skin lesions, there is an inflammatory phase that is characterized by tissue infiltration by T-cells, macrophages, mast cells and B-cells,[30,55] and the release of fibrinogenic cytokines.[34,35]

Hasegawa et al have produced a model linking systemic autoimmunity and tissue fibrosis in SSc and TSK/+ mice (tight skin heterozygous mice – genetic model for SSc).[23] This model is illustrated in Figure 1 and described subsequently.

B-cell signaling is regulated by response regulators that augment or diminish B-cell signals during response to self and foreign antigens. Of the regulators, CD19 is a critical cell surface signal transduction molecule and it is the most potent positive response regulator. Transgenic mice, which overexpress CD19 by approximately threefold, lose tolerance, and generate autoantibodies spontaneously.[78] In SSc patients, B-cells have been shown to overexpress CD19 and are chronically activated.[65] This chronic activation is believed to result in two important processes detected in SSc patients; firstly, these cells produce auto-antibodies (as a result of breakdown of peripheral tolerance). Indeed, loss of CD19 in TSK/+ mice (which have significantly elevated serum levels of autoantibodies) completely abrogates production of these antibodies. Secondly, they secrete cytokines (e.g., transforming growth factor β (TGFβ) and interleukin 6 (IL-6)), which are potent stimulators of tissue fibrosis and differential activation of T-cells (see subsequent discussion).[23]