

Modern Pathogenetic Mechanisms of Systemic Scleroderma

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Summary: Systemic scleroderma is a chronic and often progressive autoimmune inflammation of the connective tissue, characterized by fibrosis of the skin and internal organs, widespread vascular lesions with unknown etiology, and heterogeneous clinical manifestations. Systemic scleroderma is a violation of the synthesis and accumulation of collagen in the skin (scleroderma) and other internal organs, especially in the connective tissue of the lungs, gastrointestinal tract (gastrointestinal tract), heart and kidneys. Over time, patients develop signs of a progressive structural and functional impairment of blood vessels and internal organs due to fibrosis. This review article presents current data on the pathogenetic mechanisms of systemic scleroderma.

Key words: Systemic scleroderma, antinuclear antibodies (ANA), T cells, Raynaud's syndrome, connective tissue growth factor

Systemic scleroderma is a disease characterized by systemic escalating immune inflammation of the connective tissue and fibro-sclerotic and widespread vasospastic disorders in the skin and subcutaneous tissue, internal organs, i.e. obliterative endarteriolitis [10, 28, 29, 28]. Although the concept of scleroderma in general was first described by Lusitanus in 1634 [4, 32], the term "scleroderma" was first used by Gintrak in 1847 [32]. Although the term "systemic progressive sclerosis" is widely used abroad [22], it is now widely accepted as "systemic scleroderma". For many years, scleroderma was considered only a skin disease, and the changes in the internal organs that determine the end of the main disease were overlooked by doctors. Matsui in 1924 [31], in turn, described a widespread degenerative-sclerotic process in connective tissue associated with obliterative disorders in arterioles. The phenomenon shown by the French neurologist Maurice Raynaud in 1862 in a patient and later named Raynaud's disease was actually a symptom associated with vasospastic changes occurring in 96% of systemic scleroderma - Raynaud's syndrome, without knowing it [30]. In fact, in practice and in many literature data [2, 12, 16, 30, 24, 19, 23] it is confirmed that "Raynaud's syndrome" in systemic scleroderma is one of the main symptoms of the disease.

In the modern world view of this disease, scientists confirm that the main causes of it, as well as a complex process underlie its pathogenesis [16]. Currently, the causes of systemic scleroderma, that is, the etiology, are unclear. But according to some scientists [29, 19, 28], both endogenous and exogenous factors play a role in the origin of this disease. According to these theories, toxins cause immune responses by damaging the vascular endothelium, leading to vascular inflammation and tissue sclerosis. Indeed, according to studies cited in the literature, fibrosis occurs in the tissues of patients with prolonged contact with polyvinyl chloride [16]. According to the proponents of the effect of infectious factors [17, 18, 28, 24], an immune mechanism develops in the body due to the virus, that is, immune complexes formed due to antibodies, antigens and complements, without elimination, settle in susceptible tissues and lead to immune inflammation. According to information in the literature [12], factors such as vibration in their profession, long contact with chemicals, dust and long exposure to cold also play an important role in patients suffering from systemic scleroderma. But another group of scientists emphasizes the importance of genetic predisposition in the origin of systemic scleroderma [20, 12]. According to data [14, 16, 23], Ag HLA-10, -V35, -Cw4 association is observed in the genes of patients with systemic scleroderma. In the research of another group of scientists who studied the genetic aspects of the problem [15, 27, 18], 90% of patients with systemic scleroderma show changes in chromosomes: chromatid breaks, edge and circle fragments of chromosomes. In conclusion, diffuse sclerosis occurs in connective tissues as a result of pathological reactions in the immune system under the influence of certain exogenous and endogenous factors in genetically predisposed individuals.

It is known that the main three processes in the pathogenesis of systemic scleroderma: metabolism, immune disorders and vascular changes attract the attention of scientists. Given this, what processes occur in

metabolism? Metabolic disorder is mainly observed in collagen and its components [32, 17, 29, 24]. Fibrosis is the central process in this joint, and the increased activity of fibroblasts and other collagen-forming cells (including smooth muscle cells in the vessel wall) in the synthesis of collagen, fibronectin, biopolymers - proteoglycan and glycoprotein [16, 32, 13, 19, 23]. According to other available literature sources [26, 28, 25], there is an organic connection between fibroblasts and immunocomplex cells, that is, lymphokines and monokines are involved in controlling the functional activity of fibroblasts. Therefore, in the pathogenesis of systemic scleroderma, the increased functional activity of fibroblasts and other collagen-forming cells with a non-stop phenotypic character takes a leading role, which leads to the exacerbation of the pathological process. Also, the role of the autoimmune mechanism in the development of such a fibrosis process is large, that is, the increase in the synthesis of incompletely formed collagens due to the increase in the functional activity of fibroblasts is foreign to the body [12, 18, 16]. This, in turn, causes the appearance of "collagen" autoantigens. According to the information in the literature [21, 13, 14, 25, 18], autoantibodies appear at the expense of those autoantigens, which lead to the renewal of immune complexes. According to the evidence of the established medicine, the detection of antinuclear factor in 90% of the patients under observation indicates the involvement of the autoimmune process in the pathogenesis of systemic scleroderma [17, 31, 25]. In addition, T-cells of immunity in the blood: the total amount of T-lymphocytes and their subpopulations - T-suppressor, T-helper decrease, found their place in the research of scientists [31, 30, 1, 28]. The increase of circulating immune complexes and autoantibodies in the blood is mainly the result of T-cell deficiency of immunity [18, 26, 28, 19]. Because the lack of T-cells plays a key role in the development of the autoimmune process.

Changes in blood vessels are one of the directions of great importance in the pathogenetic process of systemic scleroderma. As mentioned above, increased functional activity of fibroblasts leads to a specific pathological process in the vessel (endoarteriolitis): microcirculation disorder - changes in serum and cell properties in the blood. According to literature reports [29, 17, 19], the cytotoxic effect of blood increases in this process. As a result, blood solubility increases, collagen synthesis increases, and damage to endothelial cells increases. Therefore, their place is filled by collagen-synthesizing smooth muscle cells, vascular wall hyperplasia and spasms occur [8, 3, 18]. In this process, damage to the vascular endothelium leads to adhesion and aggregation of elements in the blood - leukocytes, erythrocytes, and platelets, that is, blood stasis, intravascular coagulation, and microthrombosis processes take their place [16, 14, 28, 19, 31]. These, in turn, are represented by Raynaud's phenomenon in the clinic of systemic scleroderma [17, 13]. Other scientists who have studied this problem have stated [32, 25, 16, 25] that disturbances in microcirculation flow are the result of changes in immunogenesis. According to the evidence of these scientific works, the formed immune complexes damage the humoral joint of the immune system, especially the vascular endothelium of the compliment system, in the process of settling (fixation) in prone areas. The interaction of immune complexes with the special receptors of platelets in the blood leads to the activation of platelet aggregation properties and blood clotting [4, 7, 14]. Of course, in this case, there is the release of biologically active substances into the blood, its swelling and thickening due to plasmatic absorption into the vessel wall, and the deposition of fibrin [13, 6, 18]. Therefore, intravascular narrowing, microcirculation disturbance, platelet adhesion and damage to the vessel wall, in turn, stimulate the migration of "substitute" factors: smooth muscle cells to the vascular intima [7, 27, 19]. In this case, as mentioned above, due to the proliferation of cells, fibroblasts' ability to synthesize collagen increases, and too much secreted collagen leads to perivascular fibrosis [32]. During the phagocytosis of immune complexes, the adhesive property of neutrophils increases, that is, they have a greater chance of sticking to the vessel wall, continuing the inflammatory process [30, 5, 16]. Degranulation of neutrophils during phagocytosis of immune complexes causes the release of lysosomal enzymes. As a result, the basement membrane is damaged, and its remnants turn into autoantigens. This condition ensures the re-emergence of autoantibodies and immune complexes [26].

So, at the end of the conclusion, it can be noted that the pathogenesis of systemic scleroderma includes three main mechanisms: fibrosis, autoimmune process, and angiopathy, due to the functional activation of fibroblasts. But in recent years, scientists have been interested in the interdependence of the mentioned three processes, the problem of their sequence. It is known that in systemic scleroderma, the main clinical manifestation is the continuous synthesis of low-quality collagens by fibroblasts, which leads to the

escalation of the sclerotic process in the skin and internal organs. But collagens themselves also have antigenic properties, and this, in turn, is a driving factor for the development of the autoimmune process. Also, vascular changes are associated with specific disorders of both immune and smooth muscle cells. The pathological changes that we have considered can be thought of as a "chain ring" process. However, the important processes mentioned above do not answer all the questions you want. The reason is that autoimmune diseases are more common in women. According to data [11, 8], autoimmune thyroiditis is 40 times more common in women compared to men, systemic lupus erythematosus is 9 times more common, rheumatoid arthritis and Sjögren's disease are 3 times more common. In particular, women suffer from systemic scleroderma 3 times more than men [31], according to some data [3], 6 times more often. This situation, in turn, attracts attention to gender differences in the pathogenesis of the disease.

In scleroderma, connective tissue growth factor (CTGF), also known as SSN2, is a small secreted protein of the SSN family of three original members, including cysteine-rich (Syr61/ SSN 1), STGF / SSN2, overexpressed in nephroblastoma /SSN 3) STGF is a cysteine-rich extracellular matrix protein composed of four domains or modules. This protein, like other members of the SSN family, contains four different structural modules: an amino terminal insulin-like domain that binds growth factor; cysteine-rich domain; and the carboxyl domain of the terminal cystine node stimulates the synthesis of STGF, a growth factor-like profibrotic cytokine discovered in 1991. Connective tissue growth factor regulates various cellular functions, including the proliferation, migration, adhesion, differentiation and synthesis of extracellular matrix proteins in various types of cells, as well as participates in angiogenesis, chondrogenesis, osteogenesis, wound healing, fibrosis and other more complex biological processes. An increase in STGF is primarily observed in pathological conditions associated with fibrosis. As an extracellular matrix protein, connective tissue growth factor is thought to integrate various extracellular signals into complex biological responses. The importance of STGF in various fibrosis-related diseases is being actively studied by world scientists, including the fact that this protein plays an important role in the process of fibrosis in lung and heart diseases. However, studying the role of this protein in the process of skin fibrosis in systemic scleroderma is one of the most pressing issues today.

In conclusion, it can be noted that the main morphological unit of systemic scleroderma is the uncontrolled synthesis of collagens by fibroblasts, resulting in fibrosis in the skin, blood vessels, and internal organs. This, in turn, is related to immunogenesis disorder, and the autoimmune process is its basis.

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