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# Early Systemic Scleroderma – A Modern Diagnostic Algorithm

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**Annotation:** Systemic connective tissue diseases encompass a group of chronic disorders affecting the connective tissues of the body, with systemic scleroderma (SSD) being one of the most severe forms. SSD is characterized by progressive fibrosis, which involves excessive collagen deposition in the skin and internal organs, leading to functional impairment and tissue damage. This disease also results in significant vascular abnormalities, including Raynaud's syndrome, as well as immune system dysregulation, manifesting in autoantibody production. The clinical course of SSD is often aggressive, with multiple organ involvement such as the lungs, heart, and kidneys. Patients may experience a range of complications, including pulmonary fibrosis, hypertension, and renal crisis. Given the disease's complexity, early diagnosis and a multidisciplinary treatment approach are essential to improve outcomes and manage symptoms. Current therapeutic strategies focus on symptom management, preventing further organ damage, and improving quality of life for those affected.

**Keywords:** Systemic scleroderma, connective tissue disease, Raynaud's syndrome, fibrosis, immune system, organ damage, vascular abnormalities.

## INTRODUCTION

Systemic scleroderma (SSD) is a prominent representative of the scleroderma group of diseases, united by the sign of excessive fibrosis formation. This group also includes focal scleroderma, diffuse eosinophilic fasciitis, Buschke's scleroderma, induced scleroderma, paraneoplastic or tumor-associated scleroderma, some genetically determined diseases, scleroderma-like syndromes in metabolic diseases, skin lesions in chronic transplant rejection reaction ("adjuvant" disease), IgG4-associated systemic diseases (including multifocal fibrosis), etc. [1].

SSD (according to ICD-10 – progressive systemic sclerosis, M34.0) is a multi-organ disease that progresses in stages with characteristic vasospastic vascular reactions and progressive generalized vasculopathy with ischemic disorders, in which specific autoimmune disorders develop, accompanied by the activation of fibrosis formation with excessive deposition of collagen and other components of the extracellular matrix in tissues.

The pathogenesis of SSD is schematically represented as a complex multi-stage process, apparently beginning with microvascular damage [2, 3]. Already in the early stages of the disease, generalized vasculopathy is observed, the progression of which leads to fibrous hyperplasia of the intima, adventitial fibrosis, severe narrowing and/or obliteration of vessels and subsequent ischemia [4, 5]. It is assumed that damage to the endothelium of microvessels is associated with autoimmune and inflammatory reactions [2, 5]. A direct and indirect consequence of these processes is the activation of fibroblasts, a key event in the development of fibrosis [3, 6]. Activated fibroblasts in damaged tissues are transformed into myofibroblasts, which begin to synthesize extracellular matrix proteins in excess, which ends in fibrosis of tissues and organs. Thus, the staged course of SSD naturally leads to the development of irreversible widespread fibrotic changes, which determine high disability of patients and a generally poor prognosis for the disease.

SSD as an independent nosological entity related to systemic autoimmune rheumatic diseases is characterized by great clinical and pathogenetic heterogeneity. There is no generally accepted classification of SSD, while the classifications of the disease in different countries have much in common [1, 7, 8].

The entire diversity of clinical variants of SSD is reduced to several main forms:

1. Diffuse scleroderma.
2. Limited scleroderma, including the so-called CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal hypotension, sclerodactyly, telangiectasia).
3. Scleroderma without scleroderma (lesion of visceral organs only) is a rare form of the disease, which is diagnosed in approximately 2% of cases.
4. Cross forms, when SSD is combined with rheumatoid arthritis, systemic lupus erythematosus, inflammatory myopathies, etc. Thus, the term “Overlap syndrome”, which is widespread abroad, means a combination of nosologically independent diseases in a patient that satisfy the existing criteria for their diagnosis.

A more detailed classification of SSD was proposed by N.G. Guseva [4]. This classification includes, in addition to the above-mentioned clinical forms, juvenile SSD with the onset of the disease before the age of 16. Juvenile SSD is a rare disease of childhood. Among adult patients with SSD, the frequency of the juvenile form is estimated at 1.5–11.5%. The spectrum of clinical manifestations of the disease is similar to that in adults, but there are certain differences. Visceritis occurs as often as in adults and determines the prognosis of the disease, but in general the prognosis is better than in adults: 5-year survival is 95% [9]. The domestic classification of SSD also includes the definition of the nature of the course and rate of progression (acute rapidly progressive, subacute moderately progressive and chronic slowly progressive) and the stage of the disease

(initial, generalized and late, or terminal) [10]. Specification of all three parameters of the domestic classification – clinical form, course variant and stage of the disease – is important for diagnosis, selection of a therapeutic program and determination of the prognosis [3]. It is important that in SSD the formation of visceral pathology and the nature of the course of the disease are determined at an early stage, the duration of which depends on the rate of progression of the disease [11].

Different forms of SSD differ significantly in the mechanisms of development of pathological reactions, clinical manifestations and prognosis.

Already at the onset, there are clear differences between these forms of SSD [11]. Thus, in diffuse SSD (dSSD), the polysyndromic picture of the disease, including characteristic skin lesions, Raynaud's syndrome, joint manifestations, is formed already in the first 3-6 months of the disease, in 2/3 of patients such general symptoms as fever and significant weight loss are observed. Active formation of the symptom complex of the disease, including visceritis, occurs quickly, and the diagnosis can be established already in the first year of the disease. In the limited form (lSSD), the onset of the disease is monosymptomatic, manifested by a long-term, often many-year Raynaud's phenomenon, and the first symptoms of skin lesions of the hands and face appear on average 5 years after the onset of Raynaud's syndrome. Ischemic and trophic changes in the fingers (scars and ulcers, decreased volume of soft tissues of the distal phalanges, osteolysis), moderately expressed sclerotic lesions of the internal organs gradually join. The full picture of the disease is formed on average 3–5 years after the appearance of the first “non-Raynaud’s” symptom.

A definitive diagnosis of SSD is currently established based on the preliminary classification criteria proposed by the American College of Rheumatology (ACR) in 1980, i.e., more than 30 years ago [16]. According to these criteria, a definitive diagnosis of SSD is established in the presence of a major criterion or at least two minor criteria. The major criterion is proximal scleroderma, i.e., typical scleroderma skin changes (hardening, thickening) observed proximal to the metacarpophalangeal and metatarsophalangeal joints and also involving other parts of the extremities, face, neck, or trunk (chest or abdomen); these changes are usually bilateral and symmetrical. The minor criteria include only three signs: sclerodactyly, ischemic digital scars, and bilateral basal pulmonary fibrosis (on chest X-ray). When creating these criteria, patients with a detailed, vivid clinical picture of the disease were analyzed, allowing to distinguish SSD from other diseases. It is known that approximately 20% of patients with SSD (mainly with a limited form) do not meet these criteria. Being aimed at identifying a detailed picture of the disease, the criteria practically do not identify early stages, the most promising in terms of therapy. When using these criteria, the diagnosis is often delayed.

The difficulties in diagnosing SSD are often objective in nature and are primarily related to the fact that Raynaud's syndrome, a marker of SSD, which occurs in 90-95% of patients, can occur in isolation for a long time, preceding the development of other clinical manifestations of the disease, especially in the limited form. The development of characteristic clinical symptoms in some patients occurs gradually, and visceral pathology may be absent even during the period of skin manifestations. At the same time, it is this time interval - between the onset of Raynaud's syndrome and the first "non-Raynaud" symptom of SSD - that is essentially the "window of therapeutic opportunity" when it is possible to stop the progression of the process and prevent irreversible sclerotic damage. However, to establish a diagnosis of SSD and determine adequate therapeutic approaches at this initial stage of the disease, the existing ACR criteria are insufficient. Attempts to create criteria aimed at a more adequate and early diagnosis of SSD have been repeated many times and are ongoing.

One of the approaches to early diagnosis of SSD consisted of prospective observation of patients with Raynaud's phenomenon. Raynaud's phenomenon is a polyetiological peripheral vascular vasospastic disease, which is based on episodes of vasoconstriction of digital arteries, precapillary arterioles and cutaneous arteriovenous shunts under the influence of cold temperature and emotional stress, apparently associated with a defect in the central and local mechanisms of

vascular tone regulation. An attack of vasospasm occurs in three phases - pallor, cyanosis and hyperemia, which successively replace each other. The frequency of Raynaud's phenomenon in the population is approximately 5-10%. In most cases, it is benign, not affecting the prognosis of life (the so-called primary phenomenon, or Raynaud's disease). At the same time, this phenomenon is often associated with a number of different diseases, including rheumatic diseases (systemic lupus erythematosus, mixed connective tissue disease, rheumatoid arthritis with systemic manifestations, dermato/polymyositis, etc.) and is "secondary" to the underlying disease, i.e. a syndrome of a certain disease. The algorithm for differential diagnostics of primary and secondary Raynaud's syndrome is the subject of publications that detail the examination scheme for such patients [17–19]. Dynamic observation of patients with Raynaud's phenomenon in terms of "waiting" for the development of a systemic rheumatic disease (RD) confirmed the pattern of RD occurrence in a number of patients, but turned out to be very labor-intensive, expensive, and ineffective. Thus, the evolution of primary Raynaud's phenomenon into secondary, associated with different RD, occurred only in 14.9% of cases during prospective observation of 236 patients for an average of 11 years [20]. At the same time, the annual transformation of the primary phenomenon into a secondary one occurred in only 1% of cases. A meta-analysis of 10 studies in which patients with Raynaud's phenomenon were prospectively (on average, 4 years) observed, its secondary nature, i.e. association with systemic diseases, was shown in 13% of cases with an average observation period of 4 years [21]. It has long been obvious that it is necessary to search for additional informative parameters on the basis of which a physician can suspect SSD in patients with Raynaud's phenomenon who do not have clinical signs of systemic RD.

The accumulated knowledge on the specificity of the capillaroscopic picture in SSD and the features of autoimmune shifts formed the basis for new classification criteria for SSD proposed in 2001 [29]. These criteria, along with such well-characterized skin forms as diffuse and limited, also included the earliest stage, when skin manifestations have not yet developed and a specific clinical form has not yet formed. The authors called this initial stage of SSD development "prescleroderma", or unclassifiable (by form) SSD, and for its detection they included new diagnostic parameters for the first time - "scleroderma" capillaroscopic picture and detection of SSD-specific autoantibodies.

Variant of classification criteria for SSD according to E.C. Le Roy, T.A. Medsger [29]

1. Limited systemic sclerosis: unclassifiable SSD, or "pre-scleroderma" (unclassible/pre-scleroderma).
2. Limited cutaneous systemic sclerosis.
3. Diffuse cutaneous systemic sclerosis.
4. Diffuse fasciitis with eosinophilia: proximal skin changes without criteria 1 and 2.

## Conclusion

Early SSD is a period of active formation of the clinical symptom complex and is characterized by high immunological activity and characteristic vascular changes. The initial stages of the disease are potentially reversible, so early SSD is the most promising for achieving the maximum effect using modern therapy, since modern methods of pharmacotherapy are effective only in the early stages of the disease [11, 31]. Approaches to antifibrotic therapy are still in the realm of hypotheses and experimental studies [2].

Since practical medicine does not yet have effective antifibrotic agents, the main really available goal of treating SSD is currently to prevent the development of fibrosis [33]. For this purpose, basic agents are used that act in the early stages of immune inflammation. Thus, early diagnosis determines therapeutic tactics, which can be quite successful using currently available antirheumatic drugs and improve the prognosis. It has been proven that improving the quality of life, as well as reducing the severity of the course and mortality of patients with SSD is possible

with timely detection of damage to internal organs using modern therapy with glucocorticoids and immunosuppressants aimed at suppressing damaging processes in the lungs, blood vessels, and kidneys [13]. Therefore, it is necessary to organize training for primary care physicians to identify the earliest signs of scleroderma ("red flags") in order to ensure timely referral of patients to specialized rheumatology clinics.

**LITERATURE**


1. Гусева Н.Г. Системная склеродермия. В кн.: Ревматология. Национальное руководство. М., 2008;447–66.
2. Varga J., Abraham D. Systemic sclerosis: a prototypic multisistem fibrotic disorder. J Clin Invest 2007;117:557–67.
3. Hunzelmann N., Brinckmann J. What are the milestones in the pathogenesis of systemic sclerosis? Ann Rheum Dis 2010;69(Suppl. I): i52–i56.
4. Гусева Н.Г. Системная склеродермия. В кн.: Я.А. Сигидин, Н.Г. Гусева, М.М. Иванова. Диффузные болезни соединительной ткани. М.: Медицина, 2004;343–487.
5. Sakkas L.I., Chikanza I.C., Platsoucas C.D. Mechanisms of disease: the role of immune cells in the pathogenesis of systemic sclerosis. Nat Clin Pract Rheumatol 2006;2:679–85.
6. Abraham D.J., Krieg T., Distler J., Distler O. Overview of pathogenesis of systemic fibrosis. Rheumatology 2009;48(Suppl.):iii3–iii7.
7. Wigley F.M., Hummers L.K. Clinical features of systemic sclerosis. In: Rheumatology. Eds: M.C. Hochberg, A.J. Silman, J.S. Smolen et al. 3rd ed. Philadephia: Mosby, 2003;1463–5.
8. Medsger T.A. Classification, prognosis. In: Systemic sclerosis. Eds: P.J. Clements, D.E. Furst. 2nd ed. Baltimore: Lippincott Williams&Wilkins, 2004;7–22. 9. Scalapino K., Arkachaisri T., Lukas M. et al. Childhood onset systemic sclerosis: classification, clinical and serologic features, and survival in comparasion with adult onset disease. J Rheumatol 2006;33:1004–13.
9. Гусева Н.Г. Системная склеродермия и псевдосклеродермические синдромы. М.: Медицина, 1993;13–25.
10. Гусева Н.Г. Системная склеродермия: ранняя диагностика и прогноз. Науч-практич ревматол 2007;1:39–46.
11. Wollheim F.A. Classification of systemic sclerosis. Vision and reality. Rheumatology 2005;44:1212–6.
12. Nihtyanova S.I., Tang E.C., Coghlan J.G. et al. Improved survival in systemic sclerosis in assiciated with better ascertainment of internal organ disease: a retrospective cohort study. QJM 2010;103:109–15.
13. Al-Dhaher F.F., Pope J.E., Quimet J.M. Determinants and mortality of systemic sclerosis in Canada. Sem Arthr Rheum 2010;39(4):269–77.
14. Hudson M., Thombs B., Baron M. Time to diagnosis in systemic sclerosis: is gender a factor? Arthr Rheum 2007;56(Suppl.):487.
15. Spenser-Green G. Outcomes in primary Raynaud phenomenon: a meta-analysis of the frequency, rates, and predictors of transition to secondary diseases. Ann Intern Med 1998;158:595–600.
16. Maricq H.R., Gordon G., Le Roy E.C. Studies in patients with connective tissue disorders. Bibl Anat 1977;16(Pt 2):135–41.
17. Maricq H.R. Widefield capillary microscopy: Technique and rating scale for abnormalities seen in scleroderma and related disorders. Arthr Rheum 1981;24:1159–65.

18. Maricq H.R., Harper F.E., Khan M.M. et al. Microvascular abnormalities as possible predictors of disease subsets in Raynaud phenomenon and early connective tissue disease. Clin Exp Rheumatol 1983;1:195–205.
19. Najmiddinov A., Ibragimova N., Muxitdinova G. SILIKOZ PATOGENEZIDA KREMNIY DIOKSIDI VA YALLIG‘LANISH MEDIATORLARINING O‘RNI //Евразийский журнал медицинских и естественных наук. – 2023. – Т. 3. – №. 12. – С. 63-77.
20. Шодикулова Г. З., Мухитдинова Г. З., Атоев Т. Т. ОЦЕНКА СОСТОЯНИЯ ЦЕНТРАЛЬНОЙ ГЕМОДИНАМИКИ У БОЛЬНЫХ С ХРОНИЧЕСКИМИ БОЛЕЗНЯМИ ПОЧЕК В САМАРКАНДСКОМ РЕГИОНЕ //Достижения науки и образования. – 2021. – №. 8 (80). – С. 59-63.
21. Zikriyayevna S. G., Zoxirovna M. G., To’raqulovna Q. S. PREVENTION OF CHRONIC KIDNEY DISEASE AND CHRONIC HEART FAILURE //Spectrum Journal of Innovation, Reforms and Development. – 2022. – Т. 4. – С. 408-414.
22. Zikiryayevna S. G. et al. Kidney Damage in Patients with Chronic Cardiac Insufficiency and Obesity //Texas Journal of Medical Science. – 2022. – Т. 13. – С. 72-78.
23. Bozorova Chekhroza Sodik kizi , M. G. Z. . , K. T. A. U. . ,. (2024). Clinical and Immunological Features of the Diffuse Form of Systemic Scleroderma. American Journal of Pediatric Medicine and Health Sciences (2993-2149), 2(3), 433–436. Retrieved from https://grnjournal.us/index.php/AJPMHS/article/view/4018
24. Zohirovna, M. G. (2024). Changes in the Structural and Functional State of Myocardium in Patients with Chronic Kidney Disease at Different Stages of Development. *International Journal of Alternative and Contemporary Therapy*, *2*(5), 73–76. Retrieved from https://medicaljournals.eu/index.php/IJACT/article/view/321