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# Early Diagnosis of Systemic Scleroderma

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**Annotation.** Systemic scleroderma (SSD) is an autoimmune disease, which is based on generalized microangiopathy and activation of the processes fibrosis of the skin and internal organs. Most patients develop visceral complications, which usually cause death. SSD are often diagnosed late, when pathological changes in organs are irreversible, and treatment is less effective. At the same time, the results of a large study showed that the mortality rate of patients with SSD reaches 68 per 1000 people per year. So, timely diagnosis of SSD is a difficult, but very important task for a doctor.

**Keywords:** Systemic scleroderma, diagnosis, Raynaud's syndrome, sclerodactyly.

Systemic scleroderma (SSc) is a general microangiopathy, as well as an autoimmune disease based on the activation of fibrotic processes in the skin and internal organs. In the early stages, the disease manifests itself as severe swelling of the fingers and skin changes in the form of Raynaud's syndrome, but the patient may not show signs of deterioration or damage to internal organs (dysphagia, shortness of breath, etc.), so patients often do not seek medical help ahead of time. In this regard, systemic scleroderma is often diagnosed late after the onset of irreversible pathological changes in organs and with ineffective treatment. According to Canadian researchers, the diagnosis of systemic scleroderma in 408 patients was established 6 years after the development of Raynaud's syndrome and 2.7 years after the onset of primary “cutaneous manifestations” [21]. In Russia, systemic scleroderma was diagnosed 2.0-2.7 years after Raynaud's syndrome, and with diffuse and limited forms of the disease - 4.8-6.5 years, depending on the degree of damage to various internal organs, as well as the rate of development of the disease [ one]. However, the results of a large study show that the mortality rate of patients with this disease is 68 out of 1000 patients per year. [36]. Thus, the timely diagnosis of systemic scleroderma is a difficult but very important task for a doctor.

Systemic scleroderma is currently being actively studied within the framework of the EUSTAR (European League Against Rheumatism Scleroderma Trials and Research Group) project. (31)

Epidemiology and risk factors. Women with systemic scleroderma are more susceptible to infection than men (3: 1); most patients are between the ages of 25 and 50. The incidence of the disease varies from region to region. In Northern Europe and Japan, the incidence is less than 10 per 1 million populations per year, and in Southern Europe, North America and Australia - 14–21 per 1 million populations per year [11]. The prevalence of the disease among African Americans, American Indians, Australians and Japanese is higher than among Europeans and the white population of the United States [29].

Several genes involved in the regulation of immune system activity have been shown to increase the risk of developing systemic scleroderma, including BANK1, C8orf13-BLK, IL-23R, IRF5, STAT4, TBX21, and TNFSF4 [7]. Also the role of potential epigenetic mechanisms and environmental factors, including silica dust, organic solvents, drugs (bleomycin, carbidopes, etc.), pesticides, rapeseed oil, cocaine [25].

The etiology of SJS is not fully understood. The development of the disease can occur due to a genetic predisposition along with the influence of negative exogenous and endogenous factors. There is a wealth of data attempting to link the occurrence of SJS with various triggers such as infection, chemical agents, stress, neuroendocrine shifts, trauma, vibration, cooling, and so on.

Metabolism of collagen types I and III and other components of connective tissue play a key role in the pathogenesis of the disease due to dysfunction of fibroblasts and smooth muscle cells of the vascular wall. Vasoconstructive stimulation (cold, emotions, thromboxane A2, serotonin) leads to further vasoconstriction and the formation of Raynaud's phenomenon in the skin and internal organs. Damage to the renal vessels stimulates the renin-angiotensin system and leads to the formation of vasoconstriction. The activated platelets release factors that increase vascular permeability and procoagulant factors. Fibrosis of tissues is the result of contact of fibroblasts with interstitial tumors.

Clinic. There are two main forms of SSD - diffuse and limited. In a limited form, skin thickening is located in the distal region from the elbow and knee joints, while in a diffuse form, skin changes can be found in the trunk, thighs and shoulders (facial skin lesions occur in both forms). The differences between the two forms of the disease are not limited to the spread of the skin process, but the diffuse form is also characterized by frequent damage to internal organs and a more rapid progression of the disease. If the 10-year survival rate for the diffuse form of the disease is 65%, then for the limited form this figure reaches 92% [9].

Raynaud's phenomenon. Raynaud's phenomenon occurs in 95% of patients with systemic scleroderma and is usually the first sign of the disease [19]. Clinically, it has two, and sometimes three stages - whitening, cyanosis and redness of the skin of the fingers, which develops under the influence of cold, can also be accompanied by pain syndrome [13]. Primary Raynaud's syndrome differs from Raynaud's phenomenon in SJS in that changes in video-capillary microscopy of the nail base, antinuclear antibodies, signs of ischemic tissue damage (gangrene, wounds, scars), and normal ECG are not detected [41].

Damage to the skin. Another symptom of SJS is skin damage that develops in three stages: edema (eg, severe swelling of the hands), thickening (eg, sclerodactyly), and atrophy. At the first stage, there is a decrease in the elasticity of the skin and tissues and dense edema, then "scleroderma" is formed, and at the stage of atrophy, the skin becomes thinner and becomes bluish-brown, a kind of shine, hair loss appears. [8]. The number of "cysts" (radial folds around the mouth) and telangiectasias increases [16]. Ischemic skin damage due to microvascular injury is common, resulting in lesions in the distal phalanx of the fingers that look like "rat bites" and, in rare cases, like dry necrosis or gangrene [22]. However, there are signs of other SJS-specific skin lesions, such as hypo- and hyperpigmentation, skin calcification [10]. Internal organ damage.

Most patients with SJS (70-98%) develop lesions of the gastrointestinal tract, in particular hypotension of the esophagus, which is manifested by dysphagia and gastroesophageal reflux. Against the background of the development of malabsorption syndrome and slowing down of chyme movement, symptoms such as the proliferation of pathogenic flora, as well as damage to the colon (diarrhea, retention of feces) develop [35]. Local studies have found an association between the severity of gastroesophageal reflux and pulmonary fibrosis [4].

Cardiovascular pathologies and related complications (heart attack, stroke, sudden coronary death) are one of the most common causes of early death in autoimmune rheumatic diseases, despite the constant improvement of diagnostic and treatment methods. Heart damage in SS occurs in 15–35% of cases [33] and manifests itself as heart failure, arrhythmias and pain syndrome [2]. In rare cases,

mitral stenosis develops, including mitral heart failure [23]. In SJS, primary heart disease may be accompanied by changes occurring primarily in the myocardium, pericardium, and heart valves. In some cases, heart damage in patients with SJS develops secondarily after acute renal scleroderma and pulmonary arterial hypertension. In SS, vasculopathy is characterized by a progressive restructuring of microcirculation, which leads to the development of various signs of cardiovascular damage. Endothelial dysfunction specific to SJS and hemorrhagic disorders in SJS are risk factors for the early development of atherosclerosis. Several authors have suggested the existence of a common pathogenetic mechanism of vascular damage in SJS and atherosclerosis [30], and that this process leads to various forms of macro- and microvascular myocardial damage in SJS [27].

One of the main manifestations of SS is vascular lesions, since morphological examination of the skin and internal organs in these patients in all cases reveals signs of angiopathy (vasopathy, vasculopathy) [32]. They manifest themselves in the form of necrosis of the phalanges of the fingers, digital arteritis, chronic kidney disease with changes in the glomerular capillaries and arterioles, damage to the carotid and coronary arteries. It is known that angiopathy in SS leads to impaired microcirculation with organ ischemia [39].

In the first years of the disease, interstitial lung disease is detected in about 75% of patients, which develops gradually and leads to pulmonary fibrosis of varying severity [14]. L.V. Teplova et al. Using high-resolution computed tomography, it was found that 82% of 138 patients with SJS showed signs of interstitial lung lesions [6]. SJS is sometimes characterized by the development of severe pulmonary arterial hypertension (OAG). According to the latest data, 60 of 132 patients with SJS died from complications of pulmonary hypertension on average within 4 years. It is known that the survival rate since the diagnosis of OAS was only 4 (2.2–6.2) years [26]. Pulmonary hypertension in patients with SJS can result from: OAG (including due to the accumulation of collagen in the vascular wall), pulmonary venous occlusive disease and hemangiomatosis of the pulmonary capillaries, left ventricular dysfunction, pulmonary lesions with hypoxemia, chronic thromboembolism [18].

Kidney damage occurs in 19% of patients. In the diffuse form of TSD in 10-15% and in a limited form in 1-2% of cases, the development of an acute crisis of scleroderma with a sharp deterioration in renal function (acute kidney damage) was revealed [37]. For the first time in a scleroderma crisis of the kidneys, blood pressure was 150/85 mm.w. one can suspect that it is higher than. Over the next 24 hours, other parameters were observed, such as an increase in the ball filtration rate by 10% or a decrease in the ball filtration rate (KFT) by 90 ml / min. Additional symptoms of scleroderma renal crisis may include hematuria and proteinuria, sudden pulmonary edema, oliguria or anuria, and, for the first time, retinopathy [34].

Diagnostics. SJS should be considered in all patients with Raynaud's phenomenon. Signs of skin damage (hardening of the skin, cat's mouth symptoms, facial disguise, sclerodactyly, calcification (pigmentation) are important diagnostic points. Symptoms of internal organ damage such as dyspnea and dysphagia should also be considered during the examination. (ACR) and classification criteria developed by experts from the European Anti-Rheumatic Association (EULAR) (Table 1) are used to diagnose SJS.20 It should be noted that the ACR-EULAR criteria are not fully informative in the early or very early stages of SJS. The results of the EUSTAR study showed that that the period between the development of Raynaud's syndrome and other symptoms of SJS averaged 4.8 years for a limited form of the disease and 1.9 years for a diffuse form [40]. This is called a "window of opportunity" for preventing internal organ damage and slowing the progression of the disease. In this sense, criteria for the early diagnosis of systemic scleroderma have been developed (VEDOSS; Table 2) [12]. At the first stage of diagnosis, it is recommended to identify the main symptoms of the disease (the so-called "warning signs"), such as Raynaud's syndrome and severe swelling of the fingers. At the second stage, video capillary microscopy of the nail base is performed and specific antibodies (for example, anticentromeres or topoisomerase-1) are detected [24]. In the very early stages of SJS, there is no internal injury, but in the early stages of SJS there

are signs of subclinical damage such as echocardiography, left ventricular diastolic dysfunction, an initial decrease in lung diffusion capacity <80%, and LESP <15 mmHg. decreases from 0.1 [38].

Table 1. Criteria for the classification of systemic scleroderma

(ACR-EULAR 2013)

| **Criteria** | **Points** |
|---|---|
| Thickening of the skin of the metacarpophalangeal joints of both hands (sufficient criterion) | 9 |
| Thickening of the skin of the fingers (index only)<br>Sclerodactyly of all fingers (on the distal side of the palmar interphalangeal joints and proximally on the interphalangeal joints)<br>Dense swelling of the fingers | 4<br><br>2 |
| Digital ischemia (high score only)<br>Scars<br>Ulcers | <br>3<br>2 |
| Pulmonary arterial hypertension and / or interstitial lung disease | 2 |
| Telangiectasia | 2 |
| Specific antibodies (ACA, anti-Scl-70, anti-RNA pol III) | 3 |
| Raynaud's phenomenon | 3 |
| Changes in capillaroscopy video | 2 |

If the overall score is 9 or higher, the diagnosis is systemic scleroderma. It should be noted that SJS without scleroderma is also present without signs of skin damage (hardening and fibrosis) in the early and late stages of the disease. In this case, the diagnosis is made on the basis of the presence of Raynaud's syndrome, lesions of the fingers, specific antibodies, changes in video capillaroscopy, and damage to internal organs [17]. The disease is also diagnosed with CREST syndrome, that is, skin calcification, Raynaud's syndrome, esophageal motility disorders, sclerodactyly and telangiectasia, as well as the detection of centromeric antibodies. [28]

Among the laboratory and instrumental studies conducted to confirm systemic scleroderma, the following indicators are important:

- the presence of antinuclear (anti-Scl-70) and anticentromeric antibodies;
- Detection of antibodies and anti-nuclear factors against DNA;
- evidence of rheumatoid factor;
- When examining the immune system, a deficiency status and changes in immunoglobulin fractions are observed.
- Conversion of tissue into a fibrous process and the presence of vascular changes in the skin, synovium and muscle biopsy.

Помимо специфических тестов, перечисленных выше, ряд неспецифических показателей системной склеродермии играют важную роль в диагностике заболевания (диспротеинемия, особенно высокий уровень G-глобулина, анемия, лейкопения, повышение ЭКГ, повышение фибриногена), и т. д. Важным лабораторным критерием диагностики ССД является наличие


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этих антител, например, антител к топоизомеразе I (анти-Scl-70), антицентромерных антител (ACA), антител к рибонуклеопротеазе III (анти-РНК). III) исследования показали, что большинство пациентов с ССД (n = 300) имели антиядерный фактор (83,8%) и анти-Scl-70 (50,0%), ACA (14,6%), анти-U1RNP (8,6%). ) Выяснилось, что это пороговое значение III (5,5%)[5]. Различные антитела могут быть связаны с конкретными клиническими проявлениями ССД (таблица 3), поэтому их исследование является не только диагностическим, но и прогностическим).

Table 3. Types of antibodies found in systemic scleroderma

| Autoantitella | Autoantigen | Clinical and laboratory associations |
|---|---|---|
| anti-Scl-70ACA | DNA topoismerase | • Diffuse skin lesions, scars.<br>• X-ray signs of pulmonary fibrosis.<br>High mortality |
| ACA | Centromeric protein | • This is with CREST syndrome.<br>• Occurs with limited skin lesions.<br>• Absence of radiological signs of pulmonary fibrosis.<br>• Protects against scleroderma kidney crisis. |
| anti-RNA pol III | Multiprotein RNA polymerase III complex | • Severe diffuse skin damage.<br>• High incidence of scleroderma kidney crisis. |
| anti-Th/To | Small nucleoproteins, RNA-PAase and myeloid binding protein (mRP) | • Limited skin damage<br>• Interstitial injury and pulmonary fibrosis.<br>• Pulmonary hypertension |
| anti-U3RNP/Fibrillarin | Component complex U3-RNP (U3-RNA, fibrillin, etc.) | Severe course of the disease.<br>• Diffuse skin lesions.<br>• Pulmonary hypertension<br>• Myositis<br>• Injury to the heart |
| anti-U1RNP | Component set (U1-RNP, A, C, B/B, D-G) | Formation of "overlap" syndrome |
| anti-PM/Scl | Exosomal protein complex (Pm-Scl-100, Pm-Scl-75) | Limited skin damage<br>SJS / polymyositis / rheumatoid arthritis cross syndrome<br>• Pulmonary fibrosis |

Changes during video capillaroscopy are of great diagnostic value. Patients with SJS are conventionally divided into the following stages: changes detected by video capillariroscopy of the nail bed: early, active and late. At different stages, changes in scleroderma, giant capillaries, capillary bleeding, a decrease in the number of capillaries or the identification of avascular areas, impaired capillary branching and “branched” capillaries can be detected [15].

**Conclusion.** Early diagnosis of systemic scleroderma is one of the most difficult tasks facing a doctor. After all, early diagnosis of this disease allows you to start treatment in the early stages of the disease, up to pathological changes in internal organs and achieve high results in treatment. To

date, insufficient work has been done on the early detection of this disease, which indicates the need for a deeper study of systemic sclerosis.

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