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SYSTEMIC LESIONS IN SCLERODERMIA

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✓ ***Resume***

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.

СИСТЕМНЫЕ ПОРАЖЕНИЯ ПРИ СКЛЕРОДЕРМИИ

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✓ ***Резюме***

Системная склеродермия (ССД) – это аутоиммунное заболевание, в основе которого лежат генерализованная микроангиопатия и активация процессов фиброза кожи и внутренних органов. У большинства пациентов развиваются висцеральные осложнения, которые обычно становятся причиной смерти. Нередко диагностируют поздно, когда патологические изменения в органах необратимы, а лечение менее эффективно. При этом результаты исследования показали, что смертность пациентов с ССД достигает 68 на 1000 человек в год. Таким образом, своевременная диагностика представляет собой сложную, но очень важную задачу для врача.

Ключевые слова: Системная склеродермия, диагностика, синдром Рейно, склеродактилия.

СКЛЕРОДЕРМИЯДА ТИЗИМЛИ ЗАРАРЛАНИШ

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✓ ***Резюме***

Тизимли склеродермия (ТСД) – умумий микроангиопатия ва тери ва ички органларда фиброз жараёнларнинг фаоллашишига асосланган аутоиммун касаллик бўлиб, кўп ҳолларда беморларда висцерал асоратлардан ўлим ҳолати кузатилади. Тизимли склеродермияда кўпинча органларда қайтмас патологик ўзгаришлар вужудга келгандан сўнг ва даволаниш самарасиз бўлгач, кечикиб ташхис қўйилади. Тадқиқотлар шуни кўрсатадики, мазкур касаллик билан беморларнинг ўлим даражаси йилига 1000 бемордан 68 тани ташкил этади. Тизимли склеродермияни ўз вақтида ташҳислаш шифокор учун мураккаб, аммо жуда муҳим вазифадир. Шуни инобатга олган ҳолда, мазкур мақолада касалликни эрта ташҳислаш мезонлари ҳақида кенг фикр юритилади.

Калит сўзлар: Тизимли склеродермия, ташҳис, Рейно синдроми, склеродактилия.

Relevance

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 in advance. In this regard, systemic scleroderma is often diagnosed late after the appearance 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 sclerosis 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 per 1000 patients annually [36]. Therefore, 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 infections than men [3,1]; most patients are between the ages of 25 and 50. The incidence varies from region to region. In Northern Europe and Japan, the incidence is less than 10 per million inhabitants per year, and in Southern Europe, North America and Australia - 14-21 per million inhabitants per year [11]. The prevalence of the disease is higher among African Americans, American Indians, Australians, and Japanese than among Europeans and whites in the United States [29].

The influence of several genes involved in the regulation of the activity of the immune system on an increase in the risk of developing systemic scleroderma was revealed, 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 CCD is not fully understood. The development of the disease can occur due to a genetic predisposition, coupled with the influence of negative exogenous and endogenous factors. There is a wealth of evidence that attempts to link the occurrence of SSS to various triggering factors such as infection, chemical agents, stress, neuroendocrine changes, trauma, vibration, cooling, and so on.

Metabolism of collagen types I and III and other components of connective tissue plays a fundamental 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 STO - distributed and limited. In a limited form, thickening of the skin is located distal to the elbow and knee joints, while in a diffuse form, skin lesions occur on the trunk, thighs and shoulders (facial 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 reduced 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 SS in that changes are not detected on video-capillary microscopy of the nail base, antinuclear antibodies, signs of ischemic tissue damage (gangrene, wounds, scars), and normal ECG [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 swelling, 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 [16] increases. Ischemic skin damage from

microvascular injury is common, resulting in lesions in the distal phalanx of the fingers that look like "rat bites" and, in rare cases, dry necrosis or gangrene [22]. However, there are signs of other skin lesions specific for SJS, 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 disease. Against the background of the development of malabsorption syndrome and slowing down of the movement of the chyme, symptoms such as the proliferation of pathogenic flora, as well as lesions of the colon (diarrhea, fecal retention) develop [35]. Local studies have found an association between the severity of gastroesophageal reflux disease and pulmonary fibrosis [4].

Cardiovascular diseases 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. Damage to the heart in SS occurs in 15–35% of cases [33] and is manifested by heart failure, arrhythmias and pain syndrome [2]. Rarely, mitral stenosis, including mitral heart failure, develops [23].

With SJS, primary heart disease may be accompanied by changes that occur mainly in the myocardium, pericardium, and heart valves. In some cases, heart damage develops secondary to acute renal scleroderma and pulmonary arterial hypertension in patients with SJS. In SS, vasculopathy is characterized by a progressive restructuring of microcirculation, which leads to the development of various symptoms of damage to the cardiovascular system. SJS-specific endothelial dysfunction and hemorrhagic disorders in SJS are risk factors for the early development of atherosclerosis. Several authors have suggested a general 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 are manifested 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 organic 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. High-resolution computed tomography showed that 82% of 138 patients with SJS had symptoms of interstitial lung disease [6]. SJS is sometimes characterized by the development of severe pulmonary arterial hypertension (PAH). According to the latest data, 60 of 132 patients with SJS died on average within 4 years from complications of pulmonary hypertension. It is known that the survival rate with a diagnosis of PAH was only 4 (2.2–6.2) years [26]. Pulmonary hypertension in patients with SJS can result from PAH (including the accumulation of collagen in the vessel wall), pulmonary vein occlusive disease and pulmonary capillary angioma, left ventricular dysfunction, hypoxemic pulmonary lesions, chronic thromboembolism [18].

Kidney damage occurs in 19% of patients. In the diffuse form of SS 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 crisis of renal scleroderma, blood pressure was 150/85 mm. 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 glomerular filtration rate (GFR) by 90 ml / min. Additional symptoms of renal crisis in scleroderma 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 (skin tightening, cat's mouth symptoms, facial disguise, sclerodactyly, calcification (pigmentation)) are important diagnostic points. During the examination, symptoms of internal organ damage, such as shortness of breath and dysphagia, should also be considered. (ACR) and classification criteria developed by experts from the European Association for Antirheumatica (EULAR) (Table 1) are used to diagnose SJS [20]. It should be noted that the ACR-EULAR criteria are not entirely meaningful in the early or very early stages of STS. The results of the

EUSTAR study showed that the mean time between the development of Raynaud's syndrome and other symptoms of SJS was 4.8 years for the limited form of the disease and 1.9 years for the diffuse form [40]. This is called a "window of opportunity" for preventing internal organ damage and slowing the progression of the disease. possible. 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)	4 2
Sclerodactyly of all fingers (on the distal side of the palmar interphalangeal joints and proximally on the interphalangeal joints)	3 2
Dense swelling of the fingers	2
Digital ischemia (high score only)	2
Scars	3
Ulcers	3
Pulmonary arterial hypertension and / or interstitial lung disease	2

If the total 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 videocapillaroscopy, 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 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.

In addition to the specific tests listed above, a number of nonspecific indicators of systemic scleroderma play an important role in the diagnosis of the disease (dysproteinemia, especially high levels of G-globulin, anemia, leukopenia, increased ECG, increased fibrinogen), etc. An important laboratory criterion for diagnosing SJS is the presence of these antibodies, for example, antibodies to topoisomerase I (anti-Scl-70), anti-centromeric antibodies (ACA), antibodies to ribonucleoprotease III (anti-RNA). III) studies

have shown that the majority of patients with SJS (n = 300) had an antinuclear factor (83.8%) and anti-Scl-70 (50.0%), ACA (14.6%), anti-U1RNP (8 , 6%).) Выяснилось, что это пороговое значение III (5,5%)[5]. Various antibodies can be associated with specific clinical manifestations of SJS (Table 3), therefore, their study is not only diagnostic, but also prognostic.

Table 3. Types of antibodies found in systemic scleroderma

Autoantitella	Autoantigen	Clinical and laboratory associations
anti-Scl-70ACA	DNA topoismerase	• Diffuse skin lesions, scars.
ACA	Centromeric protein	• X-ray signs of pulmonary fibrosis.
anti-RNA pol III	Multiprotein RNA Polymerase III Complex	High mortality
anti-Th/To	Small nucleoproteins, RNA-PAase and myeloid binding protein (mRP)	• This is with CREST syndrome.
anti-U3RNP/Fibrillarin	Component complex U3-RNP (U3-RNA, fibrillin, etc.)	Severe course of the disease.
anti-U1RNP	Set of components (U1-RNP, A, C, B / B, D-G)	• Diffuse skin lesions.
anti-PM/Scl	Exosomal protein complex (Pm-Scl-100, Pm-Scl-75)	• Pulmonary hypertension

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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