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The Importance of Early Diagnosis of Systemic Scleroderma

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ABSTRACT

Systemic scleroderma (SSc) is a progressive and severely debilitating autoimmune disease characterized by inflammation, vasculopathy, and extensive fibrosis. SSc is highly heterogeneous in its clinical presentation and severity of skin and internal organ lesions, and it has also the highest mortality rate among connective tissue diseases. Recently, Raynaud's phenomenon (RP), puffy fingers turning into sclerodactyly, and antinuclear antibody (ANA) positivity are considered the three red flags for the suspicion of a very early SSc. Further signs such as positivity of other specific autoantibodies and/or video capillaroscopy pattern may allow very early SSc diagnosis. No current therapy is able to reverse or stop the natural progression of SSc, which reflects its complex pathogenesis. In our article, we analyzed a clinical case of SSc and modern methods of pathogenetic therapy, substantiating the importance of new diagnostic approaches for the early detection of the disease, and increasing the effectiveness of treatment. An ultrasound examination of the internal organs revealed a change in the structure of the thyroid gland. SSc was diagnosed and the proper medication prescribed. Further diagnosis revealed diffuse form of SSc, and activity of the II degree. Later on, a seroma of the right groin area was diagnosed. After some times, pulmonary arterial hypertension associated with SSc was verified. Revealed signs of fibrosis in the myocardium of both ventricles indicated heart damage. Therefore, Bosentan was prescribed. It was revealed that drugs cannot be canceled and replaced, since even a short-term cancellation of specific therapy for pulmonary arterial hypertension leads to a rapid progression of the disease with the possible development of a fatal outcome.

GRAPHICAL ABSTRACT

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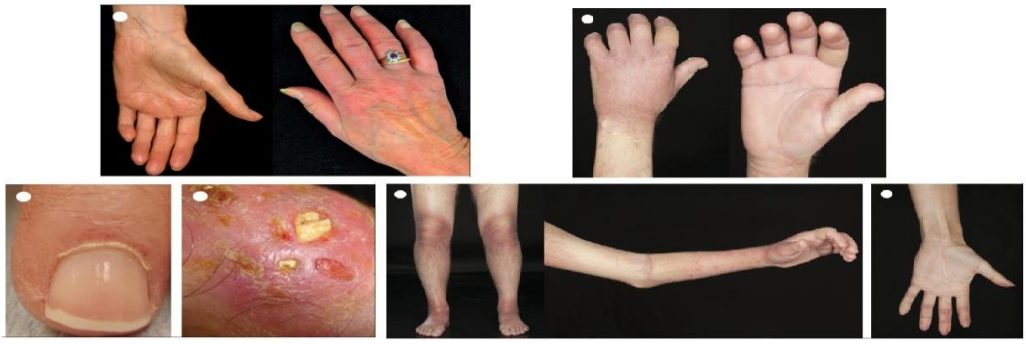

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Introduction

Systemic scleroderma (SSc) is a rare chronic disease of an unknown cause characterized by diffuse fibrosis and vascular abnormalities in the skin, joints, and internal organs (especially the esophagus, lower gastrointestinal tract, lungs, heart, and kidneys). Common symptoms include: RP, polyarthralgia, dysphagia, heartburn, swelling, skin tightening, and fingers contractures. Lung, heart, and kidney involvement accounts for most deaths. Diagnosis is clinical, but laboratory tests support the diagnosis and aid in prognostication. Specific treatment is difficult, and emphasis is often on complications treatment [1–3]. Trigger factors of this pathology are heredity, exposure to low temperatures, vibration, prolonged exposure to chemicals, various infectious agents, and interruptions in the work of the nervous and endocrine systems. This leads to damage to endothelial cells and their apoptosis, provoking vascular depletion, which manifests itself in the early clinical stages in the form of tissue edema. The vascular compartment is further impaired by altered angiogenesis by decreasing the number of endothelial progenitor cells. The release of vasoconstrictor agents exceeds the release of vasodilator agents leading to vascular instability. The affected endothelium is a focus of platelet activation, which leads to the formation of blood clots and reactive oxygen species [4–6].

Adhesion molecules, together with chemokines, are activated by the damaged endothelium to attract leukocytes, which ensures the development of both innate and adaptive immune responses, including loss of tolerance to autoantigens, for instance, topoisomerase I [7,8]. Antibodies against topoisomerase I form immune complexes, are absorbed through Fc-receptors and activate endosomal Toll-like receptors in immune cells, which leads to the production of type I interferon. Antibodies to the stimulating platelet-derived growth factor receptor provoke the production of reactive oxygen species by fibroblasts. Dysregulation of TGF-B and activation of fibroblasts and myofibroblasts promotes excessive the deposition of collagen and other extracellular matrix proteins, which ultimately leads to tissue fibrosis seen in SSc [9].

Autoantibodies in SSc are conventionally divided into 2 groups - specific (characteristic only for this disease) and nonspecific. Specific antibodies are a heterogeneous group of immunoglobulins that bind to nucleic acids and associated proteins of the cell nucleus. These antibodies are antinuclear antibody (ANA) and are found in patients with SSc in 90-95% of cases. In accordance with clinical guidelines [10,11], the ANA identification underlies the SSc laboratory diagnosis, especially at the initial stages of the disease development [12].

SSc in the initial stages proceeds with small signs of the disease. It has been proven that the time between the development of Raynaud's phenomenon (RP) and the onset of more severe symptoms is 3 to 10 years. This period is called the "window of opportunity". Treatment started during this period slows the progression of the disease and prevents more severe symptoms from developing. That is why the early diagnosis of SSc patients is important based on a specific algorithm [13]. RP is the clinical reflection of diffuse microvascular damage in SSc. Occurring in more than 90% of patients, RP often precedes skin and visceral fibrosis by years or decades. Hence, at initial RP presentation, there is a need for novel predictors to help physicians in identifying the patients who are at risk of the SSc development or another connective tissue disease [14].

According to clinical guidelines [15], every physician, regardless of specialization, should suspect SSc when RP is detected in combination with hand edema. Such a patient needs to determine the level of antinuclear factor (ANF) in the blood. Positive ANF, RP, and hand edema are considered "red flags" and are the initial stages of the diagnostic search. As a result, the patient should be referred to an experienced rheumatologist who knows the SSc clinic well [16,17]. At the second stage, the rheumatologist prescribes vidiocapillaroscopy and other specific examination methods: scl 70 and /or ACA and antibodies to RNA polymerase III. If even one of these predictors of SSc is found, the diagnosis of

the early SSc is made. Furthermore, an additional examination is prescribed to identify intraorgan pathologies [18].

For the diagnosis of connective tissue diseases in the regions of the Russian Federation, immunoblotting is often mostly used. The result of autoantibody detection is displayed in crosses for each antigen, and the test itself is semi-quantitative. The increase in the seropositivity level, to some extent, reflects the level and affinity of autoantibodies. This method does not give an idea of the quantitative content of autoantibodies in the blood serum of the patient and is not used in the early stages of the disease [19,20].

For screening autoantibodies in the early SSc diagnosis, the "gold standard" is the indirect immunofluorescence test (IRIF), which is the most accurate, economic, and affordable laboratory test for most medical organizations that does not require expensive laboratory equipment for its implementation. The expediency of this method lies in a quick response, as well as in the availability of a wide range of diagnostic kits. IRIF is carried out by using antiglobulin serum labeled with fluorochrome and is aimed at detecting antigen-antibody-complexes. The obtained IRIF results are evaluated by displaying the highest ANF titer in the studied sera [21]. However, labor-intensive and time-consuming procedures and unsatisfactory reproducibility because of the subjective interpretation of results are considered to be the IRIF drawbacks [22].

The most common substrate for the SSc diagnosis is the HEP-2 cell line culture, which is characterized by a good morphology and an ease of cultivation [23,24]. A fluorescent microscope is used to record the results. The most common and specific for SSc is the granular type of luminescence, in which autoantibodies interact with granules in the nucleus, which are complexes of nucleoproteins. This type is characteristic of such autoantibodies as anti-Ro/SS-A, anti-La/SS-B, antibodies to Scl-70, and antibodies to RNP-70. Centromeric luminescence, observed in the presence of antibodies to chromosome centromeres, is specific for anticentromeric antibodies. This type of luminescence is found only in those cells that are in a division state [25–27].

Using cells of the HEP-2 line, the diagnostic criterion is a titer of 1: 40-1: 80. With such titer values in healthy people, the frequency of weakly positive results is less than 5%, while in people suffering from systemic connective tissue diseases, it is almost impossible to miss significant ANA titers. During the period of SSc exacerbation, ANF titers of more than 1: 640 are recorded, decreasing during the period of remission to 1: 160-1: 320 [28]. In this paper, we looked at a clinical case of SSc and modern pathogenetic therapy methods, demonstrating the usefulness of novel diagnostic methodologies for the early illness detection and treatment efficacy.

Material and Methods

Analysis of a clinical case

Patient G., born in 1976, disabled group II, gas station operator was under observation (2010-2016). Since May 2010, the patient began to notice swelling of the feet and legs, later joined by dense swelling of the hands and face, a decrease in the oral aperture, and polydipsia. She applied to the Central Regional Hospital in September 2010. The general practitioner explained these symptoms as impaired kidney function and prescribed treatment that did not work.

In October of the same year, she turned to an endocrinologist at her place of residence. An ultrasound examination of the internal organs revealed a change in the structure of the thyroid gland. Blood test was done for thyroid hormones (free T3, free T4, and TSH) within normal limits.

Within six months, the patient developed diffuse hyperpigmentation and skin induration, complaints of arthralgia of the hands, difficulty in swallowing solid food, heartburn, fatigue, shortness of breath during exercise (which later appeared at rest), episodes of rapid heartbeat, and interruptions in the work of the heart. Several months later, the umbilical edema and hyperemia with a large amount of pus developed, telangiectasias were noted on the anterior surface of the chest.

In mid-January 2011, the patient again consulted an endocrinologist (Saransk) at the rheumatology

department of the Mordovian Republican Clinical Hospital. The doctor suggested that the disease has a rheumatologically etiology. In this regard, the patient was referred to a rheumatologist and hospitalized in April 2011.

Results and Discussion

During the examination, based on the history of life and illness, objective data of the patient, the rheumatologist made a presumptive diagnosis of SSc (without the study of ANA). Prescribed treatment: Penicillamine (250 mg 2 r/d) and Prednisolone (10 mg in the morning). After 3 weeks, an allergic reaction to Penicillamine developed. During treatment, the condition of the patient was worsened: hypersensitivity to drugs of the penicillin group appeared. Due to the lack of therapy effect, the patient was referred for a consultation at the V.A. Nasonova Research Institute of Rheumatology to verify the diagnosis and select a better therapy. The diagnosis was confirmed in accordance with the standard to determine ANA by the IRIF method, which greatly increases the reliability of the diagnosis: diffuse form of SSc and activity of the II degree (see Table 1).

Table 1: Antibody levels over time in a patient with SJS

Index	06.06.2011	15.04.2012	02.05.2012	31.10.2012
ANF (IRIF)	1/640 n	1/640 n	1,0	
Antibodies to SS-A	4,7		2,1	
Antibodies to SS-B	4,5		1,8	
Antibodies to Scl-70	0,2	0,2		
Antibodies to RNP-70	0,1	0,1		
Antibodies to CENT-B	1,3	1,7		
Rheumatoid factor		9,5		
Antibodies to Sm			0,1	
Antibodies to dsDNA			0,9	
Antibodies to C3c			1,51	
Antibodies to C4			0,21	
Antibodies to TG				34,1
Antibodies to TPO				14,5

The patient was prescribed a drug with an immunosuppressive effect Cyclophosphamide (20 mg 1 r/week) and a glucocorticosteroid Methylprednisolone (April 2011 - 4 mg 2 r/day, from June 10, 2011 12 mg 1 r/day, in 2015-2016 14 mg 2 r/day, from 2017 - 4 mg 1 r/day). Against the background of the use of Cyclophosphamide, induration, and hyperpigmentation of the skin decreased; however, the therapy brought only temporary relief, the condition worsened: vomiting of black mass, shortness of breath with attacks of suffocation, and pain throughout the body. With a slight rise in blood pressure, the state of health was significantly complicated, up to syncope.

In January 2012, the condition of the patient was deteriorated sharply - fever of 38.5°C, hyperemia of the skin of the right thigh, due to the appearance of granulomatous abscessing lymphadenitis in the right groin area. Dyspnea intensified, dense edema of the lower extremities, anterior abdominal wall, sacrum, and pain in the eyeballs appeared. A seroma of the right groin area was diagnosed. In this regard, the drug Cyclophosphamide was canceled.

Due to the insufficient effectiveness of therapy, the patient developed digital scars, telangiectasias on the skin of the back, anterior surface of the chest, masklike face, induration of the skin of the hands, face, feet, legs, thighs, diffuse hyperpigmentation of the skin, sclerodactyly, signs of lymphostasis of the right lower extremity, and the beginning of the formation of vertical folds around the mouth. The

patient noted pressing pain in the left side of the chest, poor sleep, pain in the eye socket, interruptions in the work of the heart, episodes of rapid heartbeat, decreased memory, and increased fatigue.

In May 2012, pulmonary arterial hypertension associated with SSc was verified. The fibrosis signs in the myocardium of both ventricles indicated heart damage. In a laboratory study, the titer of myocardial autoantibodies is 1:20.

During catheterization of the right heart in dynamics, an increase in the cardiac index was noted in combination with a significant decrease in pulmonary artery pressure, pulmonary vascular resistance, and mean pressure in the right atrium (see Table 2).

Table 2: Dynamics of the function of the cardiovascular system during PAH therapy

Index	04.05.2012	02.11.2012	26.05.2013	15.11.2013	12.12.2014	N
FC, NYHA	III	III	III	III	III	0
RAP, mm Hg	9	24	18	8	5	2 - 6
RVP, mm Hg	87/3/39	69/12/36	66/6/33	59/2/25	44/5/17	15-25/0-8
PAP, mm Hg	89/41/59	72/30/46	68/26/43	58/20/36	13/15/27	20/11/14
CO, L / min	–	3,5	5,2	6,8	6,6	2,5-4
PCWP, mm Hg	–	13	12	12	–	6-12
SV, mL	–	86	73	101	118	60-100
SVI, mL / m^2	–	48	41	56	6,5	33-47
SVR, dyne / sec / cm^{-5}	–	863	1154	882	1224	600-1200
PVR, dyne / sec / cm^{-5}	–	419	477	282	–	< 250
6MWT, m	215	313	300	295	300	> 551

Within six months from the start of therapy, the test distance changed from 6 to 100 minutes, which indicates a positive trend in this situation. For health reasons, the continuous pathogenetic therapy of pulmonary arterial hypertension of FC III with an antagonist of receptors to endothelin I Bosentan was prescribed (from May 2016 - 125 mg 2 r/day for life. Endothelins are the most powerful vasoconstrictors (10 times more active than angiotensin II). Blockade of these receptors leads to persistent vasodilation, which decreases both pulmonary and systemic vascular resistance, leading to increased cardiac output without an increase in heart rate. Against the background of the treatment, the condition of the patient was stabilized.

In 2012 (before the Bosentan appointment), the patient began to notice the appearance of painful ulcers on the hands. About six months after the appearance of the formations, their contents were easily separated. At the site of the removed ulcer, necrotic dark brown tissue without blood vessels remained. Within one year, 2 pigment spots of black-brown color with a diameter of 1-2 cm were formed on the face, after healing, and scars formed in their place. After the start of taking the Bosentan drug, the appearance of new ulcerative lesions was not observed that indicated the trophic effects of this drug described in the literature.

Besides the background of the use of the drug Bosentan, there was a positive trend in the form of a decrease in edema, shortness of breath, and an increase in exercise tolerance. However, there appeared pasty feet and legs to the knee joints, flexion contractures of the fingers of the hands, de-figuration, and aching pains in the knee joints against the background of aseptic necrosis of the tibia. In SSc, the neurological syndrome is represented mainly by polyneuritic manifestations associated with vascular changes and fibrotic processes in the connective tissue. Yet, the patient developed dis-circulatory encephalopathy, manifested by migraine-like headache, memory loss, confusion with signs of dementia, speech impairment, depression, and uncontrollable actions [29].

Due to the patient's irregular intake of the drugs Bosentan and Sildenafil (since May 2016 - 20 mg 3 r/d) - the patient has a worsening condition in

in the form of an increase in shortness of breath, the appearance of edema, an increase in the right heart, the diameter of the inferior vena cava, changes in CRP, leukocytes (neutrophils, lymphocytes, monocytes), and ESR (see Table 3).

Table 3: Dynamics of indicators of general blood analysis and CRP levels in a patient with SJS

	CRP, mg /L	Leukocytes, * 109 / L	ESR, mm / h	H, L, M - thousand / µL
22.04.11	Negative	7,6	30	-
28.12.11	Negative	8,5	10	H - 5,31 L - 1,47 M - 0,82
28.03.12	14,9	10,2	3	H - 5,23 L - 1,54 M - 0,7
02.05.12	2,6	26,7	2	H - 5,31 L - 1,68 M - 0,47
14.05.12	-	27,1	6	H - 5,15 L - 1,40 M - 0,82
18.05.12	0,17	26	2	L - 12,4 M - 0,83
21.05.12	0,17	21,3	-	L - 4,6 M - 1,3
28.05.12	-	23,4	-	L - 5,3 M - 1,21
02.11.12	10,4	11,1	6	H - 5,6 L - 1,33 M - 0,47
24.05.13	10,8	7,2	16	H - 5,75 L - 1,12 M - 0,47
15.11.13	4,4	7,9	30	H - 5,82 L - 1,12 M - 0,35
12.12.14	10,7	6,6	72	H - 5,31 L - 1,54 M - 0,59
01.04.15	-	6,1	50	H - 5,31 L - 1,26 M - 1,70
07.04.15	-	10,5	45	H - 75,6 L - 1,55 M - 1,70

Conclusion

In the course of treatment, it was revealed that drugs cannot be canceled and replaced, since even a short-term cancellation of specific therapy for pulmonary arterial hypertension leads to a rapid progression of the disease with the possible development of a fatal outcome. With the patient, this study was carried out to increase the degree of adherence to therapy. At the present time, besides the background of the use of the drugs Bosentan, the patient's condition is stable. However, weakness, shortness of breath, arrhythmia, and pain in the knee joints is felt. The prognosis for this patient in the future depends on the patient's compliance with therapy and promptly correction of treatment, taking into account the individual disease development.

The SSc timely diagnosis by using the methods reflected in the clinical guidelines makes it possible to identify the disease at the initial stages and prevent the complications development. This will give the opportunity for the early and proper treatment [30]. The SSc availability will allow regional rheumatologists to recognize this formidable disease and begin treatment promptly. It should be noted that IRIF is not an expensive diagnostic method and requires a fluorescent microscope, diagnostic kits, and, most importantly, a specialist.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

There are no conflicts of interest in this study.

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