ЎЗБЕКИСТОН РЕСПУБЛИКАСИ СОҒЛИҚНИ САҚЛАШ ВАЗИРЛИГИ
ТОШКЕНТ ТИББИЁТ АКАДЕМИЯСИ

2023 №11

2011 йилдан чиқа бошлаган

TOSHKENT TIBBIYOT AKADEMIYASI
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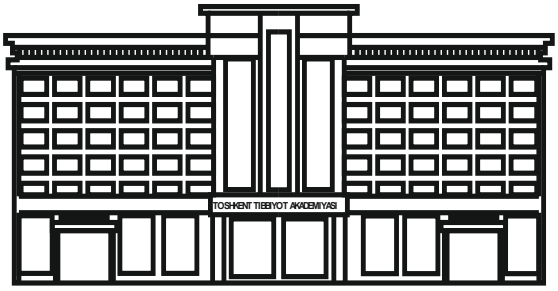

ВЕСТНИК
ТАШКЕНТСКОЙ МЕДИЦИНСКОЙ АКАДЕМИИ

Тошкент

Выпуск набран и сверстан на компьютерном издательском комплексе

редакционно-издательского отдела Ташкентской медицинской академии

Начальник отдела: М. Н. Аслонов

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Компьютерная корректура: З.Т. Алюшева

Учредитель: Ташкентская медицинская академия

Издание зарегистрировано в Ташкентском Городском управлении печати и информации
Регистрационное свидетельство 02-00128

Журнал внесен в список, утвержденный приказом № 201/3 от 30 декабря 2013года

реестром ВАК в раздел медицинских наук

Рукописи, оформленные в соответствии с прилагаемыми правилами, просим направлять по адресу: 100109, Ташкент, ул. Фароби, 2, Главный учебный корпус ТМА,

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Формат 60x84 1/8. Усл. печ. л. 9,75.

Гарнитура «Cambria».
Тираж 150.
Цена договорная.

Отпечатано на ризографе редакционно-издательского отдела ТМА.
100109, Ташкент, ул. Фароби, 2.

Journal edited and printed in the computer of Tashkent Medical Academy editorial department

Editorial board of Tashkent Medical Academy

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Organizer: Tashkent Medical Academy

Publication registered in editorial and information department of Tashkent city

Registered certificate 02-00128

Journal approved and numbered under the order 201/3 from 30 of December 2013 in Medical Sciences department of supreme attestation comission

complited manscipts please send following address:

2-Farobiy street, 4 floor room 444. Administration building of TMA. Tashkent. 100109, Toshkent, ul. Farobi, 2, TMA bosh o'quv binosi, 4-qavat, 444-xona.

Contact number:71- 214 90 64

e-mail: rio-tma@mail.ru. rio@tma.uz

Format 60x84 1/8. Usl. printer. l. 9.75.

Listening means «Cambria».

Circulation 150.

Negotiable price

Printed in TMA editorial and publisher department risograph

2 Farobiy street, Tashkent, 100109.

СОДЕРЖАНИЕ

НОВЫЕ ПЕДАГОГИЧЕСКИЕ ТЕХНОЛОГИИ

ОБЗОРЫ

КЛИНИЧЕСКАЯ МЕДИЦИНА

616.12-008.46-06:616.12-008.331.1- 616.5-004.1

PATHOPHYSIOLOGICAL AND CLINICAL SIGNIFICANCE OF ANTI-NUCLEAR ANTIBODIES IN SYSTEMIC SCLEROSIS

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Systemic sclerosis (M34.0) is a polysyndromic autoimmune disease characterized by progressive fibrosis of the skin, musculoskeletal system, internal organs (lungs, kidneys, heart, digestive system) and vasospastic disturbances. It occurs in around 30 people per million population per year and there are an estimated 125,000 active cases in the United States and perhaps 2.5 million worldwide. Although systemic sclerosis is infrequent, it has a high morbidity and mortality and serious life threatening complications. The main marker of an abnormal immune response is circulating autoantibodies, which are found in more than 95% of patients with systemic sclerosis. It is important to study the clinical, immunological, diagnostic and prognostic significance of autoantibodies.

Key words: *Systemic sclerosis, anti-nuclear antibodies, fibrillarin-(U3-RNP), AFA- anti-fibrillarin antibodies, Raynaud's phenomenon.*

Systemic sclerosis is a chronic autoimmune connective tissue disease, characterized by endothelial dysfunction, immune abnormalities and progressive fibrosis of skin and multiple inner organs. Systemic sclerosis is divided into two subgroups depending on the degree of skin involvement – limited scleroderma (lcSSc) and diffuse systemic sclerosis (dsSSc). In limited scleroderma, the acral parts of the body - the face and limbs (up to the knees and elbows) are affected, in diffuse systemic sclerosis, skin fibrosis is observed in the proximal parts of the body and limbs. In limited scleroderma, Raynaud's phenomenon begins earlier than skin damage, and is accompanied by damage to the lungs and esophagus, but in limited scleroderma, damage to internal organs is relatively late and slow, so the prognosis is good, and the 10-year survival rate of patients exceeds 90%. Patients with diffuse systemic sclerosis have a poor prognosis, which is characterized by rapid damage to the skin and internal organs, damage to the cardiovascular system, lungs, kidneys, digestive system, and even the central and peripheral nervous system. The sinus scleroderma type of systemic sclerosis occurs in 5% of patients with systemic sclerosis, has typical systemic sclerosis symptoms (positive autoantibodies, Raynaud's phenomenon, lung damage), but it is characterized bay absence of skin fibrosis.

In 2013, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EU-LAR) published new classification criteria, presented in the following table.

The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis*

Item	Sub-item(s)	Weight/score†
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)	-	9
Skin thickening of the fingers (only count the higher score)	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions (only count the higher score)	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
Pulmonary arterial hypertension and/or interstitial lung disease (maximum score is 2)	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	-	3
SSc-related autoantibodies (anticentromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III) (maximum score is 3)	Anticentromere	3
	Anti–topoisomerase I	
	Anti–RNA polymerase III	

These criteria are applicable to any patient considered for inclusion in a systemic sclerosis study. The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (eg, nephrogenic sclerosing fibrosis, generalised morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).

The total score is determined by adding the maximum weight (score) in each category. Patients witha total score of ≥9 are classified as having definite systemic sclerosis.

SSc, systemic sclerosis.

Many scientific studies are being conducted to determine the etiology and pathogenesis of systemic sclerosis. The most important factor in the origin of the disease is genetics, as well as viruses, stress, injuries, endocrine and other disorders take the leading place among the factors that cause the disease. As knowledge about the pathogenesis of systemic sclerosis expands, factors that cause or affect the development of fibrosis, such as infections, chemical (silicon, vinyl chloride) and physical factors, are still being analyzed. Their activation is associated with the presence of specific susceptibility genes: HLA (for example, A23, B18 or DR11) and non-HLA (for example, CD247, signal transducer and activator of transcription protein 4 (STAT4) and interferon regulatory factor 5 (IRF5), ankyrin of B cells with repetitive skeletal protein gene (BANK1), autophagy protein-5 (ATG5) or c-SRC tyrosine kinase (CSK) variants are predicted to be key susceptibility genes. Systemic sclerosis is based on immunity, fibrosis, and microcirculation disorders, which interact at the level of tissues (immunocompetent cells - fibroblasts - endothelium - blood cells) and receptor ligand system. It is based on the excessive production of collagen, which is followed by connective tissue disorganization in the areas of injury. In the pathogenesis of the disease, an increase in the process of collagen and fibrosis formation as a result of a violation of cellular and humoral immunity, as well as proliferation of vascular endothelium and smooth muscle cells, basement membrane reduplication, thickening of the wall of microvessels, and narrowing of the cavity play an important role. Also, occurrence of obliterating microangiopathies as a result of aggregation and stasis of blood-shaped elements plays an important role. Systemic sclerosis, like other autoimmune diseases of the connective tissue, is characterized by chronic activation of B-lymphocytes and loss of tolerance to specific antigens. In this disease, a wide spectrum of autoantigens circulates, which may be caused by ischemia-reperfusion damage to internal organs and tissues as a result of vasospastic reactions. Subpopulations of T-lymphocytes autoreactive to endothelium and fibroblasts are synthesized in the body against autoantigens. Autoantibodies and fibrogenic cytokines, which cause fibrosis characteristic of scleroderma, play an important role in the pathogenesis of the disease. Disorganization of the connective tissue is accompanied by immune disorders, inflammatory reactions dominated by proliferative and degenerative processes. Peripheral vasospasm (Raynaud's syndrome) is characteristic for vascular damage. In this case, the capillary wall becomes sclerosed and loses its contractile properties. Obliteration of these vascular surfaces occurs from the connective tissue structures, which in turn leads to a violation of blood supply to all organs and tissues involved in the pathological process. Inadequate blood supply to tissues leads to thinning (for example, mucous membranes of the esophagus and stomach) or, on the contrary, thickening (walls of lung alveoli), disruption of their basic functions (absorption of the gastrointestinal system, release of carbon dioxide from the lungs, contraction of muscle fibers).

In the pathogenesis of systemic sclerosis, the activation of the immune system leads to the production of autoantibodies. Antinuclear antibodies (ANA) are the most frequently identified autoantibodies (in 90-95% of cases) in patients with systemic scleroderma. In patients with clinical symptoms of systemic scleroderma, but without circulating antinuclear antibodies (ANA), differential diagnosis of scleroderma-like diseases is appropriate. In systemic sclerosis, there are autoantibodies associated with different types of disease, which are also important in prognosis. Autoantibodies against topoisomerase I (Topo I, ATA, Scl-70) are more common in patients with diffuse systemic scleroderma and have been found to be associated with the development of pulmonary complications, finger ulcers, and hand disability. Anti-centromere autoantibodies (ACA) are predominantly detected in limited scleroderma and increase the risk of pulmonary fibrosis and pulmonary hypertension. Antibodies against RNA polymerase III are detected in some patients with diffuse systemic sclerosis, which increases the risk of kidney disease. They are also present in patients with adjacent neoplastic processes. Antibodies against Th/To are less common. Th/To is characteristic of limited scleroderma.

Anti-fibrillarin autoantibodies are associated with pulmonary arterial hypertension and cardiovascular complications.

Materials and methods

We examined 70 patients with Systemic sclerosis aged 18 to 50 years,51 women and 19 men who received inpatient treatment in the Rheumatology department of the for 2022-2023 years. Medium duration of the disease was 7,5±3,3 years. 45 patients had a limited form of SSc (lSSD) and 25 patients had a diffuse form (dSSD). All patients underwent clinical, laboratory, instrumental and immunological (to identify AFA- anti-fibrillarin (U3-RNP) antibodies) research methods and the Diagnosis of disease was confirmed according to the 2013 EULAR/EUSTAR diagnostic criteria.

Results

All patients had characteristical peripheral and visceral symptoms of systemic sclerosis. Almost all patients suffered from different skin changes, such as- edema-34 patients (48,6%), induration - 35 patients (50%) digital ulcers- 18 patients (25,7%), sclerodactyly - 28 patients (40%). Raynaud's phenomenon was detected in all patients. Musculoskeletal manifestations included arthritis (7 patients -10%), flexion contractures (8 patients -11,4%) muscle weakness (6 patients- 8,6%). Dysphagia was the most frequent visceral symptom among examined patients (71,4%).

Anti-fibrillarin antibodies were detected in 10 patients. In the comparative analysis it was noted that the patients who had autoantibodies against fibrillarin showed early onset of the disease, the progressive course of systemic sclerosis, rapid fibrosis of lungs and

skin. Pulmonary hypertension was detected overall in 12 patients and 8 of them had AFA.

Conclusion

The results of the study confirm pathophysiological, clinical, diagnostic and prognostic significance of anti-anti-nuclear antibodies. AFA in Systemic sclerosis can be considered as a predictor of the progressive fibrosis of skin and lungs. Based on the early detection of AFA, it is possible to identify patients with a progressive course of the disease who need immunosuppressive and anti-fibrotic therapy and increase the effectiveness of the treatment.

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