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PROFILE OF AUTOANTIBODIES IN SYSTEMIC SCLERODERMA

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ABSTRACT: The aim is to determine the frequency of autoantibody detection in a cohort of Uzbek patients with systemic scleroderma (SSD), to study the clinical associations of the detected antibodies.

Material and methods. From 2021 to 2024. The study included 60 patients (12 men and 48 women) who met the criteria of the American College of Rheumatology/European Antirheumatic League (ACR/EULAR) SSDs. All patients underwent an immunological examination, including determination of antinuclear antibodies, antibodies to topoisomerase I (anti-Scl-70), to centromeres (ACA), to ribonucleoproteins (anti-UI-RNP), to ribonucleoprotease III (anti-RNCP III).

Results and discussion. The vast majority of patients were female, middle-aged, with a moderate duration of the disease. Patients with a limited form prevailed (55.3%), 37.4% patients had diffuse, 5.9% – cross (overlap syndrome); <1% - visceral and juvenile forms of SSD. The vast majority (83.8%) of patients had an antinuclear factor. The most common of the SSD-associated antibodies (approximately half of the patients) were antiScl-70. ACA occurred in only 9 (14.6%) patients. A combination of ACA positivity and anti-Scl-70 was observed in three patients with limited SSD, including one with an early form of the disease. 5 patients were positive for anti-UI-RNP. Among them, patients with limited and cross-sectional forms of SSD prevailed. Anti-RNCP III was detected in 5.5% of cases, mainly in the group patients with a limited form of SSD; in one case, they were detected in a patient with diffuse skin lesions and severe interstitial lung damage. Kidney damage was not observed in this group of patients.

Conclusion. The peculiarities of the Russian cohort are the predominance of the limited form of SSD and the frequent detection of anti-Scl-70 in both diffuse and limited forms of SSD; the absence of correlations of anti-Scl-70 with rapid progression of the pathological process, kidney pathology.

Key words: Systemic scleroderma; limited form; diffuse form; autoantibodies; associations.

INTRODUCTION

Systemic scleroderma (SSD) is characterized by excessive fibrosis, microangiopathy and the presence of circulating antibodies to various autoantigens.

The pathogenesis of SSD has not yet been fully studied. In particular, the role of autoimmunity in the development of clinical and pathogenetic phenotypes remains unclear. Various autoantibodies are found in SSD that are associated with certain clinical manifestations, but the pathogenetic role of these antibodies has not been sufficiently proven.

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The presence of antinuclear antibodies is a distinctive feature of diabetes, they are detected in the vast majority (approximately 95%) of patients. The best studied are anti-topoisomerase antibodies (anti-Scl-70) and anti-centromeric antibodies (ACA), which were found in SSD in the late 70s of the XX century. At least seven types of antibodies associated with with SSD: anti-Scl-70, ANA, antibodies to ribonucleoprotease III (onti-NCTP III), anti-Th/To, antibodies to U3 ribonucleoprotein (anti-U3 RNP), antibodies to PM-Scl (anti PM-Scl), antibodies to U1 ribonucleoprotein (ANTIU1 RNP). Their frequency varies according to different authors.

These SSD-bound antibodies target various nuclear components involved in basic cellular processes, namely, nuclear division and transcription. These antibodies are rarely found in patients with other connective tissue diseases and are therefore important diagnostic markers. Their detection helps to determine the subtype of SSDs, since they can be associated with characteristic clinical phenotypes.

SSD-associated antibodies are detected along with the initial symptoms of SSD and do not change throughout the disease. They persist regardless of whether the patient receives treatment or not. It is also believed that the circulation of certain autoantibodies is not associated with the severity or activity of SSDs.

Two or more SSD-associated autoantibodies are rarely found in the same patient.

The traditional method for determining antibodies is indirect immunofluorescence on human cell culture. This technique is recommended as the first screening method, as it is highly sensitive and provides information about the titer of antibodies and the type of their glow.

In recent decades, many studies have confirmed a strong association between specific autoantibodies and the unique clinical phenotype of SSD. Nevertheless, it remains unclear whether these antibodies play a direct pathogenetic role or simply serve as markers of particular manifestations of the disease.

Recent research has suggested the possible role of anti-Scl-70 in the development of SSD. In particular, in vivo experiments have shown that antibodies from patients with SSD can stimulate adhesion and activation of macrophages, although the entire pathogenesis remains completely uncertain. At the same time, immunization in mice leads to the production of antibodies, but does not induce the development of SSD.

The detection of immunological disorders is a new direction in the early diagnosis of SSD. Thus, anti-Scl-70, anti-RNCP III and ACA specific for diabetes were included in the new diagnostic criteria for DIABETES proposed by the European Antirheumatic League (EULAR) and the American College of Rheumatology (ACR); the presence of these autoantibodies is estimated by 3 points, whereas to confirm the diagnosis of DIABETES, it is necessary to score 9 points. Thus, the importance of autoantibodies cannot be overestimated.

The aim of our work was to determine the frequency of specific autoantibodies in a cohort of Uzbek patients with SSD, and to study the clinical associations of the identified antibodies.

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MATERIALS AND METHODS OF RESEARCH

From 2021 to 2024, the study included 60 patients (12 men and 48 women) who meet the criteria of the ACR/EULAR SSD. There were no patients with pulmonary arterial hypertension (PAH) among them, catheterization of the right heart was not performed All patients with PAH were observed separately and were not included in the study group. All patients underwent conventional clinical and laboratory tests, electrocardiography (ECG), echocardiography (EchoCG), and function was studied respiratory organs with the determination of the diffusion capacity of the lungs. Immunological examination: antinuclear factor (ANF) was determined on

NONER2 cells by indirect immunofluorescence reaction using a commercial set of Immco reagents (USA; upper limit of norm <1/160); anti-Scl-70 (upper limit of norm 25.0 U/ml); ACA (upper limit of norm 10.0 U/ml); anti-UI-RNP (upper limit of the norm of 25.0 U/ml) – using commercial reagent kits from Orgentec (Germany), anti-RNCP III (upper limit of the norm of 28.0 U/ml) – Medical & Biological Laboratories CO (Japan). Statistical data processing was carried out using the Statistica 6.0 program, descriptive statistics methods and nonparametric methods were used. The relationship between the signs was assessed by Spearman's rank correlation method. Differences and association of features were considered statistically significant at $p<0.05$.

THE RESULTS AND THEIR DISCUSSION

The vast majority of patients were female, middle-aged, with a moderate duration of the disease. Patients with a limited form prevailed (55.3%), 37.4% of patients had diffuse, 5.9% – cross (overlap syndrome); <1% – visceral and juvenile forms of SSD. More than half of the patients had a slowly progressive course of the disease. The average duration of the disease was 8.1±7.6 years. In all patients, the clinical picture of the disease it was polysymptomatic; in addition to the characteristic lesion the skin had vascular pathology, damage to joints and internal organs (lungs, heart, gastrointestinal tract), laboratory changes (mainly immune).

SSD-specific autoantibodies were identified. In the vast majority (83.8%) of patients, ANF was determined. Anti-Scl-70 was detected most frequently among the SSD-associated antibodies, in about half of the patients. ACA occurred in only 44 (14.6%) patients. Almost 1/3 (26.7%) of patients with a reliable diagnosis of SSD with ANF positivity had ACA and anti-Scl-70 have not been identified. A combination of ACA positivity and anti-Scl-70 was observed in three patients with limited SSD (one of them with an early form of the disease). 26 were positive for anti-U1NP (8.6%) of patients. Among them, patients with limited and cross-sectional forms of SSD prevailed. In addition, anti-RNCP III was detected in 5.5% of cases. They were found mainly in the group of patients with a limited form of SSD; only one patient positive for anti-RNCP III had diffuse skin lesions correlating with pronounced interstitial lung damage. Kidney damage was not observed in this group. It seems interesting that the patient with the highest level of these antibodies (42 U/ml) had an early form of the disease, lasting <3 years, with limited skin damage and erased Raynaud's syndrome. The clinical characteristics of patients with SSD, depending on the type of autoantibodies. As can be seen the main clinical manifestations of SSD were pronounced in the group of patients positive for anti-Scl-70, with the exception of signs such as swelling of the hands,

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characteristic mainly of the early form of the disease, and necrosis, mainly digital, characterizing the progressive course of Raynaud's syndrome. The identified type of autoantibodies determined the clinical heterogeneity of the disease. Thus, in the group positive for anti-Scl-70, the predominance of fibrosing processes in general was noted: more frequent development of diffuse induration of the skin and periarticular tissues, leading to the formation of flexion contractures of the hands in the vast majority of patients.

Interstitial lung damage was detected in almost 70% of cases. Also in this group, there was severe heart damage with rhythm and conduction disorders, including the development of large-focal myocardial fibrosis exclusively in the group of patients with CVD associated with antiScl-70. In addition to the predominant fibrotic processes, severe vascular disorders have been reported. Raynaud's syndrome developed in 100% of cases, was progressive in nature with the development of trophic disorders and the formation of digital scars in more than 50% of cases. The group of patients positive for ACA had a relatively benign course of the disease. It was characterized by less pronounced lesions of the skin and internal organs, although interstitial lesions lungs were detected in almost half of the cases. Among the clinical features of SSD common to both groups, acroosteolysis, swelling of the hands (detected in approximately 1/3 of patients), telangiectasia, damage to the gastrointestinal tract and kidneys; increased systolic pressure in the pulmonary artery (SDLA) according to EchoCG data - in 10% of patients. Anti-Scl-70 was significantly more often detected in patients with diffuse skin lesions, including its diffuse hyperpigmentation, as well as in the presence of flexion contractures of the hands. In addition, these antibodies they prevailed in the group of patients with pulmonary fibrosis. The presence of anti-Scl-70 was also correlated with sclerodermic cardiopathy, mainly with impaired heart rhythm and conduction. ACA was found mainly in patients with a limited form of the disease. In patients with dense edema of the hands, anti-Scl-70 and ACA occurred with approximately the same frequency. There was no association between positivity according to anti-Scl-70 and ACA and the main vascular manifestations such as Raynaud's syndrome, digital ischemic disorders; as well as pulmonary hypertension, gastrointestinal tract lesions and sclerodermic nephropathy.

According to the literature, anti-nuclear antibodies are detected in more than 90% of patients with SSD. Although their role in the pathogenesis of SSD remains unclear, they are often associated with clinical heterogeneity, severity and course of the disease. ACA, anti-Scl-70, and less often anti–RNCP III are detected in patients with SSD. Serum antibodies such as anti-Th/To; anti-U3RNP, anti-U1RNP, antibodies to Ku (anti-Ku), anti-Pm-Scl are also found in SSD and determine its clinical diversity. Thus, anti-Th/To and anti-Pm-Scl are associated with a limited form, while anti-U3RHP – with a diffuse form of SSD. In addition, anti-Th/To and anti-U3RHP can serve as predictors of the development of organ lesions such as pulmonary fibrosis, PAH and renal crisis. Other antibodies, such as anti-Ku, anti-U1NP, antibodies to U11/R U12, are generally less common, but can also determine the clinical variant of SSD. It is known that the frequency of various SSD-related antibodies and the clinical picture of SSD can be influenced by the ethnicity of patients. There is still interest in the world literature in studying the significance of these antibodies, their relationship to the classification forms of SSD, and the population characteristics of the disease. This work is carried out within the framework of registers and cohort studies, which analyze regional and ethnic differences in the main clinical forms and autoantibodies. By now, many national registers are in operation. All national cohorts have a number of features

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in terms of the prevalence of clinical forms of the disease, the frequency of specific SSD-associated autoantibodies. Comparable data with Russian data were obtained in a cohort of German patients with SSD, where limited scleroderma occurred in half of the patients, and the diffuse form was slightly more than 1/3 of the cases.

Despite the wide range of immunological disorders, ACA and anti-Scl-70 are considered classic autoantibodies associated with SSD. A high level of anti-Scl-70 in SSD was detected in the vast majority (up to 80%) of the ethnic population of the USA and Australia. In the Russian cohort, these autoantibodies were found in more than half (59.9%) of patients with SSD. In a number of countries, the most common There were aces. Among "white" Australians, they were detected in 51% of cases; among the "white" population of the United States, as well as Denmark and Greece – in more than 30%. In our study, ACES were relatively rare (in 14.6% of cases). Our results were consistent with the Brazilian and Chinese cohorts of patients. Thus, Uzbek patients were comparable in clinical forms with German ones, and in the frequency of the main autoantibodies with Chinese and Brazilian registers. It is known that the immunological profile correlates with the clinical picture, course and prognosis of the disease. Thus, ACA is associated primarily with limited skin lesions and isolated pulmonary hypertension, while anti-Scl-70 is associated with the diffuse nature of the skin syndrome and pulmonary fibrosis. ACA is also a predictor of a relatively favorable, and anti-Scl-70 – an unfavorable course and outcome of SSD. Despite the prevalence of a limited form of SSD in our group, antiScl-70 was most often detected, which were present in almost half of the patients, while ACA was detected in only 14.6% patients, i.e. there was no strict correspondence between the serological profile and the clinical phenotype of the disease, which can also be attributed to the characteristics of the cohort.

The combination of anti-Scl-70 and ACA in one patient is extremely rare. So, in the European cohort EUSTAR out of 5,323 patients, a similar association was found in 28 (0.52%) people. Among these patients was one patient from the Russian group we studied. Among all the examined 300 patients with SSD, the association of both antibodies was detected in 1% of cases (in 3 people). All of these patients had a limited form of SSD, while according to the world literature, such a combination of antibodies correlates with the diffuse nature of the pathological process. According to the literature, the absence of autoantibodies in patients with SSD is also rare and may be associated with less pronounced symptoms and a better prognosis. Thus, according to a large Canadian cohort study, among 874 patients, 15 (1.7%) people were negative for autoantibodies. In the German group, autoantibodies were absent in 38 (4.4%) of 853 patients. And in the international database EUSTAR the proportion of such patients was 8% of 5,378 people. Patients had less pronounced vascular disorders, such as Raynaud's syndrome and digital ulcers, LAG was less frequently recorded, but at the same time flexor contractures formed more often. In the studied Russian cohort, the proportion of patients negative for autoantibodies turned out to be quite large and it amounted to almost 1/3 (26.7%). This subgroup was generally characterized by relatively slow progression and lower severity of symptoms; perhaps this is due to the fact that in this study only four of the most SSD-specific autoantibodies were evaluated. In our observation, anti-U1NP in the general cohort occurred mainly in patients with limited and cross-forms of SSD, in only 8.6% of cases. At the same time, they were found in almost one in four in the group of anti-Scl-70 and ACA-negative patients. This observation deserves further study.

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CONCLUSIONS

Thus, the peculiarities of the Uzbek cohort are the predominance of the limited form of the disease and the frequent detection of anti-Scl-70 in both diffuse and limited forms of SSD. The identified associations reflect, in general, the trends in the development of the disease presented in the literature. However, the absence of correlations of anti-Scl-70 described by other authors with the rapid progression of the pathological process and kidney pathology, as well as the detection of this type of antibodies in groups of patients with a limited form of SSD, with slow progression, may probably be they are related to the geo-epidemiological features of the Uzbek cohort. The study of SSD-associated antibodies may be important for monitoring, better understanding of the prognosis and therapy of this category of patients.

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