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Clinical and Prognostic Characteristics of "Disease-specific" Autoantibodies in Systemic Scleroderma

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Authors' contributions

This work was carried out in collaboration among all authors. Author ANA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors DER and NDA managed the analyses of the study. Author GNA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Systemic sclerosis (SSc) is a connective tissue disease of autoimmune nature characterized by the triad of vascular injury, autoimmunity (cellular and humoral) and tissue fibrosis. Autoantibodies do not seem to be simply epiphenomena, but are involved in disease pathogenesis. It is believed that the SSc-specific autoantibodies are responsible both for amplifying immune response and targeting cell types that are relevant in the pathophysiology of SSc. In the current understanding of the pathogenesis of SSc, the leading role is assigned to the vascular lesion of the microvasculature arising against the background of immunity dysregulation and the intensification of fibrosis processes associated with the action of various growth factors and cytokines. In SSc, as in other systemic autoimmune diseases, chronic B-lymphocytic activation is observed, which results in a loss of tolerance to self antigens. Circulation of a wide range of autoantibodies (antibodies) is a characteristic feature of SSc. It is possible that autoantigens in SSc are released during ischemia-

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reperfusion tissue damage that occurs against the background of vasospastic vascular reactions characteristic of this disease. In the process of B-cell presentation of autoantigens through costimulatory surface molecules, activation of T-lymphocytes occurs, followed by clonal expansion of T-cell subpopulations, which are autoreactive towards endothelium and fibroblasts. It is believed that B cells play an important role in the initial mechanisms of fibrosis in SSc, and chronic activation of B cells is directly related to the development of sclerodermic fibrosis through the production of antibodies and fibrogenic cytokines. Despite many years of efforts, a complete concept explaining the role of antibodies in the pathogenesis of SSc has not yet been created. At the same time, a huge amount of information has been accumulated on the diagnostic and prognostic significance of circulating antibodies, the importance of which for the supervision of the patient can hardly be overestimated.

Keywords: Systemic sclerosis; antinuclear autoantibodies; anticentromere autoantibodies; antitopoisomerase autoantibodies; anti-RNA polymerase III antibodies; nonspecific autoantibodies.

1. INTRODUCTION

Systemic sclerosis (SSc) is a systemic autoimmune rheumatic disease (RD) characterized by progressive fibrosis of the skin and internal organs. The disease, heterogeneous in clinical manifestations and variants of the course, includes both fatal, rapidly progressive forms, and long-term benign variants of the disease, manifested subclinical. SSc is characterized by the presence of components of the nucleus, cytoplasm and surface cellular antigens in the circulation of antibodies. For the convenience of presenting the extensive material, antibodies in SSc are conditionally divided into two subgroups - specific, which are characteristic mainly for this disease, and nonspecific [1,2]. SSc-specific antibodies are a heterogeneous group of immunoglobulins that react with various components of the cell nucleus, that is, they are antinuclear (antinuclear) antibodies (ANA). SSc is characterized by an exclusive set of auto antigens targets, which are localized in the nucleoli, chromatin, and nucleoplasm. The detection rate of ANA in SSc is 90–95% [3]. Their role in the pathogenesis of the disease remains poorly understood. Along with the idea that antibodies is an epiphenomenon associated with tissue damage, there are still unproven hypotheses that assign ANA an important role in the onset and / or progression of SSc. It has been shown that, in addition to specific ANA, other antinuclear antibodiess circulate in the blood of about half of SSc patients, including those found in various RD, for example, antibodies to SS-A / Ro polypeptides with molecular weights of 60 and 52 kDa, etc. Nonspecific antibodies targets such targets as endothelial cells and fibroblasts, functional molecules (various cellular receptors), extracellular matrix proteins, enzymes, etc. An example is antiendothelial, anticardiolipin antibodies, antibodies to fibroblasts, etc.

2. ANTINUCLEAR AUTOANTIBODIES ASSOCIATED WITH SYSTEMIC SCLERODERMA

Of the large spectrum of antibodies associated with SSc, seven have been most studied, called the "standard profile". It is known that 85–95% of SSc patients have one of the antibodies of this series in their blood [4]. These include antibodies to centromeres (ACA), to topoisomerase 1 (ATA) and ANA to ribonucleoprotease III (ARNP), Th / T0, Pm / Scl, as well as antibodies to ribonucleoproteins (RNP). The primary screening method for the determination of antinuclear scleroderma antibodies in blood serum is an indirect immunofluorescence reaction using human Hep-2 cell culture as a substrate. ANA tested by the immunofluorescence method are called antinuclear factor (ANF) [5].

The presence of ANF in the sera of SSc patients is manifested by the nuclear luminescence of Hep-2 cells, the type of which depends on the topography of the autoantigen. The nature of the luminescence allows the identification of various autoantigen-specific scleroderma antibodies (see Fig. 1). Centromeric luminescence is associated with ACA (see Fig. 1a), small speckled (reticulated) - with ATA (see Fig. 1b). The nucleolar type of fluorescence (see Fig. 1c) is characteristic of the antibodies group, which includes antibodies to fibrillarin / U3-RNP, ARNAP I, II, III, Th/To, and Pm-Scl [6]. NRIF-HEp-2 is considered the most sensitive and specific method for the determination of ACA for the diagnosis of SSc, which eliminates the need for further study of these autoantibodies using confirmatory laboratory tests. Measurement in patients with positive results of NRIF-HEp-2 of other subtypes of antinuclear scleroderma antibodies (ATA, ARNAP III, antibodies to U3RNP, PM / Scl, Th / To, U1RNP, etc.) is carried out using confirmatory immunodiagnostic methods, to which include counter-immunoelectrophoresis (CIEF), double immunodiffusion (DID), immunoprecipitation (IP), enzyme-linked immunosorbent assay (ELISA), immunoblotting (IB) and, in recent years, multiplex immune analysis (MIA) [7]. Multiplex diagnostic test systems based on the use of planar and suspension microarrays have high analytical sensitivity and allow simultaneous determination of an extended antibody profile in a small volume of serum (up to 50 µl). To determine the antibodies profile in SSc, sets of 10-15 autoantigens are used, including, along with the "standard set" of antigenic targets, other antigens - SS-A / Ro polypeptide with a molecular weight of 52 kDa (Ro-52), platelet-derived growth factor receptor (RTFR), hUBF / NOR-90 (human Upstream-Binding Factor), etc. In a large group of patients with SSc and control sera (360 people), it was shown that the method has high specificity (97-100%) for all antibodiess (except for antibodies to SS-A / Ro-52) and is able to detail the immunological profile of antibodies in patients with a nucleoli type of fluorescence in the NIF and negative for the most common antibodies, ATA and ACA [3,6].

As noted above, SSc-specific ANA are present in the blood of almost all (90–95%) SSc patients. However, each of the antibodies is individually detected in a small group of patients [3]. The production of one type of SSc-specific antibodies is exclusive for each patient, and two or more types of SSc-specific antibodies are rarely found in a particular patient [4]. The dominant type of antibodies persists throughout the disease, and, as a rule, in the process of its development, new types of antibodies do not appear [8]. Despite the wide range of known antibodies, only two types of antibodies are found in 50-60% of patients - ACA and ATA (Scl-70). These antibodies are highly specific for SSc and are usually not combined in one patient. Other antibodies highly specific for SSc - to U3RNP and Th / To - are rare. Antibodies to Pm / Scl, Ku, U1RNP, which are more characteristic of syndromes overlapping with SSc, are also rare.

It is also known that a small proportion of patients (6–10%) with SSc can be negative for antibodies. It should be borne in mind that "seronegativeness" in relation to SSc is conditional and directly depends on the methods for determining antibodies. Thus, with the simultaneous use of several modern sensitive methods for the determination of antibodies in patients with SSc using a wide panel of auto antigens M. Hudson et al. [6] found only 1.7% of 874 sera in which antibodies was not detected by any of the methods. The authors also noted that antibodies negativity in SSc was associated with a milder course and a more favorable prognosis of the disease.

There are some reports that antibodies may disappear during the course of the disease, which also suggests its more benign course [9], including against the background of successful treatment [8].

To date, there is strong evidence that SSc-specific antibodies are predictors of disease progression and outcome. A clear association between the type of antibodies, the nature of organ complications, and survival has been well studied [10]. Antibodies are more stringent predictors of the outcome and severity of viscerites than the severity of skin lesions (in the context of diffuse and limited forms of the disease) [3]. These clear associations make testing for antibodies for diagnosis, assessment of the course and prognosis indispensable in the modern supervision of patients with SSc.

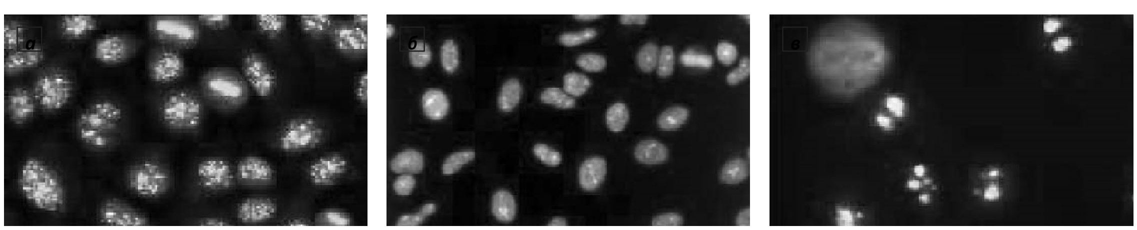

Fig. 1. Types of nuclear fluorescence in the determination of sclerodermic antibodies by the NRIF-Hep-2 method: a - centromeric (ACA); b - small speckled (mesh; ATA); c - nucleolar (antibodies to RNA polymerases I, II, III, U3-RNP, To / Th, PM / Scl)

3. ANTICENTROMERIC ANTIBODIES

The target autoantigens are 6 centromeric nucleoproteins (designated by letters from A to F), of which peptide B (CENR-B), a DNA-binding protein with a molecular weight of 80 kDa, is one of the main autoantigens that react with almost all ACA-positive sera [11]. On average, the frequency of detection of ACA in patients with SSC is 16–39% and varies in different ethnic groups. Approximately 30% of Caucasians are positive for ACA, while this frequency is lower among African Americans and Taiwanese [12]. In childhood SSc patients, the incidence of ACA is significantly lower (8%) than in adolescent and adult patients [3]. In other systemic RDs, these antibodies practically do not occur, with the exception of Sjogren's disease (SJ). ACAs are also detected in primary biliary cirrhosis and, rarely, in healthy elderly people [2]. In the NIF reaction (to Hep-2), these antibodies have a typical luminescence in the form of clearly delineated dotted specks, evenly distributed in the nucleus (see Fig. 1a). The diagnostic specificity of ACA is 97–99% [13]. In persons who are positive for ACA, the disease has certain features that make it possible to speak of a special clinical and immunological subtype of SSc. The debut of the disease with Raynaud's syndrome is characteristic. Between the onset of Raynaud's syndrome and the onset of other manifestations of the disease, it takes from 3 to 9-10 years. Swelling of the hands is often the first non-Raynaud symptom. Subsequently, a limited form of the disease is formed with limited lesions of the skin of the hands, feet and face. Sclerodermas renal crisis (SRC) or interstitial lung injury (ILI) is almost never developed, therefore ACAs are considered "protective" for progressive pulmonary fibrosis and acute sclerodermas kidney. Typical development of digital ischemic ulcers, the incidence of which ranges from 40-60% in Caucasians and Africans and only in 11-17% of cases complicates the course of the disease in Japanese. This variant of the SSc is characterized by a long and relatively favorable course. In the later stages of the disease, it diagnosed in about 10% of cases, which is the main cause of death in this subtype of the disease.

An association was noted between the presence of ACA and the carriage of human leukocyte antigens - HLA (human leukocyte antigen) -DR1, -DR4, -DR8, -DR11 and -DQ7 (DQB1 * 0301) [6]. Recently, a new genetic marker not associated with HLA was identified in tumor necrosis factor (TNF) polymorphisms, namely, TNF-863A and TNF-1031C alleles [14]. These data indicate the immunogenetic dependence of the antibody response or the clinical subtype of SSC [15].

4. ANTITOPOISOMERASE AUTOANTIBODIES

Topoisomerase 1 is considered as a possible autoantigen [2]. This intranuclear enzyme is released during cell apoptosis and has the ability to bind to the surface of fibroblasts. Topoisomerase 1 on the surface of fibroblasts can be detected by reacting with antibodies from the sera of patients with SSc. Under in vitro conditions, the complex of topoisomerase 1 with the corresponding antibody bound to the fibroblast surface stimulates adhesion and activation of co-cultured monocytes. It is believed that activated mononuclear cells release cytokines, which, in turn, locally stimulate fibroblasts to secrete profibrotic mediators [4]. This theory is confirmed by the relationship (in 100% of cases) of ATA with antibodies to fibroblasts in SSc.

With NIF (on Hep-2), ATA usually give a speckled type of glow in high titers - more than 1/320 (see Fig. 1b). ATA for SSc is high (97–100%) when compared with healthy controls and with patients with other systemic inflammatory RD when using the DID method [3]. The specificity depends on the method and decreases with the use of ELISA. On average, the detection rate of antibodies is 10–40% and depends on the geographic region and race [16]. Thus, in France, ATA in SSC is detected in 35% of patients, in Japan - in 27%, in the United States among whites - in 20% and among African Americans - in 11% of cases [3]. Another study found similar data. Thus, in France, the frequency of ATA detection was significantly higher, and ARNCP III - lower than in the United States [14]. In Japan, 31% of ATA-positive patients have a limited form of the disease [5]. In the USA, 18% of patients with the limited form are positive for ATA [13]. In a later study, it was shown that in the United States, 65% of ATA-positive patients have a diffuse form, which is significantly higher than in ATA-positive patients from France (38%) [6].

ATA are associated with HLA-DRB1, -DQB1, and -DPB1 [17]. Among these antigens, the carriage of HLADRB1 * 1104 is characteristic of all ethnic groups (including Japanese) and occurs in 65% of ATA-positive patients and only in 8% of ATA-negative patients. Carriage of HLADRB1 * 1101 was more common among whites and African Americans, and HLA-DRB1 * 1502 - among Spaniards [18]. ATA are found in different clinical forms of SSc, but mainly in diffuse. Approximately 60% of patients with diffuse disease are ATA-positive. Carriage of ATA is associated with a rapidly progressive course, the development of widespread cutaneous and severe pulmonary fibrosis, early onset digital ulcers, and high mortality [19]. Scleroderma skin lesions in carriers of ATA are less pronounced and proceeds more slowly than in patients positive for ARNCP III. ATA positivity is considered a predictor of pulmonary fibrosis and digital ulcers [10]. It has been shown that the development and progression of IPL is characteristic of almost all ATA-positive patients with SSc, while a higher level of these antibodies is associated with a more severe course of the disease [11]. ATA positively correlates with skin score and is considered a predictor of poor prognosis in IPL: patients with severe progressive pulmonary fibrosis die on average 10 years after the onset of the process in the lungs.

With persistence of ATA, the clinical manifestations of skin syndrome and ILI were more pronounced than in patients with the disappearance of these antibodies during treatment. A case of a decrease in the level of ATA and their disappearance against the background of successful treatment with glucocorticoids of cutaneous syndrome in SSc, which served as the basis for discontinuation of the drug, is described. However, 10 months after discontinuation of therapy, ATA reappeared in high titers in parallel with the deterioration of the skin process. This case indicates a possible pathogenic role of ATA in the development of both the disease and its exacerbations [13]. It has been observed that patients in whom ATA disappears over time have a milder course of the disease and better survival [14]. However, the assumption about the possibility of using the ATA level to assess the severity, activity, and prognosis of SSc in later studies was not developed and confirmed.

5. ANTI-RNA POLYMERASE III ANTIBODIES

Highly specific for SSc - 98–100%. In patients with ARNCP III, less specific ARNCP I and II (which sometimes occur in SLE or cross syndromes) can be simultaneously detected. The detection rate of ARNCP varies widely and averages 4–6% [15]. It is high among Caucasians in the USA and Great Britain (20–25%) and low in France (5%) [16]. In a large Japanese cohort, ARNCP III in SSc were detected by ELISA in 10.7% of cases, in other RD - in 1.2% and were not detected in healthy subjects [17]. These antibodies are rarely found in patients with childhood (4%). A meta-analysis of 30 publications, which included more than 8.4 thousand patients with SSc from different centers, revealed fluctuations in frequency from 0 to 41%. The frequency of detection of ARNCP III depended on geographic factors. Probably, the appearance of these antibodies is determined by both genetic predisposition and environmental influences [18]. The presence of these antibodies is associated with the carriage of HLADRB1 * 0301.

This type of antibodies is associated with onset in old age, a diffuse form of the disease, in which positivity for ARNCP III reaches 70–100%, a rapidly progressive course, and is more common in men [19]. ARNCP III is a predictor of acute SSc, which develops within 1 year from the onset of skin lesions in 26–43% of patients [20]. The clinical picture of SSc in carriers of ARNCP III is characterized by the rapid progression of severe persistent skin syndrome with the formation of contractures; however, severe damage to the lung parenchyma develops infrequently. Ischemic peripheral disorders (digital ulcers) are also uncommon. In the absence of kidney damage, the prognosis for this form of the disease is better than for carriers of ATA. On the contrary, the combination of diffuse cutaneous syndrome and SSc makes the management of these patients very difficult. These antibodies are associated with the detection of HLA-DRB1 * 0301. The ten-year survival rate is about 70% [21].

In recent years, there have been convincing data that positivity for ARNCP III is associated with an increased incidence of malignant neoplasms [22]. As you know, SSc is associated with an increased risk of developing cancer compared to the population. According to various authors, solid cancers (lung, breast, gastrointestinal and urogenital tract organs, skin) are more common, less often - hematology oncology. Further special studies have shown that with SSc in cancer patients, ARNCP III is more often detected. Thus, when examining more than 2000 patients with SSc, the incidence of cancer in patients with ARNCP III was 14.2%, while in the rest - 7.1% [23]. Carriers of ARNCP III have a 2-fold increased risk of cancer in comparison with carriers of other antibodies (relative risk 2.55).

Moreover, cancer in carriers of ARNCP III develops in chronological connection with the onset of SSC and is more often diagnosed at an early stage - in the first 36 months of the disease, and the risk of developing early cancer increases 6 times [24]. When ARNAP III is positive, breast cancer develops more often, and increased expression of nuclear RNA proteinase was detected in the tumor tissue [25]. There are other examples of the detection of activated RNA proteinase - in lung carcinoma, breast cancer and fibroblasts infected with polyomavirus. Based on these associations, it has been suggested that the subtype of SSc patients with breast cancer may represent a model for the development of paraneoplastic autoimmunity [26]. A hypothesis has been formulated according to which antibodies to a tumor-associated antigen (mutant RNA proteinase III in a tumor cell) arise as antitumor immunity and, thus, initiate an immune response to specific targets in healthy tissues, contributing to tissue damage. Thus, cross-immune reactions can occur and be directed to an autoantigen, which is expressed both by mutated tumor cells and targeted tissues in individuals with a genetic predisposition and, possibly, against the background of the influence of special environmental factors. According to this hypothesis linking oncogenesis and autoimmunity, the subtype of SSc patients with breast cancer and lung carcinomas may represent a model for the development of paraneoplastic immunity, ie, it is considered as a consequence of a specific cancer, and not an etiologically independent disease [27].

6. ANTIBODIES TO Th / To

They occur only in 2–5% patients with SSc [18]. It is highly specific for SSc (up to 99%) and are associated with HLA-DRB1 * 11. They are more common in Caucasians and in 80% of cases are associated with a limited form of the disease. In contrast to patients with a limited form, positive for ACA, carriers of antibodies to Th/To have a shorter interval between the onset of Raynaud's syndrome and the development of hand edema, but the development of digital ulcers or gangrene is not typical. At the same time, patients with these antibodies can develop quite early on all the severe internal organ lesions characteristic of the disease, so their prognosis is worse than in patients with a limited form without an antibodies to Th / To.

7. ANTIBODIES TO UI RNP (ANTI-U1RNP)

Antibodies to UI RNP in NIF give a pure speckled type of glow in high titers, are detected mainly in Africans, African Americans and people of eastern nationalities. Patients with antibodies to UI RNP are often positive for antibodies to Ro / SSA, La / SSB, and Sm antigen [6]. The presence of antibodies to UI RNP is associated with features of SLE, RA, myositis, and many patients meet the criteria for mixed connective tissue disease [21]. The disease begins at a younger age, often subacutely, with signs of inflammatory arthropathy and myopathy. Raynaud's syndrome and hand edema occur early in the disease. Over time, the disease evolves into a typical SSc, predominantly limited form. Internal organ involvement is less common than for other SSc subtypes; however, lung damage and IPL - can be severe.

8. ANTIBODIES TO U3RNP (ANTI-U3RNP)

First described in 1985 [28]. The autoantigen to which they are produced is the fibrillarin protein with a molecular weight of 34 kDa. It is one of the main components of the nucleolar U3-ribonucleoprotein complex [23]. When using RIF, these antibodies have a nucleolar type of luminescence; in patients with SSc, they occur in 4–10% of cases [24]. Antifibrillarin antibodies are highly specific for SSc, although they have also been described in SLE patients [5]. In the United States, they are more common in African American patients than in Caucasians [26]. There are certain clinical differences in SSc patients who are positive for anti-U3RNP and belong to different ethnic groups. Compared to the Japanese, in African Americans and Caucasians, the presence of these antibodies is more often associated with damage to internal organs (IPL, PAH), and the prognosis in these patients is worse [27]. Anti-U3RNPs are associated with diffuse disease and peripheral vasculopathy, including digital gangrene, and muscle damage. About 25–33% of patients with these auto-ATs have proximal muscle weakness in combination with at least one of the following features: increased creatinine phosphokinase levels, myopathic changes on electromyograms and muscle biopsies [28]. Patients with anti-U3RNP often develop all the visceritis characteristic of SS, including renal and gastrointestinal lesions with pseudo-obstruction and malabsorption.

9. ANTIBODIES TO PM / Scl

Antibodies to PM / Scl (about 2% of patients) have a homogeneous nucleolar type of luminescence, rarely found in non-Caucasoids. Positive patients often have inflammatory myopathy in the clinical picture against the background of the classic manifestations of Raynaud's syndrome and skin lesions typical of the limited form of SSc. About 1/4 of patients with SSc and myositis are positive for these antibodies. Myositis is usually relatively mild, responding well to moderate-dose glucocorticoid therapy. Severe damage to internal organs is not typical, therefore the prognosis is favorable [29].

10. ANTIBODIES TO Ku (ANTI-Ku)

They were first described 20 years ago in patients with SSC combined with PM and positive for antibodies to PM / SSc [30]. Subsequently, these antibodies were occasionally detected in other systemic diseases of the connective tissue - in patients with SLE and in patients with such overlapping syndromes as SLE / PM or SLE / PM [31]. In a group of 14 patients positive for anti-Ku, 85% had SSc features [2]. More recent studies have confirmed the association of anti-Ku with muscle damage in SSc [13].

Summarizing the data presented, we can conclude that each of the antibodies is individually detected in a small number of patients with a certain clinical picture, the nature of the course of SSc, prognosis, and has clear genetic associations. It is obvious that the determination of SSc-specific antibodies is very important for assessing the risk of organ manifestations and prognosis. When studying the outcomes of SSC, it was shown that mortality from all causes over 15 years differed in patients with different types of antibodies. Thus, in carriers of ATA, it was 57%, ACA - 78%, anti-URNP - 78%, and ARNCP III - 93% [14].

In the clinical interpretation of the indicators, it should be borne in mind that not all antibodies have one hundred percent sensitivity or specificity in relation to organ pathology. Therefore, dynamic observation is necessary to detect lesions of internal organs, despite the presence of "protective" in relation to the prognosis of antibodies. The determination of antibodies is mainly of qualitative importance; therefore, quantitative measurement has no clinical application, since the repeated determination of antibodies is not very informative.

To what extent clinical differences between subgroups reflect pathogenetic differences in immune dysregulation remains unclear. The connection of sclerodermic auto-ATs with pathogenesis is evidenced by the fact that their circulation in the blood is associated with changes in the levels of cytokines circulating in the plasma.

11. THE VALUE OF SPECIFIC AUTOANTIBODIES IN THE DIAGNOSIS OF SYSTEMIC SCLERODERMA

The initial stages of the disease are potentially reversible, so the early stage of SSc is the most promising in terms of preventing fibrosis. At the same time, the heterogeneity of clinical forms and polymorphism of the clinical picture complicate the timely diagnosis of SSc. For example, Raynaud's syndrome, a marker of SSc, which occurs in 90–95% of patients, is a long-term isolated course, many years before the development of other clinical manifestations of the disease, especially in the limited form. Special studies have shown that the presence of ANF and specific antibodies is an independent predictor of the development of SSc in Raynaud's disease [25]. At the same time, in patients with Raynaud's phenomenon with SSc-specific antibodies and microangiopathy (detected by capillaroscopic examination), the likelihood of SSc development increased 60 times. With long-term follow-up, almost 80% of these patients developed SSc. On the contrary, the absence of these parameters practically excludes the development of SSC in individuals with Raynaud's phenomenon. Long-term prospective observations and modern diagnostic capabilities have allowed the development of new, more sensitive criteria for SSc [16].

It is important that SSc-specific antibodies appear already at the earliest stages - even before the developed clinical picture of the disease (in particular, with "isolated" Raynaud's syndrome), therefore their determination is of diagnostic value at all stages of the disease, including the early one. A doctor of any specialty should be suspected of early SSc if, on examination or in history, the patient has Raynaud's phenomenon, especially in combination with swelling of the hands, even if the swelling occurs intermittently. For such a patient, it is necessary to determine ANF in the blood serum. Raynaud's phenomenon, hand edema and a positive test result for ANF are regarded as justification for a deeper examination, including, first of all, a consultation with a rheumatologist and determination of ATA (Scl-70), ACA and ARNCP-III, as well as video capillaroscopy of the nail bed (revealing dilated capillaries , a decrease in the number of capillaries and other typical signs of scleroderma microangiopathy). If at least one of these predictors of SSc is found, a patient with Raynaud's syndrome and / or swelling of the hands is diagnosed with early scleroderma and must be monitored by a rheumatologist. In the management plan of such a patient, a rheumatologist includes additional studies for the timely detection of pathology of internal organs.

The new criteria turned out to be more sensitive at all stages of SSc. Our own experience with these criteria has shown that they allow the detection of SSc at earlier stages of the disease than the old criteria.

12. AUTOANTIBODIES TO CELL SURFACE (MEMBRANE) AND EXTRACELLULAR ANTIGENS

These antibodies are directed against antigens expressed on the surface of various cells, in particular, fibroblasts and endothelial cells, as well as against matrix metalloproteinases (MMPs), various growth factors, and other extracellular antigens. It is assumed that such antibodies have pathogenetic significance, since they are able to activate signaling intracellular pathways involved in fibrosis and vascular damage in SSc. Having low specificity for SSC, they are common (in 20–100% of cases) and do not always have definite clinical associations.

13. ANTIBODIES TO THE PLATELET-DERIVED GROWTH FACTOR RECEPTOR

A stimulatory profibrotic effect of anti PGFR is assumed, since their binding to the ligand leads to the activation of fibroblasts and the subsequent hyperproduction of reactive oxygen radicals (ROR), which, in turn, support fibroblasts in a state of activation, stimulating cell proliferation and the synthesis of components of the extracellular matrix [27]. The authors found anti PGFR in all patients with SSc, but not in healthy people with SLE, RA, idiopathic pulmonary fibrosis, and primary Raynaud's phenomenon. Interestingly, against the background of B-cell depletion after rituximab treatment, anti PGFR phosphorylation is suppressed in the skin of SSc patients, which may indirectly reflect the "cancellation" of the agonistic effect of antibodies to TGF [28].

Thus, stimulatory antibodies against anti PGFR may have a pathophysiological role in stimulating collagen formation, and these antibodies may be an example of the relationship between immune disorders and the development of fibrosis. However, the data on the high specificity and association with impaired signaling activity of these antibodies remain contradictory and have not been confirmed in other studies. Therefore, their role in the pathogenesis of SSc requires clarification. It should be added that in later studies on large groups of patients, the detection rate of anti PGFR was low and amounts to about 6%.

14. ANTI-ENDOTHELIAL ANTIBODIES (AEAT)

Antiendothelial antibodies (AEAB) are found in 25–85% of patients with SSc, but they are also detected in other RDs. It is known that in SS, the circulation of AEAT is associated with severe vascular disorders - severe Raynaud's syndrome, digital scars and ulcers, pulmonary hypertension, as well as pulmonary fibrosis. High titers of AEAT were associated with severe microangiopathy according to capillaroscopy data [20]. It is believed that after the binding of antibodies to the endothelial surface, the processes of activation of microvascular endothelial cells begin and, possibly, the development of antibody-dependent cell-mediated cytotoxicity [21]. Under the action of AEAT on the surface of endothelial cells, the expression of adhesion molecules (ICAM1, VCAM1, E-selectin) is enhanced, and as a result of activation, the production of interleukin (IL)-1 increases [32]. These changes promote the infiltration of mononuclear cells in the areas of tissue damage, and also induce apoptosis of endothelial cells. Probably, it is the development of endothelial cell apoptosis that triggers the fibrosing process characteristic of SS. Thus, the serum stimulated an increase in the formation of RCP of SSC patients containing AEAT, when added to the culture of endothelial cells, stimulates their apoptosis, and the culture supernatant increases the lifespan of fibroblasts and induces myofibroblast differentiation, as well as collagen production [33]. The antigen to which

AEATs are synthesized has not yet been determined. It is believed that the molecular target (autoantigen) for AEAT on endothelial cells is topoisomerase 1, possibly with the expression of neoepitopes. It is also known that the centromeric B antigen can be expressed on the cell surface, which makes real antibody-mediated induction of apoptosis. The binding of AEAT to nuclear centromeric protein B (CENTR-B) has been shown [34].

It cannot be ruled out that the formation of AEAT may be an epiphenomenon following cell death. At the same time, the possible pathogenetic significance of AEAT is confirmed by new data. Thus, it has recently been shown that immunoglobulins (IgG) of SSC and SLE patients with PAH and AEAT-positive (as opposed to negative patients and healthy individuals), when added to the culture of umbilical human venous endothelial cells, caused an increase in the expression of adhesion molecules on the surface of these cells (ICAM1 and VCAM1) and E-selectin, as well as an increase in the synthesis of IL6, IL8 and CC-chemokine ligand 2 (CCL2). This means that by rearranging endothelial cells to the proadhesive and proinflammatory state of IgG, AEAT can play a pathogenetic role, inducing inflammatory damage to the endothelium, a key moment in the initiation and progression [35]. These results are consistent with data from S.I. Wolf et al. [30], who showed that in patients with diffuse SSc in 32% of cases and limited SSc in 39%, antibodies to ICAM-1 was detected. The authors believe that AEATs from SSc patients cause pro-inflammatory activation of endothelial cells and are not only a marker of the disease, but also participate in its progression. They postulate that one of the specific endothelial surface autoantigens is ICAM1.

15. ANTI-FIBROBLAST ANTIBODIES (AFA)

Antiendothelial antibodies (AEAB) are found in 26–58% of patients with SSc. The presence of AFA in SSc is strongly associated with ATA positivity and pulmonary fibrosis. The binding of AFA to the surface of fibroblasts stimulates the increased production of profibrous and proangiogenic chemokines in them, which can directly or indirectly affect the process of fibrosis [36]. By interacting in vitro with the surface molecules of fibroblasts, AFA stimulate the production of IL1 and IL6, ie, fibroblasts acquire a proinflammatory phenotype [25]. It was shown that alpha-enolase is an autoantigen target for AFA [11]. AFA binding to fibroblasts can also stimulate the production of metalloproteinases and matrix degradation, potentiating tissue inflammation [37]. It is also known that dermal fibroblasts of SSc patients in culture secrete increased amounts of endothelin 1 in comparison with healthy ones, which may be important for the development of Raynaud's syndrome or pulmonary arterial hypertension (PAH) [1].

16. AUTOANTIBODIES TO THE TYPE I RECEPTOR OF ANGIOTENSIN II (ANGIOTENSIN II RECEPTOR TYPE 1 - PIAII) AND THE ENDOTHELIN TYPE A RECEPTOR (PTAE)

It is believed that they induce a profibrotic response of fibroblasts [34]. These antibodies also correlated with vascular manifestations and poor disease prognosis. Further study showed that PIAII and PTAE are expressed on the surface of human peripheral mononuclear cells (monocytes, T- and B-cells), but their expression was reduced in SSC patients compared with healthy people and decreased throughout the disease. The IgG fraction from SSC patients, positive for both antibodies, stimulated peripheral mononuclear cells to more pronounced synthesis of IL8 and CCL18 compared to healthy controls. These effects were significantly suppressed when using selective PIAII and PTAE antagonists. IL8 induction in SS was more pronounced at an early stage of the disease, and high CCL18 concentrations were associated with pulmonary fibrosis and vascular complications [25]. The authors believe that a decrease in the expression of these proteins on mononuclear cells in SSc, the profibrotic and pro-inflammatory effect of autoantibodies to these receptors and the association of these changes with clinical manifestations indicate their participation in antibody-induced activation, mediated through PIAII and PTAE, of immune cells, which may be one of the mechanisms of the pathogenesis of SSc. Antibodies directed against PIAII and PTAE are associated with the leading features of SSc - vasculopathy, inflammatory and fibrotic disorders, which suggests their involvement in the pathogenesis of the disease. The IgG fraction from SSc patients, positive for PIAII and PTAE, in vitro activated human endothelial cells (of microvascular origin), as a result of which the levels of proinflammatory IL8 and VCAM1 increased. At the same time, the ability of endothelial cells to heal wounds decreased. The IgG fraction from SSc patients stimulated fibroblasts (both healthy and sick) to produce type I collagen. All the observed effects were absent when using IgG from healthy donors [16]. The results of these studies are of interest both for substantiating the pathogenetic role of antibodies to PIAII and PTAE in SSc, and for choosing a new target for therapeutic action.

Antibodies to extracellular antigens may also be involved in the development of SSc. In particular, the pathogenetic significance of antibodies to fibrillin 1 and MMP is discussed. The effect of antibodies to fibrillin 1 on fibroblasts in vitro leads to activation of cells through a pathway dependent on transforming growth factor β (TGFβ; Smad3), and their acquisition of a profibrous "scleroderma" phenotype, increasing the production of components of the extracellular matrix. Patients with SS also have elevated levels of antibodies to MMP1 and MMP3, enzymes involved in the degradation of the extracellular matrix [17]. By suppressing the activity of MMPs, they contribute to excess fibrosis. The levels of MMP antibodies in the blood of SSC patients correlate with the severity of cutaneous and visceral fibrosis.

Antibodies to phospholipids, tissue plasminogen activator, etc. are nonspecific for SSC, but apparently involved in the genesis of sclerodermic vasculopathy. Phosphatidylserine-dependent antibodies to thrombin (from the AFA group) activate platelets, their molecular level in the blood correlates with platelet activation markers. Clinically, the circulation of antibodies to phospholipids is associated with arterial thrombosis and peripheral trophic disorders in SSC. The frequency and clinical correlations of antiphospholipid antibodies were studied in 940 patients with SSC. One or more types of antiphospholipid antibodies were found in 24% of them. IgG antibodies to cardiolipins (ACL) have been associated with PAH, especially at high titers, as well as with IPL, including complicated pulmonary hypertension and digital ulcers. Apparently, dysfunction of the endothelium and thrombosis of small vessels can play a role in the pathogenesis of the disease [18].

In recent years, numerous new targets for antibodies, both nuclear and non-nuclear, continue to be studied [19]. Thus, in a small number of SSC patients, in particular in the Japanese and in the American population, antibodies to RuvBL1 / 2 were found, which were associated with moderately increased titers in the RNIF and had a speckled type of luminescence [9]. Searches for an autoantigen using purification, mass spectrometry, and further evaluation using immunoblot resulted in the identification of a complex containing two components, RuvBL1 (pontin) and RuvBL2 (reptin). Examples of the search for new antibodies can form the subject of a separate literature review; they reflect the active process of studying the pathogenesis of SSC and attempts to approach the creation of new options for targeted therapy in this severe suffering.

17. CONCLUSION

SSc-specific antibodies appear at the earliest stage of the disease, before the detailed clinical picture of the disease. Early, before the development of pronounced fibrosis of vital organs, the establishment of a diagnosis allows timely determination of the correct therapeutic tactics; therefore, early detection of disease-specific antibodies is of great practical importance [13]. In connection with their diagnostic significance and inclusion in the new classification criteria for SSc, it is important to introduce the definition of ACA, ATA and ARNCP III into routine clinical practice [25]. Determination of antibodies to RNA proteinase III is of particular importance due to the importance of isolating a special subtype of SSc potentially having a poor prognosis, including due to the increased incidence of cancer. It seems appropriate when formulating the diagnosis of SSc to indicate the positivity for the main "sclerodermic" antibodies [19].

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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