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Assessment of the Relationship between Clinical and Immunologic Parameters in Patients with Rheumatoid Arthritis

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Abstract **Introduction.** Rheumatoid arthritis (RA) is one of the most common forms of rheumatologic pathology (0.5-1.3% of the total population), often developing in people of working age, leading to rapid formation of disability and reduced life expectancy of patients. **The aim of the study** was to investigate clinical and immunologic interrelationships in patients with rheumatoid arthritis. **Material and methods.** To solve the tasks set in the work, 125 RA patients (78% women, 22% men) were examined. The age of the patients ranged from 18 to 76 years (mean age 57.3±1.6 years). The early rheumatoid arthritis group consisted of 85 patients with disease duration from 1 to 12 months (mean duration was 9.7±1.4 months). The comparison group included 40 patients with disease duration of more than 1 year (mean duration was 11.7±1.8 years). The control group consisted of healthy people comparable in sex and age. **Results of the study.** At the first stage of the study, we studied the occurrence of signs characterizing the joint syndrome in RA at different stages of the disease course. These signs included the presence of arthralgias in the hand joints, swelling of at least 1 hand joint, symmetrical arthritis (defined as involvement of any joints within 1 anatomical zone), and swelling of at least 1 major joint (knee, ankle, elbow, shoulder). In addition, the incidence of arthritis of the small joints of the feet was assessed, as well as the presence and duration of morning stiffness. **Conclusions.** Thus, the identified features of cytokine status depending on the serologic variant according to ACCP are in good agreement with our data on the presence of an inverse correlation between clinical parameters of disease activity and the content of TNF-α and IL-4 in the serum of RRA patients and the known unfavorable prognostic value of antibodies to citrullinated proteins. The above changes may indicate in favor of the important diagnostic role of ACCP at the stage of early rheumatoid arthritis.

Keywords Rheumatoid arthritis, Antibodies to citrullinated proteins, Proinflammatory cytokines

1. Introduction

It is known that in recent years in the developed countries of the world there has been a significant increase in the incidence of diseases of the musculoskeletal system and, above all, inflammatory diseases of the joints. Of particular medical and social importance is rheumatoid arthritis (RA), which is a chronic systemic autoimmune disease of connective tissue, accompanied by a predominant lesion of peripheral joints with the development of erosive-destructive changes and ankylosing [1]. Rheumatoid arthritis is one of the most common forms of rheumatologic pathology (0.5-1.3% of the total population), often developing in people of working age, leading to rapid disability and decreased life expectancy of patients [2].

Currently, the concept of early rheumatoid arthritis (ERA) - a conditional clinical and pathogenetic stage of the disease with the duration of active synovitis not more than 1 year, characterized by antigen-specific activation of SE4+ T-lymphocytes, hyperproduction of proinflammatory cytokines in the absence of a number of characteristic morphological features of this disease (formed pannus).

The classical concepts of RA pathogenesis were based on several complementary ideas, including the following. First, the leading role in the initiation and maintenance of the immunoinflammatory process belongs to SB4 T cells [7,11,13]. Cells of monocytic-macrophage origin play a leading role in the local production of proinflammatory cytokines [9]. Destruction of articular cartilage and pannus formation at late stages of RA is caused by the development of autonomous non-immune mechanisms that determine "tumor-like" growth and proliferation of synovial tissue [8].

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It has been established that circulating immune complexes containing autoantibodies can cause hyperproduction by immunocompetent cells of a number of cytokines, in particular TNF-α, IL-1, IFN-α, which occurs in such autoimmune diseases as RA and systemic lupus erythematosus (SLE) [3-6]. It should be noted that so far there has been no direct evidence of the pathogenic role of rheumatoid factor and antibodies to cyclic citrullinated proteins (ACCP), the main families of autoantibodies found in RA patients.

In-depth study of molecular targets of antifilaggrin antibodies allowed us to identify citrulline-containing fragments of the filaggrin molecule as antigenic epitopes. Citrulline is an unusual amino acid formed by the deamination of arginine by the enzyme peptidyl arginine deaminase and is incorporated into the structure of a number of proteins. The necessity of using a combination of peptides was determined by a wide spectrum of anti-citrulline antibodies presented in the serum of RA patients. The possibility of synthesis of ACCP by plasma cells of synovial membrane and synovial fluid in patients seropositive for these autoantibodies was shown [12]. Currently, ACCP are one of the most promising laboratory markers of rheumatoid arthritis, since the use of ELISA technique makes the test easily standardizable and allows quantitative consideration of the obtained result.

At the same time, the American College of Rheumatologists (ACR) classification criteria used since 1987 do not allow to establish the diagnosis of early RA with high accuracy and differential diagnosis with other forms of arthritis. The only laboratory criterion, rheumatoid factor (RF), which is included in the ACR criteria, is often negative at the onset of the disease and is characterized by low specificity.

It is proved that immune disorders in early rheumatoid arthritis are diverse and cover the cellular and humoral parts of the immune system. Of particular interest is the study of SB-antigens of lymphocytes, as well as indicators of the cytokine spectrum, which play a key role in the development of the immunoinflammatory process. In recent years, a number of studies have been devoted to the study of lymphocyte phenotype and cytokine immunity parameters, with only a few of them conducted at the early stage of RA. However, there have been no comprehensive studies of immunologic changes in RA in comparison with clinical parameters in dynamics. The system of anti-inflammatory cytokines attracts unremitting interest of researchers. This is due to the dominant ideas that among the mechanisms of immunoinflammatory process observed in autoimmune diseases, including rheumatoid arthritis, the most important is the balance between pro- and anti-inflammatory cytokine systems, rather than an isolated increase in any component of the proinflammatory link.

The anti-inflammatory cytokines involved in the realization of synovitis primarily include IL-lα, IL-1β, IL-6, and TNF-α [10]. This group unites cytokines of predominantly monocytic -macrophage origin. These are key effector molecules that trigger most pathogenetic mechanisms of inflammation, including cell activation and proliferation, expression of adhesion molecules, adhesion mechanisms, destruction of bone and cartilage tissue, as well as affecting angiogenesis, which has been shown in many in vivo and in vitro models of inflammation.

Thus, due to the absence of characteristic clinical and laboratory changes at the early stage of rheumatoid arthritis, verification of the diagnosis is often difficult, which raises the question of the need for further search for additional immunologic diagnostic criteria and predictors of an unfavorable clinical course of this disease.

The aim of the study was to investigate the clinical-immunologic relationships in patients with rheumatoid arthritis.

2. Material and Methods

Table 1. Clinical characteristics of patients with early RA

Indicators	Number of Patients (n=85)	% ratio to total number
women	64	75,3
men	21	24,7
Age:		
- up to 20 years	4	4,7
-21-40 years	11	12,9
- 41-60 years	48	56,5
- over 60	22	25,9
Duration of symptoms (months):		
- up to 3 months	22	25,9
-3-6 months	37	43,5
- 6-9 months	8	9,4
- 9-12 months	18	21,2
Clinical and anatomical characterization :		
- joint form	38	44,7
- joint-visceral form	47	55,3
Clinical and immunologic type of RA :		
- seropositive	36	42,3
- seronegative	49	57,7
The nature of the joint syndrome:		
- monoarthritis	1	1,2
- oligoarthritis	33	38,8
- polyarthritis	51	60
Degree of RA activity:		
I - low	24	28,2
II - media	47	55,3
III - high	14	16,5
X-Ray stages:		
I	52	61,1
II	33	38,9
III	0	0
IV	0	0

To solve the tasks set in the work, 125 RA patients (78% women, 22% men) were examined. The age of the patients ranged from 18 to 76 years (mean age 57.3±1.6 years). The early rheumatoid arthritis group consisted of 85 patients with disease duration from 1 to 12 months (mean duration was 9.7±1.4 months). The comparison group included 40 patients with disease duration of more than 1 year (mean duration was 11.7±1.8 years). The control group consisted of healthy people comparable in sex and age (n=26).

The clinical characteristics of patients with early RA are presented in Table 1.

Only 42.3% of patients with early RA (ERA) were seropositive for rheumatoid factor. Joint involvement was predominantly characterized by oligoarthritis of large joints (38.8%). Among the examined patients of the main group, the average degree of activity of the immunoinflammatory process prevailed (55.3%), as well as the 1-P radiologic stages of the disease (Steinbroker classification) (61.1% and 38.9%, respectively). Predominantly articular form of RA was diagnosed in 38 (44.7%) patients. Systemic manifestations of RA were detected in 47 (55.3%) patients. The most frequent of them were fever (in 38.8%), weight loss (in 21.2%), lymphadenopathy (in 10.6%), anemia (in 10.6%), amyotrophies (in 7.1%). Such systemic manifestations as rheumatoid nodules (in 3.5%), rheumatoid vasculitis (in 4.7%), cardiovascular system damage in the form of myocarditis and/or pericarditis (in 3.5%) were diagnosed less frequently in the examined patients. Anemic syndrome was recorded in 10.6% of cases, and the frequency of anemia in women was significantly higher than in men ($p < 0.01$). The comparison group consisted of rheumatoid arthritis patients with disease duration of more than 1 year (n=40). Clinical characteristics of patients with long-term current RA are presented in Table 2.

The age and sex composition of the group of patients suffering from long-term current RA was comparable to that of RRA patients. Women (90.0%) of middle and older age groups (40-70 years) also prevailed among them.

The majority of RA patients were seropositive for rheumatoid factor (82.5%). In 100% of cases there was symmetric polyarthritis. Among the examined patients of the comparison group the average degree of activity of the immunoinflammatory process prevailed (50%), as well as II-III radiologic stages of the disease (Steinbroker classification) (60% and 30%, respectively). Predominantly articular form of RA was diagnosed in 3 (7.5%) patients. Systemic manifestations of RA were recorded in 37 (92.5%) patients. The most frequent of them were lymphadenopathy (in 30%), weight loss (in 40%), amyotrophies (in 85%), anemia (in 50%), fever (in 52.5%), rheumatoid nodules (in 32.5%). At the same time, such systemic manifestations as rheumatoid vasculitis (in 7.5%), diffuse interstitial pulmonary fibrosis (in 10%), nephropathy (in 2.5%), cardiovascular system damage (in 10%) were diagnosed less frequently in this group of patients.

Table 2. Clinical characteristics of RA patients

Indicators	Number of Patients (n=40)	% ratio to total number
women	36	90
men	4	10
Age:		
-up to 20 years	0	0
-21-40 years	4	10
- 41-60 years	28	70
- over 60	8	20
Duration of symptoms (months):		
- up 2 year	1	2,5
-2-10 year	24	60
- более 10 year	15	37,5
Clinical and anatomical characterization:		
- joint form	3	7,5
- joint-visceral form	37	92,5
Clinical and immunologic variant of RA :		
- seropositive	33	82,5
- seronegative	7	17,5
The nature of the joint syndrome:		
- monoarthritis	0	0
- oligoarthritis	0	0
- polyarthritis	40	100
Degree of RA activity:		
I - low	11	27,5
II - media	20	50
III - high	9	22,5
Radiologic stage:		
I	0	0
II	24	60
III	12	30
IV	4	10

Thus, the group of patients with early RA was characterized by a not quite typical joint syndrome (oligoarthritis of large joints), a significantly lower frequency of the seropositive form of the disease, and a different spectrum of extraarticular manifestations of the disease. The frequency of visceral manifestations in patients of both groups is presented in Table 3.

It can be seen that the frequency of detection of fever and weight loss as indicators reflecting the activity of the immunoinflammatory process did not depend on the duration of the disease. The frequency of detection of rheumatoid nodules, diffuse interstitial pulmonary fibrosis, cardiovascular lesions, and nephropathy was significantly higher in patients with long-term RA.

Table 3. Visceral manifestations of RA in patients with early and long-standing rheumatoid arthritis

Extra-articular manifestations	Patients ERA (n=85)	% ratio to total number	Patients RA (n=40)	% ratio to total number
Amyotrophy	6	7Д	34	85
Lymphadenopathy	9	10,6	12	30
Anemia	9	10,6	20	50
Weight loss body weight	18	21,2	16	40
Fever	33	38,8	21	52,5
Rheumatoid nodules	3	3,5	13	32,5
Rheumatoid vasculitis	4	4,7	3	7,5
Myocarditis and/or pericarditis	3	3,5	4	10
Diffuse interstitial pulmonary fibrosis	0	0	4	10
Nephropathy	0	0	1	2,5

The most frequently diagnosed comorbidities in patients with early RA were hypertension (30.6%), CHD (21.2%), chronic pyelonephritis (19.1%), thyroid diseases (14.7%) in the form of diffuse nodular nontoxic goiter and autoimmune thyroiditis. Indications of gastrointestinal pathology were found in 39.3% of RA patients. According to the results of instrumental examination and anamnestic data, 14.1% of patients were diagnosed with chronic gastritis, 12.9% - with peptic ulcer disease of the stomach and 12-perintestine (out of exacerbation), 12.3% - with biliary stone disease. Chronic bronchitis was less common - in 8.2% of cases, bronchial asthma - in 1.4% of cases. Type P diabetes mellitus was observed in 7.1% of RA patients. Chronic viral hepatitis C was diagnosed in 2.3% of patients. The spectrum of concomitant pathology in patients of the comparison group was comparable to that in the main group. However, it should be noted that the frequency of CHD and hypertension was higher (34.7% and 35.5%, respectively).

Studies of immunologic status were carried out in laboratories of the City Hospital of the Central medical association of Samarkand city.

Blood samples from patients were collected according to standard methodology into vacutainer tubes and transported to the laboratory. Immunologic study included determination of the RF content, the level of ACCP, and cytokine profile indicators.

The study included determination of a wide spectrum of cytokine immunity link in peripheral blood, including the following indicators: IL-6, IL-10, TNF-α.

3. Results of the Study

At the first stage of the study, we studied the occurrence of signs characterizing the joint syndrome in RA at different stages of the disease course. These signs included the presence of arthralgias in the hand joints, swelling of at least 1 hand joint, symmetrical arthritis (defined as involvement of any joints within 1 anatomical zone), and swelling of at least 1 major joint (knee, ankle, elbow, shoulder). In addition, the incidence of arthritis of the small joints of the feet was assessed, as well as the presence and duration of morning stiffness. The frequency of the above signs was assessed at three points: from anamnesis during the first month from the onset of the joint syndrome (ascertained from the patient by filling out a formalized questionnaire), during examination by a rheumatologist in the process of establishing the diagnosis, and during prospective follow-up after 1 year.

One of the most frequent symptoms of arthritis is pain in the affected joint - arthralgia. We evaluated the frequency of arthralgias of the hand joints in patients with early RA at different stages of the disease course.

Arthralgias of small joints of the hands were described by 52.5% of patients in the main group during the first month of the disease, and by 92.5% of patients with early RA at the time of diagnosis verification. Differences in the frequency of this sign between patients at the debut of rheumatoid arthritis and at the time of diagnosis were highly statistically reliable ($p<0.001$). However, in patients under prospective follow-up for 1 year after diagnosis verification, we found a decrease in the occurrence of this symptom to 67.5%. Significant differences in the frequency of detection of these signs between the subgroups of patients with early RA at the time of diagnosis and after 1 year of prospective follow-up are also reliable ($p<0.01$). The differences between the subgroups of patients with early RA at the disease debut and after 1 year from the moment of diagnosis are not reliable.

An important diagnostic sign of RA, along with symmetric lesions of small joints of the hands, is the involvement of small joints of the feet in the pathologic process. This is reflected in the well-known statement that "hands and feet are the visiting card of a patient with rheumatoid arthritis". The average duration of morning stiffness in patients with early RA was 20.3±29.4 minutes at the disease debut, 123.8± 181.3 minutes at the time of diagnosis, and 105.7±114.8 minutes after 1 year of prospective follow-up. Differences between this index in RA patients at the disease debut and at the time of diagnosis were statistically reliable ($p<0.01$).

We studied the occurrence of rheumatoid factor and ACCP. In patients with early rheumatoid arthritis, RF is

detected in 44% of cases. At the same time, ACCP are detected much more frequently - in 62% of cases. Differences in the frequency of detection of these autoantibodies in patients of the main group are reliable in favor of ACCP ($p<0.05$). On the other hand, in patients with long-term rheumatoid arthritis the occurrence of RF and ACCP is 88% and 82%, respectively. When conducting a comparative study to establish relationships between the levels of ACCP and the severity of the joint syndrome assessed by the Ritchie index, DAS index, HAQ, VAS pain score, as well as the presence of systemic manifestations, we were able to identify significantly higher values of indicators characterizing the severity of the joint syndrome, as well as VAS pain parameters in ACCP -seropositive patients with RA.

Thus, the mean values of DAS index in the group of patients seropositive for ACCP amounted to 5.54±1.3, while in patients seronegative for this autoantibody - 4.74±1.04 ($p<0.05$). The validity of the above-mentioned differences was confirmed by the detection of direct correlation between DAS value and ACCP titer ($r=0,32$ $p<0,05$), as well as between the number of painful joints and ACCP titer ($r=0,33$ $p<0,05$). The mean value of VAS pain score was 55.4±25.4 mm in the group of patients with early RA seropositive for ACCP, and ~42.7±23.8 mm among seronegative patients.

Along with this, activation of anti-inflammatory cytokines was observed both in patients with early and in patients with long-term rheumatoid arthritis. This was manifested by a significant increase in IL-10 content in serum in patients of both groups in comparison with the control group. These unidirectional shifts in the system of pro- and anti-inflammatory cytokines in patients with rheumatoid arthritis can be considered as a manifestation of endogenous homeostatic mechanisms aimed at limiting the intensity of the immunoinflammatory process.

To verify this assumption we determined correlations between the content of pro- and anti-inflammatory cytokines in patients with early and long-term RA. The obtained results are presented in Table 5.

It follows from the data presented in Table 5 that the revealed highly significant positive correlations between the serum levels of IL-4 and IL-10, on the one hand, and the content of key proinflammatory cytokines, on the other hand, in both groups of examined patients confirm the assumption of increased production of anti-inflammatory interleukins in response to hyperproduction of proinflammatory cytokines in RA patients.

The revealed significant differences in IL-10 content between the groups of patients with early and long-term RA seem to reflect the depletion of such compensatory homeostatic mechanisms mediating the regulatory anti-inflammatory potential as the disease progresses.

At the same time, we thought it was important to study the relationship between the degree of disease severity and cytokine levels in peripheral blood.

Table 4. Clinical characteristics of ERA patients depending on the presence of various autoantibodies (n=85)

Parameter	CCP		RF	
	+	-	+	-
Number of swollen joints	9,7±8,4	7,5±6,5	8,1±9,2	9,4±7,3
Number of painful joints	24,3±13,0	22,4±9,8	22,7±13,1	24,2±11,7
The Ritchie Index	46,4±23,9	38,3±19,8	47,7±29,0	42,2±19,6
The DAS Index	5,3±1,3	4,8±1,0	5,6±1,4	4,9±1,1
Vas pain, mm	51,1±24,8	45,0±24,1	46,3±27,6	50,7±23,3
HAQ, points	0,9±0,5	1,1±0,5	1,0±0,6	1,0±0,6
ESR, mm/hours	35,0±26,2	32,3±20,0	38,5±27,2	32,2±23,1
C-reactive protein, mg/l	65,8±89,1	23,0±29,2	68,5±106,8	45,8±61,3
Duration morning stiffness, min	151,2±209,8	60,0±46,7	60,0±63,8	154,6±210,8

Note: *p<0.05; ACCP - antibodies to cyclic citrullinated peptide

Table 5. Correlative relationship between levels of some pro- and anti-inflammatory cytokines in patients with early and long-standing rheumatoid arthritis

		IL-6	TNF-α	IL-1β	ESR	C-reactive protein
Early RA (n=40)	IL-4	insufficient data	н/д	0,36*	insufficient data	insufficient data
	IL-10	insufficient data	0,33*	n/d	insufficient data	insufficient data
Long-term RA (n=40)	IL-4	insufficient data	0,43**	0,36**	insufficient data	insufficient data
	IL-10	insufficient data	0,53***	0,63***	insufficient data	insufficient data
All RA patients (n=80)	IL-4	insufficient data	0,28**	0,28**	insufficient data	insufficient data
	IL-10	insufficient data	0,41***	0,37***	insufficient data	insufficient data

Note: *p<0.05; **p<0.01; ***p<0.001; insufficient data - correlation relationship is statistically insignificant

It turned out that in RRA patients there was a direct correlation between the number of painful joints and the levels of IL-10 and IL-4 in blood serum ($r=0,31$ $p<0,05$ and $r=0,36$ $p<0,05$ respectively). It is known that against the background of immunopathologic process progression there is an increase not only of proinflammatory but also of anti-inflammatory cytokines. It should be noted that in patients with early RA a negative correlation between IL-4 content and ESR was revealed ($r=-0,30$ $p=0,05$), which reflects the anti-inflammatory property of this cytokine. These data may explain the fact that IL-10 and IL-4 hyperproduction is aimed at limiting the immunoinflammatory process.

The above data may indicate in favor of the important diagnostic role of ACCP at the stage of early rheumatoid arthritis. Determination of blood levels of IL-1β, IL-4, IL-6 can be used as additional laboratory and prognostic criteria of rheumatoid arthritis.

4. Conclusions

Thus, the identified features of cytokine status depending on the serologic variant according to ACCP are in good agreement with our data on the presence of an inverse correlation between clinical parameters of disease activity and the content of TNF-α and IL-4 in the serum of RRA patients and the known unfavorable prognostic value of antibodies to citrullinated proteins. The above changes may indicate in favor of the important diagnostic role of ACCP at the stage of early rheumatoid arthritis. Determination of cytokine immunity parameters, especially IL-1β, IL-4, IL-6, TNF-α, can be used to assess the degree of RA activity and as prognostic criteria.

Conflict of Interest

The authors declare no conflicts of interest or special funding for the current study.

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