CLINICAL AND IMMUNOLOGICAL RELATIONSHIP BETWEEN COVID-19 AND RHEUMATOID ARTHRITIS

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Abstract: Rheumatoid arthritis is the most common inflammatory disease of the joints, characterized by erosive symmetrical polyarthritis in combination with systemic immune-inflammatory damage to internal organs. One of the most severe and widespread inflammatory diseases of the joints. Rheumatoid arthritis is a common disease, occurring in all countries in approximately 1% of the total population. New data have shown that respiratory viral infections may increase the risk of autoimmune inflammatory arthritis, such as rheumatoid arthritis. In addition, infections may worsen the disease in patients with inflammatory arthritis.

Key words: COVID-19, immune-inflammatory rheumatic diseases, diagnostics, cytokines.

Relevance: The incidence of the new coronavirus COVID-19 is considered by the world community as an emergency of international concern. Along with its enormous social significance, the COVID-19 pandemic has highlighted a number of fundamentally new clinical and fundamental problems in the immunopathology of human diseases. This problem is extremely relevant for patients suffering from immune-mediated inflammatory rheumatic diseases, due to their higher susceptibility to infectious complications [1]. The coronavirus disease 2019 (COVID-19) pandemic, etiologically associated with the SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) virus, has drawn attention to new clinical and fundamental problems in the immunopathology of human diseases associated with virus-induced autoimmunity and autoinflammation [2]. Currently, the infection caused by the new coronavirus – COVID-19, is considered by the world community as a global emergency. Rheumatologists are particularly concerned about this problem, since patients with immune-inflammatory rheumatic diseases (IIRD) have an increased risk of developing infectious diseases and are treated with drugs that have an immunosuppressive effect [3,8,9]. The early period of rheumatoid arthritis plays a decisive role in the development and progression of immune complex inflammation. At the same time, early diagnosis of RA allows for adequate treatment and a more significant clinical effect, as well as improving the prognosis of this disease [5,10,12]. Early diagnosis, regular monitoring of disease activity, and a treat-to-target strategy are recommended for both CPA-positive and -negative RA, but the efficacy of individual drugs in these

subtypes may vary significantly. The development of autoimmune and rheumatic diseases in patients who have had COVID-19 is a pressing public health issue. COVID-19 may unmask previously undiagnosed rheumatic conditions or trigger the disease denovo [6,10]. As noted earlier, patients with IVR3 have a higher risk of developing infections than the general population, which reflects the immunopathological disorders inherent in these diseases. In addition, the risk of infection is clearly associated with the degree of activity of the process [7,10,11].

Materials and methods of the study: The study included 120 patients with rheumatoid arthritis (meeting the criteria of EULAR/ACR, 2010). During the study, patients were divided into 2 groups: the main group - 60 patients with rheumatoid arthritis who had COVID-19, and the control group - 60 patients with rheumatoid arthritis who had not had COVID-19. Patients were studied in comparison based on the analysis of clinical, laboratory and instrumental parameters.

Results of the study: At the time of the study, the average age of patients was 41.7±11.7 years, the average duration of the disease was 10.7±5.8 years. According to the anamnesis, 75 (62.5%) patients with RA had a gradual onset of the disease, and 35 (29%) had an acute onset. The course of the disease in the main group (RA patients who had COVID-19) differed in a number of aspects. According to current scientific data, viral infections can increase the severity of inflammation or aggravate an existing immune imbalance in autoimmune diseases, including RA. According to our observations: morning sickness was observed in 89% of patients in group I and in 82% of patients in the control group. The duration of morning stiffness averaged 89±19.3 minutes in group I and 70±14.8 minutes in group II. Thus, it was found that both the percentage of morning stiffness and its duration were higher in RA patients who had COVID-19. Participants in Group I experienced frequent fatigue, general malaise, and even sleep disturbances or constant weakness, which are symptoms of “post-Covid syndrome”. In Group II, these symptoms were observed comparatively less frequently. Patients who recovered from COVID-19 showed elevated levels of almost all indicators. This is explained by the fact that in RA, the existing autoimmune process is further aggravated by a viral infection, triggering a cascade of inflammatory reactions. Thus, previously unobserved or rare complications may also be more pronounced in RA patients who have had COVID-19 in clinical practice (Table 1).

Table 1

Clinical signs	Group I (abs)	Group I (%)	Group II (abs)	Group II (%)
Increased subfebrile temperature	26	43.3	15	25.0
Myalgia	34	56.7	23	38.3
Lymphadenopathy	12	20.0	9	15.0
Rheumatoid nodule	9	15.0	7	11.7
Defiguration	24	40.0	21	35.0
Deformation	24	40.0	20	33.3
Ankylosis	6	10.0	5	8.3
Contracture	11	18.3	9	15.0
Cutaneous vasculitis	5	8.3	3	5.0
Keratoconjunctivitis (Sjögren's syndrome)	4	6.7	2	3.3
Pleurisy / pericarditis	6	10.0	3	5.0
Interstitial lung injury	10	16.7	6	10.0
Systemic vasculitis	5	8.3	4	6.7

Note: "Abs" is the absolute number (how many out of 60 people it occurred in). "%" shows how many out of 60 it occurred in as a percentage.

Laboratory and instrumental data of patients with RA who had COVID-19: It is known that the assessment of disease activity in patients with RA is important for further treatment of the patient and prognosis of the disease course. In the study groups, the level of C-reactive protein was 1.5 times higher in the main group than in the control group, and 11.3 times higher than in healthy people ($p<0.05$). The level of C-reactive protein in the control group was 5.9 times higher than in the control group ($p<0.05$). Thus, coronavirus infection affects the activity of the disease in patients with RA, and the severity of the inflammatory process aggravates the course of the disease. In Group II, the duration of RA was up to 6 months, it was detected in 40.3% of patients ($p<0.05$). Isolated erosions were detected in another 9% of patients in this group ($p<0.05$). Most patients in group III (60.6%) showed signs of osteoporosis, small cystic foci of luminal changes at the site of the disease, and 18.8% of patients had single erosions ($p<0.05$).

The main group had the highest frequency of stage III sacroiliitis (35%, i.e. 21 patients). The control group had a higher incidence of stage II sacroiliitis (52.5%, i.e. 21 patients). Stage I sacroiliitis was also quite common in the control group (25%, 10 patients). Stage III sacroiliitis (with joint erosions and bone narrowing) was 2.5 times more common in patients with COVID-19. Thus, severe cases of sacroiliitis are more common in patients who have had COVID-19. This condition may be associated with a long course of the disease and high inflammatory activity.

Dynamics of proinflammatory cytokines in selected groups: in local inflammation foci in RA patients, immune cells and proinflammatory cytokines, including IL-6, IL-17 and TGF β1, play a decisive role in the pathogenesis of autoimmune inflammation. Activation of cytokines and immunity in patients with COVID-19 is similar to that in patients with RA. Based on these data, we examined the cytokines IL-6, IL-17 and TGF β1. When studying the concentration of TGF β1 in blood plasma, it was 26±0.6 ng/ml and 21±0.6 ng/ml in the main and control groups, respectively, and in healthy individuals – 15±0.6 ng/ml. The IL-6 level increased by 1.5 times compared to the control group and averaged 32.31±1.6 pg/ml ($p<0.05$). It is known that IL-6 directly induces the synthesis of acute phase proteins in hepatocytes and stimulates the production of antibodies by B cells, controlling the differentiation of plasma cells. Based on the findings of scientific studies, IL-17. It was found that its level in the blood serum of patients with early RA was three times higher than that of patients in the control group (19.30±2.79 pg/ml and 6.23±2.98 pg/ml, respectively; $r<0.05$). Elevated cytokine levels indicate more active inflammation in patients with COVID-19 (Table 2).

Table 2

Serum cytokine frequencies in RA patients and control subjects with COVID-19

Cytokines pg/ml	Control group (n=20)	Patients with RA who have had covid (n=55)	Reliability of differences (p)
IL-6	13,89±4,56	32,31 ±1,6*	p<0,05
IL-17	6,23± 2,98	19,30±2,79*	p<0,05
TGF β1	7,72±3,98	26±0.6 ±9,96*	p<0,05

Note: * p<0.05. Significant difference from healthy people

When monitoring the amount of cytokines in dynamics, it took the following form according to the table:

Dynamics of cytokine indicators in patients

	Main group			Control group		
Indicator	1-month	3 month	6-month	1-month	3 month	6-month
Interleukin 6 (1,3 - 6,8 пг/мл)	32,31 ±1,6*	24,31 ±1,3*	13,31 ±2,6*	23,89±4,56	13,89±4,56	7,9±4,56
Interleukin 17 (87-104 пг/мл)	159,30±2,79*	142,30±3,79*	135,30±2,79*	148,23± 2,98	110,23± 2,98	98,23± 2,98

When comparing the results of immunoinflammatory markers, a directly proportional increase in IL-6 and IL-17A was noted compared to C-reactive protein.

Expression of radiographic features in groups

Radiological sign	Patients with RA who had COVID-19 (%)	RA patients who did not have COVID-19 (%)
Periarticular osteopenia (decreased bone density)	77	60
Accumulation of fluid in the joint cavity	67	54
Changes in the composition of the joint space (narrowing of the joint space)	57	50
Erosion	62	55
Subluxation/dislocation (dislocation of joints)	37	30
Deformation of joints	46	39
Cystic changes	33	25

Patients with RA who had COVID-19 had higher rates of many radiographic features (periarticular osteopenia, joint effusion, erosions, subluxation/dislocation, joint deformity, and cystic changes) compared with patients who did not have COVID-19. This is explained by the fact that COVID-19 infection negatively affects the course of RA, causing additional inflammation and tissue damage.

Conclusions: The pandemic and COVID-19 are not only an emergency in global health care, but also a major factor in global problems. This problem is especially relevant for patients with IVRZ. Thus, the revealed data may testify in favor of an important diagnostic role of RA. Evaluation of laboratory and instrumental parameters can be used as prognostic criteria for rheumatoid arthritis.

LIST OF REFERENCES

1. Belov B.S., Muravyova N.V., Tarasova G.M. COVID-19: rheumatological aspects // Effective pharmacotherapy. 2020. T. 16. № 16. C. 18–25. DOI 10.33978/2307-3586-2020-16-16-18-25
2. Nasonov E.L. Coronavirus disease 2019 (COVID-19) pandemic and autoimmune rheumatic diseases: results and prospects. Scientific and practical rheumatology. 2024;62(1):32-54. https://doi.org/10.47360/1995-4484-2024-32-54
3. Belov B.S., Karateev A.E. COVID-19: a new challenge for rheumatologists. Modern Rheumatology. 2020;14(2):110-116. https://doi.org/10.14412/1996-7012-2020-2-110-116
4. Sokolova V.V., Lapin S.V., Moskalov A.V., Mazurov V.I. Clinical and immunological relationships in early rheumatoid arthritis. Medical Immunology. 2007;9(6):635-642. https://doi.org/10.15789/1563-0625-2007-6-635-642
5. Dibrov D.A. ACCP-negative rheumatoid arthritis — clinical and immunological features. Scientific and practical rheumatology. 2022;60(3):314-326. https://doi.org/10.47360/1995-4484-2022-314-326
6. G.G. Taradin, T.E. Kugler, I.S. Malovichko, L.V. Kononenko. Acute arthritis associated with COVID-19. Almanac of Clinical Medicine. 2022; 50 (2): 139–148. doi: 10.18786/2072-0505-2022-50-015.
7. Belov B.S., Muravyova NV, Tarasova GM. COVID-19 and rheumatology: so far, so close. Medical Council. 2020;(8):135-143. https://doi.org/10.21518/2079-701X-2020-8-135-143
8. Akhmedov H.S. Features of the immune status in rheumatoid arthritis depending on the climatic, geographical and ecological zones of Uzbekistan. Scientific and practical rheumatology. 2016;54(2):183-186. https://doi.org/10.14412/1995-4484-2016-183-186

9. M.F. Beketova, V.V. Babak, M.D. Suprun, T.V. Beketova, O.A. Georginova. On the issue of late complications of COVID-19 in patients with rheumatic diseases. Scientific and practical rheumatology. 2022;60(2):162–164.
10. Mazurov V.I., Belyaeva I.B., Sarantseva L.E., Chudinov A.L., Bashkinov R.A., Trofimov E.A., Smulskaya O.A., Inamova O.V., Petrova M.S., Melnikov E.S. The influence of a new coronavirus infection on the clinical course of immunoinflammatory rheumatic diseases // Bulletin of the North-West State Medical University named after I.I. Mechnikov. 2021. T. 13. № 2. C. 39–47. DOI: https://doi.org/10.17816/mechnikov7226.
11. A.M. Kozodaeva. M.Sh. Shingarova. DEBUT OF JUVENILE RHEUMATOID ARTHRITIS AFTER CORONAVIRUS INFECTION. Russian pediatric journal (Russian journal). 2024; 27. Supplement 1 https://doi.org/10.46563/1560-9561-2024-27-S1
12. Korolev M.A., Letyagina E.A., Sizikov A.E., Bogoderova L.A., Ubshaeva Yu.B., Omelchenko V.O., Akimova A.A., Mullagaliev A.A., Chumasova O.A., Kurochkina Yu.D. Immunoinflammatory rheumatic diseases and COVID-19: analysis of clinical outcomes according to the registry of patients of the Novosibirsk region receiving therapy with genetically engineered biological drugs. Therapeutic archive. 2022;94(5):636–641. DOI: 10.26442/00403660.2022.05.201502.