CIRCULATING IMMUNE COMPLEXES IN THE PATHOGENESIS OF POST-COVID JOINT SYNDROME

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RESUME

Background. *A common manifestation of the post-COVID syndrome is damage to the articular apparatus. Considering the role of circulating immune complexes in the occurrence of postinfectious and immune lesions of joints, as well as their participation in the immunopathogenesis of the acute period of infection, it can be assumed that they are involved in the formation of joint syndrome after COVID-infection.*
The aim. *To assess the involvement of circulating immune complexes in the pathogenesis of various clinical variants of post-COVID joint syndrome.*
Materials and methods. *Sixty two patients with post-COVID syndrome and complaints of damage to the musculoskeletal system were examined. All patients had suffered coronavirus infection during the previous 12 months. All patients underwent radiographic and ultrasound examination of the joints. In the blood serum the total content of IgM, IgG and IgE was determined. Circulating immune complexes in peripheral blood were determined by precipitation method.*
Results. *The post-COVID joint syndrome in the examined patients manifested itself in four variants, which differed clinically and had different immunological characteristics. High levels of circulating immune complexes were detected in arthralgia, arthritis, and the onset of arthropathy and were accompanied by elevated titers of IgM and IgG. With the progression of arthropathy, the circulating immune complexes content in the blood of patients often corresponds to the borderline level with low IgM and IgG values.*
An increased IgE titer was recorded in the blood of patients with arthritis, onset and progression of arthropathy, and there were no manifestations of allergy and the allergic history was negative in the majority of the examined.
Conclusion. *Thus, the immunocomplex mechanism of damage plays an important role in the pathogenesis of arthralgia, arthritis and the onset of osteoarthropathy, but not its progression in post-COVID syndrome. IgE is actively involved in the formation of arthritis, the progression of osteoarthropathy, and especially in its onset.*

Key words: *post-COVID syndrome; post-COVID joint syndrome; circulating immune complexes; immunoglobulins; mast cell activation syndrome*

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РОЛЬ ЦИРКУЛИРУЮЩИХ ИММУННЫХ КОМПЛЕКСОВ В ПАТОГЕНЕЗЕ ПОСТКОВИДНОГО СУСТАВНОГО СИНДРОМА

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РЕЗЮМЕ

Частым проявлением постковидного синдрома является повреждение суставного аппарата. Учитывая роль циркулирующих иммунных комплексов в возникновении постинфекционных и иммунных поражений суставов, а также их участие в иммунопатогенезе острого периода инфекции, можно предположить их причастность к формированию суставного синдрома после COVID-инфекции.
Цель исследования: *оценить роль циркулирующих иммунных комплексов в патогенезе различных клинических вариантов постковидного суставного синдрома.*
Методы. *Обследовано 62 пациента с постковидным синдромом и жалобами на поражение мышечно-суставного аппарата. Перенесенная COVID-19-инфекция была подтверждена лабораторно. Всем пациентам проведено инструментальное обследование: рентгенография и ультразвуковое исследование суставов. В сыворотке крови оценивали общее содержание IgM, IgG и IgE. Уровень циркулирующих иммунных комплексов в периферической крови определяли методом преципитации.*
Результаты. *Суставной синдром в постковидном периоде у обследованных пациентов клинически проявлялся в виде четырех вариантов: изолированной артралгии, артрита, дебюта и прогрессирования артропатии. Высокие уровни циркулирующих иммунных комплексов были выявлены при артралгии, артрите и дебюте артропатии и сопровождались повышенными титрами IgM и IgG. При прогрессировании артропатии содержание циркулирующих иммунных комплексов в крови у пациентов зачастую соответствовало пограничному уровню при невысоких значениях IgM и IgG.*
Повышенный титр IgE зафиксирован в крови у пациентов с артритом, дебютом и прогрессированием артропатии, причем проявления аллергии отсутствовали и аллергологический анамнез был отрицательным у большинства обследованных.
Заключение. *Таким образом, иммунокомплексный механизм повреждения играет важную роль в патогенезе артралгии, артрита и дебюта остеоартропатии, но не ее прогрессирования при постковидном синдроме. В формировании артрита, а также при прогрессировании остеоартропатии и, особенно, при ее дебюте принимают активное участие IgE.*

Ключевые слова: *постковидный синдром; постковидный суставной синдром; циркулирующие иммунные комплексы; иммуноглобулины; синдром активации тучных клеток*

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INTRODUCTION

After the acute phase of SARS-CoV-2 infection, some patients may experience post-COVID syndrome (PCS). In addition to respiratory, cardiovascular, and neurological damage, joint pathology may occur, persisting and worsening over several months [1]. The incidence of joint damage in the post-COVID period (PCP) reaches 65 % [2]. Joint syndrome (JS) manifests in 80 % of cases and progresses in 20 % [3]. The development of JS depends on the severity of the acute COVID-19 infection [4]. Risk factors for JS in post-COVID patients include female gender, older age, pre-existing arthralgia, prolonged hospitalization, and a history of joint pain at the onset of the infection [5, 6]. Another significant risk factor for JS in PCP is a high body mass index [7].

Researchers' opinions on the nature of the post-COVID joint syndrome are highly contradictory. The syndrome develops in the context of high acute-phase reactant levels (ESR, CRP, and IL-6), yet the titers of antinuclear antibodies and antibodies to cyclic citrullinated peptides, as well as C3 and C4 complement system components, have changed insignificantly. This suggests that there is excess inflammation associated with the COVID-19 infection rather than autoimmune activation [8, 9]. However, the high probability of transformation of unspecified arthritis into various rheumatic conditions in 49 % of patients (most commonly into early rheumatoid arthritis), as well as exacerbation of underlying disease in 83.4 % of those with advanced rheumatoid arthritis, and significant increase in immune activity due to antinuclear antibodies in systemic connective tissue disorders do not allow us to exclude the role of autoimmune mechanism in the pathogenesis of post-COVID joint damage [10].

One of the significant mechanisms of immune tissue damage is the immune complex mechanism. This mechanism involves the formation and circulation of immune complexes, which are composed of specific immunoglobulins, complement components, and antigens. Immune complexes are formed when there is an excess of antigen, both from exogenous sources (such as viruses) and endogenous sources (products of damaged cells and tissues). The deposition of large numbers of immune complexes in tissues can initiate an enhanced signaling cascade mediated by Fc-gamma receptors. This ultimately leads to the development of vasculitis, glomerulonephritis, and arthritis in the setting of acute COVID-19. Moreover, soluble circulating immune complexes (CICs) have been found in the blood of critically ill patients with acute COVID-19, and their levels correlate with disease severity [11]. Soluble circulating immune complexes (CICs), containing IgG, have been detected in approximately 80 % of patients with severe and critical COVID-19 at levels comparable to those seen in active systemic lupus erythematosus. CICs may form before the development of a specific humoral response to SARS-CoV-2, and through excessive activation of Fc-gamma receptors, they can cause impaired immune responses in susceptible patients [12]. Given the role of CICs in the immunopathogenesis of acute COVID-19, it is possible that they may also contribute to the development of post-COVID-19 arthritis syndrome.

THE AIM OF THE STUDY

To assess the role of circulating immune complexes in the pathogenesis of various clinical manifestations of post-COVID joint syndrome.

MATERIALS AND METHODS

Study Design and Setting

The study was conducted at the outpatient clinic of the E.M. Niginsky Consultative and Diagnostic Clinic in Tyumen between 2021 and 2023. A total of 62 patients were included in the study: 19 male patients (mean age 48.84 ± 13.97 years) and 43 female patients (mean age 44.53 ± 12.47 years). All participants had signs of a joint syndrome that developed following COVID-19 infection. All patients had a laboratory-confirmed COVID-19 infection (a positive SARS-CoV-2 RNA PCR result in their medical records or a positive IgG antibody titer to SARS-CoV-2 after the acute phase of the disease had resolved and in case of asymptomatic infection). Based on the persistent asthenia following COVID-19, the diagnosis of post-acute COVID-19 syndrome (PCS) was made. The duration of the latest acute phase of infection was as follows: 1–3 months (n = 12); 3–6 months (n = 18); 6–12 months (n = 16); and 12–15 months (n = 16).

Exclusion criteria: the presence of any chronic diseases that may have triggered or exacerbated general asthenia during the PCP; lack of laboratory confirmation for a prior COVID-19 infection; refusal to participate in the study.

All patients underwent instrumental examinations, including radiography and ultrasonography of the joints.

The white blood cell count and differential in the complete blood count were determined using a Mindray BC-2800 hematology 3-frequency analyzer (Hemalight 1270, USA). Blood biochemistry parameters: C-reactive protein (CRP) and fibrinogen were measured using a Mindray BS-240Pro biochemistry analyzer (China). To assess total IgM and IgG levels in serum, a standard reagent kit from Protein Contour LLC (Russia) was used.

The analysis was conducted in accordance with the manufacturer's guidelines. Results were obtained using a Multiskan photometer (Labsystems, Finland). Total immunoglobulin E (total IgE) levels in serum were measured using an ELISA assay method and results were recorded on a Multiskan SkyHigh reader (Thermo FS, Finland). Laboratory values from healthy individuals of the same age served as a control.

Circulating immune complex (CIC) levels in peripheral blood were measured using PEG precipitation and results were recorded on an Infinity F50 ELISA reader (Austria). According to the method used, if the CIC concentration was less than 3.2 μg/ml, the result was considered negative; if the concentration was 3.3–5.0 μg/ml, the result was classified as borderline; and if the CIC level exceeded 5.0 μg/ml, the sample was considered positive.

Ethical review. The study has been conducted in compliance with the ethical standards established in accordance with the World Medical Association's Declaration of Helsinki. This is confirmed by the extract from the minutes of the local Ethics Committee meeting. The study protocol has been approved by the independent Ethics Committee of the Ilizarov National Medical Research Centre for Traumatology and Orthopedics (protocol No. 2(72) dated October 7, 2022). All participants included in the study signed voluntary written informed consent.

Statistical analysis of the results was conducted using Microsoft Excel (Microsoft Office, USA) and the Statistica 10.0 package (StatSoft, Inc., USA). A sample size was not pre-calculated. The normality of variable distribution was verified using the Shapiro – Wilk test. The data are presented as median and interquartile range Me [Q25; Q75], categorical data as frequencies and percentages. Statistical significance of intergroup differences in quantitative variables was determined using the Mann – Whitney U-test. Differences in the compared parameters were considered statistically significant at $p < 0.05$.

RESULTS

Most patients with joint syndrome (56 %, $n = 35$) experienced the acute phase of COVID-19 with mild or no symptoms. In 36 % ($n = 22$) of these cases, the acute phase was moderate, with evidence of interstitial viral pneumonia, and therefore full treatment was administered. Only 8 % ($n = 5$) of patients experienced a severe acute phase, requiring hospitalization for treatment.

Joint syndrome in the PKP patients examined manifested clinically in four different ways.

Isolated arthralgia, which was not accompanied by visual signs of joint inflammation or changes in instrumental examination, was reported by 14 women with an average age of 33.64 ± 9.11 years and 1 man, aged 27 years. Arthralgia typically manifested 1–3 months following recovery. Patients most frequently reported pain in the wrists (47 %), ankles (26 %), knees (20 %), and feet (7 %). In 76 % of cases, arthralgia affected only a single joint. In the peripheral blood, despite the normal number of leukocytes, unchanged leukogram and acute phase indices corresponding to the standards (ESR values, as well as CRP and fibrinogen), IgM and IgG titers were high (Table 1). Additionally, CIC levels were detected in blood samples from all patients except for one, exceeding the reference range (Table 2).

Postinflammatory arthritis (PIA) without cartilage destruction was observed in 30 patients: 17 women aged 47.41 ± 10.82 years and 13 men aged 45.3 ± 11.14 years. The period from COVID-19 to the onset of joint syndrome ranged from 2 to 6 months. The most commonly affected joints were the knee (39 %) and ankle (36 %), followed by the proximal and distal interphalangeal joints (34 %), the hip (10 %), the elbow (6 %), and the shoulder (4 %). All signs of inflammation were locally present: pain, swelling, hyperemia, and varying degrees of joint mobility impairment. Instrumental examination (X-ray, ultrasound of the affected joints) revealed signs of synovitis without evidence of cartilage destruction. Joint inflammation was associated with elevated acute-phase reactant levels, while white blood cell counts remained within normal ranges. IgM, IgG, and IgE titers were elevated, and circulating immune complex (CIC) levels were significantly increased in all patients (Tables 1 and 2).

Osteoarthritis with cartilage destruction, detected through instrumental examination, developed in 8 patients 6–8 months after acute COVID-19. The disease manifested as acute monoarthritis in large joints, including the knees, hips, wrists, and interphalangeal joints. Local signs of inflammation were accompanied by generalized polyarthralgia and polymyalgia. Examination revealed deformity of the affected joints and limited mobility. Instrumental examination showed signs of synovitis in nearly all cases, along with developing cartilage destruction. Increased blood levels of CRP, fibrinogen, and ESR were not accompanied by leukocytosis. However, IgM, IgG, and particularly IgE titers were elevated. The number of circulating immune complexes (CIC) was also increased (Table 2).

The joint syndrome, which was present in the period prior to COVID, progressed in 9 patients (2 men aged 59 and 68 years and 7 women with a median age of 54.7 [39.0; 72.0] years). Polyarticular symmetric lesions were more typical of the progressive joint syndrome. Ultrasound examination of the affected joints frequently revealed signs of synovitis (in 90 % of cases), osteoarthritis (in 44 %), and tenosynovitis (in 22 %). Joint radiography showed narrowing of the joint space and the presence of osteophytes. Destructive changes were seen in both knee joints in 4 out of 9 patients (44 %), ankle joints in 4 patients (44 %), wrist and elbow joints in another 4 cases (44 %), and hip joints in 3 patients (33 %). Elevated levels of acute-phase reactants in peripheral blood also indicated the presence of alterative inflammation. The total white blood cell count remained stable, but eosinophilia was noted in some cases. The IgM titer was below the expected level, and IgG titer values were not significantly different from those of the control group, but total IgE levels were elevated. The circulating immune complex (CIC) levels were within the normal range (4.29 [3.1; 5.7] μg/ml) and were significantly lower than those observed in other cases of joint syndrome.

TABLE 1

THE IMMUNOGLOBULIN CONTENTS IN PERIPHERAL BLOOD IN PATIENTS WITH VARIOUS TYPES OF POST-COVID JOINT SYNDROME, ME [Q25; Q75]

	Group I	Group II	Group III	Group IV	Group V	*p*			
	Isolated arthralgia, *n* = 15	Arthritis, *n* = 30	Debut of arthropathy, *n* = 8	Progression of arthropathy, *n* = 9	Healthy individuals (control), *n* = 25	Groups I-V	Groups II-V	Groups III-V	Groups IV-V
ESR, mm/h	7.9 [3–11]	11.7 [6–16]	16.3 [5–23]	13.4 [6–19]	6.3 [1–8]	0.162	0.007	0.000	0.001
IgM, g/l	2.27 [1.5; 3.4]	2.625 [1.9; 2.9]	2.6 [1.6; 3.4]	1.13 [0.9; 2.0]	1.39 [0.99; 1.5]	0.008	0.001	0.004	0.010
IgG, g/l	14.46 [11.5; 16.0]	12.27 [7.5; 22.9]	13.28 [11.7; 20.0]	12.44 [5.5; 12.5]	11.03 [10.2; 13.6]	0.008	0.040	0.005	0.050
Total IgE, IU/ml	40.97 [6.0; 31.0]	97.53 [25.0; 112.0]	148.82 [40.1; 172.0]	118.56 [25.4; 265.4]	32.54 [5.0; 76]	0.060	0.001	0.000	0.000

Note. *p* is the level of statistical significance for the differences between the control and treatment groups based on the Mann – Whitney U-test.

TABLE 2

THE CONTENT OF CIRCULATING IMMUNE COMPLEXES (CIC) IN PERIPHERAL BLOOD IN PATIENTS WITH VARIOUS TYPES OF POST-COVID JOINT SYNDROME, ME [Q25; Q75]

Indicator	Group I Isolated arthralgia, *n* = 4	Group II Arthritis, *n* = 5	Group III Debut of arthropathy, *n* = 6	Group IV Progression of arthropathy, *n* = 6	*p*					
					Groups I-II	Groups I-III	Groups I-IV	Groups II-III	Groups II-IV	Groups III-IV
CIC, µg/ml	8.05 [1.67; 11.45]	11.45 [9.33; 12.98]	8.58 [6.23; 14.27]	4.29 [3.1; 5.7]	0.391	0.165	0.0140	0.120	0.008	0.005

DISCUSSION

Women predominated among the patients with post-COVID-19 syndrome: 43 out of 62 presenting with complaints of joint pain, as reported in the literature [5, 6]. However, in most cases, the patients experienced initial symptoms and their development did not depend on age or the severity of the COVID-19 infection they had.

Based on clinical, laboratory, and instrumental examinations, four distinct types of post-COVID syndrome have been identified, each with its own underlying mechanism.

In our study, high levels of CICs were detected in patients with arthralgia, arthritis, and the onset of arthropathy. These findings suggest a possible role for CICs in the development of these joint conditions. CICs are known to cause tissue damage through various mechanisms. In the form of complexes with antigens, IgG and IgM antibodies activate the classical pathway of the complement system, which leads to the development of inflammation through its damaging effects. Independent of the complement, IgG-containing CICs can bind to Fc receptors expressed on various cell types, including macrophages, neutrophils, eosinophils, and platelets, leading to the release of inflammatory mediators. Through direct interaction with neutrophils via Fc receptors and activation of platelets and endothelial cells, CICs can induce neutrophil

extracellular trap (NETosis) [13]. Moreover, the pattern of chemokine secretion by macrophages is dependent on the characteristics of CICs [14]. As the arthropathy progresses, the levels of CIC, as well as IgG and IgM in patient blood, often correspond to the borderline level, indicating a reduced contribution of the immune complex pathway to the destructive process formation.

Elevated IgE titers in the blood of patients with arthritis, as well as the onset and progression of arthropathy, deserve special attention. Although most of the individuals examined did not exhibit any allergic symptoms and had a negative history of allergy, recent research has demonstrated the existence of IgE autoantibodies, and their elevated production is not linked to an increased incidence of atopic conditions in patients. IgE plays a crucial role in immune response by stimulating the secretion of type I interferons from plasmacytoid dendritic cells, attracting basophils to lymph nodes, and activating both B and T cell-mediated adaptive immune responses. Immune complexes with DNA-specific IgE antibodies stimulate plasmacytoid dendritic cells and induce a powerful differentiation of B lymphocytes and the formation of plasma cells. This process subsequently leads to the development of autoimmune humoral responses [15]. Furthermore, immune complexes formed by IgE and low-molecular weight proteins can enhance specific reactions of CD4+ T cells, thereby stimulating the Th2 immune response [16].

IgE is a trigger for mast cell activation, which can lead to the development of a secondary mast cell activation syndrome (SMAS) [17]. As suggested by numerous authors, SMAS may be one of the mechanisms underlying the formation of PCS [18, 19].

Mast cells are abundantly present in the inflamed synovial tissue. Although there is no direct evidence that mast cells themselves synthesize IL-17, it has been shown that they actively take up exogenously produced IL-17 through receptor-mediated endocytosis. This exogenous IL-17 is stored within intracellular granules and can be subsequently released in a biologically active form [20]. Mast cells represent the predominant population that expresses IL-17 within the synovial tissues during inflammation, particularly in reactive arthritis compared to rheumatoid arthritis [21-23]. The number of IL-17A-positive mast cells expressing IL-17A within target tissues correlates inversely with the level of inflammation, suggesting a role for this cytokine in mediating the inflammatory response [24, 25]. IL-17A is a proinflammatory cytokine that has the additional ability to stimulate angiogenesis and osteoclastogenesis [26].

CONCLUSION

Thus, the immune complex mechanism of injury plays a significant role in the development of isolated arthralgia, arthritis, and the onset of osteoarthropathy in post-COVID-19 joint syndrome, although it does not appear to be involved in the progression of the osteoarthritic process. High IgE titers during episodes of arthritis and the onset and progression of arthropathy in patients may be interpreted as a manifestation of an IgE-dependent autoimmune mechanism mediated by mast cell activation syndrome. The obtained results allow us to justify an individualized approach to treatment depending on the type of post-COVID-19 joint syndrome. To better predict the development and course of post-COVID-19 manifestations, further research is needed to elucidate the initial immune system changes that occur following infection.

Conflicts of interest

No potential conflict of interest relevant to this article reported.

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