CLINICAL OBSERVATIONS

Selective plasmosorption of extracellular DNA and NETs in patients with difficult-to-treat rheumatoid arthritis (first clinical experience)

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Rheumatoid arthritis (RA) associated with interstitial lung disease (RA-ILD) represents a distinct clinical and pathogenetic phenotype characterized by high inflammatory activity, seropositivity, and systemic manifestations. In recent years, increasing attention has been directed to the role of extracellular DNA and neutrophil extracellular traps (NETs) in RA pathogenesis. This report presents the first case of selective plasmosorption of extracellular DNA and NETs in a patient with RA-ILD. The therapy was associated with a decrease in joint pain and stiffness and improvement of general condition. Laboratory parameters were also monitored dynamically. This clinical case demonstrates the potential of DNA-containing structure plasmosorption as an adjunctive method to enhance the effect of therapy with biological disease modifying antirheumatic drugs in refractory RA.

Keywords: *rheumatoid arthritis; extracorporeal therapy; neutrophil extracellular traps; extracellular DNA; therapeutic apheresis.*
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Introduction

Rheumatoid arthritis (RA) is an immune-inflammatory (autoimmune) rheumatic disease of unknown etiology, characterized by chronic erosive arthritis and systemic damage to internal organs, leading to disability, development of severe comorbid pathology and, as a consequence, reduction in life expectancy of patients [1]. Among the wide range of systemic manifestations of RA, interstitial lung disease (ILD) attracts special attention as it is the most severe form of pulmonary pathology in RA (defined as RA-ILD), which is pathogenetically associated with autoimmune mechanisms underlying RA. In the development of RA-ILD, among immunological biomarkers, seropositivity for rheumatoid factors (RF), antibodies to cyclic citrullinated peptide (ACCP) and other citrullinated proteins is of particular importance. In general, RA-ILD is defined as a phenotype of RA characterized by a severe course, high inflammatory activity and an unfavorable prognosis, and patients with RA-ILD fall into the category of "difficult to treat" (D2T); so, approaches to pharmacotherapy of this disease require further research [2]. The role of autoimmune mechanisms in the development of RA is confirmed by hyperproduction of autoantibodies, including rheumatoid factors (RF), which are antibodies to the Fc fragment of IgG, and antibodies that react with proteins with an altered conformational structure induced by citrullination or other forms of post-translational modification of proteins (PTMP) [3]. It is assumed that antibodies to PTMP are involved in the development of pain, inflammation, joint destruction and systemic manifestations (generalized bone loss, atherosclerotic vascular lesions and interstitial lung disease) [4]. One of the mechanisms leading to the formation of PTMT is the process of NETosis. NETosis is one of the forms of programmed cell death of neutrophils, accompanied by the formation of "network" structures consisting of DNA strands with inclusions of intracellular neutrophil proteins, and the release of large amounts of enzymes. These structures are called neutrophil extracellular traps (NETs) [5].

NETs present in the synovial tissue of patients with RA contain the enzyme peptidyl-arginine deaminase (PAD) which is responsible for the conversion of peptidyl-arginine (with a positive charge) into peptidyl-citrulline (with a neutral charge). This process leads to the acquisition of autoantigenic properties by proteins and the formation of antibodies to citrullinated proteins (ACP) [6, 7]. Thus, NETosis is considered one of the key sources of citrullinated autoantigens. Citrullinated proteins in joint tissues stimulate the release of perforin and the formation of a membrane attack complex (a biomarker of complement activation) which causes tissue damage [8]. Neutrophil elastase released from NETs causes cartilage damage [9]. NETs also provoke the expression of the receptor activator of nuclear factor kappa-B ligand (RANKL), which stimulates osteoclasts, and, thus, leads to the destruction of bone tissue [10]. NETosis contributes to the maintenance of local inflammation, and also leads to the stimulation of T-lymphocytes and fibroblast-like synovial cells [11,12]. According to Jarzebska N. et al, potential therapeutic agents capable of suppressing NETosis may include PAD4 inhibitors, interleukin 4 and 13 in-

hibitors, N-acetylcysteine, and hydroxychloroquine. However, no proven effect of these agents has yet been obtained. The authors emphasize a potential role of the elimination of DNA-containing structures and NETs from the bloodstream using a sorption column [13]. The active ingredient of this column is an inert matrix on which the recombinant histone H1.3 protein is immobilized, specifically binding extracellular DNA (cfDNA) and NETs. As for NETosis and RA, clinical studies have revealed a positive correlation between the severity of NETosis, inflammatory activity, the dynamics of the progression of destructive changes in the joints, and development of extra-articular manifestations in these patients. Neutrophils of RA patients demonstrate an increased tendency to NETosis compared to healthy donors, and this process is enhanced by the influence of autoantibodies – RF and ACP [14].

Widespread introduction of traditional and targeted antirheumatic drugs into clinical practice allows us to effectively suppress the inflammatory activity of RA, restrain the progression of the disease and improve the quality of life of patients.

However, there are patients in whom even a change in targeted drugs does not allow to achieve the target level of activity. Serious difficulties that arise in the management of such patients have made it possible to identify a special variant of the disease – difficult-to-treat (D2T) RA [15]. The term "refractory RA" is often used to describe this form of the disease. Of course, there is still no unambiguous approach to the treatment of a difficult-to-treat patient with RA-ILD. Since this disease phenotype is often associated with seropositivity for RF, ACCP and other ACP [16], as well as with inflammatory activity [17], the removal of DNA-containing structures and NETs from the patient's bloodstream can help significantly reduce disease activity and enhance the effect of subsequent therapy with genetically engineered biological drugs (GEBD). We present the world's first clinical case of successful use of selective plasmasorption of extracellular DNA in a difficult-to-treat patient with RA-ILD.

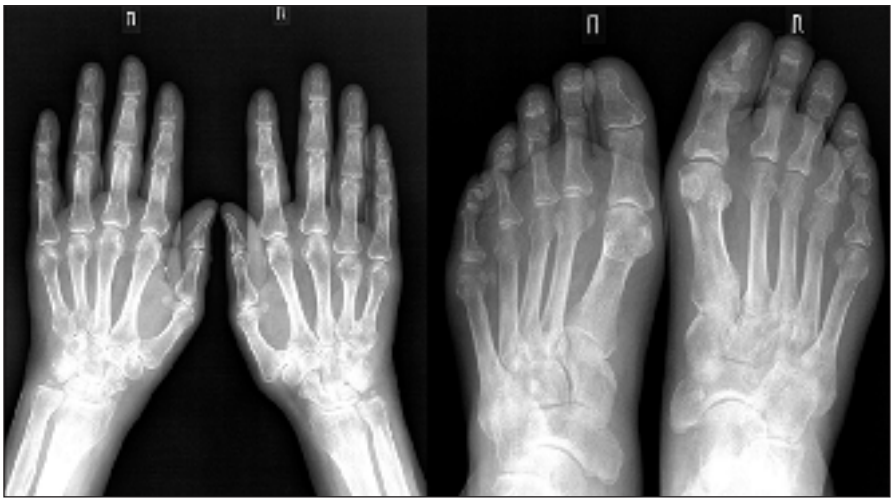

Fig. 1. *X-ray of the hands and feet of patient N.*

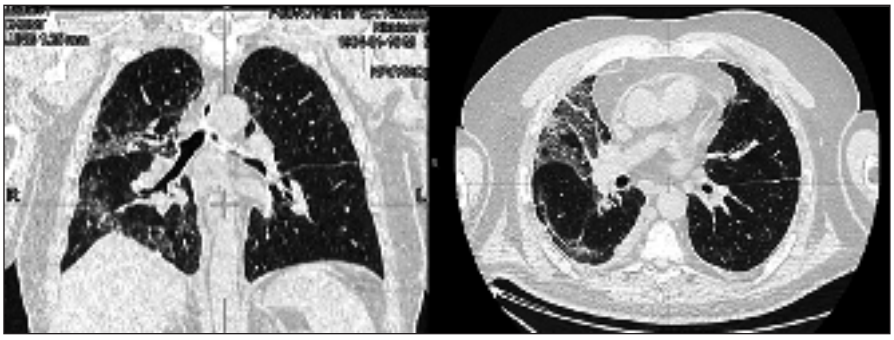

Fig. 2. *Chest CT of patient N.*

Clinical observation

***Patient N.**, a 60-year-old man, unemployed. Diagnosis: Rheumatoid arthritis seropositive, ACCP+, antibodies to modified citrullinated vimentine (AMCV)+, late stage, high disease activity (DAS28 – 7.55), erosive, radiographic stage 2, with extra-articular manifestations (rheumatoid nodules; ILD; respiratory insufficiency, stage 2). Functional class 3.*

The patient has been ill since June 2021. He debuted with pain and stiffness in the joints of the hands and knees. The examination revealed positive RF (1102 IU/ml), an increase in the level of C-reactive protein (CRP) to 31 mg/l. The patient was diagnosed with RA, and methotrexate (MT) therapy was initiated in October 2021 at a dose of 10–15 mg per week, 6-methylprednisolone (6-MP) 4 mg per day; since December 3, 2022, the MT dose was increased to 25 mg per week due to high inflammatory activity and ineffectiveness of lower doses. Examination on November 18, 2022: erythrocyte sedimentation rate (ESR) 15 mm / h, platelets 392×10^9/l, leukocytes – 9.8×10^9/l, RF 1247.8 IU / ml, CRP 46 mg / l.) The patient noted insufficient effectiveness of the therapy, complaints of neck pain in the morning persisted, morning stiffness lasted about 2 hours, there was a limitation in clenching the hand into a fist and pain in the feet and knee joints. In this regard, in December 2021, the dose of 6-MP was increased to 6 mg per day. Inflammatory activity persisted (01/17/2023: RF 1519 IU/ml, CRP 56.7 mg/l, ESR 5 mm/h, platelets 397×10^9/l, leukocytes – 15.9×10^9/l. Urinalysis: erythrocytes 100 in the field of vision, otherwise without deviations). Due to erythrocyturia, MT was canceled, and the dose of methylprednisolone was increased to 8 mg per day. The patient regularly took non-steroidal anti-inflammatory drugs (NSAIDs). In March-April 2023, he underwent inpatient treatment in V.A. Nasonova Research Institute of Rheumatology. During the examination on 03/24/2023: leukocytes 12.4×10^9/l, ESR 86 mm/h, RF 2870.0 IU/ml, ACCP 28.8 U/ml, antinuclear factor (ANF) Hep-2 1/2560 h+sp, cytopl. X-ray of the hands and feet on 03/27/2023 showed a picture that may correspond to the diagnosis of rheumatoid arthritis stage 3 according to Steinbrocker" (Fig. 1).

Due to positive ANF, in order to exclude ILD, on March 27, 2023, the patient underwent computed tomography (CT) of the chest organs which demonstrated a picture of interstitial changes in the parenchyma of both lungs with the formation of traction cylindrical bronchiectasis and multiple solid foci in both lungs (rheumatoid nodules)" (Fig. 2).

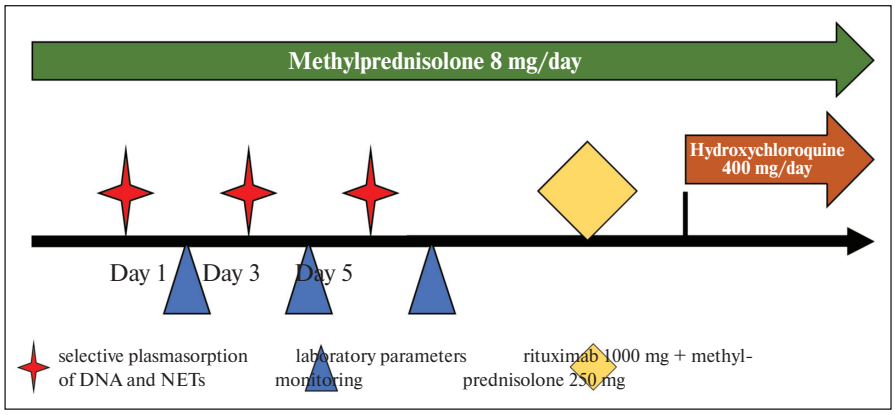

Fig. 3. *Scheme of selective plasmosorption procedures for DNA and NETs*

Fig. 4. *Selective plasmosorption procedure*

Ultrasound examination of the knee joints from 03/29/2023 showed signs of synovitis on both sides with a proliferative component, degenerative and periarticular changes and Baker's cysts on both sides."

The patient was initiated on rituximab therapy 1000 mg, infusions were performed on 03/31/2023 and 04/16/2023, tolerability was satisfactory. The effect of therapy lasted for 7–8 months. MT therapy was resumed 20 mg per week, the dose of methylprednisolone was reduced to 4 mg per day.

Exacerbation occurred in winter of 2024 in the form of severe polyarthritis and morning stiffness. Laboratory findings: ESR 140 mm/h, leukocytes – 11.4 ×10⁹/l, platelets – 608×10⁹/l, CRP 98.9 mg/l, RF >3000 IU/ml, ACCP 15.9 U/ml, ANF 1/2560.

The patient was hospitalized to V.A. Nasonova Research Institute of Rheumatology from 03/25/2024 to 04/04/2024. During additional examination, it was established that according to chest CT, changes in the lungs persisted. Diaskin test was positive. The patient was consulted by phthisiatricians and diagnosed with latent tuberculosis infection. He received anti-tuberculosis therapy for a month. MT was canceled; the introduction of rituximab was postponed. The patient was readmitted a month later (from 05/07/2024 to 05/24/2024). Upon examination: severe polyarthritis of the small joints of the hands, wrists, elbows, shoulders, stiffness throughout the day; limited movement in the shoulder, wrists; flexion contractures of the elbow joints; rheumatoid nodules in the elbow joints. The number of painful joints (NPJ): 20, number of swollen joints (NSJ): 16. Pain on the visual analogue scale (VAS): 79 mm. Disease Activity Score 28 (DAS28) index 7.55. Laboratory findings: CRP 93.2 mg/l, RF >300 IU/ml, ACCP 59.5 U/ml, antibodies to modified citrullinated vimentin (AMCV) 715 U/ml, ANF 1/1280, D-dimer 1516 μg/l, leukocytes 10.5×10⁹/l, platelets 386×10⁹/l, ESR 61 mm/h. In order to quickly relieve inflammatory activity, and taking into account the pronounced immunological disorders, a decision was made to conduct a course of 3 procedures of selective plasmasorption of DNA and NETs against the background of therapy with methylprednisolone at a dose of 8 mg/day with an interval of 24 hours between the procedures (Fig. 3).

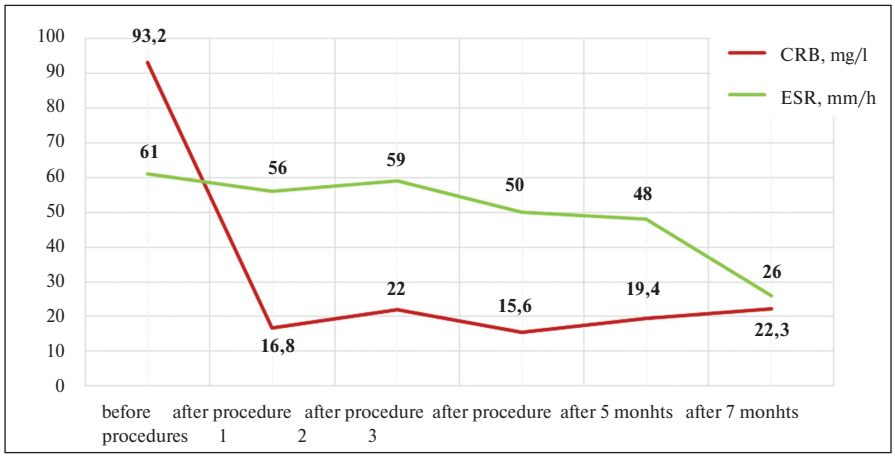

Fig. 5. *Dynamics of inflammatory activity indicators during selective plasmosorption of DNA and NETs and subsequent rituximab (RTX) therapy*

Selective plasmasorption procedures were performed on Gemma PF device using the Plasmaflo OP-5W-05W\08254 plasma separator and a sorption column (Fig. 4).

The duration of the procedures was 5 h 30 min, 5 h 15 min and 5 h 15 min, respectively. During the procedures, 15160 ml, 36120 ml, 26400 ml of blood and 4120 ml, 7620 ml, 6150 ml of plasma were processed, respectively. During the first procedure, thrombosis of the blood flow circuit was noted, due to which it was stopped. Given the pronounced hyperviscosity, the patient was additionally prescribed fraxiparine subcutaneously 0.3 ml 2 times a day. Laboratory parameters of immunological and inflammatory activity, as well as clinical parameters of the patient, were dynamically assessed. Already after the first procedure, a decrease

in the CRP level to 16.8 mg/l (-82%) was noted. After the third procedure it decreased to 15.6 mg/l (-83.5%). Laboratory results after the completion of the procedure course were as follows: leukocytes 10×10⁹/l, platelets 347 10⁹/l, D-dimer 703 mcg/l (-53.6%), RF 280 IU/ml (-7%), ACCP 78 U/ml (+31%), anti-MCV 111 U/ml (-84.4%), ANF 1/1280. Morning stiffness disappeared, flexion contractures were relieved. The number of painful and swollen joints decreased: NPJ – 12, NSJ – 10, VAS – 40 mm. The DAS28 index after the treatment was 6.26 (-17%). The dynamics of laboratory parameters of inflammatory and immunological activity, as well as the DAS28 activity index are shown in Figures 5, 6 and 7. Three days after the completion of the plasmasorption course and recording of laboratory and clinical parameters, 250 mg of methylprednisolone and 1000 mg of rituximab were administered intravenously by drip. Before discharge, hydroxychloroquine 400 mg/day was added to the therapy and methylprednisolone was continued at a dose of 8 mg per day.

In June 2024, the patient was readmitted to Nasonova Research Institute of Rheumatology for administration of a loading dose of rituximab 1000 mg. The clinical effect of plasmasorption persisted: no morning stiffness or flexion contractures were observed, NPJ – 12, NSJ – 10, VAS – 45 mm. Laboratory tests showed an increase in inflammatory markers (CRP 71 mg/l, ESR 90 mm/h). The disease activity index DAS28 was 6.61. There was a continuing downward trend in RF (261 IU/ml), anti-MCV (62 U/ml). An increase in ACCP was noted (119 U/ml). In November 2024, he began to notice a deterioration in his health in the form of renewed joint pain, morning stiffness for about 1.5 hours, and limited movement in the elbow and shoulder joints due to pain. Laboratory findings: ESR 48 mm/h, CRP 19.4 mg/l. Clinically: NPJ – 6, NSJ – 13. DAS28 – 5.79.

However, according to CT data, positive dynamics were noted in the form of regression of consolidation zones located mainly in the right lung with their replacement by areas of compaction of the "ground glass" type (Figure 8A, 8B), regression of pleural thickening of the interlobar sections of the right lung (Figure 8C), a decrease in the size of the intrathoracic lymph nodes (Figure 8D).

The patient was consulted as an outpatient: due to persistent lung damage, mycophenolate mofetil was added to the therapy at a dose of 1000 mg/day. The next administration of rituximab was planned, but for technical reasons, the administration was postponed to January 2025. In January 2025 - hospitalization to V.A. Nasonova Research Institute of Radiology for the planned administration of rituximab as a maintenance regimen. Clinical findings: NPJ – 10, NSJ – 6, VAS – 50 mm. Laboratory findings: ESR – 26 mm/h, CRP – 22 mg/l. DAS28 – 5.67. The patient tolerated the administration of rituximab satisfactorily. The next administration is planned for July 2025.

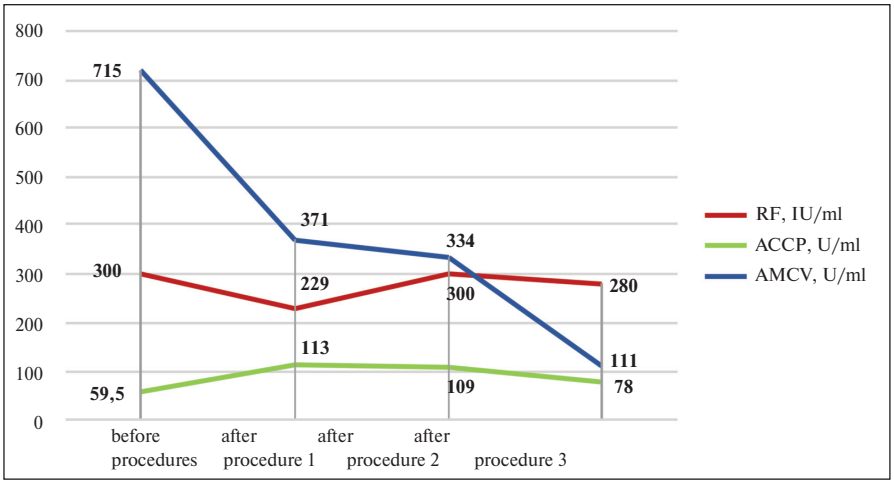

Fig. 6. *Dynamics of RF, ACPA, and AMCV levels during selective plasmosorption of DNA and NETs and subsequent RTX therapy*

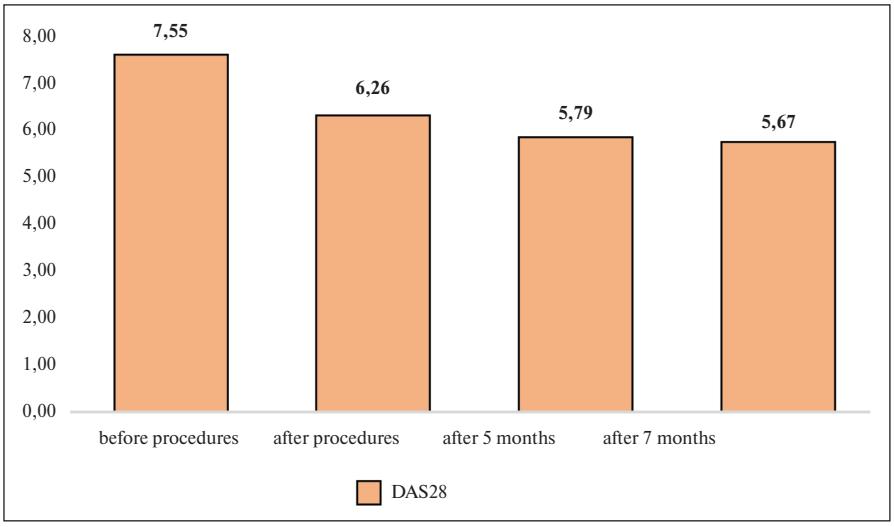

Fig. 7. *Dynamics of DAS28 during selective plasmosorption of DNA and subsequent RTX therapy*

Discussion

Patient N. is a striking example of a special phenotype of RA – RA-ILD: a man with RA debuting after the age of 50 with high rates of inflammatory activity, seropositivity for RF, ACCP and anti-MCV, and positive for ANF. Currently, the treatment tactics for RA-ILD have not been sufficiently developed [18, 19], and there are no scientifically based recommendations [20, 21]. The implementation of the Treat-to-target (T2T) strategy for RA-ILD is difficult, since this phenotype develops in elderly people with various comorbid and multimorbid conditions that complicate active anti-inflammatory therapy. Antirheumatic drugs can cause drug-induced lung pathology and increase the risk of infectious pneumonia. Thus, patients with RA-ILD automatically fall into the D2T category [22–24]. A number of authors believe that the concept of "refractoriness" also implies the persistence of active inflammation against the background of the use of synthetic disease-modifying antirheumatic drugs (DMARDs) and GEBDs. At the same time, the need for constant use of moderate or high doses of glucocorticoids (GC) should also be regarded as a sign of refractoriness to treatment [15]. Patient N. has an RA phenotype,

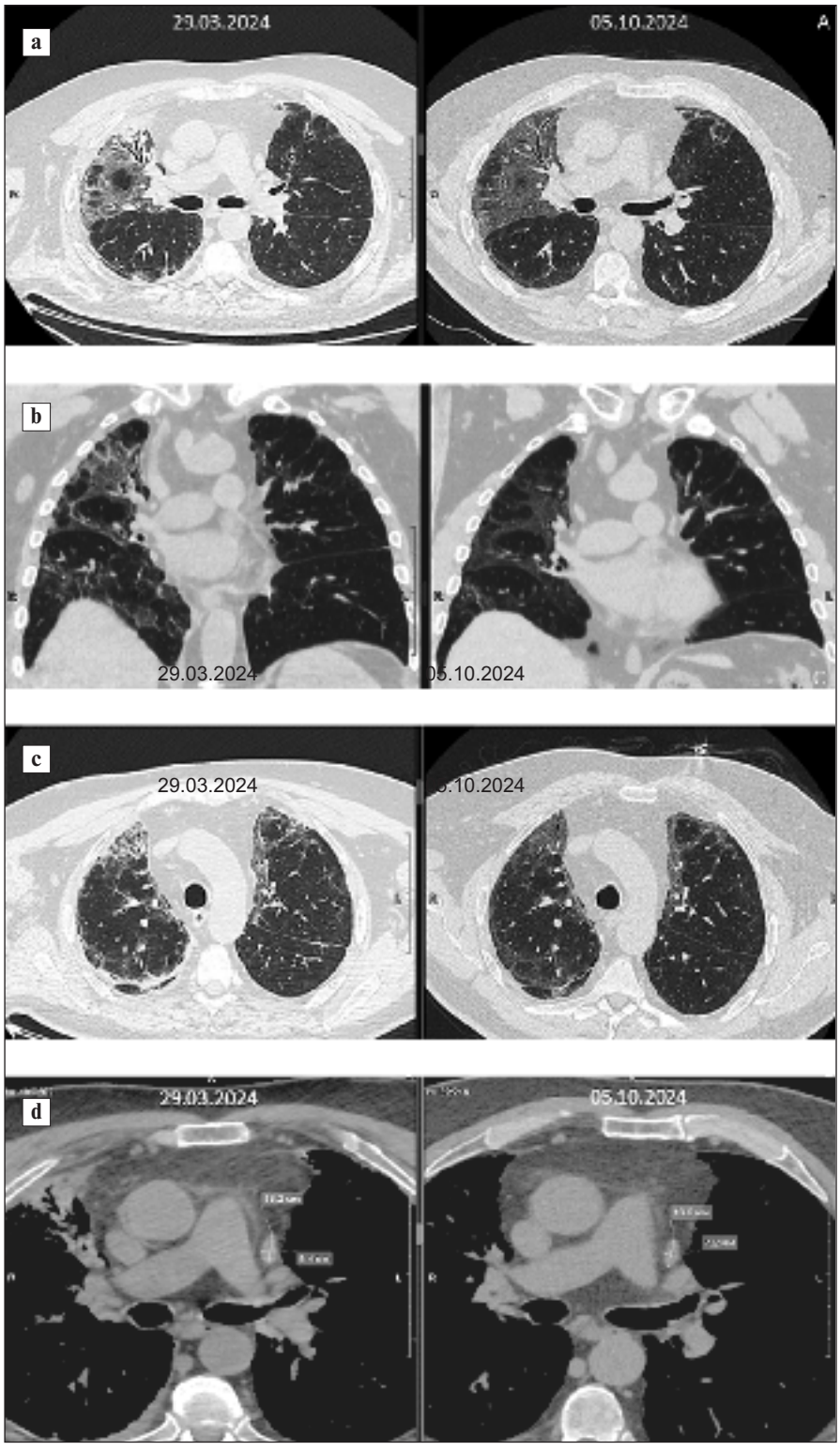

Fig. 8. *Chest CT of patient N. over time (a–d) after selective plasmosorption of DNA and NETs followed by RTX administration*

which in itself refers to D2T category, but we also observed in this patient ineffectiveness of various doses of MT in combination with 6-MP, which, in turn, is a sign of refractoriness. Until recently, various extracorporeal methods of therapy were used in the treatment of refractory forms of RA.

Thus, in 2000, S.K. Soloviev et al. used synchronous program intensive therapy in 10 patients with refractory RA with systemic manifestations. During the first stage, patients underwent 3 plasmapheresis sessions with exfusion of 1200–1500 ml of plasma, an interval between the procedures of 2-3 days and synchronous administration of 40 mg MT and 250 mg 6-MP. The second stage of therapy consisted of a similar plasmapheresis procedure once a week for three subsequent weeks. After the completion of the second stage, all patients were prescribed MT at a dose of 20 mg per week intramuscularly for 5 months. The authors note the development of a rapid therapeutic effect from the therapy in patients with refractory RA. Thus, in their opinion, plasmapheresis contributed to the suppression of systemic manifestations of RA, which are usually caused by immune complex vasculitis, by removing circulating immune complexes from circulation, while pulse therapy with MT and administration of 6-MP suppressed the production of antibodies and reduced the activity of lymphoid cells [25]. With the development of medicine, extracorporeal therapy methods are also improving. And now we are talking about sorption technologies in combination not with GC or cytostatics, but with GEBDs. In 2021, Xing Y. et al. conducted a retrospective cohort study. One hundred and fifty-three patients aged 18 years and older with active refractory RA underwent 2 procedures of cascade plasma filtration (CPF) within a week with administration of infliximab and methotrexate the day after the second procedure. The remission rate in the CPF treatment group was more than 50%, while in the infliximab and GC groups the remission rates according to the clinical disease activity index (CDAI) were 41.2% and 22.4%, and according to the simplified disease activity index (SDAI) 37.3% and 14.2% after 3 months of treatment. The authors conclude that the combination of CPF and GEBDs quickly induces remission or low disease activity in active refractory RA [26]. The effectiveness of CPF in patients with active RA has been noted by other authors [27, 28]. The advent of the technique of selective plasmasorption of extracellular DNA and NETs has expanded the therapeutic options in the treatment of RA, allowing to influence a previously inaccessible link in its pathogenesis. Preclinical studies of sorption columns have confirmed that they remove not only NETs from the bloodstream, but also circulating genomic and mitochondrial DNA, which are autoantigens involved in the development of autoimmune reactions. The first successful use of this sorption column in a

patient with SLE gave hope for success in patients with RA [29]. Both doctors and the patient noted a rapid therapeutic effect after the first procedure. The result of using three plasmasorption treatment procedures was not only an improvement in the patient's general well-being, complete relief of morning stiffness and flexion contractures, a decrease in the number of painful and swollen joints, but also a significant decrease in inflammatory activity (by 83% in the CRP level, by 20% in the ESR level). I would like to especially emphasize that in this case, neither GC nor cytostatics were used, as in the work of Solovyov S.K. et al., and the anti-inflammatory effect was comparable.

Definitely, three procedures of selective plasmasorption are not sufficient for achiev optimal results, but in combination with GERDs they will help to achieve faster and longer-lasting results, as in patient N., whose health was significantly better after 12 months. Therefore, combination with GERD therapy (rituximab) is advisable. The choice of rituximab in this case is due to its high efficiency in RA-ILD [30–32].

Conclusion

The first use of selective plasmasorption of extracellular DNA and NETs for the treatment of RA with systemic manifestations resistant to therapy can be considered successful. This method can be indicated for patients as an additional treatment method for rapid relief of inflammatory activity and ensuring a better response to subsequent GERD therapy.

REFERENCES

1. Насонов ЕЛ, Лила АМ. Ревматоидный артрит: достижения и нерешенные проблемы. Терапевтический архив. 2019; 91(5):4-7.
Nasonov EL, Lila AM. Rheumatoid arthritis: achievements and unresolved issues. *Terapevticheskii arkhiv*. 2019;91(5): 4-7. (In Russ.).
2. Насонов ЕЛ, Ананьева ЛП, Авдеев СН. Интерстициальные заболевания легких при ревматоидном артрите: мультидисциплинарная проблема ревматологии и пульмонологии. Научно-практическая ревматология. 2022;60(6):517-534.
Nasonov EL, Ananyeva LP, Avdeev SN. Interstitial lung disease in rheumatoid arthritis: A multidisciplinary problem in rheumatology and pulmonology. *Nauchno-Prakticheskaya Revmatologia*. 2022;60(6):517-534. (In Russ.).
3. Насонов ЕЛ. Проблемы иммунопатологии ревматоидного артрита: эволюция болезни. Научно-практическая ревматология. 2017;55(3):277-294.
Nasonov EL. Problems of rheumatoid arthritis immunopathology: evolution of the disease. *Rheumatology Science and Practice*. 2017;55(3):277-294. (In Russ.).
4. Catrina A, Krishnamurthy A, Rethi B. Current view on the pathogenic role of anti-citrullinated protein antibodies in rheumatoid arthritis. *RMD Open*. 2021 Mar;7(1):e001228. doi: 10.1136/rmdopen-2020-001228.
5. Mutua V, Gershwin LJ. A Review of Neutrophil Extracellular Traps (NETs) in Disease: Potential Anti-NETs Therapeutics. *Clin Rev Allergy Immunol*. 2021 Oct;61(2):194-211. doi: 10.1007/s12016-020-08804-7.
6. Авдеева АС, Алексанкин АП. Нетоз нейтрофилов: методы лабораторной оценки и роль в патогенезе иммуновоспалительных ревматических заболеваний (обзор литературы). Клиническая лабораторная диагностика. 2024;69(5):206-214.
Avdeeva AS, Aleksankin AP. NETosis: assessment methods and role in the pathogenesis of systemic autoimmune rheumatic diseases (review of literature). *Klinicheskaya laboratornaya diagnostika*. 2024;69(5):206-214. (In Russ.).
7. Foulquier C, Sebbag M, Clavel C, et al. Peptidyl arginine deiminase type 2 (PAD-2) and PAD-4 but not PAD-1, PAD-3, and PAD-6 are expressed in rheumatoid arthritis synovium in close association with tissue inflammation. *Arthritis Rheum*. 2007 Nov;56(11): 3541-53. doi: 10.1002/art.22983.
8. Насонов ЕЛ, Авдеева АС, Решетняк ТМ и др. Роль нетоза в патогенезе иммуновоспалительных ревматических заболеваний. Научно-практическая ревматология. 2023; 61(5):513-530.
Nasonov EL, Avdeeva AS, Reshetnyak TM, et al. The role of NETosis in the pathogenesis of immunoinflammatory rheumatic diseases. *Nauchno-Prakticheskaya Revmatologia*. 2023; 61(5):513-530. (In Russ.).
9. Carmona-Rivera C, Carlucci PM, Goel RR, et al. Neutrophil extracellular traps mediate articular cartilage damage and enhance cartilage component immunogenicity in rheumatoid arthritis. *JCI Insight*. 2020 Jul 9;5(13): e139388. doi: 10.1172/jci.insight.139388.
10. Schneider AH, Taira TM, Publio GA, et al. Neutrophil extracellular traps mediate bone erosion in rheumatoid arthritis by enhancing RANKL-induced osteoclastogenesis. *Br J Pharmacol*. 2024 Feb;181(3):429-446. doi: 10.1111/bph.16227.
11. Khandpur R, Carmona-Rivera C, Vivekanandan-Giri A, et al. NETs are a source of citrullinated autoantigens and stimulate inflammatory responses in rheumatoid arthritis. *Sci Transl Med*. 2013 Mar 27;5(178): 178ra40. doi: 10.1126/scitranslmed.3005580.
12. Carmona-Rivera C, Carlucci PM, Moore E, et al. Synovial fibroblast-neutrophil interactions promote pathogenic adaptive immunity in rheumatoid arthritis. *Sci Immunol*. 2017 Apr;2(10):eaag3358. doi: 10.1126/sciimmunol.aag3358.
13. Jarzebska N, Rodionov RN, Voit-Bak K, et al. Neutrophil Extracellular Traps (NETs) as a Potential Target for Anti-Aging: Role of Therapeutic Apheresis. *Horm Metab Res*. 2025 Jan 9. doi: 10.1055/a-2444-3422. Online ahead of print.
14. Sur Chowdhury C, Giaglis S, Walker UA, et al. Enhanced neutrophil extracellular trap generation in rheumatoid arthritis: Analysis of underlying signal transduction pathways and potential diagnostic utility. *Arthritis Res Ther*. 2014 Jun 13;16(3):R122. doi: 10.1186/ar4579.
15. Гордеев АВ, Олюнин ЮА, Галушко ЕА и др. Труднолечимый ревматоидный артрит. Какой он? Современная ревматология. 2021;15(5):7-11.
Gordeev AV, Olyunin YA, Galushko EA, et al. Difficult-to-treat rheumatoid arthritis. What is it? *Sovremennaya Revmatologiya = Modern Rheumatology Journal*. 2021;15(5):7-11. doi: 10.14412/1996-7012-2021-5-7-11
16. Xie S, Li S, Chen B, et al. Serum anti-citrullinated protein antibodies and rheumatoid factor increase the risk of rheumatoid arthritis-related interstitial lung disease: A meta-analysis. *Clin Rheumatol*. 2021 Nov;40(11): 4533-4543. doi: 10.1007/s10067-021-05808-2.
17. Sparks JA, He X, Huang J, et al. Rheumatoid arthritis disease activity predicting incident clinically apparent rheumatoid arthritis-associated interstitial lung disease: A prospective cohort study. *Arthritis Rheumatol*. 2019 Sep;71(9):1472-1482. doi: 10.1002/art.40904.
18. Kelly C, Emery P, Dieude P. Current issues in rheumatoid arthritis related interstitial lung disease (RA-ILD). *Lancet Rheum*. 2021; 3(11):e798-e807. doi: 10.1016/S2665-9913(21)00250-2
19. Akiyama M, Kaneko Y. Pathogenesis, clinical features, and treatment strategy for rheumatoid arthritis-associated interstitial lung disease. *Autoimmun Rev*. 2022 May;21(5): 103056. doi: 10.1016/j.autrev.2022.103056.
20. Yu KH, Chen HH, Cheng TT, Jan YJ, Weng MY, Lin YJ, et al. Consensus recommendations on managing the selected comorbidities including cardiovascular disease, osteoporosis, and interstitial lung disease in rheumatoid arthritis. *Medicine (Baltimore)*. 2022;101(1):e28501. doi: 10.1097/MD.0000000000028501 92.

21. Diesler R, Cottin V. Pulmonary fibrosis associated with rheumatoid arthritis: From pathophysiology to treatment strategies. *Expert Rev Respir Med*. 2022 May;16(5):541-553. doi: 10.1080/17476348.2022.2089116.
22. Roodenrijs NMT, Hamar A, Kedves M, et al. Pharmacological and non-pharmacological therapeutic strategies in difficult-to-treat rheumatoid arthritis: A systematic literature review informing the EULAR recommendations for the management of difficult-to-treat rheumatoid arthritis. *RMD Open*. 2021 Jan;7 (1):e001512. doi: 10.1136/rmdopen-2020-001512.
23. Buch MH, Eyre S, McGonagle D. Persistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis. *Nat Rev Rheumatol*. 2021 Jan;17(1):17-33. doi: 10.1038/s41584-020-00541-7.
24. Насонов ЕЛ, Олюнин ЮА, Лила АМ. Ревматоидный артрит: проблемы ремиссии и резистентности к терапии. Научно-практическая ревматология. 2018;56(3): 263-271.
Nasonov EL, Olyunin YuA, Lila AM. Rheumatoid arthritis: The problems of remission and therapy resistance. *Nauchno-Prakticheskaya Revmatologia*. 2018;56(3): 263-271. (In Russ.).
25. Соловьев СК, Асеева ЕА, Чикликчи АС, Лашина НЮ. Синхронная программная интенсивная терапия больных ревматоидным артритом. Научно-практическая ревматология. 2000;38(1):49-54.
Solov'ev SK, Aseeva EA, Chiklikchi AS, Lashina NYu. Synchronic intensive program therapy of patients with rheumatoid arthritis. *Nauchno-Prakticheskaya Revmatologia*. 2000; 38(1):49-54. (In Russ.).
26. Xing Y, Wang S, Liu C, et al. Efficacy and safety of dual filtration plasmapheresis combined with biological agents in active refractory rheumatod arthritis: A retrospective cohort study. *Medicine (Baltimore)*. 2020 Jul 10;99(28): e20966. doi: 10.1097/MD.00000000000 20966.
27. Yu X, Zhang L, Wang L, et al. MRI assessment of erosion repair in patients with longstanding rheumatoid arthritis receiving double-filtration plasmapheresis in addition to leflunomide and methotrexate: a randomized controlled trial. *Clin Rheumatol*. 2018 Apr; 37(4):917-925. doi: 10.1007/s10067-017-3956-3.
28. Yu X, Ma J, Tian J, et al. A controlled study of double filtration plasmapheresis in the treatment of active rheumatoid arthritis. *J Clin Rheumatol*. 2007 Aug;13(4):193-8. doi: 10.1097/RHU.0b013e318124a483.
29. Асеева ЕА, Покровский НС, Соловьев СК и др. Первый клинический опыт применения селективной плазмосорбции ДНК с использованием сорбционной колонки «НуклеоКор®» при лечении системной красной волчанки. Современная ревматология. 2024;18(2):75-80.
Aseeva EA, Pokrovskii NS, Solov'ev SK, et al. The first clinical experience with selective DNA plasmasorption using the NucleoCapture Device in the treatment of systemic lupus erythematosus. *Sovremennaya Revmatologiya = Modern Rheumatology Journal*. 2024;18(2): 75-80. (In Russ.). doi: 10.14412/1996-7012-2024-2-75-80
30. Mena-Vazquez N, Redondo-Rodriguez R, Rojas-Gimenez M, et al. Efficacy and safety of rituximab in autoimmune disease-associated interstitial lung disease: A prospective cohort study. *J Clin Med*. 2022 Feb 10;11(4):927. doi: 10.3390/jcm11040927.
31. Matteson E, Bongartz T, Ryu J, et al. Open-label, pilot study of the safety and clinical effects of rituximab in patients with rheumatoid arthritis-associated interstitial pneumonia. *Open J Rheumatol Autoimmune Dis*. 2012;2(3):53-58. doi: 10.4236/ojra.2012.23011
32. Vadillo C, Nieto MA, Romero-Bueno F, et al. Efficacy of rituximab in slowing down progression of rheumatoid arthritis-related interstitial lung disease: Data from the NEREA Registry. *Rheumatology (Oxford)*. 2020 Aug 1; 59(8):2099-2108. doi: 10.1093/rheumatology/kez673.

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