CLINICAL OBSERVATIONS

Rhupus – a combination of systemic lupus erythematosus and rheumatoid arthritis as a separate disease phenotype (a clinical case)

Nikishina N.Yu., Aseeva E.A., Mesnyankina A.A., Soloviev S.K.

V.A. Nasonova Research Institute of Rheumatology, Moscow
34A, Kashirskoe Shosse, Moscow 115522, Russia

Rhupus is a rare combination of systemic lupus erythematosus (SLE) and rheumatoid arthritis, one of the characteristic features of which is the development of erosive polyarthritis on the background of the main immunological signs of SLE.
The article presents a clinical observation in which, along with the typical immunological picture of SLE, the patient was diagnosed with erosive polyarthritis with "swan neck" type deformities of the hand joints, which required administration of anti-B-cell therapy.

Keywords: *rhupus; systemic lupus erythematosus; rheumatoid arthritis; rituximab.*
Contact: *Nina Yurievna Nikishina;* ***lashinanina@gmail.com***
For reference: *Nikishina NYu, Aseeva EA, Mesnyankina AA, Soloviev SK. Rhupus – a combination of systemic lupus erythematosus and rheumatoid arthritis as a separate disease phenotype (a clinical case). Sovremennaya Revmatologiya=Modern Rheumatology Journal. 2023;17(2): 65–71.* ***DOI:*** *10.14412/1996-7012-2023-2-65-71*

A combination of several autoimmune diseases in one patient is a frequent phenomenon that requires a special approach to treatment taking into account the prognosis and therapeutic strategy [1–4].

In 1936, Friedberg et al. [5] for the first time noted that patients with systemic lupus erythematosus (SLE) may develop polyarthritis involving small and large joints, similar to that of rheumatoid arthritis (RA). In 1950, G.W. Daugherty and A.H. Baggenstoss [6] proposed to consider arthritis as a diagnostic sign of SLE. However, over time, patients with SLE did not experience erosive changes in the joints, and subluxations were usually caused by tendinitis and tenosynovitis. At the same time, arthritis associated with SLE was regarded as a form of "malignant" RA or as a "pseudo-rheumatoid" form of SLE [7]. In 1960, Toone et al. [8] reported coexistence of SLE and RA in 15 patients. In 1971, P.H. Schur first used the term "rhupus" to describe a syndrome in which SLE and RA are combined in one patient, RA being the most common diagnosis in such cases [7, 8].

The prevalence of rhupus varies from 0.01% to 9.7%, the average age of onset of the disease is about 40 years [9–12]. Every year the number of descriptions of rhupus is growing, but the criteria for its diagnosis are still not defined. Several combinations of clinical, immunological, and radiological signs are presented in the literature to confirm the diagnosis of rhupus. Most often, this syndrome can be suspected if a patient simultaneously meets the criteria for the diagnosis of SLE SLICC (Systemic Lupus International Collaborating Clinics) 2012 or ACR (American College of Rheumatology) 1997 and the criteria of RA ACR/EULAR (European Alliance of Associations for Rheumatology) 2010 [9, 10]. However, some authors consider the presence of joint erosions [13], rheumatoid factor (RF), antibodies to cyclic citrulline peptide (ACCP) [13, 14], antinuclear antibodies (ANA), antibodies to double-stranded DNA (anti-dsDNA) or to the extracted Smith nuclear antigen (anti-Sm) [13] as mandatory for diagnosis of rhupus, which raises many debatable issues (Table 1).

We present a case report of combination of SLE with RA.

Patient P.*, a 34-year-old woman, was admitted to V.A. Nasonova Research Institute of Rheumatology (V.A. Nasonova Research Institute) in January 2021 with complaints of general weakness, increased hair loss, erythematous rashes on the face, an increase in the body temperature in the evening to 37 °C, pain in the lumbar spine, small joints of the feet and right hand, knee joints, left hip joint, morning stiffness for 3 hours, discoloration of the skin of the fingers in cold weather.*

It is known from her medical history that in childhood she was observed by a dermatologist due to rashes on the scalp, and the diagnosis of psoriasis was discussed. In 2011, she first noticed impairment of extension in the right elbow joint, then whiteness and blueness of the skin of the fingers in the cold weather. Local therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) and group B vitamins was carried out at the place of residence, but with little effect. In 2013, a non-developing pregnancy was diagnosed (at 10 weeks), after which the patient developed polyarthritis with the damage to small joints of the hands and wrists. The local rheumatologist diagnosed RA and administered intramuscular methotrexate (MT) 10 mg / week. Against the background of the therapy, there was an increase in the body temperature up to 40 °C, itching of the skin, which was regarded as an adverse reaction, and the drug was canceled. Therapy with prednisone 10 mg/day and NSAIDs per os was started for the first time. In 2016, thrombocytopenia was detected (up to $5 \cdot 10^9$/L), and the patient was hospitalized to a hematology hospital at the place of residence. Examination in November 2016 showed: CRP – 20.95 mg/L; screening for lgG-, lgM-antibodies to cardiolipin (aCL), lgG-, lgM-antibodies to β2-glycoprotein 1 (aβ2-GP1) gave a negative result; Hb – 98 g/L, leucocytes – $6.5 \cdot 10^9$/L; erythrocytes – $3.47 \cdot 10^{12}$/ L; thrombocytes – $7{,}0 \cdot 10^{12}$/ L; ESR – 33 mm/h; ferritin – 185.20 μg/L. Metypred was prescribed at a dose 64 mg / day with a gradual dose reduction to 8 mg / day with a positive effect; the platelet count returned to normal. In 2017, the

Table 1. Rhupus criteria, according to the literature data

Study	Number of patients	Inclusion criteria
H. Kondo et al, 2019 [15]	7	ACR for SLE + ACR for RA + erosions
B.B. Yang et al. 2018 [16]	20	ACR 1997 for SLE + ACR 1987 for RA
A.C. Lozada-Navarro et al, 2018 [13]	9	SLICC 2012 for SLE + ACR/EULAR 2010 for RA + erosions + RF or anti-CCP + ANA + anti-dsDNA Sm + SLE organ involvement
F. Danion et al, 2017 [17]	15	ACR 1997 for SLE + ACR 1987 for RA
J. Li et al, 2014 [10]	56	ACR 1997 for SLE + ACR 1987 for RA
C. Tani et al, 2013 [9]	10	ACR 1997 for SLE + ACR 1987 for RA
L. Andrade-Ortega et al, 2013 [18]	9	ACR 1997 for SLE + ACR 1987 for RA
K. Ikeda et al, 2013 [19]	6	ACR 1997 for SLE + ACR/EULAR 2010 for RA
T. Piga et al, 2013 [20]	6	ACR 1997 for SLE + ACR 1987 for RA + erosions
O. Malaise et al, 2012 [21]	6	ACR 1997 for SLE + ACR/EULAR 2010 for RA
E.P. Benavente and S.O. Paira, 2011 [22]	4	ACR 1997 for SLE + ACR 1987 for RA + erosions + anti-dsDNA or anti-Sm
M.T. Chan et al, 2008 [23]	12	ACR 1997 for SLE + ACR 1987 for RA + erosions
J.B. Martinez et al, 2007 [24]	5	ACR 1997 for SLE + ACR 1987 for RA + erosions
A. Fernandez et al, 2006 [25]	8	ACR 1997 for SLE + ACR 1987 for RA
L.M. Amezcua-Guerra et al, 2006 [26]	7	ACR 1997 for SLE + ACR 1987 for RA
T.S. Rodriguez-Reyna and D. Alarcon-Segovia et al, 2005 [27]	13	ACR 1997 for SLE + ACR 1987 for RA
J.A. Simyn et al, 2002 [28]	22	ACR 1997 for SLE + ACR 1987 for RA + erosions + anti-dsDNA or anti-Sm
C.A. Brand et al, 1992 [29]	11	ACR 1997 for SLE + ARA for RA
M.G. Cohen and J. Webb, 1987 [30]	11	ARA for SLE + ARA for RA + having RA as the first diagnosis

ACR: American College of Rheumatology; SLICC: Systemic Lupus Erythematosus International Collaborating Clinics; ARA: American Rheumatism Association; EULAR: European League Against Rheumatism; SLE: Systemic lupus erythematosus; RA: Rheumatoid arthritis.

patient had a fracture of the femoral neck on the right, and osteosynthesis. She sought help from a local rheumatologist who confirmed the previous diagnosis and prescribed sulfasalazine 1000 mg / day as the basic therapy, which provoked hyperemia of the skin, and difficulty in breathing. The drug was replaced with leflunomide 20 mg / day, however, after a few days it also caused adverse events (Quincke's edema, increased body temperature). The analyses (November 2017) did not reveal antibodies to cyclic citrullinated peptide (ACCPs), the test for lupus anticoagulant was weakly positive. The patient was seen by a rheumatologist again, and this time the antinuclear factor (ANF) was detected, and the diagnosis was revised in favor of SLE. Metypred was recommended at 8 mg / day, but it had little effect. Since the summer of 2020, against the background of metypred therapy (8 mg /day), pain in the small joints of the hands and in the spine increased; numbness of the tip of the tongue, upper and lower lips appeared; she noted increased weakness and fatigue.

On examination (October 2020): ANA Hep2 – 1:10240, homogeneous type of glow, аЯ2GP1 were not detected, anti-Sm – 2+, antibodies to ribonucleoprotein 70 (anti-RNP70) – 3+, anti-dsDNA >200 IU/mL (norm – 0–20 IU/mL), antibodies to nucleosomes – 3+. In January 2021, she was hospitalized to V.A. Nasonova Research Institute with the diagnosis of unspecified systemic lupus erythematosus, chronic course, high activity (Systemic Lupus Erythematosus Disease Activity Index-2K, SLEDAI-2K – 15), Raynaud's syndrome, polyarthritis, hematological disorders (anemia, leukopenia, thrombocytopenia), ANA +, anti-dsDNA +.

Upon admission, the general condition was satisfactory; the constitution normosthenic. The physique is regular, height – 157 cm, body weight – 52 kg, body mass index – 21.10, body temperature – 36.6 ℃.

Erythematous rashes on the face, two-phase Raynaud's syndrome, palmar capillaritis were noted. There was a pronounced vascular pattern on the skin of the lower extremities of livedo-vasculitis type. Lymph nodes available for palpation were not enlarged, painless. Swelling and soreness of the left knee joint, proximal interphalangeal joints of both hands, wrist joints, soreness on palpation and restriction of movements in the shoulder joints were noted. The number of painful joints was 22, the number of swollen joints - 9, pain on the visual analog scale – 80 mm. The patient had swan-neck deformity of the joints of the hands valgus deformity of the I metatarsophalangeal joints of both feet (Fig. 1, a–d), a sharply positive symptom of "compression of the feet" on both sides. The internal organs were normal. On examination: Hb – 92 g/L, leucocytes – 2,0·10⁹/ L, erythrocytes –

3,21·10^{12}/ L, hematocrit – 28.6%, thrombocytes – 116·10^{9}/L, ESR (according to Westergren) – 88.0 mm/h, total protein – 74.6 g/L, γ-globulins – 24.10%, CRP – 37.5 mg/L, RF <9.4 IU/mL, ACCP – 27.1 units/mL, lgG-aCL – 5.9 GPL, lgM-aCL – 2.0 MPL, lgG-aβ2-GP1 – 4.4 Units/mL, lgM-aβ2-GP1 – 1.9 Units/mL, direct Coombs test +/-, ANA (Hep2) – 1/2560 h+sp, anti-dsDNA >200.0 IU/mL, lgG – 19.0 g/L, lgM – 1.31 g/L, lgA – 6.16 g/L, compliment components: C3 – 0.745 g/L, C4 – 0.05 g/L, antibodies to Ro/SSA (anti-Ro/SSA) – 3.0 Units/mL, antibodies to La/SSB (anti-La/SSB) – 5.4 units/mL, anti-Sm – 46.5 units/mL, anti-centromeric antibodies – 2.7 units/mL, anti-RNP70 >200.0 U/mL, antineutrophil cytoplasmic antibodies and cryoglobulins within normal limits. General urinalysis: proteins – 0.3 g /L, leukocytes – 7–8 per high power field (pHPF), flat epithelium – 1–2 pHPF, hyaline cylinders – 2 pHPF. Daily urine: protein – 0.3 g / day.

Electrocardiogram: sinus rhythm, heart rate – 82 per minute, normal electrical axis of the heart. Predominance of left ventricular potentials. Diffuse changes in the myocardium of the left ventricle. Computed tomography of the chest organs: no recent focal and infiltrative changes in the lungs were detected. The trachea, main, lobar and segmental bronchi were patent. The intra-thoracic lymph nodes were not enlarged, with usual density and structure. Free fluid in the pleural cavity and pericardial cavity was not detected. Bones were without destructive disorders; dystrophic changes of the thoracic spine were noted. Capillaroscopy: Raynaud's syndrome. Ultrasound of the salivary glands: lymph nodes in the parotid salivary glands. Diffusely heterogeneous structure, signs of Sjogren's syndrome. Ultrasound of the abdominal cavity and kidneys: diffuse changes in the liver and pancreas; inflection of the gallbladder; hemangiomas in the right lobe of the liver.

Densitometry: The Z-criterion in $L_{I–IV}$ was 2.8, in the neck of the left femur – 2.0. Conclusion: the indicators of bone mineral density in $L_{I–IV}$ and in the left femoral neck showed osteopenia. Contrast radiography of the salivary gland and ducts (sialography): initial manifestations of parenchymal sialadenitis. Radiography of the hands and feet: osteoporosis, more pronounced in the periarticular parts; few cyst-like areas of radiolucency of bone tissue; erosion of a number of adjacent articular surfaces, mainly interphalangeal joints of the hands; intra-articular osteolysis in the area of interphalangeal joints of the thumbs; subluxations of a number of metacarpal and interphalangeal joints, mostly of the thumbs and little fingers (I and V), valgus deviation of the I metatarsophalangeal joints; joint gaps significantly narrowed, osteophytes on the edges of the articular surfaces of the distal interphalangeal joints of the hands. Conclusion: signs of chronic erosive arthritis of stage III (see Fig. 1, a–d). Consultation of an ophthalmologist revealed posterior capsular cataract.

In accordance with the classification criteria of RA ACR/EULAR (2010) and SLE SLICC (2012), the following diagnoses were made: seronegative rheumatoid arthritis (M05.3), late clinical stage, average activity (DAS28 – 5.01) with systemic manifestations (Sjogren's syndrome), erosive, radiological stage III, ACCP+, functional class II and systemic lupus erythematosus (M32.1), activity – III (SLEDAI 2K – 15 points, SLICC damage index – 3 points), with damage to joints (polyarthritis), vessels (Raynaud's syndrome, palmar-plantar capillaries, livedo-vasculitis), hematological (Coombs-positive anemia, leukopenia, thrombocytopenia) and immunological (anti-dsDNA+, anti-Sm+, anti-RNP70+, ANF+) disorders. Moderate myopia (H52.1), retinal angiopathy of both eyes, posterior capsular cataract.

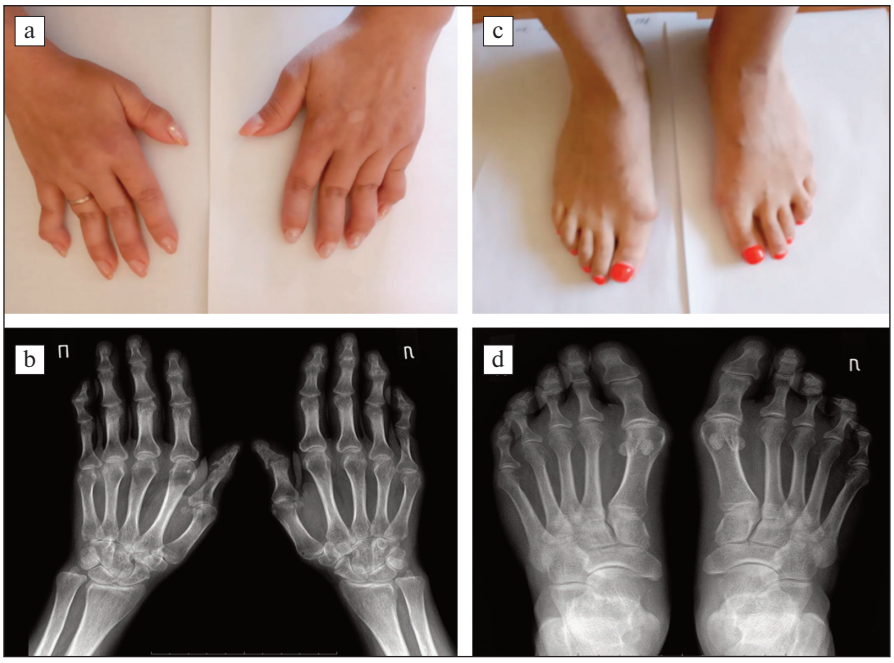

Fig. 1. *Patient P., 34 years old: a – "swan neck" type deformity of the hand joints; b – X-ray of the hands in direct projection; c – valgus deformity of the first metatarsophalangeal joints; d – radiography of the feet in direct projection (here and in Fig. 2, radiographs from the authors collection are presented)*

Taking into account the high activity of both RA and SLE, ineffectiveness of the previous therapy (MT, sulfasalazine, leflunomide), the young age of the patient, irreversible organ damage (osteopenia, hip fracture in the anamnesis, complicated posterior capsular cataract, deforming polyarthritis with impaired hand function), it was recommended to add to metypred therapy (8 mg / day) a genetically engineering biological drug (GIBD) – rituximab (RTM) 1000 mg intravenous (IV) drip, followed by the administration of mycophenolate mofetil 1000 mg / day, hydroxychloroquine 200 mg / day, which contributed to a significant improvement in the general condition and a decrease in the severity of joint syndrome. Dynamic examination after 3 and 6 months of therapy allowed to confirm the positive clinical and laboratory effect (Fig. 2, 3): pain on a visual analog scale was 10 mm, the number of painful joints – 2, the number of swollen joints – 0. After 6 months of treatment by a rheumatologist at the place of residence, the dose of metypred was reduced to 4 mg / day, no exacerbation of the disease was observed. Thus, the therapy allowed to reduce the dose of glucocorticoids (GCs) and achieve remission of the disease.

Discussion. According to A. Fernandez et al. [25], signs of RA and SLE in rhupus rarely manifest or are diagnosed simultaneously. Rheumatoid-like polyarthritis is observed in almost 2/3 of patients at the onset of the disease. Patients in whom the disease debuts with a clinical picture of RA usually have a younger age [9, 10, 12, 14].

J. Li et al. [10] analyzed the data of 56 patients diagnosed with rhupus, among whom 84% were women with an average age

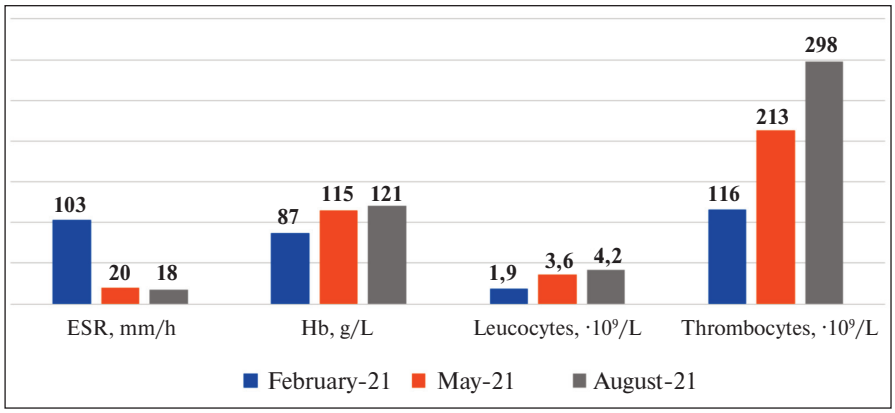

Fig. 2. *Dynamics of CBC test parameters in patient P. during therapy*

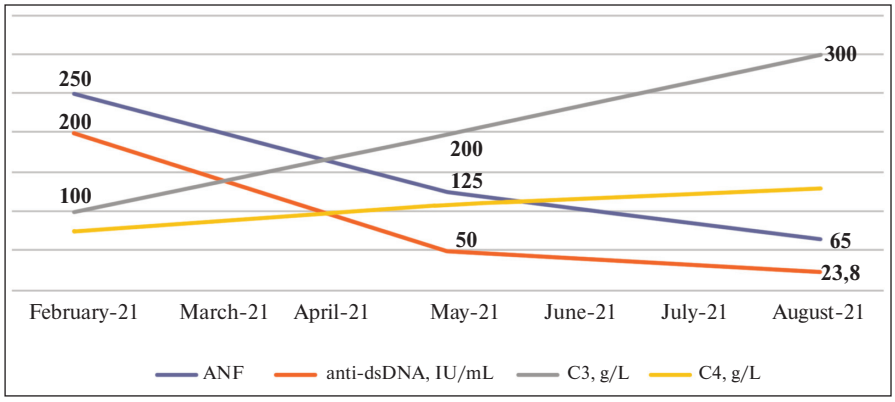

Fig. 3. *Dynamics of indicators of immunological activity of SLE in patient P. during therapy*

of disease onset of 35 years, while the average age of diagnosis verification was 45 years. Interestingly, in 66% of cases, the first sign was rheumatoid-like polyarthritis, so the diagnosis of RA was established [26]. The prevalence of rhupus in patients with SLE varies from 0.09% [28] to 9.7% [10]. In the two most recent and large studies, it was 1.3% [17] and 1.4% [14]. Such discrepancies can be explained by heterogeneity of inclusion criteria and approaches to the diagnosis of erosions, which can lead to underdiagnosis of rhupus in patients with RA and SLE. The maximum prevalence of rhupus (9.7%) was found in a prospective cohort of 103 patients with SLE who underwent systematic screening of erosions using ultrasound and magnetic resonance imaging of hands and wrists. Thus, a lower incidence of rhupus in retrospective cohorts of patients with SLE who did not undergo a complete instrumental examination may be a consequence of underdiagnosis [9]. Rheumatoid-like arthritis is the main diagnostic sign of rhupus, which must be differentiated from benign non-erosive arthritis and Jacou syndrome [7, 31–33]. L. Antonini et al. [11] presented the most common clinical manifestations in rhupus (Tabl. 2).

The most common signs of SLE in patients with rhupus are hematological disorders [12], skin and mucous membrane changes, kidney damage and serositis, and the most common skin manifestations are zygomatic rash, photosensitization and alopecia, while discoid rash is rarely recorded [10]. In our patient, the first sign of the disease was rheumatoid-like polyarthritis, 5 years later hematological disorders in the form of deep thrombocytopenia developed.

Kidney damage is a frequent manifestation of rhupus. Thus, in 24 patients with rhupus , a pathomorphological examination of a kidney biopsy revealed different classes of lupus nephritis (LN) according to 2003 ISN/RPS criteria (International Society of Nephrology / Renal Pathology Society): mainly, classes IV (45.8%; n=11) and II (25%; n=6), while classes III and V were less common (12.5% each; n=3) [9, 12, 13, 15, 18, 24, 28, 33]. Our patient did not have any criteria-based signs of LN, however, urinary syndrome was detected during hospitalization.

With Rhupus, although rarely, may be accompanied by damage to the peripheral nervous system. J.A. Simyn et al. [28] observed 3 patients with transverse myelitis and 2 patients with multiple mononeuritis; data on the development of encephalopathy and convulsive syndrome have also been published [25, 27].

In 2014, J. Li et al. [10] described 10 patients with rhupus and interstitial lung damage. S. Zaman et al. [34] reported a combination of rhupus with Liebman–Sachs endocarditis and cerebral infarction. Raynaud's syndrome and vasculitis are not uncommon, but usually benign, without the development of severe complications. Our patient also has Raynaud's syndrome and livedo-vasculitis [10, 22, 25, 27, 30].

Treatment of rhupus is based on the complex use of GCs, cytostatic therapy, hydroxychloroquine, possibly with addition of genetically engineered biological drugs (GIBD). GCs prescribed at doses from 6.5 to 15 mg / day of prednisolone equivalent [9, 17, 18, 28]; according to some authors, lower doses of GCs are required for rhupus than for SLE [10]. Intravenous administration of methylprednisolone is used less frequently in patients with rhupus than in patients with SLE [10]. The most commonly used cytostatic drug is methotrexate; azathioprine and leflunomide are less commonly used [9, 17, 18, 28]. The administration of hydroxychloroquine is mandatory, since it is effective both for SLE and RA [9, 17, 18]. In case of damage to vital organs, especially kidneys, therapy with cyclophosphamide, mycophenolate mofetil and cyclosporine is advisable [10, 17, 18, 20, 24, 33, 35–37]. Several studies have demonstrated successful treatment with GIBDs – inhibitors of tumor necrosis factor α (TNF) [16, 17], abatacept [19] and RTM [18, 20]. Tocilizumab [38], baricitinib [15] and belimumab [39] were also used. It should be noted that TNFa inhibitors, abatacept, Rituximab (RTM) and tocilizumab are approved for use in patients with rhupus [40]. Rituximab is approved for RA therapy, at the same time, it has shown effectiveness in the treatment of SLE in real clinical practice [41–44]. L. Andrade-Ortega et al. [18] in an open study evaluated the effectiveness of Rituximab therapy at a dose of 1000 mg with an interval of 2 weeks. Basic anti-inflammatory drugs and immunosuppressants (except GCs) were canceled a month before the start of the study in 9 patients with rhupus. The effectiveness was evaluated after 6 months.

Table 2. Clinical manifestations of Rhupus (n=287) [11]

Manifestations	Occurrence (%) (number of patients / number of examined patients)
Polyarthritis	88.2% (225/255)
Symmetric arthritis	87% (206/237)
Erosions	90% (251/278)
Rheumatoid nodules	16% (43/262)
Skin lesions	41% (118/287)
Oral ulcers	23% (65/287)
Photosensitivity	30% (87/287)
Alopecia	17% (47/271)
Raynaud's syndrome	9% (25/271)
Serositis	26% (74/287)
Neurological disorders	5% (14/287)
Renal involvement	35% (100/287)
Pulmonary involvement	6% (16/287)
Hematological disorders	70% (202/287)
s	
Vasculitis	4% (12/287)

There was a significant decrease in DAS28 (from 5.73 to 3.02 on average; p<0.001) and SLEDAI-2K (from 5 to 1.22; p<0.001). The average dose of prednisolone was reduced from 11.66 to 0.55 and 1.11 mg/day after 12 and 24 months, respectively. In another study, 6 patients with rhupus who did not receive basic anti-inflammatory drugs were also prescribed RTM at a dose of 1000 mg with a 2-week interval, and after 28 weeks the course of treatment was repeated. After 12 months, there was a significant decrease in DAS28 on average from 5.98 to 3.95 (p<0.01) and SLEDAI-2K from 7.1 to 1.3; (p<0.01), the average dose of GC after 6 months was reduced from 15.4 to 10.6 mg/day (p<0.05) [20]. L. Laccarino et al. [45] reported a good response according to DAS28 and SLEDAI in 2 out of 3 patients with rhupus refractory to traditional methods of treatment after the administration of RTM.

In the analyzed clinical case, the combined use of mycophenolate mofetil, hydroxychloroquine and RTM was due to the high clinical and immunological activity of the disease, as well as the presence of irreversible organ damage and intolerance to many drugs.

Conclusion. Our clinical observation illustrates a separate phenotype of SLE in combination with rheumatoid-like joint damage, which has a set of clinical and immunological markers different from other variants of the disease. In real clinical practice, it should be borne in mind that autoimmune diseases are dynamic and can evolve. Since these diseases often debut with polyarthritis, it must be remembered that polyarthritis can be a manifestation of various systemic diseases and such patients need regular monitoring for their timely detection.

REFERENCES

1. Lockshin MD, Levine AB, Erkan D. Patients with overlap autoimmune disease differ from those with 'pure' disease. *Lupus Sci Med.* 2015 May 6;2(1):e000084. doi: 10.1136/lupus-2015-000084. eCollection 2015.
2. Suzuki K, Sawada T, Murakami A, et al. High diagnostic performance of ELISA detection of antibodies to citrullinated antigens in rheumatoid arthritis. *Scand J Rheumatol.* 2003;32(4):197-204. doi: 10.1080/03009740310003677.
3. Schellekens GA, Visser H, de Jong BAW, et al. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. *Arthritis Rheum.* 2000 Jan; 43(1):155-63. doi: 10.1002/1529-0131(200001)43:1<155::AID-ANR20>3.0.CO;2-3.
4. Vannini A, Cheung K, Fusconi M, et al. Anti-cyclic citrullinated peptide positivity in non-rheumatoid arthritis disease samples: citrulline-dependent or not? *Ann Rheum Dis.* 2007 Apr;66(4):511-6. doi: 10.1136/ard.2006.058933. Epub 2006 Sep 19.
5. Friedberg CK, Gross L, Kaufman W. Nonbacterial thrombotic endocarditis: associated with prolonged fever, arthritis, inflammation of serous membranes and widespread vascular lesions. *Arch Intern Med (Chic).* 1936;58(4): 662-84. doi:10.1001/archinte.1936.00170140087006
6. Daugherty GW, Baggenstoss AH. Syndrome characterized by glomerulonephritis and arthritis Libman-Sacks disease with predominantly renal involvement. *Arch Intern Med (Chic).* 1950 Jun;85(6):900-23. doi: 10.1001/archinte.1950.00230120009002.
7. Fernandez A, Quintana G, Matteson EL, et al. Lupus arthropathy: historical evolution from deforming arthritis to rhupus. *Clin Rheumatol.* 2004 Dec;23(6):523-6. doi: 10.1007/s10067-004-0951-2.
8. Toone EC, Irby R, Pierce EL. The L.E. cell in rheumatoid arthritis. *Am J Med Sci.* 1960 Nov;240:599-608.
9. Tani C, D'Aniello A, Sedie D, et al. Rhupus syndrome: Assessment of its prevalence and its clinical and instrumental characteristics in a prospective cohort of 103 SLE patients. *Autoimmun Rev.* 2013 Feb;12(4):537-41. doi: 10.1016/j.autrev.2012.09.004. Epub 2012 Oct 11.
10. Li J, Wu H, Huang X, et al. Clinical analysis of 56 patients with rhupus syndrome. *Medicine (Baltimore).* 2014 Aug;93(10):e49. doi: 10.1097/MD.0000000000000049.
11. Antonini L, Le Mauff B, Marcelli C, et al. Rhupus: A systematic literature review. *Autoimmun Rev.* 2020 Sep;19(9):102612. doi: 10.1016/j.autrev.2020.102612. Epub 2020 Jul 12.
12. Liu T, Li G, Mu R, et al. Clinical and laboratory profiles of rhupus syndrome in a Chinese population: a single-centre study of 51 patients. *Lupus.* 2014 Aug;23(9):958-63. doi: 10.1177/0961203314526439. Epub 2014 Mar 7.
13. Lozada-Navarro AC, Castillo-Martinez D, Moreno-Ramirez M, et al. An imbalance in the T-helper phenotypes displayed by senescent CD4(+)CD28(null) T cells is associated with erosive arthritis (rhupus syndrome) in systemic lupus erythematosus. *Lupus.* 2018 Nov; 27(13):2155-2160. doi: 10.1177/0961203318793715. Epub 2018 Aug 15.
14. Gormezano NW, Silva CA, Aikawa NE, et al. Chronic arthritis in systemic lupus erythematosus: distinct features in 336 paediatric and 1830 adult patients. *Clin Rheumatol.* 2016 Jan;35(1):227-31. doi: 10.1007/s10067-015-3127-3. Epub 2015 Nov 28.
15. Kondo H, Watanabe R, Okazaki S, et al. Coexistence of rheumatoid arthritis and systemic lupus erythematosus is still rare in the biologic era: report of seven cases and literature review. *Mod Rheumatol.* 2020 Nov;30(6): 1082-3. doi: 10.1080/14397595.2019.1682795. Epub 2019 Oct 30.
16. Yang BB, Xiao H, Li XJ, Zheng M. Safety and efficacy of etanercept-methotrexate combination therapy in patients with rhupus: an observational study of nonglucocorticoid treatment for rheumatic diseases. *Discov Med.* 2018 Jan;25(135):14-20.

17. Danion F, Sparsa L, Arnaud L, et al. Long-term efficacy and safety of antitumour necrosis factor alpha treatment in rhupus: an open-label study of 15 patients. *RMD Open*. 2017 Dec 29;3(2):e000555. doi: 10.1136/rmdopen-2017-000555. eCollection 2017.
18. Andrade-Ortega L, Irazoque-Palazuelos F, Munoz-Lopez S, Rosales-Don Pablo VM. Efficacy and tolerability of rituximab in patients with rhupus. *Reumatol Clin*. 2013 Jul-Aug; 9(4):201-5. doi: 10.1016/j.reuma.2012.10.010. Epub 2013 Feb 15.
19. Ikeda K, Sanayama Y, Makita S, et al. Efficacy of abatacept for arthritis in patients with an overlap syndrome between rheumatoid arthritis and systemic lupus erythematosus. *Clin Dev Immunol*. 2013;2013:697525. doi: 10.1155/2013/697525. Epub 2013 Nov 14.
20. Piga M, Gabba A, Cauli A, et al. Rituximab treatment for 'rhupus syndrome': clinical and power-Doppler ultrasonographic monitoring of response. A longitudinal pilot study. *Lupus*. 2013 May;22(6):624-8. doi: 10.1177/0961203313482741. Epub 2013 Apr 4.
21. Malaise O, Halleux S, von Frenckell C, et al. Rhupus: when rheumatoid arthritis meets lupus. Rev Med Liege. 2012 Sep;67(9): 475-84.
22. Benavente EP, Paira SO. Rhupus: report of 4 cases. *Reumatol Clin*. 2011 Sep-Oct;7(5): 333-5. doi: 10.1016/j.reuma.2010.12.006. Epub 2011 Mar 21.
23. Chan MT, Owen P, Dunphy J, et al. Associations of erosive arthritis with anti-cyclic citrullinated peptide antibodies and MHC Class II alleles in systemic lupus erythematosus. *J Rheumatol*. 2008 Jan;35(1):77-83. Epub 2007 Dec 15.
24. Martinez JB, Valero JS, Bautista AJ, et al. Erosive arthropathy: clinical variance in lupus erythematosus and association with anti-CCP case series and review of the literature. *Clin Exp Rheumatol*. 2007 Jan-Feb;25(1):47-53.
25. Fernandez A, Quintana G, Rondon F, et al. Lupus arthropathy: a case series of patients with rhupus. *Clin Rheumatol*. 2006 Mar;25(2): 164-7. doi: 10.1007/s10067-005-1149-y. Epub 2005 Jun 25.
26. Amezcua-Guerra LM, Springall R, Marquez-Velasco R, et al. Presence of antibodies against cyclic citrullinated peptides in patients with "rhupus": a cross-sectional study. *Arthritis Res Ther*. 2006;8(5):R144. doi: 10.1186/ar2036.
27. Rodriguez-Reyna TS, Alarcon-Segovia D. Overlap syndromes in the context of shared autoimmunity. *Autoimmunity*. 2005 May;38(3): 219-23. doi: 10.1080/08916930500050145.
28. Simyn JA, Granados J, Cabiedes J, et al. Clinical and immunogenetic characterization of Mexican patients with 'rhupus'. *Lupus*. 2002;11(5):287-92. doi: 10.1191/0961203302lu189oa.
29. Brand CA, Rowley MJ, Tait BD, et al. Coexistent rheumatoid arthritis and systemic lupus erythematosus: clinical, serological, and phenotypic features. *Ann Rheum Dis*. 1992 Feb;51(2):173-6. doi: 10.1136/ard.51.2.173.
30. Cohen MG, Webb J. Concurrence of rheumatoid arthritis and systemic lupus erythematosus: report of 11 cases. *Ann Rheum Dis*. 1987 Nov;46(11):853-8. doi: 10.1136/ard.46.11.853.
31. Pipili C, Sfritzeri A, Cholongitas E. Deforming arthropathy in systemic lupus erythematosus. *Eur J Intern Med*. 2008 Nov;19(7): 482-7. doi: 10.1016/j.ejim.2008.01.017. Epub 2008 Apr 1.
32. Ceccarelli F, Perricone C, Cipriano E, et al. Joint involvement in systemic lupus erythematosus: from pathogenesis to clinical assessment. *Semin Arthritis Rheum*. 2017 Aug; 47(1):53-64. doi: 10.1016/j.semarthrit.2017.03.022. Epub 2017 Apr 4.
33. Seo SR, Lee SJ, Park DJ, et al. Successful treatment using cyclosporine in a patient with rhupus complicated by aplastic anemia: a case report and review of the literature. *Clin Exp Rheumatol*. 2011 Jul-Aug;29(4):708-11. Epub 2011 Sep 1.
34. Zaman S, Rahim MA, Sayami LA, et al. Libman-sacks endocarditis in a bangladeshi patient suffering from rhupus. *Trop Doct*. 2019 Oct;49(4):309-11. doi: 10.1177/00494755 19854623. Epub 2019 Jun 10.
35. Piga M, Saba L, Gabba A, et al. Ultrasonographic assessment of bone erosions in the different subtypes of systemic lupus erythematosus arthritis: comparison with computed tomography. *Arthritis Res Ther*. 2016 Oct 4;18(1): 222. doi: 10.1186/s13075-016-1125-8.
36. Zengin O, Onder ME, Sarica MA, et al. Systemic vasculitis in a patient with rhupus syndrome. *Reumatismo*. 2015 Dec 23;67(4): 161-4. doi: 10.4081/reumatismo.2015.858.
37. Turkcapar N, Olmez U, Ozer D, et al. A case of overlap syndrome with rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and secondary Sjögren's syndrome. *Rheumatol Int*. 2006 Jul;26(9):841-5. doi: 10.1007/s00296-005-0084-1. Epub 2005 Nov 22.
38. Kim MY, Park S, Suh CH, et al. Patient with systemic lupus erythematosus combined with erosive arthritis was treated successfully with tocilizumab: a case report. *J Rheum Dis*. 2018;25(2):144-147. doi: 10.4078/jrd.2018.25.2.144.
39. Dayer PVC, Rivas NL, Ferrin JJM, et al. Belimumab treatment in rhupus: a case report with severe skin involvement. *Dermatol Ther*. 2019 Sep;32(5):e13056. doi: 10.1111/dth.13056. Epub 2019 Aug 20.
40. Kleinmann JF, Tubach F, Le Guern V, et al. International and multidisciplinary expert recommendations for the use of biologics in systemic lupus erythematosus. *Autoimmun Rev*. 2017 Jun;16(6):650-7. doi: 10.1016/j.autrev.2017.04.011. Epub 2017 Apr 18.
41. Merrill JT, Neuwelt CM, Wallace DJ, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase ii/iii systemic lupus erythematosus evaluation of rituximab trial. *Arthritis Rheum*. 2010 Jan;62(1):222-33. doi: 10.1002/art.27233.
42. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum*. 2012 Apr;64(4):1215-26. doi: 10.1002/art.34359. Epub 2012 Jan 9.
43. McCarthy EM, Sutton E, Nesbit S, et al. Short-term efficacy and safety of rituximab therapy in refractory systemic lupus erythematosus: results from the British Isles Lupus Assessment Group Biologics Register. *Rheumatology (Oxford)*. 2018 Mar 1;57(3):470-9. doi: 10.1093/rheumatology/kex395.
44. Terrier B, Amoura Z, Ravaud P, et al. Safety and efficacy of rituximab in systemic lupus erythematosus: results from 136 patients from the French AutoImmunity and Rituximab registry. *Arthritis Rheum*. 2010 Aug;62(8): 2458-66. doi: 10.1002/art.27541.
45. Iaccarino L, Gatto M, Bettio S, et al. Overlap connective tissue disease syndromes. *Autoimmun Rev*. 2013 Jan;12(3):363-73. doi: 10.1016/j.autrev.2012.06.004. Epub 2012 Jun 26.

Received/Reviewed/Accepted
06.11.2022/15.01.2023/19.01.2023

Conflict of Interest Statement

The investigation has not been sponsored. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

Nikishina N.Yu. https://orcid.org/0000-0002-4160-7218
Aseeva E.A. https://orcid.org/0000-0002-1663-7810
Mesnyankina A.A. https://orcid.org/0000-0001-5411-7317
Soloviev S.K. https://orcid.org/0000-0002-5206-1732