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SYSTEMIC LUPUS ERYTHEMATOSUS AS A MULTIDISCIPLINARY PROBLEM (CLINICAL CASE)

V.V. Talash [*],
I.P. Katerenchuk,
Yu.A. Kostrikova,
T.I. Yarmola,
O.O. Hutsalenko,
H.L. Pustovoyt,
L.A. Tkachenko,
O.V. Mokhnachev,
S.T. Rustamian,
V.V. Talash,
L.P. Sarychev,
R.B. Savchenko

Poltava State Medical University
Shevchenko str., 23, Poltava, 36000, Ukraine
Полтавський державний медичний університет
вул. Шевченка, 23, Полтава, 36000, Україна
e-mail: pdmu@edu.ua
[*]*e-mail: viktorya.talash@gmail.com*

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Key words: *systemic lupus erythematosus, lupus crisis, lupus nephritis, renal failure*
Ключові слова: *системний червоний вовчак, вовчаковий криз, вовчаковий нефрит, ниркова недостатність*

Abstract. Systemic lupus erythematosus as a multidisciplinary problem (clinical case). Talash V.V., Katerenchuk I.P., Kostrikova Yu.A., Yarmola T.I., Hutsalenko O.O., Pustovoyt H.L., Tkachenko L.A., Mokhnachev O.V., Rustamian S.T., Talash V.V., Sarychev L.P., Savchenko R.B. *Systemic lupus erythematosus (SLE) is a prognostically unfavorable systemic connective tissue disease with heterogeneous clinical manifestations, development of complications, and an unpredictable wave-like course, which complicates the diagnosis of this pathology. The relevance of this clinical case is determined by a number of features: the debut of SLE with isolated kidney damage, an 11-year delay in the date of diagnosis, and the occurrence of an extremely rare complication – lupus crisis (LC), which became fatal for the patient. The aim of the work: to analyze a clinical case as unique in terms of the features of the debut and clinical course of systemic lupus erythematosus, which has become a multidisciplinary problem, to highlight the reasons for the delay in diagnosis verification, to assess, in dynamics, the effectiveness of the prescribed treatment and to report on the development of a multiorgan lupus crisis. The article analyzes data from the medical documents of a 31-year-old inpatient. An illustrative clinical case of SLE, which debuted with glomerulonephritis at the age of 16, 11 years before the appearance of specific clinical symptoms that met the criteria of the American College of Rheumatology and the European League Against Rheumatism 2019, is presented. The level of immunological indicators specific for SLE – antinuclear antibodies to double-stranded deoxyribonucleic acid increased in the patient in 2023, i.e. 4 years later. The patient's refusal of nephro biopsy, starting from the debut of the disease and from pathogenetic therapy at the stage of diagnosis and during the next 4 years. led to increased SLE activity, frequent relapses with the development of polymorbid pathology and, incompatible with life, multiorgan lupus crisis. The article describes in detail the dynamics of clinical manifestations of SLE and LC. The stages of diagnostic search, features of differential diagnosis and treatment of SLE and LC are discussed on the example of a clinical case. Based on the results of a review of the medical literature, analysis of articles, databases PubMed, SCOPUS, Web of Science, MedScape, the current state of the problem is highlighted, literature data on the incidence, features of the clinical course, diagnosis and treatment of SLE, its complications are summarized. The description of the clinical case, analysis of the literature is an addition to modern information about the possible clinical manifestations and consequences of SLE with the development of a severe, extremely rare complication – lupus crisis.*

Реферат. Системний червоний вовчак як мультидисциплінарна проблема (клінічний випадок). Талаш В.В., Катеренчук І.П., Кострікова Ю.А., Ярмола Т.І., Гуцаленко О.О., Пустовойт Г.Л., Ткаченко Л.А., Мохначов О.В., Рустамян С.Т., Талаш В.В., Саричев Л.П., Савченко Р.Б. *Системний червоний вовчак (СЧВ) – прогностично несприятливе системне захворювання сполучної тканини з гетерогенними клінічними проявами з розвитком ускладнень, непередбачуваним хвилеподібним перебігом, що ускладнює діагностику цієї патології. Актуальність цього клінічного випадку визначається рядом особливостей: дебютом СЧВ з ізольованого ураження нирок, 11-річним відтермінуванням дати встановлення діагнозу та виникненням надзвичайно рідкісного*

ускладнення – вовчакового кризу (ВК), який для пацієнтки став фатальним. Мета роботи: проаналізувати клінічний випадок як унікальний щодо особливостей дебюту та клінічного перебігу системного червоного вовчака, що став мультидисциплінарною проблемою, висвітлити причини відтермінування верифікації діагнозу, оцінити в динаміці ефективність призначеного лікування та повідомити про розвиток поліорганного вовчакового кризу. У статті проаналізовано дані медичної документації стаціонарної хворої 31-річного віку. Продемонстровано показовий клінічний випадок розвитку СЧВ, який дебютував гломерулонефритом у 16-річному віці пацієнтки, за 11 років до появи в неї специфічних клінічних симптомів, що відповідали критеріям Американської колегії ревматологів та Європейської антиревматичної ліги 2019 року. Рівень специфічних для СЧВ імунологічних показників – антинуклеарних антитіл до двоспіральної дезоксирибонуклеїнової кислоти підвищився в пацієнтки 4 роки по тому. Відмова пацієнтки від нефробіопсії, починаючи з дебюту захворювання, та згоди на патогенетичну терапію на етапі встановлення діагнозу призвели до підвищення активності СЧВ, частих рецидивів з розвитком поліморбідної патології та несумісного з життям поліорганного вовчакового кризу. У статті детально описана динаміка клінічних проявів СЧВ та ВК. Обговорено етапи діагностичного пошуку, особливості диференційної діагностики та лікування СЧВ і ВК на прикладі клінічного випадку. За результатами огляду медичної літератури, аналізу статей, отриманих у результаті пошуку в базах даних PubMed, SCOPUS, Web of Science, MedScape, висвітлено сучасний стан проблеми, узагальнено літературні дані, що стосуються захворюваності, особливостей клінічного перебігу, діагностики та лікування СЧВ, його ускладнень. Опис клінічного випадку, проведений аналіз літератури є доповненням до сучасних відомостей про можливі клінічні прояви та наслідки СЧВ з розвитком тяжкого, надзвичайно рідкісного ускладнення – вовчакового кризу.

Systemic lupus erythematosus is a multiorgan systemic connective tissue disease (SCTD) of unknown etiology with poorly understood pathogenesis [1, 2, 3].

Worldwide, SLE is diagnosed in 3.4 million people, 90% of whom are women [4]. The incidence of SLE in Ukraine is 0.7 cases per 100 thousand adults and 0.2-0.4 cases per 100 thousand in children under 16 years of age [5]. The prevalence of this disease is 17.1 per 100 thousand adults [6]. The ratio of women to men with SLE is 8:1 to 15:1, and in prepubertal individuals – 4:3 [7].

There are several phenotypes of SLE with different clinical manifestations – from mild mucocutaneous to severe multiorgan lesions [8, 9, 10, 11] and unpredictable complications [12, 13, 14]. From 60 to 90% [6, 15], and according to some data about 40 % of patients with SLE are suffering from lupus nephritis (LN) with the development of chronic kidney disease (CKD). In 5-20% of cases, end-stage renal failure develops after 10 years [16].

The main screening laboratory marker for SLE is antinuclear antibodies (ANA) titer. Verification of SLE diagnosis is based on the American College of Rheumatology and the European League Against Rheumatism (EULAR/ACR) 2019 classification criteria and/or the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis, according to nephro biopsy (NB) data [17, 18].

The main principles of pathogenetic therapy (PGT) are outlined in the 2019 European Renal Association and European Association for Dialysis and Transplantation (ERA-EDTA) guidelines, Kidney Disease: Improving Global Outcomes (KDIGO) 2021 and 2024, and European League Against Rheumatism (EULAR) 2023 [19, 20, 21, 22, 23, 24].

Despite significant progress in optimizing medical care, patients with SLE are still at risk of progressive organ damage, leading to a reduced quality of life and high mortality [1, 2]. The main causes of death in patients with SLE are: end-stage chronic renal failure (CRF) due to LN, nephropathy associated with antiphospholipid syndrome (APS), thrombotic microangiopathy (TMA), hemolytic uremic syndrome (HUS), sepsis, and lupus crisis (LC) [25, 26, 27, 28, 29].

Lupus crisis is a prognostically unfavourable complication of SLE. According to our data, only 32 cases of its occurrence have been described in the professional medical literature worldwide. Most of them had an aplastic lupus crisis, while others had a multi-organ crisis, in various combinations [12, 30]. Given the rarity of information on lupus crisis, its diagnosis and treatment is a complex multidisciplinary problem.

Aim of work – to analyze a clinical case as unique in terms of the features of the debut and clinical course of systemic lupus erythematosus, which has become a multidisciplinary problem, to highlight the reasons for the delay in diagnosis verification, to assess, in dynamics, the effectiveness of the prescribed treatment and to report on the development of a multiorgan lupus crisis.

MATERIALS AND METHODS OF RESEARCH

The article analyzes data from the medical documents of female patient for 15 years of the disease. In addition to the clinical and biochemical methods generally accepted in nephrology for blood and urine tests, electrocardiogram (ECG), echocardioscopy (ECHO), ultrasound examination (US) of the abdominal cavity, radiography (Rography) of the chest, esophagogastroduodenoscopy (EGDS), there were defined the presence of antibodies (AB) to human immunodeficiency virus (HIV), syphilis (Wasserman reaction (WR)), viral hepatitis: B (antiHBV), C (antiHCV), the level of erythropoietin, transferrin, ferritin, intact parathyroid hormone (PTH), C-reactive protein (CRP), D-dimer, procalcitonin, and also polymerase chain

reaction (PCR) test for COVID-19, direct Coombs test, blood and urine culture for microflora were made, general sputum analysis and detection of immunological markers: ANA, ANA to double-stranded deoxyribonucleic acid (dsDNA), level of C3 and C4 complement, anticardiolipin antibody, lupus anticoagulant index (LA) [31], antineutrophil cytoplasmic antibodies (ANCA) to myeloperoxidase (MPO) [32, 33] and to proteinase-3 (PR-3) were defined [34, 35].

The diagnosis of the disease was based on the ACR/EULAR, 2019 classification criteria [17, 36]. The SLE activity index was determined according to the Safety of Estrogen in Lupus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA SLEDAI) and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) criteria, the damage index – according to the Systemic Lupus International Collaborating Clinics/Damage Index (SLICC/DI) criteria [31], and its course – according to the classification characteristics of the course by Nasonova V.A. [37]. The stage of CKD was determined according to the clinical classification based on the Kidney Disease Outcomes Quality Initiative (KDOQI, 2012), by calculating the glomerular filtration rate (eGFR) using the online calculator [38, 39]. The morphological class of LN was verified postmortem, according to the pathomorphological study taking into account the ISN/RPS criteria, 2003 [40, 41].

Based on the results of the medical literature review, analysis of articles from the PubMed, SCOPUS, Web of Science, MedScape databases for the period from 1986 to 2024, using a combination of terms: "Systemic lupus erythematosus, glomerulonephritis, lupus nephritis, renal failure, nephro biopsy, lupus crisis", the current state of the problem is shown, literature data of the incidence, features of the clinical course, diagnosis and treatment of SLE and its complications are summarized. We selected 74 sources with documented cases of the SLE course features, 57 of which were published in English.

After analyzing the literature, making a differential diagnosis, we concluded that this clinical case is another documented fact of the SLE debut with isolated kidney damage, delayed diagnosis, and the development of an extremely rare complication – lupus crisis, the description of which, according to our data, is almost absent in the medical literature. According to our data, only 32 cases of its development have been described in the world. In most of them, aplastic lupus crisis occurred, and in others – multiorgan, in various combinations. All this determines the relevance of the problem.

The patient's written informed consent was obtained during her lifetime for the publication of her clinical history, and photographs from her own archive were also provided, which we used in the case history section.

The materials of the scientific work comply with the requirements of the Tokyo Declaration of the World Medical Association, the International Recommendations of the Helsinki Declaration on Human Rights, the Council of Europe Convention on Human Rights and Biomedicine, the Laws of Ukraine, the orders of the Ministry of Health of Ukraine, the Code of Ethics of a Doctor of Ukraine and the Code of Ethics of a Scientist of Ukraine (Excerpt from the minutes of the commission meeting on ethical issues and biomedical ethics of the PSMU No. 232 dated 11.21.2024).

Clinical case

Patient M., 31 years old, was hospitalized in the Nephrology and Dialysis Center of the Municipal Institution "Poltava Regional Clinical Hospital named after M.V. Sklifosovsky of the Poltava Regional Council" in October 10, 2023.

Complaints during hospitalization: increased abdominal volume, swelling of the eyelids and extremities, mixed shortness of breath during moderate physical exertion, cough with a small amount of mucus sputum, nausea, periodic vomiting, loss of taste, lack of appetite, headache, sometimes dizziness, weight loss (she lost 5 kg in 3 weeks), general weakness, rapid fatigue.

Medical history: she has been ill since the age 16, when in 2008, on the background of the absence of an apparent cause, she developed nausea, vomiting, and dysuric manifestations. She was hospitalized in a children's city hospital, where diagnosis was established: "Chronic renal failure II. Glomerulonephritis (GN), urinary syndrome. Chronic renal failure stage 1". She was consulted at the children's specialized hospital "Ohmatdit". Based on the detected increased titer of ANA (1:1280 (N<1:80)) the diagnosis was supplemented: "Primary immunodeficiency state with the threat of developing SCTD (SLE?)". Due to the refusal of the patient and her parents from nephro biopsy, membrane stabilizing, detoxification therapy was performed, according to existing protocols.

Deterioration of the condition was noted in 2013, when the patient started to feel increased blood pressure (BP) to 160/100 mm Hg. She sought medical help and was hospitalized. During the examination, secondary arterial hypertension (AH) of stage II, grade 2 and mild anemia were detected on the background of CKD (stage III) progression. The ANA titer at that time was: 1:1290, other indicators specific to SLE were within normal limits. The patient continued to categorically refuse nephro biopsy. Therefore, detoxification, renoprotective and antihypertensive therapy were performed. After treatment, the patient's well-being improved: the level of proteinuria and azotemia decreased, and BP stabilized at 140/90 mm Hg.

Condition worsened further in 2015, when during pregnancy she developed swelling in her legs, increased proteinuria, and not controllable blood pressure (160-180/100-110 mm Hg). Severe preeclampsia was diagnosed at 34-35 weeks of pregnancy. Delivery was performed by cesarean section.

Over the next 3 years, the patient felt satisfactory. She did not seek medical help. She constantly took an antihypertensive drug from the group of angiotensin-converting enzyme inhibitors.

The next deterioration of her condition was noted in 2019 after suffering left-sided lower-lobar pneumonia: patient was bothered by pain and swelling of the joints of her hands and feet, she noticed a change in the color of urine, frequent urination at night (up to 2-3 times), swelling of the eyelids, hair loss, brittle nails and constant fatigue. She first noted the appearance of a rash on the face and forearms in the form of erythematous plaques with follicular hyperkeratosis and peeling of the skin (Fig. 1, Fig. 2).

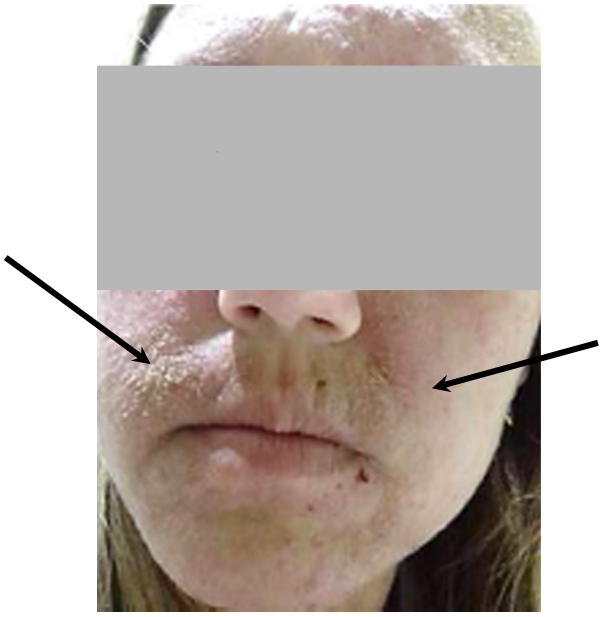

Fig. 1. Discoid lupus on the facial skin of patient M. (indicated by arrows)

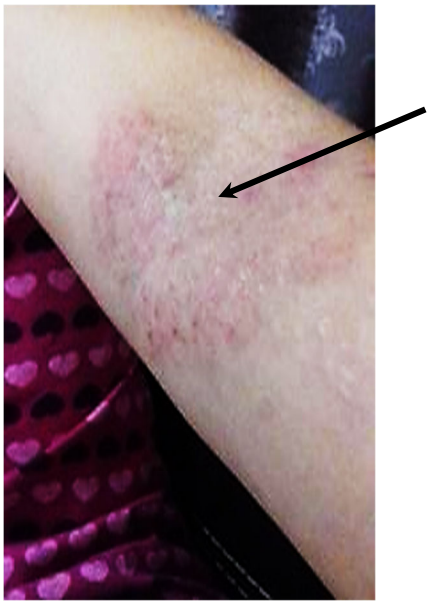

Fig. 2. Discoid lupus on the skin of the forearm in patient M. (indicated by the arrow)

She sought medical help and was hospitalized in the nephrology center. Dermatitis, arthritis, lymphadenopathy, splenomegaly, livedo reticularis, Raynaud's phenomenon, alopecia, symptoms from the bronchopulmonary and cardiovascular systems (CVS), liver, and CNS were detected on the background of anemia (Hb – 90 g/l), leukocytosis ($10x10^9$/l), accelerated erythrocyte sedimentation rate (ESR) (68 mm/h), signs of urinary syndrome, hyposthenuria, macrohematuria, azotemia (creatinine – 344 μmol/l), decreased GFR (52.4 ml/min.) and tubular reabsorption (94.5%), increased CRP (26 mg/l). All these manifestations, combined with an increased ANA titer (1:2250), indicated the necessity to revise the diagnosis. 10 points from the list of clinical domains of the EULAR/ACR 2019 classification criteria [36] and the classification characteristics of the course of SLE [37] gave grounds to establish a clinical diagnosis: "SLE, chronic course, CKD III, lupus nephritis, secondary hypertension, carditis, autoimmune hepatitis, consequences of organic CNS damage with bilateral reflexes insufficiency, autonomic, vestibular dysfunction, cephalalgia, asthenoneurotic disorders, polyarthritis, lymphadenopathy, anemia, dermatitis, Raynaud's phenomenon, alopecia. Residual effects of previous left-sided lower-lobar pneumonia. RF I". The tactics of further treatment included prescription of pathogenetic therapy, which primarily depended on the morphological class of lupus nephritis [5, 20]. However, the patient refused both kidney biopsy and immunosuppressive therapy. Therefore, treatment was carried out according to the leading syndrome of LN and the existing multiorgan pathology, which corresponded to regional standards of medical care and unified clinical protocols of the Ministry of Health of Ukraine.

Since then, the patient has periodically noted unbearable pain and swelling in the wrist, ankle, and small joints of the hands and feet, the appearance of maculo-pustular rashes on the face, boils of various localization, and hair loss. She independently took nonsteroidal anti-inflammatory, antihypertensive drugs, and topical glucocorticosteroids (GCS).

Marked worsening of the condition since February 2023, when, after a previous left-sided lower-lobar pneumonia on the background of COVID-19 infection, a cough appeared with a small amount of mucus sputum, pain in the lumbar region, edema in the lower extremities, blood pressure was poorly corrected, and an erythematous rash on the cheeks and bridge of the nose in the form of a butterfly appeared for the first time (Fig. 3).

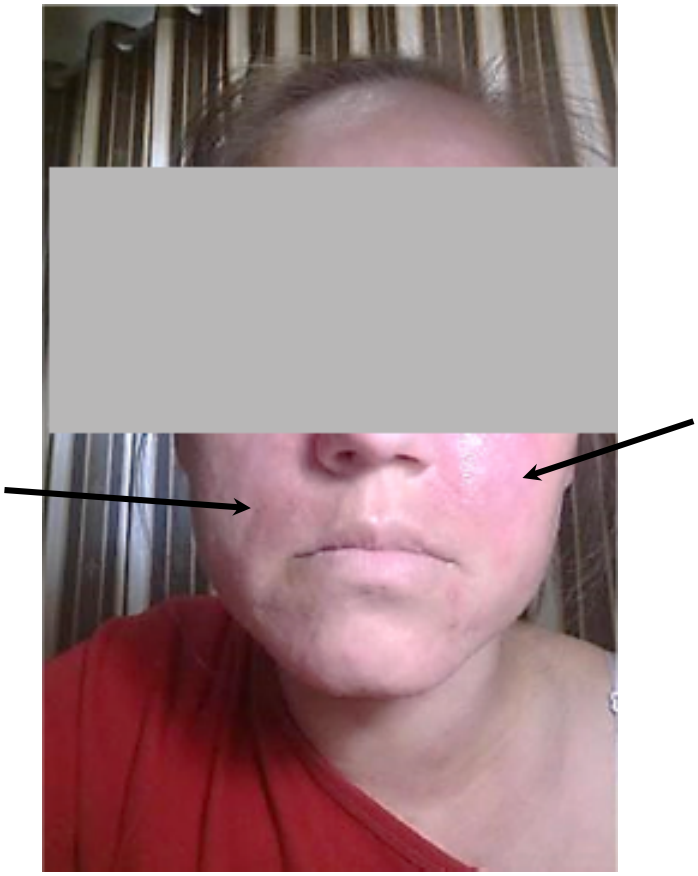

Fig. 3 Skin rash on the face of patient M. in the form of a "butterfly" (indicated by arrows)

She sought medical help only in July 2023. During inpatient treatment, signs of worsening CKD were detected (eGFR – 36.5 ml/min (CKD-ERI)). Nephrotic syndrome was diagnosed (edema, hypoproteinemia (total protein 52 g/l, daily proteinuria – 3.5 g/day). Anemia progressed (Hb – 82 g/l). Blood pressure rose to 180/120 mm Hg. Multispiral computed tomography of the chest, abdomen and pelvis revealed: small-volume encapsulated left-sided hydrothorax, decreased lung tissue pneumatization, fluid component in the lumen of subsegmental bronchi, thickening of the interlobular septa of both lungs; increased size of the left heart chambers, presence of a moderate amount of fluid in the pericardial cavity; decreased blood density in the vessels and chambers of the heart, lymphadenopathy. The first detected increase in the level of AHA to dsDNA (>379.0 /ml) at the same time with progressive growth in the titer of AHA 1:3200 indicated a high degree of disease activity and relapse of SLE. After symptomatic treatment, she was referred for consultation to the medical center "Institute of Rheumatology".

In August 2023, she was consulted by a rheumatologist. Considering the high activity of SLE (SELENA SLEDAI – 16 points), immunological syndrome (ANA 1:3200, ANA dsDNA), CKD V (GFR 13.4 ml/min/m^2 (CKD-EPI)), lupus nephritis with nephrotic syndrome, multiorgan lesions, and also – refusal of NB, initial PGT was recommended according to the KDIGO 2021 clinical recommendations [21]: GCS – methylprednisolone (MP), drug from the aminoquinoline group – hydroxychloroquine (HC),

mycophenolic acid (MPA) – mycophenolate mofetil (MCF) and sulfamethoxazole (SM).

Only in September 2023 did the patient appear for PGT. An increase in the SLE activity index to 28 according to SELENA SLEDAI, electrolyte disorders (hyperkalemia (7.21 mmol/l), hypocalcemia (1.0 mmol/l), increased signs of NS (edema syndrome, ascites, anasarca, proteinuria – 3.6 g/d), anemia (Hb – 77 g/l), the appearance of dyspeptic syndrome were noted. After normalization of electrolyte disorders, detoxification and symptomatic therapy, with the patient's consent, PGT, recommended by the rheumatologist, was initiated. Despite the prescribed treatment, her condition worsened: symptoms of intoxication increased, manifestations of asthenia intensified, and weight loss was disturbing. In this regard, after 21 days the patient independently refused treatment.

Due to worsening of her health, in October 2023, she was re-consulted by a rheumatologist and immunosuppressive therapy was adjusted.

From the anamnesis of life: in childhood – hepatolienal syndrome, lymphadenopathy, recurrent adenoiditis, encephalitis, meningitis, frequent pneumonia, exacerbation of chronic bronchitis. In 2018, autoimmune hepatitis with high activity, cholestatic syndrome, chronic gastroduodenitis, pancreatitis, and splenomegaly were detected. Since 2022 – autoimmune thyroiditis, gastroesophageal reflux disease (GERD), chronic blepharitis.

On examination: general condition is severe, conscious, malnourished. Body mass index – 14.7 kg/m^2 . Limited activity due to severe general weakness. Skin is dry, pale, maculo-papular rash on the face, neck, and décolleté area on background of areas of dyspigmentation, atrophic scars in the places of previous boils, reticular livedo on the thighs. Visible mucous membranes are pale. Facial swelling. Eyelid swelling. Diffuse swelling of the trunk and extremities. Alopecia. Enlarged submandibular lymph nodes. Body temperature – 36,8°C. Defiguration of the hands and feet joints, palpation of these joints is painful, active and passive movements are fully preserved. Saturation (SpO_2) – 97%. Respiratory rate (RR) 20/min. Dull percussion sound and weakened vesicular breathing in the lower parts of the left lung. In other areas of the lung fields – breathing with scattered dry rales. The left border of relative cardiac dullness is 1 cm outward from the midclavicular line in the 5th intercostal space. Heart sounds are rhythmic, weakened. Accent of the 2nd tone over the aorta. Systolic murmur at all points of auscultation. BP 160/100 mm Hg, pulse 100 beats/min. The abdomen is enlarged, moderately elastic due to ascites, sensitive to palpation in the hypochondrium. Hepatosplenomegaly. The percussion symptom is negative on both sides. Diuresis 1.2 l.

In the complete blood count (CBC): moderate hypochromic anemia, lymphopenia (8%), acceleration of ESR to 56 mm/h. Other indicators are within normal limits. Coagulogram without pathological changes. General urine analysis (GUA) – proteinuria (2.24 g/l), in the urinary sediment – erythrocytes – on ¼ of field/view (f/w), cylindruria (hyaline – 0-1, granular – 0-1); daily proteinuria (DP) – 2.97 g/day; in biochemical blood analysis (BCA): hypoproteinemia (total protein – 56 g/l, albumin – 32 g/l), increased creatinine level (411 μmol/l); urea (27,5 mmol/l), uric acid (692.8 μmol/l) and cholesterol (C) – (6,27 mmol/l), CRP (34 mg/l), intact PTN – 175 (N – 15-65) pg/ml, erythropoietin – 29.6 (N – 4.3-29) mU/ml; decreased serum iron (7.78 (N – 9,0-30,4) μmol/l) and electrolytes (sodium 127 (N – 130-157) mmol/l, chlorine 93.2 (N – 95-110) mmol/l and calcium (0.97 mmol/l (N – 2.15-2.5)). Antibodies to HIV, syphilis, HBsAg, antiHBV, antiHCV and LE cells were not detected. Estimated GFR was 11.7 mL/min (CKD-EPI). In sputum: general analysis: leukocytes – all f/v, erythrocytes – unchanged – 1-3 in f/v, elements of bronchial epithelium and alveolar cells – rare, fibers and acid-fast bacteria were not detected; culture: Candida albicans – 103 CFU. In immunological blood test: ANA titer (1:3250), ANA dsDNA – 330 IU/ml (N<10.0), C3 complement level – 0.84 g/l (N 0.9-1.8). C4 complement level – 0.11g/l (N 0.1-0.4). In order to exclude antiphospholipid [25] and overlap syndrome with ANCA-associated vasculitis [42], blood immunoglobulin (Ig) G to cardiolipin, VA index, blood IgG to MPA and IgG to PT_3 were determined. The results were negative (<10 G phospholipid units/ml, <1.1, <3.5 U/ml and <2.0 U/ml, respectively).

On the ECG: heart rate (HR) – 86 per minute, sinus rhythm, single atrial extrasystoles, left heart hypertrophy with dystrophic changes in the left ventricle (LV), signs of right atrial strain; EchoCS – LV hypertrophy with type I diastolic dysfunction, enlarged cavities of both atria, signs of aorta and aortic valve compaction, mitral valve insufficiency of the first degree, regurgitation on the tricuspid valve of the first degree. Signs of fluid in the pericardial cavity, pulmonary hypertension (PH) of the 1st degree. LV ejection fraction – 51%. According to the Ro-graphy, there is thickening and deformation of the lung pattern with massive pleurodiaphragmatic layering and fibrous cords, compaction of the pleura on the right, signs of small-volume bilateral hydrothorax and hydropericardium. EGDS: GERD, stage A. Erythematous gastropathy. Congestive duodenopathy. Duodenogastric reflux. Ultrasound of the abdominal cavity: signs of ascites, hepatosplenomegaly, nephritis, bilateral hydrothorax.

Taking into account hypertension, nephrotic syndrome, multi-organ pathology, critical activity of SLE, on October 17, the rheumatologist recommended pulse therapy with MP and cyclophosphamide (CP) according to the scheme, GCS – orally was started. At the same time, symptomatic therapy was carried out according to the existing unified protocols [43, 44, 45, 46].

Despite treatment, on October 19, 2023, the patient's condition suddenly worsened: the body temperature rose to 38.1°C, the cough intensified, palpitations, shortness of breath at rest, and pronounced general weakness appeared. Objectively: the general condition was extremely severe. Orthopnea, pale skin. Pasty face, peripheral edema of the upper and lower extremities. HR 24/min. Breathing was harsh, in the lower parts of the lungs – weakened. Heart sounds weakened, the accent of the II tone over the aorta, pulmonary artery (PA). BP – 90/60 mm Hg. Ps – 110/min., SpO_2 – 95%. Ascites. Liver + 4 cm from the edge of the costal arch. Urinary disorders were absent.

In the dynamics of complete blood count: pronounced leukopenia ($0{,}6x10^9$/l0), neutropenia (rod shaped – 1%, segmented cells – up to 15%) per 50 cells, severe anemia erythrocytes – $2.2x10^{12}$ /l, Hb – up to 57 g/l), thrombocytopenia (137x10 9 /l), megaloblasts (1:300) and plasma cells; in the smear – anisocytosis 2; in biochemical analysis: decreased albumin, total protein (23.4 and 43.6 g/l, respectively), increased creatinine and urea levels (512.3 and 29.3 mmol/l, respectively); in general urine analysis: proteinuria (3.58 g/l), erythrocyturia (10-13 in the f/v), cylindruria (1-3 in the f/v, granular); Coagulogram: fibrinogen, prothrombin and activated partial thromboplastin time, prothrombin index and international normalized ratio – 2.22 g/l, 11.1 and 34.9 sec., 80.2% and 1.12, respectively, eGFR – 9.0 ml/min (CKD-EPI); on ECG (cito!): heart rate increased, QRS complex voltage decreased; ultrasound revealed a small amount of free fluid in the abdominal and right pleural cavities, a significant enlargement of the liver, and signs of nephritis. According to the SLEDAI-2k criteria, the SLE activity index was up to 50 points. At the same time, the SLE damage index according to SLICC/DI was 10 points, which was interpreted as high.

Further diagnostic search involved differentiation from syndrome-like diseases and critical conditions [47, 48, 49, 50, 51]. Additional laboratory tests were performed for differential diagnosis purposes: PCR test for COVID-19 (negative), direct Coombs test (negative), D-dimer levels (0.5 μg/ml), soluble fibrin monomer complexes (3.6 mg %), transferrin (2.19 g/l), ferritin (90.9 ng/ml) and procalcitonin (0.05 ng/ml).

Multiorgan LC was diagnosed. This required emergency medical care, which included GCS, plasma and symptomatic therapy [22, 29, 44]. For this purpose, pulse therapy with MP, volume replacement therapy and vasopressor hemodynamic support, oxygen and other symptomatic therapy were performed, according to existing protocols.

Due to the ineffectiveness of the therapy, on October 19, 2023 at 10:00, the patient was transferred to the intensive care unit. Despite intensive therapy, on October 20, 2023 at 00:45, the patient experienced cardiac arrest. Immediately initiated resuscitation measures were unsuccessful - biological death was declared at 01:15.

Final clinical diagnosis:

Main: "Systemic lupus erythematosus, chronic course, with kidney damage (CKD V: (GFR 9.0 ml/min): lupus nephritis with nephrotic syndrome, stage of exacerbation); heart (carditis with paroxysms of sinus tachycardia. HFI), serositis (pericardial effusion, right-sided hydrothorax, ascites, anasarca), lungs (interstitial lung disease, LF I), liver (chronic autoimmune hepatitis with minimal activity), joints (polyarthritis mainly of the interphalangeal joints of the hands and feet. FJI I), CNS (consequences of organic CNS damage with bilateral reflexes insufficiency, autonomic, vestibular dysfunction, cephalalgia, astheno-neurotic disorders), skin (maculopapular rash, non-scarring alopecia), Raynaud's syndrome, with impaired electrolyte metabolism (hyponatremia, hypochloremia, hypocalcemia), hematological disorders (anemia, leukopenia, thrombocytopenia), lymphadenopathy and immunological phenomena (ANA + (1 : 3250), increased anti-dsDNA, hypocomplementemia C3). Activity is very high (SLEDAI-2K – 50 points), SLICC/DI – 10 points. Lupus crisis (19.10.2023)".

Complicated: Arterial hypertension stage II, grade 3, very high risk Secondary hyperparathyroidism. Hyperuricemia. Intoxication. Multiple organ failure syndrome. Acute cardiovascular failure. Cerebral edema. Pulmonary edema. Condition after cardiopulmonary resuscitation (10/20/2023).

Concomitant: Chronic bronchitis with bronchoobstructive syndrome, exacerbation phase. Chronic gastritis with preserved acid-forming function. Duodenogastric reflux. Autoimmune thyroiditis. Euthyroidism. Hypotrophy of the III degree. Chronic blepharitis.

Autopsy report: the clinical diagnosis was confirmed at autopsy and during histological examination of the sectioned material.

Pathological diagnosis: Systemic lupus erythematosus with lesions of the skin (maculopapular rash), kidneys (nephritis), lungs, serous membranes

(chronic pericarditis with adhesion of the pericardial sheets, fibrinous peritonitis, fibrinous pleurisy), heart (LV hypertrophy (wall thickness 1.8 cm)), spleen (pulp plasmacytoma, splenomegaly), joints".

Complications of the underlying disease were: ascites (3000 ml), hydrothorax (800 ml on the right). Anasarca. Abdominal adhesions. Focal pulmonary edema. Cerebral edema. Venous congestion and parenchymal dystrophy of internal organs.

The immediate cause of death was multiple organ failure.

RESULTS AND DISCUSSION

Systemic lupus erythematosus is a chronic multisystem, relapsing-remitting autoimmune disease that is pathogenetically associated with a disorder of immunoregulation and is characterized by the presence of AB to nuclear antigens, the deposition of immune complexes in the glomeruli, tubules, basement membranes of peritubular and other capillaries of target organs with the development of chronic inflammation in them [3, 4]. Under this condition, pathophysiological changes in the patient's body develop over several months or years with persistent clinical manifestations and complications. Statistically, SLE usually develops in adolescent and young female individuals. This indicates that genetic and hormonal factors play a major role in the etiology of this disease. Their influence is confirmed by the fact that the clinical manifestations of SLE in males and females differ [7].

Systemic lupus erythematosus is a heterogeneous disease, and its diagnosis can be a significant problem [10]. According to scientific literature, an average of 2 years pass from the moment symptoms appear to the time of diagnosis. However, there are also reports of delays in the established diagnosis of SLE from 3 to 7 years [52]. In this clinical case, the delay in establishing the final clinical diagnosis is 11 years. This is related both to the peculiarities of the SLE course and to the patient's attitude to her health. The organ-dominance of the disease debuted with isolated kidney damage, an increase in the basic screening test for SLE – ANA on the background of negative specific serological tests for SLE, the patient's refusal to perform nephro biopsy created diagnostic problems. Only 11 years later, after the appearance of specific clinical symptoms that met the EULAR/ACR 2019 criteria [41], was the final diagnosis established and confirmed 4 years later by the appearance of specific immunological indicators (anti-dsDNA).

Systemic lupus erythematosus has been reported to have a variety of manifestations and can affect all organ systems, including the kidneys [6]. lupus nephritis is a form of GN, which is one of the most severe manifestations of SLE. According to the literature, it develops in 30-50% [15], and to some data, up to 90% of patients, at different stages of the disease [52]. At the same time, cases of SLE debut with isolated kidney damage, especially in young women with primary immunodeficiency [53]. Our clinical case complements these data.

The appearance of glomerulonephritis symptoms at the onset of our patient's disease is consistent with data known in the literature, which indicate a high frequency of asymptomatic progressive course of CKD, especially without proper treatment, depending on its morphological type [54].

Differential diagnosis of primary and secondary glomerulonephritis causes difficulties requires an interdisciplinary approach, especially if ANA is detected in the absence of other, specific for a particular disease manifestations, as evidenced by this clinical case. The most common glomerulonephritis in Europe at present are: IgA nephropathy, membranous GN, minimal change disease, focal segmental GN, membranoproliferative GN, dense deposit disease, antineutrophil cytoplasmic (ANCA)-associated GN [55, 56, 57], hypertensive nephrosclerosis, tubulointerstitial nephritis, LN, renal amyloidosis and diabetic nephropathy [54].

In routine clinical practice, the presence of systemic connective tissue disease, including SLE, is determined by testing the ANA titer. However, a positive result of this test may also be elevated in SLE, autoimmune thyroid disease, liver disease, diabetes mellitus, and viral infections, which complicates diagnosis [47, 58]. Verification of the diagnosis is carried out according to the data of specific for SLE studies : ANA to dsDNA; and/or Smith antigen (anti-Sm); APS-AT; decreased levels of C3 and C4 complement and/or nephro biopsy, which is the gold standard, allowing not only to make a differential diagnosis and determine the morphological class of LN, but also to assess the activity and chronicity of the process, in order to prescribe adequate treatment in a timely manner and understand the prognosis of its course [59]. We believe that the key role in the timely verification of the diagnosis, in this case, would have been played by the NB, as noted in the literature. However, the patient categorically refused it throughout the disease.

Differential diagnosis of SLE causes difficulties for doctors of all levels due to the similarity of clinical symptoms with "mimics". These include: drug-induced lupus, other SCTD, infectious, oncological diseases, diseases affecting the skin and mucous membranes [53]. Verification of the disease is critically important, since the effectiveness of treatment depends on it, which confirms our case.

Publications of recent years testify to the frequent development of ANCA-associated conditions, especially in the post-covid period [33]. Since the patient's relapse occurred after COVID-19, we first excluded their presence and APS, which is often associated with SLE.

Clinical heterogeneity, unpredictable course and frequent relapses are characteristic features of SLE. In most SLE patients, the earliest complaints are: constitutional, mucocutaneous and musculoskeletal symptoms, such as fatigue, low-grade fever, skin rashes, mouth ulcers, alopecia, arthralgias and myalgias [9, 60], according to some reports, aplastic anemia [61], pancytopenia [51, 62, 63] and other manifestations [8, 11, 66, 68, 69, 70]. However, in this patient, the first manifestations were only symptoms of kidney damage on the background of an increase in ANA titer.

Considering the fact that cases of SLE development against with negative serological tests are highlighted in the medical literature, its diagnosis remains clinical until now [43, 71]. This is confirmed by our clinical case, in which symptoms that were included in the list of clinical domains of the EULAR/ACR 2019 classification clinical criteria developed in the patient only 11 years after the onset of the disease, already with the emerging multiorgan pathology, and immunological indicators specific for SLE – after 15 years.

The main criteria for determining the prognosis and treatment tactics is the study of the daily proteinuria level, hematuria and assessment of eGFR [24, 38, 39]. These indicators were regularly monitored during the patient’s inpatient treatment and indicated the progression of the disease. Juvenile lupus, elevated creatinine at diagnosis, according to the literature, is one of the main causes of unfavorable prognosis of SLE and a predictor of patient mortality [29] which is confirmed by our clinical case.

Such provoking factors as pregnancy, COVID-19, refusal of specific treatment provoked a continuous-recurrent course of SLE in a patient with the development of comorbid processes (autoimmune hepatitis, autoimmune thyroiditis), multiorgan pathology and complications. This is consistent with the literature data [66, 67, 68, 69, 70]. Among the complications of SLE, both typical and rare are noted, which is confirmed by our clinical case. It should be noted that the transition of urinary syndrome to nephrotic syndrome after COVID-19 infection indicated a transformation of the SLE course, that arose in its indicated further progression of glomerular damage and was a predictor of the lupus crisis development [29, 63, 64, 65, 72].

In view of her serious condition, severe multiple organ damage and high SLE activity index (16 points according to SELENA-SLEDAI), the patient only gave permission for specific treatment in August 2023. The choice of treatment tactics was complicated by a categorical refusal to carry nephro biopsies. Based on the recommendations of KDIGO 2021 for the appointment of aminoquinoline drugs, corticosteroids, MPC drugs, biological agents, and cytostatics [20, 21, 22, 23, 60, 61, 62, 71, 73, 74], the most effective treatment regimen was selected that minimizes the risk of side effects, in the dosage of drugs, according to the patient's body weight and eGFR. Unauthorized patient's cessation of PGT drugs provoked another relapse of SLE. On the 3rd day after resumption of adjusted immunosuppressive therapy, the patient's condition sharply worsened. This required rapid differentiation and emergency care.

The complexity of the differential diagnosis is due to the multitude of syndrome-like diseases. At the same time, the side effects of drugs, and the development of infectious complications, were not excluded.

Given the fact that the constant use of corticosteroids by patients can lead to a decrease in the body's resistance mechanisms, we first needed to differentiate her condition from coronavirus infection and sepsis [28]. A negative PCR test for COVID-19 and the result of blood culture for microflora, normal values of the procalcitonin level in the blood excluded these diagnoses.

An increase in creatinine level indicated the development of acute kidney injury (AKI), the cause of which could be: thrombocytopenic microangiopathy (TMA) associated with SLE and/or APS, disseminated intravascular coagulation (DIC), which are the main causes of the development of critical conditions in SLE and predictors of mortality in these patients [25, 48, 49, 50, 51]. Arterial hypotension, absence of pathogenic microflora in the blood and sputum, signs of hemolytic anemia (negative direct Coombs test, absence of reticulocytosis, schizocytes in the complete blood count), specific antibodies to APS and HIV, normal lactate dehydrogenase values and coagulogram parameters indicated the absence of TMA, both primary (HUS, thrombotic thrombocytopenic purpura (TTP)) and secondary – associated with APS or HIV infection [26]. At the same time, arterial hypotension, AKI could also be signs of the pulmonary embolism (PE) development. However, the symptoms, the level of D-dimer and soluble fibrin monomer complexes indicated a low clinical probability of it – 1 point on the Geneva

scale (Geneva score). Considering the seriousness of the patient's condition, it was impossible to perform a CT angiography of the pulmonary artery with contrast. In addition, we did not observe any typical changes on ECG and ECHO. Normal potassium and glucose levels allowed us to exclude acute adrenal insufficiency. At the same time, there was a suspicion of hemophagocytic syndrome development, which is usually accompanied by hyperthermia, hepatosplenomegaly, cytopenia, hypoalbuminemia, hyponatremia [53], which occurred in our patient. However, the absence of hemorrhagic skin rash, jaundice against the background of no changes in the coagulogram, normal values of transferrin and ferritin and the level of procalcitonin excluded this diagnosis.

Cytopenias due to autoimmune myelofibrosis, which are extremely rare in SLE, have been described in the literature. A sudden decrease in formed blood elements, the appearance of megaloblasts and plasma cells in the patient's blood required a bone marrow biopsy (BMB) [12, 54]. However, the extremely serious condition of the patient made this diagnostic procedure impossible. It has been reported that myelophthisis, electrolyte disturbances, and infectious complications may be a consequence of immunosuppressive drugs [13, 64]. However, we ruled out sepsis, and a single administration of cyclophosphamide could not provoke myelotoxic effects and electrolyte disturbances, as noted in the professional literature [51, 65, 73, 74], she was no longer taking mycophenolate mofetil at that time. At the same time, a search was conducted for alternative causes of the development of the critical condition. Taking into account the above, clinical and diagnostic data indicated the presence of acute kidney injury, acute cardiovascular and respiratory failure in the patient with severe pancytopenia. According to the literature, acute cardiovascular failure is a potential threat to life, due to disruption of homeostatic mechanisms, which lead to irreversible cells damage with multiple organ failure (MOF). Regardless of the heart failure causes, serious disorders of central hemodynamics and capillary circulation develop in the body, which is due to hypovolemia, hypoxia, acidosis, impaired vascular wall permeability, and vascular tone. Taking into account hyperthermia, anorexia, tachycardia, grade III hypotrophy, endogenous intoxication, microcirculatory disorders on the background of pancytopenia and progression of polyorganic failure, lupus crisis was diagnosed. According to the professional literature, this prognostically unfavorable critical state develops suddenly, as a result of acute relapse or, chronic progression of SLE in combination with immunological changes and pronounced endogenous intoxication [30], which occurred in this clinical case. Usually, lupus crisis is characterized by the development of functional insufficiency of one or another organ or all vital organs with the development of life-threatening acute multiorgan failure. Currently, several of its variants are known, namely: monoorgan (hematological, renal, cardiac, pulmonary, abdominal, cerebral, peripheral vascular crisis) and multiorgan: (renal-abdominal; renal-cardiac and cerebral-cardiac). However, with any organ localization of the lupus crisis, almost all patients also have other organs and systems affected, but without a sharp impairment of their functions [72]. Among the variants described above, in our opinion, the patient had a multiorgan lupus crisis with the development of hematological (aplastic) crisis symptoms with predominant damage to the kidneys, cardiovascular and respiratory systems. The occurrence of such a clinical picture indicates the development of a multi-system inflammatory response, as a result of a “mediator storm” in the body, which led to multi-organ failure, incompatible with the patient’s life.

Self-medication of the patient, refusal of the proposed pathogenetic therapy, starting from the moment of diagnosis and over the next 4 years led to a fatal outcome.

According to the literature, histological changes in renal tissue preparations in LN are fibrinoid necrosis of capillaries, arterioles and small arteries with destruction of the vascular wall. Under this condition, in glomeruli reveal destruction of the glomerular basement membrane, hematoxylin bodies, fibrinoid changes, hyaline and erythrocyte thrombi in the lumen of capillaries are revealed, as well as dystrophic changes in the convoluted tubules [5], nuclear pathology (karyorrhexis and karyopyknosis), sharp focal damage to the glomerular basement membranes in the form of “wire loops” [16]. This is clearly shown in the microphotograph (Fig. 4) obtained after pathological examination.

The 2003 ISN/RPS classification of lupus nephritis indicates the presence of 6 classes of morphological changes of renal tissue in LN [19,59]. Postmortem, the III morphological class of changes in the renal tissue was established, according to the LN classification ISN/RPS, 2003 [31]. It should be noted here that according to the key provisions of the KDIGO 2021 clinical recommendations, pathogenetic therapy was prescribed to the patient and was indicated for the class of histological changes in the renal tissue detected in her.

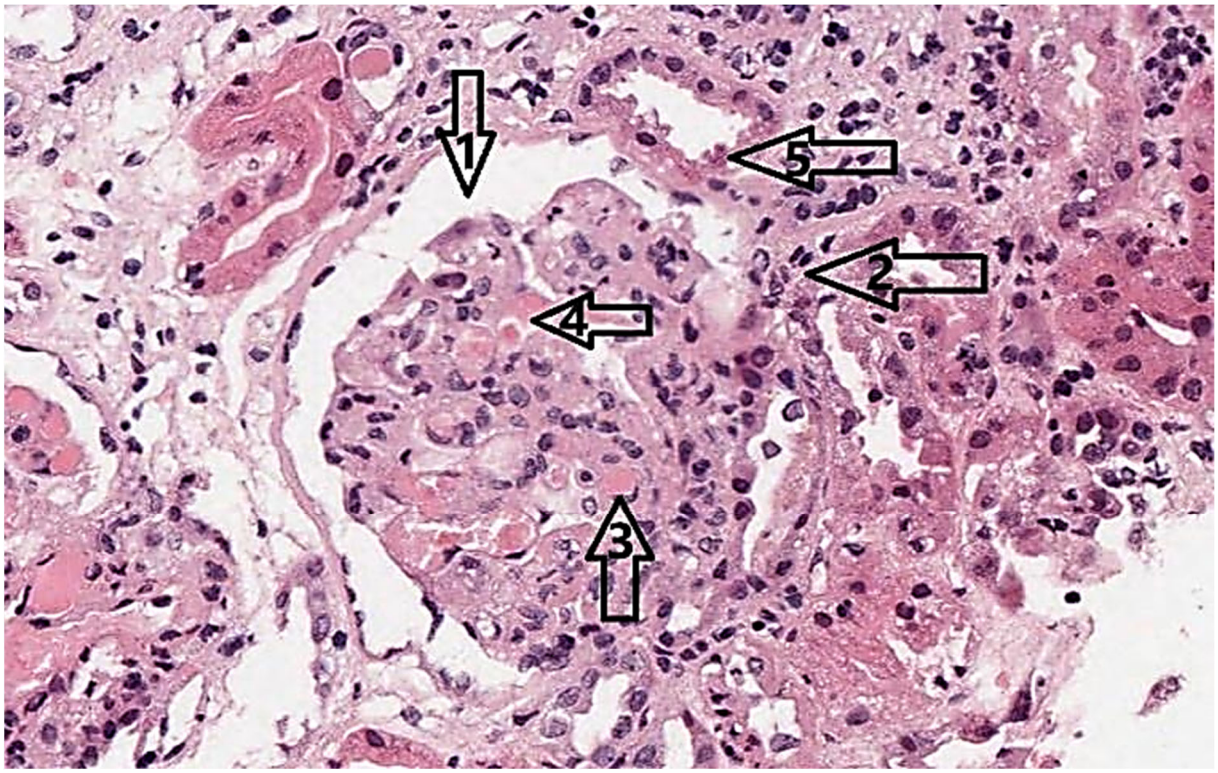

Fig. 4. Morphological picture of the kidneys of the deceased M. 1 – edema of the mesangium, 2 – foci of leukocyte infiltration, 3 – hyaline thrombi in the capillary lumen, 4 – sludged erythrocytes in the capillary lumen, 5 – epithelium of the convoluted tubules in a state of dystrophy. Microscopy. Staining with hematoxylin and eosin. Lens 25x, Eyepiece 10x

CONCLUSIONS

1. Clinical heterogeneity and unpredictable course of systemic lupus erythematosus are a multidisciplinary problem.
2. With the development of glomerulonephritis against the background of an increase in the titer of antinuclear antibodies, the diagnosis must be confirmed by nephro biopsy data, since specific immunological indicators can appear in patients with systemic lupus erythematosus much later than the onset of the disease.
3. Coronavirus disease may be a predictor of systemic lupus erythematosus course transformation.
4. Lupus crisis is a rare, potentially life-threatening complication of systemic lupus erythematosus that can develop as a result of significant immunological changes and severe endogenous intoxication.
5. Delaying pathogenetic treatment increases inflammatory activity and immune-mediated damage to many organ systems, reduces quality of life, and increases the risk of fatal outcomes, which can become an interdisciplinary problem.

Contributors:

Talash V.V. – research design, writing – original draft;

Katerenchuk I.P. – reviewing, writing – review & editing;

Kostrikova Yu.A. – editing the article in English, writing – review & editing.

Yarmola T.I. – writing – review & editing;

Hutsalenko O.O. – conceptualization, formal analysis;

Pustovoyt H.L. – resources, data analysis;

Tkachenko L.A. – resources, data analysis;

Mokhnachev O.V. – methodology, data analysis;

Rustamian S.T. – resources, investigation;

Talash V.V. – resources, investigation;

Sarychev L.P. – resources, investigation;

Savchenko R.B. – resources.

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