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DIFFICULTIES OF "COMPETITIVE" PROCESSES DIAGNOSIS: THE SYSTEMIC LUPUS ERYTHEMATOSUS IN PATIENT WITH MODERN COMORBIDITY. CLINICAL CASE

Abstract

The paper deals with the problem of recognizing systemic lupus erythematosus, which is getting a rather common disease. It presents a clinical case of a female patient with type 2 diabetes mellitus, hypertension, hyperuricemia, who developed systemic lupus erythematosus at the age of 52. The onset of a new disease in a patient with comorbidity is often concealed by the symptoms of the new disease. It troubles the well-timed diagnosis of the new disease. The diagnosis of systemic lupus erythematosus was established according to the accepted criteria in Federal Clinical Recommendations. The authors emphasize that according the Federal Clinical Recommendations a long-course of hydroxychloroquine added to the basic therapy proved to be effective in relieving clinical manifestations of systemic lupus erythematosus and preventing its exacerbations. Detailed differential diagnosis in the presented case is given in discussion. The considerable attention is paid to diagnosis and treatment of the fast-progressing lupus nephritis. The example of standard pulse-therapy is given at the fast-progressing lupus nephritis for an induction of remission and its effectiveness for reversal of a nephrotic syndrome on a concrete example is shown. The authors considered pathological processes which lead to fast progression of secondary nephrotic syndrome. Recently opened pathophysiological mechanisms of development of anemia of chronic disease are presented in the paper, which contribute to complete understanding of pathogenesis of these processes. Diagnostic search of the reason of not expressed joint syndrome with systemic manifestations was performed among probable autoimmune and metabolic diseases for people of the senior age group. Specific liver function tests indicated the diagnosis of lupus hepatitis. Probable mechanisms of liver injury in this clinical case are described. Work of authors has cross-disciplinary character and it can be useful to experts of theoretical and clinical medicine.

Key words: *systemic lupus erythematosus, nephrotic syndrome, glomerulonephritis, anemia of chronic disease, hepcidin.*

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BP — blood pressure, ALT — alanine aminotransferase, AST — aspartate aminotransferase, AB — antibody, ACD — anemia of chronic disease, ALP — alkaline phosphatase, CHF — chronic heart failure, FOV — field of view, Hb — hemoglobin, gl — globulin, GGT — gamma-glutamyl transferase, Ig — immunoglobulin, ACEI — angiotensin converting enzyme inhibitor, WBC — white blood cells, LN — lymph node, CBC — complete blood count, CU — clinical urinalysis, PTI — prothrombin index, X-ray — roentgenography, RES — reticuloendothelial system,

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DM — diabetes mellitus, SCT — spiral computed tomography, ESR — erythrocyte sedimentation rate, SLE — systemic lupus erythematosus, Pl — platelets, T° — body temperature, US — ultrasound scan, CIC — circulating immune complex, HR — heart rate, RBC — red blood cells

Systemic lupus erythematosus (SLE) is a typical autoimmune disease that has not lost its relevance with the passage of time. This disease is currently incurable. However, SLE symptoms can be controlled with appropriate therapy, which gives the majority of diagnosed patients an opportunity to lead an active and healthy life. Today, successful pharmaceutical treatment is available. Nevertheless, despite obvious medical breakthroughs, some SLE-related issues remain unsolved; the most important of them is probably timely diagnosis. Symptoms of the disease are highly diverse, and they do not always manifest themselves in typical ways, which makes diagnosis difficult and confirms its name as "the great imitator" of other diseases [1]. SLE can be diagnosed at any age; however, the onset is more common between 15 and 45 years. SLE onset can occur in elderly patients, when comorbidities are present and differential diagnosis is especially problematic. To prove this, we provide a case report of SLE.

A 52-year-old female patient was admitted at the Internal Medicine Department of Khabarovsk Railway Hospital on November 30, 2015. The patient complained of hypertension, weakness, dyspnea on exertion, low appetite, morning nausea, daily fevers of up to 37.5 °C in the morning and to 38.5 °C in the evening (without chills), pain in shoulder joints, and leg swelling by night. The patient had a medical history of type 2 diabetes mellitus for 2 years and was treated with metformin (glycemia of 5.8–6.5 mmol/L). The patient has hypertension for about 5 years (BP up to 200 mm Hg), but she did not feel sick and took beta-blockers, ACEI and Arifon irregularly. Episodes of feet, legs, hands and face swelling were registered periodically for 3 years. Tenderness in shoulder joints was observed for several years. The patient attributed these symptoms to being overweight and doing sports at younger age. She had considered herself healthy until August 2015, when abundant red rash appeared in the vermilion zone, facial skin, shoulders, upper parts of the chest and back, sometimes accompanied by itching. The patient consulted with an allergy specialist. The event was considered to be a symptom of allergic dermatitis (due to the administration of Ascorutin, vitamins B and magnesium). When these drugs administration was discontinued, the signs of dermatitis decreased significantly. Blood tests had been showing leukopenia and ESR 30 mm/h since September, and blood count was within normal limits. After high levels of uric acid had been detected, the patient was referred to a rheumatologist. Rheumatoid arthritis and psoriasis were excluded. Outpatient examinations continued. Periodic fever and ESR elevations to 60 mm/h had been registered since the second half of September. The hemogram of November 21, 2015, showed anemia (RBC — $3.3*10^{12}$/L, Hb — 97 g/L). WBC and platelet counts were within normal limits. Blood biochemistry showed dysproteinemia with normal total protein. US results: no abnormalities were detected in the liver, spleen and lymph nodes. The patient consulted with a hematologist. Iliac crest bone biopsy was performed: no abnormalities were detected. Contrast-enhanced spiral computed tomography (SCT) of the head, neck, chest, and abdominal cavity organs revealed liver hemangioma, calcified foci in the spleen, small secondary renal cysts. No abnormalities of the lymph nodes were detected. Blood tests for HIV as well as for viral hepatitis B and C all produced negative results. Tumor markers were within normal limits. Fibrogastroduodenoscopy: reflux esophagitis, incompetence of the cardia, duodenogastric reflux. The patient's health worsened progressively, and she contacted the Railway Hospital for additional examination with the following referral diagnosis: fever of unknown origin.

Patient's state at admission was satisfactory. Obesity was diagnosed (grade 3). Faint hyperemia foci with slight desquamation were present in the upper part of her chest and back. Mild swelling of the face, eyelids, lower third of the calves and feet was observed. T° 37.6 °C, BP was 150/100 mm Hg, HR — without abnormalities.

Complete blood count: RBC — $3.2*10^{12}$/L, Hb — 91 g/L, Pl — $258*10^9$/L (N: 150–390), WBC — $3.8*10^9$/L, lymphocytes — 14% (18–40) / $0.5*10^9$/L (1.2–3.0), banded neutrophils — 7%, segmented neutrophils — 75%, ESR — 69 mm/h, reticulocytes — 6 per mille (N: 2–13); peripheral blood smear: RBC hypochromia (++), mixed anisocytosis (+), occasional megalocytes and hypochromic macrocytes; clinical urinalysis: color — yellow, clarity — cloudy, specific gravity — 1,010 (N: 1,012–1,024), reaction — acidic, protein — 4.6 g/L (N: 0–0.12), glucose — absent, squamous epithelium — 2–3 per FOV, granular, waxy and WBC casts — single casts per FOV, bacteria (+); blood biochemistry: glucose — 7 mmol/L (N: up to 5.5), total protein — 49 g/L (65–85), albumins — 43.6% (46.9–61.4), α_1-gl — 5.31% (2.2–4.2), α_2-gl — 15.8% (7.9–10.9), β-gl — 14.6% (10.2–18.3), γ-gl — 20.7% (17.6–25.4), total bilirubin — 9.7 μmol/L, direct bilirubin — 2.2 μmol/L, ALP — 157 U/L (up to 270), GGT — 61 U/L (up to 32), creatinine — 128 μmol/L (up to 106), urea — 11.6 mmol/L (up to 8.3), uric acid — 732 μmol/L (up to 310), serum iron — 4.9 μmol/L (6.3–30.1), PTI — 103% (80–110), ALT and AST — within normal limits; procalcitonin — 0.23 ng/mL (up to 0.5), and serum ferritin — 887 μg/L (15–150) were detected; blood test for syphilis (rapid plasma reagin) was negative.

Clinical urinalysis on day 3: specific gravity — 1,003, reaction — acidic, protein — 1.9 g/L (0–0.12), WBC — 45–55 per FOV, abnormal RBC — 10–15 per FOV, glucose — absent, squamous epithelium — single cells per FOV, waxy casts — single casts per FOV. ECG results: sinus rhythm with HR 93 bpm, moderate changes in the left ventricular myocardium. Cardiac ultrasound: grade 1 hypertrophy of left ventricular myocardium, ejection fraction — 69%. Cardiac chambers dilation. Grade 2 mitral regurgitation, grade 1 tricuspid regurgitation. Mild pulmonary hypertension. Increased pericardial effusion (pericardial cavity thickness 0.9 cm behind the posterior wall of the left ventricle). The patient continued complaining of fatigue, low appetite and nausea.

Based on the results of laboratory and instrumental testing, the patient was given a conservative treatment of urinary infection as a possible cause of fever (empiric antibacterial treatment — ceftriaxone + ciprofloxacin). Anemia, hypertension, edema, and diabetes mellitus were treated: allopurinol, insulin Actrapid, Maltofer, vitamin B_{12}, metoclopramide, omeprazole, Arifon. However, an acute worsening of dyspnea and swelling was registered on December 5 while on therapy. Edema increased and orthopnea appeared. Examination results: moderately severe condition, massive swelling of the lower extremities (up to the groin), upper extremities, anterior abdominal wall, and anterior neck surface; oliguria. Dyspnea at rest up to 22 respiratory movements per minute, BP was 180/110 mm Hg, tachycardia at rest — 100 bpm, ECG results unchanged compared to those of December 2, 2015. The therapy was adjusted: furosemide 80 mg, intravenous bolus; spironolactone 50 mg twice a day (in the morning and in the afternoon); bisoprolol 7.5 mg in the morning, HR-controlled; enalapril 10 mg twice a day (in the morning and in the evening).

Hands X-ray results: subchondral bone sclerosis and paraarticular osteoporosis of hand bones, single subperiosteal dystrophic cysts around the base of the middle phalanx and the head of the proximal phalanx of the fifth right finger; spinous syndesmophytes along the dorsal surface of the nail phalanx of the first right finger. Narrowing of the joint space in the phalangeal joints. Conclusion: dishormonal arthropathy, necessary to differentiate from rheumatoid arthritis. During hospital stay, changes in the body temperature were irregular, from 36.8 °C to 38.9 °C. The following tests were performed to determine the cause of inflammation: colonoscopy (histological results — moderate chronic enteritis), blood culture (no growth), repeated procalcitonin test less than 0.5 ng/mL. C-reactive protein — 18 mg/L (0–6), rheumatoid factor — 16 IU/mL (0–8). Serum cryoglobulins — positive. Clinical urinalysis: specific gravity — 1,010, protein — 4.1 g/L, WBC — the entire FOV, RBC — 40 per FOV. Urinary infection secondary to other disorders was predominant in the clinical pattern; however, the autoimmune disorder was becoming more and more probable.

Despite the therapy, edema, fatigue, dyspnea and nausea persisted. Blood biochemistry results on

December 8 (compared to December 1, 2015): normalized total protein — 55 g/L, and uric acid — 595 μmol/L, worsening of hypoalbuminemia — 21 g/L, increased creatinine — 350 μmol/L, and urea — 15.2 mmol/L. IgA — 5.07 g/L (1–6.5), IgM — 0.59 g/L (0.6–2.8), IgG — 19.15 g/L (9–20). Antinuclear antibodies were detected. The analysis of homeostasis showed a tendency towards hypercoagulation with signs of intravascular coagulation, positive lupus anticoagulant, CICs without abnormalities, daily protein loss — 7 g/day (0–0.141), with diuresis — 1,300 mL/day. TSH — 1.2 pg/mL. CBC showed that the anemia parameters remained almost the same compared to December 1, 2015: RBC — $3.3*10^9$/L, Hb — 89 g/L, leukocytosis — $11.8*10^9$/L, banded neutrophils — 2%, segmented neutrophils — 88%, lymphocytes — 6% / $0.7*10^9$/L, ESR — 66 mm/h, platelet count within normal limits; microscopy showed mixed anisocytosis (+) with hypochromia (+). Tests for antineutrophil cytoplasmic antibodies, anticardiolipin antibodies, and anti-DNA antibodies were in progress. Renal ultrasound detected no abnormalities. Chest X-ray: increased pulmonary vascularity due to vascular and interstitial components, bilateral pleural effusion, signs of heart enlargement due to enlarged left chambers.

Taking into account patient's condition and test results indicating the development of nephrotic syndrome, the therapy was adjusted after consultation with a nephrologist: albumin transfusion followed by stimulation with furosemide at 1 mg/kg/day (80–120 mg/day) was added to treatment. Continued antibacterial therapy was recommended based on the glomerular filtration rate: ceftriaxone 1.0 once a day together with ciprofloxacin 500 mg/day. Due to progressive azotemia, enalapril was replaced by moxonidine 200 μg twice a day. Treatment with spironolactone (potassium- and ECG-controlled) and allopurinol was continued. Laboratory tests showed signs of disseminated intravascular coagulation. Therefore, Clexane was added to the therapy.

On December 10, the primary diagnosis was determined considering medical history, clinical pattern of the disease, and additional tests: acute SLE with serositis (pleuritis, pericarditis), skin lesions (faint erythematous rash in the upper part of the chest and back), renal involvement (rapidly progressive lupus nephritis), hematologic (anemia, lymphopenia) and immunologic disorders (elevated antinuclear antibodies, anti-DNA antibodies); high SELENA-SLEDAI score (17), and high SLICC index (5) [2, 3]. Complications: acute kidney injury, RIFLE stage I. Secondary diagnoses: urinary infection; T2DM, HbA_1c < 7.5%; stage 3 essential hypertension. NYHA class III CHF; grade 3 obesity; hyperuricemia.

SLE diagnosis is based on ACR 1997 classification — 4 of 11 criteria should be present (rash, serositis, renal involvement, abnormal titer of anti-DNA antibodies were diagnosed), or is based on SLICC 2012 — 4 criteria should be present, one of them clinical and one immunologic (the following were confirmed: nephritis, serositis, lymphopenia < $1.0*10^9$/L, a more than twofold increase in anti-DNA antibodies titer) [2]. Daily protein loss was 7 g/day (0–0.141). The patient was examined by a rheumatologist and was transferred to a specialized Rheumatology Unit; prednisolone 45 mg/day was initiated. The patient reported slight improvement. Intravenous pulse therapy was prescribed according to therapeutic indications: methylprednisolone 1,000 mg once a day (for 3 days) + cyclophosphane 1,000 mg once a day (one day). Laboratory results of December 14, 2015, after initiation of therapy: anticardiolipin IgM antibodies — 3.0 (N less than 7), IgG — 6.1 (less than 10), anti-β_2-glycoprotein IgM antibodies — 4.1 (less than 7), IgG — 5.7 (less than 10), antiphospholipid IgM — 3.6 (less than 10), IgG — 7.9 (less than 10); *serum anti-DNA antibodies* — 586.2 (0–25); CIC — 56 RU (54.24 ± 2.0 RU), IgA level — 336 mg% (91–360), IgM — 78 mg% (61–160), IgG — 864 mg% (720–1,460). During the period from December 17 till January 14, 2016: RBC count increased from 2.8 to $3.6*10^{12}$/L, Hb — from 81 to 104 g/L, lymphocytes level — from 15 to 27%; WBC count decreased from 11 to $10*10^9$/L, ESR — from 38 to 32 mm/h. During the same period, urea level decreased from 32.7 to 18.1 mmol/L, creatinine — from 245 to 98 μmol/L, total bilirubin — from 11 to 8 μmol/L; cholesterol level decreased from 6.6 to 3.2 mmol/L, with reduced enzymatic activity: ALT — from 28 to 13 U/L,

AST — from 20 to 10 U/L, and ALP — to 97 U/L. Clinical urinalysis showed regression of proteinuria from 1.4 to 0.44 g/L, and it showed regression in daily protein loss from 7 to 0.28 g/day. Subjective condition of the patient also improved: fatigue and dyspnea decreased, nausea disappeared, and appetite increased.

The patient was discharged with improvement on January 18, 2016, with the following recommendations: a rheumatologist follow-up at the place of residence, continued hypotensive therapy as before, methylprednisolone 30 mg/day, omeprazole 20 mg in the morning, torasemide 5 mg in the morning, alphacalcidol 0.5 μg in the morning, and cyclophosphamide administration scheduled in one month.

The reported case was difficult to diagnose, since this systemic, rapidly progressing, highly active disease was developing in an elderly patient with several comorbidities. Each of these comorbidities could be accompanied by cardiovascular and kidney damage. Therefore, differential diagnostics included multiple diseases. Determining the cause of kidney danage was of special interest. The absence of stable hypotensive therapy could lead to hypertensive glomerulonephritis. The patient had type 2 DM; therefore, diabetic nephropathy could not be excluded: the glomerular capillary basement membrane becomes glycosylated, which leads to impaired nutrition and hypoxia of underlying tissues, including podocytes and juxtaglomerular apparatus. A reactive increase in BP accelerates the course of hypertensive glomerulonephritis, and podocytes cell death results in diabetic glomerulosclerosis. This could lead to kidney failure and nephrotic syndrome. Secondary cysts found in the kidneys confirmed this "expected" long-term nephropathy. At the same time, nephropathy secondary to hypertension and DM leads to excretory hyperuricemia. The accumulation of urates in renal interstitium induces abnormal tubular function and proteinuria leading to chronic kidney disease, hypertension and secondary gout. The patient was taking indapamide, which significantly increased the risk of this type of kidney damage. Existing DM predisposed the patient to recurrent renal infections with anemia, fever and nephrotic syndrome. Infectious endocarditis and oncological processes can induce nephrotic syndrome and fever, but they were excluded in the differential diagnosis. Nephrotic syndrome in the absence of marked systemic manifestations also could be explained by IgA-nephropathy (atypical Berger disease or IgA-nephropathy induced by other disorders: celiac disease, psoriasis, SLE) or renal type of Henoch-Schönlein purpura. Normal blood IgA levels did not exclude these diseases, and renal biopsy was considered as a reserve diagnostic measure. Hypothyroidism as the cause of edema was also excluded. Insignificant articular syndrome with systemic symptoms required differential diagnosis with rheumatoid arthritis, psoriatic arthropathy, gout, and osteoarthritis deformans, which are common in elderly patients. The key factor in the diagnosis of nephrotic syndrome, considering a peculiar clinical pattern, was detection of abnormal anti-DNA antibodies titer. Rapidly progressive lupus nephritis has the following symptoms: twofold increase in serum creatinine within 3 months, nephrotic syndrome, erythrocyturia, severe hypertension [3]. Clinical symptoms fully corresponded to this type of lupus nephritis.

According to current recommendations, renal biopsy is the gold standard of diagnostic methods of kidney damage in SLE [2, 3]. However, some patients are ineligible for biopsy due to various reasons (obesity, coagulopathy, diabetes mellitus, risk of secondary infection, etc.). The patient had rapidly progressing kidney damage secondary to SLE; therefore, pulse therapy was indicated. In Russian guidelines, mycophenolate mofetil and belimumab in lupus nephritis treatment have higher levels of evidence. However, "classical" medications for SLE treatment, such as prednisolone, cyclophosphan and azathioprine, remain relevant. The role of hydroxychloroquine in the comprehensive therapy of SLE should be noted. This product of a 4-aminoquinoline derivative is prescribed to all patients with SLE — class of recommendation A, level of evidence 1 [2]. In the present case hydroxychloroquine administration had been postponed until comorbidities were stabilized.

The hematologic status of the patient is also interesting. Based on the clinical urinalysis and blood biochemistry results, the following disorders were considered: iron deficiency anemia (given decreased serum iron level, hypochromic RBC, and mixed anisocytosis), hyperchromic anemia (presence of megalocytes), autoimmune hemolytic anemia with antilymphocyte antibodies (based on direct to total bilirubin ratio of 1:4.4, absolute lymphopenia, and positive test for serum cryoglobulins), hereditary hemochromatosis (ferritin level 887 μg/L, with N up to 150), and blood cancer as the cause of these changes. Anemia of chronic disease should be seriously considered as a disorder that can explain the majority of these changes. Recent studies of ACD have provided a detailed description of its etiology. Pro-inflammatory factors (IL-1, IL-6, TNF-α, etc.) inhibit production of erythropoietin, suppress proliferation and differentiation of erythroid progenitors, stimulate erythrophagocytosis by cells of RES [4] and ferritin production [5], increase the number of transferrin receptors on hepatocytes [6] and, thus, increase their iron intake, and activate production of an antimicrobial peptide with a role in iron regulation — hepcidin. Hepcidin blocks exit of iron from hepatocytes and RES cells [4, 7]. Considering the presence of ferritin receptors on hepatocytes, lymphocytes and erythroblasts [8], we can expect that a decrease in number of ferritin-consuming cells will lead to an increase in its serum concentration. This can explain hyperferritinemia with low serum iron.

Observation of the patient over time revealed an interesting tendency in liver function parameters, which do not exclude a diagnosis of lupus hepatitis, in our opinion, although liver function parameters were within normal limits at admission. The patient received intensive pharmaceutical treatment during the period from December 17, 2015, to January 14, 2016: prednisolone pulse therapy (followed by oral methylprednisolone 50 mg/day with dose tapering), and other medications, with simultaneous 2-week therapy with antibiotics. During this treatment, liver function markers (ALT, AST, ALP, bilirubin) decreased from the upper limit of normal to the lower limit. We can explain this by immune-mediated (antinuclear antibodies, rheumatoid factor, etc.) damage of hepatocytes and their overload with ferritin.

Therefore, the reported case demonstrated a multidisciplinary approach to differential diagnosis in this patient. Our observation, which highlights current explanations of pathogenesis of certain disorders, may be useful for primary care physicians and hospital physicians: it is a case of SLE in female patient over 50 years old with "not uncommon comorbidity".

Conflict of Interests

The authors declare no conflict of interests.

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