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INFECTIOUS COMPLICATIONS AS PREDICTORS OF ADVERSE OUTCOME IN A PATIENT WITH SYSTEMIC LUPUS ERYTHEMATOSUS (CLINICAL CASE)

Abstract

Systemic lupus erythematosus is a systemic autoimmune disease. Over the past decades, great success has been achieved in its treatment. However, mortality in systemic lupus erythematosus is still high. An adverse outcome may occur because of kidney damage, damage of the nervous system, severe hematological disorders, etc. The factor of unfavorable prognosis is infectious complications.

The article presents a prospective clinical observation of a fatal case of severe course of systemic lupus erythematosus. The patient was treated in the rheumatology department of the State Regional Clinical Hospital in Saratov from 2007 to 2014.

The presence of high disease activity, multiple system disorders — polyarthritis, lupus nephritis, hepatitis, leukopenia, and recurrent necrotizing cutaneous vasculitis required the administration of high doses of immunosuppressive drugs. The progressive course of the disease, resistance to hormonal therapy, the rapid development of infectious complications made the prognosis for the patient's life extremely unfavorable. Persistent autoimmune leukopenia was the background condition for the development of complications.

We used combined therapy — the oral administration of high doses of glucocorticoids together with intravenous injections (pulse therapy), broad-spectrum antibacterial drugs, intravenous immunoglobulin, drugs that improve tissue trophicity and microcirculation. It was possible to decrease the disease activity, and also to restore the functional activity of the patient, to maintain low disease activity for 3 years, to prolong the life of a young patient by 8 years. The adverse combination of high activity of systemic lupus erythematosus with recurrent soft tissue infections caused difficulties for the therapy. Administration of adequate doses of cytostatic and biological agents were impossible due to leukopenia and secondary infection, which led to the death of the patient.

Key words: *systemic lupus erythematosus, severe course, necrotizing cutaneous vasculitis, leukopenia, treatment of systemic lupus erythematosus, infectious complications*

Conflict of Interests

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ANA — antinuclear antibodies, IVIG — intravenous immunoglobulin, GEB — genetically engineered biologics, GC — glucocorticoids, IC — infectious complications, MP — methylprednisolone, SLE — systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by a loss of tolerance to nuclear antigens, impaired activation of T- and B-lymphocytes with further polyclonal activation of B-lymphocytes that produce antibodies, and the formation of immune complexes that damage various organs and tissues [1]. Over the past decades, great success has been achieved in the treatment of SLE [2]. However, mortality in SLE remains high. According to the literature, the probability of fatalities in SLE is 2–5 times higher than in the general population. One of the factors of poor prognosis is the development of infectious complications (IC) [3].

According to the Rheumatology Department of the Regional Clinical Hospital data (Saratov), among eight patients who died in 2018 in the hospital, three were diagnosed with systemic lupus erythematosus. Two of three patients had a history of infection (one — history of cavernous tuberculosis, and one was diagnosed with sepsis associated with immunosuppression). At the same time, in none of these cases the infection was a direct cause of death. With the recurrent nature of the infection, the prognosis is aggravated.

Previously, we presented a case of combined severe SLE and skin infection [4]. We continued the patient's follow up.

We present the results of a prospective clinical observation of a patient M. Z., born in 1983, who was followed up in the Rheumatology Department of the SHCI "Regional Clinical Hospital" (RCH), Saratov, from 2007 to 2014.

Since February 2007, after acute respiratory infection (ARI), fever (37.7–38.1 °C), swelling of small joints of the hands, feet, redness and itching in the nasal bridge and cheeks after insolation appeared. In April 2007, she was admitted for examination and clarification of the diagnosis in the Rheumatology Department of the SHCI RCH in Saratov.

No abnormalities in the cardiovascular, respiratory, digestive, nervous systems were detected. Past medical history was without findings. An objective examination revealed polyarthritis; laboratory tests revealed leukopenia ($2.5 \times 10^9/l$), an increase in ESR to 43 mm/h, signs of nephritis (microhematuria, proteinuria — 1.2 g/l), glomerular filtration rate was normal (92 ml/min / 1.73 m² according to the MDRD formula), and anti-DNA antibodies were detected.

The diagnosis was: SLE, acute onset, moderate activity, nephritis, leukopenia, polyarthritis, photodermatitis. SLE SELENA-SLEDAI activity index amounted to 15 points. The changes of the main clinical and laboratory signs and treatment of the patient are presented in Figure 1.

The patient was treated with oral methylprednisolone (MP) 44 mg/day for a month with further dose reduction, hydroxychloroquine 200 mg/day, calcium supplements, gastroprotectors, antiplatelet agents, and angiotensin converting enzyme inhibitors (ACE inhibitors). In connection with nephritis, program pulse corticosteroid therapy (GC) of 500–1,000 mg was started in a regimen of once per month.

Over the next two years (June 2007 — May 2009), the disease progressed: cutaneous vasculitis, aphthous stomatitis, hepatitis (AST, ALT increase by 3.5–12.5 times), persistent leukopenia ($2.7–3.2 \times 10^9/l$), and moderate proteinuria (0.6–1.8 g/l) appeared. HIV and viral hepatitis were negative. With the SLE progression, SELENA-SLEDAI was 17–31 points.

Despite treatment correction in October 2007 (oral MP dose increase to 52 mg per day, program pulse MP therapy once every 3–4 weeks in combination with plasmapheresis, hepatoprotective agents), the effect was short-term and incomplete. The patient persisted with cutaneous vasculitis, hepatitis, nephritis, and leukopenia.

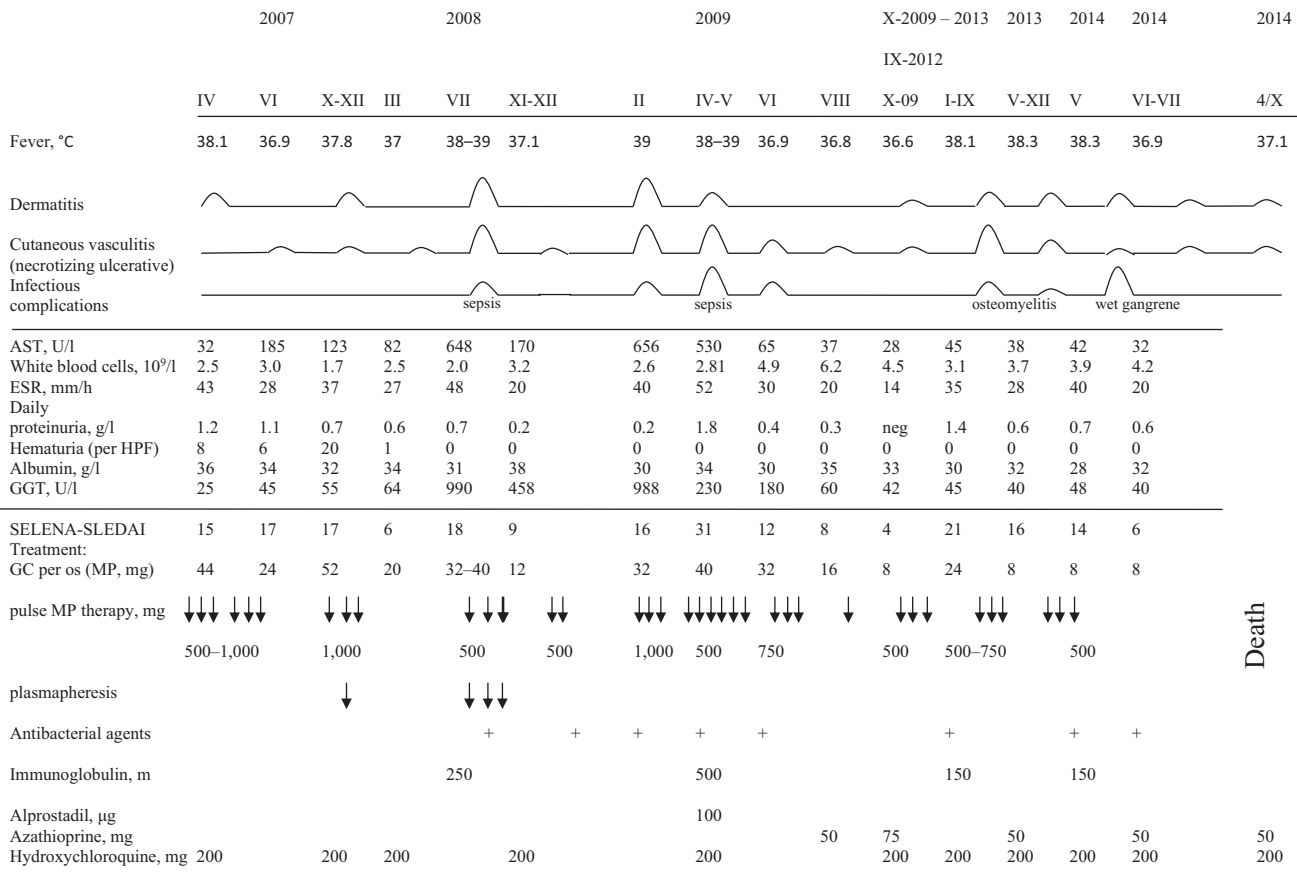


Figure 1. Changes of the main clinical and laboratory signs and the treatment of patient M.

Since July 2008, the course of SLE has been aggravated not only due to an increase in the activity of SLE, but also the addition of IC. Over the next 2–3 months, the formation of an abscess of the right buttock, left ankle joint, and suppurative bursitis of the right elbow joint were successively observed. Taking into account recurring suppurative IC, febrile fever with chills, stab shift up to 10%, the appearance of splenomegaly, sepsis was diagnosed in a patient with high SLE activity. Blood culture revealed *Staphylococcus aureus*. Antibacterial therapy was carried out with generation 3–4 cephalosporins and carbapenems, treatment with high doses of oral GC and pulse corticosteroid therapy continued, and intravenous immunoglobulin (IVIG) was administered, 250 ml in total. Short-term improvement occurred in November — December 2008 (Figure 1).

Despite the ongoing therapy, since February 2009, there has been a progression of aphthous stomatitis, dermatitis, and hepatitis (AST, ALT, GGT increase by 16.5, 6.3 and 20.0 times, respectively). There

was a worsening of the signs of cutaneous vasculitis, palmar capillaritis onset, foci of ischemic tissue on the skin of the hands, feet, chest, elbow joints, knee joints with necrosis, spontaneous opening of the left buttock abscess, and persistent fever with body temperature of up to 39 °C with chills. Due to the lack of effect, pulse GC therapy was intensified (1,000 g of No. 1–3 every 3 weeks), high doses of oral MP were still used (32–40 mg per day), and high-dose treatment with 3–4 generation cephalosporins continued.

The patient’s condition continued to deteriorate. In April — May 2009, during treatment in the Rheumatology Department of the SHCI RCH, the patient’s condition was regarded as extremely serious, which was associated with SLE activity, recurring suppurative infection of the skin and soft tissues, and sepsis. All signs of SLE aggravated: ulcerative stomatitis, digital arteritis, lupus cheilitis, leukopenia and nephritis progressed, retinal vasculitis appeared, high titer of anti-DNA antibodies (175 U/ml) and antinuclear antibody were

detected. Based on the GFR (94 ml/min / 1.73 m²) in the presence of kidney disease, stage 1 of chronic kidney disease (CKD) was diagnosed. Daily albuminuria was not evaluated.

Markers of antiphospholipid syndrome were negative, and coagulation test was within normal limits. The leading and most dreadful sign of SLE was necrotizing ulcerative vasculitis with areas of deep necrosis of the knee joint, elbow joint, the fingers of the hands, the skin of the feet and chest.

Subsequently, the patient developed dry necrosis of the distal phalanx of the second finger of the left hand. At this period, the diagnosis was as follows:

SLE, acute clinical course, severe activity (SELENA-SLEDAI — 31 points). Photodermatitis. Livedo reticularis. Palmar capillaritis. Generalized cutaneous vasculitis. Necrotizing ulcerative lesion of the skin and mucous membranes. Lupus cheilitis. Digital arteritis with the formation of dry necrosis of the distal phalanx of the second finger of the left hand. Nephritis (stage 1 CKD). Leukopenia, hepatitis, retinal vasculitis. Positive anti-DNA and antinuclear antibodies (ANA). History of polyarthritis.

Sepsis, acute clinical course. April, 2009: left thigh abscess incision and drainage (Figure 2). Infected wound of the right forearm, infiltration of the right buttock.

Complications: drug-induced Cushing's syndrome. Secondary hypertension.

On massive antibacterial therapy (generation 3–4 cephalosporins, carbapenems, fluoroquinolones, antifungal drugs), MP oral administration in a dose of 28–40 mg/day, MP pulse therapy 500–750 mg No. 6 with an interval of 14 days, additional administration of normal human immunoglobulin (500 ml) and 100 IU of anti-Staphylococcal immunoglobulin No. 4, and agents that improve trophic and microcirculation of tissues (IV infusion of pentoxifylline, actovegin, alprostadiol), the patient's condition gradually began to improve. The patient's body temperature returned to normal, a decrease in the severity

of cutaneous vasculitis, the disappearance of disorders of the retina, a decrease in hepatitis activity, an increase in the level of RBC and WBC were noted. After the formation of the demarcation line, exarticulation of the second finger of the left hand was performed.

As a result of the treatment, there was a sustained improvement in the patient's condition. A dose reduction of oral GC was initiated; taking into account hepatitis and nephritis, baseline therapy with cytostatic agents was prescribed: oral azathioprine 50 mg per day.

Over the next three years (from October 2009 to September 2012), on maintenance immunosuppressive treatment (MP 8 mg/day orally, azathioprine 50–75 mg/day, hydroxychloroquine 200 mg/day), SLE activity was minimal. Moderate dermatitis, a slight increase in the level of immunological markers, and moderate leukopenia were occasionally noted. Nephritis, hepatitis, cutaneous vasculitis and IC did not recur.



Figure 2. In the region of the upper third of the left thigh, there is a deep soft tissue ulcer with foci of necrosis, suppurative exudate and partially with bloody crusts. In the area of the lower part of the left buttock, there is a rough scar after spontaneous opening of an abscess of soft tissues

From January 2013, the patient showed an increase in SLE activity and recurrence of soft tissue infection associated with cutaneous vasculitis. The patient was repeatedly treated in the Rheumatology Department and periodically in the Septic Surgery Department of the SHCI RCH. SLE signs were the same: initially, cutaneous vasculitis, dermatitis, febrile fever, leukopenia, six months later — severe necrotizing ulcerative vasculitis with deep skin ulcers of the buttocks, thighs, mild nephritis (daily proteinuria 1.4 g/l), a significant increase in the level of anti-DNA antibodies.

In January 2013, the course of SLE was complicated by osteomyelitis of the middle and distal phalanges of the third finger of the right hand, which developed after the injury; in May 2014 — the development of wet gangrene of the right hand. Rheumatologists and surgeons carried out the treatment jointly. Oral MP doses were increased again to 24 mg/day, with a further decrease to 12 mg/day, and hydroxychloroquine was continued at a dose 200 mg/day. After the IC management, program therapy with MP 500.0–750.0 mg once every 1–2 months and treatment with small doses of azathioprine (50 mg/day) were performed. During the period of IC development, long-term (for 1.5 months) antibiotic therapy and IVIG was performed, and surgical treatment of wounds was carried out. Given IC, an adequate dose of cytotoxic drugs and GEBs could still not be prescribed. During this period, on treatment, SLE activity decreased slightly. SELENA-SLEDAI ranged from 6 to 11 points during the improvement. Relative stabilization of the patient's condition was noted in June — July 2014, after wet gangrene relief: cutaneous vasculitis, hepatitis did not recur, daily proteinuria, leukopenia did not increase. The patient took 15 mg/day MP orally, plaquenil 200 mg/day. The condition was regarded as satisfactory. The patient was discharged for outpatient treatment.

Subsequently, the patient went off the radar.

Later we managed to find out that in the fall of 2014, after contact with a sick child, the patient had a runny nose, dry cough, sore throat, muscle pain, fever (37.6–38.8 °C) with chills, general weakness, shortness of breath, and hemoptysis. She was

hospitalized in her home area. On October 4, 2014, the patient died of progressive respiratory failure. According to the documents, the cause of death was pulmonary embolism. At the same time, taking into account recurrent infections and leukopenia, toxic shock syndrome cannot be ruled out, which caused acute deterioration of the patient's condition and death.

Discussion

The clinical pattern of SLE is very diverse, and the course is often unpredictable. In the presented clinical case, a severe clinical course was not expected considering the SLE onset without severe damage to internal organs and pronounced hematological signs and a good initial response to GC therapy.

A feature of the SLE course in the patient was the development of hepatitis with severe cytolysis syndrome, cholestasis, a moderate decrease in albumin levels, the presence of necrotizing ulcerative cutaneous vasculitis, and persistent leukopenia. Another feature of the clinical course was the development of severe recurrent IC of the skin and soft tissues, osteomyelitis, and wet gangrene of the right hand.

Despite recent advances in rheumatology, treatment of SLE still poses a challenge. High-dose cyclophosphamide therapy shown in cases of severe vasculitis, nephritis, was not possible with this combination of symptoms in the patient.

The standard treatment of severe SLE using high doses of oral GC and pulse therapy, cytostatic agents and IVIG is not always effective. Given the presence of severe hepatitis, cutaneous vasculitis, the ineffectiveness of treatment, it would be advisable to add GEB, anti-B-cell therapy (rituximab), to the treatment. Rituximab, recently used in SLE “off-label”, is a promising tool for the treatment of patients, if standard therapy with GCs and cytostatic agents is ineffective [5]. However, recurrent severe IC was a contraindication to its use. It is known that IC aggravate the course of SLE, complicate the management of patients, while comprehensive immunosuppressive therapy and GEB worsen the prognosis [3].

In SLE, congenital and acquired abnormalities of the immune system increase the tendency to develop infectious diseases, including bacterial, viral and other infections [6].

ICs of soft tissues, which were repeatedly noted in the patient, are not characteristic of this disease. According to researchers, in SLE, pneumonia (36.8%), sepsis (18.1%), tuberculosis (13.5%), and urinary tract infections (12.9%) are most common [7].

According to monovariant analysis, significant causes of IC development are nephritis, SLE activity, the severity of leukopenia, high level of anti-DNA antibodies, low complement values, the use of GC in general and in a daily dose of more than 10 mg/day. According to multivariate analysis, statistically significant risk factors for the development of IC are the low complement values, the use of GC in a daily dose of more than 20 mg/day in combination with cyclophosphamide [8].

Apparently, long-term oral administration of GC in medium and high doses, as well as in the form of pulse therapy played a leading role in the development of IC in our patient. Cytotoxic drug use, in particular, azathioprine in adequate doses, was impossible due to recurrent infections, leukopenia and hepatitis. Severe ICs were a contraindication to GEB use.

For the treatment of the patient, the full range of available drugs was used both in high activity of SLE and in IC.

Prescribing treatment with GEB was not discussed due to the lack of clinical recommendations regarding their use in SLE at the time of the development of the disease, economic reasons when the patient's condition had stabilized, and contraindications associated with the recurrence of the infection.

Rheumatologists and surgeons observed the patient jointly, and because of this approach the patient lived for 8 years with such a persistent, treatment-resistant course of the disease. A fatal outcome in this patient could occur at any time, primarily related to a recurrence of IC against a

background of a severe autoimmune disease and immunosuppression.

The development of new drugs for the treatment of SLE variants is necessary. The advent of genetically engineered biologics has taken a new step in the treatment of SLE [9]. GEB use for the treatment of severe forms of SLE with bone marrow, lung and kidney damage or in the presence of contraindications to cytostatic agents, and their timely prescription can reduce the time and the dose of hormones used, improve the prognosis of the disease.

Conclusions

Despite the achievements of modern rheumatology, in some cases, SLE remains a serious disease. Infectious complications make it hard to treat SLE, making it impossible to prescribe adequate immunosuppression therapy, including the use of GEB, and they remain one of the leading causes of death in patients with SLE.

Contribution of Authors

Nikitina N.M. — collection of information, literature review, paper design, article correction after reviewing

Alexandrova O.L. — collection of information, literature review, description of the clinical part of the article

Scriabin E.N. — collection of information

Magdeeva N.A. — collecting information, translating resumes into English, posting articles on the journal's website

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