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Experience of Using Rituximab in a Girl with Severe Systemic Lupus Erythematosus

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Severe complications of systemic lupus erythematosus, such as antiphospholipid syndrome, generalized vasculitis, severe lesions of the central nervous system, remain topical. Inherent and frequent development of side effects secondary to a high-dose therapy with glucocorticosteroids and cytostatic agents remains a problem. That is why it is important to develop new methods of pathogenetic therapy of this disease, which would selectively affect its key links. The article presents a case of severe systemic lupus erythematosus accompanied by lesion of the central nervous system with pronounced clinical and laboratory activity, which led to the development of complications as a result of standard therapy regimens. The results demonstrate fast and significant efficiency of rituximab for combination therapy of severe forms of systemic lupus erythematosus.
Keywords: *systemic lupus erythematosus, lupus nephritis, antiphospholipid syndrome, vasculitis, adolescents, monoclonal antibodies, B cells, rituximab.*
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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic disease of unknown etiology characterized by systemic immunoinflammatory lesion of vital organs. This is one of the severest autoimmune human diseases. The polyetiologic concept of SLE development remains the main one; according to this concept, adverse conditions cause activity of any of the trigger factors, which eventually leads to the launch of a pathological process [1-4].
SLE is characterized by diversity of disease onsets and clinical manifestations. The disease usually sets on with one or several symptoms: idiopathic fever, weight loss, anemia, arthritis, skin lesion, Raynaud’s phenomenon, polyserositis, kidney damage, neurologic disorders (convulsions or chorea), recurrent thrombosis. Clinical pattern in the onset of the disease may significantly differ from classic descriptions of SLE; this often causes diagnostic difficulties not only among general practitioners, but also among rheumatologists. No wonder that SLE is called “the chameleon disease” or “the great disease imitator”: there is approximately fifty diseases, which require ruling SLE out, especially in the early stages of development (juvenile idiopathic arthritis, systemic vasculitis, systemic scleroderma, idiopathic inflammatory myopathies, primary antiphospholipid syndrome, drug-induced lupus, infectious diseases, lymphoproliferative processes etc.) [3].

Systemic lupus erythematosus is a disease, the most significant pathogenetic aspect whereof is associated with the development of autoantibodies and immune complexes; this leads to a chronic inflammatory process, which affects numerous organs and systems.
Contemporary treatment regimens involving high doses of glucocorticosteroids (GCS), including pulse therapy with methylprednisolone, and cytotoxic immunosuppressive agents (cyclophosphamide, azathioprine) considerably improved short- and long-term survival rate of patients with SLE. However, several severe forms of SLE, especially catastrophic antiphospholipid syndrome, generalized vasculitis and severe lesions of the central nervous system aggravate the severe prognosis on top of everything else. Expected frequent development of side effects in the setting of high-dosage therapy with GCS and cytostatic agents remains an issue. This is why it is of utmost importance to develop new methods of pathogenetic SLE therapy, which would selectively affect key links of the SLE pathogenesis [5].
Use of rituximab, including cases of development of lupus encephalitis, is of interest. This drug is a chimeric anti-CD20 monoclonal antibody, which contains human IgG1k component and a murine variable region. Antigen CD20 is expressed on surfaces of pre-, naïve and mature B lymphocytes and memory cells and never on plasmatic and stem cells. Rituximab causes depletion of B lymphocytes; this allows for successful treatment of humoral-cellular autoimmune diseases, such as SLE [6].
There is a considerable amount of published clinical cases and registry reports confirming the possibility of effective treatment of severe and resistant forms of SLE with rituximab in adults [6, 7]; however, there are few publications related to the use of rituximab for SLE in children [5]. This is why we would like to present a clinical case demonstrating difficulties of differential diagnosis of systemic connective tissue disorders and effectiveness of genetically engineered biopharmaceuticals (in the given example – of rituximab) for the therapy of severe systemic lupus erythematosus.

CLINICAL CASE

Female A. Gerel, 16 years of age, was admitted to the pediatric department of the Rostov State Medical University hospital on February 21, 2013, in severe condition; the girl complained of body temperature rises to 38-38.5 ^{o}C, pronounced weakness, drowsiness; rashes around zygomatic arches, lower and upper limbs were observed.
According to the anamnesis, the girl was born on term, of the 3rd pregnancy (the first pregnancy – daughter, 28 years of age, healthy; the second pregnancy – daughter, 25 years of age, healthy) characterized by gestosis in the first half, third term delivery, with a natal cervical spine injury, Erb's palsy on the right side and hyperbilirubinemia. Birth weight was 3 000 g, body length – 50 cm. Growth and development were age-adequate.
Infection anamnesis: acute respiratory viral infections 2-3 times per year, varicella at the age of 12 years.
Allergological anamnesis: atopic dermatitis (mother).
The girl was age-adequately vaccinated. Mantoux test – negative (2012).
The girl has been ailing since January 2013, when polymorphic rashes (including annular and maculopapular rashes) on the skin of palms, elbows, cheeks, lower limbs, as well as reddening around the maxillary gingiva, first appeared. At the same period body temperature rises to 38.8 ^{o}C in the evening were observed. The girl was examined by a local dermatologist, who diagnosed her with acute urticaria and prescribed chloropyramine, calcium gluconate, cetirizine and methylprednisolone aceponate (topically). The rashes became less pronounced after 2 weeks of treatment.
Edemata appeared on the face and lower limbs, pains occurred in the areas of ankle joints and small hand joints, body temperature rises to 38.5 ^{o}C recurred on February 11, 2013, which is why the patient was admitted to a local inpatient hospital. According to the examination results, clinical blood assay demonstrated sharp reduction in the levels of hemoglobin (47 g/l) and

erythrocytes (2.5×10^{12}/l) and increase in ESR to 48 mm/h; clinical urine assay – leukocyturia (up to 17 in the visual field) and proteinuria (1.0 g/l); no hyperazotemia was observed. The girl was examined by a pediatric cardiologist, who diagnosed her with subacute systemic lupus erythematosus (grade 2 activity), nephritis and reactive pericarditis. The girl underwent 2 transfusions of packed red blood cells in the amount of 300 ml, as well as antibacterial, antihypertensive (enalapril), diuretic (lasix, verospiron) and anticoagulant therapy (heparin), at the inpatient hospital. The edemata became smaller, however, punctate rashes appeared on lower limbs (ankle joints, foot surface); pyretic fever persisted as well. The girl was prescribed methylprednisolone on February 20, 2013; it helped to normalize body temperature, however, proteinuria (up to 3 g/l) persisted despite the absence of pathological alterations according to the biochemical blood assay.

The child was transferred to the pediatric department of the RostSMU hospital (Rostov-on-Don) due to ineffective therapy.

Objective data at admission: general condition – severe; body temperature – 38.6 ^{o}C; pronounced weakness; slow coming into contact; adequate reactions. Skin pallor; red maculopapular elements were observed around facial zygomatic arches, segments of hyperpigmentation – on the elbows, signs of capillaritis – on the palms, punctate rash, segments of hyperpigmentation – on the lower limbs (primarily on the back surface of the feet and ankle joints). Mucosae were pink and clean. Swelling of the face, lower limbs and lumbar region was observed. Mandibular, anterior and posterior cervical lymph nodes of 0.5 x 0.5 cm were palpable; they were soft, painless and not glomerated with each other and adjacent tissues. Pectoriloquy indicated harsh respiration. Cardiac borders were age-adequate. Blood pressure was high – up to 160/110 mm Hg.

Auscultation: muffled heart tones, moderate tachycardia, apical systolic murmur. The abdomen was soft and painless on palpation. The liver was situated by the costal margin. The spleen was not palpable. Murphy's punch sign was negative on both sides. Urination – 2-3 times per day; cloudy urine.

Clinical blood assay: hypochromic anemia (hemoglobin – 81 g/l, amount of erythrocytes – 3.47×10^{12}/l), leukocytosis up to 12.9×10^{9}/l, neutrophil leukocytosis (segmentonuclear neutrophils – 91%), ESR increase up to 42 mm/h. *Blood serum:* hypoproteinemia (total protein – 40 g/l), hyperkalemia (6.1 mmol/l), hyponatremia (131 mmol/l), hyperazotemia (creatinine – 165 mmol/l, urea – 13.4 mmol/l).

Immunological examination: increase in the level of $CD3^{+}$ and circulating immune complexes, sharp reduction in $CD19^{+}$ level, neutrophil link activation. Acute herpesvirus infections were ruled out on the basis of the enzyme-linked immunoassay (ELIA) and polymerase chain reaction. The ELIA also indicated a considerable increase in the level of antibodies against nDNA – 305.9 IU/ml (normally – up to 20 IU/ml), rheumatoid factor – 115.7 IU/ml (normally – up to 25 IU/ml), and cardiolipin IgM – 35.23 IU/ml (normally – 0-7 IU/ml); LE cells were observed.

Urine analysis: proteinuria – up to 3 g/l, hematuria (erythrocytes – outside the visual field), moderate leukocyturia; daily protein loss was 9.5 g.

Abdominal ultrasound examination: diffuse parenchymal changes of the liver in the form of a moderate edema, pronounced diffuse parenchymal changes of the kidneys, free fluid in the abdominal cavity.

Echocardiography: small fluid accumulation in the pericardial cavity (ca. 80-100 ml).

Thoracic spiral computed tomography (SCT) revealed bilateral pleurisy.

Brain magnetic resonance tomography (MRT) demonstrated signs of multifocal cortico-subcortical damage of both cerebellar hemispheres, as well as of the hemispheres on the right-hand side in the temporo-occipital region, on the left-hand side – in the parietooccipital region.

The child was diagnosed with systemic lupus erythematosus characterized by lesions of skin (livedo reticularis, angiitis, capillaritis, epidermolysis bullosa), kidneys (nephritis with nephrotic syndrome, hematuria, arterial hypertension, acute renal failure), central nervous system

(cerebrovasculitis with Eaton-Lambert syndrome), serosae (pleurisy, pericarditis, ascitis); acute course, high activity.

The patient was prescribed daily high-dosage GCS pulse therapy (3 x 750 ml per administration) with subsequent transfer to peroral intake in the dose of 48 mg/day; triple cytostatic pulse therapy (cyclophosphamide in the dose of 750 mg – February 26, 2013, 500 mg – March 04, 2013, 750 mg – March 25, 2013); anticoagulant and antiaggregatory therapy (enoxaparin sodium, dipyridamole); combination antihypertensive therapy (amlodipine, enalapril, metoprolol); diuretics (furosemide, torsemide); antibacterial (cefoperazone and sulbactam, meropenem, vancomycin) and antisecretory drugs (omeprazole); iron preparations, vitamins (cyanocobalamin), hemopoietic stimulators (erythropoietin).

On March 23, 2013, the girl's condition worsened sharply due to the development of impaired cerebral blood flow symptoms. Anticonvulsant therapy was corrected with Depakine Chrono (500 mg/day). In the evening of the same day the girl suffered a hypertensive emergency (BP – 190/120 mm Hg); headache intensification, primarily in the right-hand side temporal region, repeated emesis and jerking of upper and lower limbs were observed. The patient was reexamined by a neurologist and a resuscitator and transferred to the intensive care unit. First, positive dynamics in the form of fewer complaints of headache and BP reduction down to 150/100 mm Hg was observed. Thoracic SCT revealed bilateral pleurisy. However, on March 25, 2013, the patient suffered a complicated hypertensive emergency relapse: BP – 200/120 mm Hg; development of tonic-clonic seizures, nausea and emesis. The girl was examined by a neurologist, who diagnosed her with systemic lupus erythematosus, lupus encephalitis and symptomatic epilepsy. Anticonvulsant therapy was corrected with increase in the dose of Finlepsin up to 600 mg/day and gradual withdrawal of Depakine. Hypotensive (an angiotensin I receptor antagonist was prescribed) and diuretic therapy were intensified.

Sharp negative dynamics was observed on March 26, 2013: state of consciousness – sopor; occasional random arm movements; moderately dilated pupils; anergic photoreaction; BP – 190/105 mm Hg; SaO_2 – 99% in the setting of oxygen therapy and 94% in the event of no oxygen therapy. The patient was examined by a neurologist, who observed the following: state of consciousness – coma I; no photoreaction, meningeal signs; preserved tendon reflexes (arms and legs); pathological plantar signs on both sides, mydriasis. Brain SCT: signs of diffuse cortico-subcortical brain changes and of brain edema (with signs of descending transtentorial herniation).

Given the patient's extremely severe condition due to increasing cerebral failure caused by brain edema and low level of consciousness, the decision was made to intubate trachea and transfer her to artificial pulmonary ventilation (APV). Laboratory tests indicated hypokalemia (most probably in the setting of diuretic therapy [3.0 mmol/l]), hypoproteinemia (total protein – 40.9 g/l), high urea level (12.35 mmol/l) and normal sodium level (141 mmol/l). Anticonvulsant, anti-edema, antibacterial therapies and oncotic plasma correction were preserved. Despite the increase in hypotensive therapy (Pentamine), BP remained within 160-180/110 mm Hg.

The decision was made to add to the treatment regimen a genetically engineered biopharmaceutical – B lymphocyte receptor blocker rituximab – in the dose of 375 mg/m^2 (500 mg per administration once weekly). The patient featured signs of consciousness after the first administration of rituximab: she reacted to the endotracheal tube, experienced vomiturition, reached the left hand out for her head. The condition remained extremely severe, spontaneous respiration was abnormal: bradypnea of 6-8 respiratory movements per minute alternated with tachypnea of 30 respiratory movements per minute, BP – 136/91 mm Hg; convulsive twitches of the mimic muscles at emerging from a medication sleep were observed. Laboratory changes persisted: hypokalemia (3.0 mmol/l), hypoproteinemia (49.5 g/l); however, there were no signs of hyperazotemia; the sodium level was within the normal range. The day later the patient's state of consciousness was sopor; she would open her eyes on cue, clasp a hand; mobility was preserved in the upper and lower left limbs and absent in the upper right limb. Body temperature – pyretic fever, BP – 134/90-148/110 mm Hg. Diurnal diuresis – 1 560 ml, straw-colored urine.

The patient was transferred to the assisted APV. Antibacterial therapy was reinforced with the prescription of linezolid; human immunoglobulin for intravenous administration was added to the treatment regimen in order to prevent intercurrent infections. Given the lack of clear consciousness, need in long-term respiratory support, high tracheal, laryngeal and palatal reflexes, tracheostomy was performed in order to reduce the dead area within the airways. The patient reacted with rapid and significant fluctuations of hemodynamic parameters to tracheal sanitation; this was considered a dysfunction of stem structures.

On March 29, 2013, the patient was conscious, had spontaneous respiration, understood directed speech, performed simple tasks; however, mobility of the right hand remained absent. The girl was examined by an ophthalmologist who identified partial ptosis of the left eyelid. Hemodynamics was stable. BP – 130/99-140/95 mm Hg. Sponginess of the face and the upper body persisted.

On April 02, 2013, the girl underwent the second rituximab infusion. The condition continued to improve: the tracheostomy tube was removed and the girl was transferred to the pediatric department. Brain MRI revealed signs of involution of the subcortical hemispherical damage.

On April 09 and April 16, 2013, the girl underwent the next scheduled rituximab infusions, the treatment regimen was altered to include mycophenolate mofetil (1 g BID). Given stabilization of the patient's general condition and reduction of laboratory activity indicators, the therapists started to gradually decrease the methylprednisolone dose.

Further observation of the patient revealed stable positive clinical dynamics (absence of edemata; regression of skin syndrome, neurological symptoms and physical parameters in the lungs; occasional complaints of headache), and the girl was discharged in the satisfactory condition.

Rituximab was administered according to the following regimen: courses – once per 6 months, infusions – once weekly for 4 consequent weeks. No side effects due to administration were observed. The girl is hospitalized to the pediatric department of the RostSMU hospital once per 3 months for dynamic follow-up. By November 2013 the daily methylprednisolone dose was reduced down to 16 mg/day. The child continues to take mycophenolate mofetil (1 g BID) and undergoes antihypertensive (irbesartan, amlodipine), anticonvulsant (carbamazepine), hemopoietic (enoxaparin sodium, ferric [III] hydroxide polymaltosate), antiaggregatory (dipyridamole), gastro- and hepatoprotective therapies.

CONCLUSION

The described case demonstrated high effectiveness of rituximab – a chimeric anti-B lymphocyte monoclonal antibody – for severe systemic lupus erythematosus resistant to glucocorticosteroid and cytostatic therapy and accompanied by brain lesion.

CONFLICT OF INTEREST

The authors of this article have declared absence of reportable financial support / conflict of interest.

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