

„LUPUS IN FABULA”: SISTEMSKI ERITEMSKI LUPUS KOMPLIKOVAN SINDROMOM AKTIVACIJE MAKROFAGA SA FATALNIM ISHODOM

PRIKAZ SLUČAJA

CASE REPORT

"LUPUS IN FABULA": SYSTEMIC LUPUS ERYTHEMATOSUS COMPLICATED BY MACROPHAGE ACTIVATION SYNDROME WITH A FATAL OUTCOME

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SAŽETAK

Uvod/Cilj: Sindrom aktivacije makrofaga (engl. *macrophage activation syndrome – MAS*) predstavlja hiperinflamatorni sindrom i izuzetno retku, ali potencijalno životno ugrožavajuću komplikaciju sistemskog eritemskog lupusa (SEL), drugih sistemskih autoimunskih i autoinflamatornih bolesti, infekcija i maligniteta.

Prikaz slučaja: Pacijentkinja starosti 33 godine, sa istorijom ponavljanih holangitisa od detinjstva i perzistentno pozitivnim antinuklearnim antitelima (ANA) tokom više godina, simptomatski je lečena, u decembru 2022. godine, zbog febrilnosti i gastroenteroloških tegoba shvaćenih kao ponovni atak holangitisa, uprkos prisutnoj pancitopeniji, potrošnoj koagulopatiji i oštećenju bubrežne funkcije. U januaru 2023. godine dolazi do ponovne febrilnosti uz perifernu limfadenopatiju, splenomegaliju, progresiju pancitopenije i hipokomplementemiju, kada je postavljena dijagnoza SEL i započeto lečenje metilprednizolonom. Zbog novonastalih promena mentalnog statusa sa halucinacijama i izraženim kožnim promenama, razmatran je neurolupus, koji nije potvrđen usled odsustva adekvatnog neuroradiološkog korelata. Potom dolazi do progresivnog pogoršanja funkcije jetre i bubrega, produbljivanja pancitopenije, uz ekstremnu hiperferritinemiju ($> 33511 \mu\text{g/L}$), hipofibrinogenemiju i hipertrigliceridemiju, na osnovu čega je postavljena dijagnoza sindroma aktivacije makrofaga, kao komplikacije aktivnog, prethodno neprepoznatog sistemskog eritemskog lupusa (*H-score* 266). Uvođenje ciklosporina dovelo je do prolaznog poboljšanja. Međutim, uprkos primeni imunomodulatornih doza intravenskih imunoglobulina uz svu ostalu terapiju, razvijaju se anasarka, respiratorna, srčana i bubrežna slabost. Terapijske izmene plazme i intenzivne ultrafiltracije dovode do kratkotrajnog kliničkog, laboratorijskog i ehokardiografskog poboljšanja, iza čega dolazi do produbljivanja sindroma multiorganske disfunkcije. Uprkos svim primenjenim modalitetima lečenja, došlo je do fatalnog ishoda.

Zaključak: Preklapanje kliničkih i laboratorijskih manifestacija aktivnog sistemskog eritemskog lupusa i sindroma aktivacije makrofaga značajno otežava pravovremeno postavljanje dijagnoze. Poseban dijagnostički značaj ima praćenje koncentracija feritina, pri čemu se vrednosti $> 10.000 \mu\text{g/L}$ smatraju visoko sugestivnim za MAS.

Ključne reči: feritin, H-skor, sindrom multiorganske disfunkcije

ABSTRACT

Introduction/Objective: Macrophage activation syndrome (MAS) is a hyperinflammatory syndrome and an extremely rare but potentially life-threatening complication of systemic lupus erythematosus (SLE), other systemic autoimmune and autoinflammatory diseases, infections, and malignancies.

Case report: A 33-year-old female patient with a history of recurrent cholangitis since childhood and persistently positive antinuclear antibodies (ANA) for several years was treated symptomatically in December 2022 for fever and gastrointestinal symptoms interpreted as a recurrent episode of cholangitis, despite the presence of pancytopenia, consumptive coagulopathy, and impaired renal function. In January 2023, she developed recurrent fever accompanied by peripheral lymphadenopathy, splenomegaly, progression of pancytopenia, and hypocomplementemia, at which point a diagnosis of SLE was established and treatment with methylprednisolone was initiated. Due to newly developed changes in mental status with hallucinations and prominent nightmare content, neuropsychiatric lupus was considered; however, it was not confirmed because of the absence of an adequate neuroradiological correlate. Subsequently, progressive deterioration of liver and kidney function and worsening pancytopenia occurred, accompanied by extreme hyperferritinemia ($> 33,511 \mu\text{g/L}$), hypofibrinogenemia, and hypertriglyceridemia, leading to the diagnosis of macrophage activation syndrome as a complication of active, previously unrecognized systemic lupus erythematosus (*H-score* 266). Cyclosporine was introduced, resulting in transient improvement; however, despite immunomodulatory doses of intravenous immunoglobulins along with the other therapy, anasarca, respiratory, cardiac, and renal failure developed. Therapeutic plasma exchange and intensive ultrafiltration resulted in short-term clinical, laboratory, and echocardiographic improvement, followed by worsening of the multiple organ dysfunction syndrome. Despite all treatment modalities employed, the patient had a fatal outcome.

Conclusion: The overlap of the clinical and laboratory manifestations of active systemic lupus erythematosus and macrophage activation syndrome significantly complicates timely diagnosis. Monitoring ferritin concentrations is of particular diagnostic importance, with values $> 10,000 \mu\text{g/L}$ considered highly suggestive of MAS.

Keywords: ferritin, H-score, multiple organ dysfunction syndrome

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UVOD

Sindrom aktivacije makrofaga (engl. *macrophage activation syndrome* – MAS) ili reaktivna hemofagocitna limfocitocitoza (rHLH) je životno ugrožavajuće hiperinflamatorno stanje koje karakteriše nekontrolisana aktivacija T-limfocita i makrofaga, uz masivno oslobađanje citokina. Kašnjenje u dijagnostici i lečenju dovodi do razvoju sindroma multiorganske disfunkcije (engl. *multiorgan dysfunction syndrome* – MODS) [1]. Karakterišu ga febrilnost, splenomegalija, citopenija u dve ili više krvnih loza (citopenija ≥ 2 krvne loze), (hemoglobin < 90 g/l, trombociti $< 100 \times 10^9$ /l, neutrofili $< 1,0 \times 10^9$ /l), hipofibrinogenemija ($\leq 1,5$ g/l) i/ili hipertrigliceridemija ($\geq 3,5$ mmol/l), hiperferitinemija (≥ 500 μ g/l) uz nalaz hemofagocita u koštanoj srži, sniženu aktivnost NK ćelija (engl. *natural killer cells*) i povišene vrednosti α -subjedinice solubilnog interleukin (IL)-2 receptora (≥ 2400 U/ml). Za postavljanje dijagnoze sindroma aktivacije makrofaga, neophodno je prisustvo bar 5 od navedenih 8 kriterijuma [2].

Razlikuju se tri kategorije faktora koji doprinose razvoju sindroma aktivacije makrofaga: genetski (npr. urođeni poremećaji imunskog sistema), predisponirajuća stanja (sistemske autoimunske bolesti, limfoproliferativna oboljenja) i akutni okidači (infekcije, imunoterapija). U patogenezi često učestvuje više faktora istovremeno, npr. infekcije su najčešći pokretač sindroma aktivacije makrofaga kod pacijenata sa sistemskim autoimunskim bolestima i urođenim poremećajima imunskog sistema [1,3].

Iako izuzetno retka, MAS je životno ugrožavajuća komplikacija pacijenata sa sistemskim autoimunskim bolestima. Najčešće se opisuje kod pedijatrijskih pacijenata sa sistemskim juvenilnim idiopatskim artritism (sJIA) i odraslih sa Stilovom bolešću [4]. Javlja se kod 0,9%–4,6% pacijenata sa sistemskim eritemskim lupusom (SEL) [5,6].

Proгноza i ishod sindroma aktivacije makrofaga zavise od uzroka, trajanja bolesti, zahvaćenosti pojedinih organskih sistema, razvoja sindroma multiorganske disfunkcije. MAS koji je nastao kao komplikacija neke od sistemskih autoimunskih bolesti ima bolju prognozu od onog koji je nastao kao komplikacija hematoloških maligniteta. Takođe, razvoj insuficijencije jetre i bubrega je povezan sa lošijom prognozom [1]. Mortalitet kod pacijenata sa SEL varira i iznosi 5%–35% [4,6]. Nelečen, MAS ima progresivan tok zbog čega je pravovremeno prepoznavanje i uvođenje adekvatne terapije od vitalnog značaja za pacijenta.

Cilj ovog rada je da prikaže slučaj pacijentkinje sa kasno prepoznatim sistemskim eritemskim lupusom, koji se komplikovao razvojem sindroma aktivacije makrofaga sa fatalnim ishodom i da ukaže na značaj brzog

INTRODUCTION

Macrophage activation syndrome (MAS), or reactive hemophagocytic lymphohistiocytosis (rHLH), is a life-threatening hyperinflammatory condition characterized by uncontrolled activation of T-lymphocytes and macrophages, accompanied by massive cytokine release. Delayed diagnosis and treatment lead to the development of multiple organ dysfunction syndrome (MODS) [1]. It is characterized by fever, splenomegaly, cytopenia affecting two or more blood cell lineages (cytopenia in ≥ 2 blood cell lineages), (hemoglobin < 90 g/l, platelet count $< 100 \times 10^9$ /l, neutrophils $< 1.0 \times 10^9$ /l), hypofibrinogenemia (≤ 1.5 g/l) and/or hypertriglyceridemia (≥ 3.5 mmol/l), hyperferritinemia (≥ 500 μ g/l), along with the presence of hemophagocytes in the bone marrow, decreased natural killer (NK) cell activity, and elevated levels of the soluble α -subunit of the interleukin (IL)-2 receptor (≥ 2400 U/ml). For the diagnosis of macrophage activation syndrome, at least 5 of the 8 aforementioned criteria must be present [2].

Three categories of factors contribute to the development of macrophage activation syndrome: genetic factors (e.g., congenital disorders of the immune system), predisposing conditions (systemic autoimmune diseases, lymphoproliferative disorders), and acute triggers (infections, immunotherapy). Multiple factors often contribute simultaneously to MAS pathogenesis; for example, infections are the most common trigger of MAS in patients with systemic autoimmune diseases and congenital disorders of the immune system [1,3].

Although extremely rare, MAS is a life-threatening complication in patients with systemic autoimmune diseases. It is most commonly described in pediatric patients with systemic juvenile idiopathic arthritis (sJIA) and in adults with Still's disease [4]. It occurs in 0.9%–4.6% of patients with systemic lupus erythematosus (SLE) [5,6].

The prognosis and outcome of macrophage activation syndrome depend on its cause, disease duration, involvement of individual organ systems, and development of multiple organ dysfunction syndrome. MAS occurring as a complication of a systemic autoimmune disease has a better prognosis than MAS developing as a complication of hematological malignancies. In addition, the development of liver and renal failure is associated with a poorer prognosis [1]. Mortality among patients with SLE varies and ranges from 5% to 35% [4,6]. Untreated MAS follows a progressive course; therefore, timely recognition and initiation of appropriate therapy are of vital importance for the patient.

This paper aims to present the case of a patient with late-diagnosed systemic lupus erythematosus complicated by the development of macrophage activation

prepoznavanja i adekvatnog lečenja ove životno ugrožavajuće komplikacije sistemskog eritemskog lupusa.

PRIKAZ SLUČAJA

Pacijentkinja starosti 33 godine, imala je od detinjstva, a nakon operisane atrezije žučnih puteva u drugom mesecu života, ponavljane holangitise. U imunološkoj obradi su utvrđena pozitivna antinuklearna antitela (ANA) koja su perzistirala godinama unazad, uz prisutna antitela protiv Sjögrenovog sindroma (engl. *anti-Sjögren's syndrome A antibodies – ASSA*), antiglatkomišićna antitela (AGMA) i antimito hondrijalna antitela (AMA). Uprkos višegodišnjoj pozitivnosti antitela, u diferencijalnoj dijagnostičkoj obradi nije razmatrana sistemska autoimunska bolest, kao ni organ-specifična autoimunska bolest jetre i žučnih puteva. Lična i porodična anamneza su bile neupadljive.

Dominantno opšte i gastroenterološke tegobe (bolovi ispod desnog rebarnog luka, mučnina, povraćanje, tečne stolice) praćene febrilnošću do 39 °C u decembru 2022. godine shvaćene su kao samo još jedan napad holangitisa. Uz poremećaj analiza funkcije jetre i leziju bubrega, detektovana je pancitopenija (leukociti $2,87 \times 10^9/l$; eritrociti $3,05 \times 10^{12}/l$; hemoglobin 94 g/l; trombocitopenija) i poremećaj koagulacije po tipu potrošne koagulopatije (D-dimer 5,23 mg/l; fibrinogen 1,23 g/l). Ultrazvučno su opisani hepatosplenomegalija i ascites, a magnetnom rezonantnom holangiopankreatografijom isključena je opstruktivna bolest žučnih puteva. Pacijentkinja je u nadležnoj zdravstvenoj ustanovi lečena antibioticima, transfuzijama eritrocita, faktorima stimulacije granulocitne loze, ursodeoksiholnom kiselinom, uz simptomatsku terapiju što je dovelo do kratkotrajnog kliničkog poboljšanja.

U januaru 2023. godine, pacijentkinja ponovo postaje febrilna uz produktivan kašalj, perifernu limfadenopatiju, hepatosplenomegaliju i pogoršanje pancitopenije (leukociti $1,0 \times 10^9/l$; eritrociti $2,34 \times 10^{12}/l$; hemoglobin 79 g/l; trombociti $81 \times 10^9/l$). Biopsija kosti ukazala je na reaktivnu koštanu srž uz megakariocitnu trombocitopeniju. Hipoalbuminemija je bila klinički praćena otokom mekih tkiva, pleuralnim izlivima i ascitesom.

Pri inicijalnom fizikalnom pregledu, u Univerzitet-skom kliničkom centru Srbije, viđen je malarni osip uz bezbolne ulceracije u usnoj duplji. Pacijentkinja je negirala artralgijske, a klinički nije bilo znakova artritisa. U pristiglim imunološkim analizama je registrovana visokopozitivna ANA na HEp2 supstratu, homogenog bojenja nukleoplazme u titru $>> 1:640$ deobne ćelije $>> 1:640$, kao i antitela usmerena protiv dvolančane dezoksiribonukleinske kiseline (engl. *double-stranded deoxyribonucleic acid – dsDNA*) $>> 1:640$, uz potrošnju obe komponente komplementa (C3 0,16 g/l; C4 0,02 g/l).

syndrome with a fatal outcome, and to highlight the importance of rapid recognition and appropriate treatment of this life-threatening complication of systemic lupus erythematosus.

CASE REPORT

A 33-year-old female patient had been experiencing recurrent episodes of cholangitis since childhood, following surgical treatment of biliary atresia at the age of two months. Immunological evaluation revealed positive antinuclear antibodies (ANA), which had persisted for several years, along with anti-Sjögren's syndrome A antibodies (ASSA), anti-smooth muscle antibodies (ASMA), and antimitochondrial antibodies (AMA). Despite the persistent antibody positivity over several years, neither a systemic autoimmune disease nor an organ-specific autoimmune disease of the liver and biliary tract had been considered in the differential diagnosis. Her personal and family medical histories were unremarkable.

Predominantly general and gastrointestinal symptoms (right upper quadrant pain, nausea, vomiting, and loose stools) accompanied by fever up to 39 °C in December 2022 were interpreted as yet another episode of cholangitis. In addition to abnormal liver function tests and renal injury, pancytopenia was also detected (WBC $2.87 \times 10^9/l$; RBC $3.05 \times 10^{12}/l$; hemoglobin 94 g/l; thrombocytopenia), together with a coagulation disorder consistent with consumptive coagulopathy (D-dimer 5.23 mg/l; fibrinogen 1.23 g/l). Ultrasonography revealed hepatosplenomegaly and ascites, while magnetic resonance cholangiopancreatography ruled out obstructive disease of the biliary tract. At the healthcare institution in charge of her treatment, the patient received antibiotics, red blood cell transfusions, granulocyte colony-stimulating factors, ursodeoxycholic acid, and symptomatic therapy, resulting in short-term clinical improvement.

In January 2023, the patient again developed fever accompanied by a productive cough, peripheral lymphadenopathy, hepatosplenomegaly, and worsening pancytopenia (WBC $1.0 \times 10^9/l$; RBC $2.34 \times 10^{12}/l$; hemoglobin 79 g/l; platelet count $81 \times 10^9/l$). Bone marrow biopsy indicated reactive bone marrow with megakaryocytic thrombocytopenia. Hypoalbuminemia clinically manifested as soft-tissue edema, pleural effusions, and ascites.

At her initial physical examination at the University Clinical Center of Serbia, a malar rash and painless oral ulcerations were observed. The patient denied arthralgia, and there were no clinical signs of arthritis. The available immunological analyses showed strongly positive ANA on a HEp-2 substrate, with homogeneous nucleoplasmic staining at a titer of $> 1:640$, as

Na osnovu febrilnosti, malarnog osipa, oralnih ulceracija, poliserozitisa (pleuralni izliv, ascites), pozitivnih ANA, pozitivnih dsDNA, potrošnje obe komponente komplementa, leuko/limfopenije, autoimunske hemolizne anemije, trombocitopenije i lezije bubrega sa eritrociturijom i proteinurijom do 1,13 g/dan, zaključeno je da se kod pacijentkinje radi o sistemskom eritemskom lupusu sa elementima akutne lezije bubrega i jetre.

Ubrzo dolazi do promene mentalnog statusa sa halucinacijama i izraženim košmarnim sadržajima. Razmatran je neurolupus, koji nije potvrđen usled odsustva adekvatnog neuroradiološkog korelata na magnetnoj rezonanci (MR) endokranijuma. Lečenje je započeto metilprednizolonom u pulsnim dozama od po 250 mg (ukupno tri pulsa), a potom nastavljeno u dozi od 1 mg/kg telesne mase (TM).

Sprovedene su detaljne mikrobiološke analize. Isključene su bakterijske, virusne i gljivične infekcije – uredni nalazi briseva nosa i ždrela, pregleda sputuma na bakterije i gljivice, urinokulture, hemokulture na aerobe, anaerobe i gljivice uzorkovane u više navrata, serologije na *Leishmania infantum*; virus teškog akutnog respiratornog sindroma 2 (SARS-CoV-2), virusi hepatitisa B i C, virus humane imunodeficijencije, Epštajn-Bar virus – EBV i citomegalovirus; *Aspergillus* i *Candida spp.*, negativni galatkomanan i *Candida mannan* antigen.

Uprkos započetoj kortikosteroidnoj terapiji, dolazi do pogoršanja pancitopenije, uz ekstremnu hiperferitinemiju ($> 33511 \mu\text{g/l}$), hipofibrinogenemiju i hipertrigliceridemiju, kao i uz održavanje hepatosplenomegalije i periferne limfadenopatije. Primenom kriterijuma definisanih preporukama za dijagnostiku i lečenje hemofagocitne limfohistiocitoze iz 2004. godine (HLH-2004), zaključeno je da se radi o sindromu aktivacije makrofaga (H-skor 266; referentna vrednost > 250 upućuje na MAS sa verovatnoćom od preko 99%) kao komplikaciji aktivnog, više godina neprepoznatog sistemskog eritemskog lupusa. Povećava se 24 h-proteinurija na 2,48 g/dan.

Nastavljena je primena pulsnih doza metilprednizolona od po 500 mg (primila kumulativno ukupno 2,25 g) i započeta primena ciklosporina 3mg/kg TM. Nakon inicijalno kratkotrajnog kliničkog i diskretnog laboratorijskog poboljšanja, opšte stanje pacijentkinje se ponovo pogoršava u vidu febrilnosti, kašlja, tahidispnee. Primenjene su imunomodulatorne doze intravenskih imunoglobulina (IVIG) u ukupnoj dozi od 2 g/kg TM, uz nastavak terapije metilprednizolonom i ciklosporinom. Uprkos primenjenoj terapiji ne dolazi do zadovoljavajućeg kliničkog odgovora i stanje se komplikuje razvojem anasarke, sa znacima parcijalne respiratorne, srčane (EF 10–15%) i bubrežne insuficijencije (najpre kao posledica sindroma sistemskog kapilarnog curenja).

Pacijentkinja je dodatno lečena terapijskim izmenama plazme i intenzivnim ultrafiltracijama. Razmatrana je i mogućnost primene dodatnih lekova poput

well as antibodies directed against double-stranded deoxyribonucleic acid (dsDNA) at a titer of $> 1:640$, accompanied by consumption of both complement components (C3 0.16 g/l; C4 0.02 g/l).

Based on fever, malar rash, oral ulcerations, polyserositis (pleural effusion, ascites), positive ANA, positive dsDNA antibodies, consumption of both complement components, leukopenia/lymphopenia, autoimmune hemolytic anemia, thrombocytopenia, and renal involvement with erythrocyturia and proteinuria of up to 1.13 g/day, it was concluded that the patient had systemic lupus erythematosus presenting with acute kidney and liver injury.

The patient's mental status soon changed, and she experienced hallucinations and vivid nightmares. Neuropsychiatric lupus was considered but was not confirmed due to the absence of an adequate neuroradiological correlate on magnetic resonance imaging (MRI) scans of the brain. Treatment was initiated with methylprednisolone at pulse doses of 250 mg each (three pulses in total), which was continued at a dose of 1 mg/kg body weight (BW).

Detailed microbiological analyses were performed. Bacterial, viral, and fungal infections were excluded, specifically – unremarkable findings from nasal and pharyngeal swabs, sputum examination for bacteria and fungi, urine cultures, and blood cultures for aerobic and anaerobic bacteria and fungi obtained on multiple occasions, serology for *Leishmania infantum*; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), hepatitis B and C viruses, human immunodeficiency virus, Epstein–Barr virus (EBV), and cytomegalovirus; *Aspergillus* and *Candida spp.*, negative galactomannan and *Candida mannan* antigen tests.

Although corticosteroid therapy was introduced, pancytopenia worsened, accompanied by extreme hyperferritinemia ($> 33,511 \mu\text{g/l}$), hypofibrinogenemia, and hypertriglyceridemia, with persistent hepatosplenomegaly and peripheral lymphadenopathy. Applying the criteria defined in the 2004 recommendations for the diagnosis and treatment of hemophagocytic lymphohistiocytosis (HLH-2004), the condition was diagnosed as macrophage activation syndrome (H-score 266; a reference value > 250 indicates MAS with a probability of more than 99%) as a complication of active systemic lupus erythematosus that had remained unrecognized for several years. Twenty-four-hour proteinuria increased to 2.48 g/day.

Treatment with methylprednisolone pulse doses of 500 mg each was continued (a cumulative total dose of 2.25 g was administered), and cyclosporine was initiated at 3 mg/kg BW. Following an initially brief clinical and modest laboratory improvement, the pa-

Tabela 1. Laboratorijske i imunološke analize tokom lečenja pacijentkinje: po postavljanju dijagnoze SEL, uspostavljanju dijagnoze SEL sa MAS, i po razvoju sindroma multiorganske disfunkcije**Table 1.** Laboratory and immunological analyses during the patient's treatment: at the time of SLE diagnosis, upon establishment of the diagnosis of SLE with MAS, and following the development of multiple organ dysfunction syndrome

Parametri (referentne vrednosti) / Parameters (reference values)	Dijagnoza SEL (07.01.2023) / SLE diagnosis (January 7, 2023)	Dijagnoza SEL/MAS (17.01.2023) / SLE/MAS diagnosis (January 17, 2023)	MODS (06.02.2023) / MODS (February 6, 2023)
Leukociti (3,4–9,7x10 ⁹ /l) / WBC (3.4–9.7x10 ⁹ /l)	1.0	2.1	6.4
Hemoglobin (119–157 g/l) / Hemoglobin (119–157 g/l)	79	74	82
Trombociti (158–424x10 ⁹ /l) / Platelet count (158–424x10 ⁹ /l)	81	59	35
C reaktivni protein (0–5 mg/l) / C-reactive protein (0–5 mg/l)	1.1	23.1	119.7
Sedimentacija eritrocita (0–10 mm/h) / ESR (0–10 mm/h)	12	34	10
Interleukin 6 (0–7 pg/ml) / Interleukin 6 (0–7 pg/ml)	5.7	148.5	3,549
Feritin (4,6–204 µg/l) / Ferritin (4.6–204 µg/l)	> 33,511	12,236	1,798
Fibrinogen (2–4 g/l) / Fibrinogen (2–4 g/l)	2.5	2.2	2.6
D-dimer (< 0,5 mg/l) / D-dimer (< 0.5 mg/l)	1.72	2.87	8.32
Trigliceridi (0–1,7 mmol/l) / Triglycerides (0–1.7 mmol/l)	6.82	3.44	2.3
Urea (2,5–7,5 mmol/l) / Urea (2.5–7.5 mmol/l)	11.8	9.8	29.1
Kreatinin (45–84 µmol/l) / Creatinine (45–84 µmol/l)	189	50	143
eGFR (> 60 ml/min/1,73 m ²) / eGFR (> 60 ml/min/1.73 m ²)	51	60	37
Sediment urina / Urine sediment	eritrociturija, proteinurija (+++) / erythrocyturia, proteinuria (+++)		
24h proteinurija (0–0,15 g/24 h) / 24-hour proteinuria (0–0.15 g/24 h)	1.92	2.49	/
Ukupni proteini (62–81 g/l) / Total protein (62–81 g/l)	43	47	50
Albumini (34–55 g/l) / Albumins (34–55 g/l)	22	27	24
Aspartat transaminaza (0–37 U/l) / Aspartate transaminase (0–37 U/l)	1,011	82	49
Alanin transaminaza (0–41 U/l) / Alanine transaminase (0–41 U/l)	319	98	45
Gama-glutamil transferaza (0–38 U/l) / Gamma-glutamyl transferase (0–38 U/l)	621	694	198
Laktat dehidrogenaza (220–460 u/l) / Lactate dehydrogenase (220–460 u/l)	1,254	343	657
Imunološke analize / Immunological analyses	ANA HEp2 nukleoplazma homogena >> 1:640, deobne ćelije >> 1:640; anti-dsDNA >> 1:640 ENA screen ++ / ANA HEp2 homogeneous nucleoplasm >> 1:640, proliferating cells >> 1:640; anti-dsDNA >> 1:640 ENA screen ++		
C3 (0,65–1,8 g/l) / C3 (0.65–1.8 g/l)	0.18	0.23	0.27
C4 (0,1–0,4 g/l) / C4 (0.1–0.4 g/l)	0.03	< 0.027	0.03
H skor (< 169) / H score (< 169)	205	266 (> 99% verovatnoće za MAS / probability of MAS)	143

etopozida i rekombinantnog inhibitora interleukina-1 (anakinra). Zbog razvoja globalne respiratorne insuficijencije pacijentkinja je priključena na neinvazivnu, a potom na invazivnu mehaničku ventilaciju.

Nakon inicijalnog, kratkotrajnog, kliničkog, laboratorijskog i ehokardiografskog poboljšanja, u daljem toku dolazi do produbljiivanja sindroma multiorganske disfunkcije koji se, uprkos svim primenjenim modalitetima lečenja, završava fatalnim ishodom 34 dana po postavljanju dijagnoze sistemskog eritemskog lupusa.

Laboratorijske i imunološke analize tokom lečenja pacijentkinje su prikazane u Tabeli 1.

tient's general condition deteriorated again, with fever, cough, and tachypnea. Immunomodulatory doses of intravenous immunoglobulins (IVIG) were administered at a total dose of 2 g/kg BW, with continuation of methylprednisolone and cyclosporine therapy. Despite the treatment administered, there was no satisfactory clinical response, and the condition became further complicated by the development of anasarca, with signs of partial respiratory, cardiac (EF 10–15%), and renal insufficiency (primarily due to systemic capillary leak syndrome).

The patient was additionally treated with thera-

DISKUSIJA

Aktivan SEL i MAS se preklapaju u određenim kliničkim i laboratorijskim karakteristikama kao što su febrilnost, psihijatrijske tegobe, pancitopenija, znaci insuficijencije više organskih sistema. Kako i SEL i MAS mogu da obuhvate različite sisteme organa, ne postoji patognomoničan nalaz koji ih razlikuje. Mnoge od navedenih manifestacija se mogu videti i u teškim infekcijama, zbog čega diferencijalna dijagnoza između ova tri entiteta predstavlja izazov.

Postojeći dijagnostički kriterijumi za MAS su nedovoljne senzitivnosti i specifičnosti, posebno kad kod pacijenta postoje koegzistirajuća stanja (infekcije, inflamacije, maligniteti) [1]. Imajući u vidu fulminantan tok sindroma aktivacije makrofaga i veliku smrtnost, postojanje specifičnog i senzitivnog biomarkera bi bilo od izuzetnog kliničkog značaja. Evropski savez udruženja za reumatologiju (engl. *European Alliance of Associations for Rheumatology – EULAR*) i Američki koledž za reumatologiju (engl. *American College of Rheumatology – ACR*) u svojim preporukama za rano prepoznavanje MAS, ističu značaj određivanja i serijskog praćenja koncentracije feritina [1]. Feritin vezuje slobodno gvožđe smanjujući oksidativni stres i inhibirajući apoptozu endotelih ćelija, te je porast njegove koncentracije najpre kompenzatorni mehanizam u uslovima hiperinflamacije [7]. Ukoliko se isključe alternativni uzroci hiperferitinemije, kao što su preopterećenost gvožđem, hepatitisi i maligniteti, koncentracije feritina $> 10\,000\ \mu\text{g/l}$ kod odraslih pacijenata se smatraju visoko sugestivnim za MAS [1,5,8]. Kod dece se značajnim smatraju i niže koncentracije feritina ($500\text{--}2000\ \mu\text{g/l}$) [1]. Visoka koncentracija feritina, zabeležena u slučaju naše pacijentkinje – inicijalno pripisana leziji jetre, svakako je daljim porastom usmerila diferencijalnu dijagnozu ka razmatranju MAS.

Laktat dehidrogenaza (LDH) bi, uz koncentraciju feritina, mogla da bude značajan marker u prepoznavanju sindroma aktivacije makrofaga [4], ali treba imati na umu da povišen nivo LDH može da upućuje i na druge i/ili paralelne inflamatorne procese [9]. Povišene vrednosti LDH kod naše pacijentkinje su shvaćene kao posledica aktivne hemolize i lezije jetre (Tabela 1). Kako je u daljem toku došlo do normalizacije hepatograma, održavanje izuzetno povišenih koncentracija feritina je, uz produblјivanje pancitopenije, hipofibrinogemiju i hipertrigliceridemiju, primenom HLH-2004 kriterijuma dovelo do zaključka da se radi o MAS kao komplikaciji aktivnog sistemskog eritemskog lupusa [2]. Drugi biomarkeri za MAS su merenje aktivnosti T-ćelija (solubilni IL-2 receptor- α , ekspresija DR izotipa humanog leukocitnog antigena), makrofaga (npr. CD163,

peutic plasma exchange and intensive ultrafiltration. The possibility of administering additional drugs, such as etoposide and the recombinant interleukin-1 inhibitor anakinra, was also considered. Due to the development of global respiratory failure, the patient was placed first on noninvasive and subsequently on invasive mechanical ventilation.

Following an initial, short-term clinical, laboratory, and echocardiographic improvement, the subsequent course was characterized by worsening of multiple organ dysfunction syndrome which, despite all treatment modalities employed, resulted in a fatal outcome 34 days after the diagnosis of systemic lupus erythematosus was established.

Laboratory and immunological analyses obtained during the patient's treatment are presented in Table 1.

DISCUSSION

Active SLE and MAS overlap in certain clinical and laboratory characteristics, such as fever, psychiatric symptoms, pancytopenia, and signs of multiple organ dysfunction. Since both SLE and MAS can involve different organ systems, there is no pathognomonic finding that can distinguish between them. Many of the aforementioned manifestations may also occur in severe infections, making the differential diagnosis among these three entities challenging.

The existing diagnostic criteria for MAS have insufficient sensitivity and specificity, particularly when patients have coexisting conditions such as infections, inflammatory disorders, or malignancies [1]. Given the fulminant course of macrophage activation syndrome and its high mortality, the availability of a specific and sensitive biomarker would be of exceptional clinical importance.

The European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR), in their recommendations for the early recognition of MAS, emphasize the importance of determining and serially monitoring ferritin concentrations [1]. Ferritin binds free iron, thereby reducing oxidative stress and inhibiting endothelial cell apoptosis; thus, an increase in its concentration initially represents a compensatory mechanism under conditions of hyperinflammation [7]. After excluding alternative causes of hyperferritinemia, such as iron overload, hepatitis, and malignancies, ferritin concentrations $> 10,000\ \mu\text{g/l}$ in adult patients are considered highly suggestive of MAS [1,5,8]. In children, lower ferritin concentrations ($500\text{--}2,000\ \mu\text{g/l}$) are also considered clinically significant [1]. The high ferritin concentration recorded in our patient, initially attributed to liver injury, subsequently increased further and consequently directed the differential diagnosis toward MAS.

neopterin), inflamazoma (interleukin (IL)-18) i puta interferona gama (IFN γ). Iako specifičniji, ovi biomarkeri često nisu rutinski dostupni u kliničkoj praksi [1,9].

U nedostatku jedinstvenog kliničkog, laboratorijskog i/ili patološkog nalaza za MAS, razvijen je tzv. H-skor (engl. *H-score*) koji procenjuje rizik za razvoj sindroma aktivacije makrofaga. Sistem bodovanja obuhvata kombinaciju devet kliničkih, laboratorijskih i citoloških parametara: prethodna imunosuprimiranost, febrilnost, organomegalija, citopenije, koncentracija feritina, triglicerida, fibrinogena, vrednosti aspartat transaminaze, te prisustvo hemofagocita u aspiratu koštane srži. Granična (engl. *cutoff*) vrednost H-skora iznosi 169, što odgovara senzitivnosti od 93% i specifičnosti od 86%, dok vrednosti H-skora preko 250 govore sa > 99% verovatnoće da se radi o MAS [8,10].

Naknadnom evaluacijom kliničko-laboratorijskih parametara u trenutku postavljanja dijagnoze sistemskog eritemskog lupusa, kod naše pacijentkinje je utvrđen H-skor 205 koji govori sa 88-93% verovatnoće da je došlo do razvoja MAS [10]. Međutim, niža vrednost H-skora (143) u trenutku razvoja sindroma multiorganske disfunkcije bi mogla da upućuje na iscrpljenost kompenzatornih mehanizama pacijentkinje i smanjene produkcije proinflamatornih citokina. Značaj ovog sistema bodovanja se ogleda u tome što omogućava kliničarima da, na osnovu kliničke slike i rutinskih laboratorijskih analiza, brzo procene verovatnoću da je kod pacijenta došlo do razvoja MAS i blagovremeno započnu lečenje. Navedene parametre treba pratiti longitudinalno kroz vreme uz reevaluaciju H-skora, nekada i više puta dnevno, ukoliko kliničko stanje pacijenta tako nalaže.

Manifestacije centralnog nervnog sistema (CNS) nisu uključene u HLH-2004 dijagnostičke kriterijume [2], što u kliničkoj praksi može biti razlog da se ne uoče blagovremeno. Iako se češće javljaju u pedijatrijskom uzrastu, ni kod odraslih ne smeju biti zanemarene. Poremećaj mentalnog statusa ili stanja svesti, pojava konvulzija, encefalopatije, meningizma, znakovi zahvaćenosti kranijalnih nerava, zahtevaju dopunsku neurološku obradu – MR endokranijuma sa/bez angiografije, lumbalnu punkciju sa pregledom cerebrospinalne tečnosti i elektroencefalografiju (EEG) [1,11]. Kako je MR endokranijuma naše pacijentkinje isključila parenhimske promene u sklopu SEL, njene neuropsihijatrijske tegobe su shvaćene kao manifestacije sindroma aktivacije makrofaga.

Patofiziologija sindroma aktivacije makrofaga je izuzetno kompleksna i zasniva se na disfunkciji citotoksičnih ćelija (NK ćelija i CD8⁺ T-limfocita) koje u uslovima adekvatnog imunskog odgovora zaustavljaju inflamaciju eliminacijom aktiviranih antigen-prezentujućih

Lactate dehydrogenase (LDH), together with ferritin concentration, may be an important marker for the recognition of macrophage activation syndrome [4], but it should be kept in mind that an elevated LDH level may also indicate other and/or concomitant inflammatory processes [9]. The elevated LDH levels in our patient were interpreted as a consequence of active hemolysis and liver injury (Table 1). As liver function tests subsequently normalized, the persistence of extremely elevated ferritin concentrations, together with worsening pancytopenia, hypofibrinogenemia, and hypertriglyceridemia, led, upon application of the HLH-2004 criteria, to the conclusion that the patient had MAS as a complication of active systemic lupus erythematosus [2]. Other biomarkers for MAS include assessment of T-cell activity (soluble IL-2 receptor- α , expression of the DR isotype of human leukocyte antigen), macrophage activity (e.g., CD163, neopterin), the inflammasome (interleukin [IL]-18), and the interferon-gamma (IFN γ) pathway. Although more specific, these biomarkers are often not routinely available in clinical practice [1,9].

In the absence of a single clinical, laboratory, and/or pathological finding to diagnose MAS, the so-called H-score was developed to assess the risk of developing macrophage activation syndrome. The scoring system incorporates a combination of nine clinical, laboratory, and cytological parameters: previous immunosuppression, fever, organomegaly, cytopenias, ferritin concentration, triglyceride concentration, fibrinogen concentration, aspartate transaminase levels, and the presence of hemophagocytes in a bone marrow aspirate. The H-score cutoff value is 169, corresponding to a sensitivity of 93% and specificity of 86%, whereas H-score values above 250 indicate a >99% probability of MAS [8,10].

Retrospective evaluation of the clinical and laboratory parameters at the time of SLE diagnosis revealed an H-score of 205 in our patient, corresponding to an 88%–93% probability of MAS development [10]. However, the lower H-score (143) at the time of development of multiple organ dysfunction syndrome could indicate exhaustion of the patient's compensatory mechanisms and reduced production of proinflammatory cytokines. The significance of this scoring system lies in its ability to enable clinicians, based on the clinical presentation and routine laboratory analyses, to rapidly assess the probability that a patient has developed MAS and to initiate treatment promptly. These parameters should be monitored longitudinally over time, with reassessment of the H-score, sometimes several times a day, if warranted by the patient's clinical condition.

ćelija, na prvom mestu makrofaga. Kada takav imunski odgovor izostane, T-limfociti i makrofagi ostaju stalno aktivni. Makrofagi dovode do fagocitoze krvnih ćelija (hemofagocitoza) i amplifikacije inflamatornog odgovora koji kroz tzv. citokinsku oluju sam sebe održava. Pored faktora nekroze tumora (engl. *tumor necrosis factor* – *TNF*) koji je odgovoran za oštećenje tkiva, aktivirani makrofagi proizvode i brojne interleukine. IL-18 stimuliše CD8⁺ T-limfocite koje proizvode IFN γ i aktivirajući makrofage amplifikuju ovu citokinsku kaskadu. Smatra se da su IL-1 i IL-6 odgovorni za sistemsku inflamaciju u sindromu aktivacije makrofaga [3,7]. Navedeni citokini i/ili njihovi receptori mogu biti meta terapijskog delovanja (npr. anakinra je monoklonsko antitelo koje se vezuje za alfa subjedinicu IL-1 receptora). Ograničena dostupnost ciljanih bioloških lekova je glavni razlog za izostanak njihove češće primene u kliničkoj praksi.

EULAR/ACR preporučuju visoke doze glukokortikoida uz anakinru i/ili IVIG kao prvu terapijsku opciju za lečenje MAS kod odraslih, čak i pre definitivnog otkrivanja uzroka [1]. Izbor glukokortikoida je individualan i prilagođen specifičnostima sindroma aktivacije makrofaga kod pacijenta. Pulsne doze metilprednizolona (10–30 mg/kg telesne mase/dan, do 1 g dnevno) su prvi izbor u situacijama kad je potreban brži terapijski efekat. Zbog prolaska krvno-moždane barijere, deksametazon (10 mg/m²/dan) je pogodan za pacijente sa CNS manifestacijama. Naša pacijentkinja je inicijalno imala dobar klinički odgovor na pulsne doze metilprednizolona, a deksametazon je aplikovan nešto kasnije, u skladu sa kliničkim stanjem. Psihijatrijske tegobe se nisu ponavljale.

Glukokortikoide treba davati sa oprezom kad postoji sumnja da je MAS pokrenut/održavan infekcijom ili malignitetom. U tim situacijama su pogodniji IVIG ili anakinra koji omogućavaju imunomodulaciju bez imunosupresije. Oni omogućavaju veću bezbednost bez uticaja na eventualno naknadno ispitivanje etiologije MAS [1,12]. Imunomodulatorne doze IVIG su, uz metilprednizolon i ciklosporin A, kod naše pacijentkinje samo tranzitorno dovele do povoljnog terapijskog efekta. Brz početak dejstva i kratak polужivot anakinre je čini pogodnom za MAS pokrenut sistemskim autoimunskim bolestima [7,13], ali u konkretnom slučaju nije bio dostupan za brzu primenu kod naše pacijentkinje. Etoposid je takođe razmatran, ali je u kontekstu brzo napredujuće slike sindroma multiorganske disfunkcije, zaključeno da bi njegova primena pogoršala postojeću tešku srčanu insuficijenciju [14].

Ciklosporin A je, zbog svog efekta na smanjenje produkcije IL-1, IL-6 i TNF α , koji igraju ključnu ulogu u patogenezi sindroma aktivacije makrofaga, zauzeo

Central nervous system (CNS) manifestations are not included in the HLH-2004 diagnostic criteria [2], which in clinical practice may be a reason why they are not recognized on time. Although they occur more frequently in the pediatric population, they should not be overlooked in adults either. Altered mental status or level of consciousness, seizures, encephalopathy, meningism, and signs of cranial nerve involvement require additional neurological evaluation, including brain MRI with or without angiography, lumbar puncture with cerebrospinal fluid analysis, and electroencephalography (EEG) [1,11]. Since brain MRI scans in our patient excluded parenchymal changes associated with SLE, her neuropsychiatric symptoms were interpreted as manifestations of macrophage activation syndrome.

The pathophysiology of macrophage activation syndrome is extremely complex and is based on dysfunction of cytotoxic cells (NK cells and CD8⁺ T lymphocytes), which, under conditions of an adequate immune response, terminate inflammation by eliminating activated antigen-presenting cells, primarily macrophages. When such an immune response is absent, T lymphocytes and macrophages remain continuously activated. Macrophages cause phagocytosis of blood cells (hemophagocytosis) and amplify the inflammatory response, which sustains itself through the so-called cytokine storm. In addition to tumor necrosis factor (TNF), which is responsible for tissue damage, activated macrophages produce numerous interleukins. IL-18 stimulates CD8⁺ T lymphocytes, which produce IFN γ and, by activating macrophages, amplify this cytokine cascade. IL-1 and IL-6 are considered responsible for systemic inflammation in MAS [3,7]. These cytokines and/or their receptors may represent therapeutic targets (e.g., anakinra is a monoclonal antibody that binds to the alpha subunit of the IL-1 receptor). Limited availability of targeted biological agents is the main reason for their infrequent use in clinical practice.

EULAR/ACR recommend high-dose glucocorticoids with anakinra and/or IVIG as the first therapeutic option for the treatment of MAS in adults, even before the underlying cause has been definitively identified [1]. The choice of glucocorticoid is individualized and tailored to the specific characteristics of MAS in each patient. Methylprednisolone pulse doses (10–30 mg/kg body weight/day, up to 1 g/day) are the first choice when a rapid therapeutic effect is required. Because of its ability to cross the blood–brain barrier, dexamethasone (10 mg/m²/day) is suitable for patients with CNS manifestations. Our patient initially showed a good clinical response to methylprednisolone pulse doses, while dexamethasone was administered a bit later,

značajno mesto u terapijskom algoritmu. Iako to nije bio slučaj kod naše pacijentkinje, u dozi od 3 mg/kg telesne mase/dan u kombinaciji sa visokim dozama glukokortikoida i IVIG može dovesti ne samo do indukcije već i do održavanja remisije sindroma aktivacije makrofaga indukovanog sistemskim eritemskim lupusom [15].

Terapijske izmene plazme (TIP) su se pokazale kao efikasna *add-on* terapija u MAS (uz glukokortikoidnu i imunosupresivnu terapiju) dovodeći do redukcije proinflammatoryh citokina [16]. Iako postoje podaci da su TIP dovodile i do redukcije mortaliteta kod pacijenata sa MAS, ishod je u slučaju naše pacijentkinje bio nepovoljan, što je verovatno bilo uslovljeno već odmaklim stadijumom bolesti sa posledičnim sindromom multiorganske disfunkcije unutar mesec dana od započinjanja lečenja.

Prema pregledu literature o aktuelnim terapijskim modalitetima MAS u pedijatrijskom uzrastu iz 2025. godine, visoke doze glukokortikoida uz inhibitore IL-1 (anakinra) i IFN γ (emapalumab) efikasne su u terapiji sindroma aktivacije makrofaga koji je povezan sa sJIA. Podaci o eventualnoj terapijskoj efikasnosti ove kombinacije kod drugih sistemskih autoimunskih bolesti, kao što je SEL, još uvek su oskudni [17].

Emapalumab, humanizovano monoklonsko antitelo usmereno na IFN γ , pokazao je veliku efikasnost za indukciju remisije kod dece sa rekurentnim i refraktarnim primarnim HLH [18]. De Benedetti i saradnici su pokazali da je emapalumab efikasan i kod pacijenata sa sekundarnim MAS, kod kojih visoke doze glukokortikoida, kao monoterapija ili konkomitantno uz anakinru i/ili ciklosporin, nisu pokazale zadovoljavajući efekat [19]. Iako dokazano efikasna terapijska metoda, nedostupnost emapalumaba u određenim zemljama, uključujući i Srbiju, jeste razlog što se još uvek nije započelo sa njegovom primenom.

Ruksolitinib (inhibitor Janus kinaze, JAK1 i JAK2) takođe je pokazao izvesnu efikasnost kod maligniteta i MAS za koji je okidač EBV infekcija kod odraslih [1,20], ali se i dalje savetuje oprez kod MAS pokrenutog sistemskim autoimunskim bolestima [6]. Iako IL-6 ima svoju ulogu u nastanku i održavanju citokinske oluje, blokada njegovog receptora tocilizumabom, nije se pokazala kao dovoljno efikasna opcija u lečenju MAS [7].

Velika studija slučaj-kontrola u Bostonu na preko 2.000 odraslih pacijenata sa sistemskim eritemskim lupusom, pokazala je da upotreba hidroksihlorokina smanjuje šansu za razvojem MAS, najverovatnije zbog njegovog efekta na produkciju proinflammatoryh citokina koji učestvuju u patogenezi MAS. Takođe, pacijenti sa artritisa u sklopu sistemskog eritemskog lupusa su ređe imali klinički tok komplikovan sindromom ak-

in keeping with her clinical condition. The psychiatric symptoms did not recur.

Glucocorticoids should be administered with caution when MAS is suspected to have been triggered or sustained by infection or malignancy. In such situations, IVIG or anakinra are more appropriate because they enable immunomodulation without immunosuppression. They provide greater safety without interfering with subsequent investigation of the etiology of MAS [1,12].

In our patient, immunomodulatory doses of IVIG, together with methylprednisolone and cyclosporine A, resulted in only a transient favorable therapeutic effect. The rapid onset of action and short half-life of anakinra make it suitable for MAS triggered by systemic autoimmune diseases [7,13]. However, it was not available for rapid administration to our patient. Etoposide was also considered; however, in the context of the rapidly progressive picture of multiple organ dysfunction syndrome, it was concluded that its administration would worsen the existing severe cardiac insufficiency [14].

Cyclosporine A, owing to its effect on reducing the production of IL-1, IL-6, and TNF α , which play a key role in the pathogenesis of macrophage activation syndrome, has assumed an important place in the therapeutic algorithm. Although this was not the case in our patient, at a dose of 3 mg/kg body weight/day in combination with high-dose glucocorticoids and IVIG, it may lead not only to induction but also to maintenance of remission of systemic lupus erythematosus-induced macrophage activation syndrome [15].

Therapeutic plasma exchange (TPE) has been shown to be an effective add-on therapy in MAS (in addition to glucocorticoid and immunosuppressive therapy), resulting in a reduction in proinflammatory cytokines [16]. Although there are data indicating that TPE may also reduce mortality in patients with MAS, the outcome in our patient was unfavorable, probably owing to the already advanced stage of the disease, with consequent multiple organ dysfunction syndrome developing within one month of starting treatment.

According to a 2025 review of current therapeutic modalities for MAS in the pediatric population, high-dose glucocorticoids combined with IL-1 inhibitors (anakinra) and IFN γ inhibitors (emapalumab) are effective in the treatment of MAS associated with sJIA. Data on the potential therapeutic efficacy of this combination in other systemic autoimmune diseases, such as SLE, remain scarce [17].

Emapalumab, a humanized monoclonal antibody directed against IFN γ , has demonstrated high efficacy in inducing remission in children with recurrent and refractory primary HLH [18]. De Benedetti et al. demonstrated that emapalumab is also effective in

tivacije makrofaga [21]. Zbog fulminantnog toka SEL i MAS i rapidnog pogoršanja opšteg stanja naše pacijentkinje, hidroksihlorokin u kratkotrajnoj primeni nije mogao postići željeni klinički efekat.

Iako genetsko testiranje nije rutinski indikovano kod svih bolesnika sa sindromom aktivacije makrofaga u sklopu sistemskog eritemskog lupusa, treba ga razmotriti u selektovanim slučajevima, posebno kod pacijenata sa ranom pojavom bolesti, rekurentnim i/ili refraktornim MAS, pozitivnom porodičnom anamnezom ili funkcionalnim poremećajima citotoksičnosti NK i T ćelija. U ovim situacijama identifikacija genetske predispozicije može imati značajan uticaj na dijagnostiku, procenu prognoze i izbor terapije [1].

Pacijenti sa sumnjom ili već razvijenim MAS se, bez obzira na uzrok, moraju lečiti u jedinicama intenzivne nege uz kontinuirano praćenje vitalnih parametara i redovno praćenje laboratorijskih analiza. Bitno je što pre identifikovati osnovnu bolest, ali i doprinoseće faktore i lečiti ih paralelno. Individualizovan pristup pacijentu sa MAS omogućava bolje prevazilaženje izazova u kontekstu prepoznavanja osnovne bolesti, procene faktora rizika i odluke o terapiji. Formiranje multidisciplinarnog tima sačinjenog od lekara različitih specijalnosti, u zavisnosti od prezentacije i kliničkog toka bolesti, od presudnog je značaja za pravovremeno prepoznavanje i lečenje komplikacija sindroma aktivacije makrofaga [1].

ZAKLJUČAK

Preklapanje kliničkih i laboratorijskih manifestacija aktivnog sistemskog eritemskog lupusa, sindroma aktivacije makrofaga i teških infekcija značajno otežava pravovremeno postavljanje dijagnoze. Na MAS se mora misliti kod pacijenata sa aktivnim SEL i/ili znacima multiorganske disfunkcije. Praćenje specifičnih biomarkera je od presudnog značaja za pravovremeno postavljanje dijagnoze, pri čemu se koncentracije feritina > 10 000 µg/l smatraju visoko sugestivnim za MAS. Rano prepoznavanje ovog sindroma i primena adekvatne imunomodulatorne terapije su ključni za poboljšanje kliničkog ishoda i smanjenje mortaliteta ovih kompleksnih pacijenata.

Sukob interesa: Nije prijavljen.

patients with secondary MAS in whom high-dose glucocorticoids, either as monotherapy or concomitantly with anakinra and/or cyclosporine, failed to produce a satisfactory response [19]. Although this is a proven effective therapeutic modality, the unavailability of emapalumab in certain countries, including Serbia, is the reason why its use has not yet been initiated.

Ruxolitinib (a Janus kinase inhibitor, JAK1 and JAK2) has also demonstrated some efficacy in malignancies and MAS triggered by EBV infection in adults [1,20], but caution is still advised in MAS triggered by systemic autoimmune diseases [6]. Although IL-6 plays a role in the development and maintenance of the cytokine storm, blockade of its receptor with tocilizumab has not proven to be a sufficiently effective option for the treatment of MAS [7].

A large case-control study conducted in Boston involving more than 2,000 adult patients with systemic lupus erythematosus showed that hydroxychloroquine use reduced the likelihood of developing MAS, most likely because of its effect on the production of proinflammatory cytokines involved in the pathogenesis of MAS. In addition, patients with arthritis associated with systemic lupus erythematosus were less likely to have a clinical course complicated by macrophage activation syndrome [21]. Owing to the fulminant course of SLE and MAS and the rapid deterioration of our patient's general condition, short-term administration of hydroxychloroquine could not achieve the desired clinical effect.

Although genetic testing is not routinely indicated in all patients with macrophage activation syndrome associated with systemic lupus erythematosus, it should be considered in selected cases, particularly in patients with early disease onset, recurrent and/or refractory MAS, a positive family history, or functional abnormalities of NK and T-cell cytotoxicity. In these situations, identification of a genetic predisposition may have a significant impact on diagnosis, prognostic assessment, and treatment selection [1].

Patients with suspected or confirmed MAS, regardless of the underlying cause, must be treated in intensive care units with continuous monitoring of vital parameters and regular monitoring of laboratory analyses. It is important to identify the underlying disease as soon as possible, as well as the contributing factors, and to treat them concurrently. An individualized approach to patients with MAS facilitates better management of the challenges associated with identifying the underlying disease, assessing risk factors, and making treatment decisions. Establishing a multidisciplinary team comprising physicians from different specialties, depending on the presentation and clinical course

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- of the disease, is of crucial importance for the timely recognition and treatment of complications of macrophage activation syndrome [1].

CONCLUSION

The overlap of the clinical and laboratory manifestations of active systemic lupus erythematosus, macrophage activation syndrome, and severe infections significantly complicates timely diagnosis. MAS should be considered in patients with active SLE and/or signs of multiple organ dysfunction. Monitoring specific biomarkers is of crucial importance for timely diagnosis, with ferritin concentrations >10,000 µg/l considered highly suggestive of MAS. Early recognition of this syndrome and the administration of appropriate immunomodulatory therapy are essential for improving clinical outcomes and reducing mortality in these complex patients.

Conflict of interest: None declared

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