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CASE REPORT PRIKAZ BOLESNIKA

IBUPROFEN – INDUCED TOXIC EPIDERMAL NECROLYSIS – A CASE REPORT

TOKSIČNA EPIDERMALNA NEKROLIZA INDUCIRANA IBUPROFENOM – PRIKAZ BOLESNIKA

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Abstract

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe, life-threatening mucocutaneous hypersensitivity reactions. The inflammatory response is mediated by cytotoxic T lymphocytes and NK (natural killer) cells with cytotoxic proteins and cytokines as mediators in the onset of cell apoptosis. Drugs are responsible for about 95% of cases of toxic epidermal necrolysis. Although non-steroidal anti-inflammatory drugs (NSAID) are classified as drugs that can potentially lead to this hypersensitivity reaction, a small number of cases have been described in the literature regarding the occurrence of this reaction to the use of ibuprofen. We present the case of a 58-year-old man who developed symptoms of TEN seven days after using ibuprofen. The treatment of toxic epidermal necrolysis is still a matter of debate. Given that there is no uniform protocol for treatment, and the lethal outcome in such conditions occurs in about 40% of cases, each presented case is significant in terms of considering the effectiveness and improvement of the therapeutic approach.

Key words: toxic epidermal necrolysis, Stevens-Johnson syndrome, ibuprofen, sepsis

Sažetak

Stevens-Johnsonov sindrom (SJS) i toksična epidermalna nekroliza (TEN) teške su, po život opasne, mukokutane reakcije preosjetljivosti. Inflamatorni odgovor je posredovanom citotoksičnim T-limfocitima i NK (engl. *natural killer*) stanicama uz citotksične proteine i citokine kao posrednike u nastanku stanične apoptoze. Lijekovi su odgovorni za oko 95% slučajeva toksične epidermalne nekrolize. Iako se nesteroidni protuupalni lijekovi (NSAIL) svrstavaju u lijekove koji potencijalno mogu dovesti do ove reakcije preosjetljivosti, u literaturi je opisan mali broj slučajeva u vezi s nastankom ove reakcije na primjenu ibuprofena. Prezentiramo slučaj 58-godišnjeg muškarca kojemu su se simptomi TEN-a pojavili sedam dana nakon početka primjene ibuprofena. Tretman toksične epidermalne nekrolize i dalje je predmetom rasprava. Budući da ne postoji jedinstven stav i protokol za liječenje, a letalni ishod u ovakvim se stanjima događa u do 40% slučajeva, svaki je prezentirani slučaj značajan u pogledu razmatranja učinkovitosti i poboljšanja terapijskog pristupa.

Ključne riječi: toksična epidermalna nekroliza, Stevens-Johnsonov sindrom, ibuprofen, sepsa

INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe, life-threatening, mucocutaneous hypersensitivity reactions in which keratinocyte destruction occurs. (1) It is caused by a type IVc immune reaction and an inflammatory response mediated by cytotoxic T lymphocytes, especially drug-

UVOD

Stevens-Johnsonov sindrom (SJS) i toksična epidermalna nekroliza (TEN) teške su, po život opasne mukokutane reakcije preosjetljivosti u kojima dolazi do propadanja keratinocita. (1) U osnovi nastanka je imunološka reakcija tipa IVc i inflamatorni odgovor posredovanom citotoksičnim T-limfocitima, osobito

specific CD8+ T lymphocytes, and NK cells. (2) Although many theories have been developed over time about the pathophysiology of the process itself, where many cytotoxic proteins and cytokines have been considered responsible, including granulysin, Fas-Fas ligand interaction, tumor necrosis factor-α (TNF-α), apoptosis-inducing ligand (TRAIL) and perforin-granzyme B for the destruction of keratinocytes, the latest studies advocate ROS (reactive oxygen species) as an initiating factor in cell apoptosis. (3)

TEN is characterized by necrosis of keratinocytes and separation of the epidermis from the dermis. Macules on the skin appear suddenly, usually on the face, neck and upper torso. After that, they also appear on other parts of the body, they merge with each other, forming bullous changes that begin to peel off. (4)

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are clinically similar, and the diagnosis itself is declared depending on the degree of involvement of the body surface. In SJS, the changes affect <10%, and in TEN >30% of the body surface. When 15 – 30% of the body surface is affected, it is considered to be an overlap of SJS-TEN. (5)

Toxic epidermal necrolysis is most often associated with the use of sulfa drugs, antiepileptics, antibiotics, NSAIDs and some individual drugs such as allopurinol. (6,7) Also, triggers for the development of TEN can be infections such as infection with mycoplasma pneumoniae, herpesvirus 7 and vaccines (meningococcal vaccine). (8,9) The literature also describes a few cases of TEN as part of neoplastic processes such as hepatocellular carcinoma and lung carcinoma. (10)

Research has also shown a genetic predisposition for the development of SJS or TEN depending on the presence of a certain HLA locus, so meta analysis has proven the connection between the presence of the HLA-B*58 locus and the frequency of SJS and TEN in patients prescribed allopurinol. (11)

Symptoms usually begin one to three weeks after the start of drug administration in the form of weakness, elevated body temperature, headache, conjunctivitis. In severe clinical manifestations of TEN, large areas of epithelium peel off (Nikolski's sign), leaving erythematous and painful skin. (12) This is followed by the formation of erosions in the area of the oral mucosa and changes in the genitals, most often in the form of synechiae of the uterus in women. (13) The bronchial epithelium can also become desquamated, causing coughing and a breeding ground for the development of a respiratory infection. In the final stage of the disease, glomerulonephritis and hepatitis may occur. (14)

Given that there is no single protocol for its treatment, and the lethal outcome in such conditions occurs in about 40% of cases, each presented case is significant in terms of considering the effectiveness and improvement of the therapeutic approach.

CD8+ T-limfocita specifičnih za lijek, te NK stanicama. (2) Iako su se s vremenom razvijale mnoge teorije o samoj patofiziologiji procesa gdje su se različiti citotoksični proteini i citokini smatrali odgovornim, uključujući granulizin, Fas-Fas interakciju liganda, faktor nekroze tumora-α (TNF-α), ligand koji inducira apoptozu (TRAIL) i perforin-granzim B za propadanje keratinocita, najnovije studije zagovaraju ROS (engl. *reactive oxygen species*) kao inicirajući faktor u staničnoj apoptozi. (3)

TEN je karakteriziran nekrozom keratinocita te odvajanjem epidermisa od dermisa. Makule na području kože pojavljuju se naglo, obično na licu, vratu i gornjem dijelu trupa. Nakon toga se pojavljuju i na ostalim dijelovima tijela, međusobno se stapaju formirajući bulozne promjene koje se počinju ljuštiti. (4)

Stevens-Johnsonov sindrom (SJS) i toksična epidermalna nekroliza (TEN) klinički su slični, a sama dijagnoza se proglašava u ovisnosti od stupnja zahvaćanja tjelesne površine. Kod SJS-a promjene zahvaćaju <10%, a kod TEN-a >30% površine tijela. Kada je zahvaćeno 15–30% površine tijela smatra se da se radi o preklapanju SJS–TEN. (5)

Toksična epidermalna nekroliza najčešće se veže uz primjenu sulfapreparata, antiepileptika, antibiotika, nesteroidnih protuupalnih lijekova (skr. NSAIL) i nekih pojedinačnih lijekova poput alopurinola. (6,7) Uz navedene lijekove okidači za razvoj TEN-a mogu biti i infekcije, kao npr. infekcija *mycoplasmom pneumoniae*, herpesvirusom 7, te cjepiva (cjepivo protiv meningokoka). (8,9) U literaturi je također opisano nekoliko slučajeva TEN-a u sklopu neoplastičnih procesa, kao npr. kod hepatocelularnog karcinoma i karcinoma pluća. (10)

Istraživanjima je pokazana i genetska predispozicija za razvoj SJS-a ili TEN-a u ovisnosti od prisutnosti određenog HLA lokusa, pa je tako metaanalizom dokazana povezanost prisutnosti HLA B*58 lokusa s učestalom pojavom SJS-a i TEN-a kod pacijenata kojima je ordiniran alopurinol. (11)

Simptomi obično počinju jedan do tri tjedna nakon početka primjene lijeka u smislu slabosti, povišene tjelesne temperature, glavobolje, konjuktivitisa. U teškim kliničkim slikama TEN-a dolazi do ljuštenja velikih površina epitela (Nikolski znak), ostavljajući eritematoznu i bolnu kožu. (12) To prati stvaranje erozija u području oralne sluznice i promjene na genitalijama najčešće u smislu sinehija maternice kod žena. (13) Bronhalni se epitel također može ljuštiti, izazivajući kašalj i podlogu za razvoj respiratorne infekcije. U krajnjoj fazi bolesti može doći do pojave glomerulonefritisa i hepatitisa. (14)

PRIKAZ BOLESNIKA

Muškarac star 58 godina hospitaliziran je na odjelu reumatologije nakon prethodnog pregleda dermatovenerologa, gdje se postavi radna dijagnoza SJS-a i

CASE PRESENTATION

The patient, a 58-year-old male, was hospitalized in the rheumatology department, after a previous examination by a dermatovenerologist, where a working diagnosis of SJS was made and further development of toxic epidermal necrolysis (TEN) was suspected due to the progression of the changes.

On admission, the patient had extensive skin changes in the area of the face, neck, torso, upper and lower extremities in the form of a maculopapular rash with formed bullae (in the area of the head, back, abdomen and hands), as well as ulcerations in the area of the oral cavity, and hyperemia of both conjunctivae. On examination, the patient is hemodynamically stable, afebrile, cardiopulmonary compensated.

The anamnestic patient states that the changes started to appear five days earlier, accompanied by mild fever and malaise. The patient, a house painter by profession, states that he always works with the same paints and varnishes and that he was not exposed to any new chemical agent. He denies previous chronic diseases, and does not use any medical therapy. Occasionally, due to headaches, he used to take a medicine that was a combination (paracetamol, propyphenazone, caffeine and codeine phosphate sesquihydrate). He has not used the same medicine in the last month. He also denies that the skin changes were preceded by any infection.

In the laboratory tests, we found normal values of leukocytes, erythrocytes and platelets, slightly elevated values of fibrinogen 3.9 g/L (ref. 1.8–3.5 g/L) and D dimer 1.16 mg/L FEU (ref. 0–0.55 mg/L FEU) and elevated values of creatine kinase 580 U/L (ref. 0–208 U/L), lactate dehydrogenase 363 U/L (ref. 123–243 U/L). All other findings were within physiological limits.

The patient is isolated, in consultation with a dermatovenerologis therapy is prescribed: moderately high doses of methylprednisolone, low molecular weight heparin, antibiotic (myocamycin), saline solutions, local antiseptics and corticosteroids, and sterile dressing of open wounds. Due to developed conjunctivitis, the ophthalmologist included corticosteroid and antibiotic eye drops and artificial tears. On the third day of hospitalization, we get information from heteroanamnesis that seven days before the onset of the first symptoms, the patient took ibuprofen for a couple of days due to a headache. The patient has not used this drug before.

In the following days, the patient's general condition is stable, laboratory findings without significant deviations compared to the admission, with the still present massive peeling of the skin. In view of the results of the received skin swab, which came back positive for Staphylococcus aureus, with the consultation of an infectious disease specialist, the previously included antibiotic therapy is modified.

On the eighth day of hospitalization, the patient's general condition suddenly worsens with the appearposumnja na daljnji razvoj toksične epidermalne nekrolize (TEN) s obzirom na progresiju promjena.

Na prijemu su kod bolesnika u području lica, vrata, trupa, gornjih i donjih ekstremiteta bile prisutne opsežne kožne promjene u vidu makulopapuloznog osipa s formiranim bulama (u području glave, leđa, abdomena i šaka) te ulceracijama u području usne šupljine i hiperemijom obiju konjuktiva. Na pregledu bolesnik je bio hemodinamski stabilan, afebrilan, kardiopulmonalno kompenziran.

Anamnestički, bolesnik navodi da su se promjene počele pojavljivati pet dana ranije, praćene blago povišenom tjelesnom temperaturom i osjećajem malaksalosti. Bolesnik, po zanimanju soboslikar, navodi da uvijek radi s istom vrstom boja i lakova te da nije bio izložen nekom novom kemijskom agensu. Negira ranije kronične bolesti te ne koristi nikakvu medikamentoznu terapiju. Povremeno je zbog glavobolja ranije uzimao lijek koji je kombinacija paracetamola, propifenazona, kofeina i kodeinfosfat seskvihidrata). Isti lijek nije koristio posljednjih mjesec dana. Također anamnestički negira da je kožnim promjenama prethodila bilo kakva infekcija.

U laboratorijskim nalazima kod prijama nađene su uredne vrijednosti leukocita, eritrocita i trombocita, blago povišene vrijednosti fibrinogena 3,9 g/L (ref. 1,8–3,5 g/L) i D-dimera 1,16 mg/L FEU (ref. 0–0,55 mg/L FEU) te povišene vrijednosti kreatin kinaze 580 U/L (ref. 0–208 U/L), laktat dehidrogenaze 363 U/L (ref. 123–243 U/L). Vrijednost C-reaktivnog proteina (CRP) 12,4 mg/L (ref. 0–5,0 mg/L). Svi ostali učinjeni nalazi bili su u fiziološkim granicama.

Bolesnik je smješten u izolaciju, u konzultaciji s dermatovenerologom ordinira se terapija: umjereno visoke doze metilprednizolona, niskomolekularni heparin, antibiotik (miokamicin), fiziološka otopina, lokalno antiseptici i glukokortikoidi te sterilno previjanje otvorenih rana. Zbog razvijenog konjuktivitisa od strane oftalmologa uključene gukokortikoidne i antibiotske kapi za oči te umjetne suze.

Trećeg dana hospitalizacije heteroanamnestički su dobiveni podatci da je bolesnik sedam dana prije pojave prvih simptoma zbog glavobolje nekoliko dana uzimao ibuprofen. Bolesnik nije ranije koristio taj lijek.

Bolesnik je sljedećih dana bio stabilnoga općeg stanja, laboratorijski nalazi su bili bez značajnijih odstupanja u odnosu na prijam, uz i dalje prisutno masivno ljuštenje kože. S obzirom na pristigli nalaz brisa kože koji je bio pozitivan na *Staphylococcus aureus*, uz konzultaciju infektologa modificira se ranije uključena antibiotska terapija.

Osmog dana hospitalizacije kod bolesnika dolazi do iznenadnog pogoršanja općeg stanja s pojavom povišene tjelesne temperature, padom krvnog tlaka i padom saturacije kisika. Učinjene su urgentno laboratorijske pretrage, a nalazi su pokazali leukopeniju

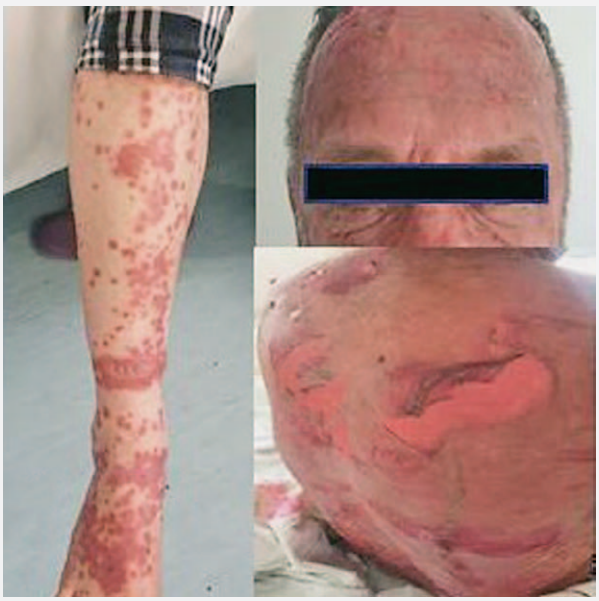

FIGURE 1 Skin lesions on the first day of hospitalization (Nikolsky sign)
SLIKA 1. Kožne lezije prvog dana hospitalizacije (Nikolski znak)

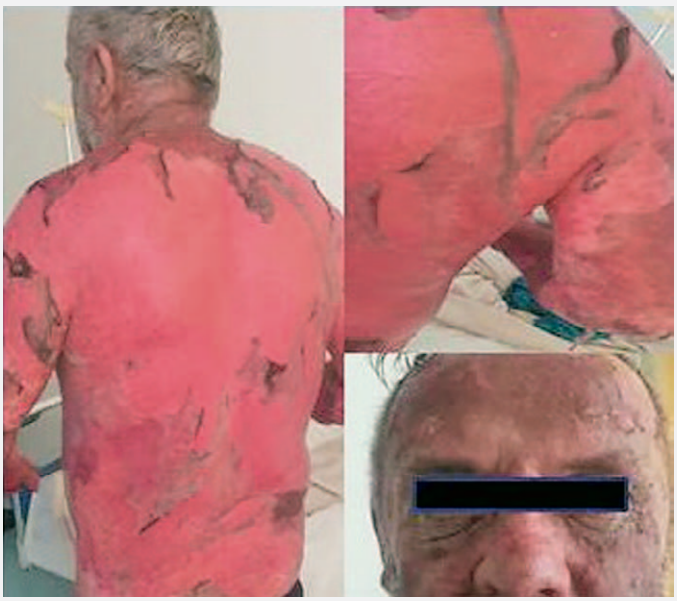

FIGURE 2 Progression of skin lesions on the fourth day of hospitalization
SLIKA 2. Progresija kožnih lezija četvrtog dana hospitalizacije

ance of elevated body temperature, a drop in blood pressure, and a drop in oxygen saturation. Urgent laboratory findings are performed, which show leukopenia 1.49 x 109/L, and an increase in CRP to 246 mg/L (ref. 0–5.0 mg/L). The patient is put on inotropic drugs, oxygen support through a mask with a tank 15L/min, bicarbonates are administered, physiological solutions are administered continuously. As the patient's condition worsens further, under the clinical picture of developed septic shock, the patient is intubated, and transported to the Department of Anesthesia and Reanimation, where he dies within a few hours.

DISCUSSION

Ibuprofen (abbreviated from the older nomenclature: iso-butyl-propane-phenolic acid) is a drug that belongs to the group of non-steroidal anti-inflammatory drugs. It works by inhibiting cyclooxygenase (COX), thus inhibiting the synthesis of prostaglandins. There are at least two variants of cyclooxygenase: COX-1 and COX-2. Ibuprofen inhibits both of these variants. It is believed that its analgesic, antipyretic and anti-inflammatory properties and action come precisely from the inhibition of COX-2. It is a relatively safe drug and in most countries in doses of 200 mg and 400 mg can be bought without a doctor's prescription, which makes it an easily accessible choice for pain management by the population. Its side effects are most often related to its effect on the mucous membrane of the digestive tract, and through its effect on the liver and kidneys. (15)

1,49 x 109/L i porast CRP-a na 246 mg/L (ref. 0–5,0 mg/L). Bolesnik je dobio inotropne lijekove, kisik preko maske s protokom 15 L/min, ordiniraju se bikarbonati te kontinuirano fiziološka otopina. S obzirom na to da dolazi do daljnjeg pogoršanja stanja bolesnika, bolesnik je intubiran i pod slikom razvijenoga septičkog šoka transportiran na Odjel za anesteziju i reanimaciju, gdje nakon nekoliko sati nastupa letalni ishod.

RASPRAVA

Ibuprofen (skraćeno iz starije nomenklature: izobutil-propan-fenolska kiselina) je lijek koji spada u skupinu nesteroidnih protuupalnih lijekova. Djeluje putem inhibicije ciklooksigenaze (COX) tako da inhibira sintezu prostaglandina. Postoje najmanje dvije varijante ciklooksigenaze: COX-1 i COX-2. Ibuprofen inhibira obje ove varijante. Vjeruje se da njegova analgetička, antipiretička i protuupalna svojstva i djelovanje dolaze prvenstveno zbog inhibicije COX-2. Relativno je siguran lijek te se u većini zemalja u dozama od 200 mg i 400 mg može kupiti bez liječničkog recepta, što ga čini lako dostupnim izborom u kupiranju boli. Njegove nuspojave najčešće se povezuju s djelovanjem na sluznicu probavnog trakta te kroz njegov učinak na jetru i bubrege. (15)

Od teških po život opasnih reakcija na ibuprofen opisani su slučajevi razvoja DRESS-a (engl. *Drug Reaction with Eosinophilia and Systemic Symptoms*). (16)

Kada je riječ o razvoju SJS-a i TEN-a iz grupe nesteroidnih protuupalnih lijekova, oksikami (melo-

Of the serious, life-threatening reactions to the drug, cases of the development of DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) have been described following the use of ibuprofen. (16)

When it comes to the development of SJS and TEN from the group of non-steroidal anti-inflammatory drugs, oxicams (meloxicam and piroxicam) are the drugs with the highest number of cases of developing these reactions. (17)

Recently, the HLA loci HLA-A*02:06 and HLA-B*44:03 were discovered, the presence of which is closely related to the predisposition to the appearance of severe manifestations of SJS and TEN in patients who used nonsteroidal anti-inflammatory drugs. (18)

In the available literature, we found two cases of TEN caused by the use of ibuprofen for comparison. The case of a then twenty-two-year-old man in Nepal, in whom the clinical picture began to develop on the third day after the administration of ibuprofen. As in the case of our patient, the maculopapular rash first appeared in the area of the chest, face and upper extremities with oral ulcerations and elevated body temperature. In the case of the patient, the treatment protocol was similar to the one we applied in the case of our patient, with the addition of plasmapheresis. The patient in this case fully recovered after five weeks. (19) The second case is that of a then twenty-one-year-old woman from Serbia, whose symptoms appeared after using ibuprofen for a headache. In this case too, the clinical picture included a maculopapular rash with the formation of bullae predominantly in the upper parts of the body. In addition to all supportive therapy, apheresis was also applied to the patient. The patient recovered after one month. (20)

In our case, the patient was admitted to the department with already advanced skin lesions and Nikolski's sign, where larger areas of the scalp, front and back of the chest were eroded and a potential site for the entry of microorganisms. Despite the prescribed therapy, only on the fourth day of hospitalization did the process of forming new bullous changes and further peeling of the skin stop, but by then the upper half of the body's skin was completely eroded. The patient did not develop a fever during hospitalization, and hypothermia was verified on the last day. Laboratory findings, except for CK and LDH, which were constantly increasing, were maintained at the same values as in the admission laboratory. On the eighth day of hospitalization, when the patient's general condition worsened, leukopenia and a high increase in CRP were verified. The patient did not require oxygen support until the development of acute respiratory failure on the eighth day.

In the past two years, four patients were treated at the rheumatology department of the University Clinical Center in Sarajevo, three with a diagnosis of TEN, one with a diagnosis of SJS. Three patients recovered successfully, and one had a fatal outcome.

ksikam i piroksikam) su lijekovi kod čije je primjene zabilježeno najviše slučajeva razvoja ovih reakcija. (17)

U novije vrijeme otkriveni su HLA lokusi HLA-A *02:06 i HLA-B*44:03 čija se prisutnost dovodi u usku vezu s predispozicijom za pojavu teških manifestacija SJS-a i TEN-a u bolesnika koji su koristili nesteroidne protuupalne lijekove. (18)

U dostupnoj literaturi pronašli smo dva slučaja TEN-a na primjenu ibuprofena. U slučaju dvadesetdvogodišnjeg muškarca u Nepalu kod kojega se klinička slika počela razvijati trećeg dana nakon primjene ibuprofena, kao i u slučaju našeg bolesnika, makulopapulozni osip najprije se javio u području prsnog koša, lica i gornjih ekstremiteta uz oralne ulceracije i povišenu tjelesnu temperaturu. Kod bolesnika je protokol liječenja bio sličan onome koji smo mi primijenili u slučaju našeg bolesnika, uz dodatno primijenjenu plazmaferezu. Bolesnik se u ovom slučaju u potpunosti oporavio nakon pet tjedana. (19) Drugi slučaj je onaj dvadesetjednogodišnje žene iz Srbije kod koje su se simptomi javili nakon primjene ibuprofena zbog glavobolje. I u ovom slučaju klinička slika je uključivala makulopapulozni osip uz formiranje bula predominantno u gornjim dijelovima tijela. Kod bolesnice je uz svu potpornu terapiju primijenjena i afereza. Bolesnica se oporavila nakon jednog mjeseca. (20)

U našem slučaju bolesnik je primljen na odjel s već uznapredovalim kožnim lezijama i Nikolskim znakom, gdje su veće površine kože glave, prednje i stražnje strane prsnog koša bile erodirane i potencijalno mjesto za ulazak mikroorganizama. Usprkos ordiniranoj terapiji tek četvrtog dana hospitalizacije uspjelo se zaustaviti proces formiranja novih buloznih promjena i daljnje ljuštenje kože, ali tada je već gornja polovica kože tijela u potpunosti bila erodirana. Bolesnik tijekom hospitalizacije nije bio febrilan, a posljednjeg dana je verificirana hipotermija. Laboratorijski nalazi, s izuzetkom CK i LDH koji su bili u konstantnom porastu, održavali su se u vrijednostima kao kod laboratorijskih nalaza kod prijama. Osmog dana hospitalizacije, kada je došlo do pogoršanja općeg stanja, u bolesnika je verificirana leukopenija i visoki porast CRP-a. Bolesnik nije zahtijevao potporu terapije kisikom sve do razvoja akutne respiratorne insuficijencije osmog dana.

Na Odjelu reumatologije Kliničkog centra Univerziteta u Sarajevu u protekle dvije godine tretirana su četiri bolesnika, tri s dijagnozom TEN-a, jedan s dijagnozom SJS-a. Tri bolesnika uspješno su se oporavila, a jedan je završio letalnim ishodom.

Kod svih bolesnika simptomi su počeli visokom temperaturom i makulopapuloznim osipom koji je kasnije progredirao u bulozne promjene. Tri bolesnika koja su preživjela primljena su na odjel u fazi makulopapuloznog osipa, dok još nije započelo formiranje bula ili su one bile ograničene na maloj površini

In all patients, the symptoms started in the form of a high temperature and a maculopapular rash that later progressed to bullous changes. The three patients who survived were admitted to the department in the stage of maculopapular rash before the formation of bullae had started, or they were limited to a small area of the body, in contrast to the patient who ended fatally, in whom the skin lesions were already advanced. Based on our experience, early recognition of symptoms, timely application of therapy and timely stopping of the process play a key role.

The treatment consists in isolating the patient in intensive care units, in order to reduce the risk of secondary infections, replenishing fluids, electrolytes, proteins, taking care of open wounds, and relieving pain. Regarding drugs, several approaches are mentioned in the literature in terms of administration of corticosteroids in moderate to high doses, administration of immunoglobulins, immunosuppressive drugs such as cyclosporins, Tumor necrosis alpha inhibitors. (21,22,23) In the literature, plasmapheresis is also mentioned as a treatment option. (24)

The treatment of toxic epidermal necrolysis in the world is still the subject of debates and conflicting opinions, and it is considered that no protocol has shown significant effectiveness, and the treatment is left to the choice of the assigned physician.

All patients who were admitted with a diagnosis of SJS or TNE in the past two years in our department were treated with moderately high doses of corticosteroids 80–100 mg methylprednisolone once a day for 7–10 days, broad-spectrum antibiotics, low molecular weight heparin 1mg/kg twice a day, albumin replacement according to the proteinogram, continuous infusion solutions, local antiseptics and corticosteroids. In the cases of our patients, the administration of immunoglobulin in the early development of the process also proved to be beneficial. Immunoglobulins were used in three patients. We did not use cytostatics, biological drugs or plasmapheresis.

The fatal outcome in such conditions in the world occurs in up to 40% of cases. In 2018, doctors from the Clinical Center of São João, Porto, Portugal published a retrospective study of 21 cases of TEN recorded in twelve years, and 15 patients (71.4%) ended with a fatal outcome. The most common complication and cause of death in these patients was sepsis, in 53% of cases. The highest mortality rate was among those patients who required mechanical ventilation (91%). (25)

CONCLUSION

Although in the literature, TEN is most often associated with the use of sulfa drugs, antiepileptics, antibiotics and some individual drugs such as allopurinol, one should definitely be careful when using non-steroidal anti-inflammatory drugs, given their frequent use in medical practice. Early recognition of symptoms, timely application of therapy and timely stopping of the process

tijela, za razliku od bolesnika koji je završio letalno u kojega su lezije na koži već uznapredovale. Na osnovi našeg iskustva rano prepoznavanje simptoma, blagovremena aplikacija terapije i pravovremeno zaustavljanje procesa igraju ključnu ulogu.

Liječenje SJS-a i TEN-a sastoji se u izolaciji bolesnika u jedinicama intenzivne njege kako bi se smanjio rizik nastanka sekundarnih infekcija, nadoknadi tekućine, elektrolita, proteina, zbrinjavanju otvorenih rana, kupiranju boli. Od lijekova u literaturi se spominje više pristupa u smislu davanja glukokortikoida u umjerenim do visokim dozama, primjene imunoglobulina, imunosupresivnih lijekova kao što su ciklosporini, inhibitori čimbenika nekroze tumora -alfa (TNF-alfa). (21,22,23) U literaturi se kao opcija liječenja spominje i plazmafereza. (24)

Tretman toksične epidermalne nekrolize u svijetu je i dalje predmet rasprava i oprečnih stavova. Kako nijedan protokol nije pokazao značajnu učinkovitost u odnosu na neki drugi, izbor liječenja je ostavljen na izbor nadležnom ordinarijusu.

Svi bolesnici koji su primljeni pod dijagnozom SJS-a ili TEN-a u protekle dvije godine na našem odjelu su liječeni umjereno visokim dozama glukokortikoida 80–100 mg metil-prednizolona jedanput dnevno 7–10 dana, širokospektralnim antibiotikom, niskomolekularnim heparinom 1mg/kg dva puta dnevno, nadoknadom albumina prema proteinogramu, kontinuiranim infuzijskim otopinama, lokalnim antisepticima i glukokortikoidima. U slučajevima naših bolesnika davanje imunoglobulina u ranom razvoju procesa također se pokazalo korisnim. Imunoglobulini su primijenjeni kod tri bolesnika. Citostatike, biološke lijekove i plazmaferezu nismo primjenjivali.

Letalni ishod u ovakvim stanjima u svijetu događa se u do 40% slučajeva. Liječnici Kliničkog centra São João, Porto, Portugal objavili su 2018. godine retrospektivnu studiju o zabilježenom dvadeset i jednom slučaju TEN-a tijekom dvanaest godina i čak petnaest bolesnika (71,4%) završilo je letalnim ishodom. Najčešća komplikacija i uzrok smrti kod tih bolesnika bila je sepsa, u 53% slučajeva. Najveća stopa smrtnosti bila je među onim bolesnicima koji su zahtijevali mehaničku ventilaciju (91%). (25)

ZAKLJUČAK

Iako se u literaturi TEN najčešće vezuje uz primjenu sulfapreparata, antiepileptika, antibiotika i nekih pojedinačnih lijekova poput alopurinola, svakako je potrebno biti na oprezu i kod primjene nesteroidnih protuupalnih lijekova, s obzirom na njihovu čestu upotrebu u kliničkoj praksi. Rano prepoznavanje simptoma, blagovremena aplikacija terapije i pravovremeno zaustavljanje procesa igraju ključnu ulogu. Izolacija

play a key role. Isolation of the patient, treatment of open wounds is extremely important, in order to prevent the development of secondary infections, which are mostly responsible for the development of complications and fatal outcome in these patients. Liquid, electrolyte, protein replacement must be carried out continuously. Application of moderately high doses of corticosteroids. In the cases of our patients, the administration of immunoglobulin at an early stage proved to be beneficial.

bolesnika i zbrinjavanje otvorenih rana iznimno je važno kako bi se spriječio razvoj sekundarnih infekcija koje su najvećim dijelom odgovorne za razvoj komplikacija i letalni ishod kod ovih pacijenata. Nadoknada tekućine, elektrolita i proteina mora se provoditi kontinuirano, uz aplikaciju umjereno visokih doza glukokortikoida. U slučajevima naših bolesnika davanje imunoglobulina u ranoj fazi pokazalo se korisnim.

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REFERENCES / LITERATURA

1. Nassif A, Bensussan A, Dorothée G, Mami-Chouaib F, Bachot N, Bagot M et al. Drug specific cytotoxic T-cells in the skin lesions of a patient with toxic epidermal necrolysis. J Invest Dermatol. 2002;118(4):728–33.
2. Valeyrie-Allanore LL, Roujeau J. Chapter 40. Epidermal necrolysis (Stevens–Johnson syndrome and toxic epidermal necrolysis). In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K. eds. Fitzpatrick's dermatology in general medicine, 8th edition. McGraw Hill: New York; 2012. Available from ACCESS MEDICINE. [accessed: 2022 Jul 25].
3. Labib A, Milroy C. Toxic epidermal necrolysis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK574530/ [accessed: 2022 Jul 25]
4. Creamer D, Walsh SA, Dziewulski P, Exton LS, Lee HY, Dart JK et al. U.K. guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults 2016. Br J Dermatol. 2016;174(6):1194–227.
5. Hsu DY, Brieva J, Silverberg NB, Silverberg JI. Morbidity and mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis in United States adults. J Invest Dermatol. 2016;136(7):1387–97.
6. Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. J Invest Dermatol. 2008;128(1):35–44.
7. Pejčić AV. Stevens-Johnson syndrome and toxic epidermal necrolysis associated with the use of macrolide antibiotics: a review of published cases. Int J Dermatol. 2021;60(1):12–24.
8. Shen MH, Liu MT, Chung WH, Lu CW. Toxic epidermal necrolysis induced by human herpesvirus 7 treated with a tumor necrosis factor-α inhibitor. J Dermatol. 2020; 47(10):1179–81.
9. Chahal D, Aleshin M, Turegano M, Chiu M, Worswick S. Vaccine-induced toxic epidermal necrolysis: A case and systematic review. Dermatol Online J. 2018;24.
10. Wu J, Lee YY, Su SC, Wu TS, Kao KC, Huang CC et al. Stevens-Johnson syndrome and toxic epidermal necrolysis in patients with malignancies. Br J Dermatol. 2015;173(5):1224–31.
11. Somkrua R, Eickman EE, Saokaew S, Lohitnavy M, Chaiyakunapruk N. Association of HLA-B*5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. BMC Med Genet. 2011;12:118.
12. Harris V, Jackson C, Cooper A. Review of toxic epidermal necrolysis. Int J Mol Sci. 2016;17(12):2135.
13. Gulanikar A, Abrol A, Sagar S. Study of genital manifestations of Stevens Johnson syndrome/toxic epidermal necrolysis. Indian J Sex Transm Dis AIDS. 2022;43(1):39–42.
14. Lee TH, Lee CC, Ng CY, Chang MY, Chang SW, Fan PC et al. The influence of acute kidney injury on the outcome of Stevens-Johnson syndrome and toxic epidermal necrolysis: The prognostic value of KDIGO staging. PLoS One. 2018;13(9):e0203642.
15. Rainsford KD. Ibuprofen: pharmacology, efficacy and safety. Inflammopharmacology. 2009;17(6):275–342.
16. Nanau RM, Neuman MG. Ibuprofen-induced hypersensitivity syndrome. Transl Res. 2010;155(6):275–93.
17. Mockenhaupt M, Kelly JP, Kaufman D, Stern RS; SCAR Study Group. The risk of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with nonsteroidal antiinflammatory drugs: a multinational perspective. J Rheumatol. 2003;30(10):2234–40.
18. Ueta M, Kaniwa N, Sotozono C, Tokunaga K, Saito Y, Sawai H et al. Independent strong association of HLA-A*02:06 and HLA-B*44:03 with cold medicine-related Stevens-Johnson syndrome with severe mucosal involvement. Sci Rep. 2014;4:4862.
19. Angadi S, Karn A. Ibuprofen induced Stevens-Johnson syndrome – toxic epidermal necrolysis in Nepal. Asia Pac Allergy. 2016 Jan;6(1):70–3.
20. Balint B, Stepic N, Todorovic M, Zolotarevski L, Ostojic G, Vucetic D et al. Ibuprofen-induced extensive toxic epidermal necrolysis – A multidisciplinary therapeutic approach in a single case. Blood Transfus. 2014;12(3):438–9.
21. Kohanim S, Palioura S, Saeed HN, Akpek EK, Amescua G, Basu S et al. Stevens-Johnson syndrome/toxic epidermal necrolysis – a comprehensive review and guide to therapy. I. Systemic Disease. Ocul Surf. 2016;14(1):2–19.
22. Ye LP, Zhang C, Zhu QX. The effect of intravenous immunoglobulin combined with corticosteroid on the progression of Stevens-Johnson syndrome and toxic epidermal necrolysis: a meta-analysis. PLoS One. 2016;11(11):e0167120.
23. Woolridge KF, Boler PL, Lee BD. Tumor necrosis factor alpha inhibitors in the treatment of toxic epidermal necrolysis. Cutis. 2018;101(1):E15–21.
24. Chaidemenos GC, Chrysomallis F, Sombolos K, Mourellou O, Ioannides D, Papakonstantinou M. Plasmapheresis in toxic epidermal necrolysis. Int J Dermatol. 1997;36(3):218–21.
25. Barreiro D, Monteiro D, Isabel O, Silva A. Twelve years of Lyell's syndrome in the burn unit of São João Hospital Centre. Ann Burns Fire Disasters. 2018;31:259–65.