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DRESS (DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS) SINDROM UZROKOVAN AMOKSICILINOM – PRIKAZ SLUČAJA

AMOXICILLIN INDUCED DRESS (DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS) SYNDROME – CASE REPORT

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Sažetak

Uvod. *Drug Reaction with Eosinophilia and Systemic Symptoms sindrom je retka, ali potencijalno životnougrožavajuća reakcija na lek. Karakteriše je odloženi početak, kožne promene, hematološke abnormalnosti kao i zahvatanje unutrašnjih organa, posebno jetre. Drug Reaction with Eosinophilia and Systemic Symptoms sindrom je najčešće povezan sa primenom antiepileptičkih lekova i alopurinola, iako su i beta-laktamski antibiotici, poput amoksicilina, takođe identifikovani kao uzročni agensi. Varijabilnost kliničke slike i preklapanje sa drugim sistemskim oboljenjima otežavaju dijagnozu, pri čemu se postavljanje dijagnoze često zasniva na kriterijumima poput RegiSCAR i J-SCAR sistema bodovanja.* ***Prikaz slučaja****. Predstavljamo slučaj 53-godišnje žene sa multiplim mijelomom, koja je razvila generalizovani makulopapulozni egzantem i sistemske simptome nakon dvonedeljne terapije amoksicilinom, propisanog za infekciju gornjih disajnih puteva. Klinička slika uključivala je povišenu telesnu temperaturu, difuzni makulopapulozni osip koji je zahvatao više od 80% površine tela, blagi edem lica, kao i laboratorijski verifikovanu izraženu eozinofiliju i povišene enzime jetre. RegiSCAR skor bio je 6, što potvrđuje definitivnu dijagnozu Drug Reaction with Eosinophilia and Systemic Symptoms sindroma. Započeta je terapija sistemskim kortikosteroidima (1 mg/kg TT) tokom dve nedelje, uz dalje postepeno snižavanje doze, što je dovelo do potpunog povlačenja simptoma u roku od mesec dana. Dva meseca nakon povlačenja simptoma sprovedeno je epikutano (patch) testiranje, kojim je utvrđeno postojanje preosetljivosti na amoksicilin.* ***Zaključak.*** *Drug Reaction with Eosinophilia and Systemic Symptoms sindrom predstavlja ozbiljnu i potencijalno životnougrožavajuću hipersenzitivnu reakciju na lek, povezanu sa značajnim morbiditetom i procenjenom stopom smrtnosti koja iznosi približno 10%, prvenstveno zbog zahvatanja više unutrašnjih organa. Ovaj slučaj naglašava važnost pažljive procene indikacije za primenu antibiotika, kao i razmatranje amoksicilina kao potencijalnog uzročnog leka kod pacijenata sa Drug Reaction with Eosinophilia and Systemic Symptoms sindromom. Nadalje, ističemo značaj patch testiranja za identifikaciju uzročnog leka, čije je pravovremeno prepoznavanje ključno u prevenciji ponovne pojave ovog potencijalno životnougrožavajućeg oboljenja.*
Ključne reči: *sindrom preosetljivosti na lekove; amoksicilin; patch testovi; eozinofilija; lekovima izazvani osip; prognoza; egzantem; oštećenje jetre izazvano lekovima i hemikalijama; ishod lečenja*

Abstract

Introduction. Drug Reaction with Eosinophilia and Systemic Symptoms is a rare but potentially life-threatening drug-induced hypersensitivity reaction characterized by delayed onset, cutaneous eruptions, hematologic abnormalities, and internal organ involvement, most commonly affecting the liver. Although the condition is most frequently associated with antiepileptic medications and allopurinol, beta-lactam antibiotics such as amoxicillin have also been reported as causative agents. Due to its clinical variability and overlap with other systemic conditions, diagnosis remains challenging and is often supported by scoring systems such as RegiSCAR and J-SCAR. **Case Report.** We present a case of a 53-year-old

female patient with multiple myeloma who developed generalized maculopapular exanthema and systemic symptoms following a two week course of amoxicillin prescribed for an upper respiratory tract infection. Clinical presentation included fever, a diffuse rash involving more than 80% of body surface area, mild facial edema, and laboratory findings significant for marked eosinophilia and elevated liver enzymes. The RegiSCAR score was 6, confirming a definite diagnosis of Drug Reaction with Eosinophilia and Systemic Symptoms syndrome. Systemic corticosteroid therapy (1 mg/kg body weight) was initiated, resulting in complete symptom resolution within one month. Epicutaneous (patch) testing performed two months after clinical recovery confirmed amoxicillin as the culprit drug. No relapse was observed during the follow-up. **Conclusion.** Drug Reaction with Eosinophilia and Systemic Symptoms syndrome represents a severe hypersensitivity reaction associated with significant morbidity and an estimated mortality rate of approximately 10%, primarily due to multiorgan involvement. This case highlights the importance of careful antibiotic prescribing and the need to consider amoxicillin as a potential trigger of Drug Reaction with Eosinophilia and Systemic Symptoms syndrome. Furthermore, identification of the culprit drug through patch testing is essential for preventing recurrence and ensuring patient safety.
Key words: eosinophilia; amoxicillin; RegiSCAR; maculopapular rash; systemic corticosteroids

Uvod

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) sindrom je teška hipersenzitivna reakcija na lek, koja se karakteriše značajnim morbiditetom i mortalitetom, sa procenjenom učestalošću koja se kreće od 1 na 1.000 do 1 na 10.000 izloženosti lekovima [1,2].

DRESS sindrom obično počinje prodromalnim simptomima kao što su opšta malaksalost, svrab i groznica, pri čemu kožne manifestacije obično prethode groznici nekoliko dana i mogu perzistirati nedeljama [3].

Klinička slika obično se karakteriše simetričnim makulopapuloznim (morbiliformnim) egzantemom, groznicom, uvećanim limfnim čvorovima, zahvatanjem unutrašnjih organa i laboratorijskim poremećajima koji uključuju leukocitozu sa hipereozinofilijom [2,4]. Iako klinička slika može varirati i uključivati urtikarijalne ili makulopapulozne osipe, u nekim slučajevima može se manifestovati pojavom bula, pustula, vezikula, purpure, target-lezija, edema lica i eritrodermije [5].

Kod većine pacijenata reakcija se javlja dve do šest nedelja nakon početka terapije lekom, pri čemu je latentni period DRESS sindroma duži nego kod većine drugih lekom izazvanih erupcija. Međutim, kod pacijenata ponovo eksponiranih uzročnom leku, kao i kod onih sa hematološkim i jetrenim poremećajima, kliničke manifestacije se mogu razviti brže, u nekim slučajevima već 24 sata nakon izlaganja leku [3,4].

S obzirom na kompleksnost i heterogenost kliničke slike, preklapajuće karakteristike sa drugim oboljenjima, tokom poslednjih godina razvijeni su različiti kriterijumi koji pomažu lekarima pri postavljanju dijagnoze. Prvobitne dijagnostičke kriterijume predložili su Boke (Bocquet) i saradnici, ali su oni od tada zamenjeni kriterijumima Japanskog istraživačkog

Introduction

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a severe drug-induced hypersensitivity reaction associated with significant morbidity and mortality, with an estimated incidence ranging from 1 in 1,000 to 1 in 10,000 drug exposures [1,2].

DRESS syndrome typically begins with prodromal symptoms such as malaise, pruritus, and fever; cutaneous manifestations usually precede systemic symptoms by several days, while fever may persist for weeks [3]. The clinical presentation most commonly includes a symmetrical maculopapular (morbilliform) rash, fever, lymphadenopathy, internal organ involvement, and hematologic abnormalities such as leukocytosis with hypereosinophilia [2,4]. However, the clinical spectrum is heterogeneous and may also include urticarial or maculopapular eruptions, bullae, pustules, vesicles, purpura, target lesions, facial edema, and erythroderma [5].

In most patients, symptoms developed two to six weeks after initiation of the causative drug, reflecting a longer latency period compared with other drug-induced eruptions. Nevertheless, in case of re-exposure or in patients with underlying hematologic or hepatic dysfunction, clinical manifestations may occur more rapidly, occasionally within 24 hours [3,4].

Due to its clinical complexity, variable presentation, and overlap with other conditions, several diagnostic criteria have been developed to assist clinicians. The original criteria proposed by Bocquet et al. have largely been replaced by the Japanese Research Committee on Severe Cutaneous Adverse Reactions (J-SCAR) and the RegiSCAR scoring system established by the European

komiteta za teške kožne neželjene reakcije na lekove (J-SCAR) i RegiSCAR skorom koji je razvijen u Evropskom registru za teške kožne neželjene reakcije na lekove [2,3,6].

DRESS sindrom se najčešće povezuje sa antiepilepticima (fenitoin, karbamazepin, lamotrigin), alopurinolom i antibioticima kao što su sulfonamidi, cefalosporini i penicilini [7]. U preglednom radu iz 2020. godine, Šarifzadeh (Sharifzadeh) i saradnici navode da je od 250 prijavljenih slučajeva DRESS sindroma, 22 slučaja pripisano penicilinima, što čini 8,6% svih slučajeva uključenih u analizu [4].

Kroz ovaj prikaz slučaja nastojimo da povećamo svest o kliničkoj prezentaciji DRESS sindroma i istaknemo mogućnost da čak i lekovi nižeg rizika mogu izazvati ovu tešku reakciju.

Prikaz slučaja

Na Klinici za kožno-venerične bolesti u Novom Sadu 53-godišnja žena je hospitalizovana zbog generalizovanog makulopapuloznog egzantema praćenog povišenom temperaturom. Dve nedelje pre pojave osipa, pacijentkinja je imala povišenu telesnu temperaturu i nazalni sekret, zbog čega je pregledao njen izabrani lekar. Započeta je oralna terapija amoksicilinom, nakon čega se, dve nedelje kasnije, razvio makulopapulozni egzantem koji je prvobitno zahvatio donji deo trupa, a potom se proširio na celo telo. Pacijentkinju je potom pregledao i dermatovenerolog koji ju je uputio na hospitalizaciju.

Pacijentkinja od ranije boluje od multiplog mijeloma i leči se po VTD protokolu (bortezomib, talidomid i deksametazon). Prateća terapija uključivala je oralni aciklovir, alopurinol, bisoprolol i acetilsalicilnu kiselinu. Prilikom prijema na Kliniku, pacijentkinja je bila stabilnog opšteg stanja, kardiopulmonalno kompenzovana, sa arterijskim krvnim pritiskom TA 90/50 mmHg, febrilna T 38,2 °C. Abdomen je bio mek, u ravni grudnog koša, bez distenzije i palpabilne hepatosplenomegalije. Vidljive sluzokože bile su bez patoloških promena. Klinički značajna regionalna limfadenopatija nije uočena.

Pacijentkinja nije imala poznatu istoriju alergijskih ili hipersenzitivnih reakcija, uključujući i alergijske reakcije na lekove. Tokom kliničkog pregleda, pacijentkinja nije navodila simptome u vezi sa respiratornim, kardiovaskularnim, gastrointestinalnim, genitourinarnim ili drugim organskim sistemima.

Registry of Severe Cutaneous Adverse Reactions [2,3,6].

DRESS syndrome is most frequently associated with antiepileptic medications (phenytoin, carbamazepine, lamotrigine), allopurinol, and certain antibiotics, including sulfonamides, cephalosporins, and penicillins [7]. A 2020 review by Sharifzadeh et al. reported that 22 out of 250 documented DRESS cases were attributed to penicillins, representing 8.6% of cases included in the analysis [4].

Through this case report, we aim to increase awareness of the clinical presentation of DRESS syndrome and emphasize that even drugs traditionally considered to carry a lower risk may trigger this potentially life-threatening reaction.

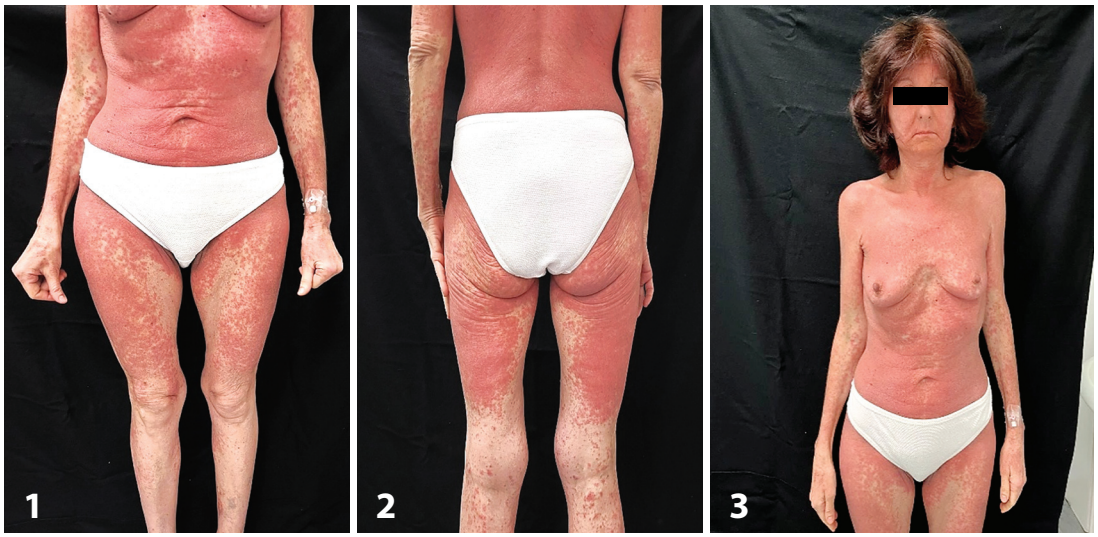
Case Report

A 53-year-old female patient was hospitalized at the Clinic of Dermatovenereology in Novi Sad due to a generalized maculopapular exanthema accompanied by fever. Two weeks prior to rash onset, the patient experienced febrile episodes and nasal discharge and was evaluated by her primary care physician. Oral amoxicillin therapy was initiated, after which she developed a maculopapular eruption that initially appeared on the lower trunk and subsequently spread to involve the entire body. She was evaluated by a dermatologist and referred for hospital admission.

Her medical history was significant for multiple myeloma diagnosed one year earlier, treated according to the VTD protocol (bortezomib, thalidomide, and dexamethasone). Concomitant medications included oral acyclovir, allopurinol, bisoprolol, and acetylsalicylic acid.

Upon admission, the patient was in stable general condition, cardiopulmonary compensated, with a blood pressure of 90/50 mmHg and a febrile temperature of 38.2 °C. The abdomen was soft and non-distended on palpation, with no hepatosplenomegaly. Visible mucous membranes showed no pathological changes. No clinically significant regional lymphadenopathy was observed.

The patient had no known history of allergic or hypersensitivity reactions, including medication allergies. During clinical evaluation, she reported no symptoms involving the



Slike 1, 2 i 3. *Makulopapulozni egzantem koji zahvata lice, trup, leđa, gornje i donje ekstremitete, posebno proksimalne delove*
Figures 1, 2 and 3. Maculopapular exanthema involving the face, trunk, back, and both upper and lower extremities, predominantly affecting proximal areas

Uočen je generalizovani makulopapulozni egzantem koji je zahvatao lice, trup, leđa, gornje i donje ekstremitete, posebno proksimalne delove, zahvatajući više od 80% ukupne površine tela **(Slike 1, 2 i 3)**.

Kožne promene su u manjoj meri zahvatale šake i obe potkolenice **(Slika 4)**. *Takođe je primećen blag edem lica sa zagasitim eritemom* **(Slika 5)**.

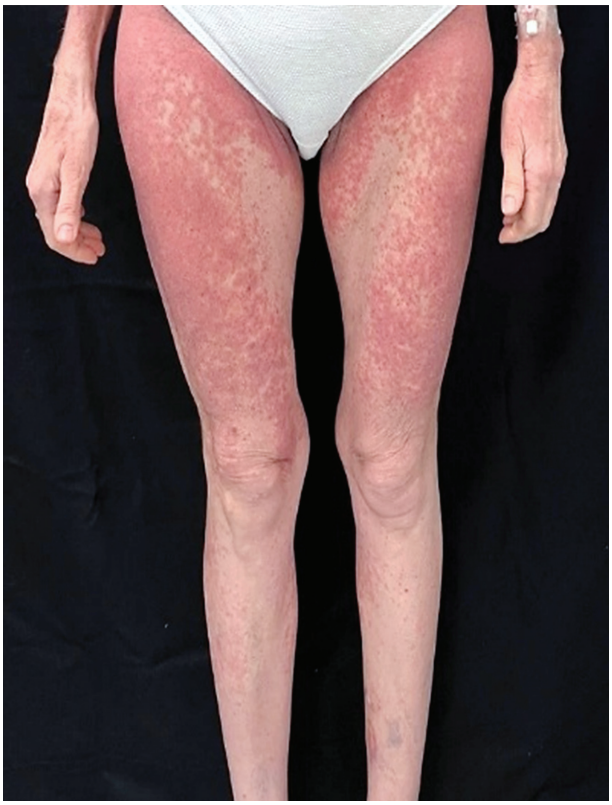
Laboratorijski nalazi ukazivali su na značajnu eozinofiliju (24,7%–1,99 × 10^9/L), četvorostruko povišene vrednosti alanin-aminotransferaze (ALT – 181 U/L), trostruko povišene vrednosti aspartat-aminotransferaze (AST – 90 U/L) i povišene vrednosti inflamatornih markera (CRP 11,7 mg/L; PCT 0,16 ng/mL).

Parametri hemostaze, vrednosti uree i kreatinina bili su u granicama referentnih vrednosti, dok su vrednosti magnezijuma i kalcijuma u serumu bile snižene.

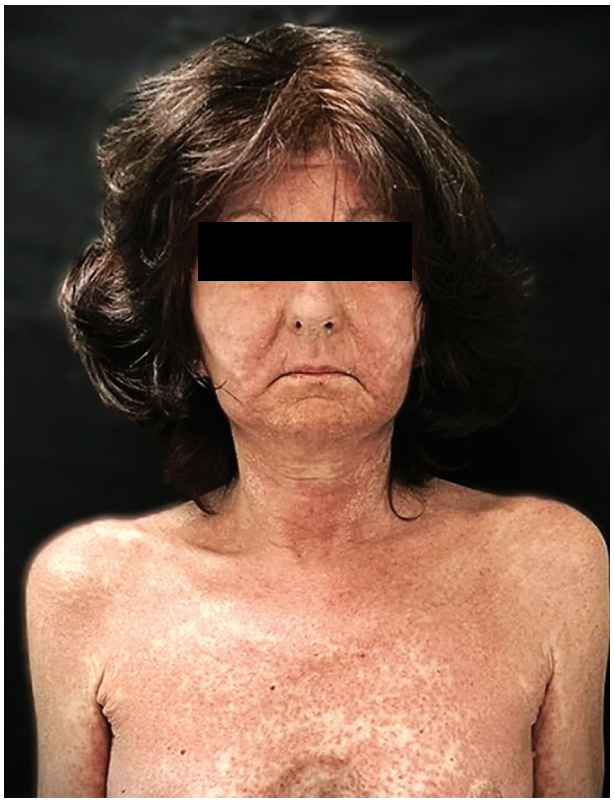
Serološki testovi na Epštajn–Barov virus (EBV), citomegalovirus (CMV), koksaki B virus, viruse influence A i B, herpes simpleks virus (HSV) tip 1 i 2, parvovirus B19 kao i hepatitise A, B i C bili su negativni.

Postavljena je dijagnoza DRESS sindroma (reakcija na lek sa eozinofilijom i sistemskim simptomima), sa RegiSCAR skorom 6.

Nakon prijema, započeta je parenteralna terapija sistemskim kortikosteroidima (1 mg/kg TT) u trajanju od dve nedelje, sa postepe-



Slika 4. *Kožne promene manjeg inteziteta prisutne na šakama i potkolenicama*
Figure 4. Lesions spared the hands and both lower legs to a minor degree



Slika 5. *Blag edem lica sa zagasitim eritemom*
Figure 5. Mild facial edema with dusky erythema

nim smanjenjem doze i prelaskom na oralnu terapiju kortikosteroidima.

Nakon mesec dana egzantem se povukao, a vrednosti jetrenih enzima, inflamatornih markera i broja eozinofila vratile su se u granice referentnih vrednosti.

Dva meseca nakon povlačenja kožnih promena sprovedeno je pač testiranje, kojim je potvrđena preosetljivost na amoksicilin. Tokom perioda praćenja nisu uočene kožne manifestacije niti dokazi o recidivu bolesti.

Diskusija

DRESS sindrom, takođe poznat i kao sindrom hipersenzitivnosti izazvan lekovima, retka je, ali potencijalno životnougrožavajuća neželjena reakcija na lek, koja se karakteriše odloženim početkom i zahvatanjem kože uz više unutrašnjih organa, najčešće jetre, bubrega, pluća i srca [8].

Aromatični antikonvulzivi (npr. karbamazepin, fenitoin, fenobarbital) i alopurinol predstavljaju najčešće lekove koji izazivaju DRESS

respiratory, cardiovascular, gastrointestinal, genitourinary, or other organ systems.

Dermatological examination revealed a generalized maculopapular exanthema involving the face, trunk, back, and both upper and lower extremities, predominantly affecting proximal areas and involving more than 80% of the total body surface area **(Figures 1–3)**.

The lesions spared the hands and both lower legs to a minor extent **(Figure 4)**. Mild facial edema with dusky erythema was also observed **(Figure 5)**.

Laboratory findings demonstrated marked eosinophilia (24.7%; 1.99 x 10^9/L), a fourfold elevation of alanine aminotransferase (ALT, 181 U/L), a threefold elevation of aspartate aminotransferase (AST, 90 U/L), and elevated inflammatory markers (CRP 11.7 mg/L; PCT 0.16 ng/mL). Hemostasis parameters, urea, and creatinine levels were within reference ranges, whereas serum magnesium and calcium levels were decreased.

Serological testing for Epstein–Barr virus (EBV), cytomegalovirus (CMV), Coxsackie B virus, influenza A and B viruses, herpes simplex virus (HSV) types 1 and 2, parvovirus B19, and hepatitis A, B, and C viruses was negative.

Based on clinical presentation and laboratory findings, a diagnosis of DRESS syndrome was established, with a RegiSCAR score of 6.

Following admission, systemic corticosteroid therapy was initiated parenterally at a dose of 1 mg/kg body weight for two weeks, followed by gradual tapering and transition to oral corticosteroid therapy.

After one month, the exanthema resolved, and liver enzymes, inflammatory markers, and eosinophil counts returned to within reference ranges.

Two months after resolution of cutaneous manifestations, epicutaneous (patch) testing was performed to identify the causative drug and confirmed hypersensitivity to amoxicillin. During follow-up, no recurrence of cutaneous manifestations or systemic symptoms was observed.

Discussion

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as drug-induced hypersensitivity syndrome, is a rare but potentially life-threatening adverse

sindrom. Međutim, postoje različiti izveštaji o DRESS sindromu izazvanom antimikrobnim lekovima, uključujući vankomicin, sulfonamide i beta laktame [2–4,7,9,10]. Kod većine pacijenata, reakcija se razvija dve do šest nedelja nakon početka primene leka, što predstavlja duži latentni period u poređenju sa većinom drugih lekom izazvanih erupcija [3].

Ovo je u skladu sa slučajem naše pacijentkinje, kod koje su se kožne promene pojavile dve nedelje nakon terapije amoksicilinom, iako je zabeležen slučaj DRESS sindroma izazvanog amoksicilinom koji se pojavio već nakon jednog dana latentnog perioda [5].

Šunkert (Schunkert) i saradnici, u svom preglednom članku iz 2021. godine, stoga preporučuju da se DRESS sindrom ne isključuje samo na osnovu kraćeg latentnog perioda između izlaganja leku i pojave bolesti [2].

Najkarakterističnija osobina DRESS sindroma je zahvatanje kože, u vidu simetričnog makulopapuloznog osipa. Hematološke manifestacije su pretežno karakterisane eozinofilijom, koja se javlja u približno 66–95% obolelih. Eozinofilni infiltrati u određenim organima doprinose širokoj heterogenosti simptoma i širokom kliničkom spektru bolesti. Najčešća sistemska komplikacija DRESS-a je oštećenje jetre. Iako je zabeleženo i zahvatanje bubrega, simptomi su obično blagi i nisu povezani sa dugoročnim strukturnim ili funkcionalnim oštećenjem. Treća najčešća sistemska manifestacija je zahvatanje pluća, koje se manifestuje kao dispneja, intersticijumska bolest pluća, pleuritis ili akutni respiratorni distres sindrom [2,6,11].

Klinička slika naše pacijentkinje bila je u skladu sa tipičnim karakteristikama DRESS sindroma, uključujući kožne, hematološke i jetrene poremećaje, u vidu opsežnog makulopapuloznog egzantema, četvorostrukog i trostrukog porasta vrednosti ALT i AST, kao i značajne eozinofilije.

Dijagnoza DRESS sindroma ponekad se postavlja kasno i predstavlja izazov zbog heterogenosti kliničke slike, varijabilnog toka bolesti i relativno kasnog pojavljivanja simptoma [3, 5–7,9,12].

Tokom poslednjih godina razvijeni su različiti kriterijumi u cilju dijagnostikovanja DRESS sindroma. Dva najčešće korišćena sistema su J-SCAR (Japanese Severe Cutaneous Adverse Reactions) i RegiSCAR (European Registry of Severe Cutaneous Adverse Reactions) [4].

drug reaction characterized by a delayed onset and multisystem involvement, typically affecting the skin, liver, kidneys, lungs, and heart [8].

Aromatic anticonvulsants (e.g., carbamazepine, phenytoin, phenobarbital) and allopurinol are the most commonly implicated medications. However, increasing evidence demonstrates that antimicrobial agents, including vancomycin, sulfonamides, and beta-lactam antibiotics, may also trigger DRESS syndrome [2–4,7,9,10].

In most cases, clinical manifestations develop two to six weeks after initiation of the offending drug, representing a longer latency period compared with other drug-induced eruptions [3]. This timeline corresponds with our patient, who developed cutaneous symptoms following a two-week course of amoxicillin therapy. Nevertheless, shorter latency periods have been described, including cases of amoxicillin-induced DRESS occurring within 24 hours [5]. Consequently, as emphasized by Schunkert et al. in their 2021 review article, clinicians should avoid excluding the diagnosis solely based on a shorter interval between drug exposure and symptom onset [2].

Cutaneous involvement is the hallmark of DRESS syndrome and typically presents as a symmetrical maculopapular (morbilliform) eruption. Hematologic abnormalities, particularly eosinophilia, occur in approximately 66–95% of patients. Eosinophilic infiltrates of various organs contributes to the heterogeneous clinical presentation and broad disease spectrum. Hepatic involvement represents the most frequent systemic complication, while renal manifestations are generally mild and rarely associated with long-term functional impairment. Pulmonary involvement, the third most common systemic manifestation, may presents as dyspnea, interstitial lung disease, pleuritis, or acute respiratory distress syndrome [2,6,11].

The clinical presentation of our patient was consistent with typical features of DRESS syndrome, including extensive cutaneous involvement, significant eosinophilia, and hepatic dysfunction, as evidenced by markedly elevated ALT and AST levels.

Diagnosis can be challenging due to clinical heterogeneity, variable disease course, and delayed onset following drug exposure [3,5–7,9,12]. Several diagnostic crite-

Tabela 1. *RegiSCAR kriterijumi za postavljanje dijagnoze DRESS sindroma*
Table 1. Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) criteria

1. *Zahvaćenost kože sa akutnim osipom*/Skin involvement with acute rash
2. *Groznica iznad 38,5 °C (u središnjem delu tela) ili ≥38 °C (u aksilarnom delu)*/Fever above 38.5 °C (core) or ≥38 °C (axillary)
3. *Limfadenopatija na najmanje dve različite lokacije*/Lymphadenopathy in at least two different sites
4. *Uključenost najmanje jednog unutrašnjeg organa*/Involvement of at least one internal organ
5. *Limfocitoza ili limfocitopenija*/Lymphocytosis or lymphocytopenia
6. *Eozinofilija*/Eosinophilia
7. *Trombocitopenija*/Thrombocytopenia

Do danas, klinički skor sistem koji je predstavila RegiSCAR grupa 2007. godine ostaje jedno od najčešće korišćenih sredstava za dijagnozu DRESS sindroma.

Prema RegiSCAR kriterijumima, potencijalni slučaj mora ispunjavati najmanje tri od sledećih uslova ***(Tabela 1).***

Prema ukupnom skoru, pacijenti se klasifikuju kao definitivni slučaj (skor > 5), verovatni (skor 4–5), mogući (skor 2–3) ili se DRESS sindrom isključuje (skor < 2) [9].

Trenutno znanje o lečenju DRESS sindroma pretežno se zasniva na prikazima slučajeva i serijama slučajeva, uz nedostatak randomizovanih kliničkih ispitivanja i dokazanih smernica zasnovanih na dokazima [8].

Najvažniji korak u lečenju DRESS sindroma je obustava primene uzročnog leka. Trenutno ne postoji dijagnostički test koji bi u aktivnoj fazi bolesti pouzdano identifikovao lek koji izaziva reakciju. Stoga zlatni standard ostaje klinička procena lekara zasnovana na detaljnoj anamnezi i prepoznavanju lekova visokog rizika za razvoj DRESS sindroma [2]. S obzirom na poteškoće u identifikaciji uzročnog leka, preporučuje se sprovođenje pač testiranja dva do šest meseci nakon povlačenja simptoma radi utvrđivanja uzročnog leka [9].

Sistemski kortikosteroidi su terapija izbora za DRESS sindrom. Šunkert i saradnici preporučuju lečenje intravenskim metilprednizolonom u dozi od 1 mg/kg TT, a potencijalno i 1,5 mg/kg TT, u zavisnosti od težine bolesti [2].

Kao i u našem slučaju, pacijentkinja je inicijalno lečena sistemskim kortikosteroidima (1 mg/kg TT) primenjenim parenteralno tokom dve nedelje, nakon čega je usledilo postepeno smanjenje doze i prelazak na peroralnu kortikosteroidnu terapiju, sa uspešnim ishodom bez relapsa tokom perioda praćenja.

ria have been proposed, among which the Japanese Research Committee on Severe Cutaneous Adverse Reaction (J-SCAR) criteria and the European Registry on Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system are most widely used [4]. The RegiSCAR scoring system, introduced in 2007, remains one of the most commonly applied diagnostic tools.

According to the RegiSCAR criteria, a potential case must present with at least three of the following independent findings **(Table 1).**

According to the total score, cases are classified as definite (>5 points), probable (4–5 points), possible (2–3 points), or excluded (<2 points) [9].

Current treatment strategies for DRESS syndrome are primarily based on case reports and observational studies, as randomized controlled trials and standardized evidence-based guidelines remain limited [8].

The cornerstone of management is immediate discontinuation of the suspected culprit drug. At present, no diagnostic test reliably identifies the causative agent during the acute phase; therefore, clinical judgment based on detailed medication history and awareness of high-risk drugs remains essential [2].

Patch testing is recommended two to six months after complete clinical resolution to help confirm drug causality [9]. In our case, epicutaneous testing performed two months after symptom resolution confirmed hypersensitivity to amoxicillin. The test was conducted using amoxicillin in petrolatum applied to the upper back, with readings obtained at 48 and 72 hours, consistent with recommendations for evaluation of delayed hypersensitivity reactions to beta-lactam antibiotics [13].

Dva meseca nakon potpune regresije kožnih promena sprovedeno je pač testiranje u cilju identifikacije uzročnog leka, kojim je potvrđena preosetljivost na amoksicilin. Pač testiranje je izvedeno primenom amoksicilina u petrolatumu na koži gornjeg dela leđa, uz očitavanje reakcija nakon 48 i 72 časa, u skladu sa preporukama za ispitivanje odloženih hipersenzitivnih reakcija na beta laktamske antibiotike [13].

Zaključak

Zaključno, autori ističu da je Drug Reaction with Eosinophilia and Systemic Symptoms sindrom ozbiljna i potencijalno životnougrožavajuća reakcija na lek, povezana sa značajnim morbiditetom i procenjenom stopom mortaliteta od oko 10%, prvenstveno zbog zahvatanja više unutrašnjih organa.

Iako se Reaction with Eosinophilia and Systemic Symptoms sindrom najčešće povezuje sa primenom antiepileptičkih lekova, lekari treba da imaju u vidu da i lekovi koji se generalno smatraju niskorizičnim, poput antibiotika, naročito amoksicilina, mogu predstavljati potencijalne uzročnike ovog oboljenja.

Predstavljeni slučaj ističe značaj pažljive procene indikacije za primenu antibiotika, kao i razmatranje amoksicilina kao potencijalnog uzročnog leka kod pacijenata sa Reaction with Eosinophilia and Systemic Symptoms sindromom.

Takođe, autori naglašavaju značaj pač testiranja u utvrđivanju etiologije Reaction with Eosinophilia and Systemic Symptoms sindroma, jer je identifikacija uzročnog leka ključna za prevenciju ponovne pojave ove potencijalno životnougrožavajuće reakcije na lek. Iako se ne smatra zlatnim standardom, pač test predstavlja bezbednu metodu koja može pomoći pri utvrđivanju uzročnika Reaction with Eosinophilia and Systemic Symptoms sindroma.

Systemic corticosteroids are currently considered the mainstay of treatment. Schunkert et al. recommend intravenous methylprednisolone at a dose of 1 mg/kg body weight, with escalation up to 1.5 mg/kg body weight in severe cases [2]. In our patient, parenteral corticosteroid therapy at 1 mg/kg body weight was administered for two weeks, followed by gradual tapering and transition to oral administration, resulting in complete clinical recovery without relapse during follow-up.

Conclusion

Drug Reaction with Eosinophilia and Systemic Symptoms syndrome is a serious and potentially life-threatening drug hypersensitivity reaction associated with significant morbidity and an estimated mortality rate of approximately 10%, primarily due to multiorgan involvement.

Although most frequently associated with antiepileptic drugs, clinicians should remain aware that medications generally perceived as lower risk, including commonly prescribed antibiotics such as amoxicillin, may act as causative agents.

This case underscores the importance of carefully evaluation of antibiotic indications and maintaining a high index of suspicion for Drug Reaction with Eosinophilia and Systemic Symptoms syndrome in patients presenting with systemic symptoms and cutaneous eruptions.

Furthermore, patch testing represents a valuable and safe adjunctive tool for identifying the culprit drug and preventing recurrence, even though it is not considered the definitive diagnostic gold standard.

Literatura/References

1. Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, et al. The DRESS syndrome: a literature review. Am J Med. 2011;124(7):588-97.
2. Schunkert EM, Divito SJ. Updates and insights in the diagnosis and management of DRESS syndrome. Curr Dermatol Rep. 2021;10(4):192-204.
3. Calle AM, Aguirre N, Ardila JC, Cardona Villa R. DRESS syndrome: a literature review and treatment algorithm. World Allergy Organ J. 2023;16(3):100673.
4. Sharifzadeh S, Mohammadpour AH, Tavanaee A, Elyasi S. Antibacterial antibiotic-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: a literature review. Eur J Clin Pharmacol. 2021;77(3):275-89.
5. Cortes M, Cho KW, Chowdhury NM, Mays JN, Shin CH. Amoxicillin-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome with acute onset of diffuse rash and acute kidney injury (AKI). Cureus. 2024;16(1):e51707.
6. Kanabaj K, Jenerowicz D, Jankowska L, Żaba Z. DRESS syndrome – a dermatological emergency –

sulfasalazine-related acute drug reaction case report. Heliyon. 2023;9(9):e20021.
7. Kulkarni MP, Chinta S, Sosa F, Nasr R, Kelly P. Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome due to vancomycin. Cureus. 2022;14(6):e26219.
8. Mąsior MN, Rostkowska OM, Furmańczyk-Zawiska A, Wieczorek-Godlewska R, Wyzgał M, Durlik M. DRESS syndrome: renal involvement in two cases – a comprehensive analysis and literature review of improved diagnosis and treatment. Am J Case Rep. 2023;25:e942315.
9. Manieri E, Dondi A, Neri I, Lanari M. Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome in childhood: a narrative review. Front Med. 2023;10:1108345.
10. Cabañas R, Calderón O, Ramírez E, Fiandor A, Prior N, Caballero T, et al. Piperacillin-induced DRESS: distinguishing features observed in a clinical and allergy study of 8 patients. J Investig Allergol Clin Immunol. 2014;24(6):425-30.
11. Dagnon da Silva M, Domingues SM, Oluic S, Radovanovic M, Kodela P, Nordin T, et al. Renal manifestations of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: a systematic review of 71 cases. J Clin Med. 2023;12(14):4576.
12. Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol. 2013;169(5):1071-80.
13. Woodruff CM, Botto N. The role of patch testing in evaluating delayed hypersensitivity reactions to medications. Clin Rev Allergy Immunol. 2022;62(3):548-61.

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