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Lamotrigine Associated DRESS Syndrome – a Case Report

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Abstract

Drug-induced delayed multiorgan hypersensitivity syndrome, also known as drug rash (reaction) with eosinophilia and systemic symptoms (DRESS) syndrome, represents a drug-induced cluster of skin, hematologic and systemic symptoms. More than forty drugs have been associated with this syndrome. We present a case of DRESS syndrome suspecting that lamotrigine was directly responsible for the patient's rash and other symptoms. A female patient presented with extensive skin rash, fever, hematologic abnormalities, organ involvement such as hepatitis, pancreatitis and respiratory symptoms. The symptoms developed four weeks after the initiation of the offending drug, and disappeared eight weeks after its discontinuation.

Key words

Drug Hypersensitivity Syndrome; Anticonvulsants; Drug-Related Side Effects and Adverse Reactions; Antipsychotic Agents; Case Reports

Drug-induced delayed multiorgan hypersensitivity syndrome (DIDMOHS) (1), also known as drug rash (reaction) with eosinophilia and systemic symptoms (DRESS) syndrome, is a severe, unexpected drug reaction which affects several organ systems at the same time (2, 3, 4). Most commonly it causes a combination of high fever, morbiliform skin rash and inflammation of one or more internal organs including the liver, kidneys, lungs and/or heart. It generally starts two to eight weeks after taking the offending medicine. The drugs most often reported with DRESS include anticonvulsants (particularly those with aromatic structures), sulfa derivatives, antidepressants, non-steroidal anti-inflammatory drugs, and antimicrobials (5, 6, 7).

Case report

We present a 44-year-old unemployed nurse with psychiatric history since her teens. She was first admitted to the Emergency Department seven days before admission to our Clinic, because of persistent symptoms of high fever (body temperature above 38°C), severe nonproductive cough, nasal secretion, facial swelling, especially around the nose, and erythema on the hands. A differential white blood cell count and urinalysis were performed, and except mild eosinophilia of 6% (normal range 0 - 5%) all other findings were within normal limits. She was advised to stop taking all drugs. The patient was using three drugs (olanzapine: an antipsychotic serotonin blocker; lamotrigine: an antiepileptic and mood stabilizer; and losartan: an antihypertensive and angiotensin II receptor blocker), since she was discharged from the Clinic of Psychiatric Diseases a month before, where she was hospitalized under the diagnosis of paranoid personality disorder. Due to persistent high temperature and worsening of respiratory symptoms, the patient was examined by the specialist for infectious diseases, who set the diagnosis of acute bronchiolitis, and introduced azithromycin 500 mg once daily

during three days; the chest X-ray was normal and the patient was advised to visit a dermatologist. At the first dermatological examination, the patient had diffuse facial flushing with mild edema, and morbiliform skin rash mainly on the extremities. In addition to azithromycin, an antihistamine levocetirizine was introduced. In spite of the therapy, the skin rash was spreading, therefore hospitalization was recommended. On admission, the dermatology examination revealed diffuse erythematous and slightly edematous face, generalized maculopapular livid erythematous rash partly confluent on the trunk and extremities involving more than 50% of the body surface (Figures 1, 2). No peripheral lympadenomegaly was detected.

Laboratory and other relevant findings

Laboratory findings on admission were as follows: erythrocyte sedimentation rate (ESR) - 13 mm/h, C-reactive protein (CRP) - 4.7 mg/L (normal range: 0 - 5 mg/L), white blood cell count (WBC) - 17.3x10^9/L (normal range: 3.4 - 9.3 x10^9/L), red blood cell count (RBC) - 4.1x10^{12}/L (normal range: 3.9 - 5.4 x10^{12}/L), platelets (PLT) - 246x10^3/L (normal range: 140 - 400x10^9/L), differential white blood cell count: neutrohils - 6.46x x10^9/L or 38.2% (normal range: 2 - 7.5x10^9/L or 50 - 75%), lymphocytes - 5.67x10^9/L or 32.8% (normal range: 0.8 - 4x10^9/L or 20 - 40%), monocytes - 0.9 x10^9/L or 5.4% (normal range: 0.08 - 1x10^9/L or 2 - 10%), eosinophils - 2.38x10^9/L or 13.8% (normal range: 0 - 0.5x10^9/L or 0 - 5%), basophils - 0.33x10^9/L or 1.9% (normal range: 0 - 0.1x10^9/L or 0 - 1%), total bilirubin - 8.2 μmol/L (normal range: 3 - 21 μmol/L), direct bilirubin - 2.0, μmol/L (normal range: 0.1 - 5.2 μmol/L), aspartate aminotransferase (AST) - 52 IU/L (normal range: 0 - 35 IU/L), alanine aminotransferase (ALT) - 136 U/L (normal range: (0 - 35 U/L), gamma glytamil transferase - 24.4 U/L (normal range: 1 - 38 U/L), creatine kinase - 65 U/L (normal range: 24 - 170 U/L), urea - 5.2 μmol/L (normal range: 2.5 - 7.5 μmol/L), creatnine - 72 μmol/L (normal range: 44 - 98 μmol/L), serum amylase - 79 U/L (normal range: 20 - 118 U/L), urine amylase - 601 U/L (normal range: 20 - 118 U/L), lipase - 48U/L (normal range: 0 - 160 U/L), urinanalysis was normal, ELISA herpes simplex virus typus 1 (HSV-1) IgM and IgG negative, HSV-2 IgM and IgG negative, anti Epstein–Barr virus (EBV) IgM negative, anti-EBV IgG 1.54 (positive > 1.1), anti cytomegalovirus (CMV) IgM and IgG negative. Peripheral blood smear: eosinophils - 15% (normal range: 0 - 5%), atypical lymphocytes - 8% (normally ‹ 5%), immature myelocytes (1%). The upper abdomen ultrasound was normal. On the third day of hospitalization, the abnormal laboratory findings improved: WBC 10.5x10^9/L, eosinophils 8.8%, AST 15 IU/L, ALT 50 IU/L.

The diagnosis of DRESS syndrome was established based on the diagnostic criteria for DRESS syndrome, including skin rash, blood count and laboratory abnormalites that were as follows: leukocytosis (>11x109/L), eosinophilia (>1.5x109/L), atypical lymphocytes (>5%) and liver abnormalities (ALT>100 IU/L) (6, 8).

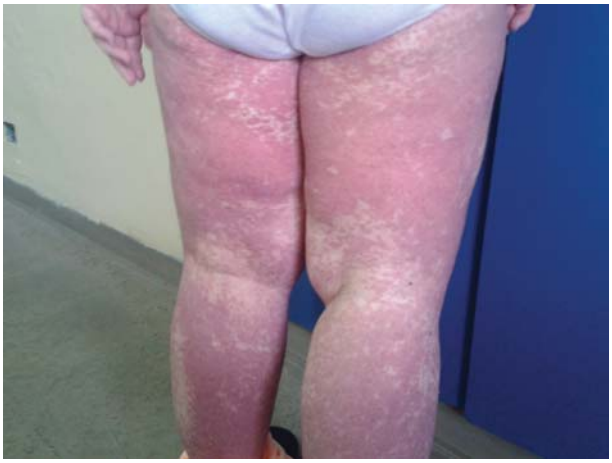

Figure 1. Maculopapular rash on admission

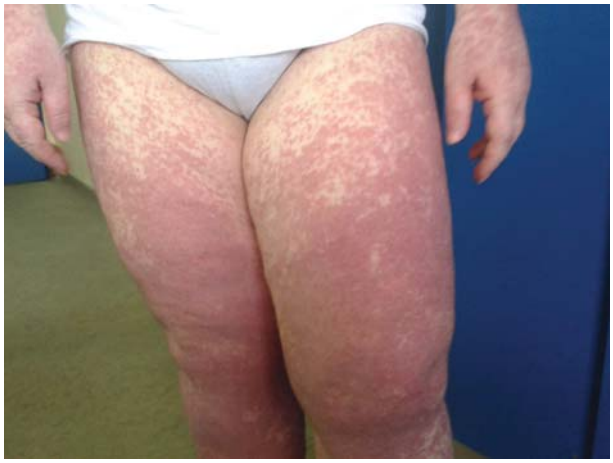

Figure 2. Maculopapular rash on admission

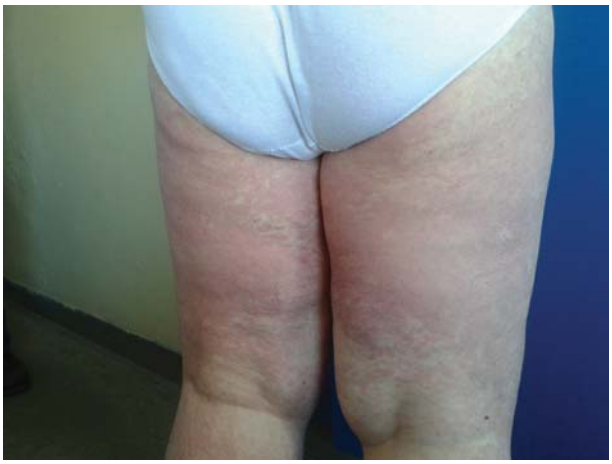

Figure 3. Maculopapular rash 2 weeks after the withdrawal of lamotrigine and olanzapine

During the seven-day hospital stay, the patient received 40 mg methylprednisolone daily, a systemic steroid, and oral ranitidine, loratadine; - an antihistaminic, butamirate citrate - an antitussic, and losartan - an antihypertensive. After being discharged, the patient continued oral corticosteroid therapy with 40 mg prednisolone daily, with dose reduction by 10 mg after every seven days. She continued taking ranitidine and losartan. On discharge, she still presented with erythematous macular rush. Three weeks later, laboratory findings (WBC with differential count, RBC, AST, ALT, urinanalysis and serum amylase) normalized, but the pale residual pinkish macular skin rash was still persistent (Figures 3 - 6). On last visit, six weeks after hospitalization

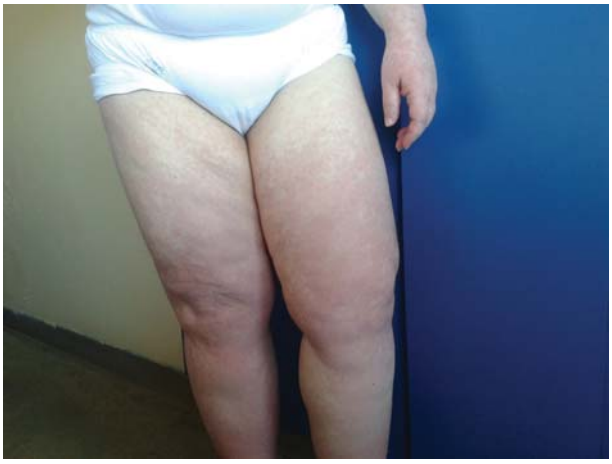

Figure 4. Maculopapular rash 2 weeks after the withdrawal of lamotrigine and olanzapine

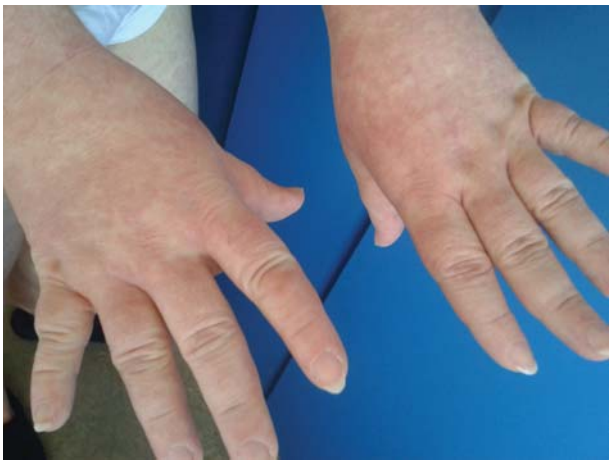

Figure 5. Maculopapular rash 2 weeks after the withdrawal of lamotrigine and olanzapine

and 8 weeks after lamotrigne and olanzapine were discontinued, the skin lesions completely resolved. Due to the psychiatrist's recommendation, olanzapine was reintroduced into the therapy, and since then the patient has been taking it without any problems.

Discussion

Before 1996, when Bouquet and associates described the DRESS syndrome, several different terms have been used such as: anticonvulsant hypersensitivity syndrome, first described in 1936 during the treatment with anticonvulsant drugs; drug hypersensitivity syndrome; drug-induced hypersensitivity syndrome (9, 10, 11). The "R" was previously used to indicate "rash" (9), now it indicates "reaction" (3).

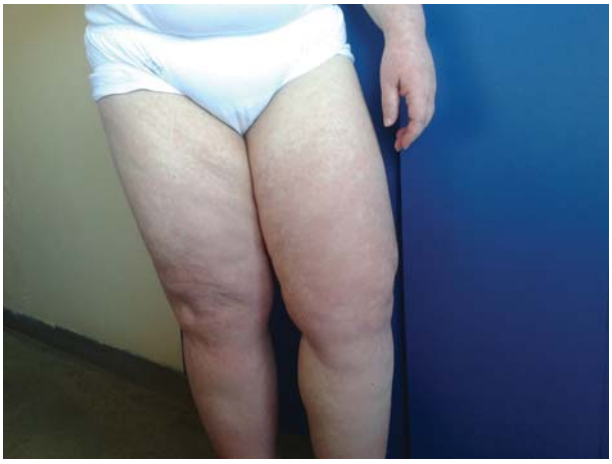

Figure 6. Maculopapular rash 2 weeks after the withdrawal of lamotrigine and olanzapine

Though DRESS syndrome was recognized as a serious form of skin drug adverse reaction from the very beginning, it is currently viewed as a drug-related syndrome with life-threatening organ dysfunctions. A long interval from first drug exposure to symptom onset and a prolonged course after discontinuation of the offending drug even with flares, represent the two highly typical features of the syndrome (12). The syndrome is also characterized by an extensive rash, fever, lymphadenopathy, hematologic abnormalities, hepatitis, and involvement of the kidneys, lungs, heart, or pancreas. Although skin lesions may rapidly aggravate from erythematous to purpuric, pustrular or turn to exfoliative dermatitis, they can be overshadowed by the severity of organ involvement, hence "reaction" instead of "rash" in the acronym DRESS (13). The onset of symptoms is often delayed, occurring 2 – 8 weeks after drug initiation (14). In our patient symptoms occurred one month after initiation of three drugs, two of which being psychoactive (olanzapine - antipsychotic serotonin blocker; lamotrigine - antiepileptic and mood stabilizers; and losartan - antihypertensive and angiotensin II receptor blockers).

The incidence of DRESS has been estimated to be between 1 in 1,000 and 1 in 10,000 drug exposures. It carries a mortality rate of 10 – 20%, with most fatalities due to liver failure (15).

The exact pathogenesis of DRESS syndrome is not yet well understood. Although it is considered an idiosyncratic reaction, three potential causative factors have been identified among multiple cases: 1) a defect in drug metabolism resulting in the failure to eliminate toxic reactive intermediates (e.g. slow acetylation and defects in enzymes responsible for drug metabolism such as arene oxidase for anticonvulsants); 2) reactivation of human herpes virus-6 (HHV-6), human herpes virus-7 (HHV-7), Epstein-Barr virus (EBV), or cytomegalovirus (CMV), which may act as a trigger for the immune reaction; 3) or genetic predisposition that alters immune response (4, 16, 17).

Two groups have developed specific criteria for making the diagnosis of DRESS syndrome: The European Registry of Severe Cutaneous Adverse Reactions Group (The RegiSCAR group) and Japanese Consensus Group (SCAR-J). The RegiSCAR study group developed a set of inclusion criteria (Table 1) and established a scoring system (total score ranges from 4 to 9), for classifying DRESS cases as definitive with final score >5, probable with final score 4 - 5, possible with final score 2 - 3, and no case with final score <2 (8).

According to RegiSCAR group criteria, our patient met all criteria except lymphadenopathy and reduced platelets. According to the RegiSCAR group scoring system, eosinophilia (>1.5x109/L), atypical lymphocytes (>5%), skin involvement (>50%), suggestive skin rash, and liver abnormalities (ALT>100 IU/L) were scored as 2+1,+1,+1, and +1, respectively (8). Since the final score was +6, the diagnosis of DRESS syndrome was definite in our patient.

According to the Japanese Consensus Group criteria for DRESS syndrome, our patient fulfilled the first five, thus being classified as having atypical DRESS syndrome (Table 2) (6). In comparison to criteria developed by the RegiSCAR group, the major difference was inclusion of HHV-6 reactivation (6). However, the use of HHV-6 reactivation as a criterion is controversial, because no definite evidence of the causative role of herpes viruses in DRESS syndrome has been reported (18). In the *in vitro* studies, it was found that drugs associated with DRESS syndrome do not only potentiate HHV-6 and EBV replication by inhibition of epigenetic control mechanisms (the two main are methylation and histone acetylation), but also induce an antiviral T-cell immune response in individuals with genetic susceptibility factors, by interacting with the major histocompatibility complex receptor (12). Since anticonvulsant drugs can induce hypogammaglobulinemia, it has been hypothesized that use of drugs associated with DRESS syndrome may promote viral reactivation by inducing immunosuppression. However, the mechanism underlying the direct drug-virus interaction remains unknown. Only a minority of transplant recipients with marked viral reactivation develop systemic manifestations. The systemic manifestations are suggested to be related to a strong immune response against the reactivated virus. Thus, DRESS syndrome, develops only in patients with both marked viral reactivation and an ability to produce a strong antiviral immune response (e.g. genetic polymorphisms for cytokines, receptors, or antagonists (as demonstrated for the TNF-receptor) (12). Meanwhile, Japanese criteria are less practical in routine clinical practice,

Table 1. RegiSCAR criteria for diagnosisof DRESS syndrome (published by RegiSCAR

All criteria fulfilled
1. Hospitalization
2. Reaction suspected to be drug-related
3. Acute rash
Three of the following four criteria
4. Fever >38°C
5. Enlarged lymph nodes at least at 2 sites
6. Involvement of at least 1 internal organ
7. Blood count abnormalities - defined either by:
o Lymphocytes above or below normal limits ; or
o Eosinophils above the laboratory limits ; or
o Platelets below the laboratory limits

as viral serologic tests are unhelpful (18). Quantitative PCR of the whole blood must be used in order to detect viral reactivations (12).

The liver is the most commonly involved organ in DRESS syndrome, and hepatitits, present also in our patient, occurs in about 80% of all cases (19, 20, 21). The degree of hepatitis is related to the interval between the onset of the syndrome and the discontinuation of the offending drug. Apart from the liver, another, most frequently affected organs are the kidneys in 40% and lungs in 33% of cases. Cardiovascular symptoms develop in 15% of cases, and pancreas is involved in about 5% of cases (22). The most common hematologic disorders that occur in DRESS syndrome are as follows: atypical lymphocytes (63%), eosinophilia (52%), lymphocytopenia (45%), and thrombocytopenia (25%) (23, 24). Our patient had leukocytosis (>11x10^9/L), eosinophilia (>1.5 x 10^9) and atypical lymphocytosis (>5%).

The outcome is usually favorable after discontinuation of the casual drug, although full symptom resolution requires at least two weeks and flares may occur. Moreover, after prompt withdrawal of the offending agent, complete resolution of skin lesions and visceral injury can be achieved in up to several weeks, which happened after 8 weeks in our patient. Although in less severe cases resolution can be achieved by using only supportive measures, in cases with internal organ impairment, moderate to high doses of corticosteroids should be commenced, but not before infection has been carefully ruled out! Corticosteroids should be gradually tapered over a period of 6 - 8 weeks as in our patient, in order to prevent relapse which may occur especially with rapid discontinuation. Time to onset is shorter after re-challenge with the same drug.

There are more than 40 drugs, including lamotrigine and olanzapine, that have been reported to be associated with DRESS syndrome (18). Aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine) and sulphonamides are the most common causative drugs, but a variety

Table 2. Japanese group's criteria for diagnosis* ** of DRESS syndrome

1. Maculopapular rash developing >3 weeks after initiation of the suspected drug
2. Prolonged clinical symptoms: 2 weeks after discontinuation of the suspected drug
3. Fever >38°C
4. Liver abnormalities (alanine aminotransferase >100U/L)
5. Blood count abnormalities - defined either by:
o Lymphocytes above or below normal limits ; or
o Eosinophils above the laboratory limits ; or
o Platelets below the laboratory limits
6. Lymphadenopathy
7. Human herpes virus-6 reactivation

*The diagnosis of typical syndrome is confirmed by the presence of all 7 criteria

**The diagnosis of atypical syndrome is confirmed by the presence of the first 5 criteria

of other drugs have been reported such as: dapsone (DDS, 4,4-diaminodiphenylsulphone), allopurinol, captopril, calcium-channel blockers, ranitidine, thalidomide, minocycline, sulfasalazine, non-steroidal antiinflammatory agents, antituberculotic drugs, α-methyldopa and antiretroviral drugs (abacavir, zalcitabine, nevirapine) (18, 20-27). Lamotrigine [6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine] is an antiepileptic drug, used in the management of a broad range of seizures in adults and children which is not an aromatic antiepileptic, thus being structurally and pharmacologically unrelated to other antiepileptic medications e.g. carbamazepine (28, 29). Lamotrigine has been repoted in association with severe skin rash, multiorgan failure, DRESS syndrome, acute hepatic failure, and disseminated intravascular coagulation. Severe rashes due to lamotrigine occurr almost regularly within the first 6 - 8 weeks of exposure, rarely after 12 weeks and almost exclusively later (30). Several reports of lamotrigine-induced DRESS syndrome have been reported in the literature (12, 27, 28, 29, 31-34). The second psychoactive drug our patient was taking in combination with lamotrigine was an antipsychotic - olanzapine, an oxazepine that is prescribed to patients with schizophrenia or recurrent bipolar disorder. Regarding cutaneous adverse drug reactions due to olanzapine, the literature contains few reports of DRESS syndrome, contrary to lamotrigine that has commonly been reported as a causative agent in DRESS syndrome. Actually, in a frequently cited review on DRESS syndrome published in 2011 by Cacoub et al, only one case involved olanzapine (35). Since then, according to available literature, there are four new published cases of DRESS syndrome associated with olanzapine (12, 36-38). Although drug-drug interactions have been reported between antiepileptic and antipsychotic drugs, there was only one report of cross-sensitization between carbamazepine (aromatic antiepileptic drug) and olanzapine (aromatic antipsychotic drug) (38).

The diagnosis of DRESS syndrome in our case was definite. However, regarding causality, due to the scoring system established by Naranjo et al, it was a probable adverse drug reaction caused by lamotrigine (final score 7); we did not confirm the adverse event by at least one objective evidence e.g. by skin testing (39). Skin tests can assist in the causality assessment, but performed at a time distance from the DRESS

syndrome episode (12). Given the fact that lamotrigine, opposed to olanzapine, is known as a common cause of DRESS syndrome, that there is no cross reactivity between them, and there was a necessity of its use in the given moment, the psychiatrist considered that olanzapine should be reintroduced into the therapy. If the psychiatrist had not reintroduced olanzapine into the therapy, patch testing would be performed in 6 months, and olanzapine would gradually be reintroduced under hospital supervision. Therefore, now we can only hypothesize that lamotrigine was directly responsible for our patient's rash, and all other symptoms and signs.

Conclusion

We present a case of a female patient who was treated with an antipsychotic - olanzapine in combination with an anticonvulsant – lamotrigine. Since both drugs were discontinued due to the development of DRESS syndrome, and with regard to the chronology of events, lamotrigine was considered the main suspected drug.

Abbreviations

DRESS - drug rash (reaction) with eosinophilia and systemic symptoms
DIDMOHS - drug-induced delayed multiorgan hypersensitivity syndrome
ESR - erythrocyte sedimentation rate
CRP - C-reactive protein
WBC - white blood cell count
RBC - red blood cell count
PLT - platelets
AST - aspartate aminotransferase
ALT - alanine aminotransferase
ELISA - enzyme-linked immunosorbent assay
HSV - herpes simplex virus
Ig – immunoglobulins
EBV - Epstein–Barr virus
CMV - cytomegalovirus
RegiSCAR - Registry of Severe Cutaneous Adverse Reactions
SCAR-J - Japanese Consensus Group.
HHV - human herpesvirus
TNF - tumor necrosis factor
PCR - polymerase chain reaction

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Lamotrigin udružen sa DRESS sindromom – prikaz slučaja

Sažetak

Uvod. Lekom izazvan odložen multiorganski sindrom poznat i pod nazivom DRESS (eng. *drug reaction with eosinophilia and systemic symptoms*), podrazumeva neočekivanu lekom izazvanu reakciju koja se klinički najčešće manifestuje visokom temperaturom, morbiliformnim osipom na koži i upalom jednog ili više unutrašnjih organa, uključujući jetru, bubrege i/ili srce, dve do osam nedelja nakon uključivanja leka u terapiju. Lekovi koji najčešće izazivaju ovaj sindrom su: aromatski antikonvulzanti, sulfa-derivati, antidepresanti, nesteroidni antiinflamatorni i antimikrobni agensi.

Prikaz slučaja. Prikazujemo slučaj četrdeset-četvorogodišnje ženske osobe koja od puberteta ima psihijatrijske tegobe. Sedam dana pre prijema na našu kliniku, javila se u Urgentni centar zbog visoke febrilnosti, intenzivnog neproduktivnog kašlja, nazalne sekrecije, otoka i crvenila lica i šaka. Rutinska laboratorijska ispitivanja ukazala su na blagu eozinofiliju od 6% (referalne vrednosti 0–5%).

Pacijentkinji je savetovano da odmah obustavi uzimanje svih lekova, s obzirom da je mesec dana ranije lečena i otpuštena sa psihijatrijske klinike, gde je zbog paranoidnog personalnog poremećaja započeto lečenje sledećim lekovima: olanzapin (antipsihotik i blokator serotonina), lamotrigin (antiepileptik) i losartan (antihipertenziv, blokator angiotenzin II receptora). Zbog perzistirajuće febrilnosti i pogoršanja respiratornih simptoma i znakova, infektolog je postavio dijagnozu akutnog bronhiolitisa i u terapiju uveo azitromicin u dnevnoj dozi od 500 mg tokom tri dana; rendgenski snimak pluća bio je u granicama referalnog nalaza, pa je pacijent upućen na pregled dermatologu.

Prilikom prvog dermatološkog pregleda, utvrđeno je prisustvo difuznog jako izrženog eritema i umerenog edema na licu i morbiliformnog eritema na koži ekstremiteta. I pored antihistaminika koji je uključen u terapiju, osip na koži se i dalje pojačavao i širio na ostale delove tela, tako da je na prijemu u bolnicu, pored difuznog eritema i edema lica, bio prisutan generalizovni lividni makulozni osip koji je zahvatao više od 50% površine tela sa tendencijom konfluencije, bez periferme limfadenomegalije (slike 1, 2).

Laboratorijski parametri koji su na prijemu odstupali od referalnih vrednosti odnosili su se na povišen broj leukocita u krvi (17,3 x 10^9/L, referalno 3,4–9,3 x 10^9/L), blagu limfocitozu (5,67 x 10^9/L, referalno 0,8–4 x 10^9/L) i eozinofiliju (2,38 x 10^9/L ili 13,8%, referalno 0–0,5 x 10^9/L ili 0–5%), povišene jetrene enzime u serumu i to aspartat aminotransferazu – AST (52 IU/L, referalno 0–35 IU/L), alanin aminotransferazu – ALT (136 U/L, referalno 0–35 U/L), povišenu vrednost amilaze u urinu (601 U/L, referalno 20–118 U/L), prisustvo u razmazu periferne krvi eozinofilije od 15% (referalno 0–5%), atipičnih limfocita 8% (referalno < 5%) i nezrelih mijelocita (1%).

Dijagnoza DRESS sindroma postavljena je na osnovu prisustva prihvaćenih dijagnostičkih kriterijuma, uključujući osip na koži i sledeća odstupanja u kompletnoj krvnoj slici i osnovnim biohemijskim parametrima: leukocitoza (> 11 x 10^9/L), eozinofolija (> 1,5 x 10^9/L), atipični limfociti (> 5%), jetreni enzimi (ALT > 100 IU/L), povišen nivo amilaze u urinu. Trećeg dana po prijemu i započinjanju lečenja, došlo je do poboljšanja vrednosti labortorijskih parametara: broj leukocita u krvi iznosio je 10,5 x 10^3/L, eozinofila u diferencijalnoj formuli 8,8%, AST je normalizovan i iznosio je 15 IU/L, dok je ALT smanjen na 50 IU/L. Za vreme sedmodnevne hospitalizacije, ordiniran je parenteralno metilprednizolon u dozi od 40 mg dnevno i peroralno ranitidin, loratadin, butamirat citrat (antitusik) i losartan (antihipertenziv). Posle otpusta iz bolnice, nastavljena je terapija kortikosteroidima putem peroralnog unošenja prednizolona (u dozi od 40 mg dnevno sa smanjenjem dnevne doze za 10 mg svakih sedam dana), ranitidina i losartana. Na otpustu je na koži i dalje bio prisutan eritematozni makulozni osip. Tri nedelje kasnije, došlo je do normalizacije svih laboratorijskih prametara, dok je na koži i dalje perzistirao značajno bleđi, rezidualni, svetloružičasti makulozni osip (slike 3–6). Kožne promene su potpuno nestale na kontrolnom pregledu šest nedelja posle otpusta iz bolnice, tj. osam nedelja posle obustave uzimanja lamotrigina i olanzapina. U terapiju je na predlog nadležnog psihijatra, ponovo uveden olanzapin koji je pacijentkinja nastavila da pije bez ikakvih tegoba.

Diskusija. DRESS sindrom klinički tipično karakterišu dug period 2–8 nedelja od prvog uzimanja leka do pojave prvih simptoma, kao i prolongirani vremenski period od trenutka obustavljanja uzimanja leka, do potpunog povlačenja svih znakova uključujući i promene na koži. Pored visoke febrilnosti, limfadenomegalije i promena na koži, sindrom karakterišu i odstupanja u hematološkim i biohemijskim parametrima koja ukazuju na zahvaćenost unutrašnjih organa, najčešće jetre, bubrega, pluća, srca ili pankreasa. Iako promene na koži mogu progredirati od purpuričnih i pustuloznih, pa sve do eksfolijativnog dermatitisa, one mogu ostati u senci u odnosu na jako izražene simptome i znake zahvaćenih unutrašnjih organa, te zato „reakcija" umesto „raš" označava „R" u akronimu DRESS. Kod naše pacijentkinje, prvi simptomi su se javili mesec dana posle uvođenja tri leka, od kojih su dva bila psihoaktivna (olanzapin, antipsihotik i inhibitor preuzimanja serotonina i lamotrigin; antiepileptik i stabilizator raspoloženja, lamotrigin; treći lek je bio antihipertenziv losartan, iz grupe blokatora angiotenzinskih II receptora).

Iako tačan patogenetski mehanizam odgovoran za nastanak DRESS sindroma nije u potpunosti razjašnjem, radi se najverovatnije o idiosinkrazijskoj reakciji zasnovanoj na jednom i/ili više od navedenih

uzroka: 1) defekt u metabolisanju leka koji rezultira neadekvatnom eliminacijom toksičnih reaktivnih intermedijarnih produkata (npr. usporena acetilacija ili poremećana aktivnost arena oksidaze, enzima odgovornog za metabolisanje antikonvulzivnih lekova; 2) reaktivacija humanog herpes virusa-6 (HHV-6), humanog herpes virusa-7 (HHV-7), Epštajn-Barovog virusa (EBV), ili citomegalovirusa (CMV), koja može da pokrene reakciju imunskog sistema; 3) genetska predispozicija za poremećan imunski odgovor.

Evropska, RegiSCAR grupa istraživača (engl. *The European Registry of Severe Cutaneous Adverse Reactions Group*) i Japanska konsenzus grupa (eng. *The Japanese Consensus Group*), utvrdile su dijagnostičke kriterijume za DRESS sindrom: Inkluzioni kriterijumi koje je uspostavila RegiSCAR groupa izneti su u Tabeli 1 i oni služe za postavljanje dijagnoze DRESS sindroma, dok se na osnovu skoring sistema (ukupni skor se kreće od -4 do +9), vrši klasifikacija dijagnoze DRESS sindroma na definitivnu (ukupnii skor > 5), verovatnu (ukupni skor 4-5), moguću (ukupni skor 2-3), ili se dijagnoza isključuje (ukupni skor < 2).

Prema RegiSCAR kriterijumima, kod naše pacijentkinje su osim trombocitopenije i limfadenopatije bili prisutni svi ostali kriterijumi, koji su skorovani: eozinofilija (> 1,5 x 10^9/L) sa +2 atipični limfociti (> 5%) sa +1, procentualna zahvaćenost kože (> 50%) sa +1, osip koji ne isključuje dijagnozu DRESS sindroma sa +1, poremećaj finkcije jetre (ALT > 100 IU/L) sa +1. S obzirom da je ukupni skor koda naše pacijentkinje iznosio +6, dijagnoza DRESS sindroma kod naše pacijentkinje je bila defnitivna.

Prema kriterijumima Japanske konsenzus grupe za postavljanje dijagnoze DRESS sindroma, naša pacijentkinja je imala pet prvih od ukupno sedam kriterijuma, što je odgovaralo dijagnozi atipičnog DRESS sindroma (Tabela 2). U odnosu na kriterijume koje je dala RegiSCAR grupa, glavna razlika je što je u kriterijume Japanske konsenzus grupe uključena i reaktivacija infekcije sa HHV-6, što je u nedostatku dokaza o direktnoj ulozi herpes virusa u nastanku DRESS sindroma izazvalo kontroverzne stavove. U *in vitro* istraživanjima utvrđeno je da lek udružen sa pojavom DRESS sindroma, ne samo da pospešuje replikaciju HHV-6 i EBV virusa putem inhibicije epigenetskih kontrolnih mehanizama (dva glavna mehanizma su metilacija i histonska acetilacija), nego kod genetski predisponiranih osoba (npr. genetski polimofizam za citokine, receptore ili antagoniste, kao što je pokazano za TNF-receptor), pokreće i antivirusni T-ćelijski imunski odgovor putem interakcije sa receptorima glavnog histokompatibilnog kompleksa. Japanski kriterijumi su se istovremeno pokazali manje praktičnm, s obzirom na mali dijagnostički značaj seroloških testova i potrebe za uključivanjem kvantitativne PCR u krvi, sa ciljem detekcije reaktivacije virusa.

Jetra je najćešće zahvaćen organ, a hepatitis, prisutan i kod naše pacijentkinje, može se javiti u preko 80% slučajeva, potom sledi zahvaćenost bubrega u 40%, pluća u 33%, kardiovaskularnog sistema u 15% i pankreasa kao kod naše pacijentkinje u 5% slučajeva.

Najčešće opisani hematološki poremaćaji u DRESS sindromu su: povećan broj atipičnih limfocita (63%), eozinofilija (52%), limfocitopenija (45%), i trombocitopenija (25%). Kod naše pacijentkinje bila je prisutna: leukocitoza (> 11 x 109/L), eozinofilija (> 1,5 x 10^9) i povišen broj atipičnih limfocita (> 5%).

Prognoza je je dobra ukoliko se na vreme isključi inkriminisani lek, iako je za postizanje kompletne remisije potrebno nekoliko nedelja, kao kod naše pacijentkinje, gde je do kompletne rezolucije bilo potrebno 8 nedelja.

Ukoliko su jače zahvaćeni unutrašnji organi, potrebno je u terapiju uključiti sistemske kortikosteroide u srednjim i visokim dozama, ali je potrebno prethodno isključiti postojanje infekcije. Ukoliko se pažljivo, tokom 6–8 nedelja smanjuje doza kortikosteroida, snižava se rizik od recidiva, što smo i mi sproveli kod naše pacijentkinje. Ukoliko se u terapiju ponovo uvede inkriminisani lek, simptomi se javljaju posle kraćeg vremenskog perioda od uključivanja leka.

Preko 40 različitih lekova među kojima su i lamotrigin i olazapin su u literaturi povezani sa razvojem DRESS sindroma, najčešće su to aromatski antikonvulzivi (fenitoin, fenobarbital, karbamazepin) i sulfonamidi, a potom slede i ostali kao što su dapson (DDS, 4,4-diaminodifenilsulfon), alopurinol, kaptopril, blokatori kallcijumovih kanala, ranitidin, talidomid, minociklin, nesteroidni antiinflamatorni lekovi, antituberkulotici, α-metildopa i antiretrovirusni lekovi (abakavir, zalcitabin, nevirapin). Lamotrigin [6-(2,3-diklorofenil)-1,2,4-triazine-3,5-diamine] nearomatski je antiepilektik, koji ne pokazuje ni

strukturne niti farmakološke povezanosti sa ostalim antiepilepticima kao što je to npr. karbamazepin. Lamotrigin može izazvati različite simptome i znake: osipe po koži uključujući i urtikariju, multiplu insuficijenciju unutrašnjih organa, DRESS sindrom, akutnu insuficijenciju jetre, kao i diseminovanu intravaskularnu koagulaciju. Egzantemi udruženi sa teškim opštim simptomima koji su izazvani lamotriginom, javljaju se najščešće unutar 6–8 nedelja od započinjanja lečenja, ređe nakon 12 nedelja, a po pravilu – nikad kasnije. U literaturi je do sada opisano nekoliko slučajeva DRESS sindroma izazvanog lamotriginom; drugi psihoaktivni lek koji je uzimala naša pacijentkinja je bio antipsihotik olanzapin. Za razliku od lamotrigina, u literaturi postoji veoma mali broj (oko pet), do sada objavljenih radova u kojima se pojava DRESS sindroma povezuje sa upotrebom olanzapina.

Dijagnoza DRESS sindroma kod naše pacijentkinje klasifikovana je kao definitivna; neposredni uzrok sindroma definisan je na osnovu skoring sistema koji je uspostavio Naranjo sa saradnicima, kao verovatna neželjena reakcija izazvana lamotriginom (finalni skor 7); mi nismo objektivno dokazali da je neželjena reakcija bila izazvana lekom, što se moglo učiniti da smo npr. sproveli kožne testove, koji su indikovani nakon određene vremenske distance od jednog do nekoliko meseci (zavisno od dužine terapije potrebne za kompletnu sanaciju svih simptoma i znakova DRESS sindroma). S obzirom da je lamotrigin poznat kao čest uzrok DRESS sindroma, za razliku od olanzapina, da među njima nema unakrsnog reagovanja, a imajući u vidu neophodnost njegove primene u datom trenutku, psihijatar je smatrao da u terapiju ponovo treba uvesti olanzapin. Mi bi za 6 meseci sproveli epikutano testiranje i postepeno ponovo uveli olazapin, kontrolisano, postepeno, u bolničkim uslovima. Iz tog razloga, možemo samo pretpostaviti da je lamotrigin direktno odgovoran za nastanak DRESS sindroma kod naše pacijentkinje, ali je za nju uzimanje ovog leka strogo kontraindikovano.

Zaključak. Prikazujemo slučaj ženske osobe sa DRESS sindromom koji se povukao nakon prestanka uzimanja antikonvulzantnog leka lamotrigina i antipsihotika olanzapina, ali se na osnovu daljeg toka moglo pretpostaviti da je lamotrigin bio uzrok oboljenja.

Ključne reči

Sindrom preosetljivosti na lekove; Antikonvulzivi; Neželjena dejstva i reakcije na lekove; Antipsihotici; Prikazi slučajeva

