



DRUG-INDUCED HYPERSENSITIVITY SYNDROME CAUSED BY LAMOTRIGINE, A CASE REPORT

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SUMMARY – Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, also known as drug-induced hypersensitivity syndrome (DIHS), is an under-recognized and potentially life-threatening hypersensitivity reaction associated with a variety of medications, many of them anti-epileptics. Patients with DRESS syndrome typically present with rash, swelling, fever, and systemic manifestations. We report a case of a patient admitted to out hospital after the administration of an anticonvulsive drug lamotrigine. She was presented with high fever, rash, face oedema and elevated liver enzymes. At admission, all previous medications were discontinued, systemic corticosteroid therapy was administered, and the patient was monitored for signs of clinical recovery. This case report suggests that in patients presenting with skin rash and systemic abnormalities after a recent change in medications, physicians should consider DRESS syndrome as a possible diagnosis and switch to a more aggressive therapy if removal of the offending agent does not result in clinical improvement. Early diagnosis can reduce the risk of complications and the mortality rate.

Key words: drug-induced hypersensitivity, drug reaction, lamotrigine

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, also known as drug-induced hypersensitivity syndrome (DIHS), is an under-recognized and potentially life-threatening hypersensitivity reaction associated with a variety of medications, many of them anti-epileptics. Patients with DRESS syndrome typically present with rash, swelling, fever, and systemic manifestations such as a severe transaminitis.¹

Isolated elevation of liver transaminases is the most common laboratory manifestation of hepatitis in DRESS syndrome. In severe cases it can progress to

Table 1. Drug groups associated with DRESS/DIHS

Drug groups:
Anticonvulsants
Antidepressants
Sulfonamides/sulfones
Anti-inflammatories
Anti-infectives
Angiotensin-converting enzyme inhibitors
Beta-blockers
Specific Examples:
phenytoin, carbamazepine, phenobarbital, lamotrigine, valproate
despiramine, amitriptyline, fluoxetine
dapsone, sulfasalazine, trimethoprim-sulfamethoxazole
piroxicam, naproxen, diclofenac, sulindac, ibuprofen
abacavir, nevirapine, linezolid, doxycycline,
nitrofurantoin
captopril, enalapril
atenolol, celiprolol

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fulminant liver failure, occurring in as many as 10% of cases and accounting for the principle cause of mortality in patients affected by DRESS syndrome.¹

These patients are typically found to have started one of a few select medications in the past two to eight weeks with aromatic anti-epileptics being the most commonly implicated.^{2,3}

Drug group's associates with DRESS/DIHS are shown in the table (Table 1.).

Although its true incidence is unknown, DRESS syndrome has been estimated to occur in approximately one out of 1,000 to 10,000 new users of anti-epileptic medications.^{4,5}

Case report

A 52-year-old woman was presented at the Emergency Department (ED) of the Clinical Hospital Sveti Duh with a high fever (40°C), maculopapular rash prominent on most parts of the chest, back, extremities, and face oedema and erythema (Fig. 1,2).

Two days prior she was administered for first time an anticonvulsive drug (lamotrigine) during the modification of chronic psychiatric therapy at the University Psychiatric Hospital Vrapčce. She was referred to the Clinical Hospital Sveti Duh for further evaluation.

There was no involvement of the oral mucosa, palms, or soles. The patient's past medical history included hypertension, diabetes type II and depression. There were no previously known allergies to drugs. Physical examination showed that heart rhythm is normal. No murmurs, gallops, or rubs were auscultated. There were no signs of respiratory distress. Lung sounds were clear in all lobes bilaterally without rales, rhonchi, or wheezes. The abdomen was soft, symmetric, and non-tender and without distention. No masses, hepatomegaly, or splenomegaly were noted. No focal deficits were appreciated on neurological examination. The initial laboratory results revealed elevated liver enzymes and leukocytosis, but no eosinophilia. The chest X-ray showed normal size and shape of the chest wall and the main structures in the chest. Covid-19 infection was excluded after negative reverse-transcription of a polymerase chain reaction (PCR) test for severe acute respiratory syndrome coronavirus (SARS COV2). The diagnostic panel for hepatitis serology showed past HBV infection. Other diagnostic



Figure 1. Maculopapular rash



Figure 2. Face erythema and swelling

tests that excluded the possible causes of the symptoms were also carried out - anti-nuclear antibodies (ANA), blood cultures, serology for chlamydia and/or mycoplasma.

She was admitted to the Clinical Hospital Sveti Duh with a presumptive diagnosis of a drug-induced hypersensitivity. At admission, systemic corticosteroid therapy was started, all previous medications were discontinued and the patient was monitored for signs of clinical recovery.

Although no formal diagnostic criteria for DRESS syndrome have been widely accepted, the Kardaun *et al.* of the Severe Cutaneous Adverse Reactions (RegiS-

Table 2. Scoring system by RegiSCAR

Criteria	No	Yes	Unknown
Fever greater than 38.5°C	-1	0	-1
Enlarged lymph nodes	0	1	0
Atypical lymphocytosis	0	1	0
Eosinophilia	0	0	0
10-19,9%		1	
>20%		2	
Skin rash			
> 50% of the skin surface	0	1	0
morphology suggestive			
of DRESS	-1	1	0
biopsy suggestive of DRESS	-1	0	0
Organ involvement	0		0
1		1	
2 or more		2	
Resolution greater than 15 days	-1	0	
Evaluation of other causes (ANA, blood cultures, serology for hepatitis A virus, hepatitis B virus, hepatitis C virus, and chlamydia and/or mycoplasma)	0	1	0

DRESS= Drug reaction with eosinophilia and systemic symptoms, ANA= Anti-nuclear antibodies

CAR) study group published a scoring system in 2007 that has been widely used to evaluate potential cases of DRESS syndrome (Table 2).⁶

The criteria for this system include: first, fever greater than 38.5°C; second, enlarged lymph nodes; third, eosinophilia; fourth, atypical lymphocytosis; fifth, skin involvement; sixth, organ involvement; seventh, resolution greater than 15 days; and eighth, evaluation of other causes (ANA, blood cultures, serology for hepatitis A virus, hepatitis B virus, hepatitis C virus, and chlamydia and/or mycoplasma). Using this scoring system, a final score of less than two indicates no case, a final score of between two and three indicates a possible case, and a final score of between four and five indicates a probable case, and a final score of greater than five indicates a definite case.

The patient in this case report had a score of five points (one each for fever greater than 38.5°C, skin rash suggestive of DRESS, affecting >50 % of the skin surface, liver involvement, and evaluation of other potential causes), indicating a 'probable case' of DRESS per the RegiSCAR scoring guidelines.



Figure 3. Confluent configuration of the rash



Figure 4. Confluent configuration of the rash

Within five days of admission and corticosteroid treatment, the laboratory results showed a slight progression of elevated liver enzymes. Other laboratory results were without significant change. Confluent configuration of the rash was noticed (Fig. 3,4).

On 10th day of the admission, the clinical improvement was obvious. There was no face erythema or swelling, and the skin rash had begun to resolve (Fig. 5, 6 and 7). The levels of transaminases began to improve, and she was discharged home, with metilprednizolon still in the therapy until a follow-up with an immunologist within four weeks.



Figure 5. Rash resolution



Figure 6. Resolution of the face oedema and erythema

Discussion

As with most severe allergic reactions, DRESS syndrome involves a rash, diffuse swelling, and eosinophilia.^{2,6,7} The hallmark of DRESS syndrome, however, is the presence of systemic manifestations, such as inflammation of the liver, kidneys, heart, or other organs.⁸ Prompt recognition of the adverse drug reaction and discontinuation of the offending medications are imperative steps in limiting the progression of DRESS syndrome. Systemic corticosteroids have become a mainstay of therapy in severe cases and often produce a marked improvement in clinical symptoms and laboratory measures within just a few days of the initiation



Figure 7. Rash resolution

of the treatment.⁹ If symptoms continue to progress despite the use of corticosteroids, other options include intravenous immunoglobulin (IVIG) and/or plasmapheresis.¹⁰ The mortality rate in patients affected by DRESS syndrome is about 10%, with the principle cause of mortality being fulminant liver failure.¹

Conclusion

In patients presenting with skin rash and systemic abnormalities after a recent change in medications, physicians should consider DRESS syndrome as a possible diagnosis and switch to more aggressive therapy if removal of the offending agent does not result in clinical improvement. Early diagnosis can reduce the risk of complications and the mortality rate.

Consent

Verbal informed consent was obtained from the patient for the publication of this case report and the accompanying images.

The authors state that this manuscript has not been published previously and is not currently being assessed for publication by any journal other than the *Acta Clinica Croatica*. The authors disclose that they did not receive any financial support for the study. No proprietary interest is involved in the study.

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Sažetak

SINDROM PREOSJETLJIVOSTI UZROKOVAN LAMOTRIGINOM; PRIKAZ SLUČAJA

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Reakcija na lijek s eozinofilijom i sistemskim simptomima (DRESS, engl. Drug Reaction with Eosinophilia and Systemic Symptoms), ili sindrom preosjetljivosti uzrokovan lijekom (DIHS, engl. Drug-induced Hypersensitivity Syndrome), je često neprepoznato i potencijalno životno ugrožavajuća reakcija preosjetljivosti povezana s uzimanjem raznih lijekova, najčešće antiepilepticima. Pacijenti s DRESS/DIHS se najčešće prezentiraju osipom, febrilitetom i zahvaćanjem unutarnjih organa. U ovom prikazu slučaja predstavljena je pacijentica koja je nakon uzimanja lamotrigina razvila osip, visoki febrilitet, edem lica te hepatitis. Po primitku u bolnicu, isključena je sva dotadašnja terapija te započeto sistemsko liječenje kortikosteroidima. Ovaj rad sugerira razmatranje dijagnoze DRESS/DIHS kod pacijenata s naglom pojavom osipa te sistemskim simptomima, a nakon uvođenja novog lijeka u terapiju te se preporuča agresivniji pristup u terapiji osim prestanka uzimanja uzročnog lijeka. Rano prepoznavanje može smanjiti rizik komplikacija i mortalitet.

Ključne riječi: *preosjetljivost uzrokovana lijekom, reakcija na lijek, lamotrigin*