**DRESS Causes Interstitial Nephritis – Mansouri M et al**

**Case Report**

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**Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) Cause Interstitial Nephritis: a case Report and Review of Literatures**

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**Introduction**

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) is a potentially life-threatening, complex, and multifaceted disease which may imitate other grave conditions. It presents with cutaneous drug eruptions, fever, hematologic abnormalities (an eosinophil count of 1500/mm3 or atypical lymphocytosis), and systemic involvement including hematologic, renal, pulmonary, hepatic, cardiac, gastrointestinal, neurologic, and endocrine abnormalities. Anticonvulsant therapies (mainly carbamazepine) are among the most important causative drugs.

**Case report:** Herein we present a 10-year-old girl who developed skin rash, systemic symptoms, marked eosinophilia, and kidney involvement following anticonvulsive treatment with phenobarbital and sodium valproate. She experienced multiple hospitalizations due to an improper diagnosis and management.

**Conclusion:** Drug Induced Hypersensitivity Syndrome (DIHS) is a severe life-threatening disorder which mostly occurs due to aromatic anticonvulsive drugs. The disease may mimic other serious conditions and delay in the diagnosis and improper treatment may cause organ involvement and more severe outcomes.

**Key words:** Drug Hypersensitivity Syndrome; DRESS Syndrome; Drug Reaction with Eosinophilia and Systemic Symptoms; Drug Eruptions; Interstitial Nephritis.

**Running Title:** DRESS Causes Interstitial Nephritis
eruptions can be purpuric, vesiculobullous, or targetoid and morbilliform. Facial edema may be detected in 25% of the patients [4,5]. Later in the course of the disease, the rashes take a violaceous pattern. The clinical features may continue for weeks or months after discontinuation of the offending drug. Lymphadenopathy is observed in 75% of the patients. Hematologic abnormalities include leukocytosis (up to 50×10^9 leukocytes/L), atypical lymphocytes (about 30%), eosinophilia (2.0×10^9 eosinophils/L), anemia, and thrombocytopenia. Lymphopenia may precede leukocytosis [4]. The involvement of other organs includes hepatitis (in 50% of the patients), nephritis (in 10% of the patients), and rarely pneumonitis, colitis, pancreatitis, encephalitis, and myocarditis [6].

Other special features are a delayed onset (2-6 weeks or even up to 3 months) after the introduction of the culprit drug and continuation of clinical symptoms despite discontinuation of the offending agent. Anticonvulsant agents (mainly carbamazepine), allopurinol, sulfasalazine, dapsone, minocycline, and mexiletine are among the most important causative drugs [2,7].

The etiology and pathogenesis of DIHS is considered to be a combination of defective detoxification of reactive metabolites of arene oxides (mainly anticonvulsants) which bind to cellular macromolecules, causing cell necrosis or a secondary immunologic response and a cascade of events that imply herpes family reactivation with HHV-6 and EBV reactivation at the onset of disease. With a delay, HHV-7, and CMV reactivate as well in the course of the disease. The same is true for graft versus host disease (GVHD) [2,4,8]. Several months to years after resolving the acute phase, however, some autoimmune diseases may develop, including diabetes mellitus, autoimmune hypothyroidism, and systemic lupus erythematosus (SLE). A dramatic decrease in serum IgG, IgA, and IgM is noted, especially at the onset, which reaches the lowest level one week following discontinuation of the culprit drug and eventually returns to normal after complete improvement [2]. There is not a standard method for the diagnosis of Dress; however, several features have been defined by some experts:

I- The original criteria established by Bocquet et al were some common elements including 1) drug eruptions 2) hematologic abnormalities (like eosinophilia or atypical lymphocytes 3) systemic manifestations (adenopathy more than 2 cm, hepatitis (more than two times increase in the transaminase level) and more than two times increase in the size of lymph nodes.

II- The second method is regarded as the RegiSCAR DRESS scoring system and its contributing factor include 1) an acute rash 2) the reaction suspected to be drug related 3) hospitalization 4) fever >38˚, 5) enlarged lymphnodes ≥ 2 sites, 6) involvement of ≥1 internal organ, 7) hematologic disorders (lymphocyte abnormalities above or below normal limits, eosinophils over laboratory limits, platelets under laboratory limits). The first 3 criteria are necessary for diagnosis and include an acute rash, suspicion of a drug-related reaction, and hospitalization.

III – Other diagnostic criteria have been proposed by the Japanese Research Committee (J-Scar) and including a maculopapular rash developing >3 weeks after starting the offending drug, prolonged clinical symptoms after discontinuation of the causative drug, fever >38 °C, liver abnormalities (ALT> 100 U/L) or other organ involvements: at least more than one from following signs: leukocytosis, atypical lymphocyte (>5%), eosinophilia (≥1.5×10^9/L), lymphadenopathy, and HHV6 reactivation. If all 7 criteria are present, the patient is diagnosed with typical DIHS; if only the first 5 criteria (1-5) are present, a diagnosis of atypical DIHS is made [2]. Differential diagnoses attributable to the most likely infectious diseases are measles and infectious mononucleosis. Other differential diagnoses include Kawasaki syndrome, serum sickness-like reaction, hypereosinophilic syndrome, autoimmune diseases, and malignancies [10].

Management relies on immediate discontinuation and lifelong avoidance of the offending drug, prompt referral of the patient to a specialized center, and high-dose glucocorticoid therapy. N acetylcysteine (NAC) may be effective alone or in combination with a glucocorticoid or intravenous immunoglobulin G (IVIG). The Follow-up should be set even for one or two years [7,11].

Case Report

Our patient, a 10-year-old girl, was on phenobarbital due to febrile seizures. One week later, she developed maculopapular eruptions and her physician decided to hold all the medications; subsequently, the seizures occurred again and phenobarbital was started for the second time as an anticonvulsive treatment. She was readmitted three weeks later due to an erythematous maculopapular rash that developed over the face...
along with facial edema and perioral scaling. At this time, phenobarbital was discontinued and sodium valproate was started. Three days later, the skin rash intensified and expanded to the trunk, proximal limbs, and eventually all over the body. The fever was accompanied by vertigo and arthralgia of both knees. The physical examination showed a pulse rate around 105/min, a normal blood pressure, a respiratory rate about 35/min, a temperature of 39°C, and mild enlargement of the liver. Blood cell counts showed a white blood cell count of 9,800/mm3 with hypereosinophilia (1142 or 19%), C-reactive protein of 104 mg/l (normal < 10), and an erythrocyte sedimentation rate of 67 mm/h (normal < 10). Other laboratory findings were as follows: lactate dehydrogenase= 280 iu/l (normal < 195 IU/l), AST=50 IU/l (normal < 18 IU/l), ALT=120 IU/l (normal < 19 IU/l), and alkaline phosphatase=1040 IU/l (normal 21–85 IU/l). Total and direct bilirubin were normal. Serologic tests were negative for antinuclear antibodies and rheumatoid factor.

Since a hypersensitivity reaction to anticonvulsant drugs was suspected, valporic acid was stopped and systemic steroid treatment was started. With a relative improvement of the skin rashes, the patient was discharged from the hospital 3 days later. She was readmitted three weeks later because of an occasional high fever and severe skin dryness, scaling, and arthralgia. A physical examination demonstrated severe xerosis, exfoliation of the skin, swelling, erythema over the knees and painful passive and active movements of the knee joints. She also had marked erythema and scaling around the anus and genitalia. Echocardiography was normal. Abdominal sonographic examination revealed that the kidneys, spleen, and the urinary bladder were normal; however, hepatomegaly and a little free fluid in the cul-de-sac were noticed on abdominal ultrasound. About 12-15 WBC's and one plus glucose were detected on urinalysis examination. Blood Na=122 mEq/l, k=4.5 mEq/l, BUN=15 mg/dl, Cr=1.3 mg/dl and venous blood gas showed a moderated metabolic alkalosis. Na fractional excretion in the urine was 1.4. A nephrology consultation was requested and interstitial nephritis was proposed. Beside the supportive care for the kidneys and skin, the patient also received 10 mg/day of oral prednisolone for one month. All the symptoms and signs and paraclinical abnormalities were resolved and systemic steroid was tapered and discontinued 2 weeks later. The patients had no problem on follow-up visits.

Discussion

DRESS syndrome is a severe and sophisticated drug reaction with an immunological basis mainly involving CD4 T cells [11]. Although there is no reliable standard criteria for the diagnosis of DRESS syndrome, there exist different scoring systems which are applied for the diagnosis of the condition, including the Regi-SCAR score and J-SCAR score which were mentioned earlier [2,4,6]. The case was consulted with the Immunology and Allergy Department in the last hospitalization. A diagnosis of DIHS probably due to phenobarbital and sodium valproate was made for her according to Table 1.

Table 1. The RegiScar-group diagnosis score for drug reaction with eosinophilia and systemic symptoms (DRESS)

<table>
<thead>
<tr>
<th></th>
<th>NO</th>
<th>Yes</th>
<th>unknown</th>
</tr>
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<tbody>
<tr>
<td>fever &gt;38 °C</td>
<td>-1</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>Lymph enlargement*</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>≥ 2 sites&gt; 1 cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical lymphocytes</td>
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<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Eosinophilia:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>700-1499 or 10%-</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>19.9%</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>≥1500 or ≥20%</td>
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<td></td>
<td></td>
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<tr>
<td>Skin rash</td>
<td>0</td>
<td></td>
<td>0</td>
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<tr>
<td>Extent &gt;50%</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>At least 2 of edema,</td>
<td>-1</td>
<td>1</td>
<td>0</td>
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<tr>
<td>infiltration, purpura,</td>
<td>-1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>scaling</td>
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<td>Biopsy suggesting</td>
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<td></td>
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<tr>
<td>DRESS</td>
<td></td>
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<td></td>
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<tr>
<td>Internal organ involved</td>
<td>0</td>
<td></td>
<td>0</td>
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<tr>
<td>One</td>
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<tr>
<td>2 or more</td>
<td></td>
<td>1</td>
<td>2</td>
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<tr>
<td>Resolution in &gt; 15 days</td>
<td>-1</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>At least 3 biological</td>
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<td>alternative diagnosis</td>
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Final score: < 2 Negative; 2-3 possible case; 4-5 probable case; >5 definite case [9]

*Lymphadenopathy enlargement

The visceral organ involvement distinguishes DRESS from other drug allergies. Among them, the liver involvement is more common (involvement rate: %50-87%) and equally more fatal than the others [5,11]. Other organs affected during the disease are the kidneys (involvement rate: 10%-%53) [12], and more rarely the lungs, large
intestine, and pancreas. Interestingly, the type of organ captivation is also related to the type of offending drug, e.g. minocycline-induced DRESS is accompanied by lymphadenopathy, while allopurinol-induced DRESS usually presents with renal failure [6]. Infrequent clinical manifestations include interstitial nephritis, colitis, arthralgia, myocarditis, and splenic rupture [11]. The liver involvement may be anicteric, which is more common and determined by an elevation in the ALT level, or icteric, which has a poorer outcome. HHV6 reactivation during the disease usually causes recurrent increment of the liver enzymes. A rise in serum creatinine and recent proteinuria implicate renal involvement. Published data shows that interstitial nephritis in the course of DRESS syndrome has a more important and prevalent role in inducing the renal failure than the tubular necrosis phenomenon [12]. As previously explained, our patient showed renal involvement in addition to mild liver abnormality, and interstitial nephritis was a compatible diagnosis for her allergic renal disease. The severity of renal impairment may vary from a mild increase in serum creatinine to end stage renal disease [11]. Our patient fortunately demonstrated a mild feature of renal dysfunction. Whether the disease could have a worse outcome if proper intervention was not performed on time is not certain. On the basis of the studies which show the role of T lymphocyte that are directed toward acting against body tissue in this disease and development of autoimmune disease in years afterward, the proper use of systemic steroid, IVIG and N acetyl cysteine can be lifesaving in the condition [11, 13].

That fact that makes the disease very mysterious is first, the very long latency between starting the offending drug and presenting the symptoms which sometimes takes up to 3 months [2,7], and second, the variability in the target organs involvement and their severity which may cause the diagnosis even more challenging [10]. Since herpes family viruses (HHV6, EBV, CMV and HHV7) reactivation has been traced in the pathogenesis of the disease (in which one can consider DRESS syndrome a kind of interaction between the culprit drug, host immune system, and herpes viruses), this similarity between the DRESS syndrome and infection with herpes family viruses may be misleading [2, 4]. The similarity between the disease and other serious illnesses like infection, lymphoreticular malignancies, and autoimmune diseases may have an important role in delaying the diagnosis and significant associated morbidities [2, 4, 6]. In addition to proper and timely diagnosis and withdrawal the offending medication which are essential for the control of the situation, another substantial issue is to start a convenient anti inflammatory medication like a systemic steroid and to continue it for a long period of time until the inflammation subsides [4]. As these proceedings were not properly performed in our case, she experiences multiple hospital admissions. It is noteworthy that an incorrect diagnosis results in continuation of the offending drug that consequently causes a more severe and uncontrollable disease, as in our case.

Conclusion
DIHS is a severe life-threatening condition that mostly occurs due to aromatic anticonvulsive drugs. The disease may mimic other serious conditions and a delay in the diagnosis and inappropriate treatment may cause organ involvement and a more severe outcome.

Conflict of Interest
None declared

Financial Support
None declared

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References