Case Report
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Lamotrigine-Induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Masquerading as A Systemic Autoimmune Process

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ABSTRACT

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a syndrome that is the consequence of a hypersensitivity reaction associated with exposure to certain medications in a population of individuals with presumed genetic predisposition to certain drugs. It is a potentially life-threatening condition that presents with rash and multi-organ system involvement. While characteristic findings include eosinophilia, lymphocytosis, and lymphadenopathy (LAD), clinical and pathological features can vary significantly. Aside from the observed immune response to certain drugs, its pathogenesis also includes reactivation of latent Herpesviridae. This suggests that drug exposure alone may not elicit the syndrome if neither active or latent Herpesviridae are present, Drug-induced hypersensitivity syndrome (DIHS) is postulated to be a consequence of the interplay between drug exposure and viral infection (latent or otherwise). With a mortality rate of approximately 10%, timely recognition and treatment is imperative. This end can only be accomplished through greater familiarity with the clinical features of DRESS/DIHS. We present a case report of a 35-year-old woman with fever, rash, and lymphadenopathy suffering from lamotrigine-associated DRESS/DIHS masquerading as a systemic autoimmune process.

Keywords: *Drug Reaction, Eosinophilia, Systemic Symptoms, Drug-Induced Hypersensitivity Syndrome, Lamotrigine, Lamictal, Regiscar, Cervical Lymphadenopathy*

Introduction

DRESS, or DIHS, represents both cutaneous and visceral manifestations of a hypersensitivity reaction to certain medications. It was first described in 1937 as exfoliative dermatitis following treatment with the antifungal sulfanilamide or related compounds (Myers *et al*., 1937). Since that time, a number of drugs have been implicated including but not limited to allopurinol, dapsone, phenytoin and other anticonvulsants (Shear and Spielberg, 1988). It has been presumed that coincident viral infection, or reactivation of latent Herpesviridae, also contributes to the pathogenesis of this syndrome (Bocquet *et al*., 1996). It is characterized by fever, lymphadenopathy, hematologic abnormalities, and multi-organ involvement. Onset tends to occur weeks after initiation of the offending drug and flares may continue to occur well after the drug has been discontinued. Due to a lack of specific features, the diagnosis is

frequently overlooked in routine clinical practice. With a mortality rate of approximately 10%, timely recognition and treatment is imperative. Criteria for diagnosis have been established by the collective work of the RegiSCAR group (Table 1) and a Japanese consensus group. We present a case report of a 35-year-old female with lamotrigine-associated DRESS/DIHS who responded well to corticosteroids following cessation of lamotrigine use.

Table 1: RegiSCAR Scoring System for Classifying DRESS applied to the Patient (Husain *et al*., 2013).

Symptoms and Laboratory Findings for DRESS	Scoring (points) For DRESS	Patient Result	Patient Score
Fever 38.5^{0}C	No/U: (-)1, Y: 0	38.8^{0}C	0
Lymphadenopathy	No/U: 0, Y: 1	Yes	1
Eosinophilia Eosinophils (per µL) Eosinophils (%), if WBC < 4000	 700-1500: 1, ≥ 1500: 2 10-19.9%: 1, ≥ 20%: 2 * Max score = 2	No	0
Atypical Lymphocytes	No/U: 0, Y: 1	Absent	0
Skin Rash -Extent (% body surface area) -Rash suggesting DRESS -Biopsy suggesting DRESS	 No/U: 0, > 50%: 1 No: (-)1, U: 0, Y: 1 No: (-)1, Y/U: 0 *Minimum score = -2, Max = 2	 > 50% Yes Unknown	 1 1 0
Organ Involvement -Liver -Kidney -Lung -Muscle/heart -Pancreas -Other	 No/U: 0, Y: 1 No/U: 0, Y: 1 No/U: 0, Y: 1 No/U: 0, Y: 1 No/U: 0, Y: 1 No/U: 0, Y: 1 *Max score = 2	 Yes No No No No No	 1 1
Resolution ≥ 15 days	No/U: (-)1, Y: 0	Yes	0
Evaluations of other potential causes -Antinuclear antibody -Blood culture -HAV/HBV/HVC -Chlamydia/mycoplasma *If none positive and ≥ 3 of above negative	 No: 0, Y: 1	 Negative Negative Negative Negative	 1
Total Score: 6 (Definite case of DRESS)			
Final Score of < 2, no case; score of 2-3, possible case; score 4-5, probable case; score > 5, definite case. Range of total score is -4 to 9. U: Unknown, Y: Yes			

Case Presentation

A 35-year-old female with past medical history significant for depression and anxiety presented to our emergency department for evaluation of two weeks of subjective fevers and intermittent chills. She denied known sick contacts and said she was without other systemic symptoms. Her medications included trazodone 50 mg daily, valproic acid 100 mg daily, lamotrigine 50 mg twice daily, and fluoxetine 30 mg daily. Vital signs were stable on presentation and physical examination revealed a diffuse maculopapular rash affecting the face, trunk, and all extremities with sparing of the palms and soles.

Right cervical LAD was also appreciated. Her laboratory results were significant for Aspartate Aminotransferase (AST) of 211 (NR <35 U/L), Alanine Transferase (ALT) of 255 (NR < 55 U/L), Alkaline Phosphatase (ALP) of 195 (NR < 140 U/L) and serum creatinine of 1.5 mg/dl with Blood Urea Nitrogen of 25 mg/dl. Urine analysis and right upper quadrant ultrasound were unremarkable for any acute findings. Rheumatology was consulted for input regarding concern of occult systemic autoimmune disease. Serologic testing for infectious etiologies included but were not limited to the following: Human Immunodeficiency Virus (HIV), Cytomegalovirus (CMV), Epstein-Barr Virus (EBV), Toxoplasmosis, viral Hepatitis (A, B, and C), Parvovirus B19, Bartonella, Brucella, RPR; all were negative. Heterophile antibody, rheumatoid factor, antinuclear antibody, QuantiFERON, and blood cultures were also negative. A surgical biopsy of the enlarged right cervical lymph node was performed. The histological findings included palisading neutrophils, histiocytes, lymphocytes, and necrosis without evidence of malignancy or infection. The findings, most notably the presence of neutrophils, were not entirely consistent with those seen in KFD, which is typically characterized by a predominance of histiocytes and absence of neutrophils.

Further questioning of the patient revealed that she had been started on lamotrigine 50 mg daily five weeks prior to her admission and that the dose had been increased to 50 mg twice daily 3 weeks prior. Given the patient's negative workup, the temporal relationship between the initiation of lamotrigine and the onset of her symptoms, the lack of another identifiable trigger, and her score per diagnostic criteria developed by the Registry of Severe Cutaneous Adverse Reactions or RegiSCAR Group (Table 1), she was diagnosed with DRESS/DIHS. Lamotrigine was discontinued and she was started on prednisone 40 mg/day with plan to taper over a 2-month course (Husain *et al*., 2013). She was subsequently discharged after resolution of symptoms and upon follow-up denied recurrence of symptoms.

Discussion

A severe cutaneous reaction that would eventually become known as DRESS was initially observed as an exfoliative dermatitis in patients receiving sulfanilamide treatment for gonorrhea or candida vulvovaginitis (Myers *et al*., 1937). It was then observed in association with exposure to phenytoin, among other anticonvulsants. There were also descriptions of erythema multiforme, exanthematous eruption, toxic epidermal necrolysis, and Stevens-Johnson syndrome (Singer and Wallace, 1986; Shear and Spielberg, 1988).

Ever since that time, many different terms were used to describe this clinical syndrome, with those terms primarily depending on the culprit drug, such as allopurinol hypersensitivity syndrome, sulfone

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syndrome, and anti-convulsant hypersensitivity syndrome. To limit confusion, Bocquet, *et al*. (1996) proposed the use of the term DRESS in hopes of providing a single umbrella term with a clear description of the nature of these exposure-related syndromes. DRESS/DIHS is a severe reaction following drug initiation that most commonly develops 3-6 weeks following initiation of therapy (Cho *et al*., 2017). Common features include rash, fever, lymphadenopathy, and hematologic abnormalities. Drugs commonly implicated include anticonvulsants such as phenytoin, carbamazepine, phenobarbital, valproic acid, and lamotrigine as well as allopurinol, minocycline, sulfasalazine, nevirapine, vancomycin, trimethoprim-sulfamethoxazole, and abacavir (Cacoub *et al*., 2011). DRESS/DIHS is relatively rare, with an incidence of approximately one case per 1,000-10,000 exposures (Chiou *et al*., 2008). The pathophysiology of DRESS/DIHS is not entirely understood, but it is believed that the interplay between viral reactivation, particularly EBV, CMV, and HHV-6, and immunologic response from regulatory T-cells is paramount in evolution of this disease.

Reactivation of latent Herpesviridae infection, specifically HHV-6, has been observed to be associated with not only more severe disease but also a protracted clinical course (Miyagawa *et al*., 2016). In patients with DRESS/DIHS, an association has been observed between the presence of higher viral load or antibody titers and poorer outcomes. Polymorphisms influencing the process of drug breakdown (e.g. N-acetylation) and mitigation of toxic metabolites are speculated to have some role in increasing one's susceptibility to developing DRESS/DIHS when exposed to specific drugs.

Skin manifestations are prevalent and tend to occur early in the disease course as an eruption of a maculopapular rash covering the trunk and extremities. The rash can eventually coalesce to form large patches of confluent erythema and facial swelling often occurs. Facial edema is a hallmark feature of the disease. Such cutaneous manifestations are estimated to occur in up to 73–100% of the patients (Cho *et al*., 2017). Erythroderma may eventually develop as rash typically involves greater than half of the body surface area. The lesions vary but many are infiltrative papules or plaques with purpuric features. These cutaneous lesions are often polymorphoric: maculopapular, urticarial, exfoliative, lichenoid, pustular, bullous, target-like, or eczematous. Desquamation tends to evolve around the time of resolution.

Both hematologic and organ system dysfunction have been observed. Eosinophilia and atypical lymphocytosis are the most common hematologic manifestation of DRESS syndrome. Liver injury is the most common type of end-organ damage and typically presents in a cholestatic pattern (Peyrière *et al*., 2006). Notably, hepatic injury can occur well before the onset of characteristic cutaneous lesions. While renal involvement is generally mild, there have been documented cases of severe interstitial nephritis and acute tubular necrosis ultimately leading to acute renal failure. The lungs are the third most involved organ. Patients may present with spectrum of conditions ranging from pleurisy and interstitial

pneumonitis to acute respiratory distress syndrome (ARDS). Cardiac involvement is primarily limited to two common entities: hypersensitivity myocarditis and acute necrotizing eosinophilic myocarditis. Involvement of other organs, albeit less likely, can be encountered including the brain, pancreas, gastrointestinal tract, and spleen (Cacoub *et al*., 2011).

Some of the short and long-term consequences of DRESS/DIHS are mentioned in Table 2. Patients with DRESS often develop signs and symptoms as early as 3 weeks following initiation of the offending drug. When compared to other familiar cutaneous hypersensitivity reactions such as Steven-Johnson Syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis, the latency period for DRESS is much longer. This fact alone could increase the likelihood of overlooking the diagnosis altogether. Further, DRESS/DIHS share clinical features common to a wide spectrum of systemic disorders which further complicates the goal of timely and accurate diagnosis. Cervical lymphadenopathy has been reported as a finding in Lamotrigine-associated DRESS/DIHS (Schlienger *et al*., 1998). Surgical biopsy can assist in identifying the etiology of cervical lymphadenopathy because many of the potential etiologies like infections, neoplasms, and inflammatory disorders have unique histopathology. Further, DRESS/DIHS is generally considered a clinical diagnosis. Several diagnostic criteria have been developed including those drafted by the RegiSCAR group (Table 1) and a Japanese consensus group.

Table 2: Short- and long-term sequelae of DRESS/DIHS

Arthralgia, reactive arthritis, rheumatoid arthritis
Autoimmune thyroiditis Colitis/enteropathy
Cutaneous autoimmune disease
Vitiligo, alopecia areata
Diabetes mellitus
Encephalitis
Fulminant hepatic failure
Hemolytic anemia
Myocarditis
Pneumonitis
Renal failure
Systemic lupus erythematosus
Venous thrombosis

If suspected, the offending agent should be discontinued with immediate initiation of supportive care. The general consensus is that systemic corticosteroids are the mainstay treatment for patients with DRESS syndrome (Husain *et al*., 2013). A starting dose of prednisolone or an equivalent of 0.5–1.0 mg/kg/day with a gradual tapering over 2–3 months is typically recommended. As anticipated, our patient experienced significant interval improvement upon cessation of Lamotrigine and administration

of systemic steroids.

It should be noted that patients with DRESS/DIHS are at risk for systemic autoimmune sequelae which can appear months to years after resolution of acute systemic involvement, this necessitating long-term monitoring aimed at its detection and subsequent management.

Conclusion

DRESS/DIHS often presents as a multi-system disorder which can mimic a systemic autoimmune process. It can be distinguished from other diagnoses by history of new drug exposure in the weeks prior to onset of rash or systemic symptoms as well as the absence of serologic and histologic findings commonly observed in autoimmune disease. This case highlights the value of early rheumatological consultation in preventing morbidity and mortality.

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