Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome: lamotrigine Associated

Kendal Allen, OMSIV; Jordan Steelquist, DO; Renee Delos Angeles, DO; He Wang, DO; Andrew Chen, DO

Background

- Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare systemic and cutaneous adverse reaction to a variety of drugs including:
  - Carbamazepine, phenytoin, phenobarbital, zonisamide, lamotrigine, mexiletine, dapsone, sulfasalazine, minocycline, allopurinol, and vancomycin[1]
- Estimated incidence is 1 case per 10,000 patients exposed to associated medications[2]
- Initial signs and symptoms: fever, diffuse morbilliform rash, facial edema, erythroderma, lymphadenopathy, and involvement of one or more internal organs[1,2]
- Common laboratory findings: leukocytosis, eosinophilia, elevated liver enzymes, and abnormal kidney function tests[2]
- Diagnosis of DRESS syndrome is widely based off the criteria from the Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples (RegiSCAR)[1]
- Gold standard for treatment: systemic corticosteroids followed by a 6-8 week taper[4]

Case Presentation

- History of Present Illness:
  - 55 year old male with past medical history of bipolar disorder, anxiety disorder, and squamous cell carcinoma
  - Presented to the ED with 1 week of sore throat, fever, chills, shortness of breath, and fatigue and a diffuse morbilliform rash
  - One month prior to onset of symptoms, the patient was placed on a psychiatric hold at a local hospital and was started on lamotrigine, bupropion, aripiprazole, and hydroxyzine
    - Four days prior to admission, he discontinued these medications
  - Review of Systems: fever, chills, lower extremity edema and mild itching
- Objective:
  - Physical exam: diffuse, non-palpable, morbilliform rash that spared the mucosa, purpura on bilateral lower extremities, inguinal lymphadenopathy, and a negative Murphy's sign
  - Significant laboratory findings:
    - Leukocytosis (WBC 22.9 k/mm^3)
    - Eosinophilia (18%)
    - Elevated total alkaline phosphatase (375 U/L), AST (52 U/L), and ALT (89 U/L)
    - Elevated serum creatinine (1.49 mg/dL)
    - Negative hepatitis panel
    - Negative for mononucleosis, streptococcus, syphilis, and HIV
  - Imaging:
    - Abdominal ultrasound: no liver, gallbladder or pancreatic abnormalities

This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

Diagnosis

RegiSCAR Criteria

Score	-1	0	1	2	Min/Max
Fever ≥ 38.5℃	No	Yes			-1/0
Lymphadenopathy		No	Yes		0/1
Eosinophilia		No	10-19.9%	≥ 20%	0/2
Atypical Lymphocytes		No	Yes		0/1
Skin Rash > 50% of body surface area		No	Yes		0/1
Skin Rash suggesting DRESS	No		Yes		-1/1
Biopsy Suggesting DRESS	No	Unknown /Yes			-1/0
Organ Involvement		No	Yes	≥ 2 organs	0/2
Resolution in ≥ 15 days	Unknown/No	Yes			-1/0
Alternative diagnoses excluded (≥ 3 biological investigations negative)		No	Yes		0/1
Total Score					-4/9

Final score < 2, no case; Final score 2-3, possible case; Final score 4-5, probable case; Final score > 5, definite case.

Clinical Course

- Continued to have elevated liver function tests and a low-grade fever
- Developed facial edema and mild desquamation of the face and upper back
- The most likely cause was concluded to be a drug reaction due to the multiple medications he was recently prescribed
- After an extensive medication review, the offending agent was concluded to be lamotrigine
- RegiSCAR score was 6, indicating a definitive case of DRESS syndrome:
  - Fever (0)
  - Inguinal lymphadenopathy (+1)
  - Eosinophilia 10-19.9% (+1)
  - Atypical lymphocytes (0)
  - Skin rash > 50% of body surface area (+1)
  - Skin rash suggesting DRESS syndrome (+1)
  - Biopsy suggesting DRESS syndrome (unknown, 0)
  - Organ involvement of ≥ 2 organ systems (hepatic and renal, +2)
  - Resolution in ≥ 15 days (unknown, -1)
  - Alternative diagnoses excluded (≥ 3 biological investigations negative, +1)

Discussion

- When reviewing the current literature, this patient's case is similar to other DRESS syndrome cases
- Four weeks prior to presentation, he was started on lamotrigine, an anticonvulsant that is frequently used as a mood stabilizer for bipolar disorder
- Experienced flu-like symptoms followed by a diffuse morbilliform rash, lower extremity purpura and lymphadenopathy
- Although not included in the RegiSCAR criteria, this patient also developed facial edema which is seen in 75% of DRESS syndrome patients[1]
- As seen in this patient, there is evidence that upper respiratory infection symptoms are often experienced as a prodrome to DRESS syndrome, suggesting that viral infections can be a potential trigger[4]
- In several DRESS syndrome cases, there was a documented use of empiric antibiotic therapy due to unfamiliarity of the syndrome[4]
  - Increasing knowledge and awareness of DRESS syndrome can limit the use of unnecessary antibiotics
  - Patients with DRESS syndrome show an unexplained increase in drug cross-reactivity with medications of differing structures[4]
  - The addition of unneeded antibiotics can cause worsening of symptoms, and may lead to relapses weeks after resolution[4]
- Over 90% of DRESS syndrome patients develop organ involvement; with acute liver injury being the most commonly described organ system[2]
  - This results in the main cause of mortality following DRESS syndrome, hepatic necrosis[2]
  - Swift follow up with PCP is essential to trend liver function tests

Conclusion

- Lamotrigine is a medication commonly associated with DRESS syndrome, with symptom onset two weeks to two months after initiation of the medication
- In patients with diffuse rash and lower extremity purpura it is important to have workup with CBC with differential, AST, ALT, total alkaline phosphatase, and serum creatinine
- Although rare, it is imperative to maintain a high suspicion for DRESS syndrome, and initiate treatment including cessation of the offending agent and systemic corticosteroids

References

1. Hama N, Abe R, Gibson A, Phillips EJ. Drug-Induced Hypersensitivity Syndrome (DIHS)/Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS): Clinical Features and Pathogenesis. J Allergy Clin Immunol Pract. 2022 May;10(5):1155-1167.e5. doi: 10.1016/j.jaip.2022.02.004. Epub 2022 Feb 15. PMID: 35176506; PMCID: PMC9201940.
2. Calle AM, Aguirre N, Ardila JC, Cardona Villa R. DRESS syndrome: A literature review and treatment algorithm. World Allergy Organ J. 2023 Apr 8;16(3):100673. doi: 10.1016/j.waojou.2022.100673. PMID: 37082745; PMCID: PMC10112187.
3. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, Roujeau JC. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol. 2007 Mar;156(3):609-11. doi: 10.1111/j.1365-2133.2006.07704.x. PMID: 17300272.
4. Shiohara T, Mizukawa Y. Drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS): An update in 2019. Allergol Int. 2019 Jul;68(3):301-308. doi: 10.1016/j.alit.2019.03.006. Epub 2019 Apr 16. PMID: 31000444.