Un-DRESSing Lithium: A Pediatric case of Lithium Induced Drug Hypersensitivity Syndrome

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INTRODUCTION

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), also known as Drug Induced Hypersensitivity Syndrome (DIHS), is a rare but severe cutaneous drug reaction characterized by rash and systemic multi-organ involvement. Given its typically delayed onset, variable clinical presentation, variety of known inciting agents, and mimicry of more commonly seen drug side effects, this illness presents a diagnostic challenge for even the most astute clinician.

Lithium has a long history of use in the management of bipolar disorder in both pediatric and adult populations. Numerous side effects of Lithium have been documented at both therapeutic and toxic doses, including dermatologic manifestations[1]. However, very few cases of DRESS secondary to Lithium has been reported, and none have been previously reported in the medical literature in a pediatric patient[2,3,4].

We present an unusual case of a 16 year old female with bipolar disorder who developed DRESS several weeks after starting Lithium salts. This case highlights the clinical challenges when considering a diagnosis of DRESS, adds DRESS to the list of potential side effects of Lithium therapy, and provides the first reported example of lithium induced DRESS in a pediatric patient.

CASE PRESENTATION

A 16 year old African American female with bipolar disorder presented to an academic medical center complaining of right upper quadrant pain for the past day associated with nausea and multiple episodes of non-bloody, non-bilious vomiting. She also reported a bi-frontal headache associated with photophobia, and intermittent nausea and vomiting for one week prior. For her headache, her mother was administering ~6 grams of Acetaminophen daily but with limited relief of symptoms.

On arrival to the hospital, her physical exam was positive for right upper quadrant tenderness and transaminitis. Poison control was contacted due to concern for chronic acetaminophen overdose and the patient was admitted to the Pediatric ICU for administration of N-acetylcysteine (NAC). Acetaminophen level on admission was undetectable and lithium level was sub-therapeutic.

HOSPITAL COURSE

On day 0-1, the patient completed 4 doses of NAC. She was noted to have developed an urticarial rash after her first or second dose. On days 2-6, she was transferred to the general floors where she developed worsening systemic symptoms including fever, urticarial rash, myalgia/myositis, facial edema, acute interstitial nephritis, and peripheral eosinophilia. Work-up for potential infectious, auto-immune, or IgE mediated etiologies of her symptoms were performed, but returned negative.

Additional history revealed that, 3 weeks prior to presentation, the patient started taking 450mg daily of Lithium carbonate upon discharge from a recent psychiatric hospitalization for her bipolar disorder. Her dose had also been increased to 900mg daily, days before her initial symptoms began, but was temporarily stopped by her primary physician 3 days prior to her arrival at the hospital.

Lithium-induced DRESS was suspected given the appropriate clinical timeline, characteristic multi-organ involvement, and diffuse rash. It was also noted that her systemic symptoms had worsened within 48 hours after receiving a one time dose of Lithium at the beginning of her hospitalization. She was subsequently treated with intravenous steroids and 4 doses of IVIG, after which her rash, myalgia, and angioedema resolved and labs improved. She was discharged home with a prolonged steroid taper and at follow up one month later, she continued to be symptom free and had normalization of all previously seen lab abnormalities.

Timeline:

- **3 weeks PTA**
  - Lithium therapy started
  - Dose Increased 1 week PTA
  - Stopped 3 days PTA
- **1 week PTA**
  - Patient develops headaches
  - Starts high doses of acetaminophen
- **Admission (HD 0)**
  - Develops RUQ pain, nausea, & vomiting
  - Found to have transaminitis
  - NAC initiated
- **HD 1-2**
  - Symptoms improve
  - Pruritic rash appears (Fig. 1)
- **HD 3-4**
  - Develops myalgia, myositis (CK 1340) & fever (100.8°F)
  - Rash worsens
- **HD 5**
  - Fever Tm 102°F
  - Develops acute kidney injury (sCr 0.9-> 1.5) & metabolic acidosis (HCO3 14)
- **HD 6**
  - Develops facial edema (Fig. 2) and cervical LAD
  - Rash extends to trunk, arms, legs (Fig. 3)
  - Myalgia worsens
- **HD 7**
  - DRESS recognized
  - IVIG (4 doses total) & IV steroids started
- **HD 8 – 11**
  - Angioedema, rash, myalgia improve
  - Discharged home with steroid taper

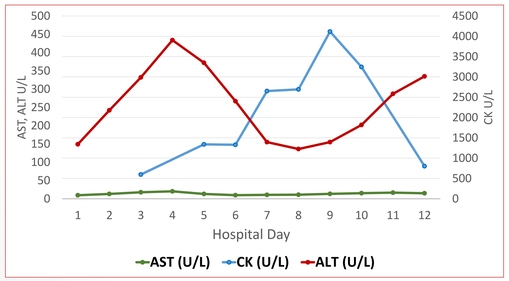
Figures:

1.

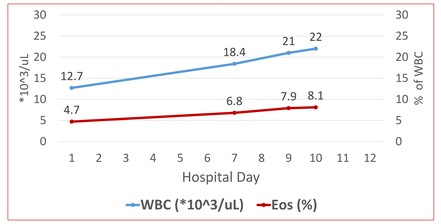
2.

3.

AST, ALT, & CK:



WBC & Eosinophils:



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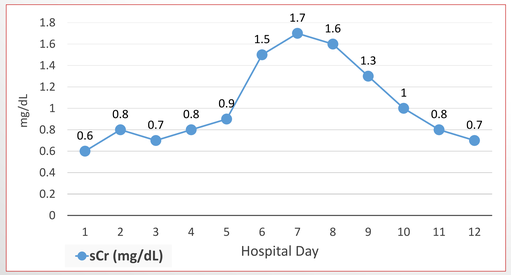

Table 1: The RegiSCAR-Group Diagnosis for DRESS

	NO	YES	UNKNOWN
Fever (≥ 38.5 °C)	- 1	0	-1
Enlarged lymph nodes (≥ 2 sites, > 1cm)	0	1	0
Atypical lymphocytes	0	1	0
Eosinophilia	0		0
700-1499 or 10-19.9		1	
≥ 1500 or ≥ 20%		2	
Skin rash	0		0
extent > 50%	0	1	0
at least 2 of: edema, infiltration, purpura, scaling	-1	1	0
biopsy suggesting DRESS	-1	0	0
Internal organ involved	0		0
One		1	
2 or more		2	
Resolution in > 15 days	-1	0	-1
At least 3 biological investigations done and negative to exclude alternative diagnosis	0	1	0

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

DISCUSSION

- DRESS syndrome is a delayed, type IV drug reaction of variable presentation typically characterized by: 1) Onset of symptoms 2-6 weeks following a new drug exposure, 2) cutaneous findings, and 3) multi-system organ dysfunction[5].
- Rash is the most common symptom reported and usually first to appear, however, dermatologic involvement need not be present for a diagnosis to be made[6].
- The additional constellation of symptoms / lab findings seen in DRESS are myriad and include fever, facial edema, lymphadenopathy, atypical lymphocytosis or eosinophilia, hepatitis, interstitial nephritis, myositis, and myopericarditis[5].
- In one case series, the most common symptoms seen in pediatric cases include: fever, lymphadenopathy, liver dysfunction, and hematologic abnormalities[7].
- Disease incidence varies widely but is most frequent in adults with use of certain anticonvulsants (carbamazepine, phenobarbital, phenytoin, lamotrigine) where rates appears to be 1:1,000 to 1:10,000[5].
- Other drugs implicated in pediatric cases include: vancomycin, valproic acid, dapsone, sulfonamides, and minocycline[7].
- DRESS may be difficult to distinguish from other severe dermatologic adverse drug reactions such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Acute Generalized Exanthematous Pustulosis (AGEP), Acute Cutaneous Lupus, and other Hypereosinophilic Syndromes[8].
- The RegiSCAR Group has laid out diagnostic criteria by which the likelihood of a DRESS diagnosis can be determined (Table 1). In our case, a score of 6 (extent of skin rash, eosinophilia, multi-organ involvement, alternative diagnosis excluded), meant the patient had a 'definite' probability of lithium related DRESS[8].

CONCLUSION

We document the first reported case of Lithium-induced DRESS in a pediatric patient. Case highlights include:

- Lithium salts should be on the differential of offending drugs when a diagnosis of DRESS is considered.
- DRESS syndrome, while infrequently seen in children, is associated with many drugs often prescribed in the pediatric population. Clinicians would be wise to have a high index of suspicion for it in the appropriate clinical setting.
- Though DRESS syndrome is most easily recognized by its dermatologic manifestations, rash is not always the first or most prominent feature of the syndrome. In our case significant hepatic injury preceded the later dermatologic and renal symptoms.

References

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