Characterizing DRESS Syndrome Recurrence

Ajay N. Sharma MD, MBA[1], Samantha Shwe BS[1], Vignesh Ravi BS[2], Melanie Miller MD[2],
Natasha A. Mesinkovska MD, PhD[1], Nathan W. Rojek MD[1], Scott Worswick MD[2]

[1] [2]Department of Dermatology, UC Irvine; [2]Department of Dermatology, USC

BACKGROUND

- Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare, serious adverse drug reaction presenting with cutaneous manifestations and internal organ involvement.
- Most patients with DRESS syndrome experience complete recovery, though the mortality risk is estimated to be approximately 10%.
- Relapse and/or recurrence is possible at any time after initial presentation, with life-long systemic damage a potential complication of unresolved symptoms.
- Given the elusive pathogenesis of DRESS and reports of the syndrome associated with newer medications, dermatologists must be increasingly prepared to predict, identify, and manage patients even after treatment of the initial presentation.

METHODS

- The PubMed and MEDLINE databases were searched for all peer-reviewed articles published until August 2020 using the following search terms entered in separate pairs: “dress syndrome or drug reaction and eosinophilia with systemic symptoms or drug induced hypersensitivity syndrome” and “recurrence or readmission or relapse”.

DEFINITIONS

- Recurrence was defined as a second presentation of DRESS syndrome at any time after treatment of the first presentation was completed or resulted in clear clinical improvement (i.e. resolution of rash, improvement in hematologic or solid organ laboratory values).
- Organ involvement was determined based on laboratory values 1.25 times (renal, cardiac, pancreatic) or 1.5 times (hepatic) above the upper limit of normal.
- Review articles, articles unavailable to the study team, letters to the editor and clinical trial proposals were excluded.

RESULTS

- **Articles**: 334 full-texts assessed --> 42 articles included
- **Overall Results (60 cases)**
  - Age (avg): 46.3 years
  - Comorbidities: rheumatologic conditions (17%), seizure disorders (15%), HIV (5%), CKD (5%), melanoma (5%)
- **Initial Episodes**
  - Causative medications: allopurinol (10%), carbamazepine (10%), lamotrigine (6%), sulfasalazine (6%)
  - Eosinophil count (avg peak): 1.45 cells x 10^9 L
  - Organ involvement: liver (90%), kidneys (28%)
- **Recurrent Episodes**
  - Time to recurrence (avg): 123 days
  - Causes: introduction of a new drug (30%), re-initiation of original offending medication (20%), steroid taper (18%)
  - Eosinophil count (avg peak): 2.81 cells x 10^9 L
- **Outcomes**
  - Survival rate: 71%
  - Viral reactivation: 40% total
    - HHV 6, CMV, EBV, HHV 7
  - Autoimmune sequelae: alopecia universalis, vitiligo, autoimmune thyroiditis, hypothyroidism, antiphospholipid syndrome.

Initial Episode		Recurrent Episode	
		Time to Recurrence (n=54)	123 days (2-1470)
Rash Characterization (n=54)		*Rash Characterization (n=37)*	
Erythroderma	29 (54%)	Erythroderma	24 (65%)
Maculopapular/Morbilliform	27 (50%)	Maculopapular	14 (38%)
Exfoliative	6 (11%)	Exfoliative	4 (11%)
Other (pustular, targetoid, polymorphous)	3 (6%)	Other (pustular, targetoid, polymorphous)	6 (16%)
Presentation		*Presentation*	
Maximum Temperature (n=27)	38.9 +- 0.86	Maximum Temperature (n=27)	39.4 +- 0.86
Rash Resolved ≤ 15 days (n=22)	16 (73%)	Rash Resolved ≤ 15 days (n=14)	8 (57%)
Facial Edema (n=22)	18 (82%)	Facial Edema (n=9)	9 (100%)
WBC Count (n=24)	15.6 +- 11.1	WBC Count (n=12)	10.8 +- 17.8
Eosinophil Absolute Peak (n=24)	1.45 +- 1.93	Eosinophil Absolute Peak (n=18)	2.81 +- 2.74
Thrombocytosis (n=6)	0 (0%)	Thrombocytosis (n=2)	0 (0%)
Atypical Lymphocytes (n=14)	11 (79%)	Atypical Lymphocytes (n=6)	5 (83%)
Lymphadenopathy (n=31)	27 (87%)	Lymphadenopathy (n=6)	5 (83%)
REGISCAR (mean, n=7)	4.4 +- 2.07	REGISCAR (mean, n=2)	7.5 +- 0.5
Infectious Workup		*Infectious Workup*	
ANA Positive (n=10)	0 (0%)	ANA Positive (n=3)	0 (0%)
Blood Culture Positive (n=13)	0 (0%)	Blood Culture Positive (n=5)	1 (20%)
HAV/HBV/HCV Positive (n=11)	1 (9%)	HAV/HBV/HCV Positive (n=5)	0 (0%)
Chlamydia/Mycoplasma Positive (n=5)	0 (0%)	Chlamydia/Mycoplasma Positive (n=0)	n/a
Organ Involvement (n=39)		*Organ Involvement (n=26)*	
Hepatitis	35 (90%)	Hepatitis	19 (73%)
Nephritis	11 (28%)	Nephritis	4 (15%)
Pneumonitis	4 (10%)	Pneumonitis	1 (4%)
Myocarditis	2 (5%)	Myocarditis	2 (8%)
Rhabdomyolysis	4 (10%)	Myositis	1 (4%)
Pancreatitis	1 (3%)	Osteomyelitis	1 (4%)
Conjunctivitis	1 (3%)	Cholestasis	1 (4%)
Enteritis	1 (3%)	Enteritis	1 (4%)
None	3 (8%)	Peritonitis	1 (4%)
Treatment (n=37)		*Treatment (n=29)*	
Methylprednisolone	13 (35%)	Prednisolone	13 (45%)
Prednisolone	12 (32%)	Methylprednisolone	7 (24%)
Prednisone	6 (16%)	Increased Dose	6 (21%)
Hydrocortisone	4 (11%)	IVIG	3 (10%)
Betamethasone	2 (5%)	Prednisone	2 (7%)
Dexamethasone	2 (5%)	Ganciclovir	2 (7%)
Withdrawal Only	2 (5%)	Cyclosporine	2 (7%)
Acyclovir	1 (3%)	Hydrocortisone	1 (3%)
Activated Charcoal	1 (3%)	Mepolizumab	1 (3%)
Liver Transplant	1 (3%)	Dexamethasone	1 (3%)
Intravenous Immunoglobulin	1 (3%)	Plasmapheresis	1 (3%)
Mycophenolate mofetil	1 (3%)	No additional treatment	1 (3%)
Cyclosporine	1 (3%)	*Biopsy Confirmed* (n=9)	9 (100%)

DISCUSSION & CONCLUSIONS

- Diagnostic and lab abnormalities exhibited in the initial episode were similarly demonstrated in the recurrent episode, but with increased severity.
  - Fever and eosinophilia, when present, both increased from initial to second presentation.
- The extent of internal organ involvement was more severe in recurrent presentations
  - In cases of associated liver involvement, the average ALT of 398 in the initial episode increased to an average ALT of 722 in the second episode.
- Relapse was most induced by the introduction of a new drug (n = 18).
  - A similar chemical structure and mechanism of action shared between the initial and new culprit drug could explain the trigger of a recurrent hypersensitivity reaction.
- An adequately high dose of systemic steroid treatment, typically equivalent to oral prednisone dosed at 1-2 mg/kg/day, should be maintained until clinical improvement or lab parameters are normalized, with a subsequent slow taper over a minimum of eight to twelve weeks.

Please email ajayns@uci.edu for any questions, comments, or references.