D.R.E.S.S. Syndrome-
An update

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• I have no disclosures
• I will be discussing off-label uses for medications
• Maculopapular
• Morbilliform
• Classic drug reaction
ID/CC: 24F h/o epilepsy controlled with topiramate recently changed to lamotrigine (lamictal)

HPI: Brother called Stanford Neurology c/o fever, skin peeling, and trouble breathing. Difficulty swallowing and facial swelling were described

PMH: URI s/p ABX 2 days after peeling began
**Vitals:** 100.8F, 122, 89/45, 98% RA

- injected sclerae
- *facial erythema/edema*
- erosions on the anterior hard palate
- lips&chest with superficial desquamation
- UE>LU w/ confluent erythematous patches
- vulva w/ superficial desquamation
- no vesiculobullous component
- *Nikolsky sign negative*
- *Cervical lymphadenopathy*
Presenting Labs

12% eosinophils
Medical Decision Making

• Neuro: lamotrigine->levetiracetam (Keppra) IV

• methylprednisolone 1 gram IV then 1 gram daily divided qid for 3 days
Hospital course

• ICU- continued high dose steroids & antibiotics
• Tapered down to 1mg/kg IV methylprednisolone before switching to prednisone 60 mg PO
• **slow taper over 3 months.**
• Facial edema improved, no new cutaneous findings, transaminitis improved.
• 24F h/o epilepsy switched to lamotrigine: Symptoms began 5 weeks after medication switch

• fever, facial edema, lymphadenopathy, morbilliform exanthem and severe transaminitis
Nomenclature

• 1959: Salztein and colleagues
  – “Drug-induced Pseudolymphoma”

• 1960s
  – “Anticonvulsant Hypersensitivity Syndrome”
  – More recently: “Drug-Induced Hypersensitivity Syndrome”

• 1996: Callot and colleagues described 21 patients with a morbilliform exanthem and acute systemic illness/inflammation and eosinophilia

• 1996: Bocquet and colleagues
  – “Drug Rash (Reaction) with eosinophilia and systemic symptoms”

• 1998: Sontheimer
  – “drug-induced delayed multiorgan hypersensitivity syndrome” or “DIDMOHS”
RegiSCAR

• International registry for SCAR syndromes
• Severe Cutaneous Adverse Reactions

• HSS (Hypersensitivity Syndrome)/DRESS/DIHS
Which Criteria to Use?


• Bocquet’s Criteria found to be efficient and appropriate to diagnose DRESS syndrome in clinical practice.

• 3 Features:
  – Skin Eruption
  – Blood eosinophilia (>1500/uL) or the presence of atypical lymphocytes.
  – Internal organ involvement or lymphadenopathy, hepatitis, nephritis, interstitial pneumonia or carditis
<table>
<thead>
<tr>
<th>Bocquet et al.</th>
<th>RegiSCAR&lt;sup&gt;1&lt;/sup&gt;</th>
<th>J-SCAR&lt;sup&gt;2,3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous drug eruption</td>
<td>Acute rash&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Maculopapular rash developing &gt;3 weeks after starting offending drug</td>
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<tr>
<td>Hematologic abnormalities</td>
<td>Reaction suspected to be drug-related&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Prolonged clinical symptoms after discontinuation of the causative drug</td>
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<tr>
<td>Eosinophils ≥ 1.5 × 10&lt;sup&gt;9&lt;/sup&gt;/L</td>
<td>Hospitalization&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Fever &gt;38°C</td>
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<tr>
<td>Presence of atypical lymphocytes</td>
<td>Fever &gt;38°C&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Liver abnormalities (ALT &gt;100 U/L) or other organ involvement</td>
</tr>
<tr>
<td>Systemic involvement</td>
<td>Enlarged lymph nodes involving ≥ 2 sites&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Leukocyte abnormalities (≥ 1)</td>
</tr>
<tr>
<td>Adenopathy: lymph nodes ≥ 2 cm in diameter</td>
<td>Involvement of ≥ 1 internal organ&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Leukocytosis (&gt;11 × 10&lt;sup&gt;9&lt;/sup&gt;/L)</td>
</tr>
<tr>
<td>Hepatitis with liver transaminases ≥ 2 times normal</td>
<td>Blood count abnormalities&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Atypical lymphocytes (&gt;5%)</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>Lymphocytes above or below normal limits</td>
<td>Eosinophilia (&gt;1.5 × 10&lt;sup&gt;9&lt;/sup&gt;/L)</td>
</tr>
<tr>
<td>Interstitial pneumonitis</td>
<td>Eosinophils over laboratory limits</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>Carditis</td>
<td>Platelets under laboratory limits</td>
<td>HHV-6 reactivation</td>
</tr>
</tbody>
</table>

For Bocquet et al. criteria, all 3 criteria are required (1 hematologic and 1 systemic feature required).

DIHS, Drug-induced hypersensitivity syndrome; HHV-6, human herpesvirus-6; J-SCAR, Japanese Research Committee on Severe Cutaneous Adverse Reaction; RegiSCAR, European Registry of Severe Cutaneous Adverse Reaction.

<sup>1</sup>J-SCAR criteria includes DIHS. Typical DIHS is defined as the presence of all 7 criteria, while atypical DIHS is defined as the presence of the first 5 criteria only.

<sup>2</sup>Necessary criteria for diagnosis according to RegiSCAR.

<sup>3</sup>Three of these 4 criteria required for diagnosis according to RegiSCAR.
Disease spectrum

- 216 cases over a 15 year period in France
- Morbilliform eruption (>70%)
- Facial edema (often mistaken for angioedema)
- Lymphadenopathy
- Longer latency period (100%) 2 weeks – 2 months
- Persistence or aggravation of symptoms despite the discontinuation of the culprit drug.
- Fever
- Hematologic (Eosinophilia- 50%)
- Involvement of at least one internal organ system
  - Liver – 60%
- Mortality: 10% with most patient dying from liver failure

RegiSCAR- prospective study of 117 patients

- 92% of patients: skin eruption persisted >15 days
- Median inpatient stay: 17 days
Day of onset of early signs and symptoms in relation to onset of erythema.

Onset of erythema is defined as Day 0.

Horizontal bars = extreme values, boxes = interquartile range, vertical bars = median.
Dysphagia- early and overlooked sign of DRESS syndrome.

May be reminiscent of a primary herpesvirus infection

Hypothesize that:
“early manifestations of DRESS syndrome, including pharyngitis, cervical lymphadenopathy and facial edema, may reflect the oropharynx as the initial site of herpesvirus reactivation”


Dysphagia, a major early manifestation in DRESS syndrome.
Descamps V.
Clinical images of patient affected by drug reaction with eosinophilia and systemic symptoms

Effects on internal organs (A) and blood (B) of drug reaction with eosinophilia and systemic symptoms

Internal organ involvement in DIHS/DRESS


- Colitis/Intestinal bleeding
- Diabetes mellitus
- Encephalitis/aseptic meningitis
- Hepatitis
- Interstitial nephritis
- Interstitial pneumonitis/respiratory distress syndrome
- Myocarditis
- Serositis
- Syndrome of inappropriate secretion of antidiuretic hormone
- Thyroiditis
Acute Management and Treatment

- Immediate withdrawal of causative drug.
- Admit to ICU or hemi unit. Fluid replacement, correction of electrolyte abnormalities, warming the environmental temperature, providing high caloric intake, treatment of superinfections, and infection, and skin care with appropriate dressings.
- Order labs: CBC, LFT, BMP, 24 hour urine protein and urinary eosinophil count, CK, LDH, ferritin, triglycerides, calcium, PTH, TSH, blood glucose, PT and PTT, lipase, protein electrophoresis, CRP, quantitative PCR for HIV-1, EBV and CMV, blood culture, ANA.
- Start high-dose systemic corticosteroids at 1 mg/kg/day. Consider other immunosuppressant medications. Topical corticosteroids for symptomatic relief.

**Hepatic Evaluation**
1. LFTs
2. PT/PTT/INR
3. Hepatitis Panel

Abnormal → Consult hepatology and/or transplant surgery
- Supportive therapy: correct coagulopathy if bleeding
- Pulmonary hepatitis/hepatic necrosis
- Liver transplant

**Cardiac Evaluation**
1. ECG
2. Echocardiogram
3. Cardiac Enzymes

Abnormal → Consult cardiology and/or cardiothoracic surgery
- Supportive therapy: fluid restriction, diuretics, ACE-inhibitor, beta-blocker
- Intractable heart failure
- VAD, cardiac transplant

**Pulmonary Evaluation**
1. Chest X-ray
2. PFTs

Abnormal → Consult pulmonology
- Chest CT
- Supportive therapy: oxygen
- ARDS
- Intubation/mechanical ventilation

**Renal Evaluation**
1. Creatinine, BUN
2. Urinalysis
3. Renal Ultrasound

Abnormal → Consult nephrology and/or transplant surgery
- Supportive therapy: IV fluids, correct electrolytes
- Intractable renal failure
- Dialysis, kidney transplant

**Endocrine Evaluation**
1. TSH/T4
2. Fasting glucose

Abnormal → Consult endocrinology
- Thyroid hormone replacement
- Supportive therapy

**Gastrointestinal Evaluation**
1. FOBT
2. Lipase

Abnormal → Consult gastroenterology
- Colonoscopy
- Supportive therapy: correct electrolytes

**Neurological Evaluation**
1. Head CT/MRI
2. EEG
3. CSF analysis

Abnormal → Consult neurology
- Seizure management
- Supportive therapy

Abbreviations:
- ANA: anti-nuclear antibody
- ARDS: acute respiratory distress syndrome
- BMP: basic metabolic panel
- BUN: blood urea nitrogen
- CBC: complete blood count
- CK: creatine phosphokinase
- CMV: cytomegalovirus
- CRP: C-reactive protein
- CSF: cerebrospinal fluid
- CT: computed tomography
- EBV: Epstein-Barr virus
- ECG: electrocardiogram
- EEG: electroencephalogram
- EGD: esophagogastroduodenoscopy
- FOBT: fecal occult blood test
- ICU: intensive care unit
- INR: international normalized ratio
- LFT: liver function test
- MRI: magnetic resonance imaging
- PT: prothrombin time
- PTT: partial thromboplastin time
- T4: thyroid
- TSH: thyroid stimulating hormone
- VAD: ventricular assist device
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<tr>
<th>Medication</th>
<th>Clinical abnormality</th>
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<td>Allopurinol</td>
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<td>Carbamazepine</td>
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<td>Dapsone</td>
<td>Hepatic and renal</td>
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<td>Minocycline</td>
<td>Hepatic, pulmonary, and cardiac</td>
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<td>Phenytoin</td>
<td>Hepatic</td>
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“Mini-DRESS”

• Patients at the mild end develop minor internal organ disturbance, drug-induced exanthem
Diagram showing percentages of culprit drugs for drug reaction with eosinophilia and systemic symptoms found in this study

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<th>Week</th>
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<th>30</th>
<th>31</th>
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</table>
# USC DRESS Database: Demographic Data

29 total patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Gender, F</td>
<td>14</td>
<td>48%</td>
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<tr>
<td>Gender, M</td>
<td>15</td>
<td>52%</td>
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<td>Age (Median)</td>
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<td>Hispanic or Latino</td>
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<td>African American</td>
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<tr>
<td>Asian</td>
<td>3</td>
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<tr>
<td>Native Pacific Islander or Hawaiian</td>
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<td>3%</td>
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<tr>
<td>Other or unknown race</td>
<td>3</td>
<td>10%</td>
</tr>
</tbody>
</table>
Culprit medications

- Vancomycin alone (8 cases)
- Multiple antibiotics* (2 cases)
- Miscellaneous** (3 cases)
- Antibiotics or anticonvulsants (6 cases)
- Anticonvulsants (7 cases)
- Kinase Inhibitors
- Ceftriaxone

*Multiple antibiotics category all contained Vancomycin as a possible suspect
**Miscellaneous includes: Diclofenac, Allopurinol, Hydrochlorothiazide, Abacavir, Lithium and Unknown)
Culprit medications

- Vancomycin alone: 8
- Multiple antibiotics: 7
- Antibiotics or anticonvulsants: 3
- Protein Kinase Inhibitors: 2
- Ceftriaxone: 1
- Phenytoin: 1
- Lamictal: 1
- Allopurinol: 1
- Hydrochlorothiazide: 1
- Abacavir: 1
- Lithium: 1
- Diclofenac: 1
- Unknown: 1
Treatment:


• Prompt diagnosis and prompt withdrawal of the offending drug
• Supportive therapy
• High Dose Systemic corticosteroids- very effective
  - At least 1 mg/kg Prednisone per day
  – Beware of relapses with tapering of steroids
  – Pemphigus style tapering
• IVIG 1gm/kg/2-3d.
  – No proven efficacy
  – 4 of 6 patients without improvement

• Non-steroidal alternatives: Cyclosporine and Cyclophosphamide. Case reports of effectiveness as therapy.

• Anti-HHV meds are just now being studied. Valganciclovir is being evaluated by Moling et al.
HHV/Viral etiology?

• Clinical and biological features of DRESS are consistent with viral infection:
  – Fever
  – Edema
  – Lymphadenopathies
  – Hematologic expansion
  – Hepatitis
HHV reactivation

• HHV-6 titers increase. > 10 fold increase
• Shiohara et al.: HHV-6, HHV-4 (EBV), HHV-7 and HHV-5 (CMV)
  – In susceptible individuals a transient hypogammaglobulinemia creates an immunological environment that permits viral reactivation.
  - Resulting expansion of virus-specific and nonspecific T-cells is thought to mediate the clinical presentation. 

  The long latency period may be explained by the time delay to viral reactivation and the prolonged presentation of clinical features may reflect sequential reactivation.


Kano Y et al. Several herpesviruses can reactive in a severe drug-induced multi-organ reaction in the same sequential order as graft-versus-host-disease. Br J Dermatol 2006; 155:301-306
Damien Picard et al. **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): A Multiorgan Antiviral T Cell Response**; Sci Transl Med 2, 46ra62

- 40 patients with DRESS syndrome
- Adverse reactions were a result of cutaneous and systemic manifestations of a **CD8+ T lymphocyte mediated process**
- Noted reactivation of **HHV-4 (EBV), HHV-6/7** in 76% of DRESS patients
- Noted that three culprit drugs (Carbamazepine, Sulfamethoxazole, Allopurinol) **induce EBV production in EBV-transformed cells from DRESS patients, but not from healthy controls.**
Damien Picard et al. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): A Multiorgan Antiviral T Cell Response; Sci Transl Med 2, 46ra62

- Excess numbers of HHV- specific CD8+ T lymphocytes (TCR sequences).
  - Confirmed by cellular stimulation by antigenic peptides from HHV-4.
- HHV-specific CD8+ T lymphocytes secreting pro-inflammatory cytokines (TNF-a and IFN-gamma)
- **HHV-specific CD8+ T lymphocytes were found in blood and involved organs (skin, liver and lung)**
- Expressed high levels of homing markers specific for the skin and lungs
• Why do these drugs induce EBV/HHV production?
Reactivation of Human Herpesvirus-6 in Natalizumab Treated Multiple Sclerosis Patients

Karen Yao1,3*, Susan Gagnon1,9, Nahid Akhyani1, Elizabeth Williams1, Julie Fotheringham1, Elliot Frohman2, Olaf Stuve2, Nancy Monson2, Michael K. Racke2*, Steven Jacobson1*

1 Viral Immunology Section, National Institutes of Health, Bethesda, Maryland, United States of America. 2 Department of Neurology and the Center for Immunology, The University of Texas Southwestern Medical Center, Dallas, Texas, United States of America. 3 Department of Biology, Johns Hopkins University, Baltimore, Maryland, United States of America

Abstract

The α4 integrin antagonist natalizumab was shown to be effective in patients with immune-mediated disorders but was unexpectedly associated with JC polyomavirus associated progressive multifocal leukoencephalopathy (PML) in two multiple sclerosis (MS) and one Crohn’s disease patients. Impaired immune surveillance due to natalizumab treatment may have contributed to the JCV reactivation. As HHV-6 has been suggested to play a role in MS, we asked whether this virus could also have been reactivated during natalizumab therapy. Matched sera and CSF from a limited set of MS patients treated with and without natalizumab were examined for evidence of HHV-6. In addition, we also superinfected a persistent JC virus infected glial cell with HHV-6A to determine if JC virus can be increased. Elevated serum HHV6 IgG and HHV-6A DNA was detected in the CSF of a subset of patients but not controls. We confirmed that superinfection with HHV-6 of a JC virus infected glial cells increased expression of JCV. These results support the hypothesis that treatment with natalizumab may be associated with reduced immune surveillance resulting in reactivation of viruses associated with MS pathogenesis.


Editor: Peter Sommer, Institut Pasteur Korea, Republic of Korea
Valpromide Inhibits Lytic Cycle Reactivation of Epstein-Barr Virus

Kelly L. Gorres, Derek Daigle, Sudharshan Mohanram, Grace E. McInerney, Danielle E. Lyons, George Miller

Department of Molecular Biophysics and Biochemistry, Department of Microbiology, Department of Pediatrics, and Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut, USA

* Present address: Kelly L. Gorres, University of Wisconsin-La Crosse, La Crosse, Wisconsin, USA.

ABSTRACT Reactivation of Epstein-Barr virus (EBV) from latency into the lytic phase of its life cycle allows the virus to spread among cells and between hosts. Valproic acid (VPA) inhibits initiation of the lytic cycle in EBV-infected B lymphoma cells. While VPA blocks viral lytic gene expression, it induces expression of many cellular genes, because it is a histone deacetylase (HDAC) inhibitor. Here we show, using derivatives of VPA, that blockade of EBV reactivation is separable from HDAC inhibition. Valpromide (VPM), an amide derivative of valproic acid that is not an HDAC inhibitor, prevented expression of two EBV genes, BZLF1 and BRLF1, that mediate lytic reactivation. VPM also inhibited expression of a viral late gene, but not early genes, when BZLF1 was exogenously expressed. Unlike VPA, VPM did not activate lytic expression of Kaposi's sarcoma-associated herpesvirus. Expression of cellular immediate-early genes, such as FOS and EGR1, is kinetically upstream of the EBV lytic cycle. VPM did not activate expression of these cellular immediate-early genes but decreased their level of expression when induced by butyrate, an HDAC inhibitor. VPM did not alter expression of several other cellular immediate-early genes, including STAT3, which were induced by the HDAC inhibitors in cells refractory to lytic induction. Therefore, VPM selectively inhibits both viral and cellular gene expression. VPA and VPM represent a new class of antiviral agents. The mechanism by which VPA and VPM block EBV reactivation may be related to their anticonvulsant activity.

IMPORTANCE Epstein-Barr virus (EBV), a human tumor virus, establishes a life-long latent infection. Reactivation of EBV into the lytic phase of its life cycle allows the virus to spread. Previously, we showed that EBV reactivation was blocked by valproic acid (VPA), an inhibitor of cellular histone deacetylases (HDACs). VPA alters the expression of thousands of cellular genes. In this study, we demonstrate that valpromide (VPM), an amide derivative of valproic acid that is not an HDAC inhibitor, prevented initiation of the EBV lytic cycle. VPA induced lytic reactivation of Kaposi's sarcoma-associated herpesvirus (KSHV), but VPM did not. Unlike VPA, VPM did not activate cellular immediate-early gene expression. VPM is a new type of antiviral agent. VPM will be useful in probing the mechanism of EBV lytic reactivation and may have therapeutic application.
**CCL17/TARC**

- Thymus and activation regulated chemokine.
  - Expressed constitutively in the thymus
  - Only transiently in phytohemagglutinin-stimulated peripheral blood mononuclear cells
  - Induces chemotaxis in T-cells through interfacing with receptor CCR4

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Serum thymus and activation-regulated chemokine (TARC) is associated with the severity of drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome (DRESS/DIHS).

Nakamura-Nishimura Y1, Miyagawa F1, Miyashita K1, Omori R1, Azukizawa H1, Asada H1.

Author information

Abstract
Drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome (DRESS/DIHS) is a severe adverse drug-induced reaction with reactivation of human herpesvirus 6 (HHV-6).1-3 We previously reported that serum thymus and activation-regulated chemokine (TARC) levels were markedly increased in patients with DIHS and suggested TARC as a useful diagnostic marker of DIHS in the early stage.4,5 In this study, we determined whether serum TARC levels correlate with the severity of clinical symptoms and laboratory data in patients with DRESS/DIHS. This article is protected by copyright. All rights reserved.
Fig. 2. Receiver operating characteristic (ROC) curve in diagnosing DIHS ($n = 84$).

- Cutoff value: 13,900 pg/mL
- Sensitivity: 100%
- Specificity: 92.3%
Differentiating features

- Late onset
- Persistence after discontinuing medications
- Facial edema
- Cervical lymphadenopathy
- Systemic symptoms
- TARC may represent a new diagnostic modality that may be sensitive and specific
- Treatment with high dose steroids followed by a long taper.
Anecdotal lessons 1  
(Take it or leave it)

• Renal and Cardiac involvement are more resistant to treatment than Hepatic:
  – 1 gram solumedrol/500mg/250mg over 1 week  
  – 1 mg/kg solumedrol  
  – 1.2mg PO  
  – Slow taper  
  – Flares often occur when we get to 10mg/day

• Hepatic/Bone Marrow involvement:  
  – 500/250 mg solumedrol and taper  
  – Slow taper
USC Treatment Protocol for Patients with Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

1. Identify patient with DRESS

   Does this patient have organ involvement?

   Yes

   - Hepatic or bone marrow involvement
     - 250mg IV methylprednisolone x3 days
     - Patient improves
       - Yes
         - 125mg IV methylprednisolone x3 days
         - 1.2 mg/kg PO prednisone
         - Pemphigus style tapering over 3-6 months
       - No
         - 250mg IV methylprednisolone x3 days
         - 125mg IV methylprednisolone x3 days
         - 1.2 mg/kg PO prednisone
         - Pemphigus style tapering over 3-6 months

   Yes

   - Renal or cardiac involvement
     - 500mg IV methylprednisolone x3 days
     - Patient improves
       - Yes
         - 250mg IV methylprednisolone x3 days
         - 125mg IV methylprednisolone x3 days
         - 1.2 mg/kg PO prednisone
         - Pemphigus style tapering over 3-6 months
       - No
         - 250mg IV methylprednisolone x3 days
         - 125mg IV methylprednisolone x3 days
         - 1.2 mg/kg PO prednisone
         - Pemphigus style tapering over 3-6 months

No

- 1mg/kg/day prednisone
Lessons 2

– Slow Taper is critical- flares often occur
– Can involve heart or Thyroid often after two months of therapy.
– Taper is painfully slow
– Mycophenolate Mofetil can be used to accelerate the taper (Not well enough studied by USC)
CASE REPORT

Is the drug-induced hypersensitivity syndrome (DIHS) due to human herpesvirus 6 infection or to allergy-mediated viral reactivation? Report of a case and literature review

Ivan Gentile*, Maria Talamo and Guglielmo Borgia

Abstract

Background: Drug-Induced Hypersensitivity Syndrome (DIHS) is a severe and rare systemic reaction triggered by a drug (usually an antiepileptic drug). We present a case of DISH and we review studies on the clinical features and treatment of DIHS, and on its pathogenesis in which two elements (Herpesvirus infection and the drug) interact with the immune system to trigger such a syndrome that can lead to death in about 20% of cases.

Case presentation: We report the case of a 26-year old woman with fever, systemic maculopapular rash, lymphadenopathy, hepatitis and eosinophilic leukocytosis. She had been treated with antibiotics that gave no benefit. She was taking escitalopram and lamotrigine for a bipolar disease 30 days before fever onset. Because the patient’s general condition deteriorated, betamethasone and acyclovir were started. This treatment resulted in a mild improvement of symptoms. Steroids were rapidly tapered and this was followed with a relapse of fever and a worsening of laboratory parameters. Human herpesvirus 6 (HHV-6) DNA was positive as shown by PCR. Drug-Induced Hypersensitivity Syndrome (DIHS) was diagnosed. Symptoms regressed on prednisone (at a dose of 50 mg/die) that was tapered very slowly. The patient recovered completely.

Conclusions: The search for rare causes of fever led to complete resolution of a very difficult case. As DIHS is a rare disease, the most relevant issue is to suspect and include it in differential diagnosis of fevers of unknown origin. Once diagnosed, the therapy is easy (steroidal administration) and often successful. However, our case strongly confirms that attention should be paid on the steroidal tapering that should be very slow to avoid a relapse.
Brief Report

Cyclosporine Treatment of Drug-Induced Hypersensitivity Syndrome

Mark G. Kirchhof, MD, PhD; Aaron Wong, MD; Jan P. Dutz, MD

IMPORTANCE Drug-induced hypersensitivity syndrome (DIHS), also known as drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, is a potentially life-threatening reaction to medications with a mortality rate up to 10%. Standard therapy involves the use of systemic corticosteroids with tapering doses extending up to 9 months after the initial reaction. Alternative treatments for DIHS are needed, especially for patients for whom systemic corticosteroids are contraindicated.

OBJECTIVE To assess a short course of cyclosporine as first-line therapy for DIHS.

DESIGN, SETTING, AND PARTICIPANTS In this case series, 2 patients referred to the dermatology service of an academic tertiary care hospital and subsequently diagnosed as having DIHS were studied from December 1, 2013, through July 31, 2014.

INTERVENTIONS Short course (3-7 days) of cyclosporine.

MAIN OUTCOMES AND MEASURES Clinical and laboratory indicators were examined to determine the timing and efficacy of cyclosporine treatment.

RESULTS Two cases are reported of drug hypersensitivity reaction that were treated with cyclosporine, resulting in rapid and significant clinical improvement. The first case involved a woman in her 40s who developed DIHS after treatment with carbamazepine. A 7-day course of cyclosporine resulted in clinical resolution of the DIHS. The second case was that of a man in his 30s with minocycline-induced DIHS. A 3-day course of cyclosporine resulted in rapid and sustained clinical improvement.

CONCLUSIONS AND RELEVANCE A short course of cyclosporine was of therapeutic benefit in the treatment of 2 patients with DIHS. Short courses of cyclosporine in the acute care setting may be an alternative to longer courses of systemic corticosteroids in the treatment of DIHS.

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Lessons 3
Acute eosinophilic myocarditis is a rare cause of acute heart failure. We present the case of a 32-year-old woman who had presumptive eosinophilic myocarditis as part of a generalized hypersensitivity reaction (Drug Rash with Eosinophilia and Systemic Symptoms [DRESS] syndrome) that exhibited a dramatic response to steroid therapy. We highlight the central role of 2-dimensional and tissue-Doppler echocardiography in the diagnosis of myocarditis and the serial evaluation of left ventricular systolic and diastolic function in this setting.

Key words: Cardiomyopathy; infiltrative; Doppler, pulsed, drug complications; echocardiography, two-dimensional; transthoracic; eosinophils; myocarditis
mmHg, and her heart rate was 120 beats/min. The electrocardiogram showed sinus tachycardia with nonspecific repolarization abnormalities. Laboratory testing revealed an elevated leukocyte count (22.6 g/L) with massive peripheral eosinophilia (51% of leukocytes), mildly elevated transaminases (aspartate aminotransferase, 101 U/L [normal level, <40 U/L]; and alanine aminotransferase, 115 U/L [normal, <55 U/L]), highly elevated B-type natriuretic peptide (BNP, 1,560 ng/L; normal level, <50 ng/L), and detectable cardiac troponin I (cTnI, 1.23 µg/L; normal level, <0.5 µg/L). Transthoracic echocardiography showed a normal-sized LV with notably and symmetrically increased wall thickness (septum, 13 mm; posterior wall, 12 mm; Fig. 1A), diffusely impaired LVEF (0.40), and notably reduced systolic (s’, 6.5 cm/s) and early diastolic (e’, 5 cm/s; Fig. 2A) LV tissue velocities as evaluated by pulsed-wave tissue-Doppler echocardiography. There was a small pericardial effusion. A skin biopsy was compatible with severe drug rash, and a bone-marrow biopsy revealed no evidence of malignant disease. A diagnosis of DRESS syndrome was made on the basis of the typical rash, eosinophilia, cardiac involvement, and the presumed involvement of the liver. Treatment with steroids was begun. After the first oral dose of 2 mg/kg body weight of prednisone (120 mg), the BNP level fell from 1,560 to 576 ng/L, and the cardiac troponin I (cTnI) level fell from 1.23 to 0.25 µg/L within 48 hours. A repeat echocardiogram 4 days after the initial study revealed a significant reduction in LV wall thickness (septum, 10 mm; posterior wall, 8 mm; Fig. 1B), normalization of LVEF to 0.70, and notable improvement (albeit not normalization) of systolic (s’=7.5 cm/s) and early diastolic (e’=10 cm/s) LV tissue velocities (Fig. 2B). The rash disappeared within days. The patient made an uneventful clinical recovery, and the steroid dose was gradually tapered (to 100 mg after 5 d, 75 mg 4 d later, 90 mg 2 d later after a minimal flare-up of cutaneous symptoms, 75 mg 7 d later, then gradual reduction to 10 mg 1 mo later). A 3rd echocardiogram obtained on an outpatient basis, 6 weeks after the 2nd echocardiogram, revealed a further reduction in LV wall thickness (septum, 8 mm; posterior wall, 6 mm; Fig. 1C), normal LVEF, and complete normalization of systolic and diastolic LV myocardial tissue velocities (s’=9 cm/s; e’=13 cm/s; Fig. 2C). The eosinophil count, the BNP (25 ng/L), and the cTnI (<0.01 µg/L) were normal. At that time, the patient was taking oral prednisone 10 mg/d, and a further reduction in 2.5-mg steps was planned. Her exercise capacity during an incremental cycle exercise test was normal (112% of predicted).
Lessons 3

• Pro-BNP- marker of cardiac contractility
• If a patient was noted to have elevated BNP early, they will respond.
• If rash recurs, recheck the BNP.
• BNP levels functioned mainly as a binary variable
Lessons 4

• There is a small cohort of patients with liver disease who do not respond to IV Solumedrol at 250 or less.
• AST/ALT in the 1000s
• No movement with 250 solumedrol
• They will improve at 500 for longer courses (>5 days) and then require long courses of IV steroids
Lessons 5

- Renal- AKI treated with Continuous Renal Replacement Therapy (CRRT)
- Difficult to monitor improvement
- Can switch them off CRRT to intermittent Hemodialysis
- Follow urine output.
- Other organs will improve. Harder to monitor the renal patients on CRRT.
Lessons 6

• Daily skin checks- The ICU skin checks are often for pressure ulcers and so they will not do a full skin examination.

• Watchful for new fevers/persisting fevers despite steroid treatment.

• CBC diff daily

• Constant vigilance
Lessons 7

- Communicate...with everyone.
1. Fever → cold (Temp dysregulation)
2. Facial Swelling
3. Antibiotic Exposure
4. Pneumonia (Pseudomonas) → covered.
5. Liver enzyme abnormality
6. Kidney - laceration → ↓ function
7. medicine to help heart harder.
8. Full morbilliform rash.
9. WBC 4P

high dose steroids

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Lessons 8

• Make the hard call
Where are we going?

• We need to work together to describe this condition.
Educate!

1. **Diagnosis of DRESS (drug reaction with eosinophilia and systemic symptoms) in the intensive care unit: essential but challenging.**
   Descamps V.
   PMID: 24135666 [PubMed - in process]
   Related citations

2. **Shock state: an unrecognized and underestimated presentation of drug reaction with eosinophilia and systemic symptoms.**
   Kimmoun A, Dubois E, Perez P, Barbaud A, Levy B.
   PMID: 24088996 [PubMed - in process]
   Related citations

3. **DRESS syndrome presenting like septic shock.**
   Parkins G, White B.
   PMID: 23474419 [PubMed - in process]
   Related citations
HLA-A*31:01


- Showed a significant association with CBZ-DRESS in Europeans (P<0.001; OR (95% CI)=57.6 (11.0-340))
- Strong association was also found in CBZ-DRESS in Chinese (P<0.001; OR (95% CI)=23.0 (4.2-125))
- No association with TEN (unlike HLA-B*15:02)
- Meta-analysis: HLA-A*31:01 had an extremely strong association with CBZ-DRESS and a specific predictor.
- Conclusion: considering the potential clinical utility, the cost-effectiveness of a combined HLA-A*31:01 and HLA-B*15:02 genetic test to prevent CBZ-SCAR in Chinese needs further investigation.
• Personalized Preventive Medicine
  – Not simply targeted therapy for gene specific mutations and cancer
  – Primary prevention of severe adverse drug reactions
    • We will be able to determine which populations are at higher risk for ADR’s and “stop the disease before it started”