U029:
Case-based Challenges in Pediatric Dermatology Hospital Consults

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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

Raegan Hunt, MD, PhD
Focus Session U029:
Case-based Challenges in Pediatric Dermatology Hospital Consults

DISCLOSURES
Pfizer: Advisory Board – Consulting Fee
Objectives

- Diagnose pediatric skin eruptions in the hospital setting
- Determine when laboratory testing or skin biopsy may be helpful in management of hospitalized pediatric patients
• 1 day-old Hispanic girl
  – 38 WGA
  – born by C-section in rural setting
  – APGARS 9/9
• Normal pregnancy, normal infectious labs in pregnancy, G6P5 mother
• Stable
• Feeding, voiding, stooling well

• Large erosions at birth
• Deep, membranous shiny plaques
• Two dark, thick fingernails
• Oral and anal mucosa clear
• No natal teeth
• No periorificial granulation tissue
What is your next step?

1. Create genetic pedigree from family history
2. Skin biopsy of an induced blister
3. Genetic testing
4. Cultures for HSV/VZV
5. ALL OF THE ABOVE
Differential Diagnosis

Epidermolysis bullosa with congenital localized absence of skin (EB + CLAS, formerly included Bart syndrome)

Erosive Candida

Congenital HSV

Congenital VZV

Transient dermolysis of the newborn

Epidermolytic ichthyosis

Dermnet.nz

Indian J of Dermatology, Venereology, & Leprology, 76, 2010
Indian Pediatr 2016;53: 269
Diagnostic Studies

- HSV and VZV cultures negative
- HSV and VZV PCR negative

- Offered induced blister biopsy for H&E and EB immunomapping
  - family declined
Biopsy with Epidermolysis Bullosa high on Differential Diagnosis: *Induced Blister*

- Select site and mark 6 mm circle
- Anesthetize area
- Twist clean pencil eraser firmly back and forth in the marked area x 15 seconds
- Blister will likely not be visible
  - May help to return after few hours
- Clean skin
- Biopsy across edge: 1/3 of induced blister, 2/3 normal skin

Images: Plastic Surgery Key.com
Offered genetic testing

- GeneDx EB panel - results: 6 weeks --- Not covered by patient’s insurance plan
  - Tests the following known EB causing genes:
    - CD151, CDSN, CHST8, COL17A1, COL7A1, CSTA, DSG1, DSG2, DSG3, DSG4, DSP, DST, EXPH5, FERMT1, GRIP1, ITGA3, ITGA6, ITGB4, KLHL24, KRT1, KRT10, KRT14, KRT5, LAMA3, LAMB3, LAMC2, MMP1, NID1, PKP1, PLEC, TGM5

- Trio Whole Exome Sequencing - results: 3 weeks
  - analyzes the exons/coding regions of thousands of genes using next-generation sequencing techniques
  - exome of a patient and their parents analyzed - compares to normal reference sequence
Diagnosis: Epidermolysis Bullosa Simplex

• Trio whole exome genetic testing results
  – *KLHL24* mutation
    • Heterozygous c.1441T>A (p.S481T) variant
    • Both parents negative for above variant

• *KLHL24*: Kelch-like protein 24
  – Kelch-like protein 24- cullin 3–RBX1 ubiquitin ligase substrate receptor interacts with keratin 14
    • Mutations that *overstabilize* *KLH24* cause excessive ubiquitination and degradation of *KRT14* in basal keratinocytes
  – AD mutation: epidermolysis bullosa simplex
KLHL24: Kelch-like protein 24 “Epidermolysis bullosa simplex”

- **Features**
  - Widespread erosions at birth
    - Healing with whorled hypopigmented, atrophic appearance
  - Aplasia cutis congenita on extremities at birth
  - Alopecia
  - Toenail fragility- improves over time
  - Skin fragility- improves over time

• Management
  • Conservative EB wound/skin care

• Whole exome sequencing
  • For this case, more prognostic information than biopsy
  • 3 week turn-around time
Case
16 year-old girl with history of ALL and refractory seizure disorder

- Skin eruption x 2 days
- Fever 38.4 °C (101 °F)
- Non-productive cough

- Cervical lymphadenopathy
- Facial and hand edema
- **Medication History**
  - Divalproex sodium (depakote)
    - 5 weeks before rash
  - Added lamotrigine (lamictal)
    - 4 weeks before rash

- **Labs**
  - Eosinophils 12%
  - AST 118
  - ALT 74
  - Free T4 0.68 (0.8 - 1.8 ng/L), TSH within normal limits
  - Cr within normal limits
  - UA within normal limits
Which additional laboratory finding may help with diagnosis?

1. Atypical lymphocytosis
2. Thrombocytosis
3. Elevated divalproex sodium serum level
4. Serum PCR positive for HHV 5
5. Positive EBV IgM titers
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Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Drug-Induced Hypersensitivity Syndrome (DIHS)

- Manifests 2 to 6 weeks after the initiation of offending drug
- 10% Mortality rate
- Fever
- Skin eruption
  - most often morbilliform
  - can demonstrate microvesiculation
- Lymphadenopathy
- Edema of face and hands
- Eosinophilia
- Atypical lymphocytosis
- Hepatitis/Transaminitis- up to 50%
- Pulmonary infiltrates
- Nephritis
- Myocarditis
This 15-year-old girl taking lamotrigine x 4 weeks for bipolar disorder has fever to 101 °F, morbilliform eruption, the lip findings shown, and a 1 cm superficial erosion on the vulvar mucosa.

Labs: ALT 68, AST 80
8.5% eosinophils

Which condition are you most concerned about?

1. Stevens-Johnson Syndrome
2. Toxic Epidermal Necrolysis
3. Erythema Multiforme
4. DRESS/drug-induced hypersensitivity syndrome
This 15-year-old girl taking lamotrigine x 4 weeks for bipolar disorder has fever to 101 °F, morbiliform eruption, the lip findings shown, and a 1 cm superficial erosion on the vulvar mucosa.

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Which condition are you most concerned about?

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2. Toxic Epidermal Necrolysis
3. Erythema Multiforme
4. DRESS/drug-induced hypersensitivity syndrome
Mucosal involvement in DRESS

- Estimated to occur in 50% of DRESS cases
- *Milder* than TEN/SJS spectrum
  - Conjunctival injection
  - Mild mucosal ulcerations

Mucosal involvement in DRESS
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Evaluation
- CBC/diff
- Liver function tests
- Creatinine
- Urinalysis
- Baseline thyroid function studies

Treatment
- Discontinue offending medication!
- Oral corticosteroids with 3-6 week taper if reaction severe
- Monitoring
  - Thyroid function tests- 2 to 3 months after
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Common Culprit Medications

<table>
<thead>
<tr>
<th>Aromatic Anticonvulsants</th>
<th>Antibiotics</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Sulfonamides</td>
<td>Terbinafine</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Minocycline</td>
<td>Dapsone</td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>Nitrofurantoin</td>
<td>Allopurinol</td>
</tr>
<tr>
<td>Lamotrigine</td>
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</table>
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

- Cross reactivity between anticonvulsant medications may be as high as 75%
- If DRESS occurs with aromatic anticonvulsant, *avoid* the other aromatic anticonvulsants

<table>
<thead>
<tr>
<th>Anticonvulsant</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin (Dilantin)</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine (Tegretol)</td>
<td></td>
</tr>
<tr>
<td>Phenobarbitone (Phenobarbital)</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine (Lamictal)</td>
<td></td>
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</tbody>
</table>
- Started divalproex sodium (depakote) - 5 weeks before rash
- Added lamotrigine (lamictal) - 4 weeks before rash
Anticonvulsant hypersensitivity syndrome/DRESS

- Among patients taking lamotrigine:
  - Rate of serious rashes - 0.1%

- Of patients with anticonvulsant hypersensitivity (DRESS) syndrome to lamotrigine, 60% also taking valproic acid derivative
  
  - Co-administration of valproic acid derivative triples the half-life of lamotrigine


**Serious Rash**

serious rashes requiring hospitalization and D/C tx incl. Stevens-Johnson syndrome, rare cases of toxic epidermal necrolysis, and rash-related deaths; incidence w/ adjunctive epilepsy tx 0.8% in 2-16 yo and 0.3% in adults; bipolar and other mood disorder incidence 0.08% as initial monotherapy and 0.13% as adjunctive tx; age is only risk factor identified as predictive for risk of rash occurrence or severity; other risk factors may incl. concurrent valproic acid derivative or exceeding initial lamotrigine dose or dose escalation recommendations; most life-threatening rashes occur in the first 2-8wk of tx w/ isolated cases after prolonged tx; though benign rashes may also occur D/C tx at 1st sign of rash unless clearly not drug related; D/C tx may not prevent rash from becoming life-threatening or permanently disabling or disfiguring

**Black Box warning**
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

- Associated with reactivation of human herpesvirus (HHV)
  - HHV 6
  - HHV 7

- HHV 6 positive DRESS is associated with a more severe course and longer hospital length of stay (LOS)
  - LOS (11.5 days vs. 5 days, P = 0.039)
  - Number of febrile days (12.5 days vs. 3 days, P = 0.032)

Hara H, et al. Dermatology 2005; 211:159-161
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

- Reported autoimmune sequelae
  - Autoimmune thyroiditis
  - Type 1 diabetes mellitus
  - Vitiligo
  - Alopecia areata
  - Systemic lupus erythematosus

- In a study of 145 adult patients with DRESS/DIHS, the most common autoimmune sequelae were
  - Autoimmune thyroiditis (4.8%)
  - Type 1 diabetes mellitus (3.4%)
    - sometimes fulminant within 1-2 months

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Summary

- Serious drug reaction
  - 10% mortality

- Clinical presentation
  - Fever
  - Lymphadenopathy
  - Facial/hand swelling
  - Erythematous skin eruption
  - May have mild mucosal involvement
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Summary

- In acute phase, may affect multiple organ systems
  - Liver
  - Lungs
  - Kidneys
  - Heart

- In subacute phase (~2-3 months after resolution), may affect
  - Thyroid

- Risk of autoimmune sequelae
Case
2-year old admitted with fever, joint swelling and edematous coalescing plaques

Edematous hands/feet
Difficulty walking
Fever 101 F
Most likely diagnosis?

1. Serum sickness
2. Serum sickness-like reaction
3. Urticaria
4. Erythema multiforme
Most likely diagnosis?

1. Serum sickness
2. Serum sickness-like reaction
3. Urticaria
4. Erythema multiforme
“Urticaria Multiforme”: A Case Series and Review of Acute Annular Urticarial Hypersensitivity Syndromes in Children

Kara N. Shah, MD, PhD, Paul J. Honig, MD, Albert C. Yan, MD

• AKA: Giant urticaria, Annular urticaria
• Common
• Benign dermal hypersensitivity reaction
• Annular, arcuate, & polycyclic urticarial lesions
• Lesions may clear centrally or have dusky centers
• +/- acral soft-tissue edema

• Sometimes mistaken for erythema multiforme and serum sickness-like reaction
<table>
<thead>
<tr>
<th></th>
<th>Annular Urticaria</th>
<th>Serum-Sickness Like Reaction</th>
<th>Erythema multiforme</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphology</strong></td>
<td>Polycyclic wheals +/- ecchymotic centers</td>
<td>Polycyclic wheals +/- ecchymotic centers</td>
<td>- Classic small target lesions - Often acral</td>
</tr>
<tr>
<td><strong>Fixed lesions</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Facial/acral edema</strong></td>
<td>Common</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Dermatographism</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Mucosal erosions</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>2 - 12 days</td>
<td>1 - 6 weeks</td>
<td>2 - 3 weeks</td>
</tr>
<tr>
<td><strong>Characteristic features</strong></td>
<td>- Low-grade fever - Viral infection symptoms</td>
<td>- High-grade fever - Sick appearing - Arthritis - Lymphadenopathy - Antibiotic exposure</td>
<td>- Sometimes low-grade fever - Mild itch, burn - HSV infection</td>
</tr>
</tbody>
</table>

Adapted from Shah, K et al. Pediatrics 2007
“Urticaria multiforme”: treatment

• Stop any unnecessary medications

• Cetirizine 2.5-5 mg by mouth every AM (weight, age based)

• Ranitidine 3-5 mg/kg/day by mouth divided twice daily

• Diphenhydramine q 6-8 hours as needed

• Self-limited

• Once “hive free” x 1-2 days, withdraw 1 antihistamine at a time
Case
18-month old admitted with fever, tachypnea, and “rash”
Infantile seborrheic dermatitis like symptoms have *not* improved with treatment in this 18-month-old child.

Biopsy will likely show what on routine histopathology?

1. Histiocytes with reniform nuclei staining positive for CD20
2. Histiocytes with reniform nuclei staining positive for CD207
3. Birbeck granules
4. Spongiotic dermatitis
5. Leukocytoclastic vasculitis
Infantile seborrheic dermatitis like symptoms have *not* improved with treatment in this 18-month-old child.

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EM: LCH -- Birbeck granules
Langerhans Cell Histiocytosis (LCH)

- Skin findings occur in 50% of children with LCH
  - “Skin-only” LCH in 10% of children

- Most often “seborrheic dermatitis”-like or diaper eruption
  - Resistant to treatment
  - *Warning sign*: petechiae in intertriginous areas

Mimic: Infantile seborrheic dermatitis
Langerhans Cell Histiocytosis

Courtesy of Teresa Wright, MD
Langerhans Cell Histiocytosis: nail changes

Nail changes in LCH are uncommon but include:

- Hemorrhagic and pustular lesions in the nail plate
- Longitudinal grooving
- Hyperkeratosis
- Subungual thickening
- Striate nail dystrophy
- Onycholysis
- Paronychia
- Loss of nail plate

Congenital Langerhans Cell Histiocytosis

Typical presentation

- Red brown papulonodules
- May evolve into crusted papules, vesicles or ulcers
- Usually present at birth

- Formerly “self-healing reticulohistiocytosis” (Hashimoto-Pritzker disease)
  - Terms no longer favored as can only be determined retrospectively

Langerhans Cell Histiocytosis

Work up: asymptomatic infant

- CBC/diff
- LFTs
- Coagulation studies
- Chest x-ray
- Urine osmolality
- Skeletal survey
LCH: “Blueberry Muffin Baby”
DDx: purpuric papules/plaques in neonate

- TORCH infection
  - Toxoplasmosis
  - Other: syphilis
  - Rubella
  - CMV
  - Herpes

- Congenital leukemia
- Congenital rhabdomyosarcoma
- Neuroblastoma
- Langerhans Cell Histiocytosis
- Hemolytic disease or the newborn
- Twin-twin transfusion
- Neonatal lupus erythematosus (atypical)
Summary: Langerhans Cell Histiocytosis (LCH)

• Skin findings occur in 50% of children with LCH
  – “Skin-only” LCH disease in 10% of children

• Often “seborrheic dermatitis”-like or diaper eruption
  – Resistant to treatment
  – Warning sign: petechiae in intertiginous areas

• “Self-healing” congenital reticulohistiocytosis (Hashimoto Pritzker disease)--- cannot be predicted reliably

• Babies with skin findings of LCH **must be followed and screened for systemic disease**
  – ~ 50% will progress to multisystem disease

THANK YOU