Focus Session U020:
Case-based Challenges in Pediatric Dermatology Hospital Consults

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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

Case

- 4-month-old healthy child
- Blistering x 2 days
- Previously with 1 localized blister on shin about 3 weeks ago, diagnosed as impetigo
- No FMHx blistering disorders
- No pregnancy complications

What is your next step?

1. Panic
2. “Google”
3. Phone a friend
4. Skin biopsy
What is your next step?

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What diagnosis do you suspect?

1. Mastocytosis
2. Linear IgA disease
3. Stevens Johnson syndrome
4. Thermal burn
5. Infantile bullous pemphigoid

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Bullous Mastocytosis

- Bullous mastocytosis:
  - Form of Diffuse Cutaneous Mastocytosis
- Mast cell infiltration of skin
  - Thick and leathery skin (“peau d’orange” skin appearance)
  - Plaques and nodules
  - Bullae can be the first presentation
    - Suspected etiology of bullae: serine protease release from mast cells

Cutaneous Mastocytosis: Revised Consensus Classification 2016

- Diffuse cutaneous mastocytosis
  - Diffuse skin thickening and erythema
  - Pronounced dermatographism
  - Bullae in some infants (“bullus mastocytosis”)
- Maculopapular cutaneous mastocytosis
  - Polymorphic (urticaria pigmentosa)
  - Monomorphic
- Cutaneous mastocytoma
  - No longer recommended: telangiectasia macularis eruptiva perstans (TMEP)

Characteristics of typical adulthood-onset and typical childhood-onset mastocytosis

- Adult onset morphology
- Classic pediatric onset morphology

ISM: Indolent Systemic Mastocytosis

Laboratory Work Up

- CBC/Diff- within normal limits
- LFTs- within normal limits
- Tryptase – 283 mcg/ L (range < 10.9 mcg/L)
- Bone marrow biopsy – no abnormal mast cell proliferation
- C-KIT mutation analysis- negative


Pediatric Mastocytosis: screening for systemic disease

- Cohort of 105 children
- Most children experienced major or complete disease resolution (57%)
- Partial improvement was observed among remaining children
- Enlargement of liver or spleen (hepatosplenomegaly) – strong indicator of systemic disease


Treatment

- Antihistamines: "around the clock"
  – Cetirizine (H1 antihistamine)
  – Ranitidine (H2 antihistamine)
- Breakthrough: diphenhydramine as needed for flushing/itch
- Good skin moisturization
- Topical corticosteroids:
  – Triamcinolone 0.1% oint
  – "Magic Masto Lotion"

Mastokids.org: "Magic Masto Lotion"

Interval viral illness with thrombocytopenia:
- Increased blistering
- Hemorrhagic appearance to bullae

Summary: Pediatric Mastocytosis

- Revised cutaneous mastocytosis nomenclature (2016):
  – Diffuse cutaneous mastocytosis
  – Maculopapular cutaneous mastocytosis
  – Polymorphic (urticaria pigmentosa)
  – Monomorphic
    – Cutaneous mastocytoma
  – No longer recommended category: telangiectasia macularis eruptiva perstans (TMEP)
- Among children with cutaneous mastocytosis
  – Urticaria pigmentosa appears to be the most sensitive predictor of systemic disease
- Antihistamines (H1&H2) +/- topical corticosteroids or “masgic mastolotion” helpful
- Prognosis good with most children improving over 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

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 microvesicles
- Lymphadenopathy
- Edema of face and hands
- Eosinophilia
- Atypical lymphocytosis
- Hepatitis/Transaminasis- up to 50%
- Pulmonary infiltrates
- Neutritis
- 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
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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

Ben Jirnucham et al., Medicine (Baltimore). 2009 May;88(3):131-40

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>
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<tbody>
<tr>
<td>Phenytoin</td>
<td>Sulfonamides</td>
<td>Terbinafine</td>
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<tr>
<td>Carbamazepine</td>
<td>Minocycline</td>
<td>Dapsone</td>
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<tr>
<td>Phenoobarbitone</td>
<td>Nitrofurantoin</td>
<td>Allopurinol</td>
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Phenytoin (Dilantin)
Carbamazepine (Tegretol)
Phenobarbitone (Phenobarbital)
Lamotrigine (Lamictal)

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

Black Box warning

Serious Rash
serious rashes requiring hospitalization and D/C tx incl. Stevens-Johnson syndrome, toxic epidermal necrolysis, incidence of adverse events vs. placebo was 0.8% in lamotrigine, and 0.2% in placebo

Reported side effects of lamotrigine include:

- Nervous system:
  • Headache
  • Exfoliative dermatitis

- Cardiovascular:
  • Angina

- Gastrointestinal:
  • Esophageal ulcer

- Respiratory:
  • Allergic rhinitis

- Ophthalmic:
  • Nystagmus

- Psychiatric:
  • Mania

- Other:
  • Orthostatic hypotension

HHV: Human Herpesvirus

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)

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

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
Case

Infantile seborrheic dermatitis like symptoms have not improved with treatment in this 18-month old child.

Biopsy will likely show what on histopathology?

1. Reniform cells staining positive for CD20
2. Reniform cells staining positive for CK20
3. Birbrick granules
4. Spongiotic dermatitis
5. Leukocytoclastic vasculitis

EM: LCH -- Birbrick 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 intertiginous areas

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

- Young babies with skin findings of LCH must be followed
  - ~ 50% will progress to multisystem disease

Summary: Langerhans Cell Histiocytosis (LCH) in young children

- 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 intertriginous areas
- "Self-healing" congenital reticulohistiocytosis (Hashimoto Pritzker disease)—cannot be predicted reliably
- Young babies with skin findings of LCH must be followed
  - ~50% will progress to multisystem disease


Case

13 year-old-boy with relapsed stage 2 Burkitt’s lymphoma hospitalized for chemotherapy

- Painful groin eruption
- Erythema appeared the morning after patient cleaned genital area with a chlorhexidine gluconate 4% wipe
- No itch
- Worsening despite topical nystatin cream
- Advancing tender border
- Afebrile, absolute neutrophil count 233

What is your next step?

1. Take careful history for contact allergens
2. Fungal/yeast culture
3. Bacterial skin culture
4. Start patient empirically on IV antibiotic and IV antifungal
5. Take careful history for recent chemotherapy agents

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5. Take careful history for recent chemotherapy agents
Oncology and urology team started treating patient with IV clindamycin and IV fluconazole

- Fungal/yeast skin culture- negative
- Bacterial skin culture- negative
- Blood cultures- negative

- Skin exposures
  - Limited to hibiclens wipes, nystatin, zinc oxide

Relapsed Burkitt’s lymphoma: TAT ANHL01P1 group C

COP-R Day 0
- cyclophosphamide 537 mg (300 mg/m²) day 0
- vincristine 1.8 mg (1 mg/m²) day 0
- prednisone 54 mg BID, day 0-6

COMRAP1 Day 8
- rituximab 670 mg (375 mg/m²) Day -2 and 0
- vincristine 2 mg (2 mg/m²) day 0
- cyclophosphamide 450 mg (250 mg/m²) day 1-3
- high dose methotrexate 14320 mg (8g/m²) day 0 NOTE: had delayed clearance
- dexamethasone 107 mg (60 mg/m²) day 1
- prednisone 54 mg BID, day 0-4 with taper over 3 days
- pegfilgrastim 6 mg day 6
- Intrathecal therapy: methotrexate, cytarabine, hydrocortisone

Toxic Erythema of Chemotherapy

Clinical features
- Erythematous patches or edematous plaques
  - Most frequently: hands, feet, intertriginous zones, scrotum
  - Less commonly: elbows, knees, neck, and ears
- Dusky hue, petechiae, and/or sterile bullae may be seen in the affected areas of erythema
- Scattered papules may be seen at the periphery of the lesions

- Timing of onset
  - 2 days to 3 weeks after chemotherapy administered

- Symptoms
  - Pain, burning, paresthesia, or tenderness, more often than pruritus
  - Spontaneous resolution without specific therapy
  - Possible recurrence if the same or higher dose is administered

Histological findings
- Vacuolar degeneration of the basal layer
- Necrotic keratinocytes
- Dymaturation of keratinocytes
- Dermal edema
- Eccrine squamous syringometaplasia and/or eccrine hidradenitis

Toxic Erythema of Chemotherapy

Clinical features
Toxic erythema of chemotherapy (TEC)
- Eccrine squamous syringometaplasia
- Palmar-plantar erythrodysesthesia
- Acral erythema
- Hand-foot syndrome
- Neurophilic eccrine hidradenitis
- Pseudocellulitis
- ‘Ara-C ears’
- Intergingival eruption of chemotherapy

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### Chemotherapeutic agents associated with TEC

**More commonly associated:**
- Cytarabine (araC)
- Anthracyclines (doxorubicin)
- 5-Fluouracil
- Capecitabine (5-FU prodrug)
- Taxanes (docetaxel > paclitaxel)
- Methotrexate

**Less commonly associated:**
- Bleomycin
- Busulfan
- Carmustine, lomustine
- Capetate, carboplatin
- Chlorambucil
- Cytarabine
- Cyclophosphamide, ifosfamide
- Etoposide
- Gemcitabine
- Hydroxyurea
- Melphalan
- 6-mercaptopurine
- Miltefosine
- Roscovitine serine threonine kinase inhibitors (meltrin, sorindol)
- Tegafur
- Thioguanine
- Vinorelbine

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### Toxic Erythema of Chemotherapy: Treatment

**Supportive**
- Cool compresses
- bland emollients
- topical corticosteroids
- topical antibiotics for erosions

**Limited data for:**
- local hypothermia, systemic corticosteroids, oral vitamin B6 (50-150 mg once daily), oral vitamin E (300 mg once daily)

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### Summary: Toxic Erythema of Chemotherapy

- **Toxic phenomenon**
  - Not immune mediated
  - Self-limited
- Frequently misdiagnosed as
  - Allergic drug reaction
  - Allergic contact dermatitis
  - Graft versus host disease
  - Cutaneous infections

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**THANK YOU**