Mimickers or Atypical Presentations of Common Childhood Rashes

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Pediatric Dermatology
February 26th, 2017
Conflict of Interest

• No conflict of interest
• Will discuss off label use of medications
Objectives

• Recognize common neonatal and childhood rashes
• Distinguish these benign rashes from conditions that require diagnostic and therapeutic interventions
• Recognize when to refer a pediatric patient to a pediatric dermatologist
Case One

- 2-week old newborn with pustules on the forehead, temples, eyelids and cheeks
- Born full-term, uncomplicated delivery
- Afebrile
- Diagnosis?
Neonatal Cephalic Pustulosis

- 20% of healthy newborns
- Appear within 2-3 weeks of life
- Pustules on forehead, eyelids, cheeks, chin
  - May involve scalp, neck, upper trunk
- Newborn sebum excretion and the presence of yeast flora are possible triggers
NCP Treatment

• Mild and self-limiting
  – Improved by 4 months
• Ketoconazole or clotrimazole cream
• OTC hydrocortisone cream
Case Two
Potential Mimicker of NCP

- Vesiculopustular eruption
- Occurred within first 2 weeks of life
- Diagnosis?
Neonatal HSV

• Classified into three main syndromes:
  – Localized skin, eye, and mouth (SEM)
    • 45% of all neonatal cases of HSV infection
    • May progress to more severe infection
  – Central nervous system (CNS) with or without SEM
  – Disseminated disease involving multiple organs
Neonatal HSV

• Localized SEM disease is characterized by:
  – Skin: clusters or coalescing 2-4 mm vesicles with surrounding erythema (progress to pustules, and later crusting)
  – Eyes: excessive tearing, conjunctival edema
  – Mouth: localized small ulcers
• Usually presents within 2 weeks of life, but may occur at any time during the first 6 weeks
Clinical Findings

- Often, lesions will occur at sites where the skin integrity has been breached
  - Scalp vertex at the site of placement of fetal scalp monitor electrodes
Diagnosis of Neonatal HSV

• Viral culture from surface sites
  – Fresh vesicular lesions of skin are often positive within 24 hrs of incubation

• HSV PCR from surface sites
  – Not well studied in neonates

• Direct fluorescent antibody study from surface sites
  – Fast, but not as sensitive as viral culture

• HSV PCR from blood
  – All neonates with suspected HSV

• HSV PCR from cerebral spinal fluid
  – All neonates with suspected HSV (even if appear to have isolated SEM)
Newborn with Suspected HSV

• Isolate (contact precautions)
• Evaluate for systemic infection
• Treat with empiric antiviral therapy
  – 60 mg/kg IV q8hr
  – 50-60% who with SEM who do not receive antiviral therapy progress to CNS or disseminated disease
• Obtain an ophthalmology consult
• All infants exposed to HSV should be monitored for evidence of infection during the first six weeks of life
Case Three

- 4-week-old male
- Erythematous plaques with greasy scale present on his face, scalp, retro auricular area and diaper area
- Diagnosis?
Seborrheic Dermatitis

• 10% of children in neonatal period
• Most common within first 4-6 weeks of life
• Predilection for scalp (“cradle cap”), face, forehead, eyebrows, trunk, intertriginous and flexural areas including diaper area
• Precise etiology is unknown, but the yeast *Malassezia furfur* has been implicated on its pathogenesis
Seborrheic Dermatitis

• Can be difficult to distinguish clinically from infantile psoriasis

• Seborrheic dermatitis tends to be less erythematous, to have thinner scaling, and to respond more quickly to topical antiinflammatory medications
Treatment

• Neonatal seborrheic dermatitis usually self-resolves within several weeks to months
• Clears quickly with topical therapy
  – Low potency topical steroid
  – Selenium or zinc shampoos
  – Anti-yeast shampoo (ketoconazole)
  – Scale can be softened before removal with mineral oil
  – Salicylic acid is not recommended because of concerns about systemic absorption
• 8% of children may have persistent SD
Case Four
Mimicker of Seborrheic Dermatitis
Langerhans Cell Histiocytosis

• LCH – disorder characterized by infiltration of Langerhans cells into various organs

• LCH may occur at any age
  – Peak incidence between 1-4 yrs
    • 3-5/1,000,000

• Pathogenesis is unknown
  – Some appear familial (multiples and siblings)
  – A clonal neoplastic disorder
    • In 2010, a significant % of LCH specimens (57%) were shown to harbor BRAF V600E mutation
LCH

• May involve multiple organ systems
• Skin and the bones most common
  – Skin is often the presenting sign
• Unifocal, multifocal, or disseminated disease
• Patients with widespread, multiorgan involvement have the poorest prognosis
• Best prognosis with isolated bone LCH
Skin Findings

- Scaly red-brown papules
- Erythematous, scaly dermatitis
- Erosion or ulceration
- Petechiae, hemorrhage
- Vesiculopustular lesions
- Red nodules or plaques
- Granulomatous plaques
Organ Involvement

- Bone: painful swelling common
  - Frequency: skull > long bones > flat bones (ribs, pelvis, vertebrae)
- Lymph nodes (cervical most common)
- Liver
- Spleen
- Lungs (diffuse micronodular pattern on radiography)
- Gastrointestinal tract
- Thymus
- Bone marrow (pancytopenia portends a poor prognosis)
- Gingivae, buccal mucosa (swelling, erythema, erosions, petechiae)
- Kidney
- Endocrine glands (diabetes insipidus most common)
- Central nervous system
Diagnosis & Evaluation

- Tissue specimen from affected organs
  - Skin biopsy -> reveals infiltrate of Langerhans cells, which can be confirmed by positive S100, CD1a or Langerin immunostaining
- Physical exam
- CBC, coags, liver function, urine osmolality
- Complete skeletal x-ray
- CXR
- More specific studies depending
Therapy

• Depends on extent of disease
• Limited to skin – can observe, may resolve spontaneously
• Severe skin disease – consider systemic therapy
• Disease limited to bone – depends on extent of bone involvement and symptoms
• Extensive disease – systemic chemotherapy
  – Vinblastine or etoposide
  – Case reports of BFRAF inhibitors
Case Five

• Infant with erythema and flaccid bullae that easily rupture, leaving a fine collarette of scale

• Diagnosis?
Bullous Impetigo

• Nearly always caused by S. aureus
• Flaccid, thin-walled bullae or tender shallow erosions surrounded by a remnant of the blister roof
• Common locations: face, extremities, diaper region
Examples of Bullous Impetigo
Bullous Impetigo Treatment

• For localized forms, may use topical mupirocin
  – Also consider adjunctive dilute bleach baths
• Oral antibiotics: cephalexin, dicloxacillin
• Empiric coverage for MRSA based on local epidemiology and infant risk factors (clindamycin)
• Follow neonates closely, as bullous impetigo may advance rapidly
Case Six
Mimicker of Bullous Impetigo

• 6 month-old male infant with a rash on the scalp, face and neck x 3 weeks
• No apparent itch or pain
• Previous treatments include mupirocin ointment TID and oral Bactrim
  – Bacterial culture from skin swab + for staph
History Continued

• ROS: No fevers or recent illness. Appetite slightly decreased, but still a “good eater”
• PMH: Born at 28 weeks, NICU x 8 weeks, supplemental oxygen x 6 more weeks
• SH: Lives with parents and six siblings
• No sick contacts
Next Step?

• Skin biopsy
  – Epidermal pallor suggestive of nutritional deficiency
• Zinc level: 22 (60-120)
• Alk phos: 72 (115-460)
  – Zinc dependent enzyme
Classification of Zinc Deficiency

• **Inadequate intake**
  – TPN, low breast milk zinc levels, poor diet, eating disorder

• **Excessive losses**
  – Digestive fluid loss (intestinal fistula, intractable diarrhea)
  – Increased urinary elimination (liver cirrhosis, infection, renal disease, diabetes mellitus, diuretics, etoh ingestion)
  – Other: burns, excessive sweating, hemodialysis

• **Malabsorption**
  – Acrodermatitis enteropathica
  – Medical conditions (IBD, cystic fibrosis, liver dysfunction, pancreatic dysfunction) and medications (chelating agents, sodium valproate) can reduce absorption of zinc in the small intestine
Classification of Zinc Deficiency

• Increased demand
  – Pregnancy: zinc requirements in the 3rd trimester are twice as high as nonpregnant women
  – Lactating women
  – Preterm infants: born in a negative zinc balance, decreased gut absorption, higher metabolic rate needed for rapid growth, higher urinary and fecal loss
    • Transfer of zinc from the mother to fetus occurs in the final trimester

• Other
  – Associated with Down syndrome and congenital thymus defects

Acrodermatitis Enteropathica

• Autosomal recessive
• Affects the Zip family of proteins required for zinc absorption in the GI tract
  • Gene SLC39A4, chromosome 8q24.3, encodes Zip4 transporter
• Symptoms manifest when the child is weaned from breast milk
  – Result of low molecular-weight binding agents in breast milk → increases the bioavailability of zinc and delay the onset of clinical symptoms
  – Seen in nonbreast-fed infants in days to weeks after birth (existing zinc stores become depleted)
Acrodermatitis Enteropathica

• Same cutaneous and noncutaneous findings as dietary zinc deficiency
  – Erythematous, scaly, erosive and crusted plaques over acral and periorificial sites

• Alopecia
• Nail changes, paronychia
• Stomatitis, cheilitis
• Bullous pustular dermatitis
Zinc Deficiency

- **Immune**
  - ↑ Allergic sensitivity
  - Recurrent infections
- **Gastrointestinal**
  - Diarrhea
  - Anorexia
  - ↓ Ability to taste
  - Abdominal pain
- **Endocrine**
  - Growth retardation
  - Hypogonadism
- **CNS**
  - Impaired concentration
  - Depression
  - Anosmia
  - Dementia
- **Musculoskeletal**
  - Bone fractures
- **Pregnancy**
  - Delayed fetal growth
  - Low birth weight
  - ↓ Fetal cognition and motor function
Treatment

• AE requires lifelong zinc supplementation
• 1-3mg/kg/day of elemental zinc
• Solicit help from pharmacist
• Symptoms begin to resolve within 1-2 days
• Skin lesions heal without sequelae, but extended periods of deficiency may have permanent effects
Case Seven – Complication of AD

• Toddler with atopic dermatitis developed fever and widespread vesicles with crusting in eczematous areas

• Diagnosis?
Eczema Herpeticum

- HSV infection
- Occurs in individuals with AD or other chronic skin disease
- Abrupt onset of fever, malaise
- Monomorphous vesicles or crusted papules
- Lesions most prominent in skin affected with or prone to AD
Complications

• Keratoconjunctivitis
  – Call ophthalmology if periocular
• Secondary bacterial infection
• Fluid loss
• Viremia
Treatment

• Antiviral therapy
  – 10-14 days
  – IV acyclovir 5 -10 mg/kg q 8 hrs
  – Oral acyclovir 15 mg/kg (400 mg max) 3-5x/day

• Topical steroids
  – Continue with limited involvement

Mimicker of Eczema Herpeticum
Case Eight
Mimicker of Eczema Herpeticum
Hand Foot Mouth Disease

• Acute viral illness caused by coxsackievirus A16 and enterovirus 71 infections
  – Spring to fall
  – Children 5 and younger

• An uncommon enterovirus strain, CV-A6 recently(ish) reported to cause atypical HFMD

Coxsackie Virus-A6

• Causes herpangina

• Since 2008, outbreaks of CV-A6-associated HFMD
  – Late fall and winter
  – Greater proportion of affected adults and hospitalizations
CV-A6 Clinical Findings

• More widespread
• Predilection for sites of dermatitis
  – Eczema coxsackium
• Widespread vesiculobullous
• Gianotti-Crosti like
• Petechial-purpuric
• Systemic symptoms
Laboratory Testing

• RT-PCR most sensitive for detecting enteroviruses
  – Type over 100 enterovirus serotypes

• Source: vesicular fluid preferred
  – Throat swab and stool samples also acceptable
  – Serum is not recommended because viremia is early and transient (except in young infants)
Case Nine

- Toddler with recent URI
- Monomorphic, edematous, erythematous papules symmetrically distributed on the face, buttocks and extremities
Gianotti Crosti Syndrome

- Papular acrodermatitis of childhood
- More common in children 1 - 6 years
- Upper respiratory symptoms, fever and lymphadenopathy may precede exanthem
- Trunk is usually (but not always) spared
- Pruritus may be present
Associations

• Multiple viral agents have been implicated
  – EBV (most common in US)
  – HBV
  – CMV
  – Coxsackie
  – Respiratory (adenovirus, respiratory syncytial virus, parainfluenza virus)
  – Parvovirus B19
  – Rotavirus
  – HHV6

• Possible association with immunizations
  – Measles-mumps-rubella
  – Haemophilus
  – Oral polio
  – Diphtheria-pertussis-tetanus
  – Japanese B encephalitis
  – Hepatitis B vaccines
Treatment

• Treatment is supportive
• Self-limited, usually within 6 weeks
  – May take 8-12 weeks to resolve
• Post-inflammatory hypopigmentation may occasionally persist for several months following resolution of the exanthem
Gianotti-Crosti Like Reaction

Gianotti-Crosti Like Reaction

• Inflammatory reactions to molluscum contagiosum are common
  – Inflamed molluscum
    • Usually sterile
  – Molluscum dermatitis
  – GCLR

• Inflamed molluscum and GCLR reflect cell mediated immune responses that may lead to viral clearance

Control of dermatitis may help to prevent the spread of MC that occurs secondary to scratching
Case Ten

A 4-year-old girl with new onset oral and skin lesions within the last two days
Erythema Multiforme

- Hallmark is the typical target lesion
- Target lesions intermixed with atypical papular target lesions with only 2 distinct color zones
- Skin findings have abrupt onset with majority of lesions appearing within 24 hours
- Remain fixed at the same site for 7 days or longer
Mucosal Lesions

• Oral lesions occur in 25-50% of children
• Typically limited to the buccal mucosa and lips
• Initially vesiculobullous and rapidly evolve into painful erosions
Pathogenesis

• Self-limited hypersensitivity syndrome
• Majority of cases precipitated by herpes simplex virus type 1 (3-14 days)
• Other associated infections: varicella, orf, EBV, histoplasmosis (endemic areas)
• EM with high fever can be a sign of Kawasaki disease, especially in infants
Treatment

• Supportive care with topical emollients, topical corticosteroids, magic mouthwash, and oral antihistamines is cornerstone

• Oral antiviral treatment has minimal impact if given after the appearance of an acute episode

• Inpatient should be considered for hydration and pain management
Case Eleven – Mimicker of EM

- Recent URI
- Erythematous to violaceous, large, serpiginous and annular plaques
- Slightly dusky center
- Duration < 24 hours
- Mild edema hands and feet
Urticaria Multiforme

- Morphologic subtype of acute urticaria
- Polycyclic, annular plaques with dusky centers lasting < 24hrs
- Dermal edema can involve the face, hands and feet (present in 60%)
- Pruritic
- Children are otherwise well, though fever and viral prodrome +/- exposure to oral antibiotics often precede skin findings
Management

- Modest leukocytosis and elevation of ESR, CRP
- Skin findings typically self-resolve within 2 weeks
- Antihistamines

Case Twelve

- 17 year-old male admitted for fever, mucositis, and rash
- PMH: Seasonal allergies, hives and angioedema with exposure to cats/dogs
- No sick contacts
- Medication history:
  - Azithromycin for PNA
  - Augmentin
  - Acyclovir
Stevens Johnson Syndrome?

Original Articles

Mycoplasma pneumoniae—induced rash and mucositis as a syndrome distinct from Stevens-Johnson syndrome and erythema multiforme: A systematic review

Theresa N. Canavan, MD, Erin F. Mathes, MD, Ilona Frieden, MD, and Kanade Shinkai, MD, PhD

Birmingham, Alabama, and San Francisco, California

Background: Mycoplasma pneumoniae infection is associated with extrapulmonary complications, including mucocutaneous eruptions. These eruptions, which have been termed either “Stevens-Johnson syndrome” or “erythema multiforme” in the literature, may differ from drug-induced Stevens-Johnson syndrome or viral-associated erythema multiforme.

Objective: We sought to review the literature characterizing morphology and disease course of M pneumoniae—associated mucocutaneous disease.

Methods: A comprehensive literature search identified 95 articles with 202 cases.

Results: Patients were often young (mean age: 11.9 years) and male (66%). Cutaneous involvement ranged from absent (34%) to sparse (47%), to moderate (19%). Oral, ocular, and urogenital mucositis was reported in 94%, 82%, and 63% of cases, respectively. Treatments included antibiotics (89%), systemic corticosteroids (35%), supportive care alone (8%), and/or intravenous immunoglobulin (8%). Complications included mucosal damage (10%), cutaneous scarring (5.6%), recurrence (8%), and mortality (3%).

Limitations: Mild cases may not have been published; thus this review may have a bias toward more severe disease.

Conclusion: M pneumoniae—associated mucocutaneous disease has prominent mucositis and sparse cutaneous involvement, although cutaneous involvement varies. Because of the distinct morphology, mild disease course, and potentially important clinical implications regarding treatment, we propose a revision of the nomenclature system and suggest the term “Mycoplasma-induced rash and mucositis” for these cases. (J Am Acad Dermatol 2015;72:239-45.)

Key words: erythema multiforme; mucositis; Mycoplasma pneumoniae; rash; Stevens-Johnson syndrome.
MIRM

• Epidemiology
  – Young (mean 11.9 yrs)
  – Male (66%)

• Morphology
  – Mucosal predominant
    • Oral 94%
    • Ocular 82%
    • Urogenital 63%
    • Mucosal alone 34%
  – Mild skin involvement
    • 46% sparse, scattered
    • 19% moderate
    • Extensive - rare

MIRM Outcomes

- No sequelae 81%
- Pigmentary alteration 6%
- Mucosal complications 8%
- Recurrence in 8%
- Mortality 3% (all in 1940s)
Back to Our Patient

- Mycoplasma PCR negative (including from oropharynx)
- Mycoplasma serologies negative
- Consulted ENT
  - Oropharyngeal sloughing extended to the subglottis
- Consulted ophthalmology
- IVIG x 3 days
- Steroids 2 mg/kg, followed by a taper
Testing for Mycoplasma

- IgM/IgG
  - Rise ~ 7-9 days after infection, peak at 3-4 weeks
  - Repeat mycoplasma serologies 11 days later positive in our patient (s/p IVIG)

- PCR
  - Increased sensitivity if sputum tested
MIRM vs SJS

• Does this matter?
• With the exception of more frequent pulmonary disease, MIRM has a milder disease course
• Treatment is (can be) different
SJS/TEN overlap to Lamotrigine
SJS/TEN overlap to Lamotrigine
TEN 2/2 Lamotrigine
SJS/TEN in Children

- Spectrum of epidermal necrolysis
- Severe cutaneous adverse reactions to drug therapy
- Mortality rate < 2%
  - Adults: 5% in SJS to 20% in TEN
Triggers in Children

Children’s Hospital Boston + Hospital for Sick Children, 2000-7

• 29 (53%) medications
  – Anticonvulsants (29%)
  – Sulfonamide antimicrobial (13%)

• 17 (31%) infection
  – M. pneumoniae (22%)
  – HSV (9%)

• Unknown (18%)
The two institutions treat patients differently. Patients treated with IVIG had higher risk of ocular sequelae.
### Outcome of SJS/TEN spectrum

**OUTCOME OF 55 CHILDREN WITH SJS, SJS/TEN OVERLAP SYNDROME, AND TEN**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total Cohort (N = 55), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Long-term sequelae</strong></td>
<td>25 (45)</td>
</tr>
<tr>
<td>Skin sequelae (e.g., hypopigmentation, scarring)</td>
<td>23 (42)</td>
</tr>
<tr>
<td>Eye sequelae (e.g., uveitis, keratitis, corneal defects, chronic conjunctivitis)</td>
<td>15 (27)</td>
</tr>
<tr>
<td>Phimosis</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Sclerosing cholangitis</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Bronchiolitis obliterans</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Stridor</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Recurrence of SJS</td>
<td>10 (18)</td>
</tr>
<tr>
<td>Recurrence of TEN</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

- 45% have long-term sequelae
- 42% skin
- 27% eye
Treatment of SJS & TEN in Children
Del Pozzo-Magana Systematic Review

• 1389 publications, included 31
• Included objective measures other than mortality
  – Time to fever cessation
  – Time to remission
  – Hospital stay
  – Complications
• Bottom line
  – Steroids and IVIG seem to improve outcomes
  – Supportive care alone may increase mortality

Approach to Steroids

• Use in SJS with evidence of ongoing inflammation (early)
• Use 1-2mg/kg/day x ~5 days
• Occasionally use in conjunction with IVIG
• Caution in kids with behavioral or psych diagnoses
Approach to IVIG

- Use it in TEN and SJS/TEN overlap
- Use high dose 4 g/kg total (1 g/kg/day x 4 days)
- Occasionally use in combination with steroids
Supportive Care

- **FEN**
  - NG tubes for almost everyone!
  - Involve nutrition
  - 1.5x daily caloric requirements

- **Airway**
  - Intubate for respiratory distress
Supportive Care

• Sterile gloves if large BSA
• Dressing changes daily
  – Rinse with isotonic saline
  – Apply petrolatum to vaseline gauze
  – Apply vaseline gauze to patient
  – Apply telfa
  – Wrap with kerlex
  – Secure with flexinet
• GU care – involve urology
Thank You!

• Questions?
  – Sarah.Cipriano@hsc.utah.edu

• Scheduling for Pediatric Dermatology
  – (801) 581-2955, Option 3
  – Expedited referral (801) 581-6465 (have me paged)