U028 – Nursery Tales: Challenging Dermatoses in Newborns

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

DISCLOSURES
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Objectives

▪ Develop a differential diagnosis for challenging dermatoses in premature and term infants

▪ Utilize laboratory testing to diagnose skin disease in neonates

▪ Formulate management plans for newborn skin eruptions
Case
2 day-old FT girl with grouped vesicles on arms

- Afebrile
- Feeding, voiding, stooling well
- No seizure activity or abnormal movements
- Maternal labs: RPR NR, rubella- Immune, hepB neg, HIV neg; GBS negative; no maternal history of herpes

- Vesicles are tense with an erythematous base and arranged in whorled linear arrays
Blisters in Neonates

- Infectious
  -- More common
  -- Need early diagnosis and treatment

- Autoimmune

- Inflammatory

- Genetic

- Other

Pregnancy:
• Good prenatal care
• Normal infectious disease screenings
• No complications or infections

Family medical history:
• no known genetic diseases
• Mother herself was adopted internationally
  ➢ no information regarding mom’s birth

• Mother’s PMHx: retinal detachment
What cutaneous finding on mother may help direct diagnostic thinking?

- Hypopigmented curvilinear streaks
- Gingival erosions
- Hyperpigmented whorling streaks
- Hypohidrosis
What cutaneous finding on mother may help direct diagnostic thinking?

• Hypopigmented curvilinear streaks
• Gingival erosions
• Hyperpigmented whorling streaks
• Hypohidrosis
Patient’s mother:
• Hypopigmentation: “Chinese Characters”

• Focal alopecia of scalp
Differential Diagnosis

Infectious?
- Infantile herpes zoster
- Infantile herpes simplex virus
- Bullous impetigo

Autimmune Bullous?
- Neonatal bullous pemphigoid
- Epidermolysis bullosa
- Incontinentia pigmenti

Genetic?

Other?
- Sucking blister

References:
Biopsy: Spongiosis with vesiculation and numerous eosinophils
Incontinentia pigmenti (IP)

- X-linked dominant disorder; *IKBKG* gene (*NEMO*)
  - Random X chromosome inactivation -> extent of disease
- Four cutaneous phases (may overlap)

- Inflammatory vesicles/bullae ➔ Verrucous lesions ➔ Hyperpigmented streaks ➔ Hypopigmented +/- atrophic streaks

IP follows Lines of Blaschko

Mane, S. Indian Pediatrics 2006; 43:1103-1104
Bruckner, A. Seminars in Cutaneous Medicine and Surgery, 2004; 23 (2) 116–124
Pacheco, T, et al. JAAD, 2006; 55(2) 251-255
Genomic rearrangement in NEMO impairs NF-kappaB activation and is a cause of incontinentia pigmenti. The International Incontinentia Pigmenti (IP) Consortium.

Incontinentia pigmenti

Dermatologic ‘clues’
• Alopecia
• Dystrophic nails

Systemic manifestations

CNS
• Seizures
• Developmental delay
• Microcephaly
• Ataxia

Dental
• Malformed ‘Peg’ teeth

Ophthalmological
• Optic nerve atrophy
• Cataracts
• Strabismus
• Retinal detachment

Bruckner, A. Sem. in Cutaneous Medicine and Surgery, 2004; 23 (2) 116–124
Chan, Y, et al. JAAD, 2003; 49 (5), 929–931
Pride, H. www.dermatlas.com
Tule, S. et al. Consultant for Pediatricians, 2012; 11(10)
Full-term baby *boy* with linear arrays of crusted erosions and vesicles
Biopsy: spongiotic intra-epidermal vesicles with numerous eosinophils
Incontinentia Pigmenti (IP): X-linked dominant

X-linked dominant disorders

- Incontinentia Pigmenti
- Focal dermal hypoplasia (Goltz syndrome)
- CHILD (Congenital Hemidysplasia with ichthyosiform erythroderma)
- Conradi-Hünerman
- Oro-Facial-Digital Syndrome
- Albright's hereditary osteodystrophy
- Bazex syndrome

- IP: X-linked dominant disorder; IKBKG gene (NEMO)
  - 97% - female
  - males born with IP: somatic mosaicism vs. XXY

Management: Incontinentia Pigmenti

- Wound care
- Counseling on expected skin changes
  - Vesicular
  - Verrucous
  - Hyperpigmented
  - Hypopigmented
- Referrals to:
  - Genetics
  - Neurology
  - Ophthalmology
  - Dental
Jenna Lyons

Diagnosed with IP

President of J Crew

- Blaschkoid patterning is *stylish* (in all 4 stages!)
  - Vesicular, Verrucous, Hyperpigmented, Hypopigmented

- High-power corporate world isn’t “just for boys”, and IP isn’t “just for girls”
34 5/7 WGA premature infant born by repeat C-section after PPROM

- Widespread erosions at birth
  - Involves face, trunk, extremities
- Normal pregnancy and prenatal ultrasound
- Normal prenatal care

- FMHX:
  - no skin disorders
  - no genetic diseases

- Afebrile, vital signs stable
- Breathing comfortably
- Feeding, voiding, stooling normally
Next diagnostic step?

- Biopsy of existing erosion
- Induced blister biopsy for immunomapping and H&E
Next diagnostic step?

• Biopsy of existing erosion
• Induced blister biopsy for immunomapping and H&E
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
Biopsy

- Hyperkeratosis
- Hypergranulosis
- Epidermolysis of superficial epidermis
Epidermolytic Ichthyosis

- Mutations in
  - \textit{KRT1}: encodes keratin 1
  - \textit{KRT10}: encodes keratin 10

- ~ 50\% new mutations
  - otherwise usually autosomal dominant

- Presentation at birth may have:
  - Erosions
  - Severe blistering
  - Erythroderma

- Later in life:
  - hyperkeratotic skin especially over joints

Spitz, J. L. Genodermatoses, LW\&W, 2005
Naik, N. Dermatology Online Journal. 2003; 9: 4
Management: Epidermolytic Ichthyosis in newborn

- Infant:
  - Conservative, gentle wound care
    - Copious petrolatum
    - Petrolatum coated gauze
  - Minimize friction with caregiving
  - Precautions to avoid infection
    - Soft bedding covered with petrolatum soaked gauze

- Counseling on expected skin changes
Case
• 1 day-old Hispanic girl
  – born by C-section in rural setting
  – 38 WGA
  – APGARS 9/9
• Normal pregnancy, normal infectious labs in pregnancy, G6P5 mother
• Stable, Afebrile
• 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
Differential Diagnosis

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

Erosive Candida

Congenital HSV

Congenital VZV

Epidermolytic ichthyosis

Transient dermolysis of the newborn

Dermnet.nz


Indian J of Dermatology, Venereology, & Leprology, 76, 2010

Indian Pediatr 2016;53: 269
Next diagnostic step?

- Biopsy of existing erosion
- Serum zinc level
- Serum alkaline phosphatase level
- Chromosomal microarray (CMA)
- Either induced blister biopsy or direct genetic testing
Next diagnostic step?

- Biopsy of existing erosion
- Serum zinc level
- Serum alkaline phosphatase level
- Chromosomal microarray (CMA)
- Either induced blister biopsy or direct genetic testing
Diagnostic Studies

- HSV and VZV cultures and PCRs negative
- Offered induced blister biopsy for H&E and EB immunomapping
  - family declined
- 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 and 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 that interacts with keratin 14
    - Mutations that overstabilize KLH24 cause excessive ubiquitination and degradation of KRT14 in basal keratinocytes
  - AD mutation: 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
Full term neonate with progressive violaceous erythema and flaccid bullae on trunk
- Full term neonate
  - C-section for non-reassuring fetal heart tones
- Respiratory distress
- Anemia
  - Reticulocytosis (retic 20%)
- Hyperbilirubinemia (direct and indirect)
- Transaminitis
- Ultrasound: Decreased hepatic perfusion
- Infant Blood Type A +
- Circulating anti-Rh antibody
  - **Diagnosis**: Hemolytic disease of the newborn
Transfusions: PRBCs, platelets
Triple phototherapy [started 7 hours-of-life]
IVIG

Patchy erythema on abdomen [noted 10-hours-of-life]
- Antibiotic coverage broadened
- Serial abdominal radiographs & blood cultures negative

Oligouria
- Furosemide x 1
- Dopamine drip

Progression of erythema on trunk
- Phototherapy was discontinued
- Patient had received a single dose of furosemide
- No other photosensitizing medications given
- No family history of photosensitivity disorders
- Skin biopsy: H&E and cultures
Skin biopsy

- full-thickness epidermal necrosis
- intravascular fibrin thrombi
- PAS-positive deposits in/around superficial dermal blood vessels
- no vasculitis or RBC extravasation
Erythropoietic protoporphyria (EPP)  Congenital erythropoietic porphyria (CEP)


Porphyrin Testing

Plasma fluorescence peak: 619nm (normal range = no peak)
[↑ uro- and coproporphyrins]

TOTAL PORPHYRINS

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Value</th>
<th>Normal Range</th>
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<tbody>
<tr>
<td>Plasma</td>
<td>19.8 mcg/dl</td>
<td>&lt; 0.9</td>
</tr>
<tr>
<td>Erythrocyte (RBC)</td>
<td>486 mcg/dl</td>
<td>&lt; 80</td>
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<tr>
<td></td>
<td>5% uroporphyrin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>55% coproporphyrin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40% protoporphyrin</td>
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</table>

RBC Protoporphyrin Fractions

- 39% zinc-protoporphyrin
- 61% free-protoporphyrin

Urine

24 nmoles/24 hrs (normal 0-300)

Porphyrin Testing

ENZYME ACTIVITY

Porphobilinogen deaminase

89 nmol/ml RBC/hr (normal 20-50)
Elevated: suggests increased circulating young RBCs

Uroporphyrinogen decarboxylase

39.7 nmol/ml RBC/hr (normal 30-60)
Normal: Inconsistent with hepatoerythropoietic porphyria
Heme biosynthetic pathway

1. Heme biosynthetic pathway starts with the mitochondrial enzymes, where glycine and succinyl CoA are converted to δ-aminolevulinic acid (ALA).
2. ALA enters the cytosol, where it is further converted to porphobilinogen (PBG).
3. In the mitochondrial matrix, PBG is converted to hydroxymethylbilane, which is then converted to porphyrinogens.
4. Uroporphyrinogen III and coproporphyrinogen III are decarboxylated to hydroxymethylbilane.
5. Uroporphyrinogen III and coproporphyrinogen III are converted to protoporphyrinogen IX in the mitochondrial matrix.
6. Protoporphyrinogen IX is then converted to protoporphyrin IX in the cytosol.
7. Heme is then synthesized from protoporphyrin IX.
Follow Up

• Healed with post-inflammatory hypopigmentation at 4 months of age
<table>
<thead>
<tr>
<th></th>
<th>Day of life 2</th>
<th>4 Months</th>
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<tbody>
<tr>
<td>Plasma fluorescence peak</td>
<td>619 nm</td>
<td>No peak</td>
</tr>
<tr>
<td>Plasma porphyrins (normal 0-0.9)</td>
<td>19.8 mcg/dl</td>
<td>0.2 mcg/dl</td>
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<tr>
<td>RBC porphyrins (normal 20-80)</td>
<td>486 mcg/dl</td>
<td>335 mcg/dl</td>
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<tr>
<td>RBC uroporphyrin (0-5%)</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>RBC coproporphyrin (0-2%)</td>
<td>55%</td>
<td>0%</td>
</tr>
<tr>
<td>RBC protoporphyrin (90-100%)</td>
<td>40%</td>
<td>100%</td>
</tr>
<tr>
<td>% Free-protoporphyrin</td>
<td>61 %</td>
<td>30 %</td>
</tr>
<tr>
<td>% Zinc-protoporphyrin</td>
<td>39 %</td>
<td>70 %</td>
</tr>
</tbody>
</table>
Transient porphyrinemia due to hemolytic disease of the newborn

- Induration and cutaneous necrosis mimicking a severe infection
Transient porphyrinemia

- Phototherapy-induced purpuric eruptions reported in 9 neonates with increased hematopoiesis
  - Hemolytic disease of the newborn (n = 8)
  - Twin-twin transfusion (n = 1)

- Clinical findings
  - Macular purpura
  - Hemorrhagic bullae

- Histopathology (n = 3)
  - Extravasated RBCs
  - No vascular changes
  - No necrosis

Acknowledgements

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Hackensack University Medical Center
Hackensack, New Jersey
Case
• 2-hour old infant
• Born with flaccid vesicles and erosions
  – Annular appearing erosions noted on face
• Normal prenatal care without complication
• Afebrile
• Feeding, voiding, stooling well
• FMH: mother- Hashimoto’s thyroiditis
Diagnostic tests recommended?

- Skin biopsy
- HSV/VZV PCR and bacterial culture
- EKG
- ANA
- All of the above
Diagnostic tests recommended?

- Skin biopsy
- HSV/VZV PCR and bacterial culture
- EKG
- ANA
- All of the above
• HSV/VZV PCR neg
• Bacterial culture neg
• Fungal/yeast culture neg
Biopsy
Histopathology: neonatal lupus

- FANA > 1:1280
- Anti-Ro neg
- Anti-La neg
- Anti-RNP neg

- EKG wnl
- Platelets wnl
- LFTs wnl
Neonatal lupus erythematous

- **Cutaneous findings**
  - Mean age of onset: ~4-6 weeks
    - Photosensitive
    - Annular scaly plaques
    - Predilection for scalp and periorbital areas
  - Present at birth in ~20%
  - Improves by age 6-9 months

- **Maternal antibodies**
  - Anti-Ro in ~95% of mothers
  - +/- anti-La
  - +/- anti-RNP
  - Majority of mothers *asymptomatic*

*Courtesy of J.V. Schaffer, MD*

Wisuthsarewong W et al Pediatr Derm 2011
Boros et al Arth Rheum 2007
Neonatal LE: associated disease

- **Classic findings**
  - *Cutaneous* neonatal LE:
    - ~25-30% of patients
  - *Cardiac* neonatal LE: heart block, prolonged QT, cardiomyopathy
    - ~ 50-60% of patients
    - *combination* of cutaneous and cardiac manifestations seen only in 4-10%
  - *Hepatic*: cholestasis, transaminitis
  - *Hematologic*: thrombocytopenia > anemia, neutropenia
    - *rare reports of DIC*

Eronen et al, Pediatrics, 2000
Lee et al, Arch Derm Res 2008
Neonatal LE: associated disease

Other manifestations

CNS:
Subclinical central nervous system (CNS)
Hydrocephalus (~10%)
Macrocephaly (~15% at 8-24 months)

Rhizomelic chondrodysplasia punctata phenotype:
Short long bones with epiphyseal stippling
Brachydactyly
Hypoplastic nasal bone

Summary: Neonatal Lupus Erythematosus

- Scaly annular plaques
- Predilection to periorbital area and scalp
- Photosensitive
- Frequently Anti-Ro positive
- Improves by 6-9 months of age