The Differential Diagnosis of Severe Atopic Dermatitis Includes Primary Immunodeficiency

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Disclosure

• There are no available commercially-approved/non-investigative products to discuss.

• Consultant, speaker or investigator for Anacor, Boeringer-Ingelheim, Celegene, Pierre Fabre, Valeant
THE BLIND MEN AND THE ELEPHANT
(A Hindoo Fable)

It was six men of Indostan
To learning much inclined,
Who went to see the Elephant
(Though all of them were blind),
That each by observation
Might satisfy his mind.

The First approached the Elephant,
And happening to fall
Against his broad and sturdy side,
At once began to bawl:
"God bless me! but the Elephant
Is very like a wall!"

The Second, feeling of the tusk,
Cried, "Ho! what have we here
So very round and smooth and sharp?
To me 'tis mighty clear
This wonder of an Elephant
Is very like a spear!"

The Third approached the animal,
And happening to take
The squirming trunk within his hands,
Thus boldly up and spake:
"I see," quoth he, "the Elephant
Is very like a snake!"

The Fourth reached out an eager hand,
And felt about the knee.
"What most this wondrous beast is like
Is mighty plain," quoth he;
"'Tis clear enough the Elephant
Is very like a tree!"
Objectives

• Become familiar with the differential diagnosis of severe, chronic inflammatory skin disease, including many conditions other than atopic dermatitis.

• Consider primary immune dysregulation or nutritional deficiency in children with chronic dermatitis + extracutaneous problems.

• Review screening evaluation options for these conditions.

• Be aware of treatment options.
Introduction

Atopic dermatitis (AD) is a the most common chronic pediatric skin disorder, affecting 10-20% of children in the US:

- 60% by age 1
- 85% by age 5
Clinical Features of AD

• Chronic or relapsing dermatitis
• Characteristic distribution that varies by age
  – Infants: cheeks, trunk, extremities
  – Children: antecubital and popliteal fossae
  – Adults: hands and feet
• Intractable pruritus
• Supporting features :
  – Onset before age 2
  – Personal or family history of atopy
  – Ichthyosis vulgaris (familial dry scaly skin)
Differential Diagnosis

• Otherwise healthy
  – Atopic dermatitis
  – Seborrheic dermatitis
  – Contact dermatitis (irritant, allergic)
  – Psoriasis
  – Overlap

• Not otherwise healthy
  (AD often trumps comorbidities)
  – Malnutrition dermatitis
  – Immune dysregulation dermatitis
  – Both
Malnutrition Dermatitis

**Differential Diagnosis**

- **Poor intake** - restricted diet*/anorexia: protein, essential fatty acids, micronutrients* (zinc, copper, biotin, essential fatty acids), vitamin D*
- **Malabsorption** - eosinophilic gastroenteritis*, gluten sensitive enteropathy*, cystic fibrosis
- **Impaired end organ response** - acrodermatitis enteropathica, PKU, Wilsons, prolidase deficiency, biotinidase deficiency

*eczema associated
Malnutrition Dermatitis

Clinical Features

- Failure to thrive
- Hair abnormalities (sparse, light, brittle)
- “Peeling paint” scale, erosions
- Accentuation at skin folds, periorificial & diaper area
Evaluation

- Trichogram
- 3 day calorie count
- Total protein, albumin
- Vitamin D
- Alkaline phosphatase, plasma zinc
- Biotin
- Copper
- Total IgA, tissue transglutaminase A
- Total IgE
- Allergy skin testing for food allergens
- Endoscopy
- CF genetic screen or sweat test
Malnutrition Complicating Severe Atopic Dermatitis
Immune Dysregulation Dermatitis

Differential Diagnosis

- Hyper IgE syndrome
- Netherton syndrome
- Wiskott Aldrich
- Leiner phenotype – Omenn, SCID
- IgA deficiency
- IgM deficiency
- NEMO ectodermal dysplasia
- Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED)
- Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX)
- DOCK 8 deficiency
- “Not Hyper-IgE”
Not Hyper-IgE

but immunocompromised, and not good candidates for myelotoxic drugs
10 Childhood Warning Signs of Primary Immune Deficiency
(Jeffrey Modell Foundation Advisory Board)

≥ 2 warning signs
1. ≥ 4 new ear infections within 1 year
2. ≥ 2 serous sinus infections within 1 year
3. ≥ 2 months on antibiotics with little effect
4. ≥ 2 pneumonias within one year
5. Failure of an infant to gain weight or grow normally
6. Recurrent, deep skin or organ abscesses
7. Persistent thrush in mouth or fungal infection on skin
8. Need for IV antibiotics to clear infections
9. 2 or more deep-seated infections including septicemia
10. Family history of primary immunodeficiency
Immune Dysregulation Dermatitis “Not Hyper-IgE Syndrome”

- Elevated tot IgE, eosinophilia, pan-pos Immunocaps, pan-pos intradermal skin testing
- Frequent otitis media, sinusitis, pharyngitis
- Severe skin infections
  - HPV, molluscipox, HSV
  - Dermatophyte
  - Strep>Staph dermatitis/folliculitis/furunculosis/cellulitis
- Additional history-delayed shedding of baby teeth, cold urticaria, hyperextensible fingers/ankles, osteoporosis/frequent fractures
- Family history of frequent upper airway infections
Additional Risks

- Persistent skin and mucosal colonization with Group A Strep
- Susceptibility to colonization and infection with resistant organisms
  - Mupirocin, clindamycin, oxacillin resistant Staph aureus
  - Acyclovir resistant HSV

Evaluation

- Total IgE
- Atopic March Immunocaps panel
- Screen for cutaneous microbes
  - skin, upper airway and mucosal carriage: Strep & resistant Staph
  - dermatophyte
  - HSV culture, DFA, PCR, serology
  - Molluscipox
  - HPV
- Trichogram
- Quantitative immunoglobulins, IgG subclasses
- Serologic responses to protein (tetanus, diptheria) and polysaccharide (pneumococcus, H flu) vaccines
- Lymphocyte proliferation
- Lymphocyte immunophenotyping
- IL17 induction
- C3, C4, CH50
- Toll-like receptor function
- Genetic testing
<table>
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<tr>
<th>Syndrome</th>
<th>Characteristic Features</th>
<th>Gene Defect</th>
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<tr>
<td>Netherton</td>
<td>Brittle hair, FTT, food allergies</td>
<td>SPINK5</td>
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<tr>
<td>Omenn</td>
<td>Eosinophilia, reticuloendotheliosis</td>
<td>RAG-1 and 2</td>
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<tr>
<td>Wiskott Aldrich</td>
<td>thrombocytopenia</td>
<td>WASP (IL-27 R)</td>
</tr>
<tr>
<td>Hyper IgE</td>
<td>Pneumatocoeles, retained baby teeth</td>
<td>STAT-3</td>
</tr>
<tr>
<td>ED with immune deficiency</td>
<td>Alopecia, abnormal dentition</td>
<td>NEMO</td>
</tr>
<tr>
<td>Type I APECED</td>
<td>Mucocutaneous candidiasis, autoimmune polyendocrinopathies</td>
<td>AIRE</td>
</tr>
<tr>
<td>DOCK 8 deficiency</td>
<td>Skin bacterial and viral infections, SCCa</td>
<td>DOCK 8</td>
</tr>
<tr>
<td>IPEX</td>
<td>Severe diarrhea, infantile onset DM</td>
<td>FOXP3</td>
</tr>
<tr>
<td>Disease (gene mutated)</td>
<td>Inheritance mode</td>
<td>Mutation phenotype</td>
</tr>
<tr>
<td>------------------------</td>
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</tr>
<tr>
<td>DOCK8 deficiency (DOCK8)</td>
<td>Autosomal recessive</td>
<td>Null</td>
</tr>
<tr>
<td>Coronin 1A deficiency (CORO1A)</td>
<td>Autosomal recessive</td>
<td>Hypomorphic</td>
</tr>
<tr>
<td>MST1 (also known as STK4) deficiency (MST1)</td>
<td>Autosomal recessive</td>
<td>Hypomorphic</td>
</tr>
<tr>
<td>MAGT1 deficiency (MAGT1)</td>
<td>X-linked recessive</td>
<td>Hypomorphic</td>
</tr>
<tr>
<td>Hypomorph RAG mutations (RAG1 or RAG2)</td>
<td>Autosomal recessive</td>
<td>Hypomorphic (missense and other mutations)</td>
</tr>
<tr>
<td>p85α deficiency (PIK3R1 (encodes p85α))</td>
<td>Autosomal recessive</td>
<td>Null</td>
</tr>
<tr>
<td>PLAID (PLCG2)</td>
<td>Autosomal dominant</td>
<td>Hypermorphic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Locus/genes</th>
<th>Genotype</th>
<th>Functional Effect</th>
<th>Phenotype</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>APLAID (PLCG2)</td>
<td>Autosomal</td>
<td>Hypermorphic</td>
<td>Increased receptor-mediated calcium flux and cellular signalling (phenotype is not temperature dependent)</td>
<td>Multiorgan autoinflammation, B cell immunodeficiency and granulomatous skin disease. The gain-of-function Pkga2 mouse model has similarities to human disease</td>
<td>50</td>
</tr>
<tr>
<td>TLR3 deficiency (TLR3)</td>
<td>Autosomal dominant and recessive</td>
<td>Null or hypomorphic</td>
<td>Impaired TLR3 signalling</td>
<td>herpes simplex encephalitis (and one case of Coxackie B myocarditis). TLR3-deficient mice show increased susceptibility to a greater range of infections</td>
<td>51, 53</td>
</tr>
<tr>
<td>UNC93B1 deficiency (UNC93B1)</td>
<td>Autosomal recessive</td>
<td>Null</td>
<td>Impaired TLR3 signalling</td>
<td>Herpes simplex encephalitis</td>
<td>54</td>
</tr>
<tr>
<td>TRAF3 deficiency (TRAF3)</td>
<td>Autosomal dominant</td>
<td>Hypomorphic</td>
<td>Impaired TLR3 signalling</td>
<td>Herpes simplex encephalitis</td>
<td>52</td>
</tr>
<tr>
<td>TRIF deficiency (TRIF)</td>
<td>Autosomal dominant and recessive</td>
<td>Hypomorphic</td>
<td>Impaired TLR3-mediated signalling</td>
<td>Herpes simplex encephalitis</td>
<td>50</td>
</tr>
<tr>
<td>TBK1 deficiency (TBK1)</td>
<td>Autosomal dominant</td>
<td>Loss-of-function</td>
<td>Not determined</td>
<td>herpes simplex encephalitis</td>
<td>101</td>
</tr>
<tr>
<td>MonoMAC, Embberger syndrome, DCML, and familial inheritance of myelodysplastic syndrome or acute myeloid leukaemia (GATA2)</td>
<td>Autosomal dominant</td>
<td>Haplo-</td>
<td>Reduced numbers of stem cells, DCs, monocytes and lymphoid cells, impaired formation of lymphatics, and genomic instability</td>
<td>Disseminated non-tuberculous mycobacterial disease, histoplasmosis, HPV, MDS, AML and lymphoedema. Mouse model suggests far broader infectious phenotype</td>
<td>59–63</td>
</tr>
<tr>
<td>IRF8 deficiency (IRF8)</td>
<td>Autosomal recessive</td>
<td>Null</td>
<td>No monocytes or DCs, and myeloproliferation</td>
<td>Disseminated BCG, oral candidiasis and haemophagocytic lymphohistiocytosis. Mimics human disease; also has effects on B cell and T cell function</td>
<td>75</td>
</tr>
<tr>
<td>IL-17RA deficiency (IL17RA)</td>
<td>Autosomal recessive</td>
<td>Null</td>
<td>No signalling in response to IL-17A and IL-17F</td>
<td>isolated mucocutaneous candidiasis</td>
<td>81</td>
</tr>
<tr>
<td>IL-17F deficiency (IL17F)</td>
<td>Autosomal dominant</td>
<td>Hypomorphic</td>
<td>Functional inhibition of IL-17F-mediated signalling</td>
<td>Staphylococcal dermatitis and mucocutaneous candidiasis</td>
<td>81</td>
</tr>
<tr>
<td>Trait</td>
<td>Genotype</td>
<td>Phenotype</td>
<td>Description</td>
<td>References</td>
<td></td>
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<tr>
<td>STAT3 deficiency (STAT3)</td>
<td>Autosomal dominant</td>
<td>Hypomorphic</td>
<td>Reduced STAT3-dependent signalling, fewer T&lt;sub&gt;H&lt;/sub&gt;17 cells, and impaired B cell and T cell memory</td>
<td>Conditional knockouts mimic T&lt;sub&gt;H&lt;/sub&gt;17 cell deficiency; mice also show some infectious or inflammatory phenotypes not seen in humans; there is no model for elevated IgE levels as a result of Stat3 mutations in mice</td>
<td></td>
</tr>
<tr>
<td>STAT1 deficiency (STAT1)</td>
<td>Autosomal recessive</td>
<td>Null</td>
<td>No STAT1-dependent signalling for type 1 or type 2 IFNs</td>
<td>Severe viral and BCG disease</td>
<td>Closely mimics human disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypomorphic</td>
<td>Impaired STAT1-dependent signalling for type 2 IFNs</td>
<td>Disseminated BCG and non-tuberculous mycobacterial infections</td>
<td>No specific mouse model</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypermorphic</td>
<td>Excessive STAT1-dependent signalling for type 1 or type 2 IFNs, and fewer T&lt;sub&gt;H&lt;/sub&gt;17 cells</td>
<td>Mucocutaneous candidiasis and disseminated dimorphic yeast infections</td>
<td>No specific mouse model</td>
</tr>
<tr>
<td>IL-21R deficiency (IL21R)</td>
<td>Autosomal recessive</td>
<td>Hypomorphic</td>
<td>No IL-21R signalling and poor B cell class-switching responses</td>
<td>Severe cryptosporidial disease, defective humoral immunity, bronchiectasis and elevated IgE levels</td>
<td>Mouse model predicts B cell phenotype but not cryptosporidial immunity</td>
</tr>
<tr>
<td>IL10R1 and IL10R2 mutations (IL10R1 and IL10R2)</td>
<td>Autosomal recessive</td>
<td>Hypomorphic</td>
<td>Impaired IL-10-mediated signalling and uncontrolled inflammation</td>
<td>Severe early onset inflammatory bowel disease and folliculitis</td>
<td>Mimics human disease</td>
</tr>
<tr>
<td>IL10 mutations (IL10)</td>
<td>Autosomal recessive</td>
<td>Hypomorphic</td>
<td>Impaired IL-10-mediated signalling and uncontrolled inflammation</td>
<td>Severe early onset inflammatory bowel disease</td>
<td>Mimics human disease</td>
</tr>
</tbody>
</table>

AML, acute myeloid leukaemia; APLAID, autoimmune PLCG2-associated antibody deficiency and immune dysregulation; BCG, bacille Calmette–Guérin; CORO1A, coro 1A; DC, dendritic cell; DCM, DC, monocyte and lymphoid cell deficiency; DOCK8, dicator of cytokinesis protein 8; EBV, Epstein–Barr virus; GATA2, GATA-binding protein 2; HPV, human papillomavirus; IFN, interferon; IL, interleukin; IL-21R, IL-21 receptor; IFN-γ, interferon-regulatory factor 8; MAGT1, MDS, myelodysplastic syndrome; MonoMAC, monocytopenia with non-tuberculous mycobacterial infections; MST1, mammalian STE20-like protein kinase 1; NK, natural killer; NKG2D, natural killer group 2 member D; APLAID, PLCG2-associated antibody deficiency and immune dysregulation; PLCG2, phospholipase Cγ2; RAG, recombination-activating gene; SCID, severe combined immunodeficiency; STAT, signal transducer and activator of transcription; STK4, serine/threonine-protein kinase 4; TBK1, TANK-binding kinase 1; T<sub>H</sub>17, T helper; TLR3, Toll-like receptor 3; TRAF3, TNF receptor-associated factor 3; TRIF, TIR-domain-containing adaptor protein inducing IFNβ; UNC93B1, protein unc-93 homolog B1.
NEMO ED with Immunodeficiency and Atopic Dermatitis
Netherton Syndrome
Netherton Syndrome

- AR, males>females, incidence 
  ~1/200,000
- Gene Defect
  - SPINK5 (encodes LEKT1, a serine peptidase inhibitor)
  - > 50 different mutations identified
- Key clinical features
  - frequent collodion baby phenotype
  - ichthyosis linearis circumflexa
    (females>males)
  - trichorrhexis invaginata
Recent Case

- 20 year old man who initially presented with congenital erythroderma, fragile skin and tape-stripping scarring
- Netherton syndrome dx age 3 mo by trichogram

- Erratic dermatology followup since early childhood
- May 2014: pediatric dermatology reevaluation after >15 year hiatus, with 6 mo hx worsening
Interval History

• ROS: ADHD, headaches, worsening ectropion
• Past Medical History
  - avascular necrosis of the femoral head
  - recurrent infections - septic arthritis (*St aureus* R hip, L knee), cellulitis, Strep pharyngitis, otitis media, sinusitis, bronchitis
• Past Surgical History
  - epiphysiodesis
  - orchiectomy
• Allergies
  - pollen, dust mites
  - multiple foods
  - amoxicillin, sulfa drugs, codeine
• Medications
  - triamcinolone, clobetasol daily as needed
  - 10d ciprofloxacin prior to visit
Physical Exam

- Generalized erythroderma with malodor
- Coarse scale accentuated at the chest, upper back and face
- Severe inguinal and gluteal fold maceration
- Brittle hair
- Upper eyelid ectropion with thickened margins OD>OS, sparse brows, absent lashes
- Increased plantar and web-space foot scale
Recent Clinical Course

- 05/13/14 initial skin culture **pos** Trychophyton sp; skin improved S/P fluconazole, bleach baths, emollients and Protopic

- 06/16/14 worsening; skin cultures **neg** fungal, **neg** Strep, **pos** MSSA; SSSS considered; Rx 2 wk doxy with transient improvement

- 10/10/14 hospitalization for treatment of septic arthritis and skin care; skin cultures **pos** Strep; IVIG candidate

- Worsening ectropion
  - S/P 3 series Guardasil prior to onset
  - Oculoplastics evaluation “not a surgical candidate”
  - Verrucoid change suggestive of HPV, with similar skin lesions at the brows and nasal bridge
  - Nasal bridge lesion skin biopsy – “benign verrucous keratosis - without obvious viral cytopathic change or invasive carcinoma”; HPV 6,11,16, 18 PCR **neg**
Immune Evaluation and Treatment

- Selective Antibody Deficiency
  - Decreased HiB pre vaccine
  - Decreased pre- and post-vaccine Pneumococcal antibodies
  - Decreased CD27+ memory B cells
  - Decreased IgD- switch B cells
  - Decreased CD4+ T cells
  - Decreased NK cytotoxicity
- Gamunex started 12/29/14 @ 30 gm (0.52 gm/kg/dose) Q3-4 wk
- Raltegravir added 2/27/15 @ 400 mg BID
S/P IVIG X 2
Autoimmune Endocrinopathy Syndromes

Infantile-onset eczema, urticaria, type I diabetes, thyroiditis, cytopenias, elevated IgE, alopecia areata, Staph skin infections

• **IPEX**- males (XLR); chronic watery diarrhea

• **APECED**- hypoparathyroidism, candidiasis

• **ALPS** (autoimmune lymphoproliferative syndrome) -hemolytic anemia, thrombocytopenia and splenomegaly

• **CD25 (IL2RA) deficiency**- CMV infections and visceral lymphocytic infiltrate
Severe AD, Asthma, IDDM, Alopecia Areata
Eczema Herpeticum Incognito: A Diagnostic and Therapeutic Challenge

- Severe extrinsic AD
- Face, periorbital involvement
- Strong FH cold sores
- Antiviral-controlled eczema flares
- Risk of thymidine-kinase resistance

# Eczema Herpeticum Incognito

Confirming the Diagnosis

<table>
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<th>Lab</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
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<tr>
<td>PCR</td>
<td>unclear</td>
<td>high</td>
</tr>
<tr>
<td>DIF</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>Culture</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>Histology</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>HSV 1 Serology</td>
<td>81% after 1 episode</td>
<td>low</td>
</tr>
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Off-Label, Immunomodulating Options for “Not-Hyper-IgE”

Avoid Systemic Immunosuppressants

- Prophylactic TMP/Sulfa
- (MTX + antiviral)
- IVIG
- Interferon $\gamma$
- Consider off-label use of new entities on a case-by-case basis.
Antiviral Options

• Acyclovir, valacyclovir, famciclovir: Short-course/high dose vs. daily prophylaxis

• Thymidine-kinase resistant HSV*
  – Increasing reports following prolonged therapy
  – request MICs
  – valacyclovir & famciclovir: more bioavailable
  – use short-course/high-dose

• Other
  – topical ciclopiroxolamine
  – oral zinc sulphate
  – oral liposomal cidofovir (not yet approved)
  – oral raltegravir

Summary

• Maintain a high index of suspicion for nutritional deficiency or immune dysregulation in children with severe dermatitis who not otherwise healthy.
• Evaluate these children in a stepwise fashion, beginning with monitoring growth and episodes of infection.
• Be aware that a definitive diagnosis is elusive for a significant number of these children.
• Initial treatment is supportive, and includes avoiding additional nutritional or immune impairment.
• Gene discovery and targeted therapy offers hope for better treatment.