Atopic Dermatitis and Primary Immunodeficiency: When Should I Worry?

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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

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F046 - Translating Evidence into Practice: Atopic Dermatitis Guidelines

DISCLOSURES

Regeneron Pharmaceuticals – clinical researcher:

Dupilumab use in adolescents with atopic dermatitis – no compensation
Objectives

• To identify presentations of eczematous dermatitis and other skin findings that should prompt consideration of a primary immunodeficiency (PID)
• To identify extracutaneous signs and symptoms to suggest that eczematous dermatitis exists in the context of PID
• To take first steps in treating eczematous dermatitis in the context of PIDs
Infantile Erythroderma
(The “Scaly Red Baby”)

- Atopic or seborrheic dermatitis
- Psoriasis
- Infections
- Congenital Ichthyoses
- Netherton Syndrome
- Mastocytosis
- Metabolic disorders
- Immunodeficiency
The “Scaly Red Baby”: When should I worry about primary immunodeficiency?

- If congenital → favor ichthyosis
- Elevated IgE and eosinophil levels are non-specific
- Consider immunodeficiency if treatment resistant, accompanying FTT, diarrhea or multiple (systemic/invasive) infections
Concern for PID: Questions to ask

• Any history of infections?
  • Specify invasive vs. noninvasive (abscesses, etc.), requiring antibiotics (viral vs. bacterial PNA) or hospital stay, recurrent
• Meningitis, otitis media, sinus infections, sepsis?
• Any problems with fungus (thrush, ringworm, nail fungus)?
• Any problems with warts, molluscum, herpes infections?
• Infection with unusual organisms?
• Any know family members with PID or frequent infections?
  • Any family members who died abruptly at a young age?
• Problems with growth or development (FTT, diarrhea)?
• Disease specific: retained primary teeth, lymphedema, bone fractures, signs of autoimmunity?
AD Hyper IgE syndrome (STAT3 LOF mutation)

- Incidence: 1-9:100,000
- Dermatitis, abscesses, recurrent sinopulmonary (PNA, AOM) and bone infections
  - Cellulitis, lymphangitis, pneumatoceles, abscesses, mucocutaneous candidiasis
- Pruritic, lichenified eruption
  - **Distribution not entirely typical for AD**
  - Lack other signs of atopy
- **Papulopustular eruption of face in infancy**
  - Hyperextensible joints
  - Retention of primary teeth
  - Cathedral (high arched) palate
  - Coarse facies in childhood
  - Increased IgE levels (can vary initially)
Treatment of dermatitis

- Hydrocortisone 2.5% or desonide ointment for face, groin and intertriginous areas
  - Topical calcineurin inhibitors
- Triamcinolone 0.1% ointment for body (or stronger as needed)
  - BID for up to 2-3 weeks
- Consider wet wrap therapy

- Superinfection?
  - Culture/treat
  - Regular bleach baths

**FOR AD HIES:**

- Prophylactic antimicrobial agents (co-trimoxazole, fluconazole)
- IVIG?

- Consider systemic agents for dermatitis (methotrexate), in consultation with Immunology
- Can consider BMT, but not standard of care
DOCK8 deficiency (AR hyper-IgE syndrome)

• **Eczematous dermatitis**
  • Atopic dermatitis-like

• **Severe food allergy, asthma**

• Frequent, severe viral infections

• Propensity to cutaneous malignancy

• NO musculoskeletal abnormalities
<table>
<thead>
<tr>
<th>Condition</th>
<th>STAT3 (AD)</th>
<th>DOCK8 (AR)</th>
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<tbody>
<tr>
<td>Eosinophilia</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Allergy</td>
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<td>++</td>
</tr>
<tr>
<td>Asthma</td>
<td>rare</td>
<td>++</td>
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<tr>
<td>Sinopulm infxn</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>++</td>
<td>rare</td>
</tr>
<tr>
<td>Eczematous skin</td>
<td>+</td>
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<tr>
<td>Bacterial skin abscess</td>
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<td>+</td>
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<tr>
<td>LCV</td>
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<tr>
<td>Viral skin infection</td>
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<td>++</td>
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<tr>
<td>Mucocutaneous candidiasis</td>
<td>++</td>
<td>+</td>
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<tr>
<td>Malignancy</td>
<td>rare</td>
<td>SCC, lymphoma</td>
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<tr>
<td>Facies</td>
<td>Coarse, retained primary teeth, arched palate</td>
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<tr>
<td>Joint hyperext</td>
<td>++</td>
<td>rare</td>
</tr>
<tr>
<td>Bone fractures</td>
<td>++</td>
<td>Rare</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>++</td>
<td>-</td>
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</tbody>
</table>
Immune dysregulation, Polyendocrinopathy and Enteropathy, X-linked (IPEX) syndrome

- Foxp3 (XLR) → T regulatory cell dysfunction
- 1:1.6 million
  - Female carriers normal

- **Autoimmune enteropathy**
  - Diarrhea
  - Most common feature

- **Endocrinopathy**
  - Autoimmune thyroiditis and IDDM
    - Cytopenias, nephritis, hepatitis

- **Eczematous dermatitis (most commonly)**
  - Lower limbs, trunk, face
  - Exfoliative erythroderma
Other skin findings in IPEX syndrome

- Psoriasiform dermatitis
- Urticaria
  - Prone to allergy
- Bullae
  - Bullous Pemphigoid
- **Cheilitis, inflammatory lip edema**
- Onychodystrophy/trachyonychia
- Autoimmune alopecia
IPEX: Diagnosis and Treatment

- Lab evaluation often shows elevated eosinophils, IgE, IgA

- Sepsis is most common cause of death
  - Combination: immunosuppression and barrier dysfunction from lymphocytic infiltration

- HSCT is only cure
- Immunosuppression variably effective
- Chronic potent/ultrapotent TS use required for relief
Wiskott Aldrich Syndrome

• XLR mutation in Wiskott Aldrich Syndrome Protein
  • Actin polymerization in hematopoietic cells → cell signaling, cellular motility, immune synapse

• 1:100,000

• Atopic dermatitis, thrombocytopenia, sinopulmonary infections
  • Small platelets (microthrombocytopenia)

• Presentation depends on location of mutation
  • XL thrombocytopenia, XL neutropenia
  • XLT an intermediate phenotype between WAS and XLN

• Bleeding: bloody diarrhea, petechiae, bleeding after circumcision, epistaxis

• Infections: OM, bacterial PNA, Pneumocystis PNA

• Prone to drug eruptions, zoster, warts, molluscum

• Lymphoreticular malignancy (EBV-related lymphoma, leukemia)

• Inc risk of autoimmunity (defect in Treg expansion)
  • AIHA, renal disease, vasculitis, HSP, IBD

• Lymphopenia, inc IgE & IgA, variable polysaccharide antigen antibody responses
Wiskott Aldrich Syndrome: Treatment

• Dx: based on flow cytometry for WASP and genetic testing

• HSCT is only cure

• Prophylactic antimicrobials: trimethoprim-sulfamethoxazole, acyclovir
  • Platelet transfusions
  • IVIG
  • Rituximab for autoimmune disease
  • Splenectomy?

• Gene therapy?
Take Home Points

• Diffusely red baby
  • Consider immunodeficiency if also FTT/diarrhea, h/o infections
  • High IgE levels ≠ Hyper-IgE Syndrome

• Papulopustular eruption with frequent infections and MSK changes
  • AD Hyper-IgE Syndrome

• Severe atopy with extensive warts/molluscum/HSV
  • AR Hyper-IgE Syndrome (DOCK8 deficiency)

• Severe eczematous (or psoriasiform) dermatitis with chronic diarrhea, FTT and DM or hypothyroidism
  • IPEX

• Atopic dermatitis with bleeding diathesis and sinopulmonary infections
  • WAS