Differential Diagnosis of Atopic Dermatitis

or

What Else to Think About When You See Atopic Dermatitis

Atopic Dermatitis Look Alikes

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Atopic Dermatitis

Diagnosis

• No diagnostic test or pathognomonic feature

• Diagnostic criteria
  – Major clinical characteristics
  – Other typical characteristics

• Consider the differential

Atopic Dermatitis Look Alikes

Objectives

• To appreciate the range of features with which atopic dermatitis patients may present

• To understand the major disease types that have clinical similarities to atopic dermatitis

• To review various disorders in the differential diagnosis of atopic dermatitis

• To consider atopic dermatitis as a constellation of pathophysiological influences that disorders with similarities may help elucidate

Atopic Dermatitis

Major clinical characteristics

– Pruritus

– Typical morphology and distribution
  • Eczematous dermatitis
  • Flexural lichenification or linearity in adults
  • Facial and extensor involvement in infants and children
  • Combinations of patterns may be seen in adults or children, hand dermatitis common in adult

Atopic Dermatitis

Diagnostic Criteria

• Major clinical characteristics
  – Chronic or chronically relapsing dermatitis
  – Personal or family history of atopy including asthma, allergic rhinoconjunctivitis, atopic dermatitis, contact urticaria

Disclosures

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Professor of Dermatology

Employment

– University of Utah, Co-Director of Immunodermatology Laboratory

Financial Interests

– Beiersdorf, Dermatology Advisory Panel

– GlaxoSmithKline, Consultant and grant; Family member is consultant, received honoraria and grant

– Novartis, Family member is speaker, received honoraria and grant

– Genentech, Family member is speaker and received honoraria

– Celgene, Family member has stock

– Dyax, Family member has grant

– Jerini, Family member has grant

Research Interests

– Family member, two NIH grants

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Organizational Interests

– National Eczema Association, Scientific Advisory Committee

Gifts

– Nothing to Disclose

Other Interests

– Nothing to Disclose
Atopic Dermatitis

Lesions

• Acute and chronic
• Primary and secondary

- Eczematous plaque
- Erythematous papule
- Eroded, crusted papules and plaques
- Excoriations
- Lichenification
- Prurigo nodularis

Diagnostic Criteria

• Other typical characteristics
  - Xerosis (dry skin)
  - Ichthyosis/palmar hyperlinearity/keratosis pilaris
  - Early age of onset
  - Cutaneous colonization and/or overt infections with susceptibility to Staphylococcus aureus, dermatophytes and viral infections including Herpes simplex, warts and molluscum

Atopic Dermatitis

Diagnostic Criteria

- Xerosis (dry skin)
- Ichthyosis/palmar hyperlinearity/keratosis pilaris

Atopic Dermatitis

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Atopic Dermatitis

Diagnostic Criteria

- Cutaneous colonization and/or overt infections with susceptibility to Staphylococcus aureus, dermatophytes and viral infections including Herpes simplex, warts and molluscum

- Other typical characteristics
  - Hand and/or foot dermatitis and irritant dermatitis
  - Nipple eczema
  - Cheilitis
  - Erythroderma
  - Pityriasis alba
  - Anterior neck folds
Atopic Dermatitis Diagnostic Criteria

- Hand and foot dermatitis

Atopic Dermatitis Diagnostic Criteria

- Nipple eczema
- Anterior neck folds

Atopic Dermatitis Diagnostic Criteria

- Erythroderma

Atopic Dermatitis Diagnostic Criteria

- Dennie Morgan infraorbital folds
- Orbital darkening "allergic shiners"

- Other typical characteristics
  - Keratoconus
  - Anterior subcapsular cataracts
  - Recurrent conjunctivitis
  - Dennie Morgan infraorbital folds
  - Orbital darkening "allergic shiners"
  - Facial pallor and facial erythema

Atopic Dermatitis Diagnostic Criteria

- Increased total serum IgE
- Immediate, Type I hypersensitivity skin test reactivity, and positive specific IgE serum tests
- Peripheral blood eosinophilia
- Increased basophil histamine release
Atopic Dermatitis

Diagnostic Criteria

- Other typical characteristics
  - Perifollicular accentuation
  - White dermographism/delayed blanch with methacholine
  - Impaired cell-mediated immunity

Atopic Dermatitis

Associated Abnormalities

- Physiological abnormalities
  - Exaggerated vasoconstriction with cold exposure, slow vasodilatation with warming
  - Flush with psychological stress
  - White dermographism
  - Piloerection
- Aberrant pharmacophysiologic responses
  - Aberrant reactivity to vasoactive mediators
    - Abnormal reactivity to histamine, substance P and allergen injection with decreased flare
  - Aberrant reactivity to other agents
    - Delayed blanch to methacholine injection
    - Blanch to topical nicotinic acid

Atopic Dermatitis

Associated Abnormalities

- White dermographism
- Delayed blanch to methacholine injection

Atopic Dermatitis

Associated Abnormalities

- Constitutional abnormalities
  - Itching with minimal provocation and sweating
  - Skin dryness/ichthyosis

Filaggrin Mutations

- Loss of function mutations disrupt stratum corneum integrity
  - R501X and 2282del4, chromosome 1q21 epidermal differentiation complex, in 18-48% of European atopic dermatitis
    - Semidominant inheritance, incomplete penetrance
  - 3321delA and S2554X novel truncation mutations present in 5.6% and 4.2% of 143 Japanese patients with ichthyosis vulgaris and atopic dermatitis
    - Severe reduction of keratohyalin granules in epidermis
  - Increased barrier permeability to water
  - Increased penetrance of allergens and pathogens

Barker et al., J Invest Dermatol 2007
Sandilands et al., Nat Genet 2007
Gan et al., Biochemistry 1990
Smith et al. Nat Genet 2006
Hudson, Nat Genet 2006
Other Skin Barrier Mutations

- Increased protease activity
  - Protease dysfunction
  - Protease inhibitor dysfunction
- KLK7, stratum corneum chymotryptic enzyme
- SPINK5
- CSTA, cystatin A


Atopic Dermatitis Look Alikes
Consider the Differential

- Infants and children
  - Primary immunodeficiencies
  - Metabolic and genetic disorders
  - Inflammatory dermatoses
  - Autoimmune disorders
  - Infections and Infestations
  - Malignancy

Atopic Dermatitis Look Alikes
Consider the Differential

- Adolescents and adults
  - Primary immunodeficiencies
  - Metabolic and genetic disorders
  - Inflammatory dermatoses
  - Autoimmune disorders
  - Infections and Infestations
  - Malignancy

Atopic Dermatitis Look Alikes
Consider the Differential

- Infants and children
  - Primary immunodeficiencies
  - Wiskott-Aldrich syndrome
  - Hyper-IgE syndrome
  - Severe combined immunodeficiency
  - DiGeorge Syndrome (congenital thymic aplasia)
  - Immunoglobulin deficiencies
    - X-linked hypogammaglobulinemia
    - Common variable immunodeficiency
    - IgA deficiency
  - Ataxia telangiectasia
Atopic Dermatitis Look Alikes
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Atopic Dermatitis Look Alikes
Consider the Differential

• Infants and children
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Atopic Dermatitis Look Alikes
Consider the Differential

• Infants and children
  – Metabolic and genetic disorders

• Netherton syndrome
• Ectodermal dysplasias
• Keratitis pilaris
• Hartnup disease
• Phenylketonuria
• Acrodermatitis enteropathica/zinc deficiency, glucagonoma syndrome
• IPEX

Atopic Dermatitis Look Alikes
Consider the Differential

• Infants and children
  – Metabolic and genetic disorders

• Acrodermatitis enteropathica/zinc deficiency, glucagonoma syndrome

Atopic Dermatitis Look Alikes
Consider the Differential

• Infants and children
  – Metabolic and genetic disorders

• IPEX (Immunodysregulation, polyendocrinopathy, enteropathy, X-linked recessive) syndrome
  – Mutations in FOXP3 gene, 20 described
  – In the absence of FOXP3, CD4+CD25+ regulatory T cells do not develop
  – CD4+CD25+ regulatory T cells suppress various immune responses including autoimmune, antimicrobial and antitumor
  – Diagnosis can be difficult
  – No female patients

More information in handout
Atopic Dermatitis Look Alikes
Consider the Differential

• Infants and children
  – Metabolic and genetic disorders
  • Other nutritional deficiencies
    – Pellagra
    – Riboflavin deficiency
    – Essential fatty acid deficiency
    – Carboxylase deficiency
    – Pro tease deficiency
    – Dietary histidine deficiency
    – Biotin deficiency
  • Organic acidurias
  • Cystic fibrosis

Atopic Dermatitis Look Alikes
Consider the Differential

• Infants and children
  – Metabolic and genetic disorders
  • Other nutritional deficiencies
    – Vitamin D
      • Affects keratinocyte barrier function
      • Growth and differentiation
      • Affects immune function
      • Cathelicidin expression

 More information in handout

Atopic Dermatitis Look Alikes
Consider the Differential

• Infants and children
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  – Infections and Infestations
  – Malignancy

Atopic Dermatitis Look Alikes
Consider the Differential

• Infants and children
  – Malignancy
  • Langerhans cell histiocytosis
    – Langerhans cell histiocytosis
    – Dense infiltrate of histiocytes with epidermotropism; LCH cell—histiocyte with irregular vesiculated nucleus and abundant cytoplasm, S100+, CD1a+, CD207+, with Langerhans cytoplasmic granules
    – Papules, vesicles, pustules, nodules, ulcers
    – Head, trunk, skinfolds; mucosal lesions are ulcerated nodules of gingiva and genital
    – Bones and bone marrow, lungs, liver, spleen, lymph nodes
    – Diabetes insipidus, exophthalmos

  • Hashimoto-Pritzker disease (skin lesions, absent symptoms, self-healing course)
    – Eosinophilic granuloma (skin and/or bone lesions, absent symptoms, indolent course)
    – Hand-Schüller-Christian disease (multiple organ lesions, symptoms, progressive course)
    – Letterer-Siwe disease (multiple organ lesions, symptoms, aggressive course with organ failure)
Atopic Dermatitis Look Alikes
Consider the Differential

- Infants and children
  - Malignancy
    - Langerhans cell histiocytosis

- Adolescents and adults
  - Malignancy
    - Cutaneous T cell lymphoma
      - Sézary syndrome, leukemic CTCL
        - Diffuse erythroderma
        - Generalized lymphadenopathy
        - Circulating Sézary cells, malignant T cells with cerebriform nuclei
      - Mycosis fungoides
        - Patch, plaque or tumor
        - More common than Sézary
      - Second most common group of extranodal lymphomas
  - Primary immunodeficiencies
  - Metabolic and genetic disorders
  - Inflammatory dermatoses
  - Autoimmune disorders
  - Infections and Infestations
  - Malignancy

- Infants & children, adolescents & adults
  - Primary immunodeficiencies
  - Metabolic and genetic disorders
  - Inflammatory dermatoses
  - Autoimmune disorders
  - Infections and Infestations
  - Malignancy

- Infections and Infestations
Atopic Dermatitis Look Alikes
Consider the Differential

- Infants & children, adolescents & adults
  - Infections and Infestations
    - Scabies
    - Dermatophytosis
    - Chronic mucocutaneous candidiasis
    - Impetigo
    - HIV-associated dermatoses
    - HTLV-1-associated infective dermatitis
    - Congenital syphilis

- Autoimmune disorders
  - Dermatitis herpetiformis (celiac disease, gluten sensitive enteropathy)
  - Pemphigoid
  - Pemphigus
  - Lupus erythematosus
  - Dermatomyositis
  - Graft-versus-host disease

- Infections and Infestations
  - Impetigo
  - HIV-associated dermatoses

- Metabolic and genetic disorders
  - Congenital syphilis

- Inflammatory dermatoses
  - Autoimmune disorders
  - Malignancy

Bullous Pemphigoid
Characteristic Lesions and Classical Presentation

- Elderly patients
- Pruritus
- Tense bullae on urticarial and/or erythematous bases in flexural areas
**Bullous Pemphigoid**

**Infantile presentation**

**Atypical nonbullous presentations**

- Eczematous lesions
- Generalized pruritus with excoriations

**Immunopathology**

- Perilesional skin biopsy
  - Linear IgG at BMZ
  - Linear C3 at BMZ
- Serum on human split skin substrate with anti IgG
- Roof of separation: Epidermal localization

**Pemphigoid**

- Total serum IgE levels correlate with disease activity
  - IgE antibodies to BP180 present in up to 86%
- Both mast cells and eosinophils play a role in blister formation
  - Mast cells are increased in lesions and mast cell degranulation is observed
    - BP180 peptides present on mast cells
  - Eosinophils are characteristic of the histology and eosinophil granule protein deposition is striking in areas of skin separation
    - MMP9 (and neutrophil elastase) degrade BP180

**New model of BP is emerging**

- Type I hypersensitivity
  - Part or all pathogenesis mediated by IgE, mast cells, eosinophils
- +/- acting in concert with IgG or IgA

**Atopic Dermatitis Look Alikes**

Consider the Differential

- Infants and children
  - Autoimmune
    - [IPEX]
Lupus Erythematosus

Atopic Dermatitis Look Alikes Consider the Differential
- Infants & children, adolescents & adults
  - Primary immunodeficiencies
  - Metabolic and genetic disorders
  - Inflammatory dermatoses
  - Autoimmune disorders
  - Infections and Infestations
  - Malignancy

Atopic Dermatitis Look Alikes Consider the Differential
- Infants & children, adolescents & adults
  - Inflammatory dermatoses
    - Seborrheic dermatitis
    - Psoriasis
    - Nummular dermatitis
    - Asteatotic eczema
    - Lichen simplex chronicus
    - Id reaction (disseminated eczema)
    - Chronic actinic dermatitis

Atopic Dermatitis Look Alikes Consider the Differential
- Infants & children, adolescents & adults
  - Inflammatory dermatoses
    - Seborrheic dermatitis
    - Psoriasis
    - Nummular dermatitis

Atopic Dermatitis Look Alikes Consider the Differential
- Infants & children, adolescents & adults
  - Inflammatory dermatoses
    - Psoriasis
Atopic Dermatitis Look Alikes
Consider the Differential
• Infants & children, adolescents & adults
  – Inflammatory dermatoses
    • Psoriasis
    • Or eczema?

Contact Dermatitis
• Two types
  – Allergic (cell-mediated, type IV hypersensitivity)
  – Irritant
• Common problem
  – Occurrence in children equal or greater than adults
• 72.3 million Americans with estimated associated costs of $1.6 billion
• Approximately 40% of Worker’s Compensation cases involve skin problems, and up to 95% of these involve job-induced contact dermatitis.
• Diagnosed with allergy patch testing

Allergic Contact Dermatitis
• Dermatitis involving
  – hands 27.4%
  – scattered/generalized 17.8%
  – face 16.1%
  – eyelids 5.6%
  – trunk 4.6%
  – feet 3.4%

**Allergens of the Year-ACDS**

- **2000-Disperse Dyes**
  - Novel & more frequent than recognized
- **2001-Gold**
  - Common and problematic
- **2002-Thimerosol (non-allergen)**
  - Common, non-relevant
- **2003-Bacitracin/Topical Antibiotics**
  - Common & iatrogenic with risk of anaphylaxis
- **2004-Cocamidopropyl Betaine**
  - Novel & problematic
- **2005-Corticosteroids**
  - Iatrogenic, often missed
- **2006-Paraphenylenediamine**
  - Common, epidemic with henna tattoo
- **2007-Fragrances**
  - Common, but of questionable relevance in many
- **2008 - Nickel**
  - More common in males and children
- **2009-Mixed dialkyl thioureas**
  - Rubber accelerator, neoprene

**Allergic Contact Dermatitis**

**Top 10 Allergens in Children**

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Description</th>
<th>Common Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nickel</td>
<td>Metal</td>
<td>Face/eyelids, earlobes, wrists</td>
</tr>
<tr>
<td>Neomycin</td>
<td>Topical antibiotic</td>
<td>Face/eyelids</td>
</tr>
<tr>
<td>Balsam of Peru/fragrance mix</td>
<td>Fragrance</td>
<td>Eyelids/face, neck, mouth, lips</td>
</tr>
<tr>
<td>Thimerosal</td>
<td>Preservative</td>
<td>Body/trunk</td>
</tr>
<tr>
<td>Cobalt</td>
<td>Metal</td>
<td>Earlobes, neckline, abdomen, hands</td>
</tr>
<tr>
<td>Chromate</td>
<td>Metal</td>
<td>Hands, abdomen</td>
</tr>
<tr>
<td>Thiuram</td>
<td>Rubber accelerator</td>
<td>Waistline, feet, hands</td>
</tr>
<tr>
<td>Lanolin</td>
<td>Emollient</td>
<td>Hands, body</td>
</tr>
<tr>
<td>Formaldehyde/formaldehyde releasing agents</td>
<td>Preservative</td>
<td>Face, ears, hands, trunk</td>
</tr>
<tr>
<td>Paraphenylenediamine</td>
<td>Oxidative chemical</td>
<td>Hairline, ears, hands, henna and other tattoo areas</td>
</tr>
</tbody>
</table>

**Epidemics occur and can be controlled…….**

- Nickel
- Chromium
- Formaldehyde
- MC/MI (Methylchloroisothiazolinone/ Methylisothiazolinone)
- Para-phenylenediamine
### Contact Dermatitis in Atopics

- Loss of function mutations in filaggrin gene (R501X and 2282del4) are associated with atopic dermatitis
- An association between these mutations and contact dermatitis to nickel is also observed
- Altered skin barrier function may represent a risk factor for contact sensitization


### Atopic Dermatitis Inflammation

- Histopathologically, atopic dermatitis lesions appear similar to delayed type hypersensitivity reactions
- Cytokine profiles comparing acute and chronic atopic dermatitis lesions support this
  - Acute atopic dermatitis lesions show TH2 activity
    - IL-4 and IL-5
  - Chronic lesions associated with TH1 and TH0 activity
    - Fewer IL-4 mRNA expressing cells, greater IL-5 (eosinophils)
    - IFN-γ production
    - IL-12 mRNA expressing cells potentially inducing TH0 to TH1 switch

### Drug Reactions

- Atopy is not generally associated with a higher risk of drug hypersensitivity
- An atopic predisposition
  - May prolong the persistence of drug-specific IgE in serum
  - Ongoing IgE-mediated allergic inflammation may aggravate the symptoms of an IgE-mediated drug hypersensitivity reaction
- Epicutaneous exposure of drug clearly increases the risk of sensitization compared to oral or parental treatments

Pichler WJ. Drug Hypersensitivity, p 168-189, Karger 2007

### Contact Dermatitis in Atopics

- Allergic contact dermatitis has consistently been reported as equally prevalent in atopic and nonatopic dermatitis patients
- Patients allergic to individual fragrances with dietary exposures (cinnamal, cinnamic alcohol, eugenol, geraniol) have reduced rates of atopic dermatitis
  - May have heightened oral tolerance to dietary haptens, in contrast to food-protein allergy
  - Haptens may interfere with food protein tolerance by binding to soluble protein and altering its configuration and immunogenic profile


### The Many Faces of Atopic Dermatitis
Photo (UV-Induced) Drug Reaction
Lichenified papules and plaques from chronic disease involving face and V of neck
Sparing of nasolabial folds, post auricular skin and anterior neck with “chin shadow”

Dermatitis Herpetiformis

Atopic Dermatitis Look Alikes
Consider the Differential
- Infants, children, adolescents and adults
  - Primary immunodeficiencies
  - Metabolic and genetic disorders
  - Inflammatory dermatoses
  - Autoimmune disorders
  - Infections and Infestations
  - Malignancy

Atopic Dermatitis Look Alikes
Consider the Differential
- Attend to distinguishing features that are helpful in disease recognition
- Consider common pathophysiological features and how they might help us understand the disease

Thank You for your attention

Additional slides follow in this handout (not used in presentation)
Atopic Dermatitis Look Alikes
Consider the Differential

- Infants and children
  - Metabolic and genetic disorders
    - IPEX (Immunodysregulation, polyendocrinopathy, enteropathy, X-linked recessive) syndrome
      - FOXP3 gene located on X chromosome and consists of 11 coding exons.
      - 20 mutations, varying effects depending on where in gene the mutation is located.
      - FOXP3 is highly expressed in CD4+CD25+ regulatory T cells; when stimulated, nuclear factor of activated T cells (NFAT) preferentially binds to FOXP3 (instead of activator protein 1, AP-1, that conventional T cells bind to) resulting in a different set of genes that cause immune suppression.
      - Initiation of immunosuppression is not very well known but requires antigen exposure; suppressive effects can extend through bystander immunosuppression.
      - Diagnosis can be difficult; clinical suspicion and family history.
      - Signs of type I diabetes, hypothyroidism, enteropathy and/or cytopenias.
      - No consistent changes in function or number of "conventional" T cells, granulocytes, complement components, or immunoglobulins.
      - Autoantibodies against erythrocytes, thyroid, and pancreas.
      - Inflammatory infiltrates in organs including pancreas, skin, and kidney.
      - Absence of normal mucosa of small bowel and colon.
      - No reported female cases (except one case thought to be autosomal regulatory locus), asymptomatic female carriers.

- Other nutritional deficiencies
  - Vitamin D
    - Keratinocytes express enzymes capable of producing active 1,25D3.
    - Vitamin D regulates keratinocyte proliferation, differentiation and formation of intact barrier.
    - May be why ultraviolet light therapy is helpful.


- Other nutritional deficiencies
  - Vitamin D
    - Cathelicidins (AMPs antimicrobial peptides) form a chemical shield on skin surface and trigger and coordinate components of innate and adaptive immunity.
    - Produced by keratinocytes, neutrophils, other cells.
    - Cathelicidins are greatly reduced in atopic dermatitis with increased susceptibility to infection.
    - Diminished inducibility of cathelicidins and defenses may be due to TH2 cytokines, IL-4 and IL-13, that suppress induction of AMPs.

- Further investigations on vitamin D, keratinocyte function and cathelicidin expression may be helpful in treating atopic dermatitis.