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Atopic Dermatitis and Allergic Urticaria: Cutaneous manifestations of Immunodeficiency

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Keywords

Atopic dermatitis; Urticaria; Immunodeficiency

“...for people who feel disgraced blush, and those who fear death turn pale.”¹

Introduction

Alterations in the skin can give the astute clinician insight into the inner workings of the immune system which may otherwise remain invisible. The skin can be altered in numerous ways via numerous pathologic mechanisms. This review will focus on two of those alterations: atopic dermatitis (AD) and allergic urticaria (AU). While AD and AU are common in themselves, they may also serve to be the presenting sign of an uncommon underlying disease. More specifically, this review will focus on how these two conditions may be accompanied by other sentinel symptoms serving to comprise a distinct syndromic phenotype. The presence of the syndromic phenotype may then serve as a clue to the presence of an underlying immune defect. The objective of this review is to provide a differential diagnosis for both conditions as they relate to those immune defects to provide a diagnostic pathway to aid in establishing a diagnosis. Infectious, oncologic, or other etiologies leading to AD and AU will not be considered here.

Atopic dermatitis

Atopic dermatitis is a chronic condition characterized by pruritic skin lesions related to epithelial barrier dysfunction with an immunologic involvement. It affects between 10–20% of children in developed countries making it one of the most common diseases of childhood². Adult presentation of AD should prompt consideration of an alternate diagnosis. AD is a complex disorder consisting of a constellation of historical and physical features but lacking a pathognomonic sign or biomarker. As such, diagnostic criteria have been established to support AD as a clinical diagnosis. The modified UK Working Party's Diagnostic Criteria for Atopic Dermatitis³ (Box 1) is widely used and validated⁴. The lesions can affect the scalp, face, and extensor surfaces in infants, whereas the flexor

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surfaces become more commonly affected in older children and adults. IgE and peripheral eosinophilia frequently accompany AD. The loss of skin epithelial barrier integrity is a key concept in understanding the structural defects leading to AD. Genetic studies of AD have been able to provide insights into some of the genes involved in epithelial integrity⁵. Treatment of AD is meant to reestablish epithelial barrier integrity and limit the effects of allergic inflammation.

Box 1

Revised criteria for the diagnosis of atopic dermatitis

- Pruritis

Plus three or more of the following:

- History of flexural dermatitis (front of elbows, back of knees, front of ankles, neck, around the eyes) or involvement of cheeks and/or extensor surfaces in children aged <18 months.
- Visible flexural dermatitis involving the skin creases (or the cheeks and/or extensor surfaces in children aged <18 months)
- History of a dry skin in the past year
- History of asthma or hay fever (or atopic disease in a 1st degree relative in children <4 years of age)
- Onset <2 years of age (for children aged 4 years at time of diagnosis)

Allergic urticaria

Urticaria can be either acute or chronic and is characterized by mast cell degranulation leading to a raised central wheal with surrounding erythematous flaring. Mast cell degranulation may be prompted by a variety of triggers. As such, urticarial lesions may be due to physical, allergic, or autoimmune causes. Physical urticarias cause direct mast cell degranulation and comprise 20% to 30% of chronic urticaria⁶. Stimuli can include heat, cold, and vibration even in the absence of specific antigens.. Additionally, autoantibodies are associated with 30% to 50% of chronic urticaria⁷. Acute urticarial lesions may develop as a result of IgE mediated responses of mast cells to a specific antigen. Treatment of urticaria is aimed at limiting the affects of products released during mast cell degranulation as well as stabilizing or otherwise preventing mast cells from degranulating in the first place. While physical and autoimmune urticaria needs to be within the differential of chronic urticaria, our review will focus on conditions for which urticaria is feature of a broader syndromic phenotype.

Alarm signs

Given that both AD and AU are common conditions affecting both children and adults alike, there must be distinguishing features that can alert the clinician to consider alternative diagnoses which would make the initially observable skin changes secondary to a primary

underlying process. The presence of other features, which can be subtle in nature, can serve to create a syndromic pattern when paired with the skin changes common to AD and AU. These features can include age of onset, severity of disease, concomitant infections unrelated to skin disruption serving as an infectious nidus, as well as a variety of other traits uncommon to AD or AU themselves. Table 1 serves to summarize these features.

Specific syndromic diseases giving rise to atopic dermatitis

Omenn Syndrome

Omenn Syndrome is characterized by severe erythroderma, lymphadenopathy, eosinophilia, and immunodeficiency both from traditional opportunistic pathogens such as pneumocystis as well as CMV and parainfluenza. The underlying defect is typically due to hypomorphic mutations in V(D)J recombination but numerous gene mutations leading to a variety of changes have been identified including changes in IL7Ralpha⁸, IL2Rgamma^{9,10}, CHD7¹¹, ADA¹², RMRP¹³, and AK2¹⁴. These mutations lead to a downstream effect of abnormal T and B cell development which can cause an activated autoreactive T cell phenotype manifested as T cells infiltrating organs, including the skin, and the formation of autoantibodies. Thymic biopsies show distorted architecture and gene expression with limited FOXP3+ cells leading to a lack of central tolerance.¹⁵

Atypical complete DiGeorge Syndrome

DiGeorge syndrome is manifested by congenital cardiac abnormalities, hypoparathyroidism, and patients who have very low T cells from the lack of thymic tissue can have complete DiGeorge Syndrome. Patients with atypical complete DiGeorge syndrome can develop symptoms similar to Omenn Syndrome. In addition, while they are more likely to have an itchy rash, and there is a strong trend that they acquire the diagnosis of atopic dermatitis more frequently than controls, one review of patients found that this was not statistically significant¹⁶. The severe atopic dermatitis can often have a later onset than other manifestations of DiGeorge syndrome.

Autosomal Dominant Hyper-IgE with Recurrent Infections Syndrome (AD-HIES)

AD-HIES (Job's syndrome) leads to atopic dermatitis-like rash,¹⁷ skin abscesses, pneumonia with pneumatocele formation, skeletal abnormalities including scoliosis, retained primary teeth, abnormal facies, and a characteristically elevated IgE level. The dermatitis is notable in that it frequently occurs immediately after birth and nearly always within four weeks of life. Its distribution is less typical than other forms of atopic dermatitis and occurs behind the scalp, ears, back, and buttocks. The phenotype is due to dominant negative mutations in STAT3^{18,19}. STAT3 is a gene encoding for a protein involved in a myriad of intracellular signaling functions. The mutation seen in AD-HIES lead to specific findings of increased serum IgE, decreased T and B cell populations, decreased Th17 cells and decreased Th17 cytokines^{20,21}, but the mechanism behind which many of these clinical features are caused remains obscure.

DOCK8 Deficiency

DOCK8 deficiency may appear similar to AD-HIES with an elevated serum IgE and associated skin findings, but includes a more atopic signal with asthma and food allergy. There is also an increased susceptibility to cutaneous viral infections. As opposed to AD-HIES, DOCK8 deficiency has an autosomal recessive inheritance pattern. In addition to the atopic and infectious manifestations of DOCK8 deficiency the underlying risk of malignancy either from lymphoma or squamous cell carcinomas are the major risk to life and the impetus for bone marrow transplantation in the treatment of this disease. DOCK8 is part of family that is implicated in cytoskeletal arrangements important for cell adhesion, migration, and structure²². DOCK8 expression is largely limited to cells of the immune system. It serves as a Rho GTPase activating CDC42. The mutations leads to profound effects on T-cell differentiation and survival²³, and cause a specific defect in lymphocyte migration to the skin, potentially explaining the predilection towards cutaneous infection²⁴.

Wiskott-Aldrich Syndrome (WAS)

WAS is an X-linked deficiency of the WASP protein which leads to poor actin polymerization and resulting dysfunction of hematopoietic cells including immune cells and platelets. There may be an analogous mechanism between the cytoskeletal defects seen in DOCK8 deficiency and WAS which are both involved in immune dysfunction. This leads to a variety of effects across many of the hematopoietic lineages. Myeloid cells fail to phagocytose properly and their chemotaxis is impaired. Lymphoid cells including T cell and NK cells have difficulty forming effective immunologic synapses, and B cell function is impaired due to poor T cell function. Platelets are small and poorly functional leading to bleeding as a prominent clinical feature. The autoimmunity seen in WAS may be due to abnormal Treg function^{25,26}.

PGM3 Deficiency

Patients with PGM3 deficiency can present with atopic dermatitis, atopy of any kind, increased serum IgE, myoclonus, neurocognitive impairment associated with dysmyelination, and recurrent EBV and sinopulmonary infections leading to bronchiectasis²⁷. The mutations in PGM3 lead to dysfunctional protein glycosylation due to impaired Pgm3 and underproduction of intracellular UDP-GlcNAc, a basic building block of n- and o-linked glycosylation²⁸. The exact mechanism as to why alterations in protein glycosylation would result in this phenotype is unclear, but these patients demonstrate and increase in Th2 and Th17 cytokine production.²⁹

Immune dysregulation polyendocrinopathy enteropathy X-linked (IPEX)

IPEX is a dysregulation of the immune system which leads to multiple autoimmune manifestations and prominent atopic dermatitis. The underlying dysfunction is the loss of function of FOXP3 and resultant absence of regulatory T cells (Treg). Treg cells play a critical role in the prevention of autoimmune disease and self-reactivity³⁰, and indeed discovering the loss of Treg cells in IPEX played a critical role as an “experiment of nature” in defining their role. The atopic dermatitis is an early manifestation of the disease and occurs early in infancy. It may be accompanied by other skin manifestations of autoimmune

disease such as alopecia universalis³¹. While enteropathy and chronic watery diarrhea is a constant feature of IPEX, the typical sentinel feature of the disease leading to its diagnosis is autoimmune phenomenon such as early type I diabetes. End organ manifestations also include thyroiditis, autoimmune cytopenias, hepatitis, interstitial lung disease, and adrenal failure. IgE mediated food allergy is an additional feature of the atopic character of IPEX³².

Netherton and SAM Syndrome

Mutations in structural skin proteins can also lead to severe atopic dermatitis. Netherton syndrome is characterized by a severe ichthyosis, atopic disease, and pathognomonic changes in the hair shaft resembling bamboo and known as trichorrhexis invaginat³³. Food allergy, asthma, and angioedema can accompany the skin disease. Immunodeficiency is also a feature of the disease with patients having an increased rate of respiratory and gastrointestinal infections. The underlying defect is in a mutation in SPINK5, which leads to loss of function of LEKTI.³⁴ SPINK5 is associated with skin epithelial barrier function which is thought to be relevant in developing ichthyosis associated with SPINK5 mutations, but patients also have poor vaccine responses. Subsequent initiation of immunoglobulin replacement therapy has been shown to help both the rate of infections as well as skin integrity³⁵.

Mutations in DSG1 and DSP, both skin junctional barrier proteins, can lead to severe dermatitis-multiple allergies-metabolic wasting (SAM) syndrome, associated with severe atopy and metabolic wasting, and can also be associated with other congenital malformations such as microcephaly and structural heart defects, amongst others.

Specific diseases giving rise to allergic urticaria

Phospholipase C γ 2 Associated Antibody Deficiency (PLAID)

Patients with PLAID were discovered in the context of familial cold urticaria that was life long³⁶. Typical cold induced urticaria, by contrast, is later onset and transient. Further elucidation of the phenotype led to an understanding that it can include antibody deficiency, frequent infections, autoimmunity, and granulomatous disease³⁷. The cold urticaria is universal whereas the other traits are seen to a lesser degree. This phenotype is caused by mutations in PLCG2 leading to alterations in the function of PLC γ 2³⁸. These mutations lead to a complex effect on intracellular signaling which is at least partially dependent on temperature. The PLCG2 mutations in PLAID patients are deletions in an autoregulatory unit of the protein which, when absent renders the protein more constitutively active, more so in the cold. This activity actually leads to activation of the mast cell at lower temperatures which accounts for the cold urticaria observed in these patients. The active enzyme paradoxically leads to impaired signaling at physiologic temperatures.

Vibratory Urticaria due to ADGRE2 Mutations

Physical causes of mast cell degranulation are well known, but at least one form of physical urticaria has been associated with a specific mutation affecting mast cell function. Vibratory urticaria inherited in an autosomal dominant pattern has been shown to be due to mutations in ADGRE2. ADGRE2 is a membrane bound autoinhibitory unit on the mast cell. Mutations

in this protein cause structural fragility which when disrupted by mechanical stress leads to easy mast cell activation with vibratory stimuli³⁹.

Autoinflammatory Syndromes

Autoinflammatory syndromes are a series of disease entities that are caused by abnormal inflammatory responses not caused by antibody or cellular attacks on self. In some cases, mutations in genes involved in the formation of the inflammasome, an intracellular complex that responds to activated pattern recognition receptors in order to induce inflammation through IL-1 β and IL-18⁴⁰, can lead to phenotypes with a variety of manifestations including what appear to be urticarial lesions. These lesions have historically been described as urticarial, however they are due to neutrophils, not mast cells, and do not result from immediate hypersensitivity. At least three such disorders are accompanied by urticarial manifestations: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal onset multisystem inflammatory syndrome (NOMID). Quite different from the allergic urticaria described above, the syndromes are also accompanied by periodic fever, arthritis, conjunctivitis, and other organ-specific and systemic inflammation.

Summary

Atopic dermatitis and allergic urticaria are commonly seen in clinical practice, but when coupled to unusual features they may constitute a syndrome distinctive for an immunological defect. These rare syndromes have been able to disclose many mechanisms within the immune system that otherwise would remain obscure. New modes of treatment have been implemented which can modulate the immune dysfunction. In some cases these immune defects necessitate replacing the immune compartment with a hematopoietic stem cell transplant. Both through mechanistic discovery and patient care, these syndromes present a unique opportunity for the observant physician.

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Key Points

- Atopic dermatitis and allergic urticaria are common conditions of the skin which can also be the presenting symptoms of uncommon diseases.
- Defects leading to immunodeficiency may be associated with atopic dermatitis or allergic urticaria.
- Unusually severe or otherwise atypical presentations of atopic dermatitis or allergic urticaria may lead to clinical suspicion of an underlying immunodeficiency

Table 1

Atopic Dermatitis	Clinical Features Seen in Addition to Skin Manifestations	Gene Mutation	Laboratory Changes	Estimated Prevalence if Known
Netherton Syndrome	Trichorrhexis invaginatam, recurrent infections, failure to thrive, food allergy, angioedema	SPINK5	High IgE	1–9/1000000
Omenn Syndrome	Lymphadenopathy, recurrent infections, eosinophilia	SCID Genes	Lymphopenia, hypogammaglobulinemia	<1/1000000
Autosomal Dominant Hyper-IgE Syndrome	Skin abscesses, pneumatoceles, joint hypermobility, abnormal facies, retained primary teeth, coronary artery aneurysm	STAT3	High IgE	1–9/100000
DOCK8 Deficiency	Viral skin infections, food allergy, asthma, malignancy	DOCK8	Lymphopenia, low IgM, high IgE	<1/1000000
Wiskott-Aldrich Syndrome	Bleeding diatheses, recurrent infections, autoimmunity	WASP	Thrombocytopenia, microplatelets	1–9/1000000
Immunodysregulation Polyendocrinopathy X-linked (IPEX)	polyendocrinopathy, chronic diarrhea	FOXP3	High IgE	<1/1000000
DiGeorge Syndrome	Congenital heart defects, abnormal facies, hypoparathyroidism	chr22q11	T-cell lymphopenia	1/2000–4000 live births
PGM3 Deficiency	myoclonus, neurocognitive impairment, recurrent EBV and sinopulmonary infections leading to bronchiectasis	PGM3	Lymphopenia, high IgE	
SAM Syndrome	Severe atopy, metabolic wasting, hypotrichosis, microcephaly	DSG	high IgE	<1/1000000
Allergic Urticaria				
PLCG2 Associated Antibody Deficiency and Immune Dysregulation (PLAID)	Cold urticaria, recurrent infections, granulomatous disease, autoimmunity	PLCG2	Decreased B cells, NK cells, Increased IgE	<1/1000000
Familial vibratory urticaria	Lifelong vibratory Urticaria, obesity	ADGRE2		
Non-allergic “urticarias”				
Neutrophilic dermatoses (formerly called urticaria)				
Familial Cold Autoinflammatory Syndrome (FCAS)	Cold urticaria, fevers, arthritis, conjunctivitis	NLRP3	Neutrophilia, thrombocytosis, increased acute phase reactants, increased serum amyloid A	
Muckle-Wells Syndrome (MWS)	Urticaria, fevers, arthritis, conjunctivitis, sensorineural hearing loss	NLRP3	Neutrophilia, thrombocytosis, increased acute phase reactants, increased serum amyloid A	
Neonatal Onset Multisystem Inflammatory Disease (NOMID)	Urticaria, fevers, arthritis, conjunctivitis, sensorineural hearing loss, cognitive impairment	NLRP3	Neutrophilia, thrombocytosis, increased acute phase reactants, increased serum amyloid A	