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PRIMARY IMMUNODEFICIENCIES WITH ECZEMATOUS MANIFESTATION: AN UPDATED REVIEW

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Abstract

Mutations in the set of genes responsible for adequate development and function of the immune system also affect the s*kin-associated lymphoid tissue (SALT)*. As a result of inborn genetic errors, patients develop one of the 430 different primary immunodeficiencies defined to date.

Globally, nearly 6 million people are living with a primary immunodeficiency, with an estimated incidence of 1 case per 10.000 inhabitants. Despite modern and accessible diagnostic technologies, patients still receive delayed diagnoses.

We conducted a search for original articles, review articles, and case reports published in scientific journals available in the PubMed database by using the following keywords: primary immunodeficiency AND eczematous rash OR skin manifestations. This review article mainly focuses on skin manifestations of primary immunodeficiencies with eczematous rash.

Keywords: primary immunodeficiency, eczematous lesions, skin manifestations, Wiskott-Aldrich Syndrome, Autosomal dominant hyper-IgE syndrome, Autosomal recessive hyper-IgE syndrome, Comèl-Netherton syndrome, Omenn syndrome, IPEX syndrome

Introduction

The immunological function of the human skin (i.e., *skin-associated lymphoid tissue*) significantly contributes to the appropriate host defense mechanisms. The skin serves as a host for an army of innate and adaptive immune cells, including Langerhans antigen-presenting cells that reside within the epidermis, and dendritic cells, macrophages, mast cells, basophils, eosinophils and subpopulations of T-cells in the underlying dermis [1-3].

Inborn genetic defects in the set of genes that drive the normal development and function of the immune system result in primary immunodeficiency disease (PID). Since Bruton's agammaglobulinemia as the first clinically defined primary immunodeficiency in the 1950s, awareness for these rare diseases has been raised. To date, nearly 430 PIDs have been recognized by the International Union of Immunological Societies (IUIS), which can affect humoral immunity, cell-mediated immunity, phagocytic immunity, and the complement system [4-7].

Despite the fast-growing medical knowledge of PIDs, 70-90% of affected patients remain undiagnosed, while those with confirmed PIDs are diagnosed with a delay of 6-9 years from the early onset of the symptoms [4, 8]. On account of the poor life quality associated with the belated diagnosis of PIDs, early suspicion and adequate treatment are imperative for clinical immunologists [6].

Besides the increased susceptibility to recurrent infections, Lehman [5] reports the association between PIDs and cutaneous manifestations in 40-70% of cases. Most early skin manifestations are non-pathognomonic, such as eczematous lesions, erythroderma, skin granulomas, dysplasia, depigmentation, telangiectasia, and autoimmune vasculitis [5, 9].

This review article covers in more detail the skin manifestations of PIDs with eczematous lesions, which are usually misdiagnosed as atopic dermatitis (AD) in children (Table 1).

This article represents a literature review published in English from October 2001. We searched for review articles, original articles, and case reports published in scientific journals in the PubMed database using the following keywords: primary immunodeficiency AND eczematous rash OR skin manifestations.

Table 1. Overview of primary immunodeficiencies manifesting with eczematous rash.

Disease	OMIM code	Gene defect	Clinical features other than eczematous manifestation
Wiskott-Aldrich syndrome	301000	*WAS gene*	Thrombocytopenia with hemorrhagic manifestation, recurrent infections, hematologic malignancies
Autosomal dominant hyper IgE syndrome	147060	*STAT3 gene*	Respiratory infections, vasculopathy, skeletal and connective tissue abnormalities, hematologic malignancies and autoimmune disorders
Autosomal recessive hyper IgE syndrome	243700	*DOCK8 gene*	Respiratory infections, acute or chronic diarrhea with failure to thrive, neurological manifestations, hematological malignancies, autoimmune disorders
Comèl-Netherton syndrome	256500	*SPINK5 gene*	Atopic diathesis, ichthyosis linearis circumflexa, trichorrhexis invaginata
Omenn syndrome	603554	*RAG1 and RAG2 gene*	Lymphadenopathy, hepatosplenomegaly, alopecia, chronic diarrhea, recurrent infections
IPEX syndrome	304790	*FOXP3 gene*	Autoimmunity, polyendocrinopathy (type 1 diabetes mellitus, autoimmune thyroiditis), enteropathy (malabsorption, watery or bloody diarrhea)

OMIM, Online Mendelian Inheritance in Man.

Wiskott- Aldrich Syndrome

Wiskott-Aldrich syndrome is a rare X-linked primary immunodeficiency syndrome caused by mutations in the *WAS* gene on the X chromosome (Xp11.22-23). Each year, 1–9 per 100,000 newborns are diagnosed with Wiskott-Aldrich syndrome, most of whom are males due to the X-linked pattern of inheritance.

The WAS gene encodes for the 502 proline-rich WAS protein (WASp), which is present exclusively in the cytoplasm of hematopoietic cells of non-erythroid origin.

Due to mutations in the *WAS gene*, WASp loses the ability to control actin cytoskeleton rearrangement and immune system development. To date, the mechanism of immune dysregulation in WAS patients is not fully understood, but the clue may lie in the downregulated expression of CD43 on the cell membrane surface [10, 12-14].

The most common cutaneous finding in up to 80% of pediatric patients diagnosed with Wiskott-Aldrich syndrome is AD-like dermatitis.

The skin lesions have an early onset, typically in the second or third month after birth. They appear as pruritic papulose-vesicular lesions with exfoliation, excoriation, and serosanguinous crusts than classical AD. The lesions usually affect the infant's cheeks, scalp, and intertriginous regions. Lesions are

histologically identical to those of the classical AD. The epidermis has a spongiform appearance and *parakeratosis*. Perivascular infiltration of lymphocytes in the underlying dermis can also be observed.

As a result of an inadequate skin barrier, secondary bacterial infections can occur with the clinical presentation of impetigo, cellulitis, and skin abscesses. Secondary viral complications have also been reported, caused mainly by the *Herpes simplex virus* or *Molluscum contagiosum* [6, 16].

Hemorrhagic manifestations. The most common extracutaneous manifestations are the hemorrhagic manifestations as a result of thrombocytopenia.

The platelet count usually varies from 20.000-50.000 per mm^3 (moderate thrombocytopenia) in patients with Wiskott-Aldrich syndrome. However, platelet counts may be above 50.000 per mm^3 (mild thrombocytopenia) or drop below 20.000 per mm^3 (severe thrombocytopenia) [15].

Recurrent infections. Due to compromised immunity, patients are at greater risk for infections. Bacterial infections are commonly presented in these patients as otitis media, pneumonia, colitis, meningitis, or sepsis and are mainly caused by *Streptococcus pneumoniae, Haemophilus influenzae*, and *Neisseria meningitides*. Viral infections caused by *Varicella-zoster virus* and *Cytomegalovirus (CMV)* or opportunistic infections (*Pneumocystis jirovecii, Molluscum contagiosum*) can be diagnosed as well [10-12].

Malignancy and autoimmunity. Patients with Wiskott-Aldrich syndrome are indeed at higher risk of malignancy. B-cell lymphoma associated with *Epstein-Barr virus* infection and leukemia are the most commonly reported malignancies. Autoimmune manifestations have also been reported, including hemolytic anemia, vasculitis, IgA nephropathy, and inflammatory bowel disease [10-12].

Several laboratory tests can be run to conclude the final diagnosis. The results from the total blood count, microscopic evaluation of a peripheral blood smear, and the flow cytometry detection of the WASp in the white blood cells (WBC) can be valuable.

Pruritic papulose-vesicular lesions with a predilection for the face, scalp, and intertriginous regions after childbirth are highly suspect. However, the gold standard for the diagnosis is genetic testing for all types of mutations in the WAS gene (missense mutations, deletions, insertions, splice mutations, etc.). As a differential diagnosis, hyper IgE syndrome, Omenn syndrome, Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX), AD, immune thrombocytopenic purpura, and congenital neutropenia should be considered [12].

Autosomal dominant hyper-IgE syndrome

The classical, autosomal dominant hyper-IgE syndrome (AD-HIES) was first identified in 1996 in two unrelated children who presented with early-onset eczema, recurrent respiratory infections, and staphylococcal "cold" abscesses. Davis et al. named this condition *Job syndrome*, later renamed *Hyper-IgE Recurrent Infection Syndrome,* when Buckley et al. discovered the increased serum IgE titter among the other clinical signs [17-19].

AD-HIES affects both males and females equally, with an estimated prevalence of 1 case per 1,000,000 newborns [20].

AD-HIES is closely associated with molecular changes in the *STAT3 gene* (17q21.2), which encodes for signal transducer and activator of transcription 3 (STAT3). The majority of molecular alterations are missense and in-frame deletions within the DNA-binding domain (DBD), Src homology 2 (SH2) domain, and C-terminal transactivation domain (TAD) with a dominant-negative effect.

The impaired function of the ubiquitous STAT3 transcription factor will compromise the signal transduction of over 50 cytokines and growth factors (e.g., IL-6, IL-11, IL-21, IL-22, etc.), thus resulting in multisystem manifestations [17, 19, 21].

The most typical early skin manifestation in 65-85% of patients with AD-HIES is the newborn eczematous rash [22].

The neonatal rash typically affects the scalp and face. Unlike AD, it appears a couple of weeks after birth [20]. Histopathologic analysis of the skin biopsy reveals eosinophil infiltration of the dermis [18]. As a result of the impaired barrier, the skin becomes colonized by *S.aureus* species, therefore evolving into a papulopustular rash with pus exudation and crust formation [19]. The staphylococcal skin infection can

further progress into cold abscess formation, which appears less severe and inflamed, unlike the expected staphylococcal abscess [5].

Scientists believe that defects in T_H17 differentiation and the IL-17A and IL-22 deficiency contribute to susceptibility to staphylococcal skin infections. By generating β-defensins and calcium-binding proteins, these two T_H17-derived cytokines stimulate the STAT3-mediated defensive mechanisms in keratinocytes against *S.aureus*.

The failure to eradicate the *S.aureus* species in patients with AD-HIES can be explained by the loss of function of the STAT3 transcription factor, as mentioned before [23].

The non-cutaneous clinical manifestations include recurrent respiratory infections, vasculopathy, skeletal and connective tissue abnormalities, and an increased risk for malignancy.

Respiratory infections. Rhinosinusitis, otitis, and mastoiditis are the most common upper respiratory infections, whereas pneumonia is the most common lower respiratory infection in 80% of AD-HIES patients [18, 19].

The most common causative microbes of upper and lower respiratory infections are *S.aureus, Streptococcus pneumoniae,* and *Haemophilus influenzae.* Patients with a late onset of adequate antibiotic treatment can experience respiratory complications (e.g., lung abscesses, bronchiectasis, bronchopleural fistulas, and pneumatocele) along with colonization by the opportunistic microbes, *Pseudomonas aeruginosa* and *Aspergillus fumigatus* [18].

Vasculopathy. An additional characteristic of AD-HIES is the presence of vascular abnormalities in the aorta, brain, heart, lungs, and skin [24]. Both arteries and veins could be affected, with a predominance of medium-sized arteries in the brain and the heart [19, 24].

The patients are prone to develop tortuosity, ectasia, and aneurysm formation as they grow older [19]. The underlying pathogenesis of vascular abnormalities is related to the deterioration of the STAT3-vascular endothelial growth factor (VEGF) axis due to STAT3 mutations with a dominant-negative effect [24].

Skeletal and connective tissue abnormalities. Early adolescence is the period in which a majority of patients acquire characteristic dysmorphic facial features, including a prominent forehead with a wide nasal bridge, deep-set eyes, prognathism, rough facial skin, increased interalar distance, and a high-arched palate [18-20]. Up to 70% of the patients may also experience retention of primary teeth.

To avoid "double dentition" phenomenon and malocclusion, Tar et al. suggest the extraction of retained primary incisors by the age of 9 and of retained primary canines and molars by the age of 13 [25].

Approximately 79% of the patients are prone to reduced bone mineral density (BMD) and minor trauma fractures, which are seen in up to 50% of the patients. Sowerwine et al. suggest a multifactorial etiology of skeletal abnormalities, including chronic inflammation, hormones, and nutrition [26].

Mutations in the STAT3 gene deteriorate the inhibitory function of STAT3 in the IL-6/STAT3/NK-kB axis, resulting in increased osteoclast activity and pro-resorptive bone metabolism [19].

Malignancy and autoimmunity. Malignancy, predominantly of hematological origin, affects about 7% of AD-HIES patients [19].

Lymphomas are particularly frequent, with an estimated risk of 200-fold greater than that of the general population [27].

Additionally, AD-HIES patients are at risk for autoimmune disorders such as systemic lupus erythematosus, membranoproliferative glomerulonephritis, vasculitis, and dermatomyositis [19, 20].

AD-HIES diagnosis is made based on the clinical presentation and the laboratory findings. The full blood count reveals eosinophilia in over 70% of the patients, with more than 700 cells per microliter. In addition, most patients undergo serological testing, which shows hyperimmunoglobulinemia E along with IgA, IgM, and IgG within normal ranges [18, 19].

The quantification of IgE antibodies usually exceeds 2000 U per microliter, but we should remember that even the normal finding does not exclude AD-HIES [18]. The immunophenotyping of IL-17-producing Th17 cells is another diagnostic tool [19].

Yet, the gold standard for AD-HIES continues to be the molecular analysis of the STAT3 gene and the clinical presentation. When evaluating a patient suspected of having AD-HIES, physicians should bear

in mind some differential diagnoses, such as chronic granulomatous disease, severe AD, and other immunodeficiencies with eczematous rash [20].

Autosomal recessive hyper-IgE syndrome

The autosomal recessive hyper-IgE syndrome (AR-HIES) is a rare primary immunodeficiency distinguished as an entity from the dominant form in 2004 by Renner et al. [18].

The epidemiological data reports a greater frequency in consanguineous populations in Middle Eastern countries. Most patients prevail molecular changes in the *DOCK8 gene* (dedicator of cytokinesis 8) located on the 9p24.3 chromosome. However, PGM3, SPINK5, and TKY2 gene mutations have also been closely associated with the AR-HIES [29, 30].

The DOCK8 protein activates the CDC42 member of the RAS family with its intrinsic guanine exchange activity. As a guanine exchange factor, DOCK8 plays a role in signal conduction for cytoskeletal rearrangements by removing the GDPs from CDC42 and binding the GTPs. Besides the cells of hematopoietic origin as the primary site of expression, DOCK8 can be found in the placenta, kidneys, lungs, and pancreas [29].

Patients with AR-HIES usually develop atopic-like dermatitis, along with skin infections and virus-driven skin carcinomas.

The differentiation of atopic-like dermatitis in AR-HIES from classical AD is a challenge. In both cases, eczema affects the scalp, face, neck, and flexural sites of extremities, with signs of excoriations [28, 29].

In general, patients with AR-HIES have a more severe eczematous rash than those with the dominant form. Another distinctive clinical feature is the neonatal rash seen in 24% of patients with the recessive form versus 65-80% of patients with the dominant form of hyper-IgE syndrome [22].

Patients with AR-HIES will likely develop severe, recalcitrant viral infections caused by *Herpes simplex virus*, *Human papillomavirus*, *Varicella-zoster virus*, and *Molluscum contagiosum* [29].

Folliculitis, impetigo, and skin abscess formation due to *S. aureus* infection and mucocutaneous candidiasis may occur [28-30].

Owing to compromised immune surveillance, in 10-36% of AR-HIES patients' malignancy can happen, with squamous cell skin cancer related to *Human papillomavirus* infection being the most frequent [29, 30].

The extracutaneous clinical features include upper and lower respiratory infections, gastrointestinal and neurological manifestations, malignancy, and autoimmune disturbances.

Respiratory infections. Patients with recessive forms of hyper-IgE syndrome can experience recurrent rhinosinusitis, mastoiditis, bronchitis, pneumonia, and otitis media, usually caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pneumocystis jiroveci*, *adenovirus*, and *respiratory syncytial virus* [18].

Gastrointestinal manifestations. Acute or chronic diarrhea in AR-HIES patients causes malabsorption and difficulties in weight gain. Biggs et al. suggest that autoimmune or allergic enteropathy may pathogenically explain the presence of digestive symptoms [29].

Neurological manifestations. Meningitis, encephalitis, and vasculopathy have been reported. Aneurisms and vasculitis can both affect the cerebral vasculature in AR-HIES patients, which leads to delayed neurodevelopment, stroke, subarachnoid bleeding, and hemiplegia [29].

Malignancy and Autoimmunity. Besides squamous cell carcinoma, patients can exhibit Burkitt lymphoma and diffuse large B-cell lymphoma caused by *Epstein-Barr virus* infection. Patients are also prone to develop autoimmune hemolytic anemia, asthma, and food, drugs, and environmental allergies as a consequence of the atopic diathesis [29, 30].

Patients suspected of AR-HIES must be evaluated as quickly as possible since the survival rate drops to 37% by the age of 30 [29]. The high morbidity and mortality rates significantly depend on life-threatening infections and malignancy.

Comèl-Netherton syndrome

Comèl-Netherton syndrome is a rare autosomal recessive disease named after Alfred Comèl and Jean Netherton. This genetic disease affects 1 in 200,000 newborns, mainly in countries with a greater rate of consanguinity [21].

A correlation between consanguinity and Comèl-Netherton syndrome was found in 88% of the diagnosed cases [31].

Mutations in the *SPINK5 gene*, located on chromosome 5q32, are associated with the genetic cause of Comèl-Netherton syndrome. This gene codes for the LEKTI (lymphoepithelial Kazal-type-5 serine protease inhibitor) protein, which plays an essential role in protease activity regulation of kallikrein 5 (KLK5) and kallikrein 7 (KLK7).

LEKTI maintains skin barrier integrity by regulating these specific epidermal serine proteases. Mutations in the SPINK5 gene result in the loss of function of LEKTI and thereby upregulated activity of serine proteases, which break down the desmoglein-1 molecules. As a consequence, the skin barrier becomes disrupted, along with enhanced skin shedding [21, 32].

Comèl-Netherton syndrome typically affects the skin, hair, and immune system, giving rise to the characteristic triad of clinical features: atopic diathesis, ichthyosis linearis circumflexa, and hair shaft abnormalities [32].

Atopic diathesis is a tendency to become sensitized and express IgE to environmental allergens after ordinary exposure. Frequent allergic manifestations include eczema, allergic rhinitis, asthma, and food allergy.

Ichthyosis Linearis Circumflexa is characterized by pruritic, annular, or serpiginous erythematous patches with double-edged scaling margins, as described by Comèl in 1949 [32]. This distinctive type of erythroderma affects nearly 86% of patients with Comèl-Netherton syndrome early after birth [31]. Epidermal hyperplasia with parakeratosis and absent immune cells dermal infiltration is observed on skin biopsies. Immunohistochemistry with anti-LEKTI polyclonal antibodies shows reduced or absent LEKTI expression in skin biopsies. Thus, skin biopsy is a valuable tool in the diagnostic algorithm [31, 34].

Trichorrhexis invaginata (Bamboo hair) is a pathognomonic abnormality defined by Netherton in 1958, characterized by hair shaft invagination at multiple locations creating a "ball in a cup," "bamboo," or "golf tee" appearance under the microscope [32]. Hair samples from the scalp, eyebrows, and eyelashes are suitable for trichoscopy [31].

Normal hair shaft appearance does not exclude the diagnosis since the hair disorder affects only 20-50% of the body hair [32].

Omenn syndrome

Omenn syndrome is a rare, severe combined immunodeficiency disease inherited in an autosomal recessive pattern. The prevalence is estimated to be less than 1 case per 1,000,000 newborns [21].

Studies on molecular mechanisms of Omenn syndrome reveal hypomorphic mutations in *RAG1* and *RAG2* genes (11p13) in most patients. In Omenn's syndrome, mutations result in reduced functionality of RAG1 and RAG2 genes, causing an impairment of variable diversity joining V(D)J recombination [21, 33].

This process is essential for the proper development of T and B cells.

However, alterations in the *RMRP*, *ADA*, *IL2RG*, *IL7RA*, *DCLRE1C, CHD7,* and *LIG4* genes associated with Omenn syndrome have also been reported [21]. As a distinctive clinical entity, Omenn syndrome was first described by Gilbert S. Omenn in 1965.

The clinical presentation typically features a triad of symptoms: neonatal erythroderma, lymphadenopathy, and hepatosplenomegaly. In addition, patients are prone to experience alopecia, chronic diarrhea, and severe recurrent pulmonary infections indeed.

Early onset neonatal Exfoliative erythroderma is a hallmark of Omenn syndrome. Skin biopsies reveal spongiosis, acanthosis, parakeratosis, and necrotic keratinocytes throughout the epidermis. Perivascular CD3+ T-cell infiltrate, and aberrant Langerhans cell distribution in the dermis are usually

observed [34]. Overall, this makes the histopathology beneficial in the differentiation of the Omen syndrome from other eczematous rashes, such as AD, Comèl-Netherton syndrome, graft-versus-host disease, and congenital ichthyosiform erythroderma [34].

Aside from the skin, T-lymphocytes usually infiltrate the intestines wall, liver, and spleen, causing chronic diarrhea, hepatomegaly, and splenomegaly [33]. Abnormalities in the T-cell immunity defense make patients vulnerable to respiratory pathogens. *Pneumocystis jiroveci*, *Cytomegalovirus*, and *Parainfluenza virus* may cause recurrent pneumonitis [35].

The diagnosis relies on the patient's medical history, physical examination, skin biopsy, and genetic confirmation. Although histopathology can differentiate the Omenn syndrome from other PIDs with eczematous lesions, genetic testing remains the gold diagnostic standard.

IPEX Syndrome

Immune dysregulation, polyendocrinopathy, enteropathy, and X-linked syndrome (IPEX Syndrome) is the first of the group of *tregopathies* described by Powell et al. in 1982 [33].

This X-linked recessive, monogenic disease occurs mainly in male newborns, with a prevalence below 1:1,000,000 [34]. IPEX Syndrome is associated with mutations in the forkhead-winged helix transcription factor (*FOXP3 gene*) mapped on the X-chromosome (Xp11.23) [34].

Most mutations (40%) occur within the DNA-binding region, while the rest are within the proline-rich terminal region, leucine helix loop, or intronic region [34].

FOXP3 is primarily expressed in CD3+CD4+CD25+(IL-2Rα)$CD127^{low}$(IL-7) regulatory T-cells (T_{reg}). When mutations in the FOXP3 gene occur, T_{reg} becomes dysfunctional, while on the contrary, the effector T-cells (T_{eff}) become overreactive [33, 34].

Eczematous rash, enteropathy, and type 1 diabetes mellitus make up the clinical triad of symptoms in IPEX syndrome patients [33].

However, patients can also experience autoimmune thyroiditis, autoimmune hepatitis, autoimmune hematological disorders, arthritis, splenomegaly, and lymphadenopathy [34].

Recurrent infections caused by *Staphylococcus spp*., *Cytomegalovirus*, and *Candida* can be life-threatening [10].

Skin rash. Typically, it appears in the first months after birth as severe eczematous lesions on the legs, trunk, and face. Ichthyosiform and psoriasiform lesions can also be observed [34, 35].

Histopathology of skin biopsies is often non-conclusive, with epidermal hyperplasia, parakeratosis, spongiosis, and lymphocytic infiltration [35].

Conclusion

This scoping review provides a comprehensive overview of the current literature on PIDs associated with eczematous skin lesions. The differential diagnosis spectrum includes hereditary, inflammatory, allergic, and certain infectious diseases. Finally, the article emphasizes the importance for physicians to be aware of these rare diseases and always make a clinical suspicion when confronting a pediatric patient with AD-like dermatitis associated with systemic manifestations.

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