



Cutaneous manifestations of primary immunodeficiency

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Purpose of review

To show that skin symptoms help in the recognition of primary immunodeficiencies (PIDs). To analyze whether recent molecular data help in understanding genotype/phenotype relations.

Recent findings

Erythroderma in Omenn syndrome may be caused by either mutations in genes associated with severe combined immunodeficiency (SCID) in which the generation of some T cells is possible, which results in potentially autoreactive lymphoid clones, or by selective proliferation of revertant CD8⁺ T cells in the skin due to clonal expansion in response to infections or autoantigens.

The newborn eczematous eruption, which occurs mainly in the signal-transducer-and-activator-of-transcription-3 (STAT3) variant, helps to differentiate STAT3 from Dedicator of Cytokines 8-related Hyper-IgE-syndrome (HIES).

Impaired T helper 17 cell (TH17) immunity [HIES and defects of autoimmune regulator element (AIRE), STAT-1, and interleukin 17 receptor (IL17R)] may give rise to localized chronic mucocutaneous candidiasis, whereas a defective innate immune system predisposes to systemic candidiasis [congenital neutropenia, neutrophil dysfunction, and caspase recruitment domain 9 (CARD9) deficiency].

Noninfectious granulomas may be the presenting symptom in innate immunity defects [such as chronic granulomatous disease (CGD) or in predominantly humoral immunodeficiencies such as common variable immunodeficiency], as well as ataxia teleangiectasia or rare recombination-activating gene-deficient cases.

Summary

The skin is important in the diagnosis of PIDs. In particular eczematous lesions, erythroderma, noninfectious granuloma, and microbial manifestations may help to direct further diagnostic laboratory analysis.

Keywords

dermatitis, erythroderma, granuloma

INTRODUCTION

Primary immunodeficiencies (PIDs) are rare. The prevalence in eight European core countries was 4.1 per 100,000 inhabitants [1].

As an easily accessible organ, the skin might be of help in recognizing a PID patient. Cutaneous manifestations in PID can lead to early suspicion and diagnosis [2]. In a prospective study of 128 children with PID, 48% presented skin manifestations, in 39% as an early feature [3].

As genotype and skin-phenotype of a PID are not always one unity, we highlight dermatological aspects of PIDs in relation to recent molecular findings.

ERYTHRODERMA

Erythroderma occurs in 7% of the PIDs [3]. A skin biopsy is helpful for etiologic diagnosis of infantile erythroderma, particularly in PID [4].

Erythroderma shortly after birth, followed by alopecia, lymphadenopathy, and hepatosplenomegaly, is considered as a classic Omenn syndrome, in which subsequent generalized edema and metabolic alterations may be caused by a high loss of proteins [5]. Recombination-Activating Gene (RAG) deficiency, among others, leads to severe combined immunodeficiency (SCID) or Omenn syndrome.

Also mutations in Artemis, DNA ligase-4, interleukin-2 (IL-2) receptor γ chain, IL-7 receptor α

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KEY POINTS

- Looking at the skin is useful when analyzing a child with PID.
- Erythroderma is a serious skin problem in some PIDs.
- In case of serious or atypical atopic dermatitis think of PID.
- Noninfectious granulomata may be the presenting sign of ataxia teleangiectasia and Rag-2 deficiency.

chain, adenosine deaminase, and RNA component of mitochondrial RNA processing endoribonuclease (RMRP) genes can cause Omenn syndrome [6]. The majority of Omenn syndrome is caused by gene-mutations associated with SCID when their function is completely abolished, but, when in a residual number of T cells their activity is partially maintained, it results in potentially autoreactive lymphoid clones [5]. This is illustrated by an atypical case of X-linked SCID (XSCID), which presented with autologous T and natural killer (NK) cells and Omenn syndrome-like manifestations. A splice-site mutation that caused most of the mRNA to be incorrectly spliced, but produced normally spliced transcript in a lesser amount, led to residual common- γ chain CD132 expression and development of T and NK cells. The skin biopsy showed massive infiltration of revertant (caused by a second-site mutation) T cells, mostly of the CD8⁺ T-cell subset, with a T-cell Receptor (TCR) repertoire restricted to a TCR-V β 2 expansion, resulting in restoration of correct splicing and normal CD132 expression and function. This highlights revertant mosaicism as a possible cause for variable phenotypic expression. Why in particular these 'normal', reverted T cells were involved in the Omenn syndrome-related skin disease remained unclear [7]. Usually, the feature of oligoclonal expansion of autoreactive T cells in the skin is the major hallmark of the skin symptoms of Omenn syndrome, although NK cells were held responsible for the manifestations in another unique case. Also in this case, the reason why the NK cells had infiltrated the skin remained unclear [8].

In some SCID patients, the erythroderma is Graft-versus-Host disease caused by maternofetal transfusion. Microsatellite analysis is used to rule out maternal T-cell engraftment when in doubt.

DERMATITIS

In various immunodeficiencies atypical dermatitis, often widespread and resistant to treatment,

presents early in the course of the disease, hard to discern from atopic dermatitis.

High total and specific IgE levels in some PIDs complicate the differentiation from atopic dermatitis. Dermatitis has been described in 81–100% of patients with Hyper-IgE-syndrome (HIES) [3,9,10^{*}]. The discovery of different genotypes led to the distinction of two phenotypes [11]. Some patients have loss-of-function mutation in, or deletions of, the gene 'Dedicator of Cytokinesis 8' (*DOCK8*), which is expressed in lymphocytes; others (the classic Job's syndrome) have dominant-negative mutations in 'signal-transducer-and-activator-of-transcription-3' (*STAT3*). Clinical findings (see Table 1) [12^{**},13–18] and family history, combined with the assessment of TH17 cells and IL-17, discriminate HIES patients with *STAT3* mutations from classical atopic dermatitis patients (patients with wild-type *STAT3*) [19].

In the autosomal recessive *DOCK8* deficiency the dermatitis is more severe than in autosomal dominant *STAT3*-negative HIES cases [12^{**},20]. A helpful skin characteristic to discern the two genotypes is the newborn eczematous rash, present in 65–80% of *STAT3* mutation patients and only in 24% of *DOCK8* mutations. See Table 1 for more details [12^{**},13–17,20].

In 80–100% of patients with Wiskott–Aldrich syndrome (WAS) [3,16] atopic dermatitis-like skin problems occur. Premature termination and deletion mutations in the *WASP* gene, located in the X-chromosome, may result in a classical syndrome showing neonatal thrombocytopenia, small dysfunctional platelets, eczema, and severe infections early in life, but missense mutations in the gene lead to residual *WASP* protein expression, and usually result in X-linked thrombocytopenia (XLT) only. *WASP*-associated or related proteins may compensate the *WASP* protein deficiency [21].

The eczema in WAS patients is reported to look like atopic dermatitis [22], but the UK Working Party's diagnostic criteria for atopic dermatitis (UKWPA) [15] were not tested. We found the hemorrhagic component of the dermatitis to be of help to distinguish it from atopic dermatitis. For more details see Table 1.

Dermatitis resembling atopic dermatitis occurs in IgA-deficient patients. IgA deficiency shares a major histocompatibility complex-linked genetic defect with the rarer common variable immunodeficiency (CVID), characterized by, in the course of life, progressive decrease in IgG, IgA, and often IgM. A review of 37 patients (4–32 years), followed for 131 patient years [23], shows, apart from infections in 84%, asthma, atopic dermatitis (UKWPA) [15] not tested), and allergic rhinoconjunctivitis,

Table 1. Classical primary immunodeficiency with high IgE levels and dermatitis

Symptoms	Autosomal dom HIES (STAT3) [12 ^{***} ,13,14]	Autosomal rec HIES (DOCK8) [14]	WAS [16] (premature termination and deletion mutations in WASP)	IPEX syndrome [18] (based on 10 cases)
Newborn rash	80/64.9/67%	In 24%	Rare	After 1st month
Coarse facies	85/90.6/47%	0%	No	No
Atopy				
Eczema	95/90.6/95% (UKWPAD +) [15]	91% (UKWPAD +)	80–100% (UKWPAD ?)	7 cases (UKWPAD ?)
Allergies	–	71%	Predisposed ?%	10 cases(?)
Asthma	?/?/23%	50%	Predisposed ?%	0
Infections				
Skin, mucous membrane				
Bacterial	87/95.3/90%	81%	12%	10 cases
Viral	?	95%	22%	Yes
Candida	83/43.1/59%	95%	22%	No
Respiratory infections	87%/45.8%	91%	65%	Yes
Lung cyst formation	70%/74.6%	?	?	No
Musculoskeletal system	Yes	No	No	No
Joint hyperextensibility	70%/52.7%/?			
Minimal trauma fractures	65%/?/45%			
Scoliosis >10°	60%/26%/?			
Retention primary teeth	70%/80%/?			
Neoplasms				?
Squamous cell carcinoma	–	19%		
Lymphoma (a.o. CTCL)	5%/?/14%	+	18% [17] (preponderance of NHL)	
Burkitt lymphoma, microcystic adnexal carcinoma, perigastric leiomyoma		+		
Coronary vascular malformations	?/60%	?	none	None
Polyendocrinopathy, enteropathy	0%	0%	0%	10 cases

CTCL, cutaneous T-cell lymphoma; HIES, Hyper-IgE-syndrome; IPEX, immune dysregulation-polyendocrinopathy-enteropathy-X-linked syndrome; NHL, Non Hodgkin lymphoma; UKWPAD, United Kingdom Working Party diagnostic criteria for atopic dermatitis [15]; WAS, Wiskott–Aldrich syndrome.

allergy being the presenting symptom in 40.5% [23]. IgA-deficient patients with concomitant defects in specific antibody production have more recurrent infections and bronchiectasis than atopic dermatitis patients [23].

Other PIDs with associated eczema, increased serum IgE levels, and recurrent infections include Omenn syndrome [24], immune dysregulation-polyendocrinopathy-enteropathy-X-linked syndrome (IPEX; caused by mutations in the gene *FOXP3*) [18] and Comel–Netherton syndrome (caused by mutations in *SPINK5*).

Seven of 10 IPEX boys showed widespread atopic dermatitis: erythematous exudative or lichenified plaques evolving into exfoliative erythroderma in two [18] (for more details see Table 1).

Comel–Netherton syndrome is characterized by a skin-barrier defect, bamboo hairs, and often abnormalities of memory B-cells and NK cells. It often presents with erythroderma and failure to thrive. The erythroderma may evolve into eczematous

lesions with allergy hard to discern from atopic dermatitis.

MUCOCUTANEOUS CANDIDIASIS

The skin barrier is the first line of defense against fungi [25], and contains antimicrobial peptides. The defense, furthermore, relies on innate and adaptive immune mechanisms.

The IL17-producing TH17 subset of T lymphocytes plays an essential role in immunity [26], illustrated by various genetic defects in the development of TH17 cells in the case of increased susceptibility to *Candida* [27,28^{***}]. The role of IL-17 is implicated by the identification of IL-17R and IL-17F mutations in pedigrees with chronic mucocutaneous candidiasis (CMC) [27]. Mutations in signaling components (STAT3 and AIRE), known to be critical for the induction of Th17 responses in T cells, are also linked to *Candida* infection [29,30]. However, the innate pathways of defense against *Candida* spp.

remain enigmatic. Complement and also phagocytes contribute to the clearance of fungal infections, illustrated by invasive *Candida* infections in Chronic Granulomatous Disease (CGD), caused by defects in the NADPH oxidase enzyme complex needed for microbial killing, and by the positive effect of granulocyte transfusion in disseminated candidiasis [31^{***},32]. In CARD9-deficiency we identified a granulocyte defect in *Candida* killing (R.P. Gazendam and T.W. Kuijpers, in preparation), which seems to contribute more to the invasive nature of the fungal infection than a reduction in the numbers of TH17 cells [33].

In mucocutaneous fungal infections, not only IL-17 or IL-22, but also receptors recognizing components of fungi, contribute. When defects occur in either IL-reaction, or the receptors, CMC infections arise [31^{***}]. Moreover, TH17 cells help in defense against other extracellular pathogens (bacteria and some parasites). Impaired cellular immunity may cause CMC, whereas a defective innate immune

system (congenital neutropenia and neutrophil dysfunction) predisposes to systemic candidiasis [31^{***}].

The PIDs with CMC are lacking factors in the defense mechanisms outlined above (Table 2) [31^{***}].

Dectin-1 deficiency is only a very mild immunodeficiency, as described in a Dutch family with three affected sisters with a homozygous mutation in Dectin-1 showing recurrent vulvovaginal candidiasis, chronic onychomycosis, or both [34]. To date the mutation is considered a modulating factor also found in the healthy population.

The *STAT1* mutations of the coiled-coil domain of STAT1 cause fungal infections in another way, leading to a reduction in the normal inactivation of phosphorylated STAT1 dimers. The STAT1 coiled-coil mutations shift the immune response to inhibition of IL-17 and thus prevent TH17 generation, resulting in an autosomal-dominantly inherited susceptibility to serious fungal infections [34].

The overlap of the skin phenotype of fungal infections in PID does not allow a definite PID

Table 2. Primary immunodeficiencies associated with chronic mucocutaneous candidiasis

Disease	Molecular defect	Associated gene/transmission	Clinical picture
AD-HIES	Dominant-negative effect on multiple intracellular signaling pathways, including impaired generation of TH17 cells, and impaired intracellular signaling by receptors of IL-17 and 22.	STAT3, AD	Serious CMC, in particular fingernail, vaginal, and oral disease
APECED	Loss of tolerance, with persistence of autoreactive T cells, including the production of autoantibodies to cytokines (e.g., IL-17 and 22).	AIRE, AR	Serious CMC, usually arising within the first decade of life
SCID	Impaired generation of T cells, with or without accompanying B and NK lymphocytopenia.	IL2RG, X-linked; JAK3, AR; IL7R α , AR; CD3 δ , AR; CD3 ϵ , AR; RAG1, AR; RAG2, AR; ARTEMIS, AR; CD45, AR	CMC possible, perianal rash and thrush arise in the first few months of life
AR-HIES	Impaired T-cell activation, possibly impaired maintenance of memory Th17 cells or impaired formation of immunological synapse.	DOCK8, AR	Serious CMC
IL-12 and IL-23 deficiency	Impaired development of Th17 cells.	IL12B, AR; IL12RB1, AR	CMC but milder than in STAT3 deficiency
IL-17 deficiency	Impaired or abolished cellular responses to IL-17, due to either impaired production of or abolished response capacity to IL-17.	IL17F, AD; IL17RA, AR	Neonatal candidiasis, serious CMC
Dectin 1 deficiency [13]	Cell surface expression of the (mutated) receptor is lost, leading to impaired IL-6, IL-17 and TNF α on stimulation <i>in vitro</i> .	Dectin-1, AR	Increased susceptibility to vulvovaginal candidiasis and onychomycosis
CARD9 deficiency	Impaired function of signalosomes for dectin (dectin 1 and dectin 2) and other recognition molecules.	CARD9, AR	Severe or recurrent oral, vaginal candidiasis, dermatophytosis, invasive candidiasis (meningitis)
TYK2 deficiency	Adaptor molecule for several receptor complexes, including IL23 receptor.	TYK2, AR	Oral candidiasis
STAT1 mutations	The mutations in the coiled-coil domain of STAT1.	STAT1, AD	Severe CMC and dermatophytosis

Modified table from ref [31^{***}]. AD-HIES, autosomal dominant-Hyper-IgE-syndrome; AIRE, autoimmune regulator element; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; AR, autosomal recessive; CMC, chronic mucocutaneous candidiasis; SCID, severe combined immunodeficiency.

diagnosis, but systemic *Candida* infections point first at neutrophil problems.

BACTERIAL SKIN INFECTIONS

Bacterial skin infections are more prevalent in patients with congenital defects in phagocyte number, function, or both than in those with combined T-cell and B-cell immunodeficiencies; in other PIDs they occur too, but the difference from the phagocyte defects is not significant [3].

Deep skin infections (folliculitis or abscess formation) are presenting features in DOCK8 and STAT3-related HIES patients [3].

In an analysis of 429 patients with CGD [67% X-linked and 33% autosomal recessive (AR)] 17% showed skin abscesses and 5% furunculosis more than once in their lifetime [32].

In Leukocyte Adhesion Deficiencies (LADs), microbial inflammation instead of overt pustules and abscesses often leads to ulcerations that can be described as pyoderma gangrenosum [35,36]. LAD1 is an autosomal recessive disorder caused by the absence of the $\beta 2$ integrin subunit (CD18), causing impairment of neutrophil migration and activation [35]. Severe LAD1 (CD11/CD18 surface expression <1% of normal) is characterized by delayed separation of the umbilical cord, recurrent skin infections without pus formation, severe invasive infections, and abnormal wound healing. LAD-1-variant syndrome (also known as LADIII) is caused by a Kindlin-3 defect; this protein is required for the induction of integrin affinity changes for leukocyte and platelet adhesion upon cell activation [37]. In contrast to LAD1, a bleeding disorder coincides with and may dominate over the inflammatory and infectious events. However, the persistent mild-to-moderate leukocytosis, poor wound healing, and late detachment of the umbilical cord are eminent features in many cases.

In antibody deficiencies, most symptomatic patients present with ear, nose, throat, and airway and not with recurrent bacterial skin infections [38].

Recognizing a specific PID is hard by bacterial skin infections only, but, when the skin infection is the presenting symptom of the PID, HIES and congenital defects in phagocyte number, function or both are the first diseases to look for.

GRANULOMA FORMATION

Noninfectious granulomatous skin lesions in immunodeficient children are a rather frequently occurring enigma. Histopathology is helpful and infectious origin can be (culture, staining, and PCR) excluded. The granulomas can occur in ataxia

teleangiectasia, in Nijmegen breakage syndrome, in SCID [due to deficiency of RAG, Artemis, and Janus kinase 3 (JAK3)], in TAP-deficiency syndrome, Griscelli syndrome, and CVID [39].

In ataxia teleangiectasia, the granulomas present in patients from 1.5 to 31 years [39]. Interestingly, in 8% of the reported patients, the onset antedated the diagnosis and other features of ataxia teleangiectasia [39]. All had lesions on the limbs; additional granulomas occurred on the face and, in 25%, on the trunk. The granulomas (5–10 cm width) were well-defined, slowly enlarging, later scaly, erythematous-indurated papules and plaques, with central atrophy or ulceration [39]. The cause seems to be related to immune dysregulation, as suggested by a reduction of peripheral CD19⁺ B cells, a low number of CD3⁺CD4⁺CD45RA⁺ naive T cells in the presence of normal NK cells and γ/δ T cells [40].

Whether granuloma formation plays a role in the prognosis of ataxia teleangiectasia patients is not reported [41].

RAG-deficient patients with granulomas are immunologically different from other RAG-deficient patients [6]. They present at later age (around 3 years old) and the immunophenotype is T⁺ B⁺ NK⁺ with low for age lymphocyte numbers. Their granulomas show histopathological features of epithelioid and noncaseating granulomas; their immunopathogenesis is unclear [6].

Cutaneous granulomas in CVID occur commonly in adults and in one-third of the children, and are mainly located on the extremities, but the face and buttocks may be involved [42]. In CVID, the histopathology is sarcoid-like [43]. The pathogenesis of granulomas in CVID is unclear; HHV8 has been suggested as a cause [44] but not confirmed afterwards.

In 2% of CGD patients, aseptic granulomas of the skin occur [32], and their cause remains not well understood.

CONCLUSION

The skin is important in the presentation of PID. On the basis of the most characteristic skin symptoms described in PIDs, we reviewed the relation between skin phenotype and PID genotype. Eczematous lesions may be present in PIDs (Table 1). Especially in HIES induced by different genotypes (deficiency of STAT3 or DOCK8), the skin phenotype may be helpful to differentiate these two variants. In erythroderma, one should think of Omenn syndrome but not exclude SCID. A bacterial skin infection may be the presenting symptom of congenital defects in phagocyte number and function as well as of HIES.

Noninfectious granulomas are in particular found in CVID, in a subpopulation of RAG-deficient patients, in CGD and in ataxia teleangiectasia (sometimes as presenting symptom). To elucidate the pathomechanism of granulomas further research is needed.

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None.

Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 546).

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