

Skin Manifestations of Primary Immune Deficiency

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Abstract Cutaneous manifestations are common in primary immune deficiency diseases, affecting between 40 % and 70 % of patients with diagnosed primary immune deficiency. Skin infections characterize many primary immune deficiencies, but there are also frequent noninfectious cutaneous manifestations seen in many of these disorders, including eczematous lesions, erythroderma, cutaneous granulomas, dysplasia of skin, hair, and nails, autoimmune conditions, and frank vasculitis. For the patient with suspected primary immunodeficiency, much can be inferred by evaluating the presenting cutaneous findings, including various infectious susceptibilities, presence of atopy, and evidence of impaired or overactive inflammatory response. The skin manifestations of primary immune deficiency diseases are often early or heralding findings of the underlying immunologic disease. Therefore, awareness of associations between skin findings and immune deficiency may aide in the early detection and treatment of serious or life-threatening immunologic defects. This review summarizes the common skin manifestations of primary immune deficiency diseases and provides the reader with a differential diagnosis of primary immune defects to consider for the most common skin manifestations.

Keywords Immunologic deficiency syndromes · Infectious skin diseases · Chronic mucocutaneous candidiasis · Erythroderma · Chronic granulomatous disease · Ectodermal dysplasia

Introduction

Primary immunodeficiency diseases (PIDDs) result from mutations to one of the various genes needed for an intact immune system. To date, more than 185 distinct genetic defects leading to PIDD have been identified [1], and new

mutations continue to be elucidated. The *sine qua non* of PIDD is an increased susceptibility to infections; however, patients with PIDD also face a wide array of non-infectious complications involving multiple organ systems. The impact of PIDD on the skin is no exception. Skin infections are characteristic of many PIDDs, but there are also frequent noninfectious cutaneous manifestations seen in many of these disorders (Table 1).

Skin manifestations are common in PIDDs. In a series of 130 children with primary immunodeficiency, Berron-Ruiz et al. reported the presence of cutaneous alterations in 69 % of these patients [2]. Moin et al. described dermatologic abnormalities in 40.5 % of a series of 210 children with PIDD [3]. Al-Herz et al. identified skin manifestations in 48 % of 128 pediatric PIDD patients [4].

All three of these case series found cutaneous manifestations to be a common early presenting sign in PIDD, present in 32–55 % of patients at the initial time of their PIDD diagnosis [2–4]. Knowledge of skin findings in well-defined primary immunodeficiency diseases will aide in the timely recognition of this group of conditions where delays in diagnosis are common and can be associated with significant morbidity [5].

This review will summarize the skin manifestations commonly found in various primary immunodeficiency diseases.

Characteristic Skin Manifestations of PIDDs

The majority of the skin manifestations found in PIDDs are not pathognomonic for immunodeficiency and may be seen in patients with normal immunity as well. However, there are several skin findings that are so characteristic of a specific PIDD that an immunological workup could be considered essential.

Along with cerebellar ataxia and variable humoral and cellular immunodeficiency, patients with ataxia-telangiectasia develop oculocutaneous telangiectasias, which are best seen in the bulbar conjunctivae and the pinnae of the ear (Fig. 1).

Several autosomal recessive disorders are characterized by partial albinism in conjunction with immunodeficiency. These include Griscelli syndrome type 2 (*RAB27A* mutation),

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Table 1 Cutaneous manifestations of primary immunodeficiencies

Cutaneous manifestations
Skin infections
Bacterial
Fungal
Viral
Eczema
Erythroderma
Cutaneous granulomas
Dysplasia of skin, hair, and nails
Autoimmune/vasculitis
Other (telangiectasias, albinism)

Chediak-Higashi syndrome (*LYST* mutation), and Hermansky–Pudlak syndrome type 2 (*AP3B1* mutation). These patients exhibit skin hypopigmentation and have a silvery-grey sheen to their hair. The immune defect of Chediak-Higashi includes neutropenia and presence of giant lysosomes in neutrophils, along with impaired killing by NK cells and cytotoxic T cells [6]. Griscelli syndrome type 2 is associated with mild neutropenia with normal lysosomal size and impaired NK cell- and T cell-cytotoxicity [6, 7]. Patients with Hermansky-Pudlak syndrome type 2 display pronounced neutropenia and thrombocytopenia, along with impaired cytotoxicity by NK cells and cytotoxic T cells [8]. All three of these defects carry a risk of developing hemophagocytic lymphohistiocytosis [9, 10].

Eczematous Rashes in PIDDs

Eczema is a very common finding in the general pediatric population, with a prevalence estimated around 11 % [11]. It appears to be even more common in pediatric primary immunodeficiency populations, affecting between 13 % and 22 % of PIDD cohorts studied [2–4]. Non-specific eczema may be

found in many children with humoral immunodeficiencies, but severe eczema often presenting shortly after birth is characteristic of various diseases of immune dysregulation associated with eosinophilia and high peripheral immunoglobulin E (IgE) levels (Table 2).

Early onset, severe eczema is a shared feature of both autosomal dominant and autosomal recessive forms of hyper IgE syndrome (AD-HIES and AR-HIES, respectively). This often coincides with food allergy in patients with AR-HIES due to *DOCK8* mutation, while the eczema of AD-HIES (mutation in *STAT3*) is not commonly driven by specific food allergy [12, 13].

Wiskott-Aldrich syndrome (WAS) is an X-linked immunodeficiency caused by a mutation in the *WAS* gene. The clinical phenotype of WAS is described as a classic triad of thrombocytopenia with small platelets, eczema, and recurrent infections, though many WAS patients do not have all three classic features [14]. Eczematous rash is found in over 80 % of WAS patients [14], and petechiae from thrombocytopenia may be another cutaneous finding.

Males affected with immunodysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance syndrome, due to mutation in *FOXP3*, typically present during the first few months of life with severe eczema, diabetes mellitus and other autoimmune phenomenon, intractable diarrhea, and failure to thrive [15].

Hypomorphic mutations of various genes related to severe combined immunodeficiency (SCID) may lead to the expansion of an oligoclonal, abnormally activated T cell population, giving a clinical phenotype of Omenn syndrome (OS) [16]. While the initial cutaneous presentation of Omenn syndrome is most commonly described as erythroderma (see below), OS may present with a neonatal eczematoid rash. Omenn patients are anticipated to have impressive clinical findings in addition to their rash, including marked lymphadenopathy, hepatosplenomegaly, failure to thrive, eosinophilia, and severe opportunistic infections.

**Fig. 1** Telangiectasias on the ear of a child with ataxia-telangiectasia**Table 2** Primary immunodeficiencies with infantile eczema

Primary immunodeficiencies
Hyperimmunoglobulin-E syndrome
Autosomal dominant (STAT3 mutation)
Autosomal recessive (DOCK8 mutation)
Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome
Wiskott–Aldrich syndrome
Omenn syndrome
Comèl–Netherton syndrome

Comèl–Netherton syndrome is an autosomal recessive disorder caused by SPINK5 mutation, characterized by congenital ichthyosis, “bamboo hair,” atopic conditions (including atopic dermatitis) with high serum IgE levels and eosinophilia, and recurrent skin, respiratory, and gastrointestinal infections [17]. The immunologic defect in Comèl–Netherton syndrome includes reduced memory B cells, impaired specific antibody responses, and deficient NK-cytotoxicity [18].

Erythroderma in PIDDs

Erythroderma is defined as the involvement of greater than 90 % of the total body surface area with erythema and/or scaling [19]. A survey of erythroderma in infancy found 48 % of cases to be due to primary immunodeficiency [20]. Erythroderma has been associated with a relatively short list of specific primary immunodeficiencies.

The initial skin abnormality in infants with Comèl–Netherton syndrome has been described as a generalized exfoliative erythroderma [19, 21]. Diagnosis is often delayed in these patients until their characteristic short bamboo hair grows in. The erythroderma rash evolves in childhood into a distinct rash with serpiginous borders, “ichthyosis linearis circumflexa,” which is the classic rash of Comèl–Netherton syndrome [22]. Superimposed atopic dermatitis also commonly develops in children with Comèl–Netherton syndrome, which is discussed earlier in this review.

The classic rash of Omenn syndrome (due to hypomorphic mutations in various SCID genes) is an exfoliative erythroderma with an onset in the early neonatal period (Fig. 2). It is associated with diffuse alopecia, lymphadenopathy, hepatosplenomegaly, recurrent severe infections, and failure to thrive [23].

Infants with classic SCID mutations may develop graft-versus-host disease secondary to engraftment of transplacentally derived maternal T cells, or of T cells derived from transfusion of unirradiated blood products. The graft-versus-host-disease that develops in these SCID patients looks identical to the clinical picture of Omenn syndrome, including the cutaneous findings of erythroderma and alopecia [24, 25].

Autoimmune/Vasculitic Lesions in PIDDs

It is well described that patients with primary immunodeficiency have increased risk of immune dysregulation and autoimmune conditions. Autoimmunity involving the skin may develop in these patients, though it is relatively uncommon, present in 1–6 % of patients in published PIDD cohorts [2–4].

Patients with mutations in the genes for the early complement components, (C1, C4, C2) often present with a photosensitive malar rash and mucocutaneous vasculitis typical of



Fig. 2 Exfoliative erythroderma on the hand of an infant with Omenn syndrome due to hypomorphic *Artemis* (DCLRE1C) mutation

systemic lupus erythematosus, but they lack antibodies to double-stranded DNA [26] (Fig. 3).

Autoimmune dermatoses such as vitiligo and alopecia are present with increased prevalence in humoral immunodeficiencies, including common variable immunodeficiency [27, 28] and selective IgA deficiency [29], compared with the general population. Vitiligo and alopecia areata are also recognized autoimmune manifestations of autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) [30], a genetic disease of impaired immune tolerance due to mutation of the *AIRE* gene. Patient with APECED have autoreactive T cells and develop autoantibodies that initiate multiple autoimmune manifestations.



Fig. 3 Mucocutaneous vasculitis in a patient with C4 deficiency

WAS is associated with a striking prevalence of autoimmunity, as high as 70 % in retrospective cohorts [14, 31]. The underlying mechanisms of the immune dysregulation observed in WAS are still being elucidated [32]. Cutaneous autoimmune disease is relatively common in these patients, with over 20 % of WAS patients develop skin vasculitis [14, 31], most commonly manifesting as Henoch-Schoenlein purpura.

Granulomatous Skin Lesions in PIDDs

Chronic granulomatous disease (CGD) is characterized by inability of phagocytes to kill certain ingested microbes and is caused by any of several defects in the NADPH oxidase complex, which generates the microbicidal “respiratory burst.” CGD is associated with skin manifestations in 60–70 % of patients. While much of this skin disease is infectious and will be discussed later in this article, the skin may also be a site of the granulomatous lesions that occur in CGD. Skin granulomas are less common than granulomas of visceral organs in CGD, but when they are present, they are typically well-formed non-necrotizing granulomas with pigmented macrophages, making them histologically similar to the granulomas found in the bowel and other organs [33].

Multisystem granulomatous disease is also a well-documented complication of common variable immunodeficiency (CVID), occurring in 8–10 % of all CVID patients [34, 35]. CVID patients with low percentage of switched memory B cells have higher frequency of granulomatous disease, along with higher morbidity and early mortality compared with the general CVID population [36–38]. CVID patients with granulomatous disease are also more prone to autoimmune complications, especially immune cytopenias. While the lung is most commonly affected, cutaneous granulomas are also found frequently in CVID. The granulomas in CVID are well-formed, noncaseating lesions, mimicking sarcoid.

Dysplasia of Skin, Nails, or Hair in PIDDs

While the name “autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED)” suggests the involvement of a primary ectodermal dystrophy, it is now felt that the common dystrophic nail and hair findings are secondary to the infectious and autoimmune processes of APECED, such as candidal nail infections and autoimmune alopecia [39]. However, there are multiple well-defined primary immunodeficiencies that have a primary dysplasia of the skin, hair, or nails as a key feature (Table 3).

X-linked ectodermal dysplasia with immunodeficiency (XL-EDA-ID) is caused by hypomorphic mutations in *IKBK* (NEMO). Cutaneous manifestations include hypohidrosis/anhidrosis and hair abnormalities; the hair is often coarse and may be essentially absent (atrachosis) or sparse

Table 3 Primary immunodeficiencies with epidermal dysplasia

Primary immunodeficiencies
Ectodermal dysplasia with immunodeficiency
X-linked (NEMO deficiency)
Autosomal dominant
Cartilage hair hypoplasia
Dyskeratosis congenita
X-linked (Hoyeraal-Hreidarsson syndrome)
Autosomal recessive
Autosomal dominant
Papillon–Lefèvre syndrome

(hypotrichosis). The immunodeficiency of XL-EDA-ID involves susceptibility to mycobacterial infection and encapsulated bacterial infections, abnormal immunoglobulin production, impaired NK cytotoxicity, and variable T and B cell defects [40]. The less commonly seen autosomal-dominant ectodermal dysplasia with immunodeficiency (AD-EDA-ID) is caused by a gain-of-function mutation in *IKBA*. While the cutaneous manifestations of AD-EDA-ID are similar to those of XL-EDA-ID, the immune defect seen in the autosomal dominant form is more specifically a T cell impairment [41].

Cartilage hair hypoplasia (CHH) is a form of short-limbed dwarfism due to autosomal recessive mutation in the *RMRP* gene, most often described in Amish and Finnish populations. Patients with CHH may present with a variable degree of immunodeficiency. Cellular immune impairment is found in 80 % of subjects [42], including multiple patients with severe combined immunodeficiency due to the *RMRP* mutation. The cutaneous manifestation of CHH is hair dysplasia; these patients have very fine, light-colored, sparse hair, but not all CHH patients have the classic hair morphology, with some having normal hair.

Dyskeratosis congenita (DKC) is a premature aging syndrome associated with short telomeres. DKC is a genetically heterogeneous disorder, with possible autosomal recessive, autosomal dominant, and X-linked inheritance. Currently, mutations in eight different genes (*DKC1*, *TERC*, *TERT*, *NOP10*, *NHP2*, *TINF2*, *CTC1*, and *TCAB1*) have been shown to cause DKC; the X-linked form of DKC due to *DKC1* mutation is the most common form of the disease.

DKC is classically defined by a triad of abnormal skin pigmentation, nail dystrophy, and leukoplakia of the oral mucosa, though not all three of these signs are always present. The cutaneous manifestations of DKC include abnormal skin pigmentation, most often manifesting as a lacy, reticular pigmentation of the neck and chest, and dysplastic fingernails and toenails. The changes in skin pigmentation may become more pronounced with age. Dysplasia of the fingernails and toenails may worsen significantly over time so that

nails may eventually “disappear.” Hyperhidrosis is also noted in some individuals with DKC, and abnormal eyelash growth may occur, including sparse eyelashes, trichiasis (misdirected eyelash growth), and ectropion or entropion of eyelids [43, 44].

The immune dysfunction in DKC is related to a progressive bone marrow failure, which occurs in over 80 % of cases. Hoyeraal-Hreidarsson syndrome is a severe variant of X-linked DKC and may present as a T+B-NK-combined immunodeficiency in infancy, combined with cerebellar hypoplasia and aplastic anemia, before any of the classic cutaneous DKC manifestations of DKC appear [45].

Papillon-Lefèvre syndrome is a rare autosomal recessive form of palmoplantar ectodermal dysplasia, with cutaneous manifestation of palmar/plantar hyperkeratosis. Papillon-Lefèvre syndrome is caused by mutation in the gene encoding cathepsin C, leading to impaired neutrophil chemotaxis. These patients develop severe periodontal disease, with loss of teeth, as well as increased susceptibility to other pyogenic infections including staphylococcal skin abscesses [46].

Skin Infections in PIDDs

Bacterial Infections

Pyogenic infections of the skin are one of the most common cutaneous findings in patients with primary immunodeficiencies. Bacterial skin infections, including folliculitis, abscesses, furunculosis, and impetigo, are a common finding in patients with abnormalities in phagocytic number or function [4]. These include, but are not limited to, congenital neutropenias due to mutations in ELANE and HAX1, CGD, and leukocyte adhesion deficiency (LAD).

Recurrent bacterial skin infections are common in untreated CGD. The most frequent causative organism is *Staphylococcus aureus*, but skin infections with other *Staphylococcus* species, *Serratia*, *Klebsiella*, *Escherichia coli*, *Pseudomonas*, *Enterococcus*, *Chromobacterium*, *Enterobacter*, *Nocardia*, and *Salmonella* are also seen [47]. Dermatitis is often one of the earliest presenting features of the chronic granulomatous disease. This infantile dermatitis represents an infectious periorificial process rather than classic infantile eczema [48].

In leukocyte adhesion deficiency type 1 (LAD1), which is due to a mutation in the gene encoding the $\beta 2$ -integrin subunit, infectious dermatologic findings include recurrent cutaneous abscesses and pyoderma gangrenosum due to infections with *S. aureus*, *Serratia*, *Klebsiella*, *Enterobacter*, *Proteus*, and *Pseudomonas aeruginosa* [49–51]. Skin infections in LAD1 are characterized by a poor inflammatory response, due to the inability of neutrophils to enter the infected tissue from the peripheral circulation (Fig. 4). Patients with leukocyte adhesion deficiency types 2 and 3 also have defective neutrophil recruitment to sites of infection



Fig. 4 *Serratia* abscess with absent pus formation in a patient with leukocyte adhesion deficiency type 1 (Courtesy of Dr. Steven M. Holland, National Institute of Allergy and Infectious Diseases, National Institutes of Health)

and are susceptible to similar cutaneous infections as those seen in patients with LAD1.

Skin abscesses in autosomal dominant hyper IgE syndrome (AD-HIES) are most often caused by *S. aureus*. Skin infections in AD-HIES are often characterized as “cold abscesses,” with minimal inflammation and less tenderness than expected of typical staphylococcal abscesses [52]. Similar to the autosomal dominant form, autosomal recessive hyper IgE syndrome due to DOCK8 mutation carries an increased susceptibility to staphylococcal skin abscesses [53].

Mutations in genes involved in the IFN- γ /IL-12 signaling axis, including IFNGR1, IFNGR2, IL12B, IL12RB1, and Stat1, lead to the clinical phenotype of “Mendelian susceptibility to mycobacterial diseases” (MSMD). These patients are susceptible to disseminated mycobacterial infections, and cutaneous mycobacterial lesions may be one component of their widespread disease. Patients with MSMD are also at risk of developing disseminated or localized cutaneous BCGosis after BCG vaccination [54]. BCGosis has also often been described in severe combined immunodeficiency [54, 55]. In chronic granulomatous disease, localized cutaneous BCGosis is common, though disseminated disease is rare [56].

Fungal Infections

Infections with *Candida* species are the most common fungal infections seen in patients with PIDD [2], specifically those in with impairment in Th17-mediated immunity [57] (Table 4). Persistent and difficult-to-treat mucocutaneous candidiasis during infancy may be a presenting sign of T cell deficiency, including SCID and DiGeorge syndrome, though in these patients, candidiasis is only one of a variety of infectious susceptibilities.

Table 4 Primary immunodeficiencies with candidiasis

Primary immunodeficiencies
T cell/combined immunodeficiencies
Severe combined immunodeficiency
DiGeorge syndrome
Hyperimmunoglobulin-E syndrome
Autosomal dominant (STAT3 mutation)
Autosomal recessive (DOCK8 mutation)
IL-17RA mutation
IL-17F mutation
Dectin-1 deficiency
CARD9 defect
STAT1 gain-of-function mutation
Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED)

Candidiasis presenting in conjunction with eczema and skin infections with *S. aureus* occurs in patients with AD-HIES. Candidiasis is also a feature of autosomal recessive hyper-IgE syndrome due to DOCK8 mutation [58].

Isolated susceptibility to mucocutaneous candidiasis is a feature of several recently described abnormalities of the IL-17 pathway (IL-17RA mutation and IL-17 F mutation) [59], as well as of Dectin-1 deficiency [60]. Gain-of-function mutations in STAT1 also result in a phenotype of chronic mucocutaneous candidiasis, related to impaired IL-17 and IL-22 production in affected patients [61, 62].

CARD9 deficiency presents with mucocutaneous candidiasis, fungal dermatophytosis, and invasive candida meningoencephalitis [63, 64]. The CARD9 protein product has been shown to function in anti-fungal immunity as a transducer of Dectin-1 signaling, and CARD9-deficiency patients have decreased IL-17-secreting cells [64].

Candidiasis in patients with autoimmune endocrinopathies is associated with APECED, caused by mutations in the autoimmune regulator (*AIRE*) gene that regulates self-tolerance. Mucocutaneous candidiasis is often the first manifestation of APECED and is the most frequent finding as well [30]. Patient with APECED have autoreactive T cells and develop autoantibodies that initiate autoimmunity, including neutralizing antibodies against the Th17 cytokines, IL-17A, IL-17 F, and IL-22, which is believed to be the reason CMC is a feature of APECED [65].

Patients with CGD are particularly susceptible to aspergillus infections. Pulmonary and disseminated aspergillosis

are most frequently seen, though necrotizing aspergillus skin lesions have been reported [66].

Viral Infections

While not as common as bacterial or fungal skin infections, cutaneous viral infections can be a feature of certain immune deficiencies. When present, these viral infections are generally more widespread and recalcitrant compared with the clinical course in individuals with intact immunity.

The presence of cutaneous viral infections is a distinguishing feature of AR-HIES due to DOCK8 mutation when compared with classic, autosomal-dominant HIES. Patients with DOCK8 mutation may experience extensive cutaneous infections with molluscum contagiosum, herpes zoster, and HSV, as well as subsequent malignancies related to these long-standing viral infections [67].

Herpesvirus infections (herpes simplex virus, Epstein-Barr virus, cytomegalovirus, varicella-zoster virus) may present with cutaneous lesions in patients with T cell deficiencies and with NK-cell deficiencies. However, infection will rarely remain isolated to the skin in these susceptible patients who are at high risk of disseminated, multi-organ disease when infected with herpesviruses.

Human papillomavirus (HPV) can cause chronic or severe warts in certain immunodeficiencies. Patients with epidermodysplasia verruciformis, caused by mutations in EVER1 or EVER2, have abnormal susceptibility to HPV and develop disseminated verrucous lesions with a high potential for malignant transformation [68]. Chronic papillomavirus infections are also a feature of WHIM syndrome (warts, hypogammaglobulinemia, infections, myelokathexis), which is due to a gain-of-function mutation in CXCR4 [69]. Due to the presence of neutropenia and hypogammaglobulinemia, patients with WHIM syndrome have frequent bacterial infections in addition to warts.

Conclusion

Many PIDDs have cutaneous features. These may be some of the earliest signs of an underlying immunodeficiency. The skin can often serve as a “window,” giving the physician a glimpse into the underlying disease state. We can learn much by carefully observing the skin disease of patients with suspected primary immunodeficiency, including infectious susceptibilities, presence of atopy, and evidence of impaired or overactive inflammatory response. Awareness of associations between skin findings and immunodeficiency diseases may lead to early detection and treatment of serious or life-threatening immunologic defects.

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