



Review Article

# Cutaneous manifestations in primary immunodeficiency diseases

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Received : 13 October 2020  
Accepted : 09 November 2020  
Published : 14 October 2021

DOI:  
[10.25259/JSSTD\\_48\\_2020](https://doi.org/10.25259/JSSTD_48_2020)

Quick Response Code:



## ABSTRACT

Primary immunodeficiency diseases (PID) or inborn errors of immunity are a group of inherited disorders characterized by defects in components of innate and/or adaptive immunity. Cutaneous manifestations are common in PIDs. The cutaneous manifestations are often the presenting symptoms which help in the diagnosis. Patients with PID are more prone to recurrent, unusual, prolonged or severe infections, and often these infections involve the skin. PID patients may also manifest non-infectious cutaneous signs such as eczema/erythroderma, granulomas, urticaria, vasculitis, and autoimmune skin diseases due to immune dysregulation. Certain PIDs also have specific cutaneous features such as telangiectasia and silvery sheen of hair. Although individual immunodeficiency syndromes are rare, the PIDs as a whole are not uncommon. This review article gives a summary of the common cutaneous manifestations in PID with a focus on the clinical clues for diagnosis.

**Keywords:** Primary immunodeficiency, Cutaneous manifestations, Hyper IgE, Chronic granulomatous disease, Leukocyte adhesion deficiency

## INTRODUCTION

Primary immunodeficiency diseases (PIDs), now called inborn errors of immunity,<sup>[1]</sup> are a heterogeneous group of inherited disorders characterized by defects in components of innate and/or adaptive immunity. A health survey in people of all ages in the United States reported a population prevalence of 1 in 1200 of diagnosed PID.<sup>[2]</sup> Abnormalities in humoral immunity account for more than 50% of PIDs.<sup>[3]</sup> T-cell anomalies account for fewer PIDs but are considerably more severe than defects in humoral immunity and are often fatal.<sup>[4]</sup> Several immunodeficiencies are associated with cutaneous manifestations and the skin being a readily accessible and easily assessable organ may provide clues to diagnosis of PIDs. This review provides a summary of the common cutaneous manifestations of PIDs with a focus on the clinical clues which help in diagnosis.

## CUTANEOUS MANIFESTATION OF PIDS

Patients with PID often present in early childhood, with cutaneous lesions as concerning signs. Moin *et al.* reported cutaneous lesions in 31.8% of children with PIDs which preceded and were the basis of the diagnosis of the underlying immunodeficiency.<sup>[5]</sup> About 48% of the 128 pediatric patients with PIDs had skin manifestations and those manifestations were the presenting features in 39% of total PIDs studied by Al-Herz *et al.*<sup>[6]</sup>

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Defects in the immune system render patients with PID more prone to recurrent, unusual, prolonged or severe infections and often these infections involve the skin. PID patients may also manifest non-infectious cutaneous signs such as eczema/erythroderma, granulomas, urticaria, vasculitis, and autoimmune skin diseases due to immune dysregulation and specific cutaneous features such as telangiectasia and silvery sheen of hair.

Of the 90 PID patients studied by Berron-Ruiz *et al.*, 69% had skin infections,<sup>[7]</sup> 29% had eczema-dermatitis, and 44% had other associated cutaneous conditions. Similarly, skin infections (30%) were the most prevalent cutaneous manifestation, followed by eczemas (19%), erythroderma (7%), diffuse alopecia (7%), telangiectasia (6%), and autoimmune skin diseases (6%) in the study by Al-Herz *et al.*<sup>[6]</sup> The summary of cutaneous manifestations serving as warning signs of specific PIDs are listed in [Table 1]. Table 2 shows the PIDs with cutaneous features grouped according to the defects in immunity.

## INFECTIONS

There are several published lists which consider the frequency of various types of infection as a warning sign of immunodeficiency. However, Costa-Carvalho *et al.* opined that the type of infection, the circumstances under which infections occur, and the organs and tissues affected (rather than the exact numbers of different infections or special definitions of severity) serve as a more effective differentiating clue to identify PIDs. In addition to repeated or severe infections, an infection with a pathogen of low pathogenicity, infection with an uncommon organism, concomitant presence of non-infectious features commonly

associated with PID or a positive family history should alert to the possibility of PID.<sup>[8]</sup>

### Bacterial infections

Al-Herz *et al.* found bacterial skin infections to be significantly more prevalent in patients with congenital defects of phagocytes, hyper-IgE syndrome, and Wiskott-Aldrich syndrome (WAS) than in those with combined T- and B-cell immunodeficiencies or predominant antibody deficiencies.<sup>[6]</sup>

Phagocytic deficiency disorders include congenital neutropenia, chronic granulomatous disease (CGD), leukocyte adhesion deficiency (LAD), and Chediak-Higashi syndrome (CHS).<sup>[9]</sup>

CGD is characterized by mutation of one of the several components of the nicotinamide adenine dinucleotide phosphate-reduced form (NADPH) oxidase complex that results in phagocytic inability to create the reactive oxygen metabolites that are necessary to destroy the microbes they have ingested. Staphylococcal abscesses were the most common cutaneous infection observed in a cohort of CGD patients.<sup>[10]</sup> Other organisms causing cutaneous abscesses were *Serratia*, *Aspergillus*, *Klebsiella*, and *Candida* spp. *Pneumonia*, suppurative adenitis, liver abscesses, and osteomyelitis were the other common types of infections.<sup>[10]</sup> A dermatitis predominantly involving the eyelids and periorbital skin, nares, perioral skin, and ears with associated chronic blepharoconjunctivitis and a serosanguineous nasal discharge has been often described in CGD, which represents an infectious periorificial process rather than classic infantile eczema.<sup>[11]</sup> Non-infectious manifestations such as granulomatous colitis, inflammatory lung disease, and autoimmune diseases such as systemic

**Table 1:** Cutaneous manifestations serving as warning signs of specific PIDs.<sup>[8]</sup>

| Cutaneous manifestation                                  | Associated PID   |
|--|--|
| Eczema   | Wiskott-Aldrich syndrome (WAS)<br>Hyper IgE syndrome (HIES)<br>Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX)<br>Severe combined immunodeficiency (SCID) |
| Cutaneous lesions by Mycobacteria                        | Combined immunodeficiencies<br>Hyper-IgM syndromes<br>Mendelian susceptibility to mycobacterial diseases (MSMD)<br>Chronic granulomatous diseases (CGD)                                  |
| Partial albinism, gray hair                              | Chediak-Higashi syndrome<br>Griscelli syndrome   |
| Telangiectasias  | Ataxia-telangiectasia  |
| Disseminated viral infections (warts, molluscum, herpes) | Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome<br>Dedicator of cytokinesis 8 (DOCK8) deficiency<br>Idiopathic CD4 lymphopenia                               |
| Fragile hair, conic teeth                                | Ectodermal dysplasia   |

PID: Primary immunodeficiency syndrome

**Table 2:** PIDs with cutaneous features grouped according to defects in immunity.

|   |
|---|
| Disorders of adaptive immunity  |
| Hyper IgE syndrome  |
| Severe combined immunodeficiency                                      |
| Omenn syndrome  |
| Wiskott-Aldrich syndrome  |
| Ataxia Telangiectasia   |
| Disorders of innate immunity  |
| Chronic granulomatous disease   |
| Leucocyte adhesion deficiency   |
| Chediak Higashi syndrome  |
| Mendelian susceptibility to mycobacterial diseases                    |
| Natural killer cell disease   |
| Disorders of immune dysregulation                                     |
| Autoimmune Polyendocrinopathy Candidiasis and Ectodermal Dysplasia    |
| Immune dysregulation-polyendocrinopathy-enteropathy-X-linked syndrome |
| PID: Primary immunodeficiency syndrome                                |

lupus erythematosus, discoid lupus erythematosus, granulomatous acne, inflammatory cutaneous nodules, and poor wound healing have been reported in CGD.<sup>[12]</sup> Specialized blood tests, such as the nitro blue tetrazolium test or flow cytometry with dihydrorhodamine, detect the abnormal intracellular bactericidal activity and thus help in diagnosis.

The genetic defects in leukocyte adhesion deficiencies (LAD) affect the different steps of the leukocyte recruitment process from the intravascular compartment to the site of infection, inflammation or injury, which is a critical step in the response of the innate immune system. LAD type-1 due to a defective  $\beta$ -2 integrin subunit is the most common form of LAD. Delayed umbilical cord separation is one of the first signs of the disease. Severe infections can occur during infancy. The absence of pus formation in lesions is a characteristic clinical marker of LAD.<sup>[13]</sup> A marked peripheral blood leukocytosis is consistently observed during infections, but the skin biopsies demonstrate inflammation devoid of neutrophils. Another feature is impaired and slow wound healing resulting in high mortality rates in infancy.<sup>[14]</sup>

CHS is an autosomal recessive disorder characterized by variable degrees of oculocutaneous albinism and recurrent skin and pulmonary infections in infancy due to *Staphylococcus* and *Streptococcus*. Neutropenia, impaired chemotaxis and bactericidal activity, and abnormal NK cell function are the immune dysfunctions noted. Deficient platelet dense bodies result in easy bruisability and bleeding. The hallmark of CHS is the presence of huge cytoplasmic azurophilic granules in circulating granulocytes and many other cell types.<sup>[15]</sup>

Bacterial skin infections are also a prominent feature of the hyper-IgE syndromes, which may be autosomal dominant (due to Signal transducer and activator of transcription 3 [STAT3] deficiency, previously called Job's syndrome – AD HIES) or autosomal recessive (due to Dedicator of Cytokinesis 8 [DOCK8] deficiency – AR HIES). Recurrent folliculitis and abscess formation were observed in 87%–100% of patients with hyper-IgE syndrome and were consistent findings in these patients on follow-up examination.<sup>[6,16]</sup> A peculiar tendency of the abscesses to localize about the scalp, face, and neck was observed in infants and younger children by Buckley.<sup>[17]</sup> “Cold” abscesses with minimal signs of characteristic inflammation which are typically observed in patients not on antibiotic prophylaxis are pathognomonic of the hyper-IgE syndrome but are not necessary for a definitive diagnosis.<sup>[18]</sup> Other manifestations include pneumonias caused by *S. aureus*, *H. influenza*, and *Streptococcus* complicated by lung abscesses, bronchiectasis, bronchopleural fistula, and pneumatocoles.<sup>[18]</sup>

Infections with certain bacteria have been reported more frequently with different types of immune deficiency. Pyogenic encapsulated bacteria (*Streptococcus pneumonia* and *H. influenza*) are frequently seen in antibody or complement deficiencies.<sup>[8]</sup> Recurrent neisserial infection is a characteristic manifestation of late complement component (C5-9, or the membrane attack complex) defects.<sup>[19]</sup> Disseminated mycobacterial infections are characteristic of defects in interleukin-12, interferon gamma, or their receptors,<sup>[19]</sup> the clinical phenotype is referred to as the “Mendelian susceptibility to mycobacterial diseases” (MSMD).<sup>[20]</sup> MSMD patients may also develop disseminated or localized cutaneous BCGosis after BCG vaccination.<sup>[21]</sup> Agammaglobulinemic patients and, to a lesser extent, patients with common variable immunodeficiency (CVID) have an increased risk of developing bloodstream bacterial infections.<sup>[22]</sup> X-linked agammaglobulinemic patients have a peak incidence of onset at 6 months of age, probably due to the decline in the maternally acquired antibodies. However, patients may remain asymptomatic even up to the age of 5 years. The age of onset of symptoms shows a biphasic distribution in common variable immunodeficiency, with peaks at 1–5 and 16–20 years.<sup>[23]</sup>

**Fungal infections**

Innate immune response forms the first-line defense against fungal infection. Although acquired immunodeficiencies are more likely to manifest as unusual fungal infections, an increasing number of PIDs are being reported as the underlying cause for fungal infections.

Chronic mucocutaneous candidiasis (CMC) is characterized by persistent or recurrent candidal infections of the mouth,

esophagus, digestive or genital mucosa, nails and/or skin, mostly with *C. albicans*.

Patients with defects in T-cell number or function (TH17 cells) such as severe combined immunodeficiency (SCID), combined immunodeficiencies (CIDs), and Di George syndrome have difficulty in eradicating *Candida* infections. In these patients, other opportunistic infections are also seen due to the absence of other T-cell subsets.<sup>[9,24,25]</sup>

CMC manifests as a common clinical presentation (in addition to other features) in AD-HIES, MSMD and caspase recruitment domain-containing protein 9 (CARD9) deficiencies. In all three, the susceptibility occurs due to defects in signaling pathway involved in IL-17 producing T-Cell development and maturation.<sup>[25]</sup> Patients with CARD9 mutations appear to have significantly impaired antifungal immunity which makes them susceptible to deep dermatophytosis and other invasive fungal infections.<sup>[26]</sup>

Autoimmune polyendocrinopathy candidiasis and ectodermal dysplasia (APECED) is a complex syndrome with mucocutaneous candidiasis as the main infectious feature.<sup>[24]</sup> APECED occurs due to mutations in the autoimmune regulator gene. Chronic *Candida* infection in early childhood is often the first sign of APECED. The initial description included a triad of CMC, hypoparathyroidism and adrenal insufficiency. Later, additional autoimmune manifestations in the skin and other organs were found to be common and expanded diagnostic criteria have been proposed, adding an adjunct triad of urticarial eruption, intestinal dysfunction, and enamel hypoplasia.<sup>[27]</sup> The presence of various autoantibodies is characteristic of APECED leading to various clinical findings. The ectodermal manifestations associated with APECED include vitiligo, alopecia, keratoconjunctivitis, dental enamel hypoplasia, nail dystrophy, and tympanic membrane calcification.<sup>[24]</sup>

Genetic analysis of patients affected with CMC suggests that IL-17 immunity plays a critical role in defense against *Candida* infections. Defects in the IL-17 pathway alone have been shown to be an underlying cause, when CMC occurs without other obvious immune defects clinically. These include STAT 1 gain of function missense mutations, complete AR IL-17RA and partial AD IL17F deficiencies, ACT1 mutation, and RORC (Retinoic acid related orphan receptor C) mutations.<sup>[9,24,25]</sup> CMC is also seen in Dectin-1 mutations, a pattern recognition receptor on antigen-presenting cells.<sup>[9]</sup>

CNS infections with *Candida* have been observed in CGD and CARD9 deficiency. Invasive aspergillosis can occur in CGD and AD-HIES patients with lung cavities. Cryptococcosis should prompt evaluation for autoantibodies against GM-CSF or against IFN- $\gamma$ . Infection with dimorphic fungi should raise the suspicion of IL-12R $\beta$ 1 deficiency,

IFN- $\gamma$ R1 deficiency, and STAT1 GOF mutation. The probability of T-cell disorders, such as SCID and CD40 ligand deficiency, to be considered when pneumocystosis is diagnosed.<sup>[25]</sup>

### Viral infections

Compared to bacterial and fungal skin infections, viral skin infections are less common manifestations in PIDs, unlike in acquired immunodeficiencies.

Recurrent, severe herpes simplex or herpes zoster infections; extensive and persistent infections with molluscum contagiosum; and human papillomavirus infections along with other features have been described in DOCK8 deficiency but not commonly in AD-HIES.<sup>[28]</sup>

Natural killer (NK) cells are part of the innate immune defense against infections and cancers and are especially useful in combating certain viral pathogens. Severe VZV infection, CMV, EBV, HSV, and unusual consequences of HPV infection have been reported in Classical NK cell deficiency (CKND) disease. In the GATA deficiency caused CNKD, HPV infection manifests the main infectious phenotype in the first decade of life.<sup>[29]</sup>

Epidermodysplasia verruciformis occurs due to mutations in EVER1 and EVER2 and develop benign, flat, wart-like papules, or plaques along with verrucous lesions with malignant potential over sun exposed areas. Other PIDs with warts as a manifestation include WHIM syndrome (warts, hypogammaglobulinemia, infections, and myelokathexis), idiopathic CD4 Lymphopenia, WILD syndrome (wart, immunodeficiency, lymphedema, and dysplasia), MST 1 deficiency, and Netherton Syndrome.<sup>[30]</sup>

### ECZEMA

Eczematous skin lesions are the second most common cutaneous manifestation in PID with a reported prevalence between 13% and 22% in pediatric PID patients.<sup>[5,7]</sup> About 100% of patients with Hyper-IgE syndromes and Wiskott-Aldrich syndrome studied by Al-Herz *et al.* had eczematous skin rashes.<sup>[6]</sup> Other PIDs in which eczematous dermatitis commonly occur are Netherton's syndrome, SCID, Omenn syndrome, immune dysregulation-polyendocrinopathy-enteropathy-X-linked (IPEX) syndrome, hyper-IgM syndrome, selective IgA deficiency, CVID, and ataxia telangiectasia (AT). In most cases, the presentation of eczema is similar to those in normal individuals but they tend to become secondarily infected, be widespread and remain unresponsive to conventional treatment. The patterns of dermatitis include atopic, seborrheic, perioral, ichthyosiform, or non-specific.<sup>[5]</sup>

AD-HIES patients often have a pruritic dermatitis that is not typical atopic dermatitis, and respiratory allergic



symptoms are usually absent.<sup>[17]</sup> Patients often have an early onset (in the 1<sup>st</sup> week/month of life) papulopustular eruption that begins on the face and scalp, but which can become generalized.<sup>[31,32]</sup> Scaling and lichenification may develop over time.<sup>[33,34]</sup> Recurrent staphylococcal infections are characteristic of the diseases and have been described previously. The serum IgE levels are greater than 2000 IU/ml in the majority of cases, although normal IgE levels are seen occasionally.<sup>[18]</sup> Facial features such as facial asymmetry, bulbous nose, prominent chin, high arched palate, and retained primary teeth and skeletal features such as scoliosis have been observed.<sup>[16]</sup> Vascular abnormalities such as aneurysms are present in many individuals with AD-HIES, increasing the risk of brain and cardiac infarcts in this cohort.<sup>[35]</sup>

In AR-HIES or DOCK8 deficiency, the dermatitis is similar to atopic dermatitis in distribution and appearance, often lacking the pustular eruption noted in AD-HIES. There is an increased occurrence of severe food allergies and asthma in AR-HIES, in contrast to AD-HIES patients. They also appear to have an increased predisposition to malignancies including lymphomas and cutaneous squamous cell carcinomas. Musculoskeletal and dental abnormalities are rarely identified in AR-HIES.<sup>[36]</sup>

Wiskott-Aldrich Syndrome (WAS) is an X-linked immunodeficiency caused by mutations in the WAS gene resulting in decreased T cell number and activity, decreased NK cell activity, reduced phagocyte function, thrombocytopenia with small platelets, and altered antibody responses.<sup>[37]</sup> The classically described triad of clinical features is thrombocytopenia with small platelets, recurrent infections, and eczematous dermatitis, but only 50% of the patients have this characteristic triad.<sup>[38]</sup> The eczematous dermatitis that commonly manifests in the 1<sup>st</sup> month of life is refractory and does not meet the clinical criteria of atopic dermatitis.<sup>[6,38]</sup> The platelet abnormalities lead to petechiae and ecchymoses in the areas of dermatitis. Other features of a bleeding diathesis including life-threatening intracranial or gastrointestinal hemorrhage can occur.<sup>[39]</sup> Infectious complications of WAS typically manifest after 3 months of age when passive immunity from the maternal antibodies wanes.<sup>[37]</sup>

Netherton syndrome (NS) is a rare, autosomal recessive genodermatosis caused by alterations in the serine protease inhibitor Kazaltype-5 (SPINK5) gene.<sup>[37]</sup> NS is characterized by the triad of congenital ichthyosiform erythroderma (CIE), trichorrhexis invaginata or “bamboo hair,” and a predisposition to atopy including reactive airway disease, allergic rhinitis, urticaria, and food allergy. As the child grows older, the dermatitis evolves into migratory, annular, serpiginous or polycyclic patches, and plaques with a doubled-edged scale, referred to as ichthyosis linearis circumflexa.<sup>[40]</sup>

IPEX syndrome is characterized by a classic triad of intractable diarrhea secondary to autoimmune enteropathy, autoimmune endocrinopathy, and eczematous dermatitis.<sup>[41]</sup>

## INFANTILE ERYTHRODERMA

Though it is a presenting feature of more common dermatoses, erythroderma in the 1<sup>st</sup> year of life can be a rare, early potential manifestation of PID.<sup>[37]</sup> In retrospective cohort studies, an underlying PIDD such as Omenn syndrome, SCID, or Wiskott Aldrich Syndrome (WAS) was associated with neonatal erythroderma in 5%–30% of cases.<sup>[42,43]</sup> Cutaneous findings such as severe pruritus, indurated and thickened skin, exaggeration of skin folds, and loss of eyebrows and eyelashes are suggestive of an underlying immunodeficiency. Systemic features such as diarrhea, failure to thrive, invasive infections due to rare or opportunistic pathogens, and cytopenias in an erythrodermic baby should prompt evaluation for a PID.<sup>[42]</sup> The histological features of spongiosis, epidermal lymphocytic exocytosis with keratinocyte necrosis and an extensive dermal infiltrate on skin biopsy is consistent with an underlying immunodeficiency.<sup>[44]</sup>

## GRANULOMATOUS SKIN REACTIONS

Non-infectious cutaneous granulomas were observed in 2% of PIDs by Nanda *et al.*<sup>[45]</sup> These can be observed in CGD, CVID (8%–20%), AT, SCID, Nijmegen breakage syndrome, cartilage hair hypoplasia, X-linked hypogammaglobulinemia, WAS, Griscelli syndrome, and Hermansky Pudlak syndrome.<sup>[9,12]</sup>

## AUTOIMMUNE MANIFESTATIONS

Diseases with an autoimmune etiological basis such as vitiligo, alopecia, SLE/DLE, vasculitis, and thyroid disease have been reported in partial C4 deficiency, APECED, WAS, CVID, selective and partial IgA deficiency, AT, AD-HIES, Griscelli syndrome, and STAT 1 GOF mutations.<sup>[24,27,46]</sup>

## URTICARIA/ANGIOEDEMA

Urticaria and angioedema are significant manifestations of complement deficiencies.<sup>[6]</sup> Urticarial eruption has been added as one of the extended triad of APECED.<sup>[27]</sup> Familial cold urticaria in phospholipase C $\gamma$ 2 associated antibody deficiency and immune dysregulation (PLAID), and vibratory urticaria due to ADGRE2 mutations affecting mast cell function and urticarial manifestations in autoinflammatory syndromes such as familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal onset multisystem inflammatory syndrome (NOMID) are other instances of urticaria in PID.<sup>[47]</sup>

## SPECIFIC CUTANEOUS FEATURES

### Dysplasia

Abnormal development of skin, hair, nails, and teeth along with immunological abnormalities can occur in ectodermal dysplasia with immunodeficiency (EDA-ID), cartilage hair hypoplasia, dyskeratosis congenita, Papillon-Lefevre syndrome, and APECED syndrome.<sup>[48-51]</sup>

### Partial albinism/silvery grey hair

Variable degree of oculocutaneous albinism is observed in CHS, Hermansky-Pudlak syndrome (HPS), and Griscelli syndrome.<sup>[15,52,53]</sup> HPS is an autosomal recessive disorder that is associated with oculocutaneous albinism, bleeding diathesis, granulomatous colitis, and highly penetrant pulmonary fibrosis in some subtypes.<sup>[52]</sup> Griscelli syndrome patients have a silvery-gray sheen to the hair, large clumped melanosomes in hair shafts, and prominent mature melanosomes in cutaneous melanocytes with sparse pigmentation of adjacent keratinocytes in addition to immunological abnormalities.<sup>[53]</sup>

### Telangiectasia

Ataxia telangiectasia (A-T) is an autosomal recessive disorder primarily characterized by cerebellar degeneration, telangiectasia, immunodeficiency, cancer susceptibility, and radiation sensitivity. Telangiectasias within the bulbar conjunctiva over the exposed sclera of the eyes usually occur by the age of 5–8 years, but sometimes later or not at all. Telangiectasia can also appear on sun-exposed areas of skin, especially the face and ears. An increased prevalence of vitiligo, and extensive, recalcitrant warts may also occur.<sup>[54]</sup>

### Congenital hypotrichosis

Cartilage hair hypoplasia presents with short-limbed short stature, hypoplastic hair, and defective immunity and erythropoiesis.<sup>[55]</sup> Hypoplastic hair may also be noted in hypohidrotic ectodermal dysplasia with immunodeficiency and Netherton's syndrome.<sup>[48]</sup>

## CONCLUSION

A single cutaneous feature is not diagnostic of a primary immune deficiency disease but rather it is the plethora of events that raises the suspicion of an underlying PID. Although individual immunodeficiency syndromes are rare, the PIDs as a whole are not uncommon. A high index of suspicion along with a thorough clinical examination can help the astute clinician to make a timely diagnosis of a primary immune deficiency disease.

### Declaration of patient consent

Not required as there are no patients in this article.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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**How to cite this article:** Thanveer F. Cutaneous manifestations in primary immunodeficiency diseases. *J Skin Sex Transm Dis* 2021;3:143-50.