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IMMUNE DEFICIENCY AND DYSREGULATION (DP HUSTON, SECTION EDITOR)

Common Dermatologic Manifestations of Primary Immune Deficiencies

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Abstract The skin is the largest organ of our body; it consists of the epidermis, dermis, hair follicles, sweat glands, blood vessels, and connective tissue matrix. Its main function is to act as a barrier to the outside world and protect us from infections. Any component of the skin is subject to insults from the environment and/or from within the body. Primary immune deficiency patients present with recurrent or prolonged infections not frequently seen in healthy individuals. Oftentimes, these infections involve the skin. Primary immune deficiency may also present with noninfectious cutaneous signs, such as eczema; erythroderma; granulomas; dysplasia of the skin, hair, nails, or teeth; pigmentary changes; angioedema; urticaria; vasculitis; or autoimmune skin disease due to immune dysregulation. Prompt recognition of the underlying diagnosis and initiation of treatment decrease morbidity. This review provides the reader with an up-to-date summary of the common dermatologic manifestations of primary immune deficiency diseases.

Keywords Chronic granulomatous disease · Chronic mucocutaneous candidiasis · Ectodermal dysplasia · Eczema · Erythroderma · Infectious skin diseases · Primary immune deficiency diseases

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Introduction

Primary immune deficiency diseases (PIDDs) consist of a group of over 200 genetic defects [1••], all of which ultimately lead to an aberrantly functioning immune system and predispose an individual to recurring, protracted, atypical, or severe infections. New mutations are being discovered constantly due to technological advances in gene identification. The overall incidence of PIDDs is rare, with an estimated prevalence of 1 in 1200 patients in the USA [2]. PIDDs are differentiated from secondary immunodeficiencies as the latter are often caused by chemotherapeutic agents, certain viral infections, or malnutrition.

Patients with PIDDs often present in early childhood, with skin manifestations as a common concerning sign. Moin et al. report cutaneous aberrations in 67 of 210 (31.8 %) children which preceded their immunological diagnosis [3]. Al-Herz et al. observed 61 out of 128 (47.7 %) cases with skin manifestations [4]. Berron-Ruiz et al. report cutaneous alterations in at least 71 of 130 (54.6 %) of their patients [5].

The most common reason for delay in diagnosis is the low index of suspicion for underlying PIDD [6]. Patients with a normal immune system may present with similar skin manifestations as those with PIDDs. While cutaneous infections may be more readily associated with immune deficiency (Table 1), noninfectious cutaneous signs, such as eczema; erythroderma; granulomas; dysplasia of the skin, hair, nails, or teeth; pigmentary changes; angioedema; urticaria; vasculitis; or autoimmune skin disease due to immune dysregulation, may also be early signs of primary immune deficiency (Table 2). Increasing familiarity of these dermatological manifestations as well as keeping a broad differential will allow the astute clinician to arrive at PIDDs as a diagnosis. Arriving at a diagnosis promptly may decrease morbidity commonly associated with PIDD and aid in providing genetic counseling to the family [7]. This review will attempt to summarize the

Table 1 Infectious skin manifestations of PIDDs

Skin infection	Primary immune deficiency diseases to consider
Bacterial	Congenital neutropenias Chronic granulomatous disease (CGD) Leukocyte adhesion deficiency (LAD) Chediak-Higashi syndrome (CHS) X-linked hyper-IgM syndrome (XHIGM) X-linked agammaglobulinemia (XLA) Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome Hyper-IgE syndromes X-linked (STAT3 mutation) Autosomal recessive (DOCK8 or TYK2 mutation) "Mendelian susceptibility of mycobacterial diseases" (MSMD)
Viral	Autosomal recessive hyper-IgE syndrome (DOCK8 mutation) Epidermodysplasia verruciformis GATA-2 deficiency Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome Warts, immunodeficiency, lymphedema, and dysplasia (WILD) syndrome Netherton syndrome serine-threonine kinase 4 (STK4) gene mutations NK cell deficiencies MCM4 deficiency CD16 mutation
Fungal	Combined immunodeficiencies (CID) Severe combined immunodeficiency (SCID) DiGeorge syndrome Hyper-IgE syndromes X-linked (STAT3 mutation) Autosomal recessive (DOCK8 or TYK2 mutation) Chronic mucocutaneous candidiasis (CMCC) Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) Chronic granulomatous disease (CGD)

frequent skin manifestations of PIDDs; it is by no means a comprehensive list. The clinician is encouraged to seek input from an immunologist or dermatologist [8] when in doubt and refer to a tertiary care center when appropriate.

Infections of the Skin in PIDDs

Skin infections are the most prevalent dermatologic manifestation of PIDDs [3–5]. Any organism may be involved, including bacteria, viruses, fungi, and/or parasites (see Table 1). The skin microbiome of PIDD patients with hyper-IgE (STAT3 deficiency), Wiskott-Aldrich, and dedicator of cytokinesis 8 (DOCK8) deficiency syndromes was recently examined by Oh et al. [9••]. They noted that in PIDDs, compared to healthy controls and patients with atopic dermatitis, the skin has increased ecological permissiveness and was colonized with species not seen in their controls. These species included *Clostridium* and *Serratia marcescens*, as well as increased populations of *Candida* and *Aspergillus*.

Bacterial Infections

Skin infections involving bacteria include folliculitis, abscesses, furunculosis, impetigo, or pyoderma gangrenosum. These may be localized initially but spread if untreated or resistant to treatment and may become disseminated in rare cases. Bacterial skin infections are seen in PIDDs that have phagocyte dysfunction as an underlying pathology.

In disorders of phagocytosis, either number or function or both may be affected. The etiology of these disorders includes congenital neutropenias due to mutations in ELANE or HAX1 genes, chronic granulomatous disease (CGD), various forms of leukocyte adhesion deficiency (LAD), and Chediak-Higashi syndrome (CHS). Neutropenia may also be seen in multiple other PIDDs including X-linked hyper-IgM syndrome (XHIGM), X-linked agammaglobulinemia (XLA), and WHIM syndrome (warts, hypogammaglobulinemia, infections, and myelokathexis syndrome).

CGD results from mutation of one of the several components of the NADPH oxidase complex that results in phagocytes unable to destroy the microbes they have ingested. In CGD, recurrent bacterial infections are frequent, with suppurative adenitis in 53 % of patients and subcutaneous as well as liver abscess due to *Staphylococcus* being the most prevalent [10]. Other organisms may also be involved, including *Serratia*, *Klebsiella*, *Escherichia*, *Pseudomonas*, *Enterococcus*, *Chromobacterium*, *Enterobacter*, *Nocardia*, and *Salmonella* [10]. Additional dermatological manifestations have been described in association with CGD including dermatitis similar to eczema but with significant deep-seated infections [11] and a range of other infectious and inflammatory lesions [12].

There are at least three defined LAD syndromes, with a growing list, that result from other adhesion protein defects. LAD type 1, due to a defective β2-integrin subunit, is the most common form. Patients have recurrent, severe bacterial infections of the skin and mucosa starting in infancy; the prototypical history is that of delayed umbilical cord separation [13]. Another hallmark feature is the absence of pus at the site of the wounds. These patients have poor wound healing and high mortality rates [14]. LAD types 2 and 3 also involve flawed recruitment or adhesion of neutrophils to sites of inflammation, with associated developmental delay in LAD2 and platelet defects in LAD3 [15].

Chediak-Higashi syndrome is associated with recurrent skin as well as pulmonary infections in infancy due to *Staphylococcus aureus* and *Streptococcus* because of neutropenia and difficulty with chemotaxis [16]. The hallmark of CHS is giant azurophilic granules in neutrophils, which impair their migration along with bactericidal activity [16].

Table 2 Noninfectious cutaneous manifestations of PIDDs

Dermatological manifestation	Primary immune deficiency diseases to consider
Eczema	Hyper-IgE syndromes
	X-linked (STAT3 mutation)
	Autosomal recessive (DOCK8 or TYK2 mutation)
	Wiskott-Aldrich syndrome
	Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX)
	Severe combined immunodeficiency/Omenn syndrome
	Netherton syndrome
Erythroderma	Netherton syndrome
	Omenn syndrome
Granulomas	Chronic granulomatous disease
	Common variable immunodeficiency
Dysplasia of skin, hair, nails, or teeth	Ectodermal dysplasia with immunodeficiency
	Cartilage hair hypoplasia
	Dyskeratosis congenita
	Papillon-Lefevre syndrome
	Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED)
Pigmentary changes	Chediak-Higashi syndrome
	Griscelli syndrome type 2
	Hermansky-Pudlak syndrome types 2 and 9
Angioedema without urticaria	Hereditary angioedema types 1–3
	Acquired angioedema
Urticaria	Cryopyrin-associated periodic syndromes (CAPS)
	Familial cold autoinflammatory syndrome
	Muckle-Wells syndrome
	Chronic infantile neurologic cutaneous articular (CINCA) syndrome
	PLCG2-associated antibody deficiency and immune dysregulation (PLAID)
Autoimmunity/vasculitis	Common variable immunodeficiency (CVID)
	Selective IgA deficiency
	Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED)
	Wiskott-Aldrich syndrome
	Early complement deficiencies
	Ataxia telangiectasia

Bacterial skin infections are also a prominent feature of the hyper-IgE syndromes, which may be inherited as autosomal dominant (due to STAT3 deficiency, also called Job's syndrome) or autosomal recessive (due to DOCK8 or Tyk2 deficiency). In both forms, the hallmark is severe recurrent skin abscesses with *S. aureus* particularly localized on the scalp, face, and neck [17]. These abscesses are often described as "cold," with minimal signs of characteristic inflammation (rubor, calor, and dolor) [18]. The patients with the autosomal dominant form tend to have distinguishing coarse facial features and form pneumatoceles after staphylococcal pneumonias [17].

Mutations affecting IFN-gamma, IL-12, or their signaling pathways (including receptors, signaling molecules such as STAT1, or transcription factors) can predispose an individual to disseminated mycobacterial infections [19]. In these patients, cutaneous mycobacterial disease may be one component of widespread infection. The clinical phenotype is referred to as the "Mendelian susceptibility of mycobacterial diseases" (MSMD). In these patients, defects in the positive feedback loop between Th1 cells and macrophages lead to susceptibility to mycobacteria and *Salmonella* species, but preserved immunity to most other pathogens. In addition to disease with ubiquitous nontuberculous mycobacteria, MSMD patients may also develop disseminated or localized cutaneous BCGosis after Bacille Calmette-Guerin (BCG) vaccination [20].

Viral Infections

Viral skin infections are a less common manifestation of PIDDs compared to bacterial skin disease. Typically, in the select PIDDs, they present as severe, prolonged, or recalcitrant infections due to the herpesvirus family or human papillomavirus (HPV).

Patients with DOCK8 deficiency present with cutaneous viral infections while patients with autosomal dominant hyper-IgE syndrome do not. Typical infections are caused by molluscum contagiosum, herpes zoster (HZV), herpes simplex (HSV), and HPV [21]. Other causes of infections by herpesvirus family of viruses (HSV, varicella zoster, Epstein-Barr virus, cytomegalovirus) and HPV include deficiencies of T cells or disorders of natural killer (NK) cells. Known defects that lead to isolated NK cell disorders include MCM4 deficiency, which is a quantitative NK cell deficiency, and CD16 mutation, which results in a functional NK cell deficiency [22•]. These disorders are characterized by extracutaneous symptoms of herpesvirus infection, as these infections become widespread quickly.

Severe warts due to HPV are also implicated in several PIDDs. Recalcitrant cutaneous warts were defined by Leiding and Holland as those that failed to respond over a 6-month time period to five treatments [23•]. Epidermodysplasia verruciformis (EV) is due to mutations in EVER 1 and EVER 2 [24]. These genes are needed for transcription of highly preserved proteins involved in zinc homeostasis [25]. In EV, the HPV infections are due to serotypes that are more often associated with malignant transformation.

Patients that present with disseminated facial warts or those on their extremities during their teenage years should be screened for GATA-2 deficiency [23•]. Other PIDDs with warts as a common manifestation include WHIM syndrome, WILD (warts, immunodeficiency, lymphedema, and dysplasia) syndrome, Netherton syndrome, and serine-threonine kinase 4 (STK4) gene mutations [23•].

Fungal Infections

The most common fungal infections of the skin in PIDDs involve Candida species. Difficulty with eradicating *Candida* occurs in patients with defects of T-lymphocyte number or T-lymphocyte function, such as combined immunodeficiencies (CIDs), severe combined immunodeficiency (SCID), and DiGeorge syndrome. In these patients, candidal disease is seen in conjunction with susceptibility to other opportunistic organisms as well. Candidiasis is also a common feature in the complex presentation of hyper-IgE syndromes [26].

Defects in the Th17 pathway have been shown to be an underlying cause of cases in which chronic mucocutaneous candidiasis (CMCC) occurs without other obvious immune defects [27, 28]. Known single gene defects causing CMCC include gain-of-function STAT1 mutation, as well as mutations in IL-17F, IL-17RA, and ACT1 [29•]. CMCC is also seen in patients with mutations in Dectin-1, a pattern recognition receptor on antigen-presenting cells. Interestingly, patients with mutations in CARD9, a component of the signaling pathway downstream of Dectin-1, appear to have more significantly impaired antifungal immunity, developing CMCC in conjunction with deep dermatophytoses and invasive fungal infections [30, 31].

CMCC presents in association with autoimmune endocrinopathies in autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) also known as autoimmune polyendocrinopathy type 1 (APS-1). In this syndrome, there is a mutation in the autoimmune regulator (AIRE) gene that results in loss of self-tolerance. Thus, patients have autoreactive T lymphocytes and make neutralizing autoantibodies to the Th17 cytokines [27].

Other types of PIDDs may involve susceptibility to fungal disease, as is seen in CGD patients with *Aspergillus* species [32]. The majority of these patients present with pulmonary aspergillosis after inhaling the spores, but there is report of purulent *Aspergillus* skin lesions in a CGD patient [33, 34].

Parasitic Infections

Infections with lice or scabies are generally not associated with PIDDs. These parasites are spread by contact and can infest immunocompetent hosts. Intracellular parasites that cause Leishmaniasis and Chagas disease have evolved mechanisms to evade the immune system and can cause more severe, life-threatening illnesses in patients with PIDDs [35].

Eczema

Atopic dermatitis or eczematous lesions tend to be the second most common cutaneous presentation of PIDDs, after infectious causes [3–5]. Eczema is a familiar finding for most pediatricians as it affects approximately 13 % of children [36]. In patients with PIDDs, this prevalence increases up to 22 % [3–5].

Severe eczema presenting in early infancy, however, is unusual. It is most often associated with peripheral eosinophilia and increased IgE concentrations, as seen in hyper-IgE syndromes. DOCK8 mutation is associated with eczema as well as asthma and food as well as environmental allergy [37]. The patients with STAT3 mutation tend to have a pruritic dermatitis that is not typical of atopic eczema [17].

A triad of eczema, thrombocytopenia with small platelets, and recurrent infections is commonly associated with Wiskott-Aldrich syndrome (WAS). Less than 50 % of patients have this characteristic triad [38]. WAS is an X-linked disease

caused by a mutation in the WAS protein (WASp), involved in cell cytoskeleton signaling [39]. The most frequent cutaneous manifestation is eczema, which occurs in 71 % of patients [38]. Bleeding complications, including epistaxis, ecchymoses, petechiae, and hemorrhage occur in greater than 80 % of WAS patients [40].

Another X-linked syndrome called IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) due to mutation in FOXP3 transcription factor presents with infantile eczema. The typical triad is eczema, type 1 diabetes, and intractable diarrhea [41]. Cutaneous manifestations occur in 70 % of infants and may range from eczema with lichenified plaques to psoriasis to painful cheilitis and alopecia [41]. Resistance to classical treatments and uncontrolled pruritus are common.

Severe combined immunodeficiency (SCID) may result from over 20 various mutations; hypomorphic mutations that lead to an atypically stimulated T lymphocyte population lead to a clinical diagnosis of Omenn syndrome [42]. An erythematous rash is present in 98 % of infants along with other clinical findings such as hepatosplenomegaly, lymphadenopathy, recurrent infections, and failure to thrive [43]. The erythematous rash is often described as erythroderma, and patients with Omenn syndrome also tend to have alopecia with loss of eyebrows and eyelashes [44].

The SPINK5 gene mutation encoding a protein involved in skin barrier function leads to an autosomal recessive disorder called Netherton syndrome or Comel-Netherton syndrome [45]. Patients present in early infancy with erythroderma and various levels of peeling; after 1 year of age, they develop hair shaft abnormalities, referred to as bamboo hair (trichorrhexis invaginata) [46]. Some patients also have congenital ichthyosis. In Netherton syndrome, the classic rash called "ichthyosis linearis circumflexa" (ILC) develops from an initial erythroderma that grows to have circular borders with scaling [48]. ILC, although found in up to 80 % of patients with Netherton, is not permanent and tends to be migratory [47]. Other typical features of this syndrome include recurrent infections, elevated IgE levels, peripheral eosinophilia, and atopy, including eczema [47].

Erythroderma

The involvement of 90 % or more total body surface area with erythema and scaling is the definition of erythroderma [49]. It is classically associated with Netherton syndrome and Omenn syndrome, reviewed above.

Granulomas

The most common disorder with granuloma formation is CGD, described earlier in this review. It is characterized by skin manifestations in 60–70 % of patients [12]. These include eczematoid or seborrheic dermatitis involving the face and pustular lesions in skin folds. The nonnecrotizing granulomas may be cutaneous or internal, with the latter being more common.

Another PIDD that presents with granulomas in 8 to 22 % of its patients is common variable immunodeficiency (CVID) [50]. The granulomas most frequently occur in the lungs, lymph nodes, and spleen, although the skin can also be involved, as can other organs such as liver, bone marrow, kidney, gastrointestinal tract, and brain. In CVID, having granulomas makes it more likely that these patients will also have autoimmune cytopenias and other complications as well as low memory switched B lymphocytes.

Dysplasia of Skin, Hair, Nails, or Teeth

PIDDs with abnormal development of hair, nails, or teeth include ectodermal dysplasia with immunodeficiency (EDA-ID), cartilage hair hypoplasia (CHH), dyskeratosis congenital (DKC), and Papillon-Lefevre syndrome (PLS).

EDA-ID may be X-linked, due to mutations in NEMO, autosomal dominant, due to mutations in IKBA [51], or autosomal recessive, due to mutations in ORAI-1 [53]. The ectoderm includes skin, teeth, hair, nails, and eccrine glands [51]. Dermatological features present in 77 % of XL-EDA-ID patients comprise recalcitrant atopic or seborrheic dermatitis, hypohidrosis, dental anomalies (i.e., delayed tooth eruption, hypodontia, conical incisors), and alopecia or hypotrichosis (scant hair) [51, 52]. Skin tends to be pale, dry, and wrinkled. Patients have variable immune defects, involving pyogenic infections with encapsulated organisms, as well as T, B, and NK cells. The autosomal dominant form of EDA-ID is rarer and presents with a similar clinical picture; immunologically, however, it is associated with more severe T lymphocyte deficits [51]. Within the past 5 years, a mutation in the calcium channel regulatory gene ORAI-1 was identified. Calcium homeostasis is involved in activating T lymphocytes. The clinical syndrome of ORAI-1 deficiency is described as an anhidrotic ectodermal dysplasia with dental enamel calcification defect as well as immunodeficiency and congenital myopathy [53].

CHH is an autosomal recessive disease due to mutations in RMRP gene. It results in short-limbed dwarfism starting prenatally and combined immunodeficiencies. Patients, often of Amish or Finnish background, have thin, fragile, light-colored, scant hair with absence of eyebrows and eyelashes and short fingernails and toenails [54]. These patients often have other extraskeletal features that vary.

With variable inheritability, DKC is a disorder with at least eight different genetic mutations; the most common is due to DKC1 mutation, which is X-linked. These defects are in the telomerase or telomere maintenance, which results in short

telomeres as well as premature aging. Patients with DKC present with abnormal skin pigmentation that worsens with age, oral mucosal leukoplakia, and nail dystrophy of the fingers and toes [55]. They may have premature hair loss, graying, or sparse eyelashes [55]. Facial and hand eczema has been reported [56]. They also have bone marrow failure, pulmonary fibrosis, and leukemia [57].

PLS is an autosomal recessive syndrome caused by mutation in the CTSC gene, which encodes for cathepsin C. These patients develop pyogenic bacterial infections as well as liver abscesses and often present with symmetrical palmoplantar ectodermal dysplasia. Psoriasis-like rashes on elbows and knees have also been described. Their periodontal disease may result in the premature loss of dentition [58].

Failure or delayed shedding of the primary teeth due to decreased root resorption is commonly seen in autosomal dominant hyper-IgE syndrome [17]. Also, in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), patients have dystrophic hair and nails due to autoimmune and infectious difficulties [59].

Pigmentary Changes

PIDDs associated with oculocutaneous albinism include Chediak-Higashi syndrome (LYST mutation), Griscelli syndrome type 2 (RAB27A mutation), Hermansky-Pudlak syndrome type 2 (AP3B1 mutation) and type 9 (PLDN mutation), and MABPIP deficiency [60]. These patients often have a silvery sheen to their hair and hypopigmentation of their skin. CHS was reviewed earlier; Hermansky-Pudlak syndrome is associated with thrombocytopenia. All of these diseases are associated with aberrant NK cell cytotoxicity function and increase the risk of acquiring hemophagocytic lymphohistiocytosis [22•].

Angioedema Without Urticaria

Hereditary angioedema (HAE) results from C1 esterase inhibitor (C1-INH) deficiency due to mutations in the SERPING1 gene. Patients have nonpitting edema without urticaria, involving both the skin as well as internal organs. The typical skin manifestation is a lacy or mottled appearing rash called erythema marginatum, which may develop before the onset of the angioedema. HAE attacks can become life threatening if the airway becomes involved; patients are at risk for asphyxia. At least two types of HAE have been defined, based on the level or function of C1-INH. Type three HAE has most recently been discovered to be due to a defect in factor XII of the coagulation pathway. This type of HAE is the rarest, and patients, most commonly females, tend to have both normal levels and functions of C1-INH. It is important to distinguish hereditary from acquired angioedema, as the latter is usually due to a significant underlying pathology [61].

Urticaria and Immunodeficiency

While rash may be a feature of several different periodic fever syndromes, the cutaneous manifestations of the cryopyrin-associated periodic syndromes (CAPSs) have been well described. In these syndromes, which consist of familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile neurologic cutaneous articular (CINCA, or neonatal-onset multisystem inflammatory disease (NOMID)), patients typically present with fever, joint pain, rash, and fatigue. The rash evolves into urticaria from maculopapular lesion after exposure to cold [62]. In allergic urticaria, the hives are generally pruritic, whereas in CAPS, the rash is described as burning or stinging. On biopsy, CAPS is associated with a neutrophilic infiltrate, compared to common allergic urticaria which has an eosinophilic infiltrate.

Recently, a deletion of phospholipase C-gamma-2 (PLCG2) which results in cold urticaria, immunodeficiency, and autoimmunity (PLCG2-associated antibody deficiency and immune dysregulation, PLAID) syndrome was described. All patients had hives after being exposed to cold temperatures, and 75 % had antibody deficiencies. Over half the patients had autoantibodies or autoimmune disease, and a quarter had granulomatous disease [63•].

Autoimmune/Vasculitis

PIDDs are associated with autoimmune disease due to the dysregulation of the immune system as a whole. Cutaneous features are uncommon in autoimmune disease, with a few exceptions. As previously mentioned, CVID patients with granulomatous disease tend to have increased autoimmune features, including vitiligo and alopecia [64]. These features are also present in selective IgA deficiency and in APECED patients [65]. IgA deficiency in particular is associated with numerous autoimmune conditions including celiac disease and type 1 diabetes. WAS patients also display signs of autoimmune disease, in up to 70 % of patients of which at least 20 % are vasculitis, particularly Henoch-Schonlein purpura [40].

Deficiency of early complement components (such as C1, C4, or C2) predisposes patients to develop lupus-like photosensitive rash in the malar distribution. These patients do not have the typical double-stranded DNA those patients with systemic lupus erythematous do [66]. In addition, patients with early complement deficiency will have recurrent infections.

Ataxia telangiectasia (AT) is an autosomal recessive disorder due to mutations in ATM, required for DNA repair. The blood vessel telangiectasias characteristic of this disorder appear around age three or four and are commonly located on the bulbar conjunctivae and face (nose, neck, and pinnae of ear). Additional cutaneous features of AT include café-au-lait macules, hypopigmented macules, melanocytic nevi, facial papulosquamous rashes, and hypertrichosis [67].

Conclusions

PIDDs are oftentimes manifested through the skin. It is a highly visible organ that should lead to an early suspicion and diagnosis. The clinician is reminded to keep PIDDs in the differential when a patient presents with cutaneous signs and symptoms.

Compliance with Ethics Guidelines

Conflict of Interest Manisha Relan and Heather K. Lehman report no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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