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# Cutaneous manifestations of genodermatoses and primary immunodeficiency

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## Abstract

Immunodeficiency is most commonly related to inherited syndromes, infections, chemotherapy, or aging. As the population of individuals with immunodeficiency continues to grow, physicians are confronted with the task of diagnosing dermatologic disease in this population. Cutaneous involvement in immunodeficiency disorders serves as a useful tool that aids diagnosis and provides prognostic value. Given that cutaneous manifestations often herald an underlying immunodeficiency disorder, understanding the complexities of these diseases is important for appropriate clinical management. Although certain diseases may present with stereotypical cutaneous lesions, others may involve more variable lesions that require specialized consultation for diagnosis and treatment recommendations. In this review, we discuss a number of cutaneous findings associated with primary immunodeficiencies. Awareness of these cutaneous associations may aid in the early detection and prompt treatment of these potentially serious immunologic disorders.

*Keywords: primary immunodeficiency disorders, secondary immunodeficiency disorders, HIV/AIDS, cutaneous manifestations, infections, HAART*

## Introduction

Cutaneous manifestations can often herald immunodeficiency disorders. Primary immune-

deficiency disorders (PIDs) are rare, chronic disorders found predominantly in children. They are characterized by inherited defects of the innate and adaptive immune systems. After the hematopoietic system, the skin is the second most commonly affected organ in PIDs, with involvement in 40-70% of cases [1-3]. In this review, we present the clinical features, in particular cutaneous manifestations, of several PIDs.

### 1.0 Disorders affecting cellular and humoral immunity

#### 1.1 Hyper-IgM syndrome

Hyper-IgM syndromes result from defective immunoglobulin class switching [4]. The most common variant is an X-linked recessive disorder, first identified in two boys with recurrent bacterial pneumonia and other bacterial infections [5], both hallmarks of the disorder. It is characterized by low levels of circulating B lymphocytes [6] and results from a defect in the CD40 ligand expressed on T lymphocytes [6-8]. CD40 ligand complexes with the B-cell protein CD40 to drive B-cell proliferation and differentiation and immunoglobulin class switching [6, 8]. Consequently, patients exhibit normal to elevated serum levels of IgM, with risk of IgM secreting lymphomas later in life, and decreased levels of IgG, IgA, and IgE [4, 6].

Affected boys typically present with a sinopulmonary infection, but also commonly experience neutropenia and increased sensitivity to

*Pneumocystis jirovecii* pneumonia, *Cryptosporidium* liver disease, and inflammatory liver and/or gastrointestinal diseases [4]. Cutaneous manifestations of hyper-IgM syndrome most frequently include warts and oral ulcers of the tongue and buccal mucosa, which are present in 87.5% of neutropenic patients [9]. In addition, widely disseminated cutaneous warts and cutaneous sarcoid-like granulomas and histoplasmosis, although rare, have been reported [4, 10, 11].

#### 1.1.2 Severe combined immunodeficiency (SCID)

SCID is a combined B- and T-cell immunodeficiency disorder that can result from numerous genetic mutations. As such, it exhibits various inheritance patterns and has the potential to produce heterogeneous clinical presentations [12, 13]. Occurring in 45% of cases [14], the most common cause of SCID is a non-functional gamma chain, a component of the interleukins and interleukin receptors inherent to proper B- and T-cell development and differentiation [12]. The disease is characterized by a marked depression in T-cell levels, with a normal or elevated number of B cells [12]. However, these B cells exhibit poor function owing to abnormal cell surface receptors [12] that accordingly results in decreased levels of immunoglobulin [12]. In essence, these children lack an immune system and are thus highly susceptible to infection.

Signs of SCID, including various microbial infections and failure to thrive, present around six months of age [15]. Cutaneous manifestations include persistent mucocutaneous candidiasis of the mouth and anus, monilial diaper dermatitis, and gangrenous vaccinia cutaneous infections [15]. Moreover, otherwise benign infections, such as varicella zoster, can be refractory to treatment or even life threatening. Omenn syndrome, an autosomal recessive variant of SCID, typically presents with exfoliative erythroderma in the early neonatal period [16].

### 1.2 Combined immunodeficiencies with associated or syndromic features

#### 1.2.1 Wiskott-Aldrich syndrome

Wiskott-Aldrich syndrome is an X-linked recessive disorder that manifests after the first month of life.

The clinical phenotype consists of a triad of thrombocytopenia with small platelet size, atopic dermatitis, and recurrent bacterial infections, though many patients do not exhibit all three features [14]. Thrombocytopenia can produce skin findings such as bleeding from mucosal sites and thrombocytopenic purpura [15-17]. Atopic dermatitis occurs in over 80% of patients [14]. Patients have low levels of IgM, normal levels of IgG, and elevated levels of IgA and IgE. Delayed-type hypersensitivity is defective, with anergy to common antigens [18]. The average individual lives about four years and the select few patients who survive into adolescence often develop lymphomas [19].

#### 1.2.2 Ataxia-telangiectasia

Ataxia-telangiectasia is an autosomal recessive disorder of abnormal DNA repair resulting in profound immunologic disturbances [20]. Unlike typical cells that cease DNA synthesis in response to double stranded breaks caused by radiation and radiation mimetic agents such as bleomycin, cells affected by ataxia-telangiectasia lack this protective mechanism and divide before errors are corrected [21, 22]. Additionally, T cells are often deficient. Autoimmune abnormalities are common and the risk of lymphoma is significantly elevated [20].

The most common clinical features of ataxia-telangiectasia are bulbar telangiectasias and ataxia resulting from progressive degeneration of the Purkinje cells of the cerebellum [20]. Bulbar telangiectasias typically appear at two years' of age, in sun-exposed areas [20]. Other common cutaneous features include *café au lait* macules, impetigo, AD, seborrheic dermatitis (SD), vitiligo, loss of subcutaneous fat, and premature poliosis [21, 23]. Most patients develop recurrent sinopulmonary infections, with pneumonia as the most common cause of death [21, 23].

#### 1.2.3 Bloom syndrome

Bloom syndrome is a rare autosomal recessive disorder that occurs primarily in Ashkenazi Jews [21, 24]. The condition is caused by a mutation in the *BLM* gene located on chromosome 15. This gene encodes RecQ helicase, which is critical for maintaining DNA stability during replication and repair. Without this protein, cells in these patients commonly display

high rates of baseline sister chromatid exchanges and chromosomal aberrations known as quadriradial figures [24]. Neonates with Bloom syndrome demonstrate low birth weight and elongation of the head [25]. Telangiectasias appear in sun-exposed areas, predominantly on the nose, malar area, and dorsum of the hands. Photosensitivity may lead to scarring and atrophy [21]. *Café au lait* macules are commonly seen. Patients also remain susceptible to infections and show low levels of immunoglobulins [25]. Avoiding exposure to ultraviolet light and consistent use of sunscreens can mitigate the cutaneous changes [25]. Patients are also predisposed to neoplasia, especially acute leukemia, lymphoma, and squamous cell carcinoma of the tongue, often leading to premature death [21, 26].

#### 1.2.4 Hyper-IgE syndrome (Job syndrome)

Hyper-IgE syndrome was discovered in two girls with severe dermatitis, recurrent staphylococcal infections with “cold” abscess formation, and an abnormal inflammatory response [27, 28]. Disease pathogenesis is attributed to sporadic or inherited autosomal dominant defects in the Janus activated kinase-signal transducer and activator of transcription (JAK-STAT) pathway, which regulates IL2 and IL6 cytokine signaling [29]. Notably, abnormalities in this pathway lead to defective differentiation of the Th17 cell type, although the specific mechanisms underlying disease pathogenesis are not well-defined.

The most common presenting manifestation of this autosomal dominant disorder is a papulopustular eruption in the first month of life primarily affecting the face and scalp [28, 30]. Later skin findings include retroauricular fissures, otitis externa, dermatitis of the axillae and groin, folliculitis of the upper back and shoulders, and pitted scarring of the face [28]. Patients are susceptible to superficial and systemic bacterial and fungal infections [28]. Specifically, *Staphylococcus aureus* often causes abscesses of the skin and lungs, *Candida albicans* leads to mucocutaneous candidiasis, and *Aspergillus* species commonly contribute to lung disease [31, 32]. Lastly, most patients develop a dermatitis that resembles atopic dermatitis [33].

### 1.3. Disorders with predominantly immunoglobulin deficiencies

#### 1.3.1 X-linked agammaglobulinemia, (Bruton hypogammaglobulinemia)

X-linked agammaglobulinemia was first described in boys with recurrent bacterial infections during the first year of life [18]. One boy developed caseating granulomas containing CD8+ cells with no infectious isolates [34]. X-linked agammaglobulinemia is caused by mutation of BTK receptors, which results in abnormal B-cell differentiation and defective antibody signaling [35]. The disease is characterized by complete absence of circulating B cells and plasma cells, with decreased (IgG) or absent (IgA and IgM) levels of immunoglobulins [38-40]. Despite absent B cells, B cell precursors are abundant, suggesting defective B-cell differentiation [38].

Maternal transfer of immunoglobulins delays infection; however, severe and repeated bacterial infections of the skin, respiratory tract, and meninges occurring by the second year of life [38]. In particular, staphylococcal infections such as furunculosis are common [15, 36, 37]. Patients may demonstrate a normal immune response to some viruses, fungi, and gram-negative bacteria given intact T cell response [37].

#### 1.3.2 Common variable immunodeficiency

Common variable immunodeficiency is the most common primary immunodeficiency [38]. Molecular pathogenesis of this disorder has not been fully uncovered; however, genetic susceptibility is seen in 20% of patients with dominant inheritance [39]. Diagnosis is based on reduced levels of IgG in addition to IgA, IgM, or both-[39]. Approximately one-third of patients also demonstrate functional impairment of T cells [39].

The majority of patients present with recurrent sinopulmonary infections. Other features include gastrointestinal disturbances, granulomatous inflammation, and unusual infectious presentations related to enterovirus and *Mycoplasma* species [39]. Cutaneous granulomas of the leg and cutaneous viral infections are common, including recurrent cutaneous enterovirus infection causing hand, foot, and mouth disease, recurrent attacks of herpes simplex virus infection, herpes zoster, and

epidermodysplasia verruciformis [40-42]. Other cutaneous manifestations include elastosis perforans serpiginosa, pyoderma gangrenosum, polymorphic light eruption, and alopecia areata [43-45].

#### 1.4 Disorders affecting phagocyte function

##### 1.4.1 Chronic granulomatous disease

Chronic granulomatous disease exists in both an autosomal recessive and X-linked form, with the latter occurring in more than 50% of patients [46]. Chronic granulomatous disease is caused by gene mutations encoding essential subunits of the NADPH oxidase complex, the enzyme required for synthesis of reactive oxygen intermediates during the respiratory burst [46, 47]. Without NADPH oxidase and resultant superoxide radicals, neutrophils fail to increase oxygen consumption for the destruction of phagocytosed bacteria and fungi [48, 49]. As a result, patients with chronic granulomatous disease develop recurrent bacterial and fungal infections complicated by granuloma formation [46]. The most common organisms associated with infection in chronic granulomatous disease are *S. aureus*, *Escherichia coli*, and species of *Klebsiella*, *Pseudomonas*, *Aspergillus*, and *Candida* [50].

Cutaneous manifestations occur in at least of 60-70% patients with chronic granulomatous disease [51]. One of the earliest features of the disease is a dermatitis, which represents an infectious periorificial process rather than classic atopic dermatitis [51]. Another cutaneous finding is draining, suppurative lymph nodes resembling scrofula in the neck and inguinal regions [51]. Bacterial skin infections, including chronic suppurative paronychia, impetigo around the nares and ears, facial pustules, furunculosis, and subcutaneous abscesses, are a recurrent feature of untreated chronic granulomatous disease [51]. Other less common cutaneous manifestation include vesicular skin lesions and cutaneous granulomas [54].

##### 1.4.2 Chediak-Higashi syndrome

Chediak-Higashi syndrome is an autosomal recessive disorder characterized by impaired phagocytosis related to defects in vesicle trafficking [52, 53]. The genetic basis for Chediak-Higashi syndrome is

generally attributed to mutations in the *CHS1/LYST* genes, although much genetic heterogeneity exists.

Chediak-Higashi syndrome exhibits features such as partial oculocutaneous albinism and recurrent infections primarily with *S. aureus*,  $\beta$ -hemolytic streptococcus, and various fungi [52, 53]. Chediak-Higashi syndrome involves defects in cytoplasmic organelles such as melanosomes, lysosomes, and cytoplasmic secretory granules. As a result, melanocytes contain giant melanosomes and myeloid and lymphoid cells exhibit defective phagocytosis [52-54]. Neutrophils in Chediak-Higashi syndrome exhibit impaired chemotaxis causing poor intracellular destruction of pathogens and natural-killer cells have poor function because of defective secretory granules [52]. Cutaneous findings include skin with a slate-gray hue and blue to brown-colored irises [55]. Hair is usually blonde but may have a metallic sheen because of clumping of melanin in the hair shaft [55].

Griscelli syndrome and Hermansky-Pudlak syndrome are disorders related to Chediak-Higashi syndrome but are significantly less common [56]. Like Chediak-Higashi syndrome, Griscelli syndrome is caused by defects in vesicle trafficking, whereas Hermansky-Pudlak syndrome involves defects in vesicle formation [57].

##### 1.4.3 Myeloperoxidase deficiency

Myeloperoxidase deficiency is an autosomal recessive disorder characterized by the absence or inactivity of the enzyme myeloperoxidase [58, 59]. Myeloperoxidase catalyzes several oxidative reactions necessary for the proper functioning of polymorphonuclear cells, notably production of the microbicidal agent hypochlorous acid and termination of the respiratory burst [58, 59]. Most patients with myeloperoxidase deficiency are relatively asymptomatic, although they exhibit increased susceptibility to systemic candidiasis in the presence of diabetes mellitus [59, 60]. Cutaneous findings include recurrent acne, skin infections, and Sweet syndrome [61, 62].

##### 1.4.4 Leukocyte adhesion deficiency

Leukocyte adhesion deficiency is an autosomal recessive disorder involving an absence of the  $\beta$ 2-

integrin subunit (CD18), which prevents neutrophils aggregation [63]. Because neutrophils cannot exit the peripheral circulation and enter infected tissue, the peripheral blood shows a persistent leukocytosis [64]. Recurrent cutaneous infections are common and are generally secondary to *S. aureus* or gram-negative bacilli such as *Pseudomonas aeruginosa* or species of *Enterobacter*, *Klebsiella*, *Proteus*, and *Serratia* [65]. Because impaired neutrophil function precludes the formation of overt pustules or abscesses, microbial inflammation results in ulcerations similar to pyoderma gangrenosum [63]. Other clinical features include delayed umbilical cord separation and omphalitis [64].

### 1.5 Other disorders

Dyskeratosis congenita is a genetically heterogeneous condition characterized by short telomeres. The disease is classically known for the triad of oral leukoplakia, nail dystrophy, and reticular skin pigmentation, but affected individuals are also at high risk for bone marrow failure, pulmonary fibrosis, and cancer [66]. Comèl-Netherton syndrome is an autosomal recessive disorder with reduced memory B cells and deficient NK cytotoxicity that presents in infancy [67]. It is characterized by congenital ichthyosis, atopic diseases, and trichorrhexis invaginate, or "bamboo hairs." Cases of exfoliative erythroderma and hypernatremia have also been reported. Papillon-Lefèvre syndrome is an autosomal recessive disorder of impaired chemotaxis featuring ectodermal dysplasia and palmoplantar hyperkeratosis [68]. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy is an autosomal recessive disorder of impaired immune tolerance, resulting in cutaneous autoimmune diseases such as vitiligo and alopecia areata [69]. Cartilage-hair hypoplasia is an autosomal recessive form of short-limbed dwarfism that

involves cell-mediated immunodeficiency and the appearance of hypoplastic, light-colored hair [70]. Lastly, selective IgA deficiency is an inherited condition that can be associated with a dermatitis similar to atopic dermatitis [71].

## Conclusion

Cutaneous lesions are common manifestations of immunodeficiency. An immunologic workup may be necessary to evaluate for a possible primary immunodeficiency disorder if a pediatric patient presents with failure to thrive, multisystem involvement, and recurrent infections. Although these disorders are rare, recognition of characteristic dermatologic manifestations can facilitate earlier diagnosis and identify appropriate therapies for patients.

## Potential conflicts of interest

Dr. Feldman is a consultant and speaker for Galderma, Abbvie, Celgene, Abbott Labs, Lilly, Janssen, Novartis Pharmaceuticals, Sanofi, Sun Pharma and Leo Pharma Inc. He has received grants from Galderma, Janssen, Abbott Labs, Abbvie, Celgene, Taro, Sanofi, Celgene, Novartis Pharmaceuticals, Quriel, Pfizer Inc. and Anacor. He is a consultant for Advance Medical, Caremark, Gerson Lehrman Group, Guidepoint Global, Kikaku, Lilly, Merck & Co Inc, Mylan, Pfizer Inc, Quriel, Sienna, Suncare Research, Valeant, and Xenoport. Dr. Feldman is the founder, chief technology officer and holds stock in Causa Research. Dr. Feldman holds stock and is majority owner in Medical Quality Enhancement Corporation. He receives royalties from UpToDate, Informa and Xlibris. The remaining Authors have no financial relationships or conflicts of interest to disclose.

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