Immunodeficiency and Skin
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Immune deficiency refers to a state in which part of immune system is missing or defective resulting into an inability to fight infections and consequences related to that and abnormal reaction patterns to various stimuli that target the immune system. Immune deficiency can be inherited as:

A. **Primary state or**
B. **Acquired due to:**
    a. HIV infection
    b. Other fulminant infections
    c. Malignancy
    d. Drugs
    e. X-Ray irradiations
    f. Metabolic disorders

Primary immunodeficiency disorders (PIDs) serve a prototype to make us understand how various immunological pathways can influence the skin and result in various skin manifestations. PIDs are a widely heterogeneous group of inherited defects of immune system consisting of more than 350 clinical phenotypes with more than 340 underlying genetic defects currently known. Depending upon the clinical features, predominant immunological abnormalities and underlying genetic defects, the International Union of Immunological Societies has classified the PIDs into nine major groups to facilitate the clinicians to settle the appropriate diagnosis. Patients with PIDs can present with diverse clinical manifestations including susceptibility to recurrent and chronic infections, autoimmune, allergic, inflammatory and/or proliferative disorders. Most patients with PIDs manifest in first year of life and 10 warning signs (Table 1) have been proposed to suspect a PID in the first year of life. Despite major advances in PIDs, many patients remain undiagnosed or are diagnosed too late, resulting in poor consequences.

Skin manifestations are encountered in 40-70% of the patients with PIDs and in around one-third of the patients they are the presenting features. Thus in many instances, dermatologist is the first clinician to suspect a PID. Skin manifestations encountered in PIDs can be divided into following groups:

1. Significant skin manifestations
2. Specific skin manifestations
3. Autoimmune skin manifestations
4. Others

Table 2 summarizes the various skin manifestations that are observed in the PIDs.

1. **Significant Skin manifestations of PIDs:** These are the skin manifestations encountered more frequently in PIDs. These manifestations are not specific to a PID, they are seen in normal population as well. When seen in PIDs, they do have some peculiar

features that make a clinician suspect an underlying PID. They tend to be associated with other cutaneous and systemic signs and symptoms of a PID including those enumerated in Table 1.

Among significant skin manifestations, recurrent **skin infections** are most prevalent. They tend to be wide spread with atypical presentations (Figures 1 - 4) and recalcitrant to various treatment modalities. All types of skin infections including bacterial, fungal, viral, parasitic and opportunistic are seen in most of the PIDs but prevalence of various infections varies related to some PIDs. Patients with *leukocyte adhesion deficiency (LAD) types 1-3*, hyper IgE syndrome (Job's syndrome), and *DOCK-8* deficiency are more prone to get bacterial infections, more so with Staphylococci.

PIDs associated with multiple, recurrent warts and viral infections include:

- WHIM (**W**arts, **H**ypogammaglobulinemia, **I**nfections and **M**yelokathexis) syndrome
- *DOCK8* (dedicator of cytokinesis 8) deficiency
- *GATA2* (zinc finger transcription factor) mutations
- Gain of function *STAT1* (signal transducer and activator of transcription 1) mutations

PIDs associated with chronic mucocutaneous candidiasis include:

- Hyper IgE syndrome
- Gain of function *STAT1* mutations
- Interleukin 17 deficiency
- APECED (**A**utoimmune **P**olyendocrinopathy, **C**andidiasis, and **E**ctodermal **D**ysplasia) syndrome

Eczemas in PIDs tend to be recurrent with atypical distribution, recalcitrant to treatment and associated with other features of PIDs (Figures 5-7). Severe and recurrent eczema is a feature of many PIDs including hyper IgE syndrome, severe combined immunodeficiency (SCID), Netherton's syndrome, etc. Severe eczema with raised serum IgE, once thought to be a feature of Hyper IgE syndrome (Job's syndrome), has now been found to be associated with a variety of PIDs including:

- Hyper IgE syndrome (Job's syndrome)
- *DOCK8* deficiency
- Netherton's syndrome
- Omenn syndrome
- Wiskott-Aldrich syndrome
- IPEX (**I**mmune dysregulation, **P**olyendocrinopathy, **E**nteropathy, **X**-linked) syndrome

Erythrodermas of infancy are seen in:

- SCID
- Omenn syndrome (Figure 8)
- Netherton's syndrome
- Maternal engraftment in a newborn with SCID

Contrary to erythroderma in congenital ichthyosis, in PIDs (except for Netherton's syndrome) erythroderma is usually not present at birth and tends to appear later after few months. It may or may not be associated with alopecia and is associated with various other signs and symptoms of PIDs.

Non-infectious cutaneous granulomas (Figures 9a and b) have been reported in various PIDs. They are seen more often in chronic granulomatous disease (CGD), common variable immunodeficiency, and ataxia telangiectasia, but have been reported in variety of other PIDs as well. They can be localized only to the skin or can be associated with systemic granulomas. Granulomas of PIDs can precede, appear simultaneously or appear later during the course of the disease. All types of granulomas including sarcoidal, tuberculoid, necrotizing have been described.

2. **Specific skin Manifestations:** Specific skin signs are not widely encountered in PIDs but when present with other features pointing to underlying immunodeficiency are very helpful in diagnosis. Silvery grey hair is the feature of:
    - Hermansky Pudlak syndrome type 2 and 10
    - Chediak Higashi syndrome
    - Griscelli syndrome type 2

    Early onset telangiectasias of conjunctiva and skin can be a feature of ataxia telangiectasia.
    Congenital hypotrichosis can be a feature of:
    - Netherton's syndrome
    - Anhidrotic ectodermal dysplasia with immunodeficiency
    - Cartilage hair hypoplasia
    - Papillon Lefévre syndrome

3. **Autoimmune Skin Manifestations:** Autoimmunity in PIDs has been a subject of interest in the recent past. Urticaria/angiodema can be a feature of C1 inhibitor deficiency, and various autoinflammatory syndromes. Early onset SLE can be associated with various complement deficiencies. Various other autoimmune skin diseases including panniculitis, vasculitis, vitiligo, psoriasis (Figure 10), and alopecia areata can be randomly encountered in association with various PIDs.

4. **Others:** Rarely other skin findings are encountered in PIDs. BCGitis (local exaggerated response) to BCGosis (disseminated disease) can be complication of underlying PIDs including SCID, CGD, MSMD, etc.

Table 1. 10 Warning Signs for the Clinicians to Suspect a PID

SN	Clinical Signs
1	Oral thrush, chronic diarrhea or failure to thrive in the first month of life.
2.	Recurrent infections with bacterial pathogens, opportunistic organisms and viruses.
3.	Pneumonitis that does not clear.
4.	Extensive skin lesions, such as erythroderma, severe eczema that do not resolve with treatment.
5.	Delayed umbilical cord detachment (more than 3 days).
6.	Hepatosplenomegaly, lymphadenopathy.
7.	Congenital heart defects, particularly conotruncal anomalies.
8.	Family history of PID or death in infancy.
9.	Laboratory findings of lymphopenia (lymphocyte count <3400 cells/μL), other cytopenias, IgM less than 0.2g/L, IgA less than 0.05g/L or hypocalcemia.
10.	Absence of thymic shadow on radiograph.

Table 2. Skin Manifestations Seen in PIDs

SN	Skin Manifestations
1	Significant: - Recurrent skin infections (bacterial; fungal; viral; parasitic; others) - Recurrent eczema/eczematoid reactions - Non-infectious Granulomas of PIDs -
2.	Specific: - Premature greying of hair - Telangiectasias - Congenital hypotrichosis - Café-au-lait spots - Other ectodermal defects
3.	Autoimmune: - Urticaria - DLE/SLE - Panniculitis - Vasculitis - Vitiligo - Psoriasis - Vitiligo - Others
4.	Others: - BCGosis/BCGitis - Skin cancers - Café-au-lait macules - Acanthosis nigricans