Review Article

Approach to a Child with Primary Immunodeficiency Made Simple

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Abstract

Primary immunodeficiency disorders (PIDs) are a group of disorders affecting the capability to fight against infection. These include defects in T cells and B cells affecting cell-mediated and humoral immunity, respectively, combined humoral and cell-mediated immunodeficiency, defects in phagocytosis, complement defects, and defects in cytokine or cytokine signalling pathways which are detrimental for immune function. Depending upon the type and severity, age at onset of symptoms can vary from neonatal period to late childhood. Clinically, this group of disorders can involve any organ system of an individual such as respiratory system, gastrointestinal system, skin and mucous membrane, bone and joints, endocrine organs, and nervous system. Common dermatological manifestations include eczema, warts, molluscum contagiosum, mucocutaneous candidiasis, recurrent nonhealing ulcers, skin abscesses, erythroderma, petechiae, and nail changes. The common skin manifestations of various PIDs include eczema (seen in Wiskott–Aldrich syndrome and autosomal dominant hyper IgE syndrome); erythroderma (in Omen syndrome); viral warts or molluscum contagiosum (in autosomal recessive hyper IgE syndrome); chronic mucocutaneous candidiasis (in hyper IgE syndrome, autoimmune polyendocrinopathy candidiasis ectodermal dysplasia syndrome, Th17 cell defects); recurrent nonhealing ulcers (in leucocyte adhesion defect); skin abscesses (in antibody defects, hyper IgE syndrome, and chronic granulomatous disease); petechial or purpuric spots (in Wiskott–Aldrich syndrome).

Keywords: *Chronic mucocutaneous candidiasis, eczema, molluscum contagiosum, primary immunodeficiency, warts*

Introduction

Primary immunodeficiency disorders (PIDs) occur due to a defect in the development and/or function of innate (macrophage, neutrophil, dendritic cell, and complement system) or adaptive (B and T lymphocytes) immune system. Humoral immune deficiencies are characterized by defective B cells resulting in impaired antibody production. On the other hand, cellular immune deficiencies are caused by defects in T cells. Majority of PIDs are single gene defects and follow a Mendelian inheritance pattern. However, some of them, such as common variable immunodeficiency (CVID), may have a complex polygenic inheritance. Till date more than 300 different PIDs have been identified.[1] Depending upon the type and severity of defect, patients can present as early as in the newborn period [such as severe combined immunodeficiency, severe combined immunodeficiency disease (SCID)] or as late as late adulthood (such as CVID). However, the most common age at presentation is infancy and early childhood. Apart from infectious complications, patients with PID are also predisposed to several noninfectious complications such as autoimmune diseases and malignancies.[2] The international union of immunological societies (IUIS) expert committee for primary immunodeficiency has classified all PIDS under 9 different subheadings [Table 1].[1]

Contrary to common perception, PIDs as a group are not rare. Studies in United States have reported prevalence of PIDs as high as 1 in 1200 population.[3,4] Prevalence rates may be higher in communities with higher rate of consanguineous and endogamous marriages.[5] There are paucity of data on the prevalence rates of PID in developing countries including India.

In 1990, the Jeffrey Modell Foundation (an international nonprofit organization established for the welfare of individuals and families affected by PIDs) proposed 10 warning signs [Table 2] to help physicians suspect the diagnosis of PID.[6]

How to cite this article: Sharma D, Jindal AK, Rawat A, Singh S. Approach to a child with primary immunodeficiency made simple. Indian Dermatol Online J 2017;8:391-405.

Received: July, 2017. **Accepted:** September, 2017.

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Access this article online

Website: www.idoj.in

DOI: 10.4103/idoj.IDOJ_189_17

Quick Response Code:

For an early diagnosis of PID, dermatologists often have important contribution. Skin manifestations (such as eczematous dermatitis, chronic mucocutaneous candidiasis, and cutaneous viral infections such as disseminated molluscum contagiosum) may be the first or a predominant clinical presentation of PIDs. In this review, we highlight a symptom-based approach for diagnosis of PIDs with focus on dermatological manifestations.

Table 1: The international union of immunological societies (IUIS) expert committee classification of primary immunodeficiency diseases

1. Immunodeficiencies affecting cellular and humoral immunity (e.g. SCID)
2. Combined Immunodeficiencies with associated or syndromic features (e.g. Wiskott Aldrich syndrome, hyper IgE syndrome and DNA repair defects such as ataxia telangiectasia)
3. Predominantly antibody deficiencies (e.g. X-linked and autosomal recessive agammaglobulinemia and CVID)
4. Diseases of immune dysregulation (e.g. familial hemophagocytic lymphohistiocytosis)
5. Congenital defects of phagocyte number, function or both (e.g. neutropenia, chronic granulomatous disease and leucocyte adhesion defect)
6. Defects in intrinsic and innate immunity (e.g. mendelian susceptibility to mycobacterial disease, STAT 1 deficiency, STAT1 gain of function and IL-17 deficiency; majority of them also predispose to CMC)
7. Autoinflammatory disorders (e.g. Familial Mediterranean fever, neonatal onset multisystem inflammatory disease [NOMID] and disorders with sterile inflammation involving skin, bone and joints that may manifest as sterile pustular eruptions such as deficiency of IL-1 receptor antagonist [DIRA], deficiency of IL-36 receptor antagonist [DITRA], and neonatal inflammatory skin and bowel disease)
8. Complement deficiencies (e.g C1q deficiency presenting as early onset lupus and C1 inhibitor deficiency presenting as hereditary angioedema)
9. Phenocopies of PID (e.g. antibodies to IL17 or IL-22 presenting as CMC and antibodies to C1-inhibitir presenting as angioedema)

CMC: Chronic mucocutaneous candidiasis, CVID: Common variable immunodeficiency, PID: Primary immunodeficiency, SCID: Severe combined immunodeficiency

Table 2: Ten warning signs of PID proposed by Jeffrey Modell Foundation

Four or more new ear infections within 1 year
Two or more serious sinus infections within 1 year
Two or more months on antibiotics with little effect
Two or more pneumonias within 1 year
Failure of an infant to gain weight or grow normally
Recurrent, deep skin or organ abscesses
Persistent thrush in mouth or fungal infection on skin
Need for intravenous antibiotics to clear infections
Two or more deep-seated infections including septicaemia
A family history of PID

Eczema

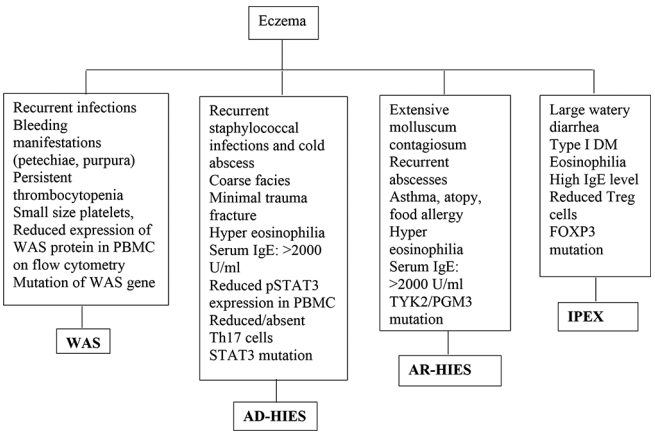
Eczema is a common skin disorder and affects approximately 10–20% of the children.[7,8] Eczema is also one of the common dermatoses seen in pediatric dermatology outpatient department.[9] Many PIDs have eczema as the predominant clinical manifestation [Table 3 and Flow Diagram 1].[10]

Wiskott–Aldrich syndrome

Wiskott–Aldrich syndrome (WAS) is characterized by a triad of eczema, thrombocytopenia, and immunodeficiency. Bleeding can occur in more than 80% of patients and may be life threatening in approximately 30%. However, intracranial bleeding occurs only in 2% of patients.[11] Patients with WAS usually present during infancy with bleeding manifestations in the form of petechiae, purpura or bloody diarrhoea, and recurrent infections (sinopulmonary infections, *Pneumocystis jirovecii*, cytomegalovirus, disseminated HSV, and varicella infection, especially hemorrhagic variant).[12] Eczema usually appears early in life [Figure 1].

Approximately 40% patients with WAS may develop autoimmunity [e.g., autoimmune haemolytic anemia (AIHA), skin vasculitis [Figure 2], neutropenia, IgA nephropathy, and chronic arthritis].[13] There is an increased risk of malignancy in WAS patients (most common is nonHodgkin lymphoma).[14] Diagnosis must be suspected in any male child presenting with eczematous dermatitis. A history of bleeding manifestations or infections or a family history suggestive of an X-linked inheritance should be actively solicited. Most important initial investigation is an assessment of platelet size on peripheral smear. WAS patients have microthrombocytopenia (small platelets).

WAS is a combined immunodeficiency and there is diminished T-cell proliferation in response to mitogen.[12]



Flow Diagram 1: Approach to PIDs presenting with eczema. PBS: Peripheral blood smear; WAS: Wiskott-Aldrich Syndrome; PBMC: Peripheral blood mononuclear cells; pSTAT3: Phosphorylated STAT3; TYK- tyrosine kinase; PGM3: Phosphoglucomutase 3; DM: Diabetes mellitus; AD-HIES- autosomal dominant hyper IgE syndrome; AR-HIES: Autosomal recessive hyper IgE syndrome; IPEX: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome

Table 3: PIDs with eczema as a predominant manifestation

	AD-HIES	AR-HIES, DOCK8 deficiency	WAS	IPEX
Key features	Early onset eczema Recurrent cold abscesses Coarse facies Skeletal defect	Eczema Recurrent severe skin infections by HSV, MCV, HPV Atopy, asthma	XL, Eczema Bleeding manifestations Recurrent infections Thrombocytopenia, small size platelets, Autoimmune diseases	XL, Eczema Autoimmune enteropathy Endrocrinopathy (hypo-/hyperthyroidism, Type I diabetes mellitus)
Newborn rash	Yes	No	No	No
Molecular defect	STAT3 mutation	Tyk2; PGM3 and DOCK8 gene	*WAS gene* mutation	FOXP3 mutation
Immunological abnormalities	IgE >2000 IU/ml, absent or reduced Th17 T cells and pSTAT3 expression, Eosinophilia	IgE >2000 IU/ml, lymphopenia, low IgM and variable IgG. T-cell defect in DOCK8 deficiency	Low IgM, normal or low IgG and high IgA and IgE; decreased T-cell number and function	Neutropenia, high IgE Normal IgG, IgA and IgM Low to absent regulatory T cells (Tregs)
Neurological involvement	Stroke, lacunar infarct	In PGM3 mutation ataxia, developmental delay, sensorineural hearing loss	No	No

AD: Autosomal dominant, AR: Autosomal recessive, DOCK8: Dedicator of cytokinesis-8, HIES: Hyper IgE syndrome, HPV: Human papilloma virus, HSV: Herpes simplex virus, IPEX: Immunedysregulation Polyendocrinopathy Enteropathy X-linked, MCV: Molluscum contagiosum virus, PGM3: Phosphoglucomutase-3, STAT: Signal transducer and activator of transcription, Tyk2: Tyrosine kinase-2, WAS: Wiskott-Aldrich syndrome, XL: X-linked

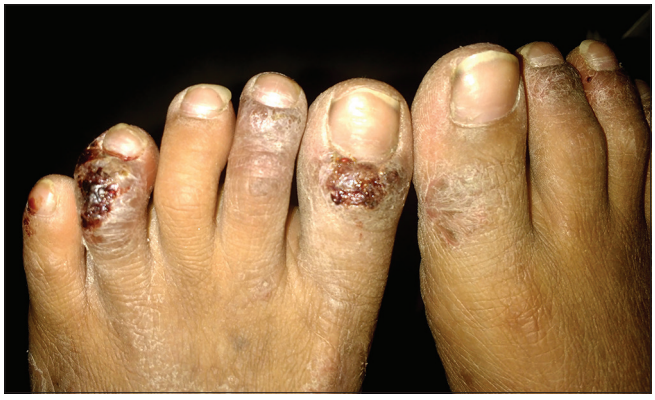


Figure 1: Eczema over toes in a 6-year-old boy, case of Wiskott Aldrich syndrome

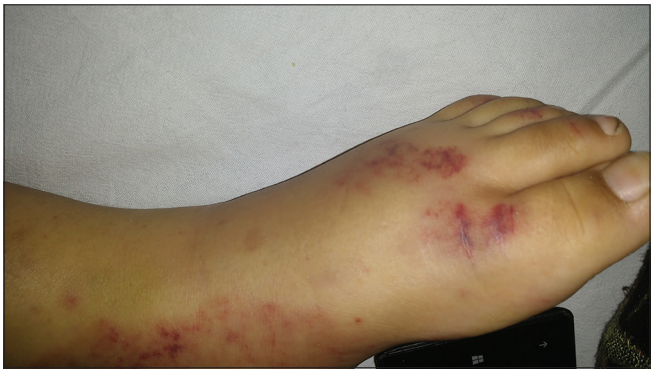


Figure 2: Erythematous, non-itchy skin lesions over foot in a 3-year-old boy, case of Wiskott Aldrich syndrome. Skin biopsy revealed leucocytoclastic vasculitis with IgA deposits

Absent or reduced expression of WAS protein in peripheral blood mononuclear cells (by flow cytometry) is another important laboratory test.

Autosomal dominant hyper IgE syndrome

AD-HIES is characterized by early-onset eczematous dermatitis; coarse facial features (usually by adolescent age) in the form of prominent forehead, widely spaced eyes, broad nasal bridge, fleshy nasal tip, facial asymmetry, prognathism, and hemihypertrophy; recurrent staphylococcal abscesses (cold abscess, no signs of inflammation); recurrent pneumonia with pneumatocele formation; chronic mucocutaneous candidiasis (CMCC); and skeletal and vascular abnormalities [Table 3].[15] Newborn rash may be the first clinical manifestation that manifests as papulopustular eruptions on the face, scalp, or generalized body surface. An important diagnostic clue is the normal C-reactive protein despite severe and extensive bacterial infections. *Staphylococcus* is the most common offending pathogen followed by *Candida* spp. Eczema usually exacerbates with *Staphylococcus* infection and tends to subside with its treatment.

Skeletal abnormalities are more apparent in older children and may include high arched palate, craniosynostosis, kyphosis, scoliosis, minimal trauma fractures of long bones, and joint hyperextensibility. In adolescents, retained primary tooth is another characteristic finding. The vascular abnormalities that these patients may develop are aneurysm of intracranial arteries leading to stroke or lacunar infarcts in the brain and myocardial infarction due to coronary

artery abnormalities (aneurysms and tortuosity). These patients are also at high risk for development of lymphoma.

Serum IgG, IgA, and IgM; T and B lymphocytes, and natural killer (NK) cells are usually normal. The National Institutes of Health (NIH) scoring system is a clinically useful tool for evaluation of patients with suspected AD-HIE syndrome.[15] NIH score of >40 has been found to correlate with presence of a molecular defect in *STAT3* gene.

Autosomal recessive hyper IgE syndrome

AR-HIES due to mutation in *TYK2* gene is characterized by recurrent viral skin infections, atopic dermatitis, asthma, food allergies, and anaphylaxis.[16,17] Though not consistent, these patients may have recurrent staphylococcal abscess, recurrent respiratory infections, strokes, and vascular aneurysms. However, unlike AD-HIES, pneumatoceles, coarse facies, dysmorphism, skeletal abnormalities, and retained primary tooth are not seen. *TYK2* mutation has recently been described in patients with predominant mycobacterial and viral infections without HIES [Table 3].[18]

Patients with phosphoglucomutase 3 (*PGM3*) mutation (another form of AR-HIES) also develop leukocytoclastic vasculitis, viral infections, and have prominent neurological features (developmental delay, ataxia, myoclonus, dysarthria, and sensorineural hearing loss).[19,20]

Patients with *PGM3* mutation may also have neutropenia, lymphopenia, low serum IgM, and variable IgG antibody responses.[19] In addition, they may also have abnormal electroencephalographic (EEG) changes and hypomyelination on brain magnetic resonance imaging (MRI).[20]

DOCK8 deficiency

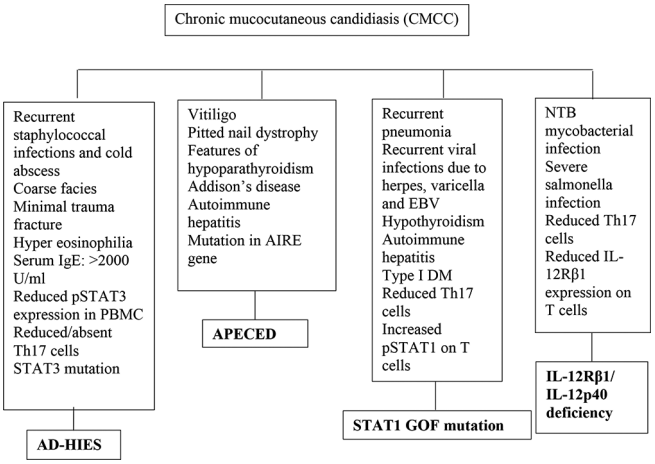
This AR form of HIES (caused by a mutation in the *DOCK-8* gene) has now been grouped under combined immunodeficiency diseases.[1] There are many overlapping features with AD-HIES such as eczema; staphylococcal and candida infections; elevated serum IgE and eosinophilia. However, patients with *DOCK-8* deficiency are more predisposed to severe viral infections such as extensive molluscum contagiosum infection and herpes infection; these patients usually have allergies, have neurological symptoms (vasculitis, meningitis, and brain infarction); do not develop somatic abnormalities such as coarse facies, delayed fall of deciduous teeth; newborn rash is less common and pneumatoceles are rarely seen.[21-23] These patients are more prone for malignancy (squamous cell carcinoma, cutaneous T-cell lymphoma and EBV related lymphomas). Th17 cells are often normal but CD4+ T cells and CD8+ T cells are often reduced. Elevated IgE and eosinophilia is present in almost all cases. IgA and IgG is usually normal or high but IgM tends to be low.[21]

IPEX

This is an X-linked disorder due to mutation in the forkhead-winged helix transcription factor (*FOXP3*) gene. *FOXP3* is involved in the development and function of CD4+ CD25+ regulatory T cells (Treg) that control effector T cells. Absence of Treg cells in IPEX leads to various autoimmune manifestations [Table 3].[24] IPEX usually manifests in neonatal period with large watery diarrhea (autoimmune enteropathy), which may sometime be mucoid or bloody and leads to failure to thrive. Skin disease may manifest in the neonatal period. Most common presentation is eczematoid dermatitis and other less common manifestations include icthysiform or psoriasiform dermatitis, urticaria, and alopecia. Autoimmune manifestations are common and include type I diabetes mellitus occurring in early infancy, hyperthyroidism or hypothyroidism, AIHA, thrombocytopenia, neutropenia, arthritis, hepatitis, and nephritis. Patients with IPEX do not have impaired response to pathogens; however, breach of physical barrier of skin and mucosa predisposes them for infections. Patients may develop lymphadenopathy and splenomegaly. If untreated, most children may die by the age of 2.

Chronic mucocutaneous candidiasis

Chronic mucocutaneous candidiasis (CMC) is a syndrome complex typified by the predominant clinical manifestation of *Candida* infection localized to skin and mucous membrane. Numerous PIDs involving both innate and adaptive immune system may have CMC as the major clinical manifestation [Table 4 and Flow diagram 2]. The innate immune response forms the initial line of defence against fungal pathogen and is eventually aided by adaptive immune system in the form of Th17 (T helper 17) cells. Toll-like receptors (TLRs) and C-type lectin



Flow Diagram 2: Approach to PIDs presenting with chronic mucocutaneous candidiasis. AD-HIES: Autosomal dominant hyper IgE syndrome; AIRE gene: Autoimmune regulator gene; APECED: Autoimmune polyendocrinopathy candidiasis ectodermal dysplasia; DM: Diabetes mellitus; pSTAT1: Phosphorylated STAT1; GOF: Gain of function; NTB: Nontubercular

Table 4: PIDs with chronic mucocutaneous candidiasis as presenting/main clinical manifestation

PID	Inheritance	Salient clinical features	Laboratory abnormalities
Hyper IgE syndrome (STAT3 mutation)	AD	Recurrent staphylococcus infection (skin abscess, pneumonia, sinusitis) with minimal signs of inflammation at the site of infection Physical abnormalities such as hyper-extensibility of joints, minimal trauma fractures, retained primary teeth, coarse facies, scoliosis, coronary and cerebral aneurysm Pruritic dermatitis, predisposition to lymphomas	Eosinophilia Elevated IgE Reduced Th17 cells and STAT3 expression Reduced memory T cells
APECED (mutation in AIRE gene)	AR	Triad of CMC, hypoparathyroidism and Addison disease Vitiligo, alopecia, enamel hypoplasia, hypothyroidism, pernicious anemia, autoimmune hepatitis, type 1 diabetes, hypergonadotrophic hypogonadism, Sjögren syndrome, pitted nail dystrophy	Low calcium, low magnesium, elevated phosphate, low PTH (if hypoparathyroidism) Low sodium, low chloride, high potassium (if Addison disease) Elevated transaminases, low albumin, elevated globulins (if autoimmune hepatitis)
STAT1 GOF mutation	AD	Recurrent sinusitis, otitis media and pneumonia; skin abscess Viral infections- herpes, varicella, EBV Vitiligo, alopecia, hypothyroidism, autoimmune hepatitis, type 1 diabetes, enamel abnormalities, cerebral aneurysm and vasculitis, squamous cell carcinoma of esophagus	Increased phosphorylation of STAT1 protein on T cells Decreased Th17 cells
IL-17 RA mutation	AR	CMC, staphylococcal dermatitis	Impaired cellular response to IL-17 A and IL-17 F
IL-17 A mutation	AD	CMC	Impaired cellular response to IL-17
IL-17 F mutation	AD	CMC	Impaired binding of IL-17 F to IL-17 RA and defective signalling
Dectin 1 mutation	AR	Vulvo-vaginal candidiasis, onychomycosis	Decreased IL-17 production
CARD-9 mutaion	AR	CMC and predisposition to invasive fungal infections	Decreased Th17 cells
IL-12Rβ1/IL-12p40 deficiency	AR	CMC, non-tubercular mycobacteria infections and severe *Salmonella* infections	Decreased Th 17 cells and decreased IL-12Rβ1 expression on T cells

AD: Autosomal dominant, AIRE: Autoimmune regulator, APECED: Autoimmune polyendocrinopathy, candidiasis and ectodermal dysplasia, AR: Autosomal recessive, CARD-9: Caspase recruitment domain-containing protein 9, CMC: Chronic mucocutaneous candidiasis, EBV: Epstein-Barr virus, GOF: Gain of function, IL-12Rβ1: interleukin-12 receptor β1, IL-17 RA: Interleukin 17A receptor, PIDs: Primary immunodeficiency diseases, PTH: Parathyroid hormone, STAT: Signal transduction and activator of transcription, Th: T helper

receptors are the primary components of innate immune system that provides protection against fungal pathogens. They bind to various fungal elements leading to the release of pro-inflammatory cytokines. These cytokines stimulate the receptors on Th17 cells that synthesize and releases interleukin 17 (IL-17). IL-17 is a cytokine which plays a crucial role for body's defence against *Candida*. A defect that involves any component in this pathway will predispose to chronic infection with candida. Human immunodeficiency virus (HIV) infection and CD4 lymphocytopenia must be ruled out in all cases of CMC.

STAT1 GOF mutation

There are 7 different types of signal transducer and activator of transcription (STAT) proteins (STAT 1, 2, 3, 4, 5A, 5B, and 6) that are involved in intracellular signalling downstream of type I and type II cytokine receptors. Gain of function mutation in *STAT1* leads to loss of dephosphorylation of this molecule and persistent or recurrent *Candida* infection affecting skin, mucosa, and nails [Figure 3] or disseminated fungal infection. Patients also have recurrent viral, bacterial infections, fungal (disseminated coccidioidomycosis and histoplasmosis), mycobacterial infections, aphthous stomatitis, and autoimmune manifestations.[25,26]

Molluscum contagiosum

Molluscum contagiosum (MC) is a viral infection of the superficial skin or mucous membrane characterized by discrete papular or nodular lesions. It is caused by molluscum contagiosum virus (a DNA virus from the Poxvirus family). MC is a common infection in children and sexually active adults. Human immunodeficiency virus (HIV) infection and use of immunosuppressant medications are well-described risk factors. PIDs that predispose to MC infection include WAS [Figure 4] and

AR hyper IgE syndrome caused by *DOCK-8* (dedicator of cytokinesis 8) deficiency.[23]

Warts

Human papilloma virus (HPV) is a large group of keratinotropic viruses that can infect the skin and mucosa leading to cutaneous and genital warts. Cellular immunity (especially T helper cells and NK cells) is an important defence mechanism that protects against HPV infection. Many PIDs are associated with predisposition to warts [Table 5 and Flow diagram 3]. A PID must be suspected if warts are recurrent, generalized or resistant to therapy, and if there are other suggestive features such as recurrent infections with other organisms or a suggestive family history.[27]

WHIM syndrome

Warts, Hypogammaglobulinemia, Infections and Myelokathexis (WHIM) syndrome is a rare autosomal dominant PID. Severe congenital neutropenia is the hallmark manifestation that develops because of myelokathexis (bone precursors of neutrophils are increased and undergo apoptosis).[28,29] Neutrophils in WHIM syndrome show a brisk release from bone marrow in response to an infection or administration of granulocyte colony stimulating factor (G-CSF), thereby suggesting no defect in the development of neutrophil but its release from bone marrow. The genetic defect lies in the *CXCR4*, a chemokine receptor belonging to G protein couple receptor (GPCR) superfamily.[30,31]

Clinical manifestations include recurrent bacterial infections that begin early in life. These include pneumonia, sinusitis, osteomyelitis, skin and soft tissue infections, and deep-seated abscesses. Patients with WHIM syndrome can handle viral infections except HPV and Epstein-Barr virus (EBV). HPV infection leads to severe and recurrent warts involving the skin and mucosal surfaces (manifesting as genital and anal condyloma acuminata in males and vulval and cervical dysplasia in females). Mucosal lesions tend to progress to frank carcinoma. Persistence of EBV infection may lead to lymphoproliferative disorder.

Bone marrow findings are characteristic and include granulocytic hyperplasia with apoptosis of granulocytic precursors (cytoplasmic vacuolization, hypersegmented nuclei, and chromatin hypercondensation)

GATA2 deficiency

Loss of function mutation in GATA binding protein 2 (GATA2) has been found to produce 4 distinct syndromes:

1. Monocytopenia and susceptibility to mycobacterial infections (MonoMac syndrome)
2. Dendritic cell, monocytes, B and NK cell lymphoid deficiency (DCML)
3. Emberger syndrome – primary lymphedema and myelodysplasia
4. Familial myelodysplastic syndrome and acute myeloid leukaemia (MDS/AML).

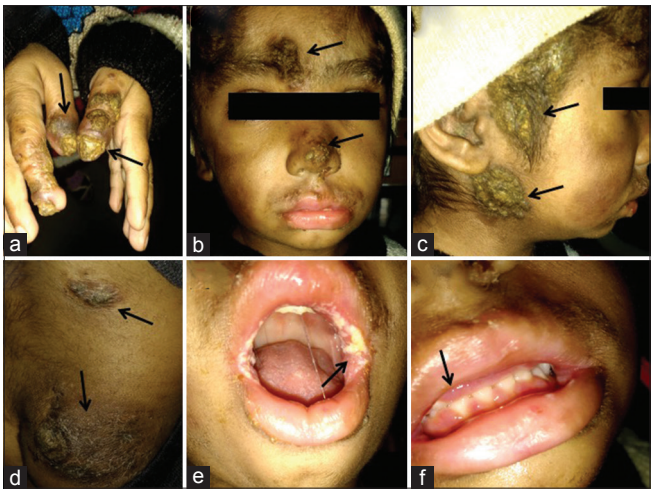


Figure 3: (a-f): Hyperkeratotic lesions involving nails of both hands (a), face (b and c), lower back (d). Oral thrush (e) and dental anomalies with almost complete loss of teeth in upper compartment in a 6-year-old-girl. Flow cytometry revealed an increased expression of STAT1 protein suggestive of *STAT1* gain of function mutation

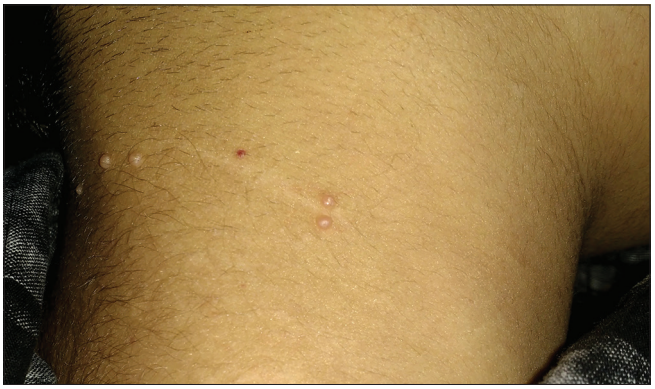
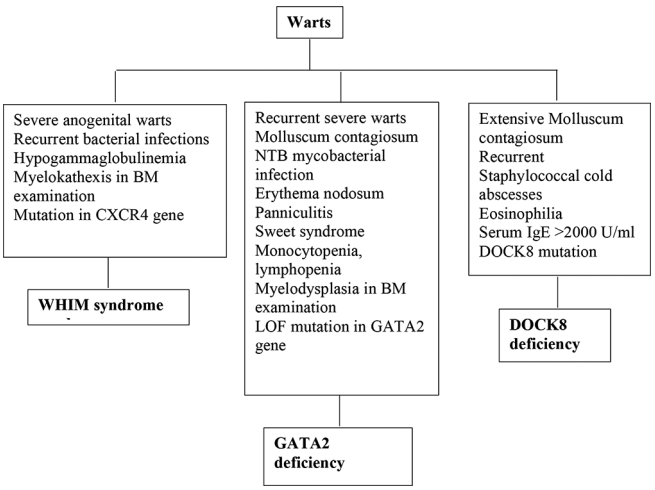


Figure 4: Molluscum contagiosum over neck region in 5-year-old boy, case of Wiskott Aldrich syndrome



Flow Diagram 3: Approach PIDs presenting with warts. BM: Bone marrow; WHIM: Warts, Hypogammaglobulinemia, Infections, Myelokathexis; NTB: Non-tubercular; LOF: Loss of function

Table 5: PIDs associated with warts

PID	Inheritance	Salient clinical features	Laboratory abnormalities
WHIM syndrome	AD	Recurrent infections (pneumonias, sinusitis, cellulitis, omphalitis, osteomyelitis, abscesses and skin infections) Severe and recurrent HPV infection in the skin and mucosa that may progress to frank carcinoma	Neutropenia, lymphopenia Hypogammaglobulinemia Low B cells and CD27+ memory B cells Bone marrow- granulocytic hyperplasia and apoptosis
GATA 2 deficiency	AD	Non tubercular mycobacterial infection, HPV infection, molluscum contagiosum Autoimmunity Lymphedema, panniculitis	Cytopenias (monocytopenia; B cell, NK cell and CD4+ T cell lymphocytopenia), CD4 to CD8 reversal; Myelodysplasia in the bone marrow
DOCK-8 deficiency	AR	Eczema, allergies Staphylococcus and Candida infections Viral infections (molluscum contagiosum, HPV and herpes)	Eosinophilia High IgE Variable degree of B/T or NK cell lymphopenia Variable antibody response
STAT1 GOF mutation	AD	Table 3	Table 3
MST1 deficiency	AR	Eczema Recurrent bacterial, viral (HPV, molluscum contagiosum, EBV) and candida infections Atrial septal defect and valvular abnormalities Autoimmunity	Neutropenia, with normal bone marrow maturation T and B cell lymphopenia
Idiopathic CD4 lymphopenia	No known inheritance pattern	Cryptococcus, non-tubercular mycobacteria and warts are the most common infections Histoplasma, candida, cytomegalovirus and varicella zoster infection may occur This disease usually present late, often in the 5th decade and when CD4 counts are done in a patient who is previously well and presents with one of these infections	CD4% <20% of all lymphocytes or absolute CD4 lymphocyte count <300 cells/μL on more than 1 occasion at least 6 weeks apart (HIV infection, any other known PID or secondary causes of low CD4 such as drugs have bene ruled out)
Netherton syndrome	AR	Icthysiform erythroderma, eczema, atopy, allergies, asthma and bamboo hair Cutaneous warts commonly in the ano-genital region Recurrent bacterial and viral (HSV) infections	High IgE, eosinophilia Normal to high IgG Low NK cells Trichorrhexis nodosa/invaginata on light microscopy of hair
NEMO deficiency	AR	Ectodermal dysplasia (conical teeth and eccrine sweat gland dysplasia leading to loss of sweating) Recurrent bacterial, viral, opportunistic infections	Low IgG, elevated IgM Normal T and B cells Impaired response to polysaccharide antgen
WAS	X-linked recessive	Table 2	Table 2
Ataxia telengiectasia	AR	Neurodegeneration leading to developmental delay appear in first 2-3 years of life and telangiectasias develop later Recurrent viral and bacterial infections, risk of malignancies May develop warts, atopic dermatitis and cutaneous granuloma	Low IgA and IgG2 subclass, high IgM Variable degree of B and T cell lymphopenia Elevated α-fetoprotein (AFP) >10 ng/mL Progressive cerebellar atrophy on magnetic resonance imaging (MRI)
X-linked hyper IgM syndrome	X-linked recessive	Combined immunodeficiency; recurrent bacterial, viral, fungal and parasitic infections; opportunistic infections; autoimmunity (haematological, hepatitis, nephritis); risk of malignancy	Low IgG, low IgA and normal to elevated IgM Normal B cells but low switch memory B cells Neutropenia in 70% cases CD40 ligand expression on activated T cells is reduced to absent

AD: Autosomal dominant, AR: Autosomal recessive, EBV: Epstein-Barr virus, GOF: Gain of function, HPV: Human papilloma virus, HSV: Herpes Simplex Virus, DOCK8: Dedicator of cytokinesis 8, MST1: Mammalian sterile 20-like 1, NEMO: Nuclear factor (NF)κ B Essential Modulator, NK: Natural killer, STAT: Signal transduction and activator of transcription, WHIM: Warts, Hypogammaglobulinemia, Immunodeficiency and Myelokathexis

GATA2 is a zinc finger transcription factor required for maturation and proliferation of early hematopoietic progenitor elements in bone marrow. There is a genotype phenotype correlation that leads to a marked variability in the age of presentation and clinical manifestations.

Various dermatologic manifestations are seen in this disease and may provide initial clue to the diagnosis. These include erythema nodosum or panniculitis [usually in the setting of an underlying infection such as *Mycobacterium avium* complex (MAC) or fungal infection]; recurrent and severe warts; MC; nontubercular mycobacterial infections involving the skin; sweet syndrome (usually in the setting of an underlying malignancy such as AML/MDS); melanoma, basal or squamous cell carcinoma; and lymphedema.[32-35]

In addition, patients with GATA2 deficiency are predisposed to recurrent systemic infections predominantly with viruses (herpes, EBV, CMV) and nontubercular mycobacteria. Hematological manifestations include variable degree of cytopenias (NK cell, B cell, monocytes, CD4+ T cells, and neutrophils). Pancytopenia is usually seen in the setting of MDS. Bone marrow is typically hypocellular in contrast to a hypercellular marrow seen in *de novo* MDS.[32] Other associated manifestations are pulmonary alveolar proteinosis,[33] risk of thrombosis, hypothyroidism, and sensorineural hearing loss.[34]

Epidermodysplasia verruciformis (EV) is another disease associated with predisposition to cutaneous warts.[36] EV is not a PID but is a rare genodermatosis caused by mutation in *EVER 1* and *EVER 2* genes (these genes regulate intracellular zinc distribution). EV is characterized by generalized and treatment resistant cutaneous warts with a potential to transform into cutaneous malignancies.

Detailed clinical description and laboratory investigations of other PIDs that may have warts as the predominant clinical manifestation is given in Table 5.

Cutaneous granuloma: Is there an underlying PID?

Cutaneous granuloma is a histopathological diagnosis on a tissue that is usually taken for the evaluation of the cause of an unexplained nodular swelling in the skin. Cutaneous infections such as tuberculosis (*Mycobacterium* and nontubercular *Mycobacteria*), *Histoplasma*, *Coccidiomycosis*, and *Meliodosis* may produce granulomatous skin lesions. However, following PIDs must be considered in the differential diagnosis:

1. Common variable immunodeficiency (CVID)[37,38]
2. Chronic granulomatous disease (CGD)[39]
3. Hypomorphic variant (clinically mild form) of severe combined immunodeficiency (due to *RAG* mutation)[40]
4. Nijmegen breakage syndrome[41,42]
5. Phospholipase C, gamma 2 (PLCγ2)-associated antibody deficiency and immune dysregulation (PLAID)[43]
6. Ataxia telangiectasia[44,45]
7. Major histocompatibility complex (MHC) class 1 deficiency
8. Blau syndrome.

Cutaneous granulomas may often be the first presenting manifestation of an underlying immune defect.[46]

Lupus erythematosus: When to suspect a PID?

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that may affect nearly every organ system of the body. Both genetic and environmental factors are involved in the pathogenesis of SLE. Patients with deficiency of early complement components C1–C4 are at a high risk of developing SLE.[47-50] Among them, C1q deficiency is most common, and approximately 90% patients with deficiency of C1q will develop lupus. The risk of lupus with C1r/s, C4, C2, and C3 deficiency is 60%, 80%, 40%, and 20%, respectively. The pathogenesis involves impaired clearance of the apoptotic bodies and immune complexes as well as impaired tolerance of B cells in the absence of early complements. In addition, impaired phagocytosis of apoptotic blebs leads to antinuclear antibody formation.

The clinical phenotype and laboratory manifestations of complement deficiency lupus differ from usual patients with SLE:

1. An early onset of the disease (usually below the age of 5 years)
2. Family history of similar illness (autosomal recessive inheritance); history of consanguinity
3. Predominant skin manifestation with less renal involvement
4. ANA is frequently positive with a speckled pattern; anti double-stranded DNA antibody is frequently normal.
5. An undue susceptibility to infections (more than the usual frequency of infection seen in SLE patients and secondary to use of immunosuppressant medications)
6. Complements level C3 and C4 will usually be normal in C1q deficiency. C4 deficiency will have undetectable to low C4 with normal C3. C3 deficiency will have undetectable C3 with normal-to-low C4 levels.
7. CH50 activity (a laboratory investigation to assess the function of the classical and terminal pathway of complement) will be very low if one of the early complement components is absent. In any other lupus patient, the activity may be reduced but is usually not very low or nearly absent.

Other PIDs that may present with SLE or SLE-like presentation include prolidase deficiency, Aicardi–Goutières syndrome (type 1 interferonopathies), protein kinase C (PRKC) delta deficiency, and carrier females of X-linked chronic granulomatous disease.[1]

Cutaneous manifestations of other common primary immunodeficiency disorders

Common variable immunodeficiency

CVID is the most common clinically significant PID with a variable clinical phenotype. The prevalence of CVID has been reported to be as high as 1 in 153 individuals. The clinical manifestations of this disease often appear slightly later (often in 2nd to 3rd decade). It is characterized by recurrent bacterial infections predominantly involving the sinopulmonary and gastrointestinal tract. In addition, these patients are predisposed to develop autoimmune manifestations that may virtually involve any organ system. Common dermatologic manifestations that have been reported in patients with CVID are vitiligo, psoriasis, and granulomatous lesions.[51-54] Laboratory investigations reveal low IgG with at least a low IgA or low IgM; normal B cells and reduced memory B cells; reduced functional antibodies (such as anti-diphtheria antibodies, anti-pneumococcal antibodies, anti-tetanus antibodies, and iso-hemagglutinins).

Leucocyte adhesion defect

LAD is a rare PID with AR mode of inheritance and characterized by a defect in the migration of neutrophils through the vascular endothelium into the extravascular space, i.e., at the site of infection. It is divided into three different types: (1) Type I with a defect in the β2 integrin gene that encodes for CD18 protein is the most common type (2) Type II with defect in the *SLC35C1* gene that encodes for CD15 protein and (iii) Type III with defect in the *FERMT3* gene that encodes for Kindlin 3 protein. Patients with LAD are predisposed to severe and life-threatening bacterial infections usually beginning in early infancy. The most distinctive feature of this PID is that there is no pus formation at the site of infection because neutrophils and monocytes do not reach the site of inflammation.[55,56] Children present with recurrent infections, nonhealing skin ulcers without any pus exudate and oral ulcers [Figure 5]. There is often a history of delayed fall of umbilical cord (beyond 2 weeks of life) and omphalitis in the neonatal period. Occasionally, children (and even adolescents) may also present with pyoderma gangrenosum-like lesions that are resistant to healing for prolonged duration.[57] Investigations reveal marked neutrophilic leucocytosis (may be up to 100×10^9 cells/L) even when there is no infection. Flow cytometry may reveal reduced expression of the defective protein on neutrophils. Final diagnosis is by molecular confirmation of the putative defective gene.

Chronic granulomatous disease

Chronic granulomatous disease (CGD) is a PID characterized by defect in the neutrophil oxidative burst and predisposition to infection with catalase positive microorganisms. It can have an X-linked or an autosomal recessive inheritance. The common clinical manifestations include pneumonia, lymphadenitis, and skin and deep-seated abscesses. *Staphylococcus aureus* and *candida spp.* are the most common organisms isolated in these infections; however, *Aspergillus spp.*, *Nocardia spp.*, *Burkholderia cepacia*, and *Pseudomonas aeruginosa* are also commonly encountered. A common clinical finding in these patients is presence of single or multiple cutaneous scars [Figure 6] that are the remnants of an incision applied for drainage of a cutaneous abscess or bacterial lymphadenitis (observed in the cervical, axillary, and groin region). Patients with CGD may also develop cutaneous granulomas. Laboratory investigations reveal elevated platelet counts, C-reactive protein, and erythrocyte sedimentation rate. Nitroblue tetrazolium (NBT) dye reduction test and dihydrorhodamine 123 (DHR) assay assess the oxidative potential of neutrophils. DHR assay is a flow cytometry based test that is more sensitive than traditional NBT test and is currently the screening test of choice for CGD.

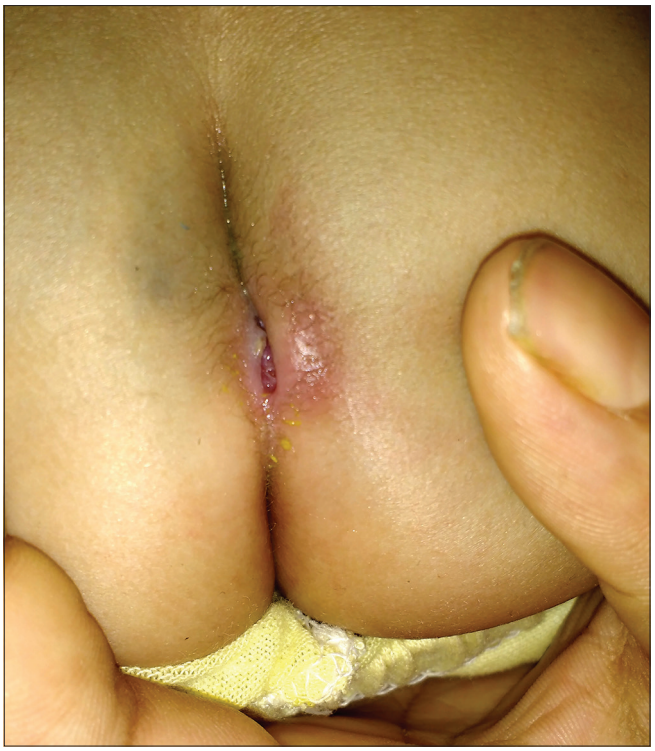


Figure 5: Ulcer in the sacral region in a 5-month-old girl with leucocyte adhesion defect type 1, there is no pus formation

Papillon–Lefèvre syndrome

Papillon–Lefèvre syndrome (PLS) is a rare AR disorder caused by mutation in the cathepsin C gene. The principal clinical manifestations of PLS include palmoplantar hyperkeratosis of variable severity that starts commonly between the age of 1 and 4 and periodontitis that begins almost simultaneously and leads to progressive loss of all

teeth.[58-60] With the eruption of deciduous teeth there is inflammation of gingiva leading to loss of periodontium and early fall of teeth. This inflammation subsides temporarily till the time of eruption of permanent teeth and then this process continues leading to complete loss of all teeth. Children are also predisposed to pyogenic infections involving skin and liver abscess with *Staphylococcus aureus* being the most common offending organism.

Severe combined immunodeficiency

SCID is the most severe form of immunodeficiency that often presents within the first 6 months of life with serious bacterial, viral, and fungal infections. Pneumonia, otitis media, persistent diarrhoea, sepsis, oral thrush, and meningitis are the common presenting clinical manifestations. SCID can have both an AR and X-linked pattern of inheritance. If these children receive an irradiated blood transfusion, they may develop an erythematous reddish maculopapular rash all over the body with frequent scaling and alopecia.[61] SCID must be suspected in an infant who develops such a reaction after a blood product transfusion. Omenn syndrome is a subtype of SCID characterized by persistence of activated and abnormal T lymphocytes in the circulation that infiltrate various tissues such as skin, bone marrow, gastrointestinal tract, and liver.[62] A scaling erythematous rash with acquired alopecia is a frequent clinical presentation [Figure 7]. Laboratory investigations reveal lymphopenia (absolute lymphocyte count $<1.5 \times 10^9$ cells/L in infancy) and low immunoglobulins. Lymphocyte subset analysis using flow cytometry reveals low T cells and variable number of NK and B cells depending upon the type of SCID.

Dermatofibrosarcoma protuberans is a rare malignant tumor involving skin and is more frequent in patients with adenosine deaminase (ADA) deficiency SCID.[63]

Primary immunodeficiency disorders presenting with hypopigmentation of skin and hair

Griscelli syndrome Type II

Griscelli syndrome (GS) is an AR disorder characterized by albinism and silver hair. Among the 3 subtypes of GS, type II has a tendency to present with recurrent hemophagocytic lymphohistiocytosis (HLH).[64] It is caused by a mutation in the *RAB27A* gene that encodes Rab27a protein. This protein belongs to the GTPase family of proteins and has a role in vesicular trafficking and fusion. GTP-bound Rab27a protein binds to Munc 13-4 and this interaction is necessary for perforin-dependent lymphocyte cytotoxicity, the defect of which is responsible for HLH. In addition, Rab27a is also responsible for distribution of pigment containing melanosomes in melanocytes.

These children often present with recurrent and severe HLH early in the life. The albinism and silvery hair may be very subtle and must be carefully looked for in all patients presenting with HLH. Neurological abnormalities may be seen in up to two-third of patients, although they are more common in GS1 [Flow diagram 4].

Laboratory investigations may reveal evidence of HLH (i.e., pancytopenia, elevated serum ferritin, transaminitis, low ESR, and elevated soluble CD25). NK cell cytotoxicity assay may reveal impaired activity, though a normal activity does not rule out the diagnosis of GS. Hair shaft examination under light microscope is an important investigation. In GS, the hair shaft will reveal irregular clumps of pigment in the centre compared to a uniform distribution in normal children and is almost confirmatory of diagnosis in the appropriate clinical settings. T cells, B cells, NK cells, immunoglobulins, and neutrophil

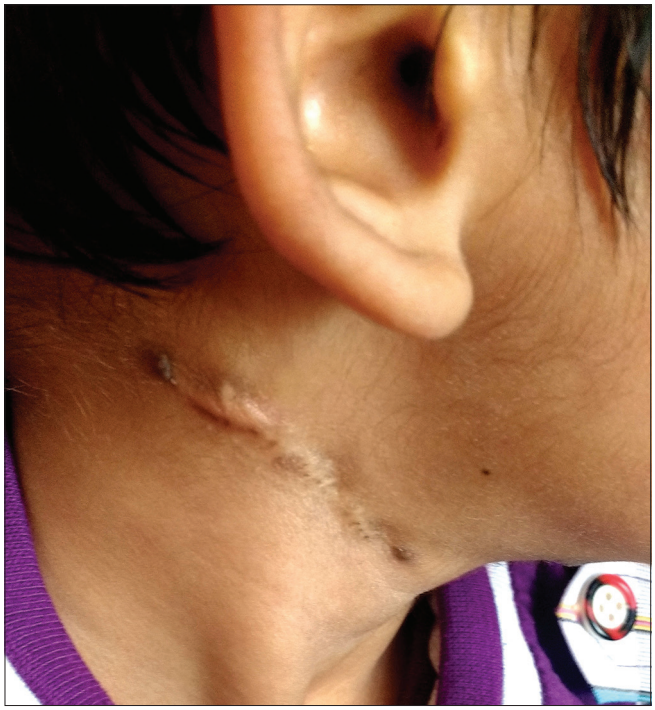


Figure 6: Scar mark in the neck region reminiscent of bacterial lymphadenitis in a 3-year-old boy, case of X-linked chronic granulomatous disease

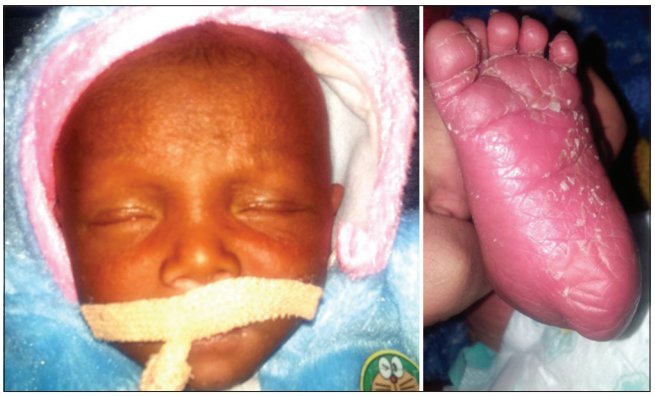
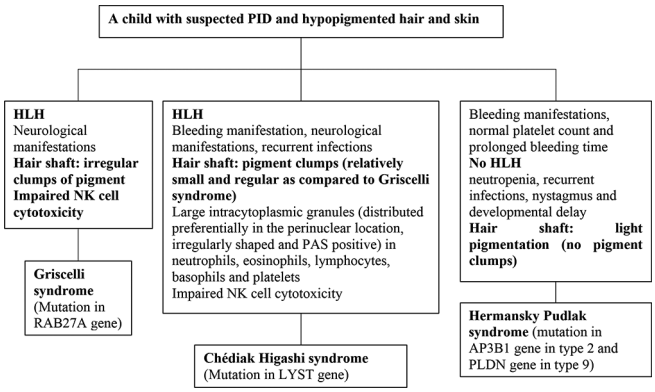


Figure 7: Erythroderma, loss of hair and skin peeling in a 2-month-old boy, case of severe combined immunodeficiency with Omenn syndrome



Flow Diagram 4: Approach to PIDs presenting with hypopigmentation of skin and hair. HLH: Hemophagocytic lymphohistiocytosis; PID: Primary immunodeficiency disease

phagocytic activity are normal in GS. Detection of mutation in the *RAB27A* gene will confirm the diagnosis.

Chediak Higashi syndrome

Chediak Higashi syndrome (CHS) is an AR disorder caused by mutation in *LYST* (lysosomal trafficking regulator) gene. This syndrome is characterized by hypopigmented skin (the skin color is at least fair than that of their parents), hypopigmented hair (the color of hair may vary from blond to dark but always exhibit a silvery tint which is more obvious in strong light), tendency for bleeding, neurological manifestations, recurrent infections, and propensity for progression to HLH (also known as accelerated phase).[65,66] The diagnosis is often suspected in the first decade of life. Neurological manifestations include peripheral neuropathy and intellectual disability.

Hair microscopy (just like GS) reveals pigment clumps but the clumps are relatively smaller compared to the hair shaft in GS. Intracytoplasmic granules in neutrophils, eosinophils, lymphocytes, basophils, and platelets provide important diagnostic clue. Other than hematopoietic cells, they may also be seen in melanocytes, fibroblasts, renal tubular cells, neurons, and Schwann cells. The immunological abnormalities include impaired cytotoxicity of lymphocytes (T and NK cells) and impaired chemotaxis and migration of neutrophils and monocytes. Mutation in *LYST* gene confirms the diagnosis, however, given its length, the sequencing of *LYST* gene is a difficult task.

Hermansky Pudlak syndrome

Hermansky Pudlak syndrome (HMS) is an AR disorder characterized by albinism due to a defect in the formation of melanosomes and bleeding tendency due to a defect in the synthesis of platelet dense granules. Among the 9 different subtypes of HPS, HPS type 2 and type 9 are associated with immunological abnormalities. HPS type 2 is caused by a mutation in the *AP3B1* gene that encodes for adaptor protein comple × 3 (AP-3) and HPS type 9 is caused by mutation in the *PLDN* gene that encodes for pallidin. HPS2 is also characterized by neutropenia, recurrent bacterial and viral infections, nystagmus, and developmental delay. These patients may also develop interstitial lung disease.

Platelet numbers are normal but bleeding time is prolonged. Though the cytotoxicity of lymphocytes is impaired, HPS patients do not often manifest with HLH. Hair microscopy reveal lighter pigmentation compared to normal, however, unlike GS and CHS there are no pigment clumps in the hair shaft.

Autoinflammatory disorders

Autoinflammatory disorders are rare monogenic disorders resulting from exaggerated activation of innate immune system. These disorders are characterized by episodes of inflammatory symptoms (periodic fever, rash, and joint symptoms) without any evidence of infection, autoimmunity, or allergy.[67-69] Cutaneous manifestations of common autoinflammatory disorders are highlighted below.

Familial Mediterranean fever

Erysipelas-like erythema occurring commonly at distal extremities such as foot and ankles is a characteristic finding in FMF. This rash occurs in association with fever, monoarthritis, or oligoarthritis (most commonly the knee joint), severe abdominal, and/or chest pain. Episodes usually last for 1–3 days. There is increase in acute phase inflammatory parameters (i.e., ESR and CRP) during episodes and sometimes in between attacks as well. Amyloidosis is the most serious complication of FMF.

Tumor necrosis factor receptor associated periodic fever syndrome

Erythematous rash which starts on the trunk or limbs and migrates distally (migratory erythema) is characteristic in Tumor necrosis factor receptor associated periodic fever syndrome (TRAPS). There is associated subcutaneous swelling and periorbital edema. In this periodic fever syndrome, febrile episodes usually last longer (more than 14 days). There is accelerated rise in ESR and increased CRP during as well as in between the episodes of attacks.

Cryopyrin associated periodic fever syndrome

Neonatal-Onset Multisystem Inflammatory Disease (NOMID), familial cold autoinflammatory syndrome (FCAS), and Muckle Wells Syndrome (MWS) fall under this category of autoinflammatory syndrome. Urticaria-like (nonpruritic) rash is characteristic of Cryopyrin associated periodic fever syndrome (CAPS). Children with CAPS are usually symptomatic since early infancy with fever and rash. Children with NOMID can have development delay, aseptic meningitis, progressive hearing loss, and bizarre enlargement of epiphysis and metaphysis of long bones (knee joint involvement is the most common). Prominent patella is a characteristic clinical finding in NOMID.

Deficiency of IL-1 receptor antagonist

Rash in Deficiency of IL-1 receptor antagonist (DIRA) is characterized by grouping of small pustules to generalized pustulosis. These are sterile neutrophilic pustules. Sterile osteomyelitis is another characteristic presentation in DIRA with onset of symptoms during neonatal period.

Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature

Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) is a recently described autoinflammatory disorder characterized clinically by presence of systemic inflammation in the form of fever; musculoskeletal manifestations in form of myositis, arthritis, and joint contractures; panniculitis (that manifest as nodular or plaque-like violaceous rash in the skin and violaceous discoloration in the periorbital region often with edema), acanthosis nigricans, and truncal obesity.[70] Skin biopsy demonstrate immature neutrophils, myeloid precursors which are myeloperoxidase positive, and activated macrophages (CD68+ and CD163+). ESR and CRP are markedly high and dyslipidemia may be present. CANDLE is caused by a loss of function mutation in proteasome beta type 8 (*PSMB8*) gene also known as proteasome associated autoinflammatory syndrome.

Stimulator of interferon genes (*STING*) associated vasculopathy of infancy (SAVI)[71] is another autoinflammatory syndrome that may resemble CANDLE. SAVI is clinically characterized by features of systemic inflammation and vasculopathic skin lesions that often manifest early in life. Skin lesions often develop over cold exposed areas such as distal extremities, nose, pinna, and face. Gangrene of fingers or toes, violaceous nodular, or plaque lesions, generalized pustules, livedo reticularis, Raynaud phenomenon, nail dystrophy, and nasal septal perforation are common cutaneous manifestation and represent the effect of vasculopathy. Interstitial lung disease is a pulmonary complication and may result in early mortality. SAVI is caused by dominant gain of function mutation in *TMEM173* gene that encodes STING.

The manifestations of Aicardi-Goutières syndrome (AGS)[70] may also resemble SAVI and CANDLE syndrome. AGS often presents very early in life with developmental delay and microcephaly. Presence of these neurological abnormalities differentiate this disorder form SAVI or CANDLE. Recurrent fever, chilblain lesions on hands, feet and ears, and hepatosplenomegaly are other common presenting manifestations. Calcification of basal ganglia, variable white matter changes, and cerebral atrophy is seen on central nervous system imaging. Cerebrospinal fluid (CSF) examination may reveal elevated interferon-α and neopterin Various gene mutations (including *ADAR*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, or *TREX1*) have been implicated in causing AGS.

Blau syndrome

Blau syndrome is an autosomal dominant autoinflammatory disorder characterized by a triad of granulomatous arthritis, uveitis, and rash.[72] It is caused by a mutation in the *NOD2* (a pattern recognition receptor) gene. These children usually present during the first year of life with rash being the presenting manifestation. Rash is erythematosus, fine maculopapular with scaling and is often misdiagnosed as eczema. It may even present in the neonatal period. Skin biopsy may reveal noncaseating granuloma. Polyarthritis with characteristic boggy swelling of synovium is typical of Blau syndrome and is often the second manifestation in chronological order after rash. The granulomatous uveitis is often bilateral and posterior with a potential to progress to panuveitis.

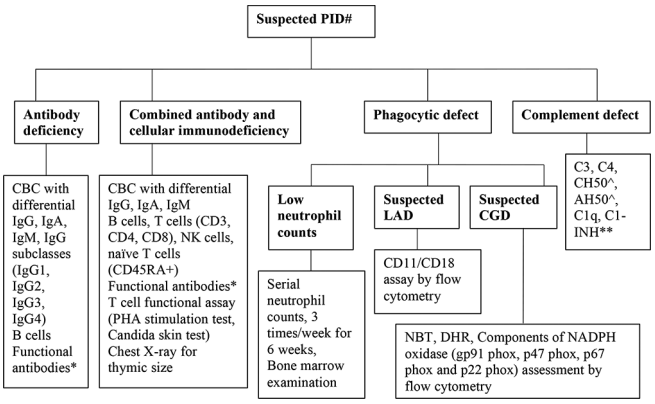
Autoinflammation with phospholipase Cγ2 – associated antibody deficiency and immune dysregulation

Autoinflammation with phospholipase Cγ2 –associated antibody deficiency and immune dysregulation (APLAID) is an autosomal dominant autoinflammatory disorder characterized by recurrent blistering skin lesions, cold urticarial, cutaneous granulomas, pulmonary involvement in form of bronchiolitis, inflammation in eyes and gastrointestinal tract, and recurrent sinopulmonary infections.[43] There are no autoantibodies. APLAID is caused by gain of function mutation in *PLCG2* gene leading to increased signaling in phospholipase Cγ2 pathway.

A prototype approach for laboratory evaluation of a case of suspected PID is given in Flow Diagram 5.

Conclusion

PIDs as a group are not rare and dermatologists have an important role in their early diagnosis. Majority of these



Flow diagram 5: Laboratory evaluation of a child with suspected PID. #Always rule out HIV infection *Functional antibodies include antidiptheria antibody titers, antipneumococcal antibody titers, antitetanus antibody titers. ** If hereditary angioedema is suspected ^CH50 and AH 50 are functional assay for assessment of classical and alternative complement pathway respectively. CBC: Complete blood count; CGD: Chronic granulomatous disease; DHR: Dihydrorhodamine 123 assay; LAD: Leucocyte adhesion defect; NBT: Nitroblue tetrazolium dye reduction test

diseases present in young age group, however, occasionally they may present in older individuals as well. Common cutaneous lesions such as eczema and warts warrant immunodeficiency evaluation when they are extensive, recurrent, recalcitrant to therapy, or if there are other features suggestive of a PID such as thrombocytopenia in WAS or neutropenia in WHIM syndrome. A detailed family history always gives important diagnostic clues to an underlying PID. Chronic mucocutaneous candidiasis and cutaneous granulomas are almost always associated with an underlying immune defect and need detailed evaluation. Recurrent skin infections, nonhealing ulcers especially if there is no pus formation, and recurrent bacterial lymphadenitis also suggest a PID. Complement defect must always be considered in patients with early onset SLE, SLE with unusual infections and family history of SLE. Simple laboratory investigation such as complete blood count and serum immunoglobulin level gives important diagnostic clue.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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