Published in final edited form as:
J Allergy Clin Immunol. 2012 November ; 130(5): 1030–1048. doi:10.1016/j.jaci.2012.07.049.

Warts and All: HPV in Primary Immunodeficiencies

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Abstract

Infection with human papilloma virus (HPV) is almost universal and eventually asymptomatic, but pathologic infection with HPV is severe, recurrent, and recalcitrant to therapy. It is also an underappreciated manifestation of primary immunodeficiency. Mutations in *EVER1, EVER2, GATA2, CXCR4*, and *DOCK8* are typically associated with extensive HPV infections, whereas several other primary immune defects have severe HPV much less frequently. We review immunodeficiencies with severe HPV infections and the mechanisms underlying them.

Keywords

Immunodeficiency; human papilloma virus; HPV; warts; squamous; carcinoma; dysplastic

Introduction

Warts are benign virus-induced tumors caused by human papilloma virus (HPV) that are common in the general population at some point in life. There are more than 100 different genotypes of HPV classified according to their tissue tropism (mucosal or cutaneous) and oncogenic potential. Along with host and environmental factors, HPV genotype influences the type and malignant potential of lesions[1]. The prevalence of cutaneous viral warts in children and adolescents is between 3-5%[2, 3] occurring with similar frequency in adults aged 25-34 years[4]. In 90% of children, warts present by age 11 and clear by 16 years[1]. Other rates of spontaneous clearance have also been reported: 23% at 2 months[5, 6] and 66% by 2 years[6]. There is no exact definition for recalcitrant cutaneous warts but an accepted rule is failure to respond after five treatments over a period of 6 months[7]. Mucosal HPV is much more common, with up to 79% of sexually active women acquiring genital HPV during their lifetime, ranging from no phenotype, to koilocytosis, to genital warts, to high grade intraepithelial neoplasms. Spontaneous regression occurs in 30% of women within 4 months[8], and median time to clearance with treatment is 6 months[9]. HPV infection is the most frequent cause of cervical cancer in women but also induces cancer of the vagina, vulva, anus, and penis. HPV has been linked to oral squamous cell carcinomas as well[10].

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Host defense against HPV relies on intact and functioning cellular immunity including T cell and natural killer (NK) cell cytotoxicity. Therefore, in patients in whom warts are severe or recalcitrant, concern for immune defects is raised. Here we review the frequency, severity, and clinical importance of warts in primary immunodeficiencies. We will discuss separately the syndromes in which HPV is a manifestation in the majority of cases and those syndromes in which HPV is less consistently recognized as a severe manifestation of immunodeficiency.

Epidermodysplasia Verruciformis (EV): EVER1 and EVER2 deficiency

EV is a rare genodermatosis characterized by increased susceptibility to cutaneous HPV. First described by Lewandowsky and Lutz in 1922[11], EV typically presents in infancy, and has two main phenotypes differentiated by their potential for malignant transformation[12]. The more benign lesions typically occur on the trunk, neck and extremities as flat, wart-like, hypo- or hyper-pigmented papules that may coalesce as scaly patches or plaques with irregular borders. Lesions with greater malignant potential present as verrucous or seborrheic keratosis-like lesions that occur more frequently on sun exposed surfaces[12]. The HPV's that cause disease in EV are beta papillomaviruses, which typically cause asymptomatic infections in the general population. At least 19 different beta HPV genotypes have been found in patients with EV and patients usually are infected with more than 1 genotype. HPV-5 is the most frequent genotype in EV patients followed by HPV-3 and HPV-10 [13]. HPV-5 is also the most common genotype to undergo malignant conversion. EV specific HPV's are acquired early in infancy [14] and are prevalent in the normal skin of healthy adults [15]. Symptomatic infections and malignant transformation may occur in patients with EV or those with other immunodeficiencies.

Although the immunophenotype of EV may be normal, it may include decreased total T lymphocyte counts[16], reduced cell mediated immunity as measured by reduced responsiveness to mitogens and antigens as well as cutaneous anergy to recall antigens[16-22], and defective cell mediated immunity toward EV-specific HPV types[23]. Reduced cell mediated immunity may be related to the length of infection with EV specific HPV's[17, 18] and is independent of oncologic potential[18-20, 22]. NK cell cytotoxic responses are increased in EV[16, 24, 25], primarily in patients with early premalignancies or malignancies, but are reduced in disease induced by EV associated HPV-3 displaying a specific reduction of NK cell mediated cytotoxicity against disease specific target cells[25]. Hypoproductive polymorphisms of the interleukin (IL)-10 gene promoter have also been linked to EV. Low IL-10 levels allow for higher production of inflammatory cytokines and may contribute to HPV persistence by inhibiting infected Langerhan's cells from migrating to regional lymph nodes[26].

EV is historically inherited in an autosomal recessive fashion, but X-linked[27] and autosomal dominant[28] inheritance patterns have been reported. Homozygous mutations in *EVER1* or *EVER2* have been reported in ~75% of patients with EV[13]. The *EVER* genes are predicted to encode highly conserved transmembrane proteins[29] that are important regulators of zinc homeostasis[30]. EVER proteins are expressed in T and B lymphocytes, NK cells, endothelial cells, myeloid cells, and dendritic cells[29]. Products of *EVER1* and *EVER2* act as dominant restriction factors for HPV. Loss of EVER zinc homeostasis enhances expression of viral genes, specifically the pro-oncogenic E6 and E7, contributing to HPV mediated carcinogenesis[30].

EV lesions are refractory to conventional therapies. Non-surgical interventions with topical 5-fluorouracil[31], 5% imiquimod[32], tacalcitol[33], systemic retinoids combined with interferon (IFN)α[34], cimetidine[35], and topical 5-aminolevulinic acid photodynamic therapy[36] yield

inconsistent results. Approximately one third of patients go on to develop malignancy with an average of 24 years between development of benign lesions and cancer[37]. Invasive skin cancers are typically squamous cell carcinomas that often retain features of Bowen's carcinomas. They develop slowly and are locally destructive[38].

Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) Syndrome: CXCR4 deficiency

This rare autosomal dominant immunodeficiency was described by Zuelzer[39] and Krill et al [40] in 1964 in a 10 year old girl with congenital neutropenia and recurrent infections. WHIM is characterized by recurrent bacterial infections in infancy and early childhood, most commonly pulmonary, gastrointestinal, and cutaneous. Kawai and Malech pooled information from 37 published cases[41]. At first presentation, 78.6% had warts, 89.6% had hypogammaglobulinemia, and 91.7% had neutropenia. Specific clinical features and age at diagnosis were variable. All patients had recurrent bacterial infections in childhood including pneumonias, sinusitis, cellulitis, urinary tract infections, thrombophlebitis, omphalitis, osteomyelitis, deep soft tissue abscesses, and skin infections. Common pathogens include *Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella pneumoniae, Staphylococcus pneumoniae*, and *Proteus mirabilis*. Infections typically respond well to antibiotics and run a benign course. However, recurrent pneumonias can result in bronchiectasis and lead to chronic infection with *Pseudomonas aeruginosa* and *Burkholderia cepacia*[41].

HPV related disease is the predominant feature. Numerous cutaneous warts occur on the feet, hands, and trunk; genital condyloma accuminata with papillomatosis may become dysplastic or neoplastic. There are also reports of severe recurrent oral and genital herpes [42], and herpes zoster [43] as well as two reports of patients developing Epstein Barr virus (EBV) - related lymphoproliferative disorders, indicating susceptibility to herpes family viruses as well[44, 45]. HPV related carcinomas are a significant cause of morbidity with lesions of mucosal or transitional areas of the skin at the highest risk of dysplasia. Frequent monitoring with biopsies or surgical removal is often required [41].

The primary laboratory abnormality is neutropenia with bone marrow hypercellularity due to a defect in the release of mature neutrophils[41, 46]. Myeloid hypercellularity with cytoplasmic vacuolation, chromatin hypercondensation, and hypersegmented pyknotic nuclei all contribute to the pattern referred to as myelokathexis [47]. Despite severe neutropenia, patients are not at risk for overwhelming sepsis, presumably because functional neutrophils are released from the bone marrow during stress. Other laboratory abnormalities include lymphopenia of CD27+ memory B cells as well as both unswitched immunoglobulin D (IgD +) and switched (IgD-) B lymphocytes [48]. Hypogammaglobulinemia primarily involves IgG but can also affect IgM, but responses to immunization demonstrate that the defect in humoral immunity is incomplete. T lymphopenia with normal CD4/CD8 ratio and normal proliferative responses to mitogens occurs as well[48].

WHIM is caused by dominant heterozygous gain-of-function mutations in the chemokine receptor, CXCR4. Four mutations have been described: 1 frameshift and 3 nonsense mutations, which result in truncation of the cytoplasmic C-terminal portion of the receptor[49]. CXCR4 is a G-protein coupled receptor that selectively binds stromal cell derived factor – 1 (SDF-1, or CXCL12). Mutations in *CXCR4* impair SDF-1 mediated signaling due to absence of intracellular phosphorylation sites on the receptor.[43] Leukocytes expressing the truncated CXCR4 demonstrate enhanced chemotactic responses to SDF-1 which likely impairs their trafficking [43, 50]. The C-terminal portion of the receptor contains canonical phosphorylation sites that are targets of G protein coupled receptor kinases. Phosphorylation

results in binding of β-arrestins to CXCR4 and interaction with C-terminal sequences that result in endocytic internalization of the receptor and desensitization to ligand stimulation [50]. Two cases of WHIM have no mutation identified so far [43, 51]. In the patients lacking specific mutations, a marked decrease in G-protein coupled receptor kinase 3 (GRK3) has been described. Overexpression of GRK3 restored ligand-mediated internalization of CXCR4 in response to SDF-1 to normal levels, showing that CXCR4 hyperactivity is the common biochemical feature in all affected patients. SDF-1 and CXCR4 are expressed in normal Langerhans' cells and keratinocytes[52] and increased levels of SDF-1 are expressed in HPV infected dermis[43]. These observations suggest that host susceptibility to HPV infection is mediated by upregulation of CXCR4. Defects in number and function of myeloid and, more impressively, plasmacytoid dendritic cells, have also been demonstrated, likely enhancing susceptibility to HPV[53].

Early diagnosis and aggressive measures to decrease bacterial infections improves prognosis. Treatment with granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), intravenous immunoglobulin (IVIg), and prophylactic antibiotics provide benefit[41, 54, 55]. The mechanism of action of G-CSF involves a positive feedback loop that increases neutrophil counts and enhances release of neutrophil elastase. Neutrophil elastase cleaves SDF-1 and CXCR4, reducing its activity and releasing mature neutrophils from the bone marrow into the peripheral blood[54, 55]. Therapy with plerixafor, a CXCR4 antagonist, has shown promising results, reversing neutropenia in 3 WHIM patients[56].

Autosomal Recessive Hyper IgE Syndrome (DOCK8 Deficiency)

Mutations in dedicator of cytokinesis 8 (*DOCK8*) cause an autosomal recessive combined immunodeficiency with hyper IgE. Some features are in common with *STAT3* mutated hyper IgE (Job's syndrome), such as atopic dermatitis, *Staphylococcus aureus* skin abscesses and soft tissue infections, pneumonias, elevated serum IgE and eosinophilia. However, a distinguishing feature of *DOCK8* deficiency is susceptibility to cutaneous viral infections, most commonly herpes simplex virus (HSV), HPV, molluscum contagiosum virus (MCV), and varicella zoster virus (VZV). These infections are extensive, can be disfiguring, occur concurrently, and are difficult to control. Examples include chronic orolabial or anogenital infections, herpes simplex keratitis, and eczema herpeticum. HPV presents as flat and verrucous warts. In 21 patients followed at the National Institutes of Health (NIH), 62% had histories of significant warts [57]. An increased incidence of genital warts has not been reported and it is unclear whether these patients are at increased risk for them. Molluscum lesions are often confluent and can be disfiguring as well[57-59].

DOCK8 deficiency is associated with recurrent upper and lower respiratory tract infections, sinusitis, otitis media, mastoiditis, and pneumonia from a wide spectrum of Gram positive and Gram negative bacteria as well as intracellular fungi, such as *Histoplasma capsulatum*. Mucocutaneous candidiasis and recurrent infections of the gastrointestinal tract are common. DOCK8 deficiency is highly associated with the development of malignancies in childhood or young adulthood, including squamous cell carcinomas, Burkitt's and other lymphomas, and T cell leukemia [58, 59].

The lymphopenia of DOCK8 deficiency progresses with age, predominantly affecting T cells, especially CD4 T cells, and to a lesser extent NK cells and B cells. CD8 T cells from DOCK8 deficient patients fail to activate, divide, and expand following T cell receptor stimulation and have poor production of IFNγ and tumor necrosis factor (TNF)α [60]. Impaired functioning of CD8 T cells likely contributes to the viral susceptibility of DOCK8 deficiency[61]. Decreased CD4 T helper type 17 cells (Th17) may explain the increased

susceptibility of some DOCK8 deficient patients to mucocutaneous candidiasis [62]. Besides their elevated IgE, DOCK8 deficient patients have low IgM, high or normal IgG, and low, high, or normal IgA. Antibody responses to previously encountered protein antigens and polysaccharides are variable[60].

Warts are extremely difficult to eradicate; imiquimod, cidofovir, and other conventional treatments are usually unsuccessful. Eczema is frequently exacerbated by *Staphylococcus aureus*. Reduction of colonization of the skin with bleach baths is recommended, as is the use of topical corticosteroids, although the latter may exacerbate cutaneous viral infections. Patients with antibody deficiency may benefit from IVIg [63]. Mortality due to malignancy and infections is high. Hematopoietic stem cell transplant (HSCT) has led to immune reconstitution and viral eradication [64]. However, DOCK8's role in non-hematopoietic tissues and the ability of HSCT to prevent malignancies is undefined.

Idiopathic CD4 Lymphopenia

Idiopathic CD4 lymphopenia (ICL) was first defined by the Centers for Disease Control in 1992 as a disease with "a documented absolute CD4 T lymphocyte count less than 300 cells/mm^3 or of less than 20% on more than one occasion, no evidence of infection on HIV testing, and the absence of any defined immunodeficiency or therapy[65]." ICL is a heterogeneous disorder that is usually detected after an opportunistic infection in a person without a known immunodeficiency. Cryptococcosis, HPV, and nontuberculous mycobacterial infection were the three most common infectious presentations in a cohort of ICL patients followed at the NIH from 1992-2006[66]. ICL typically presents in the fifth decade. Less common infections included histoplasmosis, mucosal candidiasis, VZV, and cytomegalovirus (CMV). *Pneumocystis jirovecii* pneumonia is uncommon.

Warts in ICL typically present as disseminated verrucae or flat warts on the extremities, face, and genitals. A few reports have found HPV types -2, -3, -6, and -49 in cutaneous lesions[67-71]. HPV related dysplasia and carcinoma can be the presentation of ICL, as can juvenile laryngeal papillomatosis [72] and recurrent vulvar intraepithelial neoplasia [66]. Some patients do well with topical treatments and destructive therapies, whereas others require systemic immunomodulators, such as IFNα; some may require radical surgery. Of 40 ICL patients currently followed at the NIH, 15 have had cutaneous or genital HPV. Five of the nine patients with genital HPV have developed dysplasia or carcinoma. One patient with cutaneous HPV has developed cutaneous squamous cell cancer.

Autoimmune phenomena and autoantibodies occur frequently, with thyroid disorders and anti-nuclear antigens being the most common. Systemic lupus erythematosus, antiphospholipid antibody syndrome, autoimmune hemolytic anemia, ulcerative colitis, psoriasis, and vitiligo also occur[66]. The temporal relationship of autoimmune disease to ICL and the exact nature of this correlation are not known.

The majority of patients have an inverted CD4/CD8 ratio, but a normal CD4/CD8 ratio is found in some with concomitant depletion of CD8 T lymphocytes. Low absolute B lymphocyte counts with normal immunoglobulin production and response to vaccination and low absolute NK cells counts are common. T cells are more activated (human leukocyte antigen [HLA]-DR+), have increased CD4 T cell turnover as measured by Ki-67, higher percentages but lower absolute number of regulatory T cells as measured by forkhead box p3 (Foxp3) expression, and a lower proportion of naïve CD4 T cells as measured by expression of CD127 (the alpha chain of the IL-7 receptor, IL-7Rα) [66]. CD4 autoantibodies have been hypothesized and reported in at least one patient [73].

Despite the high rate of opportunistic infections and HPV, the overall prognosis of ICL is quite good. From the cohort followed from 1992-2006, there were 7 deaths, 4 related to opportunistic infections; there have been no deaths in the cohort followed currently. Three patients had pulmonary *Mycobacterium avium* complex (MAC), progressive multifocal leukoencephalopathy, and EBV-B cell lymphoma, respectively. One patient with severe genital HPV died of metastatic squamous cell carcinoma 42 months after initial diagnosis. All 4 deaths were in patients who had concurrent CD8 lymphopenia. The three non-opportunistic infection related deaths were due to pneumonia and metastatic prostate cancer (age 84 years). There were no deaths in the group that had no opportunistic infections and were incidentally found to have ICL [66].

GATA2 Deficiency

Deficiency in GATA2, an important transcription factor involved in hematopoiesis and maintenance of the stem cell compartment [74, 75], leads to a syndrome characterized by opportunistic infections and myelodysplasia or leukemia [76-78]. GATA2 deficiency has a variety of presentations including MonoMAC (monocytopenia and *M. avium* complex infection) [78], familial myelodysplastic and leukemia syndrome [77], DCML (dendritic cell, monocyte, B cell, and NK cell lymphoid deficiency) [76], and Emberger syndrome (a primary lymphedema with myelodysplasia or acute myelogenous leukemia) [79]. Missense and null mutations in GATA2 have been found with all four phenotypes, suggesting that the mechanism of disease is haploinsufficiency [77, 80-82]. This syndrome typically presents in later childhood or adulthood with profound circulating monocytopenia and NK, B cell, and dendritic cell lymphocytopenia [76, 78]. T cell counts and function are variable. Patients are susceptible to nontuberculous mycobacteria, HPV, *Histoplasma, Cryptococcus* and *Aspergillus*. In the largest series, HPV occurred in more than 75%, followed by herpes family viruses (HSV, VZV, and EBV) [78]. Other features include pulmonary alveolar proteinosis, panniculitis, pulmonary hypertension, thromboembolic phenomena, and recurrent miscarriages. Hypotelorism, epicanthal folds, webbed neck, long tapering fingers, and high frequency sensorineural deafness were also noted in patients described as having Emberger syndrome [83-86]. Despite specific cytopenias described, macrophages and plasma cells are seen at sites of inflammation, and patients produce normal quantities of immunoglobulin [78].

Generalized warts occur frequently and can be severe leading to dysplasia and neoplasia. In 18 patients from 5 families with GATA2 deficiency followed at the NIH, 14 had severe or disseminated HPV; in most it was the first manifestation of disease. Warts typically presented in adolescence or early adulthood as verruca plana or vulgaris on the face or extremities and genital condylomata. Severe genital HPV commonly led to cervical dysplasia and carcinoma [78].

The high rate of myelodysplasia and leukemias contributes to the high mortality rate in patients with GATA2 deficiency[78, 87, 88]. Abnormal cytogenetics are common. Allogeneic hematopoietic stem cell transplantation seems to be curative. [87]. Graft versus host disease (GVHD) has occurred both early and late after transplantation but was usually manageable.

WILD Syndrome

Warts, immunodeficiency, lymphedema, and dysplasia (WILD) syndrome is described in two cases as a combined immunodeficiency with disseminated warts, lymphedema, and anogenital dysplasias[89, 90]. Both cases had lower extremity lymphedema presenting at 6 months that progressed to involve the entire lower and upper extremities and groin. Warts began in adolescence with eventual development of anogenital dysplasia or cancer. Both

patients had B and T cell lymphopenia and depressed mitogen stimulated lymphocyte proliferation. This may well represent another manifestation of GATA2 deficiency.

Netherton Syndrome (SPINK5 deficiency)

Netherton syndrome is a rare autosomal recessive disorder characterized by congenital icthyosiform erythroderma, tricorrexis invaginata (bamboo hair), and atopy, food allergies and asthma. Chronic inflammation of the skin leads to dehydration, life threatening infections, and sepsis, leading to a high mortality rate in the first year of life [9192].

Patients with Netherton syndrome have increased susceptibility to viral skin infections, specifically HSV and HPV, although there are few published reports of the latter [92, 95-98]. The Netherton syndrome has high IgE, normal to elevated IgG, hypercomplentemia (C3 and C4), and NK cell lymphocytopenia [92]. Interestingly, IgE levels are normal at birth, reach their peak by age 4, and then decrease over time. CD4 lymphopenia, impaired skin tests to microbial antigens, and impaired lymphocyte proliferation to mitogens have also been reported [97, 99]. Susceptibility to cutaneous and systemic infections may reflect the proteolytic breakdown of antimicrobial peptides, specifically the cathelicidin carboxy fragment, LL-37.

Serine protease inhibitor Kazal-type 5 (*SPINK5*) encodes the serine protease inhibitor, lympho-epithelial Kazal-type-related inhibitor (LEKTI), which is normally cleaved into 15 active domains that suppress serine protease activity[93]. *SPINK5* mutations truncate LEKTI and permit unopposed serine protease activity. There is a strong genotype-phenotype correlation with the length of he residual LEKTI molecule [94].

Warts in Netherton syndrome typically present in adolescence or adulthood as common genitoanal, plane and verrucous lesions. Depending on the HPV type, they may progress to carcinoma. EV-associated HPV types have been found on biopsy and skin cancers occur in these patients [97]. Lesions are typically recalcitrant to therapy but there has been some success with use of retinoids, psoralen plus ultraviolet A (PUVA) therapy, and IFNα [92, 95-98].

MST1 (MST1 or STK4 deficiency)

Homozygous mutations in the serine-threonine kinase 4 (STK4) gene cause a combined immunodeficiency that is primarily characterized by a dramatically reduced amount and survival of circulating naïve T cells. Missense mutations and deletions in *STK4* in 4 patients from two consanguineous unrelated families from Turkey[100] and in 3 patients from a consanguineous Iranian family[101] result in truncation of the STK4 protein, previously named Mammalian sterile 20-like protein (MST1).

Patients with STK4 deficiency suffer from recurrent bacterial skin and respiratory tract infections; recurrent cutaneous viral infections with HSV, VZV, and MCV are common. Persistent EBV viremia is common and can lead to EBV associated lymphoproliferative syndrome and EBV related malignancies. Chronic dermatitis resembling eczema has been described in 3 patients. Autoantibodies and autoimmune hemolytic disease have occurred in 2. All 3 patients in the Iranian family, and 1 in the Turkish cohort had structural heart disease including atrial septal defect; patent foramen ovale; mitral, tricuspid, and pulmonary insufficiency; and right ventricular hypertrophy[100, 101].

Cutaneous warts were described in all 3 patients from the Iranian family. Histologic analysis showed orthokeratosis and epithelial hyperplasia secondary to HPV-57 and -84 and HPV -71, -3, and -25 in 2[101].

Progressive CD4 T cell lymphopenia with profoundly low naïve CD4 T cell counts is hallmark while CD8 T cells and NK cells are within normal range. T cell proliferation responses to both antigens and mitogens are markedly impaired. B cell counts are mildly low with hypergammaglobulinemia of IgG and variable increases in IgA and IgE. Antibody responses are defective. Persistent neutropenia occurs with normal maturation of neutrophils in the bone marrow [100, 101].

STK4 is involved in several pathways controlling T cell survival and death and its activity can be regulated by caspase-induced cleavage. STK4 is necessary for activation of forkhead box protein O1 (FOXO1), an important transcription factor in T cell homeostasis. Loss of STK4 results in significantly lower expression of FOXO1. Decreased expression of FOXO1 leads to decreased expression of IL-7Rα, CCR7, and CD62 ligand (CD62L) on naïve T cells, possibly impairing T cell homing[100, 101]. STK4 deficient T cells have enhanced apoptosis mediated through increased Fas expression, decreased B cell lymphoma 2 (BCL-2) expression[100], and loss of mitochondrial transmembrane potential[101]. STK4 deficiency may also impair development or maintenance of T regulatory cells with decreased absolute numbers described in these patients[100].

Therapy relies on treatment of the underlying infections. EBV related diseases were intermittently controlled with anti CD20 therapy. HSCT was curative in 1 patient; 2 died within 6 months due to GVHD[100].

NEMO (NEMO or IKBKG deficiency)

Hypomorphic mutations in the nuclear factor (NF)κB essential modulator (*NEMO* or *IKBKG*) gene cause a combined immunodeficiency with early susceptibility to pyogenic and mycobacterial infections. NEMO is a 419 amino acid regulatory protein encoded by 10 exons on the X chromosome that is critical for NFκB activation. After specific receptor activation, the inhibitor of κB (Iκb) kinase complex (IKK) phosphorylates IκB, leading to its degradation and the release of NFκB, which activates the transcription of various genes [102]. Amorphic NEMO mutations are lethal in boys and cause an ectodermal phenotype known as incontinentia pigmenti in girls, characterized by dermal scarring and skin hyperpigmentation. Hypomorphic mutations in boys can result in immunodeficiency with or without ectodermal dysplasia. The ectodermal dysplasia is characterized by dental abnormalities, eccrine sweat gland dysgenesis, and fine sparse hair [103] because of impaired ectodysplasin A signaling via NFκB.

Boys with defects in NEMO are susceptible to bacterial, viral, pneumocystis and mycobacterial infections starting within the first year of life. They can present with pneumonia, bacteremia, skin and soft tissue abscesses, enteritis or colitis, encephalitis or meningitis, sinusitis, or osteomyelitis. Approximately 20% of patients develop HSV, CMV or MCV. However, patients are also susceptible to severe disseminated HPV, typically flat warts[104]. Inflammatory colitis is also common [105].

The immunodeficiency of NEMO can include hypogammaglobulinemia with elevated IgM and IgA due to impaired CD40-mediated B cell class switch recombination. Toll-like receptor (TLR) signaling and NK cell cytotoxicity are diminished as well. T cell numbers and proliferation to mitogens tend to be preserved. In the patients with HPV infection, CD4 lymphopenia was common with decreased NK cell cytotoxicity in one patient [105].

Treatment of patients with defects in NEMO relies on prevention and aggressive treatment of infections. Replacement IVIg and antimicrobial prophylaxis are recommended.

Severe Combined Immunodeficiency

Severe Combined Immunodeficiency (SCID), characterized by absence of T cells and profoundly impaired adaptive immunity, has an incidence of 1 in 40,000-75,000 live births. Glanzmann and Riniker first described SCID in 1950 in Swiss infants who were profoundly lymphopenic and died of infection within the first two years of life [106]. Adenosine deaminase (ADA) deficiency was recognized in 1972 as the first molecular cause of SCID [107]. Now, mutations in more than 30 different genes have been described as causes of SCID[108].

SCID classically presents in infancy with recurrent severe infections, chronic diarrhea, and failure to thrive. Persistent mucocutaneous candidiasis, adenovirus, CMV, EBV, rotavirus, respiratory syncitial virus, VZV, HSV, measles, influenza, and parainfluenza 3, *Pneumocystis jirovecii*, and vaccine related infections with polio, rotavirus, varicella and Bacillus Calmette-Guerin are common and can be fatal. Transplacental passage of alloreactive maternal T cells or transfusion of blood products containing viable lymphocytes can cause GVHD[109].

Typical laboratory abnormalities include severe T cell lymphopenia, abnormal lymphocyte subpopulations, absent or very low T cell proliferative responses, and hypogammaglobulinemia. However, absolute lymphocyte counts may be normal in the setting of maternal T cell engraftment and hypogammaglobulinemia may be masked by transferred maternal IgG in infants less than 6 months.

Widespread seborrhea-like dermatitis, morbilliform eruptions, and extensive eczema are common in SCID. However, there are a few cases of warts as the presenting cutaneous sign of SCID. Three adults with lifelong histories of frequent sinopulmonary infections and mucosal candidiasis developed warts as adults and were found to have ADA deficiency [110-112]. Presumably, the defect in cellular immunity caused their HPV susceptibility. However, ADA is present in somatic cells in addition to the myeloid compartment and ADA itself may play a role in prevention of HPV. Widespread cutaneous and plantar warts have also been described in patients with IL-2 receptor common gamma chain (γc) and Janus kinase 3 (JAK3) deficiencies following hematopoietic stem cell transplantation [113, 114]. Laffort et al found warts a mean of 8 years after HSCT, primarily on the hands and feet, but no genital or pre-malignant lesions were seen. HPV genotypes associated with EV (HPV-5, -14, -36), common warts (HPV-2 and -57) and flat warts (HPV-3) were identified in the lesions of 6 patients. Types HPV-5 and -14 are potentially oncogenic and were noted only in patients with EV-like lesions. Chimerism patterns after transplantation were similar in patients with mutations in γc-deficient and JAK3- deficient SCID, regardless of HPV status. T and NK cells were of donor origin in all patients tested and B cells were of donor origin in 2/7 patients tested with HPV disease and 1/8 without HPV. There was no difference in NK cell number between the groups with and without HPV. One patient had complete resolution with a combination of laser therapy, acitretin, and topical imiquimod. All other patients' lesions were recalcitrant to therapy. The etiology for increased susceptibility to warts after HSCT in patients with IL2Rγc/JAK3 mutations is unknown, but IL2Rγc-dependent cytokines may induce production or amplification of immune responsive molecules in keratinocytes. [113]

CVID

Common variable immunodeficiency (CVID) is the most prevalent immunodeficiency, affecting 1 in 25,000 – 1 in 50,000 white patients, but a single unifying genetic etiology is still elusive. Most patients are diagnosed at 20-40 years but both children and adults have been described. CVID is heterogeneous with a broad range of clinical manifestations

including chronic infections, inflammatory and autoimmune disease, and increased cancer and lymphoma. CVID is characterized by low IgG, IgA, and/or IgM with poor or absent antibody production[115].

Pneumonias due to *Streptococcus pneumoniae, Haempohilus influenzae* or *Mycoplasma* species are common before diagnosis and treatment are initiated. Warts are uncommon in CVID, but severe disseminated warts are reported. Three cases with ages of wart onset of 9, 13, and 55 were associated with T-lymphopenia and impaired T cell response to mitogens[116, 117]. One had intestinal lymphangiectasia as well [118]. An 18-year-old man with CVID had normal T cell numbers but decreased T cell proliferation to antigen and multiple warts on his arms, hands, and feet. His lesions completely resolved after treatment with subcutaneous immunoglobulin replacement [119]. T cell deficiency likely contributes to susceptibility to warts in CVID. These cases may represent other recognized genetic defects masquerading as CVID.

LAD-1 (CD18 deficiency)

Leukocyte adhesion deficiency type-1 (LAD-1) was described in the 1970s [120] as an autosomal recessive disease, eventually recognized as caused by mutations in integrin B2 (*ITGB2*), encoding the common beta chain of the beta 2 integrin family (CD18) [120-122]. Mutations resulting in dramatically reduced or nonfunctional forms of CD18 also prevent surface expression of alpha subunits of the three heterodimers A1/B2 (lymphocyte function-associated 1 [LFA-1], CD11a), A2/B2 (macrophage-1 antigen [Mac-1], CD11b), and A3/B2 (p150,95, CD11c) as well as impair binding to intracellular adhesion molecules, involved in firm adhesion of leukocytes to vascular endothelium. This impairment leads to defective polymorphonuclear chemotaxis, margination, adherence, phagocytosis of complement coated particles, bacterial killing, and diminished NK cell and cytotoxic T cell activity [122, 123]. Clinical characteristics include frequent systemic, skin, and soft tissue infections, impaired wound healing, gingivitis and periodontitis, and inflammatory bowel disease, all without pus formation [122-124]. Disease phenotypes correlate with complete or partial absence of CD18[125]. Somatic reversion mutations have also been reported [126].

Uzel et al., recently reported severe warts in 5 patients with milder forms of LAD-1 [127]. Two siblings with deletions of exons 12 and 13 developed extensive warts over their upper extremities in childhood. The younger sibling had leukocytoclastic vasculitis, myositis, and Graves' disease, as well. A 30-year-old woman with extensive colitis, perianal fistula and subtotal colectomy developed extensive vulvovaginal warts at age 28. A 30-year-old man developed extensive perianal warts requiring resection and treatment with pegylated IFNα. A 37-year-old man with colitis developed warts over his hands. The exact susceptibility to HPV in LAD-1 is unknown; decreased T and NK cell cytotoxicity and immunodysregulation in patients with residual CD18 levels and inflammatory bowel disease may be related. It may be that viral susceptibility is also high in severe forms of LAD-1, but they are transplanted or die earlier in life. Allogeneic HSCT succeeds in LAD-1. Gene therapy in a canine LAD-1 model is promising [128].

Wiskott-Aldrich Syndrome (WASP deficiency)

Wiskott Aldrich Syndrome (WAS) is an X-linked immunodeficiency affecting approximately 1 in 100,000 live births first described by Wiskott in 1937 after noticing the triad of thrombocytopenia, eczema, and frequent pyogenic infections[129, 130]. This syndrome was re-discovered by Aldrich in 1954 who noted its X-linked inheritance pattern[131]. Subsequently, other clinical features of WAS have been described including specific immunodeficiency and high rates of autoimmunity and malignancy[129, 132, 133].

WAS gene encodes its cognate protein, WASP, which is present in all hematopoietic cells, where it facilitates cellular migration through cytoskeletal reorganization.[134] The severity of eczema varies considerably but usually resembles classic atopic dermatitis and occurs more frequently in the first year of life. There are at least 4 distinct WAS phenotypes that correlate with levels of protein expression:[135, 136, 137].

Immunodeficiency in WAS affects both humoral and cellular immunity and depends largely on the amount of WASP expression. In classic WAS, the lymphopenia often progresses over time; IgG and IgM are typically low or normal and IgA and IgE are often elevated[133]. Defective antibody responses to polysaccharide vaccines, diminished lymphocyte proliferation to mitogens, normal to increased numbers of NK cells but reduced cytotoxicity, and impaired chemotaxis of phagocytes are common[133, 138, 139]. Patients are particularly susceptible to *Streptococcus pneumoniae, Haemophilus influenzae*, and *Neisseria meningitidis*. Opportunistic infections include *Pneumocystis jirovecii*, MCV, systemic VZV and CMV. Fungal infections consist primarily of Candida[132, 133]. Autoimmunity occurs in 40- 70% of patients, including hemolytic anemia, vasculitis, inflammatory bowel disease, and renal diseases[133, 140]. Malignancies usually occur in adolescence and young adulthood with B cell lymphomas and leukemias being the most common[133].

Cutaneous HPV is uncommon but has been reported in WAS. Sullivan et al. reported 6/154 patients with WAS had recurrent warts[133]. Case reports of warts in WAS include a twelve year old [141]; a two year old with disseminated warts treated successfully with “transfer factor” who had complete resolution of warts within 2 weeks of treatment[142]. Most recently, a 25 year old man with 2 years of eczema and recalcitrant warts on his hands and feet [143] had complete resolution after receiving acitretin for 13 weeks. However, once it was tapered, the lesions returned. The exact etiology of HPV infection in WAS is not understood, but defects in NK cellular immunity are likely to be etiologic.

Currently, allogeneic HSCT is the only curative treatment available for WAS with the best results in recipients of matched related donors less than 5 years of age[144-146]. Gene therapy trials with a lentiviral vector[147, 148], are currently underway [149].

Ataxia Telangiectasia (ATM Deficiency)

Ataxia – Telangiectasia (A-T) is an autosomal recessive multisystem disorder characterized by progressive neurodegeneration, oculocutaneous telangiectases, radiosensitivity and combined immunodeficiency[150, 151]. In 1958 Boder and Sedgewick described 8 patients in 6 families with progressive cerebellar ataxia, oculocutaneous telangiectasia, and frequent sinopulmonary infections [152].

Sinopulmonary infections are common in A-T; chronic lung disease and bacterial pneumonia have been major causes of death [153, 154]. In 100 A-T patients recurrent sinopulmonary infections occurred in more than one third. However, infections with *P. jirovecii* or following live viral vaccination do not occur. Infections with *Candida* were rare and only in the setting of severe viral infection or chemotherapy. Viral infections include VZV, HSV, MCV, and EBV. HPV occurred in 17 patients and were severe and refractory to treatment in 7 [155].

Immunodeficiency in A-T is variable. The most common humoral abnormalities are low B lymphocytes [155]; decreased IgG, IgA, IgE, IgG4 and IgG2 [156, 157155]; impaired antibody responses [158]; and occasional hypergammaglobulinemia [159]. CD4 T lymphopenia [155, 160], decreased CD4/CD45RA lymphocytes [160, 161]; decreased NK cells [155]; and impaired lymphoproliferation to mitogens and antigens are reported[162].

A-T results from mutations in the ataxia-telangiectasia mutated (ATM) gene on chromosome 11, a phosphatidylinositol 3-kinase family member involved in mitogenic signal transduction, intracellular protein transport, and cell cycle control [151]. In the absence of ATM, repair of DNA breaks such as in V(D)J recombination and breaks caused by ionizing radiation does not occur.

Mortality typically occurs from lymphoreticular malignancies and infections of the respiratory system, further complicated by their neuromuscular deterioration. Median survival in two large cohorts was 25 and 19 years, respectively. However, life expectancy did not correlate well with neurologic impairment [163].

CD40L deficiency (X-linked Hyper IgM Syndrome, XHIGM1)

First described in the 1960's[164], the syndrome was most commonly observed in males as an X-linked recessive trait. HIGM1 is due to mutations in CD154 (CD40L, tumor necrosis factor surface family 5 [TNFSF5]), which encodes CD40L, expressed transiently on activated T cells. These mutations result in failure of T cell signaling to B cells and monocyte/macrophages, resulting in impaired B cell stimulation for class switch recombination, as well as other cell mediated defects[165, 166].

Affected males are susceptible to recurrent bacterial and opportunistic infections starting early in life, including *Pneumocystis jirovecii* pneumonia, occurring in 20-40% of cases. Chronic watery diarrhea due to infection with *Cryptosporidium* species is common. Liver and biliary tract disease with sclerosing cholangitis due to *Cryptosporidium parvum*, and infections with hepatitis B and C viruses as well as CMV can result in liver and biliary tract tumors. Neutropenia occurs in about 50% of patients, causing recurrent oral ulcers and proctitis[165]. Autoimmunity is also common in CD40L deficiency with immune thrombocytopenia, hemolytic anemia, and immune mediated nephritis

CD40L deficient patients have normal numbers of circulating B lymphocytes expressing IgM or IgD. However, cell surface expression of IgG, IgA, and IgE may be profoundly reduced. IgM is not always elevated as its name implies; 50% have normal levels at diagnosis. However, the majority of patients develop hyper IgM at some point. Patients also have low affinity antibody production to T dependent antigens and lack an amnestic response, reflecting their lack of memory B cells. T cell subsets and proliferative responses to mitogens are normal, although in vitro proliferation to T dependent antigens is often reduced. Lymph nodes contain primary follicles but characteristically lack germinal centers[165, 167].

Susceptibility to viral infections is not a hallmark of CD40L deficiency. A 3 year old boy with cutaneous histoplasmosis also had common warts on the hands [168]. He had elevated IgM, low IgG, and normal IgA as well as CD4 T cell lymphopenia, but no neutropenia. A 28 year old man with recurrent herpes labialis had 7 years of recalcitrant common warts on the elbows and dorsal surfaces of the hands and knees[169]. Allogeneic HSCT is currently the treatment of choice for CD40L deficiency[170]. Clinical management is with administration of IVIg and prophylactic antibiotics.

Discussion

Immunity leading to wart regression is essentially universal, but poorly understood. Cellular and cytotoxic immunity provided by T cells and NK cells are necessary for control of HPV infections, but the exact mechanisms are unknown.

Several lines of evidence show the importance of cellular immunity in wart regression and long-lived immunity to HPV. In vivo, delayed type hypersensitivity (DTH) reactions to purified formalin inactivated HPV antigens were highest in patients with prior warts (73%) but lower (51%) in those with active warts. The duration of warts strongly influenced DTH [171], with response highest at 6 months (65%) and 2 years (69%) and then decreasing to 20% in those with warts for more than 10 years[172]. The importance of CD4+ T cells in control of HPV became more obvious with the advent of human immunodeficiency virus (HIV) infection, in which multiple recurrences of cervical HPV infection[173] and genital warts[174] and prolonged persistence of high risk HPV occur[175] despite treatment with antiretroviral therapy [176]. Both CD4 and CD8 T cells are seen histologically in regressing genital warts along with upregulation of adhesion molecules required for lymphocyte trafficking [177]. These infiltrating lymphocytes produce pro-inflammatory cytokines including IL-12, TNFα, and IFNγ, characteristic of a Th1 phenotype[178]. Increasing evidence has shown that CD4 T cell responses to E2 and E6 specific HPV proteins are important in control of HPV-16. Strong Th1 responses to E2 and E6 occur in normal individuals without clinical signs of HPV-16 infection[179]. These are only occasionally impaired in patients with high-grade cervical intraepithelial neoplasia (CIN) but more impaired in patients with cervical cancer[180].

Antigen specific cytotoxic T cells (CTL) and NK cells are the most important effectors for viral infections, including HPV. CTL responses of both CD4 and CD8 T cells, measured by specific lysis after stimulation with HPV specific proteins are reduced in patients with previous and ongoing HPV infection[181-183]. Reduced NK cell activity against HPV-16 infected keratinocytes has been reported in patients with active HPV-induced neoplasia[184].

The importance of effective T and NK cell cytotoxic responses is further supported in host defense against recurrent respiratory papillomatosis (RRP). RRP is a rare disease of the larynx caused by HPV-6 and -11. A shift in immunologic tolerance with polarization of T cells to a Th2 and T regulatory cell phenotype as well as defective NK cell cytotoxicity of HPV infected keratinocytes have been described in patients with chronic RRP. Patients with RRP have no other infection susceptibilities and have otherwise normal immunity[185].

There is also some role of humoral immunity in the control of HPV. Eventual seroconversion and evolution of type specific antibody to L1, the major HPV coat protein, occurs 6-18 months after infection. However, 20-50% of women with detectable HPV DNA do not have type specific HPV antibodies. When present, these antibodies are long lived, persisting for more than 10 years in 20-25% of women[186]. Whether these low level antibodies are protective against future infection with the same or different HPV strains is not known.

HPV evades host defense and induces poor immune responses in normal individuals. It has an exclusively intra-epithelial life cycle, infecting basal keratinocytes via micro-abrasions of the epithelium, leaving the basal lamina intact. The subsequent life cycle, including encapsidation, viral assembly, and maturation occur in the most superficial cells of the squamous epithelium. Virus capsid entry typically leads to activating signals for dendritic cells, such as Langerhans' cells but these cells are not activated after uptake of HPV antigens [187]. HPV's are not lytic, but live in terminally differentiated cells at a high level of viral replication. Because of the infection of "dying" cells, there is little inflammatory response with release of pro-inflammatory mediators, and thus little danger signal to induce innate immune responses. Although HPV's can enter antigen presenting cells, their replication is confined to keratinocytes, thus decreasing the antigen load within the antigen presenting cell. Lastly, there is no viremic state, leaving the draining lymph nodes where adaptive responses are initiated with poor access to the HPV antigens[188, 189]. Despite the

absence of viral induced cell death, keratinocytes should be able to be activated to have type 1 interferon responses. However, HPV, like many other DNA viruses, can inhibit interferon synthesis and signaling[190-193]. HPV inhibits downstream signaling from the type 1 interferon receptor preventing translocation, transactivation, and transcription of critical elements in the type 1 interferon response (reviewed in [190]). Furthermore, HPV has evolved mechanisms to evade the effects of type 1 interferons. Several human cervical epithelial cell lines immortalized by recombinant HPV-16, -18, and -33 prevent IFNα inhibition of transcription of E6 and E7 [190, 194].

Treatment and cure of HPV in the immunocompromised is both imperative and challenging. Multiple modalities are often required including destructive treatments, topical therapies, systemic anti-virals, and immunomodulators. Two HPV vaccines, bivalent and quadrivalent, are commercially available and routine vaccination with the quadrivalent vaccine for prevention of HPV is recommended by the Advisory Committee on Immunization Practices (ACIP) for females and males ages 11-26 years [195, 196]. Successful primary treatment of HPV-associated intraepithelial neoplasia with the quadrivalent vaccine has been recently reported [197-200]. The role for HPV vaccination in the setting of immunodeficiency is undefined but is likely warranted.

When warts are numerous, recurrent, and recalcitrant, clinicians should suspect underlying immune defects, especially if occurring with other infections, atopy, autoimmunity, or malignancy. The types and locations of other infections (viral vs. fungal vs. opportunistic) can greatly help in formulating a guided differential diagnosis (see table 3). A thorough history and physical examination and focused laboratory testing should help guide an informed and prudent search for the specific immune defect (figure 1).

Host defense against HPV is multifaceted. Investigation of patients with severe recalcitrant HPV has increased our understanding of host defense and cutaneous and systemic immunity. Further study of patients with severe and recalcitrant warts will continue to yield the immune mechanisms that control one of our long-associated fellow travelers, HPV.

Acknowledgments

Financial Support: This work was supported by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health

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Abbreviations/Acronyms

ACIP	Advisory Committee on Immunization Practices
AD	autosomal dominant

ADA	adenosine deaminase
AR	autosomal recessive
A-T	Ataxia – Telangiectasia
ATM	ataxia-telangiectasia mutated gene
BAFFR	B cell activating factor receptor
BCL-2	B cell lymphoma 2
CD40L	CD40 ligand
CIN	cervical intraepithelial neoplasia
CMV	cytomegalovirus
CTL	cytotoxic T cells
CVID	Common variable immunodeficiency
DCML	Dendritic cell, monocyte, B cell, and natural killer cell deficiency
DOCK8	dedicator of cytokinesis 8
DTH	delayed type hypersensitivity
EBV	Epstein Barr virus
EV	Epidermodysplasia verruciformis
FOXO1	forkhead box protein O1
FOXp3	forkhead box protein 3
γc	common gamma chain of the interleukin 2 receptor
G-CSF	granulocyte colony stimulating factor
GM-CSF	granulocyte macrophage colony stimulating factor
GRK3	G-protein coupled receptor kinase 3
GVHD	graft versus host disease
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPV	human Papilloma Virus
HSCT	hematopoietic stem cell transplant
HSV	herpes simplex virus
IBD	inflammatory bowel disease
ICOS	inducible costimulator
ICL	Idiopathic CD4 lymphopenia
IFN	interferon
IgG, -A, -M, -E, -D	immunoglobulin –G, -A, -M, -E, -D
IκB	inhibitor of κB

IKK	IκB kinase complex
IL-7Rα	interleukin 7 receptor alpha
IL	interleukin
ITGB2	integrin beta chain β2
IVIg	intravenous immunoglobulin
JAK3	Janus kinase 3
LAD-1	Leukocyte adhesion deficiency type-1
LEKTI	lympho-epithelial Kazal-type-related inhibitor
LFA-1	lymphocyte function-associated 1
LPA	lymphocyte proliferation to antigen
LPM	lymphocyte proliferation to mitogen
MAC	*Mycobacterium avium* complex
Mac-1	macrophage-1 antigen
MCV	molluscum contagiosum virus
MonoMAC	monocytopenia, *M. avium* complex infection
MST1	mammalian sterile 20-like protein
NEMO	nuclear factor κB essential modulator
NFκB	nuclear factor κB
NIH	National Institutes of Health
NTM	nontuberculous mycobacteria
NK cells	natural killer cells
PUVA	psoralen plus ultraviolet A
RRP	recurrent respiratory papillomatosis
SCID	Severe combined immunodeficiency
SDF-1	stromal cell derived factor -1
STK4	serine-threonine kinase 4
SPINK5	serine protease inhibitor Kazal-type 5
TACI	transmembrane activator and calcium modulator and cyclophilin ligand
Th cells	T helper type cells
TLR	Toll-like receptor
TNF	tumor necrosis factor
TNFSF5	tumor necrosis factor super family 5
TNFRSF13B	tumor necrosis factor receptor superfamily 13B
VZV	varicella zoster virus
WAS	Wiskott Aldrich Syndrome

WASP	Wiskott Aldrich Syndrome protein
WHIM	Warts, hypogammaglobulinemia, infections, myelokathexis
WILD syndrome	Warts, immunodeficiency, lymphedema, and dysplasia syndrome
XHIGM1	X-linked Hyper IgM Syndrome type 1
XL	X-linked

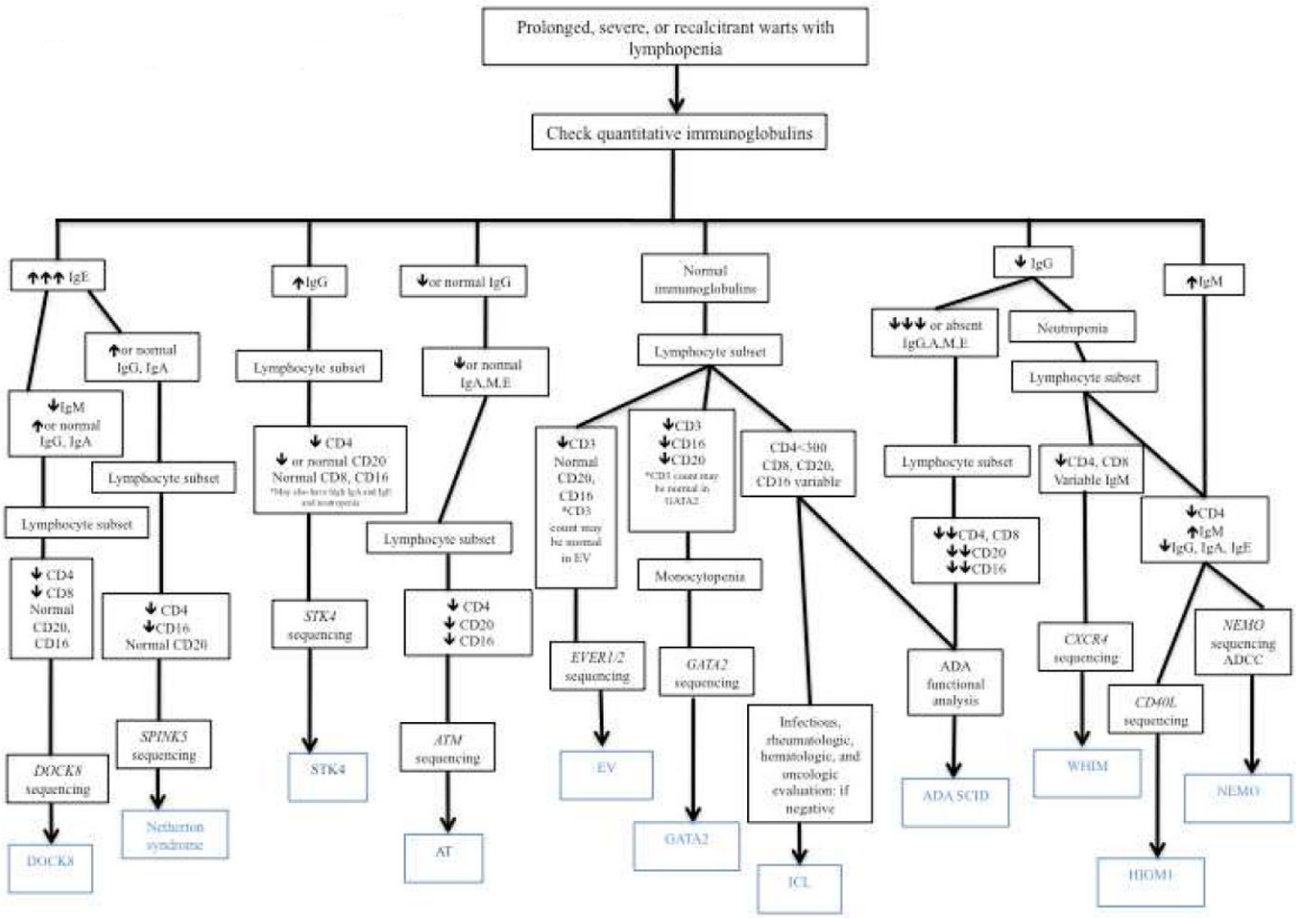


Figure I.

Algorithm for diagnosis of PID with warts and lymphopenia.

DOCK8, dedicator of Cytokinesis 8; EV, Epidermodysplasia verruciformis; ICL, Idiopathic CD4 Lymphopenia; ADA SCID, Adenosine demaminase severe combined immunodeficiency; AT, Ataxia-Telangiectasia; XHIGM1, X-linked Hyper IgM Syndrome type 1/CD40L deficiency; NEMO, Nuclear Factor κB essential modulator deficiency

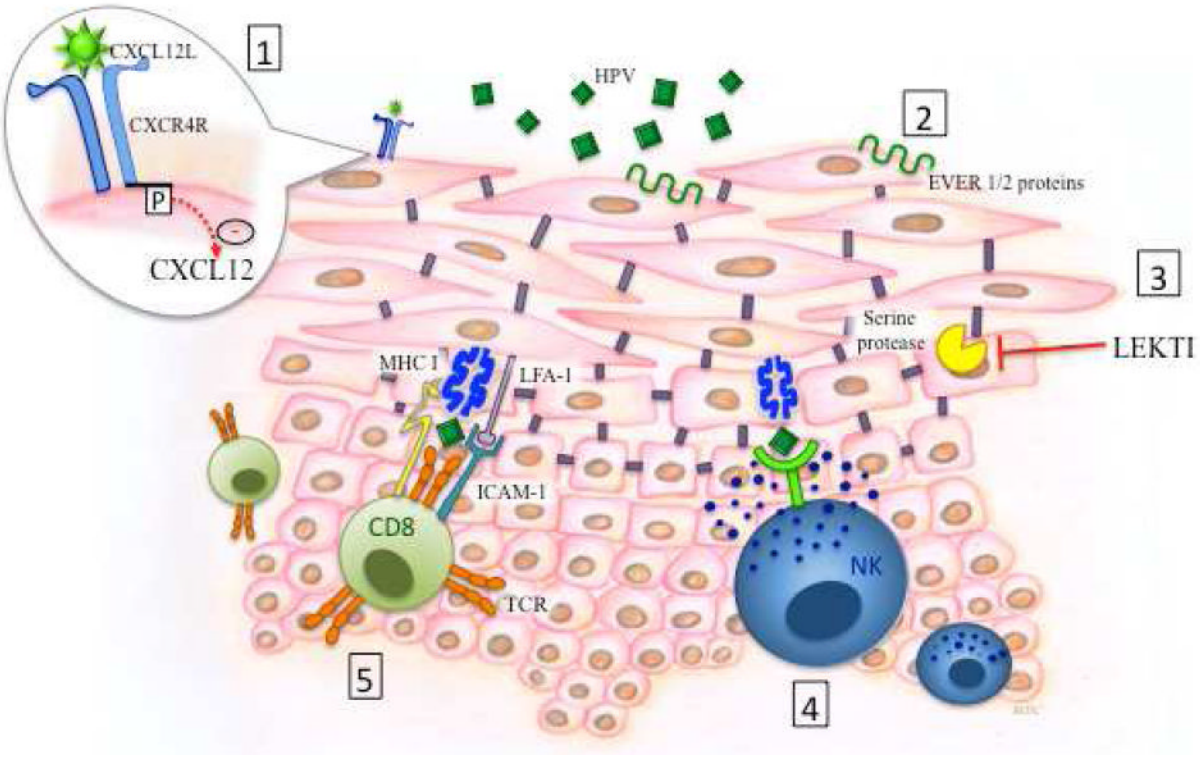


Figure II.

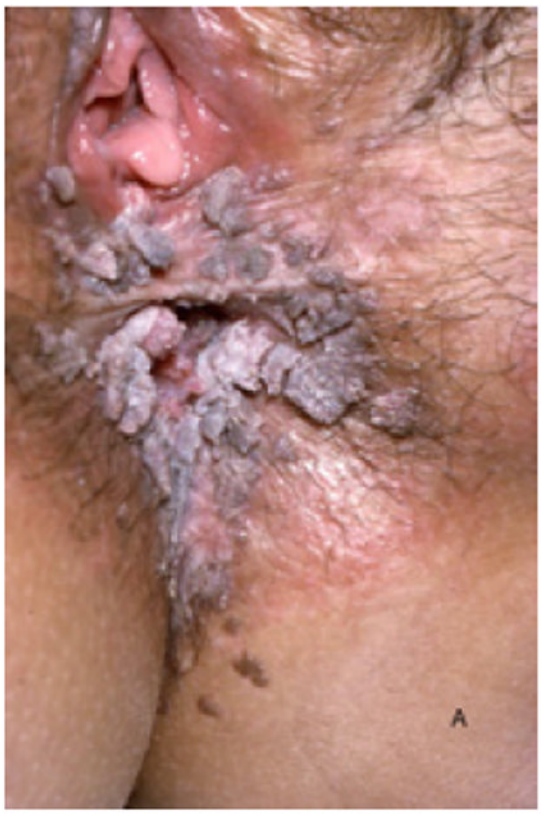
Schematic depiction of the critical elements of host defense against Human Papilloma viruses (HPV) in the skin as determined from primary immune defects.

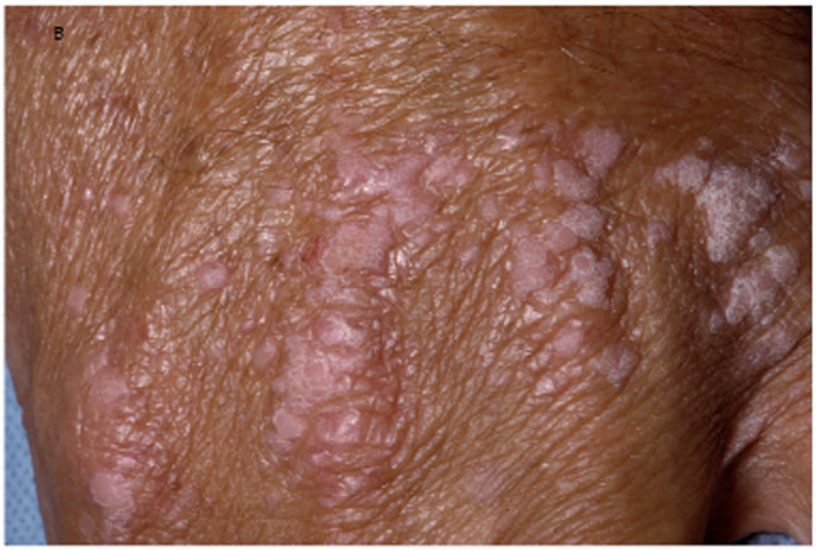
1. CXCR4: Gain of function mutations inhibit CXCL12 mediated signaling and leukocyte trafficking.

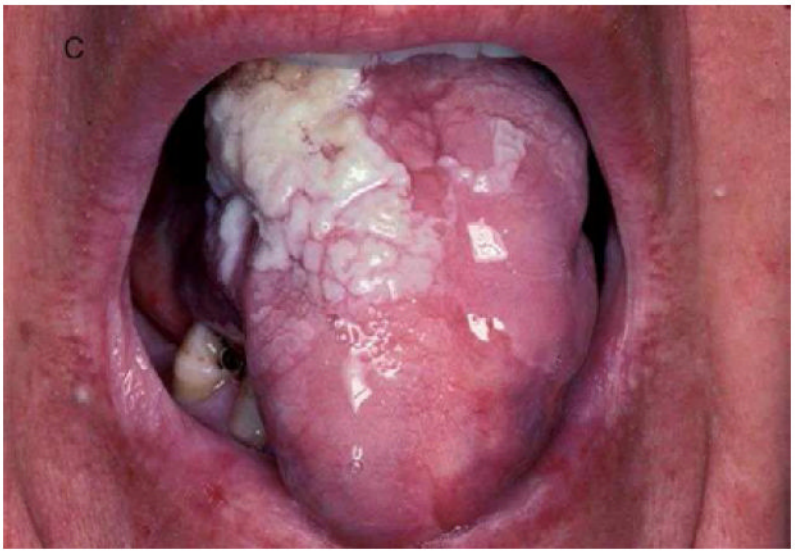
2. EVER 1 and 2: transmembrane proteins that act as restriction factors for HPV.

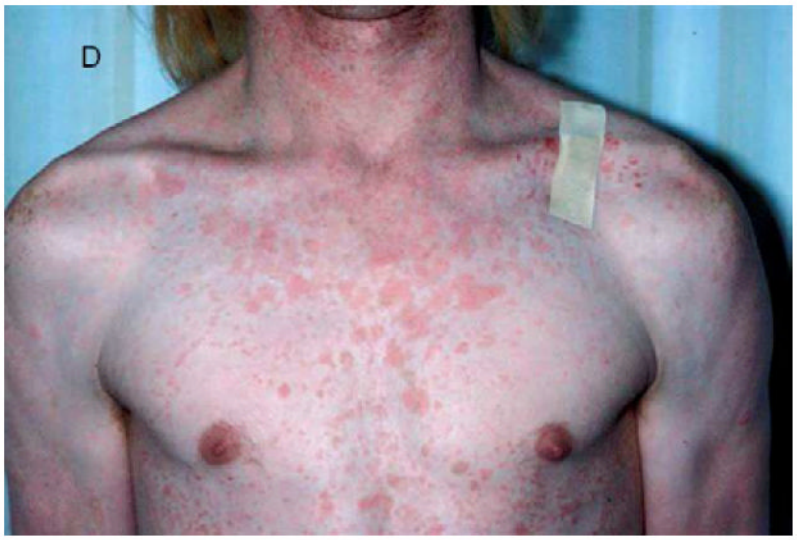
3. LEKTI inhibits serine protease activity, preventing breakdown of intercellular adhesions. Mutations in *SPINK5* lead to decreased LEKTI production and therefore impaired skin integrity.

4, 5. HPV antigen specific activation of natural killer (NK) cells and cytotoxic CD8 T cells results in degranulation of cytotoxic granules.









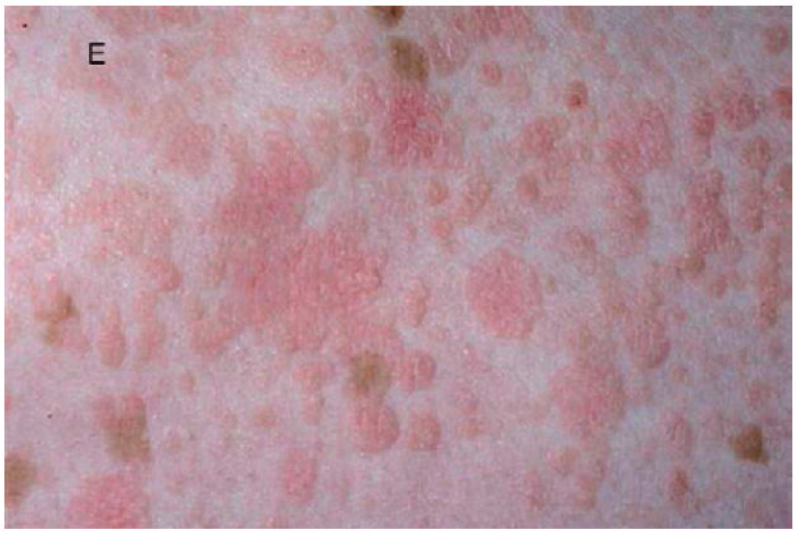


Figure III.

A, Verrucous genital HPV in a patient with GATA2 deficiency. B, Flat warts in a patient with NFκB essential modulator deficiency. C, Warts on the tongue of a patient with epidermodysplasia verruciformis. D and E, Warts on the chest of a patient with epidermodysplasia verruciformis that appear as hyperpigmented lesions similar to tinea versicolor (pictures C, D, and E courtesy of Dr. Maria Turner, NCI, NIH).

Table I

Primary Immune Deficiencies with warts as a major feature

PID	Gene / protein mutated	Inheritance	Age at presentation of warts	Types / Location of warts	Other Infections	Other clinical associations	Immune phenotype
Epidermodysplasia Verruciformis	*EVER1 and 2* / epidermodysplasia verruciformis 1 and 2	AR Reports of XL and AD	Infancy	Flat – trunk, neck, extremities Verrucous – sun exposed areas Hypo / hyper pigmented lesions resembling pityriasis versicolor		30-70% lesions undergo malignant transformation	+/-low T cells Low LPM Cutaneous anergy
WHIM	*CXCR4* / chemokine receptor 4	AD	Variable	Flat, verrucous – extremities, trunk Verrucous - genital	Pneumonia, Cellulitis, Sinusitis, UTI, Thrombophlebitis, Omphalitis, Osteomyelitis, Soft tissue abscesses, HSV, VZV		Low IgG and IgA Normal IgM Normal antibody responses Neutropenia Low B cells Low CD27+ B cells Low IgD+ and IgD-B cells Low T cells Low LPA/LPM Cutaneous anergy
DOCK8	*DOCK8* / DOCK8	AR	Variable	Flat, verrucous – trunk, face, extremities	*S. aureus* skin abscesses, Pneumonia, Sinusitis, Soft tissue infections, HSV, MCV, VZV	Eczema, Food allergies, Asthma, Lymphoreticular and squamous cell malignancies	High IgE Low IgM High or normal IgG

J Allergy Clin Immunol. Author manuscript; available in PMC 2013 November 01.

PID	Gene / protein mutated	Inheritance	Age at presentation of warts	Types / Location of warts	Other Infections	Other clinical associations	Immune phenotype
							High or normal IgA Eosinophilia +/-Low T cells Low B cells Low NK cells Variable antibody responses Low LPA/LPM
ICL	Unknown	?	Late adolescence, adult	Flat, verrucous – face, trunk, extremities Verrucous - genital	Opportunistic infections – MAC, Cryptococcus, histoplasmosis, Mucocutaneous Candida, HSV, *P. Jirovecii* rare	Autoimmune disease Autoantibodies Mucocutaneous Squamous cell cancer	CD4 <300 Low, normal, or high CD8+ T cells Normal or low B and NK cells Variable polysaccharide antibody response, Normal protein antibody response Variable T cell function
GATA2 deficiency MonoMAC DCML Emberger syndrome	*GATA2*/GATA2 binding protein	AD	Late adolescence / adult	Flat, verrucous – face, trunk, extremities,	NTM Histoplasma Aspergillus Cryptococcus VZV HSV	Myelodysplasia, leukemias, Malignancy Panniculitis Thromboembolic phenomena Pulmonary	Profound monocytopenia Low B cells Normal immunoglobulins Normal antibody responses Low NK cells Variable T cell counts

PID	Gene / protein mutated	Inheritance	Age at presentation of warts	Types / Location of warts	Other Infections	Other clinical associations	Immune phenotype
				disseminated, genital		alveolar proteinosis Lymphedema	Variable T cell function
Netherton Syndrome	*SPINK5* / LEKTI	AR	Adolescence, adulthood	Common, plane – extremities, trunk Verrucous - genital	Cellulitis Bacteremia Cutaneous HSV	Bamboo hair Icthyosis Eczema Food allergies Asthma	High IgE Normal or high IgG Low CD4+ T cells Low LPM High C3 and C4
STK4 Deficiency	*STK4* / STK4 or MST1	AR	Unknown	Cutaneous	Cellulitis Skin Abscesses Pneumonia Sinusitis HSV VZV MCV EBV	Autoimmunity EBV related malignancy Structural heart disease	Low CD4+ T cells Low CD45RA+ T cells Low CD25+T cells Normal CD8+ T cells Mildly low B cells Low IgD +IgM +CD27+ B cells Low IgD-IgM-CD27+ B cells High CD38+IgM + B cells Normal NK cells Neutropenia Absent LPM

PID	Gene / protein mutated	Inheritance	Age at presentation of warts	Types / Location of warts	Other Infections	Other clinical associations	Immune phenotype
							Abnormal antibody responses High IgG High or normal IgA and IgE

AR, autosomal recessive; AD, autosomal dominant; XL, X-linked; LPM, lymphocyte proliferation to mitogen; WHIM, warts, hypogammaglobulinemia, infections, myelokathexis; UTI, urinary tract infection; HSV, herpes simplex virus; VZV, varicella zoster virus; Ig –G, -A, -M, -E, -D, immunoglobulin –G, -A, -M, -E, -D; LPA, lymphocyte proliferation to antigen; DOCK8, dedicator of cytokinesis 8; MCV, molluscum cantagiosum virus; ICL, Idiopathic CD4 lymphopenia; MAC, *Mycobacterium avium* complex; MonoMAC, monocytopenia, *M. avium* complex infection; DCML, dendritic cell, monocyte, B cell and NK cell lymphopenia; NTM, nontuberculous mycobacteria; *SPINK5*, serine protease inhibitor Kazal-type 5; LEKTI, lympho-epithelial Kazal-type related inhibitor; STK4, serine-threonine protein kinase 4; MST1, mammalian sterile 20-like protein; EBV, Epstein-Barr virus.

Table II

Primary Immune Deficiencies with reports of warts

PID	Gene / protein mutated	Inheritance	Age at presentation of warts	Types / Location of warts	Other Infections	Other clinical associations	Immune phenotype	Reference
NEMO	*IKBKG* / NFκB essential modulator	XL	variable	Cutaneous	Opportunistic infections – *P. jirovecii* common NTM Histoplasma HSV CMV MCV	Autoimmunity Colitis Ectodermal dysplasia	High IgM Variable IgG, IgA Low antibody responses Normal T cell counts Normal T cell function	Hanson et al. [105] Tobin et al.[104]
Ataxia-telangiectasia	*ATM* / ATM	AR	Not noted	Not noted	Sinopulmonary bacterial VZV HSV EBV MCV	Progressive ataxia Lymphoreticular malignancies	Low IgG, IgA, IgG2, IgG4, IgE Hypergammaglobulinemia Low B cells Variable responses to vaccines Low T cells Low CD4/CD45RA+ T cells High γδ T cells Low LPA/LPM Cutaneous anergy	Nowak et al. [155]
SCID	ADA,γc,JAK3	XL, AR	ADA – adults; γc/JAK3 mean of 8 years following HSCT	ADA – widespread [111, 112]; hands and feet [110] γc/JAK3 – flat, EV like, no genital	Opportunistic infections Sinopulmonary Vaccine related infections Mucocutaneous candidiasis	Maternal T cell engraftment – leading to GVHD	ADA : T-B-NK- γc, JAK3: T-B+NK- Very low T cell numbers and lymphocyte responses Hypogammaglobulinemia Impaired antibody responses	Antony et al. [110], Fairbanks et al. [111], Shovlin et al. [112], Laffort et al.[113]
CVID	*ICOS* / ICOS *CD19* / CD19 *CD20* / CD20	Sporadic	Childhood, Adolescence, Adulthood	[116119]Hands and feet [117]Disseminated [118]palmoplantar	Sinopulmonary infections	Lymphadenopathy Granulomatous disease Chronic diarrhea	In general: Low IgG, variable IgA and IgM Impaired Ab production	Reid et al. [116], Uluhan et al [117]., Lynn et

PID	Gene / protein mutated	Inheritance	Age at presentation of warts	Types / Location of warts	Other Infections	Other clinical associations	Immune phenotype	Reference
	CD81/ CD81 *BAFFR* / BAFFR *TNFRSF13B* / TACI					Lymphoreticular malignancies Splenomegaly [117] Juvenile inflammatory arthritis [118]Intestinal lymphangiectasia	Variable B cell counts Normal or decreased CD27+IgD-IgM-B cells Variable T cell counts Impaired lymphocyte proliferation (20%) [116, 118] Low T cells and low T cell responses with anergy [119]Decreased lymphocyte proliferation but normal T cell counts	al. [118], Lin et al [119].
LAD-1	*ITGB2*/CD18	AR	Adolescence, adult	Disseminated, genital	Soft tissue bacterial infections Bacteremia Omphalitis Gingivitis Periodontitis	Impaired would healing Autoimmunity IBD	Neutrophilia	Uzel et al.[127]
WAS	*WASP* / WASP	XL	Child, adolescence, adult	Extremities, disseminated	Sinopulmonary Colitis Bacteremia Especially with encapsulated bacteria Opportunistic infections MCV VZV CMV Mucocutaneous Candida	Thrombocytopenia Eczema Autoimmunity IBD Lymphoreticular malignancies	Lymphopenia – decreases over time Low or normal IgG and IgM High IgE and IgA Low antibody responses Low B cell and T cells that decrease over time Low LPM High or normal NK cell numbers Low NK cell cytotoxicity	Sullivan et al. [133], Ormerod et al. [141], Stevens et al. [142], Kim et al. [143]
XHIGM1	*CD40L* gene / CD40L	XL	Childhood	Common - Extremities	Sinopulmonary Opportunistic infections *P. jirovecii* common	Autoimmunity Recurrent oral ulcers	Neutropenia High or normal IgM	Yilmaz et al. [168], Chang et al[169].

PID	Gene / protein mutated	Inheritance	Age at presentation of warts	Types / Location of warts	Other Infections	Other clinical associations	Immune phenotype	Reference
					Chronic diarrhea–Cryptosporidium HBV HCV CMV		Low IgG, IgA, IgE Low antibody responses Normal LPM Low LPA (T cell dependent)	

NEMO, nuclear factor κ B essential modulator; XL, X-linked; NTM, nontuberculous mycobacteria; HSV, herpes simplex virus; CMV, cytomegalovirus; MCV, molluscum cantagiosum virus; Ig –G, -A, -M, -E, immunoglobulin –G, -A, -M, -E; ATM, ataxia-telangiectasia mutated; AR, autosomal recessive; VZV, varicella zoster virus; EBV, Epstein-Barr virus; LPA, lymphocyte proliferation to antigen; LPM, lymphocyte proliferation to mitogen; SCID, Severe combined immunodeficiency; γc, common gamma chain of the interleukin 2 receptor; JAK3, Janus kinase 3; HSCT, hematopoietic stem cell transplantation; GVHD, graft versus host disease; CVID, Common variable immunodeficiency; ICOS, inducible costimulator; BAFFR, B cell activating factor receptor; *TNFRSF13B*, tumor necrosis factor receptor superfamily 13B; TACI, transmembrane activator and calcium modulator and cyclophilin ligand interactor; LAD-1, Leukocyte adhesion deficiency type type-1; *ITGB2*, integrin beta chain β2; IBD, inflammatory bowel disease; WAS, Wiskott Aldrich Syndrome; WASP, Wiskott Aldrich Syndrome protein; XHIGM1, X-linked Hyper IgM syndrome type 1; HBV, hepatitis B virus; HCV, hepatitis C virus

Table III

Other diagnostic features of Primary Immune Deficiencies associated with warts

Warts with other infections	Warts with other features
Pneumocystis jiroveci pneumonia	Malignancy
NEMO	DOCK8
XHIGM1	GATA2
WAS	STK4
SCID	CVID
	AT
	WAS
	Skin – EV, Netherton syndrome
Other viral infections (MCV, HSV, VZV)	Atopy
DOCK8	WAS
Netherton syndrome	DOCK8
NEMO	Netherton syndrome
WAS	
ICL	
GATA2	
STK4	
SCID	
Encapsulated bacterial infections	Autoimmunity
CVID	ICL
LAD-1	CVID
WHIM	LAD-1
AT	WAS
WAS	STK4
NEMO	
XHIGM1	
SCID	
STK4	
Nontuberculous mycobacteria	
GATA2	
NEMO	
Histoplasma capsulatum	
GATA2	
ICL	
XHIGM1	
No HPV associated infections	
EV	

Warts with other infections	Warts with other features
ICL	

NEMO, Nuclear Factor κ B essential modulator deficiency; XHIGM1, X-linked Hyper IgM syndrome type 1 or CD40 ligand deficiency; WAS, Wiskott-Aldrich Syndrome; SCID, Severe combined Immunodeficiency; DOCK8, dedicator of cytokinesis 8; ICL, Idiopathic CD4 lymphopenia; STK4, serine-threonine protein kinase 4; CVID, Combined variable immunodeficiency; LAD-1, Leukocyte adhesion deficiency type-1; WHIM, Warts, Hypogammaglobulinemia, Infections, Myelokathexis; AT, Ataxia-Telangiectasia; EV, Epidermodysplasia verruciformis