

Mechanisms of allergic diseases

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Warts and all: Human papillomavirus in primary immunodeficiencies

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Infection with human papillomavirus (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 dedicator of cytokinesis 8 (*DOCK8*) are typically associated with extensive HPV infections, whereas several other primary immune defects result in severe HPV much less frequently. We review immunodeficiencies with severe HPV infections and the mechanisms underlying them. (J Allergy Clin Immunol 2012;■■■:■■■-■■■.)

Key words: Immunodeficiency, human papillomavirus, warts, squamous, carcinoma, dysplastic

Warts are benign virus-induced tumors caused by human papillomavirus (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% and 5%,^{2,3} occurring with similar frequency in adults aged 25 to 34 years.⁴ In 90% of children, warts present by age 11 years and clear by age 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 5 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

Abbreviations used

ADA:	Adenosine deaminase
A-T:	Ataxia-telangiectasia
ATM:	Ataxia-telangiectasia mutated gene
CD40L:	CD40 ligand
CMV:	Cytomegalovirus
CVID:	Common variable immunodeficiency
DOCK8:	Dedicator of cytokinesis 8
EV:	Epidermodysplasia verruciformis
FOXO1:	Forkhead box protein O1
G-CSF:	Granulocyte colony-stimulating factor
GM-CSF:	Granulocyte-macrophage colony-stimulating factor
GVHD:	Graft-versus-host disease
HIGM1:	Hyper-IgM syndrome type 1
HPV:	Human papillomavirus
HSCT:	Hematopoietic stem cell transplantation
HSV:	Herpes simplex virus
ICL:	Idiopathic CD4 lymphopenia
IκB:	Inhibitor of κB
IVIG:	Intravenous immunoglobulin
JAK3:	Janus kinase 3
LAD-1:	Leukocyte adhesion deficiency type 1
LEKTI:	Lymphoepithelial Kazal type-related inhibitor
MCV:	Molluscum contagiosum virus
NEMO:	Nuclear factor κB essential modulator
NF-κB:	Nuclear factor κB
NIH:	National Institutes of Health
NK:	Natural killer
RRP:	Recurrent respiratory papillomatosis
SCID:	Severe combined immunodeficiency
SDF-1:	Stromal cell-derived factor 1
SPINK5:	Serine protease inhibitor Kazal-type 5
STK4:	Serine-threonine kinase 4
VZV:	Varicella zoster virus
WAS:	Wiskott-Aldrich syndrome
WASP:	Wiskott-Aldrich syndrome protein
WHIM:	Warts, hypogammaglobulinemia, infections, myelokathexis

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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

Host defense against HPV relies on intact and functioning cellular immunity, including T-cell and natural killer (NK) cell cytotoxicity (Fig 1). 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

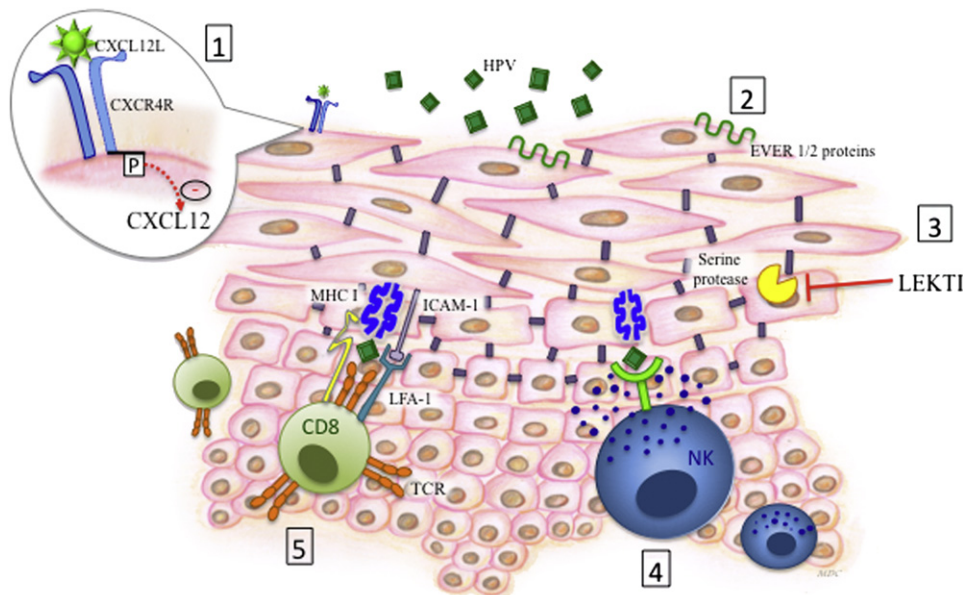


FIG 1. Schematic depiction of the critical elements of host defense against HPV in the skin, as determined from primary immune defects. 1, CXCR4: gain-of-function mutations inhibit CXCL12-mediated signaling and leukocyte trafficking. 2, EVER 1 and EVER2: transmembrane proteins that act as restriction 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 and 5, HPV antigen-specific activation of NK cells and cytotoxic CD8 T cells results in degranulation of cytotoxic granules. ICAM-1, Intercellular adhesion molecule 1.

in patients with primary immunodeficiencies. We will discuss separately the syndromes in which HPV is a manifestation in the majority of cases (Table I) and those syndromes in which HPV is less consistently recognized as a severe manifestation of immunodeficiency (Table II).

EPIDERMODYSPLASIA VERRUCIFORMIS: EVER1 AND EVER2 DEFICIENCY

Epidermodysplasia verruciformis (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 2 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, hypopigmented or hyperpigmented papules that can coalesce as scaly patches or plaques with irregular borders (Fig 2, C-E). Lesions with greater malignant potential present as verrucous or seborrheic keratosis-like lesions that occur more frequently on sun-exposed surfaces.¹² The HPVs that cause disease in patients with EV are β -papillomaviruses, which typically cause asymptomatic infections in the general population. At least 19 different β -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 patients with EV, followed by HPV-3 and HPV-10.¹³ HPV-5 is also the most common genotype to undergo malignant conversion. EV-specific HPVs are acquired early in infancy¹⁴ and are prevalent in the normal skin of healthy adults.¹⁵ Symptomatic infections and malignant transformation can occur in patients with EV or those with other immunodeficiencies.

Although the immunophenotype of EV might be normal, it can include decreased total T-lymphocyte counts¹⁶; reduced

cell-mediated immunity, as measured by reduced responsiveness to mitogens and antigens,¹⁶⁻²²; and defective cell-mediated immunity toward EV-specific HPV types.²³ Reduced cell-mediated immunity might be related to the length of infection with EV-specific HPVs^{17,18} and is independent of oncologic potential.^{18-20,22} NK cell cytotoxic responses are increased in patients with EV,^{16,24,25} primarily in patients with early premalignancies or malignancies, but reduced in patients with disease induced by EV-associated HPV-3 displaying a specific reduction of NK cell-mediated cytotoxicity against disease-specific target cells.²⁵

Hypoproliferative polymorphisms of the IL-10 gene promoter have also been linked to EV. Low IL-10 levels allow for higher production of inflammatory cytokines and might contribute to HPV persistence by inhibiting infected Langerhans' cells from migrating to regional lymph nodes.²⁶

EV is historically inherited in an autosomal recessive fashion, but X-linked²⁷ and autosomal dominant²⁸ inheritance patterns have been reported. Homozygous mutations in *EVER1* or *EVER2* have been reported in approximately 75% of patients with EV.¹³ The *EVER* genes are predicted to encode highly conserved transmembrane proteins²⁹ 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. Nonsurgical interventions with topical 5-fluorouracil,³¹ 5% imiquimod,³² tacalcitol,³³ systemic retinoids combined with IFN- α ,³⁴ cimetidine,³⁵ and topical 5-aminolevulinic acid photodynamic therapy³⁶ yield inconsistent results. Approximately one third of

patients go on to have malignancy, with an average of 24 years between the development of benign lesions and cancer.³⁷ Invasive skin cancers are typically squamous cell carcinomas that often retain features of Bowen carcinomas. They develop slowly and are locally destructive.³⁸

WARTS, HYPOGAMMAGLOBULINEMIA, INFECTIONS, MYELOKATHEXIS SYNDROME: CXCR4 DEFICIENCY

This rare autosomal dominant immunodeficiency was described by Zuelzer³⁹ and Krill et al⁴⁰ in 1964 in a 10-year-old girl with congenital neutropenia and recurrent infections. Warts, hypogammaglobulinemia, infections, myelokathexis (WHIM) syndrome is characterized by recurrent bacterial infections in infancy and early childhood, most commonly pulmonary, gastrointestinal, and cutaneous infections. Kawai and Malech⁴¹ pooled information from 37 published cases. 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 acuminata with papillomatosis can become dysplastic or neoplastic. There are also reports of severe recurrent oral and genital herpes⁴² and herpes zoster,⁴³ as well as 2 reports of patients with 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 caused by 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 (IgD⁺) and switched (IgD⁻) B lymphocytes.⁴⁸ Hypogammaglobulinemia primarily involves IgG but can also affect IgM; responses to immunization demonstrate that the defect in humoral immunity is incomplete. T lymphopenia with a normal CD4/CD8 ratio and normal proliferative responses to mitogens occurs as well.⁴⁸

WHIM syndrome 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 because of the 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 syndrome have no mutation identified thus far.^{43,51} In the patients lacking specific mutations, a marked decrease in G protein-coupled receptor kinase 3 has been described. Overexpression of G protein-coupled receptor kinase 3 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 SDF-1 levels are expressed in HPV-infected dermis.⁴³ These observations suggest that host susceptibility to HPV infection is mediated by upregulation of CXCR4. Defects in the 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 improve prognosis. Treatment with some combination of a colony-stimulating factor (usually G-CSF, but GM-CSF also works), intravenous immunoglobulin (IVIG), and prophylactic antibiotics provides 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 patients with WHIM syndrome.⁵⁶

AUTOSOMAL RECESSIVE HYPER-IGE SYNDROME (DEDICATOR OF CYTOKINESIS 8 DEFICIENCY)

Mutations in dedicator of cytokinesis 8 (*DOCK8*) cause an autosomal recessive combined immunodeficiency with hyper-IgE. Some features are shared with signal transducer and activator of transcription 3 (*STAT3*) mutated hyper-IgE (Job syndrome), such as atopic dermatitis, *Staphylococcus aureus* skin abscesses and soft tissue infections, pneumonias, increased serum IgE levels, 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

TABLE I. Primary immune deficiencies with warts as a major feature

PID	Gene/protein mutated	Inheritance	Age at presentation of warts
EV	<i>EVER1</i> and 2/epidermodysplasia verruciformis 1 and 2	AR Reports of XL and AD	Infancy
WHIM syndrome	<i>CXCR4</i> /chemokine receptor 4	AD	Variable
DOCK8	<i>DOCK8</i> /DOCK8	AR	Variable
ICL	Unknown	?	Late adolescence, adulthood
GATA2 deficiency MonoMAC DCML Emberger syndrome	<i>GATA2</i> /GATA2 binding protein	AD	Late adolescence/adulthood
Netherton syndrome	<i>SPINK5</i> /LEKTI	AR	Adolescence, adulthood
STK4 deficiency	<i>STK4</i> /STK4 or MST1	AR	Unknown

AR, Autosomal recessive; AD, autosomal dominant; DCML, dendritic cell, monocyte, B-cell and NK cell lymphopenia; LPA, lymphocyte proliferation to antigen; LPM, lymphocyte proliferation to mitogen; MAC, *Mycobacterium avium* complex; MonoMAC, monocytopenia, *M avium* complex infection; NTM, nontuberculous mycobacteria; UTI, urinary tract infection; XL, X-linked.

TABLE I. (Continued)

Types/locations of warts	Other infections	Other clinical associations	Immune phenotype
Flat: trunk, neck, extremities Verrucous: sun-exposed areas Hypopigmented/hyperpigmented lesions resembling pityriasis versicolor		30% to 70% lesions undergo malignant transformation	± Low T-cell counts Low LPM Cutaneous anergy
Flat, verrucous: extremities, trunk Verrucous: genital	Pneumonia, cellulitis, sinusitis, UTI, thrombophlebitis, omphalitis, osteomyelitis, soft tissue abscesses, HSV, VZV		Low IgG and IgA levels Normal IgM levels Normal antibody responses Neutropenia Low B-cell counts Low CD27 ⁺ B-cell counts Low IgD ⁺ and IgD ⁻ B-cell counts Low T-cell counts Low LPA/LPM Cutaneous anergy
Flat, verrucous: trunk, face, extremities	<i>S aureus</i> skin abscesses, pneumonia, sinusitis, soft tissue infections, HSV, MCV, VZV	Eczema, food allergies, asthma, lymphoreticular and squamous cell malignancies	High IgE levels Low IgM levels High or normal IgG levels High or normal IgA levels Eosinophilia ± Low T-cell counts Low B-cell counts Low NK cell counts Variable antibody responses Low LPA/LPM
Flat, verrucous: face, trunk, extremities Verrucous: genitals	Opportunistic infections: MAC, <i>Cryptococcus</i> species, histoplasmosis, mucocutaneous <i>Candida</i> species, HSV, <i>P jirovecii</i> rare	Autoimmune disease Autoantibodies Mucocutaneous Squamous cell cancer	CD4 <300 Low, normal, or high CD8 ⁺ T-cell counts Normal or low B-cell and NK cell counts Variable polysaccharide antibody response Normal protein antibody response Variable T-cell function
Flat, verrucous: face, trunk, extremities, disseminated, genitals	NTM <i>Histoplasma</i> species <i>Aspergillus</i> species <i>Cryptococcus</i> species VZV HSV	Myelodysplasia, leukemias, malignancy Panniculitis Thromboembolic phenomena Pulmonary alveolar proteinosis Lymphedema	Profound monocytopenia Low B cells Normal immunoglobulins Normal antibody responses Low NK cell counts Variable T-cell counts Variable T-cell function
Common, plane: extremities, trunk Verrucous: genitals	Cellulitis Bacteremia Cutaneous HSV	Bamboo hair Ichthyosis Eczema Food allergies Asthma	High IgE levels Normal or high IgG levels Low CD4 ⁺ T-cell counts Low LPM High C3 and C4 levels
Cutaneous	Cellulitis Skin abscesses Pneumonia Sinusitis HSV VZV MCV EBV	Autoimmunity EBV-related malignancy Structural heart disease	Low CD4 ⁺ T-cell counts Low CD45RA ⁺ T-cell counts Low CD25 ⁺ T-cell counts Normal CD8 ⁺ T-cell counts Mildly low B-cell counts Low IgD+IgM+CD27+ B cells Low IgD-IgM-CD27+ B cells High CD38+IgM+ B cells Normal NK cells Neutropenia Absent LPM Abnormal antibody responses High IgG High or normal IgA and IgE

TABLE II. Primary immune deficiencies with reports of warts

PID	Gene/protein mutated	Inheritance	Age at presentation of warts	Types/locations of warts
NEMO	<i>IKBKG</i> /NF-κB essential modulator	XL	Variable	Cutaneous
AT	<i>ATM</i> /ATM	AR	Not noted	Not noted
SCID	ADA, γc, JAK3	XL, AR	ADA: adults; γc/JAK3 mean of 8 y after HSCT	ADA: widespread ^{111,112} ; hands and feet ¹¹⁰ γc/JAK3: flat, EV like, not genitals
CVID	<i>ICOS</i> / <i>ICOS</i> <i>CD19</i> / <i>CD19</i> <i>CD20</i> / <i>CD20</i> <i>CD81</i> / <i>CD81</i> <i>BAFFR</i> / <i>BAFFR</i> <i>TNFRSF13B</i> / <i>TACI</i>	Sporadic	Childhood, adolescence, adulthood	Hands and feet ^{116,119} Disseminated ¹¹⁷ Palmoplantar ¹¹⁸
LAD-1	<i>ITGB2</i> / <i>CD18</i>	AR	Adolescence, adulthood	Disseminated, genitals
WAS	<i>WASP</i> / <i>WASP</i>	XL	Child, adolescence, adulthood	Extremities, disseminated
XHIGM1	<i>CD40L</i> gene/ <i>CD40L</i>	XL	Childhood	Common: Extremities

AR, Autosomal recessive; *ATM*, ataxia-telangiectasia mutated; *BAFFR*, B cell-activating factor receptor; γc, common γ chain of the interleukin 2 receptor; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *IBD*, inflammatory bowel disease; *ICOS*, inducible costimulator; *ITGB2*, integrin β chain β2; *LPA*, lymphocyte proliferation to antigen; *LPM*, lymphocyte proliferation to mitogen; *NTM*, nontuberculous mycobacteria; *TACI*, transmembrane activator and calcium modulator and cyclophilin ligand interactor; *TNFRSF13B*, TNF receptor superfamily 13B; *XHIGM1*, X-linked hyper-IgM syndrome type 1; *XL*, X-linked.

TABLE II. (Continued)

Other infections	Other clinical associations	Immune phenotype	References
Opportunistic infections: <i>P jirovecii</i> common NTM <i>Histoplasma</i> species HSV CMV MCV	Autoimmunity Colitis Ectodermal dysplasia	High IgM levels Variable IgG and IgA levels Low antibody responses Normal T-cell counts Normal T-cell function	Hanson et al ¹⁰⁵ Tobin et al ¹⁰⁴
Sinopulmonary bacterial VZV HSV EBV MCV	Progressive ataxia Lymphoreticular malignancies	Low IgG, IgA, IgG ₂ , IgG ₄ , and IgE levels Hypergammaglobulinemia Low B-cell counts Variable responses to vaccines Low T-cell counts Low CD4/CD45RA ⁺ T-cell counts High $\gamma\delta$ T-cell counts Low LPA/LPM values Cutaneous anergy	Nowak-Wegryzyn et al ¹⁵⁵
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
Sinopulmonary infections	Lymphadenopathy Granulomatous disease Chronic diarrhea Lymphoreticular malignancies Splenomegaly Juvenile inflammatory arthritis ¹¹⁷ Intestinal lymphangiectasia ¹¹⁸	In general: low IgG, variable IgA and IgM levels Impaired antibody production Variable B-cell counts Normal or decreased CD27 ⁺ IgD ⁻ IgM ⁻ B-cell counts Variable T-cell counts Impaired lymphocyte proliferation (20%) Low T-cell counts and low T-cell responses with anergy ^{116,118} Decreased lymphocyte proliferation but normal T-cell counts ¹¹⁹	Reid et al, ¹¹⁶ Uluhan et al, ¹¹⁷ Lynn et al, ¹¹⁸ Lin et al ¹¹⁹
Soft tissue bacterial infections Bacteremia Omphalitis Gingivitis Periodontitis	Impaired wound healing Autoimmunity IBD	Neutrophilia	Uzel et al ¹²⁷
Sinopulmonary Colitis Bacteremia, especially with encapsulated bacteria Opportunistic infections MCV VZV CMV Mucocutaneous <i>Candida</i> species	Thrombocytopenia Eczema Autoimmunity IBD Lymphoreticular malignancies	Lymphopenia: decreases over time Low or normal IgG and IgM levels High IgE and IgA levels Low antibody responses Low B-cell and T-cell counts that decrease over time Low LPM High or normal NK cell counts Low NK cell cytotoxicity	Sullivan et al, ¹³³ Ormerod et al, ¹⁴¹ Stevens et al, ¹⁴² Kim et al ¹⁴³
Sinopulmonary Opportunistic infections <i>P jirovecii</i> common Chronic diarrhea: <i>Cryptosporidium</i> species HBV HCV CMV	Autoimmunity Recurrent oral ulcers	Neutropenia High or normal IgM levels Low IgG, IgA, and IgE levels Low antibody responses Normal LPM Low LPA (T cell dependent)	Yilmaz et al, ¹⁶⁸ Chang et al ¹⁶⁹

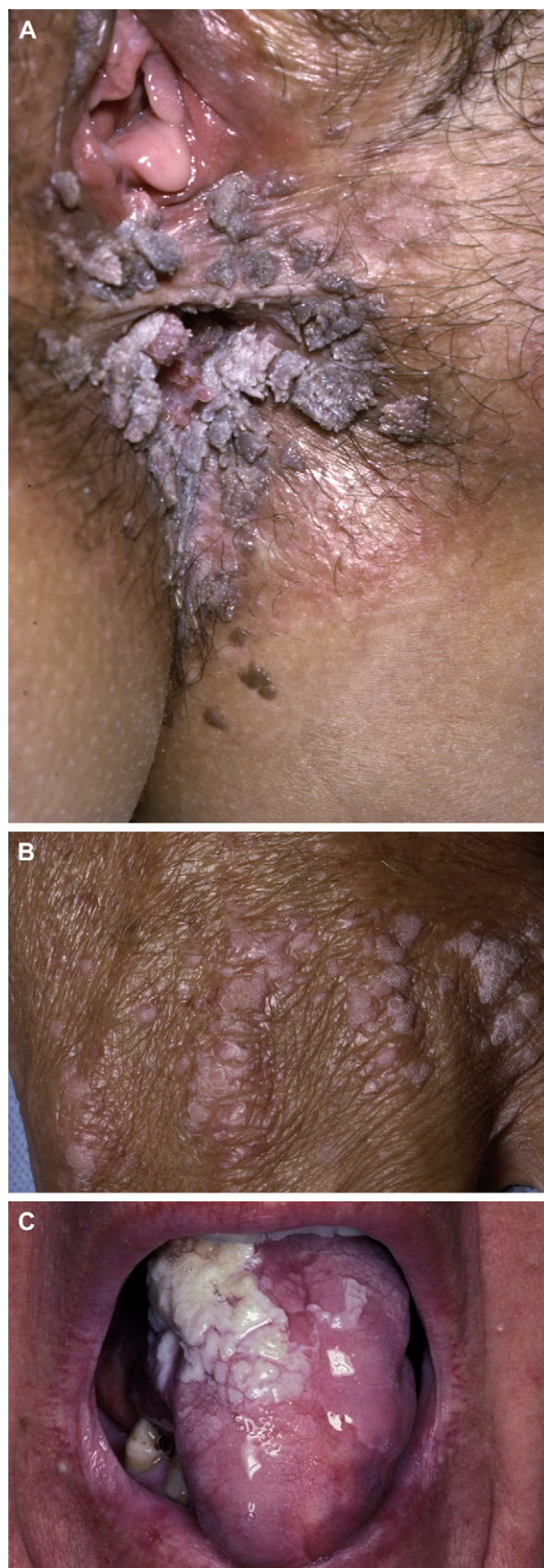


FIG 2. A, Verrucous genital HPV in a patient with GATA2 deficiency. B, Flat warts in a patient with NEMO deficiency. C, Warts on the tongue of a patient



FIG 2. (Continued)

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 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 do not activate, divide, and expand after T-cell receptor stimulation and have poor production of IFN- γ and TNF- α .⁶⁰ Impaired functioning of CD8 T cells likely contributes to the viral susceptibility of patients with DOCK8 deficiency.⁶¹ Decreased CD4 T_H17 cell counts might explain the increased susceptibility of some DOCK8-deficient patients to mucocutaneous candidiasis.⁶² In addition to their increased IgE levels, DOCK8-deficient patients have low IgM, high or normal IgG, and low, high, or normal IgA levels. Antibody responses to

with EV. D and E, Warts on the chest of a patient with EV that appear as hyperpigmented lesions similar to tinea versicolor. Fig 3, C, D, and E are courtesy of Dr Maria Turner, National Cancer Institute, National Institutes of Health.

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 *S aureus*. Reduction of colonization of the skin with bleach baths is recommended, as is the use of topical corticosteroids, although the latter can exacerbate cutaneous viral infections. Patients with antibody deficiency might benefit from IVIG.⁶³ Mortality caused by malignancy and infections is high. Hematopoietic stem cell transplantation (HSCT) has led to immune reconstitution and viral eradication.⁶⁴ However, DOCK8's role in nonhematopoietic 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 and Prevention in 1992 as a disease with "a documented absolute CD4 T lymphocyte count less than 300 cells/mm³ 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 3 most common infectious presentations in a cohort of patients with ICL 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 patients with 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 papillomatosis⁷² and recurrent vulvar intraepithelial neoplasia.⁶⁶ Some patients do well with topical treatments and destructive therapies, whereas others require systemic immunomodulators, such as IFN- α ; some might require radical surgery. Of 40 patients with ICL currently followed at the NIH, 15 have had cutaneous or genital HPV. Five of the 9 patients with genital HPV have had dysplasia or carcinoma. One patient with cutaneous HPV has had cutaneous squamous cell cancer.

Autoimmune phenomena and autoantibodies occur frequently, with thyroid disorders and antinuclear 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 cell counts are common. T cells are more activated (HLA-DR⁺) and have increased CD4 T-cell turnover, as measured by using Ki-67; higher percentages but lower absolute number of regulatory T cells, as measured by using forkhead box protein 3 expression; and a lower proportion of

naïve CD4 T cells, as measured by using expression of CD127 (IL-7 receptor α).⁶⁶ CD4 autoantibodies have been hypothesized and reported in at least 1 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 of which were related to opportunistic infections; there have been no deaths in the cohort followed currently. Three patients had pulmonary *Mycobacterium avium* complex, 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 3 nonopportunistic infection-related deaths were due to pneumonia and metastatic prostate cancer (age, 84 years). There were no deaths in the group with no opportunistic infections who 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 monocytopenia and *M avium* complex infection⁷⁸; familial myelodysplastic and leukemia syndrome⁷⁷; dendritic cell, monocyte, B-cell, and NK cell lymphoid deficiency⁷⁶; and Emberger syndrome (a primary lymphedema with myelodysplasia or acute myelogenous leukemia).⁷⁹ Missense and null mutations in GATA2 have been found with all 4 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, and *Histoplasma*, *Cryptococcus*, and *Aspergillus* species. 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 (Fig 2, A).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 HSCT seems to be curative.⁸⁷ Graft-versus-host disease (GVHD) has occurred both early and late after transplantation but was usually manageable.

WARTS, IMMUNODEFICIENCY, LYPHHEDEMA, DYSPLASIA SYNDROME

Warts, immunodeficiency, lymphedema, and dysplasia syndrome is described in 2 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 decreased mitogen-stimulated lymphocyte proliferation. This might well represent another manifestation of GATA2 deficiency.

NETHERTON SYNDROME (SERINE PROTEASE INHIBITOR KAZAL-TYPE 5 DEFICIENCY)

Netherton syndrome is a rare autosomal recessive disorder characterized by congenital ichthyosiform erythroderma, tricornis 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.^{91,92}

Patients with Netherton syndrome have increased susceptibility to viral skin infections, specifically HSV and HPV, although there are few published reports of the latter.⁹²⁻⁹⁶ Patients with Netherton syndrome have high IgE levels, normal to increased IgG levels, hypercomplementemia (C3 and C4), and NK cell lymphocytopenia.⁹² Interestingly, IgE levels are normal at birth, reach their peak by age 4 years, and then decrease over time. CD4 lymphopenia, impaired skin test results to microbial antigens, and impaired lymphocyte proliferation to mitogens have also been reported.^{95,97} Susceptibility to cutaneous and systemic infections might 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 lymphoepithelial Kazal type-related inhibitor (LEKTI), which is normally cleaved into 15 active domains that suppress serine protease activity.⁹⁸ *SPINK5* mutations truncate LEKTI and permit unopposed serine protease activity. There is a strong genotype-phenotype correlation with the length of the residual LEKTI molecule.⁹⁹

Warts in patients with Netherton syndrome typically present in adolescence or adulthood as common genital, anal, plantar, and verrucous lesions. Depending on the HPV type, they can progress to carcinoma. EV-associated HPV types have been found on biopsy, and skin cancers occur in these patients.⁹⁵ Lesions are typically recalcitrant to therapy, but there has been some success with use of retinoids, psoralen plus ultraviolet A therapy, and IFN- α .^{92,93,96}

MAMMALIAN STERILE 20-LIKE PROTEIN OR SERINE-THREONINE KINASE 4 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 naive T cells. Missense mutations and deletions in *STK4* in 4 patients from 2 consanguineous unrelated families from Turkey¹⁰⁰ and in 3 patients from a consanguineous Iranian family¹⁰¹ resulted in truncation of the STK4 protein, previously named mammalian sterile 20-like protein.

Patients with STK4 deficiency have 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 patients. All 3 patients in the Iranian family, and 1 patient 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 HPV-84 and HPV-71, HPV-3, and HPV-25 in 2 patients.¹⁰¹

Progressive CD4 T-cell lymphopenia with profoundly low naive CD4 T-cell counts is a hallmark, whereas CD8 T 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 levels. 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-7 receptor α , CCR7, and CD62 ligand (CD62L) on naive 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 expression,¹⁰⁰ and loss of mitochondrial transmembrane potential.¹⁰¹ STK4 deficiency can also impair the development or maintenance of regulatory T 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 of GVHD.¹⁰⁰

NUCLEAR FACTOR κ B ESSENTIAL MODULATOR (NEMO OR IKBKG DEFICIENCY)

Hypomorphic mutations in the nuclear factor κ B 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 nuclear factor κ B (NF- κ B) activation. After specific receptor activation, the inhibitor of κ B (I κ B) kinase complex phosphorylates I κ B, leading to its degradation and the release of NF- κ B, 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, which is 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 hair¹⁰³ because of impaired ectodysplasin A signaling through NF- κ B.

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 have HSV, CMV, or MCV. However, patients are also susceptible to severe disseminated HPV, typically flat warts (Fig 2, B).¹⁰⁴ Inflammatory colitis is also common.¹⁰⁵

The immunodeficiency of NEMO can include hypogammaglobulinemia with increased IgM and IgA levels caused by impaired CD40-mediated B-cell class-switch recombination. Toll-like receptor 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 1 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 the absence of T cells and profoundly impaired adaptive immunity, has an incidence of 1 in 40,000 to 75,000 live births. Glanzmann and Riniker¹⁰⁶ first described SCID in 1950 in Swiss infants who were profoundly lymphopenic and died of infection within the first 2 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 syncytial virus, VZV, HSV, measles, influenza and parainfluenza 3, *P jirovecii*, and vaccine-related infections with poliovirus, rotavirus, varicella and BCG 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 can be normal in the setting of maternal T-cell engraftment, and hypogammaglobulinemia might be masked by transferred maternal IgG in infants less than 6 months of age.

Widespread seborrhea-like dermatitis, morbilliform eruptions, and extensive eczema are common in patients with 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 had 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 might play a role in the prevention of HPV. Widespread cutaneous and planar warts have also been described in patients with IL-2 receptor common gamma chain (γ c) and Janus kinase 3 (JAK3)

deficiencies after HSCT.^{113,114} Laffort et al¹¹³ found warts a mean of 8 years after HSCT, primarily on the hands and feet, but no genital or premalignant lesions were seen. HPV genotypes associated with EV (HPV-5, HPV-14, and HPV-36), common warts (HPV-2 and HPV-57), and flat warts (HPV-3) were identified in the lesions of 6 patients. HPV-5 and HPV-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 γ c-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 of 7 patients tested with HPV disease and 1 of 8 patients without HPV. There was no difference in NK cell numbers 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 cause for increased susceptibility to warts after HSCT in patients with IL-2R γ c/JAK3 mutations is unknown, but IL-2R γ c-dependent cytokines might induce production or amplification of immune responsive molecules in keratinocytes.¹¹³

COMMON VARIABLE IMMUNODEFICIENCY

Common variable immunodeficiency (CVID) is the most prevalent immunodeficiency, affecting 1 in 25,000 to 1 in 50,000 white patients, but a single unifying genetic cause is still elusive. Most patients receive diagnoses at 20 to 40 years of age, 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 rates. CVID is characterized by low IgG, IgA, and/or IgM levels with poor or absent antibody production.¹¹⁵

Pneumonias caused by *S pneumoniae*, *H influenzae*, or *Mycoplasma* species are common before diagnosis and treatment are initiated. Warts are uncommon in patients with CVID, but severe disseminated warts are reported. Three cases with ages of wart onset of 9, 13, and 55 years were associated with T lymphopenia and an 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 patients with CVID. These cases might represent other recognized genetic defects masquerading as CVID.

LEUKOCYTE ADHESION DEFICIENCY TYPE 1 (CD18 DEFICIENCY)

Leukocyte adhesion deficiency type 1 (LAD-1) was described in the 1970s¹²⁰ as an autosomal recessive disease that was eventually recognized as being caused by mutations in integrin B2 (*ITGB2*), encoding the common β chain of the β_2 -integrin family (CD18).¹²⁰⁻¹²² Mutations resulting in dramatically reduced or nonfunctional forms of CD18 also prevent surface expression of α subunits of the 3 heterodimers $\alpha 1\beta 2$ (lymphocyte function-associated 1 [LFA-1], CD11a), $\alpha 2\beta 2$ (macrophage-1 antigen, CD11b), and $\alpha 3\beta 2$ (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 al¹²⁷ recently reported severe warts in 5 patients with milder forms of LAD-1. Two siblings with deletions of exons 12 and 13 had 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 had extensive vulvovaginal warts at age 28 years. A 30-year-old man had extensive perianal warts requiring resection and treatment with pegylated IFN- α . A 37-year-old man with colitis had warts over his hands. The exact susceptibility to HPV in patients with LAD-1 is unknown; decreased T-cell and NK cell cytotoxicity and immunodysregulation in patients with residual CD18 levels and inflammatory bowel disease might be related. It could be that viral susceptibility is also high in patients with severe forms of LAD-1, but they undergo transplantation or die earlier in life. Allogeneic HSCT succeeds in patients with LAD-1. Gene therapy in a canine LAD-1 model is promising.¹²⁸

WISKOTT-ALDRICH SYNDROME (WISKOTT-ALDRICH SYNDROME PROTEIN DEFICIENCY)

Wiskott-Aldrich syndrome (WAS) is an X-linked immunodeficiency affecting approximately 1 in 100,000 live births that was first described by Wiskott in 1937 after noticing the triad of thrombocytopenia, eczema, and frequent pyogenic infections.^{129,130} This syndrome was rediscovered 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}

The WAS gene encodes its cognate protein, Wiskott-Aldrich syndrome 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.¹³⁵⁻¹³⁷

Immunodeficiency in patients with WAS affects both humoral and cellular immunity and depends largely on the amount of WASP expression. In patients with classic WAS, the lymphopenia often progresses over time; IgG and IgM levels are typically low or normal, and IgA and IgE levels are often increased.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 *S pneumoniae*, *H*

influenzae, and *Neisseria meningitidis*. Opportunistic infections include *P jirovecii*, MCV, systemic VZV, and CMV. Fungal infections consist primarily of *Candida* species.^{132,133} Autoimmunity occurs in 40% to 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 patients with WAS. Sullivan et al¹³³ reported 6 of 154 patients with WAS had recurrent warts. Case reports of warts in patients with WAS include a 12-year-old¹⁴¹ and a 2-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 feet¹⁴³ had complete resolution after receiving acitretin for 13 weeks. However, once it was tapered, the lesions returned. The exact cause of HPV infection in patients with WAS is not understood, but defects in NK cellular immunity are likely to be causative.

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 multi-system disorder characterized by progressive neurodegeneration, oculocutaneous telangiectasias, radiosensitivity, and combined immunodeficiency.^{150,151} In 1958, Boder and Sedgewick¹⁵² described 8 patients in 6 families with progressive cerebellar ataxia, oculocutaneous telangiectasia, and frequent sinopulmonary infections.

Sinopulmonary infections are common in patients with A-T; chronic lung disease and bacterial pneumonia have been major causes of death.^{153,154} In 100 patients with A-T, recurrent sinopulmonary infections occurred in more than one third. However, infections with *P jirovecii* or after live viral vaccination do not occur. Infections with *Candida* species were rare and occurred 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 patients.¹⁵⁵

Immunodeficiency in patients with A-T is variable. The most common humoral abnormalities are low B-lymphocyte counts¹⁵⁵; decreased IgG, IgA, IgE, IgG₄, and IgG₂ levels¹⁵⁵⁻¹⁵⁷; impaired antibody responses¹⁵⁸; and occasional hypergammaglobulinemia.¹⁵⁹ CD4 T lymphopenia,^{155,160} decreased CD4/CD45RA lymphocyte counts,^{160,161} decreased NK cell numbers,¹⁵⁵ and impaired lymphoproliferation to mitogens and antigens have been 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, which are further complicated by neuromuscular deterioration. Median survival in 2 large cohorts was 25 and 19 years, respectively. However, life expectancy did not correlate well with neurologic impairment.¹⁶³

CD40 LIGAND DEFICIENCY (X-LINKED HYPER-IgM SYNDROME TYPE 1)

First described in the 1960s,¹⁶⁴ hyper-IgM syndrome type 1 (HIGM1) was most commonly observed in male subjects as an X-linked recessive trait. HIGM1 is caused by mutations in CD154 (CD40 ligand [CD40L], TNF surface family 5), 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 male subjects are susceptible to recurrent bacterial and opportunistic infections starting early in life, including *P jirovecii* pneumonia, which occur in 20% to 40% of cases. Chronic watery diarrhea caused by infection with *Cryptosporidium* species is common. Liver and biliary tract disease with sclerosing cholangitis caused by *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 patients with 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 can be profoundly reduced. IgM levels are not always increased, as the name implies; 50% have normal levels at diagnosis. However, the majority of patients have hyper-IgM at some point. Patients also have low-affinity antibody production to T-dependent antigens and lack an anamnestic 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 increased IgM, low IgG, and normal IgA levels, 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 (Fig 1) 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.

TABLE III. Other diagnostic features of primary immune deficiencies associated with warts

Warts with other infections	Warts with other features
<i>Pneumocystis jirovecii</i> 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	
<i>Histoplasma capsulatum</i>	
GATA2	
ICL	
XHIGM1	
No HPV-associated infections	
EV	
ICL	

XHIGM1, X-linked hyper-IgM syndrome type 1 or CD40L deficiency.

In vivo delayed-type hypersensitivity 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 delayed-type hypersensitivity,¹⁷¹ with the 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 the control of HPV became more obvious with the advent of HIV infection, in which multiple recurrences of cervical HPV infection¹⁷³ and genital warts¹⁷⁴ and prolonged persistence of high-risk HPV occur¹⁷⁵ 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 proinflammatory cytokines, including IL-12, TNF- α , and IFN- γ , which are characteristic of a T_H1 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 T_H1 responses to E2 and E6 occur in healthy subjects without clinical signs of HPV-16 infection.¹⁷⁹ These are only

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, as reviewed by Kanodia et al.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, HPV-18, and HPV-33 prevent IFN- α 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 antiviral agents, 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 for female and male patients aged 11 to 26 years.^{195,196} Successful primary treatment of HPV-associated intraepithelial neoplasia with the quadrivalent vaccine has been recently reported.¹⁹⁷⁻²⁰⁰ A role for HPV vaccination in the setting of immunodeficiency is undefined but 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 (Table III). A thorough history and physical examination and focused laboratory testing should help guide an informed and prudent search for the specific immune defect (Fig 3).

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.

Additional note: Deficiency in Ras homolog family member H (RHOH), an intracellular transducer from T and B cell receptors has recently been identified in 2 patients with susceptibility to EV-HPVs. The immunophenotype of RHOH deficiency includes low numbers of naive T cells, expansion of memory T cells, abnormal integrin profiles, and abnormalities in T cell receptor mediated activation with these abnormalities likely contributing to HPV susceptibility in these patients.²⁰¹

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