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;130:1030-48.)

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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 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

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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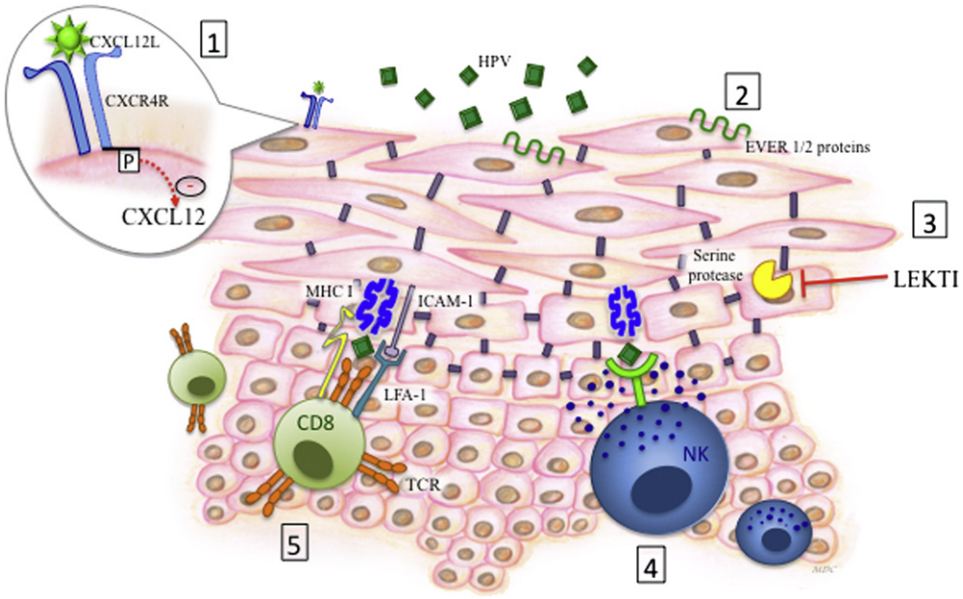

FIG 1. Schematic depiction of the critical elements of host defense against HPV in the skin, as determined from primary immune defects. *1*, CXCR4: gain-of-function mutations inhibit CXCL12-mediated signaling and leukocyte trafficking. *2*, EVER 1 and EVER2: transmembrane proteins that act as restriction 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 infancy[14] 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 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 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]

Hypoproductive 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-linked[27] and autosomal dominant[28] 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 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. 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 therapy[36] yield inconsistent results. Approximately one third of