Review

HPV-Related Skin Phenotypes in Patients with Inborn Errors of Immunity

Assiya El Kettani 1,2,3,*, Fatima Ailal 1,4, Jalila El Bakkouri 1,5, Khalid Zerouali 1,2,3, Vivien Béziat 6,7,, Emmanuelle Jouanguy 6,7, Jean-Laurent Casanova 6,7,8 and Ahmed Aziz Bousfiha 1,4

1 Laboratory of Clinical Immunology, Inflammation and Allergy LICIA, Faculty of Medicine and Pharmacy, Hassan II University, Casablanca 20250, Morocco; drailalfatima@gmail.com (F.A.);
jalilaelbakkouri@gmail.com (J.E.B.); khalid.zerouali2000@gmail.com (K.Z.); profbousfiha@gmail.com (A.A.B.)
2 Laboratory of Bacteriology, Virology and Hospital Hygiene, Ibn Rochd University Hospital, Casablanca 20250, Morocco
3 Laboratory of Bacteriology and Virology, Faculty of Medicine and Pharmacy, Hassan II University, Casablanca 20250, Morocco
4 Clinical Immunology and Infectious Pediatrics Department, Abderrahim Harouchi Hospital, Ibn Rochd University Hospital, Casablanca 20250, Morocco
5 Immunology Laboratory, Ibn Rochd University Hospital, Casablanca 20250, Morocco
6 Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Institut National de la Santé et de la Recherche Médicale (INSERM), 75015 Paris, France; vivien.beziat@inserm.fr (V.B.);
emmanuelle.jouanguy@inserm.fr (E.J.); casanova@mail.rockefeller.edu (J.-L.C.)
7 Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, Rockefeller University, New York, NY 10065, USA
8 Howard Hughes Medical Institute, Chevy Chase, MD 20815, USA
* Correspondence: assiyaelkettani@gmail.com

Abstract: Patients with inborn errors of immunity (IEI) are prone to develop infections, either due to a broad spectrum of pathogens or to only one microbe. Since skin is a major barrier tissue, cutaneous infections are among the most prevalent in patients with IEI due to high exposures to many microbes. In the general population, human papillomaviruses (HPVs) cause asymptomatic or self-healing infections, with spontaneous clearances reported: 23% at 2 months and 66% by 2 years [3,4]. The transmission is from skin-to-skin or mucous-to-mucous contact. Seroprevalence is variable, and genetic patterns of IEI related to severe HPV cutaneous infections and propose an algorithm for diagnosis of IEI with severe warts associated, or not, with lymphopenia.

Keywords: HPV; skin; inborn errors of immunity

1. Introduction

Human papillomaviruses (HPVs) are DNA viruses with a specific tropism to keratinocytes, which are the main component of stratified epithelia, including skin, genital, and laryngeal mucosa. There are more than 200 different genotypes of HPVs classified in five (∝-, β-, γ-, µ-, and ν-) genera. HPV subtypes of all genera infect the skin, and only some HPVs of ∝-genus infect the mucosal epithelia. Some ∝- and β-HPV types are oncogenic and are associated with benign genital condyloma, cervical and anogenital cancers, and non-melanoma skin cancers, respectively [1,2].

In the general population, HPVs cause asymptomatic or self-healing infections, with spontaneous clearances reported: 23% at 2 months and 66% by 2 years [3,4]. The transmission is from skin-to-skin or mucous-to-mucous contact. Seroprevalence is variable,
depending on the HPV genus, age, and screening policy of each country. However, it is estimated to be <40% and 20–65% for oncogenic α-HPV and β-HPVs, respectively. Cervical cancer is the main clinical concern following HPV infection, as it is the fourth most frequent female cancer, with a death rate around 7.5%. In addition, more than 85% of deaths due to cervical cancer are in developing countries. The incidence of cutaneous warts varies with age, with a range from 1 to 12% in the adult general population, but could be over 24% in school age children [5].

Inborn errors of immunity (IEI) are characterized by an impaired immune response, affecting tissue-intrinsic immunity that is either, innate, adaptive, or both. IEI could be associated with higher susceptibility to infections, auto-inflammation, and/or autoimmunity. Unusual clinical expression of HPV infection is frequently observed in patients with IEI. The spectrum of the clinical phenotype is large from epidermodysplasia verruciformis (EV) (a rare disease due to β-HPV) to profuse, persistent and recalcitrant warts (due to α-, γ-, and µ-genera) [6]. Very rare individuals develop tree man syndrome (TMS) due to HPV2 [7].

There are some published reviews and case reports that describe clinical, immunological, and genetic patterns of IEI related to severe HPV cutaneous infections, but there are too many aspects of these issues that are still unknown and are being discovered continuously. Here, we present an up-to-date review of the major clinical, immunological, and genetic patterns of IEI related to severe HPV cutaneous infections, and we propose an algorithm for diagnosis of IEI with severe warts in order to help clinicians who may encounter patients with recurrent and recalcitrant warts due to an underlying inherited immunodeficiency.

2. Clinical Phenotypes

Depending on the HPV genera, there are different characteristics of HPV skin lesions. Macroscopy and histology analyses could help with an appropriate diagnosis.

2.1. Epidermodysplasia Verruciformis

With less than 250 cases reported worldwide, epidermodysplasia verruciformis (EV) is a rare disease that appears at young ages: infancy (7.5% of cases), childhood (61.5% of cases), and adolescence (22% of cases). Lesions are characterized by progressive onset hyperpigmented or achromic flat verrucous lesions, irregular patches of a reddish-brown color, keratotic seborrheic lesions, and pityriasis versicolor-like macules. The lesions are found mainly on sun-exposed areas, such as the face, trunk, neck, forearms, hands, and feet (Figure 1). Although various genotypes of β-HPVs are detected in EV lesions, HPV5 and -8 are found in 80% of cases. Histologic features of an EV lesion are characterized by a flat wart and showing mild to moderate hyperkeratosis, hypergranulosis, and acanthosis of the epidermis. The keratinocytes in the upper layer of the epidermis are enlarged and exhibit a vacuolated nucleus and a pale blue-gray color [8].

EV can be isolated (typical EV) or syndromic (atypical EV) associated with other clinical manifestations, infectious, or not. [9]. Among 40–50-year-old patients, 30 to 60% of EV patients develop non-melanoma skin cancer, particularly squamous cell carcinoma, occurring in sun-exposed areas. People with black skin have a much lower incidence of skin cancer. Most squamous cell carcinomas remain localized. Metastases are not frequent [8,10].

2.2. Profuse Warts (PWs)

Profuse warts (PWs) are defined as more than 20 lesions in more than one area of the body. If they do not disappear after 6 months of treatment, they are also classified as recalcitrant [11]. PW cauliflower-like papules have a rough, hyperkeratotic surface but they can be flat depending on the HPV involved (Figure 2). PWs are the consequence of an infection with α- or γ-HPV, and less frequently with μ- and ν-HPVs [12]. Histologic analyses of PWs have shown markedly papillomatous epidermis with hypergranulomatosis and overlying tiers of parakeratosis. The upper epidermis may contain large pink inclusions, particularly in cases arising on acral skin. Other lesions have shown smaller basophilic
granules. Classically, in the upper epidermis, koilocytes or vacuolated keratinocytes which have a small shrunken nucleus surrounded by a perinuclear halos are observed [13].

![Figure 1](image1.png)

**Figure 1.** Epidermodysplasia verruciformis lesions initially localized on the face, and then generalized to the neck and the trunk in a 12-year-old male patient with STK4 deficiency.

![Figure 2](image2.png)

**Figure 2.** Profuse cauliflower and flat warts in a 26-year-old female patient with GATA2 deficiency (DCML syndrome).

2.3. **Tree Man Syndrome**

In exceptional cases, the warts can also transform into exophytic cutaneous lesions and giant horns, resulting in tree man syndrome [7]. TMS presents with the most extensive warts developing into cutaneous horns, which can be giant and generalized. These lesions start as cutaneous warts, slowly spreading over the hands and feet before transforming into cutaneous horns, characteristic of the TMS phenotype (Figure 3). This condition is extremely rare, with less than 10 cases reported so far. All cases were sporadic with no family history. Due to the paucity of reported cases, it is unclear whether these lesions in TMS have malignant potential [7].
3. Immunological Phenotypes and Inborn Errors of Immunity

3.1. No immunological Phenotype in Blood (Skin-Intrinsic Immunity Disorder)

Isolated EV is due to autosomal recessive (AR) mutations in TMC6 and TMC8, which encode EVER1 and EVER2, two endoplasmic reticulum plasma membrane proteins, respectively, and in CIB1, which encodes calcium and integrin binding protein [9,14] (Table 1). Patients with isolated EV did not show any major leukocyte abnormalities, neither quantitative nor qualitative, in terms of proliferation or antibodies production. The HPV proteins, E5 and E8, targeted the EVER1–EVER2–CIB1 complex, strongly suggesting that this complex is acting as a restriction factor to HPVs in keratinocytes. In terms of the physiological mechanism, the dominant hypothesis is that isolated EV is the consequence of IEI affecting the keratinocyte-intrinsic immune response [14].

Table 1. Etiologies and immunological phenotypes of isolated EV.

| HPV Phenotype | Gene/protein (Mode of Inheritance) | Clinical Phenotypes | T Cell Counts | T Function | Other Immunological Features | Reference |
|---------------|-----------------------------------|---------------------|---------------|------------|-----------------------------|-----------|
| Isolated EV   | TMC6/EVER1 (AR) EV                | Normal              | Normal        | Normal     | None                        | [9,14]    |
|               | TMC8/EVER2 (AR) EV                | Normal with slightly high proportions for skin-homing subsets | Normal       | None       |                             |           |
|               | CIB1 (AR) EV                       | Normal              | Normal        | Normal     | None                        |           |

AR, autosomal recessive; EV, epidermodysplasia verruciformis; TMC6, transmembrane channel-like protein 6; TMC8, transmembrane channel-like protein 8.

3.2. Immunological Phenotype with Qualitative or/and Quantitative T Cells Defects Only

In contrast to isolated EV, syndromic EV is related to IEI affecting T cells. Some of these IEI are also associated with PW phenotype. For some of them, warts are a major clinical symptom (Table 2) [6]. For instance, in AR DOCK8 deficiency, warts were reported in >40% of patients that were characterized by T and NK cell lymphopenia, and some patients developed α-HPV-induced malignancies [15]. Furthermore, AR mutations in the serine/threonine kinase 4 (STK4) gene are primarily characterized by a reduced amount and survival of circulating naïve T cells. 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 hypergamaglobulinemia of IgG and variable increases in IgA and IgE [16].

Table 2. Etiologies, clinical phenotypes, and immunological phenotypes of warts associated with IEI with qualitative or/and quantitative T cell defects.

| HPV Phenotype   | Gene/Protein (Mode of Inheritance) | Other Clinical Phenotypes | T Cell Counts | T Function | Other Immunological Features | Reference |
|-----------------|------------------------------------|---------------------------|---------------|------------|-----------------------------|-----------|
| Syndromic EV    | RHOH (AR)                          | Cutaneous viral infections, bronchopulmonary disease, Burkitt lymphoma | Low naïve CD4+ Tc, high memory CD4+ and CD8+ Tc counts, low proportions of skin-homing Tc subsets | Mildly impaired antigen-induced Tc proliferation, no anti-CD3-induced proliferation | -         | [18,19] |
| Syndromic EV or profuse warts  | STK4 (AR)                         | Bacterial, candida infections, EBV lymphoproliferation, lymphoma, congenital heart disease | Low Tc Low terminal differentiated effector memory cells Low naïve Tc | Poor proliferation Impaired mitogen (PHA, PMA/ionomycin)- and antigen (candida, tetanus toxoid, tuberculin)-induced proliferation | Intermittent neutropenia, autoimmune cytopenia, low Bc | [16,20,21] |
| Syndromic EV or profuse warts  | DOCK8 (AR)                         | Cutaneous staphylococcal and viral infections, severe eczema, severe atopy | Low Tc CD4+ | Poor production of antiviral cytokines (TNFa, IFNγ) | Hyper IgE, hyper eosinophilia Low IgM |         |
| Syndromic EV or chronic warts  | CORO1A (AR)                       | Severe varicella, molluscum contagiosum and aggressive EBV infection | Low Tc | - | Defective number and/or cytolytic activity of NK cells, hypogammaglobulinemia, and defective antibody responses | [18,23] |
| Syndromic EV    | RASGRP1 (AR)                       | Recurrent pneumonia, herpes virus infections, EBV-associated lymphoma | Low Tc | Tc: poor activation, proliferation, motility | Increased IgA, Bc: poor activation, proliferation, motility | [6,18,24] |
| Syndromic EV    | LCK (AR)                           | Failure to thrive, severe diarrhea, opportunistic infections | Low CD4+ Low Tregs, restricted Tc repertoire | Poor TCR signaling | Autoimmunity, high IgM | [18,20,24] |
| Syndromic EV    | TPP2 (AR)                          | Evans syndrome (immune thrombocytopenic purpura and autoimmune hemolytic anemia), progressive Leukopenia, mild viral infections, mild developmental delay | Normal or slightly low CD4+ Tc counts | Senescent CD8+ Tc (impaired proliferation, enhanced staurosporine-induced apoptosis) | Premature immunosenesence (Tc and Bc and antinuclear antibodies), normal IgA and IgE levels, IgG and IgM levels high | [18,24] |
| Profuse warts   | CARMIL2 (AR)                       | Recurrent bacterial, fungal and mycobacterial infections, molluscum contagiosum, EBV lymphoproliferative syndrome and other malignancy, atopy | Low Tregs, high frequency of naïve CD4+, but normal CD4+ overall | Poor Tc dependent antibody response Poor Tc function | Low frequency of memory B cells Ig normal or low | [17,25] |
| Warts           | IKBKG/NFkB essential modulator (XL) | Opportunistic Infections: P. jiroveci, common, NTM, histoplasma, HSV, CMV, MCV infections | Tc normal or low | TCR activation impaired | Low memory and isotype switched Bc, monocyte dysfunction, low IgG, some elevated IgG, IgM | [18,20,24] |
Table 2. Cont.

| HPV Phenotype                      | Gene/Protein (Mode of Inheritance) | Other Clinical Phenotypes | T Cell Counts | T Function | Other Immunological Features | Reference |
|-----------------------------------|------------------------------------|---------------------------|--------------|-----------|------------------------------|-----------|
| Tree man syndrome or common warts | CD28 (AR)                          | None                      | Low Tregs, Low central memory CD4 and CD8 T cells | Abolished CD28 costimulation response, impaired T cell proliferation upon antigens stimulation | Low NK cells | [7] |

IEI, inborn errors of immunity; AR, autosomal recessive; XL, X-linked; Tc, T cells, Tregs, T regulators; EV, epidermodysplasia verruciformis; HSV, herpes simplex virus; VZV, varicella zoster virus; DOCK8, dedicator of cytokinesis 8; STK4, serine/threonine protein kinase 4; EBV, Epstein–Barr virus; NTM, nontuberculous mycobacteria; HSV, herpes simplex virus; CMV, cytomegalovirus; MCV, molluscum contagiosum virus; CARMIL2: capping protein regulator and myosin 1 linker 2; RHOH, Ras homolog family member H; IFNγ, interferon γ; TNFα, tumor necrosis factor α; NF-κB, nuclear factor kappa B; IKBKG, inhibitor of nuclear factor kappa B kinase regulatory subunit gamma.

More recently, patients with CARMIL2 and CD28 deficiencies were associated with HPV susceptibility [7,17]. These IEI both affect the CD28 signaling pathway, which is the major costimulatory pathway of TCR. Patients with CARMIL2 deficiency developed disseminated warts among other infectious manifestations, and they also had decreased memory B cells [17], whereas CD28 deficiency was associated with PW only. Interestingly, one of the CD28 patients developed TMS [7].

3.3. Immunological Phenotype with Several Impaired Leukocyte Subsets

This category includes warts, hypogammaglobulinemia, infections, myelokathexis (WHIM) syndrome, and classical CID and SCID syndromes (Table 3). The warts are also due to α-HPV and the immunological phenotypes of these diseases are variable but qualitative or/and quantitative T cell defects are common to all of them [24]. For example, in WHIM syndrome, between 60 and 80% of patients develop warts after α-HPV infection, and about 16% of these patients develop HPV-related cancers. This disease is associated with mutations in the CXCR4 gene, encoding a chemokine receptor. The immunological phenotype is characterized by neutropenia, low counts of dendritic cells (DC), memory B cells, and naïve CD4+ and CD8+ T cells [26]. In GATA2 haploinsufficiency, α-HPV infections occur in more than 50% of the cases, and genital cancers are frequent. Low monocyte, DC, B cell, CD4+ T cell, and NK cell counts are the most common immunological features of the patients [18,24].

Table 3. Etiologies, clinical phenotypes, and immunological phenotypes of warts associated with several impaired leukocyte subsets.

| Disease Name                           | Gene/Protein (Mode of Inheritance) | Other Clinical Phenotypes | T Cell Counts | T Function | Other Immunological Features | Reference |
|----------------------------------------|------------------------------------|---------------------------|--------------|-----------|------------------------------|-----------|
| WHIM syndrome                          | CXCR4 gof (AD)                     | Warts, genital dysplasia, pneumonia, cellulitis, sinusitis, urinary tract infection, thrombophlebitis, orchitis, osteomyelitis, soft tissue abscesses, HSV infections, VZV infections | Low | Low LPA/LPM Cutaneous anergy | Low IgG and IgA, normal antibody responses | [26] |
| MonoMac syndrome DCML Embberger syndrome or WILD syndrome | GATA2 (AD)                         | Warts, susceptibility to mycobacteria, histoplasmosis, lymphedema, pulmonary alveolar proteinosis, myelodysplasia | Variable, Low Tc | Variable, impaired T cell proliferation upon mitogen stimulation | Monocytopenia, Low Bc Low NK | [18,24] |
Table 3. Cont.

| Disease Name | Gene/Protein (Mode of Inheritance) | Other Clinical Phenotypes | T Cell Counts | T Function | Other Immunological Features | Reference |
|--------------|-----------------------------------|---------------------------|---------------|------------|-----------------------------|-----------|
| LAD syndrome | LAD1/ITGB2 (AR)                   | Warts, delayed cord separation with omphalitis, no pus formation, lack in inflammation is observed in infection area, periodontitis | Leukocytosis | - | Low CD18+ neutropenia | [18,20,24] |
| Warts        | CD154/CD40L, tumor necrosis factor surface family 5 (XL) | P. jirovecii pneumonia, chronic watery diarrhea due to infection with cryptosporidium, 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 | Variable | Defect in CD40L production | Neutropenia, autoimmunity with immune TNFSF5 thrombocytopenia, hemolytic anemia, and immune mediated nephritis | [18,20] |
| Syndromic EV | DCLRE1C/ARTEMIS (hypomorphic, AR) | Recurrent respiratory and gastrointestinal infections | Low CD4+ Tc | Impaired proliferative response and reduced counts of naïve T cells, restricted T cell receptor repertoire | Low B cell numbers and serum IgA levels increased sensitivity to ionizing radiation of fibroblasts | [18,27] |
| Warts        | SPINK5 (AR)                       | Congenital ichthyosis, bamboo hair, atopic diathesis, bacterial infections | Normal T cell counts, the proportion of naïve CD4+ T cells is reduced and the proportion of CD8+ T central memory elevated | - | Switched and non-switched Bc are reduced hyper IgE and IgA | Other Ig: variably decreased impaired NK cytotoxicity | [18,20,28] |
| Warts        | ADA (XL)                          | Chondrostenal dysplasia, deafness, pulmonary alveolar proteinosis, cognitive defects | Low Tc | - | Low Bc absent or reduced ADA activity (<1% of normal) | [18,20,24] |

IEI, inborn errors of immunity; AR, autosomal recessive; AD, autosomal dominant; XL, X-linked; Tc, T cell; Bc, B cell; Treg, T regulators; NK, natural killers; LPA, lymphocyte proliferation to antigen; LPM, lymphocyte proliferation to mitogen; gof, gain of function; CXCR4, C-X-C motif chemokine receptor 4; WHIM, warts, hypogammaglobulinemia, infections, and myelokathexis; LAD-1, leukocyte adhesion deficiency type; ADA, adenosine deaminase; 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; WILD syndrome: Warts, immunodeficiency, lymphedema, and dysplasia syndrome; DCLRE1C, DNA cross-link repair 1C; ITGB2, integrin beta chain β2.

4. Warts and IEI: Diagnostic Strategy

When an HPV-related clinical manifestation is severe, meaning profuse, chronic or recalcitrant and resistant to treatment, an IEI should be suspected especially if there are other infections, atopy, autoimmunity, or malignancy. Together with familial and patient history and physical examination, a guided differential diagnosis hypothesis should be formulated. Afterwards, focused laboratory testing should be investigated starting with immunoglobulin levels, T cell counts, and T cell subpopulation counts [29]. In Figure 4, we propose an algorithm for laboratory testing orientation for diagnosis of IEI related to HPV susceptibility, with or without impaired leukocyte populations.
Figure 4. Algorithm for laboratory testing orientation to diagnosis IEI with severe warts and lymphopenia. DOCK8, dedicator of cytokinesis 8; EV, epidermodysplasia verruciformis; ADA, adenosine desaminase severe combined immunodeficiency; NEMO, nuclear factor κB essential modulator deficiency; TPP2, tripeptidyl peptidase 2; LCK, lymphocyte-specific protein tyrosine kinase; SPINK5, serine peptidase inhibitor Kazal type 5; STK4, serine/threonine kinase 4; CXCR4, C-X-C motif chemokine receptor 4; CORO1A, coronin 1A, CARMIL2, capping protein regulator and myosin 1 linker 2, RHOH, Ras homolog family member H.
5. Conclusions

HPV skin lesions are a common symptom during infancy to childhood. Although recalcitrant warts, or even EV, are a rare clinical manifestation, physicians, including dermatologists and pediatricians, should consider IEI for a patient with recurrent or disseminated HPV skin lesions. The diagnosis strategy is crucial for a prompt and appropriate treatment of those patients. Furthermore, investigations of patients with EV or PW will increase our understanding of skin-intrinsic host immunity against HPVs.

Author Contributions: Conceptualization, A.E.K.; writing—original draft preparation, A.E.K.; writing—review and editing, F.A., J.E.B., K.Z., VB., E.J., J.-L.C. and A.A.B.; supervision, J.-L.C. and A.A.B. All authors have read and agreed to the published version of the manuscript.

Funding: The Laboratory of Human Genetics of Infectious Diseases is supported by the Howard Hughes Medical Institute, the Rockefeller University, the St. Giles Foundation, the National Institutes of Health (NIH) (R01AI143810), the National Center for Advancing Translational Sciences (NCATS), the NIH Clinical and Translational Science Awards (CTSA) program (UL1TR001866), the French National Research Agency (ANR) under the “Investments for the Future” program (ANR-10-IAHU-01), the Integrative Biology of Emerging Infectious Diseases Laboratory of Excellence (ANR-10-LABX-62-IBEID), the French Foundation for Medical Research (FRM) (EQU201903007798), ANR CARMIL2 (ANR-21-CE15-0034), ITMO Cancer of Aviesan and INCa within the framework of the 2021–2030 Cancer Control Strategy (on funds administered by Inserm), the French national reference center for primary immunodeficiencies (CEREDIH), the French Society of Dermatology, the Square Foundation, Grandir-Fonds de solidarité pour l’Enfance, Institut National de la Santé et de la Recherche Médicale (INSERM), and the University of Paris Cité.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors have no conflict of interest to declare.

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