A Human Papillomavirus–Associated Disease With Disseminated Warts, Depressed Cell-Mediated Immunity, Primary Lymphedema, and Anogenital Dysplasia

WILD Syndrome

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Background: Epidermodysplasia verruciformis (EV) is a rare genodermatosis associated with infections with specific human papillomaviruses (HPVs) belonging to the β genus of HPV. Patients with EV usually have a selective defect in cell-mediated immunity. Although skin cancer frequently develops in the sun-exposed cutaneous lesions of patients with EV, the anogenital area is usually not affected by squamous cell carcinomas related to mucosal HPV types.

Observations: We report the case of a patient with clinical similarities to EV who also presented with primary lymphedema, anogenital dysplasias, and depressed cell-mediated immunity. Swab samples and biopsy specimens from various body sites collected over a 28-month period were screened by different protocols for DNA of the HPV groups alpha, beta, and mu/nu. Seventeen β-HPV types could be demonstrated. Interestingly, β-HPVs (HPV-22 and HPV-23) were detectable only in plucked eyebrows and in 1 skin swab sample. None of the specimens from lesional biopsies carried β-HPV. Consistently found α-HPV types included HPV types 6, 51, 52, 61, and 84 in the genitoanal region and HPV-57 in skin lesions. Histological and cytological evaluation revealed multifocal anogenital dysplasia and benign genital and cutaneous warts.

Conclusions: To our knowledge, only 1 other similar case of an EV-like syndrome with impaired, cell-mediated immunity and primary lymphedema has been described in the literature. Based on the characteristic clinical and virological findings in the present case and the previously published case, we speculate that both patients could have a previously unknown syndrome that has clinical similarities to EV but notably differs in the associated HPV types. We suggest the acronym WILD (warts, immunodeficiency, lymphedema, dysplasia) to characterize this syndrome.

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Epidermodyplasia verruciformis (EV), first described in 1922 by Lewandowsky and Lutz,1 is a rare genodermatosis characterized by a generalized infection with EV-specific human papillomaviruses (HPVs). Clinically, it is characterized by the formation of disseminated flat warts beginning in childhood.2 Epidermodysplasia verruciformis has a worldwide distribution and is found in many races.3,4 Patients with EV are at high risk for malignant conversion of cutaneous lesions to squamous cell carcinomas predominantly in sun-exposed areas.5 Several HPV types causing EV have been determined, including HPV types 5, 8, 9, 12, 14, 15, 17, 19 through 25, 36, 38, 47, and 50, of which especially HPV types 5, 8, 17, 20, and 47 have been reported to be associated with malignant transformation.6,8 Infections with HPV-16 and HPV-18, the 2 most common mucosal high-risk HPV types, are not increased in patients with EV.

Twenty years ago in the Archives, Ostrow et al9 reported the case of a patient with clinical features of EV and 2 additional findings that are not characteristic of patients with EV: congenital lymphatic dysplasia and HPV-16–positive carcinoma in situ of the thumb. Moreover, their patient had a history of squamous cell carcinoma of the foot and the groin presenting as large, ulcerative lesions, again not typical conditions for patients with EV. We report the case of a patient presenting with similar findings. Based on the virological and molecular analyses performed in our patient, we speculate that the clinical characteristics of both individuals could represent a specific syndrome.
A 37-year-old German woman with primary lymphedema presented for evaluation of persisting generalized warts that appeared during adolescence, initially affecting the palms and soles. The patient's history excluded consanguinity in her family, and none of her relatives had similar findings. Lower extremity edema was first noted at 6 months of age, and later progressed to involve the groin, vulva, anal region, and distal upper extremities (Figure 1). During adolescence, the patient developed disseminated reddish and brownish flat warts on areas including the facial skin, palms, and soles. There was no history of opportunistic or other notable bacterial or fungal infections, and no other relevant medical history.

The first physical examination at our institution, performed in November 2004, showed numerous plane warts, particularly located on the dorsa of the hands and limbs (Figure 2A). Her palms and soles demonstrated confluent warts in a bas relief–like pattern, destroying the conventional plantar lines and fingerprints (Figure 2B). The face, upper trunk, and extremities were predominantly affected by disseminated reddish flat warts and pityriasis versicolor–like macules. The genitoanal region showed widespread flat, brownish warts and several red papules and plaques ranging from 5 to 15 mm in diameter (Figure 3A). Genital and anal mucosa showed numerous verrucous lesions suspicious for condylomata acuminata (Figure 3B and Figure 4). The oral mucosa appeared normal.

Histopathologic evaluation of the red and brown wartlike lesions showed hyperkeratosis, acanthosis, and elongation of the rete ridges and enlargement of squamous cell nuclei with surrounding halos characteristic of cutaneous
warts (Figure 5A).\textsuperscript{10} A biopsy specimen taken from a pityriasis versicolor–like area revealed similar but less pronounced changes. No signs of dysplasia were present. Specimens of several verrucous lesions of the anogenital region including the vulva, perianal skin, and anal canal revealed irregular nuclei, dyskeratosis, and mitotic alterations in the lower two-thirds of the epidermis consistent with intraepithelial neoplasia grades I to II (Figure 5B). Cytological swab samples obtained from the anal and genital (vulva, vagina, cervix) area showed high-grade squamous intraepithelial lesions (according to the Bethesda classification) consistent with severe dysplasia in several samples.

All lesional biopsy specimens and additional swab samples obtained from the trunk, leg, intra-anal and perianal skin, vulva, vagina, cervix, and plucked eyebrows were analyzed for the presence of 18 different low-risk \( \alpha \)-HPV types, 18 different high-risk \( \alpha \)-HPV types, and 25 different \( \beta \)-HPV types, as previously reported.\textsuperscript{11,12} In addition, \( \alpha \)-2/\( \alpha \)-4 HPV group–specific polymerase chain reactions (PCRs) and \( \mu \)/\( \nu \) group–specific PCRs were performed on all samples as well as type-specific, real-time PCRs for HPV-5 and HPV-8.\textsuperscript{13-15} The results of HPV type analyses are detailed in Table 1. Interestingly, none of the cutaneous and anogenital biopsy specimens carried (EV-defining) \( \beta \)-HPVs. Only 2 \( \beta \)-HPV types (HPV-22 and HPV-23) were found in the plucked eyebrows and in a skin swab sample from the abdominal wall, respectively. However, 17 different high- and low-risk \( \alpha \)-HPV types were detected in both cutaneous and mucosal biopsy specimens and swab samples taken within a 28-month observation period. The HPV types consistently found (in more than two-thirds of the samples) included HPV types 6, 51, 52, 61, and 84 in the anogenital region; HPV-57 in the skin biopsy specimens; and HPV types 51, 52, 57, 61, and 84 in the skin swab samples (Table 1). The HPV types found in the plucked eyebrows were \( \alpha \)-HPV types 57, 61, and 84 and the \( \beta \)-HPV type 22. We could not detect HPV DNA in 2 ethylene-diamine-tetraacetic acid blood samples.

Results of laboratory investigations revealed findings within the reference range for a hemogram, blood cell count, and serum chemical analysis and a notable lymphopenia level of 500/\( \mu \)L (reference range, 1000-4050/\( \mu \)L), a low total protein level of 5.4 g/dL (reference range, 6.4-8.3 g/dL), and low albumin levels (in the serum electrophoresis) of 53.6% (reference range, 57%-68%). (To convert protein to grams per liter, multiply by 10.0.) Lymphocyte subpopulation studies showed a consistently severe reversal of the \( CD^{+} / CD^{8^{+}} \) T-cell ratio of 0.59 (reference range, 1-2), with notably decreased \( CD^{+} \) T cells of 64/\( \mu \)L (reference range, 410-1590/\( \mu \)L). A decrease was also observed in the B-lymphocyte count (66/\( \mu \)L; reference range, 90-660/\( \mu \)L) (to convert lymphocytes to \( \times 10^{9} \) per liter, multiply by 0.001). Immunoglobulin levels were also within reference range. Further immunologic evaluation revealed anergy to routine skin testing and a completely depressed mitogen-stimulated lymphocyte transformation. The presence of sexually transmitted diseases, including human immunodeficiency virus (HIV) and infection...
with *Treponema pallidum*, was excluded. A bone marrow aspirate excluded concomitant hematological disorders. Molecular investigations for mutations in the chemokine receptor gene CXCR4 (GenBank AF052572) (as seen in WHIM syndrome [warts, hypogammaglobulinemia, infections, myelokathexis]) and NF-1 gene (GenBank

| Table 1. Human Papillomavirus (HPV) Types Detected on Different Locations of the Body During a 28-Month Observation Period

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Skin Swab Samples&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Mucosal Swab Samples</th>
<th>Biopsy Specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abdominal Wall</td>
<td>Left Thigh</td>
<td>Vulvar (LSIL-HSIL)</td>
</tr>
<tr>
<td></td>
<td>LR α-HPV</td>
<td>HR α-HPV</td>
<td>β-HPV</td>
</tr>
<tr>
<td>HPV-6</td>
<td>NP</td>
<td>NP</td>
<td>8/9</td>
</tr>
<tr>
<td>HPV-44</td>
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<td>1/9</td>
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<tr>
<td>HPV-54</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>HPV-57</td>
<td>2/2</td>
<td>1/2</td>
<td>1/9</td>
</tr>
<tr>
<td>HPV-61</td>
<td>1/2</td>
<td>2/2</td>
<td>9/9</td>
</tr>
<tr>
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<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>HPV-72</td>
<td>NP</td>
<td>NP</td>
<td>1/9</td>
</tr>
<tr>
<td>HPV-83</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>HPV-84</td>
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<td>7/9</td>
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<td>HPV-89</td>
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<tr>
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</tr>
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<td>HPV-66</td>
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<td>HPV-73</td>
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</tr>
<tr>
<td>HPV-23</td>
<td>1/2</td>
<td>NP</td>
<td>NP</td>
</tr>
</tbody>
</table>

Abbreviations: AIN1/2, anal intraepithelial neoplasia grade 1 to 2; HR, high-risk; HSIL, high-grade squamous intraepithelial lesion; LR, low-risk; LSIL, low-grade squamous intraepithelial lesion; NP, not present; VIN1, vulvar intraepithelial neoplasia, grade 1.

<sup>a</sup>Analyses for LR α-HPV included HPV types 6, 11, 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82 (see Kreuter et al<sup>11</sup> and references therein). Analysis for β-HPV included HPV types 1, 41, and 63 (no µ/H9263-types were detected).<sup>14</sup> The numerator shows the number of samples in which the respective HPV type was detected, the denominator shows the total number of samples that were analyzed. The eyebrow sample contained 5 plucked eyebrow hairs including the hair bulb.

<sup>b</sup>The size of the area swabbed was 20 cm².

<sup>c</sup>Brown warty lesions.

<sup>d</sup>Pink warty lesions.
AH000834) (as seen in neurofibromatosis type 1) excluded these syndromes. Mutational analysis of the vascular endothelial growth factor receptor 3/FLT4 gene (GenBank X68203) did not reveal mutations previously associated with Milroy disease (primary congenital lymphedema). A silent mutation (CCC→CCT) with unclear significance was found in exon 23 (position c.3198/p.1066) of the FLT4 gene.

All anogenital lesions were treated with imiquimod cream, 5%, for a total of 16 weeks, and all verrucous lesions larger than 5 mm were electrosurgically removed. However, early relapses occurred after therapy was completed.

Although the clinical findings have similarities to EV, the presented case differs in several decisive points: (1) The HPV types of the EV-defining species ß-HPV, including HPV types 5, 8, 9, 12, 14, 13, 17, 19-25, 36, 38, and 47, were absent in all analyzed biopsy specimens. This, and the lack of histologic features characteristic of EV, excludes the diagnosis of EV in our patient. (2) Epidermodysplasia verruciformis does not involve the mucosa, whereas our patient experienced widespread infections with numerous genital high- and low-risk ß-HPVs, resulting in multifocal genitoanal dysplasia. (3) Several of these genital HPV types were also detected in cutaneous lesions, skin swab samples, and the eyebrows, none of which is usually observed in patients with EV or in the general population. (4) Primary lymphedema, a prominent finding of our patient, has so far not been described in association with EV. (5) Our patient showed no signs of premalignant changes in the sun-exposed areas, which frequently appear in persons with EV between the ages of 30 and 40 years.

To our knowledge, the combination of the clinical symptoms seen in the present patient has only been reported once before, by Ostrow et al. In their patient, a 37-year-old white man without family history of lymphedema and warts, congenital lymphatic disease was also present on all 4 extremities, and disseminated flat warts and pityriasis versicolor-like papules developed during adolescence. Further features shared with our patient were anergy to routine skin testing, depressed mitogen-stimulated lymphocyte transformation, severe CD4 T-cell and B-cell depletion, low albumin and low total serum protein levels, and condylomatous (partially dysplastic) lesions. The patient described by Ostrow et al had an in situ carcinoma of the thumb and a history of squamous cell carcinoma of the groin. Virological analyses in their patient showed that EV-defining ß-HPVs were also absent. The only cutane-
ous HPV type found was HPV-3, which is frequently found in flat warts. The only high-risk mucosal HPV type discovered in their patient was HPV-16. Because many of the HPV types found in our patient were still unknown when the article by Ostrow et al was published (in 1987), one might speculate that a broad spectrum of α-HPVs would have been detectable nowadays.

The detection of multiple β-HPVs is frequent in the eyebrows and on the healthy skin of normal individuals, whereas genital α-HPV types are rarely found in these locations (see de Koning et al17 and Hazard et al18 and references therein). The only β-HPVs found in our patient were HPV-22 (eyebrows) and HPV-23 (skin swab sample) in 1 sample each, but several mucosal α-HPVs were present in her skin swab samples and eyebrows. Virological analyses over a 28-month observation period showed that high-risk HPV types 51 and 52 and low-risk HPV types 6, 61, and 84 persisted in our patient. The median duration of incident genital HPV infection in women usually ranges from 7 to 10 months.19 The persistence of specific α-HPV types in our patient might point to a selective immunodeficiency against these types, especially because HPV-16 and HPV-18, the 2 most common high-risk HPV types, and bacterial or fungal infections were absent.

Extensive warts have been reported in some other inherited syndromes, including WHIM syndrome (warts, hypogammaglobulinemia, infections, myelokathexis), X-linked hyper-IgM immunodeficiency syndrome, Wiskott-Aldrich syndrome, Netherton syndrome, Klinefelter syndrome, Mulvihill-Smith syndrome, or Clouston syndrome.20-26 Characteristic clinical findings of these syndromes are summarized in Table 2. However, except in WHIM syndrome, viral warts are not a consistent finding in these syndromes, and other typical features were absent in our patient. In WHIM syndrome, mutations of CXCR4 have been demonstrated to predispose for HPV infection by aberrant chemokine receptor function.27 The presence of WHIM syndrome in our patient was excluded by chemokine receptor gene CXCR4 analysis.

Besides extensive HPV infection, congenital onset of lymphedema dominates the clinical picture of the present case. The advent of molecular medicine elucidated at least 3 different types of primary lymphedema: lymphedema-distichiasis syndrome, hypotrichosis-telangiectasia-lymphedema syndrome, and Milroy disease.28-30 All these conditions were excluded based on the missing typical features (Table 2). In addition, sequence analysis of the FLT4 gene did not reveal mutations previously associated with Milroy disease.

Our decision to initiate imiquimod therapy, a topical immune response modifier that relies on the host immune response, might seem counterintuitive considering the severely compromised T-cell status of the patient. In a recently published pilot study31 by our group on imiquimod treatment of anal intraepithelial neoplasia (AIN) in HIV-positive men, even patients with very low CD4-cell counts showed complete clinical and histological clearance of AIN after therapy. Moreover, imiquimod led to a significant decline in the number of HPV types and high-risk HPV DNA load in these patients. This observation encouraged us to use imiquimod for a multifocal condition in which the morbidity after ablative treatment is usually high.

In conclusion, sufficient evidence exists to support our hypothesis that both our patient and the patient described by Ostrow et al have an as-yet undescribed syndrome. An extensive review of the literature failed to detect other reports of individuals with comparable unique clinical characteristics. Future genetic and biochemical studies are now warranted to help in elucidating the molecular background of this unknown disease. Until then, based on the prominent features, we suggest using the acronym WILD to characterize this condition.

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Author Contributions: Dr Kreuter had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Kreuter, Hochdorfer, and Wieland.

Analysis and interpretation of data: Kreuter, Hochdorfer, Brockmeyer, Altmeyer, Pfister, and Wieland.

Drafting of the manuscript: Kreuter, Hochdorfer, and Wieland.

Critical revision of the manuscript for important intellectual content: Hochdorfer, Brockmeyer, Altmeyer, and Pfister.

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Study supervision: Kreuter, Hochdorfer, Brockmeyer, Altmeyer, Pfister, and Wieland.

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C ongratulations to the winner of our December quiz, John Starling III, MD, Department of Dermatology, University of Michigan, Ann Arbor. The correct answer to our December challenge was *multicentric reticulohistiocytosis*. For a complete discussion of this case, see the Off-Center Fold section in the January Archives (Tallon B, Rademaker M. Asymptomatic papules over the proximal nail fold in a child. *Arch Dermatol*. 2008;144[1]:105-110).

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