Skin Autografts in Epidermodysplasia Verruciformis: Human Papillomavirus-associated Cutaneous Changes Need Over 20 Years for Malignant Conversion

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Abstract

Epidermodysplasia verruciformis (EV) is regarded as a model for cutaneous oncogenesis associated with specific human papillomaviruses (HPVs). Because genital HPV-associated carcinogenesis is a very long-lasting process requiring 20-30 years and epidemiological studies of this type for HPV-associated skin cancers are impossible in such a rare disease as EV, we observed for up to 20 years EV patients having surgery for carcinomas with consecutive autografts from uninvolved and non-sun-exposed skin. We noticed the appearance of premalignant and malignant changes around the grafts, whereas within the grafted skin, only benign lesions developed within several years after transplantation. Thus, skin HPV-associated carcinogenesis appears to be a very slow process comparable to the genital carcinogenesis associated with high-risk HPVs.

Introduction

EV is a rare life-long disease associated with HPVs specific for EV, which are harmless for the general population (1-3). These viruses do not induce cutaneous lesions in healthy persons, and the abnormal susceptibility of EV patients to specific HPVs is genetically determined (4). This disease is of special importance because about one-half of the cases show surgical skin cancers; thus, it presents a model of HPV-associated cutaneous oncogenesis. The interest in EV has been substantially raised recently due to detection of EV-related HPVs in a majority of cutaneous cancers in an immunosuppressed and immunocompetent population (5-8). Benign macular, verruca plana-like or pityriasis versicolor-like lesions start to develop at the age of 5-7 years. The extent of cutaneous involvement and the progression of the disease differ considerably; however, one characteristic of the disease is the persistence of skin changes throughout life (4).

Benign lesions in EV were found to be induced by at least 20 EV HPVs, and the patients are in general infected with several HPV types, whereas developing carcinomas contain usually HPV5, some HPV8, and only rarely other EV HPVs (9).

It is not clear why the lesions never start to appear in newborns and children before 4-5 years of age. Also, the time of development of malignancies in patients with high-risk EV HPVs 5 and 8 is quite unpredictable. A considerable time lag between the primary infection by high-risk genital HPVs and the development of HPV-associated changes is well established by epidemiological studies (10). High rates of HPV detection were reported in young persons between 16 and 20 years with no signs of infection and no cytological abnormalities (11); the peak incidence for cervical intraepithelial neoplasia was found in age groups 25-35 years, whereas the peak incidence for cervical cancer was found in age groups 55-65 years (12). Thus, progression toward invasive growth associated with high-risk genital HPVs requires 20-30 years (13, 14).

Epidemiological data of this type are not possible to collect in such a very rare disease as EV. We had a unique opportunity to follow up for over 20 years several EV patients who had extensive surgery because of multiple carcinomas, mainly on the forehead, with wound covered by autograft from the uninvolved, non-sun-exposed skin.

Patients and Methods

Five EV patients who constantly developed multiple malignant, locally destructive changes involving the whole forehead in spite of cryosurgery and some experimental therapies with retinoids, IFNs, and others have been operated, and the excision area was covered with a free graft taken with the use of Humby's knife from the uninvolved skin of the internal aspect of the arm. The skin of the forehead was removed with the margin of seemingly uninvolved skin of at least 1 cm from both sides. The healing was uneventful, and the cosmetic results were quite satisfactory. The main data of the patients, EV HPV types, and appearance of lesions are shown in Table 1. The progressive process of carcinogenesis around the graft and appearance of benign lesions in the graft is presented in Figs. 1-3.

In two patients treated previously with X-rays, there was invariably deterioration of the disease in spite of clearance of the irradiated tumor, and benign changes showed a rapid progression into malignancy.

In all patients, within about 1-2 years after surgery, at the graft margins of both sides, numerous premalignant lesions of actinic keratosis type started to appear in previously seemingly uninvolved skin; the actinic keratoses became progressively deeper and more hyperkeratotic. Histological examination showed Bowen's atypia but with preserved dermal-epidermal border, i.e., consistent with actinic keratosis and/or carcinoma in situ. Within 3-6 years, some of the actinic keratoses progressed into superficial microinvasive carcinomas. Two patients, previously treated with X-rays, developed locally destructive cancers but with no metastatic potential.

Within grafts, first single macular benign lesions started to appear 2.5, 3, 4, or 10 years after grafting, and the rate of appearance was very slow. No malignant changes developed within the period of over 20 years.

Results and Discussion

This study has shown that the time lag between the development of EV HPV-associated benign lesions within the grafted skin, previously displaying no visible changes, was about 2.5-10 years, and progression toward malignancy did not occur within 20 years of follow-up, i.e., similar to conversion of genital high-risk HPV-induced lesions into invasive cervical cancer (14). However, around the grafts appeared, much earlier than expected, multiple, partly coalescent actinic keratoses, probably related to a life-long sun exposure. These premalignant lesions developed mainly in temporal areas, an usual site of actinic keratoses in the general population.

The recent findings strongly suggest that EV-related HPVs are...
Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Gender</th>
<th>Family history</th>
<th>Year of birth</th>
<th>Age at onset of disease</th>
<th>EV HPVs of benign lesions</th>
<th>Activity (development of new lesions)</th>
<th>Age at first malignant conversion</th>
<th>Date of grafting/appearance of benign lesions</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>Yes</td>
<td>1940</td>
<td>5y</td>
<td>5, 8, 9, 14, 17, 19, 20, 22, 24, 30, and HPV3</td>
<td>++++</td>
<td>++++</td>
<td>~29y</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>No</td>
<td>1935</td>
<td>5y</td>
<td>5 and HPV3</td>
<td>++</td>
<td>++++</td>
<td>~39y</td>
</tr>
<tr>
<td>3&quot;</td>
<td>M</td>
<td>Yes</td>
<td>1926</td>
<td>5y</td>
<td>9</td>
<td>++</td>
<td>++++</td>
<td>~43y</td>
</tr>
<tr>
<td>4&quot;</td>
<td>M</td>
<td>No</td>
<td>1937</td>
<td>7y</td>
<td>5, 14, 15</td>
<td>++++</td>
<td>++++</td>
<td>~18y</td>
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<tr>
<td>5</td>
<td>M</td>
<td>Yes</td>
<td>1955</td>
<td>5y</td>
<td>5, 18, 20, 23, 36, 50</td>
<td>++++</td>
<td>++++</td>
<td>~30y</td>
</tr>
</tbody>
</table>

a EV HPVs were typed by Southern blot, as described previously (2, 3).
b +++, hands, face, legs, single plaques on the thorax; ++++, face, upper and lower limbs, and the trunk.
c +++, new lesions within 1–2 years; ++++, extensive spreading at the time of studies.
d Before EV was recognized, the patient was treated for two cancers with X-irradiation in 1969 and 1979; he was lost to follow-up due to accidental death.
e Treated in 1967 with X-rays for two cancers on the forehead, in 1976 for cancers of the lip and the ear, and in 1978 for periauricular carcinoma; the cancers were invasive, and benign lesions appeared much earlier than in others.

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ubiquitous (5–8) and are probably present in a latent state in all individuals, possibly in hair follicles (15). EV develops, however, only in genetically predisposed persons with abnormal susceptibility to infection by specific, phylogenetically related EV HPV types, and especially to potentially oncogenic HPV type 5 variants displaying a very high intratypic diversity (16). It is conceivable that the variability of HPV type 5 constitutes a mechanism by which infected cells escape from immune surveillance (17). Although the immunogenetics of EV is not entirely clear (18), some specific HLA DR-DQ haplotypes were reported to be associated with this disease (19).

A characteristic feature of EV is local immunosuppression and immunotolerance to EV HPV-harboring cells, which facilitates long-life persistence of the lesions and could be, at least in part, related to UVB-induced local production of tumor necrosis factor α and TGF-β1, cytokines found to be overexpressed in the skin of these patients (20). Overexpression of TGF-β1 was found to inhibit tumorigenesis (21, 22) or contribute to the progression and invasiveness of cancer (23), depending on different mechanisms, mainly on cooperation with oncogenes c-myc (23) and ras (24). Of critical importance are the types of cells, because nontumorigenic keratinocytes were found to be sensitive, whereas cervical carcinoma cells were resistant to the growth-inhibitory effect of TGF-β1 (25). In in vivo conditions, a number of cellular alterations, growth-stimulating factors, mitogens, and cytokines may also contribute to the inhibition or progression of cancer. A low metastatic potential of EV cancers might be related in part to the capacity of TGF-β1 to inhibit the matrix metalloproteinases and stimulate the matrix constituents and endogenous antiangiogenic factors. Overexpression of TGF-β1 is probably also responsible for rapid wound healing in EV (4). However, the appearance of premalignant and malignant changes in the temporal areas, partly

![Fig. 1. Patient no. 1, 4 years after grafting. A few small benign macular lesions within the graft are shown. Around the graft at the right temporal area are numerous actinic keratoses.](image1)

![Fig. 2. The same patient as in Fig. 1, 11 years after grafting. Within the graft, single benign lesions. Around the graft, more numerous actinic keratoses, some transforming into early carcinomas.](image2)

![Fig. 3. The same patient as in Fig. 1, 20 years after grafting. Within the graft are only single benign lesions, but at the temporal area, several early and some microinvasive carcinomas are seen.](image3)
covered by hair, is suggestive of the role of some other factors in addition to UVB.

This idea is supported by a relatively low frequency of DNA mutations characteristic of UVB (17), including p53 mutations. Such factors, in addition to UVB (18), are X-rays (4, 26), because the most severe course of the disease was in our EV patients treated with gamma irradiation for cancers. The deleterious effect of X-rays in EV is comparable to that in laryngeal papillomatosis and other HPV-associated carcinomas. However, if no co-carcinogens are applied, the metastatic potential of EV cancers is weak, the malignant conversion occurs slowly, and the tumors are only locally destructive (4).

It is of interest that malignant proliferation in EV patients usually starts within and around hair follicles (4, 18). It is tempting to speculate that oncogenic EV HPVs (HPV type 5 and its variants) are in a dormant state in hair follicles in EV patients, as found for UV-related HPVs in both immunosuppressed and the general population (15). However, in contrast to oncogenic EV HPVs, the role of EV-related DNA sequences in cutaneous carcinogenesis is not established.

In conclusion, skin grafting in EV patients provided a unique opportunity to determine the time lag necessary for the development of benign cutaneous EV lesions in seemingly uninvolved skin. Because benign macular lesions started to appear within several (3–10) years after grafting, this time lag could explain why EV lesions in children do not appear before the age of 4–7 years. Most importantly, this study showed that development of premalignant and malignant EV lesions is a very long-lasting process (in our observation, no less than 20 years), comparable to that in cervical HPV-associated carcinogenesis.

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References

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