Human Papillomavirus Type 5 Related Epidermodysplasia Verruciformis in A Patient with Systemic Lupus Erythematosus
— Report of Two Cases and Review of the Literature

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Epidermodysplasia verruciformis (EV) is a rare cutaneous human papilomavirus (HPV) infection characterized by an unusual susceptibility to a specific group of HPVs, so-called epidermodysplasia verruciformis associated human papillomaviruses (EV-HPVs). We herein report a 42-year-old women with a history of systemic lupus erythematosus (SLE) who initially showed multiple erythematous flat-topped papules on the neck and medial forearms and progressively developed numerous brownish macules on her face, neck, upper chest and back in the following three years. The histopathology revealed characteristic viral cytopathic changes in an acanthotic epidermis: multifocal enlarged keratinocytes with cytoplasmic vacuolization in granular layer and upper spinous layer. The diagnosis of EV was thus made. Besides, the presence of human papillomavirus type 5 (HPV 5) DNA was detected on the lesional and peri-lesional skin. The patient was then treated with different modalities including Erbium-YAG laser, cryotherapy with liquid nitrogen, and topical 5% imiquimod. Partial clearing of the lesions were observed by all these three modalities up to a 6-month period of follow-up. In addition, we make a review of the relationship between EV, EV-HPV and development of non-melanoma skin cancers (NMSCs). (Dermatol Sinica 24: 278-284, 2006)

Key Words: Epidermodysplasia verruciformis, Human papillomavirus, Systemic lupus erythematosus, Non-melanoma skin cancers

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INTRODUCTION

Epidermodysplasia verruciformis (EV) is a rare cutaneous disorder characterized by an unusual susceptibility to a generalized infection by human papillomaviruses (HPVs). There are a specific group of HPVs involved in the disease process called epidermodysplasia verruciformis associated human papillomaviruses, or EV-HPVs. EV is manifested by the appearance of widespread, polymorphic skin eruptions of verruca-like lesions and pityriasis versicolor-like macules. The lesions may undergo malignant transformation to non-melanoma skin cancers in 30% to 50% of cases, with a predilection for sun-exposed sites.1,2

CASE REPORT

A 42-year-old Taiwanese woman presented with multiple erythematous flat-topped papules on the neck and medial forearms since 1995. The initial diagnosis was verrucae planae. She therefore received topical tretinoin 0.05% once daily before sleep. In addition to the original flat wart-like lesions, numerous brownish macules progressively developed on her face, neck, upper chest and back over the subsequent three years. The newly developed pityriasis versicolor-like lesions varied in size from 3 mm to 1 cm in diameter; Koebner phenomenon was observed (Fig. 1). All the skin lesions were asymptomatic. She had no family history of similar skin lesions. The patient had been diagnosed as systemic lupus erythematosus (SLE) 12 years before the onset of the skin problem. The initial presentation of SLE was symmetrical arthritis on knees and ankle joints, malar rash and oral ulcer. Elevated titer of ANA (1:1280X+) and low levels of C3 and C4 were also noted. She had been treated elsewhere with systemic corticosteroid, plaquenil and azathioprine. During the ensuing years, she had been admitted for more than ten times because of
various infections. Her SLE was controlled by prednisolone 5mg every other day over the last few years.

At the time of presentation, complete blood cell counts revealed pancytopenia (WBC: 1,920 cells/µl, normal: 5,200-12,400; RBC: 3.29 cells/µl, normal: 4.2-6.1 / 10⁷; platelet: 7.1 fL, normal: 7.2-11.1) and lymphopenia (absolute peripheral lymphocyte count: 267 cells/µl, normal: 1,600-2,400). In addition, the CD4 and CD8 count was 36 and 88 cells/µl, respectively, and the CD4/CD8 ratio was 0.41. Blood biochemistry studies showed elevated C-reactive protein level (3.80 mg/dl, normal: < 0.8). Liver and renal functions were within normal limits; HIV serology and a potassium-hydroxide (KOH) examination for fungal element from forearm lesions were negative. An incisional skin biopsy was performed from the left forearm.

The histopathologic result revealed viral cytopathic changes in an acanthotic epidermis i.e. multifocal enlarged keratinocytes with vacuolated cytoplasm in granular layer and upper spinous layer. Moreover, some basophilic keratohyalin granules were occasionally seen in those enlarged cells (Fig. 2). In addition, the skin scrapings from the lesional and peri-lesional skin were sent for polymerase chain reaction (PCR) followed by DNA sequencing (Fig. 3).

The result demonstrated the presence of human papillomavirus type 5 (HPV 5).

The protocols for PCR and DNA sequencing have been described. Briefly, the PCR solution (25 µl) contained 0.75 µM (each) FAP59 and FAP64 primers which were designed from two relatively conserved regions of the L1 open reading frame of most HPV, 2.0% bovine serum albumin (Sigma-Aldrich, Steinheim, Germany), 0.2 mM (each) deoxynucleoside triphosphate, 0.625 U of AmpliTaqGold DNA polymerase, GeneAmp PCR buffer II, 3.5 mM MgCl₂ (Applied Biosystems, Foster City, CA, U.S.A.), and 5 µl of the sample. Forty cycles of amplification were performed after denaturation for 10 min at 94°C; each cycle consisted of 94°C for 90 s, 50°C for 90 s, and 72°C for 90 s. Subsequently, the clones were sequenced (ABI 310 automatic sequencer, Advanced Biotechnologies, Foster City, CA, U.S.A.) with both forward and reverse primers. The DNA sequences obtained were compared with all sequences in Gen Bank through the BLAST server (National Center for Biotechnology Information; http://www.ncbi.nlm.nih.gov/blast/bl2seq.cgi).

The patient was then treated with different modalities including Erbium-YAG laser, cryotherapy with liquid nitrogen, and topical 5% imiquimod (Aldara cream, 3M). Partial clearing of the lesions were observed by all

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**Fig. 2**
Enlarged keratinocytes are found in granular layer and upper spinous layer of epidermis, with occasional presentation of basophilic keratohyalin granules. (H&E, x400)

**Fig. 3**
Human papillomavirus type 5 is detected on the lesional and peri-lesional skin, confirmed by DNA sequencing.
DISCUSSION

Lewandowsky and Lutz first described EV in 1922. It can be hereditary or sporadic, and no sexual, racial, or geographic preference is noted.\(^5\) Autosomal recessive transmission of the disease has been postulated as a main mode of inheritance, although autosomal dominant and sex-linked inheritance has also been described.\(^5\) However, the sporadic form of EV remains to be the most commonly reported form of the disease.\(^7\)

The pathogenesis of EV is largely unknown. There has been accumulating evidence which suggests that dysfunction in cell-mediated immunity may play a role. While the activity of non-specific nature killer cells and antigen presentation by Langerhans cells seem to be normal,\(^8,9\) reduced natural cell-mediated cytotoxicity against EV-HPV harboring keratinocytes has been demonstrated.\(^10\) All these findings indicate that there may be defects in cell-mediated immunity which result in the immunotolerance to these viruses.\(^12\)

There are two subsets of cutaneous lesions in EV; one is malignant form and the other benign. The benign form presents as monomorphous lesions that are plane wart-like and is associated with HPV types 3 and 10. The malignant subset is characterized by polymorphic skin manifestations, e.g. pityriasis versicolor-like lesions, flat wart-like papules, red macules, pre-malignancies such as actinic keratosis, and non-melanoma skin cancers. This form of EV is strongly associated with HPV types 5, 8, 9, 12, 14, 15, 17, 19-25, 36-38, 47, 49, 50, 75, 76 and 80; among them, only a few (predominantly type 5, 8 and occasionally type 14, 17, 20 and 47) have been demonstrated to have an association with carcinoma.\(^2,6,7,13,14\)

Noteworthily, the onset of initial cutaneous changes is often in the childhood\(^1\) while malignant transformations, if any, usually occur in the third to fourth decades with preferential localization at the sun-exposed areas, especially the forehead.\(^1\) All these imply that both prolonged infection with EV-HPVs and ultraviolet irradiation may contribute to the development of skin cancers in EV patients.

HPVs are small double-stranded DNA viruses that are strictly epitheliotropic and induce wide diversity of highly proliferating epithelial lesions.\(^17,18\) HPV infection is known to be linked to around 10% of the tumor burden worldwide and has been regarded as an important carcinogen in various epithelial tumors, such as the cancers of the cervix, squamous cell carcinoma (SCC), and verruca vulgaris. Their linkage to the development of non-melanoma skin cancers (NMSCs), namely SCCs, basal cell carcinomas (BCCs), comes first from some observational studies in transplant patients.\(^19\)

Studies on the detection of HPV DNA in NMSCs gave confusing results before early 1990s because of the technical difficulties in detecting the diversities of genomes which belong to the numerous different types of HPVs. It was not until the introduction of a highly sensitive degenerate PCR method by Shamanin et al. that the technique of HPV-DNA detection made a breakthrough.\(^20\) With the subsequent combination of degenerate, nested and type-specific PCR followed by direct sequencing, hybridization or cloning, the prevalence of HPV DNA in transplant SCCs ranges from 69% to 88%, of which the EV-HPV types usually predominate and mixed infection with two or more HPV types are common.\(^21\) EV-HPV DNA is also detected in SCCs from other immunosuppressed subjects, including those treated with psoralen-ultraviolet A (PUVA).\(^22,23\) The prevalence of HPV-DNA in transplant premalignant lesions (actinic keratoses, SCC in situ, keratoacanthomas) are as high as in their invasive counterparts.\(^24\) In contrast, most studies reported a lower prevalence of HPV in transplant BCCs than in SCCs.\(^22,25,26\)

There are only two previous case reports regarding the association between EV and SLE,\(^27,28\) while EV / EV-like eruptions have been described in organ transplantation, Hodgkin’s disease, leukemia, thymoma, lepro-
matous leprosy and HIV infection. These "sporadic" cases all demonstrated derangement of immune status, either due to immunosuppressive agents, hematologic neoplasms, or HIV infection. They showed characteristic clinicopathologic features and viral evidences of EV as were seen in classical (familial) EV, except in some patients (i.e. Hodgkin's disease), the EV-like lesions were almost exclusively present on irradiated and UV-exposed skin. One of the two SLE-related cases was a 32-year-old female with EV who had been diagnosed with of SLE for 13 years and had been treated with 33 pulses of intravenous cyclophosphamide, 3 pulses with methylprednisolone, oral prednisone (15-30 mg daily) and oral azathioprine (75-150 mg daily). Consequently, she had experienced multiple complications such as Aspergillus pulmonary infection, Hemophilus influenza pneumonia, and Salmonella diarrhea during the course of the disease. In this sporadic case, HPV 17 DNA was found on the cutaneous lesion while HPV 20 DNA was identified in both lesional and adjacent normal skin. The authors thus presumed that the long-standing use of immunosuppressive agents could result in the wide distribution of latent HPV that in turn contribute to the formation of EV.

In addition to the prolonged immunosuppressive treatment, the role of autoimmunity itself in the genesis of EV-HPV is interesting. Anti-HPV 5 antibodies were detected (20%) in some autoimmune disorders with cutaneous involvement, such as SLE and systemic scleroderma; whereas HPV DNA sequences were detected in a much higher percentage (90%) of the patients in this group. Another study demonstrated that damaged hair follicles in both of the diseases harbor EV-HPV DNA sequences, which could partly account for the high detection rate of HPV DNA. Given the low yield rate of HPV 5 antibodies identified from the sera of neurological autoimmune diseases without skin lesions of epidermal proliferation (multiple sclerosis: 4.6%; myasthenia gravis: 8.0%) used for control, autoimmunity by itself appeared not to be sufficient for generation of anti-HPV 5 antibodies, if not associated with keratinocyte proliferation.

The possible relationship between the development of EV and the immune status in SLE deserves further investigation. It has been demonstrated that SLE is caused by polyclonal activation of B lymphocytes, with subsequent generation of autoantibodies against a variety of self-antigens, including antibodies to nuclear, cytoplasmic, and extracellular components. In our case, the prolonged use of prednisolone and azathioprine may not only reduce the production of B-cell antibody but also inhibit the actual function of T-cell mediated immunity, thus increases the risk of various infection, including that of the HPV. Additionally, local immune responses play important roles during HPV infection in which CD4-positive T lymphocytes and macrophages predominate. A number of studies concerning interferon-resistant anogenital warts demonstrated reversed CD4/CD8 ratio (range, 0.38 to 0.97). Depleted infiltration of CD4 and, to a lesser extent, CD8 lymphocytes in this group of warts was found in comparison with interferon-responding ones. In EV patients, it has been reported that the levels of CD3+ and CD4+ T lymphocytes were decreased with maintenance of CD8+ levels, and thus inversion of the CD4/CD8 ratio, however, the ratio may be variable according to duration and severity of disease. Furthermore, impairment of cell-mediated immunity was manifested by the cutaneous anergy to a variety of common skin antigens and, by the reduction of the lymphocyte transformation to phytohaemagglutinin. To sum up, we assumed that depleted CD4 lymphocytes, resulting in reversed CD4/CD8 ratio, may attribute to impaired local immune response and are associated with prolonged HPV infection.

Given the rarity of cases of EV associated with SLE to date; it is likely that the larger reservoir of EV-HPV in autoimmune disease, the immunocompromised state secondary to drug treatments, and lastly, the genetic predisposition may all play certain roles in such a rare occurrence. With the disclosure of two suscepti-
ble loci mapped to chromosome 2p21-p24 and 17q25 by linkage analysis, it sheds light on advancing our knowledge to the innermost of EV. Unfortunately, we are unable to verify the genetic status in this patient because she loses her mother earlier in her life and there was no other affected member in her family.

**CONCLUSION**

EV is a rare cutaneous disorder characterized by persistent infection of EV-HPVs. This case is the third reported case of EV in a SLE patient. Although the pathogenesis of EV in this particular scenario remains to be elucidated, the finding of polymorphic skin lesions and presence of HPV type 5 in our patient warrants possible evolution to malignant cutaneous tumors and thus mandates strict sun protection and careful surveillance for pre-malignant and malignant lesions.

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