Association of HPV type 16 and 49 in Multiple Acral Squamous Cell Carcinomas

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We report a case with multiple acral squamous cell carcinomas (SCCs) associated with human papillomavirus (HPV) type 49 and 16 infection in separate lesions. HPV 49 belongs to the epidermodysplasia verruciformis (EV)-HPV group. It has only been detected in flat warts and one SCC in a renal transplant patient in the past literature. Our report showed the first case of SCC associated with HPV 49 in an immunocompetent patient. In addition, the high risk mucosal HPV 16 DNA was also detected in a palmar wart as well as the digital SCC of this patient. This finding indicates that HPV 16 might be a risk factor in the continuum of malignant progression from wart to cutaneous SCC. The local recurrence rate of the HPV 16-associated digital SCC was reported to be higher than HPV-negative digital SCC, and more aggressive treatment and long-term follow-up were indicated. (Dermatol Sinica 25: 153-158, 2007)

Key words: Human papillomavirus, HPV 16, HPV 49, Cutaneous Squamous Cell carcinoma

我們在此報告一個在肢端發生多個鱗狀細胞癌，同時合併有第49及16型人類乳突病毒感染之病例。第49型人類乳突病毒是屬於疣狀表皮增生不良型之人類乳突病毒。在過去的文獻上只有被報告過與腎臟移植病人之扁平疣及鱗狀細胞癌有關。我們的病例顯示在免疫健全的病人身上，第49型人類乳突病毒也可能跟鱗狀細胞癌有關。另外，高危險性之黏膜型第16型人類乳突病毒也在這個病人的手掌疣及鱗狀細胞癌上被發現，顯示第16型人類乳突病毒可能是表皮疣發展為鱗狀細胞癌之高危險因子之一。因為有第16型人類乳突病毒感染之肢端鱗狀細胞癌局部復發率較高，故臨床上需要更積極之治療及長期追蹤。 (中華皮誌 25: 153-158, 2007)
INTRODUCTION

Cutaneous squamous cell carcinoma (SCC) is the second most common nonmelanoma skin cancer after basal cell carcinoma (BCC). Although less common than BCC, SCC carries a risk of metastasis. Risk factors associated with the development of SCC include male gender, old age, precursor lesions such as actinic keratosis and Bowen’s disease, ultraviolet light exposure, ionizing radiation, some genodermatosis such as xeroderma pigmentosum and albinism, burns, chronic venous ulcer, arsenic, exposure to chemical carcinogen, immunosuppression, and some high risk HPV infections.1 The oncogenic role of HPV has been elucidated in many published reports and HPV infection has been linked to the development of SCCs in immunocompromised patients, as well as patients with epidermodysplasia verruciformis (EV). Furthermore, recent studies have identified HPV infection in approximately 30% SCCs in immunocompetent patients, especially HPV types of oncogenic potential, including high-risk mucosal types and EV types.2, 3 Here we report an immunocompetent case with multiple acral SCCs which involved EV-HPV (type 49) and high risk mucosal HPV (type 16) infections in independent lesions. To our knowledge, this was the first such case reported in the literature.

CASE REPORT

A 87-year-old man without arsenic exposure was a case of colon cancer status post operation 6 years ago, hypertension under regular medical control, viral hepatitis B carrier with liver cirrhosis, and benign prostate hyperplasia. He was followed up regularly for colon cancer and the carcinoembryonic antigen (CEA) level was within normal limit. About 6 months prior to presentation, he noted a gradually enlarging, painless plaque over his left thumb. On examination, there was a 1.8x1.5 cm, erythematous plaque with verrucous surface and crusts on the radial aspect of his left thumb (Fig. 1A). Skin incisional biopsy revealed a SCC (Fig. 1B). Two additional lesions were also noted: one 1.0x1.0 cm, scaly erythematous plaque over his right palm, and another 1.2x1.0 cm, verrucous plaque over his left fourth toe. Surgical removal of the SCC on the left thumb with split-thickness skin graft (STSG), and total excision of tumors on the right palm and left fourth toe were performed. The pathology examination showed a SCC from the left thumb and SCC in situ from the other two lesions. In addition, the specimens were sent for viral typing by polymerase chain reaction (PCR) and DNA sequencing. We used general consensus primers MY09/MY11 for the first PCR to amplify the corresponding part of the HPV L1 gene, followed by nested PCR primers GP+5/GP+6 as previously published.4 Each PCR was carried out in Geneamp PCR SYSTEM 9700. The DNA sequences obtained were compared with all sequences in GenBank through the BLAST server, and the result revealed HPV 49 infec-
tion. The patient was referred to the oncologist for post-operation radiotherapy.

One month later, the patient reported an erosive protruding nodule over his left big toe (Fig. 2) and the biopsy result showed a SCC. In addition, multiple hyperkeratotic, pea-sized papules were also noted over the both hands (Fig. 3A). Biopsy of the lesion from the right hand showed a verruca vulgaris (Fig. 3B). Viral typing of both lesions revealed HPV 16. The patient received liquid nitrogen treatment for the common warts but refused surgical excision of the SCC on the left big toe.

Eight months later, a recurrent eroded nodule over the previous STSG site on the left thumb and a newly onset erythematous hyperkeratotic plaque over the left fifth toe were noted. Because the patient refused surgical excision of the tumors, photodynamic therapy of 5-ALA with red-light irradiation was performed under the impression of SCC over the left thumb and left fifth toe. However, there was no obvious response. The patient was lost follow-up thereafter and came back to our clinic six months later. On examination, there were erythematous eroded nodules over the left thumb, left big toe, and left fifth toe. Skin biopsy of the left big toe and fifth toe revealed SCCs. The patient received surgical treatment at another hospital.

DISCUSSION

Human papillomaviruses (HPVs) are small, double-stranded DNA viruses of the Papovaviridae family. They are well-known as an etiologic agent for benign warts of the skin. Recently, HPV has been detected in malignant skin and mucosal disease suggesting that HPV infection might induce malignant tumors. Over 100 different types of HPV have been identified, and phylogenetic classification based on DNA sequence homology has been introduced, dividing all papillomaviruses into supergroups A through E. Each HPV type affects certain parts of the body preferentially. In cutaneous malignancy, HPV types 6 and 11 are associated with Buschke-Lowenstein tumors and Bowenoid papulosis; whereas the so-called “high risk” HPV type 16, 18, 31, 33-35, 39-40, 51-60 have been frequently identified in genital and perianal SCC, suggesting the possibility of genital-digital spread.

In our patient, there were multiple SCCs associated with different types of HPV DNA on his distal extremities. SCC of the left thumb...
contained HPV 49 DNA. HPV 49 was found to share 74% of its base pairs with HPV 5 DNA, corresponding to 78% identical amino acids. It belongs to the EV-HPV group (EV-HPV types include HPV 5, 8-9, 12, 14, 15, 17, 19-25, 36-38, 47 and 49). It was originally isolated from pooled flat warts of a Polish renal transplant patient, and subsequently sequenced by Dr. H. Delius. Favre et al. screened benign lesions from 134 patients (including 51 immunosuppressed patients and 35 patients with EV), premalignant cutaneous lesions from 64 patients, and invasive skin carcinomas from 48 patients, for HPV 49 DNA. Despite its similarity to HPV 5, HPV 49 was only detected in the flat warts of two additional Polish renal transplant patients, and in none of the EV patients. Later, Harwood et al. found co-infection of HPV 49 and HPV 23 in a SCC of a renal transplant patient. This was the first case which showed a possible relationship between HPV 49 infection and cutaneous SCC in an immunocompromised patient. However, in addition to its presence in immunocompromised patients, some studies showed that HPV 49 could also be detected in normal skin and follicle. The prevalence of HPV DNA in SCCs of immunocompetent individuals was much lower than that of immunocompromised patients (27% versus 84%), and the EV-HPV types predominate. It was as yet unclear whether HPV 49 contributed to the oncogenesis at all, and if so, by what mechanism. Unlike HPV 16 and 18, which are capable of acting alone in the development of cervical cancer, EV-HPV types associated with cutaneous SCC probably act as cocarcinogens. Ultraviolet radiation (UVR) is almost certainly involved in the SCC of sun-exposed area. It is possible that HPV contribute to oncogenesis via local immunosuppression, release of growth factors, or deactivation of tumor suppressor genes. Recently, an important interaction between UVR, cutaneous HPV E6 proteins and a cellular pro-apoptotic protein, Bak, was revealed. It has been observed that E6 from both high- and low-risk mucosal HPV inhibits Bak-induced apoptosis by stimulating its degradation. Moreover, Jackson and Storey found E6 from HPV 5 also inhibited UV-induced apoptosis in a p53-independent manner by abrogation of the apoptotic functions of Bak. It seemed such anti-apoptotic E6 activity not only enhanced the survival of HPV-associated lesions exposed to UVR damage, but might also allow the persistence of UVR-induced genetic damage. In our patient, the oncogenic role of the HPV 49 obtained from the left thumb remains to be elucidated.

HPV 16 is well-known for its high potential for malignant mucosal lesions. Although HPV 16 infection is less common in cutaneous SCC, Alam et al. reviewed 51 reported cases of HPV-associated digital SCCs and found that HPV 16 was noted in the greatest number of tumors (94%, 48/51). They also reviewed another series of 23 cases of HPV-positive digital SCCs and the preponderant HPV type was 16. Moreover, 10% (7/72) of patients had an antecedent genital dysplasia or carcinoma containing the same HPV type as their digital SCC. It could be speculated that HPV 16 might be involved in the pathogenesis of digital SCCs and the mechanism might be genital-digital spread. Therefore, it was reasonable to search if there were any mucosal or genital lesions and follow up the patient regularly.

Another point to be mentioned is the association of HPV infection and colorectal cancer. There have been some studies demonstrated that HPV may infect the mucosa of the colon and suggests a possible association between HPV and colorectal cancer. In the large series of Weinberger et al., they demonstrated significant association between the presence of viral antigens and tumor in a subset of 447 colorectal adenocarcinomas. In another report of Perez et al., they found HPV DNA was detected in 33% (10/30) of the normal colon tissue, and 74% (40/54) of the colorectal cancer. It is speculated the mere presence of HPV DNA in human tumors supports a possible association with colorectal cancer but does not confirm an aetiological role.

In our case, there was recurrent SCC on
the left thumb despite of standard total excision and post-operation radiotherapy. Leibovitch et al. found the recurrence rate was 2.6% in patients with primary SCC and 5.9% in patients with recurrent SCC. However, in the study of HPV-associated digital SCCs of Alam et al., they found a recurrence rate of 26% (6/23) after treatment by Mohs surgery and one patient died of metastasis. This recurrence rate was very much higher than the average recurrence rate of non HPV associated cutaneous SCC. This might be explained by the existence of oncogenic HPV at the margins of the tumor-free plane. For this reason, other suspicious lesions, even far from the primary SCC, should be treated at the same time. The diagnosis of digital SCCs should prompt consideration for HPV typing though this is not a cheap experimental tool and may also not alter clinical management. These tumors are best treated with Mohs surgery or amputation. Given the higher risk of recurrence, local adjuvant therapy, such as radiotherapy or cryotherapy to destroy intact epidermis at the perimeter of the surgical defect, might be considered. In addition, recurrence might be delayed for many years, necessitating long-term follow-up. In our case, although his palmar warts did not show malignant change after one-year follow-up, they should be completely treated because they were caused by HPV 16 infection.

In summary, we reported an immunocompetent case of multiple acral SCCs associated with HPV 49 and HPV 16 in independent lesions. In immunocompetent patients, the associated HPV types in cutaneous SCC were predominately EV-HPV. As in the HPV-associated digital SCCs, HPV 16 was the most common type and yielded a higher recurrent rate. Therefore, more aggressive treatment and long-term follow-up were indicated.

REFERENCES
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