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SHORT COMMUNICATION

Detection of Human Papillomavirus Type 58 in Periungual Bowen's Disease

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Bowen's disease (BD) is an *in situ* squamous cell carcinoma characterized by reddish, well-defined, scaly, erythematous and eczematous plaques. Human papillomavirus (HPV) infection is associated with BD on the hands and genitalia (1, 2). Nail BD presenting with longitudinal melanonychia has frequently been reported to be associated with HPV type 56. We describe here a case of periungual verrucous BD with HPV type 58 infection.

MATERIALS AND METHODS

A 36-year-old man suffered an injury to his right middle finger. He then noted a small nodule on the injured finger that slowly increased in size. The patient had neither a significant past medical history nor a significant family history. Physical examination revealed an elevated, well-demarcated, slightly pigmented plaque with a keratotic surface measuring 12 × 7 mm in diameter on the periungual area of his middle finger (Fig. 1a). The patient reported no subjective symptoms. Histopathological examinations revealed the presence of hyperkeratosis, parakeratosis, papillomatosis, dyskeratotic cells and irregularly arranged tumour cells with atypical nuclei (Fig. 1b). Koilocytosis was seen in some areas. Laboratory tests, including a complete blood cell count and a serum chemistry assay, revealed no abnormalities. The lesion was surgically excised and grafted with full-thickness skin under local anaesthesia. There has been no recurrence over a 1-year follow-up period. The resected skin specimen was examined by HPV typing with PCR, *in situ* hybridization and immunohistochemistry.

Formalin-fixed and paraffin-embedded samples were then cut into 10-μm sections. The method used and PCR conditions have all been described previously (3). DNA was extracted using Dexpat® (Takara, Kyoto, Japan). HPV PCR was performed with L1C1/L1C2 consensus primers (4). The PCR products were subjected to direct sequencing. DNA extracted from bowenoid papulosis of another patient was used as a control, in which HPV type 16 was detected (3).

The catalysed signal amplification method (GenPoint System; Dako, Kyoto, Japan) was used for detection of HPV by *in situ* hybridization (3). Formalin-fixed, paraffin-embedded specimens were used. The probe was a biotinylated high-risk HPV probe cocktail (GenPoint HPV; Dako) that contains type 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 HPV DNA. Immunohistochemistry was performed using an anti-HPV antibody (K1H8; Dako) and the avidin-biotin complex method.

RESULTS

The amplified PCR products were electrophoresed on 2% agarose gel, and a PCR band was seen at the expected position of 256 bp. The PCR product was analysed by direct DNA sequencing, which revealed that the sequence corresponded to the L1 gene of HPV type 58 (GenBank: D90400) (Fig. 2). The sequence of the patient showed one missense mutation that had not been reported previously (data not shown).

HPV-58-positive cells with nuclear staining were observed in the upper epidermis and stratum corneum of the lesion by *in situ* hybridization (Fig. 1c). Furthermore, HPV immunohistochemistry revealed that the vi-

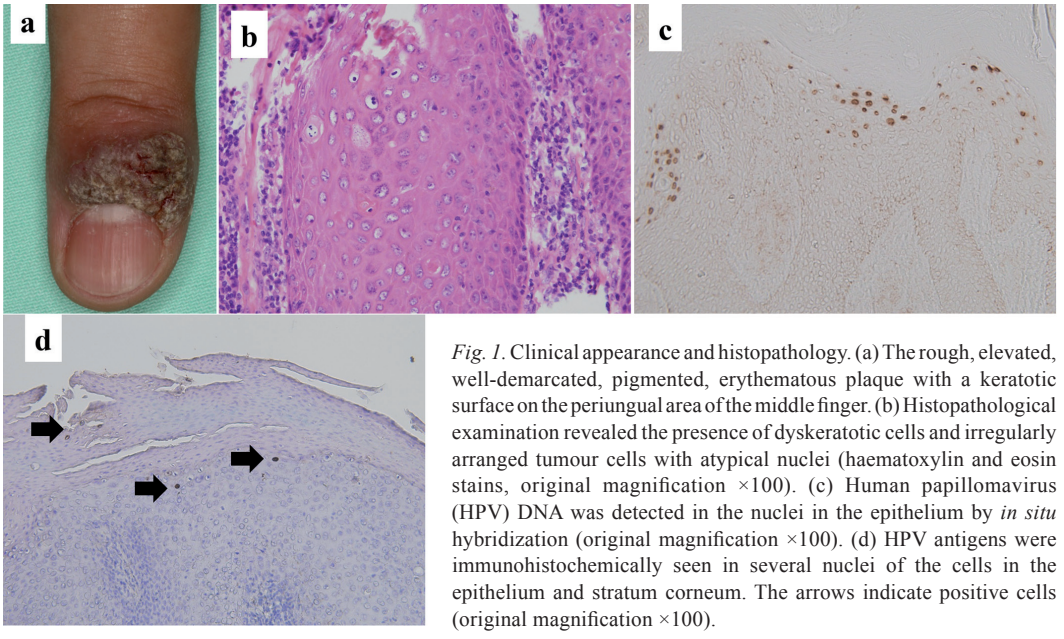

Fig. 1. Clinical appearance and histopathology. (a) The rough, elevated, well-demarcated, pigmented, erythematous plaque with a keratotic surface on the periungual area of the middle finger. (b) Histopathological examination revealed the presence of dyskeratotic cells and irregularly arranged tumour cells with atypical nuclei (haematoxylin and eosin stains, original magnification ×100). (c) Human papillomavirus (HPV) DNA was detected in the nuclei in the epithelium by *in situ* hybridization (original magnification ×100). (d) HPV antigens were immunohistochemically seen in several nuclei of the cells in the epithelium and stratum corneum. The arrows indicate positive cells (original magnification ×100).

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ral protein localized in the upper epidermis and stratum corneum (Fig. 1d).

DISCUSSION

HPV type 58 was initially identified in cervical intraepithelial neoplasias and invasive cervical carcinomas. The virus belongs to the HPV-16-related group (HPV-16, -31, -33, -35, -52, -58, and -67) (5, 6). HPV type 58 is considered to be a high-risk type (7, 8). Only 5 cases of BD associated with HPV type 58 infection have been reported (7–11). Although the prevalence of HPV type 58 in cervical cancer was not limited to Japan and Asian countries (12), the HPV type 58-associated BD may have regionality, because 4 of these cases were from Japan (7, 8, 10, 11). It is of note that 3 out of 4 cases were BD of the fingers and toes (9–11). Hara et al. (10) reported a case of polydactylous BD on the hands and feet that was clinically similar to our case. Longitudinal melanonychia is frequently associated with HPV type 56 infection, and thus some HPV genotype-phenotype correlation may exist between periungual BD and HPV type 58 infection, but the number of cases of HPV type 58 infection is still too limited to draw definitive conclusions.

Nail BD tends to be associated with HPV infection, compared with BD of other body parts (13). As in the current case, it is sometimes difficult to distinguish BD of the fingers and toes from verruca vulgaris; therefore a biopsy should be performed for recalcitrant periungual warts.

We demonstrated the presence of HPV infection by 3 different methods, HPV typing with PCR, *in situ* hybridization and immunohistochemistry. High-risk HPV capsid antigen is often not detected by immunohistochemistry (2, 10). Our immunohistochemical study showed that the viral protein was translated in the upper epidermis, indicating that the HPV infection was productive.

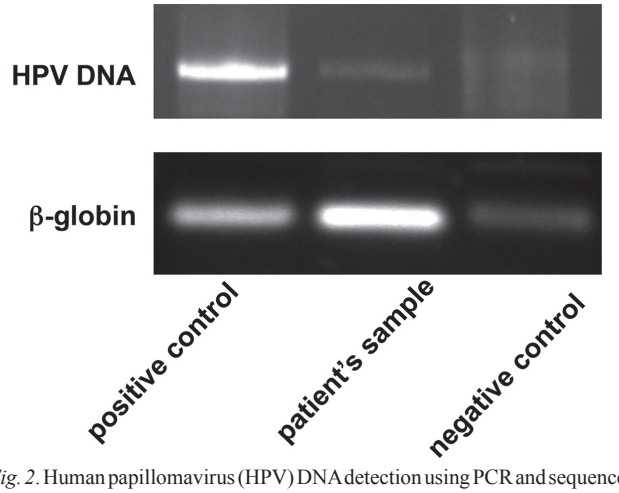

Fig. 2. Human papillomavirus (HPV) DNA detection using PCR and sequence analysis. The detection of HPV DNA using the L1C1/L1C2 primer pair. *Lane 1*: a positive control (Bowen's disease with HPV type 16 infection); *Lane 2*: the sample from the patient's finger; *Lane 3*: a negative control (normal healthy skin).

The biopsy specimens in the present case showed milder histopathological atypia in comparison with typical BD. BD sometimes develops after ultraviolet (UV) exposure, intake of arsenic, or HPV infection. Kreuter et al. (14) reported that HPV-positive BD showed more p16INK4a positive staining than did HPV-negative BD; thus there may be some histopathological characteristics of BD with HPV infection. The clinical significance of HPV in cutaneous malignant tumour needs further investigation.

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