

# Immunohistochemical findings and differential diagnosis of papillary-type cutaneous verrucous carcinoma of the neck: A case report

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**Abstract.** Verrucous carcinoma (VC) is a rare subtype of squamous cell carcinoma, with the majority of cases occurring in the oral cavity and genital area. The present study describes a rare case of cutaneous VC of the neck manifesting as a semi-pedunculated multinodular protrusion. Histological analysis revealed thickening of the epidermis and papillary growth. Although cellular atypia was generally mild, a large number of mitoses were observed, of which a small number were abnormal. Additionally, bulbous subepidermal invasion was observed. The lesion was differentiated from papillary squamous cell carcinoma, another rare subtype of squamous cell carcinoma, based on the presence of epidermal verrucous growth and the lack of remarkable nuclear atypia. Benign disorders, including seborrheic keratosis, fibroepithelial polyp, verruca vulgaris and pseudocarcinomatous hyperplasia, were also differentiated from the lesion. Immunohistochemical analysis of cytokeratin (CK)10 expression revealed attenuated staining of the lesion, therefore, anti-CK10 immunohistochemistry may be valuable in the diagnosis of VC.

## Introduction

Verrucous carcinoma (VC) is a variant of well-differentiated squamous cell carcinoma and is considered to be associated with human papilloma virus (HPV) infection. The majority of VCs occur in the oral cavity, genital area or plantar surface. VCs are rarely detected in the head and neck region; however, in such instances they predominantly occur in the mucosa of the respiratory or digestive tracts (1,2). Additional locations in the head and neck region include the larynx, nasopharynx, paranasal sinuses and esophagus. Furthermore, dermal lesions are rarely observed (1); cutaneous VCs of the head and neck

region predominantly occur on the scalp (3), and cervical epidermal lesions are rare (4). While the incidence of VC is 5-24% of all penile cancers and 2-12% of all oral carcinomas, dermal VC of sites other than the inguinal region and legs has been reported simply as rare or uncommon, without an accurate incidence rate (1,2). Surgical resection is the preferred treatment strategy for patients with VC, however, anal and perianal lesions have a high recurrence rate of ~70%, and a mortality rate of 20-30%. Although radiation therapy is not considered to be as effective as surgery, its efficacy as an adjuvant treatment strategy remains a topic of debate (4,5). The present case report describes a rare case of papillary-type cutaneous VC of the neck, including the immunohistochemical findings, which have not previously been well described. Additionally, the current study includes discussion of the diseases that VC should be differentiated from.

## Case report

**Clinical presentation.** An 80-year-old man was referred as an outpatient to Osaka Medical College Hospital (Takatsuki, Japan) in November 2011 exhibiting a cutaneous tumor at the anterior of the neck (Fig. 1). The tumor was observed as a flesh-colored multinodular protrusion measuring 1.7 cm in diameter. The patient reported that the lesion had gradually grown in size; however, precise details of its development were unclear. The patient had undergone a colonoscopic polypectomy 14 years prior to referral and, 2 years ago, experienced an angina attack. Following a clinical diagnosis of fibroma (November 2011), the lesion was excised with a margin of the intact skin on April 5, 2012. Recurrence was not observed in the 3 years following the resection of the tumor. Written informed consent was obtained from the patient.

**Histopathological analysis.** The surgical specimen was fixed in 10% buffered formalin, processed and embedded in paraffin. Paraffin sections were cut to a thickness of 4  $\mu$ m, and stained with hematoxylin and eosin. Immunohistochemical staining was also performed with antibodies for Ki-67, p53, cytokeratin (CK)7, 8, 10, 13, 18 and 20, and HPV, using the avidin-biotin-peroxidase complex technique. The thickened epidermis had proliferated in a papillary pattern (Fig. 2A) and exhibited swelling rete ridges indicating downgrowth. Cellular atypia was low in the majority of keratinocytes (Fig. 2B). The

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Figure 1. Multinodular semi-pedunculated lesion measuring 1.7 cm in diameter.

basilar nuclei were plump and, in general, the nuclei contained a single enlarged nucleolus. Mitoses were easily identified and abnormal karyokinesis was observed in a small number of cells (Fig. 2C). Clusters of cancer cells invading into the subepidermal layer were surrounded by a large number of lymphocytes and a small number of lymph follicles had formed. Cellular atypia of the invasive nests was greater than that of intraepidermal cells. Furthermore, immunohistochemical analysis of Ki-67 and p53 did not reveal any differences in the expression of these proteins in the lesion compared with the surrounding healthy epidermis. Additional immunostaining revealed a positive signal for CK10 in all layers, excluding the basal layer of the healthy epidermis. By contrast, CK10-positive staining was observed in the upper half of the intraepidermal carcinoma, but was not expressed in the deeper layer. CK10 expression was not observed in any of the epidermal layers of the lesion (Fig. 2D). Furthermore, the neoplastic and surrounding non-neoplastic epidermis were identified to be immunonegative for CK7, 8, 13, 18 and 20, and HPV immunostaining was negative. The aforementioned histopathological and immunohistochemical findings were used to determine a diagnosis of VC and dismiss the previous clinical diagnosis of fibroma.

## Discussion

VC is a low-grade variant of squamous cell carcinoma. The majority of VCs in the head and neck region occur in the oral cavity, rarely arising in the respiratory or digestive tracts of the neck (1,2). VC presenting on the buccal and gingival mucosa is known as florid papillomatosis, while VC located on the plantar surface is referred to as carcinoma cuniculatum (3). Cutaneous VC of the head and neck predominantly occurs on the scalp, however, cutaneous VC of the neck is rare. Macroscopically, VC typically forms a flat or exophytic elevation, the surface of which exhibits aggregation of small nodules (6). However, due to papillary growth of the epidermis, the present lesion formed a multinodular semi-pedunculated protrusion. VC histology is commonly characterized by a wart-like appearance with hyperkeratosis and/or hyperparakeratosis, and minimal cell atypia (2). In addition, VC typically grows in an expansive manner towards surrounding tissue, with a well-circumscribed margin. Infiltrating irregular nests,

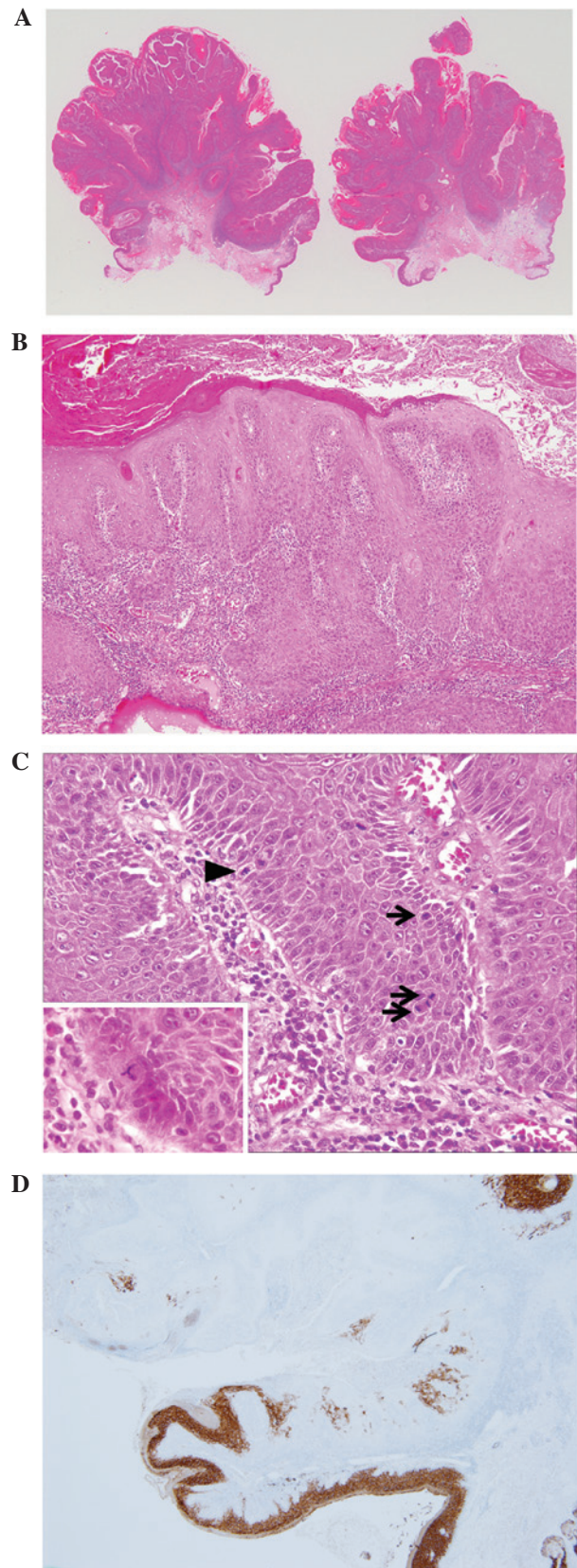


Figure 2. Pathological findings. (A-C) Hematoxylin and eosin staining revealing a (A) semi-pedunculated lesion of the cervical skin (magnification, x3), (B) swelling rete ridges indicating downgrowth and an invasive subepidermal cluster surrounded by numerous lymphocytes (magnification, x100). (C) Neoplastic cells with plump nuclei and one or two nucleoli, mitotic figures (arrows) and abnormal mitosis (arrow head and inset) were also observed (magnification, x400). (D) Attenuated staining for cytokeratin (CK)10 in the neoplastic epidermis (upper region) compared with the healthy epidermis (lower region; CK10 immunohistochemical staining; magnification, x40).



observed in normal squamous cell carcinoma, are not present in VC. A case of pedunculated VC previously reported by Shimizu *et al* exhibited similarities to the present lesion (7). However, the current study emphasizes the histological papillary growth pattern of the VC, as the epidermal growth pattern determines the macroscopic form of the lesion.

It is necessary to differentiate VCs from lesions that grow in the same pattern. In particular, the present lesion should be clinically and histologically differentiated from papillary squamous cell carcinoma and a number of other benign lesions, including seborrheic keratosis, fibroepithelial polyp, verruca vulgaris and pseudocarcinomatous hyperplasia. As with VC, papillary squamous cell carcinoma is a rare variant of squamous cell carcinoma (8). The present VC lesion proliferated in the same pattern as papillary squamous cell carcinoma, but did not share its characteristic nuclear atypia and pleomorphism (9). Condylomatous carcinoma also demonstrates high-grade cytological atypia (6). Although it was previously unclear whether Buschke-Löwenstein tumor (BLT) should be classified as non-neoplastic giant condyloma or as a type of VC, a recent study recognized BLT as VC localized in the anogenital region (10). The histological attributes of BLT are similar to those of the present lesion (11). Thus, condyloma acuminatum should also be differentiated from VC. Pseudocarcinomatous hyperplasia is caused by a proliferation of epithelial cells in response to infection, neoplasia, inflammation or trauma, and may resemble well-differentiated squamous cell carcinoma by exhibiting pseudoinvasion (12). However, the presence of nuclear atypia, individual necrotic keratinocytes and numerous mitoses favored the diagnosis of the present lesion as squamous cell carcinoma over pseudocarcinomatous hyperplasia (12).

Immunostaining for CK10 revealed reduced CK10 protein expression in the present lesion. CK10 has previously been described as a valuable tool in the diagnosis of oral squamous cell carcinoma and clonal seborrheic keratosis (13,14). Therefore, immunostaining for CK10 may aid in the diagnosis of cutaneous VC. However, the hypothesis that numerous immunohistochemical analyses are useful in the diagnosis of papillary-type cutaneous VC was confuted by the current study. CK13, 8 and 18 are reported to be useful markers in the diagnosis of squamous cell carcinoma in the head and neck region (13,15), and CK8 and 18 appear to be associated with the invasion and metastasis of squamous cell carcinoma (16). However, these CKs stained negatively in the neoplastic and surrounding healthy epidermal tissue of the present lesion, and, therefore, were not useful in the differential diagnosis of the present case. Furthermore, an increase in Ki-67 labeling and positivity for p53 were not observed in the present case. In agreement with this finding, immunohistochemistry for Ki-67 and p53 expression in VC is reported to be more similar to that of healthy epidermis than that of squamous cell carcinoma (17).

Immunostaining for HPV did not reveal positivity in the present case. However, HPV 16 and 18 have been detected in laryngeal VC, and HPV 6 and 11 infections appear to be associated with oral VC (2,17). Additionally, ano-urogenital VCs are closely associated with these viruses (18). There appears to be no association between HPV infection and rare cutaneous VC occurring at sites other than oral, ano-urogenital and palmoplantar regions (3). However, a previous study did identify an association between HPV infection and cutaneous

VCs (19). HPV-induced carcinogenesis and progression of VC may involve amino acid changes caused by mutations in an HPV oncogene, leading to the degradation of a p53 tumor suppressor gene (17). However, the present case demonstrated no abnormal immunostaining for p53. To date, the presence of HPV has yet to effect the therapeutic strategies used for VC.

In conclusion, the current study reports a rare case of papillary-type cutaneous VC arising in the neck, an uncommon location for this tumor type. Unlike VC lesions that occur at more common sites of VC development, HPV infection was not identified in the present case. Furthermore, CK10 exhibited a weak staining pattern compared with the surrounding intact epidermis.

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