—Case Reports—

Two Cases of Verrucous Carcinoma: Revisiting the Definition

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Verrucous carcinoma (VC) is an uncommon, distinct type of well-differentiated squamous cell carcinoma. Here we present two cases of VC, one arising from the lower leg and the other from genital skin. Case 1, a female patient, aged 95 years, had a brownish verrucous plaque on her right lower leg. Histopathologically, epithelial tumor cells grew pushing the stroma, while the basement membrane was intact. No prominent cellular atypia or hyperchromatin was found. Case 2, a male patient, aged 53 years, had a verrucous plaque at the border between his scrotum and inner aspect of his thigh. A pathological diagnosis of VC was made using an excisional specimen. Making a definitive diagnosis of VC is challenging but crucial. Pathological diagnosis using a small specimen might cause underdiagnosis or overdiagnosis. To avoid this, pertinent pathological diagnosis using an ample specimen is required. We also revisited the definition of VC to precisely understand its nature. (J Nippon Med Sch 2018; 85: 47–50)

Key words: verrucous carcinoma, fibrovascular core, basement membrane, benign condyloma, squamous cell carcinoma

Introduction

The term, verrucous carcinoma (VC) was coined by Ackerman[1]. It originally referred to the condition which manifests verrucous exophytic nodules arising from the oral mucosa, a locally aggressive malignancy with minimal dysplasia and a low incidence of metastasis[1]. VCs can be grouped into four main types, based on the anatomical site, and have several different names related to those sites: anourogenital VCs (giant condyloma acuminatum, Buschke Loewenstein tumors (BLT), giant malignant condyloma, carcinoma like-condyloma and condylomatoid precarcinosis), oro-aerodigestive VCs (Ackerman's tumor and oral florid papillomatosis), plantar VCs, (epithelioma cuniculatum) and other cutaneous VCs (cutaneous VC, papillomatosis cutis carcinoides and papillomatosis cutis)[2]. VC tends to appear in three major sites (anourogenital, oroaerodigestive and planter areas) and rarely in other sites[2]. The term VC is widely used[2–4]. VC usually presents as a verrucous lesion and masquerades as a giant wart. Diagnosis is often challenging. Here we present two cases of VC, one arising from the lower leg and the other from genital skin, the former being a rare site. We also revisit the definition of VC to precisely understand its nature.

Case Report

Case 1

A female patient, aged 95 years, had noticed a dark violet eruption on her right lower leg approximately 15 years previously. It gradually spread and enlarged, and she was then admitted to our facility. A well-circumscribed, brownish exophytic verrucous plaque, 40× 40 mm in size, was observed on her right lower leg (**Fig. 1A**). She had no venous insufficiency or chronic wound in her legs. A small skin biopsy revealed epithelial proliferation with prominent papillomatosis (data not shown). Although the tentative pathological diagnosis of verruca vulgaris was made, considering the clinical appearance, the tumor was completely resected under the clinical diagnosis of VC and the defect was reconstructed with a split thickness skin graft. Histopathologically, the tumor consisted of massively hyperplastic and papillomatous folded epidermis with parakeratosis (**Fig. 1B**). Epithelial tumor cells grew pushing into the underlying stroma (**Fig. 1C**). Epidermal acanthosis, with bulbous rete ridges, was observed and the basement membrane was intact.

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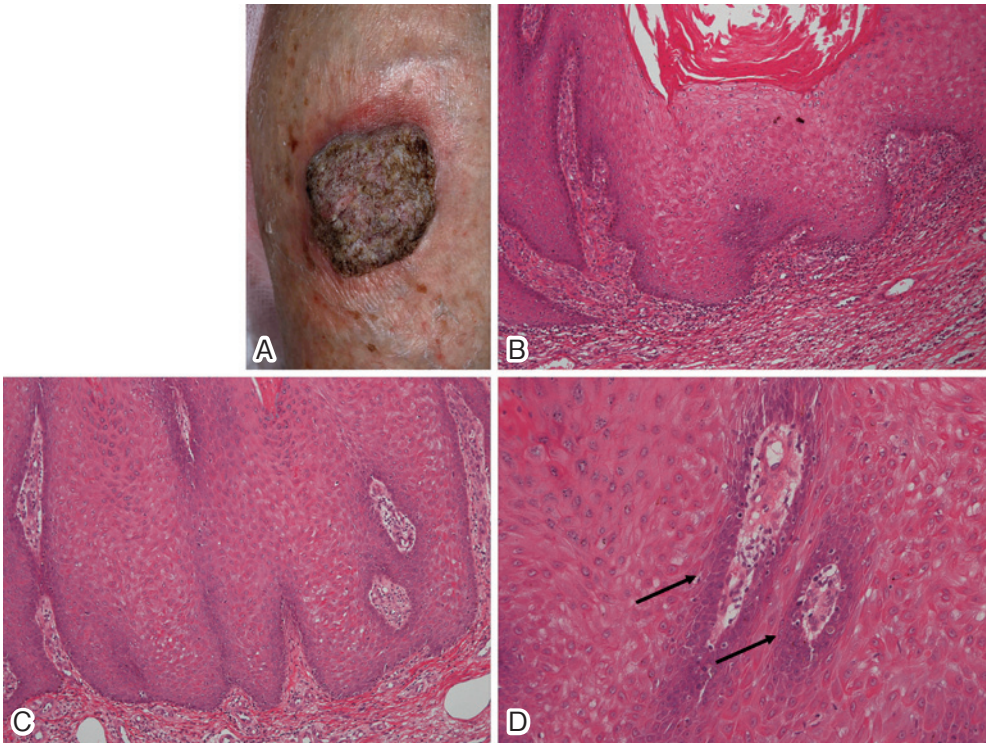

Fig. 1 Clinical and pathological features of verrucous carcinoma on the leg.
(A) A well-circumscribed, brownish, exophytic verrucous plaque, 40×40 mm in size, was observed on the right lower leg. The patient had no lower limb venous insufficiency.
(B) Epithelial tumor cells consisting of massively hyperplastic and papillomatous folded epidermis with marked hyperkeratosis and parakeratosis (HE ×40).
(C) Epithelial tumor with acanthosis pushing into the underlying stroma. The basement membrane was virtually intact. (HE ×100)
(D) Fibrovascular core observed at the surface of the tumor (HE ×100).

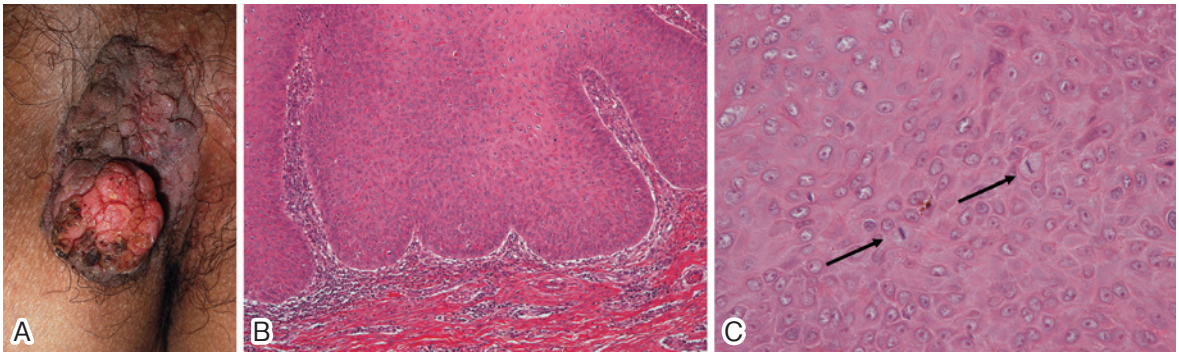

Fig. 2 Clinical and pathological features of genital verrucous carcinoma.
(A) A well-circumscribed, pinkish to brownish verrucous plaque, 60×30 mm in size, was observed at the border between the scrotum and inner aspect of the thigh. A pinkish, verrucous exophytic nodule, 27×25 mm in size, was also observed on the plaque.
(B) Epithelial tumor pushing into the underlying stroma. Epidermal acanthosis with bulbous rete ridges were observed. The basement membrane was intact (HE ×100).
(C) Mitotic figures close to the basal layer of the bulbous rete ridge were observed at times (HE ×200).

The stroma was edematous and an inflammatory reaction was prominent. The keratinocytes were well differentiated and no prominent cellular atypia or hyperchromatin was observed. Thin fibrovascular cores were observed only on the surface of the tumor (**Fig. 1D**). A diagnosis of VC was made. The surgical margin was negative. No local or distant metastasis was detected one year after the operation.

Case 2

A male patient, aged 53 years, had noticed a genital verrucous plaque. It gradually spread and enlarged, and he was admitted to our facility. A well-circumscribed, pinkish to brownish verrucous plaque, 60×30 mm in size, was observed at the border between the scrotum and inner aspect of the thigh (**Fig. 2A**). A pinkish verrucous exophytic nodule, 27×25 mm in size, was observed on the plaque. Small skin biopsy revealed epithelial proliferation with prominent papillomatosis with koilocytic cells (data not shown). The tumor was completely resected under the clinical diagnosis of VC and the defect was sutured simply. Histopathologically, fingers of epithelium grew pushing without disrupting the basement membrane (**Fig. 2B**). Epidermal acanthosis, with a club-shaped rete ridge, was also observed. The stroma was edematous and an inflammatory reaction was prominent. Mitotic figures close to the basal layer of the rete ridge were observed at times (**Fig. 2C**). The keratinocytes were well differentiated and no prominent cellular atypia or hyperchromatin was found. We diagnosed it as VC. The surgical margin was negative. No local or distant metastasis was detected 1.5 years after the operation.

Discussion

Ackerman coined the term VC to refer to a distinct type of well-differentiated squamous cell carcinoma originating from the oroaerodigestive region[1]. Initially, VC shows indolent downgrowth of fingers of epithelium that gradually push rather that infiltrate. He emphasized that the epithelium is well differentiated and that the basement membrane is virtually intact[1]. VC could rarely metastasize to regional lymph nodes but in no instance have distant metastases appeared[1]. The term VC is widely used, though it has several different names, such as giant condyloma acuminatum and BLT, as described above[2]. Anourogenital, oroaerodigestive and plantar areas are major sites of VCs. Other cutaneous VCs are rare and are thought to arise in association with chronic inflammation, including ulcers, abscesses, and sinuses, which seem to play important roles in the pathogenesis of VCs[2]. The lower limbs are less frequently affected and occurrences in this region are mostly associated with chronic venous ulceration[2], which was not present in our patient. The definition and interpretation of VC seem to differ among reports[3,5,6]. Most BLTs (Giant condyloma acuminatums) are caused by human papillomavirus (HPV) type 6 or 11, and VCs are caused by HPV type 16 or 18. Thus BLTs and VC can be distinguished[5]. Though VC and BLTs are essentially the same, they are not always associated with HPVs[2,4,7]. Of course, some anourogenital and oroaerodigestive VCs are associated with HPV type 6, 11, 16 or 18[3]. However, the BLT is reported to be the continuum between giant condyloma and VC[8]. Currently, differentiation between BLT and VC is controversial[2,3,8]. The basement membrane adjacent to the epithelium has been reported to be often intact[3,6]. However, the basement membrane should be virtually intact[1,2,4]. In this report, we assumed that VC and the BLT were the same and the basement membrane was intact in VC.

Histopathologically, the appearance of VC may be surprisingly benign[2–4]. The following findings are generally agreed on to date[2,4]. VC is a papillomatous, well-differentiated epithelial tumor. A prominent granular layer with hyperkeratosis, papillomatosis and sometimes parakeratosis is characteristic and the deeper layers show acanthosis. The tumor margin is well-demarcated and epithelial tumor cells grow, pushing the stroma rather than infiltrating, which is predominantly found in weight-bearing plantar lesions. VC demonstrates blunt projection of well-differentiated stratified squamous epithelium, with deep bulbous rete ridges, showing minimal atypia[4]. Edematous stroma, filled with chronic lymphohistiocytic inflammatory cells, surround these ridges[2,3]. Tumor cells are often enlarged with minimal or no dysplasia and prominent nuclei and nucleoli[2]. Etiological factors discussed include HPV infection and chemical carcinogenesis, such as tobacco or betel quid chewing[9,10].

Differential diagnosis considering benign condyloma and well-differentiated squamous cell carcinoma is helpful. To distinguish VC from benign condyloma, the central connective tissue support is important[11]. In VC, fibrovascular cores are not observed or limited to the superficial layer[11]. However, fibrovascular cores extend from the superficial to deep layer in the benign condyloma. In well-differentiated squamous cell carcinoma, anaplastic tumor cells grow, infiltrating the stroma, and mitotic figures are common[12]. Cellular atypia and hyperchromatin are usually found. Tumor cells travel beyond the dermal-epidermal border into the dermis at varying depths[13]. Disruptions of the basement membrane are often observed[2,3].

Superficial biopsies are often taken but a positive diagnosis of VC cannot be made in such cases[2,4]. The main pitfall in the diagnostic process is pseudocarcinomatous hyperplasia caused by non-representative small biopsies. Moreover, tumor cells of granular layers may be vacuolated and indistinguishable from koilocytes of viral

warts[14]. Even with deep biopsies, diagnosis may be difficult because of their intact basement membrane and well-differentiated nature. Therefore excisional biopsy is preferable. However, we should bear in mind that pathological diagnosis can be highly challenging even for experienced dermatopathologists, especially if they have little clinical information and suboptimal samples[2–4,15].

Given the locally destructive and rarely metastatic nature of VC, local resection is recommended, as in the cases decsribed above. Other options include cryosurgery, topical chemotherapy (mostly based on cisplatin, 5-fluorouracil and imiquimod), electrocautery, and photodynamic therapy[3,5,15]. Radiation therapy for VC is controversial[2,8]. This is because radiation was thought to cause anaplastic transformation with corresponding dedifferentiation and increased rates of metastasis, but a recent report indicates that chemoradiotherapy was effective[16]. However, given the possibility that invasive squamous cell carcinoma can arise from VC, we recommend surgical treatment with histologic margin control in order to make the pathological diagnosis as accurately as possible[17].

In conclusion, accurate diagnosis of VC is crucial. To avoid underdiagnosis or overdiagnosis, pathological diagnosis using an ample specimen is required.

Conflict of Interest: None.

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