

CASE REPORT

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Rare cutaneous verrucous carcinoma in the femoral region: a case report

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ABSTRACT

BACKGROUND

Verrucous carcinoma (VC) is a well-differentiated variant of squamous cell carcinoma (SCC) characterized by slow growth and low metastatic potential. Cutaneous verrucous carcinoma (CVC) or papillomatosis cutis carcinoides is the term used for VC in other locations than the oral, anogenital, and plantar regions. This rare tumor has a contradictory “benign” histology, but markedly aggressive clinical behavior. We present this case as background knowledge to corroborate clinical course, diagnosis, histopathology, and treatment options for this infrequent disease.

CASE DESCRIPTION

We report a verrucous carcinoma on a 79-year-old man’s left thigh. Clinical examination showed a fungating mass with cauliflower-like appearance measuring 5x3x1 cm. Excisional biopsy revealed exo-endophytic proliferation of well-differentiated squamous epithelium invading the dermis with marked hyperkeratosis, parakeratosis, acanthosis, papillomatosis, pushing margins, and minimal cellular atypia (T₂N₀M₀). It was successfully treated by wide local excision, inguinal lymph node dissection, and adjuvant radiotherapy. Follow-up after 1 year showed good wound healing without any loss of function or recurrence.

CONCLUSION

Cutaneous verrucous carcinoma is a subtype of a low-grade SCC and is not an SCC with a verrucous presentation. Identification of the clinicopathological features is essential to distinguish CVC from its mimics and to make an early diagnosis. Although slow growth and confusing early-stage appearances can lead to delay in diagnosis or to misdiagnosis, this case has not raised many diagnosis problems regarding the cardinal manifestations of CVC. Regardless of any available therapeutic methods, surgical excision with safety margins is still a priority and CVC requires aggressive treatment.

Keywords: Cutaneous verrucous carcinoma, papillomatosis cutis carcinoides, squamous cell carcinoma

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INTRODUCTION

Verrucous carcinoma (VC) or verrucous SCC is a rare, well-differentiated, locally invasive, low-grade form of squamous cell carcinoma, with low metastatic potential.⁽¹⁻³⁾ It typically affects the oral, anogenital, and plantar regions, but rarely anywhere else on the skin.⁽⁴⁻⁶⁾ It has a variety of different names; each is distinguished by its unique location but has identical histology.⁽⁷⁾

The sites of occurrence and the corresponding clinical entities are: i) oro-aerodigestive region: oral florid papillomatosis or Ackerman's tumor; ii) anourogenital region: Buschke-Löwenstein tumor or giant condyloma acuminatum; iii) palmoplantar region: carcinoma/epithelioma cuniculatum; and iv) other cutaneous sites: cutaneous verrucous carcinoma or papillomatosis cutis carcinoides.⁽⁸⁻¹⁰⁾ Regardless of its locations, VC has the same histopathological appearance. The tumor growth pattern is exo-endophytic, with a conspicuous granular layer, hyperkeratosis, parakeratosis, acanthosis, and papillomatosis.⁽⁷⁾ The tumor consists of large keratinocytes with prominent nuclei, visible nucleoli, and slight cellular atypia.⁽⁷⁾ The squamous epithelium is well-differentiated and clearly stratified.⁽⁷⁾

Cutaneous verrucous carcinoma (CVC) or papillomatosis cutis carcinoides is the rarest form of VC^(2,11) and is the term used for VC at any other location than the plantar, oral, genital, and perianal regions.⁽²⁾ The most commonly affected sites are the lower limbs, sacrum, scalp, and buttocks. The prevalence of VC is 1–3 cases for every 1 million people (0.075 per 100,000).^(3,9) Meanwhile, CVC has only been reported as uncommon or rare with no accurate incidence.⁽¹⁾ Cutaneous verrucous carcinoma occurs mostly in elderly individuals (60–70 years old) with a male predominance.^(1,7)

Patients most commonly present with fungating and cauliflower-like tumor with ulcerated and mamelonated surface, mimicking a vegetative form of squamous cell carcinoma.^(2,9) This type of carcinoma has to be named

“verrucous” because on the surface it appears as an exophytic lesion that consists of epithelial projections and invaginations filled with keratin without any noticeable fibrovascular core.⁽⁷⁾

While the broad category of VCs are histologically similar, the distinct etiology of VC can be dependent on its location.⁽¹¹⁾ The etiopathogenesis of CVC remains unclear, but several contributing factors have been proposed, including chronic inflammation (scars, ulcers), local repetitive trauma, and poor local hygiene.^(1,2,9) The differential diagnosis depends on the tumor location and appearance. These include verrucous hyperplasia, squamous papilloma, and conventional squamous cell carcinoma.⁽¹²⁾ Verruca vulgaris, keratoacanthoma, and seborrheic keratosis are also sharing the same clinical features of CVC.⁽¹²⁾ All the above should be considered as the differential diagnosis for CVC.

The recommended treatments are surgical excision with safety oncological margins and Mohs surgery (serial excision for microscopic analysis), both of which are associated with a high cure rate and a low recurrence rate.⁽³⁾ Other treatment modalities include chemotherapy, immunotherapy, cryosurgery, laser ablation, intradermal injection of interferon- α , photodynamic therapy (PDT), and radiation.⁽¹⁻³⁾ Regardless of the therapeutic methods used, there is consensus regarding the priority of making surgical excision.⁽²⁾

We report a patient with CVC that developed in the upper leg and showed “verruroid” features as classical hallmark of this tumor. Cutaneous verrucous carcinoma is a rare and unfamiliar variant of SCC with locally aggressive behavior.

CASE REPORT

A 79-year-old Indonesian male farmer was admitted to our public health center on April 5, 2021 with a papillomatous mass on the anteromedial aspect of his left thigh (Figure 1). The tumor grew gradually 3 years earlier from a prior small nodule and eventually became cauliflower-like in appearance.



Figure 1. A verrucous tumor with cauliflower-like appearance on the anteromedial aspect of a 79-year-old man's left thigh (April 5, 2021)

Within 3 days, the lesion was seen to be friable, ulcerated, and easily bleeding due to manipulation (scratching, squeezing) by the patient (Figure 2). Clinical examination showed a circumscribed, fungating mass measuring 5x3x1 cm with a verrucous surface. The patient was then referred to a hospital as an outpatient for further treatments. Radiography of the left femur showed no bone involvement; abdominal ultrasound and chest radiograph excluded metastatic spread. Wide local excision and inguinal lymph node dissection was performed

simultaneously by an oncologist. The defect was sutured by primary closure without skin grafting.

Excisional biopsy revealed exo-endophytic proliferation of well-differentiated squamous epithelium invading the dermis with marked hyperkeratosis, parakeratosis, acanthosis, papillomatosis, pushing margins, and minimal cellular atypia (Figure 3). Histopathological diagnosis confirmed a verrucous carcinoma with clear resection margins and there was reactive hyperplasia of lymphoid follicles without evidence of nodal metastasis (stage II, T₂N₀M₀).



Figure 2. The 5 x 3 x 1 cm fungating mass was seen to be friable, ulcerated, and easily bleeding due to manipulation (scratching, squeezing) by the patient (April 8, 2021)

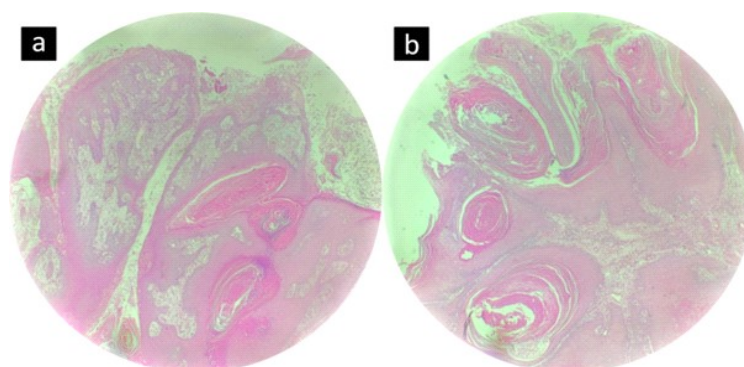


Figure 3. Histopathological features of cutaneous verrucous carcinoma (CVC). (a) Exo-endophytic proliferation of well-differentiated squamous epithelium invading the dermis with marked (b) hyperkeratosis, parakeratosis, acanthosis, papillomatosis, pushing margins, and minimal cellular atypia (hematoxylin-eosin x4)

Considering the tumor diameter, its locally destructive nature, and for locoregional disease control, the patient still underwent post-operative radiotherapy. Follow-up after 1 year showed good wound healing without any loss of function or recurrence (Figure 4).

Written informed consent from the patient was obtained and ethics approval was granted by the Ethics Committee of PKU Muhammadiyah Gombong Hospital (830/IV.6.AU/D/VI/2021).

DISCUSSION

In the last 2 decades, only sporadically have case reports, but no serial studies, of cutaneous verrucous carcinoma (CVC) appeared in the literature.⁽¹⁾ To understand how rare this tumor

site is, we know of only 12 cases that were presented in the literature within the last 10 years (Table 1). To our knowledge, this is the first published case of CVC of the upper leg, whereas the lower legs are more at risk due to chronic venous insufficiency.

Cutaneous verrucous carcinoma is a subtype of low-grade SCC and not an SCC with a verrucous presentation. This rare tumor has a contradictory “benign” histology and cytology, but markedly aggressive clinical behavior.⁽⁷⁾ CVC may progress to a large, necrotic, and infected state; the margins will often show aggressive borders which may extend into the adjacent structures causing destruction of the local connective tissue, muscle, cartilage, or bone.^(10,13,14)



Figure 4. Clinical aspect after surgical excision of the lesion. (a) day 3 post-op, (b) at 3 months follow-up, and (c) at 1 year follow-up

Table 1. Summary of 12 cutaneous verrucous carcinoma case reports published in the last 10 years

Reference	Age	Sex	Location	Size	Lesion	Therapy	Follow-up
Brito et al. ⁽¹⁴⁾	54	M	Scalp (left occipital)	5.5 cm	Coexisting with trichoblastoma	Extensive excision with adequate margins	Discharged after re-debridement
Jung et al. ⁽⁹⁾	91	F	Left zygomatic area	5 x 4 cm	Arising from actinic keratosis	Excision with 0.4 cm free tumor margins; sutured by primary closure	Good wound healing after surgery; no signs of facial nerve injury
Ito et al. ⁽¹³⁾	68	M	Neck (right cervical)	17 cm	A giant papillary tumor covered the entire right side of the neck	Tumor resection with negative margins and right neck lymph node dissection (levels I–V, 14 in total); reconstruction with pectoralis major myocutaneous flap and grafting	No evidence of nodal metastasis; no recurrence was observed 9 months after surgery
Long et al. ⁽¹¹⁾	64	M	Scalp (left occipital)	6 cm	Coexisting with syringocystadenoma papilliferum	Wide radical excision with full-thickness skin graft harvested from the lower abdomen	N/A
Hannah et al. ⁽¹⁷⁾	Late 30s	F	Left upper arm	9 cm	Arising from burn scar	Wide local excision with 1 cm margins	Good wound healing 3 weeks after surgery
Mai et al. ⁽⁶⁾	78	M	Right wrist & 2 nd interdigital space	N/A	Arising from previous surgically removed nodule	Surgical excision with 1 cm clear resection margins; reconstruction with semi-thick skin graft	Good aesthetic results 3 months after surgery; no signs of recurrence after 1 year follow-up
Shimizu et al. ⁽⁸⁾	95	F	Right lower leg	4 x 4 cm	No history of chronic venous insufficiency	Complete resection with negative surgical margins; reconstruction with split-thickness skin graft	No local or distant metastasis was detected 1 year after surgery
Nagarajan et al. ⁽¹⁶⁾	63	M	Right dorsum pedis	N/A	Arising from chronic non-healing ulcer	Wide local excision with assessment of margin status; reconstruction with split-thickness skin graft	Discharged with fully functional limb and excellent cosmesis
Pandiaraja ⁽¹⁰⁾	34	M	Presternal region	2 x 2 cm	The second published case of presternal VC (previously in 2000)	Wide local excision with 2 cm clear margins	No evidence of recurrence after 2 years follow-up
Park et al. ⁽¹⁵⁾	78	F	Right medial canthus	0.5 x 0.5 cm	Arising from previous tumor treated with laser	Complete excision and eyelid reconstruction with bilobed flap	No complication in functional or cosmetic aspects and no evidence of recurrence 7 months after surgery
Părașcu et al. ⁽²⁾	40	M	Right arm	7 x 6 cm	A vegetating mass	Excision with safety oncological margins	N/A
Kurisu et al. ⁽⁵⁾	80	M	Neck (anterior)	1.7 cm	Multinodular semi-pedunculated lesion	Excision with a margin of the intact skin	No recurrence was observed 3 years after surgery

In contrast to classical SCC, most of CVC cases are located in sun-protected areas.^(1,9) This suggests that there might be differences in the pathogenesis of CVC and SCC; ultraviolet B (UVB) is not as important in the pathogenesis of CVC as it is in SCC.⁽¹⁾ There has been speculation about chronic cutaneous inflammatory lesions triggering an oncogenic-like overdrive of growth factors which stimulate the epithelial cells constantly to undergo neoplastic transformation. In contrast to tumors of the oral, anourogenital, and palmoplantar regions, there is weak association between HPV infection and CVC.⁽⁵⁾ The diagnosis of CVC relies largely on clinical features and histopathological characteristics. Upon pathological examination, the resected tumor was diagnosed as CVC based on the observation that a well-differentiated squamous rete ridge appeared to push into the underlying tissue and no major cytologic atypia could be found within the tumor.

Histologically, the diagnosis can be difficult because of the misleading benign aspect of the tumor with very few cellular and nuclear atypia and low mitotic activity.⁽⁶⁾ Multiple biopsies are often necessary to establish the diagnosis, as the slow growth and confusing early-stage appearances can lead to delay in diagnosis or to misdiagnosis and hence under-treatment.⁽⁶⁾ Initially, CVC shows indolent downgrowth of fingers of epithelium that gradually push rather than infiltrate.⁽⁸⁾ The tumor margin is well-demarcated and inside the tumor, there is epithelial tumor cell growth, often presenting a verrucous or hyperkeratotic surface with a deep endophytic and broad blunted rete ridge, which pushes down the basement membrane rather than infiltrate into the dermis.⁽⁸⁾ Therefore, the histological criteria for the diagnosis of CVC include the exo-endophytic growth pattern, blunt acanthosis with pushing margins, invasion of the reticular dermis, and severe dermal inflammation, that are significantly more prevalent in CVC.⁽¹⁾

The differential diagnosis of CVC includes verruca vulgaris, keratoacanthoma, seborrheic keratosis, verrucous hyperplasia, and conventional

squamous cell carcinoma (Table 2).^(12,15) In their early stages, CVC may represent a diagnostic challenge because they are easily mistaken for other benign entities. Verrucous hyperplasia (VH) is a forerunner of CVC. Verrucous hyperplasia does not extend into deeper tissues generally and is superficial in nature, whereas CVC extends more deeply. It should be kept in mind that VH may transform into CVC or SCC, acting as a potential precancerous lesion. Keratin pearls are the hallmark for SCC, but are not so common in CVC.⁽¹⁰⁾ Other characteristic features are infiltration of lymphocytes, histiocytes, eosinophils, and plasma cells.⁽¹⁰⁾

Histopathological examination is especially important, highlighting the appearance of a well-differentiated squamous cell carcinoma. Because of this particular biological behavior, extensive biopsies of the lesion are important, including the transitional area between the tumor and healthy skin in order to facilitate the final histological diagnosis. Superficial biopsies are not recommended because they may become the main pitfall in the diagnostic process caused by non-representative small biopsies.^(8,10) Even with deep incisional biopsies, diagnosis may be difficult because of the intact basement membrane and well-differentiated nature.⁽⁸⁾ Therefore, in the presence of clinical suspicion of CVC, excisional biopsy is preferable in order to be able to highlight the presence of carcinoma.⁽⁸⁾

Treatment should prioritize surgical procedure, which will depend on lesion size and location. Wide local excision is the treatment of choice for CVC rather than a marginal excision since the margins are not always apparent or well-defined intraoperatively, due to structural distortion of adjacent tissue.^(10,16) The probability of local recurrence is very high when there is a tumor-positive margin.⁽¹⁰⁾ A free surgical margin of at least 1 cm should be left in order to avoid recurrences. However, detecting tumors at an earlier stage is preferable since localized disease is frequently treatable with an appropriate surgical excision with sufficient margins.⁽⁴⁾

Table 2. Differential diagnosis of cutaneous verrucous carcinoma based on histopathological features⁽¹²⁾

Verruca vulgaris (VV)	Keratoacanthoma (KA)	Seborrheic keratosis (SK)	Verrucous hyperplasia (VH)	Cutaneous verrucous carcinoma (CVC)	Conventional squamous cell carcinoma (SCC)
1. The exophytic papillae may lie above the level of normal epidermis	1. The exophytic papillae lie below the level of normal epidermis	1. Papillae are predominantly above the surface of normal epidermis (exo >> endo)	1. Exophytic pattern only	1. Exophytic papillae are present but with thin/without fibrovascular cores	1. Exophytic papillary component is absent
2. Compact (tight) hyperkeratosis filling the entire cup and plugging the mouth	2. Acantholytic (loose) type of hyperkeratosis, partially filling the cup and open mouth	2. Hyperkeratosis is seen but is less compared to VV & KA	2. Papillae are absent; well-differentiated squamous cells	2. Always well-differentiated	2. Tumor may be well, moderately, or poorly differentiated
3. The rete ridges end at the same level	3. May not end at same level and show pseudo-infiltrating margins mimicking a carcinoma	3. The rete ridges end at the same level	3. Rete ridges lie at the same level as the normal epithelium; inflammatory stroma	3. Pushing broad margins	3. Infiltrating margins with extensive desmoplasia in stroma
4. Koilocytosis is present	4. Koilocytosis is absent	4. Koilocytosis is absent	4. Orthokeratosis only	4. Hyperkeratosis with parakeratosis is seen; no crypts seen	4. Keratin filled crypts are not seen; variable keratinization
5. Cytological and nuclear atypia is absent	5. Cytological and nuclear atypia may be seen	5. Cytological and nuclear atypia is absent	5. No cellular atypia	5. Atypia is never present	5. Atypia is always present in variable degrees and proportions
6. Keratin pearls not seen in the acanthotic epidermis	6. Keratin pearls may be seen in the acanthotic epidermis	6. Keratin pearls/horn cysts are always seen in the acanthotic epidermis	6. Koilocytotic atypia is absent	6. Koilocytotic atypia is absent	6. Koilocytotic atypia is absent
			7. May progress to CVC	7. Not aggressive; no propensity to metastasis	7. Locally aggressive and may show distant metastasis
			8. Considered as a precursor to CVC	8. Very good prognosis	8. Bad prognosis

Surgical excision is usually curative; risk of local recurrence is low and may be further reduced with Mohs surgery and adjuvant radiotherapy.⁽¹⁷⁾ Mohs surgery effectively allows total tumor removal and offers the possibility to examine all the margins of the tumor (lateral and deep), including remaining areas of invading carcinoma.⁽⁷⁾ This procedure is important in the therapy of cases with perineural invasion and offers the advantage of preserving a maximum amount of healthy tissue.⁽⁷⁾ Regional lymphadenopathy may be present secondary to reactive changes due to inflammation and not to metastatic disease.

Radiotherapy is debatable as a treatment choice. Radiation as a monotherapy or primary radiotherapy has an 11–30% risk of anaplastic transformation into poorly differentiated squamous cell carcinoma.^(4,10,14) Radiation therapy should not be applied in cases of associated HPV infection and should not be used over bony structures because of the risk of osteonecrosis.⁽⁷⁾ Photodynamic and CO₂ laser therapies have been reported to be useful preoperatively to reduce tumor size.⁽¹⁾

The prognosis of CVC is better than that of other types of life-threatening malignant tumors. The long-term prognosis for definitively treated CVC is good, with cure rates of up to 99%.⁽¹⁶⁾ For this patient, both the location of the tumor and differentiation were favorable for good prognosis. However, the tumor size presents a higher risk of metastasis. The patient follow-up is mandatory, as recurrence of verrucous carcinoma has been reported despite clear histological resection margins. Whichever treatment is used, the rate of recurrence varies from 30–50% and is not usually the result of incomplete surgical interventions.^(3,7,14)

CONCLUSION

Accurate diagnosis of cutaneous verrucous carcinoma (CVC) is crucial. Because recurrent tumors have a worse prognosis and highly infiltrative potential, the primary lesion must be

totally resected with at least 1 cm safety margins, regardless of the treatment option.

CONFLICT OF INTEREST

The authors affirm that there is no conflict of interest in this study.

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AUTHOR CONTRIBUTIONS

All authors contributed equally to the content of the study. RNR contributed to revision of the manuscript. MY was responsible for the management of this patient. SHNS contributed to diagnosis. All authors have read and approved the final manuscript.

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