

## Verrucous Carcinoma of the Foot - Report of Two Cases

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### Abstract

Verrucous carcinoma (VC) is a rare variant of a well-differentiated squamous cell carcinoma (SCC) with a low grade of malignancy. Epithelioma cuniculatum (EC) is a subtype of VC, usually found on the sole of the foot.

Two patients, a 55-year-old female, and a 77-year-old male, with VC were treated at the Clinic of Dermatology and Venereology, Clinical Center of Serbia, from 2002 to 2011. Both patients presented with a tumor on the foot. Incisional biopsies showed a well differentiated squamous cell carcinoma. Foot x-rays showed bone involvement in one case. One patient underwent surgical amputation of the lower extremity, while the other had a partial amputation of the affected foot.

In the initial stage of the disease, it is difficult to distinguish pseudoepitheliomatous hyperplasia from verrucous carcinoma. The superficial biopsy of EC lesion may mislead to a histopathological diagnosis of warts or condylomas. Multiple deep biopsies are necessary for accurate and timely diagnosis of verrucous carcinoma.

### Key words

Carcinoma, Verrucous; Foot Diseases; Diagnosis; Skin Neoplasms; Biopsy; Amputation

Verrucous carcinoma (VC) is a rare variant of a well-differentiated squamous cell carcinoma (SCC) with a low grade of malignancy (1). It is usually found in the oral cavity (Ackerman, 1948) (2), lower legs (Gottron, 1932) (3), perianal or genital area (Buschke and Lowenstein, 1925) (4) and soles. Epithelioma cuniculatum (EC), first described by Ian Aird in 1954, is a subtype of verrucous carcinoma usually found on the sole of the foot (5). EC has a local invasive growth with destruction of all substructures including the bone tissue (6).

### Case reports

#### Patient 1

A 55-year-old female patient was admitted to the Clinic of Dermatology and Venereology, Clinical Center of Serbia in March 2002 due to a widespread polymorphous skin eruption, with erythematous exudative patches, tense blisters, and with a warty-

like formation located on the left plantar and dorsal side of the 4<sup>th</sup> and 5<sup>th</sup> metatarsals (Figure 1). The Tzanck test showed a large number of eosinophils, and histopathological and direct immunofluorescence examinations confirmed the diagnosis of bullous pemphigoid. A deep biopsy was taken from the foot lesion, and the histopathological examination confirmed VC (Figure 2). Foot x-ray findings showed no bone involvement. A partial amputation of the patient's left foot was performed. No signs of recurrence were noted at 10-year-follow-up.

#### Patient 2

A 74-year-old male patient, with a ten-year history of a lesion on the left sole, was admitted to the Clinic of Dermatology and Venereology in December 2011. He presented with an irregularly shaped enlarging ulceration, 6 x 4 cm in diameter, covered by fibrin and granulation tissue and centrally localized

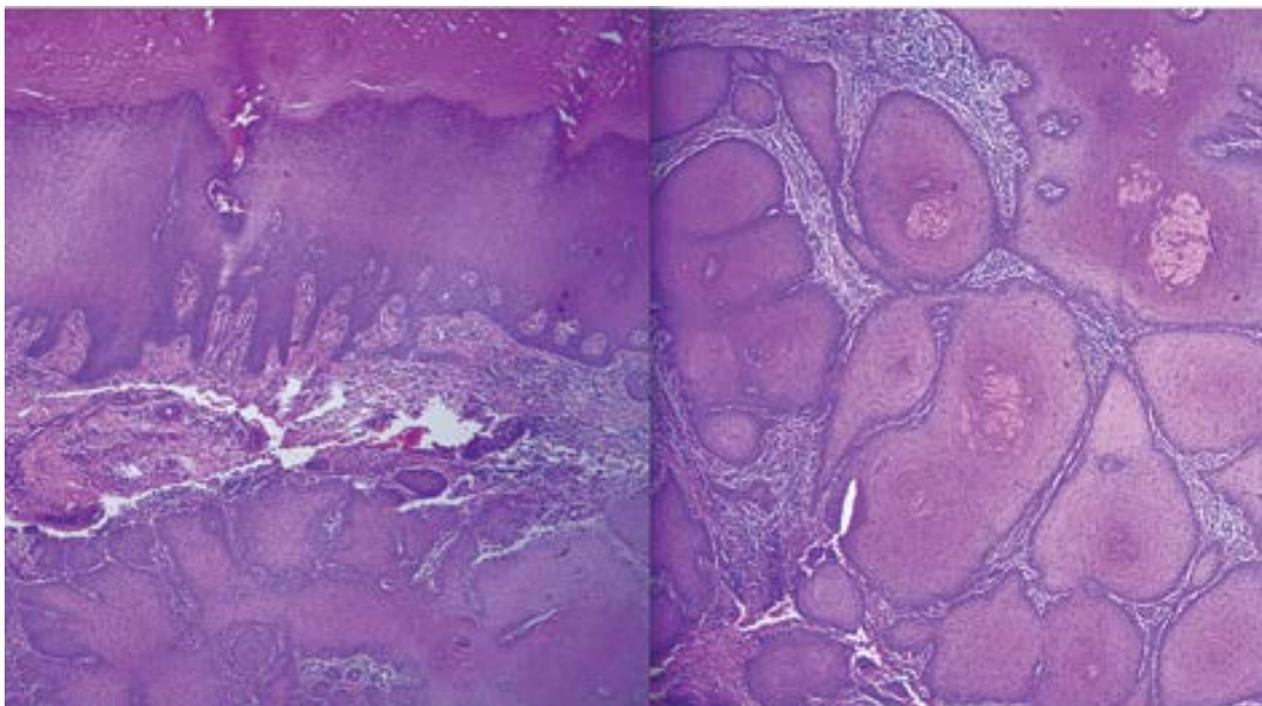


**Figure 1.** Hyperkeratotic tumefaction on the left sole

verrucous formations (Figure 3). The patient's history showed a prior total surgical excision of a lesion in 2007. At that time, the histopathological findings correlated with pseudoepitheliomatous hyperplasia. Due to the recurrence, a second surgical intervention was performed in 2009. The histopathological examination revealed VC, a tumor tissue on the lower line of the resection (Figure 4). A repeated foot x-ray showed progression of osteolytic changes (Figure 5). Amputation of the patient's left lower leg was performed in February 2012. Eleven months later, the patient's general condition was good and his rehabilitation has been going well.

### Discussion

VC is a rare tumor with uncertain incidence, although it is known that it is more common in men, and in the sixth decade of life (79 - 89% of patients) (7, 8). VC is usually found on the soles, but it may occur on palms, as well as in other regions (esophagus, oral cavity, larynx, nail, penis) (9, 10, 11, 12, 13, 14). It is well known that chronic irritation and inflammation have an important role in the pathogenesis of VC, while the role of human papilloma virus (HPV) infection

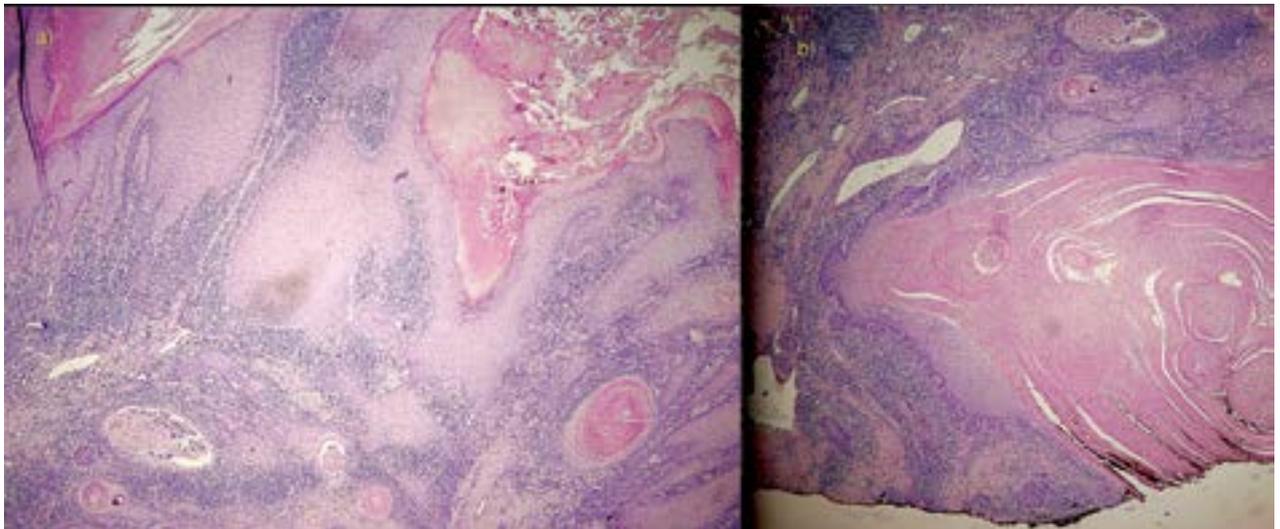


**Figure 2.** Verrucous carcinoma: exophytic component – hyperkeratosis; endophytic component – a well differentiated squamous epithelium growing downward into the underlying tissue (Hematoxylin-eosin, 40x)

is still controversial (15, 16). HPV types 1, 4, 6, 11, 16, 18 have been cited as possible etiologic factors involved in the pathogenesis of EC (17, 18). EC usually appears on the metatarsal region of the foot or area that is most exposed to mechanical trauma during movement (8). Typical lesions have exophytic and endophytic growth patterns and papillomatous surface with keratin filled sinuses. EC has a progressive dorsal growth leading to the destruction of local tissue, first the plantar fascia, then the metatarsal bone (19). Penetrating and profound tumor growth creates deep sinuses and clefts, resembling rabbit holes in the original description, hence the term *cuniculatum*, Latin for “rabbit hole”. The diagnosis of EC in the initial stage is extremely difficult because of its similarity to plantar warts. The differential diagnosis also includes reactive epidermal hyperplasia, adnexal tumors, giant seborrheic keratosis, giant keratoacanthoma, verruciform xanthoma and verrucous melanoma (20, 21). The course of our male patient’s disease supports the fact that a long-term callus or recurrent epidermal hyperplasia, usually on a site of chronic irritation or infection, may precede the appearance of EC (21). Regardless of its localization, typical clinical and histopathological presentation of EC shows an exophytic and endophytic component. The exophytic component consists of massive hyperkeratosis, often parakeratosis, acanthosis and papillomatosis. The



**Figure 3.** Ulcer with verrucous formation on the left sole



**Figure 4.** Histopathological presentation of verrucous carcinoma: (a) massive hyperkeratosis, often parakeratosis, acanthosis and papillomatosis, well differentiated squamous epithelium showing a characteristic pushing margin (Hematoxylin-eosin, 40x) (b) tumor tissue on the lower line of resection (Hematoxylin-eosin, 40x)



**Figure 5.** Repeated x-ray of the left foot. Primarily, osteolysis of the proximal phalanx of the 3<sup>rd</sup> toe, a year later extended on the 4<sup>th</sup> metatarsal head. On the last x-ray in December 2011, osteolysis of the 3<sup>rd</sup> metatarsal bone was verified, as well as the involvement of the 3<sup>rd</sup> proximal and middle phalanx, 2<sup>nd</sup> and 4<sup>th</sup> metatarsal bones

endophytic component consists of well-differentiated squamous epithelium growing downward into the underlying tissues, showing characteristic pushing margin. In most cases, squamous cell carcinoma, in contrast to EC, has an infiltrative border. The well-differentiated proliferation refers to tumor cells with minimal atypia, very low mitotic activity and extensive keratinization (1). Superficial biopsy of EC lesion may mislead to a histopathological diagnosis of warts or condylomas (22). In the initial stage of the disease it is difficult to distinguish the clinical presentation of pseudoepitheliomatous hyperplasia from verrucous carcinoma (21, 22). Therefore, small and superficial biopsies may give a false result leading to the wrong diagnosis (22). Multiple deep biopsies are necessary for accurate and timely diagnosis of verrucous carcinoma (6, 7, 8, 22). Searching the MEDLINE database we did not find any association between EC and bullous

pemphigoid. Needless to say, our second patient is the first reported case of coexistence between EC and bullous pemphigoid.

Treatment of EC includes surgical excision of the tumor when the localization is adequate for the procedure. A histopathological verification on the line of resection should be mandatory (23). In inoperable cases, radiotherapy, retinoids, interferon- $\gamma$  and photodynamic therapy can be efficient, but the number of such reports is limited, therefore they are not widely accepted (24, 25, 26). In severe cases when the bone tissue is affected, amputation is the main therapeutic modality (7, 8, 19).

In conclusion, in the early development, EC can easily be mistaken for a various number of hyperkeratotic disorders. A proper incisional biopsy and histopathological examination may be considered crucial in the differential diagnosis. The timely

diagnosis and treatment can prevent significant surgical disfigurement of these patients.

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## Verukozni karcinom stopala – prikaz dva slučaja

### Sažetak

Uvod. Verukozni karcinom predstavlja dobro diferencijirani oblik skvamocelularnog karcinoma sa niskim stepenom maligniteta. *Epithelioma cuniculatum* je podtip verukoznog carcinoma, najčešće lokalizovan na tabanima.

Prikaz slučajeva. Dva pacijenta, uzrasta 55 i 77 godina,

kojih je dijagnostikovano verukozni karcinom lečeni su na našoj klinici u period od 2002. do 2011. godine. Oba pacijenta su imali prisutnu tumefakciju na stopalu. Incizionim biopsijama potvrđen je dobro diferencijirani skvamocelularni karcinom. Zahvaćenost kostiju bila je prisutna kod jednog pacijenta.

Kompletna amputacija donjeg ekstremiteta urađena je kod jednog od pacijenata, dok je kod drugog urađena parcijalna amputacija zahvaćenog stopala.

Zaključak. U inicijalnom stadijumu bolesti teško je klinički razlikovati pseudoepiteliomatoznu hiper-

plaziju od verukoznog karcinoma. Površne biopsije *Epithelioma cuniculatum* mogu lažno navesti na dijagnozu kondiloma ili bradavica. Ponavljane duboke biopsije neophodne su za tačnu i pravovremenu dijagnozu verukoznog karcinoma.

### **Ključne reči**

Verukozni karcinom; Bolesti stopala; Dijagnoza; Kožne bolesti; Biopsija; Amputacija