

## CASE REPORTS

# Cutaneous verrucous carcinoma – report of three cases with review of literature

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## Abstract

Verrucous carcinoma is a rare variant of squamous cell carcinoma. It is well differentiated and rarely metastases but can sometimes be very aggressive locally in depth. The paper presents three cases of cutaneous verrucous carcinoma with different localizations. The first patient shows a lesion in the sacrogluteal region, the second one presented a tumor localized on the auricle (external ear), and the third patient showed a tumor on the sole of the foot. All patients underwent tumor excision and the histopathological diagnosis was verrucous carcinoma. In the first two cases, the surgery was completely curative by excision of the tumors. In the last case, the patient had relapsed and due to the aggressive nature of the tumor, which infiltrated the deeper plans, the tumor had reached the bone. None of the patients showed any metastases.

**Keywords:** cutaneous verrucous carcinoma, local aggressiveness, immunohistochemical tests.

## Introduction

Verrucous carcinoma (Ackerman's tumor) was first described in 1948 by Dr. Ackerman, in the oral cavity [1]. In 1954, Aird *et al.* were the first one who described cutaneous verrucous carcinoma also known as "carcinoma cuniculatum" or "epithelioma cuniculatum" [2]. It is a rare variant of well-differentiated, low-grade squamous cell carcinoma, characterized by slow-growth and low metastatic potential; but the tumor can be locally aggressive and recurrence is not uncommon [3]. Patients with verrucous carcinoma have a good survival prognosis [4]. This tumor occurs in elderly (generally 60–70-year-old patients), with a white male predominance [5].

Verrucous carcinoma is usually associated with HPV (human papillomavirus) in palmo-plantar, ano-genital and oral sites, with smoking, leukoplakia, poor oral hygiene, low socio-economic status, alcohol consumption and chronic inflammations. Schistosomal infection is associated with verrucous carcinoma of the bladder [6]. Rare sites of verrucous carcinoma have been previously described in sacral region, temporal bone and in the ear, respectively. The rarity of this tumor is highlighted by the only three cases of the verrucous carcinoma of the ear described so far [7].

Morbidity in verrucous carcinoma is due to local aggressiveness of the tumor (consisting in skin and soft tissue destruction) and perineural, muscle and bone invasion. Metastases in verrucous carcinoma are so rare that the mortality is more often due to local invasion.

Our work is dealing with three such cases of this

rare entity of squamous cell carcinoma: three cases of verrucous carcinoma of the skin, each one with a different localization (buttock, auricle, foot).

These case reports prove the rarity of this pathology as well as the specificity of verrucous carcinoma in comparison with other squamous cell carcinomas (SCCs). The lack of malignancy criteria and the local invasive potential are only two of the diagnosis features which helps distinguish this tumor from SCCs.

## Materials and Methods

Starting from one case of cutaneous verrucous carcinoma diagnosed in 2012, the archive files of the Emergency University Hospital of Bucharest, Romania, were searched for all cases labeled with 8051/3 ICD-O (*International Classification of Diseases for Oncology*) diagnosis code. According to *WHO (World Health Organization)* latest histological classification of tumors, this number is the diagnosis code for verrucous carcinoma. This way, another two cases of verrucous carcinoma were found and further information were obtained from the medical and pathology reports; also, the representative slides from the archive were reexamined.

During 2010–2012, three cases of cutaneous verrucous carcinoma were identified in the Emergency University Hospital of Bucharest. Patients aged between 54 and 86 years presented skin lesions were directed to the Department of Plastic Surgery of the same hospital for treatment.

First, the tissue fragments were analyzed with

extemporaneous histological examinations and complete surgical was recommended as the lesions looked infiltrative and well-differentiated squamous cell carcinoma could not be excluded.

After surgical excision of the tumor, it was sent to the Department of Pathology, where a specific fragment from the tumor was frozen at  $-30^{\circ}\text{C}$  and was sectioned at cryotome and stained with routine Hematoxylin–Eosin (HE) staining. The tissue pieces were sent for the histopathological processing where they were fixed in 10% buffered formalin for 24 hours; representative tissue blocks were taken and embedded in paraffin; afterwards sectioned at 3  $\mu\text{m}$  and then HE stained. The obtained slides were examined by light microscopy.

For immunohistochemical staining, we used an indirect tristadial Avidin–Biotin complex method (deparaffination in toluene and alcohol series, rehydration, washing in PBS (phosphate buffered saline), incubation with normal serum, for 20 minutes, incubation with primary antibody overnight, DAKO LSAB kit, washing in carbonate buffer and development in 3,3'-diaminobenzidine (DAB) hydrochloride/hydrogen peroxide nuclear counterstaining with Mayer's Hematoxylin.

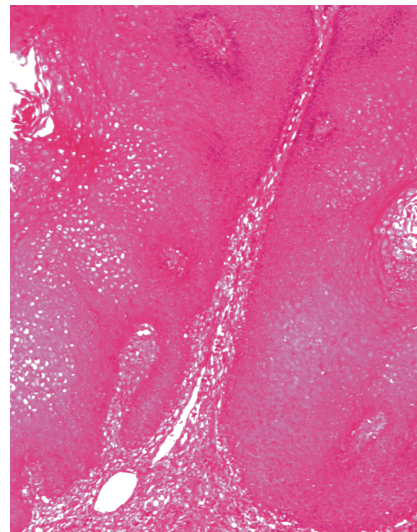
Immunohistochemical tests were made on a single case, that showed recurrence of the tumor, and the following antibodies from NeoMarkers LabVision were used: PanCytokeratin, clone AE1/AE3 (Thermo Fisher Scientific Inc., USA, 1:100 dilution), Cytokeratin 5/6, clone D5/16 B4 (Thermo Fisher Scientific Inc., USA, 1:20 dilution), P53 protein, clone DO-7 (Thermo Fisher Scientific Inc., USA, 1:200 dilution), Vimentin, clone V9 (Thermo Fisher Scientific Inc., USA, 1:200 dilution), High Molecular Weight Cytokeratin, clone 34 $\beta$ E12 (Thermo Fisher Scientific Inc., USA, 1:50 dilution), Epithelial Membrane Antigen, clone E29 (Thermo Fisher Scientific Inc., USA, 1:50 dilution), Ki-67, clone SP6 (Thermo Fisher Scientific Inc., USA, 1:200 dilution), bcl-2, clone 8C8 (Thermo Fisher Scientific Inc., USA, 1:100 dilution).

The immunoreactive cells were evaluated as follow: diffuse positive, >75% positive cells; positive, 25–75% positive cells; focal positive, <25% positive cells and negative cells.

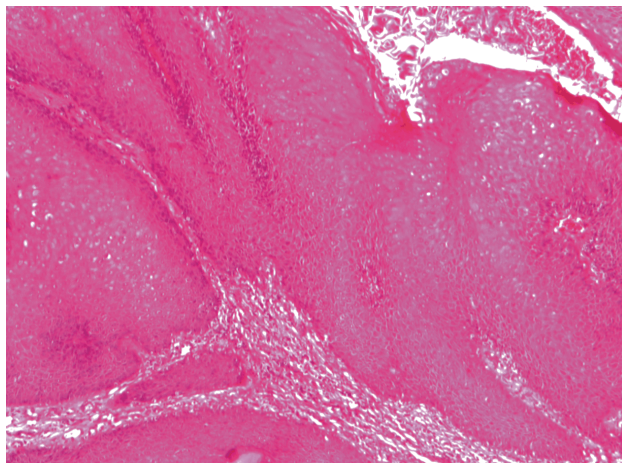
## Results

### Case No. 1

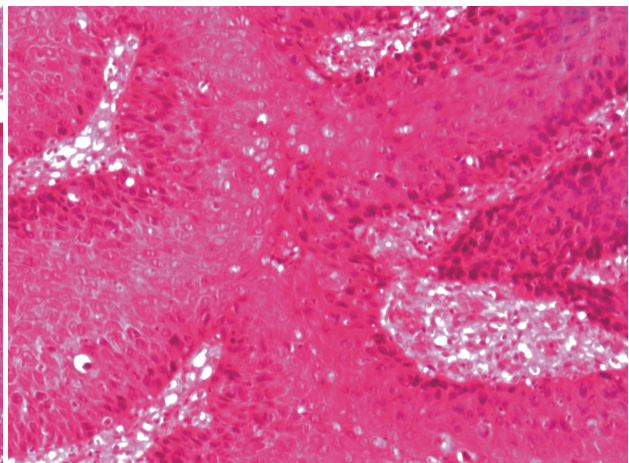
First case belonged to a 54-year-old man who was hospitalized in the Department of Plastic Surgery with the diagnosis of sacrogluteal tumor. No medical record was available at the moment of the study. The appearance of the lesion raised suspicion of malignancy and was excised. The tissue fragment sent to the Department of Pathology was a cutaneous fragment sized 130/100/40 mm, which showed an ulceration in the central portion of 50/20 mm with irregular edges. Moreover, there were described many prominent “nodular” structures with sizes ranging from 20/18 mm to 3 mm diameter. Extemporaneous histological examinations confirmed the suspicion of malignancy whereas histopathological images (HE staining) showed a papillomatous and hyperkeratotic tumor with acanthosis. Many well-demarcated exophytic and endophytic projections/islands formed by proliferations of keratinocytes with keratin-filled clefts and inflammatory infiltrate at the periphery of the islets are seen. Mild to moderate cytological atypia can also be observed. All these criteria suggested the diagnosis of ulcerated verrucous carcinoma, therefore the excision of the tumor was completely performed (Figures 1–3). No immunohistochemical tests were available.



**Figure 1 – Cutaneous verrucous carcinoma: infiltrative tumoral islands of squamous epithelial cells, surrounded by chronic inflammatory cell infiltrate. HE staining,  $\times 40$ .**



**Figure 2 – Cutaneous verrucous carcinoma: infiltrative tumoral islands of squamous epithelial cells with minimal nuclear pleomorphism. HE staining,  $\times 40$ .**

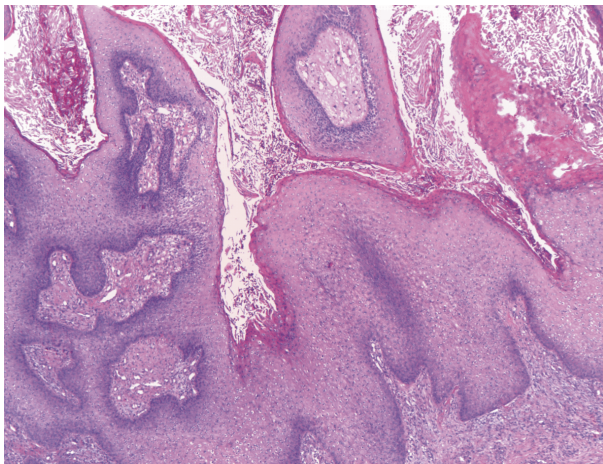


**Figure 3 – Cutaneous verrucous carcinoma: infiltrative tumoral islands of squamous epithelial cells with rare mitoses in the basal layer. HE staining,  $\times 200$ .**



### Case No. 2

Second case belonged to an 86-year-old woman who presented with a tumor on the right ear auricle, which was slowly progressing from over a year. No other symptoms were specified. The lesion was excised in the Department of Plastic Surgery and sent to the Department of Pathology as 20/10 mm piece of skin, with a whitish irregular zone in the central portion, slightly prominent from the surface, and with a firm consistency. After conventional staining, the classical image of a verrucous carcinoma was displayed (numerous round-shaped proliferations of well-polarized squamous cells with little atypia and rare mitotic figures; the exophytic component present hyperkeratosis and acanthotic papillary processes) without exceeding the resection limits (Figure 4). No immunohistochemical stains were performed.



**Figure 4 – Cutaneous verrucous carcinoma: the exophytic component present hyperkeratosis and acanthotic papillary processes. HE staining, ×40.**

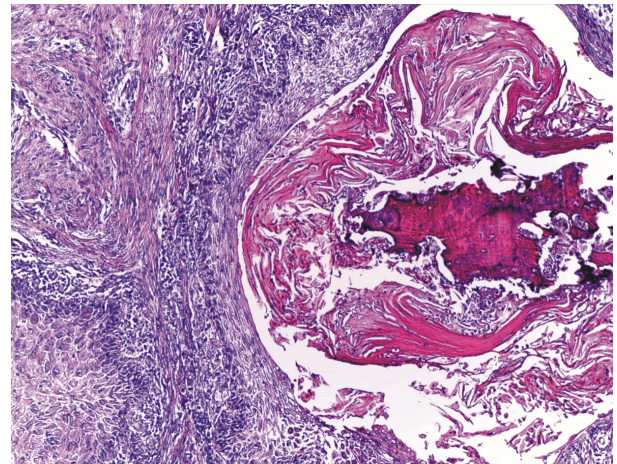
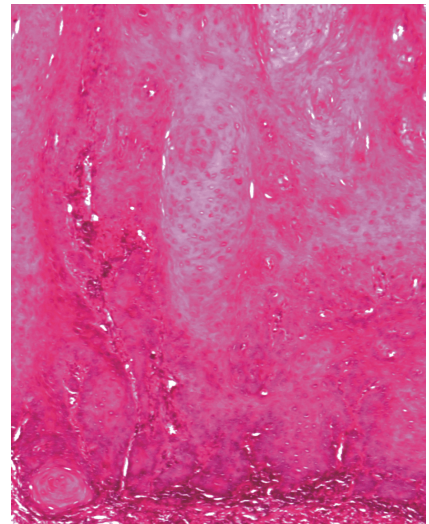
### Case No. 3

Third case belonged to a 65-year-old man who presented with a chronic plantar ulceration. The tumor was excised in the Department of Plastic Surgery and the pathologist received a skin fragment of 56/42/14 mm with a central portion ulceration of 30/20 mm, white colored and with increased consistency. The histopathological features included various islets of proliferating epithelial cells originated in spinous layers with cytological atypia, rare mitoses, moderate grade of pleomorphism. The islets tend to infiltrate the dermis, creating a mild desmoplastic reaction (Figure 5).

The resection margins were infiltrated – on extemporaneous histological examinations. The patient underwent a new surgical intervention with the excision of an ulcerated tissue fragment of 47/32/16 mm, which presented in the deeper tissue layers a bone fragment of 20/10/10 mm. At histological examination, the periosteum was infiltrated by tumoral cells (Figure 6).

Immunohistochemical tests were performed in this case and revealed diffuse appearance of positive AE1/AE3 in tumor cells (Figure 7), diffuse appearance of positive CK5/6 in tumor cells (Figure 8); Ki-67 positive in nuclei of basal and parabasal cells (Figure 9), and P53 show positive reaction in many nuclei cells (Figure 10).

**Figure 5 – Cutaneous verrucous carcinoma: the endophytic component with bulbous processes consist of well-differentiated squamous epithelium. HE staining, ×40.**



**Figure 6 – Cutaneous verrucous carcinoma: infiltrative tumoral islands of squamous epithelial cells, with deep crypts filled with horny material, destroying the periosteum. HE staining, ×40.**

Considering the features of the cases presented above, even though oral verrucous carcinomas are the most frequent, all three cases were localized on the skin and they are all included in the group of cutaneous verrucous carcinoma. Each case had a different location on the skin: the buttocks (sacrogluteal region), the auricle (external ear) and the sole of the foot. These are rare locations of verrucous carcinoma and the foot tumor represents the most common form of cutaneous verrucous carcinoma.

The size of the tumors varied from 20 to 130 mm in their largest dimension. The smallest was located on the auricle and the largest on the buttocks.

Two of the tumors presented ulcerations: the one located on the buttocks (and the largest) and the one located on the foot. The patient with the foot verrucous carcinoma had a history of chronic plantar ulcer.

According to their macroscopic features, these cutaneous carcinomas had an increased consistency, whitish color and irregular margins. The tumor of the sacrogluteal region presented multiple “nodular” structures.

All three patients, late after the clinical debut, received the elective surgical treatment and the final diagnosis of cutaneous verrucous carcinoma. In the first case, the patient presented after the tumor reached 130 mm and developed an ulcer. In the second case, the patient received

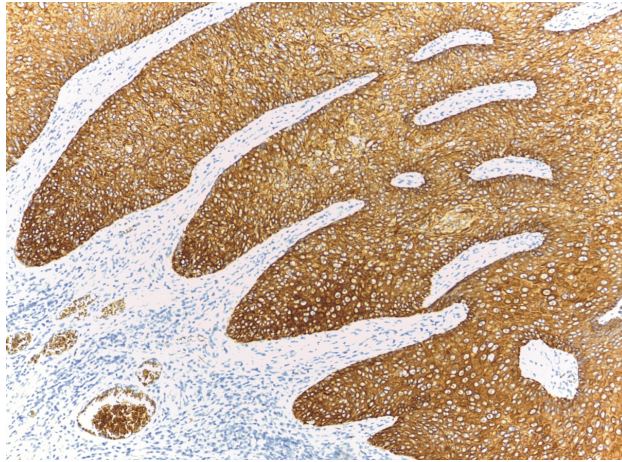


the treatment after the tumor slowly grew for one year and the third patient presented with a chronic plantar ulcer.

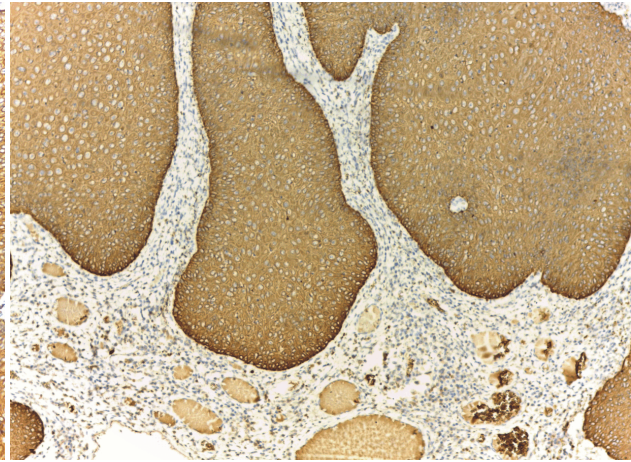
The surgical treatment was curative for the first two patients, while the patient with verrucous carcinoma of

the foot (and chronic plantar ulcer) needed another intervention for local recurrence. In this last case, the tumor reached the bone.

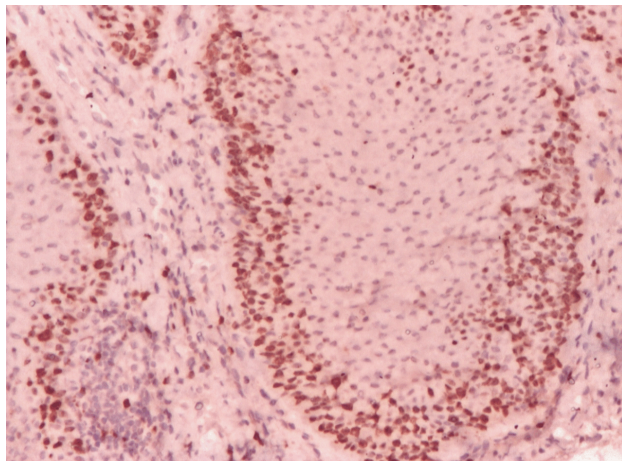
Metastases were not found in any of our cases.



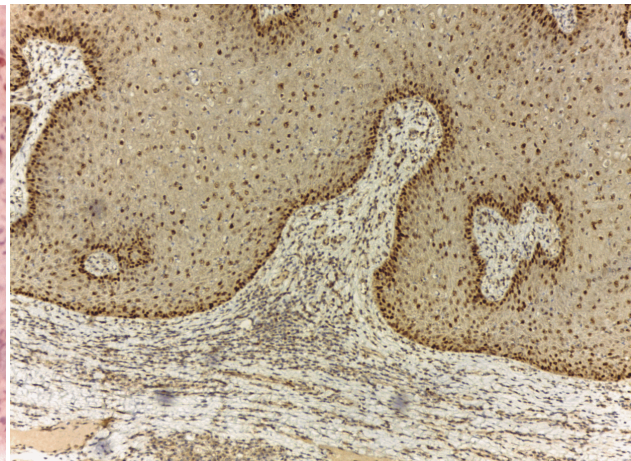
**Figure 7 – Cutaneous verrucous carcinoma: AE1/AE3 diffuse positivity of tumoral cells ( $\times 40$ ).**



**Figure 8 – Cutaneous verrucous carcinoma: CK 5/6 diffuse positivity of tumoral cells ( $\times 40$ ).**



**Figure 9 – Ki-67 expression: positive in nuclei of basal and parabasal cells of tumoral islands ( $\times 100$ ).**



**Figure 10 – Cutaneous verrucous carcinoma: P53 expression; many nuclei cells of tumoral islands show positive reaction ( $\times 40$ ).**

## Discussion

Verrucous carcinoma is a rare neoplasm with contradictory, “benign” histology and cytology but markedly invasive clinical behavior [8]. Verrucous carcinomas are said to be predominant in males and most patients are older than 60 years in more nearly 75% of the cases reported so far [5]. We found two males and one female with cutaneous verrucous carcinoma and one of the male patients was 54-year-old. Moreover, the oldest patient was the female and had the smallest tumor with the least troubling appearance. The males presented larger tumors with ulcerations.

Typically, verrucous carcinoma appears as a large hyperkeratotic nodule in the oral cavity (Ackerman’s tumor) [1, 5, 9, 10], palmo-plantar region (“epithelioma cuniculatum”) [11] and ano-genital region (Buschke–Löwenstein tumor) [12]. Those locations are the most common sites of the tumor [13]. Also, more rarely, it can involve the larynx, esophagus, ear, sino-nasal tract, nose, temporal bone, nasopharynx, mandible, tongue, lip, endometrium and bladder [14–20]. To understand

how rare are this sites, we recall that only three cases of verrucous carcinoma of the ear were presented in the literature and 14 cases of verrucous carcinoma of the temporal bone.

Oral verrucous carcinoma (Ackerman’s tumor or oral florid papillomatosis) although is the most common site of occurrence, it has a low incidence regarding oral carcinomas accounting for almost 5% of all oral carcinomas [21]. Leukoplakia, lichen planus, chronic lupus erythematosus, cheilitis and candidiasis may be precursor lesions for verrucous carcinoma [22].

Anogenital verrucous carcinoma presents itself as a cauliflower-like tumor and only the histopathological examination can differentiate it from a condyloma. This type of carcinoma is characterized by the high rate of recurrence, the tendency to invade deep in the tissue and the frequent occurrence in males and in immune compromised patients.

Palmo-plantar verrucous carcinoma has a slow growth and a long evolution in time. Fifty percent of those cases have plantar lesions.



In this paper, the first patient had a less common site of the tumor, sacrogluteal region, while the last one had a classic location – plantar region. Rare cases of sacrogluteal tumors were mentioned in the literature [11] as well as for the auricular region [7, 15]. All the cases presented with local invasion of the tumoral cells but without any metastases. The last case had a more aggressive extension of the carcinoma but still without any distant dissemination, proving the slow evolution of this tumor but the locally destructive potential of it.

Clinically and macroscopically verrucous carcinoma appears as a papillary gray-white or red mass with a very broad base of attachment and measuring up to several centimeters [23]. This type of carcinoma have 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 noticing any fibrovascular core [24]. We found two cases with nodular appearance: the auricular tumor presented as a prominent nodule, while the sacrogluteal tumor presented multiple such nodules. Another case presented as a white mass in a preexisting ulcerated plantar area. In our cases, the tumor size varied depending on the location. The auricle tumor was the smallest, followed by the foot tumor and the buttock tumor. It looks like exposed areas and those covered by a thin skin tends to be smaller. Furthermore, only the two largest tumors (the buttock and foot verrucous carcinomas) showed ulcerations, noting that the foot tumor developed in a preexisting ulcerated area, while the largest tumor located on the buttock ulcerated afterwards.

Microscopically, verrucous carcinoma, regardless of the site where is situated, has the same histopathological features. The epithelium displays an endo-exophytic growth pattern, prominent granular layer, hyperkeratosis, parakeratosis, acanthosis and papillomatosis [13]. It consists of large keratinocytes with prominent nuclei, visible nucleoli and minimal cellular atypia. The squamous epithelium is well differentiated with evident stratification. Deeply, the tumor consists of “bulbous” projections in broad that resemble rete ridges with acanthotic downgrowths into the surrounding dermis. The surrounding dermis displays inflammatory infiltrate and the epithelium may form sinuses and cysts filled with keratin.

Our cases have not raised many diagnosis problems regarding the microscopic images; the first two were almost specific for verrucous carcinoma, were as the last was more interesting considering the invasive nature of the tumor. In order to certify the final diagnosis, the last case was stained with specific immunohistochemical markers. From all the markers used, only AE1/AE3 and CK5/6 were positive but in a diffuse way in comparison with SCC were they should have been positive in all the epidermal layers.

In evolution, cutaneous verrucous carcinoma has a slow growth and that is why years may pass until the invasive features install themselves. When this carcinoma becomes invasive, tumor margins tend to extend towards surrounding structures with the destruction of the soft tissue, the muscles and the neighboring bony structures [24]. As it can be seen in our study, the tumor sizes reached almost 50 mm without being invasive in the neighboring structures.

Still, in the last case, the tumor sized a total dimension of almost 90 mm and was infiltrating deep in the periosteum. Therefore, in conclusion, this type of tumor can reach marked sizes without threatening the life of the patient.

There are reports of “hybrid” tumor cases that shares the same features of verrucous carcinoma mentioned earlier, but, focally, it may appear some areas of tumor cells with invasive characteristics resembling the classic squamous cell carcinoma [17, 25, 26]. Because of the clinical and treatment implications, these cases must be diagnosed as squamous cell carcinoma [27].

Both types of tumor stain positive for bcl-2, Ki-67 and P53 protein but in a different manner. In verrucous carcinoma, the cell's nucleus stains positive for Ki-67 and P53 but only in the basal proliferating layers of the epithelium [28]. In squamous cell carcinoma, the cell's nucleus stains positive in all layers of the epidermis, including the nests of invading cells. Bcl-2 appears positive in the cytoplasm of sporadic cells in verrucous carcinoma, while in squamous cell carcinoma has a more diffuse pattern [29].

The differential diagnosis of verrucous carcinoma is being made with verruca vulgaris, keratoacanthoma, pyoderma vegetans and other types of squamous cell carcinoma. According to our results, these cases, especially at their debut, represent a diagnostic challenge because they are easily mistaken for other benign entities. Correlations between the clinical history, the tumor behavior, the clinical presentation and pathological characteristics are needed for an accurate diagnosis.

First line treatment of the verrucous carcinoma consists of surgical excision of the tumor [30]. Morbidity in verrucous carcinoma is due to local aggressiveness of the tumor (consisting in skin and soft tissue destruction) and perineural, muscle and bone invasion. Metastases in verrucous carcinoma are so rare that the mortality is more often due to local invasion. Regarding our presented cases, none of the patients died or presented metastases. The surgical treatment proved to be curative in two of the cases (the auricle and buttock cutaneous verrucous carcinomas). On the other hand, in the verrucous carcinoma of the foot, which developed on a chronic plantar ulcer, the surgical margins were invaded. Also, the re-excised margins of this case showed invasion that reached the bone indicating an recurrence of this carcinoma. Recurrent verrucous carcinoma has a poor prognosis and highly infiltrative potential.

Surgical excision of the tumor recommends a 4 mm margin of healthy tissue. There are some cases when the margins are positive for verrucous carcinoma implying a new surgical intervention.

Mohs surgery extirpates the tumor and offers the possibility to examine all the margins of the tumor (lateral and deep), including remaining areas of invading carcinoma. This procedure is important in the therapy of cases with perineural invasion and offers the advantage of preserving healthy tissue.

Radiation therapy should not be applied in young and middle aged patients, in cases of associated HPV infection and should not be used over bone structures because of the risk of osteonecrosis.



## ✉ Conclusions

The low incidence of this pathology is proven in this case report because of the two special sites of the tumor, the auricle and sacral region, as well as the good prognosis but local aggressiveness of those lesions. In contrast to others SCCs, this type of carcinoma is not related to any sun exposure but with repetitive trauma or toxin exposure, explaining the common sites like oral mucosa or plantar region were frequently trauma and pressure points occur. The repetitive trauma could also be considered the main cause for the two unusual sites. Verrucous carcinoma of the skin can sometimes be very aggressive locally in depth as it can be also seen in this case report. When it becomes locally invasive, it tends to affect the surrounding tissues and it can reach the bone, as seen in the last case presented. The problem for this pathology is to distinguish it from other types of squamous cell carcinoma, which are more aggressive and with poorer prognosis. In conclusion, if it looks benign or "borderline" but infiltrative it is, probably, a verrucous carcinoma and further following of the patient is mandatory in order to detect any recurrent lesions since recurrence ranges from 30 to 50% of the cases.

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