

Verrucous Carcinoma - Observations on 4 Cases

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ABSTRACT: Verrucous carcinoma (VC) is a rare well-differentiated squamous cell carcinoma with the clinical forms: oral florid papillomatosis, epithelioma cuniculatum, papilomatosis cutis and Buschke-Löwenstein tumor. We present four patients and the four clinical forms of VC. The diagnosis we held after clinical examination and histopathological examination of the balance sheet expansion. First described by Ackerman in the oral mucosal, today it has a reported incidence of 1-3 cases per million inhabitants. VC can involve both skin and mucous membranes. Etiopathogenesis is uncertain, but participation HPV is widely accepted. WHO recognizes the VC as a rare form of well-differentiated squamous cell carcinoma with slow and continues evolution, with the invasion of underlying tissues, frequent relapses and very low risk of metastasis. The elective therapy is surgical excision with safety oncological margins. Diagnosis involves corroboration of clinical data with histopathological appearance and evolutive behavior of the tumor. Given the increased risk for recurrence, the patient should be reviewed quarterly to finding healing.

KEYWORDS: Verrucous carcinoma, oral florid papillomatosis., epithelioma cuniculatum, papilomatosis cutis carcinoides, Buschke-Löwenstein tumor

Introduction

Verrucous carcinoma (VC) it is considered a rare form of well-differentiated squamous cell carcinoma, with recidive tendency, local invasion capacity, but low potential for metastasis [1].

Regarding the VC location can be distinguished the following clinical entities: oral florid papillomatosis, epithelioma cuniculatum, papilomatosis cutis carcinoides and Buschke-Löwenstein tumor [2].

We present four patients, illustrating the 4 VC clinical forms, interesting both by localization and also by the pre and post-therapy evolution.

The VC diagnosis we have established after the clinical examination, histopathology examination and the extension balance.

Case 1 – Female, 74 years old, hospitalized for the presence of two vegetant tumoral masses in the left oral commissure, with verrucous surface and an oval keratotic plaque on the semimucosa of the upper lip (Fig.1). On the cheek mucosa there were present multiple leukoplasic plaques and multicentric papillomatosis masses covered by a white filing and painful erosions (Fig.2). The patient was known with hepatitis C, decompensated cirrhosis and leukoplasia at the semimucosa of the upper lip, surgically removed, 2 years ago. The lesion appeared on the upper lip semimucosa after 4 months from surgery on the old scar growing slowly, and the other injuries appeared 3 months ago.



Fig.1. Two vegetant tumoral masses in the left oral commissure, with verrucous surface and an oval keratotic plaque on the semimucosa of the upper lip



Fig.2. On the cheek mucosa multiple leukoplasic plaques and multicentric papillomatosis masses covered by a white filing and erosions

The histopathological examination of the semimucosa from upper and lower lips lesions revealed squamous epithelium with parakeratosis, intraepithelial microabscesses, acanthosis, papillomatosis, an intraepithelial and dermal acute and chronic inflammatory infiltrate and areas of moderate and severe dysplasia. On the base of pathology report our diagnosis was oral florid papillomatosis. (Fig.3,4).

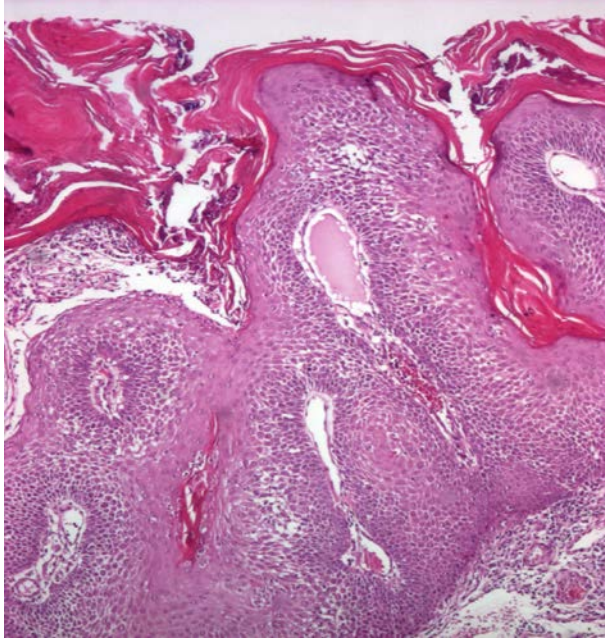


Fig.3. Squamous epithelium with parakeratosis, acanthosis, papillomatosis, an intraepithelial and dermal acute and chronic inflammatory infiltrate and areas of moderate and severe dysplasia, HE stain, x40

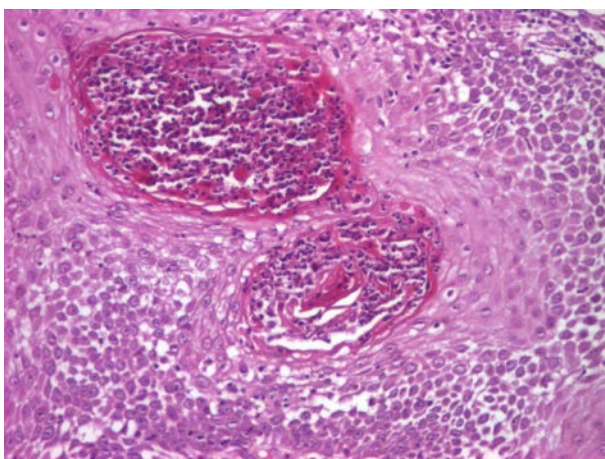


Fig.4. Intraepithelial microabscesses HE stain, x100

Considering the location and the lesions extension, patient age and the other diseases, we have used electric cautery on lesions from lips, buccal commissure and cheek mucosa.

Case 2 – Male, 71 years old, with type 2 diabetes for 28 years. Five years ago electro cautery was used on a keratotic plaque at the right foot plant. Afterwards, starting from that level, it developed an exophytic, vegetant, with verrucous surface tumor, placed on the third anterior part of the foot, extending on the inner edge (Fig.5,6). The x-ray revealed osteolytic lesions on the underlying bones.



Fig.5. Exophytic, vegetant, with verrucous surface tumor, placed on the third anterior part of the foot, extending on the inner edge



Fig.6. Exophytic, vegetant, with verrucous surface tumor, placed on the third anterior part of the foot, extending on the inner edge

The histopathological examination specified malignant squamous cells, with mature, differentiated appearance, acantholysis aspects and blister formation, with central keratin columns (Fig.7).

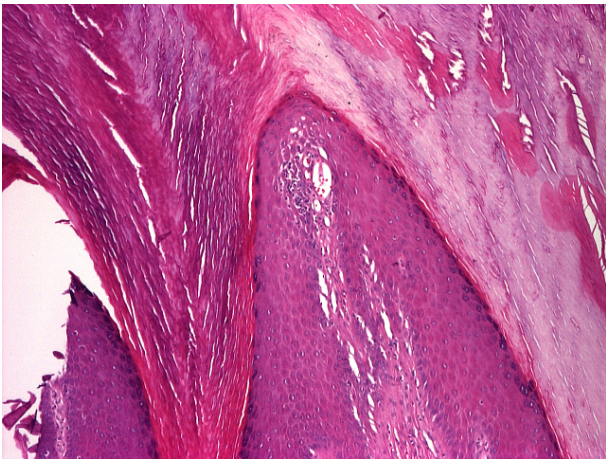


Fig.7. Malignant squamous cells, with mature, differentiated appearance, acantholysis aspects and blister formation, with central keratin columns, HE stain, x40

Tumor cells have showed a low number of malignant criteria, and morphometric, the cells have larger sizes than the ones of a conventional squamous cell carcinoma. In the periphery, the malignant cells have lightly larger nuclei, voluminous nucleoli and bulk chromatin. Mitotic activity was minimum, rare atypically mitosis were specially present in the germinal layers, massive chronic inflammatory infiltrate, predominantly composed of lymphocytes and plasma cells, intraepithelial abscess (Fig.8).

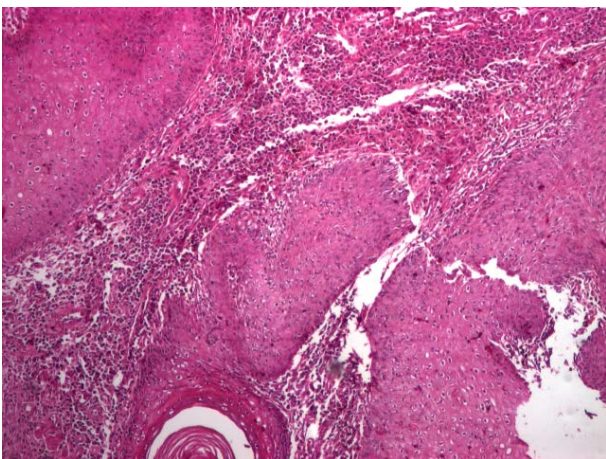


Fig.8. Intradermic massive chronic inflammatory infiltrate, predominantly composed of lymphocytes and plasma cells, HE stain, x40

After the pathology report which revealed the verrucous carcinoma, the epithelioma cuniculatum form, it was used the radical surgical treatment, the anterior leg excision.

Case 3 – Male, 40 years old, presented to dermatology examination with a vegetant

mass of 7/6 cm, placed on the right arm. The tumor surface was irregular, crossed by deep grooves, which contained inner purulent exudate (Fig.9,10).



Fig.9. Vegetant mass, placed on the right arm with irregular surface, crossed by deep grooves, which contained inner purulent exudate



Fig.10. Vegetant mass, placed on the right arm with irregular surface, crossed by deep grooves, which contained inner purulent exudate

Disease history is 10 years. First the tumor growth was slow, accelerated over the last year. After the clinical and the histopathological examination (Fig.11, 12) we have diagnosed papillomatosis cutis carcinoides. Tumor excision was practiced, with oncological safety margin.

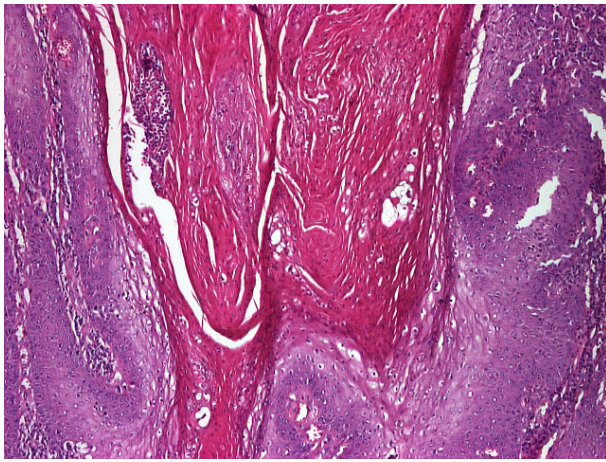


Fig.11. Hyperkeratosis, papillomatosis, acanthosis, neoplastic squamous cell looking differentiated, mature, with central keratin columns, HE stain, x40

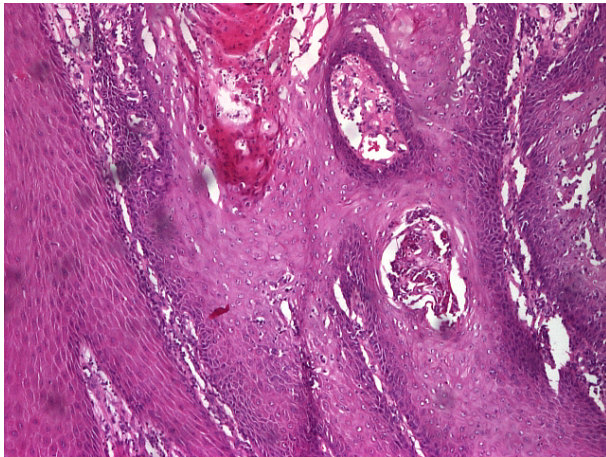


Fig.12. Hyperkeratosis, papillomatosis, acanthosis, neoplastic squamous cell looking differentiated, mature, with central keratin columns, HE stain, x40

Case 4 – Male, 44 years old, married, heterosexual, diagnosed with perianal giant condyloma Buschke-Löwenstein. Since he was 23 years old he had untreated perianal condylomas acuminati. For 5 years, the lesions gained a cauliflower appearance. The local examination demonstrated a vegetant perianal tumor by 12/8 cm, with an ulcerated, bleeding and anfractous surface, crossed by deep grooves. On palpation is detected a hard consistency and the tumor is fixed by the deep infiltration of the underlying tissues. Peritumoral are present many condylomas acuminati (Fig.13). The patient was treated on surgery department where an elliptical incision was performed, circumscribing the perianal tumor mass. During

excision, using the electric surgical knife, was noticed the tumor extension in deepness, to the ischiorectal fossa, on 7-8 cm. After tumor removal, hemostasis was made by transfixing surgical sutures and a hemostatic bud of the residual cavity was performed (Fig.14).



Fig.13. Vegetant perianal tumor with ulcerated, bleeding and anfractous surface, crossed by deep grooves, many condylomas acuminati peritumoral- preoperator view



Fig.14. Postoperator view

Histopathological examination relieved an epidermis with marked papillomatosis, acantholysis and parakeratosis hyperkeratosis. Many keratinocytes were showing a koilocytotic figure with perinuclear vacuolization and the irregularity of the nuclear contour ("raisin"-like aspect) (Fig.15). The epidermis sometimes express pseudoepitheliomatous hyperplasia changes, but those areas were not areas of clear invasion of the underlying tissue because the cell islands were limited by a basal cells layer. Within the dermis was noticed a massive chronic inflammatory infiltrate (Fig.16).

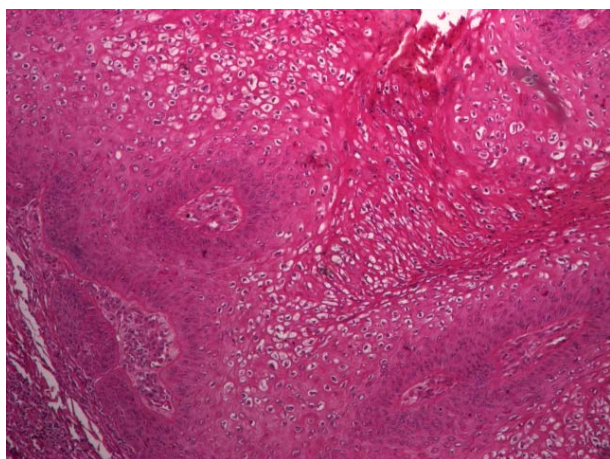


Fig.15. Epidermis with marked papillomatosis, acantholysis and parakeratosis, many keratinocytes showing koilocytotic figure ("raisin"-like aspect), HE stain, x40

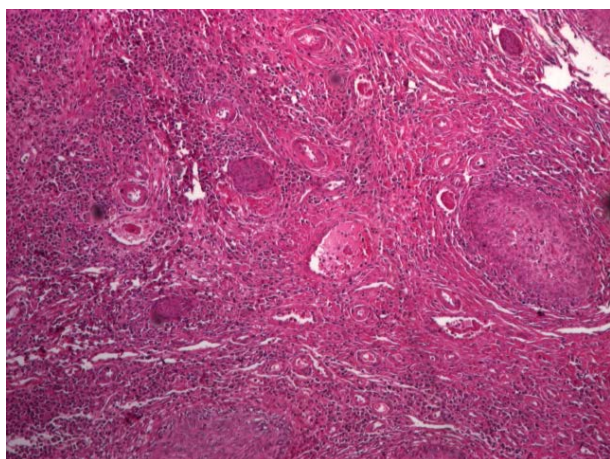


Fig.16. Intradermic massive chronic inflammatory infiltrate, predominantly composed of lymphocytes and plasma cells, HE stain, x40

Discussions

VC was first described by Lauren V. Ackerman, in the 1948, at the buccal mucosa level [3]. Reported incidence is 1-3 cases for every million people [4]. The VC appearance risk is higher in males, specially after 6th decade [5].

The etiopathogeny is not well known [6]. It seems that repeated microtrauma, chronic inflammatory process (osteomyelitis fistulas, ulcers, scars, lipoidica necrobiosis) and viruses (especially HPV-6 and HPV-11) are involved in the appearance of this type of cancer [7].

World Health Organisation admits verrucous carcinoma as a rare form of well differentiated squamous cell carcinoma with slow growing, frequent recidive and very low risk of metastasis.

Verrucous carcinoma is defined by slow and continuous grow, destroying the underlying tissues. Bones involving is present in 10% of the cases and the regional lymph node metastasis in 15% of the cases. No visceral metastasis was pointed excepting the anaplastic transformation cases after radiotherapy [8].

It is assumed that this tumor has malign macroscopic aspect and soft microscopic aspect [9]. Although, the histopathologic diagnosis is very complicated and needs one or more large biopsy [10]. The appearance is very close to that of a pseudoepitheliomatous epidermal hyperplasia with large epidermal peaks, dips in the derm. Histologically it is noted papillomatosis with acanthosis, variable degree of dysplasia and without penetration of the basement membrane.

VC may affect both skin and mucosae [11].

Regarding the verrucous carcinoma location there are distinguished the following clinical entities:

Oral florid papillomatosis (sin. Ackerman verrucous carcinoma, panoral verrucous carcinoma, oral mucosa verrucous hyperplasia) represents a form of the verrucous carcinoma with oral localization.

It was first described by Ruck and Fischer in 1960 and is about 3% of the buccal carcinomas [12].

It is a rare illness, diagnosed on 1-3 cases/year at one million people in the USA [13].

It is more frequently in males and the patients average is 60 – 70 years old.

In 1966, Kraus and Perez-Mesa have reported the first laryngeal VC cases [14].

The study of the causes of disease are: smoking, chewing tobacco, alcohol, poor oral hygiene, repeated local trauma, inadequate prostheses [15].

In 1960, based on the ultrastructural features Barnett and Hyman revealed the connection between the HPV viruses and the Ackerman verrucous carcinoma. Recent studies certified the link of oral florid papillomatosis – HPV, through detecting types 2, 3, 6, 11 HPV by PCR and Slot Blotting hybridization [16].

As contributing factors incriminated in the development of the oral verrucous carcinoma are known several types of long term oral mucosa lesions: lichen planus, leukoplasia, chronic eritematous lupus, chronic candidosis.

There were described verrucous carcinomas developed in 2-8 years from the appearance of the lichen planus associated with eritematous

and erosive oral lesions, but always containing a keratotic component [17].

Frequently affects cheek mucosa, gums, oral floor and rarely the palate, tongue and commissures. The patient presented both cheek mucosa and left commissure lesions, the last one being less frequent.

Secondary infections are frequent encountered, can occur regional lymph node inflammation.

Oral florid papillomatosis doesn't tend to regress spontaneously, often relapses after treatment and in 10% of cases evolves to a conventional squamous carcinoma, after a 10 year latent period.

Although rare, there have been reported regional metastatic cases in patients with oral florid papillomatosis [18].

Epithelioma cuniculatum (sin. Thenar verrucous carcinoma)

This tumor was described by Ian Aird and co. in 1954. It touches more frequently males (79-89% of cases) with the average age of 60 years [19]. In the disease etiology are involved 6 and 11 HPV and also the immunosuppression.

Epithelioma cuniculatum is predominant located on the anterior thenar third (53%), followed by the toes (21%) and the calcaneal region (16%) [20].

Recently there were rescribed rare cases of epithelioma cuniculatum with bilateral involvement of the legs [21].

Clinically it starts as an exophytic tumor with warty surface sometimes ulcerated or resembles a plantar wart. The tumor size can reach a diameter of 7-15 cm. The tumor infiltrates deeper tissues, having a predominantly endophytic development.

There have been described cases with involvement of plantar fascia and metatarsal bone changes [22].

In-depth it forms sinuses as rabbit burrows, appearance that suggested the name of epithelioma cuniculatum.

They are tumoral masses often centered by pseudocystic spaces that are filled with keratotic material.

A foul-smelling whitish-yellow sebum secretion can be expressed from the lesions.

Papilomatosis cutis carcinoides (also known as "Gottron's carcinoid papillomatosis" and "Papillomatosis cutis carcinoides of Gottron-Eisenlohr").

The term is used for verrucous carcinoma with another location than the plantar, oral cavity, genital and perianal region.

In 1931 Gottron used the term "cutis papilomatosis" for the papillomatous and cauliflower-like lesions from the thighs, and the full-term paternity (papilomatosis cutis carcinoides) belongs to Mischer who consider this lesions as being squamous cell carcinoma.

Papilomatosis carcinoides cutis is the rarest form of verrucous carcinoma. Can have multiple locations such as the cheeks, nose, ears, trunk, thighs, calves, buttocks, scalp, hands, etc. [23-26].

The tumor is exophytic, cauliflower-like with ulcerated and mamelonated surface, mimicking a vegetative form of squamous cell carcinoma.

A number of factors have been implicated in its development, including chronic inflammation. The tumor can develop on osteomyelitis fistulas, chronic ulcers (venous, pressure ulcer, post-traumatic ulcer), lupus scars or at the amputation stump scar.

Buschke-Lowenstein tumor (BLT)

Buschke - Löwenstein tumor represents the verrucous carcinoma which affects the genital and perianal region and is the most frequent form of VC. Represents 5 to 24% of penile cancers and occurs most often in men aged 30-50 years.

BLT is a rare tumor, infiltrating and destructive, slow-growing with a cauliflower-like morphology. The incidence of this tumor is estimated to be 0.1% in the general population.

It affects primary the genital or perianal region. It is preferentially seen in men and immunocompromised patients (the M/F sex ratio 3:1).

This tumor has been described in 1886 by Buschke on the glans penis and in 1925, Buschke and Löwenstein called it "carcinoma-like condyloma acuminatum". Later in 1965 Dawson et al. described the first case with anorectal involvement. It occurs most often on the glans penis, although it may also develop on the preputial mucosa.

Much less often BLT is located on the vulva, vagina, cervix in women, in the scrotum in men and may involve the perianal region in both sexes.

As regards its etiology, the HPV-6 and HPV-11 are the most common types identified but may be associated oncogenic types 16,18,31,33.

BLT is always preceded by preexisting lesions (condyloma acuminatum), and the immune system is probably suppressed.

Other factors implicated in the BLT development include poor hygiene, chronic irritation, promiscuity, and immunosuppression

determined by infections such as HIV and HTLV-1.

In our patient, BLT was located in the perianal region. The onset was characteristic by condyloma acuminatum - like papillomatous lesions. After 18 years the tumor had taken cauliflower-like appearance.

Despite the benign histological appearance of BLT, it presents local malignancy, destroying adjacent tissues. In our patient the tumor has infiltrated the ischioanal fossa on about 7-8 cm depth, but fortunately did not emerge anal stenosis or rectal strictures despite the long-term evolution.

If the tumor is located in female genital area, it can infiltrate the pelvic organs.

In our case the main problems of differential diagnosis were verrucous tuberculosis (diagnosis was disproved by histopathology) and typical squamous cell carcinoma. The history of disease, histopathological findings of the tumor and especially the absence of metastases were excluded this latest diagnosis.

Malignant transformation occurs in a proportion of 30-56% and the premonitory signs are represented by the rapid growth in size of the tumor, local pain, and bleeding.

The risk of recurrence after surgical excision is 60-66% at 10 months after treatment, reason why it is necessary to monitor our case treated surgically.

Treatment. Complete surgical excision with safety margins is the treatment of choice. In three of the four cases presented we have performed radical excision followed by favorable development. Incomplete resection can accelerate tumor growth [33].

Walvekar et al. studied 101 cases of oral verrucous carcinoma and found an excellent prognosis after surgical excision [34].

Radiotherapy is considered by many practitioners to be contraindicated in verrucous carcinoma management because of the risk of anaplastic transformation.

In their study, Perez et al. [36] shows that after radiotherapy in 10.7% of cases is recorded anaplastic transformation.

However, radiotherapy combined with chemotherapy (Vinblastine, Methotrexate and Bleomycin) is an effective alternative for inoperable CV from cephalic region [37]. It can be also indicated as a complementary therapy in the event of incomplete surgical excision [38].

According Heinzerling et al. favorable effects have been reported after CO₂ laser ablation and then applying of topical imiquimod [39].

Other treatments used with varying degrees of success are: cryotherapy, electrocautery, topical or systemic chemotherapy (bleomycin, 5-fluorouracil, cisplatin, methotrexate), intralesional or systemic interferon alpha [40] and photodynamic therapy [41].

According to a recent article, intra-arterial administration of methotrexate resulted in complete remission of tumors in all 15 patients studied, without recurrence at 43 months after intervention [42].

Regardless of the therapeutic methods used, there is consensus regarding the priority of making surgical excision.

Unfortunately, given the size of the tumor is often necessary a graft reconstruction after radical excision [43].

Conclusions

-verrucous carcinoma is characterized by slow-growing and continuous invasion of underlying tissues;

-to establish the diagnosis of verrucous carcinoma is required to corroborate clinical data with histological appearance and with evolutionary aspect of the tumor;

-treatment of choice is surgical excision, but given the increased risk for recurrence, the patient should be examined quarterly until healing is complete.

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