

Acral Verrucous Carcinoma

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ABSTRACT: Introduction. The verrucous carcinoma is a type of squamous carcinoma that is highly differentiated, relatively uncommon, locally aggressive, with slow growth and minimal metastatic potential. Clinical case. A 48-year old man was admitted to the Dermatology department of the Craiova Hospital for a round-oval tumoral mass that was hyperkeratotic, with central ulceration, covered by a hematic crust, approximately 1.5cm in size, localized at the distal phalanx of the third finger left hand, with perilesional edema and erythema. The wart-like lesion appeared 8 months beforehand, which the patient has traumatized repeatedly in the last 2 months. The histopathological examination confirmed the diagnosis of verrucous carcinoma. The X-ray examination revealed external margin osteolysis of the distal epiphysis in the third finger, left hand. The patient was transferred to the Plastic surgery department where the distal phalanx of the third finger, left hand was amputated. Discussions. Risk factors for the development of verrucous carcinoma are HPV infection, carcinogenic chemicals, smoking, chronic inflammation, repeated trauma, etc. Diagnosis is suspected by clinical appearance and confirmed histopathologically. The treatment of choice is surgical excision due to the high risk of recurrence and local invasiveness, and in the case of an advanced tumor with acral localization, amputation is preferred, as is our case. Conclusions. Verrucous carcinoma is a type of squamous carcinoma that is highly differentiated, with slow and continuous invasion of the underlying tissues. In order to establish the diagnosis of verrucous carcinoma, it is necessary to corroborate the clinical examination with histopathological and evolutionary examinations. The treatment of choice is surgical excision, but given the increased risk of recurrence, the patient should be evaluated periodically until complete healing. Our case is interesting by localization and rapid evolution with the invasion of the underlying tissues.

KEYWORDS: Verrucous carcinoma, acral location, etiopathogenesis, treatment.

Introduction

The verrucous carcinoma is a type of squamous carcinoma that is highly differentiated, relatively uncommon, locally aggressive, with slow growth and minimal metastatic potential [1].

It can affect the skin as well as the mucous membranes [2].

Depending on its location, the verrucous carcinoma is also known in medical literature as florid oral papillomatosis/Ackerman verrucous carcinoma (localized in the oral cavity), epithelioma cuniculatum/plantar verrucous carcinoma, the giant condyloma of Buschke and Löwenstein (affecting the genital or perianal region), papillomatosis cutis carcinoides (the verrucous carcinoma occurring in other locations) [3-6].

In 1948, Ackerman first described the verrucous carcinoma (VC) of the oral cavity as a clinical and pathological variant of the well-differentiated squamous cell carcinoma [7].

Aird et al. have described cutaneous VC in 1954, naming it epithelioma cuniculatum due to its characteristic crypt-like spaces in the histopathological report [8].

VC usually occurs in the fifth through sixth decades of life although it was noticed in patients that were younger than 16, more common in men than in women (sex ratio 5.3/1.2) [9].

The incidence is one to three cases for every 1 million persons [10].

Case report

A 48-year old man was admitted to the Dermatology department of the Craiova County Hospital with a round-oval tumor mass that was hyperkeratotic, with central ulceration, covered by a hematic crust, approximately 1.5cm in size, localized at the distal phalanx of the third finger of the left hand, with perilesional edema and erythema (Fig.1,2).

The wart-like lesion appeared 8 months before presentation to the hospital.

The patient mentioned that he had cut the tumor with his nail clippers (repeatedly traumatizing the lesion) and applied Duofilm.



Fig.1. Acral verrucous carcinoma, localized at the distal phalanx of the third finger left hand, with perilesional edema and erythema



Fig.2. X-ray reveals external margin osteolysis of the distal epiphysis in the third finger, left hand

Past medical history: unremarkable

Social history: smoker, 20 cigarettes a day for 15 years

Physical examination: phototype III, BMI 32.65 (grade I obesity)

Laboratory tests revealed normal CBC, GOT, GPT, creatinine, GGT, glucose, blood urea nitrogen, urine analysis, ESR.

X-ray revealed external margin osteolysis of the distal epiphysis in the third finger, left hand.

Soft tissue ultrasound: the left elbow pit and axilla without adenopathy.

We have excised the tumoral mass which was followed by curettage while noticing the presence of fragile tissue that extended deeply until reaching the bony structure of the phalanx.

Histopathological report: fragment covered by epidermis with marked keratinization and exulcerated areas, acanthosis, papillomatosis, marked pseudoepitheliomatous hyperplasia (Fig.3), solid invasion front, with parakeratosis centers corresponding to foci of typical aspect of an well-differentiated squamous carcinoma, minimal atypia and rare atypical mitosis (Fig.4).

At the deep limit of the fragment it is noticed a very abundant inflammatory infiltrate with lymphocytes and plasma cells and dermis edema, dilated, tortuous blood vessels within the dermal papillae (Fig.5).

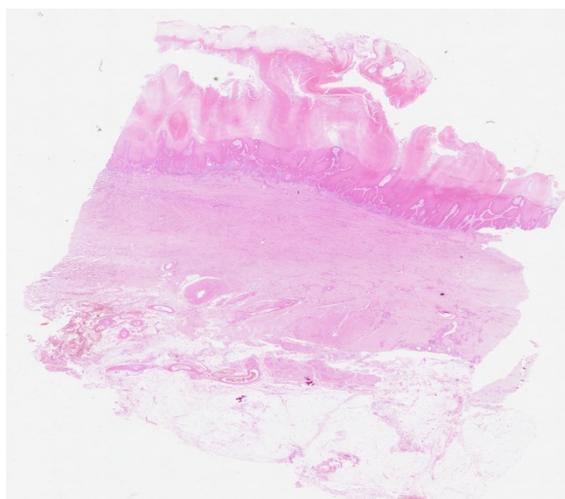


Fig.3. Acral verrucous carcinoma: epidermis with hyperkeratosis, papillomatosis, hypergranulosis, acanthosis, col. HE, whole scan

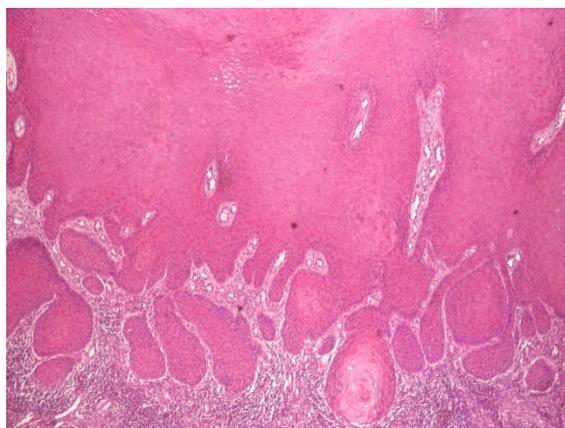


Fig.4. Acral verrucous carcinoma: solid invasion front, parakeratosis centers, Col. HE, ob X5

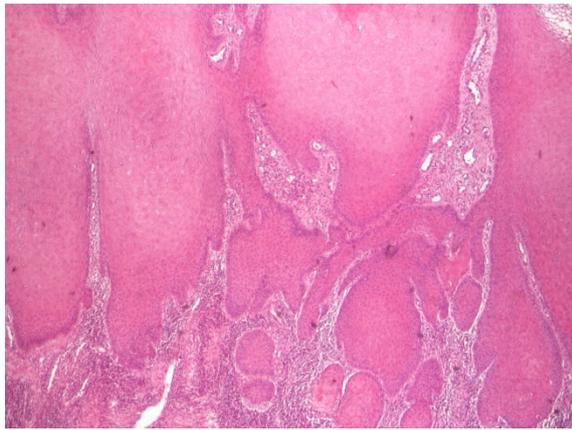


Fig.5. Inflammatory lymphocytic infiltrate at the level of the invasion front and dermis edema, dilated, tortuous blood vessels within the dermal papillae, Col. HE, ob X5

Given that the lab and imaging tests corroborated the clinical exam, we diagnosed the patient with *Acral verrucous carcinoma*.

The patient was transferred to the Plastic surgery department where the distal phalanx of the third finger, left hand was amputated (Fig.6).



Fig.6. Clinical aspect after the amputation of the distal phalanx of the third finger

The repeated histopathological examination from the tumour in toto, following radical surgery, reconfirmed the diagnosis of verrucous carcinoma.

The postoperative outcome was favorable. The patient will be clinically examined quarterly

over the next three years, although the probability of recurrence after amputation is minimal. We will recall the patient and explore the regional lymph node groups each semester.

Discussion

The etiopathogenesis of VC is not completely known [11].

One theory mentions the HPV infection, especially for the following locations: the oral cavity, the anogenital area, the foot and a small subset of cutaneous verrucous carcinoma [12].

Chemical carcinogenesis for oral lesions is also considered, such as the one induced by smoking, chewing tobacco and betel nuts [13].

Another theory mentions the role played by chronic inflammation in the pathogenesis of VC. Schistosomiasis was associated with urinary bladder VC [14].

HPV may play a role in developing VC. Types 6 and 11 are the ones most frequently associated with anogenital lesions [15].

In the case of plantar lesions, the reported types were 16 and 11 [16]. HPV 33 was described in a case of VC arising on the scalp [12].

Garven et al. have described a case of VC of the foot which was investigated for subtypes 11,16,18 through DNA in situ hybridization, with positive results for subtypes 11 and 18 [17].

Viral carcinogenesis is most probably caused by the suppression or mutation of the p53 gene which is responsible of tumor cell suppression.

Yet only the presence of a viral infection is not enough to consider it a certain cause of malignant transformation because most HPV-infected patients never develop cancer. Consequently, some cofactors are needed [18].

Chronic inflammation seems to play a role in developing VC. For example, VC can arise in a decubitus ulcer or on areas chronically affected by hidradenitis suppurativa [15,19].

Moreover, lichen sclerosus can be a risk factor for developing penile VC [20].

Similarly, VC of the oral cavity has been described in some patients with ulcerative lichen planus and chronic candidiasis.

Oral VC was reported in patients who chewed or inhaled tobacco and betel nuts or in chronic alcohol consumers.

The lesions developed in the areas where tobacco was repeatedly placed in the mouth.

Other risk factors may be immunodepression, poor dental care, inadequate prostheses and low socioeconomic status [21].

In this multi-step process, inflammation seems to play a role both in the initiation as well as in the progression of cancer.

The important components of this association are the cytokines and chemokines produced by the activated innate immune cells which stimulate the growth and progression of tumors.

Moreover, the genetical susceptibility and the interactions between genes and the environment play an important role.

Mechanical trauma induces carcinogenesis through two mechanisms.

Repeated irritation may cause DNA damage and may induce cancer.

This statement is supported by the increased activity of poly (ADP-ribose) polymerase in cases of chronic trauma.

The second proposed mechanism is that inflammation triggers the release of chemical mediators like cytokines, prostaglandins, TNF which lead to oxidative stress.

The latter may induce genetical and epigenetical modifications that inhibit DNA repair, modify transcription factors, prevent apoptosis and stimulate angiogenesis, factors responsible for the carcinogenetic process [22,23].

The positive diagnosis of VC is clinically suspected and is confirmed by histopathological examination.

Clinically, VC takes on the appearance of a white-gray verrucous papula/plaque.

It evolves slowly from a discrete focal lesion to a deeply penetrating tumor mass.

Slow growth and confusion in early stages may lead to delayed diagnosis.

The histopathological diagnosis is difficult and needs one or more broad biopsies going into depth [2].

Hyperkeratosis and parakeratosis, soft verrucous acanthosis with enlarged key-shaped papillae and prominent perilesional inflammatory infiltrates are present.

Epidermal hyperplasia presses on the basement membrane and the dermis, but the basement membrane remains intact.

Cellular atypia is not outstanding and keratin plugs are not frequent.

Mitosis and dyskeratotic cells can be seen at the base of the lesion [24].

Depending on the clinical aspect and location, the differential diagnosis is made with keratoacanthoma, cutaneous carcinoma, viral verruca, amelanotic melanoma, histoplasmosis, secondary syphilis, white spongy nevus (for the

oral location), Darier's disease and chronic erythematous lupus lesions, pyoderma vegetans [2].

Evolution and prognostic

VC grows slowly and continuously.

Morbidity results from the local destruction of skin and soft tissues and occasionally, from the perineural, muscular and even bony invasion.

Skin infiltration is present in 10% of cases.

Regional lymphatic ganglia metastasis is rare as found in 5% of cases, without any data published for hand lesions as is our case.

The VC has a high risk of local relapse.

No matter which treatment is used, the rate of recurrence varies from 30% to 50% and is not usually the result of incomplete surgical interventions [25,26].

Treatment

The main purpose is local tumor control since VC metastases are rare but the tumor has a local invasive effect with a high risk of recurrence.

The treatment of choice is the complete surgical excision with safety margins.

Residual defects can then be covered with a skin graft [27].

Mohs micrographic surgery is preferred because it reduces the rate of recurrence and it has a 98% cure rate [28].

Other therapeutical options include topical chemotherapy, electrocauterization, cryotherapy and laser therapy [29].

Imiquimod and cidofovir therapy is taken into consideration given the association with HPV [16].

Radiotherapy is not recommended.

Although it was curative in some reports, it can lead to carcinoma anaplastic transformation.

In a study, Perez et al. have shown that the anaplastic transformation takes place in 10.7% of cases after radiotherapy [30,31].

Yet some authors have described the VC response to radiotherapy as comparable to that of classical SCC [squamous cell carcinoma]. Jothirmayi R et al. have studied 53 patients with oral VC. 42 patients underwent primary radiotherapy and 11 patients underwent primary surgery as treatment.

Complete response to radiotherapy was achieved in 76% of patients and partial response in 24%.

None of the 16 VC patients that had recurrences after radiotherapy has shown any anaplastic transformation features [32].

Partial or radical amputations are necessary in case of an aggressive, invasive tumor, similar to our case or in case of tumor recurrence after incomplete excisions.

Other authors have reported the curative treatment of VC with intra-arterial administration of methotrexate or with photodynamic therapy using topical application of 5-aminolevulinic acid [33].

Chaw-Ning Lee et al. have published in 2018 a case of VC of the lip, resistant to other topical treatments and where the patient refused the surgical treatment, that was systemically treated with acitretin (20mg/day) one day after CO2 laser ablation.

The dose was increased to 30mg/day on the second week of treatment.

No tumor was detected at 15 months of follow-up and the patient continued to take acitretin [34].

Beneficial effects were also noticed after CO2 laser ablation and topical imiquimod [35].

Some authors perceive immunotherapy with ipilimumab or with anti-PD-1 (nivolumab and pembrolizumab) as a future therapeutical alternative [36].

Conclusion

The verrucous carcinoma is a variant of the well-differentiated squamous cell carcinoma, with slow and continuous invasion of underlying tissues.

In order to establish the diagnosis of verrucous carcinoma, it is necessary to corroborate the clinical exam, the histopathological report and the evolution of the disease.

The treatment of choice is surgical excision but given the high risk of recurrence, the patient has to be regularly evaluated until the cure is complete.

Our case report is interesting as a result of the location and the rapid evolution leading to the invasion of the underlying tissues.

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