PENILE INVASIVE SQUAMOUS CELL CARCINOMA ARISING ON BOWENOID PAPULOSIS - CASE REPORT

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Case presentation

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Abstract

Penile squamous cell carcinoma (PSCC) is a rare type of cancer that occurs in the penis. It usually appears after the age of 50 years, is more common in uncircumcised men with phimosis, and is often associated with high-risk human papillomavirus (HPV) infection. PSCC can develop on pre-existing genital lesions such as vulvar intraepithelial neoplasia, Bowenoid papulosis, and other precancerous conditions.

We present a case of a 56-year-old man with a history of Bowenoid papulosis who developed an invasive penile squamous cell carcinoma. Circumcision was performed with a good postoperative outcome, and the patient has been followed for three years with no complications.

In conclusion, persistent high-risk human papillomavirus infection in a smoker, uncircumcised man can cause squamous cell carcinoma.

Introduction

Penile squamous cell carcinoma has a high degree of malignancy and localizes predominantly on the glans, the balanopreputial fold or the foreskin’s inner mucosa. It usually occurs in uncircumcised males after 50 years, commonly with phimosis.

Human papillomavirus (HPV) types 16 and 18 are considered to be high-risk oncogenic HPV associated with genital intraepithelial neoplasia and cancer. For penile cancer, 22 types of HPV have recently been detected. Its prevalence in cervical cancer is 90% compared to 50% in penile cancer, for both HPV type 16 being common. Other proposed etiological factors include tobacco smoking, sexual promiscuity, poor hygiene and lichen sclerosus.

According to some recent retrospective studies on patients with psoriasis treated with PUVA therapy, squamous cell carcinoma has been reported in an increased number of patients, highlighting the role of ultraviolet radiation in the occurrence of this type of cancer.

Bowenoid papulosis is a premalignant anogenital disorder, induced by HPV. In penile localization, this intraepithelial neoplasia, although very rare,

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may evolve into invasive squamous cell carcinoma, which has also happened in our patient.

Case report

A 56-year-old man without other specific medical history was referred to our department with an infiltrated erythematous plaque, located on the mucous membrane of the foreskin.

He was initially evaluated for genital papillomatosis on the mucosa of the foreskin six years before. After one year of evolution, all lesions were treated by electrocautery. The lesions have relapsed after a few months but have been neglected by the patient. Six months later, biopsy and electrocautery of several brown papules from the foreskin were done. The result of the histopathological examination revealed acanthosis, nuclear atypia, mitosis and cellular diskretosis. In addition, areas of carcinoma in situ were identified.

The patient denied history of sexually transmitted infections and reported being in a monogamous relationship with his wife from 20 years of age. He was a heavy smoker with 30 pack-year smoking history. The patient was otherwise healthy and family history was noncontributory.

Physical exam was significant for a 4 x 2 cm infiltrated plaque, with erythematous and erosive surface, on the inner foreskin, 1 cm from the coronal sulcus, surrounded by leucoplastic mucosa (Fig. 1) and several isolated papules. Systemic examination findings were normal. The bilateral inguinal regions appeared normal.

Laboratory findings showed elevated serum levels of erythrocyte sedimentation rate (20/40 mm). Syphilis and HIV tests were negative.

Circumcision was performed with very good postoperative evolution (Fig. 2). The patient has been followed-up for three years, during which no problems appeared.

The histopathological examination revealed a poorly differentiated squamous cell carcinoma, invasive until the striated muscle fibers (Figures 3 & 4).

The immunohistochemical exam revealed positive staining of Cytokeratin 34 beta E12, p63 and ki67 positive diffuse in the tumor proliferation (Fig. 5a-c).

Discussion

In France, the incidence of penile cancer is 1/100,000 inhabitants and commonly affects men between 50 and 70 years of age. In the United
In our patient, there were at least three risk factors: lack of circumcision, HPV infection and smoking.

Penile squamous cell carcinoma may develop on the following precancerous lesions (1, 3, 4):

- **Erythroplasia of Queyrat (EQ)** is now generally considered to be Bowen's disease of the mucous membrane. It is a squamous cell carcinoma *in situ*. Several factors may participate in the development of EQ such as: oncogenic HPV types (including HPV 16 and HPV 18) and poor hygiene. Lesions in EQ are usually sharply defined plaques, which have a smooth, velvety, bright red appearance. Subsequently, in the invasive stage, the lesion becomes infiltrated and the edges are accentuated, with a verrucous surface. Bleeding or ulceration of the surface are also warning signs.

- **Penile cutaneous horn** - the name is suggested by the clinical appearance of a miniature horn. It appears mainly on the skin, but cases of penile horn on the penile glans, balanopreputial sulcus or in the inner foreskin have also been described. In one third of cases, histopathological examination revealed signs of malignancy.

- **Genital lichen sclerosus** is a chronic disease of unknown etiology involving the genital mucosa. The relationship with penile squamous cell carcinoma is still being discussed. It seems that phimosis secondary to lichen sclerosus is the most important risk factor for penile cancer.

- **Genital leukoplakia** can be located on the glans penis or on the inner foreskin. It is rarely encountered and usually complicates a genital lichen sclerosus almost exclusively in uncircumcised boys and men. Squamous cell carcinoma occurs more commonly in female genital leukoplakia than in men.

- **Pseudoepitheliomatous, keratotic micaceous balanitis** - this rare idiopathic condition is defined by clinical and histological criteria. It primarily affects uncircumcised men over 60-year-old. Patients develop well circumscribed, hyperkeratotic lesions with a lamellated (micaceous) appearance. The histopathological examination highlights acanthosis, papillomatosis and hyperkeratosis. There is a dermal superficial perivascular and periadnexal lymphocytic infiltrate. There is a risk of malignant transformation into verrucous carcinoma.

- **Giant condyloma accuminatum (Bushke-Lowenstein tumor)** is clinically characterized by warty, exophytic growths, evolving into slowly invading tumors (5). Untreated, it can penetrate deeply into the underlying tissue (cavernous bodies, urethra). The involvement of human papillomavirus type 6 or 11 DNA has been...
demonstrated with molecular hybridization techniques. Malignant transformation has been reported in 20 to 40% of cases.

- **Bowenoid papulosis (BP)** – Clinically, it manifests as multiple, warty, red-brown papules, similar to condyloma acuminatum but histological examination favors squamous cell carcinoma *in situ*. Bowenoid papulosis occurs primarily in sexually active young people, with a slight female predominance, and it is commonly associated with HPV 16 (in 80% of cases), HPV 18 and HPV 31. Lesions are isolated or confluent en nappes with imprecise delimitation. In women, they are located on the vulva and/or the perianal area, while in men, papules occur primarily on the penile shaft or mons, although they can also occasionally arise on the glans and prepuce. However, the evolution to invasive carcinoma is more common in elderly women or in the context of immunosuppression.

It is now well documented the oncogenic potential of certain types of HPV in the etiology of cervical cancer (6). Most cervical cancers arise at the squamo-cylinder junction area due to the fact that this area has mechanical and immunological fragility (low density of Langerhans cells).

Currently, there is a large number of oncogenic HPV (HPV 16, 18, 31, 32, 33, 35, 45, 51, 52, 56, 58, 59, 68, etc). The risk of malignant transformation is higher in patients with HPV-16 and HPV-18 infection and medium in those infected with HPV 31, 33 and 51.

HPV infection is responsible for the development of preneoplastic lesions and of certain types of squamous cell carcinoma (3-6):
- vulvar intraepithelial neoplasia (VIN), vulvar Bowen’s disease, vulvar bowenoid papulosis;
- penile intraepithelial neoplasia or (PIN), erythroplasia of Queyrat, penile bowenoid papulosis;
- vaginal intraepithelial neoplasia (VAIN);
- cervical intraepithelial neoplasia – CIN (CIN 1 - mild dysplasia; CIN 2 - Moderate dysplasia; CIN 3 - severe dysplasia; carcinoma *in situ*);
- giant condyloma accuminatum (Bushke-Lowenstein tumour);
- cervical cancer;
- penile cancer.

A large number of studies have shown that the intraepithelial neoplasia (IN) - IN 1 (low dysplasia) ≥ IN 2 (moderate dysplasia) ≥ IN 3 (severe dysplasia, carcinoma *in situ*) are the most common lesions of the cervix and anus, with no involvement of the penis and vulva. In these regions, oncogenic HPV infections induce from the beginning IN 3 (Bowen’s disease and Bowenoid papulosis) (7).

In addition, vulvar epidermoid carcinomas occur in most cases (70%) on precancerous non-HPV-induced lesions (8).

The molecular mechanisms of carcinogenesis induced by HPV have not been completely elucidated. However, there are a few things mentioned such as the integration of the viral genome into a host cell chromosome. As a result of this process, the synthesis of protein E2 is disrupted, while proteins E6 and E7 are synthesized as a priority (9). The E6 and E7 proteins also appear to have p53- and Rb-independent activities.

The HPV E6 protein can associate with the p53 tumor suppressor protein. This interaction promotes the degradation of p53 by the ubiquitin-proteasome pathway. The cell loses its ability to stop during the G1 phase of the cell cycle, involving natural DNA repair systems (e.g., excision repair). The p53 protein inhibits cellular proliferation, and after repair, the cells retake their cycle. If DNA damage is very important, then p53 induces programmed cell death, by promoting the Bax gene and diminishing the expression of the Bcl2 gene (10, 11).

Binding of the human papillomavirus (HPV) E7 oncoprotein to the p105RB protein causes release of the E2F transcription factor. The overexpression of this factor drives cells inappropriately into the S phase, leading to genomic instability.

The incidence of penile cancer is much higher in men whose female partner has cervical carcinoma *in situ*, which highlights the importance of oncogenic, high-risk HPV infection. In addition, the risk of cervical carcinoma in wives of men with penile carcinoma is about five times higher than in other women.

Also, multiple studies have clearly shown that women with persistent infection with high-risk oncogenic HPV types have a 116-fold higher risk of CIN 3 compared with unaffected women. All these arguments fully justify the necessity of examining (clinical, colposcopy, virological) the female partners of any man with penile cancer (12).

Clinically, squamous cell carcinoma most commonly appears as an infiltrated and/or ulcerated plaque, as in our patient, but also as a vegetative proliferation. Over time, in patients with associated phimosis, infection and tumor necrosis occur. In addition to penile squamous cell carcinoma, leukoplakia, lichen sclerosis, erythroplasia of Queyrat or bowenoid papulosis, which are premalignant penile lesions, may also be present (13).

Squamous cell carcinoma of the penis is most commonly located on the glans penis (48% of cases), followed by prepuce (21% of cases), glans penis and prepuce (9%), coronal sulcus (6%), and shaft (2%) (14).

The spread of penile cancer usually occurs in depth (invasion of cavernous bodies, urethra), regional lymph node metastasis (approximately
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with five-year survival rates of 93%.

Outcomes are good in the absence of lymph node metastases, penile cancer is 70-80% of cases. Outcomes are
occurs in bones, brain, and skin (15).

The following factors were associated with poor prognosis (1):
- inappropriate initial treatment;
- size of the tumor;
- low-grade and undifferentiated tumors;
- presence of metastases.

The overall 10-year survival rate for patients with penile cancer is 70-80% of cases. Outcomes are good in the absence of lymph node metastases, with five-year survival rates of 93%.

The treatment of penile cancer is based on the tumor size and extension, tumor location, histologic grade, patient age etc (16).

Once the tissue diagnosis is confirmed, penile tumors may be successfully treated with surgical excision (circumcision, partial or total penile amputation), Mohs micrographic surgery, radiotherapy with iridium, chemotherapy (17).

The location of the tumor in our patient allowed us to perform circumcision, with very good post-operative outcome. After that, the patient was directed to the Department of Oncology for chemotherapy.

Prophylaxis – There are epidemiological studies that support the major role of circumcision in the first childhood in the prevention of penile squamous cell carcinoma.

Regarding the prevention of oncogenic HPV infection, this is difficult to achieve due to their high prevalence and especially the presence of latent infections. The most recent data show that 20-30% of the sexually active people are infected with HPV, but only 1-2% of them have visible clinical manifestations. What is more important is that we do not currently have any treatments that can definitely cure HPV. Although treatment can result in the disappearance of clinical lesions, this does not mean that virusological eradication is achieved. Finally, condom use reduces the risk of HPV infection without providing total protection (18, 19).

There is no doubt that HPV infection represents a major public health problem with a very high impact from the psychosexual point of view. In an optimistic point of view, we hope that vaccination will prevent cervical cancer and will indirectly result in a reduction of patients with penile squamous cell carcinoma.

Conclusion

Persistent high-risk human papillomavirus infection in a smoker uncircumcised man can cause squamous cell carcinoma.

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Patient consent obtained.

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