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Erythroplasia of Queyrat Treated with 5% Imiquimod Cream — Case Report Emphasizing the Role of Human Papilloma Virus Testing in a Clinical Setting

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ABSTRACT

Background: Anogenital premalignancies and malignancies often affect females and males, and human papillomavirus infection plays a crucial role in their etiopathogenesis. These lesions are very important and represent an immense public health burden. **Case presentation:** A 78-year-old Caucasian male presented to the Dermatology Unit for persistent, slowly progressing, well-demarcated, erythematous plaques on the glans penis, observed by the patient 18 months prior to the consultation. Variable topical treatments were applied, with no improvement and with the denial of a punch biopsy. A clinical diagnosis of erythroplasia of Queyrat was established and the test for HPV revealed an association with subtype 16 (which excluded other benign inflammatory conditions). Positive results were obtained after 4 weeks of topical application of 5% imiquimod cream, once daily, 5 times a week. **Conclusion:** Erythroplasia of Queyrat should be diagnosed in a non-compliant patient based on the clinical picture and HPV testing even in the absence of a biopsy, and a non-surgical treatment should be initiated immediately.

Keywords: erythroplasia of Queyrat, treatment, human papilloma virus

BACKGROUND

Anogenital premalignancies (and malignancies) often affect both females and males, and human papillomavirus (HPV) infection plays a crucial role in their etiopathogenesis. These lesions are very important and represent an immense public health burden. In males, the most frequent anogenital pre-malignancies are Bowen's disease, bowenoid papulosis and erythroplasia of Queyrat (EQ), all

representing forms of squamous intraepithelial neoplasia. Although from a histopathological point of view these 3 entities are indistinguishable, from a clinical point of view they have very dissimilar features.[1,2]

High-risk HPV types have been linked with genital carcinomas and premalignant conditions. Very few studies have been carried out on the link between EQ and HPV infection. While some of these studies have detected HPV 18 subtype in association with EQ, others did not find EQ to be positive for the presence of HPV-DNA.[3,4]

We present here the case of a 78-year-old Caucasian male who presented to the Dermatology Unit for persistent, slowly progressive erythematous plaques on the glans penis. Because the patient was non-compliant and refused the biopsy, a clinical diagnosis supported by an HPV test was performed and treatment was established accordingly.

CASE REPORT

A 78-year-old Caucasian male presented to the Dermatology Unit for persistent, slowly progressing, well-demarcated, shiny and erythematous plaques on the glans penis. He reported the first lesion 18 months prior to the consultation, accompanied by pruritus. Slow progression of the lesions was noted despite topical steroid and antifungal treatments prescribed by the general practitioner for weeks. He was in good general health state, with no drug intake, no history of allergy, and no other complaints.

The patient agreed to the publication of his data and the institution where the patient had been admitted, approved the publication of the case.

The potassium hydroxide (KOH) test was negative, and no growth was observed in the wound culture and fungal culture, excluding a mycotic infection. He was against the idea of a 4 mm punch biopsy and of any type of surgery, despite the information regarding the precise diagnosis and a correct therapeutic approach and follow-up. However, the patient underwent a single brush cytology smear of the penile mucosa and was found to be positive for HPV subtype 16. Based on the clinical aspect, long evolution of the lesions, no previous response to topical steroids and positive HPV test, a presumptive diagnosis of erythroplasia of Queyrat was formulated, and topical treatment with 5% imiquimod cream was started once daily, 5 times a week, for the following 4 weeks. Positive results with minor side effects (local pain, itching, inflammatory local reaction) were achieved. At the 6-month follow-up there was no evidence of disease recurrence. He was well monitored, with clinical control at six-month intervals for the following two years, and no recurrence was diagnosed.

DISCUSSION

Primary malignant penile cancer has an incidence of less than 1 per 100,000 males.[5] Among this category, squamous cell cancer represents more than 95% of cases of penile cancer, the rest being represented by malignant melanoma and rarely by basal cell cancer of the penis.[6]

EQ is described as a variant form of squamous cell carcinoma in situ, also named squamous intraepithelial neoplasia; up to 30% of EQ cases progress to invasive squamous cell carcinoma.[7] The lesion was initially described in 1911 by L. Queyrat as "erythroplasie du gland", and that is why it is known in the literature as erythroplasia of Queyrat. The etiology of EQ is linked to HPV infection (8, 16, 39 and 51 subtypes), but risk factors have also been described (social and cultural habits, hygienic procedures, religious practices, heat, friction, trauma and co-infection with human papillomavirus type 8.[7–9]

EQ is characterized clinically by the presence of unique or multiple well-demarcated, velvety, shiny, intense red plaques on the glans penis, the foreskin, or the urethral meatus of elderly male patients.[7] These are clinical features in favor of EQ.

Various other benign conditions may affect the penile skin: different types of balanitis, Zoon's balanitis, eczema, lichen planus, lichen sclerosus, psoriasis. Zoon's balanitis or balanitis circumscripta plasmacellularis lesion (plasma cell balanitis) presents clinically as a unique, shiny, red-to-orange plaque of the glans or prepuce of an uncircumcised male.[10] Recent reports have drawn attention to the possibility of association of Zoon's balanitis and EQ.[11,12] However, neither Zoon's balanitis nor the other benign conditions are associated with HPV infection.

Biopsy (and histopathological examination) is mandatory for certifying the diagnosis, establishing the histological subtype (an important factor for predicting prognosis and metastatic risk) and choosing the appropriate treatment. However, in this case the patient declined any type of surgical procedure, including a punch biopsy, but accepted a single brush cytology smear of the penile mucosa. The cytology was found to be positive for HPV subtype 16, which supported the diagnosis of EQ since all the other penile benign conditions are negative for HPV.

Standard therapy consists in surgical removal (total glansectomy), with the lowest recurrence rate of 2%.[13] More recently, non-invasive alternative procedures have been successfully used such as photodynamic therapy, la-

ser therapy, cryosurgery, topical therapy with 5-fluorouracil or 5% imiquimod cream.[14,15] Imiquimod is a topically active immunomodulator agent, chemically described as a heterocyclic imidazoquinolinamine drug that binds to toll-like receptor (TRL) 7 and 8, followed by the release of pro-inflammatory cytokines including interferon (IFN)-alpha, tumor necrosis factor (TNF)-alpha and interleukin (IL)-12, and the activation of cytotoxic functions of CD8+ cells.[16,17] It also induces apoptosis and binds to adenosine receptors (ADORAs) expressed in tumor lesions. Imiquimod activates the acquired immune system through IFN-alpha and IL-12.[18,19] Local skin reactions: itching, erythema, crusting, vesicles, erosion, and scaling have been reported during imiquimod application.[16]

Topical 5% imiquimod cream could be recommended for patients diagnosed with EQ in whom surgical biopsy and excision cannot be performed, even in case of clinical suspicion only. Imiquimod cream is a relatively low-cost option with tolerable side effects. Close follow-up is mandatory for treating the recurrences.

CONCLUSION

Early diagnosis of EQ is vital to improve prognosis, even when the diagnosis is based only on clinical examination and HPV testing and is not sustained by histology, stressing the role of a multidisciplinary team in the management of anogenital premalignancies. In a delayed diagnosis, treatment options are linked to several complications, significant negative effects on the patient's mental status and quality of life, and poor prognosis.

CONFLICT OF INTEREST

The authors declare no competing interests, financial or otherwise. Also, the authors report no conflicts of interest.

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