Human Papillomavirus Type-6 in Penile Intraepithelial Neoplasia of the Urethra: A Case Report

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Abstract

The increasing incidence of precancerous and cancerous lesions in the genito-urinary area in young adults over the last years is correlated with certain sexually transmitted diseases; the most common of them is infection with Human Papillomavirus (HPV). Penile intraepithelial neoplasia (PeIN) is a rare premalignant lesion known to have a close association with oncogenic genotypes of HPV. It can affect any part of the penis surface, rarely the urethra. We report a case of a 25-year-old male with a urethral PeIN caused by HPV-6 infection with emphasis on the diagnostic challenges of the disease.

INTRODUCTION

Human papillomavirus is the most common sexually transmitted infection worldwide [1]. Its significance has taken on a new dimension since HPV has been shown to be closely associated with precancerous lesions and invasive carcinomas of the genito-urinary area [2].

Penile intra-epithelial neoplasias are precancerous lesions, from which squamous cell carcinomas (SCC) can arise [3]. Although all HPV types appear to be able to stimulate proliferation of specific cells, HPV-6 and -11 induced lesions are believed to be of low risk of malignant conversion [4]. However, HPV-6 DNA was detected within the cells of a urethral PeIN in a Tunisian young patient. Our aim, by reporting this atypical case, is to increase awareness about this condition among practitioners.

CASE PRESENTATION

We present the case of a 25-year old male, with no particular personal history, serving in the Tunisian army as an active duty soldier, who presented with a 5-month history of an exophytic formation in the meatus. Physical examination revealed an otherwise healthy adult with a 1cm-papillomatous pink tumor with a bristly and filiform surface conferring a “cauliflower” aspect to the lesion, located in the urethral meatus (Figure 1). During comprehensive questioning, the patient reported a serious urethral discharge evolving for three months, with no history of dysuria, urethrorrhagia or voiding problems. According to his statement, the last unprotected sexual intercourse dates back to two years. Syphilitic, hepatic (hepatitis B and C), and HIV serologies returned all negative. Urethroscopy was performed to detect the presence of warts beyond the navicular fossa (distal penile urethra and bladder). The urethro-vesical mucous membranes were not involved. On the basis of these findings, the diagnosis of condyloma acuminata was established. The patient underwent an urological surgery under general anesthesia with an excision of the condyloma, a regularization of the urethral meatus, and a placement of a urinary catheter to avoid urethral stenosis for 5 days. Histological examination of the 1.3 x 0.7 cm excision piece was performed with hematoxylin and eosine staining revealed a high grade intraepithelial neoplasia, developed on a condyloma of the urethral meatus, with adequate margins (Figures 2,3). After one month, the patient presented with a relapse of the lesion. Detection and typing of HPV by multiplex Polymerase chain reaction (PCR) revealed DNA sequences of HPV type 6 and gave negative results with other HPV-types (Figure 4). Treatment was continued with Topical Imiquimod 4% three times a week.
Central HPV-induced PeINs, the former being linked to a Papillomavirus infection, the latter occurring most often in chronic penile dermatosis (lichen sclerosus and lichen planus) [3]. The frequency of HPV-induced PeINs is difficult to assess, however an epidemiological approach can be made through the screening of cervico-vulvar intraepithelial neoplasia in female partners [5]. The average age of onset of PeIN is becoming earlier (30-40 years) in recent years, as for vulvar intraepithelial neoplasia in females [5]. This is being correlated with an increased incidence of unprotected sexual outcources among young adults.

Figure 2 Acanthosis, abundant koilocytes and atypical parakeratosis in the histological examination of the excision piece.

- a. Hematoxylin and Eosin (H&E) Stain, original magnification x20 showing acanthotic squamous mucosa
- b. H&E Stain, High magnification x200 demonstrating abundant binuclear koilocytes, and atypical parakeratosis with marked cytological abnormalities.

DISCUSSION

Penile intraepithelial neoplasia is a histological entity corresponding clinically to penile dysplasia [5]. It is characterized by architectural and cytological abnormalities of the genital epithelium. These PeINs are often clinically and histologically similar to vulvar intraepithelial neoplasia occurring in women, and it is classic to grade them in low- and high-grade categories, depending on the height of the cytologic atypia in the epithelium [5].

The originality of this case report leans mainly on three features: the young age of the patient, the challenging diagnosis considering the location and the clinical aspect of the lesion, and the detection of a low-risk HPV genotype in a precancerous lesion.

It is classic to distinguish HPV-induced PeINs from non-HPV-induced PeNs, the former being linked to a Papillomavirus infection, the latter occurring most often in chronic penile dermatosis (lichen sclerosus and lichen planus) [3]. The frequency of HPV-induced PeINs is difficult to assess, however an epidemiological approach can be made through the screening of cervico-vulvar intraepithelial neoplasia in female partners [5]. The average age of onset of PeIN is becoming earlier (30-40 years) in recent years, as for vulvar intraepithelial neoplasia in females [5]. This is being correlated with an increased incidence of unprotected sexual outcources among young adults.

Figure 3 Architectural disorientation and dyskeratotic cells.

- A) H&E Stain, Original stain x40 showing architectural disorientation.
- B) H&E stain, High magnification x200 showing dyskeratotic cells located at the base of proliferation.
- C) H&E Stain, High magnification x400 showing multiple koilocytes in the superficial layers: some are binuclear; others are crumpled containing hyperchromatic nuclei with irregular contours surrounded by a clear halo.
Central

Figure 4 Polymerase chain reaction (PCR) revealed DNA sequences of HPV type 6 in the urethral lesion of the patient.

In most cases, PeIN are located on the glans or the foreskin, with a maculopapular erythoplastic clinical aspect [6]. Urethral involvement is uncommon and little recognised, and usually limited to the distal 3cm of the meatus [1]. Given the misleading clinical appearance suggestive of a simple condyloma acuminata in our patient, the lesion could have been destroyed by cryotherapy, electrocoagulation or carbon dioxide laser without verification of its histological nature. Hence the need to perform a biopsy at the slightest doubt to allow early diagnosis, especially in cases of atypical forms or locations as in our case.

Detection and typing of the virus by PCR in PeINs mostly reveal simultaneous infection with several genotypes, mainly oncogenic papillomaviruses (HPV-16, 18,33) [5]. The detection of HPV-6 DNA within the excision tissue was a surprising finding in our patient. In spite of the general experience that HPV-6 is found in benign lesions, there have been some reports about the presence of HPV-6 DNA in malignant and precancerous lesions [4]. Gissman et al., recorded HPV-6 and 11 DNA sequences in several cervical cancers [7]. Zachow et al also detected HPV-6 DNA hybridizing to DNAs of a penile bowenoid papulosis in a 33yo male, of a penile carcinoma in a 17yo male, and of a vulval carcinoma in-situ in a 77yo female [8].

Therapeutic management of PeIN is mainly based on a conservative treatment, either a thermal destruction, preferably by laser, or a surgical excision of the lesion [5]. Other therapeutic methods such as 5-fluorouracil, interferon or imiquimod are proposed but still to be evaluated [3]. Over time, these lesions can regress, persist, recur, or progress, in some cases to invasive SCC. Rate of progression of PeIN is not known. Natural history of cervical intraepithelial neoplasia is best studied: progression to invasive SCC occurs in 36% of cases over a 20-year period [9].

Clinical surveillance is essential after treatment because HPV may persist in the latent state in the genital mucosa despite a complete excision of the lesion, explaining the risk of recurrence, as in our case.

CONCLUSION

In conclusion, meatal and urethral PeINs are rare. However, their incidence is higher when they are routinely and actively investigated as careful analysis ultimately permits their diagnosis.

REFERENCES

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Cite this article


