International Journal of STD & AIDS 2004; 15: 836–838

CASE REPORT

HPV 16/18-associated condyloma acuminatum of the urinary bladder: first international report and review of literature

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Summary: Condyloma acuminatum is an anogenital lesion caused by human papillomavirus (HPV) infection, a common sexually transmitted disease. It usually affects the external genitalia while urethral and/or bladder involvement is rare. HPV types are classified into three categories depending on their oncogenic potential: low risk (type 6, 11, 42, 43, 44, 59, 66, 68, 70), intermediate risk (type 30, 31, 33, 34, 35, 39, 40, 49, 51, 52, 53, 57, 58, 63, 64) and high risk (type 16, 18, 45, 56). High-risk and intermediate-risk HPV-DNA types, together with other co-factors still to be defined, are responsible for over 90% of the cases of anogenital pre-malignant and malignant tumours. We report a unique case of a urinary bladder condyloma acuminatum positive for HPV 16/18 DNA, presented as the primary and only site of the disease in an immunocompetent patient. We review the treatment and follow-up strategies of this rare lesion.

Keywords: condyloma acuminatum, HPV, bladder, carcinogenesis

Introduction

Human papillomavirus (HPV) infection is pathogenetically related to a variety of benign and malignant lesions involving the anogenital region[1]. More than 70 types of HPV have been identified. Based on their oncogenic potential, they are subdivided into three groups: low-risk (types 6, 11, 42, 43, 44, 59, 66, 68, 70), intermediate-risk (types 30, 31, 33, 34, 35, 39, 40, 49, 51, 52, 53, 57, 58, 63, 64) and high-risk (types 16, 18, 45, 56) HPV-DNA[1]. High-risk and intermediate-risk are implicated in over 90% of anogenital pre-malignant and malignant tumours[1].

We present a unique case of intravesical primary condyloma acuminatum secondary to high-risk HPV 16/18 DNA urinary bladder infection. We review the treatment and follow-up strategies of this rare lesion.

Case report

A 33-year-old female with a medical history of recurrent urinary tract infection was investigated for irritative lower urinary tract symptoms and microscopic haematuria. Physical examination including inspection of the introitus, vagina and perineum was normal. Urine culture was negative while voided urine cytology showed no evidence of malignancy. Cervical smear was negative for malignancies and *Chlamydia trachomatis* or HPV infection. Genitourinary ultrasound and excretory urogram demonstrated no pathological findings.

Cystoscopy revealed numerous white flecks resting on a diffusely reddish mucosa of the bladder trigone. Transurethral resection (TUR) of the lesion followed. Light microscopy revealed a hyperplastic, flat squamous epithelium with foci of hyperkeratosis and rare presence of koilocytic cells with abundant clear cytoplasm and hyperchromatic nuclei. No papillary configuration was evident. No evidence of extension to the submucosa or presence either of abnormal maturation patterns or significant atypia was found. The diagnosis of a flat condyloma was made. On *in-situ*-hybridization (ISH) analysis (Kreateck Diagnostic Digoxegenin label In-situ Hybridization Kit, Rembrand Series, Amsterdam, The Netherlands) tissue samples were mainly positive for HPV 16/18 sequences (Figure 1), while a weak signal was detected for HPV 6/11 sequences. Immunological evaluation of the patient revealed no immune-deficiency. Cystoscopy at three and six months, the former accompanied with biopsies of the involved area, revealed no condyloma acuminatum morphology or HPV DNA. The patient remains asymptomatic on a nine-month follow-up.

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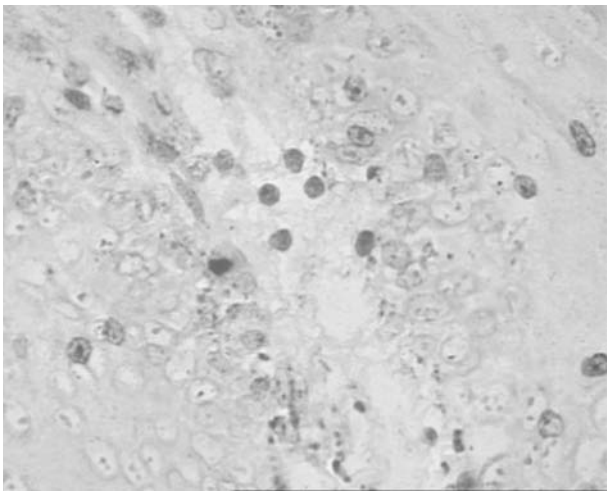

Figure 1. Positive nuclei for HPV 16/18 in metaplastic squamous epithelium (ISH, ×250). (This figure is reproduced in colour online)

Discussion

Condyloma acuminatum, a sexually transmitted disease caused by human papillomavirus infection, predominantly affects the mucocutaneous surfaces of the anogenital region. Urethral involvement occurs in up to 20% of cases, mainly in the distal portion[1–3]. Intravesical localization is rare and is usually accompanied with urethral, vulval, vaginal, anal or perineal involvement, frequently in immunocompromised patients[4,5]. Isolated bladder lesion is extreme as less than 10 cases, including the current one, have been reported (Table 1)[3,4,6–10]. Of them, only five have been tested for HPV-DNA sequences. HPV 6/11 and HPV 11 were identified in three and two, respectively[10]. Our finding is unique in that HPV 16/18 was found in a primary condyloma acuminatum of the bladder of an immunocompetent patient.

HPV 16/18 is considered a high-risk type for carcinogenesis type, due to its high detection in various malignant tumours[1]. Controversy exists on the role of HPV in bladder carcinogenesis. Current evidence indicates little role of HPV in the development of urothelial carcinoma[11–12]. However, an overall rate of HPV positivity in transitional cell carcinoma of 32.9% has been reported, with 20.3% of cases positive for HPV 16, 3.8% for HPV 18 and 8.9% positive for both types[13]. In addition, Kitamura *et al*. detected HPV-DNA 16 in carcinoma *in situ* of the urinary bladder in an immunocompromised patient, which suggests that the bladder epithelium could be susceptible to the oncogenic potential of HPV 16[14].

HPV 16/18 DNA was detected in 31% of the invasive squamous cell carcinoma (SCC) of the penis, and HPV 16 in 29% of SCC of the male urethra and in 59% of SCC of the female urethra[12]. Although condyloma acuminatum of the bladder may undergo malignant transformation to SCC and its variants[15–17] to date, the literature has only addressed the association between HPV and SCC of the bladder in less than 10 cases[12]. Of these, HPV was detected in two, and these contained low-risk HPV 11 DNA and high-risk HPV 18 DNA, respectively[12]. The latter patient was immunocompromised (post-renal transplantation). A variety of treatment modalities have been used to cure bladder condyloma acuminatum. Transurethral resection has been proposed to be effective in solitary lesions (Table 1). As malignant transformation has occurred following TUR monotherapy, intravesical instillation of virostatic agents such as podophyllin, colchicine, 5-FU, BCG and interferon have been occasionally used as an adjuvant therapy[6–10]. This seems to be a reasonable approach for high-risk HPV types. However, in most reported cases condyloma of the bladder was refractory to conservative therapy, necessitating cystectomy[5]. As condyloma may relapse and malignant transformation has been reported even two years after initial resection[4], close cystoscopic follow-up is recommended, especially for these lesions positive for high-risk HPV-DNA.

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Table 1. Condylomata acuminata in the urinary bladder as a primary site (clinical data)

Reference	Age	Sex	Initial treatment	Prognosis
Kleiman, 1961[6]	Unknown	M	Podophyllin–bismuth	Recurrence 16 months later
Kleiman, 1962[6]	38	M	Oxophenarsine–radiation	Malignant change
DeBenedicts, 1977[3]	27	M	TUR–podophyllin-colchicine–5-FU	Clear after 13 months
Masse 1981[7]	76	M	TUR	Clear after 14 months
Poppel, 1986[8]	55	M	TUR	Clear after 6 months
Walther, 1986[9]	43	F	TUR	Malignant change
Mistro, 1988[4]	50	F	Surgical excision	Recurrence 2 years later
Iwasawa, 1992[10]	49	F	TUR	Clear after 14 months
Our case 2003	33	F	TUR	Clear after 6 months

M = male; F = female; TUR = transurethral resection

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(Accepted 10 March 2004)