Case Report

Human papillomavirus infection causing refractory lower urinary tract symptoms in a young female

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ABSTRACT

We describe a rare case of refractory lower urinary tract symptoms in a young woman caused by human papillomavirus (HPV) infection. Concurrently, vulvar and vaginal warts were present, particularly near the external urethral meatus. Biopsy of the whitish plaque in the trigone of the bladder demonstrated signs of HPV infection and bladder leukoplakia; polymerase chain reaction analysis of this tissue was positive for HPV16. Systemic and local treatments for HPV infection were prescribed. All symptoms resolved. Follow-up examination revealed negative HPV DNA in the bladder tissue.

INTRODUCTION

Human papillomavirus (HPV) has more than forty subtypes that infect the anogenital area, oropharynx, and skin in females. HPV-associated clinical conditions include asymptomatic infection, different types of warts, dysplastic lesions, and invasive cancers of the vulva, vagina, cervix, anus, and oropharynx. The genital HPV infection prevalence among females is 39.9% (95% confidence interval: 36.8%–43.1%), making it the most common sexually transmitted infection in the world.[1] It is known that HPV infection may also occur in the urethra and urinary bladder, playing a role in the development of recurrent cystitis and bladder cancer. Herein, we report a case of HPV-associated refractory lower urinary tract symptoms in a young female.

CASE REPORT

A 23-year-old woman presented to the urology department with a 4-year history of urinary frequency, urgency, and dysuria. These symptoms persisted despite multiple courses of antibiotics. According to the 3-day bladder diary, she voided 125 ml on average, 23 times daily with 4.7 urinary urgency episodes. Urinary ultrasonography and uroflowmetry revealed no abnormalities; postvoid residual volume was 45 ml. She had never smoked, and her past medical history was nonsignificant. During the past 5 years, she had four sexual partners, and barrier contraceptives were used inconsistently. Pelvic examination revealed multiple vulvar and vaginal warts, particularly near the external urethral orifice. She was not vaccinated against HPV. Her Papanicolaou smear and high-risk HPV test were normal.

Complete blood count, serum biochemistry, and urine culture showed no abnormalities; however, thirty red blood cells/high power field were found on urinalysis. Microbiome composition of the urogenital tract was normal, and polymerase chain reaction (PCR) tests of cervical swabs for Neisseria gonorrhea, Chlamydia trachomatis, Trichomonas vaginalis, Ureaplasma urealyticum, Mycoplasma genitalium, and Mycoplasma hominis were negative. PCR tests of

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urethral swabs for herpes simplex virus types 1 and 2, Epstein–Barr virus, and cytomegalovirus were also negative. Cystoscopy demonstrated a whitish plaque with debris, approximately 2 cm × 2.5 cm in size, located in the trigone of the urinary bladder [Figure 1], and multiple petechiae of the mucosa after hydrodistention. Biopsy of those plaques was performed, and histopathological examination revealed papillary hyperplasia of squamous epithelium with koilocytosis and scant lymphocytic infiltration [Figure 2]. PCR analysis of the paraffin-embedded bladder tissue biopsies detected HPV16, confirming active HPV infection.

For the systemic treatment of the HPV infection, 5 ml of sodium deoxyribonucleate with Ferrum 1.5% solution intramuscularly once daily for 10 days was prescribed. Imiquimod 5% cream application thrice weekly for 10 weeks was used to remove vulvar and vaginal warts. No other concomitant therapy was used. Three months later, all lower urinary tract symptoms resolved. Six months after the treatment, cystoscopic findings were the same, whereas histopathological examination showed mild inflammatory infiltration and solitary koilocytes. PCR analysis of the bladder tissue biopsies came back negative.

DISCUSSION

HPVs are highly contagious double-stranded DNA viruses that are transmitted through direct physical contact. HPV transmission rate after unprotected sexual intercourse is up to 60%.[2] Approximately 80% of the entire female population is exposed to HPV sometime in their life. HPV infection incidence in women normally peaks between ages 20 and 25 years, when most women initiate sexual activity.[3] Most HPV infections are asymptomatic and in 70%–90% of cases are cleared within 12–24 months.[3,4] Only a small fraction of those infected have a persistent HPV infection that may cause cellular changes in the host, as in our case. Recent studies suggest that multiple sexual partners, the absence of HPV vaccination, bacterial vaginosis, immunosuppressive conditions, and smoking contribute to the persistence of HPV infection.[2,3]

Microscopic hematuria, absence of both bacteriuria and leukocyturia, and normal urine culture are signs of a viral lower urinary tract infection.[4-6] Avascular whitish plaque in the trigone of the urinary bladder with the histologic features of squamous metaplasia of the urothelium is characteristic of bladder leukoplakia. Papillary hyperplasia of squamous epithelium is a histopathologic sign like the one observed in genital warts. Koilocytosis and detection of HPV16 DNA in bladder tissue biopsy confirm active HPV infection in our patient.

Among high-risk HPV types, HPV16 and HPV18 are most associated with persistent HPV infection. HPV16 is implicated in ~60% of invasive cervical cancers and ~85% of HPV-related noncervical cancers worldwide.[7] Recent meta-analyses suggested a significant correlation between HPV infection and bladder cancer, particularly tumor stage, tumor grade, and recurrence rate.[8] However, the role of high-risk HPV types in the development of persistent voiding disorders is not well understood yet. Jimenez-Pacheco *et al.* showed that high-risk HPV types can cause benign bladder lesions, such as squamous metaplasia of urothelium.

The etiological factors of leukoplakia vesicae are not defined. The widely accepted theory is that the transitional epithelium is capable of metaplastic and neoplastic transformation in response to chronic irritation or inflammation, hormonal changes, Vitamin A deficiency, and bladder stones. In our case, persistent HPV infection of the lower urinary tract contributed to the development of leukoplakia vesicae.

Currently, there is no recommended systemic treatment for HPV infection. Sodium deoxyribonucleate and Ferrum complex has antiviral and immunomodulating effects, being

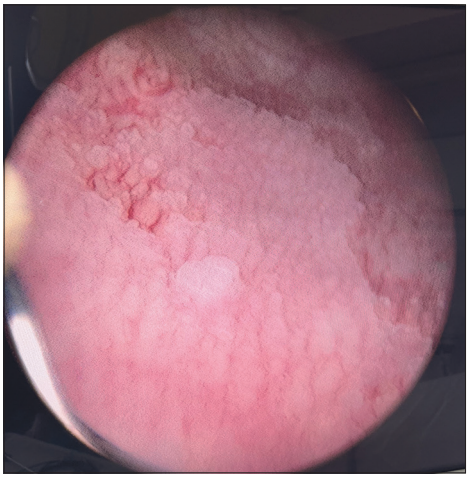

Figure 1: Cystoscopy demonstrating a whitish plaque in the trigone of the bladder

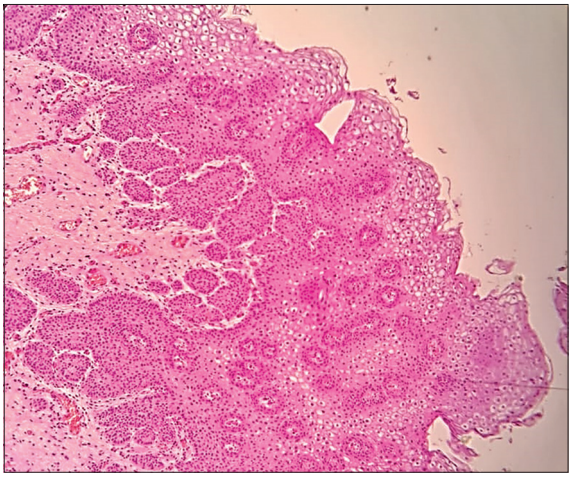

Figure 2: Histology of the bladder tissue biopsy revealed papillary hyperplasia of squamous epithelium with koilocytosis and scant lymphocytic infiltration (H and E, ×20)

active against persistent HPV infection. Refractory lower urinary tract symptoms were successfully managed with that medication, although it is not clear whether the antiviral activity or enhanced cell-mediated immunity contributed to that.

CONCLUSION

Persistent HPV infection may cause histological changes in the urinary bladder and refractory LUTS in females. Further studies are required to better understand the etiology, pathophysiology, and systemic treatment of those disorders.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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