Introduction to problems associated with HPV infection in urology

Sławomir Dutkiewicz
University Natural and Humanistic J.K. in Kielce, Poland

KEY WORDS

HPV ◗ Human Papillomaviruses ◗ HPV-infections ◗ premalignant lesions ◗ penile intraepithelial neoplasia ◗ penile cancer ◗ cancer of uterine cervix ◗ prophylactic vaccines

ABSTRACT

The paper presents problems of infections with different types of Human Papillomaviruses (HPV) which are the most frequently occurring sexually transmitted infections. Their prevalence in males is comparable to that in females. The majority of HPV infections in males produce no clinical symptoms and are transient in nature. The most frequently encountered clinical manifestation of an HPV infection is genital warts which occurs in about 1% of sexually active men and are predominantly located at the distal parts of the penis. In more than 90% of cases warts are caused by low-oncogenic-risk HPV types 6 and 11. Persistent infections with high-risk HPV types 16 and 18 are associated with the development of nearly 50% of penile squamous cell cancers. These cancers usually arise from penile intraepithelial neoplasia, which is HPV positive in the majority of cases (above 80%). Recently an increased incidence of PIN, which should be monitored, could be observed especially in partners of women with diagnosed CIN. Penile cancers are usually non-keratinizing, of a verrucous or basaloid nature. Squamous cancers of the anus are related to high-risk HPV infections. Moreover, the role of HPV infections in the etiology of prostate cancers has been suggested, although a currently available body of evidence is not sufficient for consistent confirmation.
The article also presents the diagnostic methods to detect sublinical infections, which suggest performing cytology and peniscopy, with necessary follow-up examinations such as virusology and histopathology. Moreover, there is information on HPV prevention using vaccines and less invasive treatment.

Genital tract infections are caused by a large number of microorganisms, which are frequently sexually transmitted in both sexes [1]. The following microorganisms are sexually transmitted: *Chlamydia, Mycoplasma, Trichomonas vaginalis,* Herpes viruses type 1 and 2 (HSV-1 and HSV-2), as well as Human Papillomavirus (HPV). Especially *Chlamydia trachomatis,* HSV-2 and nicotine play a role that is similar to pro-oncogenes [2,3]. Infections with genital HPV types (there are about 40 of such types) are the most common sexually transmitted viral infections. A man having intercourse with a woman whose cytology results demonstrated HPV infection markers such as koilocytes, dyskeratocytes or keratotic scales, requires an andrological examination in order to detect, whether he is infected with this virus. In approximately 70% of people between 15 and 25 years of age the infection is transient and may regress within one year, while in others it becomes persistent. In immunosuppressed patients have wide lesions of a severe character. A persistent HPV infection may lead to mucous membrane dysplasia and eventually to cancer. Genital cancers have been reported in patients with symptomatic and subclinical HPV infections [4, 5, 6].

Preneoplastic and neoplastic lesions of the genital and anal area are caused by the following HPV types: 16, 18, 31, 32, 41, 45, 51 and 56. Benign lesions with a low risk of neoplastic transformation (HPV: 6, 11, 42, 43 and 44) include, for example genital warts, pointed condyloma, giant Buschke-Lowenstein condyloma, bowenoid papulosis, Paget's disease [8]. The consequences of sexually transmitted diseases (STDs) are as follows: organ inflammations, infertility, ectopic pregnancies in women, cervical cancer, neoplasms in the transitional epithelium of the urinary tract, and fetal infections. Perigenital ulcers facilitate infections with other microorganisms, including HIV. On the other hand, viral infections of the mucous membranes favor bacterial infections [5, 9].

HPV viruses belong to the Papillomaviridae family, Papillomavirus genus and they include more than 120 types. Their genetic material consists of a double-stranded DNA molecule. They infect skin and mucosal epithelial cells and their developmental cycle is associated with the differentiation of infected cells [8].

The HPV genome consists of about 8 thousand base pairs, and double-stranded DNA contains several genes. Open reading frames (ORF) that code information necessary for viral replication are located on one strand of nucleic acid and have been divided into early (E) and late ones (L). In all HPV types they are positioned similarly to each other. Moreover, the genome contains a long control region (LCR) which does not code structural proteins, but plays a role in the regulation of the DNA synthesis and a viral life cycle [5, 8].

Moreover, the genome comprises regions supporting the transformation of an infected cell. They affect the development of glycosaminoglycan receptors, which are also necessary for other viruses, as well as bacteria, in the course of epithelial adhesion [9, 10]. At the same time epithelial damage opens a way for other factors taking part in cancerogenesis and inflammatory responses. Furthermore, cells changed by inflammation produce: cytokines, chemokines, and growth factors, which also stimulate oncogenesis [11, 12].

HPV multiplies only in proliferating cells. Inflammatory conditions of genital organs and factors increasing epithelial proliferation favor the infection and multiplication of HPV [5]. HPV infection may cause expressional disturbances of host cell genes regulating a cellular cycle. With regard to the neoplastic transformation, the important role is played by proteins coded by the genes in the early regions, E6, E7, and E2. E6 and E7 proteins are called viral oncoproteins. They form complexes with products of cellular antioncogenes and increase cell proliferation by disrupting DNA repair processes. The interactions of E6 and E7 products of the viral genome with human proteins, p53 and Rb may lead to neoplasia (5, 13, 14). However, a neoplastic condition rarely develops (within many years after infection). HPV is not

the only variable taking part in this process. The action of about six factors is necessary for the malignant tumor to develop [15].

An HPV infection is directly related to penile, anal and vulvar cancer, although the relationship between the infection and neoplasm development has not been definitively explained [15]. Squamous anal cancers develop as a consequence of mucosal infection with high-risk oncogenic HPV types. Anal intercourse contributes to this.

The HPV structure and patho-oncogenesis with elements of antiviral immunity will be presented in the following articles. The fact that oncogenic HPV types 16 and 18 cause precancerous lesions and cancers of the external genital organs should be especially emphasized [11, 12]. Chronic infection with these HPV types in men is often associated with the development of penile squamous cell carcinomas. They are based on penile intraepithelial neoplasia (PIN) and are mainly nonkeratinizing carcinomas of a verrucous or basaloid type. The detection of HPV DNA during molecular tests (*in situ* hybridization or PCR) is equal to the detection of penile intraepithelial neoplasia. Penile squamous cell carcinomas develop on the mucosal membrane of the prepuce, coronal sulcus, and glans penis. The following conditions contribute to this: phimosis, inflammatory states, lichen, papillomas and nicotine. Squamous cell carcinoma *in situ* corresponds with penile intraepithelial neoplasia (PIN) III, namely the highest grade. Superficial carcinomas are usually well-differentiated, whereas the ones that penetrate deeply are not differentiated. Another mechanism of carcinogenesis of keratinizing carcinomas is poorly associated with an HPV infection. The lesions in men are located outside the penis, in the urethra, scrotum and perianal area. In Poland, L. Walczak has the best clinically documented cases [16, 17].

The subsequent article presents the diagnostics of HPV infections, including PCR, which is based on the detection of viral genetic material (which allows for HPV serotyping), and the detection of subclinical infections using peniscopy, vulvoscopy or anoscopy. The results of nucleic acid hybridization and PCR are crucial for a urologist to make a decision regarding the extent of a surgical procedure; moreover, they provide pathomorphologists with information allowing for the differentiation of cellular lesions associated with HPV infections from lesions characteristic for neoplasia [11].

Treatment of lesions caused by HPV includes prevention measures, pharmacological therapy and surgical treatment including saving procedures and radical measures which eliminate tissues to a large extent [5, 12]. In patients with lesions located on the penis the extent of a surgical procedure is a problem (sexual functions, the quality of life). The detection of HPV infection markers in the squamous epithelium is the basis for an organ-saving procedure of eliminating the inner layer of the prepuce [15, 17]. In cases with low grade lesions, e.g. PIN I, only anti-inflammatory therapy results in their regression [18].

Currently the fundamental measures to fight with HPV include prophylaxis against infections with oncogenic HPV types and of the resulting lesions. Of great importance is the fact that prophylactic vaccines have been developed and introduced into the clinical range of prophylactic vaccines and they have been available for some time. Such vaccines prevent the development of precancerous and cancerous lesions, namely cancers. So far a great number of tests have reported a high efficacy in terms of preventing persistent HPV infections and cytological and histological lesions caused by oncogenic types of the virus. These vaccines also prevent from precancerous lesions of an early and advanced nature such as cervical intraepithelial neoplasia (CIN) in women and penile intraepithelial neoplasia (PIN) in men [19].

Based on the data of The American Cancer Society, 18% of cancers worldwide are caused by infectious factors [20]. The report indicating a relationship between prostate cancer and HPV infection is noted. HPV type 18 is suspected to be one of the carcinogenesis factors, as its tropism towards the glandular tissue has been reported [21]. Important epidemiological data also indicates the possibility that infection factors (XMRV retrovirus) initiate and promote prostate cancer. Research involving men with prostatitis or with sexually transmitted infections indicates a significantly higher risk of prostate cancer development in these subjects [22].

REFERENCES

1. Schneede P, Tenke P, Hofsteter AG: *Sexually Transmitted Diseases a synoptic overview for urologists.* Eur Urol 2003; 44: 1-7.
2. Dutkiewicz S: *Zakażenia układu moczowo-płciowego przez Mycoplazmy.* Zakażenia 2003; 1: 116-117.
3. Bosch FX, Manos N, Munoz N et al: *Prevalence of HPV in cervical cancer: a worldwide prospective.* J Natl Cancer Inst 1995; 87: 796-802.
4. Stone KM: *Human papillomavirus infection and genital warts: update on epidemiology and treatment* Clin Infect Dis 1995, 20 (suppl 1): 591-597.
5. Majewski S, Sikorski M: *Szczepienia przeciw HPV. Profilaktyka raka szyjki macicy i innych zmian związanych z zakażeniem HPV.* Lublin: Czelej, 2006; pp 25-32.
6. Majewski S, Pniewski T, Goyal-Stec M: *Rola wirusów brodawczaka w rozwoju zmian łagodnych i złośliwych okolicy narządów płciowych.* Zakażenia 2006; 62: 73-83.
7. Parrat JR, Hay DP: *Sexually transmitted infections.* Curr Opin Obstet Gynecol 2003; 13: 224-231.
8. Silins L, Dillner J: *Papillomavirus Report*, 8; 3, Leeds U. P., 2000.
9. Superti F, Longhi C: *Herpes simplex virus type 2 modulates the susceptibility of human bladder cells to uropathogenic bacteria.* Med Microbiol Immunol 2001; 189: 201-208.
10. Haves SE, Kivat NB: *Are genital infections and inflamation cofactors in the pathogenesis of invasive cervical cancer?* J Natl Cancer Inst 2002; 94: 1592-1593.
11. Dutkiewicz S, Szkoda T, Witeska A: *Wpływ zakażeń Human Papillomavirus (HPV) na powstanie raka prącia* Urol Pol 2002; 55: 2, 9-14.
12. Mroczkowski TF (ed): *Choroby przenoszone drogą płciową*, Warszawa: PZWL 1998.
13. Bonnez W: *Papillomavirus report*, 9; 2, Leeds U. P., 1998.
14. Thomas JT, Launins LA, Ruesch MN: *Papillomavirus report*, 9; 3, Leeds U. P., 1998.
15. Griffiths TRJ, Mellon JK: *Wirus brodawczaka ludzkiego i nowotwory urologiczne: Wiedza podstawowa i rola w raku prącia.* BJU Intern (wyd. pol.) 1999, 4 (5): 37-45.
16. Walczak L, Dutkiewicz S, Witeska A, Majewski S: *Zakażenie wirusem brodawczaka ludzkiego HPV – Human Papilloma Virus – problem wenerologiczno-ginekologiczno-urologiczny (aspekt profilaktyki nowotworowej).* Pamiętniki XXIII Konferencji Naukowo-szkoleniowej Urologów Wojska Polskiego, Krynica 25-27. 09. 2003: 44.
17. Walczak L, Dutkiewicz S, Nowakowski R, Witeska A, Majewski S: *Diagnostyka i leczenie łagodnych i złośliwych zmian na prąciu w materiale Kliniki CSK MSWiA w latach 2000-2005.* Pamiętniki Sekcji Urologów Wojskowych PTU, Bełchatów 21-23 marzec 2006: 78-79.
18. Lacey CJN: *Therapy for genital human papillomavirus – related disease.* J Clin Virol 2005; 32S: S82-S90.
19. Lowy D R, Schiller JT: *Prophylactic human papillomavirus vaccines.* J Clin Invest 2006, 116, 1167-1173.
20. The Cancer Atlas Available at www.cancer.org.
21. Weijerman PC, van Drunen E, Konig JJ et al: *Specific cytogenetic aberrations in two novel human prostatic cell lines immortalized by human papillomavirus type 18 DNA.* Cancer Genet Cytogenet 1997; 99: 100-115.
22. Klein E, Silverman R: *Viral integration sites for new prostate cancer virus.* AUA News 2007, v. 12 , issue 8, pp. 1-2.

Correspondence

Sławomir Dutkiewicz
2/56 Lachmana Street
02-786 Warsaw
phone: +48 502 025 8807
sad1947@wp.pl