Cervical Cancer: Open Access

Mini Review Open Access

Review of In Situ Immunopathological Occurrences in Cervical Cancer and Intraepithelial Neoplasia in Humans

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Abstract

Immunosuppressive treatment of organ transplant recipients is associated with an increase in the occurrence of human papillomavirus (HPV) related anogenital malignancies. This cohort study investigated the genotype-specific prevalence of HPV infections in a large cohort of female renal transplant recipients (RTRs). Participants self-collected a cervicovaginal sample for detection and genotyping of HPV. Besides, they completed a questionnaire regarding sociodemographic variables, medical data and sexual behavior. Anogenital screening was offered to all HPV-positive participants. A total number of 218 female RTRs were included. The prevalence of mucosal HPV infections was 27.1% and 17.4% for high risk HPV in particular.

Keywords: Immunopathology; Uterine cancer; Cytokines; Leukocytes; Progression

Introduction

The studied cohort showed a broad range of HPV genotypes and multiple HPV genotypes were found in 27.1% of HPV-positive patients. Seven participants were identified with occult premalignant anogenital lesions. In conclusion, this study shows a high point-prevalence of HPV in female RTRs with a shift in the distribution of genotypes as compared with the general population. Moreover, a substantial number of patients with occult premalignancies were identified. The introduction of self-sampling for HPV positivity can help in early detection of (pre) malignant anogenital lesions in this vulnerable population. Loop electrosurgical excision procedure (LEEP) is the most common, efficient, and conservative treatment for cervical intraepithelial neoplasia and it consists of removing the transformation zone with abnormal cells from cervix. Millions of reproductive-age women undergo LEEP, which is considered the "first line method" in the treatment of women with cervical intraepithelial neoplasia who want to have a baby. However, direct or indirect physical effects, structural changes of the cervical tissue and the process of inflammation and subsequent healing after LEEP could cause an unfavorable microenvironment for pregnancy. As a result many investigators have tried to analyze the correlation between the effect of cervical surgical procedures and the pregnancy outcome [1-4].

Discussion

Most of published studies are retrospective, focusing on preterm delivery, low birth weight, and premature rupture of the membranes, and only a few of these articles investigated the correlation between LEEP and risk of miscarriage in the subsequent pregnancy. Acyclic nucleoside phosphonates (ANPs) are well-known for their antiviral properties, three of them being approved for the treatment of human immunodeficiency virus infection, chronic hepatitis B (tenofovir and adefovir) or human cytomegalovirus retinitis. In addition, cidofovir is mostly used off-label for the treatment of infections caused by several DNA viruses other than cytomegalovirus, including papilloma- and polyomaviruses, which do not encode their own DNA polymerases. There is considerable interest in understanding why cidofovir is effective against these small DNA tumor viruses. Considering that papilloma- and polyomaviruses cause diseases associated either with productive infection or transformation (where only a limited number of viral proteins are expressed without synthesis of viral particles), it can be envisaged that cidofovir may act as antiviral and/or antiproliferative agent. The aim of this review is to discuss the advances in recent years in understanding the mode of action of ANPs as antiproliferative agents, given the fact that current data suggest that their use can be extended to the treatment of non-viral related malignancies. A complete economic evaluation requires accurate data concerning the resources used outcomes, and utilities (patient's preferences) to properly value the cost utility of human papillomavirus (HPV) vaccination strategies. This study was designed to measure the utility loss in health states affected by a broad range of HPV-induced pathologies in both sexes in Italy. As a secondary objective, risk factors influencing the viral transmission and development of HPV infections were also investigated. Patients with a diagnosis of several HPV-induced pathologies including atypical squamous cells of undetermined significance (ASC-US), cervical intraepithelial neoplasia (CIN), cervical and anal-colorectal cancer, head and neck squamous cell carcinoma (HNSCC) and anogenital warts (AWs) were evaluated. Human papilloma virus (HPV) infection causes cancers and their precursors (high-grade squamous intraepithelial lesions) near cervical and anal squamocolumnar junctions. Recently described cervical squamocolumnar junction cells are putative residual embryonic cells near the cervical transformation zone. These cells appear multipotential and share an identical immunophenotype (strongly CK7-positive) with over 90% of high-grade squamous intraepithelial lesions and cervical carcinomas. However, because the number of new cervical cancers discovered yearly world-wide is 17-fold that of anal cancer, we posed the hypothesis that this difference in cancer risk reflects differences in the transition zones at the two sites. Primary cancer of the vagina comprises approximately 3% of all malignant neoplasms of the female genital tract. Approximately 3000 cases are diagnosed annually in the United States, with almost 900 deaths. The incidence of in situ or invasive squamous cell cancer of the vagina is one per 100,000 women.

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Most vaginal cancers occur in postmenopausal or elderly women. When occurring in younger women, the disease seems to be etiologically related to cervical neoplasia, and thus human papillomavirus (HPV) dependent. Vaginal carcinoma is increasingly seen in younger women possibly due to infection with high-risk HPV infections. Squamous cell carcinoma is the most common histologic type of cancer occurring in the vagina. Squamous cell carcinoma tends to occur more commonly in the proximal third of the vagina especially the posterior vaginal wall. Adenocarcinoma may also arise in the vagina, the majority of these being clear cell histology, in young women exposed to diethylstilbestrol (DES) in utero. DES-associated tumors are mostly seen in the anterior upper vaginal wall. Recent studies have suggested potential roles of the microbiome in cervicovaginal diseases. However, there has been no report on the cervical microbiome in cervical intraepithelial neoplasia (CIN). We aimed to identify the cervical microbiota of Korean women and assess the association between the cervical microbiota and CIN, and to determine the combined effect of the microbiota and human papillomavirus (HPV) on the risk of CIN. The cervical microbiota of 70 women with CIN and 50 control women was analysed using pyrosequencing based on the 16S rRNA gene. The associations between specific microbial patterns or abundance of specific microbiota and CIN risk were assessed using multivariate logistic regression, and the relative excess risk due to interaction (RERI) and the synergy index (S) were calculated. The phyla Firmicutes, Actinobacteria, Bacteroidetes, Proteobacteria, Tenericutes, Fusobacteria and TM7 were predominant in the microbiota and four distinct community types were observed in all women. Vaginal intraepithelial neoplasia is an uncommon Human Papilloma Virus-related premalignant lesion of the lower genital tract. There is still no consensus regarding its management. Therapeutic modalities include observation, laser ablation, topical agents, radiation and surgical approach. Due to the current increasing adherence to minimally invasive therapies the aim of this study is to identify and characterize non-excisional treatment modalities. Expectant management is the first therapeutical option in low-grade lesions management. Up to 81% of lesions through an expectant approach regressed spontaneously and most of them were low-grade lesions. In contrast, high-grade lesions, due to its higher potential to invasion progression and low regression rate, require treatment, which should be selected depending on its characteristics and the patient's preference. Cervical cancer is a global health concern. Persistent oncogenic human papillomavirus (HPV) infection is a prerequisite for the development of cervical cancer. Emerging research indicates that the vaginal microbiota may play both protective and harmful roles in the acquisition and persistence of HPV and the development of cervical cancer. This multicenter cohort study mainly aims to reveal the association of vaginal microbiota with the outcome of HPV infection in six months in women of reproductive age. We will recruit 50 research centers and enroll a total of about 10,000 female volunteers with a series of strict inclusion and exclusion criteria across China, including HPV positive and HPV negative women [6-10].

Conclusion

A unified questionnaire will be used to obtain the sociodemographic information, clinical data and lifestyle of all volunteers. Specimens including vaginal secretions swabs and cervical exfoliated cells will be collected at the first visit and follow-up after six months. We will use 16S rRNA sequencing to characterize the vaginal microbiota of volunteers' vaginal swabs. Twenty-one HPV genotypes and other sexually transmitted pathogens, including Neisseria gonorrhoeae, Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma hominis, Mycoplasma genitalium and Herpes simplex type will be examined using flow-through hybridization and gene chip. The association of HPV infection and vaginal microbiota will be investigated, and the core microbiota attributes to the persistent HPV infection will be analyzed in this study.

Acknowledgment

None

Conflict of Interest

None

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